

Nickel-catalysed intramolecular alkene insertion into cyclobutanones†

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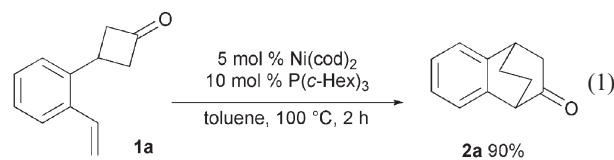
A nickel(0) catalyst converted 3-styrylcyclobutanones into benzobicyclo[2.2.2]octenones by an intramolecular insertion of the vinyl moiety into the cyclobutanone skeleton.

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 catalyses its cleavage.³ Such insertion reactions provide expanded carbon frameworks in a highly atom-economical manner.

We have reported just such a rhodium-catalysed 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 proceeds *via* (i) oxidative cyclisation 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-catalysed ring-expansion reaction of cyclobutanones. However, all attempts at accomplishing this transformation have failed thus far, which led us to examine an intramolecular variant using the alkenyl-substituted cyclobutanones. Herein, we report the nickel-catalysed intramolecular alkene insertion reaction of cyclobutanones, which affords a result complementary to that obtained with rhodium catalysts.

3-(*ortho*-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 mol%). Chromatographic isolation on silica gel afforded benzobicyclo[2.2.2]octenone (**2a**)⁶ in 90% yield [eqn (1)].‡

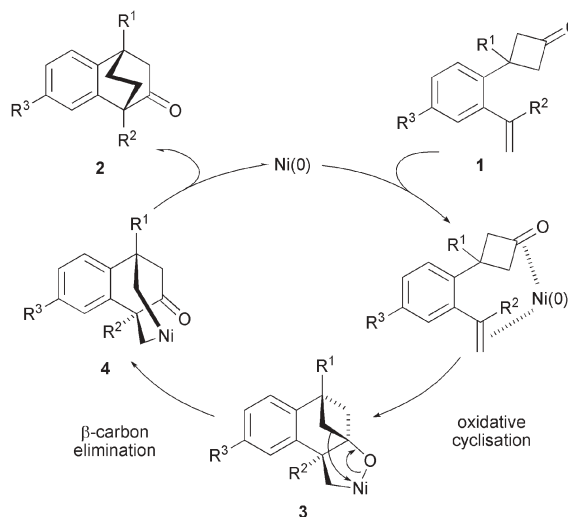
Shown in Scheme 1 is a mechanism proposed for the production of **2** from **1** on the basis of the mechanism reported for the reaction



of carbonyl compounds and olefins with nickel(0)⁷ and our previous work on the intermolecular variant using alkynes. Initially, intramolecular oxidative cyclisation 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**,⁹ which is conceivable as an alternative oxidative cyclisation intermediate, is considerably more strained than **3**. This likely accounts for the complete regioselectivity of the alkene insertion process.

Listed in Table 1 are results obtained with other ligands for nickel. Tributylphosphine and an *N*-heterocyclic carbene (IPr)¹⁰ were both comparable to tricyclohexylphosphine.

Various substrates were subjected to the nickel-catalysed 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



Scheme 1 Proposed mechanism.

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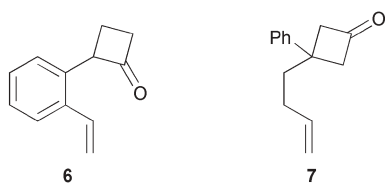
† Electronic supplementary information (ESI) available: Experimental details and selected spectral data for the new compounds. See DOI: 10.1039/b611522e

Table 1 Nickel-catalysed 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(<i>c</i> -Hex) ₃	2	90
4	10 mol% PBu ₃	2	82
5	5 mol% IPr	6	83

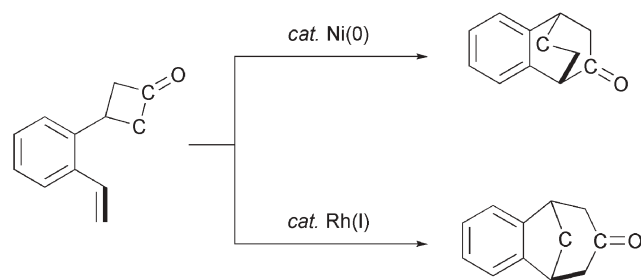
^a 3-Styrylcyclobutanone **1a**, Ni(cod)₂ (5 mol%) and ligand were heated in toluene at 100 °C. ^b Isolated yield.

substrate **1c** to give the corresponding product **2c** in 82% yield (entry 2).¹¹ 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.



As mentioned in the introduction, we have already reported the rhodium-catalysed 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 catalysed 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.



In summary, we have developed a new nickel-catalysed 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.

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Table 2 Nickel-catalysed reaction of **1**^a

Entry	1	2 (% yield ^b)	Entry	1	2 (% yield ^b)
1			5		
2			6		
3			7		
4					

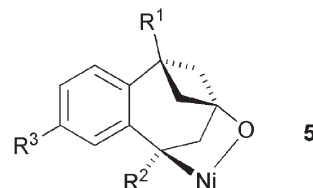
^a 3-Styrylcyclobutanone **1**, Ni(cod)₂ (10 mol%) and P(*c*-Hex)₃ (20 mol%) were heated in toluene at 100 °C for 2–12 h. ^b Isolated yield.

Notes and references

‡ **General procedure:** 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 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**.

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- 9 The structure of **5**:



- 10 IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.
- 11 Although the relative configuration of **2c** was not determined, it was obtained as a single diastereoisomer (dr = >95 : 5) from **1c** (E : Z = >95 : 5).