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Stille Coupling of Stereochemically Defined α-Sulfonamidoorganostannanes

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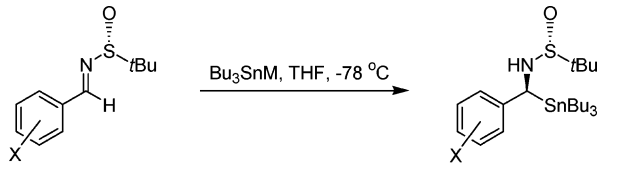
The Stille coupling of organostannanes has emerged as an important tool in modern organic synthesis.[1] Many applications have been documented, particularly with aryl and vinylstannanes. For vinylstannanes, overall retention of configuration has been well established. In contrast, there are relatively few reports where groups with an sp^3-carbon attached to the tin atom are employed[2] and even fewer reports where a chiral, nonracemic group is transferred from an organostannane. In fact, the only stereochemical studies published in this area are with an α-deuteriobenzylstannane, wherein inversion of stereochemistry was observed,[3] and with an α-benzoyloxyorganostannane, where "ca. 98% retention of configuration" was noted.[4]

The use of stereochemically defined α-aminostannanes in Stille couplings could significantly enhance this synthetic methodology, allowing access to a wide variety of enantiomerically pure amine derivatives, such as α-amino acids, α-amino ketones, and arylmethylamines. It is known that α-aminostannanes can undergo Sn−Li exchange with retention of configuration,[5] but the stereochemistry of Sn−Pd exchange (as in Stille couplings) is not known. Although it has been stated that α-amino- and α-alkoxystannanes undergo couplings with retention of configuration and with a citation to Falck's work,[6] retention of stereochemistry was only demonstrated for an α-alkoxyalkyl group. In the report by Falck and coworkers, the only α-amino derivative examined was a (racemic) phthalimidoalkyl-tributylstannane, which gave a modest (45%) yield of product along with considerable amounts (28%) of competing butyl transfer. Poor results in attempted Stille couplings of aminostannanes Bu_3SnCH_2NRR' have also been noted by Merck researchers who made elegant use of Vedejs' stannatranes[7] to efficiently transfer a CH_2NRR' unit.[8] We now report that stereochemically defined α-sulfonamidobenzylstannanes can be readily prepared and undergo Stille couplings with acid chlorides with essentially complete inversion of configuration.

We have previously shown that additions of Bu_3SnLi to imines derived from (*R*)- or (*S*)-*tert*-butanesulfinamide[9] and aliphatic aldehydes proceed with high diastereoselectivities and are an efficient means of accessing stereochemically defined α-aminostannanes.[10] Since benzylic α-aminostannanes are much more likely to participate efficiently in Stille couplings, we examined the addition of tributylstannylmetallics to *tert*-butanesulfinimine derivatives of aryl aldehydes. Addition of Bu_3SnLi to benzaldehyde-derived imine **1a** gave adduct **2a** as a single diastereomer (Table 1). Other sulfinimines with electron-donating groups (EDGs) also reacted with Bu_3SnLi with high diastereoselectivities (entries 2−4), but substrates with electron-withdrawing groups (EWGs) gave disappointing results (entries 5, 7, and 9). Fortunately, use of $Bu_3SnZnEt_2Li$, a reagent we had previously shown to react with high selectivities (and the same sense of diastereoselection as Bu_3SnLi) with aliphatic sulfinimines, restored the high selectivities (entries 6, 8, and 10) observed with other substrates. The stereochemistry of Bu_3SnLi addition to alkyl *tert*-butanesulfinimines can be rationalized by a six-membered chair transition-state model,[9] and it is reasonable to assume that the same model is operative here, especially as it has been shown that alkyl and aryl groups behave similarly in related reactions with organometallics.[11]

Table 1. Addition of Bu_3SnM to *tert*-Butanesulfinimines



1 **2**

entry	X	M	product	yield[a]	dr[b]
1	H	Li	**2a**	73	>99:<1
2	*p*-Me	Li	**2b**	77	>99:<1
3	*p*-OMe	Li	**2c**	84	>99:<1
4	*p*-NMe_2	Li	**2d**	91	>99:<1
5	*p*-Cl	Li	**2e**	80	73:27
6		$ZnEt_2Li$	**2e**	94	>99:<1
7	*p*-Br	Li	**2f**	25	50:50
8		$ZnEt_2Li$	**2f**	59	>99:<1
9	*p*-CF_3	Li	**2g**	0[c]	
10		$ZnEt_2Li$	**2g**	80	>99:<1

[a] Isolated yields (%) of chromatographed products. [b] Determined by $^1H/^{13}C$ NMR spectroscopy. The ">99:<1" denotes that signals for only one diastereomer were observed. [c] Compound **1g** was consumed, but only unidentifiable products were observed.

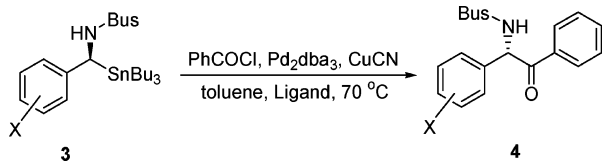
The difference in results observed with Bu_3SnLi and $Bu_3SnZnEt_2Li$ may be due to a change in the reaction mechanism. Perhaps Bu_3SnLi reacts with substrates **1a**−**d** via an ionic mechanism, while with imines **1e**−**g** (which possess EWGs), competing single electron-transfer processes[12] give rise to lower selectivities (**1e**), no selectivity (**1f**), or side reactions (**1g**). With $Bu_3SnZnEt_2Li$, reactions occur exclusively via an ionic pathway so high diastereoselectivities are observed.

Attempted coupling of sulfinamides **2** with a variety of electrophiles under Stille-type conditions proved to be fruitless. Fortunately, oxidation of sulfinamides **2** could be readily accomplished (*m*CPBA)[13] in high yields to produce sulfonamides **3**, which could be coerced to participate in Stille-type couplings. From a synthetic viewpoint, it is relevant that stereochemically defined aminostannanes **3** can be easily (three steps from commercially available materials) prepared and are essentially amines protected with a *tert*-butanesulfonyl (Bus) group, a functionality previously shown to be a useful protecting group that can be removed under acidic conditions.[14]

Stannane **3a** could be coupled with benzoyl chloride under conditions similar to those used by Falck in his work with α-amino- and α-alkoxystannanes.[4] With Ph_3P as the ligand, a respectable 66% yield of **4a** was observed (Table 2, entry 1).

10.1021/ja044354s CCC: $27.50

Table 2. Stille-type Coupling of Sulfonamides **3** with Benzoyl Chloride[a]

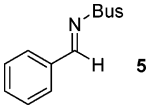


3 **4**

entry	X	ligand[b]	product	yield[c]
1	H	Ph_3P	**4a**	66
2	H	$(o\text{-tol})_3P$	**4a**	17
3	H	dppe	**4a**	0
4	H	PA-Ph	**4a**	75
5	H	TTMPP	**4a**	90
6	*p*-Me	TTMPP	**4b**	98
7	*p*-OMe	Ph_3P	**4c**	80
8	*p*-OMe	TTMPP	**4c**	85
9	*p*-Cl	Ph_3P	**4e**	63
10	*p*-Cl	$(Fu)_3P$	**4e**	23
11	*p*-Cl	Ph_3As	**4e**	37
12	*p*-Cl	TTMPP	**4e**	86
13	*p*-CF_3	TTMPP	**4g**	78

[a] Reactions were carried out with 5 mol % $Pd_2(dba)_3$, 5−10 mol % CuCN, and 20 mol % ligand. [b] Ligands dppe = 1,2-bis(diphenylphosphino)ethane, $(o\text{-tol})_3P$ = tri(*o*-tolyl)phosphine, $(Fu)_3P$ = tri(2-furyl)phosphine, TTMPP = tris(2,4,6-trimethoxyphenyl)phosphine, and PA-Ph = 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (ref 15). [c] Isolated yields (%) of chromatographed products.

By varying the ligand, the yield of **4a** could be increased to 90% (Table 2, entry 5). With trialkylphosphines (e.g., *n*-Bu_3P, *t*-Bu_3P), considerable decomposition of **3a** was observed, and with the chelating diphosphine 1,2-bis(diphenylphosphino)ethane (dppe), imine **5** was isolated in high yield. Imine **5**, likely the product of a β-hydride elimination process,[16] was also isolated from reactions that gave lower yields of **4a**.



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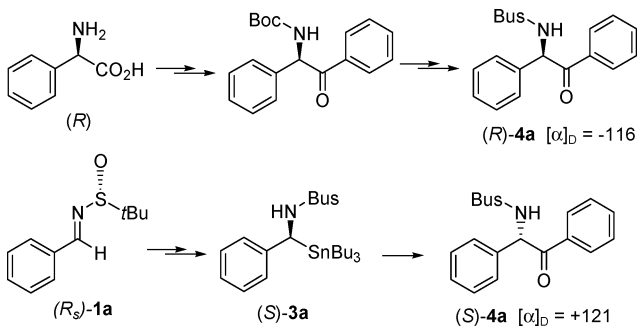
Other α-sulfonamidostannanes, including those with EDGs or EWGs on the aryl ring, also couple well under these reaction conditions (Table 2, entries 5−13). The most effective ligand for these Stille couplings is the highly basic tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP), whereas many Stille couplings are best performed using ligands of lower donicity, such as $(2\text{-furyl})_3P$ and Ph_3As.[17] This may be because the less basic ligands facilitate the Sn−Pd transmetalation step but do not help suppress the competitive β-hydride elimination observed here.

Analysis of the enantiomeric purity of the sulfonamido ketones **4** by HPLC on a chiral column (ChiralCel OD) showed >98% ee in all cases. Thus, there was <1% loss of stereochemical integrity in the conversion of **3** → **4**.

To determine the stereochemical outcome of these coupling reactions, a sample of (*R*)-**4a** was prepared from (*R*)-phenylglycine (Scheme 1).[18] Comparison (HPLC, ChiralCel OD) of ketone **4a** prepared via Stille coupling (and originally derived from sulfinimine **1a**) with this material showed that they were enantiomers. Thus, the Stille coupling of stannane **3a** proceeds with inversion of stereochemistry. This is consistent with an S_E2-type mechanism for the Sn−Pd transmetalation step, as originally proposed by Stille for benzylstannanes.[3]

Scheme 1



Other acid chlorides (e.g., *p*-$ClC_6H_4C(O)Cl$, 77%; *n*-$C_3H_7C(O)Cl$, 42%; $PhCH{=}CHC(O)Cl$, 58%) could be coupled with **3a** to yield the expected ketones, albeit in lower (unoptimized) yields.

The demonstration that α-sulfonamidobenzylstannanes can be easily prepared in high enantiomeric purity and can undergo Stille-type couplings with benzoyl chloride to give the expected ketones in high yields and with inversion of stereochemistry at the benzylic carbon is of synthetic and mechanistic interest. Efforts to expand the scope of this chemistry to other α-heteroatom-substituted stannanes and electrophiles are underway.

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

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