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Preparation of highly functionalized arylmagnesium reagents by the addition of magnesium phenylselenide to arynes

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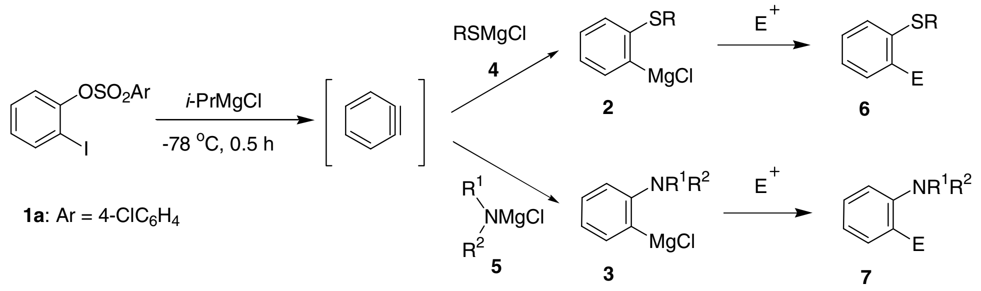
Abstract—The described polyfunctional arylmagnesium reagents, resulting from the highly regioselective addition of magnesium phenylselenide to functionalized arynes, can be trapped by a range of electrophiles, yielding polyfunctional selenoethers in 45–85% yields. Furthermore, these Grignard reagents can be used in Negishi cross-coupling reactions with iodoarenes after transmetalation to the corresponding arylzinc compounds, furnishing functionalized biaryl products in 55–73% yields.

Arynes are highly reactive intermediates, which have found numerous applications in organic synthesis.[1] Of special interest is the addition of nucleophiles to arynes.[1–3] 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**.[4] Application of this method enabled the preparation of functionalized arylmagnesium reagents **2** and **3** by the addition of magnesium arylthiolates **4** and amides **5** to aryne.[5] In contrast to previous methods, these aryl magnesium reagents can be trapped by electrophiles giving rise to aryl thioethers of type **6** and aryl amines of type **7** (Scheme 1).[5]

Arylselenoethers are very useful compounds, which can be converted to various compounds.[6] Two examples have been reported for the addition of magnesium phenylselenide (**8**) to benzyne, followed by trapping with electrophiles.[5] Herein, we report the regioselective addition of magnesium phenylselenide (**8**) to arynes generated by our previously reported procedure, providing 2-seleno-substituted aryl magnesium species of type **9**. The resulting arylmagnesium reagents **9** can be trapped by a range of electrophiles, yielding aryl selenoethers of type **10** (Scheme 2 and Table 1).

Thus, the addition of *i*-PrMgCl (2.0 equiv) to phenylselenol (1.0 equiv) in THF (−78 °C, 0.5 h) followed by



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

Keywords: Aryne; Organomagnesium reagent; Selenoether.

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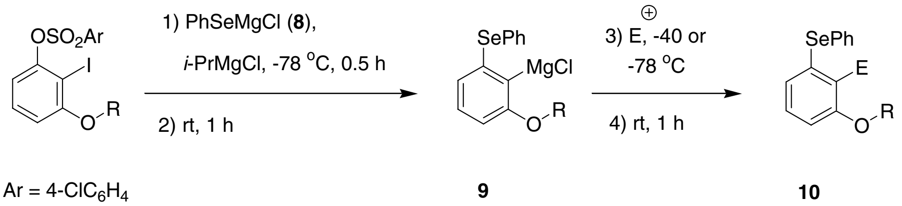
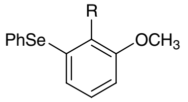
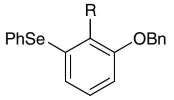
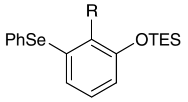


Ar = 4-ClC_6H_4
1b: R = Me
1c: R = Bn
1d: R = TES

Scheme 2. Preparation of aryl selenoethers by addition reactions to arynes.

Table 1. Synthesis of selenoethers of type **10** by the addition of magnesium phenylselenide **8** to arynes followed by the trapping of the intermediate Grignard reagents **9** with an electrophile (see Scheme 2)

Entry	1	Electrophile	Product of type 10	Yield (%)[a]
				
1	**1b**	H_2O	**10a**: R = H	85
2		DMF	**10b**: R = CHO	70
3		Allyl bromide[b]	**10c**: R = allyl	82
4		PhCOCl[c]	**10d**: R = COPh	77
				
5	**1c**	H_2O	**10e**: R = H	84
6		DMF	**10f**: R = CHO	72
7		Allyl bromide[b]	**10g**: R = allyl	74
8		PhCOCl[c]	**10h**: R = COPh	76
				
9	**1d**	I_2	**10i**: R = I	51
10		Allyl bromide[b]	**10j**: R = allyl	45

[a] Yield of analytically pure isolated product.

[b] The reaction was performed with 0.5 equiv CuCN·2LiCl.

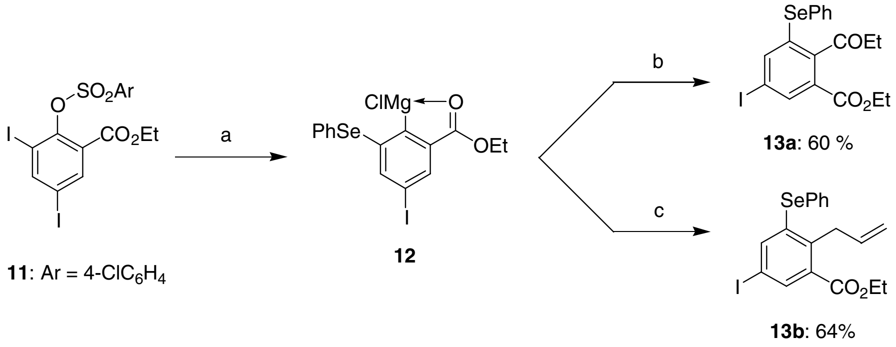
[c] The reaction was performed with 1.0 equiv CuCN·2LiCl.

the addition of 2-iodo-3-methoxyphenyl 4-chlorobenzenesulfonate (**1b**) (1.0 equiv; −78 °C, 0.5 h) and subsequent stirring at ambient temperature for 1 h led to the aryne-addition product **9b**, which upon quenching with water provided 1-methoxy-3-(phenylseleno)-benzene (**10a**) in 85% isolated yield (Table 1, entry 1). Similarly, intermediate Grignard reagent **9b** was formylated with DMF (1.5 equiv, −40 °C to rt, 1 h), leading to 2-methoxy-6-(phenylseleno)-benzaldehyde (**10b**) in 70% yield (entry 2).[7,8] Allyl bromide and benzoyl chloride (in the presence of CuCN·2LiCl) also served as excellent electrophiles, yielding **10c** and **10d** in 82% and 77%, respectively (entries 3 and 4).

The intermediate Grignard reagent **9c**, which was formed from 2-iodo-3-benzyloxyphenyl 4-chlorobenzenesulfonate (**1c**) under the same reaction conditions as **9b**, was successfully quenched with a range of electrophiles to give rise to the corresponding products **10e** (84% yield), **10f** (72% yield), **10g** (74% yield), and **10h** (76% yield), respectively (entries 5–8).

Even the more sterically hindered Grignard reagent **9d** generated from 2-iodo-3-triethylsilanyloxyphenyl 4-chlorobenzenesulfonate (**1d**), was successfully trapped with iodine (1.5 equiv, −78 °C to rt, 1 h) to give rise to **10i** in 51% yield (entry 9). Furthermore, the reaction of **9d** with allyl bromide gave rise to the allylated selenoether **10j** in 45% yield (entry 10).

Interestingly, functionalized arynes displayed a remarkable regioselectivity in the addition step.[5] Thus the polyfunctional sulfonate **11** was selectively magnesiated at the *ortho*-position of the sulfonate group, and its reaction with magnesium phenylselenide (**8**) provided selec-



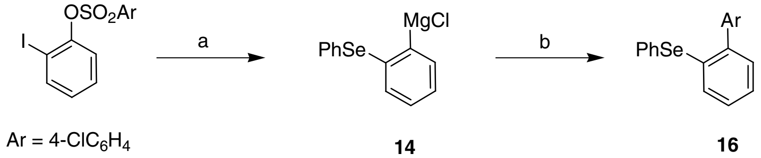
11: Ar = 4-ClC_6H_4

12

13a: 60 %

13b: 64%

Scheme 3. Reagents and conditions: (a) THF, PhSeMgCl (2.0 equiv), *i*-PrMgCl (1.0 equiv), −78 °C, 0.5 h; rt, 2 h; (b) CuCN·2LiCl (1.0 equiv), −78 °C, 10 min; EtCOCl (3.0 equiv), −78 °C to rt, 1 h; (c) CuCN·2LiCl (0.5 equiv), −78 °C, 10 min; allyl bromide (3.0 equiv), −78 °C to rt, 1 h.



1a **14** **16**

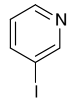
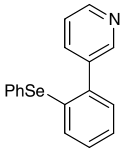
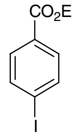
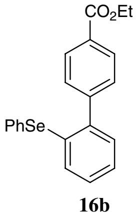
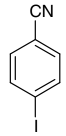
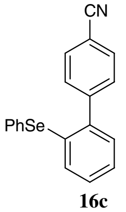
Scheme 4. Reagents and conditions: (a) THF, PhSeMgCl (1.0 equiv), *i*-PrMgCl (1.0 equiv), −78 °C, 0.5 h; 0 °C, 10 min; (b) $ZnBr_2$ (1.0 equiv), −78 °C, 10 min; iodoarenes (1.5 equiv), $Pd(dba)_2$ (5 mol %), tfp (10 mol %), −40 °C to rt, 5 h.

tively the magnesiated reagent **12**, which was stabilized by chelation. Its reaction with various electrophiles, such as an acid chloride, or allyl bromide in the presence of CuCN·2LiCl, furnished the tetrasubstituted selenoethers **13a** (60% yield)[8] and **13b** (64% yield), respectively (Scheme 3).

Furthermore, the arylmagnesium reagent **14**, which resulted from the reaction of **8** with **1a** under similar reaction condition, can be subjected to Negishi cross-coupling reaction. After transmetalation with $ZnBr_2$, the corresponding zinc reagents can react with various iodoarenes **15a**–**c** under standard reaction conditions, furnishing functionalized biaryls **16a**–**c**[8] in 55–73% yields (Scheme 4 and Table 2).

In summary, we have developed a general procedure for the selenomagnesiation of arynes. The resulting functionalized arylmagnesium species can be trapped with numerous electrophiles including iodoarenes, which undergo smooth Negishi cross-coupling reactions, in contrast to most previously reported addition reactions. Further extensions of this work, utilizing other heteroarynes, are currently underway in our laboratories.

Table 2. Synthesis of selenoethers of type **16** from **14** by Negishi cross-coupling reaction with an electrophile (see Scheme 4)

Entry	Electrophile	Product of type **16**	Yield (%)[a]
1	 **15a**	 **16a**	73
2	 **15b**	 **16b**	69
3	 **15c**	 **16c**	55

[a] Yield of analytically pure isolated product.

Acknowledgements

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7. Typical procedure: A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of phenylselenol (157 mg, 1.00 mmol) in dry THF (3 mL). After cooling to −78 °C, *i*-PrMgCl (1.88 mL, 2.01 equiv, 1.07 M in THF) was added dropwise and stirred for 30 min. 2-Iodo-3-methoxyphenyl 4-chlorobenzenesulfonate (**1b**) (424 mg, 1.00 mmol) dissolved in dry THF (2 mL) was then added. The resulting mixture was stirred vigorously for 30 min at −78 °C and immediately warmed to room temperature. After 1 h, the reaction mixture was cooled to −40 °C and DMF (0.12 mL, 1.5 equiv) was added. The mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with satd aq NH_4Cl solution, extracted with CH_2Cl_2 (3×40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (*n*-pentane/diethyl ether = 10:1) yielded **10b** as a yellow solid (207 mg, 70%).
8. Selected data: Compound **10b**: mp 77.4–79.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 10.65$ (s, 1H), 7.70–7.66 (m, 2H), 7.46–7.37 (m, 3H), 7.15 (t, ^{3}J(H,H) = 8.2 Hz, 1H), 6.71 (d, ^{3}J(H,H) = 8.2 Hz, 1H), 6.47 (d, ^{3}J(H,H) = 8.2 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 190.0$, 164.0, 142.6, 137.4, 134.4, 129.6, 129.1, 128.6, 122.2, 120.9, 107.1, 55.8. MS (70 eV, EI): *m*/*z* (%): 294 (20), 293 (20), 292 (100) [M^+], 291 (29), 290 (49), 289 (28), 288 (22), 215 (21), 214 (52), 212 (28), 135 (21), 134 (19), 77 (25), 76 (19). IR (KBr): ν (cm^{-1}) = 2888 (w), 1650 (s), 1579 (s), 1564 (vs), 1463 (s), 1437 (m), 1396 (m), 1295 (w), 1267 (vs), 1212 (w), 1187 (w), 1033 (m), 827 (w), 776 (w), 743 (w), 693 (w). HRMS for $C_{14}H_{12}O_2Se$ (292.0002): found: 292.0027. Compound **13a**: mp 64.5–65.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.23$ (d, ^{4}J(H,H) = 1.8 Hz, 1H), 7.82 (d, ^{4}J(H,H) = 1.8 Hz, 1H), 7.48–7.42 (m, 2H), 7.35–7.29 (m, 3H), 4.33 (q, ^{3}J(H,H) = 7.1 Hz, 2H), 2.85 (q, ^{3}J(H,H) = 7.1 Hz, 2H), 1.36 (t, ^{3}J(H,H) = 7.1 Hz, 3H), 1.26 (t, ^{3}J(H,H) = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 206.0$, 164.0, 146.1, 145.9, 138.0, 133.6, 130.3, 129.7, 129.6, 129.3, 128.4, 94.3, 62.1, 37.0, 14.0, 7.6. MS (70 eV, EI): *m*/*z* (%): 488 (60) [M^+], 486 (29), 459 (59), 457 (26), 431 (30), 413 (26), 355 (23), 353 (100), 351 (51), 349 (20), 57 (20). IR (KBr): ν (cm^{-1}) = 2983 (w), 2938 (w), 1723 (vs), 1700 (s), 1558 (m), 1543 (w), 1438 (w), 1366 (w), 1279 (s), 1253 (s), 1196 (m), 1113 (m), 1020 (w), 948 (w), 868 (w), 785 (w), 765 (w), 742 (m), 722 (w), 692 (m). HRMS for $C_{18}H_{17}IO_3Se$ (487.9388): found: 487.9415. Compound **16b**: mp 105.3–105.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.20$–8.10 (m, 2H), 7.57–7.45 (m, 4H), 7.38–7.17 (m, 7H), 4.46 (q, ^{3}J(H,H) = 7.1 Hz, 2H), 1.46 (t, ^{3}J(H,H) = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 166.2$, 146.0, 142.4, 134.5, 132.0, 131.9, 130.0, 129.9, 129.4, 129.3, 129.2, 129.0, 128.5, 127.8, 126.7, 60.8, 14.3. MS (70 eV, EI): *m*/*z* (%): 382 (100) [M^+], 337 (15), 308 (12), 274 (7), 229 (63), 207 (7), 168 (4), 152 (31), 113 (3), 77 (3), 51 (1). IR (KBr): ν (cm^{-1}) = 2987 (m), 2906 (m), 1961 (w), 1709 (vs), 1609 (s), 1459 (m), 1440 (m), 1401 (m), 1275 (vs), 1178 (s), 1110 (s), 1027 (s), 858 (s), 746 (vs), 446 (m). HRMS for $C_{21}H_{18}O_2Se$ (382.0472): found: 382.0449.