Selective Cyclotrimerization of Enones and Alkynes by a Nickel and Aluminum Catalytic System

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Abstract: Enones **1** reacted with two molecules of alkynes **2** (R = R′ in eq 1) in the presence of a nickel(0) and aluminum catalytic system to give cyclotrimerization adducts regioselectively. Aluminum phenoxide ($Me_nAl(OPh)_{3-n}$ ($n = 0-3$)) functions as a Lewis acid cocatalyst and activates **1**. Stoichiometric experiments suggest that the cycloaddition of **1** and **2** proceeds via nickelacyclopentadiene intermediates, which are formed by the oxidative coupling of Ni(0) species with **2**. In addition, the selective cyclotrimerization of **1** and two different alkynes **2** and **2′** (R ≠ R′ in eq 1) was also accomplished in the presence of a binary metal catalytic system. The reaction occurs effectively when an alkyl- or aryl-substituted alkyne (alkyne B, 1 equiv vs **1**) is added slowly to a mixture of **1** and a bulkier alkyne (alkyne A, 1 equiv vs **1**) such as *tert*-butylacetylene (**2f**) or (trimethylsilyl)acetylene (**2g**).

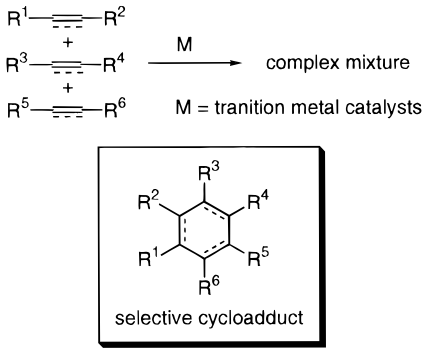
Introduction

[2 + 2 + 2] Cycloaddition of unsaturated molecules by transition metal complexes leads to six-membered cyclic compounds with the formation of three new carbon−carbon bonds. Since the first catalytic reaction was reported by Reppe,[1] these reactions have been extensively studied by various research groups.[2] Whereas the intramolecular and partially intermolecular modes of cyclotrimerization have been used as efficient synthetic methods,[3] many difficulties have been encountered with completely intermolecular modes. The major problem concerns controlling the combination of the three different starting substrates. Chemo- and regioselection leads to a complex mixture of cycloadducts which severely limit the utility of this reaction (Chart 1).

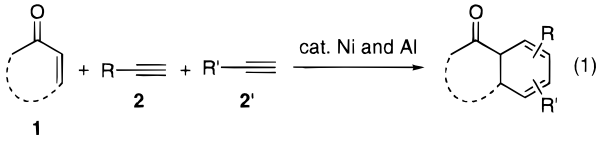
In this area, Wakatsuki et al. found that an unsymmetrical cobaltacyclopentadiene complex, prepared from a cyclopentadienyl cobalt(I) complex and two different alkynes, reacted with a third alkyne to give a benzene derivative.[4] Recently, Takahashi et al. reported the more efficient formation of benzene derivatives by the copper(I)-mediated coupling of unsymmetrical zirconacyclopentadienes with a third alkyne.[5] However, the transition metal-promoted cyclotrimerizations of three different molecules are limited to stoichiometric (not catalytic) processes.

In a preliminary report,[6] we showed that a binary metallic system of nickel and aluminum effectively catalyzed a cyclo-

Chart 1



addition of α,β-unsaturated enones **1** with two molecules of alkynes **2** (R = R′ in eq 1). We now describe in detail our studies



on the reaction. In addition, we also report the cyclotrimerization of **1** and two different alkynes **2** and **2′** (R ≠ R′ in eq 1). The reaction is a first example of the catalytic selective cyclotrimerization of three different unsaturated molecules.

Results and Discussion

Cyclotrimerization of Enones and Alkynes.[6] When 2-cyclopenten-1-one (**1a**) was treated with 1-hexyne (**2a**) (2 equiv vs **1a**) (eq 2) in the presence of nickel acetylacetonate ($Ni(acac)_2$, 5 mol %), triphenylphosphine (PPh_3, 10 mol %), and trimethylaluminum (Me_3Al, 40 mol %) in tetrahydrofuran (THF) at room temperature for 2 h, a mixture of cycloadducts (1:2 adducts) derived from one molecule of **1a** and two molecules of **2a** was

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(1) Reppe, W.; Schweckendiek, W. J. *Justus Liebigs Ann. Chem.* **1948**, *560*, 104.

(2) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 9.4. Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. Trost, B. M. *Science* **1991**, *254*, 1471. Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon Press: Oxford; 1995; Vol. 12, Chapter 7.4. Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(3) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.

(4) Wakatsuki, Y.; Kuramitsu, T.; Yamazaki, H. *Tetrahedron Lett.* **1974**, 4549.

(5) (a) Takahashi, T.; Kotora, M.; Xi, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 361. (b) Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, T.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672.

(6) Ikeda, S.; Mori, N.; Sato, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4779.

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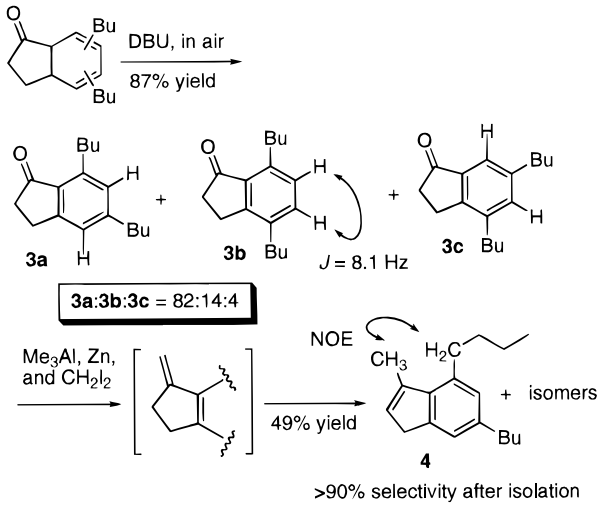
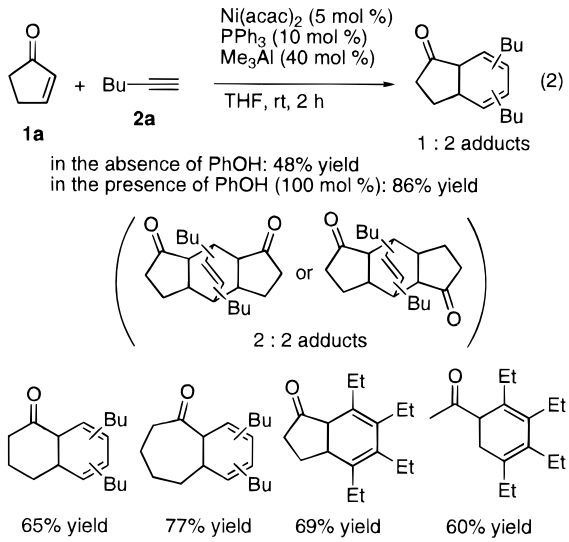
Scheme 1

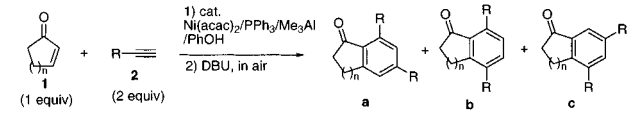


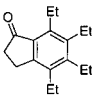
obtained in 48% yield. The addition of phenol (PhOH, ca. 100 mol %) to the reaction medium increased the yield of the cycloadducts to 86%. The 1:2 addcuts did not react with another **1a** to give the 2:2 adducts, even under THF reflux conditions. Moreover, benzenes derived from the cycloaddition of three molecules of **2a** were not also detected. Other **1** and **2** could also be applied to the cyclotrimerization.



A notable feature is that regioselective cyclotrimerization occurred in the reaction with terminal alkynes.[7] Since the regiochemistries of the cycloadducts obtained in eq 2 were equivocal by spectroscopic analyses, they were determined after aromatization by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in air (Scheme 1). The resulting aromatic compounds **3** (87% isolated yield based on the cyclohexadienes) were identified to be a mixture of three different isomers (ratio = 82:14:4) by ^{1}H NMR spectral analyses. One of the minor products (14% selectivity) was considered to be 4,7-dibutyl-1-indanone (**3b**) on the basis of the coupling constant (J = 8.1 Hz) between two aromatic protons. The major isomer was determined to be 5,7-dibutyl-1-indanone (**3a**) on the basis of spectral analyses of **4** derived from further chemical transformation by treatment of the aromatic compounds with Me_3Al, zinc dust, and diiodomethane.[8]

Table 1. Regioselective Cyclotrimerization of Enones and Alkynes[a]



entry	enone **1**	alkyne **2**	product(s)	total yield,[b] % (ratio of **a**:**b**:**c**)[c]
1	**1a**: n = 1	Et—≡—Et (**2b**)		60
2	**1a**: n = 1	R = Bu (**2a**)	**3**	71 (**3a**:**3b**:**3c** = 82:14:4)
3[d]	**1a**: n = 1	R = ^{t}BuMe$_2$SiO(CH$_2$) (**2c**)	**5**	42 (**5a**:**5b**:**5c** = >99:0:0)
4[d]	**1a**: n = 1	R = ^{t}BuMe$_2$SiO(CH$_2$)$_2$ (**2d**)	**6**	81 (**6a**:**6b**:**6c** = 93:7:0)
5	**1b**: n = 2	**2a**	**7**	83 (**7a**:**7b**:**7c** = 91:7:<2)
6	**1b**: n = 2	R = Me (**2e**)[e]	**8**	50 (**8a**:**8b**:**8c** = 90:10:0)
7	**1c**: n = 3	**2a**	**9**	70 (**9a**:**9b**:**9c** = 85:0:15)
8[d,f]	**1a**: n = 1	R = ^{t}Bu (**2f**)	**10**	45 (**10a**:**10b**:**10c** = 11:89:0)
9[d]	**1a**: n = 1	R = Me$_3$Si (**2g**)	**11**	33 (**11a**:**11b**:**11c** = 0:>99:0)

[a] All reactions were carried out with the following procedure: a solution of **1** (1.0 mmol), **2** (2.0 mmol), Ni(acac)$_2$ (0.05 mmol), PPh_3 (0.1 mmol), Me_3Al (1.0 M in hexane, 0.4 mL), and PhOH (1.0 mmol) in THF (5 mL) was stirred at room temperature for 2 h, followed by treatment with DBU in air overnight. [b] Isolated yield based on **1**. [c] Determined by integration of the aryl protons of ^{1}H NMR. [d] The reaction was carried out with Ni(acac)$_2$ (0.1 mmol), PPh_3 (0.2 mmol), Me_3Al (0.8 mmol), and PhOH (2.0 mmol). [e] Gaseous material (ca. 25 mmol) was used. [f] The conversion to aromatized compounds was carried out with 0.2 M NaOH in MeOH instead of DBU.

The results of the cyclotrimerization of a variety of **1** and **2** and the subsequent aromatization are shown in Table 1. The reaction of **1a** with propargyl silyl ether **2c** gave **5a** as a sole product (entry 3). When homopropargyl silyl ether **2d** was treated with **1a**, the regioselectivity of **6a** decreased to 93% (entry 4). Six- and seven-membered cyclic enones **1b** and **1c** also reacted to provide **7a** (from the reaction with **2a**, 91% selectivity (entry 5)), **8a** (from the reaction with gaseous propyne **2e**, 90% selectivity (entry 6)), and **9a** (from the reaction with **2a**, 85% selectivity (entry 7)) as major products, respectively. In entry 6, a commercially available **8c**[9] was not formed. In contrast to entries 2−4, 4,7-disubstituted indanones **10b** (89% selectivity) and **11b** (>99% selectivity) were synthesized from the reaction of **1a** with *tert*-butylacetylene (**2f**) and (trimethylsilyl)acetylene (**2g**), respectively (entries 8 and 9).

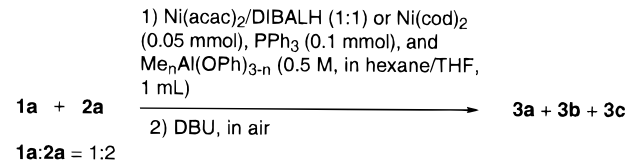
Consideration of the Reaction Mechanism: (a) Activity of the Cocatalyst $Me_nAl(OPh)_{3-n}$ (n = 0−3). The cycloaddition proceeded effectively in the presence of a nickel and aluminum catalytic system. A precatalyst Ni(acac)$_2$ reacts with a portion of the added Me_3Al to be converted into an active Ni(0) species. The residual Me_3Al functions as a Lewis acid and activates **1** (**1**−aluminum complex (**1**−*Al*)). When PhOH is added to the reaction medium, a more acidic aluminum phenoxide species ($Me_nAl(OPh)_{3-n}$ (n = 0−2)) is generated from the reaction with Me_3Al in situ (standard method, see Table

(7) For other regioselective cyclic cotrimerization of alkenes and alkynes, see: Heimbach, P.; Ploner, K.-J.; Thöme, F. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 276. Chalk, A. J. *J. Am. Chem. Soc.* **1972**, *94*, 5928. Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc.* **1993**, *115*, 1581.

(8) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698.

(9) This compound was purchased from Aldrich Chemical Co., Inc.

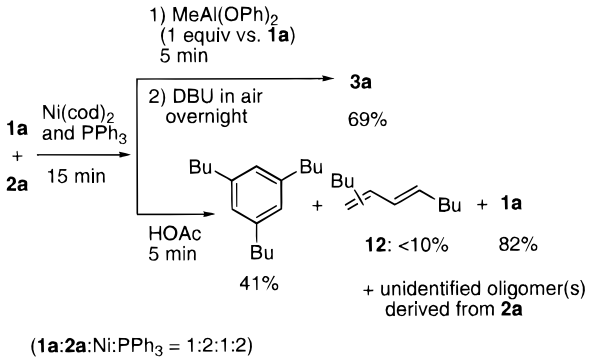
Table 2. Cyclotrimerization of **1a** and **2a** in the Presence of $Me_nAl(OPh)_{3-n}$ ($n = 0-3$)[a]



Ni cat.	$Me_nAl(OPh)_{3-n}$[a]	yield,[b] % (**3a**:**3b**:**3c**)[c]
$Ni(acac)_2$/DIBALH	$n = 0$	57 (74:26:0)
$Ni(acac)_2$/DIBALH	$n = 1$	65 (82:18:0)
$Ni(acac)_2$/DIBALH	$n = 2$	50 (80:20:0)
$Ni(acac)_2$/DIBALH	$n = 3$	30 (93:7:0)
$Ni(cod)_2$	$n = 1$	61 (86:14:0)
cf. standard method[d]		71 (82:14:4)

[a] Preparation of $Me_nAl(OPh)_{3-n}$ ($n = 0-3$): to a solution of PhOH ((3-*n*) mmol) in THF (1 mL) was added Me_3Al (1.0 M in hexane, 1 mL), and then the mixture was stirred at room temperature for 1 h. [b] Isolated yield based on **1a**. [c] Determined by integration of the aryl protons of ^1H NMR. [d] See Table 1.

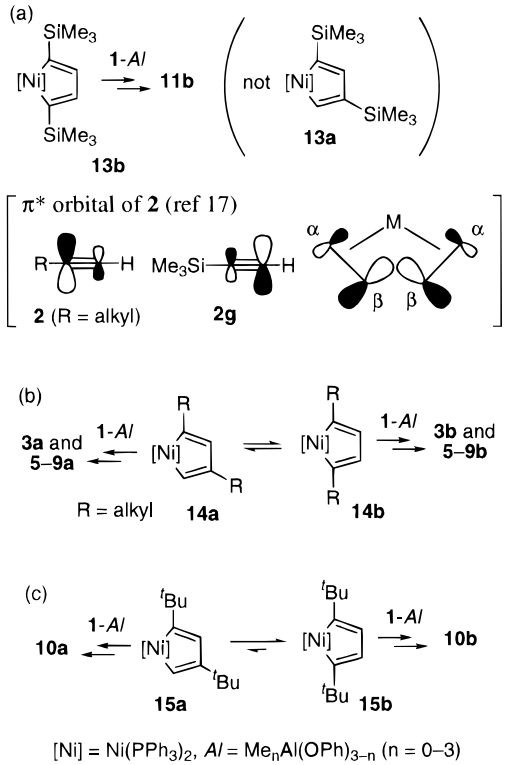
Scheme 2



1). Therefore, we investigated the effect of $Me_nAl(OPh)_{3-n}$, which had been previously prepared from PhOH and Me_3Al, in this reaction.[10] The results are shown in Table 2. Compared to the results with Me_3Al ($n = 3$), the more acidic $Me_nAl(OPh)_{3-n}$ ($n = 0-2$) increased the yields of the cycloadducts, although their regioselectivities were reduced. $MeAl(OPh)_2$ appears to mainly function as a cocatalyst in the standard method.

(b) Stoichiometric Experiments. In the cyclotrimerizations of **1** and **2**, there are two possible metallacyclic intermediates, i.e., nickelacyclo*pentadiene*[11] and nickelacyclo*pentene*.[12] We examined stoichiometric experiments to get insight into the reaction mechanism (Scheme 2). A mixture of **1a** (1 equiv) and **2a** (2 equiv) was treated with bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$, 1 equiv) at room temperature for 15 min. Although the reaction mixture was monitored by NMR, no helpful information regarding intermediates was obtained. However, **3a** was obtained in 69% yield when the mixture was treated with $MeAl(OPh)_2$ (1 equiv) and then DBU. In addition, when the reaction mixture was treated with HOAc instead of $MeAl(OPh)_2$, a small amount of diene **12**[13,14] was obtained with a tributylbenzene.[15] In this reaction, **3a** was not detected and the starting enone **1a** was recovered. On the basis of these results, it seems

Scheme 3



reasonable to conclude that the cycloaddition of **1** and **2** proceeds via nickelacyclopentadiene intermediates,[16] which are formed by the oxidative coupling of Ni(0) species with **2**.

(c) Occurrence of Regioselection. The occurrence of regioselection in this cycloaddition can be explained by considering the reaction via nickelacyclopentadienes (Scheme 3). The formation of metallacycles is controlled by electronic and steric factors. Hoffmann et al. reported that the large lobes of polarized π^* of the starting substrates face each other in the β-positions of metallacycles.[17] An alkyne **2g** reacted with **1a** to give **11b** predominantly (entry 9 in Table 1). Metallacycle **13b** is predicted to be a favorable intermediate on the basis of electronic factors (Scheme 3 (a)). On the other hand, the cycloadditions of alkyl-substituted alkynes such as **2a** and **2c**−**e** with **1** selectively gave **3a** and **5a**−**9a** derived from the corresponding intermediate **14a**, respectively (entries 2−7 in Table 1). Intermediate **14a** would be more reactive than **14b**, since the less-hindered α-carbon atom of **14a** smoothly couples with the carbon atom in the β-position of **1** (Scheme 3 (b)).[16] The reaction with **2f**, which has a bulkier *tert*-butyl group, selectively gave **10b** derived from **15b** (45% yield for 2 h, **10a**:**10b** = 11:89, see entry 8 in Table 1). Interestingly, the regioisomeric ratio was different from that at the beginning of the reaction, i.e., 11% yield for 5 min, **10a**:**10b** = 31:69. These results suggest that the final product ratio of **10a** and **10b** is governed by equilibrium between **15a** and **15b**, although **10a** was also produced via more reactive **15a** in the initial stage (Scheme 3 (c)).[18]

(10) Maruoka, K.; Yamamoto, H. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 1074 and references therein.

(11) Eisch, J. J.; Damasevitz, G. A. *J. Organomet. Chem.* **1975**, *96*, C19. Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1975**, *96*, C23. Eisch, J. J.; Aradi, A. A.; Han, K. I. *Tetrahedron Lett.* **1983**, *24*, 2073. Hoberg, H.; Richter, W. *J. Organomet. Chem.* **1980**, *195*, 355.

(12) Kaschube, W.; Schröder, W.; Pörschke, K. R.; Angermund, K.; Krüger, C. *J. Organmet. Chem.* **1990**, *389*, 399.

(13) HRMS data of **12**: $C_{12}H_{22}$ (M^+) Calcd, 166.1721; Found, 166.1750.

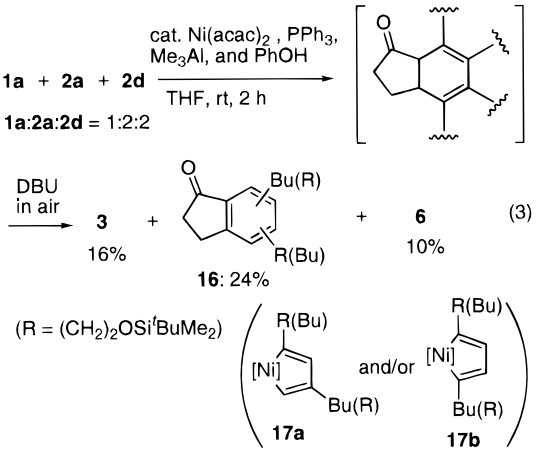
(14) Eisch et al. reported that tetraphenyl-1,3-butadiene was intercepted (5% yield) in the oligomerization of diphenylacetylene by $Ni(cod)_2$. See: Eisch, J. J.; Galle, J. E.; Aradi, A. A.; Boleslawski, M. P. *J. Organomet. Chem.* **1986**, *312*, 399.

(15) Eapen, K. C.; Tamborski, C. *J. Org. Chem.* **1988**, *53*, 5564.

(16) It is not clear whether the reaction of the metallacycle with the activated **1a** (**1a**-aluminum complex (**1a**-*Al*)) proceeds via the concerted (Diels−Alder type)[16a] or the stepwise insertion route.[16b] (a) McAlister, D. R.; Bercaw, J. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 1666. (b) See ref 5b.

(17) Stockis, A.; Hoffmann, R. *J. Am. Chem. Soc.* **1980**, *102*, 2952.

Selective Cyclotrimerization of Enones with Two Different Alkynes. Next we investigate a more challenging target, i.e., the selective cyclotrimerization of three different starting substares. An enone **1a** was treated with a mixture of two different alkynes **2a** (2 equiv vs **1a**) and **2d** (2 equiv) in the presence of the nickel and aluminum catalytic system in THF at room temperature. After the cycloadducts were treated with DBU in air, the resulting compounds were identified to be a mixture of **16** (24% yield, the regioselectivity was not determined),[19] **3** (16% yield), and **6** (10% yield) (eq 3). Thus, the



cycloadducts were formed in a ratio of 2:1:1, respectively, in this reaction.

As mentioned above, regioselection is closely related to the stability and the reactivity of the nickelacyclopentadiene intermediates. This consideration led us to the conclusion that the alkynes used in the cycloadditions can be classified into two groups. One group includes bulkier alkynes such as **2f** or **2g**, with which oxidative coupling forms a thermodynamically favored intermediate such as **13b** or **15b**, and the other group includes alkyl-substituted alkynes such as **2a** or **2d**, with which the cycloaddition tends to give a product derived from reactive **14a**. We investigated the reaction using different alkynes, e.g., **2d** and **2g**. When **1a** was reacted with a mixture of **2d** (2 equiv vs **1a**) and **2g** (2 equiv), subsequent aromatization gave **18** along with **6a**. The formation of **11b**, which was derived from the reaction of **1a** with **2g**, was completely suppressed (run 1 in Table 3). A similar result was obtained at −10 °C (run 2).[20] On the other hand, when the reaction was carried out at 50 °C, all of the cycloadducts **6**, **11**, and **18** were obtained (run 3).

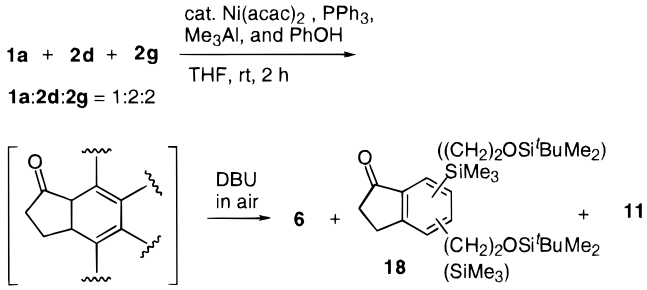
The cyclotrimerization of **1a** with **2d** and **2g** can be explained by the following mechanism (Scheme 4). The alkyne(s) **2d** and/or **2g** combine reversibly to the Ni(0) catalyst to give three intermediates, **13**, **14** (R = ^{t}BuMe$_2$SiO(CH$_2$)$_2$), and **19**. The reaction of **1a**−*Al* with these intermediates leads to the cycloadducts. When the reaction is carried out under higher temperature, **6**, **11b**, and **18** are all produced. The formation of **11b** would result from a shift in the equilibrium to thermodynamically favored **13b**. However, the product ratio of **6**, **11**, and **18** is essentially due to the kinetic preferences of the metallacycle intermediates. Thus, under lower temperature, **1a**−*Al* reacted rapidly with the most reactive **14a** to give **6a**, and the formation of **11b** derived from relatively inert **13b** was completely suppressed.

(18) Wakatsuki, Y.; Nomura, O.; Kitaura, K.; Morokuma, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 1907.

(19) HRMS data of **16**: $C_{17}H_{25}O_2Si$ (M^+ − Bu) Calcd, 289.1624; Found, 289.1612.

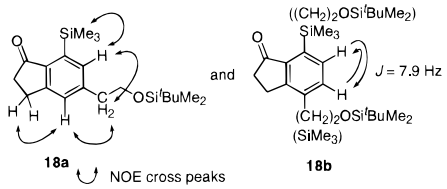
(20) The reaction did not occur at −20 °C to give the cycloadducts.

Table 3. Cyclotrimerization of **1a** with **2d** and **2g**[a]

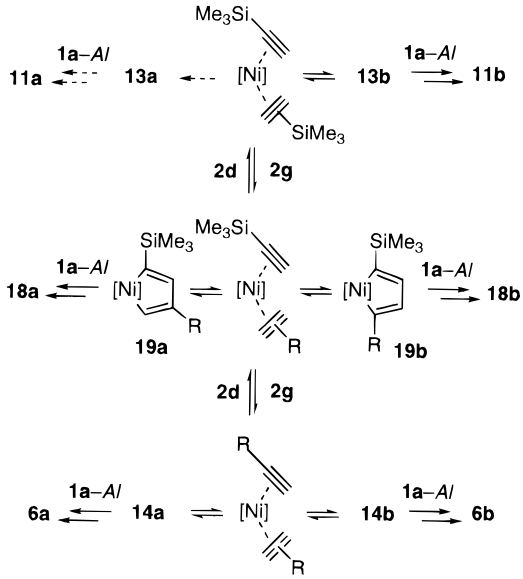


			yield,[b] %		
run	temp	time, h	**6** (**6a**:**6b**)	**18** (**18a**:**18b**)	**11** (**11a**:**11b**)
1	rt	2	42 (93:7)	28 (86:14)	0
2	−10 °C	2	50 (94:6)	15 (86:14)	0
3	50 °C	2	35 (93:7)	29 (81:19)	23 (0:100)

[a] Reaction conditions: Ni(acac)$_2$ (0.1 mmol), PPh$_3$ (0.2 mmol), Me$_3$Al (1.0 M in hexane, 0.7 mL), PhOH (2.0 mmol), **1a** (1.0 mmol), **2d** (2.0 mmol), and **2g** (2.0 mmol) in THF (5 mmol) under N_2 and followed by treatment with DBU in air. [b] Isolated yield based on **1a**.



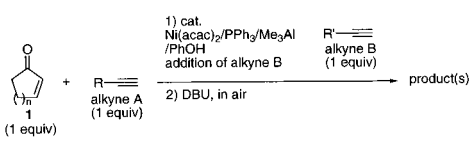
Scheme 4[a]

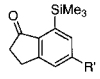
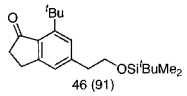
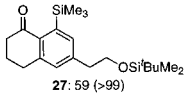
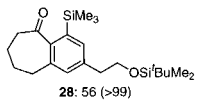


[a] [Ni] = Ni(PPh$_3$)$_2$, *Al* = Me$_n$Al(OPh)$_{3-n}$ (n = 0−3) R = (CH$_2$)$_2$OSi^{t}BuMe$_2$.

Since attempts to control the selective formation of the desired **18** failed under a variety of reaction temperatures and times, we focused on the most reactive **14a**. To suppress the formation of **14a** in situ, the concentration of **2d** in the reaction mixture should be kept low. To this end, when a THF solution of **2d** (1 equiv vs **1a**) was added dropwise over 2 h at room temperature to a mixture of **1a** and another alkyne **2g** (1 equiv vs **1a**), the desired product **18** was obtained predominantly (51% yield, see entry 1 in Table 4). Undesired **6** and **11b** were not detected. The major isomer **18a** (86% selectivity) was determined to be 5-[(2-*tert*-butyldimethylsilyl)oxyethyl]-7-(trimethylsilyl)-1-in-

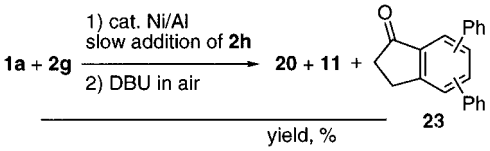
Table 4. Selective Cycotrimerization of Enones and Two Different Alkynes[a]



entry	enone **1**	alkyne A R	alkyne B R'	addition time h	product yield,[b] % (regioselectivity,[c] %)
					
1	**1a**: n = 1	**2g**: Me_3Si	**2d**: $^tBuMe_2SiO(CH_2)_2$	2	**18**: 51 (**18a**: 86)
2	**1a**: n = 1	**2g**: Me_3Si	**2a**: Bu	2	63 (83)
3[d]	**1a**: n = 1	**2g**: Me_3Si	**2h**: Ph	6	**20**: 52 (>99)
4[e]	**1a**: n = 1	**2g**: Me_3Si	**2i**: *p*-MeC_6H_4	4	**21**: 56 (>99)
5	**1a**: n = 1	**2g**: Me_3Si	**2j**: *p*-$MeOC_6H_4$	2	**22**: 60 (>99)
6	**1a**: n = 1	**2f**: ^tBu	**2d**: $^tBuMe_2SiO(CH_2)_2$	2	 46 (91)
7	**1b**: n = 2	**2g**: Me_3Si	**2d**: $^tBuMe_2SiO(CH_2)_2$	6	 **27**: 59 (>99)
8	**1c**: n = 3	**2g**: Me_3Si	**2d**: $^tBuMe_2SiO(CH_2)_2$	6	 **28**: 56 (>99)

[a] All reactions were carried out with the following procedure: a solution of alkyne B (1.0 mmol) in THF (6 mL) was added dropwise by syringe pump to the mixture of **1** (1.0 mmol), alkyne A (1.0 mmol), $Ni(acac)_2$ (0.1 mmol), PPh_3 (0.2 mmol), Me_3Al (1.0 M in hexane, 0.7 mL), and PhOH (2.0 mmol) in THF (4 mL) at room temperature, followed by treatment with DBU in air overnight. [b] Isolated yield based on **1**. [c] Determined by integration of the aryl protons of ^1H NMR. [d] Also see Table 5. [e] Also see Table 6.

Table 5. Cyclotrimerization of **1a** with **2g** and **2h**



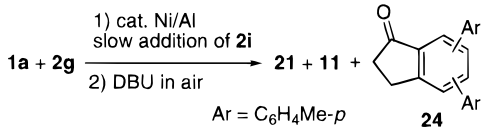
addition time	yield, % **20**	**11**	**23**
2 h	18	0	21
4 h	33	0	trace
6 h	52	0	0

danone, in which the trimethylsilyl group is adjacent to the carbonyl group, on the basis of spectral analyses.[21]

We explored the scope of the selective cyclotrimerization of a variety of enones **1** and two different alkynes with subsequent aromatization (Table 4). The reaction occurred when an alkyl- or aryl-substituted alkyne (alkyne B, 1 equiv vs **1**) was added slowly to a mixture of **1** and a bulkier alkyne such as **2f** and **2g** (alkyne A, 1 equiv vs **1**) at room temperature. Aryl-substituted acetylenes **2h**−**j** reacted with **1a** and **2g** to afford cycloadducts **20**−**22** as sole products, respectively (entries 3−5). When phenylacetylene (**2h**) was added dropwise over 2 h to a mixture of **1a** and **2g**, **20** was obtained along with undesired **23** (see Table 5). This reaction was overcome by an even slower addition (6 h) of **2h** (entry 3 in Table 4). The cycloadduct **21** was obtained effectively when *p*-methyl-substituted **2i** was added over 4 h (entry 4). Undesired **24** was not detected under these

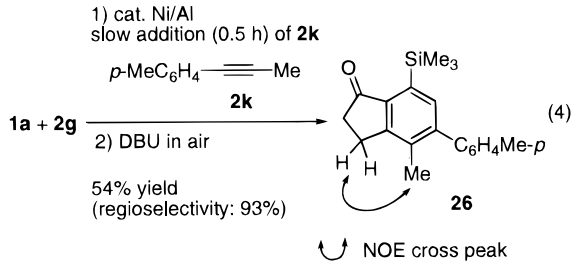
(21) Hoffmann's group previously predicted that the oxidative coupling with an alkyl-substituted alkyne and **2g** would give a metallacycle such as **18a** by the electronic factor control, see ref 17.

Table 6. Cyclotrimerization of **1a** with **2g** and **2i**



addition time	yield, % **21**	**11**	**24**
2 h	31	0	trace
4 h	56	0	0
6 h	24	0	0 + $(Me_3Si)_3C_6H_3$ (**25**)

reaction conditions. Prolonging the duration of addition to 6 h led to the formation of tris(trimethylsilyl)benzene (**25**) (see Table 6).[22] The presence of an electron-releasing group (e.g., *p*-Me or *p*-MeO group) on the arylacetylene tended to reduce the reactivity of the intermediate **14a** (R = *p*-MeC_6H_4 or *p*-$MeOC_6H_4$), compared with that of diphenyl-substituted **14a** (R = Ph). However, neither *p*-cyano- nor *p*-chlorophenylacetylenes gave corresponding cycloadducts. A biaryl product **26** was synthesized from the reaction with an aryl-substituted internal alkyne **2k** (eq 4). When the reaction was carried out with addition over



2 h, a small amount of **25** was also obtained. The alkyne **2f** instead of **2g** could also be used in the cyclotrimerization (entry 6). The reactions with six- and seven-membered cyclic enones **1b** and **1c** gave **27** and **28** as sole products, respectively (entries 7 and 8).

Conclusion

The reaction of **1** with **2** (only 2 equiv vs **1**) proceeded smoothly in the presence of nickel(0) species as a transition metal catalyst and aluminum phenoxide as a Lewis acid catalyst to give cycloadducts regioselectively. In particular, the first catalytic cyclotrimerization of three different unsaturated molecules was accomplished by reacting **1** and two different alkynes **2** and **2′** (ratio of the starting materials: **1**:**2**:**2′** = 1:1:1). This reaction should offer a solution to a long-standing problem in cyclotrimerization.

Experimental Section

General Comments. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. THF was distilled from sodium benzophenone ketyl under N_2. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Me_4Si as internal standard.

Typical Procedure (Entry 1 in Table 4). To a solution of $Ni(acac)_2$ (32 mg, 0.1 mmol) and PPh_3 (53 mg, 0.2 mmol) in THF (4 mL) were added Me_3Al (1.0 M in hexane, 0.8 mL) at 0 °C under N_2. After stirring for 5 min, PhOH (190 mg, 2.0 mmol) was added, and the mixture was stirred for 5 min. To the resulting dark red solution were added **2g** (100 mg, 1.0 mmol) and **1a** (84 mg, 1.0 mmol) at 0 °C. A THF solution

(22) van der Linden, A.; Schaverien, C. J.; Meijboom, N.; Ganter, C.; Orpen, A. G. *J. Am. Chem. Soc.* **1995**, *117*, 3008.

(6 mL) of **2d** (185 mg, 1.0 mmol) was added dropwise over 2 h by syringe pump to the reaction mixture with stirring at room temperature. After the addition was completed, the whole mixture was stirred at the same temperature for an additional 15 min. DBU (350 mg, 2.3 mmol) was added to this reaction mixture in air, and this was again stirred at room-temperature overnight. Aqueous HCl (0.2 M, 30 mL) was added, and stirring was continued for 10 min. The aqueous layer was extracted with ether. The combined organic layer was washed with $NaHCO_3$ and then with brine, dried over $MgSO_4$ for 30 min, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to yield a mixture of aromatic compounds **18** involving two different regioisomers (185 mg, 51%). The structure of the major isomer **18a** (regioselectivity: 86%) was determined by an NOE experiment (see text). An analytical sample was obtained by bulb-to-bulb distillation.

5-[(2-*tert*-Butyldimethylsilyl)oxyethyl]-7-(trimethylsilyl)-1-indanone (18a, entry 1 in Table 4): 86% isomeric purity; a colorless oil; bp 120 °C (2 mmHg); $R_f = 0.29$ (hexane:AcOEt = 14:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.03 (s, 6 H), 0.33 (s, 9 H), 0.85 (s, 9 H), 2.62−2.67 (m, 2 H), 2.88 (t, $J = 6.7$ Hz, 2 H), 3.08−3.12 (m, 2 H), 3.05 (t, $J = 6.7$ Hz, 2 H), 7.30 (br s, 1 H), 7.36 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.46, −1.05, 18.27, 25.82, 25.85, 36.10, 39.86, 64.03, 127.89, 135.15, 139.72, 139.82, 145.18, 155.92, 207.46; IR (film) 1711 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 362 (M^+, 0), 347 (M^+ − Me, 23), 305 (100). Anal. Calcd for $C_{20}H_{34}O_2Si_2$: C, 66.24; H, 9.45. Found: C, 66.00; H, 9.52.

5-Butyl-7-(trimethylsilyl)-1-indanone (entry 2 in Table 4): 83% regioselectivity; a colorless oil; bp 120 °C (1 mmHg); $R_f = 0.40$ (hexane:AcOEt = 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.33 (s, 9 H), 0.92−0.98 (m, 3 H), 1.35−1.45 (m, 2 H), 1.57−1.70 (m, 2 H), 2.61−2.70 (m, 4 H), 3.05−3.11 (m, 2 H), 7.25 (br s, 1 H), 7.33 (br s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −1.02, 13.89, 22.45, 25.84, 33.50, 36.08, 126.94, 134.39, 139.48, 139.78, 148.75, 156.12, 207.37; IR (film) 1711 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 260 (M^+, 16), 245 (100). Anal. Calcd for $C_{16}H_{24}OSi$: C, 73.79; H, 9.29. Found: C, 73.97; H, 9.24.

5-Phenyl-7-(trimethylsilyl)-1-indanone (20, entry 3 in Table 4): >99% regioselectivity; colorless crystal (MeOH); mp 112−113 °C; R_f = 0.23 (hexane:AcOEt = 14:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.39 (s, 9 H), 2.71 (t, $J = 6.0$ Hz, 2 H), 3.20 (t, $J = 6.0$ Hz, 2 H), 7.41−7,51 (m, 4 H), 7.62−7.65 (m, 2 H), 7.75 (br s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −1.00, 26.02, 36.23, 125.86, 127.57, 128.12, 128.91, 133.17, 140.52, 140.61, 140.68, 145.88, 156.26, 207.49; IR (disk) 1711 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 280 (M^+, 7), 265 (100). Ana1. Calcd for $C_{18}H_{20}OSi$: C, 77.09; H, 7.19. Found: C, 76.85; H, 7.37.

5-(4-Methylphenyl)-7-(trimethylsilyl)-1-indanone (21, entry 4 in Table 4): >99% regioselectivity; a colorless crystal (MeOH); mp 124−125 °C; $R_f = 0.26$ (hexane:AcOEt = 14:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.37 (s, 9 H), 2.42 (s, 3 H), 2.68−2.72 (m, 2 H), 3.16−3.21 (m, 2 H), 7.29 (d, $J = 8.1$ Hz, 2 H), 7.53 (d, $J = 8.1$ Hz, 2 H), 7.62 (br s, 1 H), 7.73 (br s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −1.00, 21.15, 26.02, 36.21, 125.55, 127.40, 129.65, 132.97, 137.74, 138.13, 140.29, 140.50, 145.80, 156.28, 207.46; IR (disk) 1705 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 294 (M^+, 12), 279 (100). Anal. Calcd for $C_{19}H_{22}OSi$: C, 77.50; H, 7.53. Found: C, 77.25; H, 7.65.

5-(4-Methoxyphenyl)-7-(trimethylsilyl)-1-indanone (22, entry 5 in Table 4): >99% regioselectivity; a colorless crystal (MeOH); mp 110−111 °C; $R_f = 0.17$ (hexane:AcOEt = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (s, 9 H), 2.70 (t, $J = 6.1$ Hz, 2 H), 3.18 (t, $J = 6.1$ Hz, 2 H), 3.87 (s, 3 H), 7.01 (d, $J = 8.8$ Hz, 2 H), 7.57 (d, $J = 8.8$ Hz, 2 H), 7.60 (br s, 1 H), 7.71 (br s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −1.00, 26.03, 36.23, 55.39, 114.40, 125.19, 128.67, 132.71, 133.04, 140.01, 140.52, 145.45, 156.34, 159.89, 207.39; IR (disk) 1705 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 310 (M^+, 25), 295 (100). Ana1. Calcd for $C_{19}H_{22}O_2Si$: C, 73.51; H, 7.14. Found: C, 73.53; H, 7.15.

5-[2-(*tert*-Butyldimethylsilyl)oxyethyl]-7-*tert*-butyl-1-indanone (entry 6 in Table 4): 91% regioselectivity; a pale yellow oil; bp 125 °C (2 mmHg); $R_f = 0.31$ (hexane:AcOEt = 14:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.03 (s, 6 H), 0.85 (s, 9 H), 1.44 (s, 9 H), 2.64−2.69 (m, 2 H), 2.86 (t, $J = 6.6$ Hz, 2 H), 3.03−3.07 (m, 2 H), 3.85 (t, $J = 6.6$ Hz, 2 H), 7.13 (br s, 1 H), 7.17 (br s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.43, 18.28, 25.62, 25.86, 29.72, 35.66, 37.53, 39.90, 63.93, 125.19, 126.08, 132.93, 146.37, 151.80, 158.86, 206.13; IR (film) 1705 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 346 (M^+, 0), 289 (M^+ − Bu, 100). Anal. Calcd for $C_{21}H_{34}O_2Si$: C, 72.78; H, 9.89. Found: C, 72.69; H, 10.18.

4-Methyl-5-(4-methylphenyl)-7-(trimethylsilyl)-1-indanone (26, eq 4): 93% regioselectivity; a colorless crystal (MeOH); mp 122−123 °C; $R_f = 0.37$ (hexane:AcOEt = 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.33 (s, 9 H), 2.25 (s, 3 H), 2.43 (s, 3 H), 2.72 (t, $J = 5.9$ Hz, 2 H), 3.07 (t, $J = 5.9$ Hz, 2 H), 7.23 (d, $J = 8.2$ Hz, 2 H), 7.27 (t, $J = 8.2$ Hz, 2 H), 7.42 (s, 1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ −0.92, 15.60, 21.21, 25.39, 36.23, 127.42, 128.95, 129.01, 129.65, 133.97, 136.09, 136.44, 137.11, 140.24, 155.63, 208.04; IR (disk) 1705 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 294 (M^+, 40), 293 (100). Ana1. Calcd for $C_{20}H_{24}OSi$: C, 77.87; H, 7.84. Found: C, 77.79; H, 7.76.

6-[2-(*tert*-Butyldimethylsilyl)oxyethyl]-8-(trimethylsilyl)-1-tetralone (27, entry 7 in Table 4): >99% regioselectivity; a pale yellow oil; bp 150 °C (2 mmHg); $R_f = 0.38$ (hexane:AcOEt = 14:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.03 (s, 6 H), 0.28 (s, 9 H), 0.85 (s, 9 H), 2.11 (quintet, $J = 6.3$ Hz, 2 H), 2.65 (t, $J = 5.9$ Hz, 2 H), 2.83 (t, $J = 6.8$ Hz, 2 H), 2.95 (t, $J = 5.9$ Hz, 2 H), 3.83 (t, $J = 6.8$ Hz, 2 H), 7.11 (br s, 1 H), 7.41 (br s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.44, 0.50, 18.28, 23.15, 25.86, 30.69, 39.41, 39.63, 63.95, 130.61, 135.22, 142.95, 143.81, 144.99, 198.76; IR (film) 1682 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 376 (M^+, 0), 361 (M^+ − Me, 97), 319 (100), 229 (23). Anal. Calcd for $C_{21}H_{36}O_2Si_2$: C, 66.96; H, 9.63. Found: C, 66.68; H, 9.72.

7-[(2-*tert*-Butyldimethylsilyl)oxyethyl]-9-(trimethylsilyl)-1-benzosuberone (28, entry 8 in Table 4): >99% regioselectivity; a colorless oil; bp 150 °C (1 mmHg); $R_f = 0.33$ (hexane:AcOEt = 14:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.03 (s, 6 H), 0.25 (s, 9 H), 0.85 (s, 9 H), 1.74−1.85 (m, 4 H), 2.60−2.65 (m, 2 H), 2.74−2.83 (m, 4 H), 3.82 (t, $J = 6.8$ Hz, 2 H), 6.98 (br s, 1 H), 7.33 (br s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.42, 0.37, 18.29, 21.54, 25.23, 25.89, 32.28, 39.45, 41.53, 64.18, 130.78, 134.42, 138.11, 139.79, 141.35, 143.83, 211.41; IR (film) 1682 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 390 (M^+, 0), 375 (M^+ − Me, 64), 333 (100). Anal. Calcd for $C_{21}H_{36}O_2Si_2$: C, 67.63; H, 9.80. Found: C, 67.50; H, 9.80.

5,7-Diphenyl-1-indanone (23): >99% regioselectivity; a colorless crystal; mp 148 °C; $R_f = 0.28$ (hexane:AcOEt = 3:1);^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71−2.75 (m, 2 H), 3.20 (t, $J = 6.2$ Hz, 2 H), 7.38−7.51 (m, 9 H), 7.64−7.67 (m, 3 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 25.44, 37.14, 123.96, 127.47, 127.77, 127.90, 128.38, 128.86, 128.94, 129.35, 131.98, 138.02, 139.92, 141.80, 146.88, 157.13, 205.05; IR (disk) 1711 cm^{-1}; DI/MS (EI, 70 eV) *m*/*z* (rel int) 284 (M^+, 86), 283 (100). Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.73; H, 5.88.

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