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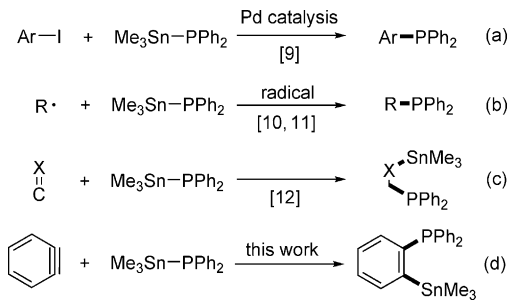
Ortho-Trialkylstannyl Arylphosphanes by C–P and C–Sn Bond Formation in Arynes

*Yuanming Li, Shyamal Chakrabarty, Christian Mück-Lichtenfeld, and Armido Studer**

Abstract: *A novel and efficient approach to ortho-trialkylstannyl arylphosphanes by the reaction of arynes generated in situ with stannylated phosphanes ($R_3Sn–PR_2$) is described. Concurrent C–P and C–Sn bond formation occurs with high yields, and stannylated products are easily transformed into valuable ortho-substituted arylphosphanes. The reaction features high efficiency, good regioselectivity, and excellent practicality.*

During the past forty years, phosphanes have been widely used in organic synthesis,[1] polymer science,[2] and for preparation of functional materials.[3] Particularly in homogeneous catalysis, arylphosphanes with *ortho*-substituents have played an important role.[4] Although much progress has been achieved, development of new methods for preparation of substituted arylphosphanes is still of importance. Existing processes in some cases lack generality and harsh reaction conditions, and often expensive transition metals have to be used.[5] Insertion of arynes into stannylated phosphanes ($R_3Sn–PR_2$) appears to be a promising alternative to ionic and transition-metal-mediated reactions for preparation of *ortho*-functionalized arylphosphanes.

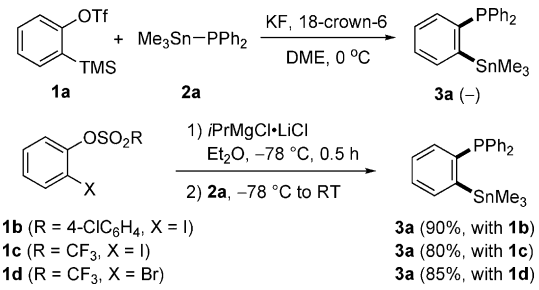
Stannylated phosphanes have been known for 50 years.[6,7] However, they have found only little application in synthesis.[8] Stille and Tunney reported the use of Me_3SnPPh_2 in Pd-catalyzed C–P couplings with aryl halides to give unsymmetrical triarylphosphanes (Scheme 1a),[9] and Schmidt and co-workers found that multiple bonds insert into Me_3SnPPh_2 via radical intermediates.[10] Recently, we reported mild and highly efficient radical phosphanylation of C-radicals with stannylated phosphanes as radical acceptors in chain reactions (Scheme 1b).[11] Some C=X double bonds also insert into the tin–phosphorus bond of stannylated phosphanes (Scheme 1c).[12]



Scheme 1. Various reactions involving $Me_3Sn–PPh_2$.

As a continuation of our aryne studies,[13] we decided to investigate the reaction of $R_3Sn–PR_2$ with arynes as a new approach to valuable 1,2-bifunctional arenes (Scheme 1d). Arynes have found widespread applications in organic synthesis.[14] The groups of Yoshida,[15] Larock,[16] Stoltz,[17] and others[18] have disclosed that various σ-bonds insert into arynes (such as C–N, C–O, C–Si, N–Si, N–P, O–Si, F–Sn, B–H).[19] To the best of our knowledge, the direct stannylphosphanylation of arynes is unprecedented.

We first investigated the reaction of 2-(trimethylsilyl)-phenyl triflate (**1a**) as an aryne precursor with KF, 18-crown-6, and phosphane **2a** in DME. However, the targeted **3a** was not formed, which is likely due to the instability of **2a** towards the F-anion (Scheme 2). The Knochel procedure[20] comprising addition of *i*PrMgCl·LiCl (1.7 equiv) to **1b** (1.5 equiv) in Et_2O (−78 °C) was suitable. For Mg–I exchange, the solution was stirred at −78 °C for 0.5 h, **2a** (1.0 equiv) was added, and the reaction mixture was allowed to warm to room temperature to deliver **3a** in excellent 90% isolated yield.[21] Slightly lower but still very good yields were obtained with aryne precursors **1c** and **1d**.[20]



Scheme 2. Testing of various aryne precursors.

Under optimized conditions, we studied the reactivity of **2a** with various arynes generated in situ (Table 1). Symmetrical arynes, such as 2,3-naphthalyne (from **1e**) and a cyclohexane-annellated aryne (from **1f**) provided the 1,2-bifunctionalized arenes **3b** and **3c** in moderate to good yields. For unsymmetrical arynes, owing to the electron-withdrawing effect of the methoxy and fluoro substituents, high regioselectivity was obtained with 3-methoxy-1,2-benzyne (from **1g**)

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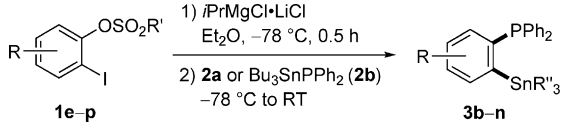
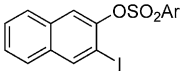
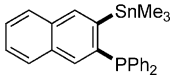
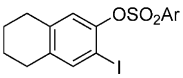
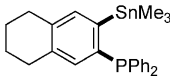
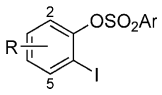
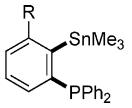
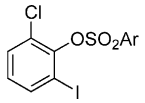
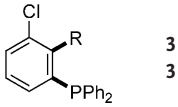
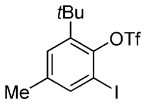
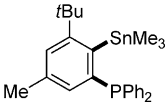
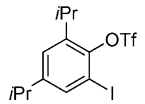
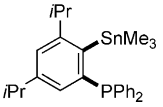
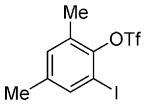
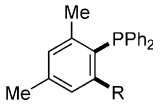
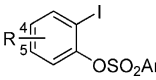
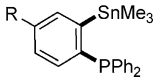
Table 1: Stannylphosphanylation of aryne precursors **1e–p** (Ar = 4-Cl-C_6H_4).[a]



Precursor		Product[b]		Ratio[c]	Yield [%][d]
	**1e**		**3b**	–	55
	**1f**		**3c**	–	71
	**1g** (R = 2-OMe) **1h** (R = 5-OMe) **1i** (R = 5-F)		**3d** (with **1g**) **3d** (with **1h**) **3e** (with **1i**)	> 20:1 > 20:1 6.8:1	44 52 50
	**1j**		**3f** (R = $SnMe_3$) **3g** (R = $SnBu_3$)	2.3:1 3.2:1	62 74
	**1k**		**3h**	> 20:1	90
	**1l**		**3i**	5.5:1	72
	**1m**		**3j** (R = $SnMe_3$) **3k** (R = $SnBu_3$)	2.4:1 2.0:1	75 75
	**1n** (R = 4-OMe) **1o** (R = 5-CF_3) **1p** (R = 4-CO_2Me)		**3l** (R = OMe) **3m** (R = CF_3) **3n** (R = CO_2Me)	1.8:1 1.1:1 1:1	88 62 48

[a] Reaction conditions: **1** (0.30 mmol), **2** (0.20 mmol) and *i*PrMgCl·LiCl (0.34 mmol) in Et_2O (2.0 mL) at RT for 2 h. [b] Major regioisomer drawn. [c] Regioisomer ratio determined by ^{31}P NMR spectroscopy on the crude product. [d] Combined isolated yield of both regioisomers.

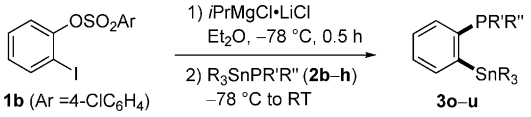
and 3-fluoro-1,2-benzyne (from **1i**) to give **3d** and **3e**. The P-substituent was installed distal to the MeO/F-substituent, indicating a nucleophile-type addition to the aryne with the phosphorous in **2a** acting as a nucleophile.[15a] As expected, the regioisomeric precursor **1h** provided **3d** with the same regioselectivity as **1g**. Selectivity was lower with 3-chloro-1,2-benzyne (from **1j**) to give **3f** and only a slight increase in selectivity was obtained with the bulkier phosphane **2b** (see **3g**). 3-Alkyl substituted arynes derived from **1k** and **1l** reacted with good to excellent selectivity: the *tert*-butyl system was converted with complete regiocontrol into **3h** and the smaller 3-isopropyl-1,2-benzyne gave **3i** with 5.5:1 regioselectivity. The isomers were readily assigned by NOE experiments. This selectivity trend can be explained by unfavorable steric repulsion between the alkyl substituent in the arynes and the incoming **2a**. Surprisingly, with the methyl congener a reversal of selectivity was observed (see **3j**). Switching to the tributylstannylphosphane **2b** did not significantly change selectivity (see **3k**). As expected, *meta*-substituted arynes do not react with high regioselectivity as shown for 4-methoxy-1,2-benzyne (from **1n**) to provide **3l**. Along these lines, 4-trifluoromethyl-1,2-benzyne (from **1o**) and 4-methoxycarbonyl-1,2-benzyne (from **1p**) reacted with **2a** with little or no selectivity (see **3m** and **3n**), supporting formation of arynes as intermediates. To show practicality, we ran a gram scale experiment with **1b** to give **3a** in 85% yield (1.8 g prepared).

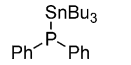
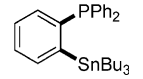
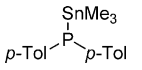
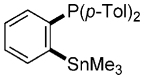
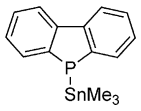
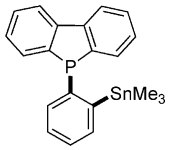
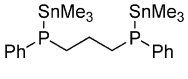
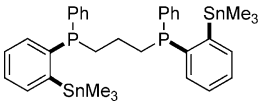
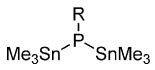
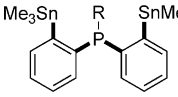
We further explored the scope by varying the stannylated phosphane using mainly **1b** as the aryne precursor (Table 2). With **2b**, a good yield of **3o** was obtained. The *p*-tolyl-substituted phosphane **2c** reacted in high yield to give **3p**. A slightly lower yield was achieved with phosphole **2d** to provide **3q**. Double aryne functionalization with the bisphosphane **2e** gave **3r** in a good yield. Notably, this sequence comprises four σ-bond formations. Along these lines, **2f** provided the formal double insertion product **3s** and the distannylated phosphanes **2g** and **2h** reacted in analogy with benzyne to provide **3t** and **3u**.

We next explored whether the stannyl substituent in the phosphane can be replaced by a silyl group and tested diphenyl(trimethylsilyl)phosphane (Me_3SiPPh_2, **4**). Pleasingly, **1b** reacted under the optimized conditions with **4** to give the targeted *ortho*-trimethylsilylphenyldiphenylphosphane (**5**) in 64% (not shown; see the Supporting Information).

Based on the results obtained from the reaction of 3-methoxybenzyne with **2a** where **3d** was formed as a single regioisomer, an ionic mechanism with initial P-attack onto the aryne is likely.[22] However, it is not clear whether stannyl transfer from P to the incipient aryl anion is occurring in a concerted process via an asynchronous cycloaddition-type reaction, where an aryl anion is not generated as an intermediate. To address that issue we performed DFT studies (PW6B95-D3//TPSS-D3/def2-TZVP; for details, see the Supporting Information). Attempts to locate a transition structure for the reaction of **2a** with 1,2-benzyne failed, even when different classes of functional were used. Optimizing a reaction path starting connecting a pre-reactive structure (d(P–C) ≈ 3 Å) with the product confirmed that there is no energetic (enthalpic) barrier to the addition (Figure 1). The formation of **3a** is highly exothermic ($\Delta H(Et_2O) = -75.6$ kcal mol^{-1}) and thus occurs under diffusion control. At the same time, the reaction path reveals the asynchronous character of the addition: the P–C bond is formed much earlier on the reaction coordinate than the C–Sn bond,

Table 2: Reaction of **1b** with various stannylated phosphanes.[a]



$R_3SnPR'R''$		Product		Yield [%][b]
	**2b**		**3o**	80[c]
	**2c**		**3p**	83[c]
	**2d**		**3q**	50[c]
	**2e**		**3r**	62[d]
	**2f** (R = Ph) **2g** (R = *n*Oct) **2h** (R = Fc)		**3s** (R = Ph) **3t** (R = *n*Oct) **3u** (R = Fc)	49[d,e] 36[d] 48[d]

[a] Reaction conditions: **1** (0.30 or 0.60 mmol), **2b**-**h** (0.20 mmol) and *i*PrMgCl·LiCl (0.34 or 0.68 mmol) in Et_2O (2.0 mL) at RT for 2 h. [b] Yield of isolated product. [c] **1c** was used. [d] **1b** was used. [e] Reaction conducted at −40 °C for 16 h. Fc = ferrocenyl.

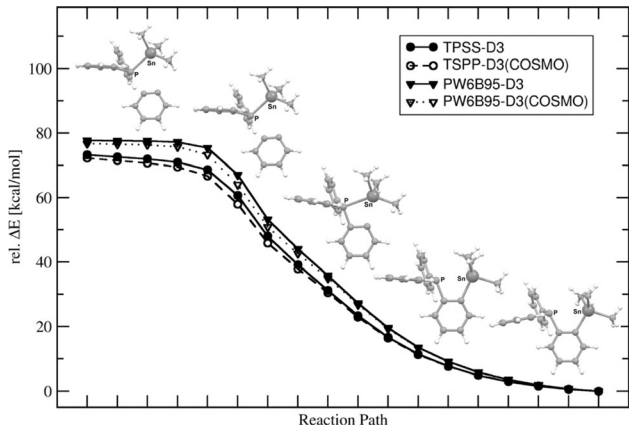


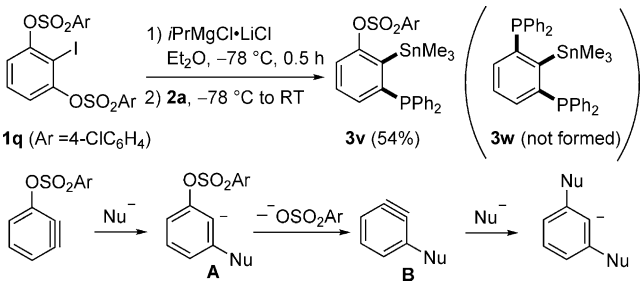
Figure 1. Optimized reaction path (TPSS-D3) of the addition of **2a** and 1,2-benzyne. PW6B95-D3 energies (triangles) and paths including solvation contributions (Et_2O) with the COSMO model (broken lines) are single point values for the TPSS-D3 structures. The def2-TZVP basis set was used for all calculations.

although the concertedness excludes the formation of an ion pair intermediate.

The high regioselectivity found for the formation of **3d** via 3-methoxy-1,2-benzyne can only be rationalized by preferential nucleophilic attack of **2a** at the C1 position of the reactive intermediate. A slightly more positive partial charge and the larger LUMO coefficient at the C1 of the aryne formed from **1g**/**1h** indicated a larger electrophilic character of this atom and thus explain the observed selectivity (see the Supporting Information).

The concerted cycloaddition type mechanism is further supported by the reaction of aryne precursor **1q** with **2a** to give **3v** (54%) and **3w** was not identified (Scheme 3). The aryne derived from **1q** should react with nucleophiles in a domino sequence,[23] where the aryl anion **A**, initially formed by nucleophilic addition, undergoes renewed β-sulfonate elimination to generate aryne **B** that further reacts with a second equivalent of the nucleophile. The absence of **3w** indicates that aryne stannylphosphanylation does not occur by a longer lived aryl anion of type **A**.

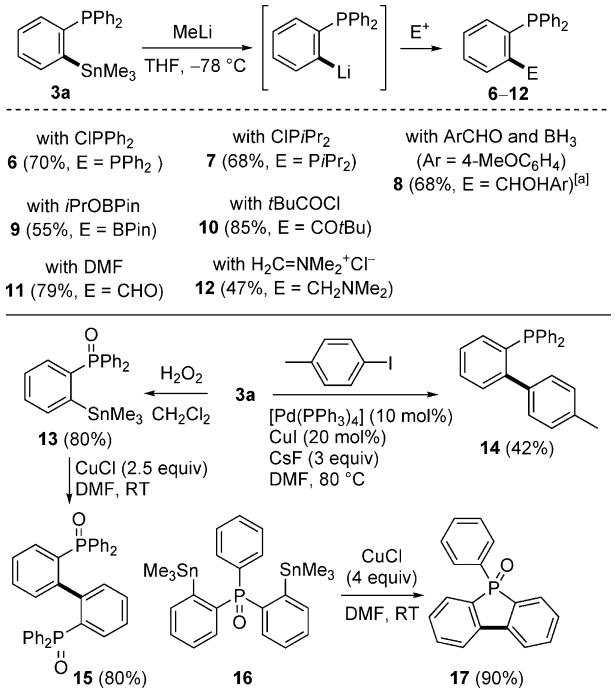
To document the synthetic value of the process, follow-up chemistry on **3a** was investigated.[24] Considering the importance of *ortho*-substituted arylphosphanes, lithiation and subsequent trapping of the intermediate Li species with electrophiles was studied (Scheme 4). Sn–Li exchange of **3a** with MeLi in



Scheme 3. Stannylphosphanylation of **1q**.

THF and treatment with chlorodiarylphosphanes afforded the bisphosphanes **6** and **7** in good yields. Trapping with *p*-anisaldehyde (**8**), borylation (**9**), acylation (**10**), formylation (**11**), and aminomethylation (**12**) worked equally well. Moreover, the P atom in **3a** was readily protected upon oxidation with H_2O_2 to give phosphane oxide **13.** Considering the importance of BINAP-type ligands, we further converted **13** in high yield into bisarylphosphane oxide **15** by CuCl-mediated homocoupling. In analogy, phosphane oxide **16** (obtained by oxidation of **3s**) reacted in excellent yield to phosphole oxide **17**. Buchwald-type ligands are accessible in moderate yield by Stille reaction of **3a** (see **14**).

In summary, we have presented direct insertion of arynes into stannylated phosphanes for concomitant C–P and C–Sn bond formation, providing functionalized stannylated arylphosphanes in high yields and in some cases with high regioselectivities. Computational studies have given insights into the mechanism of that aryne stannylphosphanylation. In



Scheme 4. Follow-up chemistry. [a] Isolated as BH_3 adduct.

a series of follow up reactions, the synthetic value of the *ortho*-stannylarylphosphanes was documented. As shown in an example, silylated phosphanes react with arynes generated in situ in analogy to give the corresponding *ortho*-silylarylphosphanes.

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[21] Upon adding **2a** in combination with *para*-methoxybenzaldehyde at −78 °C (0.5 h after *i*PrMgCl·LiCl addition), we only identified the secondary benzyl alcohol derived from direct aldehyde trapping of the *ortho*-magnesated arene, revealing that aryne formation occurs at higher temperature while warming the

reaction mixture to RT. Importantly, successful formation of **3a** shows that **2a** is stable towards the intermediate *ortho*-magnesated arene at lower temperatures.

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