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Regioselective Functionalization of the Thiazole Scaffold Using TMPMgCl·LiCl and $TMP_2Zn·2MgCl_2·2LiCl$

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Supporting Information

ABSTRACT: A general method for the synthesis of 2,4,5-trisubstituted thiazoles has been developed. Starting from commercially available 2-bromothiazole, successive metalations using TMPMgCl·LiCl or $TMP_2Zn·2MgCl_2·2LiCl$ lead to the corresponding magnesated or zincated thiazoles which readily react with various electrophiles providing highly functionalized thiazoles.

Thiazoles are an important class of heterocycles which are present in many natural products[1] possessing antitumor, antifungal, antibiotic, or antiviral effects.[2] Some functionalized thiazoles have found applications as liquid crystals,[3] while others are used as cosmetic sunscreens.[4]

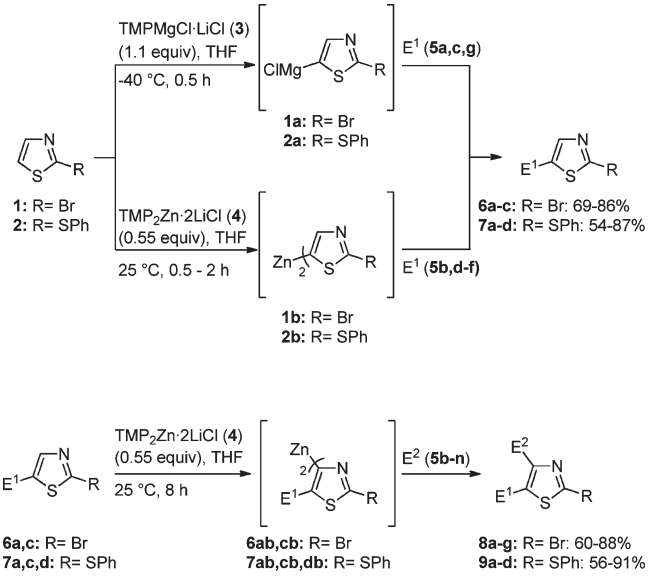
The standard syntheses of substituted thiazoles are cyclization reactions such as the Hantzsch reaction, where an α-haloketone reacts with a thioamide.[5] Furthermore, electrophilic and nucleophilic substitution sequences or functionalizations via halogen dance have been described.[6]

Herein, we wish to report a new approach for the regioselective functionalization of the thiazole scaffold using successive metalations. Starting from 2-substituted thiazoles such as 2-bromothiazole (**1**) or 2-(phenylthio)-1,3-thiazole (**2**), directed metalations using TMPMgCl·LiCl[7] (**3**; TMP = 2,2,6,6-tetramethylpiperidyl) or $TMP_2Zn·2MgCl_2·2LiCl$[8] (**4**, abbreviated $TMP_2Zn·2LiCl$ for the sake of clarity) occurred exclusively in position 5 and led, respectively, to the 5-metalated thiazoles **1a**,**2a** and **1b**,**2b** (Scheme 1).[9] Subsequent reaction with electrophiles (**5a**−**g**) afforded 2,5-disubstituted thiazoles **6a**−**c** and **7a**−**d** in 54−86% yield.

Thus, starting from readily available 2-bromothiazole **1**, a selective magnesation using TMPMgCl·LiCl (**3**, 1.1 equiv, −40 °C, 0.5 h) led to the Grignard reagent **1a**. Alternatively, the zincated intermediate **1b** can be prepared using $TMP_2Zn·2LiCl$ (**4**, 0.55 equiv, 25 °C, 0.5 h).

The magnesated thiazole **1a** reacted with TMSCl, NC−CO_2Et, or allyl bromide (20% CuCN·2LiCl), furnishing the 2,5-disubstituted thiazoles **6a**−**c** in 69−86% yield (Table 1, entries 1−3). Similarly, 2-(phenylthio)-1,3-thiazole (**2**) was metalated within 0.5 h using TMPMgCl·LiCl **3** (1.1 equiv) at −40 °C or using $TMP_2Zn·2LiCl$ **4** (0.55 equiv, 2 h) at 25 °C. The metalated reagent **2a** reacted with TMSCl, giving 2-(phenylthio)-5-(trimethylsilyl)thiazole **7a** in 80% yield (entry 4). A Pd-catalyzed acylation[10] of **2b** (2% $Pd(PPh_3)_4$) provided the ketone **7b** in 78% yield (entry 5). Negishi cross-coupling[11] reaction with the aryl iodide **5e** using 3% $Pd(dba)_2$ (dba = *trans*,*trans*-dibenzylideneacetone) and 6% P(*o*-furyl)$_3$[12] afforded the arylated

Scheme 1. Functionalization of the Thiazole Scaffold at the 5- and 4-Position



thiazole **7c** in 83% yield (entry 6). Chlorination with 1,1,2-trichloro-1,2,2-trifluoroethane led to the 5-chlorinated thiazole **7d** (−50 °C, 4 h) in 54% yield (entry 7).

After protecting the 5-position with a TMS group, a subsequent zincation at position 4 was achieved at 25 °C within 8 h using $TMP_2Zn·2LiCl$ (**4**, 0.55 equiv, Scheme 1). The zincated species **6ab** reacted with I_2 and yielded the iodinated thiazole **8a** in 85% yield (Table 2, entry 1). Copper(I)-catalyzed allylation[13] (20% CuCN·2LiCl) with various allylic bromides such as ethyl 2-(bromomethyl)acrylate[14] (**5h**) or 3-bromocyclohex-1-ene (**5i**) led to the 4-allylated products **8b**,**c** in 72−77% yield (entries 2 and 3). The 4-arylated and alkenylated thiazoles **8d**−**f** and **9a**

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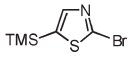
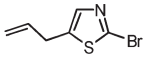
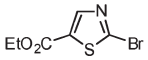
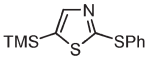
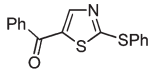
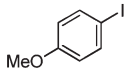
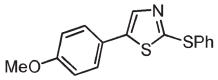
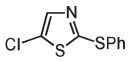
Table 1. Products of Type 6 and 7 Obtained by Metalation at the 5-Position of Thiazoles 1 or 2 and Reaction with Electrophiles

entry	substrate, (metalation conditions)	electrophile E^1, (conditions)	functionalized product, yield (%)[a]
1	 **1** (**3**, –40 °C, 30 min)	TMSCl **5a** (–50 °C, 30 min)	 **6a** (86)
2	**1** (**4**, 25 °C, 30 min)	 **5b** (0 to 25 °C, 1 h)[b]	 **6b** (69)
3	**1** (**3**, –40 °C, 30 min)	NC–CO_2Et **5c** (25 °C, 5 h)	 **6c** (80)
4	 **2** (**3**, –40 °C, 30 min)	TMSCl **5a** (–50 °C, 30 min)	 **7a** (80)
5	**2** (**4**, 25 °C, 2 h)	 **5d** (25 °C, 1 h)[c]	 **7b** (78)
6	**2** (**4**, 25 °C, 2 h)	 **5e** (25 °C, 3 h)[d]	 **7c** (83)
7	**2** (**3**, –40 °C, 30 min)	 **5f** (–50 °C, 4 h)	 **7d** (54)

[a] Isolated yield of analytically pure product. [b] After transmetalation with 20% CuCN·2LiCl. [c] 2% $Pd(PPh_3)_4$ catalyzed acylation reaction. [d] 3% $Pd(dba)_2$, 6% P(*o*-furyl)$_3$ catalyzed cross-coupling reaction.

were obtained by Negishi cross-coupling reactions with various aryl or alkenyl iodides (3% $Pd(dba)_2$, 6% P(*o*-furyl)$_3$) in 65−91% yield (entries 4−7). Due to oligomerization side reactions, Pd-catalyzed cross-coupling reactions of the zincated 2-bromothiazoles afforded lower yields compared to the same cross-coupling reactions with the zincated 2-(phenylthio)-5-(trimethylsilyl)thiazole derivatives **6ab**. The ketone **9b** was obtained by a Pd-catalyzed acylation reaction (2% $Pd(PPh_3)_4$) with benzoyl chloride in 78% yield (entry 8).

Interestingly, using $TMP_2Zn·2LiCl$ (**4**), a regioselective zincation at the 4-position of thiazoles bearing an ester, an aryl, or a halogen group (**6c** and **7c,d**) was achieved leading to the corresponding zincated thiazoles (**6cb**, **7cb,db**).

Reaction with various electrophiles provided the 4,5-disubstituted thiazoles in 60−88% yield (entries 9−11). Thus, reaction with iodine afforded the 4-iodinated thiazole **8g** in 60 yield (entry 9). Pd-catalyzed cross-coupling reactions with aryl iodides led to the trisubstituted thiazoles **9c,d** in 80−88% yield (entries 10 and 11).

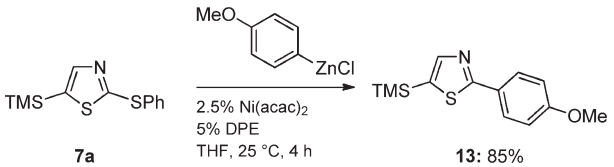
Deprotection of the TMS group with TBAF provided the 2,4-difunctionalized thiazoles **10** and **11** in 80% yield (Table 3, entries 1 and 2). Alternatively, by addition of ICl,[15] the 5-iodothiazoles **12a,b** (entries 3 and 4) were obtained in 92% yield. These heterocyclic iodides can be further used in Pd-catalyzed cross-coupling reactions.[6,16]

The resulting 2-thiophenyl thiazoles undergo further cross-coupling reaction at position 2 with various organometallic reagents.[17] Thus, the Ni-catalzyed cross-coupling reaction of the disubstituted thiazole **7a** using 2.5% $Ni(acac)_2$, 5% DPE,[18] and (4-methoxyphenyl)zinc chloride afforded the thiazole **13** at 25 °C within 4 h in 85% yield (Scheme 2).

Thiazolopyridazines have useful biological properties.[19] They are readily obtained by cyclization of 4,5-diketothiazoles with hydrazine hydrate. Starting from the 5-ketothiazole **7b**, a direct metalation with $TMP_2Zn·2LiCl$ (**4**) afforded the zincated thiazole at 25 °C within 8 h (Scheme 3). The resulting zinc organometallic undergoes a Pd-catalyzed acylation reaction with benzoyl chloride (2% $Pd(PPh_3)_4$), furnishing the trisubstituted thiazole **14** in 73% yield. A smooth cyclization occurred when **14** was treated with hydrazine hydrate (25 °C, 10 min), leading to the functionalized thiazolopyridazine **15** in 80% yield.

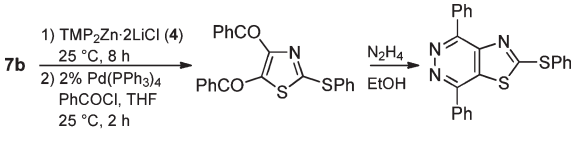
In summary, we have reported the full functionalization of the thiazole core using highly reactive TMP bases TMPMgCl·LiCl (**3**) or $TMP_2Zn·2MgCl_2·2LiCl$ (**4**). After functionalization with

Scheme 2. Ni-Catalyzed Cross-Coupling of the 2-Thiophenyl Thiazole (7a)



7a **13:** 85%

Scheme 3. Preparation of a Functionalized Thiazolopyridazine (15) from the Thiazole 7b



14: 73% **15:** 80%

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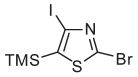
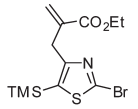
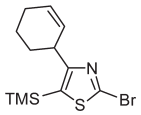
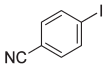
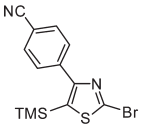
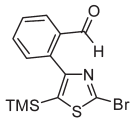
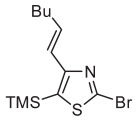
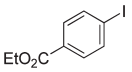
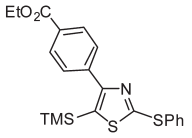
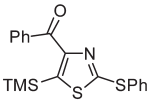
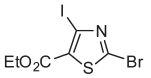
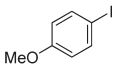
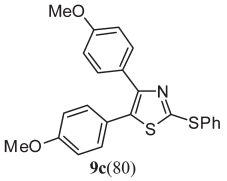
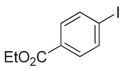
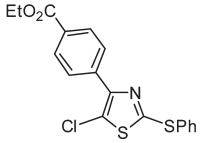
Table 2. Products of Type 8 and 9 Obtained by Zincation of Thiazoles (6a,c and 7a,c,d) at the 4-Position Using $TMP_2Zn \cdot 2LiCl$ (4) at 25 °C and Reaction with Electrophiles

entry	substrate, (metalation conditions)	electrophile E^2, (conditions)	functionalized product, yield (%)[a]
1	**6a**	I_2	
	(8 h)	**5g** (10 min)	**8a** (85)
2	**6a**		
	(8 h)	**5h** (5 h)[b,c]	**8b** (72)
3	**6a**		
	(8 h)	**5i** (2 h)[b]	**8c** (77)
4	**6a**		
	(8 h)	**5j** (15 h)[d]	**8d** (71)
5	**6a**		
	(8 h)	**5k** (5 h)[d]	**8e** (70)
6	**6a**		
	(8 h)	**5l** (2 h)[d]	**8f** (65)[e]
7	**7a**		
	(8 h)	**5m** (3 h)[d]	**9a** (91)
8	**7a**		
	(8 h)	**5d** (3 h)[f]	**9b** (78)
9	**6c**	I_2	
	(2 h)	**5g** (10 min)	**8g** (60)
10	**7c**		
	(2 h)	**5n** (2 h)[d]	**9c**(80)
11	**7d**		
	(2 h)	**5m** (0.5 h)[d]	**9d** (88)

[a] Isolated yield of analytically pure product. [b] After transmetalation with 20−100% CuCN·2LiCl. [c] At 0−25 °C. [d] 3% $Pd(dba)_2$, 6% P(*o*-furyl)$_3$ catalyzed cross-coupling reaction. [e] Exclusively the *E*-isomer was observed. [f] 2% $Pd(PPh_3)_4$ catalyzed acylation reaction.

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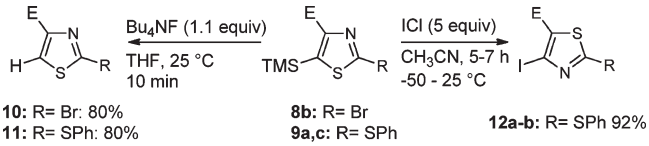
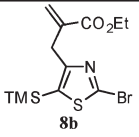
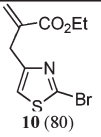
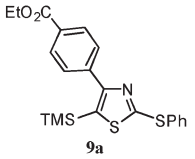
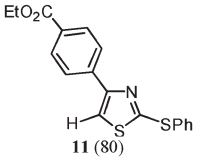
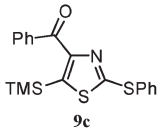
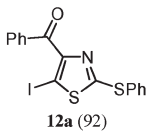
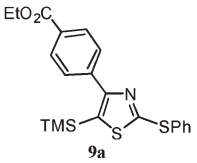
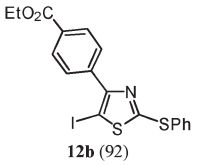
Table 3. Products of Type 10, 11, and 12 Obtained by Transformations of Silylated Thiazoles of Type 8 and 9



entry	substrate	reagent (conditions)	deprotected product, yield (%)[a]
1	 **8b**	Bu_4NF (25 °C, 10 min)	 **10** (80)
2	 **9a**	Bu_4NF (25 °C, 10 min)	 **11** (80)
3	 **9c**	ICl (–50 - 25 °C, 5 h)	 **12a** (92)
4	 **9a**	ICl (–50 - 25°C, 7 h)	 **12b** (92)

[a] Isolated yield of analytically pure product.

various electrophiles, a selective zincation at the 4-position of the thiazole core can be achieved. Electrophilic trapping leads to a broad range of highly functionalized trisubstituted thiazoles.

EXPERIMENTAL SECTION

General: All reactions were carried out in a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar. TMPMgCl·LiCl, $TMP_2Zn·2MgCl_2·2LiCl$, $ZnCl_2$, and CuCN·2LiCl were prepared according to literature.[7,8] *i*PrMgCl·LiCl solution (1.3 M) in THF was purchased from Aldrich.

Typical Procedure for the Metalation with TMPMgCl·LiCl (TP1): The starting material was dissolved in THF (1 M). Then, TMPMgCl·LiCl (1.1 equiv) was dropwise added at −40 °C and stirred for 0.5 h.

Typical Procedure for the Metalation with $TMP_2Zn·2MgCl_2·2LiCl$ (TP2): The starting material was dissolved in THF (1 M). Then, $TMP_2Zn·2MgCl_2·2LiCl$ (1.2 equiv) was dropwise added at 25 °C and stirred for the indicated time.

Typical Procedure for the Cu(I)-Catalyzed Allylation Reactions of Zincated Thiazoles with Allylic Bromides (TP3): CuCN·2LiCl (20 mol %) was added at 0 °C to the zincated thiazole (prepared according to TP2) followed by addition of the corresponding allylic bromide (1.2 equiv). The resulting solution was warmed to 25 °C and stirred for the indicated time. Purification according to P1 yielded the product.

Typical Procedure for the Pd-Catalyed Cross-Coupling Reactions of Zincated Thiazoles with Aryl Iodides (TP4): $Pd(dba)_2$ (3 mol %) and P(*o*-furyl)$_3$ (6 mol %) were added to the zincated thiazole (prepared according to TP2) followed by addition of the corresponding aryl iodide (1.2 equiv) at 25 °C. The resulting solution was stirred for the indicated time. Purification according to P1 yielded the product.

Typical Procedure for the TMS Deprotection with Bu_4NF (TP5): The starting material was dissolved in THF (1 M). Then, Bu_4NF (1.1 equiv) dissolved in THF (1 M) was dropwise added at 25 °C and stirred for 10 min. Purification according to P1 yielded the product.

Typical Procedure for the TMS Deprotection with ICl (TP6): The starting material was dissolved in acetonitrile (1 M). Then, ICl (5 equiv) was dropwise added at −50 °C and the resulting solution was warmed to 25 °C for 5−7 h. Purification according to P2 yielded the product.

Typical Procedure for the Purification of Allylated or Arylated Thiazoles (P1): The reaction mixture was quenched with saturated NH_4Cl solution (10 mL per mmol), and the resulting mixture was extracted with ether (3 × 10 mL per mmol). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure.

Typical Procedure for the Purification of Iodinated Thiazoles (P2): The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution (10 mL per mmol), and the resulting mixture was extracted with ether (3 × 10 mL per mmol). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure.

Synthesis of 2: *i*PrMgCl·LiCl (1.1 equiv) was dropwise added to a solution of **1** (1.64 g, 10 mmol) in THF (10 mL) at −40 °C and stirred for 0.5 h. (*S*)-Phenylbenzenethiosulfonate (1.1 equiv) was added at −40 °C, and the mixture was stirred for 0.5 h. Purification according to P1 and flash chromatography (pentane/ether 5:1) yielded **2** (1.78 g, 92%) as yellow oil. Analytical data matches the literature.[9]

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Synthesis of 6a: Compound **6a** was prepared according to TP1 from **1** (3.3 g, 20 mmol). TMSCl (2.2 equiv) was added at −50 °C to **1a** and was stirred for 0.5 h. Purification according to P1 and flash chromatography (pentane/ether 19:1) yielded **6a** (4.02 g, 85%) as a yellow oil. Analytical data matches the literature.[9]

Synthesis of 6b: Compound **6b** was prepared according to TP2 from **1** (1.6 g, 10 mmol) [0.5 h] following by reaction with allyl bromide according to TP3. Flash chromatography (pentane/ether 50:1) yielded **6b** (1.40 g, 69%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 7.27 (t, J = 1.11 Hz, 1H), 5.97−5.84 (m, 1H), 5.20−5.12 (m, 2H), 3.52−3.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) = 141.3, 139.8, 134.6, 134.3, 117.6, 31.2; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1408 (s), 1000 (vs), 919 (m), 841 (m), 695 (m); MS (EI, 70 eV) m/z (%) = 203 (M^+ − ^{79}Br, 50), 124 (60), 98 (49), 97 (100); HRMS (EI) calcd for C_6H_6BrNS 202.9404, found 202.9406 (M^+).

Synthesis of 6c: Compound **6c** was prepared according to TP1 from **1** (1.64 g, 10 mmol). Ethyl cyanoformate (1.5 equiv) was added to **1a** at −40 °C and was stirred for 0.5 h. Purification according to P1 and flash chromatography (pentane/ether 5:1) yielded **6c** (1.88 g, 80%) as a colorless oil. Analytical data matches the literature.[20]

Synthesis of 7a: Compound **7a** was prepared according to TP1 from **2** (4.83 g, 25 mmol). TMSCl (2.2 equiv) was added to **2a** at −50 °C and was stirred for 0.5 h. Purification according to P1 and flash chromatography (pentane/ether 10:1) yielded **7a** (5.30 g, 80%) as a yellow oil; ^{1}H NMR (DMSO, 400 MHz) δ (ppm) = 7.80 (s, 1H), 7.67−7.64 (m, 2H), 7.52−7.48 (m, 3H), 0.23 (s, 9H); ^{13}C NMR (DMSO, 100 MHz) δ (ppm) = 169.9, 149.5, 133.9, 133.9, 130.6, 130.1, 130.1, −0.3; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1474 (m), 1252 (s), 1036 (m), 1014 (s), 1000 (m), 834 (vs), 750 (s), 738 (s), 702 (m), 688 (s), 624 (m); MS (EI, 70 eV) m/z (%) = 265 (M^+, 87), 264 (89), 115 (100); HRMS (EI) calcd for $C_{12}H_{15}NS_2Si$ 265.0415, found 265.0401 (M^+).

Synthesis of 7b: Compound **7b** was prepared according to TP2 from **2** (967 mg, 5 mmol) [2 h]. $Pd(PPh_3)_4$ (2 mol %) and benzoyl chloride (1.5 equiv) were added to **2b** and were stirred for 1 h. Purification according to P1 and flash chromatography (pentane/ether 5:1) yielded **7b** (937 mg, 63%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 8.03 (s, 1H), 7.81−7.77 (m, 2H), 7.72−7.69 (m, 2H), 7.61−7.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) = 186.4, 178.2, 149.4, 138.9, 137.4, 135.2, 132.7, 130.9, 130.3, 129.3, 128.8, 128.6; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1626 (s), 1598 (m), 1502 (s), 1472 (m), 1354 (s), 1320 (m), 1306 (s), 1294 (s), 1276 (s), 1164 (s), 1130 (m), 1052 (s), 1024 (m), 868 (s), 708 (s), 688 (vs), 650 (m); MS (EI, 70 eV) m/z (%) = 297 (M^+, 83), 296 (100), 105 (23), 77 (26); HRMS (EI) calcd for $C_{16}H_{11}NOS_2$ 297.0282, found 297.0275 (M^+); mp (°C) 87−89.

Synthesis of 7c: Compound **7c** was prepared according to TP2 from **2** (967 mg, 5 mmol) [2 h] and reaction with 1-iodo-4-methoxybenzene according to TP4 for 3 h. Flash chromatography (pentane/ether 5:1) yielded **7c** (1.24 g, 83%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 7.74 (s, 1H), 7.65−7.60 (m, 2H), 7.42−7.33 (m, 5H), 6.90−6.85 (m, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) = 163.1, 159.8, 141.0, 137.7, 133.3, 132.3, 129.7, 129.3, 127.8, 123.6, 114.5, 55.3; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1605 (m), 1490 (s), 1463 (m), 1440 (m), 1304 (m), 1246 (vs), 1178 (s), 1158 (m), 1031 (s), 1015 (s), 1000 (m), 824 (vs), 794 (m), 741 (s), 688 (s); MS (EI, 70 eV) m/z (%) = 299 (M^+, 100), 298 (46), 132 (22); HRMS (EI) calcd for $C_{16}H_{13}NOS_2$ 299.0439, found 299.0430 (M^+).

Synthesis of 7d: Compound **7d** was prepared according to TP1 from **2** (967 mg, 5 mmol). 1,1,2-Trichloro-1,2,2-trifluoroethane (1.2 equiv) was added to **2a** at −50 °C and stirred for 4 h. Purification according to P1 and flash chromatography (pentane/CH_2Cl_2 10:1) yielded **7d** (606 mg, 54%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 7.62−7.58 (m, 2H), 7.46 (s, 1H), 7.45−7.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) = 164.9, 141.1, 134.5, 133.9, 130.9, 129.9, 129.9; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1489 (m), 1440 (m), 1034 (vs), 1006 (s), 999 (s), 840 (m), 747 (s), 734 (s), 702 (m), 688 (vs), 643 (m); MS (EI, 70 eV) m/z (%) = 228 (45), 227 (M^+, 64), 226 (100), 109 (18); HRMS (EI) calcd for $C_9H_6ClNS_2$ 226.9630, found 226.9619 (M^+).

Synthesis of 8a: Compound **8a** was prepared according to TP2 from **6a** (236 mg, 1 mmol) [8 h]. Iodine (2 equiv) was added to **6ab** and was stirred for 10 min. Purification according to P2 and flash chromatography (pentane/ether; 39:1) yielded **8a** (308 mg, 85%) as a yellow oil. **^{1}H NMR ($CDCl_3$, 300 MHz):** δ (ppm) = 0.41 (s, 9H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) = 140.0, 139.9, 99.3, −0.9; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1428 (s), 1364 (s), 1248 (s), 1152 (s), 1012 (m), 992 (s), 832 (vs), 796 (s), 748 (s), 696 (m), 628 (s), 524 (m). **MS (EI, 70 eV):** m/z (%) = 361 (M^+ - ^{79}Br, 39), 348 (100), 346 (90), 241 (32). **HRMS (EI)**: calcd. for $C_6H_9BrINSSi$: 360.8453, found: 360.8468 (M^+).

Synthesis of 8b. Compound **8b** was prepared according to TP2 from **6a** (236 mg, 1 mmol) [8 h] and reaction with ethyl 2--(bromomethyl)acrylate according to TP3 for 5 h. Flash chromatography (pentane/ether 20:1) yielded **8b** (249 mg, 72%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) = 6.28 (d, J = 1.19 Hz, 1H), 5.28 (d, J = 1.19 Hz, 1H), 4.21 (q, J = 7.15 Hz, 2H), 3.77 (d, J = 1.55 Hz, 2H), 1.29 (t, J = 7.15 Hz, 3H), 0.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) = 166.6, 159.1, 138.5, 138.4, 133.7, 126.5, 60.8, 33.7, 14.2, 0.0; IR (diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 1711 (m), 1407 (m), 1251 (s), 1191 (m), 1133 (s), 1025 (m), 1003 (s), 836 (vs), 751 (m), 633 (m); MS (EI, 70 eV) m/z (%) = 347 (M^+ − ^{79}Br, 15), 303 (63), 301 (59), 75 (85), 73 (100); HRMS (EI) calcd for $C_{12}H_{18}BrNO_2SSi$ 347.0011, found 347.0006 (M^+).

Synthesis of 8c: Compound **8c** was prepared according to TP2 from **6a** (236 mg, 1 mmol) [8 h] and reaction with 3-bromocyclohex-1-ene according to TP3 for 2 h. Flash chromatography (pentane/ether 20:1) yielded **8c** (242 mg, 77%) as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 5.87−5.80 (m, 1H), 5.58−5.53 (m, 1H), 3.58−3.49 (m, 1H), 2.20−1.84 (m, 5H), 1.69−1.57 (m, 1H), 0.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) = 167.0, 138.2, 131.1, 128.7, 128.5, 39.7, 30.2, 24.6, 22.0, 0.3; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1488 (m), 1400 (m), 1251 (s), 1002 (s), 834 (vs), 750 (s), 722 (m), 694 (m), 668 (m), 636 (m), 617 (m); MS (EI, 70 eV) m/z (%) = 317 (59), 315 (M^+ − ^{79}Br, 66), 288 (57), 286 (43), 236 (100); HRMS (EI) calcd for $C_{12}H_{18}BrNSSi$ 315.0113, found 315.0106 (M^+).

Synthesis of 8d: Compound **8d** was prepared according to TP2 from **6a** (236 mg, 1 mmol) [8 h] and reaction with 4-iodobenzonitrile according to TP4 for 15 h. Flash chromatography (pentane/ether 20:1) yielded **8d** (239 mg, 71%) as a white solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) = 7.71−7.66 (m, 4H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) = 159.8, 140.3, 139.5, 135.6, 132.0, 129.6, 118.6, 112.3, 0.6; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 2228 (m), 1604 (m), 1412 (m), 1252 (s), 1008 (s), 988 (s), 836 (vs), 748 (s), 676 (s), 632 (s), 568 (m), 548 (s), 520 (m); MS (EI, 70 eV) m/z (%) = 338 (100), 336 (M^+ − ^{79}Br, 92), 323 (48), 322 (71), 320 (63); HRMS (EI) calcd for $C_{13}H_{13}BrN_2SSi$ 335.9752, found 335.9759 (M^+); mp (°C) 98−99.

Synthesis of 8e: Compound **8e** was prepared according to TP2 from **6a** (236 mg, 1 mmol) [8 h] and reaction with 2-iodobenzaldehyde according to TP4 for 5 h. Flash chromatography (pentane/ether 10:1) yielded **8e** (239 mg, 70%) as an orange oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) = 9.84 (s, 1H), 7.99 (dd, J = 7.75 Hz, 1H), 7.62−7.59 (m, 1H), 7.54 (t, J = 7.63 Hz, 1H), 7.38 (dd, J = 7.63 Hz, 1H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) = 191.1, 158.0, 139.0, 139.0, 136.6, 135.0, 133.2, 131.3, 129.4, 127.7, 0.1; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1695 (s), 1597 (m), 1451 (m), 1292 (m), 1250 (s), 1194 (m), 998 (s), 834 (vs), 817 (s), 755 (s), 742 (s), 695 (s), 650 (m); MS (EI, 70 eV) m/z (%) = 339 (M^+ − ^{79}Br, 18), 311 (100), 309 (91), 260 (62), 73 (62), 57 (62); HRMS (EI) calcd for $C_{13}H_{14}BrNOSSi$ 338.9749, found 338.9757 (M^+).

Synthesis of 8f: Compound **8f** was prepared according to TP2 from **6a** (236 mg, 1 mmol) [8 h] and reaction with $Pd(PPh_3)_4$ (2 mol %)

and (*E*)-1-iodohex-1-ene (1.5 equiv) for 5 h. Purification according to P1 and flash chromatography (pentane/ether 150:1) yielded **8f** (128 mg, 65%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) = 6.69−6.65 (m, 1H), 6.32−6.29 (m, 1H), 2.23−2.19 (m, 2H), 1.48−1.43 (m, 2H), 1.39−1.33 (m, 2H), 0.91 (t, J = 7.18 Hz, 3H), 0.34 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) = 159.6, 138.7, 136.2, 131.1, 122.5, 32.5, 31.1, 22.2, 13.9, 0.2; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1469 (m), 1418 (m), 1003 (s), 964 (m), 834 (vs), 756 (m), 624 (m); MS (EI, 70 eV) m/z (%) = 317 ($M^+ - {}^{79}$Br, 32), 290 (91), 288 (75), 238 (52), 73 (100); HRMS (EI) calcd for $C_{12}H_{20}BrNSSi$ 317.0269, found 317.0266 (M^+).

Synthesis of 8g: Compound **8g** was prepared according to TP2 from **6c** (236 mg, 1 mmol) [2 h]. Iodine (2 equiv) was added to **6cb** at 25 °C and was stirred for 10 min. Purification according to P2 and flash chromatography (pentane/ether 20:1) yielded **8g** (169 mg, 60%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) = 4.36 (q, J = 7.00 Hz, 2H), 1.37 (t, J = 7.05 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) = 159.1, 142.8, 131.4, 101.1, 62.3, 14.1; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1711 (vs), 1478 (m), 1466 (s), 1376 (s), 1250 (vs), 1181 (vs), 1120 (m), 1082 (vs), 1027 (vs), 831 (s), 806 (s), 754 (vs); MS (EI, 70 eV) m/z (%) = 363 (100), 361 (M^+ - ^{79}Br, 96), 335 (75), 333 (74), 318 (88), 316 (85); HRMS (EI) calcd for $C_6H_5BrINO_2S$ 360.8269, found 360.8257 (M^+); mp (°C) 106−109.

Synthesis of 9a: Compound **9a** was prepared according to TP2 from **7a** (265 mg, 1 mmol) [8 h] and reaction with ethyl 4-iodobenzoate according to TP4. Flash chromatography (pentane/ether 10:1) yielded **9a** (372 mg, 91%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 8.09−8.05 (m, 2H), 7.70−7.64 (m, 3H), 7.63−7.61 (m, 1H), 7.44−7.39 (m, 3H), 4.37 (q, J = 7.00 Hz, 2H), 1.39 (t, J = 7.05 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) = 169.6, 166.2, 161.2, 141.0, 134.1, 131.3, 130.5, 130.0, 129.7, 129.7, 129.2, 128.9, 60.9, 14.2, 0.6; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1716 (s), 1458 (m), 1408 (m), 1256 (s), 1124 (m), 1044 (m), 1016 (m), 994 (s), 830 (vs), 780 (m), 762 (s), 744 (s), 708 (s), 686 (s), 660 (m), 632 (s); MS (EI, 70 eV) m/z (%) = 413 (M^+, 100), 412 (28), 263 (21), 73 (20); HRMS (EI) calcd for $C_{21}H_{23}NO_2S_2Si$ 413.0939, found 413.0934 (M^+); mp (°C) 69−71.

Synthesis of 9b: Compound **9b** was prepared according to TP2 from **7a** (265 mg, 1 mmol) [8 h] and reaction with $Pd(PPh_3)_4$ (2 mol %) and benzoyl chloride (1.5 equiv) at 25 °C for 3 h. Purification according to P1 and flash chromatography (pentane/ether 20:1) yielded **9b** (288 mg, 72%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) = 8.15 (dd, J = 8.35 Hz, 2H), 7.70−7.67 (m, 2H), 7.56−7.53 (m, 1H), 7.47−7.43 (m, 1H), 0.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) = 188.1, 168.8, 158.8, 145.9, 137.4, 134.4, 132.7, 131.1, 130.8, 129.9, 129.9, 128.0, −0.25; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1648 (m), 1406 (m), 1248 (m), 1214 (s), 1178 (m), 1000 (m), 836 (vs), 812 (s), 746 (s), 728 (s), 686 (vs), 658 (s), 642 (s), 622 (s); MS (EI, 70 eV) m/z (%) = 369 (M^+, 3), 355 (24), 354 (100), 145 (18); HRMS (EI) calcd for $C_{19}H_{19}NOS_2Si$ 369.0677, found 369.0665 (M^+).

Synthesis of 9c: Compound **9c** was prepared according to TP2 from **7c** (297 mg, 1 mmol) [2 h] and reaction with 1-iodo-4-methoxybenzene according to TP4 for 3 h. Flash chromatography (pentane/ether 5:1) yielded **9c** (324 mg, 80%) as a white solid: ^{1}H NMR (DMSO, 400 MHz) δ (ppm) = 7.73−7.69 (m, 2H), 7.52−7.48 (m, 3H), 7.37−7.33 (m, 2H), 7.18−7.14 (m, 2H), 6.90−6.84 (m, 4H), 3.72 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (DMSO, 100 MHz) δ (ppm) = 161.9, 159.3, 158.9, 149.1, 133.6, 132.2, 130.6, 130.5, 130.1, 130.0, 129.6, 126.3, 122.8, 114.4, 113.7, 55.1, 55.0; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1605 (m), 1439 (m), 1290 (m), 1242 (vs), 1218 (m), 1180 (s), 1048 (s), 1031 (s), 1008 (s), 842 (s), 830 (s), 753 (s), 735 (m), 688 (s), 655 (s), 628 (s); MS (EI, 70 eV) m/z (%) = 405 (M^+, 95), 299 (100), 298 (56), 149 (48); HRMS (EI) calcd for $C_{23}H_{19}NO_2S_2$ 405.0857, found 405.0848 (M^+); mp (°C) 100−102.

Synthesis of 9d: Compound **9d** was prepared according to TP2 from **7d** (297 mg, 1 mmol) [2 h] and reaction with ethyl 4-iodobenzoate according to TP4 for 1 h. Flash chromatography (pentane/ether 20:1) yielded **9d** (331 mg, 88%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) = 8.11−8.08 (m, 2H), 8.03−8.00 (m, 2H), 7.68−7.65 (m, 2H), 7.47−7.42 (m, 3H), 4.38 (q, J = 7.02 Hz, 2H), 1.39 (t, J = 7.12 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) = 166.1, 164.2, 149.0, 136.4, 134.5, 130.3, 130.1, 130.0, 130.0, 129.5, 127.9, 121.5, 61.0, 14.3; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1705 (vs), 1607 (m), 1433 (s), 1364 (m), 1265 (vs), 1101 (vs), 1045 (s), 1028 (m), 1014 (m), 863 (m), 776 (s), 754 (vs), 701 (vs), 691 (vs), 660 (m); MS (EI, 70 eV) m/z (%) = 377 (45), 376 (M^+, 100), 371 (48), 57 (33); HRMS (EI) calcd for $C_{18}H_{14}ClNO_2S_2$ 375.0154, found 375.0147 (M^+); mp (°C) 87−88.

Synthesis of 10: Compound **10** was prepared according to TP5 from **8b** (348 mg, 1 mmol). Flash chromatography (pentane/ether 10:1) yielded **10** (220 mg, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 6.90 (t, J = 0.83 Hz, 1H), 6.27−6.26 (m, 1H), 5.61 (q, J = 1.39 Hz, 1H), 4.16 (q, J = 7.10 Hz, 2H), 3.74−3.73 (m, 2H), 1.23 (t, J = 7.05 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) = 166.3, 154.4, 137.4, 135.1, 127.3, 118.6, 60.8, 33.9, 14.1; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1698 (s), 1408 (m), 1264 (s), 1218 (s), 1126 (m), 1114 (s), 1054 (m), 1012 (s), 860 (m), 756 (vs), 698 (s), 664 (m); MS (EI, 70 eV) m/z (%) = 275 (M^+, 15), 231 (100), 229 (94), 203 (77), 97 (62); HRMS (EI) calcd for $C_9H_{12}BrNO_2S$ 274.9616, found 274.9611 (M^+).

Synthesis of 11: Compound **11** was prepared according to TP5 from **9a** (414 mg, 1 mmol). Flash chromatography (pentane/ether 10:1) yielded **11** (273 mg, 85%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 8.09−8.05 (m, 2H), 7.95−7.91 (m, 2H), 7.71−7.65 (m, 2H), 7.47−7.65 (m, 4H), 4.38 (q, J = 7.21 Hz, 2H), 1.40 (t, J = 7.17 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) = 167.3, 166.3, 154.9, 137.9, 134.3, 131.2, 130.1, 130.0, 129.9, 129.9, 126.1, 115.5, 61.0, 14.3; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1698 (s), 1606 (m), 1428 (m), 1266 (vs), 1246 (s), 1198 (m), 1122 (m), 1106 (s), 1046 (s), 1022 (s), 1014 (s), 862 (m), 754 (s), 728 (vs), 710 (s), 692 (s), 664 (m); MS (EI, 70 eV) m/z (%) = 341 (M^+, 100), 340 (49), 161 (20); HRMS (EI) calcd for $C_{18}H_{15}NO_2S_2$ 341.0544, found 341.0548 (M^+); mp (°C) 124−125.

Synthesis of 12a: Compound **12a** was prepared according to TP6 from **9c** (370 mg, 1 mmol). Flash chromatography (pentane/ether 10:1) yielded **12a** (3.1 g, 92%) as a yellow oil: ^{1}H NMR (DMSO, 400 MHz) δ (ppm) = 7.91−7.89 (m, 2H), 7.70−7.68 (m, 2H), 7.64−7.60 (m, 1H), 7.55−7.47 (m, 5H); ^{13}C NMR (DMSO, 100 MHz) δ (ppm) = 187.2, 170.2, 153.9, 136.2, 134.3, 133.3, 130.6, 130.3, 130.1, 129.3, 128.3, 82.1; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1642 (m), 1415 (s), 1249 (m), 1179 (s), 1049 (s), 1030 (m), 1012 (m), 959 (m), 791 (m), 753 (s), 721 (s), 705 (s), 689 (vs), 678 (vs), 650 (s), 614 (s); MS (EI, 70 eV) m/z (%) = 423 (M^+, 96), 296 (78), 128 (78), 127 (44), 109 (70), 77 (100); HRMS (EI) calcd for $C_{16}H_{10}INOS_2$ 422.9248, found 422.9243 (M^+).

Synthesis of 12b: Compound **12b** was prepared according to TP6 from **9a** (2.1 g, 5 mmol). Flash chromatography (pentane/ether 10:1) yielded **12b** (3.1 g, 92%) as a yellow solid: ^{1}H NMR (DMSO, 400 MHz) δ (ppm) = 8.05−8.02(m, 2H), 7.99−7.96 (m, 2H), 7.74−7.72 (m, 2H), 7.59−7.52 (m, 3H), 4.33 (q, J = 7.15 Hz, 2H), 1.32 (t, J = 7.12 Hz, 3H); ^{13}C NMR (DMSO, 100 MHz) δ (ppm) = 170.6, 165.3, 155.9, 138.0, 134.4, 130.7, 130.4, 129.6, 129.4, 129.2, 128.6, 72.1, 60.9, 14.2; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1694 (s), 1659 (m), 1461 (m), 1412 (m), 1387 (m), 1277 (vs), 1172 (m), 1096 (s), 1068 (m), 1039 (s), 1016 (s), 1004 (m), 838 (m), 774 (s), 755 (s), 710 (s), 696 (m), 688 (s); MS (EI, 70 eV) m/z (%) = 467 (M^+, 100), 205 (94), 160 (27); HRMS (EI) calcd for $C_{18}H_{14}INO_2S_2$ 466.9511, found 466.9507 (M^+); mp (°C) 112−113.

Synthesis of 13: Ni(acac)$_2$ (2.5 mol %), DPEphos (5 mol %), and (4-methoxyphenyl)zinc chloride (prepared by adding *i*PrMgCl·LiCl (1.5 mmol) to 1-iodo-4-methoxybenzene (1.5 equiv, 1.0 M in THF) at 25 °C and stirring for 1 h and further transmetalation with $ZnCl_2$ (1 equiv)) were added to a solution of **7a** (133 mg, 0.5 mmol) in THF (0.5 mL) at 25 °C and stirred for 4 h. Purification according to P1 and

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flash chromatography (pentane/ether 9:1) yielded **13** (112 mg, 85%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 7.89 (d, J = 8.75 Hz, 2H), 7.78 (s, 1H), 6.93 (d, J = 8.75 Hz, 2H), 3.83 (s, 3H), 0.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) = 172.8, 161.1, 149.1, 131.8, 128.2, 126.7, 114.3, 55.4, −0.3; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1606 (m), 1482 (m), 1242 (s), 1185 (m), 1028 (s), 970 (m), 827 (vs), 749 (s), 633 (m); MS (EI, 70 eV) m/z (%) = 263 (M^+, 58), 248 (43), 115 (100), 73 (22); HRMS (EI) calcd for $C_{13}H_{17}NOSSi$ 263.0800, found 263.0808 (M^+); mp (°C) 56−58.

Synthesis of 14: Compound **14** was prepared according to TP2 from **7b** (595 mg, 2 mmol) [8 h]. $Pd(PPh_3)_4$ (2 mol %) and benzoyl chloride (1.5 equiv) were added to **7bb** and stirred for 2 h at 25 °C. Purification according to P1 and flash chromatography (pentane/ether 5:1) yielded **14** (586 mg, 82%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 7.87−7.84 (m, 2H), 7.77−7.74 (m, 2H), 7.62−7.59 (m, 2H), 7.54−7.48 (m, 4H), 7.47−7.41 (m, 1H), 7.39−7.34 (m, 2H), 7.29−7.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) = 187.9, 187.1, 173.1, 155.0, 139.3, 137.3, 136.3, 135.3, 133.4, 133.3, 131.0, 130.4, 130.0, 129.5, 128.8, 128.4, 128.3; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1619 (m), 1461 (m), 1241 (m), 942 (m), 836 (m), 786 (m), 773 (vs), 761 (m), 736 (m); MS (EI, 70 eV) m/z (%) = 401 (M^+, 93), 324 (61), 296 (59), 105 (100), 77 (82); HRMS (EI) calcd for $C_{23}H_{15}NO_2S_2$ 401.0544, found 401.0541 (M^+).

Synthesis of 15: N_2H_4 (5 equiv) was added dropwise to a solution of **14** (314 mg, 0.78 mmol) in ethanol (2 mL) at 25 °C and stirred for 5 min. Purification according to P1 and flash chromatography (CH_2Cl_2/EtOH 20:1) yielded **15** (310 mg, 80%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 8.58−8.55 (m, 2H), 8.00−7.97 (m, 2H), 7.77−7.74 (m, 2H), 7.61−7.44 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) = 178.2, 152.9, 151.0, 149.8, 136.5, 135.6, 135.1, 134.8, 131.4, 130.4, 130.2, 129.9, 129.8, 128.9, 128.3, 128.3, 127.8; IR (diamond-ATR, neat) $\tilde{\nu}$/cm^{-1} = 1413 (m), 1382 (m), 1017 (m), 773 (m), 753 (s), 693 (vs), 681 (m), 608 (m); MS (EI, 70 eV) m/z (%) = 397 (M^+, 78), 320 (100), 288 (95), 121 (33); HRMS (EI) calcd for $C_{23}H_{15}N_3S_2$ 397.0707, found 397.0704 (M^+); mp (°C) 193−195.

■ ASSOCIATED CONTENT

Supporting Information. Additional experimental procedures and NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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