Nickel-Catalyzed Diastereodifferentiative Tandem Coupling of α,β-Enones, Norbornenes, and Organometallics

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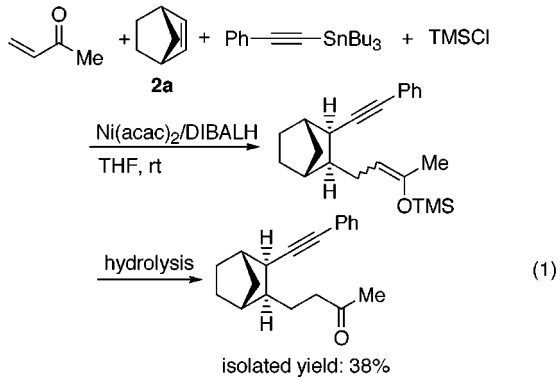
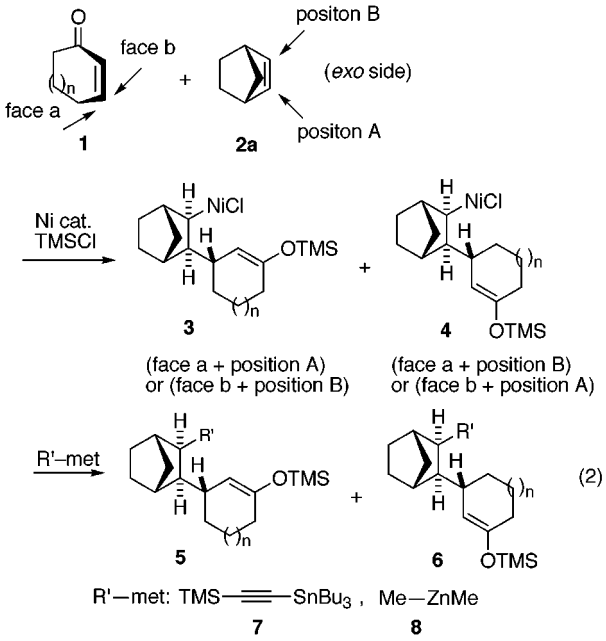
Received December 16, 1997

We recently found that a tandem reaction of α,β-enones **1**, alkynes, organotin or organozinc, and chlorotrimethylsilane (TMSCl) regio- and stereoselectively gave the coupling products in the presence of nickel catalyst.[1] We have since been interested in examining this reaction with alkenes in place of alkynes. While cycloalkenes such as cyclopentene and cyclohexene did not react in the presence of a nickel catalyst, the reaction of 2-norbornene (**2a**, 1.1 equiv) with methyl vinyl ketone (1 equiv), (phenylethynyl)tributyltin (1.2 equiv), and TMSCl (1.2 equiv) occurred at room temperature in THF to give the corresponding coupling product (eq 1).[2] When a cyclic enone **1** is applied to the reaction with **2**, either intermediate **3** or **4** preferentially should be formed to give a diastereomeric product **5** or **6** (eq 2). We report here a new example of a diastereodifferentiative reaction.[3]



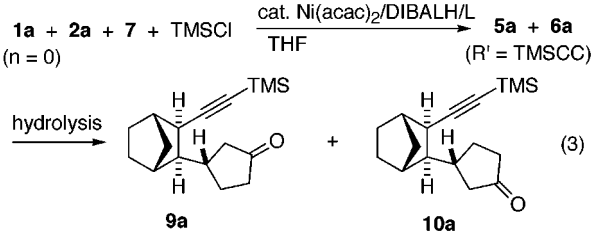
(1)

This nickel-catalyzed (5 mol %) reaction of **2a** (1.1−3.0 equiv) with 2-cyclopenten-1-one (**1a**) (1.0 equiv), tributyl[(trimethylsilyl)ethynyl]tin (**7**) (1.2 equiv), and TMSCl (1.2 equiv) in THF (5 mL) only occurred in the presence of pyridine (10 mol %) at reflux to give a coupling product **5a** or **6a** (eq 3). After hydrolysis of the resulting enol silyl ether **5a** or **6a** by treatment with aqueous acid, a corresponding carbonyl compound **9a** or **10a** was isolated as only one isomer (>98% diastereomeric excess (de) by capillary GLC analyses) by silica gel column chromatography. The structure was determined to be **9a** by X-ray crystallographical analysis. While the use of 2,2′-bipyridine (5 mol %) instead of pyridine was not efficient, 4-isopropyl-2-(2-pyridinyl)-2-oxazoline (**11**)[4] (5 mol %) improved the yield of **9a** to 76% (>98% de). When (*S*)-**11** was used, the resulting **9a** showed optical



(2)

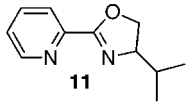
activity ($[\alpha]^{25}_D$ −8.8° (*c* 0.56, $CHCl_3$)), and the enantiomeric excess (ee) was determined to be 6% by GLC analysis of a diastereomeric mixture of dioxolane **12**



(3)

1a/2a	L	condition	isolated yield
1:1.1	Py	rt, 24 h	0%
1:1.1	Py	reflux, 4 h	22% (**9a**/**10a** = 99:1)
1:3	Py	reflux, 4 h	31% (**9a**/**10a** = 99:1)
1:1.3	Bipy	reflux, 4 h	<20%
1:1.3	**11**	reflux, 2 h	76% (**9a**/**10a** = 99:1)

Py: pyridine, Bipy: 2,2'-bipyridine



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prepared from optically active **9a** and (2*R*,3*R*)-2,3-bu-

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(1) (a) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. (b) Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. *Organometallics* **1995**, *14*, 5015. (c) Ikeda, S.; Kondo, K.; Sato, Y. *J. Org. Chem.* **1996**, *61*, 8248. Also see: Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099. Montgomery, J.; Seo, J.; Chui, H. M. P. *Tetrahedron Lett.* **1996**, *37*, 6839. Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911.

(2) For recent examples of *nonselective* Pd-catalyzed coupling of **2** with carbon nucleophiles and organoelectrophiles, see: Torii, S.; Okumoto, H.; Ozaki, M.; Nakayasu, S.; Kotani, T. *Tetrahedron Lett.* **1990**, *31*, 5319. Kosugi, M,; Kimura, T.; Oda, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3522. Oda, H.; Kobayashi, T.; Kosugi, M.; Migita, T. *Tetrahedron* **1995**, *51*, 695.

(3) The diastereodifferentiative coupling of **2** with *a chiral center-containing* alkenyl iodide and carbon nucleophiles by Pd catalyst are reported. Torii, S.; Okumoto, H.; Ozaki, H.; Nakayasu, S.; Tadokoro, T.; Kotani, T. *Tetrahedron Lett.* **1992**, *33*, 3499. Torii, S.; Okumoto, T.; Kotani, T.; Nakayasu, S.; Ozaki, H. *Tetrahedron Lett.* **1992**, *33*, 3503.

(4) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499. Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173.

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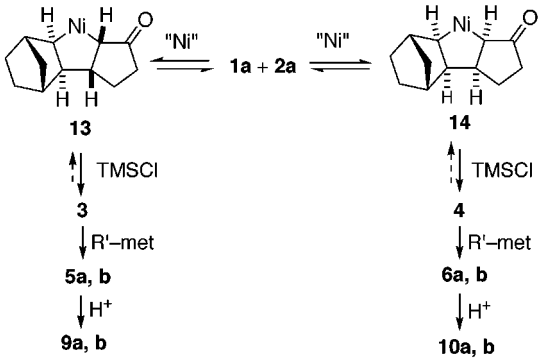
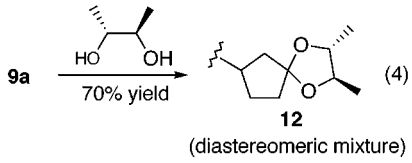
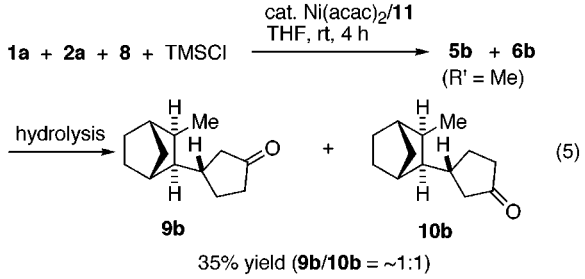
Scheme 1



tanediol (eq 4).



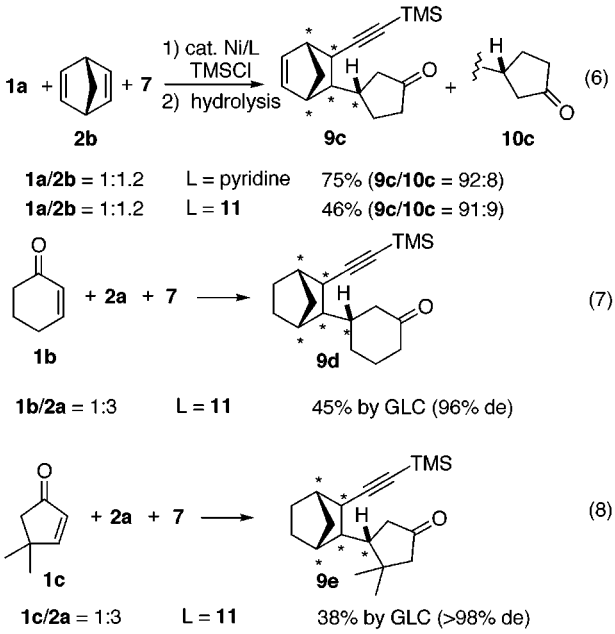
Interestingly, when the reaction of **1a** with **2a** and dimethylzinc (**8**) was carried out at room temperature, both coupling products **9b** and **10b**, which were derived from **5b** and **6b**, were obtained as a diastereomeric mixture (eq 5). Varying the reaction conditions and ligands did not improve diastereoselectivity.



Although the detail is unclear, these remarkable differences are explained by noting the following mechanism (Scheme 1). The kinetic mixture of both nickelacyclopentane intermediates **13** and **14** is initially formed by **1a**, **2a**, and the nickel species.[1c,5] The subsequent thermodynamic equilibration between **13** and **14** would control the mutual recognition between the enantiotopic face of **1a** and the enantiotopic position of **2a**, causing diastereodifferentiative coupling.[6] Since the reaction with an alkynltin **7** takes place at reflux, complete equilibration to the more thermodynamically favored intermediate **13** (or **3**) leads to the formation of a single isomer of the coupling product **5a** (i.e., hydrolyzed product **9a**). On the other hand, the reaction of **1a** with **2a** and **8** occurred at room temperature to give a diastereomeric mixture of **5b** (i.e., hydrolyzed product **9b**) and **6b** (i.e., hydrolyzed product **10b**). This means that the coupling reaction with **8** would proceed under conditions of kinetic control.[7,8]

(5) Ikeda, S.; Mori, N.; Sato, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4779.
(6) The equilibration would also occur at the conversion(s) of **13** (and **14**) to **3** (and **4**).
(7) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 3182. Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4424.

The results of diastereodifferentiative coupling of a variety of combinations of **1a**−**c** and **2a,b** with **7** are shown in eqs 6−8. The reaction with 2,5-norbornadiene (**2b**) effectively occurred in the presence of pyridine rather than **11** to give **9c** (75% yield, 84% de) (eq 6). Both a six-membered cyclic enone **1b** and a substituted cyclic enone **1c** reacted diastereoselectively with **2a** to give the corresponding products **9d** and **9e**, respectively (eqs 7 and 8).



In summary, we have shown the diastereodifferentiative tandem coupling of enones **1**, norbornenes **2**, alkynyltin **7**, and TMSCl in the presence of nickel catalyst. The present reaction has the potential to create new contiguous chiral carbon centers (asterisked carbons in eqs 3 and 6−8) by causing mutual recognition between the enantiotopic face of **1** and the enantiotopic position of **2** in a one-pot assembly.

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.

General Procedure. To a solution of $Ni(acac)_2$ (0.05 mmol) and ligand (0.05−0.1 mmol) in THF (5 mL) was added DIBALH in a 1.0 M hexane solution (0.06 mL) at 0 °C under N_2 and the resulting solution stirred for 5 min. To this solution were added tributyl[(trimethylsilyl)ethynyl]tin (**7**) (1.1 mmol), norbornene **2** (1.1−3.0 mmol), α,β-enone **1** (1.0 mmol), and chlorotrimethylsilane (1.2 mmol) at 0 °C, and then the mixture was stirred at reflux for 2−4 h. To this was added aqueous acid (2 mL, acetone/HCl(aq) = 5:1), and it was again stirred at room temperature for 15 min; aqueous NH_4F (30 mL) was then added and stirring continued for 30 min to remove the chlorotributyltin. After filtration through Celite, the aqueous layer was extracted with Et_2O (30 mL × 3). The combined organic layers were washed with aqueous $NaHCO_3$ (50 mL) and then with brine (50 mL), dried over $MgSO_4$ for 30 min, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel) to yield product **9**. The diastereoselectivities of the obtained

(8) For a direct comparison with eq 3, the reaction with dialkynylzinc prepared from lithium (trimethylsilyl)acetylide and $ZnCl_2$ was carried out. However, a complex mixture was obtained, and the desired product(s) **9a** and/or **10a** could not be detected.

products were determined by capillary GLC. An analytical sample was obtained by bulb-to-bulb distillation or recrystallization.

4-[3-(phenylethynyl)bicyclo[2.2.1]hept-2-yl]butan-2-one: >98% isomeric purity; a pale yellow oil; bp 150 °C (2 mmHg); R_f = 0.35 (hexane/AcOEt = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (dt, J = 10.4, 1.8 Hz, 1 H), 1.19−1.22 (m, 2 H), 1.50−1.56 (m, 3 H), 1.60−1.67 (m, 1 H), 1.71−1.79 (dt, J = 10.4, 1.8 Hz, 1 H), 1.88−1.95 (m, 1 H), 2.00 (s, 1 H), 2.11 (s, 3 H), 2.41 (s, 1 H), 2.41−2.49 (m, 1 H), 2.61−2.64 (m, 1 H), 2.66 (d, J = 9.1 Hz, 1 H), 7.23−7.28 (m, 5 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 27.15, 28.16, 29.91, 30.02, 34.24, 39.26, 41.62, 43.32, 44.79, 45.39, 82.67, 91.48, 124.07, 127.42, 128.18, 131.40, 209.32; IR (neat) 2955, 1716, 768 cm^{-1}; GC/MS (EI, 70 eV) m/z (rel intensity) 266 (M^+, 70), 115 (100). Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.57; H, 8.45.

(3*R,1′*S**,2′*S**,3′*S**,4′*R**)-3-[3′**-[(Trimethylsilyl)ethynyl]bicyclo[2.2.1]hept-2′-yl]cyclopentanone (9a): 98% de; a colorless crystal (hexane); mp 53.5−54.5 °C; R_f = 0.31 (hexane/AcOEt = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 9 H), 1.11−1.17 (c, 3 H), 1.42 (t, J = 9.2 Hz, 1 H), 1.48−1.60 (c, 3 H), 1.66−1.70 (m, 1 H), 1.73 (ddd, J = 18.0, 9.4, 1.5 Hz, 1 H), 2.08−2.17 (m, 1 H), 2.20−2.30 (c, 4 H), 2.36 (br s, 1 H), 2.48 (dd, J = 8.6, 1.2 Hz, 1 H), 2.76 (ddt, J = 18.0, 6.7, 1.2 Hz, 1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 0.02, 27.28, 28.95, 30.48, 34.39, 38.41, 38.51, 39.11, 39.59, 44.95, 46.02, 52.94, 86.14, 109.21, 219.86; IR (neat) 2959, 2164, 1742, 1249, 843, 760, 637 cm^{-1}; GCMS (EI, 70 eV) m/z (rel intensity) 274 (M^+, 3), 259 (100). Anal. Calcd for $C_{17}H_{26}$OSi: C, 74.39; H, 9.55. Found: C, 74.20; H, 9.58.

(3*R,1′*S**,2′*S**,3′*S**,4′*R**)- and (3*S**,1′*S**,2′*S**,3′*S**,4′*R**)-3-(3′-Methyl[2.2.1]hept-2′-yl)cyclopentanone (9b and 10b):** 1:1 mixture; a colorless oil; bp 125 °C (1 mmHg); R_f = 0.28 (hexane/AcOEt = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, J = 7.3 Hz, 1.5 H), 0.96 (d, J = 7.3 Hz, 1.5 H), 0.90−1.28 (c, 3 H), 1.33−1.63 (c, 8 H), 1.70−2.51 (c, 6 H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 16.38, 16.62, 29.03, 29.11, 29.66, 30.49, 30.67, 31.17, 32.77, 32.95, 37.00, 37.29, 38.33, 38.55, 39.34, 40.35, 40.40, 40.50, 45.01, 45.05, 45.17, 47.00, 52.26, 53.73, 219.74, 220.29; IR (neat) 2955, 2872, 1741, 1462, 1165, 733 cm^{-1}; GC/MS (EI, 70 eV) m/z (rel intensity) 192 (M^+, 59), 109 (100). Anal. Calcd for $C_{13}H_{20}$O: C, 81.20; H, 10.48. Found: C, 81.17; H, 10.51.

(3*R,1′*S**,4′*R**,5′*R**,6′*R**)-3-[6′-[(Trimethylsilyl)ethynyl]bicyclo[2.2.1]hepten-5′-yl]cyclopentanone (9c):** 84% de; a colorless oil; bp 80 °C (1.5 mmHg); R_f = 0.37 (hexane/AcOEt = 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 9 H), 1.37−1.45 (m, 2 H), 1.56−1.67 (m, 1 H), 1.72−1.83 (c, 2 H), 2.08−2.23 (m, 1 H), 2.24−2.38 (c, 4 H), 2.82 (br s, 1 H), 2.89 (dd, J = 18.6, 7.5 Hz, 1 H), 2.95 (br s, 1 H), 6.06 (dd, J = 8.5, 3.1 Hz, 1 H), 6.16 (dd, J = 8.5, 3.1 Hz, 1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 0.04, 28.94, 34.58, 38.44, 39.62, 44.02, 46.29, 49.52, 50.45, 85.16, 109.67, 135.75, 138.62, 219.76; IR (neat) 2959, 2164, 1744, 1460, 1250, 1161, 845, 760, 710 cm^{-1}; GC/MS of major (EI, 70 eV) m/z (rel intensity) 272 (M^+, 6), 207 ($M^+ - C_5H_5$, 29), 191 (52), 73 (40), 66 (100); GC/MS of minor (EI, 70 eV) m/z (rel intensity) 272 (M^+, 13), 257 (M^+ − Me, 59), 73 (100); HRMS for $C_{12}H_{19}$OSi ($M^+ - C_5H_5$) calcd 207.1205, found 207.1215.

(3*R,1′*S**,2′*S**,3′*S**,4′*R**)-3-[3′-[(Trimethylsilyl)ethynyl]bicyclo[2.2.1]hept-2′-yl]cyclohexanone (9d):** 96% de; a pale yellow oil; bp 120 °C (1 mmHg); R_f = 0.40 (hexane/AcOEt = 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 9 H), 1.08−1.19 (c, 3 H), 1.30 (t, J = 7.7 Hz, 1 H), 1.42−1.55 (c, 3 H), 1.61−1.71 (c, 2 H), 1.96−2.12 (c, 4 H), 2.21−2.38 (c, 4 H), 2.52 (dd, J = 8.4 Hz, 1 H), 2.69 (m, 1 H); ^{13}C NMR (125.4 MHz, $CDCl_3$) δ 0.05, 24.82, 27.79, 29.39, 31.06, 34.69, 37.57, 39.57, 39.93, 41.45, 44.70, 48.26, 50.93, 86.60, 108.57, 211.70; IR (neat) 2955, 2874, 2162, 1713, 1250, 843, 760 cm^{-1}; GC/MS (EI, 70 eV) m/z (rel intensity) 288 (M^+, 3), 273 (100). Anal. Calcd for $C_{18}H_{28}$OSi: C, 74.94; H, 9.78. Found: C, 74.56; H, 9.57.

(4*R,1′*S**,2′*S**,3′*S**,4′*R**)-3,3-Dimethyl-4-[3′-[(trimethylsilyl)ethynyl]bicyclo[2.2.1]hept-2′-yl]cyclopentanone (9e):** >98% de; a colorless oil; bp 130 °C (1 mmHg); R_f = 0.36 (hexane/AcOEt = 10:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.09 (s, 9 H), 0.97 (s, 3 H), 1.11−1.18 (c, 3 H), 1.33 (s, 3 H), 1.43−1.54 (c, 3 H), 1.63−1.87 (c, 2 H), 2.03−2.23 (c, 3 H), 2.36−2.49 (c, 3 H), (dd, J = 19.0, 8.0 Hz, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 0.02, 21.96, 27.55, 30.42, 30.78, 34.31, 38.65, 39.01, 40.31, 44.85, 45.48, 47.35, 50.62, 57.23, 86.13, 109.52, 218.18; IR (neat) 2961, 2874, 2164, 1741, 1250, 841 cm^{-1}; GC/MS (EI, 70 eV) m/z (rel intensity) 302 (M^+, 4), 287 (100); HRMS for $C_{18}H_{27}$OSi (M^+ − Me) calcd 287.1831, found 287.1825.

Preparation of Dioxolane 12. Ketone **9a** ($[\alpha]^{25}_D$ −8.8° (*c* 0.56, $CHCl_3$), 68 mg, 0.25 mmol), (2*R*,3*R*)-2,3-butanediol (120 mg, 1.332 mmol), and *p*-toluenesulfonic acid (8 mg, 0.04 mmol) were placed in a 30-mL round-bottom flask and dissolved in 20 mL of dry toluene. The flask was fit with a Dean−Stark trap, and the mixture was refluxed for 24 h. The solution was concentrated, and the product was purified by silica gel chromatography (hexane/AcOEt = 10:1) to give dioxolane **12** (60 mg) in 70% yield. This procedure was repeated with racemic ketone **9a**, which provided racemic dioxolane **12**. The optically active ketone **9a** obtained from the nickel-catalyzed coupling reaction in the presence of (*S*)-**11** was determined to be 6% ee by capillary GLC analysis of both diastereomers of dioxolane **12**. Spectral data for **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 9 H), 1.04−2.11 (c, 20 H), 2.25−2.50 (m, 3 H), 3.45−3.58 (m, 2 H); IR (neat) 2961, 2872, 2166, 1249, 1097, 842, 760 cm^{-1}; GCMS (EI, 70 eV) m/z (rel intensity) 346 (M^+, 38), 127 (100); HRMS for $C_{21}H_{34}O_2$Si (M^+) calcd, 346.2328, found, 346.2335.

Acknowledgment. D.M.C. was supported by the Ministry of Education, Science and Culture, Japan.

Supporting Information Available: Copies of ^{13}C NMR spectra for **9c** and **9e** and X-ray crystallographic details for **9a** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO972278O

Additions and Corrections

Volume 63, 1998

A. Sofia E. Karlström, Magnus Rönn, Atli Thorarensen, and Jan-E. Bäckvall*. A Versatile Route to 2-Substituted Cyclic 1,3-dienes via a Copper(I)-Catalyzed Cross-Coupling Reaction of Dienyl Triflates with Grignard Reagents.

Page 2522. The number of pages of Supporting Information should be changed from 14 to 28.

JO984983I

S0022-3263(98)04983-4
Published on Web 04/17/1998