Synthesis of 2-Substituted Cyclohexene Derivatives through Cross-Coupling Reactions via π-Allylmetal Intermediate Using N-Heterocyclic Carbenes (NHCs) as Ligands

Tetsuro Yamazaki, Yoshihiro Sato*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan
Fax +81(11)7064982; E-mail: biyo@pharm.hokudai.ac.jp

Received 8 July 2008

Abstract: Palladium- or nickel-catalyzed cross-coupling reactions of 2-substituted cyclohexenes, which are generally less reactive than those having no substituent at the C2 position, with organotin reagents (Migita–Kosugi–Stille coupling) or with Grigard reagents (Kumada–Tamao–Corriu coupling) using a NHC as a ligand was investigated. It was found that NHCs are effective as ligands for these reactions, giving the corresponding cross-coupling products in good yields.

Key words: N-heterocyclic carbene (NHC), cross-coupling, Migita–Kosugi–Stille reaction, Kumada–Tamao–Coriiu reaction, palladium, nickel

Cyclohexene derivatives **1**, having a substituent at the C2 position on the alkene, are useful synthetic intermediates for various natural products.[1] We have already reported syntheses of natural products from cyclohexene derivatives, including the synthesis of (–)-mesembrine from **1a**[1a] and the syntheses of (–)-tubifoline[1d,f] and (–)-strychine[1e,f] from **1b**, respectively (Figure 1).

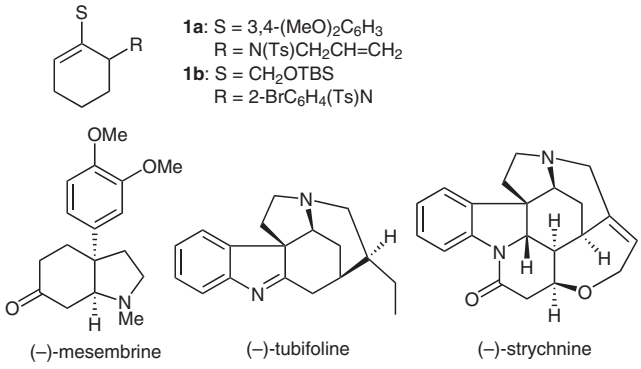
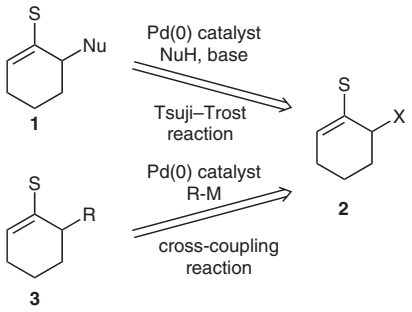


Figure 1 Synthetic utility of 2-substituted cyclohexenes

In the previous syntheses, the desired 2-substituted cyclohexene derivatives **1a** and **1b** were synthesized via palladium-catalyzed Tsuji–Trost reaction of allylic substrate **2** and nucleophiles in the presence of a base (Scheme 1).[2]

The versatility of 2-substituted cyclohexenes as a useful synthon prompted us to develop an alternative route to synthesize such compounds **3** via cross-coupling reaction of **2** and an organometallic reagent (R-M). Cross-coupling reactions are widely used to form C–C bonds in the field of synthetic organic chemistry.[3] Recently, N-heterocyclic carbenes (NHCs) have been found to be very effective as ligands for various cross-coupling reactions.[4] Thus, we decided to investigate the utility of NHCs for the cross-coupling reaction between 2-substituted allylic substrate **2** and organometallic reagents.



Scheme 1 Synthetic route for 2-substituted cyclohexenes

Although there have been a number of studies on transition-metal-catalyzed cross-coupling reactions using NHC ligands between an sp^2 carbon center in the substrate (e.g., aryl halide, vinyl halide) and various organometallic reagents, examples of the reactions between allylic substrates and organometallic reagents are limited. In addition, our previous studies on the palladium-catalyzed Tsuji–Trost reaction of 2-substituted allylic substrates **2** revealed that the reactivity of **2** is relatively low due to the bulkiness of the C2 substituent compared to those having no substituent at C2 position. Herein we report a palladium-catalyzed cross-coupling reaction of **2** with an organotin reagent (Migita–Kosugi–Stille coupling)[5] and a nickel-catalyzed cross-coupling reaction of **2** with a Grigard reagent (Kumada–Tamao–Corriu coupling)[6] using an NHC as a ligand.

Initially, we investigated the cross-coupling reaction of 2-substituted cyclohexene derivative **2a** with tributyl(phenyl)stannane using various Pd–NHC complexes, generated in situ from $Pd_2dba_3{\cdot}CHCl_3$ (1.5 mol%) and various imidazolium salts as precursors of the NHC in the presence of cesium carbonate (Table 1, Figure 2). A tetrahydrofuran solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (1.5 mol%), triphenylphosphine (3.0 mol%), and 1,3-dimesityl-4,5-dihydro-1*H*-imidazolium hydrochloride (IMes·HCl, 3.0

SYNTHESIS 2008, No. 17, pp 2830–2834
Advanced online publication: 06.08.2008
DOI: 10.1055/s-2008-1067222; Art ID: C04008SS

mol%) was stirred at 50 °C for 10 minutes. To the $Pd(PPh_3)(NHC)$ catalyst solution was added a tetrahydrofuran solution of **2a** and tributyl(phenyl)stannane and the mixture was stirred at 50 °C for 132 hours. After the usual workup, the desired coupling product **3a** was obtained in 64% yield along with β-eliminated product **4** in 9% yield (Table 1, entry 1). The use of IPr and the use of SIPr under similar conditions improved the yields of **3a** to 86% and 77%, respectively (Table 1, entries 2 and 3). NHCs having an alkyl substituent on the nitrogen in the imidazole ring such as I^{t}Bu or I^{i}Pr were less effective for the coupling reaction (Table 1, entries 4 and 5). The cross-coupling reaction using a Pd–IPr catalyst prepared from $Pd_2(dba)_3{\cdot}CHCl_3$ (1.5 mol%), IPr·HCl (3.0 mol%), and cesium carbonate in the absence of triphenylphosphine gave the best result, providing **3a** in 90% yield (Table 1, entry 6). On the other hand, the reaction of **2a** with tributyl(phenyl)stannane using triphenylphosphine instead of NHCs gave **3a** in 76% yield (Table 1, entry 7), indicating that the NHC ligand is superior to the phosphorus ligand in this reaction system.

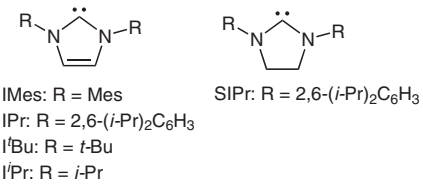
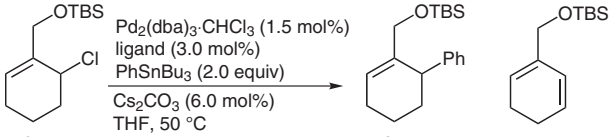


Figure 2 NHC ligands used

Table 1 Cross-Coupling Reaction of **2a** with Tributyl(phenyl)stannane

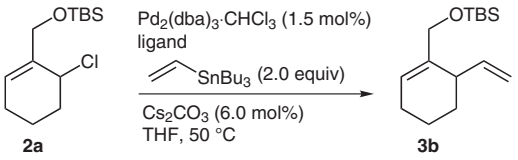


Entry	Ligand	Time (h)	Yield (%)	
			3a	**4**
1[a]	IMes	132	64	9
2[a]	IPr	113	86	–
3[a]	SIPr	138	77	5
4[a]	I^{t}Bu	36	–	12
5[a]	I^{i}Pr	129	67	6
6[b]	IPr	144	90	7
7[c]	Ph_3P	75	76	–

[a] Reaction conditions: $Pd(PPh_3)(NHC)$ complex generated in situ from $Pd_2(dba)_3{\cdot}CHCl_3$ (1.5 mol%), imidazolium salts (3.0 mol%), Ph_3P (3.0 mol%), Cs_2CO_3 (6.0 mol%), THF, 50 °C, 10 min.
[b] Pd–IPr complex generated in situ from $Pd_2(dba)_3{\cdot}CHCl_3$ (1.5 mol%), IPr·HCl (3.0 mol%), Cs_2CO_3 (6.0 mol%).
[c] In the absence of Cs_2CO_3.

Next, the reactions of **2a** with vinylstannane were investigated, and the results are shown in Table 2. The reaction of **2a** with tributyl(vinyl)stannane using triphenylphosphine gave the desired product **3b** in 55% yield along with β-eliminated product **4** in 20% yield (Table 2, entry 1). In this reaction system, the use of NHCs gave superior results. Thus, the reaction using a mixed ligand complex, $Pd(PPh_3)(NHC)$, formed from $Pd_2(dba)_3{\cdot}CHCl_3$ (1.5 mol%), triphenylphosphine (3.0 mol%), and IPr·HCl (3.0 mol%) in the presence of cesium carbonate, produced **3b** in 71% yield (Table 2, entry 2).

Table 2 Cross-Coupling Reaction of **2a** with Tributyl(vinyl)stannane



Entry	Ligand (mol%)	Time (h)	Yield (%)	
			3b	**4**
1[a]	Ph_3P (6.0)	84	55	20
2	IPr–PPh_3 (3.0:3.0)	84	71	20
3	IPr (3.0)	90	74	4

[a] Reactions were carried out in the absence of Cs_2CO_3.

In the reaction of **2a** with tributyl(vinyl)stannane using a Pd–IPr catalyst prepared from $Pd_2(dba)_3{\cdot}CHCl_3$, IPr·HCl, and cesium carbonate in the absence of triphenylphosphine, the yield of **3b** was improved to 74% (Table 2, entry 3).

The reaction of **2a** with functionalized tributyl(1-ethoxyvinyl)stannane (**5**) would provide the coupling product **3c**, which could be converted into methyl ketone derivatives and should be a useful synthon. In the reaction of **2a** with **5** using triphenylphosphine as a ligand, however, the desired product **3c** was not obtained, only isomerized product **6** (Figure 3) was obtained in 25% yield (Table 3, entry 1). On the other hand, the reaction using a mixed ligand complex, $Pd(PPh_3)(NHC)$, gave the desired product **3c** in 50% yield along with β-eliminated product **4** (3%) and **6** (8%) (Table 3, entry 2). The use of Pd–IPr was less effective in this reaction system, giving **3c** in 22% yield (Table 3, entry 3). Although the yield of **3c** was still modest, these results suggest the superiority of NHCs to the phosphorus ligand in the Migita–Kosugi–Stille coupling reaction of 2-substituted cyclohexenes.

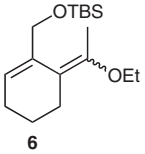
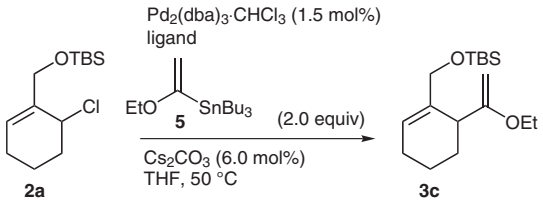


Figure 3

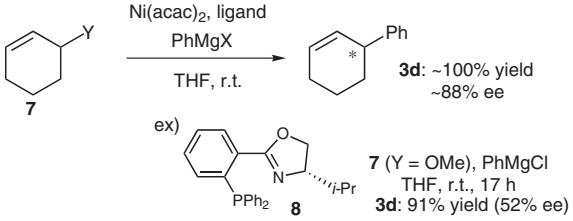
Table 3 Cross-Coupling Reaction of **2a** with Tributyl(1-ethoxyvinyl)stannane



Entry	Ligand (mol%)	Time (h)	Yield (%)	
			3c	**4**
1[a,b]	Ph_3P (6.0)	84	–	–
2[b]	IPr–PPh_3 (3.0:3.0)	84	50	3
3	IPr (3.0)	90	22	5

[a] Reactions were carried out in the absence of Cs_2CO_3.
[b] Byproduct **6** was also obtained in 25% (entry 1) or 8% yield (entry 2).

Next, we turned our attention to the synthesis of 2-substituted cyclohexenes through a nickel-catalyzed Kumada–Tamao–Corriu coupling reaction. Recently, Uemura and co-workers have reported an asymmetric Kumada–Tamao–Corriu coupling reaction of simple cyclohexene derivatives **7** with Grignard reagents using nickel complexes (Scheme 2).[7]

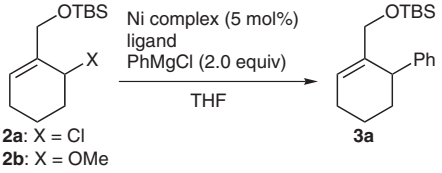


Scheme 2 Asymmetric Kumada–Tamao–Corriu coupling reaction of nonsubstituted cyclohexene derivatives reported by Uemura and co-workers

In their study, the yield and enantiomeric excess of **3d** varied up to 100% yield and 88% ee, depending on the reaction conditions and the properties of the ligands. For example, the reaction of **7** (Y = OMe) with phenylmagnesium chloride using $Ni(acac)_2$ (5 mol%) and chiral ligand **8** gave the product **3d** in 91% yield and 52% ee. However, the reaction of the corresponding 2-substituted cyclohexene derivative **2b** with phenylmagnesium chloride under the same conditions did not give the coupling product **3a**, indicating the low reactivity of 2-substituted cyclohexene substrates toward this cross-coupling reaction (Table 4, entry 1).

Thus, combinations of catalyst and ligand were screened in the reaction of **2a** or **2b** with phenylmagnesium chloride, and the results are summarized in Table 4. The reaction of **2b** with phenylmagnesium chloride in the presence of $Ni(acac)_2$ (5 mol%) and triphenylphosphine (20 mol%) also gave no desired product **3a** (Table 4, entry 2). The

Table 4 Nickel-Catalyzed Cross-Coupling Reaction of 2-Substituted Cyclohexenes **2** with Phenylmagnesium Chloride



Entry	Substrate	Catalyst, ligand (mol%)	Conditions	Yield (%)	
				3a	**9**
1[a]	**2b**	$Ni(acac)_2$, **8** (10)	r.t., 17 h	–	–
2[a]	**2b**	$Ni(acac)_2$, Ph_3P (20)	r.t., 17 h	–	–
3[a,b]	**2b**	$Ni(cod)_2$, IPr–PPh_3 (5:5)	r.t., 48 h	–	–
4	**2a**	$Ni(cod)_2$, Ph_3P (10)	r.t., 2 h	38	35
5[b]	**2a**	$Ni(cod)_2$, IPr–PPh_3 (5:5)	r.t., 2 h	48	37
6[b]	**2a**	$Ni(cod)_2$, IPr (5)	r.t., 1.5 h	82	4

[a] The starting material **2b** was recovered in 84% (entry 1), 82% (entry 2), or 87% (entry 3).
[b] The reaction was carried out in the presence of Cs_2CO_3 (6 mol%).

use of a mixed ligand complex, Ni(IPr)(PPh_3), which was generated in situ from $Ni(cod)_2$ (5 mol%), IPr·HCl (5 mol%), and triphenylphosphine (5 mol%) in the presence of cesium carbonate (6.0 mol%), was not effective in this reaction (Table 4, entry 3). On the other hand, the substrate **2a** was found to be more reactive toward this reaction than **2b**, and the reaction of **2a** with phenylmagnesium chloride in the presence of $Ni(cod)_2$ (5 mol%) and triphenylphosphine (20 mol%) gave the desired product **3a** in 38% yield along with the dimer **9** (Figure 4) in 35% yield (Table 4, entry 4). The use of a mixed ligand complex slightly improved the yield of **3a** to 48%, but a significant amount of the dimer **9** was also obtained (Table 4, entry 5). On the other hand, the use of Ni–IPr complex, generated in situ from $Ni(cod)_2$ (5 mol%) and IPr·HCl (5 mol%) in the presence of cesium carbonate (6 mol%), gave the best result, giving **3a** in 82% yield and also suppressing the formation of **9** (Table 4, entry 6).

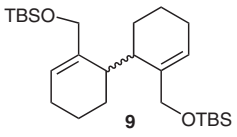


Figure 4

In summary, a palladium- or nickel-catalyzed cross-coupling of 2-substituted cyclohexene derivatives **2** with organotin reagent (Migita–Kosugi–Stille coupling) or with Grigard reagent (Kumada–Tamao–Corriu coupling) was investigated using NHC as a ligand. Although 2-substituted cyclohexenes **2** are generally less reactive as substrates toward these types of cross-coupling reactions due to the bulkiness of the C2 substituent, compared to those having

no substituent at the C2 position, it was found that NHCs are effective as ligands for these reactions and can suppress the formation of byproducts such as a β-eliminated product for Migita–Kosugi–Stille coupling and a dimeric product for Kumada–Tamao–Corriu coupling.

All manipulations were performed under an argon atmosphere. THF was purified using a Glass Contour Solvent Purification System, and all other solvents and reagents were purified when necessary by standard procedures. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh), and flash chromatography on silica gel (Merck, 230–400 mesh) with the indicated solvent as eluent. IR spectra were obtained on a Jasco FT/IR-460 plus, and ^{1}H and ^{13}C NMR spectroscopy were carried out on a Jeol EX270 or a Jeol AL400 NMR spectrometer. Mass spectra were obtained on a Jeol JMS-700TZ for LRMS (EI) and HRMS (EI), and a Shimadzu GCMS-QP5050A for LCMS (EI).

1-[(*tert*-Butyldimethylsiloxy)methyl]-6-chlorocyclohex-1-ene (2a)

To a soln of 2-[(*tert*-butyldimethylsiloxy)methyl]cyclohex-2-enol[1d] (410 mg, 1.7 mmol) in CH_2Cl_2 (3.5 mL) was added *i*-Pr_2NEt (0.4 mL, 2.5 mmol) and MsCl (0.2 mL, 2.5 mmol) and the mixture was stirred at 0 °C for 2 h then at r.t. for 3 h. To the mixture was added sat. aq NH_4Cl soln at 0 °C, and the soln was extracted with CH_2Cl_2. The combined organic layers were washed with sat. NaCl and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography (silica gel, hexane–EtOAc, 19:1) to give **2a** (400 mg, 90%) as a colorless oil.

IR (neat): 2953, 1742, 838, 777 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.85 (m, 1 H), 4.68 (m, 1 H), 4.22–4.29 (m, 1 H), 4.05–4.12 (m, 1 H), 1.54–2.19 (m, 6 H), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8, 127.1, 64.7, 55.2, 32.3, 26.1, 24.9, 18.6, 17.4, –5.0.

LR-MS (EI): *m*/*z* = 259 [M – 1]$^+$, 225 [M – Cl]$^+$, 203 [M – *t*-Bu]$^+$.

HRMS (EI): m/z [M – *t*-Bu]$^+$ calcd for $C_9H_{16}ClOSi$: 203.0659; found: 203.0649.

1-[(*tert*-Butyldimethylsiloxy)methyl]-6-methoxycyclohex-1-ene (2b)

To a suspension of NaH (60% dispersion in mineral oil, 160 mg, 4.0 mmol) in THF (2.5 mL) were successively added a soln of 2-[(*tert*-butyldimethylsiloxy)methyl]cyclohex-2-enol (485 mg, 2.0 mmol) in THF (2.5 mL) and MeI (1.3 mL, 20 mmol) at 0 °C, and the mixture was stirred at r.t. for 2 h. To the mixture was added sat. aq NH_4Cl soln and the soln was extracted with Et_2O. The combined organic layers were washed with sat. NaCl and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography (silica gel, hexane–Et_2O, 40:1) to give **2b** (497 mg, 97%) as a colorless oil.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.83 (m, 1 H), 4.21–4.27 (m, 1 H), 4.03–4.09 (m, 1 H), 3.76 (m, 1 H), 3.35 (s, 3 H), 1.54–2.19 (m, 6 H), 0.91 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H).

1-[(*tert*-Butyldimethylsiloxy)methyl]-6-phenylcyclohex-1-ene (3a) by Migita–Kosugi–Stille Coupling (Table 1, Entry 6); Typical Procedure

A soln of $Pd_2(dba)_3{\cdot}CHCl_3$ (4.8 mg, 0.0047 mmol), IPr·HCl (3.9 mg, 0.0094 mmol), and Cs_2CO_3 (6.0 mg, 0.019 mmol) in degassed THF (3 mL) was stirred at 50 °C for 10 min to generate, in situ, Pd–IPr complex. To the catalyst soln was added a soln of **2a** (81 mg, 0.31 mmol) in THF (3 mL) and $PhSnBu_3$ (0.2 mL, 0.62 mmol) and the mixture was stirred at 50 °C for 144 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by column chromatography (KF/SiO_2,[8] hexane) to give **3a** (85 mg, 90%) as a colorless oil.

IR (neat): 3060, 2929, 1601 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.15–7.27 (m, 5 H), 5.97 (m, 1 H), 3.86 (m, 2 H), 3.44 (m, 1 H), 1.45–2.14 (m, 6 H), 0.84 (s, 9 H), –0.07 (s, 3 H), –0.08 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 138.6, 129.2, 128.8, 126.6, 124.8, 66.5, 41.7, 32.9, 26.5, 25.6, 19.2, 19.0, –4.9.

LR-MS (EI): *m*/*z* = 302 [M]$^+$, 287 [M – Me]$^+$, 245 [M – *t*-Bu]$^+$.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{19}H_{30}OSi$: 302.2066; found: 302.2054.

1-[(*tert*-Butyldimethylsiloxy)methyl]-6-vinylcyclohex-1-ene (3b)

IR (neat): 2930, 1634, 913, 836 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.69–5.82 (m, 2 H), 5.02 (br s, 1 H), 4.96 (m, 1 H), 3.99 (m, 2 H), 2.78 (m, 1 H), 2.03 (m, 2 H), 1.53–1.76 (m, 4 H), 0.90 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.0, 137.4, 122.6, 114.6, 65.6, 39.4, 29.1, 26.2, 25.2, 19.1, 18.6, –4.9.

LR-MS (EI): *m*/*z* = 252 [M]$^+$, 237, 219, 195, 75.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{28}OSi$: 252.1909; found: 252.1897.

1-[(*tert*-Butyldimethylsiloxy)methyl]-6-(1-ethoxyvinyl)cyclohex-1-ene (3c)

IR (neat): 2931, 1649, 1068 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.82 (m, 1 H), 4.05 (m, 2 H), 3.93 (d, *J* = 1.6 Hz, 1 H), 3.80 (d, *J* = 1.6 Hz, 1 H), 3.69 (m, 2 H), 2.82 (m, 1 H), 1.47–2.04 (m, 6 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 0.90 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 136.4, 123.7, 82.2, 65.7, 62.7, 40.6, 27.4, 26.2, 25.0, 18.9, 18.7, 14.7, –5.08.

LR-MS (EI): *m*/*z* = 296 [M]$^+$, 267, 239, 75.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{32}O_2Si$: 296.2172; found: 296.2174.

1-[(*tert*-Butyldimethylsiloxy)methyl]-6-phenylcyclohex-1-ene (3a) by Kumada–Tamao–Corriu Coupling (Table 4, Entry 6); Typical Procedure

A soln of $Ni(cod)_2$ (4.3 mg, 0.016 mmol), IPr·HCl (6.7 mg, 0.016 mmol), and Cs_2CO_3 (11.0 mg, 0.032 mmol) in degassed THF (3 mL) was stirred at r.t. for 1 h to generate, in situ, Ni–IPr complex. To the catalyst soln was added a soln of **2a** (81 mg, 0.31 mmol) in THF (3 mL) and 1.7 M PhMgCl in THF (0.36 mL, 0.62 mmol) and the mixture was stirred at r.t. for 1.5 h. To the mixture was added sat. aq NH_4Cl soln at 0 °C and the soln was extracted with EtOAc. The combined organic layers were washed with sat. NaCl and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography (silica gel, hexane) to give **3a** (77 mg, 82%) as a colorless oil along with the dimer **9** (2.6 mg, 4%).

2,2′-Bis[(*tert*-butyldimethylsiloxy)methyl]-1,1′-bi(cyclohex-2-ene) (9)

^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.78–5.84 (m, 2 H), 4.04–4.14 (m, 4 H), 2.46–2.53 (m, 2 H), 1.23–1.78 (m, 12 H), 0.91 (s, 9 H), 0.89 (m, 9 H), 0.03 (s, 6 H), 0.01 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 138.1, 123.9, 122.9, 65.7, 38.3, 36.1, 27.7, 26.2, 25.4, 25.3, 24.2, 22.5, 22.2, 18.6, –4.99.

LR-MS (EI): *m*/*z* = 450 [M]$^+$, 393 [M – *t*-Bu]$^+$, 318 [M – OTBDMS]$^+$.

Acknowledgment

This work was financially supported by a Grant-in-Aid for Scientific Research (B) (No. 19390001) from the Japan Society for the Promotion of Science (JSPS) and by the Akiyama Foundation, which are gratefully acknowledged.

References

(1) (a) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263. (b) Nishimata, T.; Mori, M. *J. Org. Chem.* **1998**, *63*, 7586. (c) Nishimata, T.; Yamaguchi, K.; Mori, M. *Tetrahedron Lett.* **1999**, *40*, 5713. (d) Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. *Org. Lett.* **2001**, *3*, 1913. (e) Nakanishi, M.; Mori, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 1934. (f) Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801. (g) Nishimata, T.; Sato, Y.; Mori, M. *J. Org. Chem.* **2004**, *69*, 1837.

(2) Other examples of the synthesis of 2-substituted cyclohexenes via an asymmetric Tsuji–Trost reaction, see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262. (b) Hamada, Y.; Sakaguchi, K.; Hatano, K.; Hara, O. *Tetrahedron Lett.* **2001**, *42*, 1297.

(3) (a) Farina, V. In *Comprehensive Organometallic Chemistry II*, Vol. 12; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: Oxford, **1995**, 161. (b) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, **1995**.

(4) (a) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768. (b) Glorius, F. *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Springer Verlag: Heidelberg, **2007**. (c) Nolan, S. P. *N-Heterocyclic Carbenes in Synthesis*; Wiley-VCH: Weinheim, **2006**.

(5) (a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. For Migita–Kosugi–Stille coupling using Pd–NHC complexes, see: (c) Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 342. (d) Herrmann, W. A.; Böhm, V. P. W.; Gstöttmayr, C. W. K.; Groshe, M.; Reisinger, C.-P.; Weskamp, T. *J. Organomet. Chem.* **2001**, *617-618*, 616.

(6) (a) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144. (b) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (c) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268. For Kumada–Tamao–Corriu coupling using Pd–NHC complexes, see: (d) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889. (e) Frisch, A. C.; Zapf, A.; Briel, O.; Kayser, B.; Shaikh, N.; Beller, M. *J. Mol. Catal.* **2004**, *214*, 231. (f) Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403.

(7) Chung, K.-G.; Miyake, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2725.

(8) Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004**, 1968.