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Metalation

Preparation and Regioselective Metalation of Bis(trimethylsilyl)methyl-Substituted Aryl Derivatives

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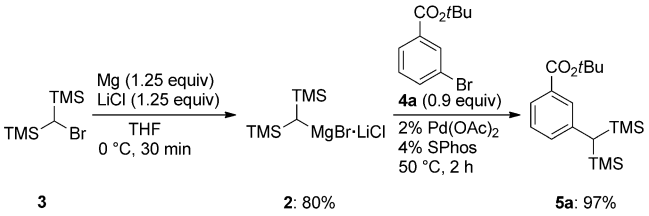
Abstract: A range of bis(trimethylsilyl)methyl-substituted aryl derivatives was prepared by using a Kumada–Corriu cross-coupling reaction. The regioselective metalation of the resulting bis(trimethylsilyl)methyl-substituted aryl derivatives bearing this bulky silyl group allowed the generation of functionalized aromatics. A regioselective switch in the presence or in the absence of the bis(trimethylsilyl)-methyl group has been demonstrated. Furthermore, this silyl group was converted into a formyl group or a styryl group, enhancing the scope of application of such bis(trimethylsilyl)methyl-substituted arenes.

The regioselective metalation of aromatics is an important synthetic task as functionalized arenes are essential building blocks for pharmaceuticals and agrochemicals.[1] Additionally, functionalized silyl substituents have found an increasing application in organic chemistry.[2] Numerous strategies have been elaborated for performing regioselective lithiations,[3] and the use of the $(Me_3Si)_2CH$ group (BTSM)[4] was pioneered by Snieckus and was shown to trigger the directed lithiation of benzamides with great efficiency.[5] In addition, this bulky silicon group has been successfully used as a remote control in the synthesis of isolable atropisomeric amides by Xia and Xu.[6] Recently, the bis(silyl)methyl moiety has also been used for Wittig rearrangements and Prins cyclization.[7] Also, we have shown that the pyrazine scaffold can be fully functionalized starting from a BTSM-substituted pyrazine[8] by using the magnesium base $TMP_2Mg{\cdot}2LiCl$ (**1**; TMP = 2,2,6,6-tetramethylpiperidyl).[9] Herein, we report a simple way to introduce the BTSM substituent onto an aromatic system by using a Kumada–Corriu cross-coupling reaction[10] between $(Me_3Si)_2CHMgBr{\cdot}LiCl$ (**2**)[11] and various aryl bromides. We show that the BTSM group allows regioselective magnesiation or lithiation of these functionalized aromatics. In some cases, a regioselective switch was demonstrated (in the presence or absence of the BTSM group). In addition, several transformations of the BTSM group were performed.

Thus, $(Me_3Si)_2CHMgBr{\cdot}LiCl$ was prepared by the reaction of $(Me_3Si)_2CHBr$ (**3**, 1.0 equiv) with magnesium turnings (1.25 equiv) in the presence of LiCl (1.25 equiv), furnishing the desired Grignard reagent **2** within 30 min at 0 °C. Titration of the organomagnesium reagent with iodine in THF indicated a concentration of 0.6 M (80% yield).

In preliminary experiments, $(Me_3Si)_2CHMgBr{\cdot}LiCl$ (**2**) underwent a smooth Kumada–Corriu cross-coupling reaction with *tert*-butyl 3-bromobenzoate (**4a**, 0.9 equiv, 50 °C, 2 h) by using 2% $Pd(OAc)_2$ and 4% SPhos.[12] The BTSM-substituted benzoic ester (**5a**) was obtained in 97% yield (Scheme 1).



Scheme 1. Preparation of **5a** and subsequent cross-coupling reaction.

This cross-coupling procedure could be extended to a range of aromatic bromides bearing either electron-donating or electron-withdrawing substituents. Thus, the *meta*-substituted aryl bromides **4b–4f** underwent the cross-coupling reaction with the Grignard reagent **2** and the corresponding BTSM-functionalized aromatic derivatives (**5b–5f**) were isolated in 88–95% yield (Table 1, entries 1–5). Also, the *para*-substituted methyl 4-bromobenzoate (**4g**) was converted into the corresponding cross-coupling product **5g** in 89% yield (entry 6). Even a keto function could be tolerated in this cross-coupling and the bromobenzophenone **4h** was converted to **5h** in 72% yield (entry 7). Also, the unprotected aniline derivative **4i** furnished the corresponding cross-coupling product **5i** by using 3 equivalents of the Grignard reagent **2** and toluene as co-solvent (THF/toluene = 2:1, 80 °C, 24 h). The resulting aniline **5i** was isolated in 60% yield (entry 8).

The prepared BTSM-substituted aromatics of type **5** were submitted to metalation reactions employing various Li or Mg

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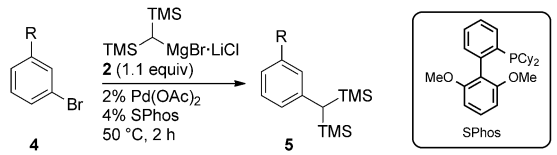
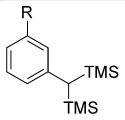
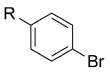
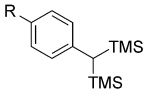
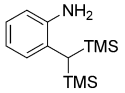
Table 1. Products of type **5** obtained by Kumada–Corriu cross-coupling reaction of various aryl bromides with **2**.



4 5

Entry	Electrophile	Product[a]
		
1	**4b**: R = F	**5b**: 92%
2	**4c**: R = CF_3	**5c**: 91%
3	**4d**: R = CO_2Et	**5d**: 91%
4	**4e**: R = OMe	**5e**: 95%
5	**4f**: R = NMe_2	**5f**: 88%
		
6	**4g**: R = CO_2Me	**5g**: 89%
7	**4h**: R = COPh	**5h**: 72%
8		
	4i	**5i**: 60%[b]

[a] Yields of isolated, analytically pure product. [b] The cross-coupling reaction was performed by using 2.5 equivalents of **2** in a 2:1 mixture of THF/toluene at 80 °C for 24 h.

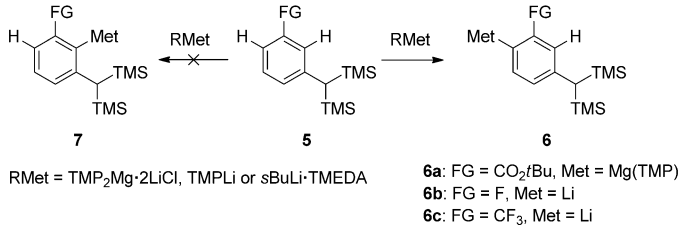
bases. In all cases, a regioselective metalation at the least hindered position of the aromatic substrate **5** was observed, leading to the lithiated or magnesiated species **6** and not to the more sterically hindered organometallic species **7** (Scheme 2).

For the metalation of benzoate **5a**, bearing a sensitive ester function, the use of TMPMgCl·LiCl did not lead to complete conversion. Therefore, the stronger base TMP_2Mg·2 LiCl was applied for a selective metalation. Thus, treatment of **5a** with TMP_2Mg·2 LiCl (**1**, 1.5 equiv) in THF (25 °C, 2 h) led to the Grignard reagent **6a**. After transmetalation with $ZnCl_2$ (1.6 equiv), a Pd-catalyzed Negishi cross-coupling[13] reaction with ethyl 4-iodobenzoate (**8a**) or 4-iodoanisole (**8b**; Table 2, entries 1–2) in THF (50 °C, 12 h) by using 2% $Pd(dba)_2$ (dba = dibenzylideneacetone) and 4% tfp (tfp = tri(2-furyl)phosphine)[14] led to the corresponding biphenyls **9a** and **b** in 88 and 93% yield, respectively. The cross-coupling reaction with 4-bromobenzonitrile (**8c**) with 2% $Pd(OAc)_2$ and 4% SPhos as the catalytic system (50 °C, 12 h), furnished the nitrile **9c** in 88% yield (entry 3). In the presence of CuCN·2 LiCl (1.6 equiv), reaction with ethyl (2-bromomethyl)acrylate[15] (**8d**) gave the allylated product **9d** in 92% yield (entry 4). The less sensitive substrate **5b** was conveniently lithiated with TMPLi (2 equiv) in THF (−60 °C, 1 h), leading to the aryllithium reagent **6b** (Scheme 2). Transmetalation with $ZnCl_2$ (2.1 equiv) and subsequent cross-coupling reaction with the aryl bromide **8e** led to the expected product **9e** in 95% yield (entry 5). Moreover, the cross-coupling reaction with 2-iodothiophene (**8f**) furnished the biaryl **9f** in 96% yield (entry 6). For the metalation of **5c**, *s*BuLi (1.5 equiv) and TMEDA (tetramethylethylenediamine, 1.5 equiv) in hexane[16] (−30 °C, 1.5 h) were used, leading to the *ortho*-lithiated species **6c**, which underwent, after transmetalation with $ZnCl_2$ (1.5 equiv), a copper-catalyzed allylation with **8d** to give the allylated product **9g** in 57% yield (entry 7). The aryllithium species **6c** reacted directly with the sulfur electrophile **8g** to afford the thioether **9h** in 60% yield (entry 8). Transmetalation to the magnesium species (with 1.6 equiv $MgCl_2$) and subsequent reaction with *N*,*N*-dimethylenemethaniminium trifluoroacetate (**8h**)[17] furnished the corresponding benzylamine **9i** in 62% yield (entry 9). Transmetalation of **6c** with $ZnCl_2$ and subsequent Pd-catalyzed cross-coupling reactions with aryl halides **8i** and **8j** gave the biphenyls **9j** and **9k** in 64–77% yield (entries 10 and 11).

The presence or absence of the BTSM group allowed switching of the metalation regioselectivity. Thus, an aryl bromide of type **4** (FG is an electron-withdrawing substituent) is preferentially metalated in position 2, leading to products of type **10** after quenching with an electrophile E (Scheme 3). On the other hand, the metalation of substrate **5** proceeds at the least sterically hindered position, 6, leading to products of type **9** after quenching with an electrophile. In this sequence, the final group, R, present in **9** or **10** is either a BTSM group or a formyl group (CHO).

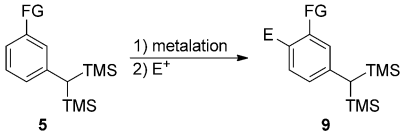
Thus, ester **4a** was smoothly metalated by TMPMgCl·LiCl[9] (1.5 equiv) in THF (0 °C, 45 min; Scheme 4). Direct addition to 4-chlorobenzaldehyde furnished the lactone **11a** in 75% yield. Alternatively, transmetalation of the magnesiated species with $ZnCl_2$ (1.6 equiv) and subsequent Pd-catalyzed cross-coupling reactions with 4-iodo-anisole (**8b**) or ethyl 4-iodobenzoate (**8a**) gave the biphenyls **11b** and **11c**, respectively, in 61–72% yield. A Kumada cross-coupling reaction of the *ortho*-substituted substrates **11a–c** with Grignard reagent **2** required harsher conditions (80 °C, 12 h) and the BTSM products **10a–c** were isolated in 32–47% yield. The resulting products **10a–c** have a complementary regioisomeric substitution pattern compared to the BTSM-substituted arenes **9a–d** already described in Table 2 (entries 1–4).

A similar regioselectivity switch was found with the 3-substituted aryl fluorides **4b** and **5b** (Scheme 5). Thus, treatment of **4b** with

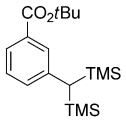
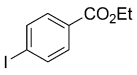
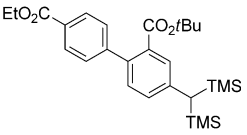
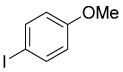
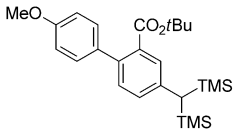
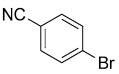
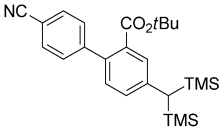
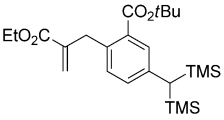
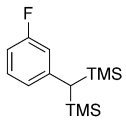
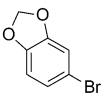
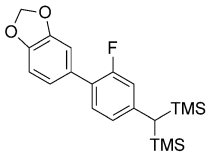
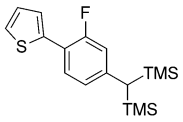
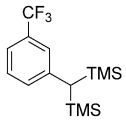
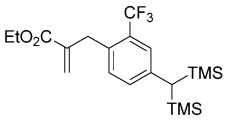
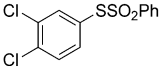
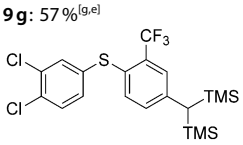
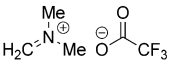
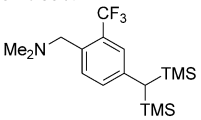
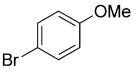
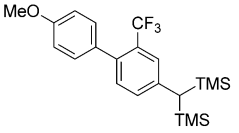


Scheme 2. Regioselective metalation of aromatics of type **5** by using various Li or Mg bases.

Table 2. Products of type **9** obtained by metalation of **5** followed by reaction with different electrophiles.



5 **9**

Entry	Substrate	Electrophile	Product[a]
1			
	5a	**8a**	**9a**: 88%[b,c]
2			
	5a	**8b**	**9b**: 93%[b,c]
3			
	5a	**8c**	**9c**: 88%[b,d]
4			
	5a	**8d**	**9d**: 92%[b,e]
5			
	5b	**8e**	**9e**: 95%[f,d]
6			
	5b	**8f**	**9f**: 96%[f,c]
7			
	5c	**8d**	**9g**: 57%[g,e]
8			
	5c	**8g**	**9h**: 60%[g]
9			
	5c	**8h**	**9i**: 62%[g,h]
10			

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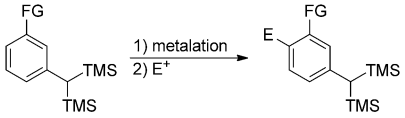

5 **9**

Entry	Substrate	Electrophile	Product[a]
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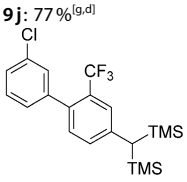
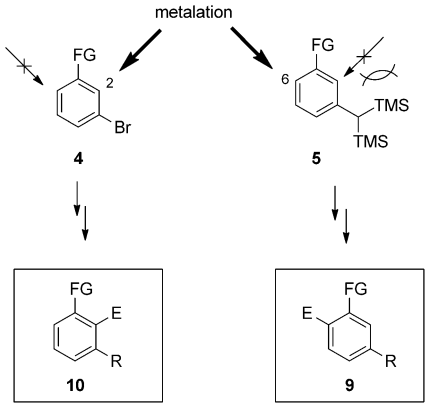
			
	5c	**8j**	**9k**: 64%[g,c]

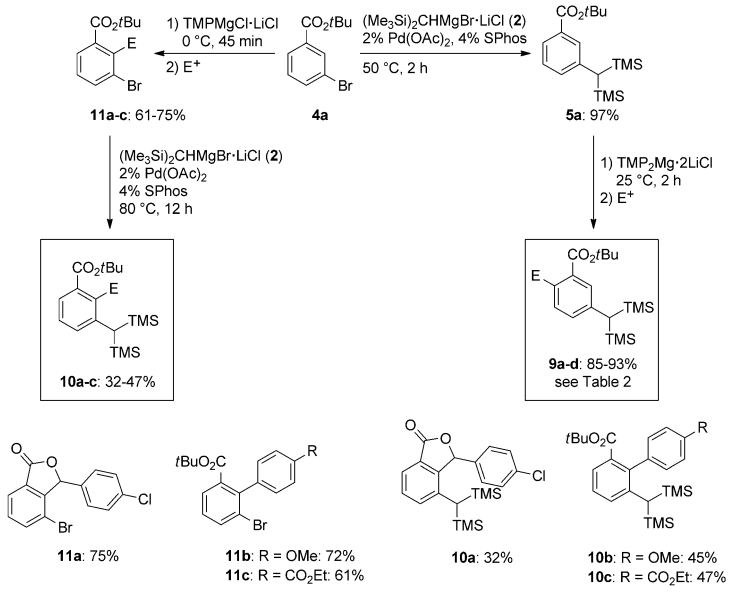
[a] Yields of isolated, analytically pure product. [b] Metalation conditions: $TMP_2Mg{\cdot}2LiCl$ (1.5 equiv), 25 °C, 2 h. [c] Cross-coupling conditions: $ZnCl_2$, 2% $Pd(dba)_2$, 4% tfp, 50 °C, 12 h. [d] Cross-coupling conditions: $ZnCl_2$, 2% $Pd(OAc)_2$, 4% SPhos, 50 °C, 12 h. [e] CuCN·2 LiCl (1.6 equiv) was added. [f] Metalation conditions: TMPLi (2 equiv), −60 °C, 1 h. [g] Metalation conditions: *s*BuLi (1.5 equiv), TMEDA (1.5 equiv), hexane, −30 °C, 1.5 h. [h] $MgCl_2$ (1.6 equiv) was added.



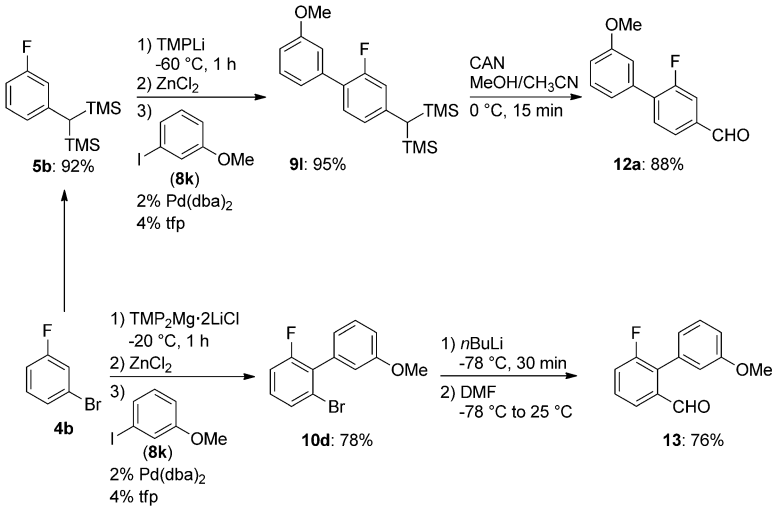
Scheme 3. Regioselective metalation of substrates of type **4** and **5**.

$TMP_2Mg{\cdot}2LiCl$ (1.1 equiv, −20 °C, 1 h) led to a 2-magnesiated intermediate that, after transmetalation with $ZnCl_2$ (1.2 equiv), underwent a Pd-catalyzed cross-coupling reaction with 3-iodoanisole (**8k**) to furnish the biphenyl **10d** in 78% yield. A Br/Li exchange was then performed on the arene **10d** with *n*BuLi (1.1 equiv) in THF (−78 °C, 30 min) to afford a lithiated species, which was trapped with DMF (2 equiv) to give the benzaldehyde **13** in 76% yield. Complementarily, the metalation of **5b** with TMPLi (2 equiv, −60 °C, 1 h) followed by transmetalation with $ZnCl_2$ (2.1 equiv) and subsequent Negishi cross-coupling with **8k**, afforded the biphenyl **9l** in 95% yield. Oxidation of **9l** with CAN (ceric ammonium nitrate, 5 equiv, 0 °C) according to the methodology developed by Palomo et al.[18] in a 3:1 mixture of methanol/acetonitrile (0 °C, 10 min) furnished the benzaldehyde derivative **12a** in 88% yield.

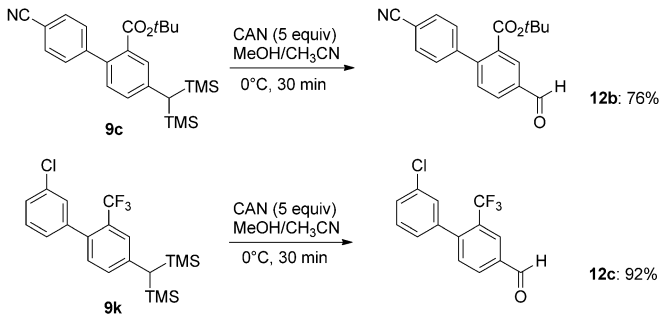
Finally, to show the utility of the BTSM group, we have converted several polyfunctional BTSM-substituted arenes to the



Scheme 4. Orthogonal functionalization of **4a** and **5a** by a regioselective magnesiation by using TMPMgCl·LiCl or $TMP_2Mg·2LiCl$.



Scheme 5. Generation of orthogonal-functionalized benzaldehydes **12** and **13**.



Scheme 6. Oxidation of **9c** and **9k** into the corresponding aldehydes **12b** and **12c**.

corresponding aldehydes by using the oxidation method of Palomo. Thus, the biphenyls **9c** and **9k** provided, after treatment with CAN (5 equiv), the corresponding aldehydes **12a** and **b** in 76 and 92% yield, respectively (Scheme 6).

Additionally, we have performed Peterson olefinations[19] of the biphenyls **9a**, **9e**, and **9j** by using benzaldehyde (**14a**), 3,4,5-trimethoxybenzaldehyde (**14b**), or thiophene-2-carbaldehyde (**14c**, 1.2 equiv) in the presence of 10% tetra-*n*-butylammonium fluoride (TBAF)[20] in THF (−20 °C, 15 min), leading to the stilbene derivatives **15a–c** (>99% *E*) in 62–98% yield (Scheme 7).

In summary, we have developed a simple procedure for the preparation of BTSM-functionalized arenes by using a Kumada–Corriu cross-coupling reaction. A range of functional groups, such as esters, ketones, and amino groups were tolerated in the cross-coupling reactions. The bulky BTSM group allows the regioselective metalation of various substrates as well as the synthesis of orthogonally functionalized compounds. Transformation of the BTSM group into aldehydes or *E*-stilbenes has been performed, confirming that the BTSM group is a versatile substituent of aromatics that allows highly regioselective lithiation or magnesiation. Extension of this methodology for the metalation of heterocycles is currently underway in our laboratories.

Experimental Section

tert-Butyl 3-(bis(trimethylsilyl)-methyl)benzoate (5a)

tert-Butyl 3-bromobenzoate (**4a**, 257 mg, 1.00 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol%), and SPhos (16.4 mg, 0.04 mmol, 4 mol%) were suspended in dry THF (3.50 mL) in a dry, argon-flushed Schlenk flask. Then, $(TMS)_2CHMgBr·LiCl$ (**2**, 1.83 mL, 1.10 mmol, 0.6 M in THF) was added and the reaction mixture was stirred for 2 h at 50 °C. After full conversion was detected by GC analysis of quenched reaction aliquots, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents in vacuo and purification by column chromatography (silica gel, *i*hexane/Et_2O = 50:1) afforded the desired product **5a** (326 mg, 97%) as colorless oil.

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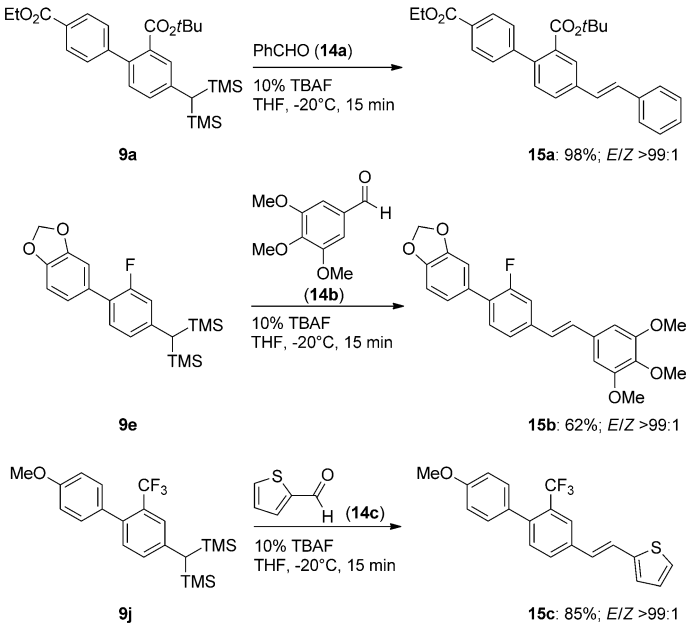

Scheme 7. Peterson olefination of substrates of type **9** to stilbene derivatives of type **15**.

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Keywords: aromatics · lithiation · magnesium · metalation · silyl reagents

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COMMUNICATION

Metalation

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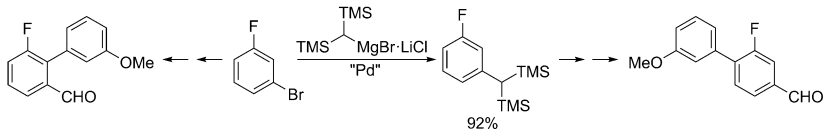
Preparation and Regioselective Metalation of Bis(trimethylsilyl)methyl-Substituted Aryl Derivatives



Metalation with bulky groups: A range of bis(trimethylsilyl)methyl-substituted aryl derivatives was prepared by using a Kumada–Corriu cross-coupling. The regioselective metalation of the resulting arenes bearing this bulky silyl group allowed the generation of functionalized aromatics. A regioselective switch in the presence or in the absence of this silyl group has been demonstrated. Furthermore, the bis(trimethylsilyl)methyl group was converted into a formyl group or a styryl group.