

Tin-Mediated CH Activation and Cross-Coupling in a Single Flask

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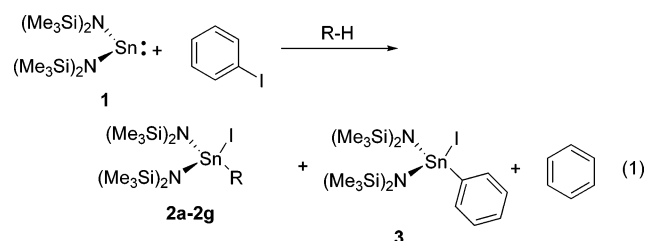
Summary: Tin-mediated CH activation and cross-coupling in a single flask has been achieved by employing a mixed stannylene/phenyl iodide reagent followed by Stille cross-coupling. The reagent has been successfully employed for alkanes and ethers and shows radical-like regioselectivity.

Carbon–hydrogen (C–H) bond activation has been the focus of many academic and industrial studies.^{1–3} The vast majority of these studies have involved transition-metal-mediated C–H activation reactions. Significant progress has been made in recent years applying this transition-metal-based approach to practical problems in organic synthesis.^{4–8} Considerably less progress has been made in the discovery and development of CH activation reactions that generate an E–C bond, where E is a main-group element. In principle, such reactions are highly desirable, since they generate a product containing an E–C bond which could be directly employed in carbon–carbon bond forming reactions. A notable success in this area is the work of Crabtree et al. using Hg to both activate CH bonds and subsequently form new carbon–carbon bonds by cross-coupling.^{9–11} Electrophilic arene activations are well-precedented for Hg, Tl, Pb, and Sn.¹² In addition, substantial progress has been made in CH activation to form B–C bonds.^{13,14}

Recently, we reported the C–H activation of ethers and alkanes by a mixed germylene/aryl halide reagent as well as the salt-catalyzed insertion of germynes into nitrile C–H bonds, ketones, and phenones.^{15,16} Unfortunately, methods to

form C–C bonds using Ge–C reagents are extremely limited.^{17–20} To improve the utility of this method for the direct formation of main-group-metal to carbon bonds, we explored the extension of this chemistry to stannylenes. We now report that the stannylene $\text{Sn}[\text{N}(\text{SiMe}_3)_2]_2$ (**1**)^{21–23} can be employed in conjunction with an aryl halide for C–H activation of alkanes and ethers and that the products derived from these reactions can be used in subsequent Stille-type $\text{C}(\text{sp}^3)$ – $\text{C}(\text{sp}^2)$ cross-coupling reactions^{24–26} to form new carbon–carbon bonds.

C–H activation is observed when equimolar amounts of **1** and phenyl iodide (0.060 mmol, 0.03 M) are mixed in hydrocarbon solvent (eq 1). Activation of C–H bonds in



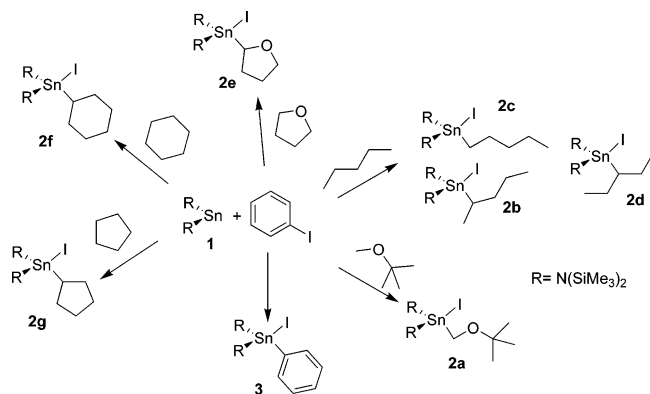
cyclohexane, cyclopentane, pentane, tetrahydrofuran (THF), and *tert*-butyl methyl ether were observed (Scheme 1). A new Sn–C bond is formed, and 1 equiv of benzene is formed. The cyclohexane case was also run using C_6D_{12} and *m*-iodotoluene. Mass spectroscopy indicated the formation of monodeuterio-toluene. When the reactants are simply mixed, a substantial amount of the oxidative addition product **3** is also formed. Similar to the results previously observed for $\text{R}_2\text{Ge}/\text{PhI}$,¹⁵ CH activation preferentially occurs α to the oxygen in THF and the secondary sites are preferred over the primary sites for pentane ($\sim 6.2:1$, secondary to primary).

The amount of CH activation product (**2a–g**) could be maximized and the amount of oxidative-addition product (**3**) minimized by performing the reaction under highly dilute conditions. In a typical reaction, 25 mL of a 0.018 M solution

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Scheme 1. Activation of Alkanes and Ethers by a Stable Stannylenes and Phenyl Iodide


of stannylenes in the solvent of choice was added slowly via a syringe pump (0.07 mL/min) to a stirred 25 mL solution of 0.02 M PhI. Reactions in which the yellow color of the stannylenes instantly disappears (cyclopentane and cyclohexane) yield no detectable **3**. However, reactions in which the yellow color of the stannylenes builds up (pentane, THF, *tert*-butyl methyl ether, diethyl ether) still yield appreciable amounts of **3** (11, 36, 32, and 63%, respectively). The rates of addition used for this chemistry are ~4–6 times slower than were required for the analogous germylene chemistry.¹⁵

Slow addition techniques effectively eliminated the side product **3** and made it possible to isolate pure [(Me₃Si)₂N]₂SnIR for R = cyclohexyl, cyclopentyl. The cyclopentyl product was also characterized by X-ray crystallography (Figure 1).²⁷ Although the mixture of primary and secondary CH activation products and **3** that resulted from the reaction with *n*-pentane did not prove amenable to separation, pure [(Me₃Si)₂N]₂SnI-(CH₂)₄CH₃ (**2c**) was obtained by the oxidative addition of 1-iodopentane with **1**. The NMR assignments from this material were then used to positively identify the presence of the primary pentyl product in the CH activation reaction mixture. For THF and *tert*-butyl methyl ether, neither reducing the concentration of the solutions further (as low as 0.01 M) nor further slowing the rate of addition (as low as 0.023 mL/min) was effective at lowering the amount of **3** below 36 and 32%, respectively. The solubilities of **2a** and **3** are virtually identical, and we were unable to separate these materials by recrystallization from hydrocarbon, aromatic, or ethereal solvents or using mixtures such as diethyl ether/acetonitrile. Attempts to separate **2a** from **3** using sublimation also failed as a purification method, as the materials cosublimed. Fortunately, the presence of **3** does not prevent the cross-coupling reaction.

The use of phenyl bromide and phenyl chloride was also tested. Similar to the previously reported case for germylenes, CH activation could be achieved using phenyl bromide but was dramatically slower. For example, refluxing **1**, phenyl bromide, and cyclohexane for 24 h resulted in 15% and 25% conversion to CH activation and oxidative addition products, respectively. The remaining 60% of **1** did not react. Neither CH activation nor oxidative addition was observed for reaction of phenyl chloride, even under refluxing conditions. The relative rates of

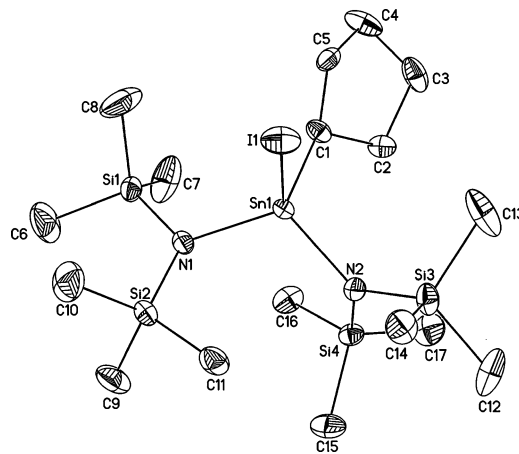


Figure 1. ORTEP diagram of [(Me₃Si)₂N]₂SnI(C₅H₉) (**2g**). Selected bond lengths (Å) and angles (deg): Sn–C1, 2.169(2); Sn–N1, 2.049(2); Sn–N2, 2.055(2); Sn–I, 2.727(5); C1–Sn–N1, 118.19(7); C1–Sn–N2, 108.82(7); C1–Sn–I, 103.67(5); N2–Sn–I, 110.32(4); N1–Sn–I, 102.23(5); N1–Sn–N2, 112.84(6).

PhI > PhBr >>> PhCl are consistent with the trend in both strengths with respect to homolytic C–X bond cleavage.

Fouquet et al. have previously demonstrated that this class of tin reagents provides excellent substrates for the Stille cross-coupling reaction.^{28–31} Products obtained from the CH activation reaction can be directly applied to the cross-coupling reactions. The Fouquet conditions are restricted to primary C–Sn bonds; thus, **2a,c** are the only CH activation products with the appropriate structure. These compounds were smoothly converted into benzyl *tert*-butyl ether and amylbenzene, respectively. The reaction conditions employed differ in terms of an increase in catalyst load (3% vs 1% for Fouquet) and a greater degree of dilution.

Ideally, the CH activation and cross-coupling could both be performed in the same reaction flask without an isolation step. Indeed, this proved to be the best way to run these reactions. In a typical one-pot reaction, 25 mL of a 0.018 M solution of **1** in *tert*-butyl methyl ether was dripped into an equimolar 25 mL stirred 0.02 M solution of phenyl iodide over a period of 5 h (Scheme 2). After 12 h of stirring to ensure completion of the reaction, the volatiles (excess *tert*-butyl methyl ether and benzene) were removed, leaving a yellow powder. The cross-coupling reagents were then added to the same flask in order: phenyl iodide (0.440 mmol, 1 equiv), tetrabutylammonium fluoride (TBAF, dissolved in THF; 1.32 mmol, 3 equiv), tetrakis(triphenylphosphine)palladium as a catalyst (15 mg, 3% catalyst load), and 10 mL of dioxane as solvent. The solution was refluxed for 12 h and then cooled to room temperature (20 °C).

The resulting dark yellow solution, also containing black sediment, was filtered through 1 in. of Celite in a glass pipet, resulting in a light yellow solution. Milliliter aliquots were used for GC/MS experiments. A 67% yield (by GC/MS) of cross-coupled product was obtained for *tert*-butyl methyl ether (overall 26% yield from **1**), and a yield of 65% was obtained for pentane (overall 5% from **1**).

(27) Crystal data for **2g**: C₁₇H₄₅N₂Si₄ISn, *M*_r = 635.50, orthorhombic, *Pbca*, colorless block, *a* = 13.481(2) Å, *b* = 17.536(3) Å, *c* = 23.734(4) Å, *V* = 5610.8(2) Å³, *T* = 123(2) K, *Z* = 8, *R*(*F*, observed data) = 0.0202, GOF = 1.104. Data were collected on a Bruker SMART CCD-based X-ray diffractometer. The structure was solved and refined using Bruker SHELXTL software. Hydrogen atoms were placed in idealized positions and refined isotropically; non-hydrogen atoms were refined anisotropically.

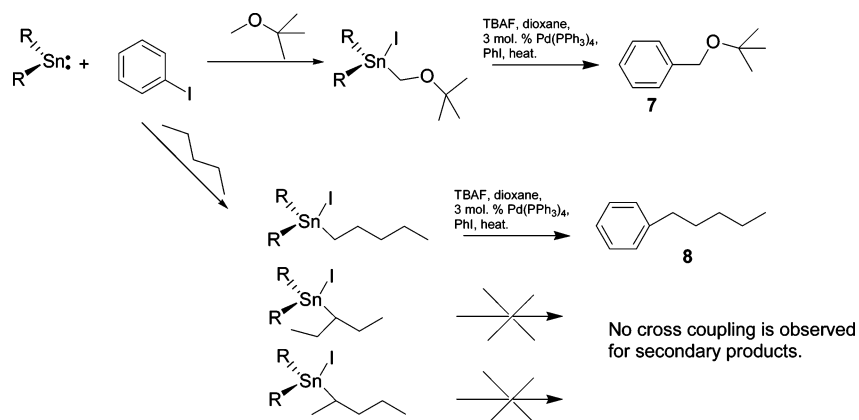
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Scheme 2. One-Pot C–H Activation and Cross-Coupling



In summary, a new method for CH activation of alkanes and ethers is reported that leads directly to the formation of a Sn–C bond. The products derived from the activation of primary carbons can be carried forward directly for C–C bond formation reactions using Stille cross-coupling methodology without need of further isolation. Additional studies are underway to explore the mechanism of this reaction and develop synthetically useful applications.

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Supporting Information Available: Text giving complete experimental preparation details and a CIF file giving crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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