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Preparations and Reactions of SF_5-Substituted Aryl and Heteroaryl Derivatives via Mg and Zn Organometallics

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The physico-chemical and pharmacological properties of organic molecules are often significantly modified by the incorporation of fluorine atoms.[1] The preparation of fluoro- or trifluoromethyl-substituted aromatics and heteroaromatics has become an active research field.[2] Recently, it has been shown that the replacement of CF_3 groups with SF_5 substituents may increase the biological activity of pharmacologically active substances.[3] Also, due to its specific physico-chemical properties[4] and to the increased availability of SF_5-substituted starting materials,[5] this fluorous group is beginning to find many applications in material sciences.[3,6] However, synthetic methods leading to SF_5-substituted aryl and heteroaryl derivatives are rare.[3]

The SF_5 group is sensitive to polar organometallic species such as organolithiums, for example 1-bromo-4-(pentafluorosulfanyl)benzene with *n*-butyllithium in THF at −78 °C. In contrast, the reaction with *t*BuLi in diethyl ether at −78 °C produced the desired lithium intermediate without side reactions.[7] Additionally, halogen–lithium exchange reactions require low temperatures and are not compatible with several important functional groups, such as ketones, aldehydes, or esters. In contrast, the halogen–magnesium exchange has been found to be the method of choice for preparing new functionalized organomagnesium reagents of considerable synthetic utility.[8] Recently, we have developed several preparations of aryl- and heteroarylzinc and -magnesium compounds displaying high functional group compatibility. These include a Br/Mg exchange using *i*PrMgCl·LiCl,[8] and directed metalation of aromatics and heteroaromatics using kinetically highly active bases such as TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidyl),[9] $TMP_2Mg{\cdot}2\,LiCl$,[10] TMPZnCl·LiCl,[9,11] and $TMP_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$.[12] Herein, we report a range of organometallic transformations that allow the preparation of various SF_5-substituted aromatics and heteroaromatics.

We initially investigated the Br/Mg exchange to prepare SF_5-substituted magnesium intermediates (Table 1). The commercial SF_5-substituted aryl bromide **1** furnished, after treatment with *i*PrMgCl·LiCl (1.1 equiv), the arylmagnesium halide **2** within 1 h at 0 °C in 80 % yield.[13] This magnesium reagent **2** reacted with various electrophiles in good yields. Thus, after a transmetalation with $ZnCl_2$, a Pd-catalyzed cross-coupling with 4-bromobenzonitrile (**3a**) or 5-bromopicolinonitrile (**3b**) (2 % PEPPSI-*i*Pr[14]) furnished the functionalized SF_5-substituted biphenyls **4a** and **4b** in 83–79 % yield (Table 1, entries 1 and 2). Remarkably, the Grignard reagent **2** underwent Negishi cross-couplings[15] with aryl bromides bearing *unprotected* anilines,[16] such as 4-bromoaniline (**3c**) or 3-amino-4-bromobenzoic acid ethyl ester (**3d**), providing the functionalized amines **4c** and **4d** in 71–88 % yield (Table 1, entries 3 and 4). The acylation of theMg reagent **2** with ethyl cyanoformate (**3e**) yielded the SF_5-substituted ester **4e** in 80 % yield (Table 1, entry 5). Addition of **2** to electron-poor aldehydes, such as 2,3-dichlorobenzaldehyde (**3f**) as well as electron-rich aldehydes such as 4-methoxybenzaldehyde (**3g**) led to the SF_5-functionalized alcohols **4f** and **4g** in 81–84 % yield (Table 1, entries 6 and 7). After transmetalation with $CuCN{\cdot}2\,LiCl$ (1.1 equiv),[17] substitution with benzoyl chloride (**3h**) provided the ketone **4h** in 84 % yield (Table 1, entry 8).

Also, the SF_5 substituent showed a good compatibility in the performance of directed metalations using $TMP_2Mg{\cdot}2\,LiCl$. Thus, the treatment of the SF_5-substituted benzoic acid ethyl ester **4e** with $TMP_2Mg{\cdot}2\,LiCl$ led to the functionalized arylmagnesium reagent **5** after 12 h at −40 °C in approximately 82 % yield[13] (Table 2). After transmetalation with $ZnCl_2$ (1.1 equiv) the resulting zinc reagent underwent a Negishi cross-coupling[15] with 1-iodo-4-methoxybenzene (**3i**) or 4-iodobenzonitrile (**3j**) in the presence of 2 % $[Pd(dba)_2]$ (dba = dibenzylideneacetone) and 4 % tfp[18] (tfp = tri-(2-furyl)phosphine) (25 °C, 12 h), providing the SF_5-substituted biphenyl derivatives **6a** and **6b** in 52–83 % yield (Table 2, entries 1 and 2). A copper-catalyzed allylation (20 % $CuCN{\cdot}2\,LiCl$) with 3-bromocyclohexene (**3k**) provided the trisubstituted benzene **6c** in 70 % yield (Table 2, entry 3). Furthermore, a Cu^I-mediated acylation with benzoyl chloride (**3h**) led to the corresponding ketoester **6d** in 87 % yield (Table 2, entry 4).

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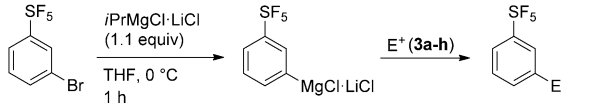
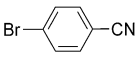
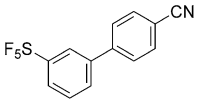
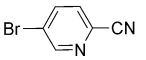
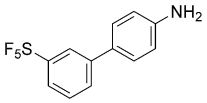
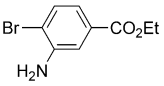
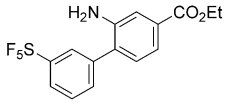
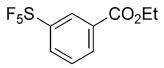
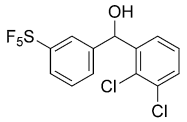
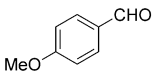
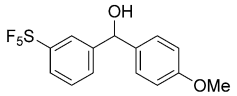
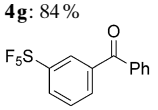
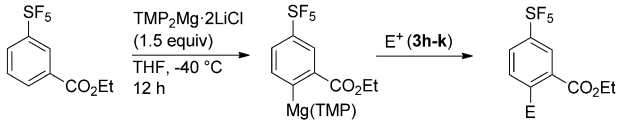
Table 1. Products of type **4** obtained by Br/Mg exchange with *i*PrMgCl·LiCl followed by reaction with various electrophiles.

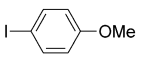
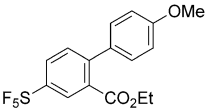
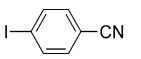
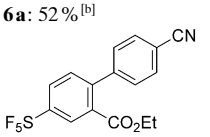
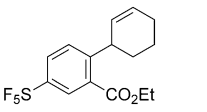
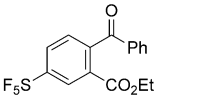


Entry	Electrophile	Product[a]
1	**3a** 	**4a**: 83 %[b] 
2	**3b** 	**4b**: 79 %[b] 
3	**3c** 	**4c**: 88 %[c] 
4	**3d** EtO_2C-CN	**4d**: 71 %[c] 
5	**3e** 	**4e**: 80 % 
6	**3f** 	**4f**: 81 % 
7	**3g** PhCOCl	**4g**: 84 % 
8	**3h**	**4h**: 84 %[d]

[a] Isolated yields of analytically pure product. [b] Cross-coupling conditions: $ZnCl_2$ (1.1 equiv) / 2 % PEPPSI-*i*Pr. [c] Cross-coupling conditions: $ZnCl_2$ (1.1 equiv) / 2 % $Pd(OAc)_2$, 4 % S-Phos, 23 °C, 12 h. [d] CuCN·2 LiCl (1.1 equiv) was added.

Table 2. Products of type **6** obtained by directed metalation of the ethyl benzoate **4e** using TMP_2Mg·2 LiCl followed by quenching with electrophiles.

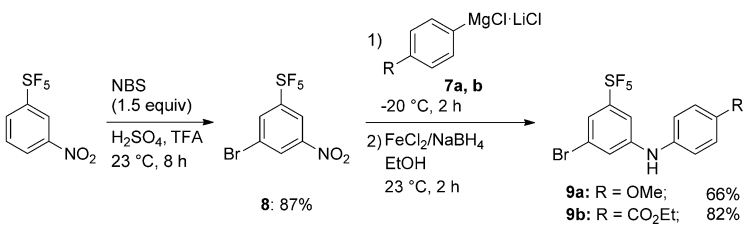


Entry	Electrophile	Product[a]
1	**3i** 	**6a**: 52 %[b] 
2	**3j** 	**6b**: 83 %[b] 
3	**3k** 	**6c**: 70 %[c] 
4	**3h** PhCOCl	**6d**: 87 %[d] 

[a] Isolated yields of analytically pure product. [b] Cross-coupling conditions: $ZnCl_2$ (1.1 equiv) / 2 % $[Pd(dba)_2]$, 4 % tfp, 23 °C, 12 h. [c] 20 % CuCN·2 LiCl was added. [d] CuCN·2 LiCl (1.1 equiv) was added.

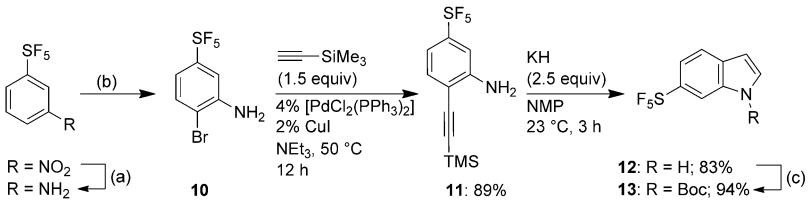
Arylamines are an important class of pharmaceuticals, due to their ability to undergo highly specific interactions with proteins. Therefore, we have also prepared SF_5-substituted arylamines. Recently, we have shown that the amination of arylmagnesium reagents with nitroarenes provides after reductive workup polyfunctional diarylamines.[9,19] This method proved to be well suited for the preparation of SF_5-substituted diarylamines. Br/Mg exchange on 1-iodo-4-methoxybenzene or 4-iodobenzoic acid ethyl ester with *i*PrMgCl·LiCl[8] (THF, −20 °C, 0.5 h) produced the corresponding functionalized Mg reagents **7a** and **b**. These organometallics reacted smoothly with 1-bromo-3-nitro-5-pentafluorosulfanylbenzene (**8**), prepared[20] from 3-nitro-5-pentafluorosulfanylbenzene. After reductive treatment with $FeCl_2/NaBH_4$, the SF_5-substituted diarylamines **9a** and **9b** were obtained in 66–82 % yield (Scheme 1).

Heterocyclic building blocks are ubiquitous in medicinal chemistry. Thus, we have prepared SF_5-substituted indoles. Starting from 2-bromo-5-(pentafluorosulfanyl)aniline[21] (**10**), the synthesis of 6-pentafluorosulfanyl-1*H*-indole (**11**) was achieved in two steps (Scheme 2). First, we performed a Sonogashira cross-coupling[22] by treating 2-bromoaniline **10** with (trimethylsilyl)acetylene (1.5 equiv, 50 °C, 12 h), pro-



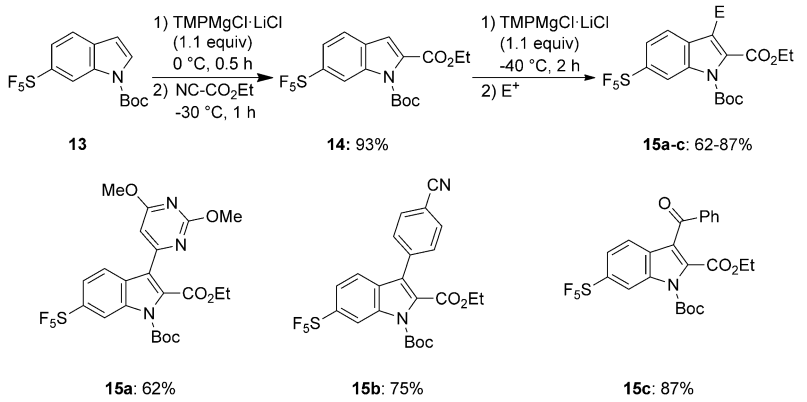
Scheme 1. Synthesis of diarylamines **9a** and **9b** using arylmagnesium halides **7a** and **7b** and the SF_5-substituted nitroarene **8**.

viding the SF_5-substituted 2-((trimethylsilyl)ethynyl)aniline (**11**) in 89% yield. A subsequent cyclization reaction was performed by treatment with KH (2.5 equiv) in *N*-methylpyrrolidone (NMP) (23 °C, 3 h) to afford the indole **12** in 83% yield.[23] The indole **12** was readily protected at nitrogen with Boc_2O leading to the *N*-Boc indole **13** in 94% yield (Scheme 2).



Scheme 2. Synthesis of the SF_5-substituted indole **12** and subsequent Boc-protection. Reagents and conditions: a) Fe powder (6.0 equiv) HCl/EtOH 1:20, 23 °C, 1 h, 91%; b) NBS (1.0 equiv), dioxane, 23 °C, 8 h, 79%; c) Boc_2O (1.5 equiv), 7% DMAP, 23 °C, 1.5 h.

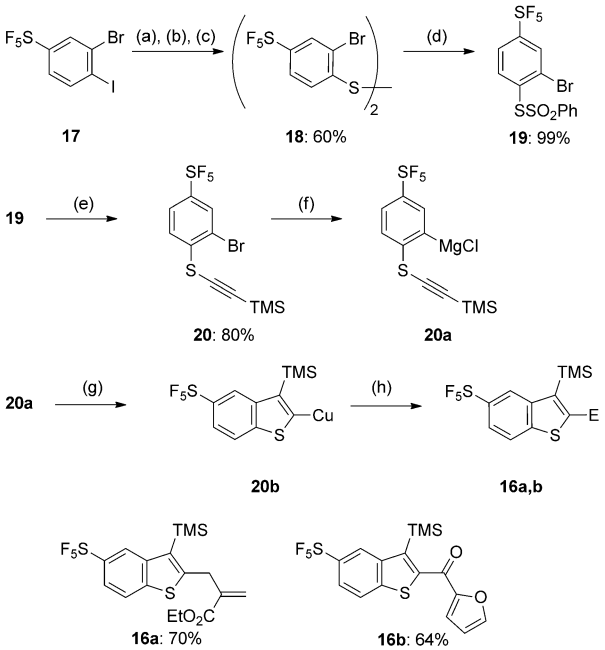
Further functionalization of the *N*-protected indole **13** could be achieved by using TMPMgCl·LiCl.[9] The selective magnesiation of **13** at position 2 of the indole ring with TMPMgCl·LiCl (1.1 equiv, 0 °C, 0.5 h), and subsequent trapping with cyanoformic acid ethyl ester (**3e**, 1.1 equiv, −30 °C, 1 h), afforded the *N*-protected ethyl 6-(pentafluorosulfanyl)-1*H*-indole-2-carboxylate **14** in 93% yield. Subsequent treatment of the indole **14** with TMPMgCl·LiCl (1.1 equiv, −40 °C, 2 h) led to a fast magnesiation at position 3 (Scheme 3).



Scheme 3. Functionalization of position 2 and 3 of the *N*-protected indole **13** by using TMPMgCl·LiCl.

After the transmetalation with $ZnCl_2$ (1.1 equiv), Negishi cross-coupling reactions[15] (2% PEPPSI-*i*Pr,[14] 23 °C, 10 h) with 4-iodo-2,6-dimethoxypyrimidine or 4-iodobenzonitrile provided the corresponding indoles **15a** and **15b** in 62–75% yield. Alternatively, a transmetalation with CuCN·2 LiCl (1.0 equiv) allows an efficient benzoylation (PhCOCl (1.2 equiv), −40 °C, 12 h) affording smoothly the 2,3-disubstituted indole **15c** in 87% yield (Scheme 3).

Besides indoles, benzo[*b*]thiophenes are of particular interest, as they are potential drug candidates[24] and are also widespread in materials chemistry.[25] Functionalized benzo[*b*]thiophenes can be prepared by the intramolecular copper-catalyzed carbomagnesiation of alkynyl(aryl)thioethers.[26] Herein, we have applied this method to the synthesis of SF_5-substituted, functionalized benzo[*b*]thiophenes of type **16** (Scheme 4). The readily available SF_5-substituted 1,2-bromoiodoarene **17**[27] was converted to the corresponding organic disulfide **18** by a I/Mg-exchange reaction (*i*PrMgCl·LiCl,[8] −80 °C, 10 min), subsequent transmetalation with $ZnCl_2$, and reaction with sulfur monochloride.[28] The sulfonothioate **19** was obtained by treating the disulfide **18** with iodine and sodium benzenesulfinate.[29] This sulfonothioate reacted with trimethylsilylethynylmagnesium chloride providing the desired alkynyl(aryl)thioether **20** in 80% yield. Thus, the treatment of the thioether **20** with *i*PrMgCl·LiCl (1.1 equiv, 23 °C, 1 h) provided the corresponding magnesium reagent **20a**. In the presence of stoi-



Scheme 4. Reaction sequence towards the SF_5-substituted alkynyl(aryl)thioether **20** and subsequent cyclization/allylation and acylation reaction sequence. Reagents and conditions: a) *i*PrMgCl·LiCl (1.05 equiv), THF, −80 °C, 10 min; b) $ZnCl_2$ (1.1 equiv), −80 °C; 10 min; c) S_2Cl_2 (0.49 equiv), −80 °C, 10 min; d) $PhSO_2Na$ (3.2 equiv), I_2 (2.0 equiv), CH_2Cl_2, 23 °C, 48 h; e) ethynyltrimethylsilane (1.5 equiv), *i*PrMgCl·LiCl (1.2 equiv), THF, −60 °C, 15 min; f) *i*PrMgCl·LiCl (1.1 equiv), THF, 23 °C, 1 h; g) CuCN·2 LiCl (1.1 equiv), 23 °C, 12 h; h) E^+ (0.8 equiv), 23 °C, 12 h.

chiometric amounts of CuCN·2 LiCl cyclization occurred at 23 °C within 12 h producing the copper reagent **20b**. A subsequent allylation reaction with 2-(bromomethyl)acrylic acid ethyl ester (0.8 equiv) afforded the polyfunctional benzothiophene **16a** in 70% yield. Similarly, the acylation with furan-2-carbonyl chloride (0.8 equiv) provided the acylated benzothiophene **16b** in 64% yield.

In conclusion, we have prepared a range of polyfunctional SF_5-substituted aromatic and heterocyclic compounds using zinc and magnesium intermediates. A library of SF_5-substituted molecules should become available using these organometallic methodologies and should allow their use for the discovery of new biologically active compounds.

Acknowledgements

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Keywords: C–C coupling reactions · fluorinated substituents · heterocyclic compounds · metalation · organometallic compounds

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C–C Coupling Reactions

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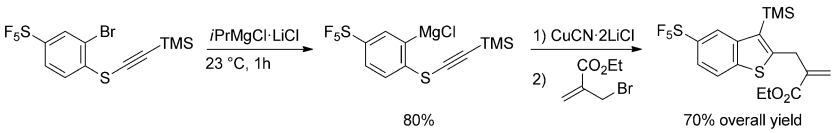
Preparations and Reactions of SF_5-Substituted Aryl and Heteroaryl Derivatives via Mg and Zn Organometallics



Polyfunctional SF_5-substituted cycles: Several organometallic sequences using zinc, copper, and magnesium intermediates were developed to prepare a broad range of SF_5-substituted aromatic and heterocyclic compounds of potential interest for pharmaceutical applications.