Cycloaddition

DOI: 10.1002/ange.201106174

[3+2] Cycloaddition Reaction of Cyclopropyl Ketones with Alkynes Catalyzed by Nickel/Dimethylaluminum Chloride**

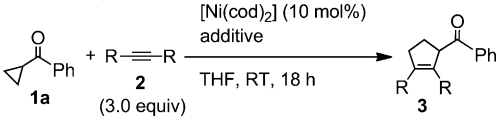
*Takashi Tamaki, Masato Ohashi, and Sensuke Ogoshi**

Transition-metal-catalyzed cycloaddition reactions have received increasing attention as straightforward methods for the synthesis of a five-membered-ring framework. The reaction of cyclopropanes having an unsaturated bond such as methylenecyclopropanes or vinylcyclopropanes has been studied intensively for use in the preparation of five-membered-ring compounds by [3+2] cycloaddition with unsaturated compounds.[1] However, the reaction of alkynes with alkylidenecyclopropanes,[2] vinylcyclopropanes,[3] and cyclopropyl imines[4] gave only seven-membered-ring products by either [3+2+2] or [5+2] cycloadditions. To date, only one example of a nickel-catalyzed intermolecular [3+2] cycloaddition reaction of methylenecyclopropanes with alkynes to afford cyclopentene derivatives has been reported by Binger et al.,[5a] although some intramolecular reactions have been known.[5]

Previously, both the group of Montgomery as well as our group simultaneously reported that cyclopropyl ketones can react as a three-carbon unit in the presence of a nickel catalyst to give cyclopentane derivatives.[6] In this reaction, a six-membered oxa-nickelacycle played an important role as a key reaction intermediate and its molecular structure was determined by X-ray crystallography.[7] Although enones reacted with the six-membered oxa-nickelacycle to give an η^3-oxa-allylnickel complex, alkynes did not react at all. In his pioneering work, Fujisawa and co-workers reported that the ring-opening reaction of cyclopropyl phenyl ketone with $AlMe_3$ to give butyl phenyl ketone is promoted by a nickel catalyst without ligands.[8] This result indicates that organoaluminum reagents might play an important role in the oxidative addition of cyclopropyl phenyl ketone to nickel(0). Herein we report the nickel-catalyzed [3+2] cycloaddition reaction of cyclopropyl ketones with alkynes to give cyclopentenes in the presence of organoaluminum reagents.[9]

In the presence of 10 mol% of $[Ni(cod)_2]$ and 100 mol% of $AlMe_3$, the reaction of cyclopropyl phenyl ketone (**1a**) with 2-butyne (**2a**) was conducted in THF at room temperature (Table 1, entry 1). The expected [3+2] cycloaddition reaction occurred to give **3aa** in 80% yield.[10] In the absence of $AlMe_3$, **3aa** was not obtained at all, thus indicating that $AlMe_3$ is crucial for the reaction (entry 2). In the absence of alkynes, the nickel catalyst was immediately decomposed to give a black precipitate. When $AlMe_3$ was employed as an additive, the formation of undesired side-reaction products, such as the methylated compound and its derivatives, was inevitable because of the high reactivity of $AlMe_3$. Therefore, other additives were examined to suppress the formation of undesired side-reaction products. In the presence of Me_2AlOAc or Me_2AlOTf, the [3+2] cycloaddition of **1a** with **2a** gave **3aa** in 99 and 84% yield, respectively (entries 3 and 4). Me_2AlCl was also very effective for the reaction (entry 5). Even a catalytic amount of Me_2AlCl was sufficient to give **3aa** quantitatively (entry 6). Other Lewis acids such as $AlCl_3$, $TiCl_4$, and $ZnMe_2$ did not promote the reaction at all (entries 7–9).[9] In the presence of PCy_3, no reaction occurred

Table 1: Reaction optimization and control studies.[a]



Entry	2	Additive	[mol%]	3	Yield [%][b]
1	**2a** (R = Me)	$AlMe_3$	100	**3aa**	80
2	**2a**	none	–	**3aa**	0
3	**2a**	Me_2AlOAc	100	**3aa**	99
4	**2a**	Me_2AlOTf	100	**3aa**	84
5	**2a**	Me_2AlCl	100	**3aa**	100 (98)
6	**2a**	Me_2AlCl	20	**3aa**	100
7	**2a**	$AlCl_3$	100	**3aa**	0
8	**2a**	$TiCl_4$	100	**3aa**	0
9	**2a**	$ZnMe_2$	100	**3aa**	0
10	**2a**	PCy_3	20	**3aa**	0
11	**2b** (R = Et)	Me_2AlCl	100	**3ab**	100
12	**2b**	Me_2AlCl	20	**3ab**	29
13[c]	**2b**	Me_2AlCl	20	**3ab**	100 (88)

[a] Unless otherwise specified, the reaction was performed on a 0.2 mmol scale. [b] Yield as determined by GC analysis of the crude reaction mixture. Yield of isolated product is given within parentheses. [c] The reaction mixture was stirred at 50°C for 3 h. cod = 1,5-cyclooctadiene, Cy = cyclohexyl, Tf = trifluoromethylsulfonyl, THF = tetrahydrofuran.

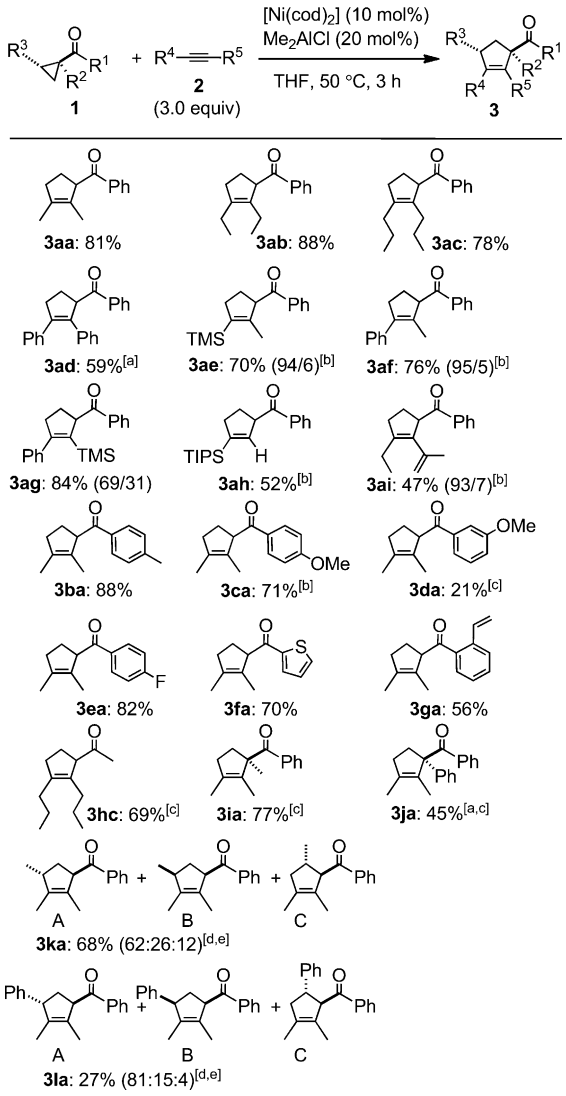
[*] T. Tamaki, Dr. M. Ohashi, Prof. S. Ogoshi
Department of Applied Chemistry, Faculty of Engineering
Osaka University, Suita, Osaka 565-0871 (Japan)
E-mail: ogoshi@chem.eng.osaka-u.ac.jp
Dr. M. Ohashi
Center for Atomic and Molecular Technologies
Osaka University, Suita, Osaka 565-0871 (Japan)

[**] This work was supported by the Grants-in-Aid for Scientific Research (No. 21245028) and "Molecular Activation Directed toward Straightforward Synthesis (No. 23105546) from MEXT. T.T. expresses his special thanks for the research fellowships for young scientists from the Japan Society for the Promotion of Science (JSPS) and the Global COE Program "Global Education and Research Center for Bio-Environmental Chemistry" of Osaka University.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201106174.

(entry 10). The reaction of **1a** with 3-hexyne (**2b**) proceeded to give **3ab** (entry 11). A decrease in the amount of Me_2AlCl from 100 mol% to 20 mol% lead to the low conversion and yield of **3ab** (entry 12). Thus, in the presence of 20 mol% of Me_2AlCl, the reaction was carried out at 50°C and **3ab** was obtained quantitatively (entry 13).

We next examined the scope of this cycloaddition reaction. The reaction of **1a** with symmetric internal alkynes gave the corresponding cyclopentene derivatives in high yields (Scheme 1; **3aa**–**3ad**). Unsymmetric alkynes were also applicable for this reaction, and both 1-trimethylsilylpropyne (**2e**; R^4 = TMS, R^5 = Me) and 1-phenylpropyne (**2f**; R^4 = Ph, R^5 = Me) reacted with **1a** to give the corresponding cyclopentenes (**3ae**, **3af**) with high regioselectivity. The reaction of 1-trimethylsilyl-2-phenylacetylene (**2g**; R^4 = Ph, R^5 = TMS) with **1a** gave a mixture of regioisomers, however, a reduced regioselectivity was observed compared with the reactions of either **2e** or **2f**. These results suggest that the regioselectivity might be controlled by the steric bulk of the substituents. The molecular structure of the major regioisomer of **3ag** was determined by X-ray crystallography.[11] Although terminal alkynes are prone to undergoing dimerization or trimerization in the presence of nickel(0) species, the cycloaddition of triisopropylsilyl acetylene (**2h**; R^4 = TIPS, R^5 = H) with **1a** occurred to give the expected cyclopentene product as a single regioisomer (**3ah**).[12] Use of activated alkynes of functional groups containing ester, ether, or carbonyl groups led to the recovery of starting material presumably because of the coordination to Me_2AlCl, thus decreasing its reactivity. The reaction of **1a** with 2-methyl-1-hexen-3-yne (**2i**; R^4 = Et, R^5 = 2-propenyl) gave the expected cyclopentene derivatives **3ai** in moderate yield.



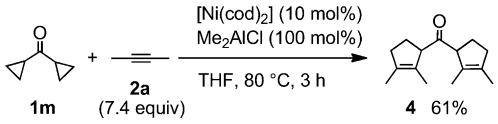
Scheme 1. [3+2] Cycloaddition reaction of **1** with **2**. Reaction conditions: cyclopropyl ketone (1.0 mmol), alkyne (3.0 mmol), $[Ni(cod)_2]$ (0.1 mmol), and Me_2AlCl (0.2 mmol) in THF (1.0 mL) at 50°C for 3 h. Yield of isolated product given; the regioisomer ratio is given in parentheses. The major product is depicted. [a] Run at 80°C. [b] Used 40 mol% of Me_2AlCl. [c] Used 100 mol% of Me_2AlCl. [d] Used 100 mol% of Me_2AlOAc. [e] The isomer ratio of 1,4-*trans* (A)/1,4-*cis* (B)/1,5-*trans* (C) is given in parentheses. TIPS = triisopropylsilyl, TMS = trimethylsilyl.

A broad range of cyclopropyl aryl ketones were successfully employed for the cycloaddition reaction (**3ba**–**3ga**). Electronic variation on the phenyl ring of the cyclopropyl ketones had little effect on the reaction efficiency, except for the methoxy group. The methoxy group is supposed to decrease the reactivity of Me_2AlCl by coordinating to Me_2AlCl. Moreover, cyclopropyl 3-methoxyphenyl ketone (**1d**; R^1 = 3-$MeOC_6H_4$, R^2 = H, R^3 = H) gave the product (**3da**) in 21% yield even in the presence of a stoichiometric amount of Me_2AlCl. Cyclopropyl 4-fluorophenyl ketone (**1e**; R^1 = 4-FC_6H_4, R^2 = H, R^3 = H) was also converted into the desired product. Cyclopropyl 2-thienyl ketone (**1f**; R^1 = 2-thienyl, R^2 = H, R^3 = H) also underwent the reaction to give **3fa** in moderate yield. Although the oxidative addition of C_{sp^2}–F and C_{sp^2}–S bonds in fluoroarenes and thiophenes, respectively, to nickel(0) is known,[13,14] neither of them underwent the oxidative addition under the reaction conditions. Cyclopropyl methyl ketone (**1h**; R^1 = Me, R^2 = H, R^3 = H) reacted with **2c** efficiently to give the expected product (**3hc**) in 69% yield with a stoichiometric amount of Me_2AlCl. This observation could be rationalized by the difference in coordination ability between **1a** and **1h**.[15] Ethyl cyclopropanecarboxylate did not proceed the reaction at all.

Although the reaction of disubstituted cyclopropanes required a stoichiometric amount of Me_2AlCl or Me_2AlOAc, both **1i** (R^1 = Ph, R^2 = Me, R^3 = H) and **1j** (R^1 = Ph, R^2 = Ph, R^3 = H) also underwent the cycloaddition reaction with **2a**. The reaction of *trans*-1-benzoyl-2-methylcyclopropane (**1k**; R^1 = Ph, R^2 = H, R^3 = Me) or *trans*-1-benzoyl-2-phenylcyclopropane (**1l**; R^1 = Ph, R^2 = H, R^3 = Me) with **2a** each gave a mixture of three isomers: 1,4-*trans* (A), 1,4-*cis* (B), and 1,5-*trans* (C; **3ka**, **3la**). In these reactions, Me_2AlOAc was more effective than Me_2AlCl. By monitoring the progress of the reaction of **1k** with **2a** using GC, it was observed that the isomer ratio of **3ka** remained unchanged during the reaction. In addition, when two different mixtures of **3ka** (A/B/C = 62:26:12 and 46:45:9) were heated at 50°C for 3 hours in the presence of 10 mol% of $[Ni(cod)_2]$, 100 mol% of Me_2AlOAc, and **2a**, the isomer ratio of **3ka** also remained unchanged.[11]

Thus, it was found that isomers A and B did not undergo the interconversion under the catalytic reaction conditions.

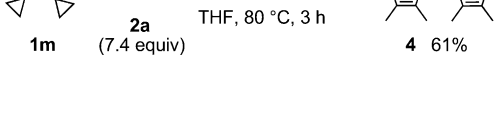
Although both a stoichiometric amount of Me_2AlCl and a higher reaction temperature were required, dicyclopropyl ketone (**1m**) reacted with two molecules of **2a** to yield dicyclopentenyl ketone **4** [Eq. (1)]. It is noteworthy that



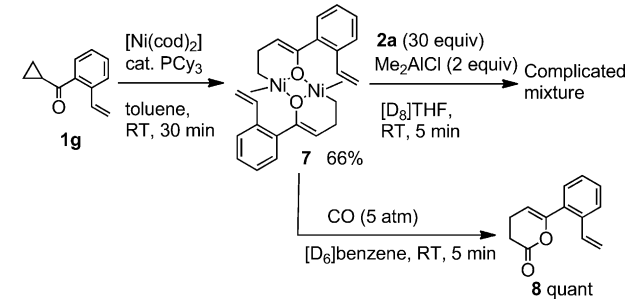
(1)

cyclopentenyl cyclopropyl ketone was not observed at all in the reaction, which suggests that the second [3+2] cycloaddition occurs much faster than the first one. The intramolecular reactions of the [3+2] cycloaddition were unsuccessful,[16] although ruthenium catalyst efficiently proceeded.[17] Thus, nickel catalysts and ruthenium catalysts are complementary in [3+2] cycloaddition of cyclopropyl ketones with alkynes.

To gain deeper insight into the reaction mechanism, we examined the reaction of the isolable six-membered oxa-nickelacycle **5** with **2a** and Me_2AlCl. However, it ended up leading to very rapid generation of the π-allylnickel complex **6** [Eq. (2)].[18] Thus, we synthesized the six-membered oxa-nickelacycle **7**, which does not contain 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) in its structure (Scheme 2). Elemental analysis showed the expected composition. The ^1H and ^{13}C NMR chemical shifts of the nickel enolate moiety (-NiOC(2-vinylphenyl)=CH-) are in the range of those for reported nickel enolates.[6a,7,19] The upfield shift of the vinyl group indicates the η^2-coordination to nickel(II) center. The treatment of **7** with carbon monoxide (5 atm) led to the formation of the expected lactone **8** quantitatively,[20] which is consistent with the structure of **7** depicted in Scheme 2. The stoichiometric reaction of **7** with **2a** and Me_2AlCl did not give **3ga** at all (Scheme 2), but **3ga** was produced in 56% yield in the catalytic reaction (Scheme 1). These results suggest that a six-membered oxa-nickelacycle intermediate does not seem to be generated in the [3+2] cycloaddition.[7]

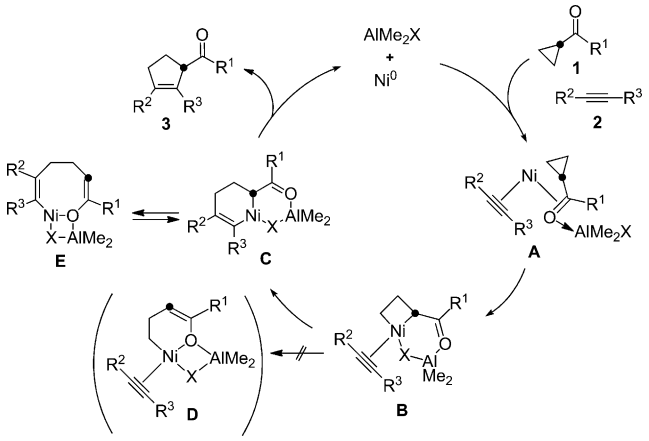


(2)



Scheme 2. Synthesis and reactivity of **7**.

A plausible reaction path is depicted in Scheme 3. The coordination of the unsaturated bonds of cyclopropyl ketones and alkynes occurs to give the η^2:η^2-coordinated nickel complex **A**. Organoaluminum reagents might enhance the coordination ability of cyclopropyl ketones toward the nickel(0) center by the coordination of the oxygen atom of the carbonyl group.[21] The oxidative addition of the proximal carbon–carbon bond of the cyclopropyl ketones to nickel(0) occurs to give the nickelacyclobutane intermediate **B**. Recently, we reported the isolation of oxa-nickelacyclopentene by the oxidative cyclization of an alkyne and an aldehyde with nickel(0) promoted by Me_2AlOTf, in which the coordination of one oxygen atom of a OTf group to a nickel(II) center was observed.[21] Thus, the substituent X of organoaluminum reagents such as Me,[22] Cl,[23] and OAc groups would also coordinate toward the nickel(II) center to stabilize the reaction intermediates by forming a chelate structure. The insertion of an alkyne into the carbon–nickel bond of **B** affords the nickelacyclohexene intermediate **C**. The experimental results of stoichiometric reactions with **7** and very rapid formation of **6** by the reaction of **5** with Me_2AlCl suggest that the generation of the intermediate **D** is unlikely. Reductive elimination from **C** gives the cyclopentene derivative **3** to regenerate nickel(0) species and organoaluminum reagents. The formation of 1,4-*cis* products in the reaction of 1,2-*trans*-disubstituted cyclopropanes was observed, which implies that a key step to invert the stereochemistry at the α position (marked carbon atom) must be included in the catalytic cycle. Thus, the interconversion between **C** and **E** might occur prior to the reductive elimination because the generation of η^1-*O*-nickel enolate complex and its inversion of stereochemistry have been reported.[19b,24]



Scheme 3. A plausible reaction pathway.

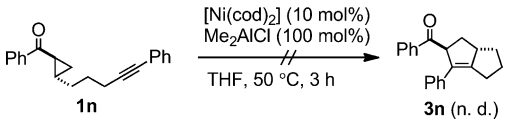
In summary, we have demonstrated the nickel-catalyzed intermolecular [3+2] cycloaddition reaction of cyclopropyl ketones with alkynes in the presence of organoaluminum

reagents. The key to success is the organoaluminum reagents, which activate the carbonyl group of cyclopropyl ketones and stabilize the reaction intermediates. This reaction provides a new method for the synthesis of cyclopentene derivatives. Additional studies to elucidate the reaction mechanism and expand the reaction scope are underway in our laboratory.

Received: August 31, 2011
Published online: October 17, 2011

Keywords: carbocycles · cycloaddition · homogeneous catalysis · nickel · transition metals

[1] For review to see: M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117 – 3179.
[2] a) S. Saito, M. Masuda, S. Komagawa, *J. Am. Chem. Soc.* **2004**, *126*, 10540 – 10541; b) S. Komagawa, S. Saito, *Angew. Chem.* **2006**, *118*, 2506 – 2509; *Angew. Chem. Int. Ed.* **2006**, *45*, 2446 – 2449; c) S. Saito, S. Komagawa, I. Azumaya, M. Masuda, *J. Org. Chem.* **2007**, *72*, 9114 – 9120; d) K. Maeda, S. Saito, *Tetrahedron Lett.* **2007**, *48*, 3173 – 3176.
[3] a) P. A. Wender, H. Rieck, M. Fuji, *J. Am. Chem. Soc.* **1998**, *120*, 10976 – 10977; b) P. A. Wender, A. J. Dyckman, C. O. Husfeld, M. J. C. Scanio, *Org. Lett.* **2000**, *2*, 1609 – 1611; c) P. A. Wender, C. M. Barzilay, A. J. Dyckman, *J. Am. Chem. Soc.* **2001**, *123*, 179 – 180.
[4] P. A. Wender, T. M. Pedersen, M. J. C. Scanio, *J. Am. Chem. Soc.* **2002**, *124*, 15154 – 15155.
[5] a) P. Binger, Q.-H. Lü, P. Wedemann, *Angew. Chem.* **1985**, *97*, 333 – 334; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 316 – 317; Intramolecular cycloaddition of methylenecyclopropanes with alkynes: b) S. A. Bapuji, W. B. Motherwell, M. Shipman, *Tetrahedron Lett.* **1989**, *30*, 7107 – 7110; c) H. Corlay, R. T. Lewis, W. B. Motherwell, M. Shipman, *Tetrahedron* **1995**, *51*, 3303 – 3318; d) M. Lautens, Y. Ren, P. H. M. Delanghe, *J. Am. Chem. Soc.* **1994**, *116*, 8821 – 8822; e) M. Lautens, Y. Ren, *J. Am. Chem. Soc.* **1996**, *118*, 9597 – 9605; f) A. Delgado, J. R. Rodríguez, L. Castedo, J. L. Mascareñas, *J. Am. Chem. Soc.* **2003**, *125*, 9282 – 9283; g) R. García-Fandiño, M. Gulías, L. Castedo, J. R. Granja, J. L. Mascareñas, D. J. Cárdenas, *Chem. Eur. J.* **2008**, *14*, 272 – 281; h) B. Yao, Y. Li, Z. Liang, Y. Zhang, *Org. Lett.* **2011**, *13*, 640 – 643; Nickel-catalyzed isomerization of vinylcyclopropane: i) M. Suginome, T. Matsuda, T. Yoshimoto, Y. Ito, *Organometallics* **2002**, *21*, 1537 – 1539; j) G. Zuo, J. Louie, *Angew. Chem.* **2004**, *116*, 2327 – 2329; *Angew. Chem. Int. Ed.* **2004**, *43*, 2277 – 2279; Intramolecular cycloaddition of vinylcyclopropanes with alkynes: k) L. Jiao, M. Lin, Z.-X. Yu, *Chem. Commun.* **2010**, *46*, 1059 – 1061.
[6] a) S. Ogoshi, M. Nagata, H. Kurosawa, *J. Am. Chem. Soc.* **2006**, *128*, 5350 – 5351; b) L. Liu, J. Montgomery, *J. Am. Chem. Soc.* **2006**, *128*, 5348 – 5349; c) G. C. Lloyd-Jones, *Angew. Chem.* **2006**, *118*, 6942 – 6944; *Angew. Chem. Int. Ed.* **2006**, *45*, 6788 – 6790.
[7] T. Tamaki, M. Nagata, M. Ohashi, S. Ogoshi, *Chem. Eur. J.* **2009**, *15*, 10083 – 10091.
[8] T. Ichiyanagi, S. Kuniyama, M. Shimizu, T. Fujisawa, *Chem. Lett.* **1997**, 1149 – 1150.
[9] $TiCl_4$ was known as an effective Lewis acid to mediate the [3+2] cycloaddition of cyclopropyl ketones with alkynes: V. K. Yadav, V. Sriramurthy, *Angew. Chem.* **2004**, *116*, 2723 – 2725; *Angew. Chem. Int. Ed.* **2004**, *43*, 2669 – 2671.
[10] H.-U. Gonzenbach, K. Schaffner, B. Blank, H. Fischer, *Helv. Chim. Acta* **1973**, *56*, 1741 – 1752.
[11] See the Supporting Information for details.
[12] The bulkiness of triisopropylsilylacetylene retards its homodimerization: a) N. Matsuyama, H. Tsurugi, T. Satoh, M. Miura, *Adv. Synth. Catal.* **2008**, *350*, 2274 – 2278; b) N. Matsuyama, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 3576 – 3578; c) M. Shirakura, M. Suginome, *Org. Lett.* **2009**, *11*, 523 – 526.
[13] a) D. R. Fahey, J. E. Mahan, *J. Am. Chem. Soc.* **1977**, *99*, 2501 – 2508; b) L. Cronin, C. L. Higgitt, R. Karch, R. N. Perutz, *Organometallics* **1997**, *16*, 4920 – 4928; c) S. A. Johnson, C. W. Huff, F. Mustafa, M. Saliba, *J. Am. Chem. Soc.* **2008**, *130*, 17278 – 17280.
[14] a) D. A. Vicic, W. D. Jones, *J. Am. Chem. Soc.* **1999**, *121*, 7606 – 7617; b) M. Hernández, G. Miralrio, A. Avévalo, S. Bernès, J. J. García, C. López, P. M. Maitlis, F. del Rio, *Organometallics* **2001**, *20*, 4061 – 4071.
[15] Although an η^2-ketone complex of **1a** was formed in the reaction of **1a** with $[Ni(cod)_2]$ and PCy_3 quantitatively, **1h** gave the corresponding η^2-ketone complex only in 15% yield under the same reaction conditions.
[16] The cyclopropyl ketone **1n** was employed in Ref. [17] and did not undergo intramolecular [3+2] cycloaddition reaction. See the Supporting Information for details.



1n **3n** (n. d.)

[17] Z. Lu, M. Shen, T. P. Yoon, *J. Am. Chem. Soc.* **2011**, *133*, 1162 – 1164.
[18] a) S. Ogoshi, T. Yoshida, T. Nishida, M. Morita, H. Kurosawa, *J. Am. Chem. Soc.* **2001**, *123*, 1944 – 1950; b) S. Ogoshi, H. Kamada, H. Kurosawa, *Tetrahedron* **2006**, *62*, 7583 – 7588.
[19] a) K. K. D. Amarasinghe, S. K. Chowdhury, M. J. Heeg, J. Montgomery, *Organometallics* **2001**, *20*, 370 – 372; b) H. P. Hratchian, S. K. Chowdhury, V. M. Gutiérrez-García, K. K. D. Amarasinghe, M. J. Heeg, H. B. Schlegel, J. Montgomery, *Organometallics* **2004**, *23*, 4636 – 4646; c) J. Cámpora, C. M. Maya, P. Palma, E. Carmona, C. Graiff, A. Tiripicchio, *Chem. Commun.* **2003**, 1742 – 1743.
[20] The treatment of nickel compounds with carbon monoxide can yield $[Ni(CO)_4]$ (extremely toxic). The reaction mixture must be handled in a well-ventilated fume hood.
[21] η^2-Coordination of carbonyl group to nickel(0) enhanced by Me_2AlOTf has been reported: M. Ohashi, H. Saijo, T. Arai, S. Ogoshi, *Organometallics* **2010**, *29*, 6534 – 6540.
[22] S. Ogoshi, M. Ueta, T. Arai, H. Kurosawa, *J. Am. Chem. Soc.* **2005**, *127*, 12810 – 12811.
[23] M. Ohashi, M. Ikawa, S. Ogoshi, *Organometallics* **2011**, *30*, 2765 – 2774.
[24] S. Ogoshi, A. Nishimura, M. Ohashi, *Org. Lett.* **2010**, *12*, 3450 – 3452.
[25] CCDC 841838 (**3ag**) and 841839 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

