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Stille Cross-Coupling of Activated Alkyltin Reagents under "Ligandless" Conditions

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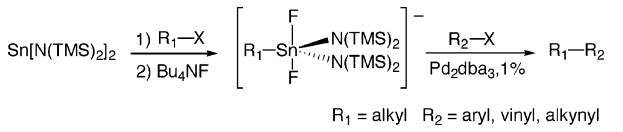
Received November 24, 2004



Monoalkyltins activated by a fluoride source are shown to be as reactive as their vinyl or aryl homologues in the Stille coupling reaction, thus providing an easy entry into the pallado-catalyzed formation of Csp^3-Csp^2 bonds. In addition to this uncommon reactivity, this methodology holds several advantages such as (i) a quantitative preparation of stable and easy to handle alkyltin reagents **2**, (ii) a simplified coupling procedure without any phosphine added ligand under neutral conditions, and (iii) a facile purification step of the organic products from the inorganic nontoxic tin byproducts.

Cross-coupling reactions represent an extremely versatile tool in organic synthesis for the C−C bond formation. In the past two decades most of the efforts have been focused on the Csp^2-Csp^2 bond formation[1] with applications ranging from organic materials to the total syntheses of complex natural molecules. Recent advances in the field of Csp^3-hybridized coupling reactions are actually emerging, the alkyl moiety being either on the substrate or the organometallic partner.[2] Among the variety of transition metals used for this purpose, such as nickel,[3] copper,[4] or iron,[5] palladium remains undoubtedly the catalyst of choice as it offers the best balance in terms of easiness of use, wide scope of reactions, and efficiency of the catalytic system.[6] In most cases, these works appear to be closely related to the use of special ligands or additives as well as careful optimization of the reaction conditions,[7] in order to overcome the reluctance of alkyl halides to undergo oxidative addition and to suppress the tendency of the resulting alkyl-metal intermediate for destructive β-hydride elimination. Interestingly, the construction of Csp^2-Csp^3 bonds implies essentially alkyl halides or triflates as substrates, the alkenyl or aromatic moieties being brought by the organometallic reagent.

However, a few recent examples can be found of pallado-catalyzed cross-coupling reactions with alkylorganoboranes,[8] dialkylzincs,[9] Grignard reagents,[10] or alkylorganoindiums.[11] Contrary to these organometallics, alkyltins have been underemployed in comparison with the large number of publications dedicated to the Stille coupling reaction. There are indeed very few works stating the possibility of transferring alkyl groups, other than methyl, from alkyltins.[12] In the course of finding nontoxic and easily removable tin reagents, we recently reported the synthesis of new monoorganotins **2** and their Stille cross-coupling with halides[13] and triflates[14] as electrophiles. The general and easy preparation of the monoorganotins[15] by oxidative addition of the corresponding alkyl halides to the stannylene **1**,[16] associated with the great functional group tolerance and the neutral

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(5) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297−1299.

(6) For Suzuki cross-coupling see: (a) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910−3912. (b) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945−1947. (c) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099−10100. (d) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691−694. For Negishi cross-coupling: (e) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12 527−12 530. For Kumada cross-coupling: (f) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056−4059. With organozirconiums: (g) Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82−83.

(7) (a) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749−5752. For Stille cross-coupling: (b) Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5079−5082. (c) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348.

(8) (a) Kirchhofff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662−13663. (b) Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761−3764.

(9) (a) Yus, M.; Gomis, J. *Eur. J. Org. Chem.* **2002**, 1989−1995. (b) Piber, M.; Jensen, A. E.; Rottländer, M.; Knochel, P. *Org. Lett.* **1999**, *1*, 1323−1326. (c) Boudier, A.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 687−690.

(10) (a) Gagneur, S.; Montchamp, J.-L.; Negishi, E. *Organometallics* **2000**, *19*, 2417−2419. (b) Messner, M.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **2000**, 1137−1155.

(11) Perez, I.; Perez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155−4160.

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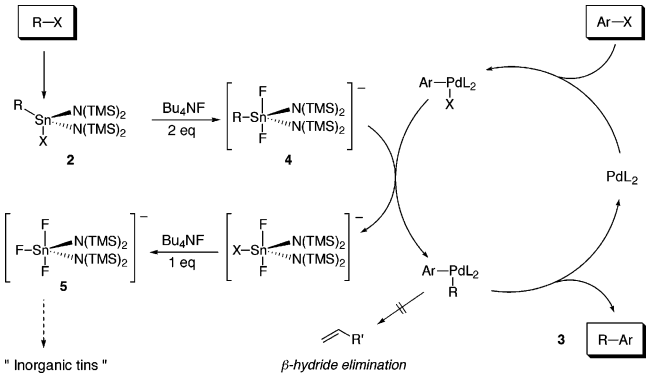
(14) Fouquet, E.; Rodriguez, A. L. *Synlett* **1998**, 1323−1324.

(15) Fouquet, E.; Pereyre, M.; Rodriguez, A. L.; Roulet, T. *Bull. Soc. Chim. Fr.* **1997**, *134*, 959−967.

10.1021/jo047907q CCC: $30.25
Published on Web 02/08/2005

SCHEME 1



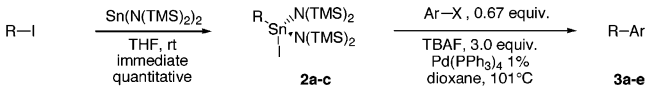
conditions of the Stille reaction, prompted us to assess the ability of monoalkyltins to achieve Csp^2-Csp^3 couplings.[17]

The coupling reaction is believed to proceed via an activated hypervalent organostannate intermediate **4** prepared in situ by adding a fluorine source (Scheme 1). Such nucleophilic activation is a well-established strategy in organosilicon-mediated coupling reactions,[18] and was, more recently, applied to organoboron[19] and organotin chemistry.[7b,13,14,20] It is noteworthy that the trifluorostannate **5** is a nontoxic and easily removable inorganic byproduct, which allows the coupling product **3** to get rid of tin residues.

***n*-Alkyl transfer:** We were first interested in transferring *n*-alkyl groups. Based on our earlier results, we chose to perform the reaction in refluxing dioxane with a 1.5-fold excess of the monoalkyltin partner. Palladium tetrakis(triphenylphosphine) (2%) was elected as catalyst and 3 equiv of TBAF was used as additive. These conditions did yield the expected products in the range 68−91% (Table 1).

Thus, methyl-, butyl-, and decyltins **2a**, **2b**, and **2c** appeared to be efficient reagents for the Stille coupling

TABLE 1. *n*-Alkyl Transfer



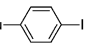
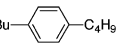
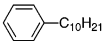
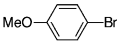
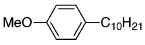
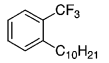
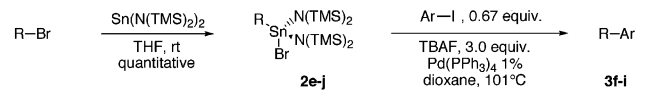
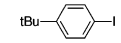
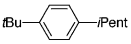
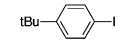
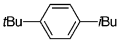
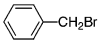
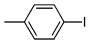
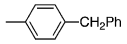
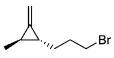
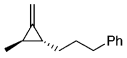
entry	RI	Alkyltin	ArX	time (h)	product		yield (%)
1	CH_3I	**2a**		4		**3a**	91
2	C_4H_9I	**2b**		12		**3b**	73
3	$C_{10}H_{21}I$	**2c**		12		**3c**	71
4	$C_{10}H_{21}I$	**2c**		12		**3d**	75
5	$C_{10}H_{21}I$	**2c**		6		**3e**	68

TABLE 2. Branched-Alkyl Transfer



entry	RBr	Alkyltin	Halide ArX	time (h)	product		yield (%)
1		**2e**		12		**3f**	76
2		**2f**		36		**3g**	63
3		**2g**		72	Iodobenzene unreacted	-	-
4		**2h**		72	Iodobenzene unreacted	-	-
5		**2i**		17		**3h**	54
6		**2j**		8		**3i**	52

reaction (Table 1). The reaction is effective with iodides (entries 2 and 3) as well as with bromides (entries 1, 4, and 5) as the electrophilic substrates. Increasing the length of the alkyl chain did not lower the reactivity of the organotin. In terms of yields, these results have to be compared with the transfer of the *n*-dodecyl group from tetra(*n*-dodecyl)tin, which furnished the cross-coupling product in only 25% yield.[12d] Importantly, the substrate−substrate homocoupling was the sole side reaction isolated and no trace of the β-hydride elimination product (i.e. *n*-decene) was observed, which suggested a quite fast reductive elimination step. Furthermore, the method is tolerant of all substitutions (electron poor or rich) on the aryl ring with only modest changes in yields.

Branched alkyl tranfer: We have also examined the cross-coupling of branched alkytins **2e**−**j** (Table 2). We observed that the reaction was sensitive to the substitution of the alkyl chain. Indeed, while γ substitution had no effect on the reaction rate and yield (entry 1), β substitution had significant effects as demonstrated by the slightly lengthened reaction time (36 h) and the reduced yield (63%) (entry 2). Not surprisingly, α substitution forbade the reaction to proceed either with an electron-donating group (entry 3) or with an electron-withdrawing group (entry 4) as substituents. As a consequence, we were unfortunately unable to transfer secondary alkyl groups under these conditions. The

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(17) A range of monoalkyltins **2a**−**m** were quantitatively prepared by oxidative addition of the corresponding alkyl halides to the stannylene **1**. They were fully characterized by ^{119}Sn, ^{1}H, and ^{13}C NMR spectroscopy and cross-coupled without further purification.

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SCHEME 2

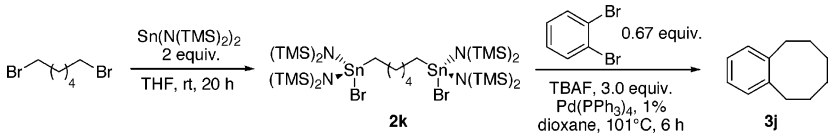
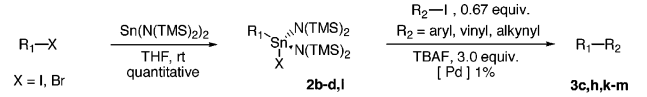
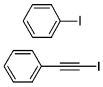
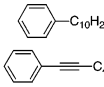
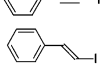
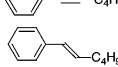
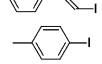
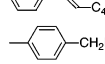
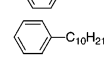


TABLE 3. Ligands Effect



entry	RX	Alkyltin	ArX	catalyst solvent (°C)	time (h)	product		yield (%)
1	$C_{10}H_{21}I$	**2c**		$Pd(Ph_3)_4$ dioxane (101)	12		**3c**	71
2	$C_{10}H_{21}I$	**2c**		$Pd(PPh_3)_2Cl_2$ dioxane (90)	6		**3c**	58
3	$C_{10}H_{21}I$	**2c**		$Pd_2dba_3/P(O\textit{i}Pr)_3$ dioxane (101)	2		**3c**	66
4	$C_{10}H_{21}I$	**2c**		$Pd_2dba_3/AsPh_3$ dioxane (80)	12		**3c**	68
5	$C_{10}H_{21}I$	**2c**		$Pd_2dba_3/Pfur_3$ dioxane (101)	2		**3c**	70
6	C_4H_9I	**2b**		$Pd_2dba_3/P(O\textit{i}Pr)_3$ dioxane (101)	3		**3k**	60
7	C_4H_9I	**2b**		$Pd_2dba_3/P(O\textit{i}Pr)_3$ dioxane (101)	3		**3l**	72
8	$PhCH_2Br$	**2i**		$Pd_2dba_3/P(O\textit{i}Pr)_3$ dioxane (101)	3		**3h**	67
9	$C_{10}H_{21}I$	**2c**		Pd_2dba_3 dioxane (101)	1		**3c**	79
10	$C_{20}H_{41}Br$	**2d**		Pd_2dba_3 dioxane (101)	1		**3m**	82

benzyltin reagent **2i** was cross-coupled with 4-methylphenyl iodide and provided the desired product **3h** (entry 5) in comparable yield with that obtained with the β-substituted alkyltin. Moreover, the reaction allowed the transfer of a more sensible alkyl group (entry 6), furnishing the cross-coupled product **3i** in a non-optimized 52% yield, without opening the methylenecyclopropyl unit.

Finally, the process showed promise for cyclization reactions by using distannylated reagents (Scheme 2). Thus, intermolecular cross-coupling of the organotin **2k** followed by an intramolecular one occurred to give the eight-membered cyclized product **3j** in a 38% yield. A simple dilution of the reaction mixture by a factor of 2 resulted in an improved yield up to 48%.

Ligand effects: These promising results led us to turn our attention to the optimization of the catalytic system (Table 3). The choice of the catalyst generally has a substantial impact on the course of the reaction. The use of $Pd(PPh_3)_2Cl_2$ in place of $Pd(PPh_3)_4$ allowed the reaction to be done with a Pd:PPh_3 ratio of 1:2, which is believed to be the optimal one for the reaction to proceed.[21] We observed a significant acceleration (entry 2 versus entry 1); however, under these conditions, the quantity of biphenyl that arose from the competitive homocoupling of the halide was isolated in 18% yield. To find the most effective catalyst, we surveyed an array of ligands of different donating effect, as the nature of the ligand can exert as well a dramatic influence on the rate of cross-coupling reactions. The catalyst was then formed in situ by introducing the weakly coordinated tris-(dibenzylideneacetone)dipalladium and 2 equiv of the ligand for each Pd atom. Replacing triphenylphosphine by less donating ligands such as triisopropyl phosphite (entry 3) and triphenylarsine (entry 4) resulted in an enhancement of the reaction rate and the ability to proceed at lower temperature. The cross-coupling was successfully extended to other types of substrates such as a iodoalkyne (entry 6) and a iodoalkene (entry 7) to yield the desired products in good yields (60% and 72%, respectively). A large rate enhancement was also observed with tri-2-furylphosphine[22] recommended by V. Farina as the ligand of choice for the Stille cross-coupling (entry 5). Nevertheless, the best results were obtained under the simplest "ligandless" conditions, i.e., by using Pd_2dba_3 as the catalyst (entry 9). Originally, even C20-alkyltin **2d** was efficiently cross-coupled with iodobenzene yielding the corresponding aromatic compound **3m** in 82% yield (entry 10).

Perfluoroalkyl transfer: The scope of our methodology was investigated with the synthesis of perfluoroalkylated aryl compounds. Indeed, perfluoroalkylated derivatives have attracted great interest in recent years not only in the field of catalysis—with the concept of Fluorous Biphasic Catalysis[23]—but also in the field of combinatorial organic synthesis.[24] Nevertheless, only a few approaches have been developed for the introduction of an ethylene or a propylene spacer between the aromatic ring and the perfluoroalkyl unit, whenever this spacer was proved to be necessary to reduce the strong electron-withdrawing effect of the perfluoroalkyl tail.[23d] Most frequently, cross-coupling methodology involves the Heck[25] reaction of perfluoroalkenes with the subsequent hydrogenation of the perfluoroalkenyl-substituted aromatic compounds. To the best of our knowledge, only one Stille coupling reaction has been described to introduce perfluoroalkyl substituents on an aromatic ring.[26]

We first studied the cross-couplings of perfluoroethyltin **2*l*** and perfluoropropyltin **3m** by applying our optimized conditions, i.e., in refluxing dioxane with a 1.7-fold excess

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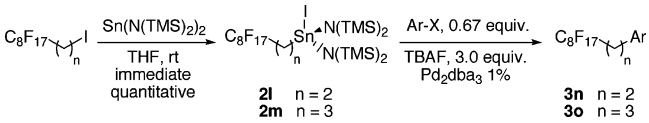
TABLE 4. Pefluoroalkyl Transfer



2l n = 2
2m n = 3
3n n = 2
3o n = 3

entry	alkyl tin	ArX	solvent (°C)	time, h	product	yield, %
1	**2l**	PhI	dioxane (101)	1.75	$Ph(CH_2)_2C_8F_{17}$ (**3n**)	62
2	**2m**	PhI	dioxane (101)	1.75	$Ph(CH_2)_3C_8F_{17}$ (**3o**)	63
3	**2m**	PhI	THF (65)	12	$Ph(CH_2)_3C_8F_{17}$ (**3o**)	89

of the organotin, 3 equiv of TBAF as additive and 2% of Pd_2dba_3 as catalyst. As shown in Table 4, the desired products **3n** and **3o** were obtained in 62% and 63% yields, respectively, within only 1 h 45 min (entries 1 and 2). This difference in terms of reactivity between perfluoroalkyltin and simple alkyltin reagents is presumably related to a faster reductive elimination step in the Stille catalytic cycle. This led us to perform the reaction at lower temperature in view of decreasing some substrate−substrate homocoupling process. Thus, the cross-coupled product **3o** was isolated in 89% yield by carrying out the reaction in refluxing THF (entry 3). This result offered us the possibility of conceiving a one-pot procedure.

In conclusion, we have described the first ligandless-palladium based method for transferring alkyl groups via a cross-coupling reaction of aryl halides with original monoalkyltin reagents. These compounds are easily and quantitatively available through direct oxidative addition of the corresponding halides with a low-valent tin species. Moreover, these reagents met with the criteria of reduced toxicity and easiness of purification, thus solving the major drawbacks of the Stille cross-coupling. Indeed all the organic products were free of organotin contamination as the trifluorostannate byproduct was easily removed by a simple filtration. This methodology was successfully applied to the synthesis of perfluoroalkylated aromatic compounds. Further extensions are currently underway in our laboratory.

Experimental Section

All reactions were carried out under an argon atmosphere in flame-dried glassware. THF and dioxane were distilled under argon from sodium/benzophenone. Commercially available materials were used without further purification. Anhydrous tin chloride was stored under argon before used. The Bu_4NF used in the coupling reactions is the commercially available 1 M solution. Reactions were monitored by gas chromatography (GC) analysis of worked up reaction aliquots. Analytical thin-layer chromatography (TLC) was performed using silica gel plates (0.25 mm). Column chromatography was performed with 40−63 μm silica gel. NMR spectra were recorded at ambient temperature in $CDCl_3$, on a 250 or 300 MHz NMR spectrometer for ^1H and ^{13}C and a 200 MHz spectrometer for ^{119}Sn.

Bis(*N*,*N*-bistrimethylsilylamino)stannylene 1. *n*-butyllithium (41.3 mL of a 2.5 M hexane solution) was added dropwise to a precooled (−78°C, acetone/dry ice) solution of freshly distilled hexamethyldisilazane (21.8 mL, 1 equiv) in anhydrous Et_2O (50 mL) and THF (30 mL). The resulting mixture was allowed to reach room temperature and stirred over a period of 1 h. The resulting lithium amidure was then added dropwise to a suspension of tinchloride(II) (10 g, 1 equiv) in anhydrous Et_2O (50 mL). The resulting reaction mixture was stirred at room temperature for an additional 3 h. The solution was transferred to a flask where the solvents were removed in vacuo to give an orange oil that was distillated under reduced pressure (0.1 mmHg, 110 °C) to furnish bis(*N*,*N*-bistrimethylsilylamino)-stannylene **1** in 89% yield (20.6 g).

General Procedure for the Preparation of Monoalkyltin Compounds 2a−m. In a typical procedure, alkyl halide (1 equiv) was added to a solution of bis(*N*,*N*-bistrimethylsilylamino) stannylene **1** (1 g) in anhydrous THF (10 mL) under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature until the reaction mixture turned pale yellow. The solution was then concentrated in vacuo to yield quantitatively the monoalkyltin **2a−m**.

General Procedure for the Stille Cross-Coupling. A solution of TBAF (5.9 mL, 3 equiv, 1 M in THF) was added in situ, at room temperature, to the monoorganotin reagents **2a−m** (1.85 mmol) prepared following the above procedure.. The reaction mixture was concentrated in vacuo before adding the anhydrous solvent (THF or dioxane, 8 mL), the catalyst (1% or 2%), and the halide (1.23 mmol, 0.67 equiv). The reaction mixture was heated until the complete consumption of the halide before cooling at room temperature. Removal of the solvent in vacuo yielded an oily residue, which was subjected to chromatography on silica gel (eluent: petroleum ether) to furnish the cross-coupled product **3a−o**.

Selected Data for Monoorganotin 2j and 2k: Bromobis-(*N*,*N*-bistrimethylsilylamino)(3-(3-methyl-2-methylencyclopropyl)propyl)tin 2j. Solvent: THF. Temperature: room temperature. Reaction time: 2 h. Quantitatively prepared following the general procedure. ^{119}Sn NMR (74.6 MHz, $CDCl_3$) δ −57.2; ^1H NMR (250 MHz, $CDCl_3$) δ 5.30−5.28 (m, 2H), 1.72−1.31 (m, 6H), 1.09−0.81 (m, 5H), 0.23 (s, 36H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 143.3, 102.3, 36.2 ($^3J_{Sn-C}$ = 72 Hz), 30.5 ($^1J_{Sn-C}$ = 607 Hz), 25.7, 22.9, 17.5, 17.1, 5.8 (12C).

1,6-Bis[bromobis(*N*,*N*-bistrimethylsilylamino)stannyl]-hexane 2k. Solvent: THF. Temperature: room temperature. Reaction time: 3 h. Quantitatively prepared following the general procedure. ^{119}Sn NMR (74.6 MHz, $CDCl_3$) δ −58.8; ^1H NMR (250 MHz, $CDCl_3$) δ 1.83−1.35 (m, 12H), 0.22 (s, 72H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.8 (2C, $^3J_{Sn-C}$ = 139 Hz), 30.7 (2C, $^1J_{Sn-C}$ = 622 Hz), 25.7 ($^2J_{Sn-C}$ = 36 Hz), 5.7 (24C).

Selected Data for Coupling Products 3i and 3j: 1-Phenyl-3-(3-methyl-2-methylencyclopropyl)propane 3i. Solvent: dioxane. Reaction time: 8 h. Temperature: 101 °C. Catalyst: Pd(PPh$_3$)$_4$ 1%. Yield: 52%. ^1H NMR (250 MHz, $CDCl_3$) δ 7.38−7.21 (m, 5H), 5.60−5.58 (m, 2H), 2.68 (br t, J = 7.6 Hz, 2H), 1.87−1.29 (m, 4H), 1.20−0.94 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 144.0, 142.7, 128.5 (2C), 128.4 (2C), 125.7, 101.8, 35.7, 32.4, 31.5, 23.6, 17.6, 17.1; MS (EI) *m/z* (rel intensity) 186 (M^+, 6), 171 (20), 157 (27), 143 (17), 129 (43), 117 (56), 104 (32), 91 (100); HRMS (EI) calcd for $C_{14}H_{18}$ 186.1409, found 186.1412.

Bicyclododec[6.4.0]-1,9,11-triene 3j. Solvent: dioxane. Reaction time: 15 h. Temperature: 101 °C. Catalyst: Pd(PPh$_3$)$_4$ 1%. Yield: 48%. ^1H NMR (250 MHz, $CDCl_3$) δ 7.19−7.03 (m, 4H), 2.85−2.73 (m, 4H), 1.78−1.61 (m, 4H), 1.45−1.33 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 141.3 (2C), 129.0 (2C), 126.2 (2C), 32.34 (2C), 32.29 (2C), 25.9 (2C); MS (EI) *m/z* (rel intensity) 160 (M^+, 100), 131 (54), 117 (76), 104 (93), 91 (45); HRMS (EI) calcd for $C_{12}H_{16}$ 160.1252, found 160.1255.

Supporting Information Available: Experimental procedures and NMR spectroscopic data including ^1H and ^{13}C for compounds **1**, **2a−m**, and **3a−o** as well as ^{119}Sn for compounds **2a−m**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO047907Q