Arene Functionalization

Preparation of Functionalized Aryl Magnesium Reagents by the Addition of Magnesium Aryl Thiolates and Amides to Arynes**

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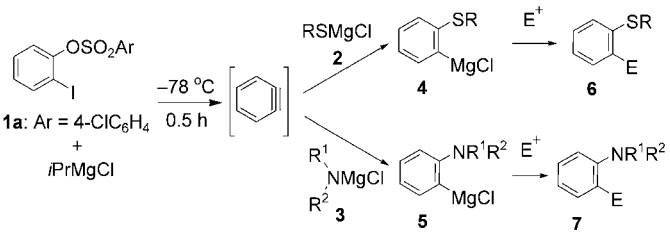
Dedicated to Professor Reinhard W. Hoffmann

The functionalization of arenes is an important synthetic task.[1] A potential approach is the addition reaction of nucleophiles to intermediate arynes.[2] The addition of heteroatom–metal bonds (Nu–Met; Nu = OR, NR_2, SR, PR_2) to alkynes is usually a difficult process due to the high energy of the Nu–Met bond and to the high nucleophilicity of the resulting C–Met bond of the adduct, which is prone to undergo polymerization and other side reactions.[3] In the presence of a catalytic amount of a metal catalyst, various heteroatom–hydrogen bonds can be added to triple bonds.[3,4] However, in this case, the reactivity of the C–Met bond of the adduct cannot be exploited. By using a very reactive alkyne, such as an aryne,[5] the addition of nucleophiles should be facilitated and should afford useful arylmetal complexes, which should react with various electrophiles. Although the addition of various nitrogen nucleophiles to arynes has been reported,[5,6] the successful trapping of the intermediates with electrophiles has been reported in only a few cases.[7]

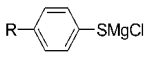
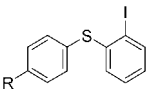
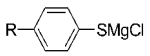
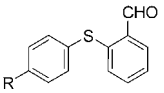
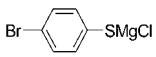
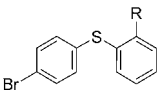
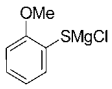
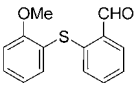
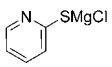
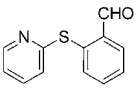
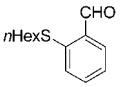
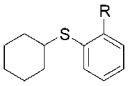
Recently we have described a new preparation of polyfunctional arynes by the elimination of 2-magnesiated diaryl sulfonates prepared from the corresponding iodides of type **1**.[8] Herein, we report the selective addition of magnesiated thiols and amines of types **2** and **3** to arynes generated by our previous procedure, providing 2-thio- and 2-amino-substituted aryl magnesium species of types **4** and **5**, respectively (Scheme 1). In contrast to previous methods,[2,5d,6] these aryl magnesium reagents can be trapped by a range of electrophiles giving rise to thioethers of type **6** and arylamines of type **7** (Table 1 and Table 2).

Thus, the addition of *i*PrMgCl (2.0 equiv) to thiophenol (1.0 equiv) in THF (−78 °C, 10 min) followed by the addition of 2-iodophenyl 4-chlorobenzenesulfonate (**1a**) (1.0 equiv; −78 °C, 0.5 h) and subsequent warming to 0 °C within 10 min led to the benzyne-addition product **4a**, which, upon quenching with iodine in THF at −78 °C, provided 2-iodophenyl



Scheme 1. Preparation of aryl thioethers and aryl amines by addition reactions to benzyne.

Table 1: Synthesis of thioethers of type **6** by the addition of magnesium thiolates **2** to benzyne followed by the trapping of the intermediate Grignard reagent **4** with an electrophile (see Scheme 1).

Entry	2	Electrophile	6	Yield [%][a]
1	PhSMgCl (**2a**)	I_2	 **6a**	83
				
2	**2b**: R = F	I_2	**6b**: R = F	90
3	**2c**: R = Cl	I_2	**6c**: R = Cl	84
4	**2d**: R = Br	I_2	**6d**: R = Br	82
				
5	**2b**	DMF	**6e**: R = F	78
6	**2c**	DMF	**6f**: R = Cl	73
7	**2d**	DMF	**6g**: R = Br	75
				
8	**2d**	EtCOCl	**6h**: R = COEt	90
9	**2d**	PhCOCl	**6i**: R = COPh	88
10	**2d**	PhCHO	**6j**: R = CH(OH)Ph	85
11	 **2e**	DMF	 **6k**	80
12	 **2f**	DMF	 **6l**	82
13	*n*-HexSMgCl (**2g**)	DMF	 **6m**	67
				
14	*c*-HexSMgCl (**2h**)	DMF	**6n**: R = CHO	73
15	**2h**	PhCOCl	**6o**: R = COPh	83

[a] Yield of isolated, analytically pure product.

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[**] We thank the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft (DFG), and Merck Research Laboratories (MSD) for financial support, as well as Chemetall GmbH (Frankfurt) and BASF AG (Ludwigshafen) for generous gifts of chemicals. I.S. thanks Sanofi-Aventis (Frankfurt) for a fellowship.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/anie.200500443

phenyl sulfide (**6a**) in 83% yield (entry 1, Table 1). Various substituted thiophenolates, such as **2b–d**, reacted as well affording after iodolysis the 2-iodophenyl thioethers **6b–d** in 82–90% yield (entries 2–4).

Similarly, the intermediate Grignard reagents were formylated with DMF (2.5 equiv, −40°C to RT, 1 h) leading to aldehydes **6e–g** in 73–78% yield (entries 5–7, Table 1). Acid chlorides (in the presence of CuCN·2 LiCl) and aldehydes were also excellent trapping agents, leading to ketones **6h–i** and to the benzylic alcohol **6j**, respectively, in 85–90% yield (entries 8–10). The *ortho*-substituted magnesium thiolate **2e** (entry 11) and the heterocyclic thiolate **2f** (entry 12) both underwent the addition reaction followed by formylation with DMF giving rise to **6k** (80% yield) and **6l** (82% yield), respectively. Aliphatic thiolates, such as **2g** and **2h**, added to benzyne under the same reaction conditions affording the functionalized alkyl aryl thioethers **6m–o** in 67–83% yield (entries 13–15).

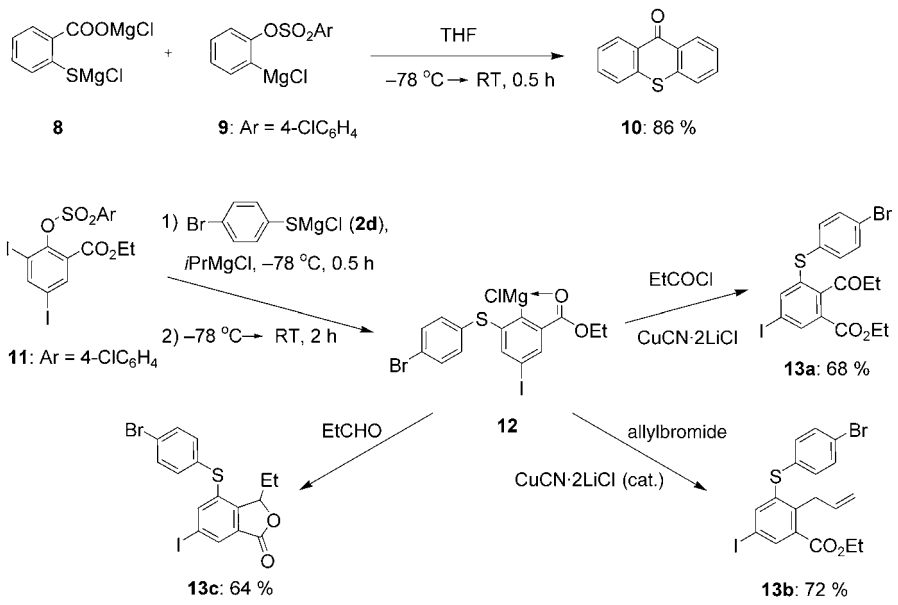
The high strain of the generated aryne ensures a smooth addition and excellent functional-group compatibility. Thus, the reaction of the magnesium thiolate **8**, bearing a carboxy group in position 2, with the 2-magnesiated benzenesulfonate **9** provided the desired addition aryl magnesium species, which reacted intramolecularly with the carbonyl group in *ortho*-position leading to thioxanthone (**10**) in 86% yield (Scheme 2).

Interestingly, functionalized arynes displayed remarkable regioselectivity in the addition step. Thus, the polyfunctional sulfonate **11** was selectively magnesiated in the α-position to the sulfonate group (inductive activation of the *ortho*-carbon–iodine bond), and its reaction with the magnesium thiolate **2d** provided only the magnesium reagent **12**, which was stabilized by chelation. Its reaction with various electrophiles, like an acid chloride, allyl bromide in the presence of CuCN·2 LiCl, or an aldehyde, furnished the tetrasubstituted thioethers **13a–c** in 64–72% yield (Scheme 2).

Remarkably, all the previous reactions involved the conversion of the magnesium–sulfur bond of **2** into the magnesium–carbon bond in **4**. We have also examined the addition of a magnesium amide of type **3** to benzyne; this results in the conversion of a nitrogen–magnesium bond to a carbon–magnesium bond in the product **5** (Scheme 1). Thus, the reaction of magnesiated *N*-methylaniline (**3a**) with the 2-magnesiated benzenesulfonate **9** provided the desired addition product of type **5** (−78°C, 30 min, then 0°C for 10 min). After the addition of CuCN·2 LiCl and allyl bromide, the desired product **7a** was obtained in 83% yield (entry 1, Table 2). Typical electrophiles, such as benzoyl chloride, benzaldehyde, and DMF, reacted similarly furnishing the diarylamines **7b–d** in 74–85% yield (entries 2–4). Related phenyl-substituted secondary magnesium amides, such as **3b** and **3c** (entries 5–7), reacted in a similar way leading to the benzaldehyde **7e** (71% yield) and the indolines **7f** and **7g** (62–66% yield), respectively. The bulky aliphatic amide *i*Pr_2NMgCl (**3d**) was less prone to add to benzyne, and the desired product **7h** (after formylation) was obtained only in 25% yield (entry 8). Interestingly, a functionalized magnesium amide, such as **3e**, underwent the benzyne addition providing a polyfunctional aryl magnesium species, which was efficiently trapped with DMF and EtCOCl according to our standard procedure furnishing the tertiary amines **7i** (73% yield, entry 9) and **7j** (76% yield, entry 10), respectively.

During this study, we realized that the rate of addition to the aryne strongly depended on the nucleophilicity of the magnesium reagent (Nu–MgX) as noted previously by Huisgen.[5a] Thus, whereas magnesium amides are basic reagents, magnesium thiolates are more nucleophilic and therefore add more readily.[9] We anticipated that highly nucleophilic reagents, like phenylselenyl magnesium chloride **14**, would react well with benzyne. Preliminary experiments confirmed this hypothesis. Thus, the addition of **14** to **9** lead via the magnesiated intermediate **16**[10] to the products **15a** (85% yield) and **15b** (87% yield) under standard conditions (Scheme 3).

In summary, we have developed a general procedure for the thio-(seleno-) and aminomagnesiation of arynes. The resulting aryl magnesium species can be trapped with numerous electrophiles in contrast to most previously reported addition reactions. Further extensions utilizing other nucleophiles are currently underway in our laboratories.

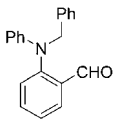
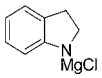
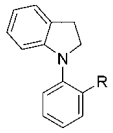
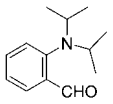
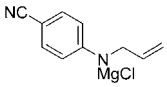
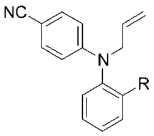


Scheme 2. Preparation of polyfunctional thioethers using the addition of magnesium thiolates to arynes.

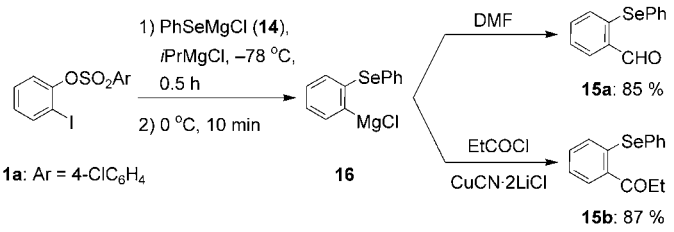
Experimental Section

Typical procedure: Preparation of **6g**: A dry and argon-flushed 25-mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 4-bromothiophenol (190 mg, 1.0 mmol) in dry THF (3 mL). This solution was cooled to −78°C, *i*PrMgCl (1.88 mL, 2.0 equiv, 1.07 M in THF) was

Table 2: Synthesis of tertiary amines of type **7** by the addition of magnesium amides **3** to benzyne followed by the trapping of the intermediate Grignard reagent **5** with an electrophile.

Entry	3	Electrophile	7	Yield [%][a]
				
1	Ph(Me)NMgCl (**3a**)		**7a**: R = allyl	83
2		PhCOCl	**7b**: R = COPh	85
3		PhCHO	**7c**: R = CH(OH)OPh	80
4		DMF	**7d**: R = CHO	74
5	Ph(Bn)NMgCl (**3b**)	DMF	 **7e**	71
				
6	**3c**		**7f**: R = allyl	66
7	**3c**	EtCOCl	**7g**: R = COEt	62
8	 **3d**	DMF	 **7h**	25
				
9	**3e**	DMF	**7i**: R = CHO	73
10	**3e**	EtCOCl	**7j**: R = COEt	76

[a] Yield of isolated, analytically pure product.



Scheme 3. Preparation of aryl selenoethers by addition reactions to benzyne.

added dropwise, and the reaction mixture was stirred for 10 min. A solution of **1a** (394 mg, 1.0 mmol) in dry THF (2 mL) was added, and the reaction mixture was stirred vigorously for 30 min at the same temperature. The resulting mixture was immediately warmed to 0 °C and stirred for 10 min. Then the reaction mixture was cooled to −40 °C, and DMF (0.20 mL, 2.5 equiv) was added. Thereafter, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed by evaporation in vacuo. Purification by flash chromatography (*n*-pentane/diethyl ether 20:1) furnished the thioether **6g** as a yellow solid (220 mg, 75 %).

Preparation of **7d**: A dry and argon-flushed 25-mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of *N*-methylaniline (107 mg, 1.0 mmol) in dry THF (3 mL). This solution was cooled to −20 °C, *i*PrMgCl (0.94 mL, 1.0 equiv, 1.07 M in THF) was added dropwise, and the reaction mixture was stirred for 30 min. The reaction mixture was cooled to −78 °C, and *i*PrMgCl (0.94 mL, 1.0 equiv, 1.07 M in THF) was added. A solution of **1a** (394 mg, 1.0 mmol) in dry THF (2 mL) was added, and the reaction mixture was stirred vigorously for 30 min at the same temperature. The resulting mixture was immediately warmed to 0 °C and stirred for 10 min. Then, the reaction mixture was cooled to −40 °C, and DMF (0.20 mL, 2.5 equiv) was added. Thereafter, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed by evaporation in vacuo. Purification by flash chromatography (*n*-pentane/diethyl ether 250:1) furnished the amino aldehyde **7d** as a yellow oil (156 mg, 74 %).

Received: February 5, 2005
Published online: June 7, 2005

Keywords: amination · arynes · Grignard reagents · heterocycles · thioethers

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[9] Low steric hindrance is also essential for an efficient addition reaction, since bulky amides add significantly less efficiently.

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