Sequential Electrophilic Trapping Reactions for the Desymmetrization of Dilithio(hetero)arenes

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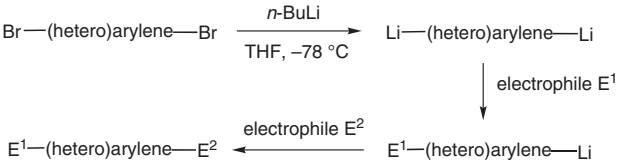
Abstract: Double bromine–lithium exchange and sequential trapping of the dilithio intermediate with different electrophiles gives rise to the formation of unsymmetrically substituted (hetero)arenes in a one-pot fashion.

Key words: arenes, bromine–lithium exchange, dianions, heterocycles, one-pot reactions

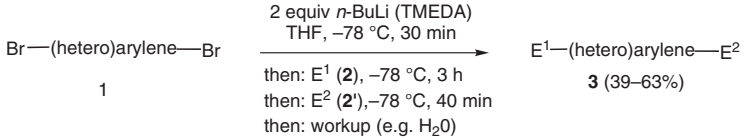
Halogen–metal exchange is a general way to transform electrophilic precursors into carbon nucleophiles that are trapped in a one-pot fashion by the addition of a broad variety of electrophiles.[1] In the case of dihalogen-substituted substrates, it is often possible to perform a double halogen–lithium exchange. Starting from symmetrical dibromo(hetero)arenes unsymmetrical target molecules have generally been synthesized by stepwise repetitive bromine–lithium exchange followed by electrophilic trapping, workup, and purification.[2] Upon reaction of symmetrical dilithio species with two equivalents of a suitable electrophile symmetrically functionalized products can be easily obtained. However, direct sequential electrophilic trapping in a one-pot fashion to furnish unsymmetrically substituted targets can be attractive with respect to efficiency and efficacy. In addition, desymmetrization of a dilithio intermediate by sequential addition of different electrophiles paves the way to a plethora of new sequences and becomes a playground for developing and inventing new one-pot, multicomponent processes[3,4] that are of particular interest in diversity-oriented syntheses,[5] combinatorial and solid-phase strategies.[4d,6] Therefore, one-pot sequences promise manifold opportunities for generating novel lead structures of pharmaceuticals, catalysts, and even novel molecule-based materials. To the best of our knowledge sequential one-pot syntheses of unsymmetrical molecules derived from dibromo(hetero)arenes have not been reported (Scheme 1). Here we communicate a facile one-pot desymmetrization of dilithio(hetero)arenes by sequential electrophilic trapping.



Scheme 1 General scheme for the one-pot desymmetrization of dibromo(hetero)arene by sequential addition of different electrophiles to the dilithio intermediate

Upon reacting dibromo(hetero)arenes **1** with *n*-BuLi in anhydrous THF at –78 °C under nitrogen the dilithio species are readily obtained. In all cases a reverse addition was chosen, i.e. the dibromo compound was added by syringe to the precooled solution of *n*-BuLi, to ensure complete conversion.[7] For 2,5-dibromothiophene, 3,6-dibromo-9-octyl-9*H*-carbazole, and 4,4′-dibromobiphenyl, and TMEDA (2 equiv) were added to *n*-BuLi solutions prior to the addition of the dibromides in order to increase the reactivity of *n*-BuLi by disaggregation. In course of the reaction turbidity could be observed, presumably due to the formation of aggregated dilithio(hetero)arenes. Then, two different electrophiles **2** and **2′** were sequentially added at –78 °C. The first was slowly added (over 3 h) to maintain a small stationary concentration while the latter was added quickly. After workup and chromatography the unsymmetrically substituted (hetero)arenes were obtained in 39–63% yield (Scheme 2, Table 1).[8,9]

Apparently, this one-pot desymmetrization by sequential electrophilic trapping is quite general for dibromo(hetero)arenes. A critical role, however, plays the inherent stability of the dilithio intermediate, e.g. it was not possible to generate and trap the 1,4-dilithiobenzene under these conditions. On the other hand, the nature of the first trap-



Scheme 2 One-pot synthesis of unsymmetrically substituted (hetero)arenes by sequential electrophilic trapping

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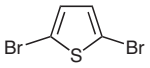
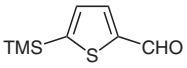
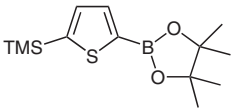
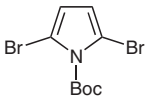
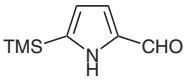
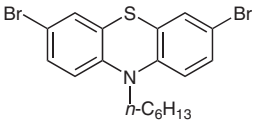
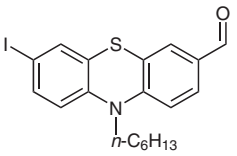
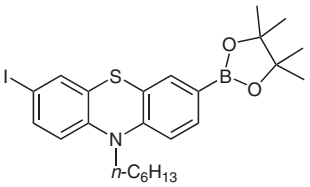
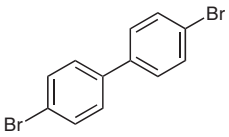
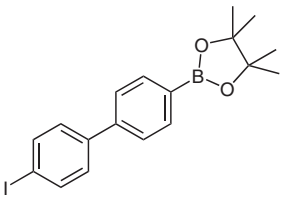
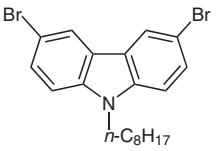
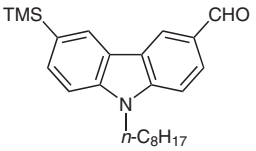
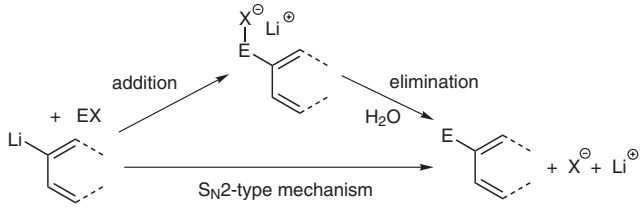
Table 1 Overview of Synthesized Products

Entry	Dibromo(hetero)arene **1**		Electrophile E^1 (**2**)	Electrophile E^2 (**2′**)	Unsymmetrical (hetero)arene **3** (isolated yield, %)[a]		
1[b]	**1a**		TMSCl (**2a**)	DMF (**2b**)	**3a**		61
2[b,c]	**1a**		**2a**	$B(OMe)_3$ (**2c**)	**3b**		55
3	**1b**		**2a**	**2b**	**3c**		58
4	**1c**		I_2 (**2d**)	**2b**	**3d**		63
5[c]	**1c**		**2d**	**2c**	**3e**		58
6[c]	**1c**		**2c**	**2d**	**3e**		40
7[b,c]	**1d**		**2d**	**2c**	**3f**		45
8[b]	**1e**		**2a**	**2b**	**3g**		39

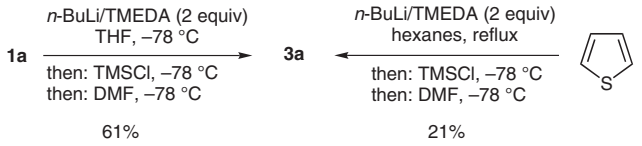
[a] Yields of the isolated and chromatographed products **3**.
[b] Addition of TMEDA (2 equiv).
[c] Addition of pinacol and stirring for 1 h, addition of AcOH and stirring for several hours prior to aqueous workup.

ping electrophile is important, since two different trapping pathways are possible: an addition–elimination route or a S_N2-type mechanism (Scheme 3).

In case of the addition route an anion results after addition of the first electrophile. As a consequence of Coulomb interactions of the two anionic sites in the intermediate affect the attack of the second electrophile and lead to minor yields (entries 5 and 6). Therefore, the first electrophiles were chosen to follow the S_N2 pathway. Interestingly, also the mode of generation of dilithio(hetero)arenes becomes relevant. An alternative access to quite stable dilithiated heterocycles such as 2,5-dilithiothiophene can be achieved for instance by double deprotonation of thiophene with BuLi and TMEDA. If the sequence is then performed under otherwise identical conditions as significantly lower yield of compound **3a** is obtained (Scheme 4). This result is somehow surprising as 2,5-dilithio thiophene usually give good to excellent yields upon symmetrical trapping with DMF.[10] The same holds true for *tert*-butyl 2,5-dibromo-1*H*-pyrrole-1-carboxylate (**1b**) as a substrate giving better yields than the dilithio deriva-



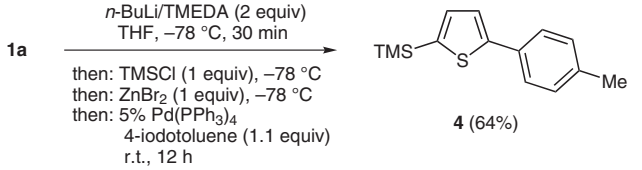
Scheme 3 Reaction pathways depending on the sequence of added electrophiles



Scheme 4 Sequential electrophilic trapping of 2,5-dilithiothiophene generated via two different routes

tive obtained from double deprotonation of Boc-protected pyrrole.

Finally, it was also possible to use anhydrous zinc bromide as the second electrophile giving rise to an organozinc derivative. This intermediate was in situ applied as an entry for a subsequent and terminating Negishi coupling[11] with 4-iodo toluene giving rise to the formation of the coupling product **4** in 64% yield (Scheme 5). With respect to five-bond transformations within a consecutive one-pot reaction this novel multicomponent process is quite promising for further elaboration.



Scheme 5 A one-pot, three-component bromine–lithium exchange–sequential electrophilic trapping–Negishi coupling sequence

In conclusion, we have developed a sequential electrophilic trapping of symmetrical dilithiated (hetero)arenes that leads to unsymmetrically substituted (hetero)arene in a one-pot fashion. Additionally, this practical and diversity-oriented procedure can be elaborated to novel multicomponent reactions also by terminating with cross-coupling reactions. Studies to expand the scope of these sequential trapping reactions and combinations with subsequent cross-coupling are currently under way.

Acknowledgment

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(8) **Representative Procedure – Synthesis of Trimethyl[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]silane (3b; Table 1, Entry 2)**
In a flame-dried Schlenk flask under N_2 atmosphere *n*-BuLi (2.5 M in *n*-hexane, 0.83 mL, 2.00 mmol) and TMEDA (0.3 mL, 2.0 mmol) were dissolved in anhyd THF (30 mL) at –78 °C. 2,5-Dibromothiophene (**1a**, 242 mg, 1.00 mmol) was added slowly to the solution, and the mixture was stirred for 30 min. Then, TMSCl (**2a**, 0.11 g, 1.00 mmol) in anhyd THF (10 mL) was added dropwise to the stirred solution over a period of 3 h. The reaction mixture was stirred for another 30 min and $B(OMe)_3$ (**2c**, 208 mg, 1.00 mmol) was added. After stirring for 40 min pinacol (130 mg, 1.10 mmol) in anhyd THF (5 mL) was added to the mixture. The solution was allowed to warm to r.t., a few drops of AcOH were added, and the solution was stirred for 14 h. After aqueous workup and extraction with Et_2O the combined organic layers were dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel (hexane–EtOAc, 10:1) gives 156 mg (55%) of **3b** as a colorless solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.30 (s, 9 H), 1.33 (s, 12 H), 7.31 (d, ^3J = 3.3 Hz, 1 H), 7.67 (d, ^3J = 3.3 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.1, 24.8, 84.1, 135.0, 137.9, 148.5. MS (EI): *m/z* (%) = 282(21) $[M]^+$, 267(100) $[C_{12}H_{20}BO_2SSi]^+$, 233(4), 209(5), 183(7), 167(11). HRMS (EI): *m/z* calcd for $C_{13}H_{23}BO_2SSi$ $[M]^+$: 282.1281; found: 282.1274.
5-(Trimethylsilyl)thiophene-2-carbaldehyde (3a)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.34 (s, 9 H), 7.29 (d, ^3J = 3.6 Hz, 1 H), 7.77 (d, ^3J = 3.6 Hz, 1 H), 9.92, (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.5, 134.5, 136.7, 148.2, 152.7, 182.6. MS (EI): *m/z* (%) = 184(19) $[M]^+$, 189(100) $[C_7H_9OSSi]^+$. HRMS (EI): *m/z* calcd. for $C_8H_{12}OSSi$ $[M]^+$: 184.0378; found: 184.0368.

5-(Trimethylsilyl)-1*H*-pyrrole-2-carbaldehyde (3c)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.24 (s, 9 H), 6.37–6.48 (m, 1 H), 6.91–6.93 (m, 1 H), 9.46 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.02, 120.5, 122.8, 137.4, 143.1, 180.4. MS (EI): *m/z* (%) = 167(36) $[M]^+$, 152(100) $[C_7H_{10}NOSi]^+$.

10-Hexyl-7-iodo-10*H*-phenothiazine-3-carbaldehyde (3d)
^{1}H NMR (300 MHz, acetone-d_6): δ = 0.82–0.86 (m, 3 H), 1.27–1.30 (m, 4 H), 1.43–1.48 (m, 2 H), 1.74–1.84 (m, 2 H), 4.00 (t, *J* = 7.0 Hz, 2 H), 6.89 (d, *J* = 8.5 Hz, 1 H), 7.17 (d, *J* = 8.5 Hz, 1 H), 7.45 (d, *J* = 1.8 Hz, 1 H), 7.47 (dd, *J* = 8.5, 1.8 Hz, 1 H), 7.52 (dd, *J* = 8.5, 1.9 Hz, 1 H), 7.60 (d, *J* = 2.2 Hz, 1 H). ^{13}C NMR (75 MHz, acetone-d_6): δ = 14.1, 23.1, 26.8, 27.1, 31.9, 48.2, 85.8, 116.5, 119.1, 124.9, 127.0, 128.5, 130.8, 132.6, 135.8, 137.3, 144.6, 150.9, 190.3. MS (EI): *m/z* (%) = 437(100) $[M]^+$, 366(42), 352(76), 239(14), 255(20), 196(22).

10-Hexyl-7-iodo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-10*H*-phenothiazine-3-carbaldehyde (3e)
^{1}H NMR (300 MHz, acetone-d_6): δ = 0.82–0.86 (m, 3 H), 1.27–1.28 (m, 16 H), 1.40–1.46 (m, 2 H), 1.71–1.81 (m, *J* = 6.9 Hz, 2 H), 3.93 (t, *J* = 7.0 Hz, 2 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 7.02 (d, *J* = 8.1 Hz, 1 H), 7.42–7.44 (m, 2 H), 7.48 (dd, *J* = 2.2, 8.5 Hz, 1 H), 7.56 (dd, *J* = 1.5, 8.1 Hz, 1 H). ^{13}C NMR (75 MHz, acetone-d_6]): δ = 14.1, 23.1, 25.0, 26.9, 27.2, 32.0, 48.7, 84.4, 84.8, 116.1, 123.7, 127.9, 134.1, 135.2, 135.6, 135.8, 136.9, 145.6, 148.3. MS (EI): *m/z* (%) = 535(100) $[M]^+$, 450(24), 409(2). Anal. Calcd for $C_{24}H_{31}BINO_2S$ (535.3): C, 53.85; H, 5.84; N, 2.62; S, 5.99. Found: C, 57.84; H, 8.13; N, 1.97.

2-(4′-Iodobiphenyl-4-yl)-4,4,5,5-tetramethyl-1,3-dioxaborolane (3f)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 12 H), 7.34 (d, ^3J = 8.50 Hz, 2 H), 7.55 (d, ^3J = 8.23 Hz, 2 H), 7.75 (d, ^3J = 8.50 Hz, 2 H), 7.90 (d, ^3J = 8.23 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 83.9, 93.4, 126.2, 128.8, 129.0, 135.4, 137.9, 140.5, 142.6. MS (EI): *m/z* (%) = 406(100) $[M]^+$, 306(48) $[C_{12}H_8BOI]^+$, 179(23) $[C_{12}H_8BO]^+$, 152(15). HRMS (EI): *m/z* calcd for $C_{18}H_{20}BIO_2$ $[M]^+$: 406.0601; found: 406.0556.

9-Octyl-6-(trimethylsilyl)-9*H*-carbazole-3-carbaldehyde (3g)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.35 (s, 9 H), 0.84 (t, ^3J = 6.7 Hz, 3 H), 1.16–1.47 (m, 10 H), 1.80–1.94 (m, 2 H), 4.30 (t, ^3J = 7.2 Hz, 2 H), 7.45 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.66 (dd, ^3J = 1.0, 0.4 Hz, 1 H), 7.99 (dd, *J* = 8.3, 1.3 Hz, 1 H), 8.32 (s, 1 H), 8.64 (d, ^3J = 1.3 Hz, 1 H), 10.09 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.7, 0.7, 14.1, 22.6, 27.2, 28.9, 29.1, 29.3, 31.8, 43.4, 108.9, 122.8, 123.9, 125.6, 127.1, 131.0, 131.5, 141.7, 144.1, 191.8. MS (EI): *m/z* (%) = 379(100) $[M]^+$, 364(84) $[C_{23}H_{30}NOSi]^+$, 280(28) $[C_{17}H_{18}NOSi]^+$, 150(11). HRMS (EI): *m/z* calcd for $C_{24}H_{33}NOSi$ $[M]^+$: 379.2331; found: 379.2358. Anal. Calcd for $C_{24}H_{33}NOSi$: C, 75.94; H, 8.76; N, 3.69. Found: C, 76.37; H, 8.79; N, 3.61.

Trimethyl(5-*p*-tolylthiophen-2-yl)silane (4)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.33 (s, 9 H), 2.35 (s, 3 H), 7.18 (m, 3 H), 7.31 (d, ^3J = 3.4 Hz, 1 H), 7.51 (d, ^3J = 8.2 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.4, 21.2, 123.9, 126.0, 129.5, 131.7, 133.8, 134.9, 137.3, 139.4. MS (EI): *m/z* (%) = 246(61) $[M]^+$, 231(100) $[C_{13}H_{15}SSi]^+$. HRMS (EI): *m/z* calcd for $C_{14}H_{18}SSi$ $[M]^+$: 246.0898; found: 246.0920.

(9) Interestingly, the expected byproducts, i.e. symmetrical disubstitution with the first electrophile and monosubstitution with the first electrophile followed by proton quenching are only found in minor quantities and were identified by GC-MS analysis in the crude ethereal extract during workup.

(10) (a) Mitsumori, T.; Inoue, K.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1995**, *117*, 2467. (b) Feringa, B. L.; Hulst, R.; Rikers, R.; Brandsma, L. *Synthesis* **1988**, 316.

(11) For recent reviews, see for example: (a) Knochel, P.; Calaza, M. I.; Hupe, E.; Negishi, E.-I.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**, 619–670. (b) Negishi, E.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**, 815–889.