

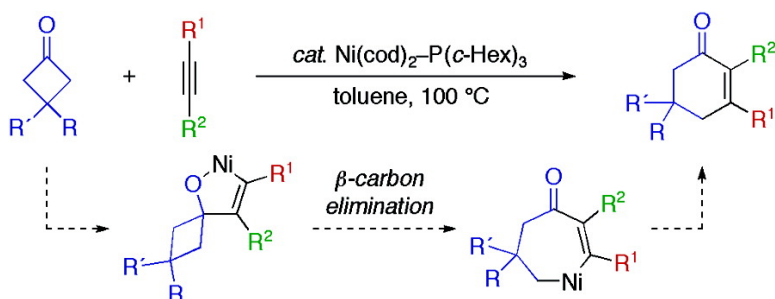
Communication

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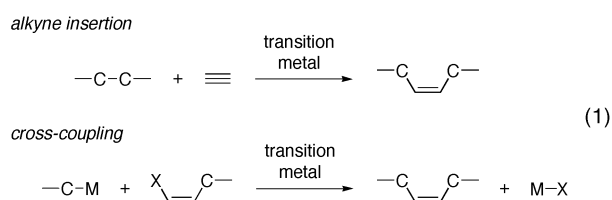
## Nickel-Catalyzed Intermolecular Alkyne Insertion into Cyclobutanones

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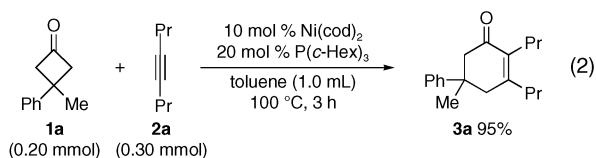
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Transition-metal-catalyzed or -mediated reactions involving carbon–carbon bond cleavage have gained significant attention because they provide new organic transformations that are otherwise difficult to achieve.<sup>1,2</sup> For example, cleaving an unreactive carbon–carbon single bond by inserting an unsaturated organic functionality like a carbon–carbon triple bond into it would be a potentially useful protocol for constructing carbon frameworks. Such an insertion reaction is highly atom-economical, in contrast to cross-coupling reactions which produce significant amounts of undesirable metal salts (eq 1).



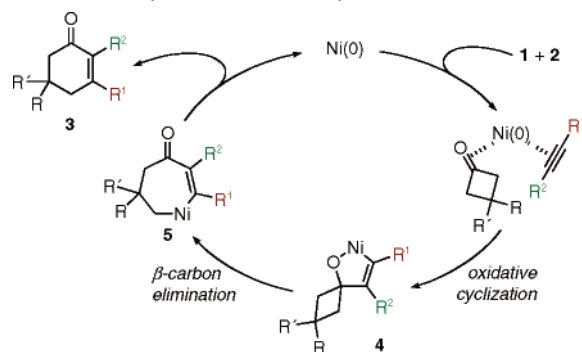
We have reported a related rhodium-catalyzed *intramolecular* alkene insertion reaction using cyclobutanone derivatives.<sup>3</sup> Our attempts to achieve *intermolecular* insertion of an alkene or an alkyne into the carbon–carbon bond of a cyclobutanone using a rhodium catalyst have all failed so far, which encouraged us to switch to nickel. Recently, nickel(0)-catalyzed carbon–carbon bond forming reactions of an aldehyde with an alkyne via oxidative cyclization forming an oxanickelacyclopentene have been developed.<sup>4,5</sup> On the other hand, the ring-opening processes of transition metal cyclobutanolates by  $\beta$ -carbon elimination have been exploited in catalytic reactions.<sup>6,7</sup> We now report the nickel-catalyzed intermolecular insertion reaction of alkynes into cyclobutanones that achieves ring-expansion of the four-membered ring skeleton by two carbons, producing substituted 2-cyclohexenones.<sup>8</sup>

When 3-methyl-3-phenylcyclobutanone (**1a**) and 4-octyne (**2a**, 1.5 equiv) were heated in the presence of a nickel catalyst prepared in situ from bis(1,5-cyclooctadiene)nickel(0) (10 mol %) and tricyclohexylphosphine (20 mol %) in toluene at 100 °C for 3 h, six-membered ring ketone **3a** was obtained in 95% yield (eq 2).<sup>9</sup>



The nickel complex effected formal insertion of the alkyne between the carbonyl carbon and the  $\alpha$ -carbon of the cyclobutanone. A conceivable mechanism is shown in Scheme 1. Oxanickelacyclopentene **4** is initially formed by oxidative cyclization of the carbonyl group of cyclobutanone and an alkyne with nickel(0). The four-membered ring is then opened by  $\beta$ -carbon elimination, resulting in ring-expansion to form seven-membered nickelacycle **5**. Finally, reductive elimination gives the product **3** with nickel(0)

**Scheme 1.** Postulated Mechanism for the Nickel-Catalyzed Intermolecular Alkyne Insertion into Cyclobutanones



regenerated. Although oxidative cyclization of a ketonic carbonyl group with an alkyne on nickel(0) is hitherto unknown, the carbonyl group of **1a** seems to possess a higher reactivity presumably due to its ring strain. The carbonyl  $sp^2$  carbon changes to an  $sp^3$  carbon upon oxidative cyclization, thereby diminishing the ring strain.

Under optimized reaction conditions, various substituted cyclohexenones were synthesized from cyclobutanones and alkynes (Table 1). Symmetrical 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 (entry 3). The methyl group was located  $\alpha$  to the carbonyl group in the major product. Alkynes **2e** and **2f** were subjected to the coupling reaction in order to see if any electronic effects impact the regioselectivity (entries 4 and 5). The electron-donating and -withdrawing substituents at the *para*-positions of the phenyl group had little effect on the regioselectivity. Terminal alkynes, such as 1-octyne and phenylacetylene, failed to participate in the reaction due to rapid oligomerization of the alkynes.<sup>10</sup> Cyclobutanone **1b** also reacted with **2a** and **2d**, affording the corresponding products in 91 and 69%, respectively (entries 6 and 7). The reaction of 3,3-diethylcyclobutanone (**1c**) required 20 mol % of the nickel catalyst to gain an acceptable yield (entries 8 and 9) because of its lower reactivity compared with the that of phenyl-substituted **1a** and **1b**. The reaction with cyclobutanones possessing substituents at the 2-position, like 2-phenylcyclobutanone, failed to take place, presumably due to steric reasons.

The situation with cyclobutanones having a hydrogen at the 3-position turned out to be somewhat different (Table 2). The reaction of monoalkyl-substituted cyclobutanone **1d** afforded a mixture of the desired product **3k** (37%) and linear unsaturated ketone **6a** (37%) and linear unsaturated ketone **6a** (37%).  $\beta$ -Hydride elimination occurred from intermediate **5**, leading to the formation of **6a** through reductive elimination and subsequent olefin isomerization. Although 3-phenylcyclobutanone (**1e**) exhibited a higher reactivity than **1d**, the linear ketone **6b** was produced even predominantly over **3l** (entry 2). Several ligands of nickel(0) were examined to improve the

**Table 1.** Nickel-Catalyzed Reaction of **1** and **2** Forming 2-Cyclohexenone **3**<sup>a</sup>

entry	<b>1</b>	<b>2</b> (R <sup>1</sup> , R <sup>2</sup> , equiv)	mol % Ni	<b>3</b> (%yield) <sup>b</sup>
1			10	<b>3b</b> (97)
2		<b>2c</b> (Ph, Ph, 3.0)	10	<b>3c</b> (84)
3		<b>2d</b> (Ph, Me, 3.0)	10	<b>3d</b> <sup>c</sup> (78)
4		<b>2e</b> ( <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> , Me, 3.0)	10	<b>3e</b> <sup>c</sup> (58)
5		<b>2f</b> ( <i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> , Me, 3.0)	10	<b>3f</b> <sup>c</sup> (65)
6			10	<b>3g</b> (91)
7		<b>2d</b> (Ph, Me, 3.0)	10	<b>3h</b> <sup>c</sup> (69)
8			20	<b>3i</b> (61)
9		<b>2d</b> (Ph, Me, 3.0)	20	<b>3j</b> <sup>c</sup> (47)

<sup>a</sup> Cyclobutanone **1**, alkyne **2** (1.5–3.0 equiv to **1**), Ni(cod)<sub>2</sub> (10 mol %), and P(*c*-Hex)<sub>3</sub> (20 mol %) were heated in toluene at 90–110 °C for 3–6 h. <sup>b</sup> Isolated yield. <sup>c</sup> Regioisomeric ratios of the methyl group  $\alpha$ : $\beta$  to the carbonyl group were determined by <sup>1</sup>H NMR to be as follows: **3d** (92:8); **3e** (90:10); **3f** (91:9); **3h** (93:7); **3j** (90:10).

**Table 2.** Ligand Screening in the Reaction of Cyclobutanones **1d** and **1e** with 4-Octyne (**2a**)<sup>a</sup>

entry	<b>1</b> (R)	mol % Ni	L (mol %)	<b>3</b> (%) <sup>b</sup>	<b>6</b> (%) <sup>b</sup>
1	<b>1d</b> (Oct)	10	P( <i>c</i> -Hex) <sub>3</sub> (20)	<b>3k</b> (37)	<b>6a</b> <sup>c</sup> (37)
2	<b>1e</b> (Ph)	10	P( <i>c</i> -Hex) <sub>3</sub> (20)	<b>3l</b> (41)	<b>6b</b> (54)
3	<b>1e</b> (Ph)	10	PPh <sub>3</sub> (20)	<b>3l</b> (37)	<b>6b</b> (26)
4	<b>1e</b> (Ph)	10	IPr (10)	<b>3l</b> (61)	—
5	<b>1e</b> (Ph)	20	IPr (20)	<b>3l</b> (79)	—

<sup>a</sup> Cyclobutanone **1** (0.20 mmol), alkyne **2a** (0.30 mmol), and nickel catalyst were heated in toluene (1.0 mL, 100 °C, 3 h for entries 1–3; 2.0 mL, 110 °C, 18 h for entry 4; 4.0 mL, 110 °C, 15 h for entry 5). <sup>b</sup> Isolated yield. <sup>c</sup> A mixture of *Z*- and *E*-isomers with respect to the 2-methyldec-1-enyl moiety was obtained.

product selectivity for **3**. To our delight, an *N*-heterocyclic carbene (NHC)<sup>11</sup> afforded cyclohexenone **3l** selectively in 61% yield without any detectable formation of **6b**, although the reaction became slower (entry 4). The yield was increased to 79% when 20 mol % of the nickel catalyst was employed (entry 5).

In summary, we have developed a new nickel-catalyzed transformation, in which a formal alkyne insertion between the carbonyl carbon and the  $\alpha$ -carbon of the cyclobutanone was achieved by combining a ketone–alkyne coupling reaction with a  $\beta$ -carbon elimination process. It was demonstrated for the first time that  $\beta$ -carbon elimination from transition metal cyclobutanolates can take place with nickel(II) as well as with palladium(II)<sup>7</sup> and rhodium(I).<sup>6</sup> This new reaction uses cyclobutanones as a four-carbon unit and provides a concise and efficient access to substituted cyclohexenones.

**Acknowledgment.** We thank H. Fujita for his assistance in the structure determination by NMR. This work was supported by a Grant-in-Aid for Young Scientists (B) (No. 15750085) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

**Supporting Information Available:** Experimental details and selected spectral data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (8) For related catalytic reactions of cyclobutenones, see: (a) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 8617–8618. (b) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 2771–2772. Therein,  $\eta^4$ -vinylketene metal complexes are presumably formed as the intermediate from cyclobutenones, which are much more labile thermally as well as catalytically than cyclobutanones.
- (9) P(*c*-Pent)<sub>3</sub> and P(*i*-Pr)<sub>3</sub> worked equally well to give **3a** in 92 and 94% yield, respectively. Use of PBu<sub>3</sub> led to incomplete conversion and afforded an inseparable mixture of **3a** (82%) and **1a** (13%). PPh<sub>3</sub> and P(*t*-Bu)<sub>3</sub> gave only a trace amount of **3a**.
- (10) Internal silylalkynes as a surrogate for 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 under the standard reaction conditions.
- (11) IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. 1,3-Dimesitylimidazol-2-ylidene (IMes) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (SIPr) showed lower reactivities.

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