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Practical Synthesis of *N*-Boc- and *N*-Cbz-α-Amido Stannanes from α-Amido Sulfones Using $TMSSnBu_3$ and CsF

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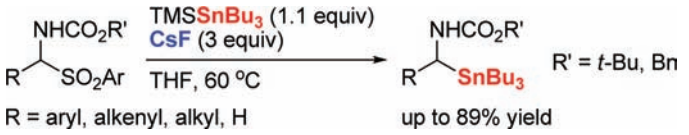
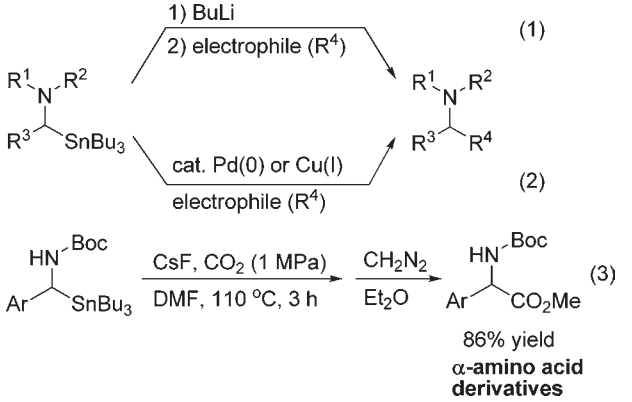
ABSTRACT



In the presence of $TMSSnBu_3$ and CsF, stannylation of *N*-Boc- and *N*-Cbz-α-amido sulfones proceeded very well to afford the corresponding α-amido stannanes in moderate-to-high yields. This reaction tolerated α-aryl-, alkenyl-, and alkyl-substituted α-amido sulfones as well as substrates containing either an ester or cyano moiety, which might be reactive with lithium or magnesium stannides employed in conventional stannylation.

α-Amino stannanes are robust and useful synthetic intermediates because of their high stability and the latent nucleophilic character of their sp^3 carbons adjacent to the nitrogen, which usually possess a positive charge in classical organic chemistry. Taking advantage of this umpolung reactivity,[1] several transformations that use α-amino stannanes have been developed (Scheme 1): These include the Sn−Li exchange reaction triggered by *n*- or *sec*-BuLi and the subsequent reaction with many electrophiles, such as aldehydes, ketones, CO_2, chloroformates, chlorophosphates, silyl chlorides, alkyl halides, and deuterides, which were all incorporated into the α-position of the bis-protected nitrogen (eq 1).[2] Palladium- or copper-catalyzed Stille-type couplings[3] have also been reported (eq 2).[4] This methodology was successfully applied in the synthesis of carbapenem derivatives by Merck researchers[5] using Vedejs' α-amino stannane.[6] Recently, our research group developed a highly efficient carboxylation of *N*-Boc-α-amido stannanes using CO_2 as a C1 unit mediated by CsF, which provided the corresponding α-amino acids in moderate-to-high yields (eq 3).[7]

Scheme 1. Various Transformations of α-Amino Stannanes



Although many powerful transformations that use α-amino stannanes have been reported thus far, the

(1) For reviews on umpolung of amine reactivity, see: (a) Seebach, D.; Enders, D. *Angew. Chem., Int. Ed.* **1975**, *14*, 15. (b) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275.

(2) For selected examples of tin−lithium exchange of α-amino stannane followed by its functionalizations, see: (a) Pearson, W. H.; Lindbeck, A. C. *J. Org. Chem.* **1989**, *54*, 5651. (b) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546. (c) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220. (d) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715. (e) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574. (f) Iula, D. M.; Gawley, R. E. *J. Org. Chem.* **2000**, *65*, 6196. (g) Ncube, A.; Park, S. B.; Chong, J. M. *J. Org. Chem.* **2002**, *67*, 3625. (h) Fraser, D. S.; Park, S. B.; Chong, J. M. *Can. J. Chem.* **2004**, *82*, 87. (i) Coeffard, V.; Beaudet, I.; Evain, M.; Grognec, E. L.; Quintard, J.-P. *Eur. J. Org. Chem.* **2008**, 3344. (j) Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A. *J. Am. Chem. Soc.* **2010**, *132*, 7260.

(3) (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. For a review on Stille coupling, see: (b) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704 and references cited therein.

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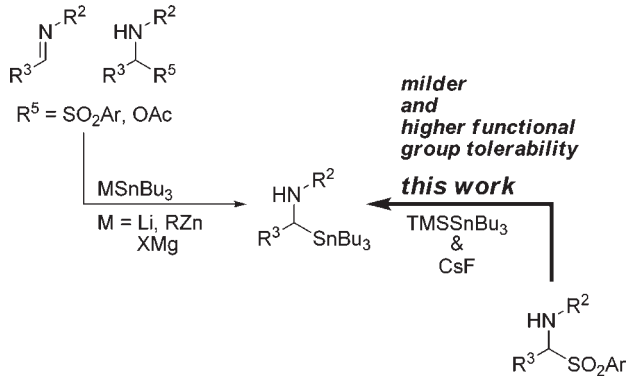
straightforward synthesis of α-amino stannanes from simple imines[4d,8] or an equivalent, such as an α-amino sulfone[9] or an α-acetoxy amine,[4a] have all employed strongly nucleophilic organometallic species such as $LiSnBu_3$, $Et_2ZnLiSnBu_3$, $ClMgSnBu_3$, $RZnSnBu_3$, and Bu_3Sn-LiCuCN (Scheme 2). These methods lack functional group tolerability and often need a low reaction temperature.

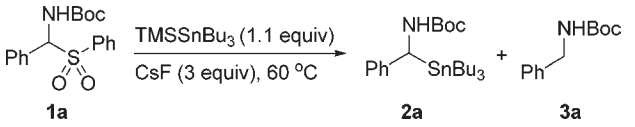
Scheme 2. Synthetic Strategy of α-Amino Stannanes



During the course of our study on α-amino acid synthesis from *N*-Boc-α-amido sulfone and CO_2,[7] the combined use of CsF and $TMSSnBu_3$,[10] both commercially available and stable chemicals, was found to be very effective for the preparation of *N*-Boc-α-amido stannanes from the corresponding *N*-Boc-α-amido sulfones, where the tributylstannyl anion was being generated *in situ*.[10] Moreover, *N*-Boc-α-amido sulfones can be readily prepared in stable crystalline form from the corresponding aldehydes and sodium sulfinate according to Engberts' method.[11] A precedented example of the stannylation of *N*-Cbz-α-amido sulfones, reported by Pearson and co-workers,[9b] showed that the substrate scope was not satisfactory and that the synthetically more useful *N*-Boc-α-amido sulfones could not be stannylated even when using several potential organometallic stannides that contained lithium, zinc, or magnesium as the countercation. Also, the stannylation would proceed through a radical mechanism, which required at least 2 equiv of alkali metal stannide. Hence, we have circumvented these problems by using the reagent combination of $TMSSnBu_3$ and CsF[12] and disclose, herein, the first mild and general stannylation of *N*-Boc- and *N*-Cbz-α-amido sulfones.

First, different solvents for the stannylation of *N*-Boc-α-amido sulfone **1a** were investigated in the presence of $TMSSnBu_3$ (1.1 equiv) and CsF (3 equiv) at 60 °C (Table 1). When the reaction was performed in THF, the desired α-amido stannane **2a** was obtained exclusively in 96% yield (entry 1). The use of 1,4-dioxane decreased the yield (67%) and unidentified products were generated (entry 2). When CH_3CN, DMSO, and DMF (entries 3−5) were used, the protiodestannylation product **3a** was produced as a byproduct.[7]

Table 1. Solvent Screening



1a **2a** **3a**

			yield (%)[a]	
entry	solvent	time (h)	**2a**	**3a**
1	THF	2	96	<1
2	1,4-dioxane	2	67	<1
3	CH_3CN	0.5	58	27
4	DMSO	0.5	24	47
5	DMF	1	58	22

[a] Yields were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

Having decided the optimal solvent for suppressing the generation of protiodestannylation product **3a**, various α-amido sulfones were subjected to this stannylation (Figure 1). All α-amido stannanes **2a**−**2r** were purified by column chromatography using 10% K_2CO_3/silica gel as a stationary phase to remove organotin impurities following Harrowven's novel method reported recently.[13] Substrates (**1a**−**1g**) possessing electron-donating and -withdrawing groups on an aromatic ring were all tolerated regardless of the location of the groups on the ring, with not only *N*-Boc-amido sulfone **1a** but also *N*-Cbz-amido sulfone **1b** being effectively stannylated. It is noteworthy that cyano and ester

(4) (a) Nativi, C.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1990**, *31*, 2637. (b) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1. (c) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973. (d) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666.

(5) Jensen, M. S.; Yang, C.; Hsiao, Y.; Rivera, N.; Wells, K. M.; Chung, J. Y. L.; Yasuda, N.; Hughes, D. L.; Reider, P. J. *Org. Lett.* **2000**, *2*, 1081.

(6) Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556.

(7) Mita, T.; Chen, J.; Sugawara, M.; Sato, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 1393. We also disclosed herein one-pot synthesis of α-amino acids from α-amino sulfones using CsF and $TMSSnBu_3$.

(8) (a) Kells, K. W.; Chong, J. M. *Org. Lett.* **2003**, *5*, 4215. (b) He, A.; Falck, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6586.

(9) (a) MacLeod, D.; Quayle, P.; Davies, G. M. *Tetrahedron Lett.* **1990**, *31*, 4927. (b) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622.

(10) For its application to organic synthesis, see: (a) Mori, M.; Kaneta, N.; Isono, N.; Shibasaki, M. *Tertahedron Lett.* **1991**, *43*, 6139. (b) Mori, M.; Isono, N.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1993**, *58*, 2972. (c) Honda, T.; Mori, M. *Chem. Lett.* **1994**, 1013. (d) Kinoshita, A.; Mori, M. *Chem. Lett.* **1994**, 1475. (e) Imai, A. E.; Sato, Y.; Nishida, M.; Mori, M. *J. Am. Chem. Soc.* **1999**, *121*, 1217.

(11) (a) Engberts, J. B. F. N.; Strating, J. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 942. (b) Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238. (c) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970.

(12) $TMSSnBu_3$ reacted with an aldehyde in the presence of CsF−CsOH. See: Busch-Petersen, J.; Bo, Y.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 2065.

(13) 10% K_2CO_3/silica gel was employed as a stationary phase on column chromatography to remove organotin residues. See: Harrowven, D. C.; Curran, D. P.; Kostiuk, S. L.; Wallis-Guy, I. L.; Whiting, S.; Stenning, K. J.; Tang, B.; Packard, E.; Nanson, L. *Chem. Commun.* **2010**, *46*, 6335.

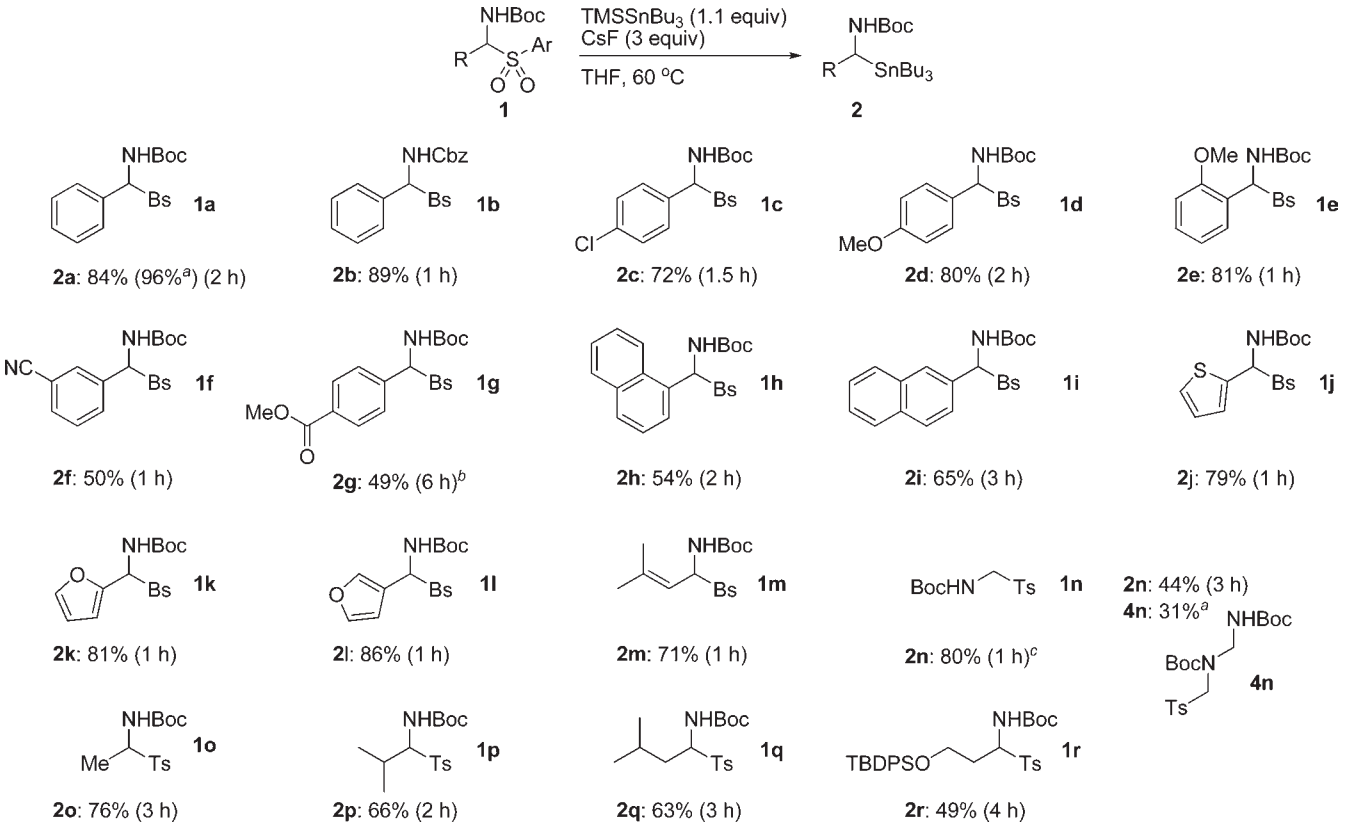
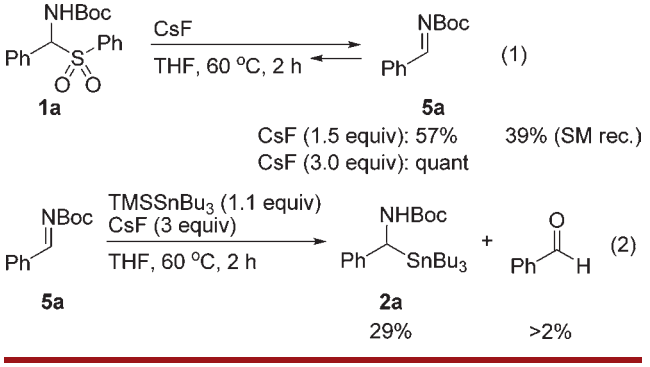


Figure 1. Reagents and conditions: Reaction was run using **1** (0.1 mmol), 1.1 equiv of $TMSSnBu_3$, and 3 equiv of CsF in THF (2 mL) at 60 °C. Isolated yields are shown unless otherwise noted. [a] Yield was determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [b] Reaction was performed at 0 °C. [c] Tetramethylammonium fluoride (TMAF) was used instead of CsF. Bs = benzenesulfonyl. Ts = toluenesulfonyl.

functionalities in substrates **1f** and **1g** remained intact during the stannylation. Moreover, both α- and β-naphthyl amido sulfones (**1h**–**1i**) as well as heteroaromatic substrates (**1j**–**1l**) were applicable. Stannylations of α-amido sulfones bearing a vinyl group as well as a variety of alkyl chains (**1m**–**1r**) also produced the corresponding α-amido stannanes in moderate-to-good yields. However, the reaction of α-amido sulfone **1n** yielded a dimer **4n** as a byproduct, the generation of which could be suppressed by using tetramethylammonium fluoride (TMAF) instead of CsF. All substrates shown in Figure 1 could be transformed into the corresponding α-amido stannanes with a slight excess of $TMSSnBu_3$ (1.1 equiv), which is a synthetic advantage due to this contributing to a reduction in the amount of potentially toxic organotin reagents needed to effect a satisfactory reaction.

In order to gain a mechanistic insight into this process, the reaction was performed without $TMSSnBu_3$ (Scheme 3, eq 1). As a result, imine **5a** was generated in 57% yield along with recovery of **1a** (39%) when using 1.5 equiv of CsF. Furthermore, complete conversion to imine **5a** was achieved with an increased amount of CsF (3.0 equiv). During this imine formation, which might be an equilibrium favoring imine **5a**, CsF works as a base to facilitate the deprotonation–elimination sequence. Based on these observations, stannylation of **1a** is most likely to proceed via imine **5a**, which was further supported by the fact that this stannylation required a nearly equal amount of $TMSSnBu_3$ and 3 equiv of CsF. However, when imine **5a** was itself used instead of **1a**, stannylation did not proceed efficiently, affording **2a** in only 29% yield along with benzaldehyde produced via imine hydrolysis as well as some unidentified peaks observed by ^1H NMR analysis (eq 2). Due to the inherent instability of *N*-Boc-imine, a high concentration of imine **5a** under the reaction conditions promoted its decomposition,

Scheme 3. Imine Formation and Stannylation of Imine **5a**



and rapid stannylation of **5a** is therefore necessary as soon as imine **5a** is generated through an equilibrium.

In summary, we have developed a practical stannylation of *N*-Boc- and *N*-Cbz-α-amido sulfones with synthetically useful yields (49−89%). We believe that this method is milder and tolerates more functionally than previously reported methods that employ organometallic stannides. Considerable effort toward the development of enantioselective variants of this transformation is now ongoing.

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Supporting Information Available. Details of experimental procedures and physical properties of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.