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A Facile Construction of Bi- or Tricyclic Skeletons by Nickel-Catalyzed Stereoselective Cyclization of Alkynylcycloalkanone

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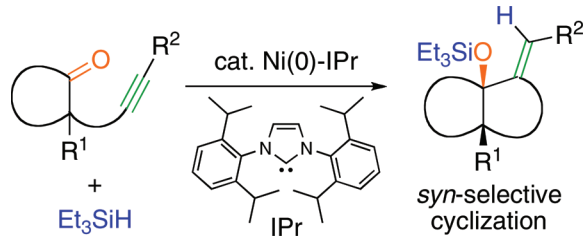
ABSTRACT



A nickel-catalyzed intramolecular cyclization of alkynylalkanone in the presence of Et_3SiH using an NHC ligand produced various carbo- and heterocycles in a stereoselective manner. The reaction would proceed via formation of oxanickelacycle followed by σ-bond metathesis with silane to give a bi- or tricyclic compound.

The development of a novel strategy for efficient construction of polycyclic skeletons is important in synthetic organic chemistry because such carbo- or heterocyclic frameworks are ubiquitous in many biologically active compounds.[1] A transition-metal-catalyzed cyclization of multiple bonds is a powerful and promising methodology for the synthesis of various types of cyclic compounds in recent organic synthesis.[2] We have reported nickel-catalyzed stereoselective cyclization of 1,3-diene and tethered aldehyde in the presence of silane.[3,4] In this reaction, a variety of cyclic alcohol derivatives having an olefin tether were produced in a highly stereoselective manner, and synthesis of biologically active natural products by using the cyclization as a key step was also demonstrated.[3c−e,j] A nickel-catalyzed reductive coupling between alkynes and carbonyl groups is also an attractive strategy for the construction of cyclic molecules, and many excellent examples of alkyne−aldehyde coupling by a nickel catalyst have been demonstrated.[5] On the other hand, nickel-

(1) For a recent review on cyclization reactions, see: *Handbook of Cyclization Reactions*; Ma, S., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2010.

(2) For reviews on transition-metal-catalyzed cyclization reactions, see: (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (c) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (d) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (e) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (f) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307.

(3) For intramolecular cyclization of 1,3-diene and tethered aldehyde, see: (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (b) Sato, Y.; Takimoto, M.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 887. (c) Sato, Y.; Takimoto, M.; Mori, M. *Synlett* **1997**, 734. (d) Sato, Y.; Saito, N.; Mori, M. *Tetrahedron Lett.* **1997**, *38*, 3931. (e) Sato, Y.; Saito, N.; Mori, M. *Tetrahedron* **1998**, *54*, 1153. (f) Sato, Y.; Takanashi, T.; Hoshiba, M.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 5579. (g) Sato, Y.; Takanashi, T.; Mori, M. *Organometallics* **1999**, *18*, 4891. (h) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624. (i) Sato, Y.; Saito, N.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 2371. (j) Sato, Y.; Takimoto, M.; Mori, M. *Chem. Pharm. Bull.* **2000**, *48*, 1753. (k) Sato, Y.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 9310. (l) Sato, Y.; Takanashi, T.; Hoshiba, M.; Mori, M. *J. Organomet. Chem.* **2003**, *688*, 36. For cyclization of 1,3-diene and aldehyde using $Me_3SiSnBu_3$ instead of silane, see: (m) Sato, Y.; Saito, N.; Mori, M. *Chem. Lett.* **2002**, 18. (n) Saito, N.; Mori, M.; Sato, Y. *J. Organomet. Chem.* **2007**, *692*, 460.

(4) (a) Kimura, M.; Tamaru, Y. In *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005; pp 137−170. (b) Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* **2001**, *3*, 2181.

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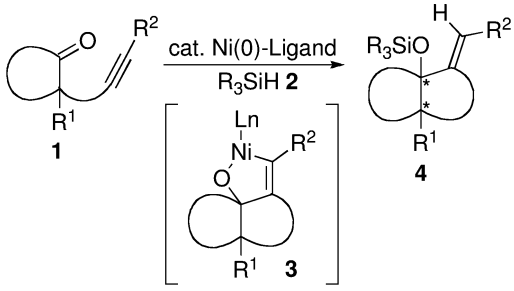
Scheme 1

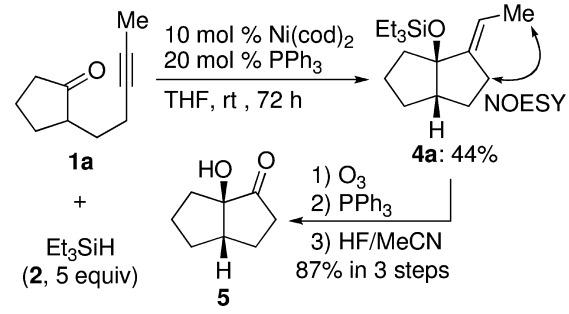


catalyzed reductive coupling between alkynes and ketones has been limited to a few cases: coupling of 1,3-enynes and aromatic ketones or α,β-unsaturated ketone[6] or coupling reaction of alkynes and cyclobutanones.[7] In this context, we planned nickel-catalyzed cyclization of alkynlcycloalkanone in the presence of silane as a new method for the construction of polycyclic skeletons (Scheme 1). That is, oxidative cycloaddition of a carbonyl group and alkyne part to a zerovalent nickel complex could proceed to give oxanickelacycle **3**.[8,9] The reaction of nickelacycle **3** with silane would afford bicyclic compound **4** including an allylic alcohol part at the bridgehead carbon, which might be used for further transformations.[10]

To examine the feasibility of this plan, we investigated the cyclization of 2-(pent-3-ynyl)cyclopentanone **1a** (Scheme 2).

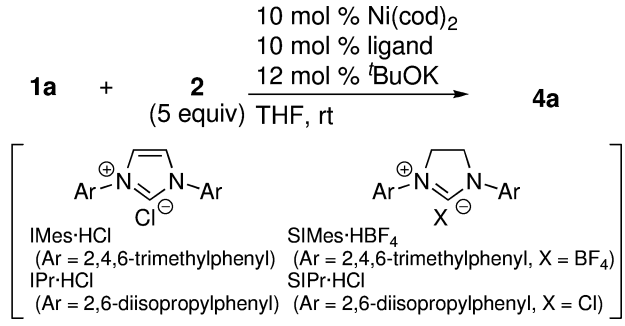
Treatment of **1a** with Et_3SiH (**2**, 5 equiv) in the presence of $Ni(cod)_2$ (10 mol %) and PPh_3 (20 mol %) in THF at room temperature provided the bicyclo[3.3.0]octane derivative in 44% yield as a single isomer. The regiochemistry of the alkene part in **4a** was determined to be the *E* configuration by a NOESY experiment. Furthermore, the product **4a** was transformed into the bicyclic compound **5**, whose ^1H and ^{13}C NMR spectral data were identical to those reported previously.[11,12] Therefore, the stereochemistry of the ring junction of **4a** was assigned to be the *syn*-orientation.

Scheme 2



Encouraged by these results, we investigated the cyclization using various ligands to improve the yield of **4a**. The results are summarized in Table 1. The reaction of **1a** and **2** using PBu_3 as a ligand gave **4a** in 72% yield (run 1). After screening various types of ligands, we found that *N*-heterocyclic carbene (NHC) ligands were effective for cyclization of **1a** in the presence of Et_3SiH (**2**) (runs 2−5). Among the NHC ligands employed, IPr [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] gave the best result. That is, when IPr was used as a ligand, the reaction proceeded smoothly to give **4a** in quantitative yield (run 4).

Table 1. Effect of Ligand



run	ligand	time (h)	yield (%)
1[a]	PBu_3	48	72
2	IMes·HCl	8	84
3	SIMes·HBF_4	9	79
4	IPr·HCl	1	quant
5	SIPr·HCl	1	93

[a] The reaction was carried out in the presence of 20 mol % of phosphine ligand without ^{t}BuOK.

(5) For recent reviews, see: (a) Ikeda, S.-i. In *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005; pp 102−106. (b) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890, and references cited therein. (c) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441, and references cited therein. For recent reports on Ni(0)-catalyzed reductive coupling of alkynes and aldehydes, see: (d) Knapp-Reed, B.; Mahandru, G. M.; Montgomery, J. *J. Am. Chem. Soc.* **2005**, *127*, 13156. (e) Luanphaisarnnont, T.; Ndubaku, C. O.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 2937. (f) Miller, K. M.; Colby, E. A.; Woodin, K. S.; Jamison, T. F. *Adv. Synth. Catal.* **2005**, *347*, 1533. (g) Moslin, R. M.; Jamison, T. F. *Org. Lett.* **2006**, *8*, 455. (h) Sa-ei, K.; Montgomery, J. *Org. Lett.* **2006**, *8*, 4441. (i) Moslin, R. M.; Miller, K. M.; Jamison, T. F. *Tetrahedron* **2006**, *62*, 7598. (j) Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 9568. (k) Moslin, R. M.; Jamison, T. F. *J. Org. Chem.* **2007**, *72*, 9736. (l) Chrovian, C. C.; Knapp-Reed, B.; Montgomery, J. *Org. Lett.* **2008**, *10*, 811. (m) Saito, N.; Katayama, T.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829. (n) Malik, H. A.; Chaulagain, M. R.; Montgomery, J. *Org. Lett.* **2009**, *11*, 5734. (o) Sa-ei, K.; Montgomery, J. *Tetrahedron* **2009**, *65*, 6707. (p) Malik, H. A.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2010**, *132*, 6304.

(6) Miller, K. M.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 3077.

(7) (a) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932. (b) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2006**, *128*, 2166. (c) Murakami, M.; Ashida, S.; Matsuda, T. *Tetrahedron.* **2006**, *62*, 7540. (d) Murakami, M.; Ashida, S. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 885.

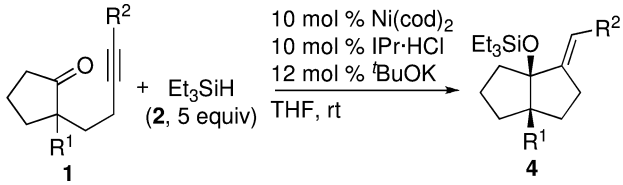
(8) For the isolation of oxanickelacyclopentene from alkyne and aldehyde, see: Ogoshi, S.; Arai, T.; Ohashi, M.; Kurosawa, H. *Chem. Commun.* **2008**, 1347.

(9) For computational studies on the mechanism of Ni(0)-catalyzed reductive coupling of alkyne and aldehyde, see: (a) McCarren, P. R.; Liu, P.; Cheong, P. H.-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6654. (b) Liu, P.; McCarren, P.; Cheong, P. H.-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 2050.

(10) Jamison reported one example of Ni(0)-catalyzed reductive cyclization of a ketone and an alkyne in their synthetic study of (−)-terpestacin and related molecules. When an alkynal including a cyclopentanone moiety was treated with a Ni(0)−PBu_3 catalyst and Et_3B, the intramolecular cyclization of the alkyne and the cyclopentanone part proceeded unexpectedly as a side reaction to give the corresponding cyclized product. See: Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 10682.

With optimal conditions in hand, we investigated the effects of substituents on the formation of a bicyclo[3.3.0]octane skeleton (Table 2). The reaction of 2-(but-3-ynyl)cyclopentanone (**1b**) and Et_3SiH (**2**) gave **4b** in 83% yield (run 1). The cyclization of alkynylcyclopentanones having a siloxymethyl group **1c** or a phenyl group **1d** on the alkyne part afforded the corresponding cyclized products **4c** or **4d** in high yields (runs 2 and 3). On the other hand, the reaction of **1e** or **1f** gave the cyclized product **4e** or **4f** in moderate yield (runs 4 and 5). Furthermore, 2,2-disubstitued cyclopentanone **1g** or **1h** also reacted with Et_3SiH (**2**) in the presence of a Ni−IPr catalyst to give the cyclic compound **4g** or **4h** having two consecutive tetrasubstituted carbon centers in high yield, respectively (runs 6 and 7).

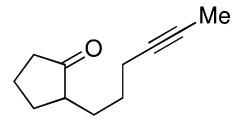
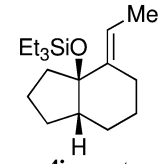
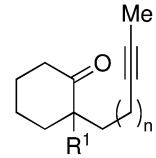
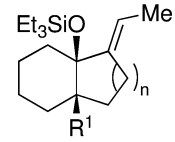
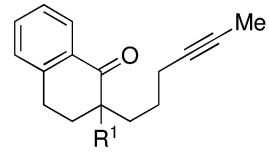
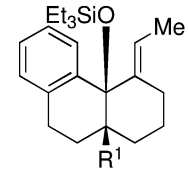
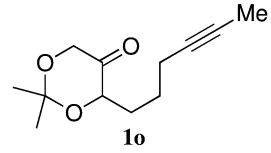
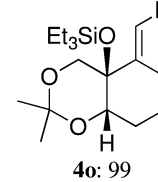
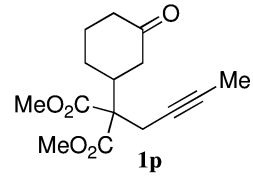
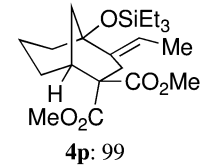
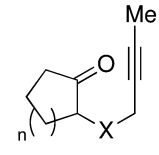
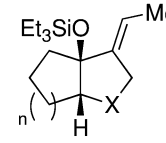
Table 2. Effects of Substituents



run	substrate	time (h)	product (%)
1	**1b**: $R^1 = R^2 = H$	0.5	**4b**: 83
2	**1c**: $R^1 = H$, $R^2 = CH_2OTBS$	0.5	**4c**: 99
3	**1d**: $R^1 = H$, $R^2 = Ph$	0.5	**4d**: 97
4	**1e**: $R^1 = H$, $R^2 = CO_2Me$	48	**4e**: 26
5	**1f**: $R^1 = H$, $R^2 = TMS$	40	**4f**: 26
6	**1g**: $R^1 = R^2 = Me$	0.5	**4g**: quant
7	**1h**: $R^1 = CH_2OTBS$, $R^2 = Me$	0.5	**4h**: 96

Next, we turned our attention to the construction of various cyclic skeletons (Table 3). The reaction of 2-(hex-4-ynyl)-cyclopentanone (**1i**) and Et_3SiH (**2**) provided *cis*-hydrindan derivative **4i** in quantitative yield (run 1). Cyclohexanone derivatives **1j**−**l** were also applicable to the nickel-catalyzed cyclization, and the corresponding cyclic compounds having *cis*-hydrindan or *cis*-decalin skeletons **4j**−**l** were obtained in good yields (runs 2−4). The cyclization of alkynyl-α-tetralones **1m** and **1n** with Et_3SiH (**2**) provided the corresponding hexahydrophenanthrene derivatives **4m** and **4n** in 73% and 79% yields, respectively (runs 5 and 6). The 1,3-dioxan-5-one derivative **1o** was also applicable to the cyclization, giving **4o** in 99% yield (run 7). When cyclohexanone **1p** bearing an alkynyl group on *β*-position was reacted with Et_3SiH (**2**), bicyclo[3.3.1]octane derivative **4p** was obtained in 99% yield as a single diastereomer (run 8). On the other hand, the reaction of cycloalkanone derivatives having an oxygen atom in a tether **1q** and **1r** was carried out under the same conditions, giving corresponding bicyclic furan derivatives **4q** and **4r** in good yields (runs 9 and 10). Furthermore, nitrogen heterocycles **4s** and **4t** were also synthesized by cyclization of **1s** and **1t** in the presence of Et_3SiH (**2**) in 92% and 95% yields, respectively (runs 11 and 12).

Table 3. Cyclization of Various Substrates[a]

run	substrate	time (h)	product (%)
1	 **1i**	0.5	 **4i**: quant
2	 **1j** (n = 1, R^1 = H)	0.5	 **4j**: quant
3	**1k** (n = 2, R^1 = H)	0.5	**4k**: quant
4	**1l** (n = 2, R^1 = CO_2Et)	25	**4l**: 76%
5	 **1m** (R^1 = H)	0.5	 **4m**: 73
6	**1n** (R^1 = CO_2Et)	3	**4n**: 79
7	 **1o**	0.5	 **4o**: 99
8	 **1p**	0.5	 **4p**: 99
9	 **1q** (X = O, n = 1)	0.5	 **4q**: 96
10	**1r** (X = O, n = 2)	0.5	**4r**: 87
11	**1s** (X = NTs, n = 1)	0.5	**4s**: 92
12	**1t** (X = NTs, n = 2)	0.5	**4t**: 95

[a] Reaction conditions: $Ni(cod)_2$ (10 mol %), IPr·HCl (10 mol %), ^{t}BuOK (12 mol %), Et_3SiH (**2**, 5 equiv), THF, room temperature

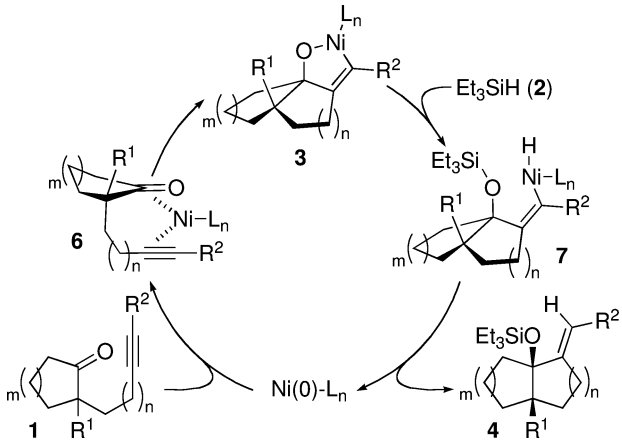
A possible reaction mechanism of the cyclization is shown in Scheme 3. First, coordination of alkyne and carbonyl group in substrate **1** to a zerovalent nickel complex (depicted as **6**) followed by oxidative cyclization would proceed to give

(11) Shono, T.; Kise, N.; Fujimoto, T.; Tominaga, N.; Morita, H. *J. Org. Chem.* **1992**, *57*, 7175.

(12) Determination of the stereochemistry is described in the Supporting Information.

oxanickelacycle **3** in a stereoselective fashion. Then cleavage of the nickel−oxygen bond by σ-bond metathesis of the nickelacycle **3** with Et_3SiH (**2**) would afford hydridenickel species **7**. Finally, the reductive elimination from **7** would give the cyclized product **4** as a single stereoisomer.

Scheme 3



In summary, the cyclization of 2- or 3-alkynylcycloalkanone with Et_3SiH in the presence of a zerovalent nickel complex and IPr as a ligand provided various carbo- and heterocyclic compounds having two consecutive stereogenic centers including tetrasubstituted carbon in a stereoselective fashion. The reaction would proceed via the formation of oxanickelacycle followed by σ-bond metathesis of the nickelacycle and silane to give bi- or tricyclic compounds.

Further studies along this line are in progress.

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Supporting Information Available: Experimental procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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