The First General Method for Palladium-Catalyzed Negishi Cross-Coupling of Aryl and Vinyl Chlorides: Use of Commercially Available $Pd(P(t\text{-}Bu)_3)_2$ as a Catalyst

Chaoyang Dai and Gregory C. Fu*

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received November 14, 2000

Abstract: With a single protocol, commercially available $Pd(P(t\text{-}Bu)_3)_2$ can effect the Negishi cross-coupling of a wide range of aryl and vinyl chlorides with aryl- and alkylzinc reagents. The process tolerates nitro groups, and it efficiently generates sterically hindered biaryls. In addition, a high turnover number (>3000) can be achieved.

Introduction

The palladium-catalyzed cross-coupling of aryl and vinyl halides/triflates with organozinc reagents (Negishi reaction)[1] represents a powerful method for generating aromatic compounds such as styrene derivatives and biaryls, which are important synthetic targets in disciplines ranging from materials science[2] to medicine.[3] The ready availability and the functional-group compatibility of organozinc reagents[4] significantly enhance the utility of this cross-coupling process.

Among aryl halides, chlorides are arguably the most useful class of substrates for coupling reactions, due to their lower cost and the wider diversity of available compounds.[5] Unfortunately, although palladium-catalyzed reactions of aryl bromides and aryl iodides have been commonplace for a number of years,[6] until quite recently the corresponding couplings of aryl chlorides were generally unsuccessful.[5,7]

Since 1998, however, noteworthy strides have been made in the development of palladium-based catalyst systems for reactions of aryl chlorides.[8] For example, versatile methods have been reported for classic coupling processes such as the Suzuki,[9] Heck,[10] and Stille[11] reactions, as well as for more recently discovered amine,[12] ketone,[13] and alcohol[14] arylations. To date, however, there have been only isolated instances of palladium-catalyzed Negishi reactions of aryl chlorides,[15] although methods for the corresponding nickel-catalyzed process have been described.[16,17] In this report, we establish that commercially

(1) For a review, see: Negishi, E.-i. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 1.

(2) For example, see: *Step Growth Polymers for High-Performance Materials*; Hedrick, J. L., Labadie, J. W., Eds.; ACS Symp. Ser. 624; American Chemical Society: Washington, D.C., 1996.

(3) For example, see: (a) A review of vancomycin antibiotics: Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096−2152. (b) Reviews of sartans and Losartan: Birkenhager, W. H.; de Leeuw, P. W. *J. Hypertens.* **1999**, *17*, 873−881. Goa, K. L.; Wagstaff, A. J. *Drugs* **1996**, *51*, 820−845.

(4) (a) *Organozinc Reagents, A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999. (b) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: Boston, 1996.

(5) (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062. (b) Grushin, V. V.; Alper, H. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer-Verlag: Berlin, 1999; pp 193−226.

(6) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.

(7) The low reactivity of chlorides is usually attributed primarily to the strength of the C−Cl bond (bond dissociation energies for Ar−X: Cl = 96 kcal/mol; Br = 81 kcal/mol; I = 65 kcal/mol). See ref 5.

(8) Stürmer, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 3307−3308.

(9) For early examples, see: (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387−3388. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (c) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. (d) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93−96. Weskamp, T.; Bohm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348−352.

(10) (a) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11. (b) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123−2132.

(11) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413.

(12) For early examples, see: (a) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807−4810. (b) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. (c) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370. (d) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174.

(13) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370. (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478.

(14) (a) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225. (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369−4378. (c) Watanabe, M.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1999**, *40*, 8837−8840.

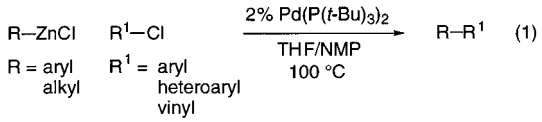
(15) We are aware of only one example of a palladium-catalyzed Negishi cross-coupling of an unactivated aryl chloride: Herrmann, W. A.; Bohm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23−41 (coupling of PhZnBr with chlorobenzene).

(16) For reports of nickel-catalyzed Negishi cross-couplings of unactivated aryl chlorides, see: (a) House, H. O.; Ghali, N. I.; Haack, J. L.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 1807−1817. (b) Lebedev, S. A.; Sorokina, R. S.; Berestova, S. S.; Petrov, E. S.; Beletskaya, I. P. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1986**, *35*, 620−622. (c) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 6441−6444. (d) Lipshutz, B. H.; Blomgren, P. A.; Kim, S.-K. *Tetrahedron Lett.* **1999**, *40*, 197−200. Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 5819−5820.

(17) For discussions of the advantages of palladium over nickel, see: (a) Negishi, E.-i. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; p 38. (b) Negishi, E.-i. In *Organozinc Reagents, A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999; pp 214−215 and Table 11.1.

10.1021/ja003954y CCC: $20.00
Published on Web 02/22/2001

available $Pd(P(t\text{-}Bu)_3)_2$ serves as a versatile catalyst for the Negishi cross-coupling of aryl- and alkylzinc reagents with aryl and vinyl chlorides (eq 1).



Results and Discussion

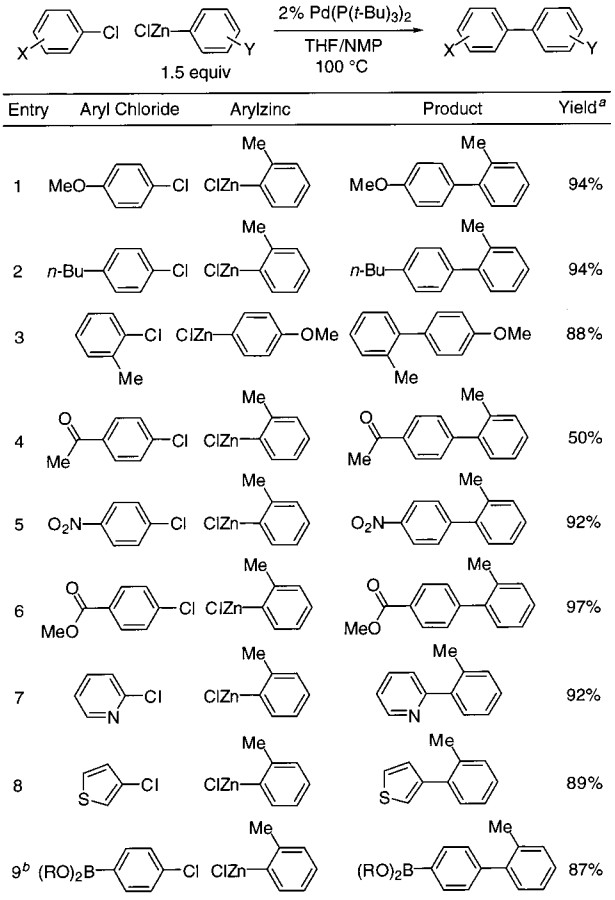
In early studies, we determined that $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyzes the challenging Negishi coupling of electron-rich 4-chloroanisole with sterically demanding *o*-tolylzinc chloride (100 °C, THF/NMP).[18,19] On the basis of our observation that a Pd:$P(t\text{-}Bu)_3$ ratio of 1:2 appeared to be optimal, we decided to examine the catalytic activity of $Pd(P(t\text{-}Bu)_3)_2$.[20,21] We were pleased to discover that this air-stable complex does indeed serve as an effective catalyst for the Negishi cross-coupling of aryl chlorides.

Using a standard set of reaction conditions (2% $Pd(P(t\text{-}Bu)_3)_2$, THF/NMP, 100 °C), we can couple a diverse array of aryl chlorides and organozinc reagents. Electronic variation in both reaction partners is tolerated, as illustrated by entries 1−6 of Table 1. Whereas coupling of a ketone-containing substrate is accompanied by the generation of unidentified byproducts (entry 4), nitro groups (which interfere with nickel catalysts[22]) and esters are compatible with the reaction conditions (entries 5 and 6). Heteroaromatic aryl chlorides are also suitable coupling partners (entries 7 and 8), and with this protocol Negishi cross-coupling proceeds in preference to Suzuki cross-coupling (entry 9).

With our standard reaction conditions, we can also efficiently synthesize quite hindered biaryls (Table 2). For example, we can generate 1,1′-dimethylbiphenyl in 96% yield from 2-chlorotoluene and *o*-tolylzinc chloride (entry 1). Furthermore, we can produce tri-ortho-substituted biaryls in excellent yield (entries 2 and 3), and we can even synthesize tetra-ortho-substituted biaryls (entry 4);[23] to the best of our knowledge, this is the first example of a Negishi coupling that furnishes a tetra-ortho-substituted biaryl.

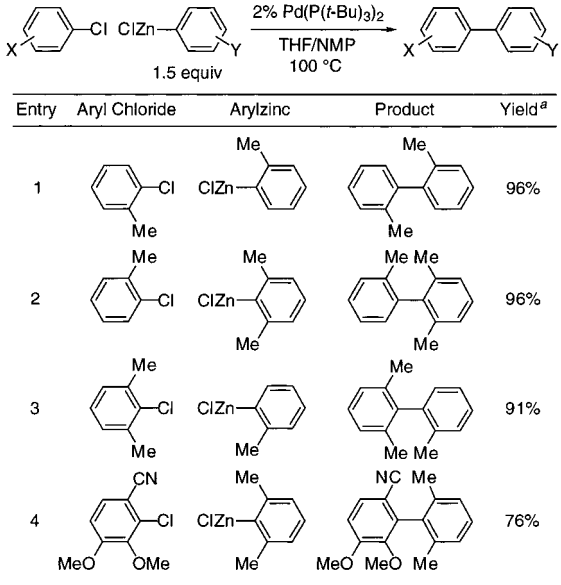
We have established that we can apply the same protocol to the Negishi reaction of vinyl chlorides,[24] thereby producing styrene derivatives in very good yield (Table 3). Thus, 1-chlorocyclopentene couples cleanly with a range of arylzinc reagents, including very hindered ones (entries 1−3). A substituent cis to chlorine is also tolerated, as illustrated in entries 4−6.

Table 1. Negishi Cross-Couplings of Aryl Chlorides to Generate Biaryls



[a] Isolated yield, average of two runs. [b] $(RO)_2B$ = pinacolboronate.

Table 2. Negishi Cross-Couplings of Aryl Chlorides to Generate Hindered Biaryls



[a] Isolated yield, average of two runs.

Finally, we have examined the $Pd(P(t\text{-}Bu)_3)_2$-catalyzed Negishi cross-coupling of aryl and vinyl chlorides with *alkyl*zinc reagents (Table 4).[25] The reaction of a primary alkylzinc reagent proceeds uneventfully (entry 1). In the case of a branched alkylzinc, for Negishi couplings catalyzed by other Pd/(monodentate phosphine) complexes, products derived from isomerization of the

(18) $Pd_2(dba)_3/PCy_3$ is also an effective catalyst.

(19) $Pd_2(dba)_3/P(t\text{-}Bu)_3$ effects clean coupling of 4-bromoanisole and *o*-tolylzinc chloride at room temperature.

(20) (a) Otsuka, S.; Yoshida, T.; Matsumoto, M.; Nakatsu, K. *J. Am. Chem. Soc.* **1976**, *98*, 5850−5858. (b) Yoshida, T.; Otsuka, S. *Inorg. Synth.* **1990**, *28*, 113−119. This report states that $Pd(P(t\text{-}Bu)_3)_2$ is "stable in air in the solid state". We have observed slight decomposition after extended (>1 month) exposure to air (A. F. Littke, unpublished results).

(21) $Pd(P(t\text{-}Bu)_3)_2$ is available from Strem Chemicals.

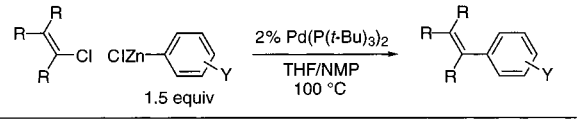
(22) In his original report of the Negishi cross-coupling process, Negishi notes that "the nitro group...destroys the catalytic ability of the Ni complexes": Negishi, E.-i.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821−1823.

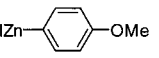
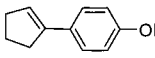
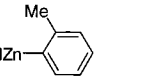
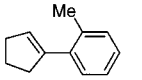
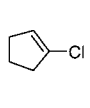
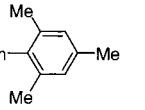
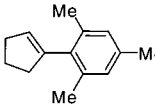
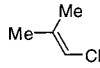
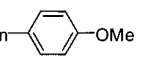
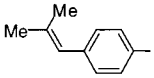
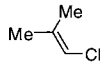
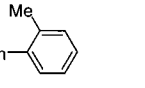
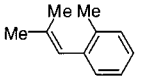
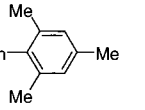
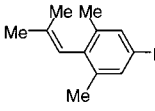
(23) For Negishi reactions that generate tetra-ortho-substituted biaryls, we have found homocoupling to be a significant side reaction.

(24) We are only aware of a few examples of palladium-catalyzed Negishi reactions of vinyl chlorides: (a) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257−1258. Minato, A. *J. Org. Chem.* **1991**, *56*, 4052−4056. (b) Sinha, S. C.; Keinan, E.; Reymond, J.-L. *J. Am. Chem. Soc.* **1993**, *115*, 4893−4594.

(25) Under the same conditions, vinyl- and alkynylzinc reagents are not suitable coupling partners.

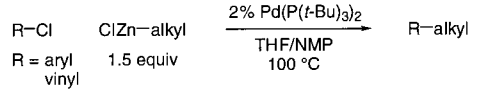
Table 3. Negishi Cross-Couplings of Vinyl Chlorides to Generate Styrenes

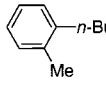
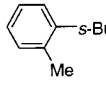
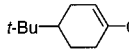
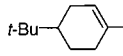


Entry	Vinyl Chloride	Arylzinc	Product	Yield[a]
1				82%
2				94%
3				96%
4				81%
5				87%
6				92%

[a] Isolated yield, average of two runs.

Table 4. Negishi Cross-Couplings of Aryl and Vinyl Chlorides with Alkylzincs

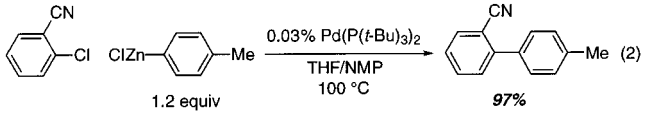


Entry	Chloride	Alkylzinc	Product	Yield[a]
1		ClZn–*n*-Bu		83%
2		ClZn–*s*-Bu		70%[b]
3		ClZn–*s*-Bu		86%[c]

[a] Isolated yield, average of two runs. [b] Includes 8% 2-*n*-butyltoluene. [c] Includes 2% 4-*tert*-butyl-1-*n*-butylcyclohexene.

alkyl group (secondary → primary) can be predominant.[26] With $Pd(P(t\text{-}Bu)_3)_2$, we generate the desired compound with ~10:1 selectivity (entry 2) for the coupling of an aryl chloride with *s*-BuZnCl and with ~40:1 selectivity (entry 3) for the reaction of a vinyl chloride.

2-Cyano-4′-methylbiphenyl is a key intermediate in the synthesis of angiotensin II receptor antagonists that are used for the treatment of hypertension.[27] We have produced this target in 97% yield through a Negishi cross-coupling of *o*-chlorobenzonitrile with *p*-tolylmagnesium bromide in the presence of 0.03% $Pd(P(t\text{-}Bu)_3)_2$ (eq 2). This corresponds to a turnover number (TON) >3000, which is the highest TON that we are aware of for a Negishi reaction of an aryl chloride.[28,29]



Conclusions

For the Negishi reaction, we have developed a single protocol that efficiently cross-couples a variety of aryl and vinyl chlorides with organozinc reagents. Noteworthy features of this method include the following: use of a commercially available, air-stable catalyst, $Pd(P(t\text{-}Bu)_3)_2$; tolerance of nitro functionality; synthesis of very hindered biaryls; coupling of sterically demanding vinyl chlorides and arylzinc reagents; reaction of alkylzincs, including secondary alkylzincs; and high turnover number.

This represents the first general method for accomplishing palladium-catalyzed Negishi reactions of aryl and vinyl chlorides. Mechanistic investigations and the development of other applications of $Pd/P(t\text{-}Bu)_3$ in cross-coupling processes are underway.

Experimental Section

General. THF was distilled from sodium-benzophenone ketyl. 1-Methyl-2-pyrrolidinone (NMP; Aldrich; anhydrous, in a Sure-Seal bottle), $Pd_2(dba)_3$ (Aldrich), $PdCl_2$ (Strem), and $P(t\text{-}Bu)_3$ (Strem) were used as received. 2-(4-Chlorophenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane[30] was prepared through the treatment of 4-chlorophenylboronic acid with pinacol in toluene. 1-Chloro-4-*tert*-butylcyclohexene[31] was prepared according to a literature procedure. Other aryl and vinyl chlorides were purchased from commercial sources (Aldrich, Alfa-Aesar) and distilled or recrystallized prior to use. Zinc chloride (0.5 M solution in THF) and all Grignard reagents were purchased from Aldrich in Sure-Seal bottles.

All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring, unless otherwise indicated.

$Pd(P(t\text{-}Bu)_3)_2$. $Pd(P(t\text{-}Bu)_3)_2$ is available from Strem Chemicals (catalog no. 46-0252). Alternatively, it may be prepared according to the following procedure: In a glovebox, $Pd_2(dba)_3$ (459 mg, 0.50 mmol), $P(t\text{-}Bu)_3$ (425 mg, 2.1 mmol), and DMF (anhydrous; 10 mL) were added to a vial equipped with a stir bar. The vial was capped, and the reaction mixture was stirred for 3 h at room temperature. The resulting precipitate was collected by filtration, washed thoroughly with DMF, and then dissolved in hexane. The hexane solution was filtered and concentrated, yielding 422 mg (83%) of white crystals. $^{31}P\{^1H\}$ NMR (C_6D_6) 85.2; ^1H NMR (C_6D_6) 1.53 (t, J = 5.7) [$Pd(P(t\text{-}Bu)_3)_2$ is not stable in $CDCl_3$].[32]

General Procedure: 4-Nitro-2′-methylbiphenyl (Table 1, entry 5).[33] Under argon, $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol) was added by syringe to a Schlenk tube. *o*-Tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol) was then added dropwise, and the resulting mixture was stirred at room temperature for 20 min. Next, NMP (2.2 mL) was added by syringe, followed after 5 min by $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol) and 1-chloro-4-nitrobenzene (158 mg, 1.0 mmol). The Schlenk tube was closed at the Teflon stopcock, and the reaction mixture was stirred in a 100 °C oil bath for 2 h. It

(26) For example, see: Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163. See also ref 1.

(27) For leading references, see: Goubet, D.; Meric, P.; Dormoy, J.-R.; Moreau, P. *J. Org. Chem.* **1999**, *64*, 4516−4518.

(28) With 0.01% $Pd(P(t\text{-}Bu)_3)_2$, this Negishi cross-coupling does not proceed to completion: we isolate a mixture of 76% of the desired product (⟹ 7600 turnovers), along with 10% of the unreacted aryl chloride.

(29) To date, we have conducted only preliminary mechanistic studies of the $Pd(P(t\text{-}Bu)_3)_2$-catalyzed Negishi cross-coupling process. Two of our observations may be of interest: (a) During the course of the reaction of 4-chloroanisole with *o*-tolylzinc chloride, $Pd(P(t\text{-}Bu)_3)_2$ is the only phosphorus-containing species that can be seen in the ^{31}P NMR spectrum. (b) Excess $P(t\text{-}Bu)_3$ inhibits cross-coupling (which likely implicates a role in the reaction for a palladium/monophosphine complex).

(30) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164−168.

(31) Lambert, J. B.; Wang, G.-t.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838−7845.

(32) Otsuka, S.; Yoshida, T.; Matsumoto, M.; Nakatsu, K. *J. Am. Chem. Soc.* **1976**, *98*, 5850−5858.

was then allowed to cool to room temperature, and aqueous HCl was added (1.0 M; 6 mL). The resulting mixture was extracted with Et_2O (4 × 8 mL), and the organic extracts were combined, washed with water (5 × 10 mL), dried ($MgSO_4$), and concentrated, affording a yellow solid. Flash chromatography (3% Et_2O in hexanes) furnished 200 mg (94%) of the title compound as a pale-yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.27 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 7.30−7.20 (m, 4H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 148.9, 139.7, 135.2, 130.8, 130.2, 129.5, 128.6, 126.3, 123.5, 20.6.

4-Methoxy-2′-methylbiphenyl (Table 1, entry 1).[34] The general procedure was followed with use of 4-chloroanisole (143 mg, 1.0 mmol), *o*-tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 24 h at 100 °C, workup and column chromatography (5% Et_2O in hexanes) yielded 190 mg (95%) of the title compound as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.27−7.21 (m, 6H), 6.95 (d, J = 9.0 Hz, 2H), 3.85 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 158.6, 141.6, 135.6, 134.5, 130.4, 130.4, 130.0, 127.1, 125.9, 113.6, 55.5, 20.8.

4-Butyl-2′-methylbiphenyl (Table 1, entry 2). The general procedure was followed with use of 1-(4′-chlorophenyl)butane (168 mg, 1.0 mmol), *o*-tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 3 h at 100 °C, workup and column chromatography (hexanes) yielded 209 mg (93%) of the title compound as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.25−7.21 (m, 8H), 2.65 (t, J = 7.7 Hz, 2H), 2.28 (s, 3H), 1.65 (quintet, J = 7.7 Hz, 2H), 1.40 (sextet, J = 7.7 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 142.0, 141.5, 139.3, 135.5, 130.4, 130.0, 129.2, 128.2, 127.1, 125.8, 35.7, 33.9, 22.8, 20.9, 14.3. IR (neat, cm^{-1}): 2955, 2928, 2857, 1483, 1456, 1007, 836, 759. HRMS (EI, *m*/*z*) calcd for $C_{17}H_{20}$ (M^+) 224.1565, found 224.1561.

4-Methoxy-2′-methylbiphenyl (Table 1, entry 3).[34] The general procedure was followed with use of 2-chlorotoluene (127 mg, 1.0 mmol), 4-methoxyphenylmagnesium bromide (0.5 M solution in THF; 3.0 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 24 h at 100 °C, workup and column chromatography (5% Et_2O in hexanes) yielded 175 mg (88%) of the title compound as a colorless liquid.

4-Acetyl-2′-methylbiphenyl (Table 1, entry 4).[35] The general procedure was followed with use of 4′-chloroacetophenone (155 mg, 1.0 mmol), *o*-tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 2 h at 100 °C, workup and column chromatography (10% Et_2O in hexanes) yielded 105 mg (50%) of the title compound as a pale-yellow liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.01 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.30−7.20 (m, 4H), 2.65 (s, 3H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 198.0, 147.1, 140.8, 135.7, 135.3, 130.6, 129.6, 129.6, 128.4, 128.0, 126.1, 26.9, 20.7.

4-Carbomethoxy-2′-methylbiphenyl (Table 1, entry 6).[36] The general procedure was followed with use of methyl 4-chlorobenzoate (171 mg, 1.0 mmol), *o*-tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 2 h at 100 °C, workup and column chromatography (10% Et_2O in hexanes) yielded 221 mg (98%) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.07 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.30−7.18 (m, 4H), 3.94 (s, 3H), 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 167.1, 146.8, 140.9, 135.3, 130.6, 129.6, 129.5, 129.4, 128.7, 127.9, 126.0, 52.4, 20.7.

2-*o*-Tolylpyridine (Table 1, entry 7).[37] The general procedure was followed with use of 2-chloropyridine (114 mg, 1.0 mmol), *o*-tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 2 h at 100 °C, workup (water, rather than aqueous HCl, was used for the extraction) and column chromatography (30% Et_2O in hexanes) yielded 157 mg (93%) of the title compound as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.70 (ddd, J = 4.8 Hz, 1.8 Hz, 0.9 Hz, 1H), 7.74 (apparent triplet of doublets, 1H), 7.42−7.38 (m, 2H), 7.31−7.22 (m, 4H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 160.1, 149.3, 140.5, 136.2, 135.9, 130.9, 129.7, 128.4, 126.0, 124.2, 121.8, 20.5.

3-*o*-Tolylthiophene (Table 1, entry 8).[38] The general procedure was followed with use of 3-chlorothiophene (119 mg, 1.0 mmol), *o*-tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol)), Pd(P(*t*-Bu)$_3$)$_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 20 h at 100 °C, workup and column chromatography (pentane) yielded 161 mg (92%) of the title compound as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.34 (dd, J = 4.7 Hz, 2.7 Hz, 1H), 7.31−7.28 (m, 1H), 7.26−7.18 (m, 4H), 7.14 (dd, J = 4.9 Hz, 1.4 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 142.3, 136.7, 135.8, 130.6, 129.9, 129.0, 127.4, 125.9, 125.0, 122.7, 21.1.

2-(2′-Methylbiphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (Table 1, entry 9). The general procedure was followed with use of 2-(4-chlorophenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (238 mg, 1.0 mmol), *o*-tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 2 h at 100 °C, workup and column chromatography (10% Et_2O in hexanes) yielded 256 mg (87%) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.85 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.25−7.20 (m, 4H), 2.26 (s, 3H), 1.36 (s, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): 145.0, 141.9, 135.4, 134.6, 130.5, 129.8, 128.7, 127.5, 125.9, 84.0, 25.2, 20.7. IR (neat, cm^{-1}): 2977, 2928, 1611, 1397, 1360, 1145, 1091, 962, 860, 661. HRMS (EI, *m*/*z*) calcd for $C_{19}H_{23}BO_2$ (M^+) 294.1786, found 294.1783.

2,2′-Dimethylbiphenyl (Table 2, entry 1). The general procedure was followed with use of 2-chlorotoluene (127 mg, 1.0 mmol), *o*-tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 20 h at 100 °C, workup and column chromatography (hexanes) yielded 170 mg (93%) of the title compound as a colorless liquid that was identical to authentic material (TCI) by ^{1}H NMR, GC, and TLC.

2,6,2′-Trimethylbiphenyl (Table 2, entry 2).[39] The general procedure was followed with use of 2-chlorotoluene (127 mg, 1.0 mmol), 2,6-dimethylphenylmagnesium bromide (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 18 h at 100 °C, workup and column chromatography (hexanes) yielded 196 mg (96%) of the title compound as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.31−7.09 (m, 6H), 7.03−6.99 (m, 1H), 1.97 (s, 3H), 1.94 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): 141.2, 140.7, 136.0, 135.8, 130.1, 129.0, 127.4, 127.1, 127.1, 126.2, 20.6, 19.7.

2,6,2′-Trimethylbiphenyl (Table 2, entry 3).[39] The general procedure was followed with use of 2-chloro-*m*-xylene (141 mg, 1.0 mmol), *o*-tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 24 h at 100 °C, workup and column chromatography (hexanes) yielded 186 mg (91%) of the title compound as a colorless liquid.

(33) Hecht, S. S.; El-Bayoumy, K.; Tulley, L.; LaVoie, E. *J. Med. Chem.* **1979**, *22*, 981−987.

(34) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434−5444.

(35) Wirth, H. O.; Kern, W.; Schmitz, E. *Makromol. Chem.* **1963**, *68*, 69−99.

(36) Ananthakrishnanadar, P.; Kannan, N. *J. Chem. Soc., Perkin Trans. 2* **1984**, 35−37.

(37) Terashima, M.; Seki, K.-I.; Yoshida, C.; Ohkura, K.; Kanaoka, Y. *Chem. Pharm. Bull.* **1985**, *33*, 1009−1015.

(38) Hartman, G. D.; Halczenko, W.; Phillips, B. T. *J. Org. Chem.* **1986**, *51*, 142−148.

(39) Kamikawa, T.; Hayashi, T. *Synlett*, **1997**, 163−164.

2,3-Dimethoxy-6-cyano-2′,6′-dimethylbiphenyl (Table 2, entry 4). The general procedure was followed with use of 2-chloro-3,4-dimethoxybenzonitrile (198 mg, 1.0 mmol), 2,6-dimethylphenylmagnesium bromide (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 18 h at 100 °C, workup and column chromatography (1:2 EtOAc/hexanes) yielded 207 mg (77%) of the title compound as a pale-yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.50 (d, J = 8.5 Hz, 1H), 7.25−7.11 (m, 3H), 6.97 (d, J = 8.5 Hz, 1H), 3.96 (s, 3H), 3.54 (s, 3H), 2.06 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): 156.8, 146.5, 138.9, 136.1, 133.9, 129.9, 128.5, 127.6, 117.9, 111.6, 105.6, 60.5, 56.2, 20.5. IR (neat, cm^{-1}): 2222 (CN), 1589, 1480, 1277, 1125, 1045, 1012. HRMS (EI, m/z) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1259, found 267.1253.

1-(4′-Methoxy)cyclopentene (Table 3, entry 1).[40] The general procedure was followed with use of 1-chlorocyclopentene (103 mg, 1.0 mmol), 4-methoxyphenylmagnesium bromide (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 8 h at 100 °C, workup and column chromatography (2.5% Et_2O in pentane) yielded 145 mg (83%) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.36 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.48 (apparent triplet, 1H), 3.80 (s, 3H), 2.70−2.63 (m, 2H), 2.52−2.46 (m, 2H), 2.05 (apparent quintet, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 158.6, 141.9, 129.8, 126.8, 124.1, 113.8, 55.5, 33.6, 33.5, 23.7.

1-(*o*-Tolyl)cyclopentene (Table 3, entry 2).[41] The general procedure was followed with use of 1-chlorocyclopentene (103 mg, 1.0 mmol), *o*-tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 2 h at 100 °C, workup and column chromatography (pentane) yielded 153 mg (97%) of the title compound as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.19−7.10 (m, 4H), 5.75 (apparent triplet, 1H), 2.70−2.62 (m, 2H), 2.56−2.49 (m, 2H), 2.35 (s, 3H), 1.98 (apparent quintet, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 143.4, 138.3, 135.6, 130.6, 129.5, 128.1, 126.7, 125.6, 36.9, 33.9, 24.1, 21.5.

1-Mesitylcyclopentene (Table 3, entry 3). The general procedure was followed with use of 1-chlorocyclopentene (103 mg, 1.0 mmol), mesitylmagnesium bromide (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 3 h at 100 °C, workup and column chromatography (pentane) yielded 170 mg (91%) of the title compound as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.85 (s, 2H), 5.48 (apparent triplet, 1H), 2.57−2.40 (m, 4H), 2.26 (s, 3H), 2.18 (s, 6H), 2.03 (apparent quintet, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 143.0, 136.2, 136.1, 136.0, 128.6, 128.0, 36.8, 33.6, 24.4, 21.3, 20.2. IR (neat, cm^{-1}): 2936, 2919, 1612, 1480, 1444, 1041, 849. HRMS (EI, m/z) calcd for $C_{14}H_{18}$ (M^+) 186.1409, found 186.1405.

2-Methyl-1-(4′-methoxyphenyl)propene (Table 3, entry 4).[42] The general procedure was followed with use of 1-chloro-2-methylpropene (91 mg, 1.0 mmol), 4-methoxyphenylmagnesium bromide (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 8 h at 100 °C, workup and column chromatography (2.5% Et_2O in pentane) yielded 131 mg (81%) of the title compound as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.15 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.20 (broad s, 1H), 3.80 (s, 3H), 1.88 (d, J = 1.1 Hz, 3H), 1.84 (d, J = 1.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 157.7, 134.1, 131.4, 129.9, 124.6, 113.6, 55.5, 27.1, 19.6.

2-Methyl-1-*o*-tolylpropene (Table 3, entry 5).[43] The general procedure was followed with use of 1-chloro-2-methylpropene (91 mg, 1.0 mmol), *o*-tolylmagnesium chloride (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 2 h at 100 °C, workup and column chromatography (pentane) yielded 132 mg (90%) of the title compound as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.14−7.12 (m, 4H), 6.21 (broad s, 1H), 2.23 (s, 3H), 1.91 (d, J = 1.5 Hz, 3H), 1.70 (d, J = 1.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.0, 136.5, 135.2, 129.7, 129.5, 126.3, 125,4, 124.2, 26.4, 20.2, 19.6.

2-Methyl-1-mesitylpropene (Table 3, entry 6).[44] The general procedure was followed with use of 1-chloro-2-methylpropene (91 mg, 1.0 mmol), mesitylmagnesium bromide (1.0 M solution in THF; 1.5 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 3 h at 100 °C, workup and column chromatography (pentane) yielded 160 mg (92%) of the title compound as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.84 (s, 2H), 6.00 (broad s, 1H), 2.26 (s, 3H), 2.13 (s, 6H), 1.88 (d, J = 1.4 Hz, 3H), 1.42 (d, J = 1.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 136.5, 135.6, 135.1, 135.0, 127.8, 123.2, 25.4, 21.3, 20.5, 19.4.

2-Methylbutylbenzene (Table 4, Entry 1).[45] The general procedure was followed with use of 2-chlorotoluene (127 mg, 1.0 mmol), *n*-butylmagnesium chloride (2.0 M solution in THF; 0.75 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 20 h at 100 °C, workup and column chromatography (pentane) yielded 120 mg (83%) of the title compound as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.15−7.02 (m, 4H), 2.59 (t, J = 7.8 Hz, 2H), 2.30 (s, 3H), 1.55 (quintet, J = 7.2 Hz, 2H), 1.41 (sextet, J = 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 141.2, 135.9, 130.2, 128.9, 125.9, 125.8, 33.3, 32.8, 23.1, 19.6, 14.4.

2-Methyl-*s*-butylbenzene (Table 4, entry 2).[45] The general procedure was followed with use of 2-chlorotoluene (127 mg, 1.0 mmol), *s*-butylmagnesium chloride (2.0 M solution in Et_2O; 0.75 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 24 h at 100 °C, workup and column chromatography (pentane) yielded 105 mg (71%) of the title compound as a colorless liquid that contained ∼8% of 2-*n*-butyltoluene (determined by GC and by ^{1}H NMR).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.15−7.02 (m, 4H), 2.87 (sextet, J = 6.9 Hz, 1H), 2.32 (s, 3H), 1.59 (dq, J = 7.2 Hz, 7.0 Hz, 2H), 1.19 (d, J = 7.8 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 145.9, 135.6, 130.2, 126.2, 125.5, 125.3, 36.4, 30.8, 21.5, 19.9, 12.6.

4-*t*-Butyl-1-*s*-butyl-1-cyclohexene (Table 4, entry 3). The general procedure was followed with use of 4-*tert*-butyl-1-chlorocyclohexene (173 mg, 1.0 mmol), *s*-butylmagnesium chloride (2.0 M solution in Et_2O; 0.75 mL, 1.5 mmol), $ZnCl_2$ (0.5 M solution in THF; 3.15 mL, 1.6 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol), and NMP (2.2 mL). After 5 h at 100 °C, workup and column chromatography (pentane) yielded 169 mg (87%) of the title compound as a colorless liquid that contained ∼2% 4-*tert*-butyl-1-*n*-butylcyclohexene (determined by GC).

^{1}H NMR ($CDCl_3$, 300 MHz): 5.38 (broad s, 0.5H), 5.37 (broad s, 0.5H), 2.05−1.70 (m, 6H), 1.41−1.05 (m, 4H), 0.96 (d, J = 6.9 Hz, 1.5H), 0.95 (d, J = 6.9 Hz, 1.5H), 0.86 (s, 9H), 0.81 (t, J = 7.3 Hz, 1.5H), 0.78 (t, J = 7.3 Hz, 1.5H). ^{13}C NMR ($CDCl_3$, 75 MHz) (two diastereomers): 141.8, 141.6, 120.47, 120.45, 44.79, 44.76, 42.86, 42.76, 32.52, 28.15, 27.97, 27.5, 27.1, 26.8, 26.4, 24.71, 24.68, 19.96, 19.34, 12.54, 12.33. IR (neat, cm^{-1}): 2960, 2865, 1458, 1435, 1362. HRMS (EI, m/z) calcd for $C_{14}H_{26}$ (M^+) 194.2035, found 194.2037.

Negishi Cross-Coupling of *o*-Chlorobenzonitrile and 4-Methylphenylzinc Chloride with 0.03% $Pd(P(t\text{-}Bu)_3)_2$ (eq 2). The general procedure was followed with use of 2-chlorobenzonitrile (137 mg, 1.0 mmol), *p*-tolylmagnesium bromide (1.2 mL, 1.0 M solution in THF,

(40) Caldwell, R. A.; Cao, C. V. *J. Am. Chem. Soc*. **1982**, *104*, 6174−6180.

(41) Baddeley, G.; Chadwick, J.; Taylor, H. T. *J. Chem. Soc.* **1956**, 451−456.

(42) Arrastia, I.; Cossio, F. P. *Tetrahedron Lett*, **1996**, *37*, 7143−7146.

(43) Rottendorf, H.; Sternhell, S.; Wilmshurst, J. R. *Aust. J. Chem.* **1965**, *18*, 1759−1773.

(44) Maxwell, R. W.; Adam, R. *J. Am. Chem. Soc*. **1930**, *52*, 2959−2972.

(45) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc*. **1984**, *106*, 158−163.

1.2 mmol), $ZnCl_2$ (0.5 M solution in THF; 2.52 mL, 1.26 mmol), Pd-($P(t\text{-}Bu)_3)_2$ (0.0010 M stock solution in THF; 0.30 mL, 0.00030 mmol), and NMP (2.2 mL). After 24 h at 100 °C, workup and column chromatography (10% Et_2O in hexane) yielded 185 mg (97%) of 2-cyano-4′-methylbiphenyl as a white solid that was identical to authentic material (Alfa-Aesar) by ^1H NMR, GC, and TLC.

Acknowledgment. Support has been provided by Bristol-Myers Squibb, Merck, the Natural Sciences and Engineering Research Council of Canada (postdoctoral fellowship to C.D.), Novartis, and Pfizer.

JA003954Y