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To be cited as: *Chem. Eur. J.* 10.1002/chem.202101124

Link to VoR: https://doi.org/10.1002/chem.202101124

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COMMUNICATION

Synthesis of Stannylated Aryl Imines and Amines *via* Aryne Insertion Reactions into Sn–N Bonds

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Abstract: The reaction of *in situ* generated arynes with stannylated imines to provide *ortho*-stannyl-aniline derivatives is reported. The readily prepared trimethylstannyl benzophenone imine is introduced as an efficient reagent to realize the aryne σ-insertion reaction. The imine functionality is an established N-protecting group and insertions proceed with good yields and good to excellent regioselectivities. The product anilines are valuable starting materials for follow-up chemistry thanks to the rich chemistry offered by the trimethylstannyl moiety.

Ortho-functionalized aryl amines are widely found structural motifs in organic synthesis, for example as ligands in asymmetric catalysis[1-6] and as building blocks in natural product synthesis.[7] They appear as active components in materials science as well as in polymer chemistry[8-9] and are also versatile building blocks for the synthesis of biologically active compounds.[10-14]

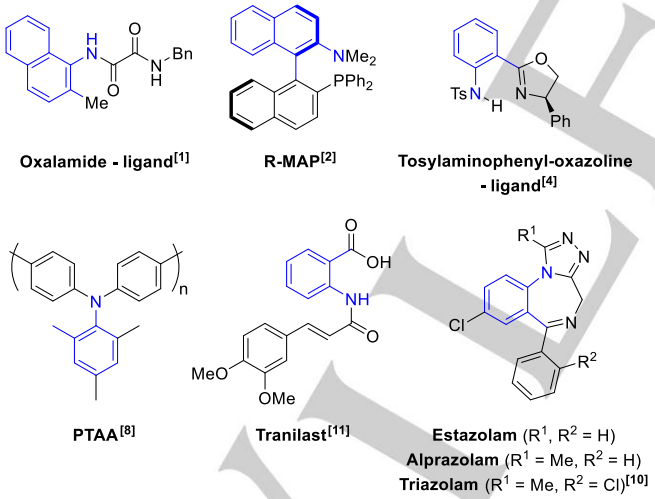
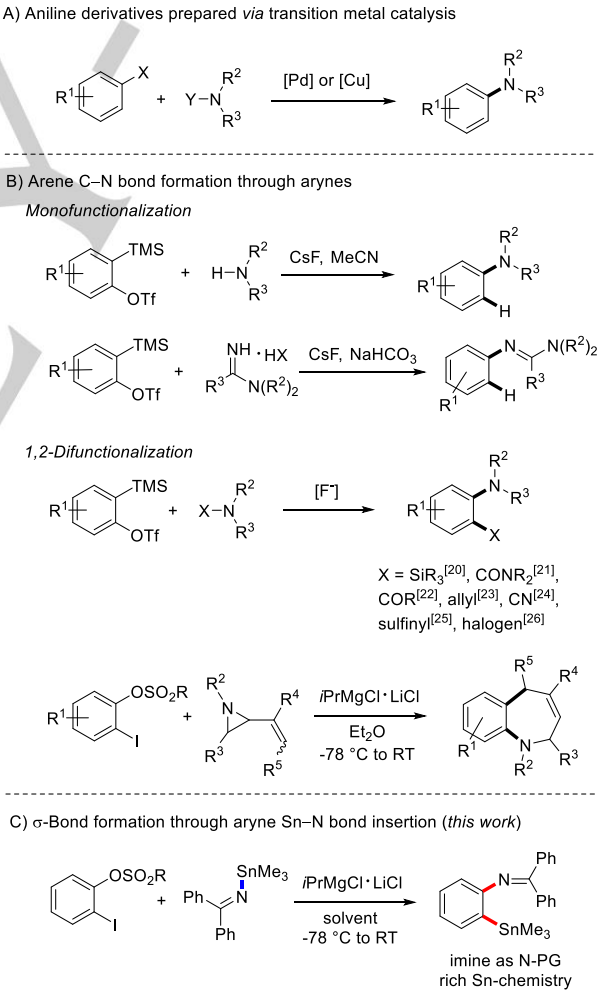


Figure 1. *ortho*-Functionalized anilines as building blocks.

Therefore, various methods for the preparation of *ortho*-functionalized anilines have been introduced over the past decades. Classical methods such as the Ullman, Buchwald-Hartwig and Chan-Lam coupling use transition metal catalysis for the amination of prefunctionalized arenes (Scheme 1A).[15-17] Aryne chemistry offers a transition metal free alternative for arene C–N bond formation (Scheme 1B). Along these lines, aryne insertions into N–H bonds have been reported.[18,19] Further leveraging aryne chemistry, 1,2-difunctionalized arenes are directly accessible through σ-insertion reactions into element-element bonds and considering the synthesis of aniline derivatives, the group of Kunai presented 1,2-aminosilylation of arynes.[20]



Scheme 1. A) Aryl amine synthesis using transition metal catalysis. B) Arene C–N bond formation through arynes.[18-27] C) Aryne insertion into the N–Sn bond of a stannylated benzophenone imine.

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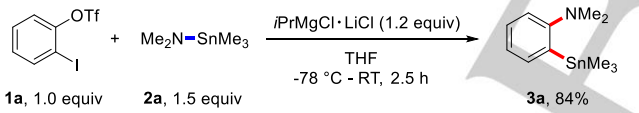
Using the same conceptual approach, aminobenzamides,[21] aminobenzophenones,[22] aminobenzonitriles,[25] sulfinylanilines[26] and haloaminoarenes[27] have been successfully prepared *via* aryne insertion reactions. An elegant route towards 2-allylanilines was presented by Greany and coworkers using allylamines as starting materials.[23] Moreover, benzazepines can be prepared by the reaction of *in situ* generated arynes with vinyl aziridines.[24] Note that the latter two processes do not rely on direct σ-bond insertion reactions. Moreover, various methods for the construction of C–N and C–Sn bonds involving aryne intermediates are known.[31-39]

Inspired by our previously reported stannylphosphanylation of aryne intermediates that uses stannylated phosphanes as reagents,[31] we herein report a practical method to implement an N-substituent to an aryl compound along with a stannyl moiety in *ortho* position *via* aryne insertion into the N–Sn bond of a stannylated imine (Scheme 1C). Notable features of the novel method are: a) the imine functionality installed serves as a protecting group and the free anilines are readily obtained upon simple hydrolysis; b) the simultaneously formed *ortho*-Sn-aryl bond has a large synthetic value which is documented by several follow-up reactions showing the diversity that can be achieved by using this approach.

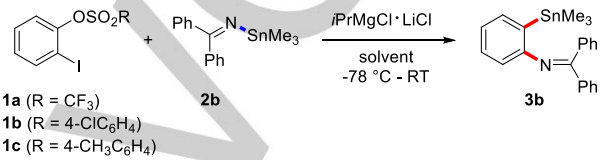
In initial experiments we found that an *in situ* generated aryne can readily insert into the σ-bond of $Me_3Sn–NMe_2$ (**2a**) to give the *ortho* stannylated aryl amine **3a** in 84% yield using the aryne precursor **1a** (Scheme 2, see Supporting Information for optimization). However, since the two N-methyl groups in **3a** are not easily removed, reagent **2a** is not of great value for the general preparation of *ortho*-stannylated anilines. Nevertheless, this result clearly showed that the aryne insertion into Sn–N σ-bonds is feasible.



Scheme 2. Aryne insertion into the N–Sn bond of the stannylated amine **2a**.

We therefore looked for other Sn-N-type reagents and identified readily prepared stannylated imines as promising candidates. N-aryl imines can be hydrolyzed easily to liberate the corresponding anilines.[28] Imine **2b**, that was previously introduced by us as a radical amination reagent,[29] was tested first. The aryne was generated using known methodology[30] by iodine-magnesium exchange on **1b** and subsequent elimination of the sulfonic acid anion at -78 °C. After 30 minutes, the imine **2b** was added and the reaction mixture was allowed to slowly warm to RT overnight. The desired product **3b** was isolated in 45% yield (Table 1, entry 1). Warming the reaction mixture to RT directly after addition of **2b** and stirring overnight increased the yield to 70% (entry 2). Upon shortening the reaction time to 2 hours at RT, the yield was further improved to 75% (entry 3). Using the aryne precursor **1b** as the limiting reagent (1.3 equiv or 1.5 equiv of **2b**) led to lower yields (59% and 55%, entry 6-7). By varying the amount of **1b** (1.3 – 2.0 equiv, entry 4-5, 8) and the amount of the Grignard reagent, the best result was noted using 2.0 equivalents of **1b** along with 2.1 equiv Grignard reagent and the desired product was isolated in a very good yield of 83% (entry 8). A further increase of the amount of **1b** to 3.0 equiv did not show any impact on the reaction outcome (entry 9). Using DCM, toluene or Et_2O as solvents led to lower yields (entry 10-12). In the case of Et_2O, the reaction mixture could not be stirred properly, because of a precipitation formed during the reaction. Therefore, this experiment was repeated at higher dilution and targeted **3b** was obtained in 86% yield (entry 13). In THF under otherwise identical conditions, yield dropped to 65% (entry 14). As compared to **1b**, the triflate **1a** and aryne precursor **1c** delivered lower yields (entry 15-20). Practicality of the process was documented by running the reaction in Et_2O at 1.0 mmol scale to provide the product **3b** in 82% isolated yield.

Table 1. Optimization of the aryne insertion into the N–Sn bond of **2b**.



entry	**1** (equiv)	**2b** (equiv)	*i*PrMgCl · LiCl (equiv)	Solvent (mL)	Yield (%)[a]
1[b]	**1b** (1.5)	1.0	1.6	THF (2)	45
2[c]	**1b** (1.5)	1.0	1.6	THF (2)	70
3	**1b** (1.5)	1.0	1.6	THF (2)	75
4	**1b** (1.3)	1.0	1.4	THF (2)	56
5	**1b** (1.7)	1.0	1.8	THF (2)	75
6	**1b** (1.0)	1.3	1.2	THF (2)	59
7	**1b** (1.0)	1.5	1.2	THF (2)	55
8	**1b** (2.0)	1.0	2.1	THF (2)	83
9	**1b** (3.0)	1.0	3.1	THF (2)	82
10	**1b** (2.0)	1.0	2.1	DCM (2)	64
11	**1b** (2.0)	1.0	2.1	toluene (2)	59
12	**1b** (2.0)	1.0	2.1	Et_2O (2)	77
13	**1b** (2.0)	1.0	2.1	Et_2O (4)	86
14	**1b** (2.0)	1.0	2.1	THF (4)	65
15[d]	**1a** (2.0)	1.0	2.1	THF (4)	49
16[e]	**1a** (2.0)	1.0	2.1	THF (2)	61
17[f]	**1a** (2.0)	1.0	2.1	THF (2)	57
18	**1c** (1.3)	1.0	1.33	Et_2O (4)	54
19	**1c** (1.3)	1.0	1.33	THF (2)	43
20	**1c** (2.0)	1.0	2.1	Et_2O (4)	72

[a] Isolated yield (reaction run at a 0.2 mmol scale. [b] After addition of **2b** the reaction mixture was slowly warmed to RT overnight. [c] Warmed directly to RT and stirred overnight. [d] After addition of **2b**, 5 minutes after the Grignard reagent at -78 °C, the mixture was warmed to RT. [e] Warmed to RT after 30 minutes. [f] **2b** was added before the Grignard reagent at -78 °C.

We next tested whether electronic effects at the benzophenone imine moiety influence reaction outcome (Scheme 3). The electron-poorer reagent **2c** bearing trifluoromethyl groups in *para* position provided the desired product **4** in lower yield, as compared to the parent reagent **2b**. The decreased nucleophilicity of the nitrogen atom in **2c** might be a reason for the decreased yield. Increasing imine nucleophilicity did also not lead to a further improvement of the yield, as documented by the reaction with the methoxy substituted congener **2d** to provide **5**. Stannylated imine

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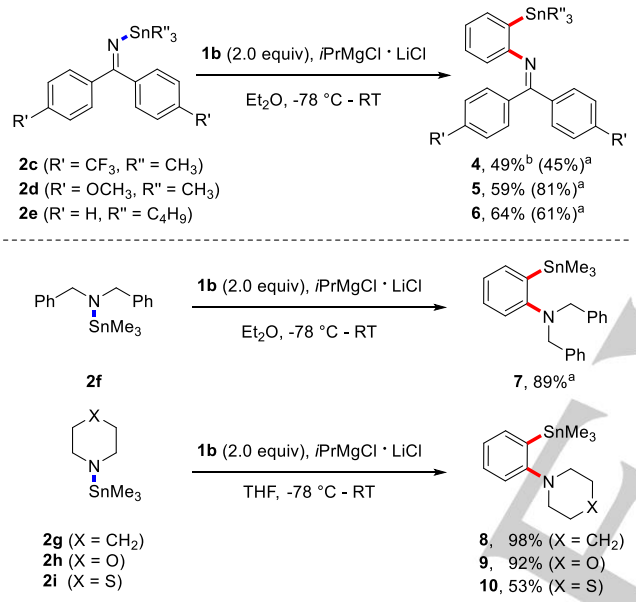
2e, in which the trimethyltin substituent is replaced by a tributyltin moiety, was also tested in the aryne insertion reaction. The desired product **6** was isolated in 64% yield. Likely, the increased steric demand of the tributyltin moiety as compared to the Me_3Sn-group is responsible for the decrease in the yield upon replacing **2b** by **2e**. The structures of the stannylated imines **2b** and **2d** were confirmed by X-ray crystal structure analysis (Figure 2). To document scope, some additional stannylated amines were tested in the σ-insertion reaction. With **2f** bearing removable N-benzyl protecting groups the desired product **7** was obtained in 89% yield. Stannylated piperidine **2g** and morpholine **2h** could be converted into the desired products **8** and **9** in almost quantitative yields, while stannylated thiomorpholine **2i** afforded **10** in 53% yield. Of note, these stannylated amines can readily be prepared by Me_3Sn-metathesis using the commercial Me_2SnNMe_2 (**2a**) as stannylating reagent (see Supporting Information).



Scheme 3. Reaction of **1b** with various stannylated imines **2c**-**2e** and stannylated amines **2f**-**2i**. [a] Reaction run in THF. [b] Reaction run in THF with 1.5 equiv of **1b**.

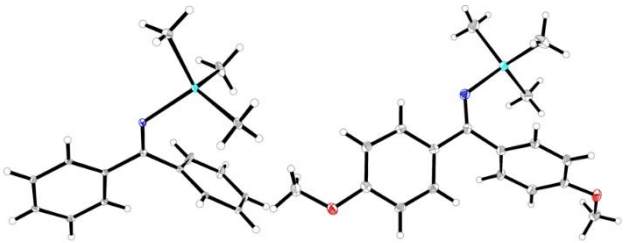
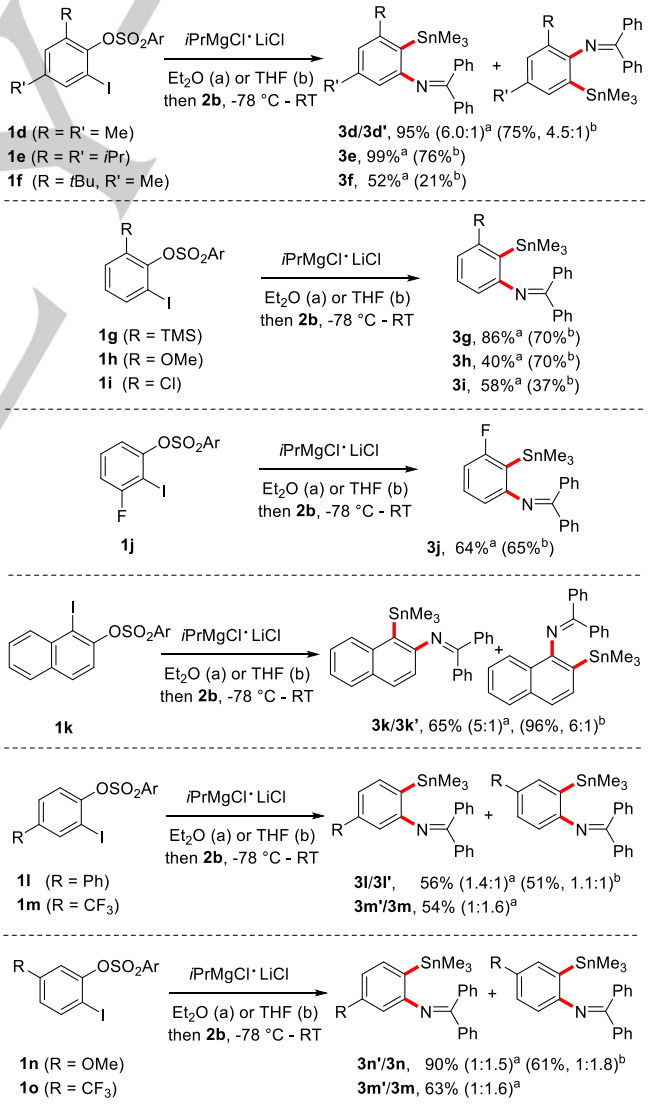


Figure 2. Crystal structures of stannylated imines **2b** (CCDC Nr.: 2063832) and **2d** (CCDC Nr.: 2063833).[40]

The scope with respect to the aryne component was studied next using imine **2b** as the amination reagent (Scheme 4). In most cases, reactions were conducted in both Et_2O as well as THF as the solvent. Arynes bearing alkyl substituents in *ortho* position provided the corresponding insertion products **3d**-**3f** in good to excellent yields. In all cases, higher yields were obtained in Et_2O. For the methyl substituted aryne derived from **1d**, the product was formed as a mixture of regioisomers **3d** and **3d'** with good selectivity. In the major isomer, the stannyl group is found *ortho* to the directing methyl substituent. Reaction of **1e** leading to an *ortho*-isopropyl substituted aryne, provided **3e** in quantitative yield with complete regioselectivity. As expected, regioselectivity was excellent with an aryne carrying the sterically demanding *tert*-butyl substituent. However, yield decreased to 52% (see **3f**). The *ortho*-TMS-substituted benzyne generated from **1g** reacted with complete regiocontrol for steric reasons to give **3g** in 86% yield. Excellent regioselectivity but a significantly lower yield was noted for the methoxy-substituted arene (**3h**, 40%). For this substrate the use of THF as the solvent gave a far better yield (70%), which is likely caused by the poor solubility of **1h** in Et_2O. Notably, halogenated aryne precursors are tolerated under our reaction conditions. Thus, reaction with the *ortho*-chloro and fluoro substituted precursors **1i** and **1j** occurred with excellent regiocontrol and good yields (see **3i** and **3j**). 2-Naphthyne generated from **1k** reacted in good selectivity and excellent yield to **3k** when THF was used as the solvent (96%, 6:1). The decrease in yield (65%) in Et_2O is likely due to the poor solubility of **1k** in this solvent.



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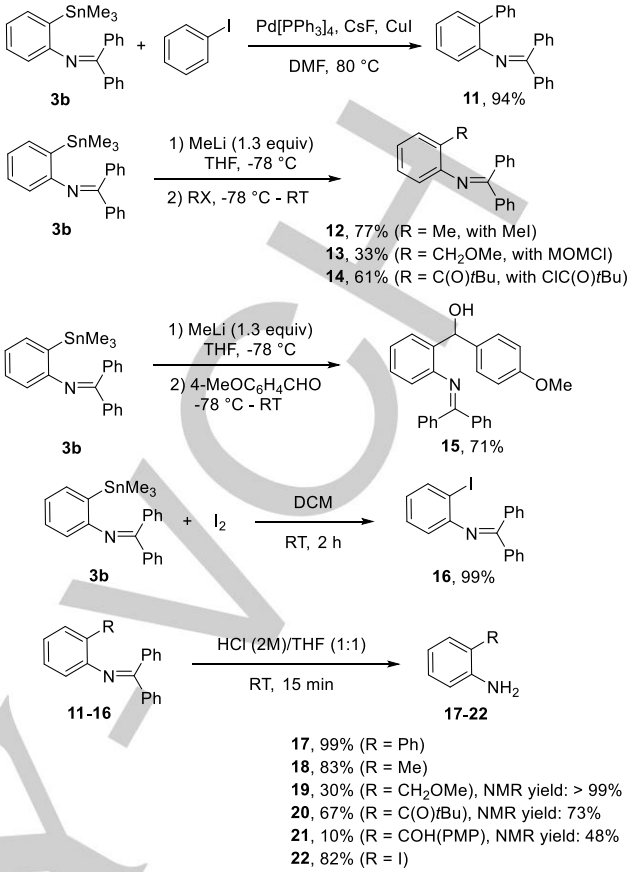
Scheme 4. Variation of the aryne precursor **1** (Ar = 4-ClC_6H_4).

Studies were continued considering *meta* substituted arynes derived from **1l**-**1o**. As expected, regioselectivities were low for all tested systems (see **3l**-**3n**).

We have studied the insertion of unsubstituted and *ortho*-TMS-substituted benzyne in the Sn-N bond of **2b** with density functional theory (DFT) calculations (see Supporting Information for details). The minimum energy path on the electronic energy surface has to overcome a barrier of 10-11 kcal/mol with respect to the isolated reactants. The highly exergonic product formation with the arynes (ΔG_{298} = -65.4 kcal/mol for **3b**, -53.5 kcal/mol for **3g**) is an asynchronous, but concerted reaction. The C^{aryne}-N bond is shorter than the C'^{aryne}-Sn distance in the transition state region (Figures S5-S7). The regioisomeric product **3g'** which is experimentally not observed ($SnMe_3$ meta to the TMS group) is more stable (ΔG_{298} = -63.7 kcal/mol) than **3g**. However, the barrier to its formation is slightly higher (0.5-1 kcal/mol), mainly due to the more synchronous (and thus less polar) nature of the structure in the TS region which leads to lower stabilization in the solvent.

Finally, to document the preparative value of the developed method, follow-up transformations were addressed (Scheme 5). Stille coupling of imine **3b** with iodobenzene provided biaryl **11** in 94% isolated yield with the imine protecting group remaining intact. The robustness of the imine protection was further documented by generating highly reactive aryl lithium compounds *via* Sn-Li exchange. Trapping with various electrophiles (iodomethane, MOM-chloride, pivaloyl chloride, aldehyde) afforded the corresponding arenes **12**-**15** in moderate to excellent yields. Furthermore, iododestannylation occurred in quantitative yield upon treatment of **3b** with elemental iodine in dichloromethane (see **16**). Imine deprotection was achieved under acidic conditions furnishing the free anilines **17-22**. Note that *ortho*-trimethylstannyl aniline is not a stable compound under acidic conditions and therefore imine deprotection must occur after chemical modification of the stannyl moiety.



Scheme 5. Follow-up reactions.

In conclusion, we introduced iminostannylation of arynes as a useful method to access versatile aniline building blocks of type **3**. Products were obtained in good to excellent yields and good to excellent regioselectivities. DFT calculations showed that the σ-insertion reaction of the aryne into the Sn–N bond of reagent **2b** proceeds *via* a concerted asynchronous process across a very low barrier without any intermediate. Finally, we could document the preparative value of the method by useful postfunctionalizations of the stannane moiety *via* Stille coupling and Sn-Li exchange reactions. The imine moiety is a robust aniline protecting group that is readily removed under aqueous acidic conditions to give *ortho*-substituted free anilines.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (DFG) for supporting this work.

Keywords: arynes • Grignard reagents • DFT calculations • main group chemistry • C-C coupling

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[40] Deposition numbers 2063832 (for **2b**) and 2063833 (for **2d**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe.

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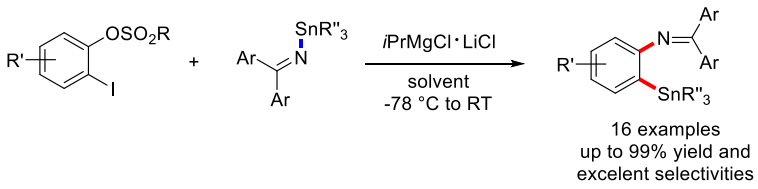

16 examples
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The synthesis of valuable *ortho*-stannylated anilines *via* aryne σ-insertion into Sn-N bonds is reported. Readily prepared stannylated imines were identified as suitable N-Sn-donors, offering the possibility to modify both introduced substituents in follow up reactions using the rich Sn-chemistry and deprotection of the imine.

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