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Development of Nickel-Catalyzed Annulation Reactions

Using Cyclobutanones as a Four-Carbon Unit

Shinji Ashida

2008

Preface

The studies presented in this thesis have been carried out under the direction of Professor Masahiro Murakami at Kyoto University during 2003-2008. The studies are concerned with nickel-catalyzed annulation reactions using cyclobutanones as a four-carbon unit and the effects of boryl substituents on thermal ring-closing reaction of vinylallens.

The author would like to express his sincerest gratitude to Professor Masahiro Murakami for his support, constant guidance, encouragement, and enthusiasm during the course of this study.

The author is deeply grateful to Assistant Professor Takanori Matsuda and Assistant Professor Tomoya Miura for their helpful discussion and suggestion. The author wishes to express his gratitude to Dr. Munehiro Hasegawa, Dr. Sho Kadowaki, Dr. Masahiko Shimada, Dr. Naoki Ishida, Mr. Masaomi Makino, Mr. Ippei Usui Mr. Taisuke Sasaki Ms. Miki Terayama, Mr. Masanori Shigeno, Mr. Motoshi Yamauchi, Mr. Tatsuro Harumashi, Mr. Tsuyoshi Goya, Mr. Yusuke Takahashi, Mr. Tomoya Tsuboi, Mr. Yoshiyuki Yamaguchi, Mr. Yoshiteru Ito, Ms. Mizuna Narumi, Mr. Keita Ueda, Mr. Tomohiro Igarashi, Mr. Taisaku Moriya, Ms. Yuki Hasegawa, Ms. Chiyo Nagae, and all other past members of Murakami's laboratory for their enthusiasm and kind consideration.

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Finally, the author expresses his deep appreciation to his family, especially his parents, Mr. Takao Ashida and Mrs. Satomi Ashida for their constant assistant and encouragement.

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Contents

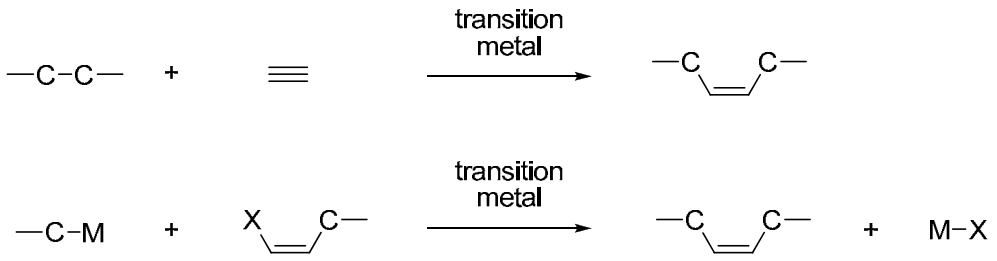
General Introduction

The construction of a variety of carbocycles has been one of the most important research topics in organic synthesis. A powerful method in assembling these ring systems is the cycloaddition class of reactions, because it can achieve multiple carbon–carbon bond formations in a single chemical operation without forming any by-products.

The author focused his research interests on using cyclobutanones as four-carbon units in cycloaddition reactions and therefore developed nickel-catalyzed formal annulation reactions of cyclobutanones with carbon–carbon multiple bonds. The author has also examined the effects of boryl substituents on thermal ring-closing reactions of vinylallenes that have been utilized in cycloaddition reactions as four-carbon units. Details of such findings are described in this thesis, which consists of five chapters. Prior to this detailed discussion, the author wishes to briefly summarize the background literature and outline important findings of his research project.

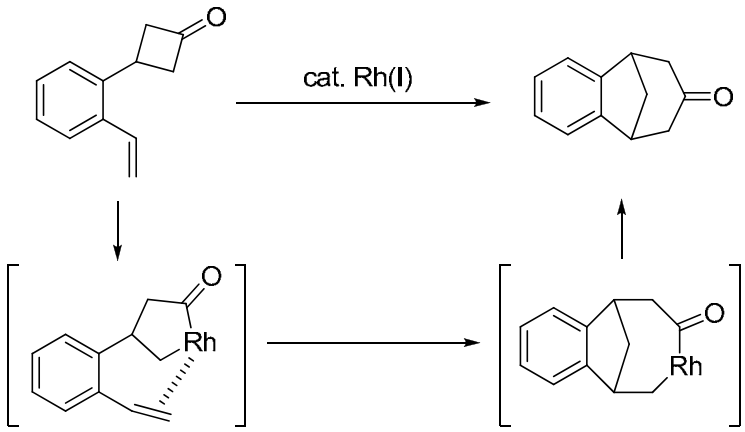
Nickel-Catalyzed Formal Annulation Reactions Using Cyclobutanones as a Four-Carbon Unit

The introduction of transition metals in organic synthesis has greatly expanded the scope, variation and utility of organic transformations, among which are included those that are otherwise difficult or even impossible to achieve.[1] A recently emerging useful protocol consists of a carbon–carbon single bond cleavage with concomitant insertion of an unsaturated organic functionality such as a carbon–carbon triple bond (Scheme 1).[2] Two carbon–carbon single bonds would be newly formed in a single chemical operation without forming any by-products.



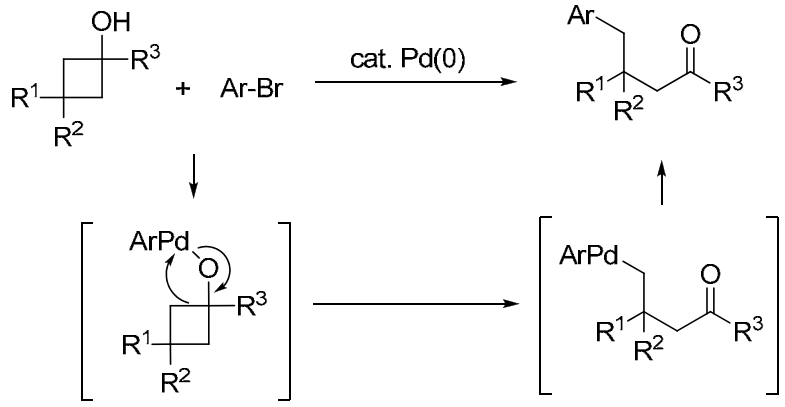
Scheme 1.

The author's group has recently achieved *intramolecular* alkene insertions into cyclobutanones,[3] which proceed through an initial insertion of rhodium(I) between the carbonyl carbon and the α-carbon of cyclobutanone, subsequent intramolecular migratory insertion of an alkene into the resulting rhodium–carbon linkage, followed by reductive elimination (Scheme 2). The author's group has also attempted to realize analogous alkene insertion in *intermolecular* reactions. However, all such endeavors have failed thus far. Since then, to the best of the author's knowledge, no literature reports of transition metal-catalyzed intermolecular insertion of carbon–carbon multiple bonds into cyclobutanones have surfaced. Therefore, the author focused his research interest on this intermolecular insertion reaction and designed a system that exploits a different elementary step for carbon–carbon bond cleavage, that is, β-carbon elimination.[4,5]



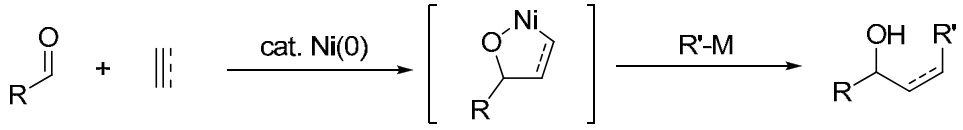
Scheme 2.

In an important recent literature contribution, Nishimura and Uemura reported the palladium-catalyzed oxidative cleavage of tertiary cyclobutanols (Scheme 3).[5a] This reaction likely proceeds via β-carbon elimination, with the palladium-cyclobutanolate acting as the provider of an alkylpalladium species. The literature has since seen several further investigations in which the four-membered carbocycle of a cyclobutylmethyl- or (cyclobutyloxy)metal is opened through β-carbon elimination.[5]



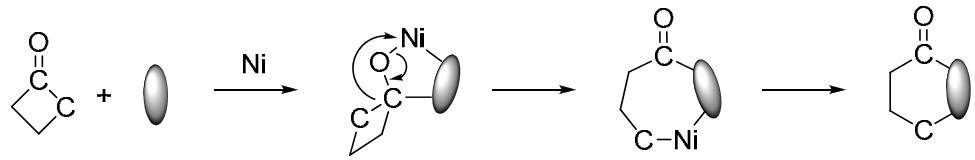
Scheme 3.

Meanwhile, several reports on nickel-catalyzed carbon–carbon bond forming reactions of carbonyl compounds with other unsaturated bonds, such as carbon–carbon double and triple bonds, have surfaced (Scheme 4).[6,7] In the initial step of the plausible mechanism shown below, an oxanickelacycle intermediate would be formed by an oxidative cyclization of a carbonyl group with an unsaturated bond using nickel(0). Compelling evidence to this mechanism was provided by the group of Ogoshi and Kurosawa that reported the direct observation of such intermediates by X-ray analysis.[8]



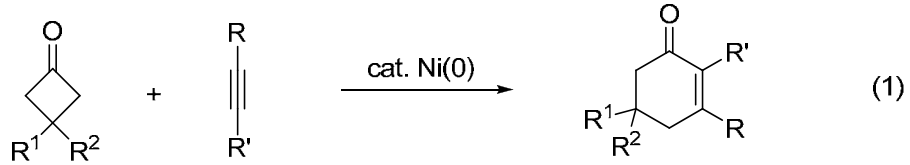
Scheme 4.

In line with these discoveries, the author envisaged that an *intermolecular* insertion of carbon–carbon multiple bonds into cyclobutanones could be achieved by combining a process of oxidative cyclization with a process of β-carbon elimination (Scheme 5). An oxanickelacycle resulting from oxidative cyclization of a cyclobutanone and an unsaturated carbon–carbon bond would contain the nickel cyclobutanolate skeleton as a spiro form. This spirocycle can then be rearranged into a nickelacycle consisting of a single, larger-membered ring through β-carbon elimination. An ensuing reductive elimination would complete the formal insertion of a carbon–carbon multiple bond.



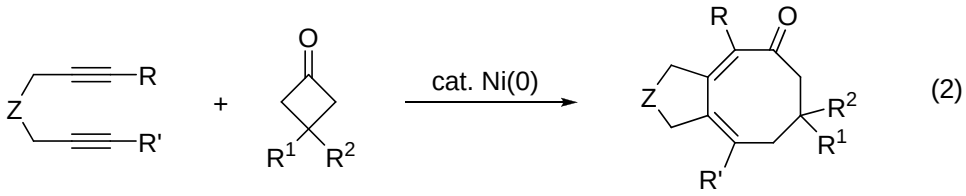
Scheme 5.

In Chapters 1-4 of this thesis, the author has directed a majority of his work onto the nickel-catalyzed insertion of carbon–carbon multiple bonds into cyclobutanones. His results demonstrate that cyclobutanones can be used as four-carbon units in nickel-catalyzed formal annulation reactions. Specifically, Chapter 1 describes nickel-catalyzed intermolecular alkyne insertions into cyclobutanones, which are equivalents of a formal alkyne insertion between the carbonyl carbon and the α-carbon, providing six-membered ring ketones (eq 1). Oxidative cyclization of the carbonyl group and the alkyne with nickel(0) was succeeded by β-carbon elimination from the resulting oxanickelacyclopentene and reductive elimination.



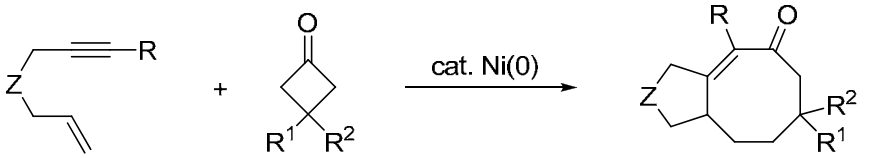
(1)

In Chapter 2, efforts are then directed toward nickel-catalyzed intermolecular [4+2+2] annulation reactions of cyclobutanones with diynes, which furnish bicyclic eight-membered ring ketones (eq 2). This type of reaction likely proceeds through a ring expansion of the oxanickelacycloheptadiene intermediate via β-carbon elimination, forming a nine-membered nickelacycle.



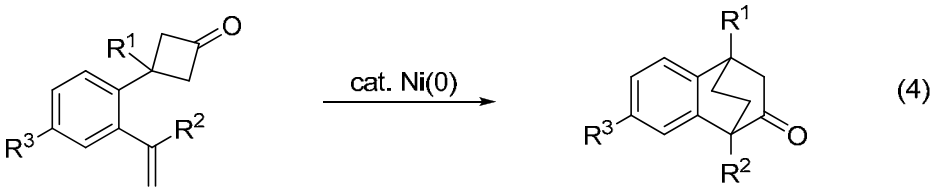
(2)

In Chapter 3, the author then shows another example describing the nickel-catalyzed [4+2+2] annulation reaction of cyclobutanones (eq 3). The nickel-catalyzed reaction of cyclobutanones with enynes afforded only single regioisomers in which the external alkyne carbon of the enyne became connected to the carbonyl carbon of the cyclobutanone.



(3)

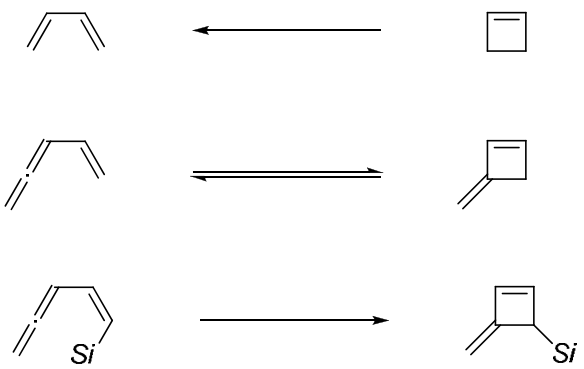
Chapter 4 explicates nickel-catalyzed intramolecular alkene insertions into cyclobutanones (eq 4). In the presence of a nickel catalyst, 3-styrylcyclobutanones were converted into benzobicyclo[2.2.2]octenones via insertion of the alkene moiety into the cyclobutanone in an intramolecular fashion.



(4)

Effects of Boryl Substituents on Thermal Ring-Closing Reaction of Vinylallenes

Analogously to 1,3-dienes, 1,2,4-pentatrienes (vinylallenes) have been utilized in transition metal-catalyzed cycloaddition reactions as four-carbon units. However, vinylallenes have occasionally displayed different chemical behaviors from 1,3-dienes. For example, the author's group reported that only vinylallenes can participate in the rhodium-catalyzed carbonylative [4+1] cycloaddition.[9] Electrocyclizations are also instances where different behaviors between 1,3-dienes and vinylallenes are observed (Scheme 6). Cyclobutene, for example, undergoes a thermal ring-opening reaction in the gas phase at temperatures ranging from 130 to 175 °C to produce 1,3-butadiene, which is thermodynamically more stable than cyclobutene.[10] In contrast, vinylallene and methylenecyclobutene display comparable thermodynamic stabilities such that thermal treatment of one or the other produces an equilibrium mixture of both.[11,12] Based on theoretical calculations, De Lera *et al.* suggested that the introduction of a methyl group at the vinylic terminus of a vinylallene renders the ring-closed methylenecyclobutene to become the thermodynamically favored form.[12b]

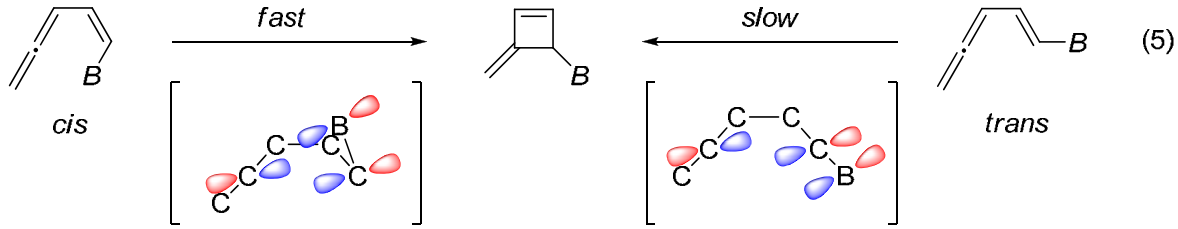


Scheme 6.

The author's group have described the remarkable effects that silyl substituents exert on the electrocyclization of vinylallenes.[13,14] A silyl substituent placed at the vinylic terminus stabilizes the ring-closed product and, in particular, lowers the temperature required for the ring-closure to 110 °C. Marked acceleration of this reaction was rationalized by assuming an electron-accepting interaction of the σ* orbital of the silicon–carbon bond with the distorted, developing bonding orbital in the transition state. Sato *et al.* have also reported that a titanium-substituted vinylallene formed as a reaction intermediate also underwent a

unidirectional ring-closing reaction even at 0 °C.[15] Unlike the previously reported elements silicon and titanium, boron possesses a vacant p orbital, which is a lower-lying electron-accepting orbital compared to the σ* orbitals described above. To investigate these electronic effects, the author focused on studying the significance of boryl substituents on thermal ring-closing reactions of vinylallenes.

Finally, Chapter 5 of this thesis describes the dramatic effect that boron substituents exert on the electrocyclization of vinylallenes, along with its electronic interpretation (eq 5). The unidirectional, thermal electrocyclic closure of *cis*-5-boryl-vinylallene to 4-boryl-3-methylenecyclobutene proceeded significantly faster than the reaction of the corresponding *trans* isomer. The large rate difference observed between the reactions of the *cis* and *trans* stereoisomers can be ascribed to the electronic participation of the vacant boron p orbital in the second highest occupied molecular orbital (SHOMO) of the transition state.



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Chapter 1

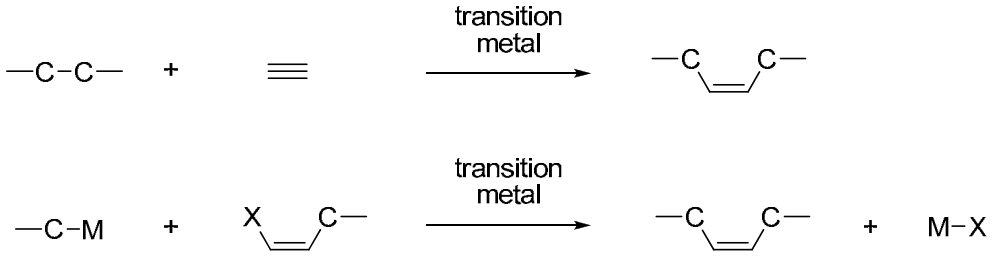
Nickel-Catalyzed Intermolecular Alkyne Insertion into Cyclobutanones

Abstract

Cyclobutanones reacted with alkynes in the presence of nickel(0) catalysts to produce cyclohexenones. Oxidative cyclization of the carbonyl group of the cyclobutanone and the alkyne with the nickel(0) was followed by β-carbon elimination from the resulting oxanickelacyclopentene, and subsequent reductive elimination. This reaction achieves a formal alkyne insertion between the carbonyl carbon and the α-carbon, providing a six-membered carbocyclic skeleton.

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 that those are otherwise difficult to achieve.[1] The author' group 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, the author's group has pursued their studies to develop various kinds of carbon–carbon bond cleavage reactions.[3] Those investigations led the author's group 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 like a carbon–carbon triple bond.[4] 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.

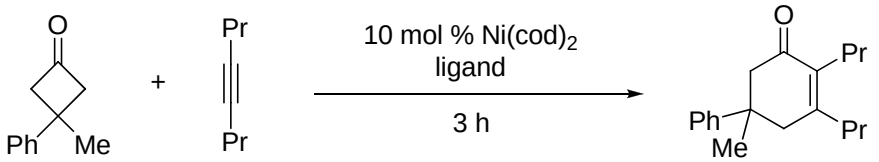
As a result of intensive studies along this line, the author's group have achieved intramolecular alkene insertion into cyclobutanones,[3d,e] which proceeds through insertion of rhodium(I) between the carbonyl carbon and the α-carbon of cyclobutanone, subsequent intramolecular migratory insertion of an alkene into the resulting Rh–C linkage, and reductive elimination. The author's group also attempted to realize analogous alkene insertion in *intermolecular* reactions. However, the reactions the author's group examined have all failed so far. The author then came up with an idea to achieve intermolecular insertion reactions, which exploits a different elementary step for carbon–carbon bond cleavage, that is, β-carbon elimination.[5] A number of reactions are known in which the four-membered carbocycle of a

cyclobutylmethyl- or (cyclobutyloxy)metal is opened through *β*-carbon elimination.[6] 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.[7,8] In the initial step, nickel(0) acts as a template to promote oxidative cyclization of a carbonyl group with an unsaturated bond on it.[9] The author 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. In this chapter, the author describes the details of his 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.[10]

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 eq) 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 eq of tricyclohexylphosphine 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 tributylphosphine resulted in incomplete conversion and afforded an inseparable mixture of **3a** (82%) and **1a** (13%) (entry 8). Triphenylphoshine and tri-*t*-butylphosphine gave only a trace amount of **3a** (entries 9 and 10).

Table 1. Optimization of Reaction Conditions[a]

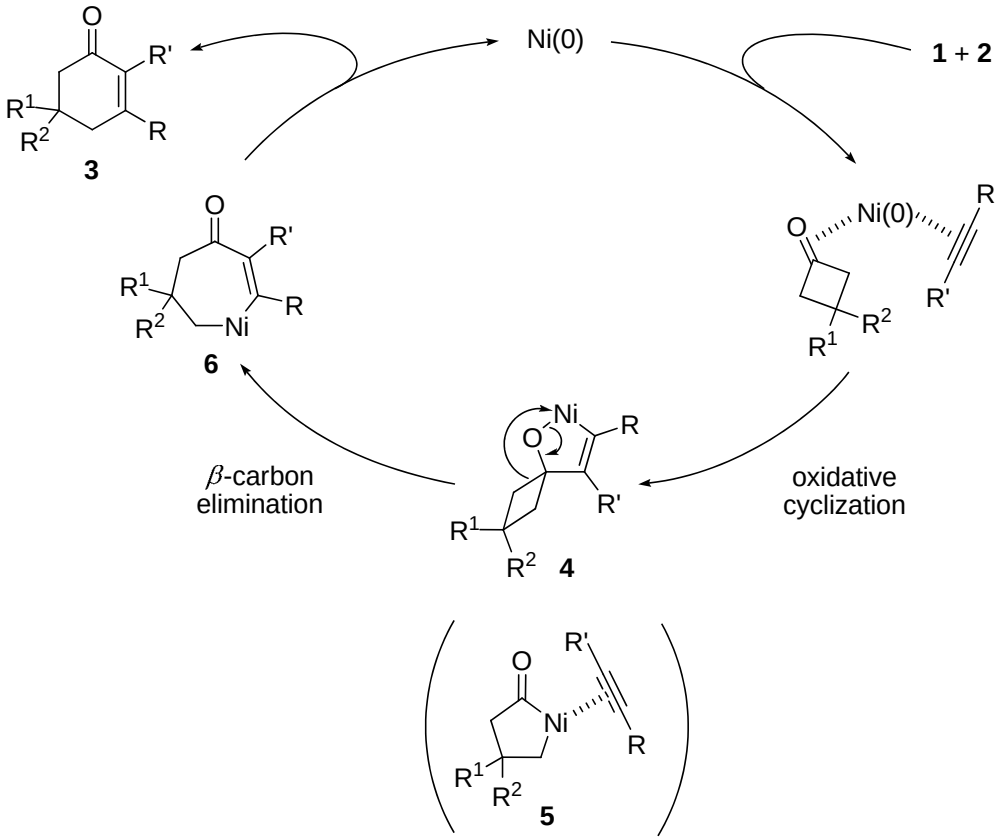


1a (0.20 mmol) **2a** (0.30 mmol) **3a**

entry	ligand	solvent	temp (°C)	yield (%)[b]
1	none	toluene	100	0
2	20 mol % P(*c*-Hex)$_3$	toluene	100	95
3	10 mol % P(*c*-Hex)$_3$	toluene	100	70[c]
4	20 mol % P(*c*-Hex)$_3$	toluene	80	50[c]
5	20 mol % P(*c*-Hex)$_3$	dioxane	100	39[c]
6	20 mol % P(*c*-Pen)$_3$	toluene	100	92
7	20 mol % P(*i*-Pr)$_3$	toluene	100	94
8	20 mol % PBu$_3$	toluene	100	82[c]
9	20 mol % PPh$_3$	toluene	100	trace
10	20 mol % P(*t*-Bu)$_3$	toluene	100	trace

[a] Cyclobutanone **1a** (0.20 mmol), alkyne **2a** (0.30 mmol), and nickel catalyst were heated in solvent for 3 h. [b] Isolated yield. [c] Obtained as an inseparable mixture of **1a** and **3a**. The yields of **3a** were calculated by ^{1}H NMR.

The author 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 an sp^3 carbon, whose ideal angle is 108°, thereby diminishing the ring strain of the four-membered carbocycle. Another mechanistic pathway leading to intermediate **5** 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**.

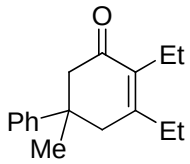
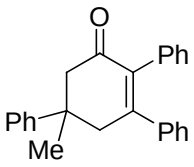
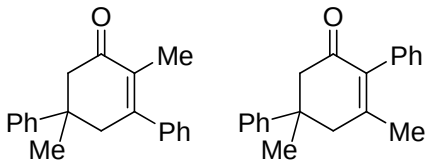
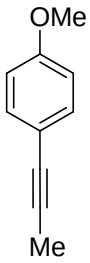
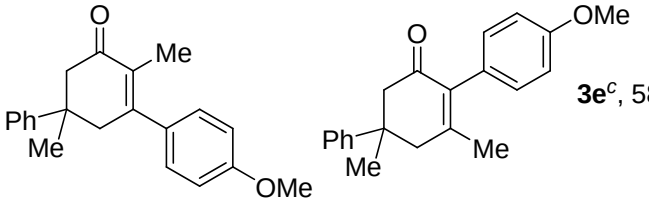
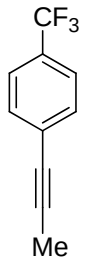
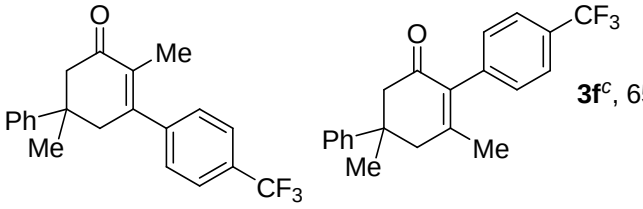


Scheme 2.

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 eq of the alkyne to the reaction mixture was required to attain a high product yield.

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

entry	alkyne **2**, eq	cyclobutanone **1a**	product **3**, yield (%)[b]
1	 **2b**, 1.5	 **1a**	 **3b**, 97
2	 **2c**, 3.0		 **3c**, 84
3	 **2d**, 3.0		 **3d**[c], 78 92 : 8
4	 **2e**, 3.0		 **3e**[c], 58 90 : 10
5	 **2f**, 3.0		 **3f**[c], 65 91 : 9

[a] Cyclobutanone **1a**, alkyne **2** (1.5-3.0 eq to **1a**), $Ni(cod)_2$ (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.

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

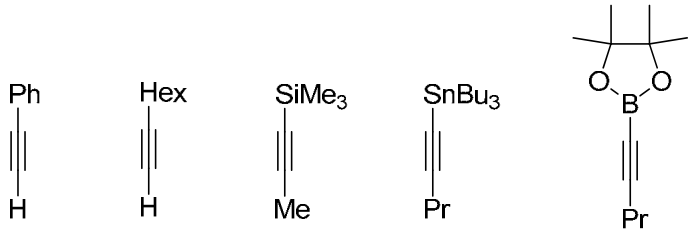
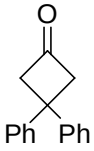
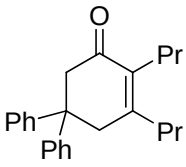
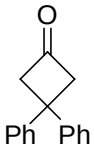
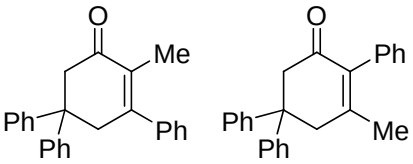
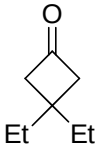
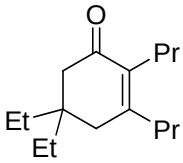
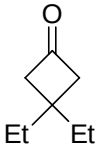
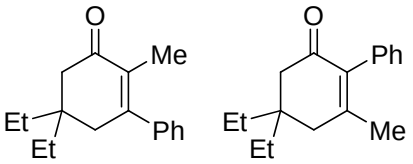


Figure 1.

The reaction of other 3,3-disubstituted cyclobutanones was also examined (Table 3). 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 (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).

Table 3. Nickel-Catalyzed Reaction of **1** and **2** Forming Cyclohexenone **3**[a]

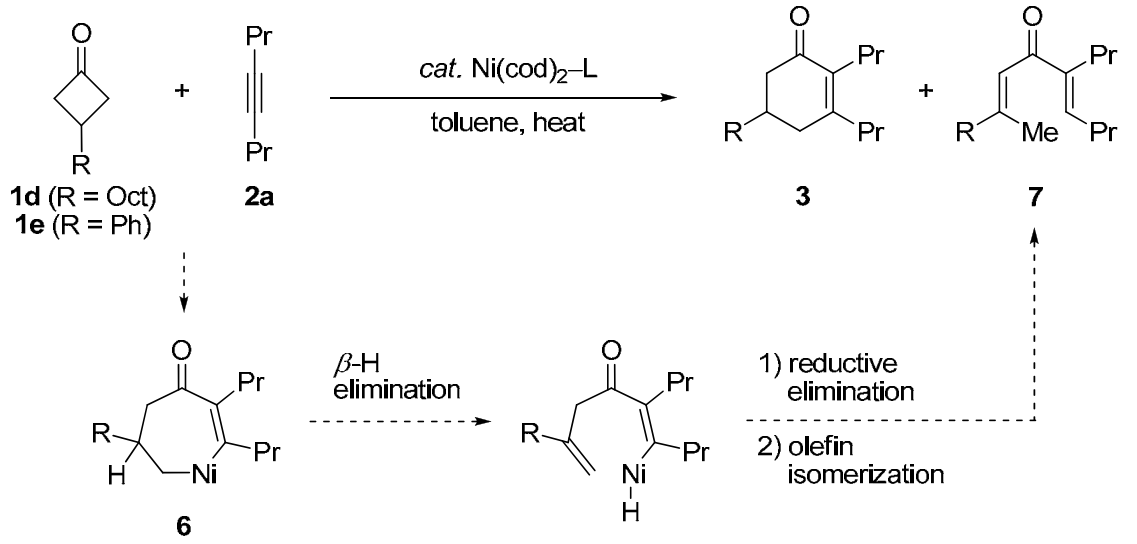
entry	cyclobutanone **1**	alkyne **2**, eq	Ni (mol %)	product **3**, yield (%)[b]
1	 **1b**	 **2a**, 1.5	10	 **3g**, 91
2	 **1b**	 **2d**, 3.0	10	 **3h**[c], 69 93 : 7
3	 **1c**	 **2a**, 1.5	20	 **3i**, 91
4	 **1c**	 **2d**, 3.0	20	 **3j**[c], 47 90 : 10

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

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)–tricyclohexylphosphine catalyst afforded 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**. Ligands of nickel(0) were again screened to improve the product selectivity in favor for **3**.

To the author's delight, the use of an *N*-heterocyclic carbene ligand (IPr) afforded cyclohexenone **3l** selectively without any detectable formation of **7b**, although the reaction became slower (entries 4 and 5).[11] 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).

Table 4. Reaction of 3-Monosubstituted Cyclobutanones and 4-Octyne (**2a**)[a]



entry	**1**(R)	Ni (mol%), ligand	toluene (ml)	conditions	**3**, yield (%)[b]	**7**, yield (%)[b]
1	**1d** (*n*-C_8H_{17})	10, 20 mol % P(*c*-Hex)$_3$	1.0	100 °C, 3 h	**3k**, 37	**7a**[c], 37
2	**1e** (Ph)	10, 20 mol % P(*c*-Hex)$_3$	1.0	100 °C, 3 h	**3l**, 41	**7b**, 54
3	**1e** (Ph)	10, 20 mol % PPh_3	1.0	100 °C, 3 h	**3l**, 37	**7b**, 26
4	**1e** (Ph)	10, 20 mol % IPr	2.0	110 °C, 18 h	**3l**, 59	-
5	**1e** (Ph)	10, 10 mol % IPr	2.0	110 °C, 18 h	**3l**, 61	-
6	**1e** (Ph)	20, 20 mol % IPr	4.0	110 °C, 15 h	**3l**, 79	-
7	**1f** (2-nap)	10, 10 mol % IPr	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.

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

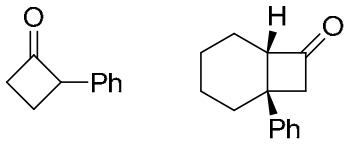


Figure 2.

Conclusion

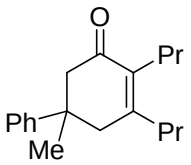
Combining a process of the carbonyl–alkyne oxidative cyclization on nickel(0) with a process of the nickel(II) cyclobutanolate ring opening by β-carbon elimination rendered it possible for alkynes intermolecularly to insert between the carbonyl carbon and the α-carbon of cyclobutanone. This new reaction uses cyclobutanones as a 1-oxobutane-1,4-diyl unit and provides a concise and efficient access to substituted cyclohexenones.

Experimental Section

General. All reactions were carried out with standard Schlenk and glove box techniques under a nitrogen atmosphere. Preparative thin-layer chromatography was performed with silica gel 60 PF_{254} (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (^{1}H 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 JOEL JMS-SX102A spectrometer. IR spectra were recorded on a Shimadzu FTIR-8100 spectrometer.

Materials. Cyclobutanones **1** were prepared by [2 + 2] cycloaddition of the corresponding olefins with dichloroketene and subsequent dechlorination with zinc dust in acetic acid.[12] 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) was prepared according to the literature procedure.[13] Toluene was distilled over sodium–benzophenone ketyl prior to use. All other commercially available chemical resources were used without further purifications.

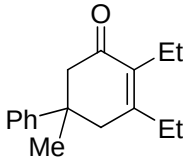
5-Methyl-5-phenyl-2,3-dipropyl-2-cyclohexenone (3a)



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}; ^{1}H 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;

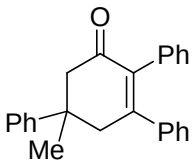
HRMS (EI) calcd for $C_{19}H_{26}O$ (M^+) 270.1984, found 270.1982. Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.55; H, 9.85.

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%): ^{1}H 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.

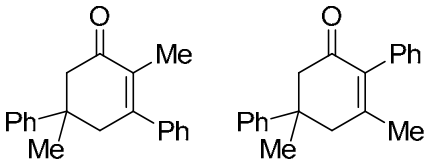
5-Methyl-2,3,5-triphenyl-2-cyclohexenone (3c)



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%): ^{1}H 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.

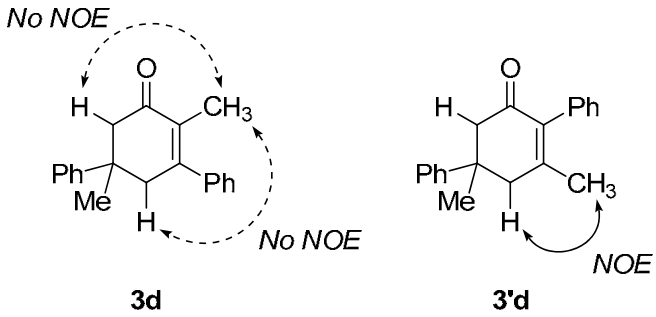
2,5-Dimethyl-3,5-diphenyl-2-cyclohexenone (3d)
and 3,5-Dimethyl-2,5-diphenyl-2-cyclohexenon (3´d)



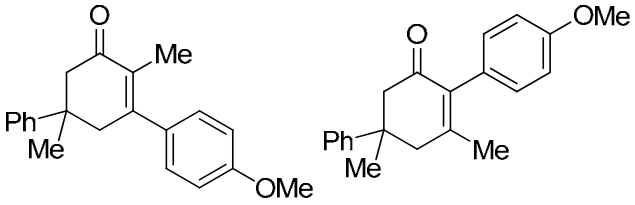
A toluene solution (0.4 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1a** (31.7 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-phenyl-1-propyne (**2d**, 69.6 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being 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%). **3d:** ^{1}H 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. **3´d:** ^{1}H 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).

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, an NOE between the methyl protons (δ 1.82) and the C4 methylene protons (δ 2.76 and 2.97) was observed for **3´d**.



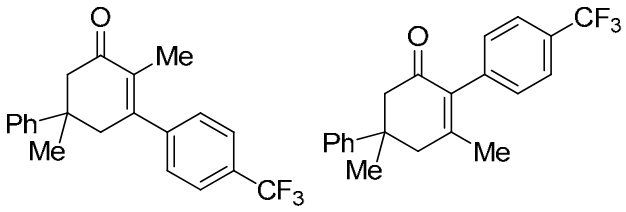
3-(4-Methoxyphenyl)-2,5-dimethyl-5-phenyl-2-cyclohexenone (3e)
and 2-(4-Methoxyphenyl)-3,5-dimethyl-5-phenyl-2-cyclohexenone (3´e)



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%). **3e:** ^{1}H NMR δ 1.43 (s, 3H), 1.71 (t, *J* = 1.8 Hz, 3 H), 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. **3´e:** ^{1}H 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,

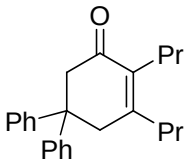
J = 15.9, 1.2 Hz, 1H), 3.80 (s, 3H), 6.83-6.90 (m, 4H), 7.20-7.27 (m, 1H), 7.30-7.35 (m, 4H); HRMS (EI) calcd for $C_{21}H_{22}O_2$ (M^+) 306.1620, found 306.1617.

2,5-Dimethyl-5-phenyl-3-(4-trifluoromethylphenyl)-2-cyclohexenone (3f)
and 3,5-Dimethyl-5-phenyl-2-(4-trifluoromethylphenyl)-2-cyclohexenone (3´f)



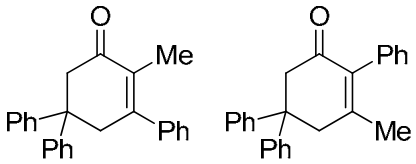
A toluene solution (0.4 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1a** (31.8 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-(4-trifluoromethylphenyl)-1-propyne (**2f**, 110.4 mg, 0.60 mmol) was added dropwise via syringe 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%). **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. **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.

5,5-Diphenyl-2,3-dipropyl-2-cyclohexenone (3g)



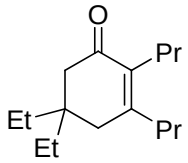
To a toluene solution (0.5 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol) and P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol) were added **1b** (44.5 mg, 0.20 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol). After being stirred for 3 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative 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.

2-Methyl-3,5,5-triphenyl-2-cyclohexenone (3h)
and 3-Methyl-2,5,5-triphenyl-2-cyclohexenone (3´h)



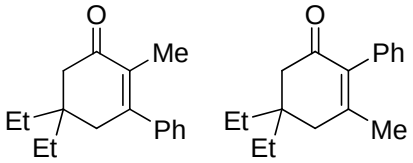
A toluene solution (0.1 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1b** (44.5 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-phenyl-1-propyne (**2d**, 69.6 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being 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%). **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. **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).

5,5-Diethyl-2,3-dipropyl-2-cyclohexenone (3i)



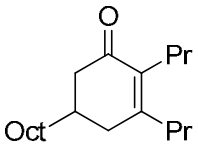
To a toluene solution (1 mL) of $Ni(cod)_2$ (11.0 mg, 0.04 mmol) and P(*c*-Hex)$_3$ (22.4 mg, 0.08 mmol) were added **1c** (24.4 mg, 0.19 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol). After being stirred for 3 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative 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.

5,5-Diethyl-2-methyl-3-phenyl-2-cyclohexenone (3j)
and 5,5-Diethyl-3-methyl-2-phenyl-2-cyclohexenone (3´j)



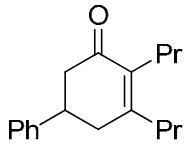
A toluene solution (0.4 mL) of $Ni(cod)_2$ (11.0 mg, 0.04 mmol), P(*c*-Hex)$_3$ (22.4 mg, 0.08 mmol), and **1c** (24.5 mg, 0.19 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-phenyl-1-propyne (**2d**, 69.6 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After 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%). **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. **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).

5-Octyl-2,3-dipropyl-2-cyclohexenone (3k)



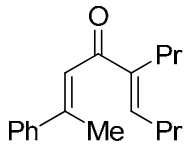
To a toluene solution (0.5 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol) and P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol) were added **1d** (36.3 mg, 0.20 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol). After being stirred for 3 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative 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.

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 minutes at 110 °C. To the stirring solution, a toluene solution (0.5ml) 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.

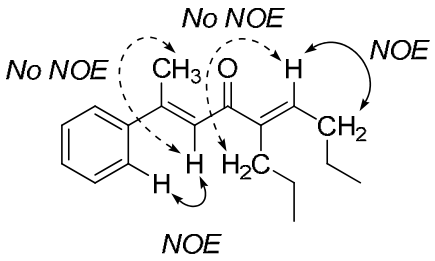
(2*E*,5*E*)-2-Phenyl-5-propyl-2,5-nonadien-4-one (7b)



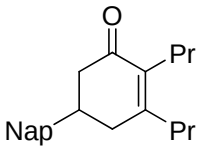
The title compound was obtained by the reaction with $Ni(cod)_2$–P(*c*-Hex)$_3$. ^{1}H NMR δ 0.94 (t, *J* = 7.8 Hz, 3H), 0.96 (t, *J* = 7.8 Hz, 3H), 1.35-1.56 (m, 4H), 2.25 (q, *J* = 7.4 Hz, 2H), 2.33-2.39 (m, 2H), 2.40 (d, *J* = 1.2 Hz, 3H), 6.62 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 1.2 Hz, 1H), 7.34-7.42 (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.

Stereochemical Assignment of 7b

Divinylketone **7b** was subjected to NOE experiments. No NOE between the vinyl proton (δ 6.78) and the metyl protons (δ 2.40) was observed. On the other hand, an NOE between the vinyl proton (δ 6.78) and the aromatic *ortho* protons (δ 7.48-7.52) was observed.



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 minutes 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

δ0.95 (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 δ14.3, 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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(7) For recent examples, see: (a) G. M. Mahandru, G. Liu, J. Montgomery, *J. Am. Chem. Soc.* **2004**, *126*, 3698. (b) K. M. Miller, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 15342. (c) T. N. Tekavec, J. Louie, *Org. Lett.* **2005**, *7*, 4037. (d) B. Knapp-Reed, G. M. Mahandru, J. Montgomery, *J. Am. Chem. Soc.* **2005**, *127*, 13156. (e) S.-S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2005**, *127*, 14194. For a review, see: (f) J. Montgomery, *Angew. Chem., Int. Ed.* **2004**, *43*, 3890.

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(10) For related catalytic reactions of cyclobutenones, see: (a) M. A. Huffman, L. S. Liebeskind, *J. Am. Chem. Soc.* **1990**, *112*, 8617. (b) M. A. Huffman, L. S. Liebeskind, *J. Am. Chem. Soc.* **1991**, *113*, 2771. Therein, η^4-vinylketene metal complexes are presumably formed as the intermediate from cyclobutenones, which are much more labile thermally as well as catalytically than cyclobutanones.

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(12) J. A. Hyatt, P. W. Raynolds, *Org. React.* **1994**, *45*, 159.

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Chapter 2

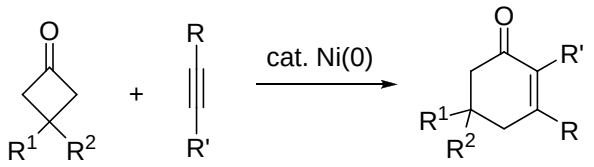
Nickel-Catalyzed [4+2+2] Annulation of Cyclobutanones with Diynes

Abstract

Cyclobutanones underwent a [4 + 2 + 2] annulation reaction with 1,6- and 1,7-diynes in the presence of nickel(0) catalysts to provide bicyclic eight-membered ring ketones. The annulation reaction proceeds through a ring-expansion of oxanickelacycloheptadiene via β-carbon elimination to form a nine-membered nickelacycle. This reaction employing cyclobutanones as a four-carbon unit constructs cyclooctadienone cores in one synthetic step.

Introduction

Transition metal-catalyzed multi-component annulation reactions[1] have been one of the most attractive research topics in synthetic organic chemistry. They have achieved the multiple carbon–carbon bond formation in a single chemical operation with good atom economy, providing a powerful method for the construction of carbon frameworks. As several carbon units and reaction modes have been developed, the variety of accessible carbocycles has been increasing. For example, [5+2+1][2] and [4+2+2][3] annulation reactions have enabled direct synthesis of eight-membered carbocycles, which are an important structural feature often found in biologically active compounds. Further exploration of new reaction modes is still expected to improve the utility of multi-component annulation reactions in synthetic organic chemistry.



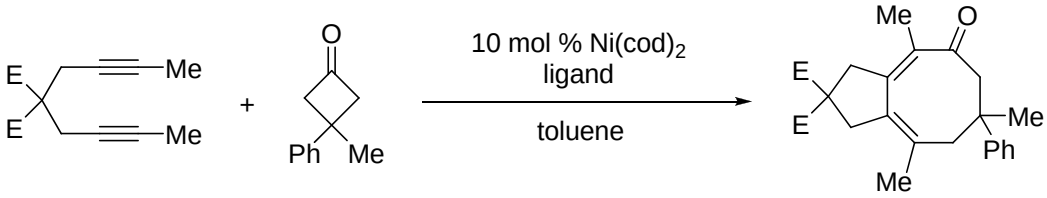
Scheme 1.

In Chapter 2, the author described a nickel-catalyzed intermolecular alkyne insertion reaction of cyclobutanones which forms six-membered carbocycles (Scheme 1).[4] An alkyne was formally inserted between the carbonyl carbon and the α-carbon through the initial formation of an oxanickelacycle intermediate by oxidative cyclization of an alkyne and the carbonyl group of a cyclobutanone with nickel(0), which was followed by β-carbon elimination and reductive elimination. This result presented an example of a [4+2] annulation reaction, in which cyclobutanones act as a four-carbon unit. The author next envisaged that incorporation of another unsaturated carbon–carbon bond into the initially formed oxanickelacycle could extend this protocol even further to a three-component annulation reaction to construct medium-sized carbocycles. In this chapter, the author describes the nickel-catalyzed [4+2+2] annulation reaction of cyclobutanones with diynes.

Results and Discussion

A solution of dimethyl 2,2-bis(but-2-ynyl)malonate (**1a**, 1.5 eq) in toluene was added dropwise to a mixture of 3-methyl-3-phenylcyclobutanone (**2a**), bis(1,5-cyclooctadiene)nickel(0) (10 mol %), and tricyclohexylphosphine (20 mol %) in toluene at 100 °C. The reaction mixture was stirred at that temperature for 3 h. A formal [4+2+2] annulation reaction took place to give bicyclo[6.3.0]undecadienone **3a** in 83% yield (Table 1, entry 1). The structure of **3a** was unambiguously assigned by NMR spectroscopy (^{1}H, ^{13}C, NOESY, HMQC, and HMBC). No formation of a six-membered ketone that might have arisen from a [4+2] annulation reaction of **2a** with the alkyne moiety was observed. Several phosphine ligands were examined under otherwise identical conditions (Table 1). Whereas triphenyphosphine and tri-*t*-butylphosphine showed low reactivities, tributylphosphine worked efficiently at 100 °C to give **3a** in 92% (entries 3-5). Self-oligomerization of the diyne **1a** was a major side-reaction, which was partially suppressed by slow addition of **1a**. Ligands other than phosphines were also examined to reveal that the use of *N*-heterocyclic carbene ligands[5] improved the catalyst activity of nickel(0) so that the [4+2+2] annulation occurred even at room temperature. In particular IPr (10 mol%) gave **3a** in the best yield of 91% (entry 8).

Table 1. Optimization of Reaction Conditions[a]

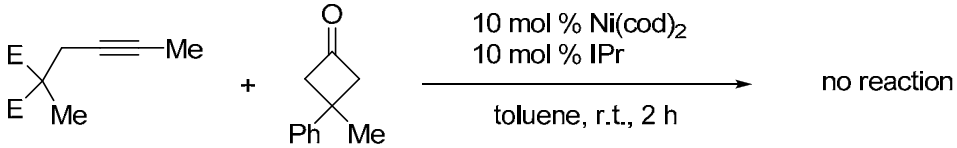


1a (E = CO_2Me) **2a** **3a**

entry	**2a** (eq)	ligand	temp (°C)	time (h)	yield (%)[b]
1	1.5	20 mol % P(*c*-Hex)$_3$	100	3	83
2	1.5	none	100	3	0
3	1.5	20 mol % PPh_3	100	3	8
4	1.5	20 mol % PBu_3	100	3	92
5	1.5	20 mol % P(*t*-Bu)$_3$	100	3	0
6	1.5	10 mol % IPr	100	1	93
7	1.5	10 mol % IPr	r.t.	1	94
8	1.2	10 mol % IPr	r.t.	1	91
9	1.2	10 mol % IMes	r.t.	12	30
10	1.2	10 mol % SIPr	r.t.	12	76
11	1.2	10 mol % I*t*Bu	r.t.	1	0

[a] A solution of diyne **1a** in toluene was added dropwise to the reaction mixture (entries 1-5). [b] Isolated yield.

The structure of alkyne **4** is given by substraction of one of two alkyne moieties from diyne **1a** with the sterically-demanding malonate moiety being retained. For comparison with diyne **1a,** alkyne **4** was subjected to reaction with cyclobutanone **2a**. The formal insertion reaction failed to occur, suggesting that simultaneous coordination of the two alkyne moieties is required for the initial oxidative cyclization to proceed.

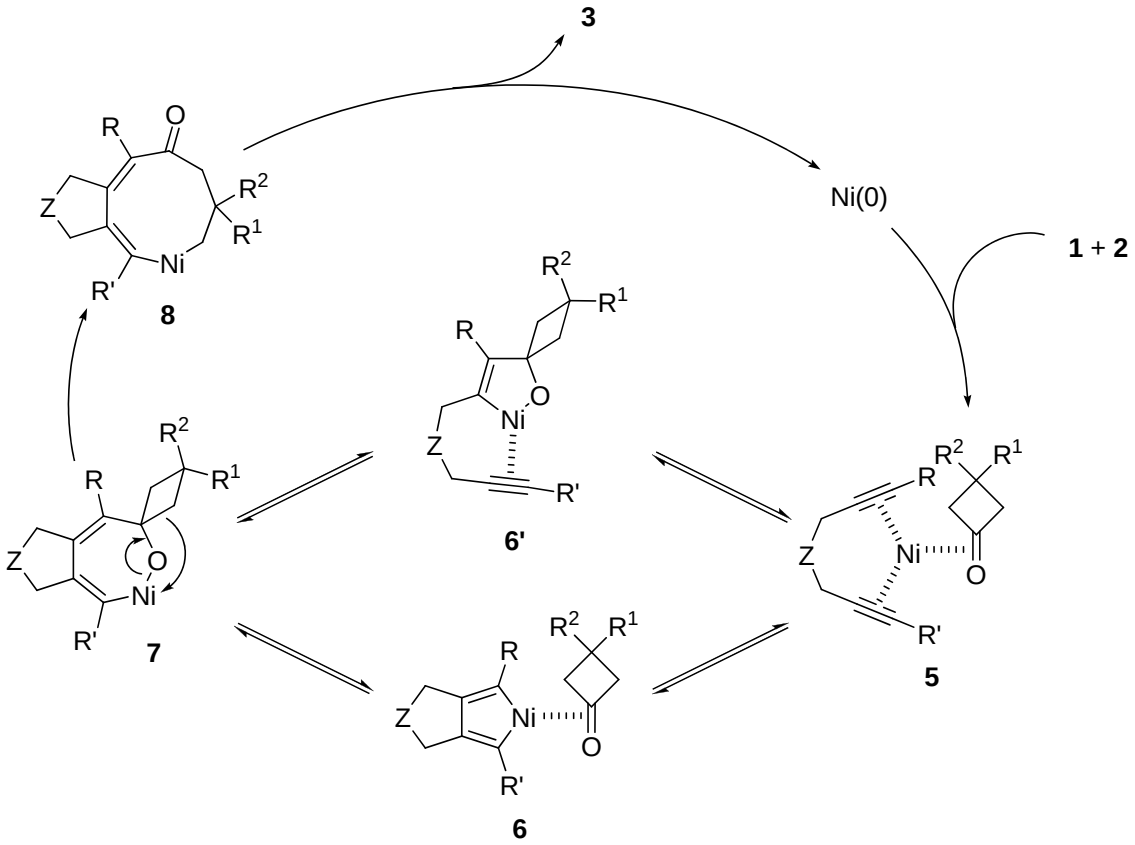


4 (E = CO_2Me) **2a**

Scheme 2.

The author postulates the mechanism shown in Scheme 3. The diyne and cyclobutanone initially bind to nickel(0) to form **5**. Subsequent oxidative cyclization leads to the formation

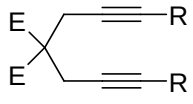
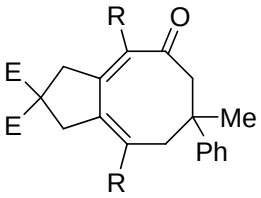
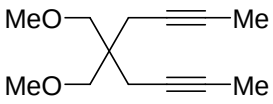
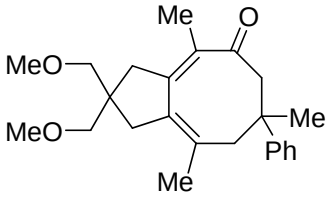
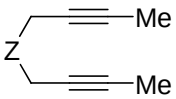
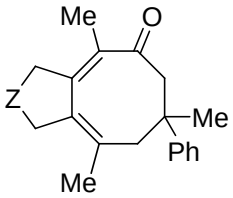
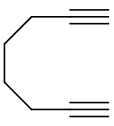
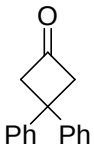
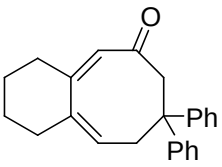
of spirocyclic oxanickelacycloheptadiene **7**. There are two species **6** and **6´** conceivable as the intermediate between **5** and **7**. Nickelacyclopentadiene **6**[6] can occur through oxidative cyclization of the two alkyne moieties on nickel(0), whereas hetero-type oxidative cyclization of the carbonyl group and one of the alkyne moieties would form another possible five-membered cyclic intermediate **6´**.[7] Subsequent incorporation of the third unsaturated functionality into the Ni–C bond of either five-membered nickelacycle **6** or **6´** leads to the formation of spirocyclic oxanickelacycloheptadiene **7**.[8,9] Then, the four-membered ring of the spiro nickelacycle **7** is opened by β-carbon elimination[10] to expand the seven-membered nickelacycle to the nine-membered nickelacycle **8**. This ring-expanding process is promoted presumably by release of the ring strain of the four-membered carbocycle of the nickel(II) tertiary cyclobutanolate. Finally, reductive elimination gives the product **3** with nickel(0) regenerated.



Scheme 3.

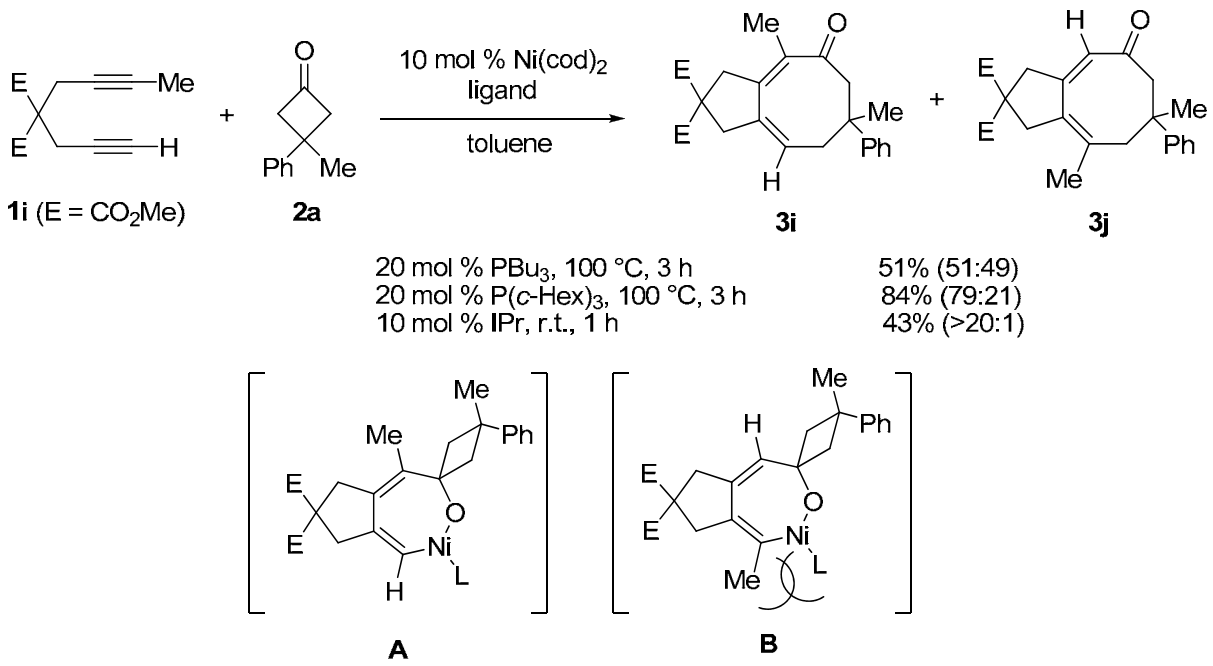
Next, various diynes **1** were subjected to the annulation reaction under the reaction conditions A (Ni–phosphine) and B (Ni–IPr) (Table 2). The reaction of diyne **1b**, possessing terminal alkyne moieties, suffered from its rapid self-oligomerization, and required the use of tricyclohexylphosphine as ligand and 3.0 equivalents of **1b** to attain 68% yield of **3b**, whereas diethyl-substituted diyne **1c** showed reactivity similar to **1a** and gave product **3c** in 85% yield (entries 1 and 2). However, diynes having either isopropyl or phenyl substituents at the alkyne terminus failed to undergo the reaction, presumably due to steric reasons. The reaction worked well with diynes having various tethers under appropriate conditions. Diyne **1e** linked by a trimethylene tether produced **3e** in 87% yield under condition B (entry 6). The reaction of oxa-1,6-diyne **1f** with **2a** afforded **3f** containing an ether linkage in its framework in 61% yield under condition A (entry 7). Whereas aza-1,6-diyne **1g** afforded product **3g** in 32% yield under condition A, condition B improved the yield to 71% (entries 8 and 9). Although octa-1,7-diyne (**1h**) whose linker was longer by one carbon could also join the [4+2+2] annulation reaction, it was less reactive than **1b** and **1d** to produce **3h** in 46% yield under the fortified condition A (entry 10).

Table 2. Screening of Diynes **1**[a]

entry	diyne **1**	cyclobutanone **2**	condition	product **3**, yield (%)[b]
				
	(E = CO_2Me)	**2a**		
1	**1b** (R = H)		A[c,d]	**3b**, 68
2	**1c** (R = Et)		A	**3c**, 85
				
3	**1d**		A	**3d**, 88
4	**1d**		B	**3d**, 91
				
5	**1e** (Z = CH_2)		A	**3e**, 78
6	**1e** (Z = CH_2)		B	**3e**, 87
7	**1f** (Z = O)		A	**3f**, 61
8	**1g** (Z = NTs)		A	**3g**, 32
9	**1g** (Z = NTs)		B	**3g**, 71
				
10	**1h**	**2b**	A[d,e]	**3h**, 46

[a] Condition A: Cyclobutanone **2**, diyne **1** (1.5 eq to **2**), $Ni(cod)_2$ (10 mol %), and PBu_3 (20 mol %) in toluene at 100 °C for 3 h. Condition B: Cyclobutanone **2**, diyne **1** (1.2 eq to **2**), $Ni(cod)_2$ (10 mol %), and IPr (10 mol %) in toluene at room temperature for 1-3 h. [b] Isolated yield. [c] P(*c*-Hex)$_3$ was used. [d] 3.0 Eq of diyne was used. [e] 20 mol % $Ni(cod)_2$ and 40 mol % P(*c*-Hex)$_3$ were used.

The reaction of unsymmetrical diyne **1i** was examined in terms of the regiochemical selectivity (Scheme 4). Whereas the tributylphosphine ligand showed no selectivity, moderate selectivity was observed with the sterically bulkier tricyclohexylphosphine ligand to give a 4:1 mixture of regioisomers **3i** and **3j**. Thus, the regioselectivity varied depending on the ligands, which were accounted for in terms of bulkiness. There are two regioisomeric intermediates **A** and **B** conceivable for **7** in Scheme 3. When a ligand is bulky enough, intermediate **A** would be favored over **B** because intermediate **B** would suffer from unfavorable steric repulsion between the methyl group at the alkyne terminus and the ligand (L). The IPr ligand would be bulkier than tricyclohexylphosphine, and therefore, produced **3i** in a more selective manner, although the chemical yield was moderate.

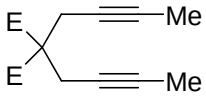
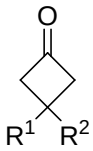
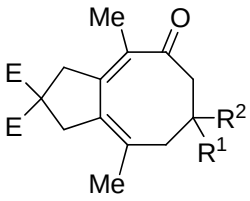


Scheme 4.

Cyclobutanones **2b** and **2c** possessing two substituents at the 3-position reacted with **1a** to give bicyclo[6.3.0]undecane derivatives **3k** and **3l**, respectively, in good yield (Table 3, entries 1 and 2). With cyclobutanones **2d** and **2e**, the hydrogen at the 3-position of the cyclobutanone might have caused β-hydride elimination with intermediate **8**. The following reductive elimination could form a monocyclic product.[4] To the author's delight, however,

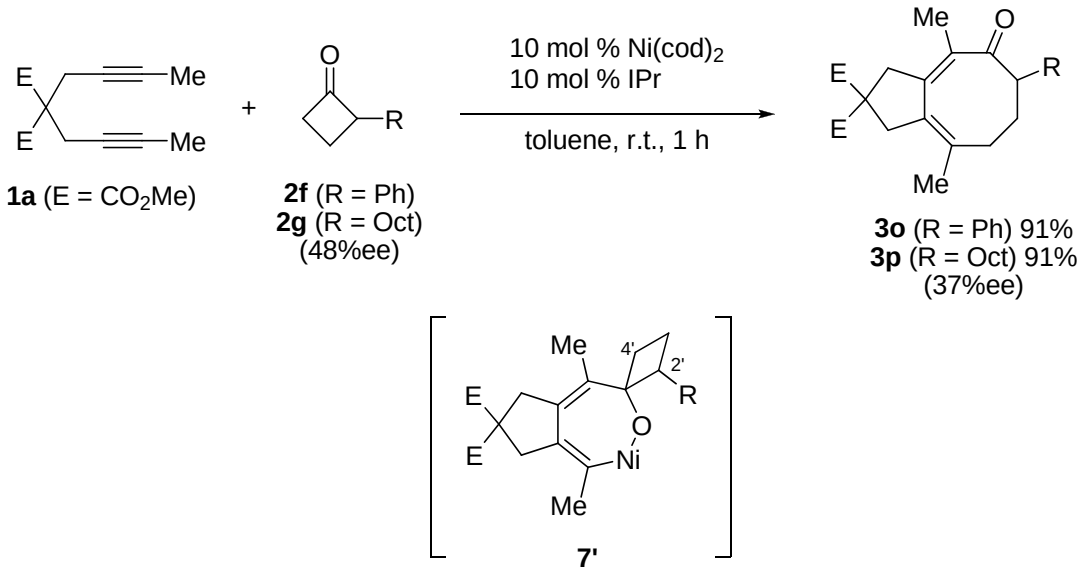
cyclobutanones **2d** and **2e** afforded the corresponding eight-membered ring products selectively without formation of such a side product (entries 3-6).

Table 3. Screening of Cyclobutanones **2**[a]

entry	diyne **1a**	cyclobutanone **2**	condition	product **3**, yield (%)[b]
	 **1a** (E = CO_2Me)			
1		**2b**, (R^1 = R^2 = Ph)	A	**3k**, 84
2		**2c**, (R^1 = R^2 = Et)	A	**3l**, 70
3		**2d**, (R^1 = Ph, R^2 = H)	A	**3m**, 83
4		**2d**, (R^1 = Ph, R^2 = H)	B	**3m**, 84
5		**2e**, (R^1 = Oct, R^2 = H)	A	**3n**, 84
6		**2e**, (R^1 = Oct, R^2 = H)	B	**3n**, 91

[a] Condition A: Cyclobutanone **2**, diyne **1a** (1.5 eq to **2**), $Ni(cod)_2$ (10 mol %), and PBu_3 (20 mol %) in toluene at 100 °C for 3 h. Condition B: Cyclobutanone **2**, diyne **1a** (1.2 eq to **2**), $Ni(cod)_2$ (10 mol %), and IPr (10 mol %) in toluene at room temperature for 1-3 h. [b] Isolated yield.

The use of unsymmetrical 2-substituted cyclobutanones **2f** and **2g** was also examined under the catalysis of Ni–IPr (Scheme 5). A high regioselectivity of >20:1 was observed for the β-carbon elimination step. The author assumes that, with intermediate **7´**, migration of the methylene carbon (C4´) is preferred over that of the methyne carbon (C2´), probably due to steric reasons. In the case of the enantiomerically enriched substrate **2g** (48% ee), the enantiopurity decreased to 37% with the product **3p**, which might be a result of enolization partially occurring with the carbonyl-containing compounds involved, e.g. **2g**, **3p**, and/or **8**.



Scheme 5.

Conclusion

In summary, the author has developed a nickel-catalyzed intermolecular [4+2+2] annulation reaction of cyclobutanones as the four-carbon unit with diynes, which incorporates β-carbon elimination for ring-expansion. This method provides a direct access to bicyclic eight-membered ring ketones.

Experimental Section

General. All reactions were carried out with standard Schlenk and glove box techniques under a nitrogen atmosphere. Preparative thin-layer chromatography was performed with silica gel 60 PF_{254} (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (^{1}H at 300.07 Hz and ^{13}C at 75.46 Hz) spectrometer or a JEOL JNM-A400 (^{1}H at 399.65 MHz and ^{13}C at 100.40 MHz) spectrometer. Proton chemical shifts were referenced to residual solvent signals in $CDCl_3$ (δ 7.26). Carbon chemical shifts were referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.00) and C_6D_6 (δ 128.00). High resolution mass spectra were recorded on a JOEL JMS-SX102A spectrometer.

Materials. Diynes **1a**,[11] **1b**,[11] **1c**,[12] **1d**,[12] **1e**,[13] **1f**,[14] **1g**,[15] **1i**,[16] and *N*-heterocyclic carbenes IPr,[17] SIPr,[17] IMes,[17] I*t*Bu[18] were prepared according to the literature methods. Cyclobutanones **2a**–**e** were prepared by [2+2] cycloaddition of the corresponding olefins with dichloroketene and subsequent dechlorination with zinc dust in acetic acid.[19] Cyclobutanones **2f** and **2g** were prepared from cyclopropylidenation of aldehyde[20] and subsequent *m*CPBA oxidation.[21] Toluene was distilled over sodium/benzophenone ketyl prior to use. All other commercially available chemical resources were used without further purifications.

General Procedure A

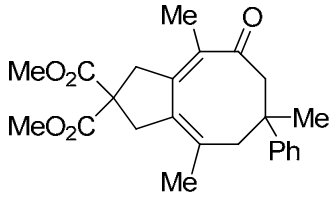
A toluene solution (0.80 mL) of $Ni(cod)_2$ (5.5 mg, 0.020 mmol), PBu_3 (8.1 mg, 0.040 mmol), and cyclobutanone **2** (0.20 mmol) was stirred at 100 °C for a few minutes. To the solution was added dropwise a toluene solution (0.20 mL) of diyne **1** (0.30 mmol) via syringe over 2.5 h. After being stirred for a further 0.5 h, the reaction mixture was concentrated. The residue was purified by preparative thin-layer chromatography of silica gel to afford product **3**.

General Procedure B

A toluene solution (0.50 mL) of $Ni(cod)_2$ (5.5 mg, 0.020 mmol) and IPr (7.8 mg, 0.020 mmol) was stirred for at least 6 h and added to a mixture of cyclobutanone **2** (0.20 mmol) and diyne **1** (0.24 mmol) in toluene (1.50 mL). After being stirred for 1–3 h at room temperature, the reaction mixture was filtered through a pad of Florisil®. The filtrate was concentrated, and the

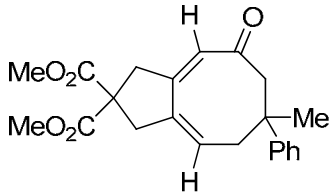
residue was purified by preparative thin-layer chromatography of silica gel to afford product **3**.

Dimethyl 2,5,7-trimethyl-5-phenylbicyclo[6.3.0]undeca-1,7-dien-3-one-10,10-dicarboxylate (3a)



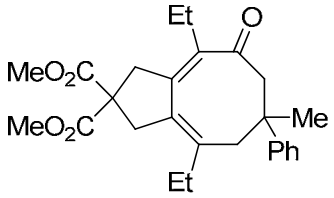
^{1}H NMR δ 1.18 (s, 3H), 1.41 (s, 3H), 1.96 (s, 3H), 2.31-2.42 (m, 3H), 2.96 (d, J = 15.3 Hz, 1H), 3.11-3.17 (m, 3H), 3.54 (d, J = 9.9 Hz, 1H), 3.72 (s, 3H), 3.75 (s, 3H), 7.20-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.0, 23.0, 29.0, 38.9, 42.0, 47.4, 49.6, 50.4, 52.9, 53.0, 55.7, 125.4, 126.2, 128.2, 131.8, 135.3, 141.3, 147.1, 148.8, 171.6, 171.7, 201.7; HRMS (EI) calcd for $C_{24}H_{28}O_5$ (M^+) 396.1937, found 396.1938.

Dimethyl 5-methyl-5-phenylbicyclo[6.3.0]undeca-1,7-dien-3-one-10,10-dicarboxylate (3b)



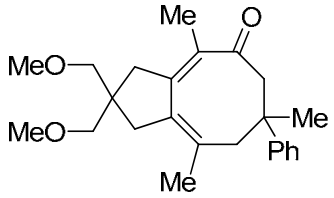
^{1}H NMR δ 1.38 (s, 3H), 2.26-2.33 (m, 1H), 2.61 (br s, 1H), 2.71 (dd, J = 12.8, 8.0 Hz, 1H), 2.98-3.36 (m, 5H), 3.73 (s, 3H), 3.74 (s, 3H), 6.00 (s, 1H), 6.08 (br t, 1H), 7.19-7.26 (m, 1H), 7.31-7.34 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 30.0, 40.8, 41.7, 42.2, 49.4, 51.6, 53.0 [two carbons], 56.2, 125.2, 126.3, 126.8, 128.4, 133.4, 140.2, 146.4, 150.7, 171.1, 171.2, 202.2; HRMS (EI) calcd for $C_{22}H_{24}O_5$ (M^+) 368.1624, found 368.1628.

Dimethyl
2,7-diethyl-5-methyl-5-phenylbicyclo[6.3.0]undeca-1,7-dien-3-one-10,10-dicarboxylate (3c)



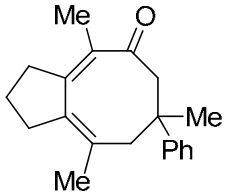
^{1}H NMR δ 0.50-0.75 (m, 3H), 0.80-1.20 (m, 3H), 1.41 (s, 3H), 1.74-1.93 (m, 1H), 2.18-2.56 (m, 6H), 3.06-3.29 (m, 4H), 3.52 (d, J = 10.8 Hz, 1H), 3.72 (s, 3H), 3.75 (s, 3H), 7.17-7.33 (m, 5H); ^{13}C NMR (C_6D_6) δ 11.5, 13.7, 24.2, 29.0, 29.6, 38.7, 41.5, 46.4, 48.0, 50.0, 52.4, 52.5, 55.9, 125.7, 126.4, 128.5, 135.5, 138.9, 146.7, 147.6, 147.7, 171.5, 171.6, 200.1; HRMS (EI) calcd for $C_{26}H_{32}O_5$ (M^+) 424.2250, found 424.2253.

10,10-bis(methoxymethyl)-2,5,7-trimethyl-5-phenylbicyclo[6.3.0]undeca-1,7-dien-3-one (3d)



^{1}H NMR δ 1.14 (s, 3H), 1.42 (s, 3H), 1.93 (s, 3H), 2.20-2.57 (m, 7H), 3.20-3.35 (m, 10H), 3.54 (d, J = 9.9 Hz, 1H), 7.18-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.1, 23.2, 29.0, 37.3, 41.0, 43.0, 47.6, 49.7, 50.5, 59.26, 59.32, 75.7, 76.1, 125.4, 126.1, 128.2, 131.8, 137.8, 140.6, 147.4, 152.6, 201.9; HRMS (EI) calcd for $C_{24}H_{32}O_3$ (M^+) 368.2351, found 368.2354.

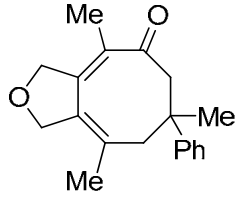
2,5,7-Trimethyl-5-phenylbicyclo[6.3.0]undeca-1,7-dien-3-one (3e)



^{1}H NMR δ 1.17 (s, 3H), 1.43 (s, 3H), 1.70-1.78 (2H), 1.97 (s, 3H), 2.31-2.70 (m, 7H), 3.59 (d, J = 9.6 Hz, 1H), 7.19-7.23 (m, 1H), 7.30-7.35 (m, 4H); ^{13}C NMR (C_6D_6) δ 16.7, 22.0, 23.3,

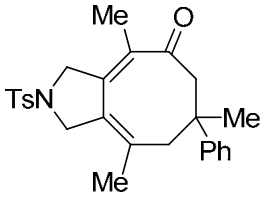
29.4, 31.9, 35.4, 47.8, 49.9, 50.2, 125.8, 126.3, 128.4, 131.4, 138.9, 139.5, 148.1, 152.6, 200.8; HRMS (EI) calcd for $C_{20}H_{24}O$ (M^+) 280.1827, found 280.1827.

2,5,7-Trimethyl-5-phenyl-10-oxabicyclo[6.3.0]undeca-1,7-dien-3-one (3f)



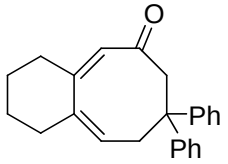
^{1}H NMR δ 1.18 (br s, 3H), 1.47 (s, 3H), 1.86 (s, 3H), 2.30-2.49 (m, 3H), 3.61 (br s, 1H), 4.51-4.66 (m, 4H), 7.20-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.5, 23.4, 29.2, 47.5, 49.9, 51.7, 71.9, 73.4, 125.3, 126.4, 128.4, 129.4, 134.9, 141.0, 146.7, 147.3, 202.2; HRMS (EI) calcd for $C_{19}H_{22}O_2$ (M^+) 282.1620, found 282.1617.

10-(4-Tolylsulfonyl)-2,5,7-trimethyl-5-phenyl-10-azabicyclo[6.3.0]undeca-1,7-dien-3-one (3g)



^{1}H NMR δ 1.11 (s, 3H), 1.44 (s, 3H), 1.86 (s, 3H), 2.15-2.42 (m, 3H), 2.43 (s, 3H), 3.27 (br s, 1H), 3.99-4.28 (m, 4H), 7.20-7.35 (m, 7H), 7.72 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 16.0, 21.5, 23.4, 29.0, 47.2, 49.7, 51.1, 52.0, 54.1, 125.2, 126.5, 127.7, 128.4, 129.8, 131.4, 132.0, 133.1, 143.0, 144.0, 144.1, 146.4, 201.2; HRMS (EI) calcd for $C_{26}H_{29}NO_3S$ (M^+) 435.1868, found 435.1868.

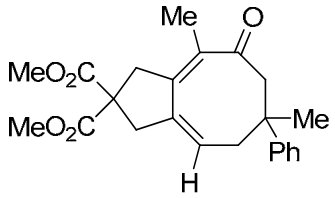
5,5-Diphenylbicyclo[6.4.0]dodeca-1,7-dien-3-one (3h)



^{1}H NMR δ 1.45-1.71 (m, 2H), 1.86-1.99 (m, 2H), 2.25-2.46 (m, 4H), 2.79 (dd, J = 12.3, 6.5 Hz, 1H), 2.91 (d, J = 10.7 Hz, 1H), 3.21 (dd, J = 12.3, 9.9 Hz, 1H), 3.79 (d, J = 10.7 Hz, 1H),

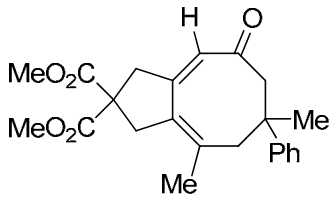
5.56 (ddd, J = 9.9, 6.5, 1.5 Hz, 1H), 5.91 (s, 1H), 7.15-7.32 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.9, 27.2, 36.7, 37.7, 38.6, 49.5, 54.9, 126.1, 126.3, 126.9, 127.0, 127.2, 128.0, 128.2, 129.1, 141.4, 146.3, 146.7, 152.9, 200.7; HRMS (EI) calcd for $C_{24}H_{24}O$ (M^+) 328.1827, found 328.1828.

Dimethyl 2,5-dimethyl-5-phenylbicyclo[6.3.0]undeca-1,7-dien-3-one-10,10-dicarboxylate (3i)



^{1}H NMR δ 1.37 (s, 3H), 1.92 (s, 3H), 2.17 (br s, 1H), 2.62 (dd, *J* = 12.1, 8.0 Hz, 2H), 2.98-3.33 (m, 5H), 3.72 (s, 3H), 3.74 (s, 3H), 5.97 (s, 1H), 7.19-7.35 (m, 5H); ^{13}C NMR δ 15.9, 30.0, 39.8, 41.6, 43.0, 48.7, 52.3, 53.0 [two carbons], 55.7, 125.3, 126.1, 128.2, 131.0, 133.1, 140.8, 146.0, 146.5, 171.3, 171.5, 202.3; HRMS (EI) calcd for $C_{23}H_{26}O_5$ (M^+) 382.1780, found 382.1780.

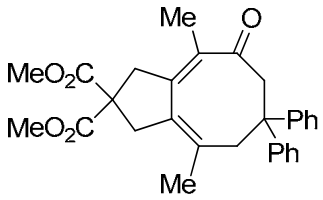
Dimethyl 5,7-dimethyl-5-phenylbicyclo[6.3.0]undeca-1,7-dien-3-one-10,10-dicarboxylate (3j)



^{1}H NMR δ 1.19 (br s, 3H), 1.42 (s, 3H), 2.34-2.60 (m, 3H), 2.90-3.30 (m, 4H), 3.46 (br s, 1H), 3.73 (s, 3H), 3.76 (s, 3H), 5.99 (s, 1H), 7.20-7.36 (m, 5H); ^{13}C NMR δ 23.1, 29.0, 38.8, 43.6, 48.1, 50.1, 50.3, 53.0, 53.1, 56.1, 125.3, 126.1, 126.4, 128.3, 134.2, 144.1, 146.8, 152.8, 171.3, 171.4, 202.5; HRMS (EI) calcd for $C_{23}H_{26}O_5$ (M^+) 382.1780, found 382.1784.

Dimethyl

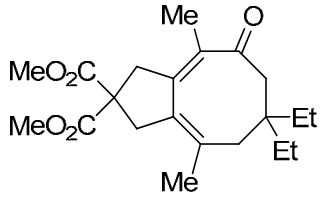
2,7-dimethyl-5,5-diphenylbicyclo[6.3.0]undeca-1,7-dien-3-one-10,10-dicarboxylate (3k)



^{1}H NMR δ 1.16 (s, 3H), 1.85 (s, 3H), 2.71-2.77 (m, 2H), 3.03 (d, J = 15.6 Hz, 1H), 3.16-3.123 (m, 4H) , 3.75 (s, 3H), 3.77 (s, 3H), 3.92 (d, J = 9.9 Hz, 1H), 7.10-7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 15.9, 23.0, 39.1 41.9, 46.6, 47.8, 53.0, 55.7, 58.2, 126.3, 127.1, 127.9, 128.2, 132.1, 136.0, 140.6, 147.0, 147.2, 148.1, 171.6, 171.7, 199.9 [Some sp^2 carbon chemical shifts are observed as nonequivalent signals due to barrier to inversion of the cyclooctadienone ring]; HRMS (EI) calcd for $C_{29}H_{30}O_5$ (M^+) 458.2093, found 458.2097. Anal. Calcd for $C_{29}H_{30}O_5$: C, 75.96; H, 6.59. Found: C, 75.72; H, 6.71.

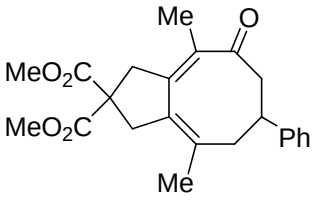
Dimethyl

5,5-diethyl-2,7-dimethylbicyclo[6.3.0]undeca-1,7-dien-3-one-10,10-dicarboxylate (3l)



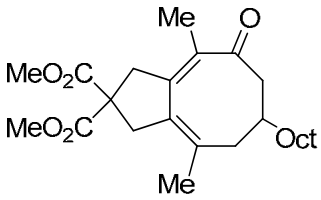
^{1}H NMR δ 0.82 (t, J = 7.1 Hz, 6H), 1.27 (br s, 4H), 1.77-2.08 (m , 3H), 1.87 (s, 3H), 1.95 (s, 3H), 2.54 (br s, 1H), 3.05-3.21 (m, 4H), 3.73 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 7.4, 16.0, 24.4, 27.9, 39.2, 42.1, 44.7, 47.5, 51.3, 53.0, 55.7, 131.8, 135.4, 140.8, 148.4, 171.6, 201.7; HRMS (EI) calcd for $C_{21}H_{30}O_5$ (M^+) 362.2093, found 362.2094.

Dimethyl 2,7-dimethyl-5-phenylbicyclo[6.3.0]undeca-1,7-dien-3-one-10,10-dicarboxylate (3m)



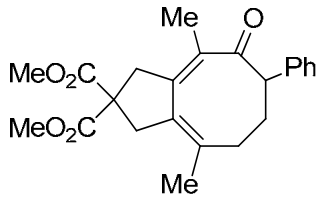
^{1}H NMR δ 1.51 (br s, 3H), 1.93 (s, 3H), 2.38 (br s, 1H), 2.56 (br s, 2H), 3.10-3.24 (m, 5H), 3.65 (br s, 1H), 3.72 (s, 3H), 3.75 (s, 3H), 7.12-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.0, 23.5, 39.0, 41.9 [two carbons], 42.4, 50.4, 52.98, 53.04, 55.7, 126.6, 126.8, 128.3, 131.1, 135.1, 139.5, 143.4, 148.4, 171.6, 171.7, 203.5; HRMS (EI) calcd for $C_{23}H_{26}O_5$ (M^+) 382.1780, found 382.1773.

Dimethyl 2,7-dimethyl-5-octylbicyclo[6.3.0]undeca-1,7-dien-3-one-10,10-dicarboxylate (3n)



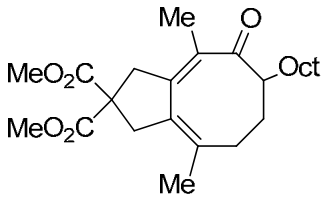
^{1}H NMR δ 0.84 (t, J = 6.6 Hz, 3H), 1.23-1.40 (m, 14H), 1.85 (s, 3H), 1.91 (s, 3H), 1.96-2.85 (m, 5H), 3.11(dd, J = 21.9, 17.4 Hz, 4H), 3.71 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 14.0, 15.8, 22.6, 23.2, 27.4, 29.2, 29.5, 29.6, 31.8, 34.7, 38.9, 40.3, 41.8, 43.2, 46.2, 52.9 [two carbons], 55.7, 131.3, 134.4, 140.2, 148.2, 171.6 [two carbons], 203.5; HRMS (EI) calcd for $C_{25}H_{38}O_5$ (M^+) 418.2719, found 418.2721.

Dimethyl 2,7-dimethyl-4-phenylbicyclo[6.3.0]undeca-1,7-dien-3-one-10,10-dicarboxylate (3o)



^{1}H NMR δ 1.89 (s, 3H), 1.96 (s, 3H), 2.06-2.19 (m, 2H), 2.45-2.63 (m, 2H), 3.14 (d, J = 15.6 Hz, 1H), 3.19 (d, J = 1.2 Hz, 2H), 3.29 (d, J = 15.3 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.46 (dd, J = 13.1, 4.1 Hz, 1H), 7.19-7.29 (m, 5H); ^{13}C NMR δ 16.3, 21.8, 34.5, 39.0, 41.0, 41.8, 51.5, 52.98, 53.04, 56.0, 126.7, 127.9, 129.1, 131.9, 134.0, 139.6, 140.4, 147.3, 171.5, 171.7, 206.1; HRMS calcd (EI) for $C_{23}H_{26}O_5$ (M^+) 382.1780, found 382.1779.

Dimethyl 2,7-dimethyl-4-octylbicyclo[6.3.0]undeca-1,7-dien-3-one-10,10-dicarboxylate (3p)



^{1}H NMR δ 0.83 (t, J = 6.6 Hz, 3H), 1.16-1.30 (m, 14H), 1.63-1.80 (m, 1H), 1.80-1.94 (m, 2H), 1.85 (s, 3H), 1.89 (s, 3H), 2.22-2.36 (m, 1H), 2.99-3.12 (m, 1H), 3.00 (d, J = 15.3 Hz, 1H), 3.10 (d, J = 0.6 Hz, 2H), 3.20 (d, J = 15.0 Hz, 1H), 3.71 (s, 3H), 3.72 (s, 3H); ^{13}C NMR δ 14.1, 16.0, 21.6, 22.6, 28.1, 29.2, 29.4, 29.8, 31.3, 31.8, 34.4, 38.9, 41.1, 41.6, 46.5, 52.9 [two carbons], 55.9, 131.5, 133.3, 140.2, 146.5, 171.6, 171.7, 209.3; HRMS (EI) calcd for $C_{25}H_{38}O_5$ (M^+) 418.2719, found 418.2720.

References and Notes

(1) For reviews, see: (a) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49. (b) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901. (c) M. Murakami, *Angew. Chem., Int. Ed.* **2003**, *42*, 718. (d) S. E. Gibson, N. Mainolfi, *Angew. Chem., Int. Ed.* **2005**, *44*, 3022.

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(3) (a) S. R. Gilbertson, B. DeBoef, *J. Am. Chem. Soc.* **2002**, *124*, 8784. (b) J. A. Varela, L. Castedo, C. Saá, *Org. Lett.* **2003**, *5*, 2841. (c) P. A. Evans, E. W. Baum, A. N. Fazal, M. Pink, *Chem. Commun.* **2005**, 63.

(4) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2005**, *127*, 6932.

(5) IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.
IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.
SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene.
I*t*Bu = 1,3-di-*t*-Butylimidazol-2-ylidene.

(6) M. Shanmugasundaram, M.-S. Wu, M. Jeganmohan, C.-W. Huang, C.-H. Cheng, *J. Org. Chem.* **2002**, *67*, 7724.

(7) For related five-membered nickelacycles, see: (a) T. N. Tekavec, A. M. Arif, J. Louie, *Tetrahedron* **2004**, *60*, 7431. (b) S. Ogoshi, M. Ueta, T. Arai, H. Kurosawa, *J. Am. Chem. Soc.* **2005**, *127*, 12810. (c) C.-Y. Ho, T. F. Jamison, *Angew. Chem., Int. Ed.* **2007**, *46*, 782. (d) M. R. Chaulagain, G. J. Sormunen, J. Montgomery, *J. Am. Chem. Soc.* **2007**, *129*, 9568.

(8) For related seven-membered nickelacycles, see: (a) H. Hoberg, D. Schaefer, G. Burkhart, C. Krüger, M. J. Romão, *J. Organomet. Chem.* **1984**, *266*, 203. (b) T. Tsuda, T. Kiyoi, T. Miyane, T. Saegusa, *J. Am. Chem. Soc.* **1988**, *110*, 8570. (c) T. N. Tekavec, J. Louie, *Org. Lett.* **2005**, *7*, 4037.

(9) We assume that the interconversion among the intermediates **5**, **6**, **6´**, and **7** is reversible and that there is equilibration before occurrence of β-carbon elimination with **7**.

(10) For β-carbon elimination from transition metal cyclobutanolates, see: (a) T. Nishimura, S. Uemura, *Synlett* **2004**, 201. (b) T. Matsuda, M. Makino, M. Murakami, *Org. Lett.* **2004**, *6*, 1257. (c) T. Matsuda, M. Makino, M. Murakami, *Angew. Chem., Int. Ed.* **2005**, *44*, 4608. (d) T. Matsuda, M. Shigeno, M. Makino, M. Murakami, *Org. Lett.* **2006**, *8*, 3379.

(11) R. S. Atkinson, M. J. Grimshire, *J. Chem. Soc., Perkin Trans. 1* **1986**, 1215.

(12) C. Liu, R. A. Widenhoefer, *Organometallics* **2002**, *21*, 5666.

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(14) B. M. Trost, M. T. Rudd, *J. Am. Chem. Soc.* **2003**, *125*, 11516.

(15) M. Nishida, H. Shiga, M. Mori, *J. Org. Chem.* **1998**, *63*, 8606.

(16) T. Shimamoto, M. Chimori, H. Sogawa, K. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 16410.

(17) A. J. Arduengo, III, R. Krafczyk, R. Schmutzler, H. A. Craig, J. R. Goerlich, W. J. Marshall, M. Unverzagt, *Tetrahedron* **1999**, *55*, 14523.

(18) A. J. Arduengo, III, H. Bock, H. Chen, M. Denk, D. A. Dixon, J. C. Green, W. A. Herrmann, N. L. Jones, M. Wagner, R. West, *J. Am. Chem. Soc.* **1994**, *116*, 6641.

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(21) H. Nemoto, J. Miyata, M. Yoshida, N. Raku, K. Fukumoto, *J. Org. Chem.* **1997**, *62*, 7850.

Chapter 3

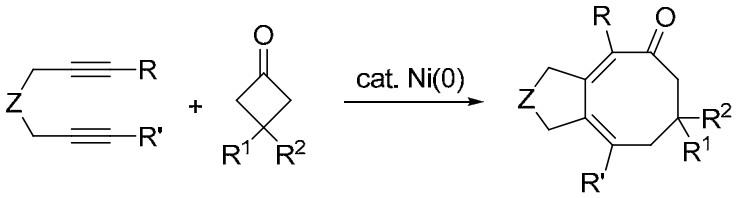
Nickel-Catalyzed [4+2+2] Annulation of Cyclobutanones with Enynes

Abstract

In the presence of a nickel(0) catalyst, cyclobutanones reacted with enynes to produce bicyclic eight-membered ring ketones. Cyclobutanones acted as a four-carbon unit in the formal [4+2+2] annulation, which proceeded through a ring-expansion of a spirocyclic seven-membered oxanickelacycle to a nine-membered nickelacycle via β-carbon elimination.

Introduction

Transition metal-catalyzed multi-component annulation reactions[1] have been one of the most attractive research topics in synthetic organic chemistry. Multiple carbon–carbon bond formations occur in a single chemical operation with good atom economy, providing a powerful method for the construction of cyclic carbon frameworks. A number of carbon units and reaction modes have been developed to expand the range of accessible carbocycles.[2] Among them, combination of different carbon units such as diene, alkene and alkyne in [4+2+2][2c] annulation reactions has provided a more useful method.



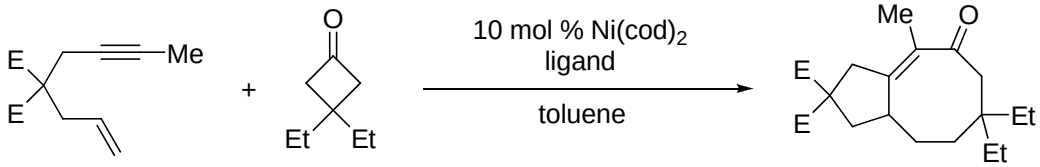
Scheme 1.

In Chapter 2, the author described the nickel-catalyzed [4+2+2] reaction of cyclobutanones with diynes, which achieved construction of cyclooctadienone cores in one synthetic step.[3] The author next examined an analogous nickel-catalyzed [4+2+2] annulation of enynes[2c] with cyclobutanones. A good regioselectivity could be expected for the three-component assembly because the alkene and alkyne moieties would possess different reactivities.

Results and Discussion

The reaction of cyclobutanone **2a** with dimethyl 2-allyl-2-(but-2-ynyl)malonate (**1a**, 1.5 eq) was carried out using the three typical ligands, tributylphosphine, tricyclohexylphosphine, and IPr (Table 1). A slow addition procedure using tricyclohexylphosphine as the ligand worked well to give the bicyclo[6.3.0]undecenone **3a** in 81% yield (entry 2). The structure of **3a** was unambiguously assigned by NMR spectroscopy (^{1}H, ^{13}C, NOESY, HMQC, and HMBC), and only one regioisomer in which the external alkyne carbon of enyne **1a** was connected to the carbonyl carbon of **2a** was detected. The use of the IPr ligand gave a lower yield at both 60 °C and 100 °C (entries 3-5).[4]

Table 1. Optimization of Reaction Conditions[a]



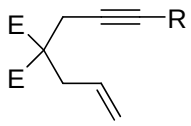
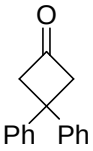
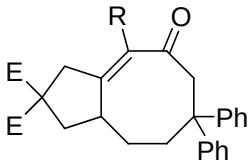
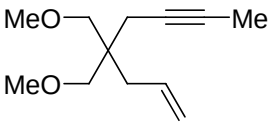
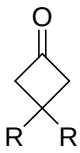
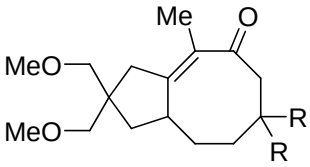
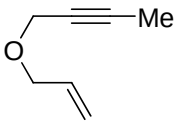
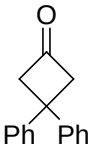
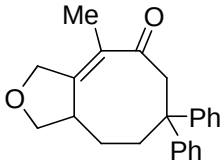
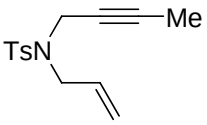
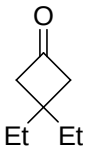
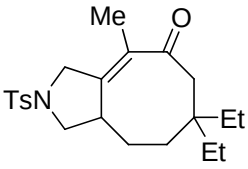
1a (E = CO_2Me) 1.5 eq **2a** **3a**

entry	ligand	temp (°C)	time (h)	yield (%)[b]
1	20 mol % PBu_3	100	3	63
2	20 mol % P(*c*-Hex)$_3$	100	3	81
3	10 mol % IPr	r.t.	3	14
4	10 mol % IPr	60	3	59
5	10 mol % IPr	100	3	63

[a] A solution of enyne **1a** in toluene was added dropwise to the reaction mixture (entries1 and 2). [b] Isolated yield.

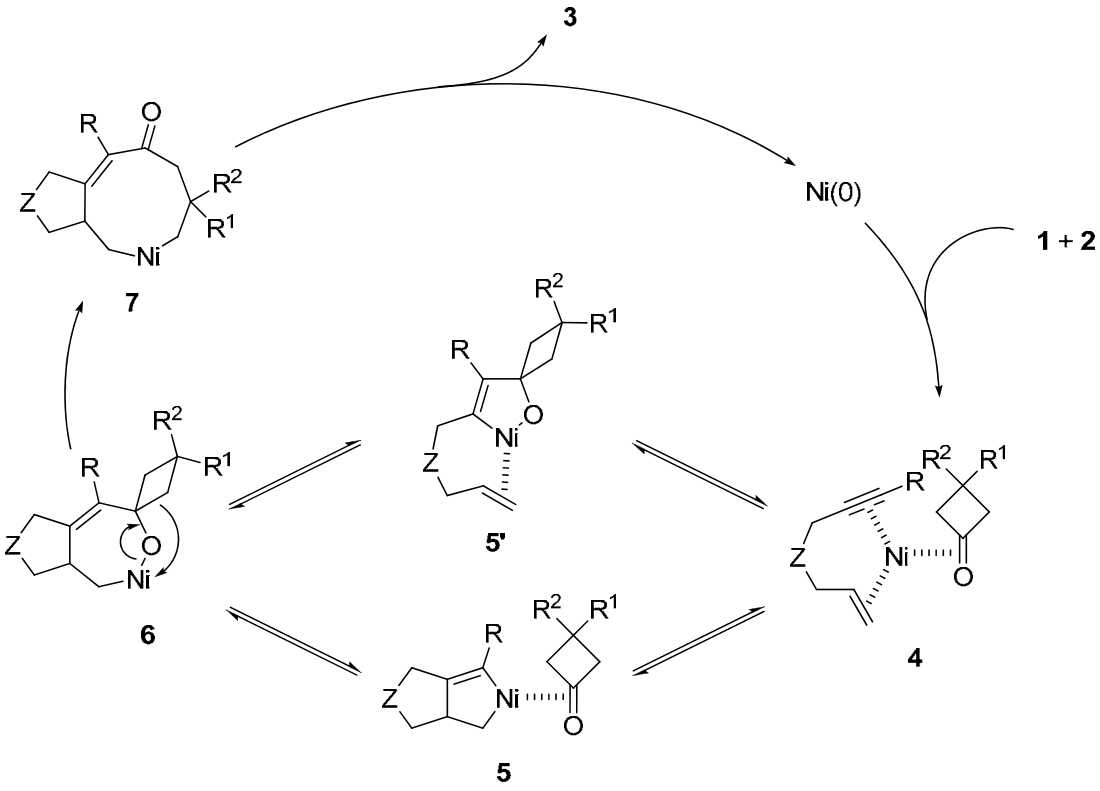
Under the optimized conditions, various bicyclo[6.3.0]undecenones were synthesized by [4+2+2] annulation of enynes **1** with cyclobutanones **2** (Table 2). Cyclobutanone **2b** possessing two substituents at the 3-position reacted with enyne **1a** to give the product in good yield (entry 1). The enyne **1b** having an ethyl substituent at the alkyne terminus afforded the product in 86% yield, whereas an enyne with a terminal alkyne moiety failed to participate in the annulation reaction due to rapid oligomerization at the terminal alkyne moiety (entry 2). The enyne having a methallyl group failed to undergo the reaction, presumably due to steric reasons. A tosylamide linker as well as an ether linker could be included in the skeleton, although the yield was less than those with malonate based linkers (entries 5 and 6).

Table 2. Reaction of Cyclobutanones **2** and Enynes **1** Forming Bicyclo[6.3.0]undecenones **3**[a]

entry	enyne **1**	cyclobutanone **2**	product **3**, yield (%)[b]
			
	(E = CO_2Me)		
1	**1a** (R = Me)	**2b**	**3b** (R = Me), 87
2	**1b** (R = Et)	**2b**	**3c** (R = Et), 86
			
3	**1c**	**2b** (R = Ph)	**3d** (R = Ph), 87
4	**1c**	**2a** (R = Et)	**3e** (R = Et), 74
			
5	**1d**	**2b**	**3f**, 32
			
6	**1e**	**2a**	**3g**, 41

[a] Cyclobutanone **2**, enyne **1** (1.5 eq to **2**), $Ni(cod)_2$ (10 mol %), and $P(c\text{-Hex})_3$ (20 mol %) in toluene at 100 °C for 3 h. [b] Isolated yield.

The mechanism of the annulation reaction of enynes would be similar to that of diynes.[5,6,7] The author assume that the intermediate **5´** is more likely to occur in order to explain the good regioselectivity observed. The higher reactivity of the alkyne moiety relative to the alkene moiety for the initial hetero-type oxidative cyclization could be the reason of the selective formation of the intermediate **5´** (Scheme 2).



Scheme 2.

Conclusion

In summary, the author have developed a nickel-catalyzed [4+2+2]-type annulation reaction of cyclobutanones with enynes, in which a spirocyclic intermediate was expanded through β-carbon elimination. In the multi-component annulation reaction, cyclobutanones acted as a useful four-carbon unit in combination with alkyne and alkene units. This method provides a new direct access to bicyclic eight-membered ring ketones.

Experimental Section

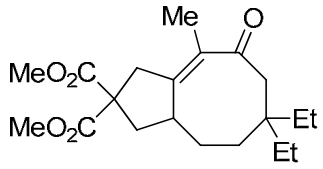
General. All reactions were carried out with standard Schlenk and glove box techniques under a nitrogen atmosphere. Preparative thin-layer chromatography was performed with silica gel 60 PF_{254} (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (^{1}H at 300.07 Hz and ^{13}C at 75.46 Hz) spectrometer or a JEOL JNM-A400 (^{1}H at 399.65 MHz and ^{13}C at 100.40 MHz) spectrometer. Proton chemical shifts were referenced to residual solvent signals in $CDCl_3$ (δ 7.26). Carbon chemical shifts were referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.00) and C_6D_6 (δ 128.00). High resolution mass spectra were recorded on a JOEL JMS-SX102A spectrometer.

Materials. Enynes **1a**,[8] **1b**,[9] **1c**,[10] **1d**,[11] **1e,**[12] and *N*-heterocyclic carbenes IPr,[13] were prepared according to the literature methods. Cyclobutanones **2a** and **2b** were prepared by [2+2] cycloaddition of the corresponding olefins with dichloroketene and subsequent dechlorination with zinc dust in acetic acid.[14] Toluene was distilled over sodium/benzophenone ketyl prior to use. All other commercially available chemical resources were used without further purifications.

General Procedure for Enynes

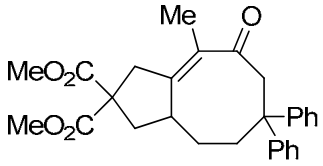
A toluene solution (0.80 mL) of $Ni(cod)_2$ (5.5 mg, 0.020 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.040 mmol), and cyclobutanone **2** (0.20 mmol) was stirred at 100 °C for a few minutes. To the solution was added dropwise a toluene solution (0.20 mL) of enyne **1** (0.30 mmol) via syringe over 2.5 h. After being stirred for a further 0.5 h, the reaction mixture was concentrated. The residue was purified by preparative thin-layer chromatography of silica gel to afford product **3**.

Dimethyl 5,5-diethyl-2-methylbicyclo[6.3.0]undeca-1-en-3-one-10,10-dicarboxylate (3a)



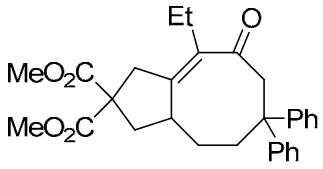
^{1}H NMR δ 0.75 (q, *J* = 6.9 Hz, 6H), 1.01-1.38 (m, 7H), 1.78-1.90 (m, 1H) 1.82 (s, 3H), 2.00 (dd, *J* = 16.5, 5.4 Hz, 1H), 2.32 (d, *J* = 12.0 Hz, 1H), 2.68 (d, *J* = 12.0 Hz, 1H), 2.81 (dd, *J* = 13.1, 8.6 Hz, 1H), 3.05 (d, *J* = 18.0 Hz, 1H), 3.22 (d, *J* = 18.0 Hz, 1H), 3.50-3.66 (m, 1H), 3.71 (s, 3H), 3.72 (s, 3H); ^{13}C NMR δ 7.2, 7.3, 15.7, 26.6, 28.9, 29.5, 31.7, 36.8, 40.9, 42.57, 42.63, 49.8, 52.88, 52.95, 58.0, 134.6, 154.0, 171.7, 171.8, 200.7; HRMS (CI) calcd for $C_{20}H_{30}O_5$ (M^+) 350.2093, found 350.2089.

Dimethyl 2-methyl-5,5-diphenylbicyclo[6.3.0]undeca-1-en-3-one-10,10-dicarboxylate (3b)



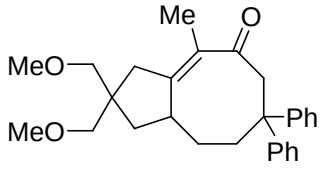
^{1}H NMR δ 1.41-1.27 (m, 1H), 1.49-1.63 (m, 1H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.97 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.23, (d, *J* = 14.4 Hz, 1H), 2.35-2.46 (m, 1H), 2.78 (dd, *J* = 13.4, 8.3 Hz, 1H), 2.99 (dd, *J* = 11.4, 1.2 Hz, 1H), 3.10 (d, *J* = 18.0 Hz, 1H), 3.32 (d, *J* = 18.0 Hz, 1H), 3.50-3.65 (m, 1H), 3.74 (s, 6H), 4.06 (d, *J* = 11.7 Hz, 1H), 7.04-7.17 (m, 3H), 7.18-7.27 (m, 5H), 7.29-7.37 (m, 2H); ^{13}C NMR δ 15.8, 29.3, 33.4, 41.0, 42.80, 42.83, 47.0, 51.2, 52.9, 53.0, 58.0, 125.9, 126.1, 127.2, 127.8, 128.3, 135.2, 146.1, 148.4, 154.0, 171.6, 171.8, 198.4 [one carbon missing]; HRMS (CI) calcd for $C_{28}H_{30}O_5$ (M^+) 446.2093, found 446.2093.

Dimethyl 2-ethyl-5,5-diphenylbicyclo[6.3.0]undeca-1-en-3-one-10,10-dicarboxylate (3c)



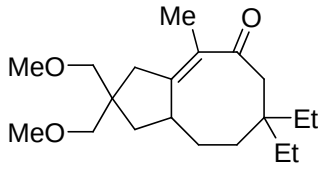
^{1}H NMR δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.15-1.27 (m, 1H), 1.51-1.65 (m, 1H), 1.91 (dd, *J* = 13.5, 5.7 Hz, 1H), 2.19-2.50 (m, 4H), 2.79 (dd, *J* = 12.5, 8.3 Hz, 1H), 2.99 (d, *J* = 11.1 Hz, 1H), 3.15 (d, *J* = 17.7 Hz, 1H), 3.33 (d, *J* = 18.0 Hz, 1H), 3.50-3.65 (m, 1H), 3.75 (s, 6H), 4.03 (d, *J* = 11.4 Hz, 1H), 7.05-7.17 (m, 3H), 7.18-7.26 (m, 5H), 7.30-7.36 (m, 2H); ^{13}C NMR δ 13.2, 23.4, 29.4, 33.4, 40.8, 41.9, 42.7, 47.0, 51.4, 52.90, 52.93, 58.0, 126.0, 126.1, 127.2, 127.8, 128.3, 141.7, 146.2, 148.2, 153.4, 171.5, 171.7, 197.8; HRMS (CI) calcd for $C_{29}H_{32}O_5$ (M^+) 460.2250, found 460.2254.

10,10-bis(methoxymethyl)-2-methyl-5,5-diphenylbicyclo[6.3.0]undeca-1-en-3-one (3d)



^{1}H NMR δ 1.26-1.40 (m, 2H), 1.54-1.68 (m, 1H), 1.85 (s, 3H), 2.03 (dd, *J* = 13.1, 8.6 Hz, 1H), 2.25 (d, *J* = 14.4 Hz, 1H), 2.38-2.65 (m, 3H), 3.00 (d, *J* = 11.1 Hz, 1H), 3.14-3.23 (m, 2H), 3.28-3.40 (m, 8H), 3.43-3.56 (m, 1H), 4.11 (d, *J* = 11.7 Hz, 1H), 7.06-7.38 (m, 10H); ^{13}C NMR δ 15.9, 30.6, 33.5, 40.8, 41.1, 42.0, 46.0, 47.0, 51.3, 59.2, 59.3, 75.5, 76.3, 125.9, 126.0, 127.2, 127.8, 128.3, 134.9, 146.4, 148.6, 158.4, 198.8 [one carbon missing]; HRMS (CI) calcd for $C_{28}H_{34}O_3$ (M^+) 418.2508, found 418.2503.

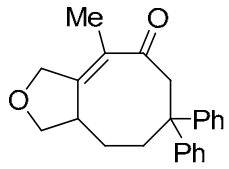
10,10-bis(methoxymethyl)-5,5-diethyl-2-methylbicyclo[6.3.0]undeca-1-en-3-one (3e)



^{1}H NMR δ 0.77 (q, *J* = 7.4 Hz, 6H), 1.06-1.40 (m, 8H), 1.80 (s, 3H), 1.81-1.94 (m, 1H), 2.09 (ddd, *J* = 12.8, 8.9, 1.1 Hz, 1H), 2.30-2.43, (m, 2H), 2.53 (d, *J* = 17.7 Hz, 1H), 2.73 (d, *J* =

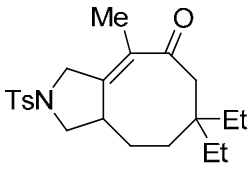
11.7 Hz, 1H), 3.11-3.18 (m, 2H), 3.27-3.31 (m, 5H), 3.33 (s, 3H), 3.41-3.54 (m, 1H); ^{13}C NMR δ 7.3, 7.4, 15.9, 26.6, 29.0, 30.9, 31.9, 36.8, 40.6, 40.9, 41.7, 45.9, 49.9, 59.2, 59.3, 75.4, 76.6, 134.4, 158.4, 201.2; HRMS (CI) calcd for $C_{20}H_{34}O_3$ (M^+) 322.2508, found 322.2502.

2-methyl-5,5-diphenyl-10-oxabicyclo[6.3.0]undeca-1-en-3-one (3f)



^{1}H NMR δ 1.41-1.63 (m, 2H), 1.78 (d, *J* = 1.2 Hz, 3H), 2.23-2.33 (m, 1H), 2.26-2.47 (m, 1H), 3.02 (dd, *J* = 12.0, 1.5 Hz, 1H), 3.47-3.55 (m, 1H), 3.69 (d, *J* = 8.7 Hz, 1H), 3.95 (dd, *J* = 8.7, 6.0 Hz, 1H), 4.17 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 15.6 Hz, 1H), 4.65 (d, *J* = 15.9 Hz, 1H), 7.03-7.09 (m, 2H), 7.12-7.18 (m, 1H), 7.19-7.30 (m, 5H), 7.31-7.38 (m, 2H); ^{13}C NMR δ 14.6, 26.7, 33.2, 42.3, 47.4, 51.4, 73.1, 76.3, 126.1, 126.2, 127.2, 127.3, 127.9 128.4, 132.1, 146.1, 148.4, 153.3, 198.2; HRMS (CI) calcd for $C_{23}H_{24}O_2$ (M^+) 332.1776, found 332.1779.

10-(4-Tolylsulfonyl)-5,5-diethyl-2-methyl-10-azabicyclo[6.3.0]undeca-1-en-3-one (3g)



^{1}H NMR δ 0.73-0.80 (m, 6H), 1.01-1.55 (m, 7H), 1.72 (s, 3H), 1.78-1.95 (m, 1H), 2.39 (d, *J* = 13.2 Hz, 1H), 2.43 (s, 3H), 2.61 (d, *J* = 12.6 Hz, 1H), 3.11 (dd, *J* = 9.0, 6.6 Hz, 1H), 3.34 (d, *J* = 9.0 Hz, 1H), 3.46-3.59 (m, 2H), 4.17 (d, *J* = 16.2 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR δ 7.26, 7.33, 14.9, 21.6, 27.0, 27.1, 29.4, 31.1, 37.3, 41.1, 50.4, 53.7, 55.4, 128.0, 129.7, 131.3, 133.9, 144.0, 149.0, 199.4; HRMS (CI) calcd for $C_{22}H_{31}NO_3S$ (M^+) 389.2025, found 389.2028.

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(2) (a) S. R. Gilbertson, B. DeBoef, *J. Am. Chem. Soc.* **2002**, *124*, 8784. (b) J. A. Varela, L. Castedo, C. Saá, *Org. Lett.* **2003**, *5*, 2841. (c) P. A. Evans, E. W. Baum, A. N. Fazal, M. Pink, *Chem. Commun.* **2005**, 63. (d) H. A. Wegner, A. de Meijere, P. A. Wender, *J. Am. Chem. Soc.* **2005**, *127*, 6530.

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(4) IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

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Chapter 4

Nickel-Catalyzed Intramolecular Alkene Insertion into Cyclobutanones

Abstract

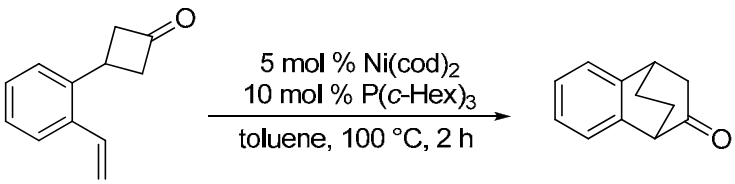
3-Styrylcyclobutanones were converted to benzobicyclo[2.2.2]octenones in the presence of nickel(0) catalysts. Intramolecular alkene insertion into cyclobutanones which proceeds through oxidative cyclization of the carbonyl group of the cyclobutanone and the alkene moiety with the nickel(0), followed by β-carbon elimination from the resulting oxanickelacyclopentane, and subsequent reductive elimination, afforded the products.

Introduction

Transition metal-mediated reactions that cleave carbon–carbon bonds have attracted considerable attention from a mechanistic point of view.[1] Metal-mediated carbon–carbon bond cleavage reactions facilitate synthetic transformations which are otherwise difficult using traditional means. Recently, a variety of catalytic reactions involving a carbon–carbon bond cleaving step have been developed.[2] For example, a carbon–carbon double or triple bond can be inserted into a carbon–carbon single bond using a transition metal complex that catalyzes its cleavage.[3] Such insertion reactions provide expanded carbon frameworks in a highly atom-economical manner.

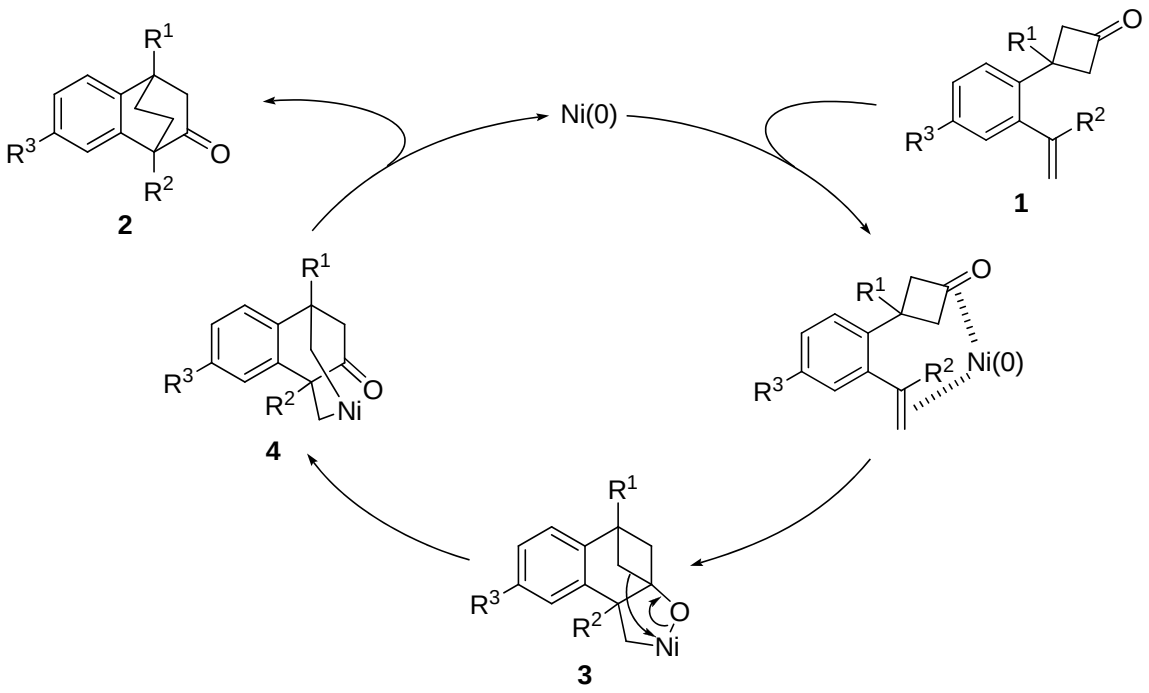
The author's group has reported just such a rhodium-catalyzed intramolecular alkene insertion reaction using alkenyl-substituted cyclobutanones as the substrates.[4] The carbon–carbon single bond between the carbonyl carbon and the α-carbon could be cleaved by oxidative addition onto rhodium(I) to allow subsequent insertion of a carbon–carbon double bond. On the other hand, the use of nickel as the catalyst brought about a different kind of reaction in which a cyclobutanone skeleton is expanded by way of an intermolecular insertion of an alkyne.[5] This procceds via (i) oxidative cyclization of the carbonyl group of a cyclobutanone and an alkyne with nickel(0), (ii) β-carbon elimination from the resulting oxanickelacycle, and (iii) reductive elimination. An analogous intermolecular insertion reaction of alkenes instead of alkynes would increase the synthetic utility of this nickel-catalyzed ring-expansion reaction of cyclobutanones. However, all attempts at accomplishing this transformation have failed thus far, which led the author to examine an intramolecular variant using the alkenyl-substituted cyclobutanones. In this chapter, the author reports the nickel-catalyzed intramolecular alkene insertion reaction of cyclobutanones, which affords a result complementary to that obtained with rhodium catalysts.

Results and Discussion



1a **2a** 90% (1)

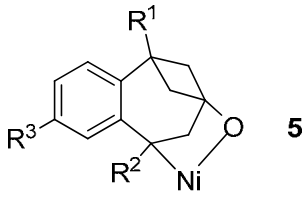
3-(*o*-Styryl)cyclobutanone **1a** was heated in toluene at 100 °C for 2 h in the presence of a nickel catalyst prepared in situ from bis(1,5-cyclooctadiene)nickel(0) (5 mol %) and tricyclohexylphosphine (10 mom %). Chromatographic isolation on silica gel afforded benzobicyclo[2.2.2]octenone (**2a**)[6] in 90 % yield (eq 1).



Scheme 1.

Shown in Scheme 1 is a mechanism proposed for the production of **2** from **1** on the basis of the mechanism reported for the reaction of carbonyl compounds and alkenes with nickel(0)[7] and the author's previous work on the intermolecular variant using alkynes. Initially, intramolecular oxidative cyclization of the vinyl moiety and the carbonyl group of the cyclobutanone with nickel(0) occurs to form the oxanickelacyclopentane **3**, which contains a nickel(II) cyclobutanolate unit. The four-membered ring is then opened by β-carbon elimination.[8] The methylene carbon γ to nickel migrates onto nickel with extrusion of the carbonyl group, resulting in the formation of the bicyclic intermediate **4**. Finally, reductive elimination gives the product **2**. Nickelacycle **5**, which is conceivable as an

alternative oxidative cyclization intermediate, is considerably more strained than **3**. This likely accounts for the complete regioselectivity of the alkene insertion process.



5

Listed in Table 1 are results obtained with other ligands for nickel. Tributylphosphine and an *N*-heterocyclic carbene (IPr)[9] were both comparable to tricyclohexylphosphine.

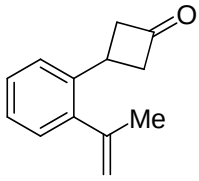
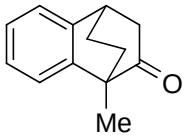
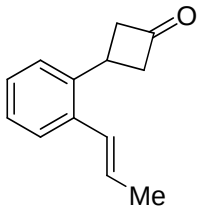
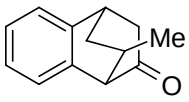
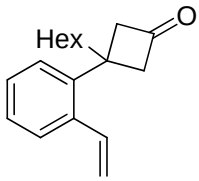
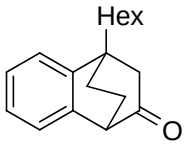
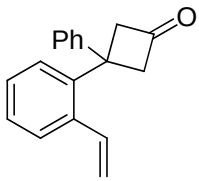
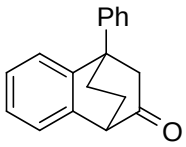
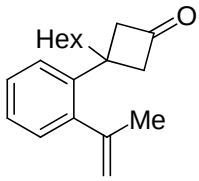
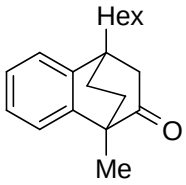
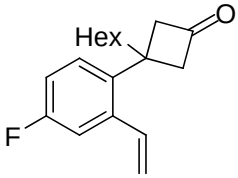
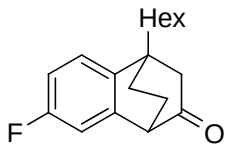
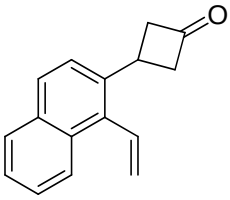
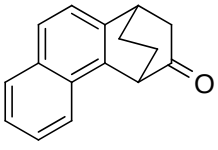
Table 1. Nickel-Catalyzed Reaction of **1a** Using Various Ligands[a]

entry	ligand	time (h)	yield (%)[b]
1	none	2	0
2	10 mol % PPh_3	2	23
3	10 mol % P(*c*-Hex)$_3$	2	90
4	10 mol % PBu_3	2	82
5	5 mol % IPr	6	83

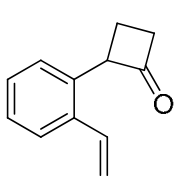
[a] 3-Styrylcyclobutanone **1a**, Ni(cod)$_2$ (5 mol %) and ligand were heated in toluene at 100 °C. [b] Isolated yield

Various substrates were subjected to the nickel-catalyzed insertion reaction using tricyclohexylphosphine as the ligand and the results are shown in Table 2. It was possible to incorporate substituents at various positions of the bicyclo[2.2.2]octenone skeleton. 3-Arylcyclobutanone **1b** with an isopropenyl group at the ortho position afforded product **2b** having a methyl substituent at the bridge head position α to the carbonyl group in high yield (entry 1). The reaction also proceeded with 1-propenyl substituted substrate **1c** to give the corresponding product **2c** in 82% yield (entry 2).[10] 3,3-Disubstituted cyclobutanones **1d** and **1e** produced benzobicyclo[2.2.2]octenones **2d** and **2e**, respectively, having a substituent at another bridge head position β to the carbonyl group (entries 3 and 4). Even benzobicyclo[2.2.2]octenone **2f** in which both bridge head positions are substituted was synthesized in high yield by the insertion reaction (entry 5). A fluoro substituent on the aryl ring retarded the reaction to furnish the product **2g** in modest yield (entry 6). Although we examined other substrates like 2-styrylcyclobutanone **6** and 3-(but-3-enyl)-3-phenylcyclobutanone **7**, they failed to participate in the insertion reaction.

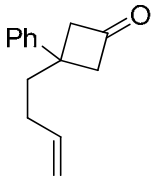
Table 2. Nickel-Catalyzed Reaction of Cyclobutanones **1**

entry	cyclobutanone **1**	product **2**, yield (%)[b]
1	 **1b**	 **2b**, 89
2	 **1c**	 **2c**, 82
3	 **1d**	 **2d**, 91
4	 **1e**	 **2e**, 40
5	 **1f**	 **2f**, 91
6	 **1g**	 **2g**, 45
7	 **1h**	 **2h**, 88

[a] 3-Styrylcyclobutanone **1**, $Ni(cod)_2$ (10 mol %) and P(*c*-Hex)$_3$ (20 mol %) were heated in toluene at 100 °C for 2-12 h. [b] Isolated yield.

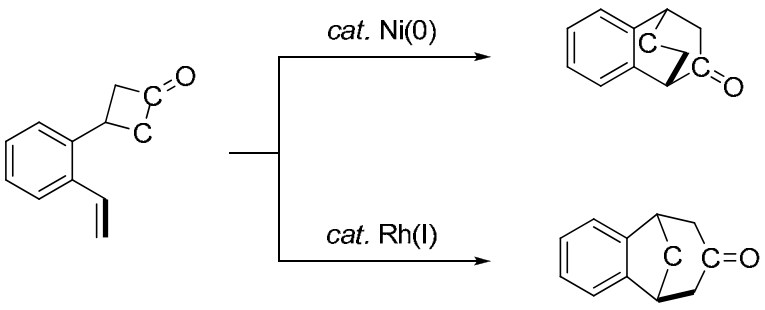


6



7

As mentioned in the introduction, the author's group has already reported the rhodium-catalyzed reaction of 3-styrylcyclobutanones which produces benzobicyclo[3.2.1]octenones by intramolecular alkene insertion. This reaction proceeds through (i) insertion of rhodium(I) between the carbonyl carbon and the α-carbon of the cyclobutanone, (ii) intramolecular migratory insertion of the vinyl group into the Rh–C linkage, and (iii) reductive elimination. During these transformations catalyzed by nickel and rhodium, the single bond between the carbonyl carbon and the α-carbon of the cyclobutanone moiety is cleaved and the pendant vinyl group is inserted between the two carbons. Distinctly different bicyclic carbon frameworks, either bicyclo[2.2.2]octenones or bicyclo[3.2.1]octenones, result depending on the regiochemistry of the vinyl insertion. The transition metal catalyst employed dictates the mechanism of the insertion, and which product is formed.



Scheme 4.

Conclusion

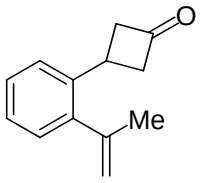
In summary, the author has developed a new nickel-catalyzed transformation of 3-styrylcyclobutanones, which are converted to benzobicyclo[2.2.2]octenone by the intramolecular insertion of an alkene moiety into the cyclobutanone skeleton.

Experimental Section

General. All reactions were carried out with standard Schlenk and glove box techniques under a nitrogen atmosphere. Preparative thin-layer chromatography was performed with silica gel 60 PF_{254} (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (^{1}H at 300.07 Hz and ^{13}C at 75.46 Hz) spectrometer. Proton chemical shifts were referenced to residual solvent signals in $CDCl_3$ (δ 7.26). Carbon chemical shifts were referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.00). High resolution mass spectra were recorded on a JOEL JMS-SX102A spectrometer.

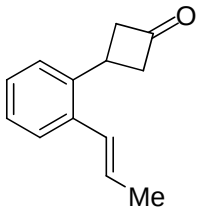
Materials. Toluene was dried and deoxygenized using an alumina/catalyst column system (GlassContour Co). $Ni(cod)_2$ was recrystallized from toluene. All other commercially available chemical resources were used without further purifications. 3-Styrylcyclobutanones **1a**, **1b** and **1c** were prepared by $Pd(P(t\text{-}Bu)_3)_2$ catalyzed coupling reaction of 3-(2-bromophenyl)cyclobutanone with the corresponding tri-*n*-butylvinyltins. Naphthalene derived substrate **1h** was prepared from 3-(1-bromonaphthalen-2-yl)cyclobutanone in an analogous manner. 3-Styrylcyclobutanones **1d**, **1f** and **1g** were prepared by 1,4-addition of the corresponding (2-vinyl-phenyl)cupurates generated from (2-vinyl-phenyl)magnesiumbromides and CuI to 3-hexylcyclobutenone. 3-Styrylcyclobutanone **1e** was prepared by an analogous 1,4-additon reaction to 3-phenylcyclobutenone.

3-(2-Isopropenylphenyl)cyclobutanone (1b)



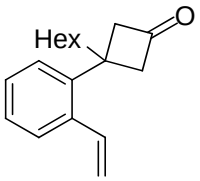
^{1}H NMR δ 2.08 (d, J = 0.6 Hz, 3H), 3.17-3.28 (m, 2H), 3.37-3.49 (m, 2H), 3.91 (quint, J = 8.3 Hz, 1H), 4.86 (t, J = 0.9 Hz, 1H), 5.25 (d, J = 1.5 Hz, 1H), 7.14-7.40 (m, 4H); ^{13}C NMR δ 25.0, 25.7, 55.0, 115.5, 124.8, 126.3, 127.4, 128.0, 139.9, 143.7, 145.1, 207.1; HRMS (CI) calcd for $C_{13}H_{15}O$ (M^+ + H) 187.1123, found 187.1124.

3-(2-Propenylphenyl)cyclobutanone (1c)



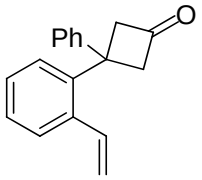
^{1}H NMR δ 1.92 (dd, *J* = 6.5, 1.7 Hz, 3H), 3.18-3.30 (m, 2H), 3.39-3.50 (m, 2H), 3.87 (quint, *J* = 8.4 Hz, 1H), 6.10 (dq, *J* = 15.5, 6.7 Hz, 1H), 6.58 (dd, *J* = 15.6, 1.5 Hz, 1H), 7.19-7.31 (m, 3H), 7.40-7.45 (m, 1H); ^{13}C NMR δ 18.9, 26.0, 53.4, 124.7, 126.6, 126.8, 127.0, 128.4, 128.6, 137.3, 139.1, 206.6; HRMS (EI) calcd for $C_{13}H_{14}O$ (M^+) 186.1045, found 186.1047.

3-Hexyl-3-(2-vinylphenyl)cyclobutanone (1d)



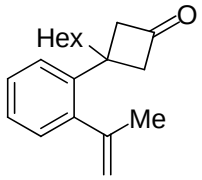
^{1}H NMR δ 0.81-0.85 (m, 3H), 1.00-1.30 (m, 8H), 1.82- 1.89 (m, 2H), 3.10-3.20 (m, 2H), 3.41-3.50 (m, 2H), 5.30 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.62 (dd, *J* = 17.3, 1.4 Hz, 1H), 6.88 (dd, *J* = 17.3, 10.7 Hz, 1H), 7.10-7.14 (m, 1H), 7.22-7.27 (m, 2H), 7.49-7.54 (m, 1H); ^{13}C NMR δ 14.0, 22.5, 25.5, 29.3, 31.6, 38.0, 41.0, 58.2, 115.8, 126.9, 127.1, 127.3, 128.1, 135.5, 136.3, 142.6, 206.9; HRMS (CI) calcd for $C_{18}H_{25}O$ (M^+ + H) 257.1905, found 257.1909.

3-Phenyl-3-(2-vinylphenyl)cyclobutanone (1e)



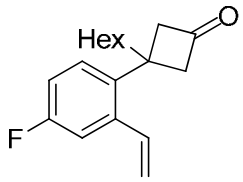
^{1}H NMR δ 3.57-3.67 (m, 2H), 3.80-3.89 (m, 2H), 5.15 (dd, *J* = 11.1, 1.2 Hz, 1H), 5.58 (dd, *J* = 17.3, 1.4 Hz, 1H), 6.47 (dd, *J* = 17.4, 11.1 Hz, 1H), 7.14-7.58 (m, 9H); ^{13}C NMR δ 41.3, 61.6, 115.8, 125.7, 126.4, 127.5, 127.6, 127.7, 127.9, 128.6, 135.7, 137.2, 142.7, 146.6, 206.3; HRMS (EI) calcd for $C_{18}H_{16}O$ (M^+) 248.1201, found 248.1203.

3-Hexyl-3-(2-isopropenylphenyl)cyclobutanone (1f)



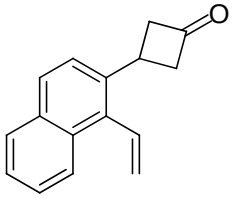
^{1}H NMR δ 0.82-0.87 (m, 3H), 1.10-1.30 (m, 8H), 1.83-1.89 (m, 2H), 2.09 (s, 3H), 3.03-3.13 (m, 2H), 3.33-3.42 (m, 2H), 4.86 (d, J = 0.9 Hz, 1H), 5.21 (t, J = 1.7 Hz, 1H), 7.07-7.15 (m, 2H), 7.19-7.25 (m, 2H); ^{13}C NMR δ 14.0, 22.6, 25.5, 26.4, 29.5, 31.6, 38.3, 42.6, 58.3, 116.4, 126.1, 126.3, 129.0, 129.5, 142.5, 142.8, 145.5, 207.6; HRMS (CI) calcd for $C_{19}H_{27}O$ (M^+ + H) 271.2062, found 271.2059.

3-(4-Fluoro-2-vinylphenyl)-3-hexylcyclobutanone (1g)



^{1}H NMR δ 0.79-0.90 (m, 3H), 1.00-1.40 (m, 8H), 1.78-1.85 (m, 2H), 3.08-3.18 (m, 2H), 3.36-3.45 (m, 2H), 5.34 (dd, J = 11.4, 0.6 Hz, 1H), 5.62 (d, J = 17.1 Hz, 1H), 6.81 (ddd, J = 17.2, 10.7, 1.4 Hz, 1H), 6.93 (dt, J = 8.3, 2.8 Hz, 1H), 7.06 (dd, J = 8.6, 5.9 Hz, 1H), 7.19 (dd, J = 9.9, 2.7 Hz, 1H); ^{13}C NMR δ 14.0, 22.5, 25.5, 29.3, 31.6, 37.7, 41.0, 58.4, 113.4 (d, $^{2}J_{C–F}$ = 21.9 Hz), 114.0 (d, $^{2}J_{C–F}$ = 20.8 Hz), 116.9, 129.8 (d, $^{3}J_{C–F}$ = 8.1 Hz), 134.5, 138.3 (d, $^{3}J_{C–F}$ = 6.9 Hz), 138.4 (d, $^{4}J_{C–F}$ = 3.5 Hz), 161.6 (d, $^{1}J_{C–F}$ = 243.2 Hz), 206.5; HRMS (EI) calcd for $C_{18}H_{23}OF$ (M^+) 274.1733, found 274.1734.

3-(1-Vinylnaphthalen-2-yl)cyclobutanone (1h)



^{1}H NMR δ 3.26-3.37 (m, 2H), 3.43-3.56 (m, 2H), 4.18 (quint, J = 8.4 Hz, 1H), 5.42 (dd, J = 17.9, 2.0 Hz, 1H), 5.84 (dd, J = 11.4, 2.1 Hz, 1H), 7.12 (dd, J = 17.9, 11.3 Hz, 1H), 7.45-7.55 (m, 3H), 7.81-7.87 (m, 2H), 8.10-8.15 (m, 1H); ^{13}C NMR δ 26.1, 54.8, 121.9, 122.6, 125.5,

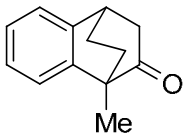
126.2, 128.0, 131.6, 132.1, 133.9, 135.1, 137.2, 207.0 (two carbons are missing); HRMS (EI) calcd for $C_{16}H_{14}O$ (M^+) 222.1045, found 222.1045.

General Procedure for Nickel-Catalyzed Reaction of 1

A toluene solution (1.0 mL) of $Ni(cod)_2$ (5.5 mg, 0.020 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.040 mmol) and 3-styrylcyclobutanone **1** (0.20 mmol) was stirred in a Schlenk-type flask under a nitrogen atmosphere at 100 °C for 2-12 h. The reaction mixture was cooled, concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane : ethyl acetate) to afford the product **2**.

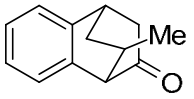
The structure of the products **2** were assigned based on the high resolution mass spectral data and ^{1}H and ^{13}C NMR data.

8-Methyltricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-trien-9-one (2b)



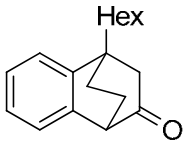
^{1}H NMR δ1.50 (d, *J* = 0.9 Hz, 3H), 1.57 (dt, *J* = 8.6, 3.7 Hz, 1H), 1.68-1.79 (m, 1H), 1.84-2.04 (m, 2H), 2.22 (dt, *J* = 18.6, 2.9 Hz, 1H), 2.40 (dd, *J* = 18.6, 1.5 Hz, 1H), 3.42 (t, *J* = 2.9 Hz, 1H), 7.20-7.30 (m, 4H); ^{13}C NMR δ15.2, 26.3, 31.1, 36.4, 41.8, 50.3, 122.7, 123.6, 126.7, 126.9, 139.0, 143.1, 212.5; HRMS (EI) calcd for $C_{13}H_{14}O$ (M^+) 186.1045, found 186.1048.

12-Methyltricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-trien-9-one (2c)



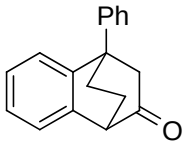
^{1}H NMR δ1.14 (d, *J* = 6.3 Hz, 3H), 1.35-1.50 (m, 1H), 1.96-2.10 (m, 2H), 2.13-2.31 (m, 2H), 3.34-3.43 (m, 2H), 7.16-7.26 (m, 4H); ^{13}C NMR δ21.9, 32.0, 34.5, 36.6, 42.4, 59.7, 123.9, 125.3, 126.8, 127.2, 137.3, 142.4, 211.4; HRMS (EI) calcd for $C_{13}H_{14}O$ (M^+) 186.1045, found 186.1045.

1-Hexyltricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-trien-9-one (2d)



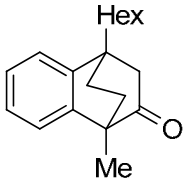
^{1}H NMR δ 0.90-0.96 (m, 3H), 1.35-1.54 (m, 9H), 1.69-2.01 (m, 5H), 2.06-2.16 (m, 1H), 2.27 (d, *J* = 18.3 Hz, 1H), 3.60 (t, *J* = 2.9 Hz, 1H), 7.18-7.34 (m, 4H); ^{13}C NMR δ 14.1, 22.7, 24.2, 24.3, 29.9, 30.2, 31.8, 35.1, 41.3, 45.6, 53.0, 121.6, 125.3, 126.6, 127.0, 137.0, 144.8, 211.8; HRMS (EI) calcd for $C_{18}H_{24}O$ (M^+) 256.1827, found 256.1825.

1-Phenyltricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-trien-9-one (2e)



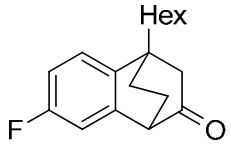
^{1}H NMR δ 1.87-1.98 (m, 1H), 2.07-2.30 (m, 3H), 2.55 (d, *J* = 18.0 Hz, 1H), 2.71 (dd, *J* = 18.3, 3.0 Hz, 1H), 3.74 (t, *J* = 2.6 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 7.11-7.26 (m, 3H), 7.35-7.50 (m, 5H); ^{13}C NMR δ 24.3, 30.9, 46.5, 53.1, 123.8, 125.4, 127.0, 127.1, 127.3, 128.6, 136.2, 141.4, 145.2, 210.6 (one carbon is missing); HRMS (EI) calcd for $C_{18}H_{16}O$ (M^+) 248.1201, found 248.1204.

1-Hexyl-8-methyltricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-trien-9-one (2f)



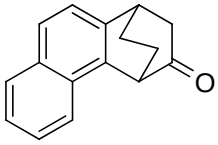
^{1}H NMR δ 0.89-0.95 (m, 3H), 1.30-1.61 (m, 13H), 1.80-2.03 (m, 5H), 2.30 (d, *J* = 18.3 Hz, 1H), 7.20-7.30 (m, 4H); ^{13}C NMR δ 14.1, 15.4, 22.7, 24.1, 30.2, 31.0, 31.8, 32.1, 35.3, 40.6, 45.5, 50.3, 121.4, 122.7, 126.5, 126.7, 139.6, 145.0, 212.5; HRMS (EI) calcd for $C_{19}H_{26}O$ (M^+) 270.1984, found 270.1981.

5-Fluoro-1-hexyltricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-trien-9-one (2g)



^{1}H NMR δ 0.88-0.96 (m, 3H), 1.30-1.54 (m, 9H), 1.66-1.99 (m, 5H), 2.05-2.16 (m, 1H), 2.26 (d, J = 18.6 Hz, 1H), 3.56 (t, J = 2.7 Hz, 1H), 6.90-7.01 (m, 2H), 7.20 (dd, J = 8.3, 5.3 Hz, 1H); ^{13}C NMR δ 14.1, 22.7, 24.2, 24.3, 29.9, 30.2, 31.8, 35.3, 41.0, 45.6, 53.0, 112.5 (d, $^{2}J_{C–F}$ = 21.9 Hz), 113.5 (d, $^{2}J_{C–F}$ = 20.8 Hz), 123.2 (d, $^{3}J_{C–F}$ = 8.1 Hz), 139.0 (d, $^{3}J_{C–F}$ = 8.1 Hz), 140.4 (d, $^{4}J_{C–F}$ = 3.5 Hz), 161.5 (d, $^{1}J_{C–F}$ = 243.2 Hz), 211.0; HRMS (EI) calcd for $C_{18}H_{23}OF$ (M^{+}) 274.1733, found 274.1736.

Tetracyclo[10.2.2.0^{2,11}.0^{5,9}]hexadeca-2,4,6,8,10-pentaen-13-one (2h)



^{1}H NMR δ 1.65-1.82 (m, 2H), 1.97-2.10 (m, 1H), 2.16-2.31 (m, 2H), 2.41 (dd, J = 18.5, 2.3 Hz, 1H), 3.60 (t, J = 2.6 Hz, 1H), 4.47 (d, J = 2.4 Hz, 1H), 7.40-7.57 (m, 3H), 7.78 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 23.3, 25.4, 37.1, 41.5, 47.6, 122.0, 123.0, 125.1, 126.4, 127.2, 128.8, 129.5, 131.6, 132.7, 140.7, 211.6; HRMS (EI) calcd for $C_{16}H_{14}O$ (M^{+}) 222.1045, found 222.1044.

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(1) For reviews, see: (a) R. H. Crabtree, *Chem. Rev.* **1985**, *85*, 245. (b) M. Murakami, Y. Ito, In Activation of Unreactive Bonds and Organic Synthesis; Murai, S., Ed.; Topics in Organometallic Chemistry, Vol. 3; Springer: Berlin, **1999**, pp 97–129. (c) M. E. van der Boom, D. Milstein, *Chem. Rev.* **2003**, *103*, 1759. (d) C.-H. Jun, *Chem. Soc. Rev.* **2004**, *33*, 610–618.

(2) For recent examples of catalytic and stoichiometric reactions, see: (a) Y. Terao, M. Nomoto, T. Satoh, M. Miura, M. Nomura, *J. Org. Chem.* **2004**, *69* 6942. (b) P. Zhao, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 11618. (c) A. Funayama, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2005**, *127*, 15354. (d) P. Zhao, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 3124.

(3) For recent examples, see: (a) C. Müller, R. J. Lachicotte, W. D. Jones, *Organometallics* **2002**, *21*, 1975. (b) T. Kondo, Y. Taguchi, Y. Kaneko, M. Niimi, T. Mitsudo, *Angew. Chem., Int. Ed.* **2004**, *43*, 5369. (c) T. L. Dzwiniel, J. M. Stryker, *J. Am. Chem. Soc.* **2004**, *126*, 9184. (d) S. Komagawa, S. Saito, *Angew. Chem., Int. Ed.* **2006**, *45*, 2446. (e) Y. Nakao, T. Yukawa, Y. Hirata, S. Oda, J. Satoh, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 7116. (f) Y. Nakao, Y. Hirata, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 7420. (g) Y. Nakao, S. Oda, A. Yada, T. Hiyama, *Tetrahedron* **2006**, *62*, 7567.

(4) (a) M. Murakami, T. Itahashi, Y. Ito, *J. Am. Chem. Soc.* **2002**, *124*, 13976. (b) T. Matsuda, A. Fujimoto, M. Ishibashi, M. Murakami, *Chem. Lett.* **2004**, *33*, 876.

(5) (a) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2005**, *127*, 6932. (b) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2006**, *128*, 2166.

(6) For the spectral data of **2a**, see: H. Morrison, K. Muthuramu, G. Pandey, D. Severance, B. Bigot, *J. Org. Chem.* **1986**, *51*, 3358.

(7) (a) S. Ogoshi, M-a. Oka, H. Kurosawa, *J. Am. Chem. Soc.* **2004**, *126*, 11802. (b) S. Ogoshi, M. Ueta, T. Arai, H. Kurosawa, *J. Am. Chem. Soc.* **2005**, *127*, 12810. (c) S.-S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2005**, *127*, 14194. (d) C.-Y. Ho, S.-S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 5362.

(8) For β-carbon elimination from transiton metal cyclobutanolate, see: (a) T. Nishimura, S. Uemura, *Synlett* 2004, 201. (b) T. Matsuda, M. Shigeno, M. Makino, M. Murakami, *Org. Lett.* **2006**, *8*, 3379.

(9) IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

(10) Although the relative configuration of **2c** was not determined, it was obtained as a single diastereoisomer (d.r. = >95:5) from **1c** (*E*:*Z* = >95:5)

Chapter 5

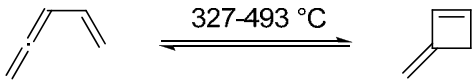
Dramatic Effects of Boryl Substituents on Thermal Ring-Closing Reaction of Vinylallenes

Abstract

The unidirectional thermal ring-closing reaction of *cis*-4-phenyl-5-borylpenta-1,2,4-triene giving 4-boryl-3-methylenecyclobutene proceeded significantly faster than that of the *trans*-isomer. The large rate difference between the *cis*- and *trans*-stereoisomers is ascribed to electronic participation of the vacant boron p orbital in the second highest occupied molecular orbital (SHOMO) at the transition state.

Introduction

Electrocyclic ring-opening and -closing reactions between cyclobutene derivatives and conjugated dienes have been a source of continuing interest.[1] Both thermodynamic and kinetic properties of the reactions change according to the structural variation with additional unsaturation. Cyclobutene undergoes a thermal ring-opening reaction in the gas phase at temperatures ranging from 130 to 175 °C producing 1,3-butadiene, which is thermodynamically more stable than cyclobutene.[2] On the other hand, 1,2,4-pentatriene (vinylallene) and methylenecyclobutene possess comparable thermodynamic stabilities such that thermal treatment produces an equilibrium mixture of them (eq 1).[3,4]

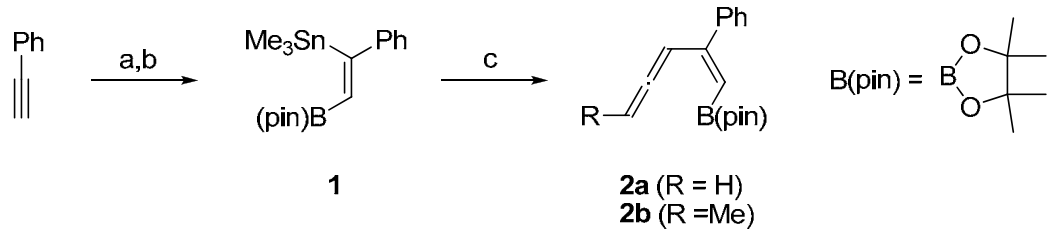


(1)

Based on theoretical calculation, De Lera et al. suggested that introduction of a methyl group at the vinylic terminus of a vinylallene renders the ring-closed methylenecyclobutene the thermodynamically favored form.[4b] The author's group have described the remarkable effects that silyl substituents have on the electrocyclization of vinyl allenes.[5,6] A silyl substituent at the vinylic terminus stabilizes the ring-closed product, and in particular, lowers the temperature required for the ring-closure to 110 °C. Recently, Sato et al. reported that a titanium-substituted vinylallene formed as a reaction intermediate underwent a unidirectional ring-closing reaction even at 0 °C.[7,8] In this chapter, the author reports the dramatic effects that a boron substituent exerts on electrocyclization of vinylallenes together with the electronic interpretation.

Results and Discussion

5-Borylpenta-1,2,4-trienes were chosen as the reaction substrates. *Cis*- and *trans*-isomers **2** and **4** were synthesized as shown in Schemes 1 and 2, respectively. The palladium-catalyzed stannaboration[9] of phenylacetylene with stannylborane afforded the *cis*-adduct **1** stereoselectively. Subsequent palladium-catalyzed coupling at the vinyltin moiety of **1** with propargyl bromide produced the *cis*-isomer **2a**. Vinylallene **2b** was synthesized in an analogous manner.

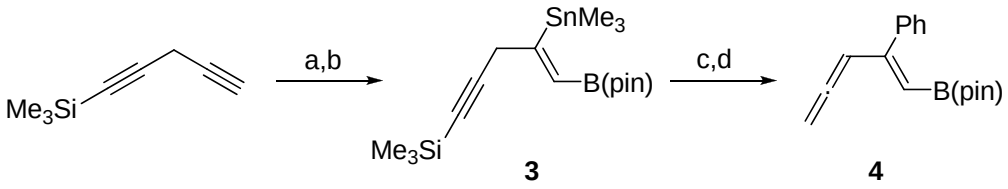


1 **2a** (R = H) **2b** (R =Me)

Reagents and conditions: (a) Me_3Sn-$B(NEt_2)_2$, $Pd(PPh_3)_4$, benzene, 60 °C. (b) pinacol, r.t. (90%, 2 steps). (c) propargyl bromide, $PhCH_2PdCl(PPh_3)_2$, CuI, DMF, r.t.-35 °C (**2a** 45%); 3-chloro-1-butyne, $PhCH_2PdCl(PPh_3)_2$, CuI, DMF, r.t.-35 °C (**2b** 11%).

Scheme 1.

Trans-isomer **4** was prepared from 1-(trimethylsilyl)penta-1,4-diyne, which was also subjected to the palladium-catalyzed stannaboration. Only the terminal acetylenic moiety reacted with the stannylborane to give adduct **3**. The phenyl group was introduced by the cross-coupling reaction of **3** with iodobenzene. Desilylation/isomerization under basic conditions afforded the *trans*-isomer **4**.[10]



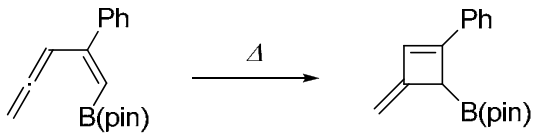
3 **4**

Reagents and conditions: (a) Me_3Sn-$B(NEt_2)_2$, $Pd(PPh_3)_4$, toluene, r.t. (b) pinacol, r.t. (52%, 2 steps). (c) iodobenzene, $PhCH_2PdCl(PPh_3)_2$, CuI, DMF, 90 °C (24%). (d) NaOH, MeOH (16%).

Scheme 2.

Heating the *cis*-isomer **2a** in xylene at 140 °C affected the electrocyclic ring-closing reaction in 3 h, providing the ring-closed product **5a** in 96% isolated yield (eq 2). The kinetics of the electrocyclization of **2a** were investigated. A dilute solution of **2a** was heated over the temperature range 90–120 °C in a sealed NMR tube and the conversion to product determined

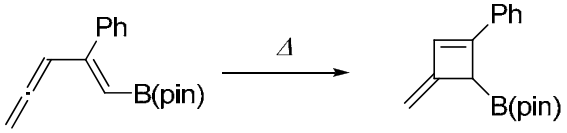
by ^{1}H NMR. The reaction was shown to be first order in **2a** and the rate described by the Arrhenius equation $k = 10^{11.4}\exp(-26.8/RT)\ s^{-1}$.



2a **5a**

$\log A = 11.4$
$E_a = 26.8$ kcal/mol (2)

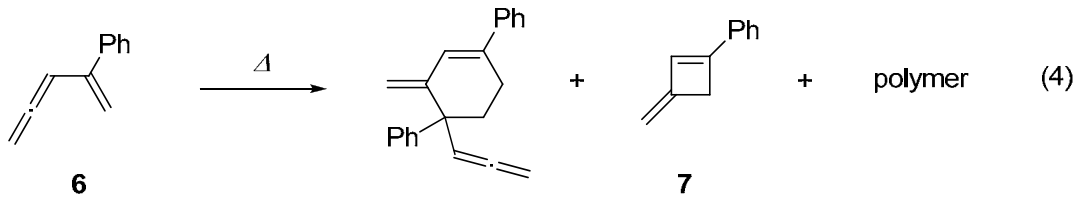
The *trans*-isomer **4** also underwent ring-closure leading to **5a** unidirectionally (eq 3). However, the reaction was much slower than that of **2a**. An Arrhenius plot provided activation parameters $k = 10^{13.6}\exp(-33.2/RT)\ s^{-1}$. It is of note that the activation energy for **4** is 6.4 kcal/mol greater than that of the *cis*-isomer **2a**.



4 **5a**

$\log A = 13.6$
$E_a = 33.2$ kcal/mol (3)

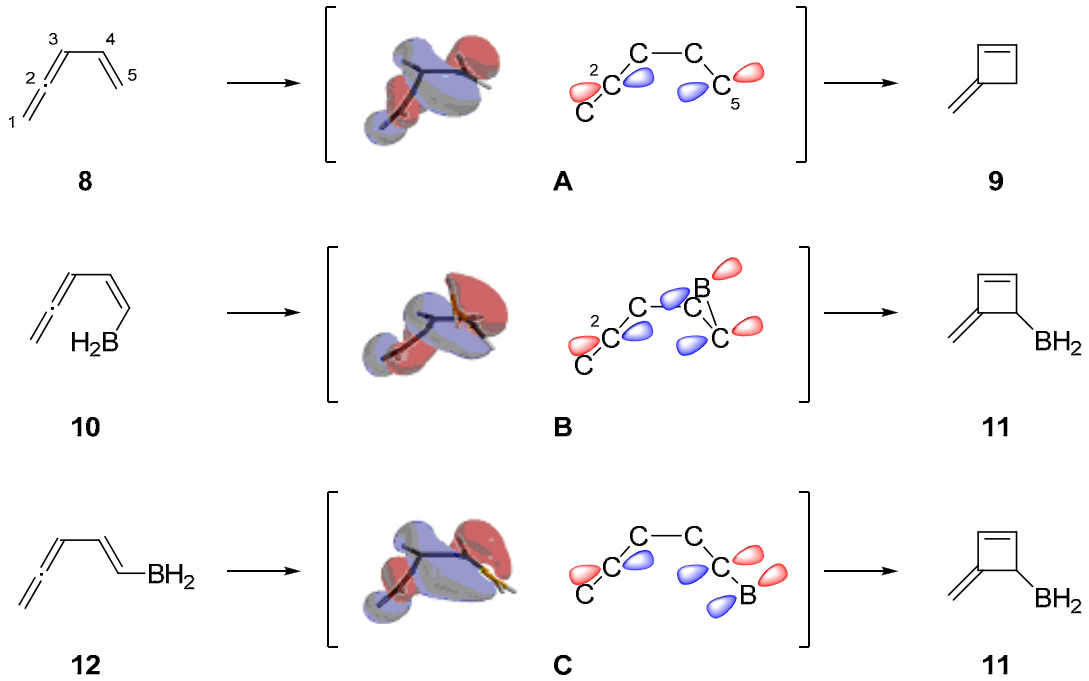
For comparison, the thermal reactivity of vinylallene **6** lacking a boryl group was examined (eq 4). Self-dimerization of **6** by [4+2] cycloaddition occurred while being stored neat even at –30 °C. Only the [4+2] cycloaddition was observed up to 90 °C. When heated at 140 °C for 8 h, the electrocyclic ring-closed product **7** was formed in ca. 20% yield (estimated by ^{1}H NMR) together with intractable polymeric compounds.[11]



6 **7** (4)

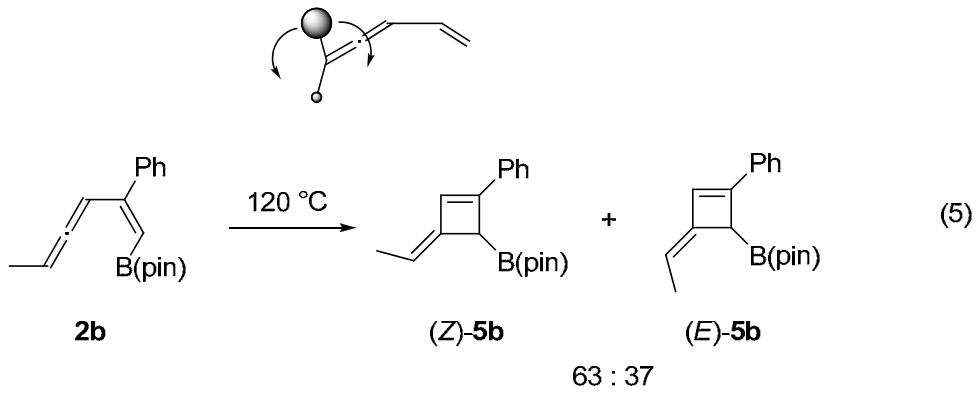
Thus, introduction of a boron substituent caused a dramatic change in the reactivity of vinylallene. It markedly facilitated the electrocyclic ring-closing reaction. Furthermore, a large difference between the activation energies for the *cis*- and *trans*-stereoisomers was

observed. These results can be understood by assuming electronic participation of the vacant p orbital of the boryl substituent, in accord with the prediction made by Houk for the ring-opening reaction of 3-borylcyclobutene.[12] The vacant p orbital interacts with the frontier orbitals of the transition states as an electron acceptor. Scheme 3 shows the second highest occupied molecular orbitals (SHOMOs) of the transition states **A** from vinylallene **8** to methylenecyclobutene **9**, **B** from *cis*-borylvinylallene **10** to borylmethylenecyclobutene **11**, and **C** from *trans*-borylvinylallene **12** to **11**.[13] A significant part of the SHOMO of **A** is concentrated along the σ bond axis developing between C2 and C5, which is still distorted as exemplified by the schematic depiction.[14] With the SHOMOs of **B** and **C**, there is extensive mixing of the distorted σ orbital with the vacant p orbital of boron. This mixing leads to a stabilizing two-electron interaction, and thus results in stabilization of the transition states. Furthermore, the mixing of the distorted σ bond with the boron p orbital is greater at **B** than at **C**, because the boron p orbital of **B** is in much closer proximity to the orbital sketched on the remote C2. Therefore, the reaction of the *cis*-isomer is more accelerated than that of the *trans*-isomer.

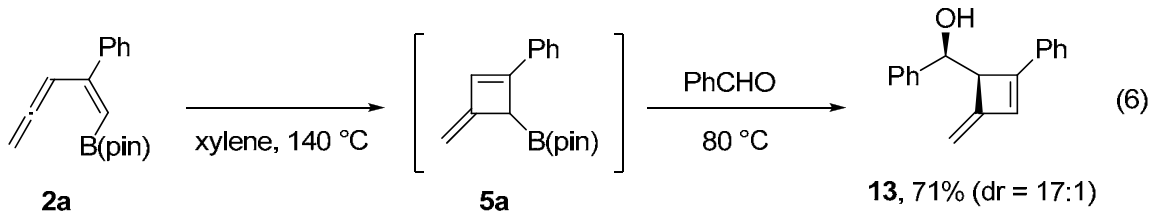


Scheme 3.

If the allene terminus is unsymmetrically substituted, torquoselection would be transferred to the stereochemistry of the ring-closed product.[4a] The ring-closing reaction of vinylallene **2b** having one methyl group at the allene terminus furnished a mixture of (*Z*)- and (*E*)-isomers (63:37 at 120 °C) (eq 5). The low selectivity observed suggests that the terminal methyl group has a limited effect on the torquoselectivity.



The products of the ring closure reaction have a doubly-allylic boron substituent, which is a competent partner in allylation chemistry. When **2a** was heated at 140 °C in xylene (5 h) and then at 80 °C with benzaldehyde (48 h), sequential ring-closing reaction and allylation took place, yielding homoallylic alcohol **13** with high diastereoselectivity (eq 6). The allylation occurs exclusively at the endocyclic position of **5a** to avoid the formation of an antiaromatic cyclobutadiene. Although the relative configuration was not determined, the author predicts, based on a six-membered cyclic chair-like transition state, the major isomer as shown in eq 6.



Conclusion

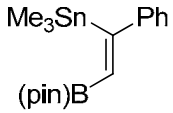
In summary, the author has shown that boryl substituents have pronounced effects on the ring-closing reaction of vinylallenes. These effects can be accounted for by considering electronic participation of the vacant boron p orbital.

Experimental Section

General. All reactions were carried out under a nitrogen atmosphere. Column chromatography was performed with silica gel 60 N (Kanto). Preparative thin-layer chromatography was performed with silica gel 60 PF_{254} (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (^{1}H at 300.07 Hz and ^{13}C at 75.46 Hz) spectrometer. ^{11}B NMR spectra were recorded on a Varian Mercury 400 (^{11}B at 128.48 Hz). Proton chemical shifts are referenced to residual $CHCl_3$. Carbon chemical shifts are referenced to $CDCl_3$. Boron chemical shifts are referenced to external standard $BF_3{\cdot}OEt_2$. High resolution mass spectra were recorded on a JEOL JMS-SX102A spectrometer.

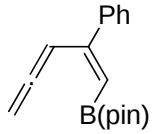
Materials. Unless otherwise noted, all chemicals and anhydrous solvents were obtained from commercial suppliers and used as received. Bis(diethylamido)(trimethylstannyl)borane and 1-(trimethylsilyl)penta-1,4-diyne were prepared according to the literature procedures.

(*Z*)-1-Phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(trimethylstannyl)ethene (1)



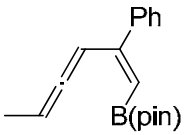
To a benzene solution (10 mL) of $Pd(PPh_3)_4$ (346 mg, 0.30 mmol) were added bis(diethylamido)(trimethylstannyl)borane (3.18 g, 10.0 mmol) and phenylacetylene (1.13 g, 10.0 mmol) at room temperature, and the mixture was stirred for 1 h. To the mixture was added pinacol (1.18 g, 10.0 mmol), and the mixture was stirred for 1 h at room temperature. The reaction mixture was passed through a plug of Florisil® (ether) and concentrated. The residue was subjected to column chromatography on silica gel (ether) to afford **1** (3.83 g, 97%). **1:** ^{1}H NMR δ 0.18 (s, $^{2}J_{Sn-H}$ = 54.9, 53.1 Hz, 9H), 1.30 (s, 12H), 6.28 (s, $^{3}J_{Sn-H}$ = 153.0, 146.4 Hz, 1H), 7.02-7.08 (m, 2H), 7.13–7.21 (m, 1H), 7.24–7.31 (m, 2H); ^{13}C NMR δ –5.5 ($^{1}J_{Sn-C}$ = 353.7, 338.7 Hz), 24.9, 83.5, 126.09 (J = 18.6 Hz), 126.12, 127.8, 133.3 (br), 149.1, 176.0; HRMS (EI) calcd for $C_{16}H_{24}BO_2Sn$ (M^+ – Me) 379.0891, found 379.0891.

(*E*)-4-Phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,2,4-triene (2a)



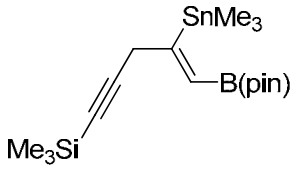
To a DMF solution (5.5 mL) of $PhCH_2PdCl(PPh_3)_2$ (59.7 mg, 0.078 mmol) and CuI (23.7 mg, 0.12 mmol) were added propargyl bromide (2.65 g, 22.5 mmol) and **1** (1.76 g, 4.5 mmol), and the mixture was stirred for 1 h at room temperature then for 18 h at 35 °C. To the mixture was added saturated KF aqueous solution, and the mixture was extracted with ether, passed through a plug of Florisil® (ether), and concentrated. The residue was subjected to column chromatography on silica gel (hexane:AcOEt = 40:3) to afford **2a** (542 mg, 45%). **2a:** ^{1}H NMR δ 1.34 (s,12H), 4.84 (dd, J = 6.8, 2.0 Hz, 2H), 5.45-5.47 (m, 1H), 7.16 (t, J = 6.8 Hz, 1H), 7.28-7.40 (m, 5H); ^{13}C NMR δ 24.9, 77.3, 83.2, 94.5, 118.8 (br), 127.5, 127.8, 127.9, 142.1, 156.1, 212.9; ^{11}B NMR δ 29.3; HRMS (EI) calcd for $C_{17}H_{21}O_2B$ 268.1635, found 268.1640.

(*E*)-2-Phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,4-triene (2b)



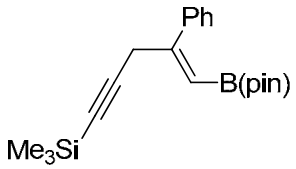
According to the procedure analogous to that described for **2a**, **2b** (59 mg, 11%) was prepared from **1** (784 mg, 2.0 mmol) and 3-chloro-1-butyne (352 mg, 4.0 mmol). **2b:** ^{1}H NMR δ 1.32 (s, 12H), 1.62 (dd, J = 7.2, 3.3 Hz, 3H), 5.15 (ddq, J = 6.3, 1.4, 7.1 Hz, 1H), 5.42 (dd, J = 1.2, 0.6 Hz, 1H), 7.05 (d sext, J = 0.6, 3.2 Hz, 1H), 7.26-7.36 (m, 5H); ^{13}C NMR δ 13.5, 24.9, 83.1, 87.7, 94.6, 118.4 (br), 127.5, 127.7, 127.9, 142.5, 157.3, 209.8; HRMS (EI) calcd for $C_{18}H_{23}O_2B$ 282.1791, found 282.1793.

(*Z*)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trimethylsilyl)-2-(trimethylstannyl)pent-1-en-4-yne (3)



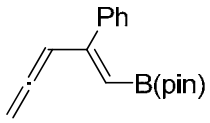
According to the procedure analogous to that described for **1**, **3** (2.23 g, 52%) was prepared from bis(diethylamido)(trimethylstannyl)borane (3.19 g, 10 mmol) and 1-(trimethylsilyl)penta-1,4-diyne (1.62 g, 12.0 mmol). **3:** ^{1}H NMR δ 0.15 (s, 9H), 0.20 (s, $^{2}J_{Sn-H}$ = 55.8, 53.4 Hz, 9H), 1.25 (s, 12H), 3.29 (d, J = 1.7 Hz, $^{3}J_{Sn-H}$ = 34.2 Hz, 2H), 6.39 (t, J = 1.7 Hz, $^{3}J_{Sn-H}$ = 149.3 Hz, 1H); ^{13}C NMR δ –6.4 ($^{1}J_{Sn-C}$ = 353.7, 338.6 Hz), 0.1, 24.8, 35.2, 83.3, 88.7, 103.9, 130.9 (br), 169.3; HRMS (EI) calcd for $C_{16}H_{30}BO_2SiSn$ (M^+ – Me) 413.1130, found 413.1129.

(*Z*)-2-Phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trimethylsilyl)pent-1-en-4-yne (3´)



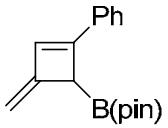
To a DMF solution (2.0 mL) of $PhCH_2PdCl(PPh_3)_2$ (37 mg, 0.050 mmol) and CuI (19 mg, 0.10 mmol) were added iodobenzene (244 mg, 1.2 mmol) and **3** (4.27 g, 1.0 mmol), and the mixture was stirred for 1 h at room temperature and then for 3 h at 90 °C. The reaction mixture was passed through a plug of Florisil® and concentrated. The residue was subjected to column chromatography on silica gel (hexane:AcOEt = 9:1) to afford **3´** (82 mg, 24%). **3´:** ^{1}H NMR δ 0.16 (s, 9H), 1.12 (s, 12H), 3.38 (d, J = 1.7 Hz, 2H), 5.91 (t, J = 1.7 Hz, 1H), 7.22-7.31 (m, 5H); ^{13}C NMR δ 0.1, 24.6, 31.2, 83.1, 88.7, 103.1, 117.6 (br), 127.5, 127.6, 127.7, 141.9, 154.5; HRMS (EI) calcd for $C_{20}H_{29}BO_2Si$ 340.2030, found 340.2030.

(*Z*)-4-Phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,2,4-triene (4)



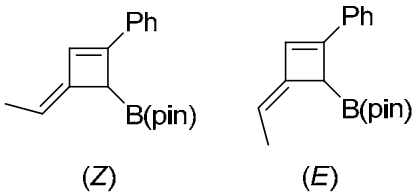
To a MeOH solution (1.0 mL) of **3´** (47.4 mg, 0.14 mmol) was added MeOH solution (1.0 mL) of NaOH (40 mg, 1.0 mmol), and the mixture was stirred for 24 h at room temperature. To the mixture were added saturated NH_4Cl aqueous solution and brine, and the mixture was extracted with ether, dried over Na_2SO_4, and concentrated. The residue was subjected to flash chromatography on silica gel (hexane:AcOEt = 9:1) followed by HPLC purification (hexane:AcOEt = 20:1) to afford **4** (6 mg, 16%). **4:** ^{1}H NMR δ 1.10 (s, 12H), 4.81 (dd, *J* = 6.5, 1.4 Hz, 2H), 5.58 (d, *J* = 0.6 Hz, 1H), 6.11 (dt, *J* = 0.6, 6.5 Hz, 1H), 7.21-7.30 (m, 5H); ^{13}C NMR δ 24.6, 78.0, 99.2, 127.1, 127.4, 128.9, 139.8, 154.3, 211.8; ^{11}B NMR δ 29.4.

3-Methylene-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutene (5a)



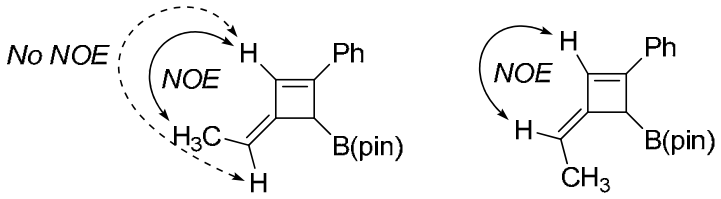
A xylene solution (5.0 mL) of **2a** (156 mg, 0.58 mol) was heated for 3 h at 140 °C. After evaporating the solvent, the residue was subjected to flash chromatography on silica gel (hexane:AcOEt = 9:1) to afford **5a** (150 mg, 96%). **5a:** ^{1}H NMR δ 1.22 (s, 6H), 1.24 (s, 6H), 3.19 (s, 1H), 4.58 (s, 1H), 4.84 (d, J = 1.5 Hz, 1H), 6.61 (s, 1H), 7.22-7.38 (m, 3H), 7.41-7.46 (m, 2H), ^{13}C NMR δ 24.5, 24.7, 35.7 (br), 83.5, 99.3, 125.6, 126.5, 128.2, 128.3, 133.7, 144.8, 151.6; HRMS (EI) calcd for $C_{17}H_{21}O_2B$ 268.1635, found 268.1636.

(*Z*)- and (*E*)-
3-Etylidene-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutene (5b)



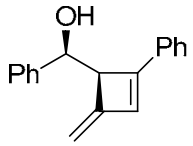
^{1}H NMR δ 1.21 (s, 12H, major and minor), 1.238 (s, 6H, major), 1.243 (s, 6H, minor), 1.72 (d, *J* = 6.9 Hz, 3H, minor), 1.79 (d, *J* = 6.9 Hz, 1H, major), 3.13 (s, 1H, major), 3.18 (s, 1H, minor), 4.96 (q, *J* = 6.9 Hz, 1H, major), 5.30 (dq, *J* = 1.5, 6.9 Hz, 1H, minor), 6.60 (d, *J* = 1.5 Hz, 1H, minor), 6.79 (d, *J* = 1.2 Hz, 1H, major), 7.19-7.45 (m, 5H); ^{13}C NMR δ 13.8, 14.4, 24.48, 24.54, 24.65, 24.71, 33.8 (br), 83.4, 83.5, 109.9, 110.2, 124.5, 125.2, 125.3, 126.4, 127.8, 127.9, 128.2, 134.2, 136.9, 138.1, 147.7, 149.7 [some signals are overlapping]; HRMS (EI) calcd for $C_{18}H_{23}O_2B$ 282.1791, found 282.1794.

Stereochemical Assignment of 5b. The two isomers, (*Z*)- and (*E*)-**5b**, were subjected to NOE experiments. No NOE between the cyclobutene vinyl proton (δ 6.79) and the ethylidene vinyl proton (δ 4.96) was observed for (*Z*)-**5b**, whereas NOE between the cyclobutene vinyl proton and the ethylidene methyl proton (δ 1.79) was observed. On the other hand, an NOE between the cyclobutene vinyl proton (δ 6.60) and the ethylidene vinyl proton (δ 5.30) was observed for (*E*)-**5b**.



(*Z*)-**5b** (*E*)-**5b**

(4-Methylene-2-phenylcyclobut-2-enyl)phenylmethanol (13)



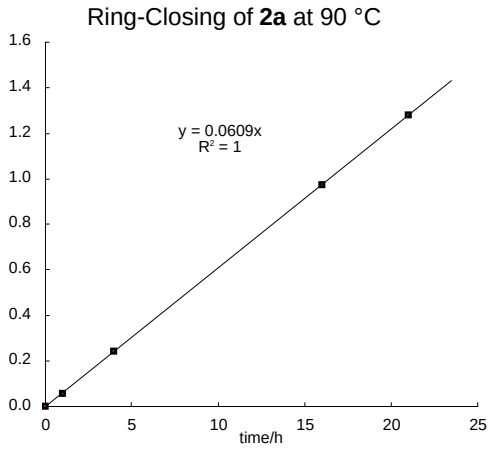
A xylene solution (2.0 mL) of vinylallene **2a** (132 mg, 0.49 mmol) was heated for 5 h at 140 °C to afford **5a**. To the solution was added benzaldehyde (72 mg, 0.68 mmol) at room temperature, and the mixture was heated for 48 h at 80 °C. The reaction mixture was acidified with 0.1 N HCl (5 mL), extracted with ether, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography on silica gel (hexane:ether = 3:1) to give **13** as a diastereomeric mixture (87 mg, 71%, 17:1 by ^{1}H NMR). **13:** ^{1}H NMR δ 2.10 (d, J = 4.8 Hz, 1H), 4.07 (dt, J = 4.5, 1.2 Hz, 1H), 4.40 (s, 1H), 4.76 (d, J = 1.5 Hz, 1H), 5.15 (t, J = 4.7 Hz, 1H), 6.63 (d, J = 0.6 Hz, 1H), 7.25-7.42 (m, 10H); ^{13}C NMR δ 55.5, 73.1, 99.9, 126.0, 126.1, 127.3, 128.0, 128.4, 128.6, 130.7, 133.0, 142.7, 145.0, 152.2; HRMS (EI) calcd for $C_{18}H_{16}O$ 248.1201, found 248.1200. For the minor diastereomer: ^{1}H NMR δ 4.02 (d, J = 6.9 Hz, 1H), 4.18 (s, 1H), 4.68 (d, J = 1.2 Hz, 1H), 4.95 (d, J = 7.2 Hz, 1H), 6.60 (s, 1H), the remaining signals were not resolved.

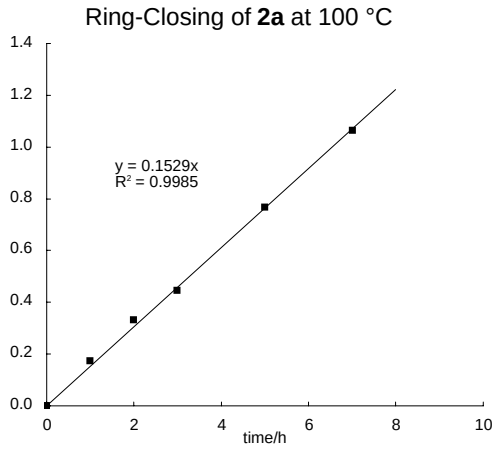
Kinetic Studies on Ring-Closing Reactions of Boryl-Substituted Vinylallenes 2a, 2b, and 4

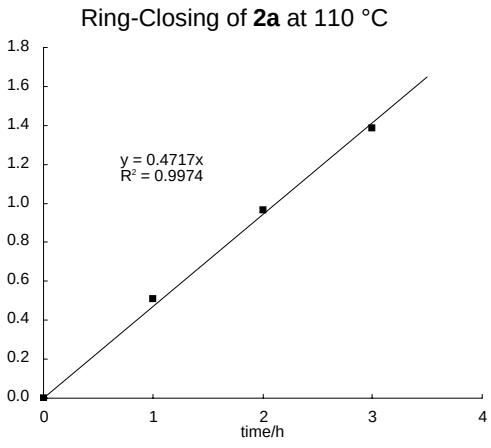
Rate Measurements: The ring-closing reactions of **2a**, **2b**, and **4** were monitored using ^{1}H NMR spectroscopy. The boryl-substituted vinylallene was dissolved in benzene-d_6 or *o*-xylene-d_{10}. The solution in an NMR tube was heated in a temperature-controlled oil bath at the specified temperature. The reaction was intercepted at intervals, and the ^{1}H NMR spectrum was recorded. The conversion was determined on the basis of the ^{1}H NMR integrations of the allenic (vinylic) protons of the reactants and products. The %conversion versus time data were subjected to least-squares analysis.

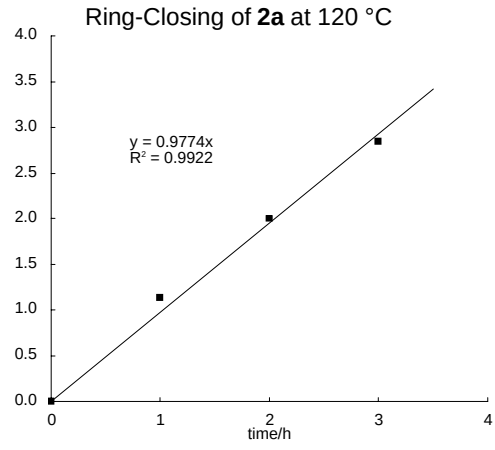
Ring-Closing Reaction of 2a

90 °C		100 °C		110 °C		120 °C	
time/h	conv./%	time/h	conv./%	time/h	conv./%	time/h	conv./%
0	0.0	0	0.0	0	0.0	0	0.0
1	5.5	1	15.8	1	39.9	1	67.9
4	21.4	2	28.1	2	62.0	2	86.5
16	62.2	3	35.9	3	75.0	3	94.2
21	72.2	5	53.6				
		7	65.5				

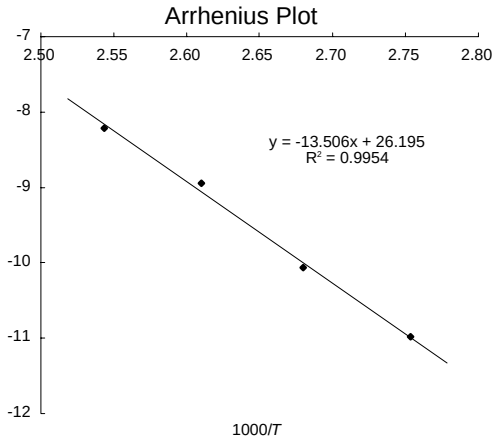








T (°C)	k (s^{-1})	1000/T (K^{-1})	ln$k$
90	1.69×10^{-5}	2.75	–11.0
100	4.25×10^{-5}	2.68	–10.1
110	1.31×10^{-4}	2.61	–8.94
120	2.72×10^{-4}	2.54	–8.21

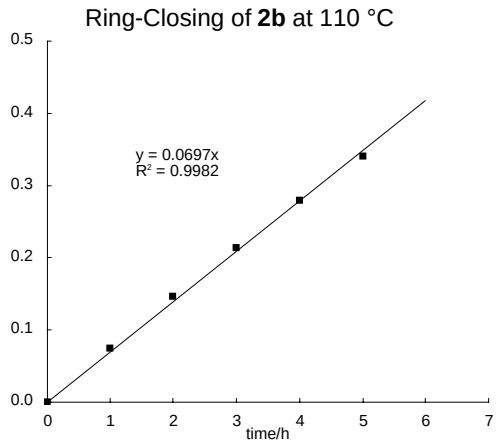


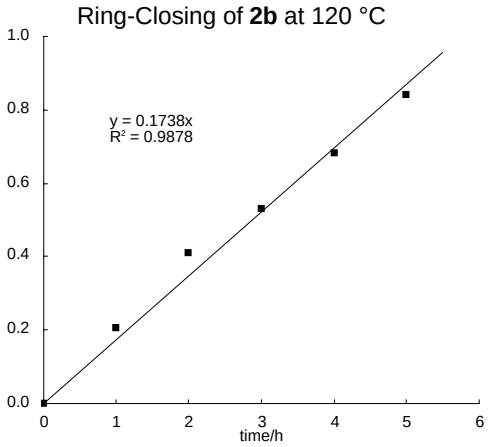
ln$A$ = 26.2; $A = 10^{11.4}$ s^{-1}

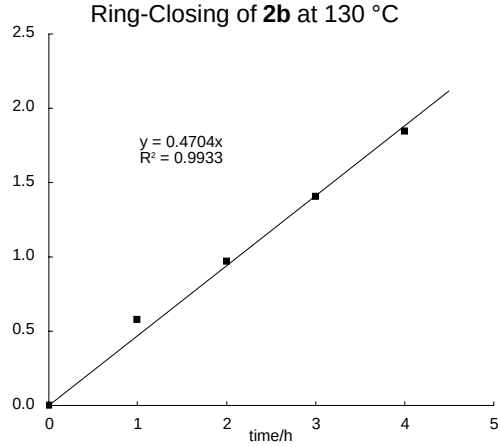
$E_a = 1000R\times13.5 = 26.8$ kcal/mol

Ring-Closing Reaction of 2b

110 °C		120 °C		130 °C	
time/h	conv./%	time/h	conv./%	time/h	conv./%
0	0.0	0	0.0	0	0.0
1	7.2	1	18.6	1	42.9
2	13.6	2	33.6	2	62.0
3	19.2	3	41.2	3	75.5
4	24.4	4	49.5	4	84.2
5	28.9	5	56.9		



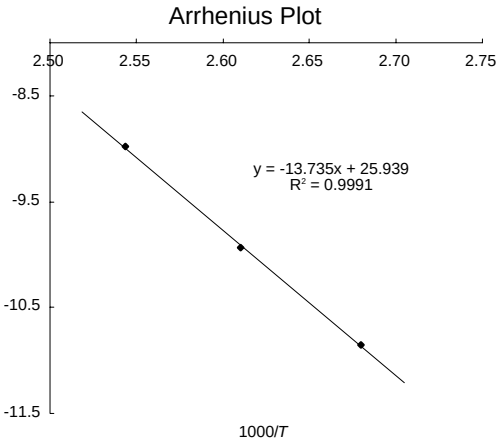




T (°C)	k (s^{-1})	1000/T (K^{-1})	ln$k$
110	1.94×10^{-5}	2.61	–10.9
120	4.83×10^{-5}	2.54	–9.94
130	1.31×10^{-4}	2.48	–8.94

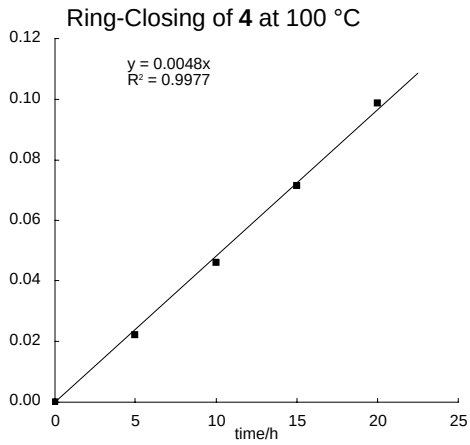
ln$A$ = 27.6; $A = 10^{12.0}$ s^{-1}

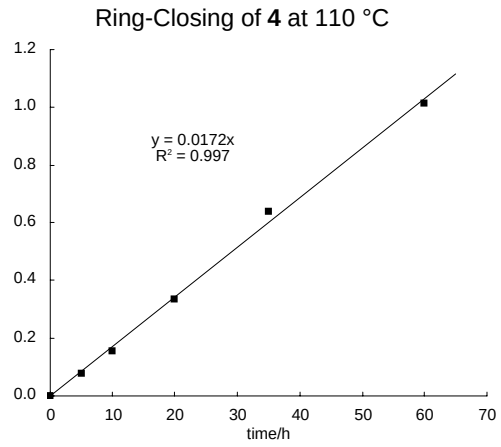
E_a = 1000R×14.7 = 29.3 kcal/mol

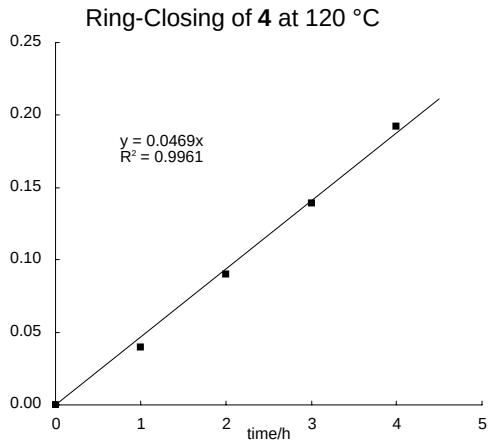


Ring-Closing Reaction of 4

100 °C		110 °C		120 °C	
time/h	conv./%	time/h	conv./%	time/h	conv./%
0	0.0	0	0.0	0	0.0
5	2.2	5	7.4	1	3.9
10	4.5	10	14.4	2	8.6
15	6.9	20	28.4	3	13.0
20	9.4	35	47.3	4	17.5
		60	63.7	5	22.1



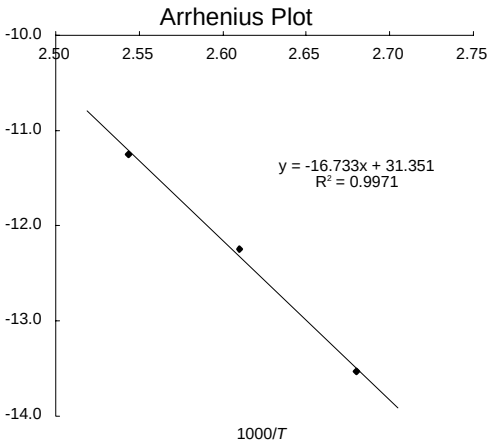




T (°C)	*k* (s^{-1})	1000/*T* (K^{-1})	ln*k*
100	1.33×10^{-6}	2.68	–13.5
110	4.78×10^{-6}	2.61	–12.3
120	1.30×10^{-5}	2.54	–11.2

ln*A* = 31.4; $A = 10^{13.6}\ s^{-1}$

$E_a = 1000R\times16.7 = 33.2$ kcal/mol



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Chapter 1
Nickel-Catalyzed Intermolecular Alkyne Insertion into Cyclobutanones
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Two-Carbon Ring Expansion of Cyclobutanone Skeletons by Nickel-Catalyzed Intermolecular Alkyne Insertion
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Chapter 2 and 3
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Chapter 5
Dramatic Effects of Boryl Substituents on Thermal Ring-Closing Reaction of Vinylallenes
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Other Publication

Stereoselective Synthesis of (*Z*)-1-Silyl-2-stannylethene by Palladium-Catalyzed Silastannation of Ethyne and Its Synthetic Transformations
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