Strueben, J., Lipfert, M., Springer, J-O., A Gould, C., Gates, P. J., Sönnichsen, F., & Staubitz, A. (2015). High Yielding Lithiation of Azobenzenes by Tin-Lithium Exchange. Chemistry - A European Journal.

Peer reviewed version

This is the accepted version of the following article: Strueben, J., Lipfert, M., Springer, J.-O., Gould, C. A., Gates, P. J., Sönnichsen, F. D. and Staubitz, A. (2015), High-Yield Lithiation of Azobenzenes by Tin–Lithium Exchange. Chem. Eur. J.. doi: 10.1002/chem.201500003, which has been published in final form at http://onlinelibrary.wiley.com/doi/10.1002/chem.201500003/abstract.

High Yielding Lithiation of Azobenzenes by Tin-Lithium Exchange

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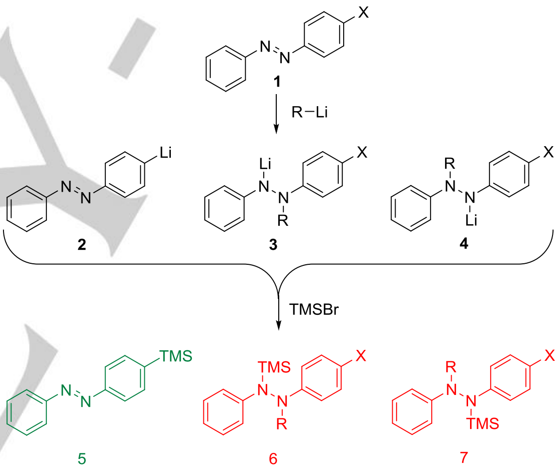
Abstract: The lithiation of halogenated azobenzenes by a halogen-lithium exchange commonly leads to a substantial degradation of the azo-group to give hydrazine derivatives besides the desired aryl-lithium species. Yields for quenching reactions with electrophiles are therefore low. This work shows that a transmetalation reaction of easily accessible stannylated azobenzenes with methyl lithium leads to a near-quantitative lithiation of azobenzenes in *para*, *meta* and *ortho* position. To investigate the scope of the reaction, various lithiated azobenzenes species were quenched with a variety of electrophiles. Furthermore, mechanistic ^{119}Sn NMR spectroscopic studies on the formation of lithiated azobenzenes are presented. A tin-ate complex of the azobenzene could be detected at low temperatures.

Introduction

Azobenzene derivatives are very important compounds in many fields of research on dyes[1,2] or photoswitchable systems: They undergo a reversible photoisomerization by irradiation with ultraviolet light from their *trans* form to their *cis* form, resulting in substantial changes in their electronic and geometric properties.[3,4] Furthermore, azobenzenes show a high resistance against photobleaching[5] and thermal decomposition.[6] These properties have led to a wide use of azobenzenes in biochemical research,[7,8] e. g. in photoswitchable cell adhesion,[9,10] in medical research e. g. photoswitchable contrast media for magnetic resonance imaging,[11] and in materials and polymer science e. g. photoresponsive polymer materials.[12-18] To be able to tailor the properties of azobenzenes exactly to their intended application, flexible and effective methodologies for the functionalization of azobenzenes are essential.

For the functionalization of aromatic rings in general, a common synthetic strategy is to convert them into organolithium or organomagnesium species and to subsequently quench the reaction with an appropriate electrophile.[19] For these systems, a metalation is usually achieved in situ by a halogen-metal exchange, direct insertion into a carbon-halogen bond or by deprotonation. Halogen-metal exchange reactions are especially selective, so long as the starting material does not contain competing halide functional groups.[20] However, if the molecule contains other electrophilic groups, these are often attacked by the lithiating reagent.[21]

In the case of the lithiation of azobenzenes, the protocols reported in literature all employ a halogen-lithium exchange reaction.[22-27] Typically, the yields are quite low (maximally 53%[22] for the *para* position, 47% for the *ortho* position, and 54 %[28] for the *meta* position). The reason for these poor yields is the low tolerance of the azo group towards reductive conditions: In competition with the halogen-lithium exchange, a nucleophilic attack by the alkyl lithium species on the azo group occurs, leading to hydrazine analogs (**3**, **4** and after quenching with TMSBr, **6** and **7**) of the starting material (Scheme 1).[29-33]



Scheme 1. Lithiation of *para*-iodoazobenzene and subsequent quenching with trimethyl bromo silane.[22]

For a successful, selective lithiation of azobenzene, the lithiation reaction on the aromatic ring must be kinetically preferred over the attack on the diazene group: the desired aryl lithium species should be much less nucleophilic than an alkyl lithium reagent. We reasoned that if a tin-lithium exchange reaction on a stannylated azobenzene of type **9** would be faster than the attack of the lithiating reagent on the diazo group, then a selective lithiation should be possible. We recently demonstrated the stannylation of azobenzenes by a Stille-Kelly cross coupling reaction of the corresponding iodinated azobenzenes **8**, catalyzed by [Pd(PPh$_3$)$_4$], using hexamethyldistannane as the nucleophilic component (Scheme 2).[34]

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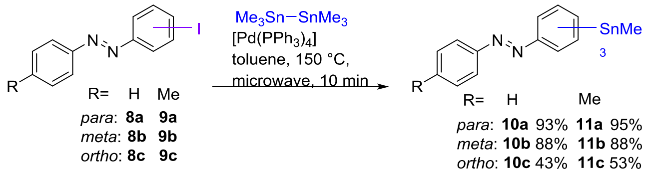
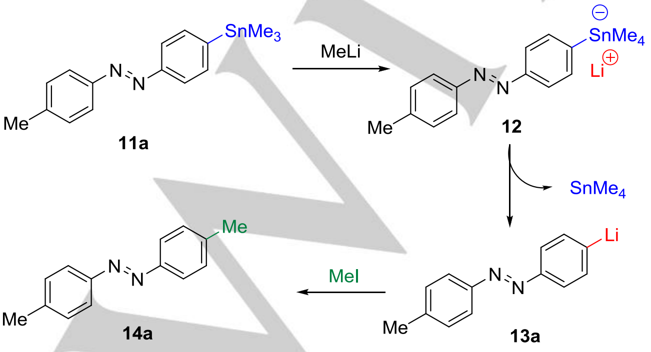


Scheme 2. Stannylation of mono iodinated azobenzenes. Compounds **8a-c**,[35] **9a**,[35] **9b-c**,[36] **10a**,[37] **11a**[34] have been reported previously, the other stannylated azobenzenes are described in this work.

In this work, we demonstrate that a transmetalation from trimethyl tin to lithium leads to a rapid and effective lithiation of azobenzenes in the *para*, *meta* and *ortho* positions without any decomposition of the azo-group. This protocol increases the yield of the lithiated species substantially and allows easy access to compounds that are difficult to obtain by other means.

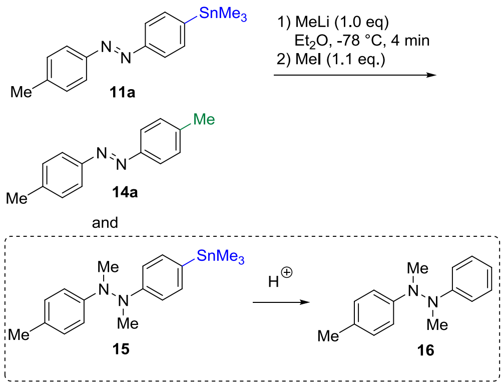
Reaction Optimization

The three most important factors that influence the selectivity of the two types of competing reactions (i. e. attack of the organolithium reagent on the azo group vs. tin-lithium exchange) are: a) the reactivity of the functional group which should be exchanged by lithium (halogen vs. trialkyl tin) b) the temperature, and c) the reactivity of organolithium complexes in the reaction solvent. We hypothesized that it should be possible to find reaction conditions where the formation of a lithium-stannate complex **12** and a subsequent rearrangement to the lithiated azobenzene **13** would be fast compared to the nucleophilic attack of the alkyllithium reagents on the azo group: As a large group 14 element, tin is able to react with nucleophiles by expanding its coordination sphere to give a penta-coordinated reactive ate-complex. Such intermediates have been described before,[38-43] and, in one instance, have even been isolated.[43] Lithium stannates typically have a lower reactivity towards electrophiles than is observed for other organolithium reagents.[40,46] The resulting lithiated azobenzene should have a significantly reduced nucleophilicity, as compared to the alkyl lithium species, and would not be capable of attacking the azo group (Scheme 3).



Scheme 3. Proposed lithiation of 4-methyl-4’-trimethyl-stannylazobenzene (**11a**) and subsequent quenching with methyl iodide.

Methyl lithium was chosen as a lithiation reagent be-cause of its high nucleophilicity. A further advantage is its comparatively high stability in tetrahydrofurans, as compared to butyl lithium reagents; [44, 45] the latter show a very short half live in THF of 107 min at 20 °C.[44, 46]
The reaction conditions were analyzed with respect to solvent, temperature and lithiation time (Table 1). To analyze the efficiency of the lithiation, methyl iodide was used as an effective electrophilic quenching reagent and the conversion was determined by quantitative gas chromatographic (GC) analysis (for details see Supporting Information - SI). All other possible side products could be expected to be chemically and thermally stable and thus suitable for GC and GC-MS analysis. To establish reaction conditions for a selective transmetalation from tin to lithium, very low temperatures of -130 °C were initially chosen. MeTHF was selected as a solvent because it has a lower freezing point than THF, -136 °C as compared to -108 °C, while maintaining comparable properties of activating organolithium reagents through deaggregation.[47,48]
At -130 °C, after 4 min of lithiation, the reaction showed no side reactions but a conversion of only 72% (Table 1, entry 1). When the temperature was raised to -78 °C, the transmetalation in MeTHF showed a full conversion to the desired product without observable side reactions (Figure 1). The same was true for THF (Table 1, entries 2, 3). To evaluate the stability of the lithiated intermediate, the total lithiation time was increased to 30 min, but no side products were detected (Table 1 entry 4). In the temperature range from -100 to -43 °C in THF, full conversion to the desired product could be observed. At -16 °C however, the reaction produced various side products: Although it was not possible to isolate these side products individually in pure form and to quantify them, they could be identified as hydrazine derivatives by GC-MS (table 1, entry 5).[49] In contrast to MeTHF and THF as solvents, the reaction proceeded entirely differently in diethyl ether: Using the same reaction conditions as for THF at -100 °C and -78 °C, the yields and the conversion were much lower with 29% and 32%, respectively (Table 1, entries 7, 8). The gas chromatograms of the reactions showed that the lithiation in diethyl ether produced various side products (Figure 1). To ensure the correct identification of the main side products, which we assumed to be the hydrazine derivatives, the lithiation reaction in ether was performed on a larger scale to isolate the side products. As a quenching reagent, methyl iodide was used. Besides the intended product **14a**, the main side product in the crude ^{1}H NMR spectrum could be identified as the hydrazine species **15**. A subsequent column chromatography gave hydrolyzed[50] species **16** in a purity of 90% and an isolated yield of 34%.[51]



Scheme 4. Lithiation reaction in diethyl ether, followed by quenching with methyl iodide.

The different reaction kinetics were also visible with the naked eye: In THF and MeTHF, the reaction mixture turned black immediately after adding the methyl lithium solution in THF, indicating the formation of an aryl-lithium species. In diethyl ether on the other hand, no significant color change could be observed at -100 °C or -78 °C. Only when the reaction mixture was allowed to warm to temperatures higher than -20 °C, an intense color change to black occurred. As the absence of by-products in THF at temperatures as high as -43 °C was striking, the tin-lithium exchange reaction was performed using an *n*-butyl lithium solution in hexanes. *n*-Butyl lithium is more commonly available and cheaper. Because of the low stability of this reagent in THF, the reaction was performed in reverse order by adding a solution of 4-methyl-4’-trimethylstannylazobenzene to a solution of *n*-butyl lithium in THF at -78 °C.[52] This reaction led to full conversion of the starting material, but unselective transmetalation of the tin group was observed: GC-MS analysis indicated a butylation of the azo group, corresponding to the side reaction in diethyl ether methyl lithium and the hydrazine synthesis as described by Katritzky and coworkers[30] (Table 1, entry 6; Scheme 4).

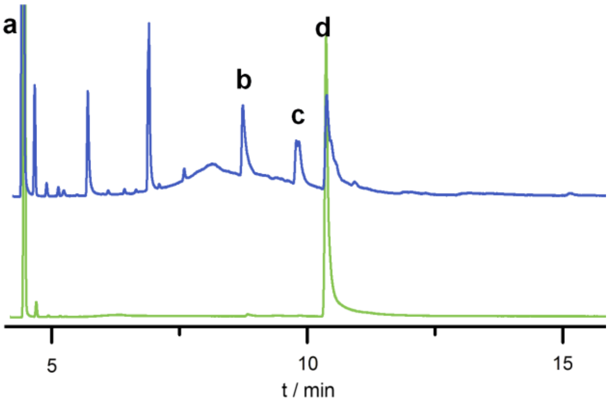
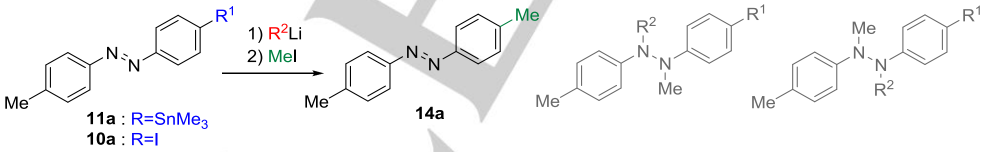


Figure 1. Gas chromatogram of the reaction mixtures after the lithiation of 4-methyl-4’-trimethylstannyl azobenzene (**11a**) in THF (table 1, entry 3) (green) and diethyl ether (table 2, entry 8) (blue). Signal a) triisopropylbenzene; b) 4-methylazobenzene; c) hydrazine **16;** d) product **14a**.

Table 1. GC optimization of the lithiation of 4-ethyl-4’-trimethylstannylazobenzene **(11a)**.



Entry	Solvent	T / °C	R^1	R^{2}Li	t/min	Starting Material / %	Yield of **14a**/%
1	MeTHF	-130	SnMe$_3$	MeLi	4	25	72
2	MeTHF	-78	SnMe$_3$	MeLi	4	<1	>99
3	THF	-78	SnMe$_3$	MeLi	4	<1	>99
4	THF	-78	SnMe$_3$	MeLi	30	<1	98
5	THF	-16	SnMe$_3$	MeLi	4	<1	63
6	THF	-78	SnMe$_3$	*n*-BuLi	4	<1	43
7	Diethyl ether	-100	SnMe$_3$	MeLi	4	<1	29
8	Diethyl ether	-78	SnMe$_3$	MeLi	4	<1	32
9	THF	-78	I	MeLi	4	22[a]	54
10	THF	-78	I	*n*-BuLi	30	<1	27

[a] Isolated from the reaction mixture, no GC quantification (see SI).

[b] Reverse order of addition; see text for details.

To provide a direct comparison with the tin-lithium exchange reaction to halogen-lithium exchange reactions, which are standard in the literature, the reaction was also performed with 4-iodo-4’-methylazobenzene. By adding either methyl lithium or butyl lithium to the iodinated azobenzene **10**, dissolved in THF, the conversion to the products was incomplete and the reaction showed various side products (Table 1, entries 9, 10).

NMR Studies

To support the mechanistic hypothesis for the reaction and to investigate why the reaction proceeded with much less selectivity in diethyl ether, in situ NMR experiments were performed. As the reaction progress in MeTHF at -130 °C was slow, those conditions were chosen to mix the reactants in a NMR tube in a glove box and immediately freeze the NMR tube within the glove box with liquid nitrogen. In this way, any reaction progress could be avoided before inserting the NMR tube into the pre-cooled NMR spectrometer (see supporting information for a detailed protocol). The reactions were then followed by ^{119}Sn NMR spectroscopy because the fast relaxation behavior of this nucleus allowed efficient sampling of the experiments. A fast scanning method was needed because of the low concentration of the ate-complex in the reaction mixture. Because of the different relaxation behaviors of symmetric and asymmetric tin species,[53] the parameters for the asymmetric, fast relaxing species could be optimized (pre-scan delay of 30 µs, relaxation delay of 1 ms).

This granted a fast recording of 3000-6000 scans with an overall recording of 132 s / 264 s per spectrum. Therefore, integration of the signals could not be correlated to the concentration of the species observed in solution and only qualitative statements can be made.[54]

The spectra were initially recorded at -103 °C[55] and then the temperature was raised stepwise by 10 K monitoring the reaction progress. First the reaction of *para* stannylated azobenzene **11a** in MeTHF was investigated.

At -103 °C, the starting material **11a** showed a chemical shift of -27 ppm. After 4 minutes, two new species appeared (Figure 2). One showed a signal at 0 ppm, which is consistent with tetramethylstannane.[56] A further ^{119}Sn NMR signal was visible at -312 ppm. This signal was assigned to the ate-complex **12**, based on literature precedent.[41,57] At -103 °C, the relative intensity for the signal of the ate-complex stayed constant, whilst the signal due to the the starting material continued to disappear and tetramethylstannane formed at the same rate (based on the percentage change of the integral of each species). The signal corresponding to the tin-ate-complex could be observed at temperatures of up to -88 °C, but when the reaction was warmed up further to -70 °C, the signal could no longer be observed. After warming up to -60 °C, the starting material had entirely disappeared and only the signal for tetramethylstannane was visible (Figure 2 and Figure SI-5 in the supporting information).

The transmetalation reactions were recorded in a similar manner for the corresponding *meta*- and *ortho*- substituted species. 4-Methyl-3'-trimethylstannylazobenzene (**11b**) showed a chemical shift of -27 ppm at -103 °C. As for the *para* congener, two new species appeared at 0 ppm[58] and -313 ppm,) also corresponding to tetramethylstannane and a lithium-tin ate-complex (**12b**). The reaction for the transmetalation in the *meta*-position was very similar to the reaction of 4-methyl-4'-trimethylazobenzene (**11a**), but appeared to be faster. The reaction was already completed at -78 °C (Figure SI-6 in the supporting information). For the reaction of 4-methyl-2'-trimethylstannylazobenzene (**11c**), the starting material showed a chemical shift at -43 ppm. Although the signal corresponding to tetramethylstannane at 0 ppm appeared, no signal for the tin-ate-complex was detectable in the temperature range of -103 °C up to -58 °C. At this temperature the reactions for the *para* and *meta* species **11a** and **11b** were almost completed, whereas the reaction for the *ortho* position only began to take place. However, as for the reaction in the *para* and *meta* positions, only tetramethylstannane could be observed as the final tin containing product, which indicates a selective tin lithium exchange. In diethyl ether, a completely different reaction progress was observed: For the treatment of 4-methyl-4'-trimethylstannylazobenzene (**11a**) with methyllithium, at -103 °C, the starting material could be observed at 27 ppm. However, after the reaction mixture had melted at -103 °C, neither a signal for tetramethylstannane nor a signal for the ate-complex could be observed. Only after warming up to -44 °C, a signal at 0 ppm, assigned to tetramethylstannane, became visible. No further changes were observed up to -15 °C. At this temperature however, the reaction displayed the formation of a third, heretofore unobserved signal at -36 ppm (Figure 2). At 27 °C, the starting materials had disappeared and only tetramethylstannane and this new stannyl species could be observed. The chemical shift of this signal indicated an aryl-stannylated compound. The reaction in the NMR tube was eventually quenched with methyl iodide. Analysis by GC-MS indicated the same side products as described in Figure 1. Based on this quenching experiment in combination with the isolated by-products (Scheme 4), the signal occurring at 36 ppm must be the *N*-lithium salt of the hydrazine derivatives, which becomes methylated upon quenching. The different reactivity of the tin-lithium exchange in diethyl ether and THF might be explained by different complexation of the lithiation agents and the different reactivity of organolithium compounds in THF/MeTHF and diethyl ether, although the situation is complex: Neither ether nor THF (or even HMPA) is a strong enough Lewis base to deaggregate the $(MeLi)_4$ complex that has been shown to form in THF.[59-62] While THF does show a significantly stronger de-aggregation effect on organolithium compounds such as phenyl lithium than does diethyl ether,[63] it has to be assumed that in the case of the tin-lithium exchange, the methyl lithium reacts in an aggregated form.[64] More detailed DFT studies on the nature of the reaction in ether and THF, and also with respect to the different reaction rates observed for different positions of the azobenzene are underway. This activation of the organolithium reagents enables reactions at much lower temperatures compared to diethyl ether. The reactions in MeTHF were already completed at -73 °C, whereas the reactions in diethyl ether only started at -15 °C.

However, at this increased temperature, the reactivity of all reactants was higher, leading to a decreased selectivity: At such high temperatures, the alkylation / metalation of the azo group can compete with the transmetalation of the trimethylstannyl group.

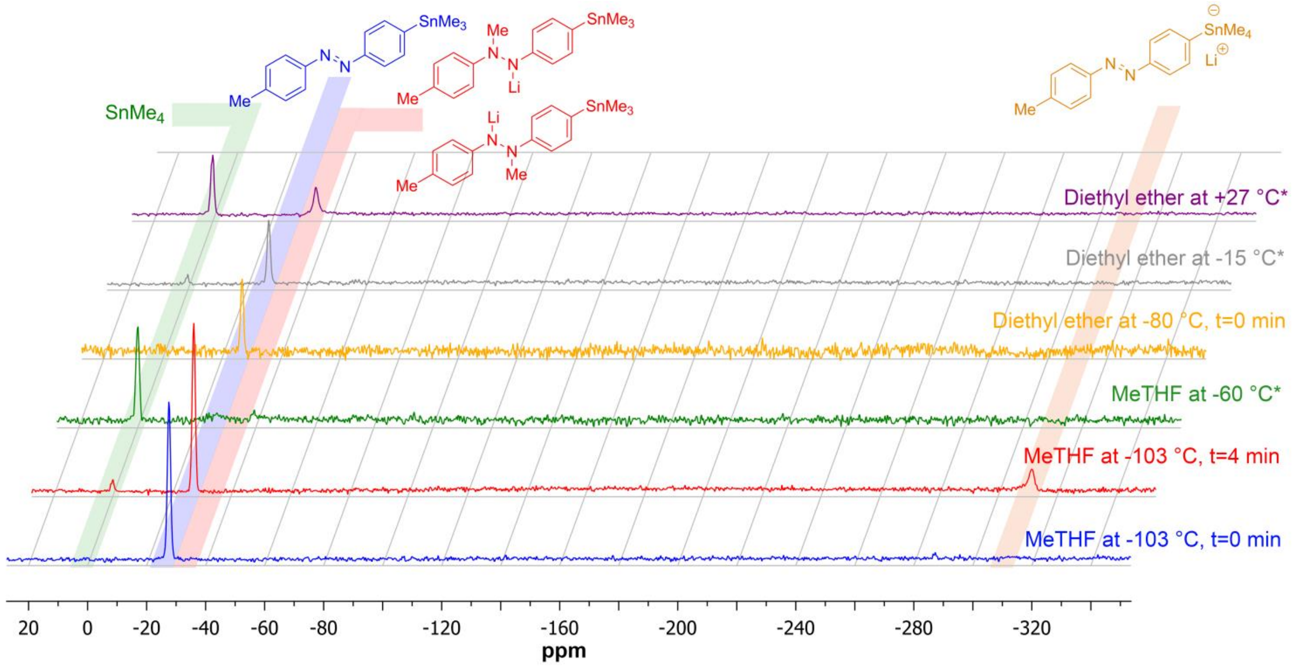
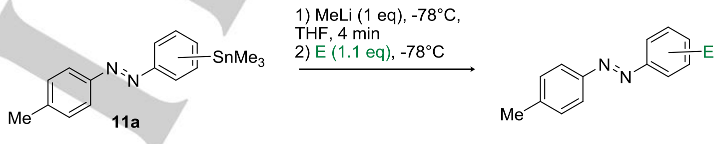


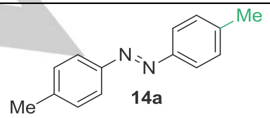
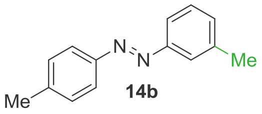
Figure 2. MeTHF: ^{119}Sn NMR signals for the reaction of the *para* stannylated azobenzene at -103 °C at t=0 min (blue) A reaction progress and the formation of the tin-stannate complex could be observed at -103 °C (t=4 min) (red), at -60 °C the reaction was finished and only tetramethylstannane was visible (green); diethyl ether: The starting material **11a** at -80 °C (yellow); at -15 °C the reaction started (grey) and 27 °C the reaction finished and tetramethylstannane and the sideproduct was visible (magenta). *= First spectrum of at this temperature, the average heating rate of the NMR was 0.2 °C/min.

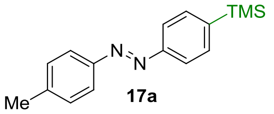
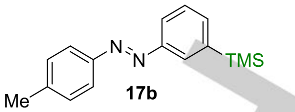
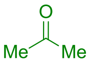
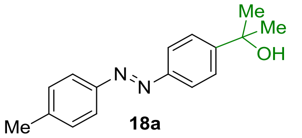
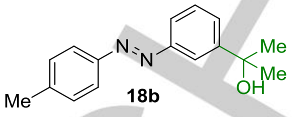
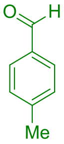
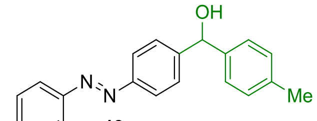
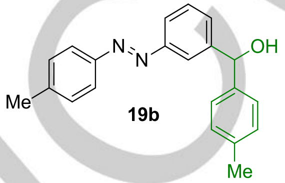
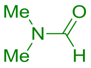
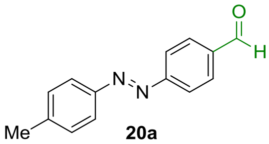
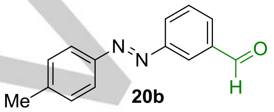
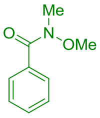
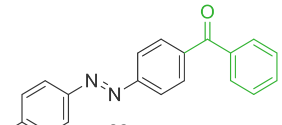
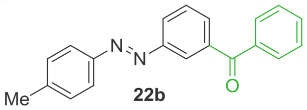
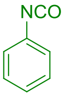
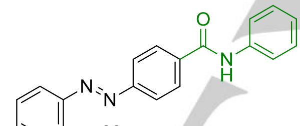
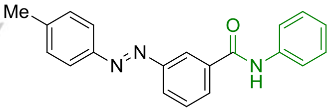
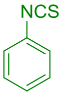
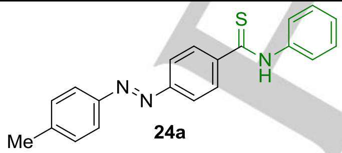
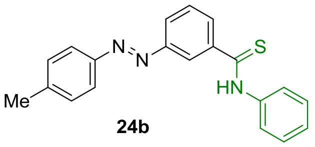
Synthetic Scope

The reaction of 4-lithio-4'-methylstannyl azobenzene (**13a**) with methyl iodide, as used in the optimization reactions, gave an excellent isolated yield of 96% of **14a**. The reaction conditions were transferred to 4-methyl-3'-trimethylstannyl azobenzene (**11b**) and a comparable yield of 95% of **14b** could be isolated (Table 2, entry 1). However, a good reaction conversion does not only depend on a successful lithiation: The electrophile used for quenching is also an important factor. To show that our newly developed methodology for the lithiation of azobenzenes is of general practical use, a variety of quenching agents were used for 4-methyl-4'-trimethylstannyl azobenzene (**11a**) and 4-methyl-3'-trimethylstannyl azobenzenes (**11b**) (Table 2). Quenching with trimethylsilyl chloride showed yields with 94% for **17a** and 95% for **17b** (entry 2). This compares favorably to previous protocols for a silylations of azobenzenes via halogen-lithium exchange: The yields reported for these reactions average around 20%[65] to a maximum yield of 42%[12] using a trimethylsilyl halogenide electrophile.

Table 2: Range of electrophiles employed for the reaction with the lithiated azobenzenes and the resulting products.



Entry	E	Product	Yield/ %	Product	Yield/ %
1	MeI	 14a	96	 14b	95

2	TMSCl	 **17a**	94	 **17b**	95
3		 **18a**	89	 **18b**	83
4		 **19a**	95	 **19b**	89
5		 **20a**	89	 **20b**	83
6	 **22**	 **22a**	98	 **22b**	71
7		 **23a**	77	 **23b**	76
8		 **24a**	80	 **24b**	81

Lithiation reactions are also often used for the introduction of functional groups such as alcohols, carbonyls or amides. The quenching reaction with acetone gave alcohol **18a** with a yield of 89% and **18b** in a slightly lower yield of 83% (entry 3). The reaction of tolulaldehyde gives **19a** and **19b** in excellent yields ranging from 89 to 95 % (table 2, entry 4). The aldehyde functionalization by quenching with *N,N*-dimethyl formamide gave product **20a** in a yield of 89% and the *meta*-compound **20b** in a yield of 83%.(entry 5). A further classical methodology of synthesizing ketones from organolithium reagents is the use of Weinreb's amide (**21**).[66] In reaction with the lithiated azobenzenes, it provided the ketones **22a** and **22b** in yields of up to 98% (entry 6).

The synthesis of amides and thioamides from aryl lithium species are typically performed by the use of phenyl isocyanate or phenyl isothiocyanate. Those compounds were also appropriate electrophiles and gave very good yields of 77% and 76%, respectively, for the *para*-lithiated species and 80% and 81%, respectively, for the *meta* lithiated species (entries 7 and 8). While simple electrophiles can only react once, other electrophiles are capable of multiple reactions. Such electrophiles are very attractive for the synthesis of dyes with multiple chromophoric groups. Various methane derivatives with two azobenzene units on one carbon atom have been reported in the literature.[67-71]

Typically, these compounds are synthesized from diamine precursors and a subsequent azocoupling.[67,69,71]

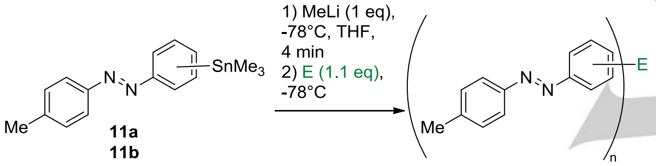
With benzoyl chloride as an electrophile, two equivalents of the lithiated azobenzenes could be added to the electrophile, where 96% of **25a** and 71% of **25b** could be obtained. Product **26a** and **26b** could be obtained by using an analogous ester that gives the product in both the *para* and *meta* positions in good yields of 79%.

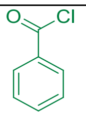
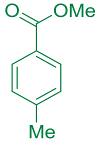
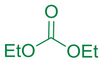
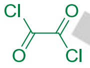
Only two protocols for the synthesis of triple azobenzene functionalized methane derivatives have been reported to date: In one procedure, the product was obtained by a condensation reaction of nitrosobenzene with tri(4-aminophenyl)methane in a yield of 35%, followed by a subsequent oxidation of the corresponding (triphenylazo)triphenyl methanol, an analog of **27a**, in a yield of 30% (which corresponds to an overall yield of 10%).[67] The second protocol entails condensation of an aldehyde functionalized azobenzene with unsubsituted azobenzenes via an electrophilic substitution in sulfuric acidutilizing very harsh conditions. No yield was reported.[68]

When three equivalents of 4-methyl-4’-trimethylstannyl azobenzene were lithiated and quenched with one equivalent of diethyl carbonate the main product was a triple azobenzene functionalized methanol derivative **27a** in a yield of 52%, and the bis-azobenzene functionalized ketone **28a** in a yield of 35%. The same reaction quenched with one equivalent of oxalyl chloride gave the triple azobenzene substituted methanol **27a** in a yield of 54% and the ketone **28a** in a yield of 23% (Table 3, entry 4).

The *meta*-substituted azobenzene analogs could be obtained in a yield of 49% for the tri-substituted methanol **27b** and 28% for the di-substituted ketone **28a** (Table 3, entry 3).

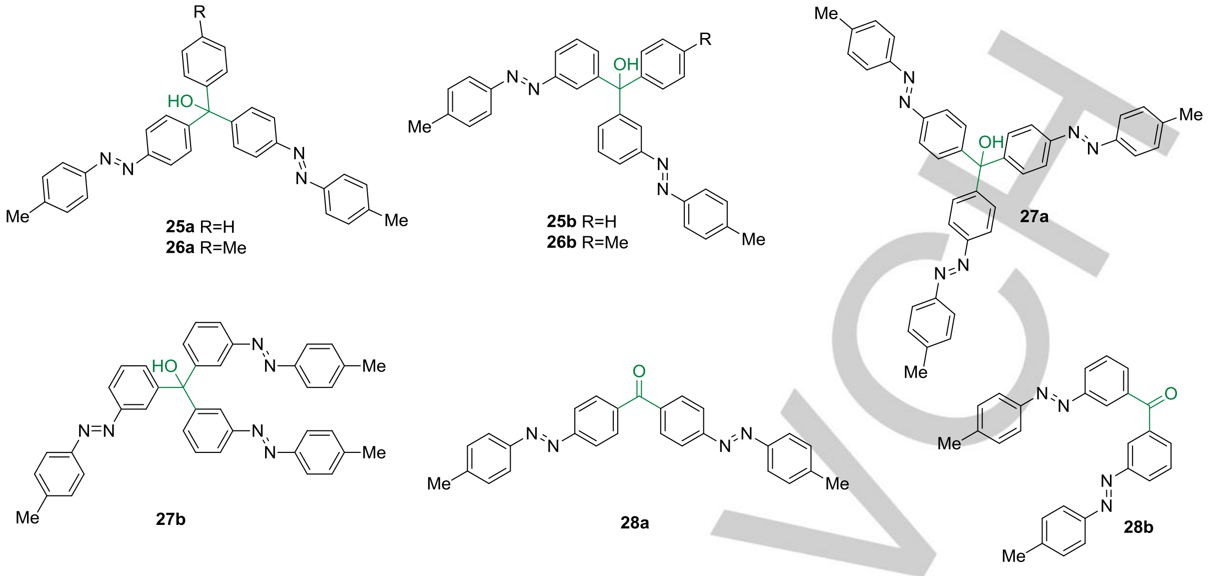
Table 3. Products with multiple azobenzenes.



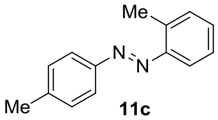
Entry	E	Products	Yield/%
1a 1b		25a 25b	96 71
2a 2b		26a 26b	79 79
3a 3b		27a 28a 27b 28b	52 35 28 49
4a 4b		27a 28a	23 54

Scheme 5. Products with multiple azobenzenes. For yields, see Table 3.

Although the *para*- and *ortho*-lithiated azobenzenes did not show a significant difference in their reactivity towards electrophiles, we suspect that this might be different for the *ortho*-lithiated azobenzene: Steric hinderence by the azo group could affect the formation of the analogous products. On the other hand, the lithiated species might be particularly stable due to additional complexation of the lithium by the lone pair of the adjacent nitrogen atom. In the literature, *ortho* lithiations typically give higher yields than a lithiation in *meta* or *para* position due to this effect.[33, 71-73] When the *ortho* lithiated azobenzene was quenched with methyl iodide, the isolated yield of the *ortho* methylated azobenzene derivative **11c** was almost quantitative (99%). Even the more sterically hindered trimethyl silyl electrophiles gave the silylated product **17c** in good 82% yield. (Scheme 6). For further *ortho*-products, see the supporting information.

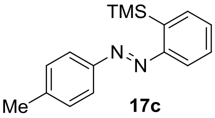


Scheme 6. *Ortho*-functionalized azobenzenes.



11c

99%



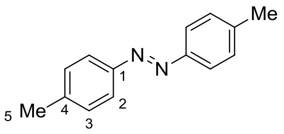
17c

82%

Conclusions

The transmetalation of stannylated azobenzenes with methyl lithium in THF led to a rapid and selective exchange of the trimethylstannyl group without any attack on the azo group. NMR spectroscopy showed that the reaction proceeded via a lithium-tin-ate complex prior to a rearrangement to the lithiated species. Analysis by gas chromatography and NMR spectroscopy showed that the reaction was rapid and selective in THF and MeTHF, but unselective in diethyl ether; in this solvent hydrazine derivatives were formed due to an attack of the organolithium reagent on the diazo group. Furthermore, optimized reaction conditions for performing the lithiation reaction in THF at -78 °C could be applied as a high yielding, general method for lithiating azobenzenes in *ortho*, *meta* and *para* positions. The lithiated azobenzenes were quenched with a wide variety of electrophiles. Products containing one azobenzene unit could be obtained in yields ranging from 71% to 98%. Quenching the lithiated azobenzenes with electrophiles with functional groups of multiple reactivity allowed the synthesis of di- and even tri- azobenzene-functionalized compounds in good yields.

Experimental Section



Representative lithiation procedure for 4,4'-dimethylazobenzene (**14a**): To a solution of 4-methyl-4'-(trimethylstannyl)-azobenzene (1.00 eq, 250 mg, 700 µmol) in THF (10 mL), a solution of methyllithium (0.99 eq, 440 µL, 700 µmol, 1.58 M in diethyl ether), diluted in THF (1.58 mL) was added at -78 °C over the course of 4 min. After 2 min, a solution of methyl iodide (1.10 eq, 50.0 µL, 800 µmol) in THF (0.32 mL) was added and the reaction mixture was warmed to 20 °C. After 6 h stirring the solvent was evaporated and the residue purified using column chromatography with DCM (Rf = 0.7) as eluent. The solvent was evaporated and yellow crystalline needles (140 mg, 666 µmol, 96%) were obtained. ^{1}H NMR (500 MHz, CDCl3): δ = 7.82 (d, 3J = 8.4 Hz, 4 H, H-2), 7.32 (d, 3J = 8.4 Hz, 4 H, H-3), 2.44 (s, 6 H, H-5) ppm. ^{13}C NMR (125 MHz, CDCl3): δ = 150.8 (C-1), 141.2 (C-4), 129.7 (C-2), 122.7 (C-3), 21.5 (C-5) ppm. IR (ATR): ṽ = 3023 (w), 2921 (w), 1601 (m), 1502 (m), 1306 (w), 1237 (w), 1149 (m), 1012 (m), 883 (m), 839 (m), 821 (s), 794 (m), 710 (m), 683 (s), 535 (m), 504 (s) 492 (s) cm^{-1}. HRMS (EI-sector): *m/z* = $[M]^{+}$ calcd. for $[C_{14}H_{14}N_{2}\ 210.1157]^{+}$; found 210.1156. Mp: 145 °C.

Acknowledgements

This project was supported by the Special Research Area 677 “Function by Switching” of the Deutsche Forschungsgemeinschaft (DFG), Project C10.

The authors thank Hans J. Reich, University of Wisconsin, for helpful discussions.

Keywords: Azo compounds• lithiation • tin • metalation • NMR spectroscopy

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[51] The substance was contaminated with starting material **11a** and product **14a** (see supporting information for details and spectra).
[52] Although at -78 °C, *n*-BuLi is relatively stable in THF, for the reaction to be conducted under the exact same conditions as for the reaction with MeLi, *n*-BuLi would need to be dissolved in THF and then transferred via syringe or cannula. This would inevitably result in an uncontrolled warming-up of the *n*-BuLi / THF solution. Therefore, this is not a reproducible way to conduct the experiment. This is especially true if one keeps in mind that Table 1 merely represents the optimization process at small scale. Azobenzenes are often used in materials, where larger amounts are required. A process where one of the reagents will undergo a time dependent, and temperature dependent decomposition would be unsuitable for scale-up.
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Entry for the Table of Contents

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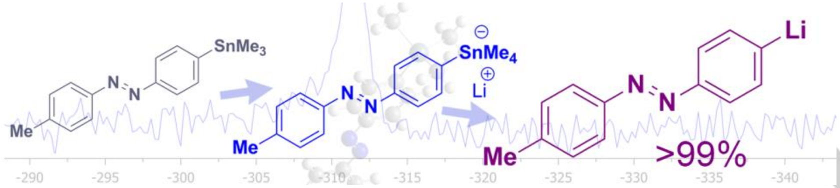
FULL PAPER



A mild and efficient method for the near quantitative lithiation of azobenzenes in any position is reported. It proceeds via a tin-lithium exchange, which could be monitored by low T ^{119}Sn NMR spectroscopy. The lithiated azobenzenes were able to react with a wide variety of electrophiles in yields ranging from 71% to 98% for mono-substitutions of azobenzenes. In addition, di- and even tri- azobenzene-functionalized compounds were obtained in good yields.

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High Yielding Lithiation of Azobenzenes by Tin-Lithium Exchange