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Eight-Membered Ring Construction by [4 + 2 + 2] Annulation Involving β-Carbon Elimination

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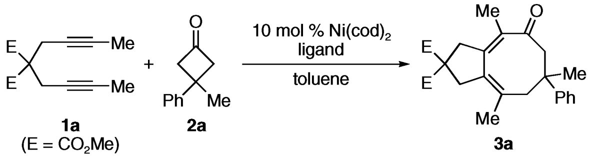
Transition-metal-catalyzed multi-component annulation reactions have created much interest in organic synthesis because they achieve the construction of difficult-to-form carbon frameworks in a single chemical operation with good atom economy.[1] For example, [5 + 2 + 1][2] and [4 + 2 + 2][3] annulation reactions have been developed to enable 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 awaited to reveal the full potential of the multi-component annulation methods.

We have previously reported the nickel-catalyzed intermolecular alkyne insertion into cyclobutanones, which constructed six-membered carbocycles.[4] This result demonstrated the synthetic potential of cyclobutanones as a C4 unit in a ring-expansion process involving β-carbon elimination. We next envisaged that this protocol could be extended even further to a three-component annulation reaction to construct medium-sized carbocycles. We now report the nickel-catalyzed intermolecular [4 + 2 + 2] annulation reaction of cyclobutanones with diynes that furnishes bicyclic eight-membered ring ketones.

A solution of dimethyl 2,2-di(but-2-ynyl)malonate (**1a**, 1.5 equiv) in toluene was added dropwise to a mixture of 3-methyl-3-phenylcyclobutanone (**2a**, 1.0 equiv) and a nickel(0) catalyst. When a nickel(0)−phosphine complex prepared in situ from bis(cycloocta-1,5-diene)nickel (10 mol %) and tri-*n*-butylphosphine (20 mol %) was used as the catalyst, a formal [4 + 2 + 2] annulation reaction took place at 100 °C to give bicyclo[6.3.0]undecadienone **3a** in 91% yield. Interestingly, the use of the *N*-heterocyclic carbene ligand IPr[5] (10 mol %) as the ligand improved the activity of the nickel(0) catalyst to promote the [4 + 2 + 2] annulation reaction at room temperature, furnishing **3a** in 92% yield.[6] 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 the [4 + 2] annulation reaction of **2a** with an alkyne[4] was observed with either ligand.

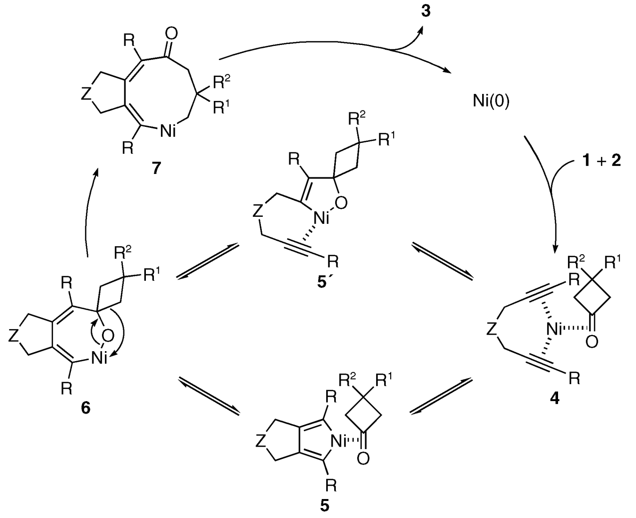


(1)

20 mol % P(*n*-Bu)$_3$, 100 °C, 3 h 91%
10 mol % IPr, r.t., 1 h 92%

We postulate the mechanism shown in Scheme 1. The diyne and cyclobutanone initially bind on nickel(0) to form **4**. There are two species, **5** and **5′**, conceivable as the next intermediate resulting from **4**. Nickelacyclopentadiene **5**[7] 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 intermediate **5′**.[8] Subsequent incorporation of the third unsaturated functionality into the Ni−C bond of either five-membered nickelacycle leads to the formation of oxanickelacycloheptadiene **6**.[9,10] Then, the four-membered ring of the spiro nickelacycle **6** is opened by β-carbon elimination[11] to expand the seven-membered nickelacycle to the nine-membered nickelacycle **7**. This ring-expanding process would be promoted by release of the strain of the four-membered tertiary cyclobutanolate. Finally, reductive elimination gives the product **3** with nickel(0) regenerated.

Scheme 1. Postulated Mechanism for the Nickel-Catalyzed Intermolecular [4 + 2 + 2] Annulation Reaction of Cyclobutanones **1** with Diynes **2**



Various substrates were subjected to the [4 + 2 + 2] annulation reaction under reaction conditions A (Ni−phosphine) and/or B (Ni−IPr), and the results are summarized in Table 1. Cyclobutanones possessing two substituents at the 3-position, such as **2b** and **2c**, reacted with **1a** to give bicyclo[6.3.0]undecane derivative **3b** and **3c**, respectively, in good yield (entries 1 and 2). Cyclobutanones **2d** and **2e** having a hydrogen at the 3-position also afforded the corresponding eight-membered ring products without formation of a side product which might have possibly arisen from β-hydride elimination (entries 3 and 4).[4] The reaction of diyne **1b**, possessing terminal alkyne moieties, suffered from its rapid self-oligomerization and required 3.0 equiv of **1b** and tricyclohexylphosphine as the ligand to attain 68% yield of **3f** (entry 5), whereas diethyl-substituted diyne **1c** showed nearly the same reactivity as **1a** and gave product **3g** in 85% yield (entry 6). However, the diyne 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. Diyne **1d** linked by a trimethylene tether produced **3h** in 87% yield (entry 7). The reaction of oxa-1,6-diyne **1f** with **2a** afforded **3j** containing an ether linkage in its framework in 61% yield (entry 9). Whereas 32% yield of product **3k** was obtained from aza-1,6-diyne **1g** under conditions A, use of IPr gave a yield more than doubled (entries 10 and 11). Octa-1,7-diyne (**1h**), whose linker is longer by one

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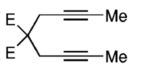
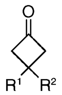
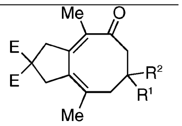
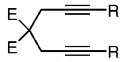
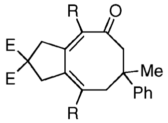
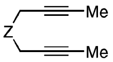
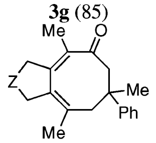
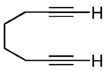
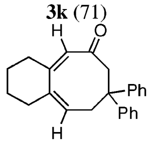
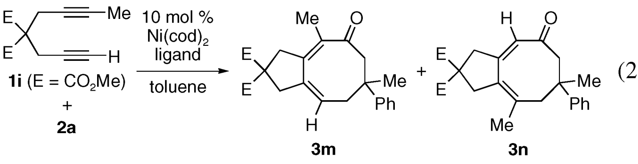
Table 1. Nickel-Catalyzed [4 + 2 + 2] Annulation Reaction of **1** and **2** Forming **3**

entry	1	2 (R^1, R^2)	conditions[a]	3 (%yield[b])
	 **1a** (E = CO$_2$Me)			
1		**2b** (Ph, Ph)	A	**3b** (83)
2		**2c** (Et, Et)	A	**3c** (70)
3		**2d** (Ph, H)	B	**3d** (84)
4		**2e** (Oct, H)	B	**3e** (91)
	 (E = CO$_2$Me)	**2a**		
5	**1b** (R = H)		A[c,d]	**3f** (68)
6	**1c** (R = Et)		A	**3g** (85)
		**2a**		
7	**1d** (Z = CH$_2$)		B	**3h** (87)
8	**1e** (Z = C(CH$_2$OMe)$_2$)		B	**3i** (91)
9	**1f** (Z = O)		A[c]	**3j** (61)
10	**1g** (Z = NTs)		A	**3k** (32)
11	**1g**		B	**3k** (71)
12	 **1h**	**2b**	A[d,e]	 **3l** (46)

[a] Conditions A: cyclobutanone **2**, diyne **1** (1.5 equiv to **2**), Ni(cod)$_2$ (10 mol %), and P(n-Bu)$_3$ (20 mol %) in toluene at 100 °C for 3 h. Conditions B: cyclobutanone **2**, diyne **1** (1.2 equiv 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] Diyne (3.0 equiv) was used. [e] Ni(cod)$_2$ (20 mol %) and P(c-Hex)$_3$ (40 mol %) were used.

carbon, could join the [4 + 2 + 2] annulation reaction, although it was less reactive than **1b** and **1d** to produce **3l** in 46% yield under fortified conditions A (entry 12).[12]

Next, the reaction of unsymmetrical diyne **1i** was examined (eq 2). Whereas a 4:1 mixture of regioisomers **3m** and **3n** was obtained with the P(c-Hex)$_3$ ligand, the sterically bulkier IPr ligand selectively produced **3m**.[13]

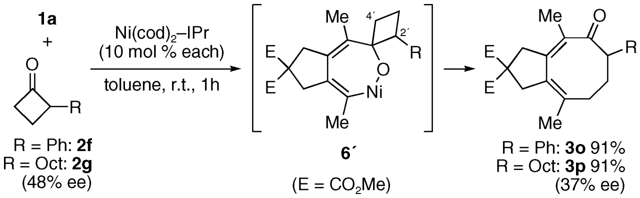


1i (E = CO$_2$Me) + **2a** → **3m** + **3n** (2)

20 mol % P(c-Hex)$_3$, 100 °C, 3 h 84% (79:21)
10 mol % IPr, r.t., 1 h 43% (>20:1)

The use of unsymmetrical 2-substituted cyclobutanones **2f** and **2g** was also examined under the catalysis of Ni−IPr (Scheme 2). A high regioselectivity of >20:1 was observed for the β-carbon elimination step. We assume that, with the intermediate **6′**, the substituent at the 2-position would sterically hamper the migration of the methyne carbon (C2′) and rather direct the methylene carbon (C4′) on the other side to migrate onto nickel. In the case of the enantiomerically enriched **2g** (48% ee), the enantiopurity decreased to 37% in product **3p**, which might be a result of enolization partially occurring with the carbonyl-containing compounds involved, such as **2g**, **3p**, and/or intermediate **7**.

Scheme 2



1a + R = Ph: **2f**; R = Oct: **2g** (48% ee) → **6′** (E = CO$_2$Me) → R = Ph: **3o** 91%; R = Oct: **3p** 91% (37% ee)

In summary, we have developed a nickel-catalyzed intermolecular [4 + 2 + 2] annulation reaction of cyclobutanones as the C4 unit with diynes, which incorporates β-carbon elimination for ring-expansion. This method provides a direct access to bicyclic eight-membered ring ketones.

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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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(1) For reviews, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901−2915. (c) Murakami, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 718−720. (d) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022−3037.

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(4) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932−6933.

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

(6) See the Supporting Information for experimental details.

(7) Shanmugasundaram, M.; Wu, M.-S.; Jeganmohan, M.; Huang, C.-W.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 7724−7729.

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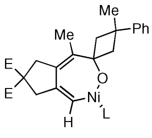
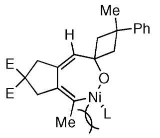
(10) We assume that the interconversion among the intermediates **4**, **5**, **5′**, and **6** is reversible and that there is equilibration before occurrence of β-carbon elimination from **6**.

(11) For β-carbon elimination from transition metal cyclobutanolates, see: (a) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201−216. (b) Matsuda, T.; Makino, M.; Murakami, M. *Org. Lett.* **2004**, *6*, 1257−1259. (c) Matsuda, T.; Makino, M.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4608−4611.

(12) The reaction of the terminal diyne **1h** under conditions B failed to afford product **3l**. Reaction of an internal diyne, deca-2,8-diyne, with **2b** gave a complex mixture of products with both the Ni−phosphine and Ni−IPr catalysts, presumably due to ensuing double bond isomerization.

(13) We assume the intermediates, such as **A** and **B**, which then undergo ring-opening through β-carbon elimination. Intermediate **A** would be more stable than **B** because intermediate **B** would suffer from unfavorable steric repulsion between the methyl group at the alkyne terminus and the ligand (L).


A


B

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