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# **Accepted Article**

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To be cited as: Angew. Chem. Int. Ed. 10.1002/anie.201812742 Angew. Chem. 10.1002/ange.201812742

Link to VoR: http://dx.doi.org/10.1002/anie.201812742 http://dx.doi.org/10.1002/ange.201812742

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# Highly Regioselective Remote Lithiation of Functionalized 1,3-bis-Silylated Arenes

#### Andreas B. Bellan and Paul Knochel\*

**Abstract:** Substituted arenes flanked by two bulky triethylsilyl groups are regiospecifically lithiated in 5-position with nBuLi•PMDTA at 25 °C. The resulting aryllithiums reacted with a broad range of electrophiles such as ketones, isocyanates, Weinreb-amides, allyl bromides or  $CO_2$  at 25 °C. These bis-silylated arenes were converted in simple reaction sequences to silyl-free tetrasubstituted arenes. This remote lithiation was extended to 2,6-bis(triethylsilyl)pyridine as well as a 3,3-bis(triethylsilyl)biphenyl.

The metalation of arenes and heteroarenes is an important functionalization method of these ring systems.<sup>[1]</sup> Usually, a functional group is required to direct such metalations in orthoposition.<sup>[2]</sup> However, metalation in meta- or para-positions are rather seldom. Recently, Mulvey and O'Hara described selective meta-functionalizations using mixed alkali-metal-mediated metalations allowing the double functionalization of various aromatics in ortho-meta' or even in meta-meta'-positions.<sup>[3]</sup> Also, Gaunt reported a copper-catalyzed oxidative C-H-coupling leading to a meta-arylation of aniline derivatives.[4] Using removable nitrile containing tethers, Yu<sup>[5]</sup> and Tan<sup>[6]</sup> were able to perform meta C-H activations using palladium-catalyzed Heck reactions. Yu performed an oxidative Pd-catalyzed Catellanireaction, changing the regioselectivity of the C-H activation from ortho to the meta position.<sup>[7]</sup> Ackermann reported a meta-selective ruthenium-catalyzed C-H alkylation using secondary alkyl halides.<sup>[8]</sup> Maiti observed a para-selective oxidative acylation of arenes employing enol ethers as acylating reagents.<sup>[9]</sup> Pioneering work of Schlosser showed that a bulky silyl-substituent between two chlorides on a benzene ring results in a buttress effect, which kinetically favors the meta-metalation relative to the halides.<sup>[10]</sup> This led us to envision the use of the direct sterical bulk of two silyl groups for achieving a remote metalation. Herein, we report a convenient, more general, 5-lithiation of arenes of type 1, leading to para-substituted aryllithiums of type 2 (Scheme 1).





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First, we have investigated metalation conditions for the lithiation of 2,6-bis(triethylsilyl)fluorobenzene (1a) as test substrate. The formation of the lithiated arene 2a was determined by quenching reaction aliquots with MeSSMe leading to the thioether 3a. No lithiation was observed with standard lithium bases (Table 1, entries 1-4). The addition of N,N,N',N'-tetramethylethylenediamine (TMEDA), a reactivity enhancing agent of alkyllithium reagents, had no effect (entries 5-6).[11] However, addition of N, N, N', N'', N''-pentamethyldiethylenetriamine (PMDTA)<sup>[12]</sup> to either nBuLi or sBuLi afforded the expected metalation product 2a in 43% and 29% yield respectively,<sup>[13]</sup> indicating that *n*BuLi is for these systems the superior alkyllithium base (entries 7-8). To improve the incomplete metalation, the base amount was increased from 1.5 equiv. to 3.0 equiv. raising the yield to 58% (entry 9). Surprisingly Schlosser's base (nBuLi•KOtBu)[14] led to a drastic product decrease (entry 10). To our delight changing from ethereal solvents to non-coordinating hexane improved the lithiation considerably and the reaction of 1a with nBuLi•PMDTA led, after quench with MeSSMe, to an increased yield of 65% isolated product of 3a (entry 11).<sup>[15,16]</sup>

Table 1: Optimization of the lithiation of bis-silylated fluorobenzene (1a).

	Et <sub>3</sub> Si	F SiEt <sub>3</sub> bar solve	se, additive Int, 25 °C, 6 h	F SiEt <sub>3</sub> –	MeSSMe E	Et <sub>3</sub> Si SMe <b>3a</b>
_	Entry	Li reagent	Additive	Equiv.	Solvent	Yield [%] <sup>[a]</sup>
	1	<i>n</i> BuLi	-	1.5	Et <sub>2</sub> O	0
1	2	sBuLi	-	1.5	Et <sub>2</sub> O	0
	3	<i>t</i> BuLi	-	1.5	Et <sub>2</sub> O	0
/	4	TMPLi	-	1.5	THF	0
	5	<i>n</i> BuLi	TMEDA	1.5	Et <sub>2</sub> O	0
	6	sBuLi	TMEDA	1.5	Et <sub>2</sub> O	0
	7	<i>n</i> BuLi	PMDTA	1.5	Et <sub>2</sub> O	43
	8	sBuLi	PMDTA	1.5	Et <sub>2</sub> O	29
	9	<i>n</i> BuLi	PMDTA	3.0	Et <sub>2</sub> O	58
	10	<i>n</i> BuLi	PMDTA/KO <i>t</i> Bu	3.0	Et <sub>2</sub> O	9
	11	<i>n</i> BuLi	PMDTA	3.0	<i>n</i> hexane	71 (65) <sup>[b]</sup>

[a] Yield of **2a** determined by GC analysis of reaction aliquots quenched with MeSSMe. [b] Yield of analytically pure isolated product.; TMP: 2,2,6,6-tetramethylpiperidyl.

The aryllithium **2a** generated under these optimized conditions was treated with various electrophiles leading regiospecifically to para-substituted fluorobenzenes **3a-I** in 61-89% yield (Scheme 2).<sup>[15,17,18]</sup>

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**Scheme 2:** Remote lithiation of fluorobenzene **1a**, leading to functionalized arenes of type **3**. [a] Yield of analytically pure isolated product. [b]  $ZnCl_2$  (3.0 equiv.) was added. [c] CuCN•2LiCl (10 mol%) was added.

To demonstrate the utility of bis-silyl derivatives of type **3**, we have converted **3b** into silyl-free tetrasubstituted fluorobenzenes of type **4** (Scheme 3). Thus, iodination of **3b** with ICI provides aryl iodide **5** in 90% yield.<sup>[19]</sup> A selective I/Mg-exchange on **5** (*i*PrMgCI•LiCI, -40 °C, 15 min) furnished a magnesium intermediate, which was quenched with a range of electrophiles (E<sup>1</sup>–X), to give the mono-silanes **6a-g** in 71-94% yield.<sup>[20]</sup> Treatment of arenes **6** with ICI afforded the silyl-free arenes **7a-b** in 91-94% yield. A subsequent I/Mg-exchange on iodoketone **7a** and quenching with a second electrophile (E<sup>2</sup>-X) led to the tetrasubstituted fluorobenzenes **4a-c** in 73-82% yield.



**Scheme 3:** Polyfunctional arenes of type **4** prepared by selective iododesilylations, followed by I/Mg-exchange and electrophile quenchings. [a] Yield of analytically pure isolated product. [b] CuCN•2LiCl (10 mol%) was added. [c] ZnCl<sub>2</sub> (1.1 equiv.), Pd(dba)<sub>2</sub> (2 mol%) and P(o-furyl)<sub>3</sub> (4 mol%) were added. [d] CuCN•2LiCl (1.1 equiv.) was added.

We were confident that the fluoro-substituent of the bis-silyl arene **1a** was essential for a fast metalation. However, after preparing analogs of **1a** such as **1b-f**, we realized that other factors than the substituent electronegativity were important for such remote lithiations. Thus, the oxazolyl derivative **1b** was smoothly metalated with *n*BuLi•PMDTA (3.0 equiv., 25 °C, 6 h) to provide the lithiated arene **2b** (Scheme 4). Quenching **2b** with MeSSMe led to the corresponding thioether **8a** in 89% isolated yield,<sup>[16]</sup> suggesting that complexation of *n*BuLi•PMDTA by the oxazolyl group was essential for an efficient metalation. Related coordinating functionalities, such as a methoxy **1c**, an amido **1d** or a carbamate **1e**, proved to be less powerful directing groups and led to lithiations with comparable efficiency than the unsubstituted substrate **1f**. After quenching **2c-f** with MeSSMe, the corresponding thioethers **9-12** were obtained in 38-48% yield. Quenching of **2b** with various electrophiles (including aldehyde, ketone, Weinreb amide, isocyanate) provided the expected products **8b-8n** in 62-96% yield (Scheme 4).<sup>[15]</sup>



Scheme 4: Remote lithiation of various functionalized arenes of type 1, leading to functionalized arenes of type 8-12. [a] *n*BuLi•PMDTA, 25 °C, 6 h. [b] MeSSMe, -20 °C, 1 h. [c] The metalation temperature was -10 °C. [d] Yield of analytically pure isolated product. [e] ZnCl<sub>2</sub> (3.0 equiv.) was added. [f] This reaction was performed on a 30 mmol scale with no yield decrease. [g] CuCN•2LiCl (10 mol%) was added.

8I. 70%<sup>[d]</sup>

8k. 86%

0

8m, 70%<sup>[d]</sup>

8n, 68%<sup>[c</sup>

The oxazolyl arenes of type **8** were converted into various silyl free amides and lactones via a short reaction sequence. Thus, in a one-pot procedure, oxazolyl arene **8c** was methylated with  $Me_3OBF_4$  (1.05 equiv., 0 °C, 2 h) followed by a new reductive ring opening with LiEt<sub>3</sub>BH (1.2 equiv., 0 °C, 4 h), affording benzamide **13** in 86% yield (Scheme 5). Treatment of **13** with ICI provided iodoarene **14** in 89% yield. Methylation of **14** with MeLi•LiBr (1.05 equiv., -78 °C, 1 h) furnished the 2-methylated arene **15** in 91% yield. <sup>[21]</sup> Subsequent iodo-desilylation with ICI afforded iodoarene **16** in 96% yield. Finally, a I/Mg-exchange followed by reactions with various electrophiles gave the desired polyfunctional arenes **17a-e** in 61-86% yield.



**Scheme 5:** Polyfunctional benzamides and lactones of type **17** prepared by reductive ring opening and selective iodo-desilylations, followed by *I/Mg*-exchange and electrophilic quench. [a] Yield of analytically pure isolated product. [b] CuCN•2LiCl (10 mol%) was added. [c] ZnCl<sub>2</sub> (1.1 equiv.), Pd(dba)<sub>2</sub> (2 mol%) and P(o-furyl)<sub>3</sub> (4 mol%) were added. [d] The crude benzylic alcohol was refluxed in 1,4-dioxane.<sup>[15]</sup>

Remarkably, this remote metalation can be extended to the pyridine scaffold.<sup>[22]</sup> Thus, 2,6-bis(triethylsilyl)pyridine (**18**) was treated with *n*BuLi•PMDTA (1.1 equiv., 25 °C, 3 h) leading to the

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4-lithiated bis-silyl pyridine **19**, which was quenched with a variety of electrophiles affording the 4-functionalized pyridines **20a-m** in 60-96% yield (Scheme 6).<sup>[15,23]</sup>



**Scheme 6:** Remote lithiation of pyridine **18**, leading to functionalized pyridines of type **20**. [a] Yield of analytically pure isolated product. [b] NEt<sub>3</sub> was used during column chromatographical purification. [c]  $ZnCl_2$  (1.1 equiv.) and CuCN-2LiCl (10 mol%) were added. [d]  $ZnCl_2$  (1.1 equiv.) and Pd(PPh<sub>3</sub>)<sub>4</sub> (2 mol%) were added. [e] MgCl<sub>2</sub> (1.0 equiv.) was added.

Silyl-free 2,4,6-trisubstituted pyridines were readily obtained by selective metalations of pyridines of type **20**. Thus, the 4-arylated pyridine **20d** was converted to the 2-bromopyridine **21** by a BF<sub>3</sub>•OEt<sub>2</sub>-mediated magnesiation with TMPMgCl•LiCl followed by the addition of bromine (83% yield).<sup>[24]</sup> TBAF-mediated protodesilylation furnished the disubstituted pyridine **22** in 98% yield. Metalation of **22** with TMPMgCl•LiCl (0 °C, 1 h) and quench with various electrophiles led to the products **23a-e** in 79-97% yield (Scheme 7).<sup>[25]</sup>



**Scheme 7:** Selective functionalization of pyridine **20d** via a sequence of TMPMgCI-LiCI magnesiations, leading to trisubstituted pyridines of type **23**. [a] Yield of analytically pure isolated product. [b] CuCN-2LiCI (10 mol%) was added. [c] ZnCl<sub>2</sub> (4.0 equiv.), Pd(dba)<sub>2</sub> (2 mol%) and P(o-furyl)<sub>3</sub> (4 mol%) were added.; TBAF: tetrabutylammonium fluoride

Finally, this remote lithiation has been briefly extended to biphenyl derivatives. The readily prepared bis-silyl derivative **24** was metalated with *n*BuLi•PMDTA (25 °C, 6 h) providing the 5-lithiated biphenyl **25**, as sole meta-metalation product (Scheme 8). A subsequent reaction with MeSSMe afforded thioether **26** in 38% yield.



Scheme 8: Remote lithiation of biphenyl 24, leading to thioether 26. [a] Yield of analytically pure isolated product.

In summary, we have found that the *n*BuLi•PMDTA complex is an exceptionally active base for the regioselective remote lithiation of various 1,3-bis(triethylsilyl)arenes, including the bis-silylated pyridine **18**. We have converted the resulting para-functionalized arenes into a variety of tetrasubstituted arenes, demonstrating the utility of our procedure for remote lithiations. Further extensions of this method are currently being studied in our laboratories.

#### Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (DFG) for financial support. We thank Albemarle (Frankfurt, Germany) for the generous gift of chemicals. We thank Dr. Johannes Nickel for preliminary experiments.

Keywords: lithiation • pyridines • remote metalation • silanes

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(s) = SiEt3>95%96%41% over 6 stepsLithiation in para-position: The regiospecific remote lithiation of easily prepared<br/> $o_io^2$ -bis(triethylsilyl)arenes and heteroarenes using nBuLi+PMDTA (PMDTA =<br/>MeN(CH2CH2NMe2)2) is reported. These lithiated (hetero)arenes react with a broad<br/>range of electrophiles leading after further functionalizations to silyl-free<br/>tetrasubstituted products.

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