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[1,4]-S- to O-Silyl Migration: Multicomponent Synthesis of α-Thioketones through Chemoselective Transformation of Esters to Ketones with Organolithium Reagents

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Abstract: A [1,4]-S- to O-silyl migration has been exploited to chemoselectively transform esters into ketones by using organolithium reagents, allowing multicomponent synthesis of α-thioketones. Mechanistic studies reveal that this migration proceeds in an intramolecular manner and is more favorable than the corresponding [1,5]-S- to O- and [1,3]-C- to O-silyl migrations. The resulting α-thioketones are valuable building blocks for the synthesis of cyclic or multifunctionalized organosulfur compounds.

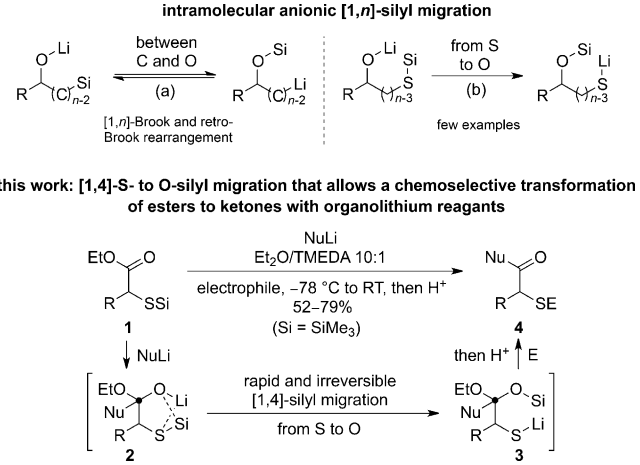
Keywords: multicomponent reactions · nucleophilic addition · organolithium reagents · silyl migration · thioketones

Introduction

Intramolecular anionic silyl migration[1] allows the efficient, site-specific transfer of negative charge "through-space" to create a new anion center, which can undergo transformations in a sequential manner. Such silyl migration between a carbon and an oxygen atom is better known as Brook rearrangement (from C to O) and retro-Brook rearrangement (from O to C). Both rearrangements have been applied in new synthetic methodologies and natural product synthesis (Scheme 1a).[2] In sharp contrast, intramolecular anionic silyl migration between two hetero atoms, especially the migration from a sulfur to an oxygen atom, has been studied to a much more limited extent (Scheme 1b).[3] Because Si–O bonds are stronger than Si–S bonds (ca. 110 vs. 70 kcal mol^{-1}),[4] the migration from S to O should be thermodynamically favorable and, indeed, has been observed under some circumstances.[5] Surprisingly, the migration has not been investigated extensively and few applications in organic synthesis have so far been reported, despite the potential for forming organosulfur compounds.[6]

As part of our continuing investigation of silyl migration,[7] we became interested in the ease with which silyl groups can be made to migrate from S to O. We speculated that this process might be exploited to achieve otherwise challenging selectivity in reactions, such as chemoselective transformation of esters into ketones by using organolithium reagents (Scheme 1).[8] Normally organolithium compounds react with esters of typical reactivity to cause over-addition, giving the corresponding tertiary alcohol rather than the ketone.[9] This has been attributed to the premature release of ketone from the initially formed tetrahedral adduct, which is highly unstable at −78 °C. In fact, efforts to trap this intermediate even at −100 °C by using Me_3SiCl have met with only limited success.[10]

To avoid this problem, we used an alternative approach based on an intramolecular trapping process in which [1,4]-S- to O-silyl migration of **2** was expected to proceed faster than its collapse, generating the masked ketone **3** chemoselectively (Scheme 1). The sulfur in ester **1** would act not



Scheme 1. Top: a) General description of [1,*n*]-Brook and retro-Brook rearrangement; b) general description of [1,*n*]-S- to O-silyl migration. Bottom: [1,4]-S- to O-silyl migration allowing the multicomponent synthesis of α-thioketones by chemoselective transformation of esters to ketones using organolithium reagents.

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only as carrier for the silyl migration, but also as a newly created anion center capable of forming a C–S bond with electrophiles in a sequential fashion. Indeed, thioethers appear as important linkages in many bioactive natural and pharmaceutical agents.[11] Traditional methods to synthesize this moiety often suffer from side reactions in which thioalcohols undergo oxidative coupling to form disulfides, or sulfur deactivates late transition metals.[6a] We reasoned that our multicomponent synthesis of α-thioketones **4** by using **1** as a scaffold would also provide a valuable route to thioether compounds. Herein, we report the detailed studies of this reaction.

Results and Discussion

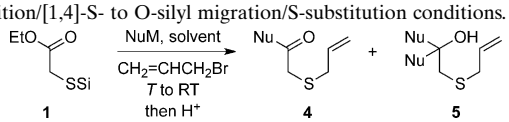
The model scaffold trimethylsilyl ethyl thioglycolate (**1a**) was prepared in 90% yield from commercially available ethyl thioglycolate and hexamethyldisilylamine.[12] The reaction was initially examined in tetrahydrofuran (THF) at −78°C by using *n*BuLi as the nucleophile and allylbromide as the electrophile. Unfortunately, severe over-addition to the ester group occurred, giving tertiary alcohol **5a** in 41% yield after acidic hydrolysis (Table 1, entry 1). Following the over-addition and either intra- or intermolecular S to O silyl migration, the allylic thioether formed. Neither addition of 1.5 equiv hexamethylphosphoramide (HMPA; usually used to promote silyl migration between C and O) nor addition of tetramethylethylenediamine (TMEDA; to stabilize alkoxide lithium **2**) effectively favored the formation of **3** (entries 2 and 3). To our delight, replacing THF with Et_2O and adding TMEDA as a co-solvent gave rise to α-allylthioketone **4a** as a single adduct and in 79% yield (entry 4). This migration proceeded reliably even when excess *n*BuLi (2.0 equiv) was used, giving **4a** in a comparably good yield of 70% and without detectable levels of over-adduct **5a** (entry 5). However, use of a higher temperature (0°C) generated a large amount of **5a** (entry 6). Switching the $SiMe_3$ group to $SiMe_2t$Bu led to no addition for **1b**. The bulky $SiMe_2t$Bu group probably shields the carbonyl carbon of the ester and prevents attack by *n*BuLi (entry 7). In contrast to the results obtained with organolithium reagents, ethyl magnesium bromide reacted with **1a** under the optimized conditions to give alcohol **5b** rather than ketone **4b** (entry 8). This is consistent with the general belief that lithium is better than magnesium as a counter ion to promote silyl migration.

The scope of electrophiles was then tested by reacting **1a** with *n*BuLi. The reaction was applicable to a range of alkyl, benzyl, allyl, and propargyl halides as well as tosylate (Table 2, entries 1–6), giving the desired α-thioketones **4c–h** in good yields. The reaction involving three epoxide derivatives revealed interesting regioselectivity. Epoxide 2-(bromomethyl)oxirane (entry 7) underwent S_N2 reaction with bromide as the leaving group, rather than epoxide opening. In contrast, the reaction of 2-(phenoxymethyl)oxirane (entry 8) proceeded by ring opening at the terminal site. The reaction with 2,3-epoxycyclohexone (entry 9) proceeded by internal attack at the α-position, followed by E_1cb elimination to give α-thiocyclohexenone **4k** in 62% yield. The process also proved suitable for thio-Michael addition to activated double C–C bonds (entries 10 and 11) and triple C–C bonds (entry 12), with a *Z*/*E* ratio of 80:20 being obtained for thioacrylate **4n**. In addition, this approach can be used to form an S–S bond, allowing the synthesis of disulfide **4o** in 72% yield (entry 13).

The multicomponent reaction was compatible with a range of organolithium compounds, including alkyl, vinyl, aryl, and heterocyclic lithium derivatives (Table 3, entries 1–9). These reactions showed reliable chemoselectivity to give α-thioketone **4p–x** with no over-addition detected. Lithium acetylide, however, did not add to the ester group (entry 10), probably because of its weaker nucleophilicity. The α-substituted compound trimethylsilyl ethyl thioglycolate (**1c**) worked well, giving **4z** in 65% yield (entry 11).

To further demonstrate the synthetic potential of our approach, we attempted to synthesize cyclic organosulfur compounds in a sequential manner. Reaction of **1a** with *n*BuLi and α,β-unsaturated ester led to an intramolecular aldol reaction of the initially formed lithium enolate with ketone (Scheme 2), giving multifunctionalized tetrahydrothiophene **6a** and **6b** in 52 and 59% yield, respectively, and with more than 95:5 diastereoselectivity. When the nucleophilic and electrophilic centers were incorporated into the same species, as in the case of α-aryl-substituted oxiranyl lithium, tetrahydrothiophenones **7a** and **7b** were obtained in 56 and 53% yield, respectively.

Table 1. Screening of addition/[1,4]-S- to O-silyl migration/S-substitution conditions.

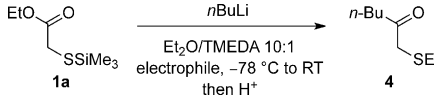


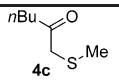
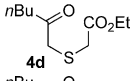
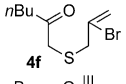
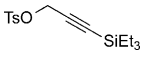
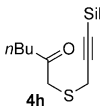
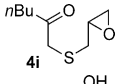
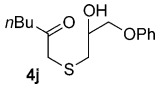
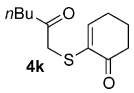
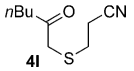
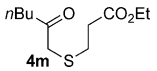
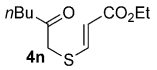
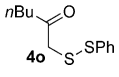
1 4 5

Entry	Si		NuM [(equiv)]	Solvent	*T* [°C]	4	Yield [%][b]	5	Yield [%][b]
1	**1a**	TMS	*n*BuLi (1.1)	THF	−78	**4a**	–	**5a**	41
2	**1a**	TMS	*n*BuLi (1.1)	THF/HMPA	−78	**4a**	–	**5a**	39
3	**1a**	TMS	*n*BuLi (1.1)	THF/TMEDA = 10:1	−78	**4a**	–	**5a**	35
4[a]	**1a**	TMS	*n*BuLi (1.1)	Et_2O/TMEDA = 10:1	−78	**4a**	79	**5a**	–
5	**1a**	TMS	*n*BuLi (2.0)	Et_2O/TMEDA = 10:1	−78	**4a**	70	**5a**	–
6	**1a**	TMS	*n*BuLi (1.1)	Et_2O/TMEDA = 10:1	0	**4a**	26	**5a**	21
7	**1b**	TBDMS	*n*BuLi (1.1)	Et_2O/TMEDA = 10:1	−78	**4a**	–	**5a**	–
8	**1a**	TMS	EtMgBr (1.0)	Et_2O/TMEDA = 10:1	−78	**4b**	–	**5a**	34

[a] Reaction conditions: **1a** (0.26 mmol) and *n*BuLi (2.5 M in hexanes, 0.29 mmol) in Et_2O/TMEDA (10:1, 5.5 mL) at −78°C; then allyl bromide (0.52 mmol), warmed to room temperature; crude products were treated with aq. HCl (0.1 N, 2.0 mL). [b] Isolated yield after purification by silica gel column chromatography.

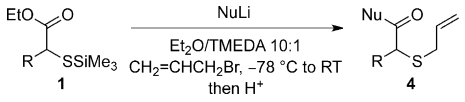
Table 2. Scope of addition/[1,4]-S- to O-silyl migration/S-substitution of **1a** and *n*BuLi with electrophiles.[a]

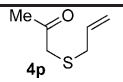
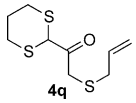
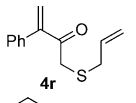
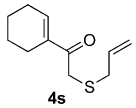
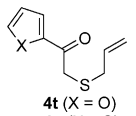
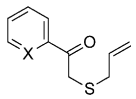
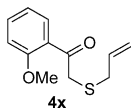
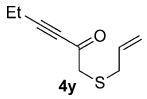
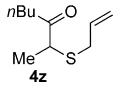


Entry	Electrophile (E)	Product	Yield [%][b]
1	MeI	 **4c**	65
2	$BrCH_2CO_2Et$	 **4d**	70
3	BnBr	 **4e**	62
4		 **4f**	67
5		 **4g**	63
6		 **4h**	56
7		 **4i**	62
8		 **4j**	64
9		 **4k**	62
10		 **4l**	61
11		 **4m**	65
12		 **4n** (Z/E = 80:20)[c]	71
13	PhSSPh	 **4o**	72

[a] Reaction conditions: **1a** (0.26 mmol) and *n*BuLi (2.5 M in hexanes, 0.29 mmol) in Et_2O/TMEDA (10:1, 5.5 mL) at −78 °C; then electrophile (0.52 mmol), warmed to room temperature; crude products were treated with aq. HCl (0.1 N, 2.0 mL). [b] Isolated yield after purification by silica gel column chromatography. [c] The ratio was determined by ^1H NMR spectroscopy.

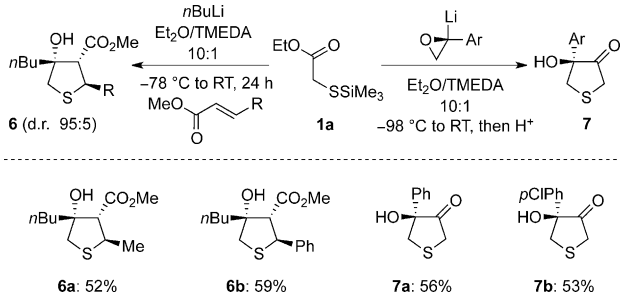
Table 3. Scope of addition/[1,4]-S- to O-silyl migration/S-substitution of **1** and allyl bromide with organolithium nucleophiles.[a]



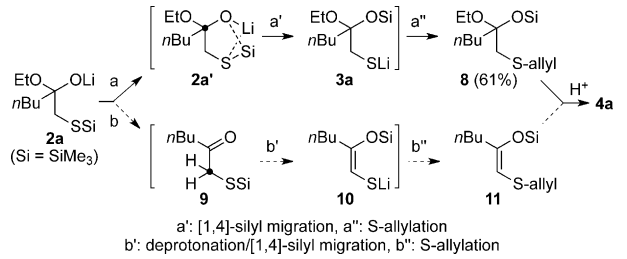
Entry	R		NuLi	Product	Yield [%][b]
1	**1a**	H	MeLi	 **4p**	61
2	**1a**	H		 **4q**	70
3	**1a**	H		 **4r**	76
4	**1a**	H		 **4s**	60
5	**1a**	H			66
6	**1a**	H		 **4t** (X = O) **4u** (X = S)	60
7	**1a**	H			63
8	**1a**	H		 **4v** (X = C) **4w** (X = N)	72
9	**1a**	H		 **4x**	71
10	**1a**	H		 **4y**	–
11	**1c**	Me	*n*BuLi	 **4z**	72

[a] Reaction conditions: **1** (0.26 mmol) and organolithium nucleophile (0.29 mmol) in Et_2O/TMEDA (10:1, 5.5 mL) at −78 °C; then allyl bromide (0.52 mmol), warmed to room temperature; crude products were treated with aq. HCl (0.1 N, 2.0 mL). [b] Isolated yield after purification by silica gel column chromatography.

Two possible reaction pathways a and b are proposed in Scheme 3 to account for the formation of **4a** from tetrahedral adduct **2a**. In pathway a, a rapid [1,4]-S- to O-silyl migration of **2a** may occur via pentacoordinated silicate **2a′** to generate thiolithium **3a**, which would undergo S-allylation to give **8**. Pathway b, on the other hand, provides another possibility; the collapse of **2a** may proceed first to release ketone **9**. In the presence of *n*BuLi and EtOLi as bases, deprotonation could occur at the α-position of ketone **9** to give the corresponding lithium enolate. Subsequent [1,4]-S- to O-silyl migration would afford thiolithium **10**, which could undergo S-allylation to give **11**. Although **8** and **11** are structurally different to each other, acidic hydrolysis of either would lead to the same thioketone **4a**.While pathway b provides a logical explanation for the mechanism, we consider that pathway a should be more reasonable based on the following evidence: first, the key intermediate **8** was isolated in 61% yield with partial decomposition on silica gel and characterized by NMR spectroscopy. Second, we did not observe the formation of either ketone **9** or silyl enol ether **11**. These results imply that the desired intramolecular [1,4]-S- to O-silyl migration of **2a** is faster, as expected, than its collapse to ketone **9**. In addition, the fact that no O-ally-



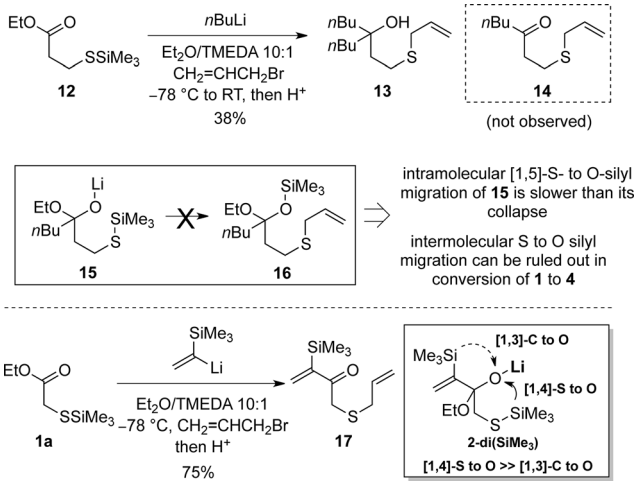
Scheme 2. Cascade transformations of **1a** to functionalized tetrahydrothiophenes **6a**, **6b** and tetrahydrothiophenones **7a**, **7b**.



Scheme 3. Two possible reaction pathways a and b for the formation of **4a** from tetrahedral adduct **2a**.

lation of **2a** was observed also implies that the [1,4]-S- to O-silyl migration is irreversible.

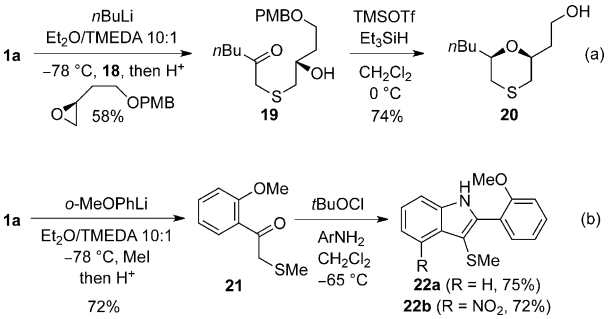
To gain further mechanistic insights into this reaction, we submitted **12** to the optimal reaction conditions. This compound contains one more methylene than **1a** between the ester and thio groups, so we expected it to undergo a long-range [1,5]-S- to O-silyl migration. However, only tertiary alcohol **13** was obtained in 38% yield by over-addition, and no desired β-thioketone **14** was produced (Scheme 4, top).



Scheme 4. Attempts to achieve [1,5]-S- to O-silyl migration of **12** (top) and [1,4]-S- to O-silyl migration/addition of **1a** and allyl bromide with 1-trimethylsilyl vinyllithium (bottom).

This result implies that, due to the longer transfer distance, the intramolecular [1,5]-S- to O-silyl migration of **15** is less favorable than the analogous [1,4]-migration[13] and it proceeds slower than its collapse. The fact that no formation of **14** was observed also excludes the possibility of intermolecular S to O silyl migration between two molecules of **2** in the conversion of **1** into **4**. Reaction of **1a** with 1-trimethylsilyl vinyllithium revealed further details about migration selectivity (Scheme 4, bottom). Even though a [1,3]-C- to O-silyl migration in intermediate **2**-diSiMe$_3$ offered a more favorable transfer distance than [1,4]-S- to O-silyl migration, the [1,4]-migration still appeared to be favored, giving **17** in 75% yield.

The α-thioketones produced by using this method are useful building blocks for the synthesis of organosulfur compounds. For example, reaction of **1a** with chiral epoxide **18** generated α-thioketone **19** in 58% yield, which underwent reductive cyclization to give (*R*,*S*)-*cis*-1,4-oxathiane **20** in 74% yield (Scheme 5a). Recently, 1,4-oxathianes have been reported to be potential muscarinic agonists, with some selectively activating the ileal M3 receptor subtype.[14] Our approach also allowed the transformation of **21**, a substrate for Gassman indolization,[15] into multifunctionalized 2-aryl-3-thioindoles **22a** and **22b** in 75 and 72% yield, respectively (Scheme 5b).



Scheme 5. a) Synthesis of **19** and its reductive cyclization to form *cis*-1,4-oxathiane **20**. b) Synthesis of **21** and its Gassman indolization to form 2-aryl-3-thioindoles **22a** and **22b**.

Conclusion

We have exploited a [1,4]-S- to O-silyl migration to chemoselectively transform esters into ketones by using organolithium reagents. This approach allows efficient multicomponent synthesis of α-thioketones. Mechanistic studies indicate that this migration proceeds in an intramolecular manner and is favored over the corresponding [1,5]-S- to O- and [1,3]-C- to O-silyl migrations. The α-thioketones synthesized in this way are valuable building blocks for the synthesis of cyclic or multifunctionalized organosulfur compounds. Further applications of this methodology are underway.

Experimental Section

Synthesis of trimethylsilyl ethyl thioglycolate (1a): Ethyl 2-mercaptoacetate (3.2 mL, 29.2 mmol) and imidazole (73.4 mg, 1.1 mmol) in hexamethyldisilazane (15.7 mL, 75.0 mmol) were heated at 130 °C for 18 h under an argon atmosphere. After cooling to RT, the excess hexamethyldisilazane was removed by distillation at atmospheric pressure. Compound **1a** (5.04 g, 90 %) was collected by further distillation of the resultant liquid under vacuum (b.p. 52–54 °C; 8 Torr); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.35 (s, 9H; CH_3), 1.28 (t, J = 7.2 Hz, 3H; CH_3), 3.20 (s, 2H; CH_2), 4.17 ppm (q, J = 7.2 Hz, 2H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.6 (CH_3), 14.0 (CH_3), 28.0 (CH_2), 61.3(CH_3), 171.1 ppm (CO); IR (neat): $\tilde{\nu}$ = 2955 (s), 2930 (s), 2854 (s), 1740 (s), 1468 (m), 1399 (w), 1245 (s), 1126 (m), 1095 (m), 939 (w), 805 cm^{-1} (s); HRMS (MALDI): m/z calcd for $C_7H_{17}O_2SSi$: 193.0713 $[M+H]^+$; found: 193.0717.

Synthesis of α-allylthioketone 4a: nBuLi (2.5 M in hexanes, 0.11 mL, 0.29 mmol) was added to a solution of **1a** (50 mg, 0.26 mmol) in anhyd Et_2O (5 mL) and anhyd TMEDA (0.5 mL) at −78 °C under an argon atmosphere. After stirring for 10 min, allyl bromide (44 μL, 0.52 mmol) was added and the resulting solution was warmed to RT with stirring for another 1 h. The reaction was quenched by the addition of H_2O (3 mL) and extracted with Et_2O (2×4 mL). The combined organic phases were stirred with aq. HCl (0.1 N, 2 mL) for 30 min followed by dilution with H_2O (3 mL) and extraction with Et_2O (2×4 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude residue by silica gel flash column chromatography (gradient EtOAc/petroleum ether, 0.2 %) afforded **4a** (35.3 mg, 79 %) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.2 Hz, 3H; CH_3), 1.29–1.35 (m, 2H; CH_2), 1.53–1.59 (m, 2H; CH_2), 2.57 (t, J = 7.2 Hz, 2H; CH_2), 3.10 (d, J = 6.8 Hz, 2H; CH_2), 3.17 (s, 2H; CH_2), 5.13 (d, J = 11.2 Hz, 1H; CH_2), 5.14 (d, J = 16.0 Hz, 1H; CH_2), 5.71 ppm (dddd, J_1 = J_2 = 6.8 Hz, J_3 = 11.2 Hz, J_4 = 16.0 Hz, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH_3), 22.2 (CH_2), 25.9 (CH_2), 34.5 (CH_2), 39.2 (CH_2), 40.4 (CH_2), 118.3 (CH_2), 132.9 (CH), 205.9 ppm (CO); IR (neat): $\tilde{\nu}$ = 2959 (s), 2953 (s), 2870 (m), 1708 (s), 1634 (m), 1580 (s), 1463 (w), 1404 (m), 1372 (m), 1333 (m), 1248 (s), 1152 (w), 1030 (m), 990 (m), 921 cm^{-1} (m); HRMS (MALDI): m/z calcd for $C_9H_{16}OSNa$: 195.0814 $[M+Na]^+$; found: 195.0819.

Synthesis of tetrahydrothiophene 6a: nBuLi (2.5 M in hexanes, 0.11 mL, 0.29 mmol) was added to a solution of **1a** (50 mg, 0.26 mmol) in anhyd Et_2O (5 mL) and anhyd TMEDA (0.5 mL) at −78 °C under argon atmosphere. After stirring for 10 min, methyl crotonate (33 μL, 0.31 mmol) was added and the resulting solution was warmed to RT with stirring for another 24 h. The reaction was quenched by the addition of H_2O (3 mL) and extracted with Et_2O (2×4 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude residue by silica gel flash column chromatography (gradient EtOAc/petroleum ether, 5 %) afforded **6a** (31.4 mg, 52 %) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.2 Hz, 3H; CH_3), 1.28–1.34 (m, 2H; CH_2), 1.34 (d, J = 6.8 Hz, 3H; CH_3), 1.44–1.50 (m, 1H; CH_2), 1.56–1.67 (m, 3H; CH_2), 2.50 (d, J = 10.8 Hz, 1H; CH), 2.89 (d, J = 11.6 Hz, 1H; CH_2), 3.04 (d, J = 11.6 Hz, 1H; CH_2), 3.45 (s, 1H; OH), 3.77 (s, 3H; CH_3), 3.82–3.89 ppm (m, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 19.9 (CH_3), 23.1 (CH_2), 26.4 (CH_2), 39.1 (CH_2), 42.3 (CH_2), 43.7 (CH), 52.2 (CH), 62.9 (CH_3), 84.9 (Cq), 173.6 ppm (CO); IR (neat): $\tilde{\nu}$ = 3500 (br. m), 2957 (s), 2930 (s), 2865 (m), 1737 (s), 1457 (m), 1438 (m), 1358 (m), 1258 (m), 1211 (m), 1166 (m), 1076 (m), 1022 (m), 924 (w), 837 cm^{-1} (w); HRMS (MALDI): m/z calcd for $C_{11}H_{20}O_3SNa$: 255.1025 $[M+Na]^+$; found: 255.1034.

Synthesis of tetrahydrothiophenone 7a: tBuLi (1.3 M in pentane, 0.21 mL, 0.27 mmol) was added to a solution of styrene oxide (32.8 mg, 0.27 mmol) in anhyd Et_2O (5 mL) and anhyd TMEDA (0.5 mL) at −98 °C under an argon atmosphere. After stirring for 5 min, **1a** (40 mg, 0.21 mmol) was added and the mixture was stirred for 10 min before warming to RT for another 30 min. The reaction was quenched by the addition of H_2O (3 mL) and extracted with Et_2O (2×4 mL). The combined organic phases were stirred with aq. HCl (0.1 N, 2 mL) for 30 min followed by dilution with H_2O (3 mL) and extraction with Et_2O (2×4 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude residue by silica gel flash column chromatography (gradient EtOAc/petroleum ether, 5 %) afforded **7a** (23.0 mg, 56 %) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.26 (d, J = 12.0 Hz, 1H; CH_2), 3.38 (d, J = 17.6 Hz, 1H; CH_2), 3.42 (d, J = 12.0 Hz, 1H; CH_2), 3.45 (d, J = 17.6 Hz, 1H; CH_2), 3.69 (s, 1H; OH), 7.35–7.41 (m, 3H; CH), 7.52 ppm (d, J = 7.2 Hz, 2H; CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.6 (CH_2), 37.1 (CH_2), 79.5 (Cq), 125.6 (CH), 128.7 (CH), 138.6 (Cq), 210.1 ppm (CO); IR (neat): $\tilde{\nu}$ = 3445 (br m), 3060 (w), 2924 (w), 2875 (w), 1740 (s), 1494 (m), 1448 (m), 1395 (m), 1350 (m), 1200 (m), 1159 (m), 1066 (s), 1031 (m), 951 (w), 918 (w), 878 (w), 820 cm^{-1} (w); HRMS (MALDI): m/z calcd for $C_{10}H_{10}O_2SK$: 233.0033 $[M+K]^+$; found: 233.0032.

Synthesis of *cis*-1,4-oxathiane 20: TMSOTf (26 μL, 0.13 mmol) was added to a solution of **19** (32 mg, 0.1 mmol) in anhyd CH_2Cl_2 (3 mL) at 0 °C under an argon atmosphere. After stirring for 20 min, Et_3SiH (36 μL, 0.2 mmol) was added and the resulting solution was warmed to RT with stirring for another 1 h. The reaction was quenched by the addition of $NaHCO_3$ (0.5 mL) and extracted with Et_2O (2×4 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude residue by silica gel flash column chromatography (gradient EtOAc/petroleum ether, 10 %) afforded **20** (15.1 mg, 74 %) as a light-yellow oil. $[\alpha]_D^{25}$ = −13.40 (c 0.5 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.4 Hz, 3H; CH_3), 1.29–1.32 (m, 3H; CH_2), 1.42–1.46 (m, 2H; CH_2), 1.52–1.54 (m, 1H; CH_2), 1.64 (s, 1H; OH), 1.69–1.83 (m, 2H; CH_2), 2.27 (t, J = 14.4 Hz, 2H; CH_2), 2.52 (dd, J_1 = 10.8 Hz, J_2 = 13.2 Hz, 1H; CH_2), 2.61 (dd, J_1 = 10.8 Hz, J_2 = 13.2 Hz, 1H; CH_2), 3.60–3.65 (m, 1H; CH), 3.78–3.79 (m, 2H; CH_2), 3.83–3.88 ppm (m, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.5 (CH_2), 27.5 (CH_2), 30.7 (CH_2), 30.8 (CH_2), 36.0 (CH_2), 38.1 (CH_2), 61.0 (CH_2), 79.0 (CH), 79.1 ppm (CH); IR (neat): $\tilde{\nu}$ = 3419 (br m), 2957 (s), 2925 (s), 2858 (m), 1738 (w), 1511 (w), 1461 (m), 1415 (m), 1380 (m), 1332 (m), 1260 (m), 1053 ppm (m); HRMS (MALDI): m/z calcd for $C_{10}H_{21}O_2S$: 205.1257 $[M+H]^+$; found: 205.1248.

Synthesis of 2-aryl-3-thioindole 22a: A solution of tBuOCl (28.8 mg, 0.22 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise to a vigorously stirred solution of aniline (20.5 mg, 0.22 mmol) in CH_2Cl_2 (1.5 mL) at −65 °C under an argon atmosphere. After stirring for 10 min, a solution of **21** (43 mg, 0.22 mmol) in CH_2Cl_2 (0.2 mL) was added and the reaction was kept at the same temperature for 5 h. A solution of Et_3N (22.2 mg, 0.22 mmol) in CH_2Cl_2 (0.2 mL) was then added and the resulting mixture was warmed to RT with stirring for 30 min. The reaction was quenched by the addition of H_2O (1 mL) and the mixture was extracted with CH_2Cl_2 (3×2 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude residue by silica gel flash column chromatography (gradient EtOAc/petroleum ether, 2 %) afforded **22a** (44.3 mg, 75 %) as a white solid. M.p. 141.2–143.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3H; CH_3), 3.91 (s, 3H; CH_3), 7.04 (d, J = 8.0 Hz, 1H; CH), 7.13 (dt, J_1 = 0.8 Hz, J_2 = 8.4 Hz, 1H; CH), 7.19–7.25 (m, 2H; CH), 7.37 (d, J = 8.8 Hz, 1H; CH), 7.40 (d, J = 8.0 Hz, 1H; CH), 7.82 (d, J = 7.6 Hz, 1H; CH), 8.16 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H; CH), 9.19 ppm (s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (CH_3), 55.8 (CH_3), 105.0 (Cq), 111.0 (CH), 111.4 (CH), 119.3 (CH), 120.1 (CH), 120.2 (Cq), 120.9 (CH), 122.6 (CH), 129.6 (CH), 130.1 (Cq), 131.9 (CH), 135.1 (Cq), 136.9 (Cq), 156.5 ppm (Cq); IR (neat): $\tilde{\nu}$ = 3551 (m), 3474 (m), 3412 (s), 2918 (m), 2838 (w), 1899 (w), 1780 (w), 1723 (m), 1638 (m), 1617 (m), 1598 (m), 1578 (m), 1530 (m), 1501 (w), 1473 (m), 1461 (m), 1450 (s), 1433 (s), 1400 (m), 1350 (m), 1324 (m), 1296 (m), 1272 (m), 1244 (s), 1224 (m), 1179 (m), 1163 (m), 1133 (m), 1118 (m), 1048 cm^{-1} (m); HRMS (MALDI): m/z calcd for $C_{16}H_{16}NOS$: 270.0947 $[M+H]^+$; found: 270.0952.

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