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Synthesis and Application of Alkenylstannanes Derived from Base-Sensitive Cyclopropenes

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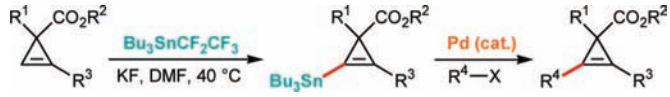
ABSTRACT



In the presence of stoichiometric potassium fluoride, a range of base-sensitive cyclopropenes undergo direct stannylation using (pentafluoroethyl)tributylstannane. The resulting stannylcyclopropenes serve as precursors to a variety of tetrasubstituted cyclopropenes that might otherwise be difficult to access using alternative methods.

The high degree of strain inherent in the three-membered ring of cyclopropenes confers upon these molecules a unique and interesting range of reactivities, which has made them the targets of significant investigation from chemists for many years.[1] A rich diversity of nucleophilic additions, substitutions, rearrangements, cycloadditions, and ring-opening reactions are among the typical reactions that cyclopropenes undergo, and new variants of these processes continue to be developed.[1,2] Due to the versatility of these compounds, the development of new methods that enable the synthesis of functionalized cyclopropenes that are otherwise difficult to access using conventional methods is in high demand.

In this regard, cyclopropenes containing a trialkylstannyl substituent on one or both of the alkene carbons could potentially serve as useful precursors to a range of other cyclopropenes through Stille cross-coupling reactions.[3−5] Surprisingly, only a few examples of these compounds have been reported previously.[6] The standard method to prepare 1- or 2-stannylcyclopropenes is through reaction of a cyclopropenyllithium species with a trialkyltin chloride.[6]

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(1) For reviews, see: (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77–151. (b) Baird, M. S. *Cyclopropenes: Transformations (Houben-Weyl)*; Thieme: Stuttgart, Germany, 1997; Vol. E17d/2, pp 2781−2790. (c) Nakamura, M.; Isabe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295–1326. (d) Fox, J. M.; Yan, N. *Curr. Org. Chem* **2005**, *9*, 719–732. (e) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221–1245. (f) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. (g) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364–7376.

(2) For recent, selected examples of investigations into the reactivity of cyclopropenes, see: (a) Alnasleh, B. K.; Sherrill, W. M.; Rubin, M. *Org. Lett.* **2008**, *10*, 3231–3234. (b) Yan, N.; Liu, X.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 563–568. (c) Rubina, M.; Woodward, E. W.; Rubin, M. *Org. Lett.* **2007**, *9*, 5501–5504. (d) Masarwa, A.; Stanger, A.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 8039–8042. (e) Trofimov, A.; Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Org. Chem.* **2007**, *72*, 8910–8290. (f) Chuprakov, S.; Malyshev, D. A.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 14868–14869. (g) Hirashita, T.; Shiraki, F.; Onishi, K.; Ogura, M.; Araki, S. *Org. Biomol. Chem.* **2007**, *5*, 2154–2158. (h) Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 3824–3825. (i) Smith, M. A.; Richey, H. G., Jr. *Organometallics* **2007**, *26*, 609–616.

(3) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.

(4) For selected reviews of the Stille reaction, see: (a) de Souza, M. V. N. *Curr. Org. Synth.* **2006**, *3*, 313–326. (b) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704–4734. (c) Mitchell, T. N. *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 3. (d) Pattenden, G.; Sinclair, D. J. *J. Organomet. Chem.* **2002**, *653*, 261–268. (e) Kosugi, M.; Fugami, K. *J. Organomet. Chem.* **2002**, *653*, 50–53. (f) Duncton, M. A.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235–1246. (g) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–652. (h) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.

(5) For Stille reactions of stannylcyclopropenes, see ref 6c.

(6) (a) Kirms, M. A.; Primke, H.; Stohlmeier, M.; de Meijere, A. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 462–464. (b) Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron* **1992**, *48*, 2045–2057. (c) Untiedt, S.; de Meijere, A. *Chem. Ber.* **1994**, *127*, 1511–1515. (d) Eckert-Maksić, M.; Golić, M.; Paša-Tolić, L. *J. Organomet. Chem.* **1995**, *489*, 35–41. (e) Eckert-Maksiæ, M.; Elbel, S.; Stohlmeier, M.; Untiedt, S.; de Meijere, A. *Chem. Ber.* **1996**, *129*, 169–174.

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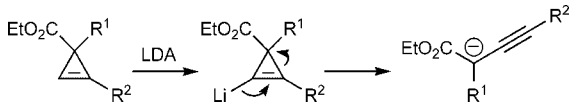
Although useful, this protocol is generally restricted to cyclopropenes lacking base-sensitive functional groups (such as esters) since these functional groups can often promote undesired side-reactions such as cyclopropene ring-opening (Scheme 1).[7]

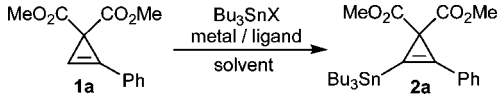
Scheme 1. Ring-Opening of Cyclopropenyl Lithium Species



Although potential solutions to this problem might lie in the inverse addition protocol employed by Eckert-Maksić and co-workers in the preparation of analogous silyl- and germyl-substituted cyclopropenes[7b,c] or in the dianion approach using cyclopropene carboxylic acids described by Fox and co-workers,[8] the development of more user-friendly cyclopropene stannylation procedures that proceed under mild reaction conditions is an attractive goal. Herein, we describe the efficient stannylation of base-sensitive cyclopropenes using the combination of (pentafluoroethyl)tributylstannane and stoichiometric potassium fluoride.

On the basis of our previous results involving the direct silylation of base-sensitive cyclopropenes using (trifluoromethyl)trimethylsilane as the silylating agent in conjunction with substoichiometric quantities of $Cu(acac)_2$ and dppe,[9,10] our exploratory experiments began with attempted stannylation of cyclopropene **1a** using Bu_3SnCF_3 in place of $TMSCF_3$ (Table 1, entry 1). Unfortunately, only a low

Table 1. Optimization of Conditions for Stannylation of Cyclopropene **1a**



entry	metal salt/ligand (equiv of each)	Bu_3SnX (2 equiv)	solvent	temp (°C)	convn (%)[a]
1	$Cu(acac)_2$/ dppe (0.05)	Bu_3SnCF_3	THF	rt	10
2	$Cu(acac)_2$/ dppe (0.05)	$Bu_3SnCF_2CF_3$	THF	rt	25
3	KF (1.0)	Bu_3SnCF_3	DMF	rt	54
4	KF (1.0)	Bu_3SnCF_3	DMF	40	67
5	KF (1.0)	$Bu_3SnCF_2CF_3$	DMF	rt	84
6	KF (1.0)	$Bu_3SnCF_2CF_3$	DMF	40	98

[a] Determined by ^1H NMR analysis of the unpurified reaction mixtures.

conversion to the desired product **2a** was observed. Efforts to increase the conversion through variation of the copper source were unproductive. However, it was noticed that use of $Bu_3SnCF_2CF_3$ improved the conversion slightly (entry 2).[11] Upon examining related reactions in the literature, we encountered a single example of a direct stannylation of an alkyne using Bu_3SnCF_3 and catalytic KF.[12] Since cyclopropenes often exhibit properties that are more similar in nature to alkynes rather than alkenes,[13] this procedure was deemed to possess potential merit, and we therefore applied these conditions to the stannylation of **1a**. Although the use of catalytic KF was not suitable, stoichiometric KF provided a promising 54% conversion to **2a** using Bu_3SnCF_3 in DMF (entry 3). Further increases in conversion were realized by raising the temperature (entry 4, and compare entries 5 and 6) and through the use of $Bu_3SnCF_2CF_3$ (compare entries 3 and 4 with entries 5 and 6, respectively).[11] The optimum conditions employed $Bu_3SnCF_2CF_3$ and stoichiometric KF in DMF at 40 °C (entry 6).

The generality of this procedure was investigated using a variety of base-sensitive 1,3,3-trisubstituted cyclopropenes (Figure 1). Dimethyl malonate-derived cyclopropenes **1a**−**1d** substituted with various aromatic groups or an alkyl group smoothly underwent the reaction to provide stannylcyclopropenes **2a**−**2d** in good to excellent yield. In addition to methyl esters, other tolerated functional groups at C3 included ethyl esters and either electron-rich or electron-deficient aromatics, resulting in stannylcyclopropenes **2e**−**2h** in 69−88% yield.

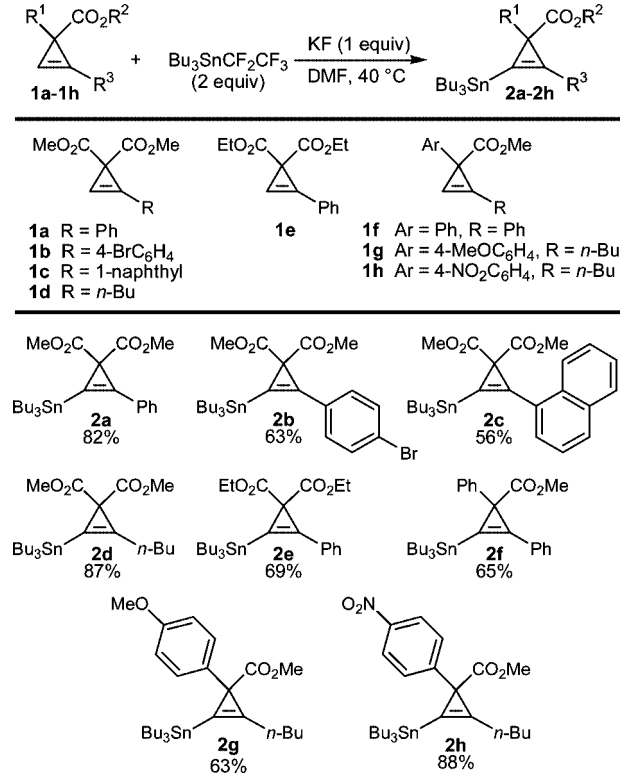
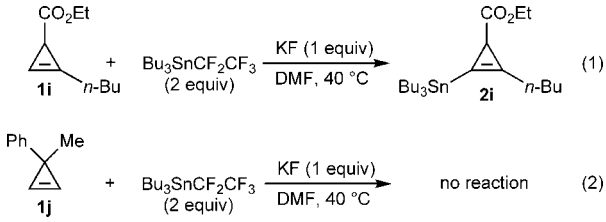


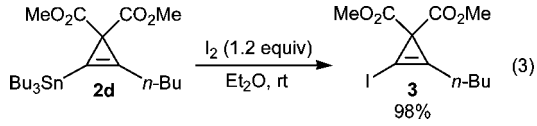
Figure 1. Direct stannylation of various cyclopropenes. Reactions were conducted using 0.20 mmol of cyclopropene, 0.20 mmol of KF, and 0.40 mmol of $BuSnCF_2CF_3$. Cited yields are of isolated material.

Two activating substituents (esters or aromatics) at C3 of the cyclopropene are required for stannylation to proceed

efficiently.[14] For example, cyclopropene **1i** provided alkenylstannane **2i** in only 29% yield (eq 1), while no reaction was observed with **1j** (eq 2).

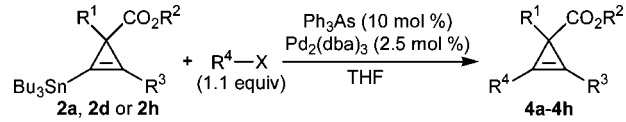


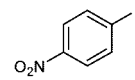
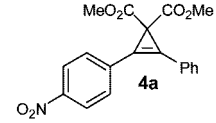
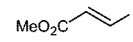
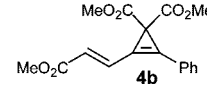
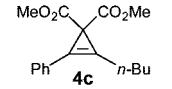
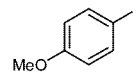
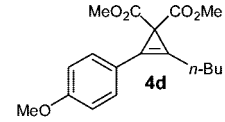
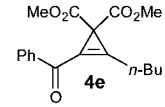
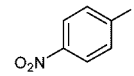
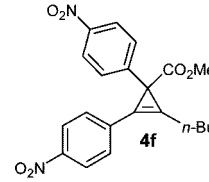
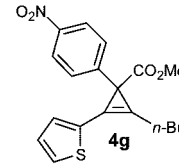
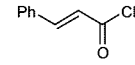
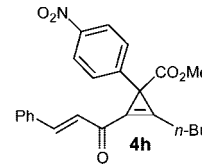
Having developed a mild protocol for the direct stannylation of base-sensitive cyclopropenes, the utility of the resulting products was investigated. We have already demonstrated that these stannylcyclopropenes undergo stereo- and regioselective iron-catalyzed carbometalation−ring-opening reactions to provide acyclic α,*β*,*β*′-trisubstituted alkenylstannanes.[15] In addition, treatment of **2d** with I_2 in Et_2O resulted in facile tin−iodine exchange to provide iodocyclopropene **3** in high yield (eq 3).[16]



However, our principal goal in this study was to establish the utility of these stannane building blocks in the synthesis of other tetrasubstituted cyclopropenes through Stille coupling reactions.[4,5] The only prior examples of these types of reactions are those reported by Untiedt and de Meijere using a limited selection of coupling partners,[6c] and it was therefore of interest to ascertain whether more highly functionalized cyclopropenes could be prepared using stannylcyclopropenes **2** and a wider selection of electrophiles. Fortunately, using a combination of $Pd_2(dba)_3$ and Ph_3As[17] as the precatalyst components, stannylcyclopropenes **2a**, **2d**, and **2h** smoothly underwent cross-coupling with a range of organic halides (Table 2). Aromatic (entries 1, 3, 4, and 6) and heteroaromatic (entry 7) iodides were found to be effective electrophiles, and as expected, the more reactive electron-deficient iodoarenes resulted in higher yields (compare entries 1 and 6 with entries 3, 4, and 7).[18] The use of an alkenyl iodide provided diene **4b** (entry 2) in 87% yield. Notably, acid chlorides were also competent electrophiles, providing cyclopropenes **4e** and **4h** that would be difficult to prepare using

Table 2. Stille Coupling Reactions of Stannylcyclopropenes[a]



entry	stannane	R^4-X	temp (°C)	product	yield (%)[b]
1	**2a**		40	 **4a**	91
2			40	 **4b**	87
3	**2d**	PhI	55	 **4c**	72
4			55	 **4d**	56
5			40	 **4e**	78
6	**2h**		40	 **4f**	99
7			60	 **4g**	61
8[c]			40	 **4h**	69

[a] Unless otherwise stated, reactions were conducted using 0.10 mmol of stannylcyclopropene and 0.11 mmol of organic halide. [b] Isolated yield. [c] Reaction conducted using 1.5 equiv of cinnamoyl chloride.

(7) (a) Zrinski, I.; Gadanji, G.; Eckert-Maksić, M. *New J. Chem*, **2003**, *27*, 1270–1276. (b) Zrinski, I.; Eckert-Maksić, M. *Synth. Commun.* **2003**, *33*, 4071–4077. (c) Zrinski, I.; Novak-Coumbassa, N.; Eckert-Maksić, M. *Organometallics* **2004**, *23*, 2806–2809.

(8) Liao, L.; Yan, N.; Fox, J. M. *Org. Lett.* **2004**, *6*, 4937–4939.

(9) Fordyce, E. A. F.; Wang, Y.; Luebbers, T.; Lam, H. W. *Chem. Commun.* **2008**, 1124–1126.

(10) For the use of similar conditions in the trifluoromethylation of aldehydes, see: Mizuta, S.; Shibata, N.; Ogawa, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Chem. Commun.* **2006**, 2575–2577.

(11) The origin of the superiority of $Bu_3SnCF_2CF_3$ over Bu_3SnCF_3 is not understood at this time.

(12) Ishizaki, M.; Hoshino, O. *Tetrahedron* **2000**, *56*, 8813–8818.

(13) For example, cyclopropene alkene protons have a pK_a of ∼30, enabling metalation with strong bases much in the same fashion as terminal alkynes. See: Fattahi, A.; McMarthy, R. E.; Ahmad, M. R.; Kass, S. R. *J. Am. Chem. Soc.* **2003**, *125*, 11746–11750.

(14) For a a study of the effect of substituents at the 3-position on the HOMO and LUMO energies of cyclopropenes, see: Diev, V. V.; Kostikov, R. R.; Gleiter, R.; Molchanov, A. P. *J. Org. Chem.* **2006**, *71*, 4066–4077.

(15) Wang, Y.; Fordyce, E. A. F.; Chen, F. Y.; Lam, H. W. *Angew. Chem., Int. Ed.* **2008**, DOI: 10.1002/anie.200802391.

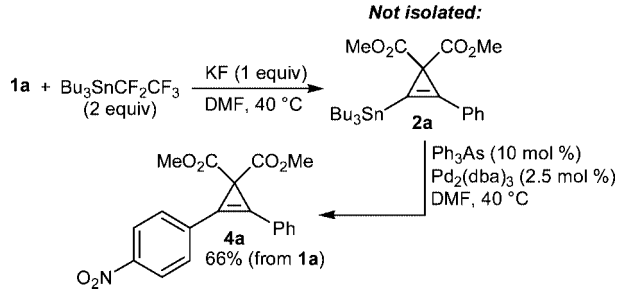
(16) Iodocyclopropene **3** was stable and could be purified by column chromatography without noticeable decomposition.

(17) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.

(18) For a useful alternative preparation of these types of compounds, see: Chuprakov, S.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 3714–3715.

existing methods (entries 5 and 8).[1] In certain cases, we have found that stannylcyclopropenes **2** sometimes undergo protodestannylation during long-term storage. In light of this observation, a one-pot direct stannylation−Stille cross-coupling reaction that obviates the requirement for isolation of the intermediate stannylcyclopropene was developed (Scheme 2). Upon completion of the stannylation of cyclopropene **2a** as observed by TLC analysis, a solution of 1-iodo-4-nitrobenzene (1.1 equiv), $Pd_2(dba)_3$ (2.5 mol %), and Ph_3As (10 mol %) in DMF was added, and heating was continued at 40 °C to eventually provide cyclopropene **4a** in 66% overall yield.

Scheme 2. One-Pot Direct Stannylation−Stille Coupling



In summary, a mild method for the direct stannylation of cyclopropenes that employs $Bu_3SnCF_2CF_3$ and KF has been developed. By use of the Stille cross-coupling reaction, the resulting stannylcyclopropenes serve as useful precursors to a variety of highly functionalized tetrasubstituted cyclopropenes that might otherwise be difficult to prepare using alternative methods. Utilization of cyclopropenes prepared using these procedures in novel catalytic processes, along with efforts to gain insight into the mechanism of the stannylation reactions,[19] will be the focus of future studies.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) In the absence of further experiments, speculation about the mechanism of these reactions would be premature at this stage.