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Award Accounts

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Construction of Carbon Frameworks through β-Carbon Elimination Mediated by Transition Metals

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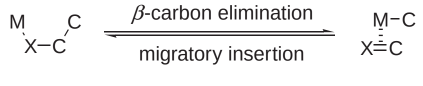
New catalytic reactions in which transition-metal cyclobutanolates undergo β-carbon elimination have been developed in our laboratory. Rhodium(I) cyclobutanolate generated by the addition of an arylrhodium(I) species to a cyclobutanone undergoes β-carbon elimination to cause ring opening of the four-membered carbocyclic framework. The synthetic potential of the ring-opening process through β-carbon elimination has been demonstrated by its application to a ring-expansion reaction forming a seven-membered ring. Furthermore, a formal alkyne insertion into the cyclobutanone framework is achieved by combining oxidative cyclization of a cyclobutanone and an alkyne on nickel(0) and β-carbon elimination from the resulting nickel(II) cyclobutanolate.

1. Introduction

A carbon–carbon single bond is a non-polar σ-bond, which is significantly stable. Interaction of such a stable σ-bond with a transition metal is so difficult that cleavage of a carbon–carbon single bond by means of transition metals has received considerable attention from the mechanistic point of view.[1] Carbon–carbon bond-cleavage processes can also provide an opportunity to achieve chemical transformations that are otherwise hardly accessible. There are two kinds of elementary steps available for cleavage of carbon–carbon single bonds with transition metals. First, insertion of a transition metal between a carbon–carbon linkage provides a direct method for its cleavage. The metal-insertion process has been studied in both stoichiometric and catalytic reactions.[1] It has also found applications in organic synthesis. Another process is β-carbon elimination occurring with transition-metal alkyls, alkoxides, and amides, in which the carbon γ to the metal migrates onto the metal with the extrusion of unsaturated carbon–carbon, carbon–oxygen, and carbon–nitrogen bonds.[2] The β-carbon elimination process has received less attention than the metal-insertion process, although the reverse process, migratory insertion of double-bond functionalities, is often involved in transition metal-catalyzed reactions (Eq. 1).



(1)

M = transition metal
X = C, O, N

We have developed a number of catalytic reactions of cyclobutanones that involve the insertion of rhodium(I) between a carbon–carbon single bond from the synthetic perspectives.[3,4] We have also been studying transition metal-catalyzed reactions that proceed through β-carbon elimination.[5–7] The key intermediates therein are transition-metal cyclobutanolates, to which there are two pathways. One is the addition of an organorhodium(I) species to the carbonyl group of cyclobutanone, and the other is oxidative cyclization of the carbonyl group of cyclobutanone and alkyne on nickel(0). The resulting metal cyclobutanolates then undergo β-carbon elimination to cleave the carbon–carbon single bond between the original carbonyl carbon and the α-carbon, constituting interesting catalytic reactions. Herein, we review the results of our recent studies on synthetic utilization of the β-carbon elimination processes and their application to ring-expansion reactions (Scheme 1).

2. β-Carbon Elimination from Rhodium(I) Cyclobutanolates

2.1 Addition/Ring-Opening Reaction of Arylboronic Acids with Cyclobutanones.[5] In the course of our studies on the C–C bond cleavage of cyclobutanones by rhodium(I) complexes, we supposed that an arylrhodium(I) species could be more easily oxidized to a rhodium(III) species through its insertion into the carbon–carbon single bond than a rhodium(I) halide or a cationic rhodium(I) species because the carbon-bound rhodium(I) is more electron-rich. An arylrhodium(I) can be generated by the transmetalation of arylboronic acid with a rhodium(I) complex.[8] Thus, we examined the reaction

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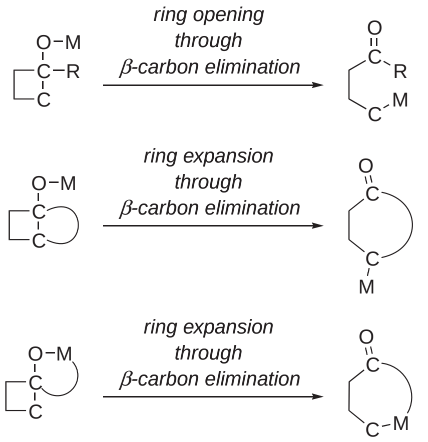
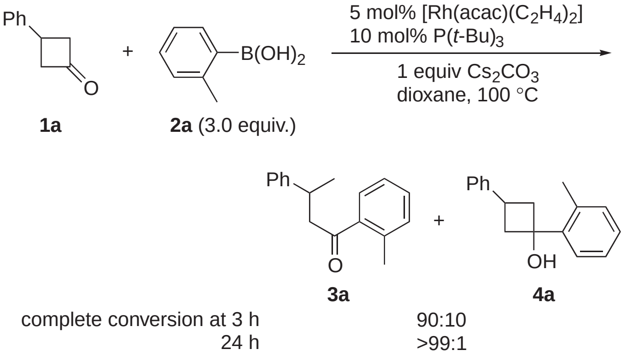


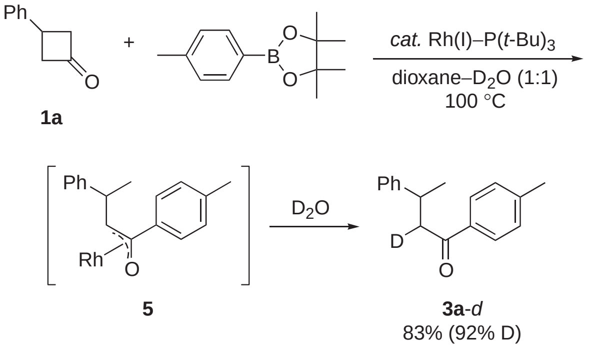
Scheme 1.

of the cyclobutanone **1a** with the boronic acid **2a** in the presence of rhodium catalysts. A range of combinations of rhodium(I) precursors and ligands were screened, and a catalyst prepared in situ from a rhodium(I)–ethylene complex, i.e., $[RhCl(CH_2{=}CH_2)_2]_2$, and tri-*t*-butylphosphine worked well (Eq. 2). The cyclobutanone **1a** was completely consumed when it was reacted with **2a** in the presence of 5 mol % of the rhodium–phosphine catalyst (Rh:P = 1:2) and 1 equiv of Cs_2CO_3 in 1,4-dioxane at 100 °C for 3 h. The ring-opened ketone **3a** and cyclobutanol **4a** were formed in a ratio of 9:1. On the other hand, when heated for a prolonged period of 24 h, **4a** disappeared to give only **3a**, indicating that the **4a** that initially formed isomerized to **3a**. The intermediacy of the cyclobutanol **4** at the earlier stage and its subsequent isomerization to **3** suggested that the insertion of rhodium into the cyclobutanone α-C–C bond giving a rhodacyclopentanone intermediate is unlikely. Other phosphine ligands like PPh_3 and $P(c\text{-}Hex)_3$ exhibited inferior activity. Rhodium(I) complexes having a cod ligand(s) such as [Rh(acac)(cod)] or $[Rh(OH)(cod)]_2$ were ineffective.

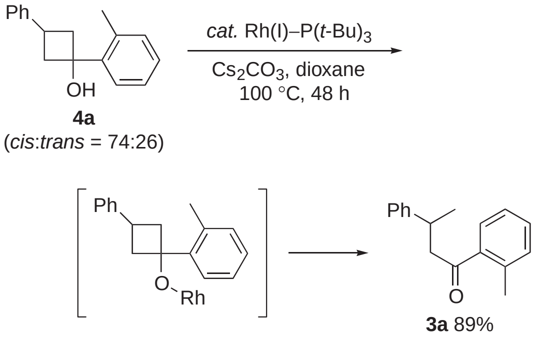


(2)

We prepared the cyclobutanol **4a** independently and examined its reactivity to open the cyclobutane skeleton. Whereas it isomerizied to **3a** through ring opening in the presence of the rhodium catalyst, the isomerization failed to occur in the absence of the rhodium catalyst (Eq. 3). These contrasting results suggested that the ring opening of the cyclobutane skeleton occurred via a rhodium(I) cyclobutanolate.



Scheme 2.



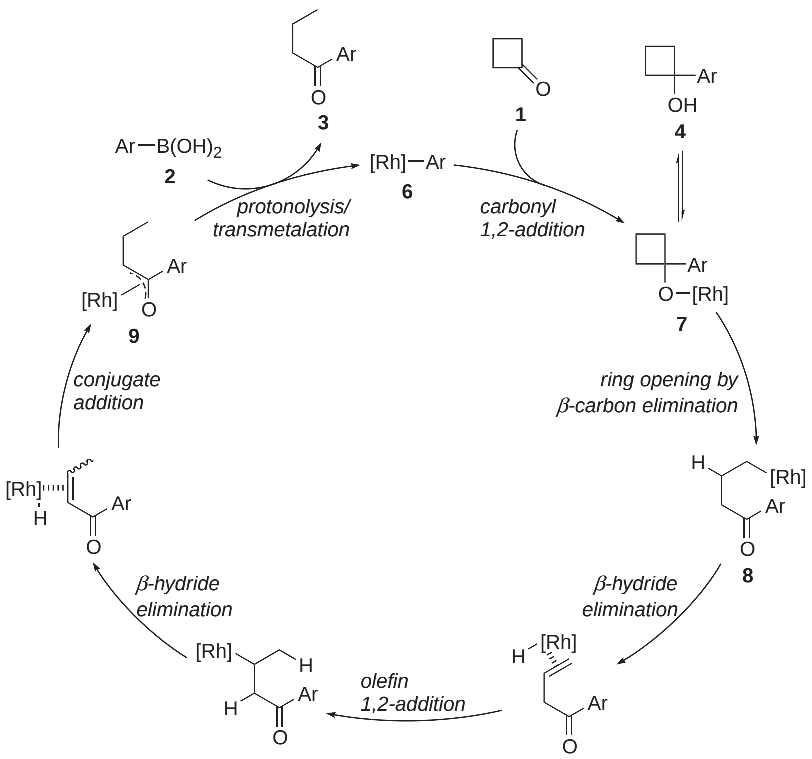
(3)

A deuterium experiment disclosed another interesting mechanistic feature. The reaction of **1a** and an arylboronate ester in 1,4-dioxane–D_2O gave the ketone **3a**-*d* with deuterium incorporated exclusively at the α-position (Scheme 2). The result indicated that an alkylrhodium species generated by β-carbon elimination eventually isomerized to the η^3-oxaallylrhodium **5** prior to protonolysis.

On the basis of the results mentioned above, we propose a mechanism for the addition/ring-opening reaction as illustrated in Scheme 3. The catalytic cycle consists of (i) the addition of the arylrhodium species **6** to the carbonyl group of **1**, (ii) the ring opening of the rhodium cyclobutanolate **7** by β-carbon elimination generating the alkylrhodium **8**, (iii) β-hydride elimination and readdition with opposite regiochemistry, shifting rhodium from γ to β to the carbonyl group, (iv) the repetition of the β-hydride elimination/readdition process leading to the η^3-oxaallylrhodium **9**, and (v) protonolysis/transmetalation generating **3** and **6**.

An attempted reaction with 4-phenylcyclohexanone lacking ring strain under identical conditions failed to occur, suggesting increased reactivity of the ketonic carbonyl group of cyclobutanone toward nucleophilic addition to an arylrhodium species.[9] This increased reactivity, which is comparable to that of an aldehydic carbonyl group,[10] can be attributed to the strained four-membered ring structure. The carbonyl sp^2 carbon changes to an sp^3 carbon upon addition of the arylrhodium, thereby diminishing the ring strain. The β-carbon elimination step would also be facilitated by release of the ring strain.

Other 3-monosubstituted cyclobutanones reacted with arylboronic acids in an analogous fashion to afford the corresponding ring-opened aryl ketones (Chart 1). While reactions with *o*-, *m*-, and *p*-tolylboronic acids worked well, reactions with boronic acids having substantially electron-donating methoxy



Scheme 3.

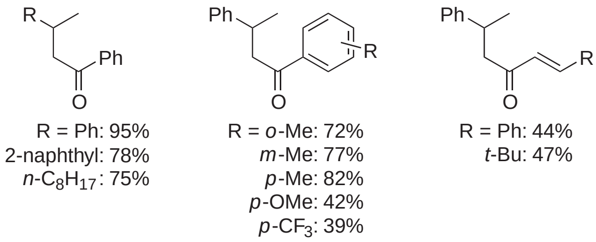
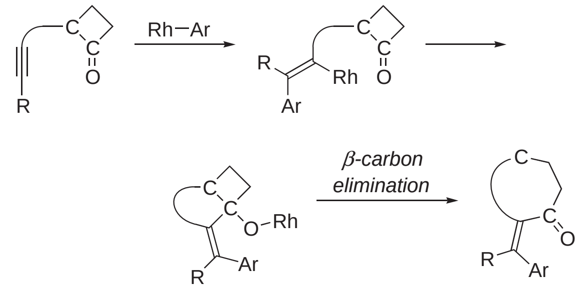


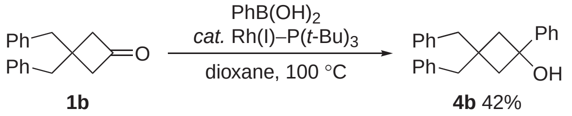
Chart 1.



Scheme 4.

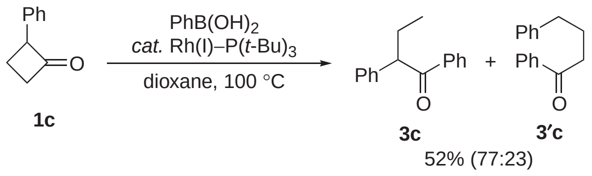
and electron-withdrawing trifluoromethyl groups were less efficient. Addition of Cs_2CO_3 as the base was crucial for sterically demanding *o*-tolylboronic acid, albeit unnecessary for ordinary phenylboronic acids. Alkenylboronic acids were less reactive than arylboronic acids, giving the corresponding α,β-unsaturated ketones in only moderate yield.

Further studies were carried out with cyclobutanones with other substitution patterns to delineate the scope and limitations. The reaction of the 3,3-disubstituted cyclobutanone **1b** was rather sluggish, and it afforded 42% yield of the cyclobutanol **4b** as the major product in addition to 2% of a ring-opened aryl ketone (Eq. 4).

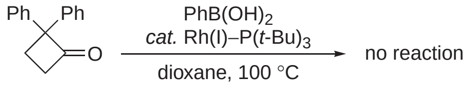


(4)

In the reaction of 2-phenylcyclobutanone (**1c**), there are two carbon–carbon bonds amenable to cleavage by β-carbon elimination (Eq. 5). β-Carbon elimination at the less-substituted carbon was preferred over that of the benzylic carbon to produce a mixture of **3c** and **3′c** in a ratio of 77:23. However, 2,2-diphenylcyclobutanone failed to react with **2a** at all under identical conditions, probably due to steric reasons (Eq. 6).



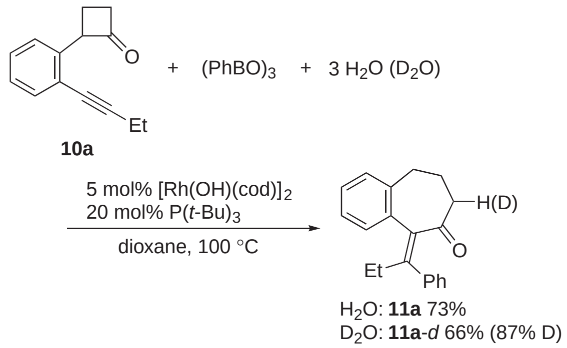
(5)



(6)

2.2 Arylative Ring Expansion of Alkyne-Substituted Cyclobutanones.[6] We next sought to develop ring-expansion reactions based on the β-carbon elimination process, and for this purpose, designed a cyclobutanone having a carbon–carbon triple bond in the molecule (Scheme 4). Addition of an arylrhodium to the alkyne moiety[9b–e,11] would trigger ensuing intramolecular addition of the resulting alkenylrhodium species to the carbonyl group of cyclobutanone. The opening of the cyclobutane ring by β-carbon elimination occurs with the resulting rhodium cyclobutanolate to achieve a ring-expansion reaction.

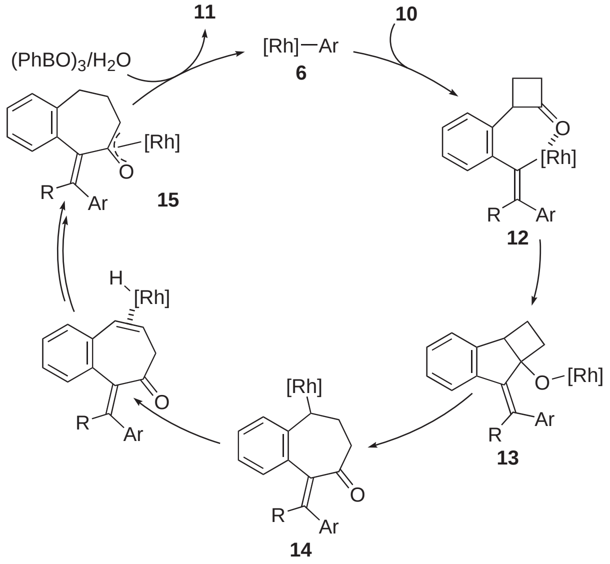
The cyclobutanone **10a** bearing a pendant alkyne moiety was reacted with triphenylboroxin, which was transformed in situ to phenylboronic acid by hydrolysis. When heated at 100 °C in the presence of Rh(I)–P(t-Bu)$_3$ catalyst and water (1 equiv to boron) in 1,4-dioxane for 6 h, the seven-membered ring ketone **11a** was produced in 73% yield from **10a** (Eq. 7). The reaction using D_2O instead of water furnished the product **11a**-*d* with deuterium incorporated exclusively at the α-position.



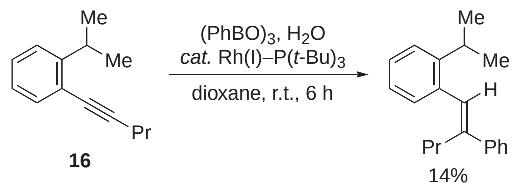
(7)

The mechanism shown in Scheme 5 that consists of two C–C bond forming and one C–C bond-cleavage events is conceivable for this transformation. The arylrhodium **6** adds regioselectively to the alkyne moiety in preference of the carbonyl group of **10** to afford the alkenylrhodium species **12**. Then, nucleophilic addition to the adjacent carbonyl group of the cyclobutanone forms the rhodium(I) cyclobutanolate **13**. β-Carbon elimination occurs regioselectively with the benzylic carbon atom, expanding the [3.2.0]bicycloheptane skeleton to a seven-membered ring. The resulting alkylrhodium **14** undergoes the repetitive β-hydride elimination/readdition processes, leading to the η^3-oxaallylrhodium **15**. Finally, protonolysis yields **11** and transmetalation regenerates **6**.

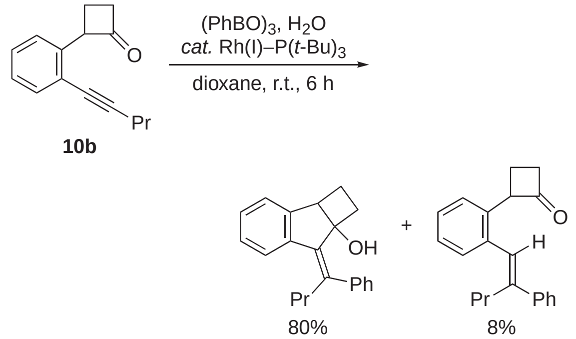
The effect of coordination of the carbonyl group was exemplified by the different reactivity observed for **10b** and **16** at room temperature. Reaction of **16**, whose steric environment around the alkyne moiety is similar to that of **10**, was sluggish at room temperature to give the 1,2-adduct in only 14% yield (Eq. 8). In contrast, the alkyne **10b** equipped with a cyclobutanone pendant furnished 80% yield of cyclobutanol together with a small amount of the 1,2-adduct (8%) (Eq. 9). The significantly enhanced reactivity of the alkyne moiety of **10b** toward the arylrhodium(I) species is ascribed to the pre-coordination of the carbonyl group.



Scheme 5.



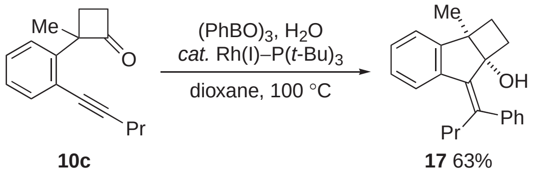
(8)



(9)

The addition/ring-expansion reaction tolerated several alkyl substituents at the alkyne terminus (Chart 2). Arylboroxins having electron-donating and -withdrawing groups at the 4-position worked well, whereas the reaction with *o*-tolylboroxin failed to give a ring-expansion product, probably due to steric reasons. The thiophene-derived substrate was also successfully transformed into the corresponding product.

The ring expansion by β-carbon elimination hardly took place with the cyclobutanone **10c**, which has a tertiary carbon at the 2-position. Instead, the cyclobutanol **17** was isolated as the exclusive product (Eq. 10). The rhodium-catalyzed ring expansion of isolated **17** failed to occur even at 160 °C, suggesting that migration of rhodium from oxygen to a tertiary carbon is very difficult.



(10)

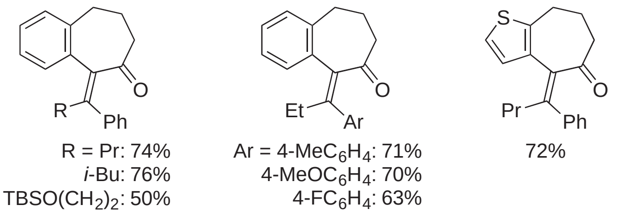
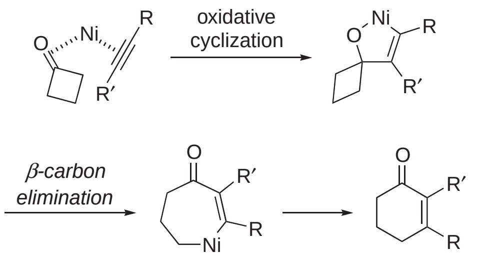


Chart 2.



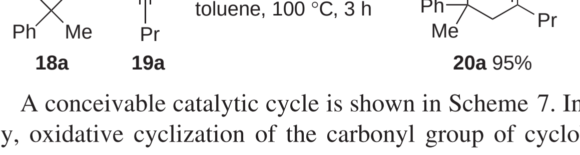
Scheme 6.

3. β-Carbon Elimination from Nickel(II) Cyclobutanolates[7]

It has been one of the ultimate goals in synthetic chemistry to construct a molecule by assembling only requisite parts, eliminating needs for any auxiliaries like protecting, directing, activating, or leaving groups. Such transformations can minimize the synthetic steps and various wastes resulting therefrom. We have explored the catalytic carbon–carbon bond-cleavage reactions of cyclobutanones, wherein a rhodium(I) complex inserts between the carbonyl carbon and the α-carbon.[3] During the course of our continuous studies on the C–C bond activation of cyclobutanones by rhodium(I) complexes, we have developed insertion reactions in which unsaturated molecules like alkenes are inserted into the cyclobutanone C–C bonds in an intramolecular way.[4] However, the intermolecular insertion reactions we have attempted so far have all been unsuccessful.[12]

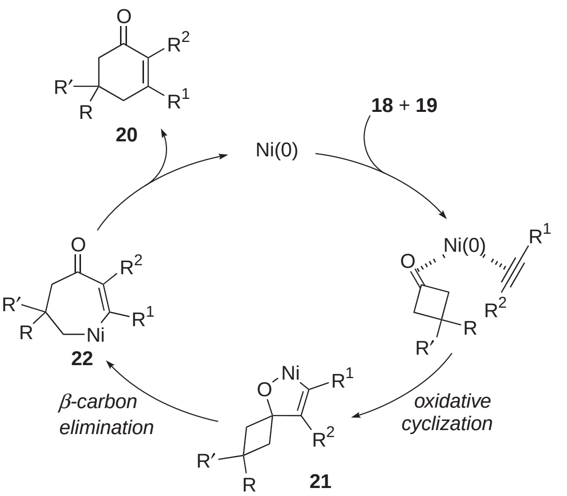
Carbonyl compounds such as aldehydes, ketones, and even carbon dioxide can undergo oxidative cyclization with an alkyne on nickel(0) to form oxanickelacyclopentenes. We envisioned that oxidative cyclization of a cyclobutanone and an alkyne would provide an alternative access to a transition-metal cyclobutanolate, which then undergoes β-carbon elimination to expand the four-membered ring skeletons through incorporation of the alkyne (Scheme 6).

Thus, the cyclobutanone **18a** was reacted with 4-octyne (**19a**) in the presence of a nickel catalyst prepared in situ from [Ni(cod)$_2$] (10 mol %) and tricyclohexylphosphine (20 mol %) (Eq. 11). The cyclohexenone **20a** was produced in 95% yield after heating the reaction mixture to 100 °C for 3 h. The reaction achieves formal insertion of the alkyne between the carbonyl carbon and the α-carbon of the cyclobutanone to construct a six-membered carbocycle.



(11)

A conceivable catalytic cycle is shown in Scheme 7. Initially, oxidative cyclization of the carbonyl group of cyclobutanone and an alkyne on nickel(0) occurs to form the oxanickelacyclopentene **21**, which then undergoes ring opening by β-carbon elimination to generate the seven-membered nickelacycle **22**. Finally, reductive elimination liberates the product **20** and regenerates nickel(0).



Scheme 7.

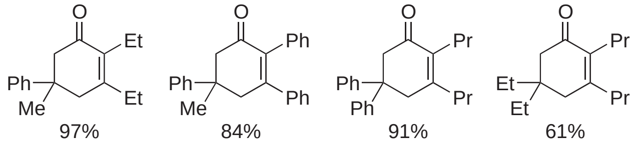
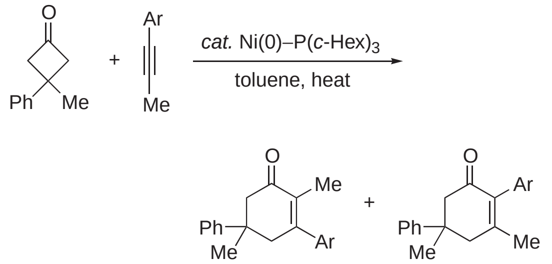


Chart 3.

The cyclohexenones shown in Chart 3 were synthesized by this formal alkyne-insertion reaction. Whereas cyclobutanones having a phenyl group(s) at the 3-position afforded the corresponding products in high yield, the reaction of 3,3-diethylcyclobutanone required 20 mol % of the nickel catalyst to gain an acceptable yield.

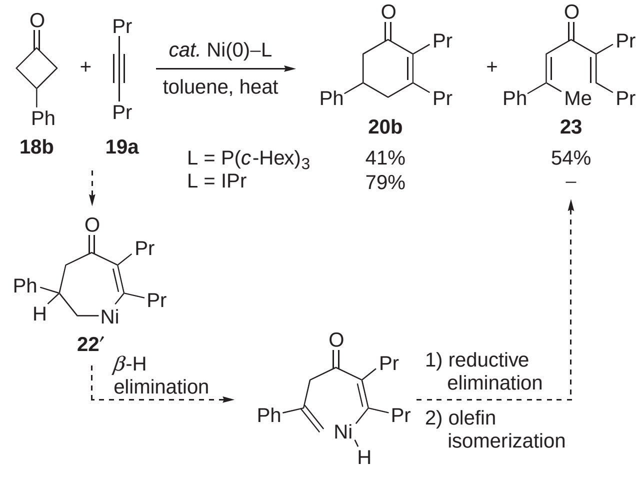
With the unsymmetrically substituted alkyne, 1-phenyl-1-propyne, oxidative cyclization occurred with excellent regioselectivity (Eq. 12). The regioselectivity was hardly affected by either electron-donating or -withdrawing *para*-substituent of the aryl group of 1-aryl-1-propyne.



(12)

Ar = Ph: 78% (92:8)
Ar = p-MeOC$_6$H$_4$: 58% (90:10)
Ar = p-CF$_3$C$_6$H$_4$: 65% (91:9)

An interesting ligand effect was observed in the reaction of 3-monosubstituted cyclobutanone. When P(*c*-Hex)$_3$ was used as the ligand of nickel(0) in the reaction of **18** with **19**, the linear unsaturated ketone **23** was obtained as the by-product in addition to the cyclohexenone **20b** (Scheme 8). The unsaturated ketone was produced via β-hydride elimination from the seven-membered nickelacycle **22′** and subsequent olefin isomerization to a conjugated system. On the other hand, the use of an *N*-heterocyclic carbene as the ligand on nickel(0) suppressed the formation of the by-product **23**, selectively giving **20b** in 79% yield, although the reason is unclear.



Scheme 8.

4. Conclusion

We have developed a carbon–carbon cleavage process involving β-carbon elimination from a rhodium(I) cyclobutanolate, which is generated by the addition of an arylrhodium(I) to a cyclobutanone. This process was applied to the ring-expansion reaction forming seven-membered ring ketones through β-carbon elimination. Furthermore, a formal alkyne-insertion reaction into cyclobutanones forming cyclohexenones was achieved by utilizing oxidative cyclization on nickel in conjunction with β-carbon elimination. These reactions demonstrated that the carbon–carbon cleavage process by β-carbon elimination can be potentially utilized for the construction of various organic frameworks.

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