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Catalytic C−H Bond Stannylation: A New Regioselective Pathway to C−Sn Bonds via C−H Bond Functionalization

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Abstract: The ubiquitous Stille coupling reaction utilizes Sn−C bonds and is of great utility to organic chemists. Unlike the B−C bonds used in the Miyaura−Suzuki coupling reaction, which are readily obtained via direct borylation of C−H bonds, routes to organotin compounds via direct C−H bond functionalization are lacking. Here we report that the nickel-catalyzed reaction of fluorinated arenes and pyridines with vinyl stannanes does not provide the expected vinyl compounds via C−F activation but rather provides new Sn−C bonds via C−H functionalization with the loss of ethylene. This mechanism provides a new unanticipated methodology for the direct conversion of C−H bonds to carbon−heteroatom bonds.

In the past few decades, transition-metal C−H bond activation[1] and catalytic functionalization have gone from an exotic branch of transition-metal reactivity without practical application to cutting-edge technology in catalytic organic transformations.[2] Reactions that convert C−H bonds into molecules bearing versatile functional groups, such as regioselective borylations,[3] have been extensively utilized to generate functionalized organics such as arylboronic esters directly from hydrocarbons and B−H or B−B bond cleavage, as depicted in Figure 1; these compounds serve as versatile starting materials used in reactions such as Miyaura−Suzuki coupling.[4]

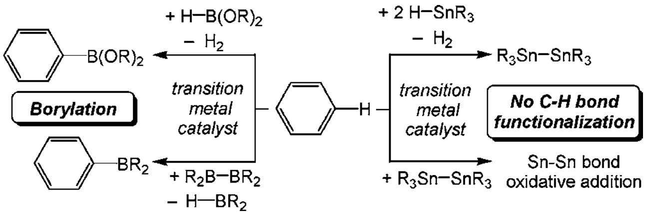

Figure 1. Examples of aryl C−H bond borylation and a comparison to the known chemistry of tin.

Unfortunately, extensions of the C−H bond borylation methodology are limited in scope. For example, although the oxidative addition of Sn−H bonds to transition metals has precedent, the catalytic conversion of trialkyltin hydrides, R_3SnH, to R_3SnSnR_3 and H_2 is often instantaneous. The oxidative addition of Sn−Sn bonds has also been reported; to date, however, this reaction has been utilized only in catalytic coupling to carbon−halide bonds and additions to carbon−carbon multiple bonds.[5] This pair of currently unsuccessful approaches to catalytic C−H bond stannylation, which are analogous to those used in borylation chemistry, are shown at the right in Figure 1. A new method for forming C−Sn bonds from C−H bonds could have significant impact as a facile route to reagents for the Stille coupling reaction,[6] which is widely utilized because of the air and moisture stability and functional group tolerance of the organonotin compounds it employs. The syntheses of these organotin reagents typically involve multiple steps from expensive functional-group-containing precursors.

We have previously shown that stoichiometric amounts of $Ni(COD)_2$ (COD = 1.5-cyclooctadiene) and the ancillary ligand $MeNC_5H_4N^iPr$ react with a variety of partially fluorinated aromatics, such as C_6F_5H, via selective C−F activation at room temperature.[7] The addition of $H_2C{=}CHSnBu_3$ and a partially fluorinated arene to catalytic amounts of $Ni(COD)_2$, and $MeNC_5H_4N^iPr$ would be expected to result in catalytic C−F bond functionalization via the Stille coupling reaction to produce a partially fluorinated styrene.[8] Remarkably, these reactions at room temperature yielded no C−F activation products and practically quantitative catalytic conversions to the products of C−H functionalization, $C_6F_nH_{5-n}SnBu_3$, as shown in Figure 2. The stoichiometric production of ethylene as a byproduct was positively identified by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy when the reaction was performed in C_6D_6 in a sealed NMR tube. The reaction was found to go to completion with as little as 1 mol % $Ni(COD)_2$ and $MeNC_5H_4N^iPr$ and provided practically pure product, as monitored by ^{19}F, ^1H, and ^{119}Sn NMR spectroscopy. The reaction could also be performed without the addition of solvent.

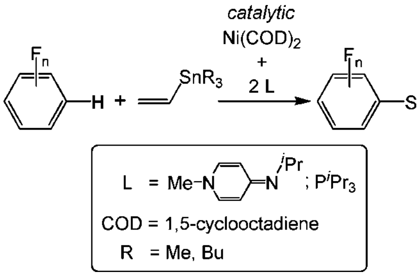

Figure 2. General reaction scheme for the catalytic stannylation of C−H bonds.

To investigate the generality of this catalytic functionalization, we examined the scope of fluorinated aromatics that undergo this reaction. A summary is shown in Table 1. Aromatic substrates with C−H bonds ortho to two fluorines, such as C_6F_5H, 1,2,4,5-$C_6F_4H_2$, 1,2,3,5-$C_6F_4H_2$, 1,2,4-$C_6F_3H_3$, 1,3,5-$C_6F_3H_3$, and 1,3-$C_6F_2H_4$ proved to be the most reactive. The monostannylated compounds **1**, **2**, **4**, **7**, and **10** were obtained with good selectivity (>91%) using a modest excess of fluorinated aromatic (∼2 equiv); the only significant impurities were the distannylated compounds **3**, **5**, **8**, and **11**, which were readily separated. The distannylated compounds could be obtained with good selectivity themselves by using 2.5 equiv of $H_2C{=}CHSnBu_3$. The distannylated isomer, 1,3-$(Bu_3Sn)_2$-2,4,5-C_6F_3H (**9**), was also present as a small impurity in the synthesis of **8**. The tristannylated derivative of 1,3,5-$C_6F_3H_3$, **12**, was also accessible using P^iPr_3

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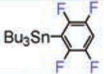
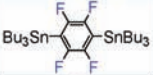
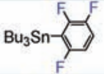
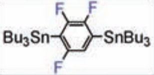
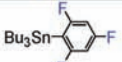
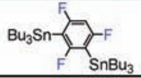
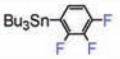
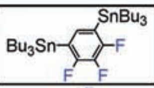
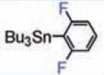
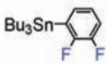
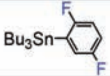
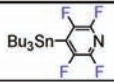
Table 1. Catalytic C−H Bond Functionalization of Fluorinated Arenes with Tributylvinylstannane

Reagent	Ancillary Ligand and Ni(COD)$_2$ Loading (%)	Conditions	Yield (%)	Products	#
C_6F_5H	MeNC$_5$H$_4$N^{i}Pr 3 % P^{i}Pr$_3$, 5 %	35 °C, 1 h 80 °C, 3 h	95^a (70^b) 98^a		**1**
1,2,4,5–$C_6F_4H_2$	MeNC$_5$H$_4$N^{i}Pr 3 % P^{i}Pr$_3$, 5 %	35 °C, 0.5 h 80 °C, 0.2 h	95^a (4^a of **3**) 93^a (7^a of **3**)		**2**
1,2,4,5–$C_6F_4H_2$	MeNC$_5$H$_4$N^{i}Pr 3 % P^{i}Pr$_3$, 5 %	45 °C, 6 h^c 80 °C, 8 h^c	85^a (11 of **2**) 99^a		**3**
1,2,3,5–$C_6F_4H_2$	MeNC$_5$H$_4$N^{i}Pr 3 % P^{i}Pr$_3$, 5 %	35 °C, 0.7 h 80 °C, 0.5 h	95^a (82^b) 90^a (10 of **5**)		**4**
1,2,3,5–$C_6F_4H_2$	MeNC$_5$H$_4$N^{i}Pr 5 % P^{i}Pr$_3$, 5 %	40 °C, 18 h^c 80 °C, 12 h^c	84^a (12 of **4**) 99^a		**5**
1,2,3,4–$C_6F_4H_2$	MeNC$_5$H$_4$N^{i}Pr 3 % P^{i}Pr$_3$, 5 %	45 °C, 12 h 80 °C, 4 h	38^a 95^a		**6**
1,2,4–$C_6F_4H_2$	MeNC$_5$H$_4$N^{i}Pr 3 % P^{i}Pr$_3$, 5 %	35 °C, 7 h 80 °C, 1 h	98^a 98^a		**7**
1,2,4–$C_6F_4H_2$	P^{i}Pr$_3$, 5 %	80 °C, 48 h^c	50^a (40^a of **7** and Bu_6Sn_2)		**8**
1,3,5–$C_6F_4H_2$	MeNC$_5$H$_4$N^{i}Pr 3 % P^{i}Pr$_3$, 5 %	40 °C, 4 h 80 °C, 0.5 h	91^a (83^b) 83^a (17 of **11**)		**10**
1,3,5–$C_6F_4H_2$	MeNC$_5$H$_4$N^{i}Pr 5 % P^{i}Pr$_3$, 5 %	40 °C, 18 h^c 80 °C, 12 h^c	38^a (55 of **10**) 45^a (50 of **12**)		**11**
1,3,5–$C_6F_4H_2$	P^{i}Pr$_3$, 5 %	80 °C, 18 h^d	95^a (5 of **11**)		**12**
1,2,3–$C_6F_4H_2$	P^{i}Pr$_3$, 5 %	80 °C, 48 h	50^a (30 of **14**)		**13**
1,2,3–$C_6F_4H_2$	P^{i}Pr$_3$, 5 %	80 °C, 72 h^c	30^a (40 of **13** and Bu_6Sn_2)		**14**
1,3–$C_6F_4H_2$	P^{i}Pr$_3$, 5 %	80 °C, 18 h	90^a		**15**
1,2–$C_6F_4H_2$	P^{i}Pr$_3$, 5 %	80 °C, 18 h^e	92^a (2 of **17**)		**16**
1,4–$C_6F_4H_2$	P^{i}Pr$_3$, 5 %	80 °C, 18 h^e	90^a (10 of **19**)		**18**
2,3,5,6–C_5F_4HN	P^{i}Pr$_3$, 5 %	80 °C, 2 h	98^a (87^b)		**22**

[a] NMR yield from integration of $^{19}F\{^1H\}$ NMR spectra. [b] Isolated yield after chromatography. [c] Using 2.5 equiv of Bu_3Sn(vinyl). [d] Using 3.5 equiv Bu_3Sn(vinyl). [e] Using a 10-fold excess of fluorinated aromatic.

as the ancillary ligand. A decrease in rate was observed with substrates with a lesser degree of fluorination; however, it proved possible to increase the turnover rate by increasing the temperature from 25 to 45 °C using the ancillary ligand MeNC$_5$H$_4$N^{i}Pr. Temperatures higher than 60 °C resulted in rapid decomposition of Ni(COD)$_2$ to nickel metal, and the yields dropped off significantly. In the cases where data for the analogous borylation reactions were available for comparison, these stannylation reactions were found to occur under milder conditions, produce higher yields, and be more selective, with no C−F functionalization products observed.[9]

The reactions of substrates where only one fluorine substituent is disposed ortho to a C−H bond were slower under similar conditions and were not efficiently catalyzed using MeNC$_5$H$_4$N^{i}Pr as the ancillary ligand. Although replacing MeNC$_5$H$_4$N^{i}Pr with traditional phosphine donors, such as P^{i}Pr$_3$, led to lower rates than using MeNC$_5$H$_4$N^{i}Pr for the substrates investigated, the thermal stability of the catalyst improved, which allowed for efficient functionalization at higher temperatures. For example, with P^{i}Pr$_3$ as the ancillary ligand, the functionalization of 1,2,3,4-$C_6F_4H_2$ occurred in 4 h at 80 °C and provided selective conversion to the monostannylated product **6**. Similar results were observed when 1,2,3-trifluorobenzene was used as the substrate, providing the monosubstituted product **13**. The distannylated product **14** was also obtained selectively in the presence of excess $CH_2{=}CHSnBu_3$ and was present as a slight impurity in the synthesis of **13**. The activation of heterocycles such as 2,3,5,6-tetrafluoropyridine also proved to be possible when phosphines were used but did not occur with the ancillary ligand MeNC$_5$H$_4$N^{i}Pr.

The monostannylated compounds **15**, **16**, and **18** were obtained from 1,3-, 1,2-, and 1,4-difluorobenzene, respectively, in >90% yield at 80 °C when P^{i}Pr$_3$ was employed as the ligand. The only significant impurities were the distannylated compounds 1,4-$(Bu_3Sn)_2$-2,3-$C_6F_2H_2$ (**17**), 1,4-$(Bu_3Sn)_2$-2,5-$C_6F_2H_2$ (**19**), and 1,3-$(Bu_3Sn)_2$-2,5-$C_6F_2H_2$ (**20**). With fluorobenzene, only 15% conversion to the monostannylated complex 1-(Bu_3Sn)-2-C_6FH_3 (**21**) was achieved. These di- and monofluorinated aromatics proved to be poor substrates when MeNC$_5$H$_4$N^{i}Pr was used as the ancillary ligand.

Both an ancillary ligand and Ni(COD)$_2$ are necessary for the desired catalytic reaction to proceed under the conditions used. Catalysis was observed even in the presence of added Hg, which argues against Ni metal particles from the decomposition of Ni(COD)$_2$ acting as the active catalyst. No direct reaction was observed between pentafluorobenzene and Bu_3Sn(vinyl) even when a toluene solution was heated to 100 °C. Similarly, no reaction was observed with the addition of the ligand MeNC$_5$H$_4$N^{i}Pr in the absence of the metal-containing catalyst precursor Ni(COD)$_2$.

The reagents Me_3Sn(vinyl), *cis*-(1-propenyl)$SnBu_3$, and *trans*-(1-propenyl)$SnBu_3$ all proved to be successful reagents for C−H bond functionalization. The replacements of these reagents with Bu_4Sn, Ph_4Sn, $Me_3SnSnMe_3$, and Bu_3SnPh were unsuccessful, as no conversion to the desired products was observed even at elevated temperatures. The reaction of Bu_3SnH and C_6F_5H using catalytic Ni(COD)$_2$ and MeNC$_5$H$_4$N^{i}Pr or P^{i}Pr$_3$ did not yield **1** but instead produced Bu_6Sn_2 instantaneously with the liberation of H_2 gas. The ratio of C−H-functionalized product to C−D-functionalized product in the reaction of the monodeuterated substrate 1,2,4,5-C_6F_4HD with $Bu_3SnCH{=}CH_2$ using catalytic Ni(COD)$_2$ and MeNC$_5$H$_4$N^{i}Pr was found to be 2.1:1 at 298 K by integration of the $^{19}F\{^1H\}$ NMR resonances of the products. This kinetic isotope effect is consistent with the equilibrium isotope effect we previously observed in the oxidative addition of 1,2,4,5-C_6F_4HD to a Ni(PEt$_3$)$_2$ synthon;[10] it supports a mechanism where oxidative cleavage of the C−H bond occurs at the transition metal during the catalytic cycle[10,11] and eliminates the possibility that the mechanism involves simple deprotonation of the fluoroarene.

Two plausible mechanistic manifolds for the functionalization of C_6F_5D with *cis*-(1-propenyl)$SnBu_3$ that invoke the oxidative addition product $L_2NiD(C_6F_5)$, where L is the ancillary ligand, are shown in Figure 3. One possibility is that the reaction occurs by

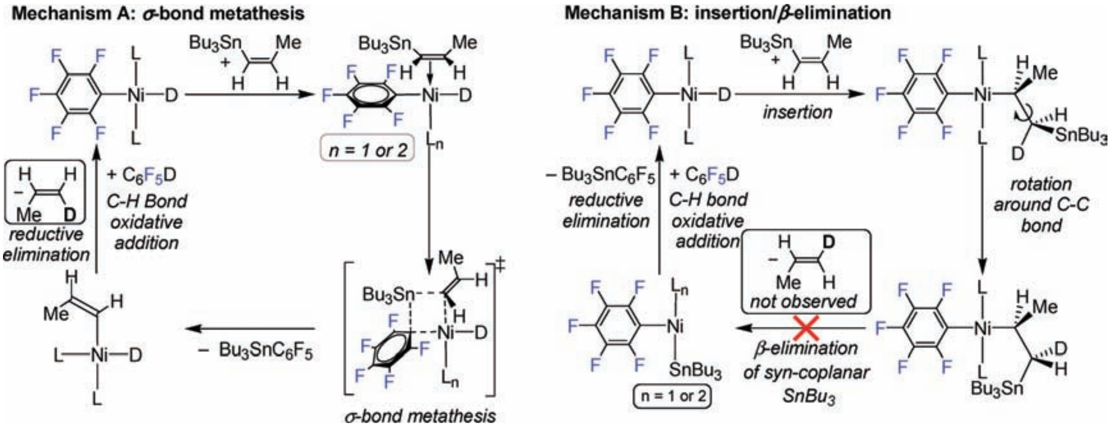


Figure 3. Two possible reaction pathways for C−Sn bond formation.

oxidative addition of C−H and Sn−C bonds to Ni centers, pure σ-bond metathesis, or some combination of these processes.[12] An example of this mechanistic manifold showing oxidative addition of the C−H bond of the fluoroarene and σ-bond metathesis to form the new C−Sn bond is shown in Figure 3 as mechanism A. In this mechanism, the double bond of the propenyl group coordinates to the metal, which brings the Bu_3Sn and C_6F_5 substituents into close enough proximity to undergo σ-bond metathesis. Reductive elimination of (*Z*)-1-deuteropropene followed by oxidative addition of C_6F_5D regenerates $L_2NiD(C_6F_5)$. Mechanism B involves 1,2-insertion of the vinyl moiety into the Ni−D bond followed by β-elimination of the $SnBu_3$ group. Mechanism B would produce (*E*)-1-deuteropropene and thus can be differentiated from mechanism A.

Experimentally, the functionalization of C_6F_5D with *cis*-(1-propenyl)$SnBu_3$ was observed to liberate almost exclusively (*Z*)-1-deuteropropene at 50% conversion, as identified by ^{1}H NMR spectroscopy. The formation of (*Z*)-1-deuteropropene supports mechanistic manifold A, where oxidative addition, σ-bond metathesis, or a combination of these processes accounts for Sn−C bond formation. Mechanism A is reminiscent of Stille coupling, where the aryl group in this case adopts the role typically played by a halide anion during the transmetalation step.[13] This reaction pathway provides an unexpected route to facile C−H bond functionalization under mild conditions.

Although the past decade has seen significant progress in the direct conversion of C−H bonds to C−C, C−N, and C−O bonds, few reactions are available that can function with a wide range of substrates and convert hydrocarbons to versatile functional-group-containing materials. The stannylation reaction reported here provides a facile route to fluorinated arenes with a range of substitution patterns from commercially available chemicals. The stannanes produced here have the potential to serve as a library of compounds for the synthesis of fluorinated pharmaceuticals bearing a variety of substitution patterns,[14] among many possible applications. It has been noted that although fluorine substituents adjacent to aromatic C−H bonds thermodynamically favor oxidative addition because of stronger carbon−metal bonds, it has been proposed that these bonds are actually more difficult to catalytically functionalize because of this increased bond strength.[15] A greater scope of substrates may be accessible with catalysts involving second- and third-row metals, which are capable of C−H bond activation of unactivated arenes such as those commonly used in borylation.[3] Also of interest is the extension of the scope of this methodology to the synthesis of other carbon−heteroatom bonds. Efforts to identify active catalysts and substrates are underway.

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Supporting Information Available: Full experimental details for the preparation and characterization of **1**−**22** and details of mechanistic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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