Functionalized Arynes

Preparation of Polyfunctional Arynes via 2-Magnesiated Diaryl Sulfonates**

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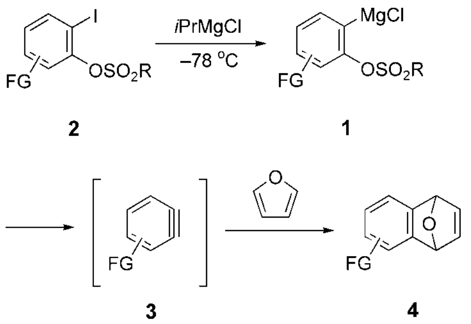
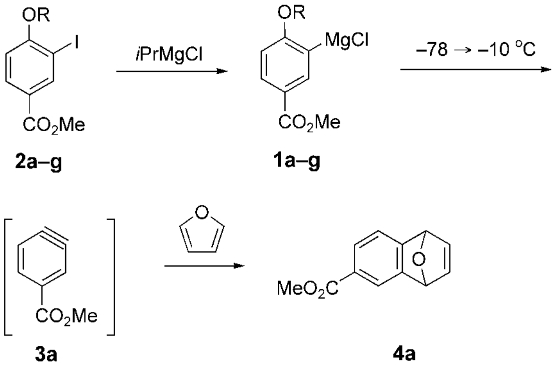
Dedicated to Professor Rolf Huisgen

Arynes are highly reactive intermediates which have found numerous applications in organic synthesis.[1] As a result of the strained nature of the ring (ca. 63 kcal mol^{-1}),[2] arynes react with a broad range of reagents (with nucleophiles in addition reactions, with alkenes in cycloadditions and ene reactions) and therefore have significant synthetic potential.[3] Whereas a number of methods for the generation of benzyne itself are known, the preparation of functionalized arynes is often incompatible with the harsh basic conditions necessary for their generation. Recently, we developed a new method for the synthesis of polyfunctionalized aryl magnesium compounds through an iodine–magnesium exchange.[4] This method can be used for the preparation of a variety of 2-magnesiated aryl sulfonates of type **1** from the corresponding 2-iodo derivates **2** (Scheme 1).

The leaving-group ability of the sulfonate group (RSO_2O^-) was found to be essential for the optimization of the reaction conditions and yield. Because of the strong metal-directing effect of the sulfonate moiety, the I/Mg exchange was complete at −78 °C within 15 min. Thus, we prepared the sulfonates **2a–g** derived from methyl 4-hydroxy-3-iodobenzoate and converted them into the corresponding Grignard reagents **1a–g**, which were in turn transformed into the products **4a** upon treatment with furan (Scheme 2 and Table 1).



Scheme 1. Generation and trapping of functionalized arynes **3**. FG = functional group.



Scheme 2. Tuning of the leaving group for the generation of the aryne **3a**; for R, see Table 1.

Table 1: Optimization of the leaving group for the generation of **3a**.

Entry	R (sulfonate)	t [h]	Yield of **4a** [%][a]
1	CF_3SO_2 (**2a**)	–	0
2	CH_3SO_2 (**2b**)	30[b]	72
3	$CF_3CH_2SO_2$ (**2c**)	–	0
4	4-$MeC_6H_4SO_2$ (**2d**)	30[b]	90
5	2,5-$Cl_2C_6H_3SO_2$ (**2e**)	1	87
6	3,5-$(CF_3)_2C_6H_3SO_2$ (**2f**)	1	78
7	4-$ClC_6H_4SO_2$ (**2g**)	4	93

[a] Yield of isolated, analytically pure compound. [b] The reaction mixture was warmed to 25 °C.

Because of the rapid decomposition of **2a** ($R = SO_2CF_3$) at −78 °C with immediate formation of the aryne, it was not possible to monitor the reaction. The product **4a** was not isolated in this case (Table 1, entry 1).[5] The corresponding mesylate **2b** required a reaction time of 30 h at 20 °C to undergo full conversion into the expected product **4a** in just 72 % yield (Table 1, entry 2). Thus, the mesylate group is only a moderate leaving group, and the rate of formation of the aryne **3a** is too slow in this case. We varied the electron-withdrawing ability of the sulfonate leaving group systematically. Although the tosylate **2d** afforded the product **4a** in 90 % yield, a reaction time of 30 h was still required. In the reactions of the 2,5-dichlorobenzenesulfonate **2e** and the 3,5-bis(trifluoromethyl)benzenesulfonate **2f** rapid formation of the aryne was observed, but **4a** was isolated in just 87 and 78 % yield, respectively (Table 1, entries 5 and 6). The best result was obtained with the 4-chlorobenzenesulfonate **2g**, from which **4a** was formed in 93 % yield after a reaction time of only 4 h at −10 °C.

This effective leaving group was used for the preparation of the functionalized arynes **3a–i** and the heteroaryne **3j**,

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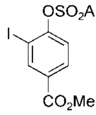
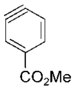
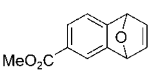
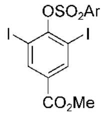
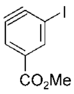
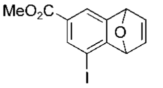
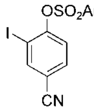
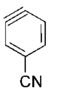
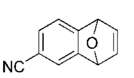
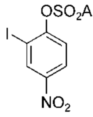
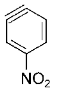
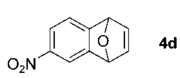
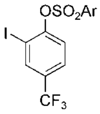
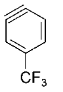
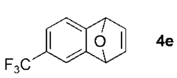
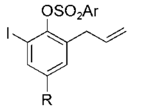
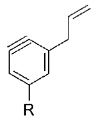
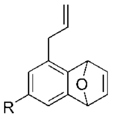
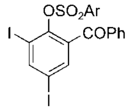
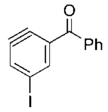
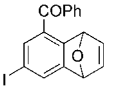
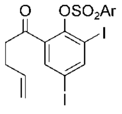
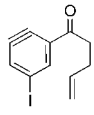
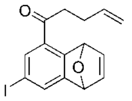
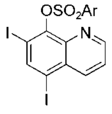
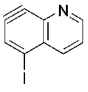
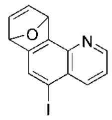
Table 2: Generation of polyfunctionalized arynes **3** and their reaction with furan.

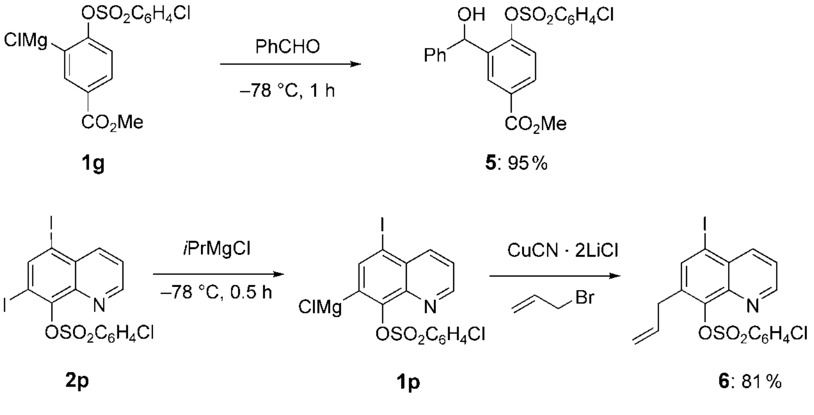
Entry	Precursor[a]	Aryne	Product	Yield [%][b]
1	 **2g**	 **3a**	 **4a**	93
2	 **2h**	 **3b**	 **4b**	71
3	 **2i**	 **3c**	 **4c**	78
4	 **2j**	 **3d**	 **4d**	78
5	 **2k**	 **3e**	 **4e**	75
6 7	 **2l**: R=I **2m**: R=H	 **3f**: R=I **3g**: R=H	 **4f**: R=I **4g**: R=H	88 83
8	 **2n**	 **3h**	 **4h**	68
9	 **2o**	 **3i**	 **4i**	71
10	 **2p**	 **3j**	 **4j**	77

[a] Ar = 4-ClC_6H_4. [b] Yield of isolated, analytically pure product.

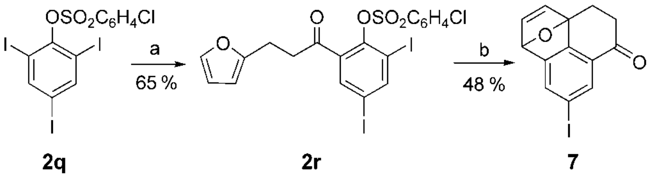
which were trapped in the presence of an excess of furan to provide the expected products **4a–j** (Table 2). Thus, a variety of functionalities, such as an iodine (Table 2, entries 2, 6, 8, 9, and 10), ester (Table 2, entries 1 and 2), nitrile (Table 2, entry 3), and trifluoromethyl group (Table 2, entry 5), are tolerated in the aryne intermediates for the first time. Interestingly, even very sensitive functional groups, such as a nitro group (Table 2, entry 4)[6] and even a ketone function (Table 2, entries 8 and 9)[7] are compatible with our preparation method. The quinolinyl sulfonate **2p** was also readily converted into the corresponding Grignard reagent, which underwent transformation via the heterocyclic aryne **3j** into the desired product **4j** in 77% yield.

The I/Mg exchange with precursors of type **2** proceeds under very mild conditions, and is therefore compatible with many functional groups. Furthermore, the intermediate Grignard reagent of type **1** is stable at low temperatures and can be quenched with a variety of electrophiles. For example, the functionalized aryl magnesium chloride **1g** reacted at low temperature (−78 °C) within 1 h with benzaldehyde to give the corresponding benzylic alcohol **5** in 95% yield (Scheme 3). The transmetalation of this Grignard reagent led to stable copper or zinc organometallic reagents, which were not prone to undergo aryne formation, so that the reactions could be performed over a broad range of temperatures. Thus, the Grignard reagent **1p** formed from the heterocyclic sulfonate **2p** (*i*PrMgCl, −78 °C, 30 min) was transmetalated to the copper derivative with CuCN·2LiCl (1 equiv, −78 °C→RT) and treated with allyl bromide (2 equiv) to give the product **6** in 81% yield (Scheme 3). Remarkably, the I/Mg exchange only occurred at the position α to the sulfonate group.

Our method allows the functionalization of the triiodoaryl sulfonate **2q**. Thus, the magnesiation of **2q** with *i*PrMgCl followed by transmetalation with CuCN·2LiCl provides a copper intermediate, which could be acylated with 3-(2-furyl)propionyl chloride[8] (−78 °C→RT, 1 h) to give the iodoketone **2r** in 65% yield (Scheme 4). This compound underwent a further I/Mg exchange at −78 °C with *i*PrMgCl. Upon warming to ambient temperature, the resulting aryne underwent an intramolecular cyclization with the furan moiety to provide the polycyclic iodoketone **7** in 48% yield. We observed competitive protonation of the magnesium intermediate as a side reaction.[9]



Scheme 3. Reactions of the magnesium reagents **1g** and **1p** with electrophiles.



Scheme 4. Intramolecular trapping of a functionalized aryne: a) *i*PrMgCl, −78 °C, 0.5 h, then CuCN·2 LiCl, −78 °C, 10 min, then 3-(2-furyl)propionyl chloride (2 equiv, −78 °C→RT, 1 h); b) *i*PrMgCl, −78 °C, 0.5 h,then −78 °C→RT, 1 h.

In summary, we have developed a new and general method for the preparation of functionalized arynes by the readily tunable elimination of 2-magnesiated aryl sulfonates. Further applications are under investigation in our laboratories.

Experimental Section

Typical procedure: **4a**: A dry, argon-flushed 10-mL Schlenk tube equipped with a magnetic stirring bar and a septum was charged with a solution of methyl iodobenzoate **2g** (452 mg, 1.00 mmol) in dry THF (5 mL) and cooled to −78 °C. *i*PrMgCl (0.920 mL, 1.05 mmol, 1.10 M in THF) was then added dropwise, and after 30 min furan (0.38 mL, 5.0 mmol) was added slowly at −78 °C. The resulting mixture was warmed to room temperature and stirred for a further 2 h. The reaction was quenched with a saturated solution of NH_4Cl, the mixture was extracted with CH_2Cl_2, and the organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (pentane/diethyl ether 2:1) furnished **4a** (188 mg, 93 %) as a colorless solid.

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Keywords:
Grignard reagents · arynes · cycloaddition · elimination · metalation

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[1] For excellent reviews, see: a) J. Sauer, R. Huisgen, *Angew. Chem.* **1960**, *72*, 294; b) R. W. Hoffmann, *Dehydrobenzene and Cycloalkynes*, Academic Press, New York, **1967**; c) L. Castedo, E. Guitian in *Studies in Natural Products Chemistry*, *Vol. 3*, Part B, (Ed.: A. U. Rahman), Elsevier, Amsterdam, **1989**, p. 417; d) S. V. Kessar in *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: B. M. Trost, I. Fleming, H. F. Semmelhack), Pergamon, Oxford, **1991**, p. 483; e) R. F. C. Brown, *Synlett* **1993**, 9; f) W. Sander, *Acc. Chem. Res.* **1999**, *32*, 669; g) H. Pelissier, M. Santelli, *Tetrahedron* **2003**, *59*, 701.

[2] C. Wentrup, *Reactive Molecules*, Wiley, New York, **1984**, p. 288.

[3] For some recent applications, see: a) T. Hamura, Y. Ibusuki, K. Sato, T. Matsumoto, Y. Osamura, K. Suzuki, *Org. Lett.* **2003**, *5*, 3551; b) T. Hosoya, T. Hamura, Y. Kuriyama, M. Miyamoto, T. Matsumoto, K. Suzuki, *Synlett* **2000**, 520; c) T. Hosoya, E. Takashiro, T. Matsumoto, K. Suzuki, *J. Am. Chem. Soc.* **1994**, *116*, 1004; d) M. Beller, C. Breindl, T. H. Riermeier, A. Tillack, *J. Org. Chem.* **2001**, *66*, 1403; e) P. Maurin, M. Ibrahim-Ouali, M. Santelli, *Tetrahedron Lett.* **2001**, *42*, 8147; f) Z. Liu, R. C. Larock, *Org. Lett.* **2003**, *5*, 4673; g) H. Yoshida, Y. Honda, E. Shirakawa, T. Hiyama, *Chem. Commun.* **2001**, 1880; h) H. Yoshida, E. Shirakawa, Y. Honda, T. Hiyama, *Angew. Chem.* **2002**, *114*, 3381; *Angew. Chem. Int. Ed.* **2002**, *41*, 3247; i) D. Peña, S. Escudero, D. Pérez, E. Guitián, L. Castedo, *Angew. Chem.* **1998**, *110*, 2804; *Angew. Chem. Int. Ed.* **1998**, *37*, 2659; j) J.-M. Becht, A. Gissot, A. Wagner, C. Mioskowski, *Chem. Eur. J.* **2003**, *9*, 3209.

[4] a) P. Knochel, W. Dohle, N. Gommermann, F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem.* **2003**, *115*, 4438; *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; b) A. Staubitz, W. Dohle, P. Knochel, *Synthesis* **2003**, 233; c) A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis* **2002**, 565; d) N. Gommermann, C. Koradin, P. Knochel, *Synthesis* **2002**, 2143; e) I. Sapountzis, P. Knochel, *Angew. Chem.* **2004**, *116*, 915; *Angew. Chem. Int. Ed.* **2004**, *43*, 897.

[5] Interestingly, the magnesium derivative of methyl 4-pivaloxy-3-iodobenzoate is also unstable and rapidly decomposes at −78 °C.

[6] For the preparation of Grignard reagents that bear a nitro group, see: I. Sapountzis, P. Knochel, *Angew. Chem.* **2002**, *114*, 1680; *Angew. Chem. Int. Ed.* **2002**, *41*, 1610.

[7] For the preparation of Grignard reagents that contain a ketone function, see: F. F. Kneisel, P. Knochel, *Synlett* **2002**, 1799.

[8] For the preparation of 3-(2-furyl)propionyl chloride we used literature procedures starting from furfural: a) M. Takeuchi, T. Taniguchi, K. Ogasawara, *Synthesis* **1999**, 341; b) A. Robertson, D. Philip, N. Spencer, *Tetrahedron* **1999**, *55*, 11365; c) A. Padwa, T. J. Wisnieff, E. J. Walsh, *J. Org. Chem.* **1989**, *54*, 298.

[9] Besides **7** (48 % yield), we also isolated an iodoketone (2-[3-(2-furyl)propanoyl]-4-iodophenyl 4-chlorobenzenesulfonate), which probably formed through protonation of the corresponding Grignard reagent.