A Synthesis of α-Lithiated Enol Ethers from α-Arenesulfinyl Enol Ethers: Ni(0)- and Pd(0)-Catalysed Coupling of Enol Triflates and Phosphates Derived from Lactones with Sodium Arenethiolates Gives α-Arenesulfanyl Enol Ethers

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Abstract: A three-step synthesis of stable and storable α-benzensulfonyl enol ethers from lactones entails (a) conversion of a lactone to an enol triflate or phosphate; (b) Ni(0) and Pd(0) cross-coupling of the enol triflate or phosphate with a sodium arenethiolate to give an α-arenethio enol ether; and (c) oxidation of an arenethio group to a sulfoxide. The α-benzensulfonyl enol ethers undergo sulfoxide–lithium exchange on reaction with n-Bu₃SnLi to give α-lithiated enol ethers thus making the α-benzensulfonyl group a surrogate for the trialkylstannyl group which has hitherto served as the most common precursor to α-lithiated enol ethers.

Key words: coupling, nickel, palladium, catalysis, sulfoxides, enol ether

α-Metallated enol ethers have been known since 1951, but it was not until their potential as acyl anion equivalents was realised by Schöllkopf and Baldwin that serious effort was invested in their synthesis. The conditions defined by Boeckman and Bruza in 1977 are currently regarded as best practice for the direct metallation of enol ethers as exemplified by the metallation of the 3,4-dihydro-2H-pyran 1 (Scheme 1) with t-BuLi in THF at −78 °C. The metallation reaction is sensitive to substitution and quantitative conversion is typically achieved with 2–4 equivalents of t-BuLi in which case heteroatom substituents (for example benzyl ethers and t-BuMe₂Si ethers) may undergo competing metallation. In order to circumvent the complications associated with the presence of excess t-BuLi, the crude α-lithiated enol ethers can be converted to an isolable 6-tributylstannyl-3,4-dihydro-2H-pyran 3 with excess Bu₃SnCl. After chromatographic purification of stannanes 3, the desired lithium derivatives 2 are regenerated by the transmetallation with n-Bu₃Li in THF at −78 °C.

The ease, generality and efficiency of the tin–lithium transmetallation reaction stimulated the development of several alternative syntheses of the stannanes 3 from lactones, thiolactones, sulfone or alkynol precursors. Of these, the methods based on Pd-catalysed coupling of enol triflates and phosphates derived from lactones are the most general and practical because of the ready availability of the starting materials. Nevertheless, serious impediments remain. For example, the Stille-type coupling of enol triflates with Me₃SnSnMe₃ is efficient (Scheme 2), but the tin reagent is very expensive and the reaction fails with 5-membered rings. Worse still, only one of the two trimethylstannyl groups is transferred and the volatile tin byproducts are hazardous. The cheaper and safer Bu₃SnSnBu₃ does not give good yields in the Stille coupling but a Cu-mediated coupling provides an alternative (5 → 7).

Environmentally safer and cheaper substitutes for tin compounds as precursors to α-lithiated enol ethers are desirable. Yu and Lin reported that α-bromo enol ethers derived from addition of HBr to 1-alkoxyalkynes undergo halogen–metal exchange with t-BuLi to give the corresponding α-lithiated enol ethers (Scheme 3). Unfortunately, this procedure cannot be easily adapted to the synthesis of cyclic α-bromo enol ethers, but Milne et al.11 has shown that enol triflates derived from lactones participate in Ni(0)-catalysed coupling with LiBr to give 6-bromo-3,4-dihydro-2H-pyran 12 that are efficiently transformed to the corresponding lithium derivatives 13.
by halogen–metal exchange. However any advantages either of these methods confer is vitiated by the instability of the α-bromo enol ethers.

We recently described a synthesis of D-erythro-sphin-
gosine that featured a very easy sulfoxide–lithium ex-
change on treatment of the α-benzenesulfinyl glycal with t-BuLi (Scheme 4) to give the α-lithiated glycal. Thus the sulfoxide group fulfilled all the requirements of economy, efficiency and safety as a tin substitute since the crystalline sulfoxide precursor was stable at room temperature and the byproduct tert-butyl phenyl sulfoxide was innocuous. In the case at hand, the sulfoxide was prepared by a β-elimination reaction, which is apt in the carbohydrate series, but which would restrict extension to a wider range of substrates.

We now report a 3-step synthesis of stable and storable α-
benzenesulfinyl enol ethers from lactones that entails (a) conversion of a lactone to an enol triflate or phosphate; (b) Ni(0)- or Pd(0)-catalysed cross-coupling of the enol triflate or phosphate with a sodium arenethiolate to give an α-arenesulfanyl enol ether; and (c) oxidation of an arenesulfanyl group to a sulfoxide. We also show that the α-benzenesulfinyl enol ethers react with Na or BuLi to give α-lithiated enol ethers. The sequence is illustrated by the conversion of the tetrahydropyranone to the 2-benzenesulfanyl-3,4-dihydro-2H-pyran (19a) in 86% overall yield after column chromatography. Similar coupling reactions performed on enol triflate with p-thiocreol and 4-methoxybenzenethiol gave the 6-arenesulfanyldihydropyran in 83% and 81% yields, respectively, but the yields of derived from 3,5-dimethylbenzenethiol and benzothiazole-2-thiol were meagre – 39 and 13%, respectively.

Step 3: S-Oxidation: The oxidation of the thioether group in 19a to the corresponding sulfoxide was accomplished by slow addition of unpurified 50% mCPBA in dichloromethane to a stirred solution of the thioether in dichloromethane at –78 °C. In contrast to the acid-sensitive O,S-ketene acetal functionality in 19a, the sulfoxide product (77% yield, dr = 1:1) was stable to silica gel chromatography and could be stored for months at room temperature exposed to air without degradation.
In order to establish the scope of the sequence depicted in Scheme 5, a series of lactones of various ring sizes were examined. Comparable efficiencies were observed with the four tetrahydropyran-2-ones 21, 24, 27 and 30 (Scheme 6) as well as the oxepanones 33 and 36; however, the enol triflate intermediate derived from the α-methyl substituted tetrahydropyran-2-one 39 did not cross-couple with sodium benzenethiolate under Ni(0) catalysis. In the case of oxocyclooctan-2-one (42) or 1-oxacyclo-hexadecan-2-one (45), the requisite enol triflate intermediates could not be generated under our standard conditions – a problem that also thwarted the use of 5-membered lactones. Two modifications to the standard protocol solved some of these problems. In the case of the lactone 39, the coupling reaction occurred on addition of the enol triflate and sodium benzenethiolate to freshly prepared Pd(PPh3)4 (10 mol%) and LiCl (6 equiv) and refluxing the mixture until consumption of the triflate. The desired 6-benzenesulfonyl dicyclopentanone 40 was thereby obtained in 95% yield. In the case of the 8- and 16-membered lactones 42 and 45, the Pd(0)-catalysed variant – but not the Ni(0)-catalysed variant – was successful on the corresponding enol phosphate intermediates generated by the simultaneous addition of the lactones and diphenylphosphoryl chloride to KHMDS in THF at –78 °C. The α-benzenesulfonyl enol ethers 43 and 46 were obtained in 33% and 58% yields, respectively.

In order to make a direct comparison of the relative efficiencies of the Ni(0)- and Pd(0)-catalysed variants, the enol triflate 18 was cross-coupled with sodium benzenethiolate using Pd(PPh3)4 and LiCl in refluxing THF whereupon the α-benzenesulfonyl enol ether 19a was obtained in 64% yield. However, the yield improved to 90% when the Pd(0) catalyst was generated in situ by reduction of PdCl2(PPh3)2 (10 mol%) with excess zinc in THF, thus solving some of these problems. In the case of the 8- and 16-membered lactones 21, 24, 27 and 30, the 6-membered ring lactones 39 were obtained in 95% yield. In the case of the 8- and 16-membered lactones 42 and 45, the Pd(0)-catalysed variant – but not the Ni(0)-catalysed variant – was successful on the corresponding enol phosphate intermediates generated by the simultaneous addition of the lactones and diphenylphosphoryl chloride to KHMDS in THF at –78 °C. The α-benzenesulfonyl enol ethers depicted in Scheme 6 were oxidised to the corresponding sulfoxides using MCPBA and NaHCO3 (60–94% yield). Sulfoxides 20, 26, 29 and 35, underwent sulfoxide–lithium exchange26–28 on treatment with n-BuLi in THF at –78 °C for 30 min to give the α-lithiated enol ethers.29 Quenching the reaction mixture with methanol at –78 °C returned the enol ethers 48–50 and 51 in quantitative yield (Scheme 7). A simple competition experiment was used to establish the relative rates of the sulfoxide–lithium exchange reaction vs the ubiquitous tin–lithium transmetallation. Thus, a mixture of 6-benzenesulfonyl-3,4-dihydro-2H-pyran (52, 0.5 equiv) and 6-tritylstannyl-3,4-dihydro-2H-pyran (53, 0.5 equiv) was treated with 0.25 equivalent of n-BuLi in Et2O at –78 °C and the mixture quenched with water after 1 minute. Integration of the H-5 signals of the remaining 52 and 53 at δ = 5.65 and 4.65, respectively, relative to methyl dodecyl ether as an internal standard showed that nearly all of the n-BuLi had reacted with sulfoxide 52 with the rate of sulfoxide–lithium exchange being 25 times faster than the transmetallation reaction.

A 3-step synthesis of α-benzenesulfonyl cyclic enol ethers from readily available lactones has been developed in two variants which is applicable to 6-, 7-, 8- and 16-membered ring lactones but not for 5-membered ring lactones. The first variant, based on Ni(0)-catalysed coupling of arenethiolates with enol triflates, is similar to the Ni(0)-catalysed cross-coupling of sodium arenethiolates with aryl mesylates previously achieved by Percec and co-workers22 using NiCl2(dppf) (10 mol%), dppf (20 mol%) and zinc (1.0 equiv) in DMF at 80 °C. The second variant, based on Pd(0)-catalysed cross-coupling of arenethiolates with enol phosphates, is suitable for 8- and 16-membered rings. It is similar to the Pd(0)-catalysed cross-coupling of sodium alkanethiolates with aryl triflates previously achieved by Zheng and co-workers30 using Pd(OAc)2 (10 mol%)

Scheme 6 Reagents and conditions: (a) PhN(Tf)2 (1.2 equiv) and KHMDS (1.4 equiv) added to lactone (1.0 equiv) THF, –78 °C; (b) PhSnNa (1.2 equiv), Ni(0) (10 mol%), –78 °C to r.t.; (c) PhOH, POCI (1.2 equiv), KHMDS (1.4 equiv), THF, –78 °C; (d) PhSnNa (1.2 equiv), Pd[PPh3]4 (10 mol%), THF, reflux; (e) MCPBA (1.0 equiv), NaHCO3 (1.4 equiv), CH2Cl2, –78 °C

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mol%) and Tol-BINAP. The higher reactivity of the lactone-derived enol triflates compared with phenol triflates allowed our reactions to be performed faster and at lower temperature in THF as solvent and we did not require the rather expensive dppf or Tol-BINAP bidentate ligands.

Finally, α-benzensulfinyl enol ethers are stable, storable intermediates that undergo easy and efficient reaction with n-BuLi to give α-lithiated enol ethers. Hence the α-benzensulfinyl group provides a cheaper and safer surrogate for the trialkylstannyl group which has hitherto served as the most common precursor to α-metalated enol ethers.

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under dry oxygen-free nitrogen, or high purity argon where stated. Anhyd solvents and reagents were distilled by distillation from the usual drying agent prior to use. All reactions were magnetically stirred unless otherwise stated.

Scheme 7

Lactones 17a and 45 were obtained from Aldrich and distilled before use. The following lactones are known compounds: 24, 26, 27, 29, 30, 33, 38, 36, 39, 40 and 42. Lactone 21 was prepared by the following procedure.

6-(tert-Butyldiphenylsilyloxyethyl)tetrahydropryan-2-one (21)

A mixture of 6-hydroxymethyltetrahydropryan-2-one\(^2\) (0.63 g, 4.9 mmol), imidazole (0.92 g, 13.5 mmol), and tert-butyldiphenylsilyl chloride (1.63 g, 5.9 mmol) in DMF (25 mL) was stirred at r.t. for 3 d. The reaction mixture was poured into H\(_2\)O (250 mL) and extracted with Et\(_2\)O (3 × 100 mL). The Et\(_2\)O extracts were combined, dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The residue (2.94 g) was purified by column chromatography on silica gel eluting with hexanes–Et\(_2\)O (gradient, 2:1 to 1:1) to give the title compound 21 (0.93 g, 58%) as a white crystalline solid; mp 96–98 °C (hexanes–Et\(_2\)O).

IR (KBr): 1732, 1110 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): δ = 8.22–7.87 (4 H, m, ArH), 7.40–7.32 (6 H, m, ArH), 3.92 (1 H, tt, J = 6.9, 4.6 Hz, OCH), 3.68 (1 H, dd, J = 11.2, 4.8 Hz, SiOCH\(_2\)H\(_3\)), 3.65 (1 H, dd, J = 10.8, 4.8 Hz, SiOCH\(_2\)C\(_2\)H\(_5\)), 2.91 (2 H, m, CH\(_2\)C=O), 1.26–1.04 (4 H, m), 1.02 (12 H, s, t-C\(_3\)H\(_9\)).

\(^13\)C NMR (100 MHz, C\(_6\)D\(_6\)): δ = 196.6 (C), 136.5 (4 CH), 134.0 (2 C), 130.5 (4 CH), 128.6 (2 CH), 79.8 (CH), 66.6 (CH\(_2\)), 30.2 (CH\(_2\)).

J = 27.4 (3 CH\(_2\)), 24.6 (CH\(_2\)), 19.8 (C), 18.7 (CH\(_3\)).

HRMS (CI mode, NH\(_3\)): m/z (%) = 386.2 [(M + NH\(_4\)]\(^+\), 100), 308 (9), 291 (33).

Anal. Calcd for C\(_{22}\)H\(_{28}\)O\(_3\)Si: C, 71.70; H, 7.66. Found: C, 71.82; H, 7.48.

6-Benzenesulfinyl-2-heptyl-3,4-dihydro-2H-pyran (19a); Procedure A Illustrating a Ni(0)-Catalysed Cross-Coupling of a Sodium Arenethiolate with an Enol Triflate

**Flask 1. Preparation of the Enol Triflate**

A solution of KH\(_2\)MS (0.38 M in toluene, 3.7 mL, 1.4 equiv) in THF (3.4 mL) was cooled to −78 °C. A mixture of N-phenyltrifluoromethanesulfonimide (0.43 g, 1.2 mmol, 1.2 equiv) and lactone 17 (0.198 g, 1 mmol, 1 equiv) in THF (5 mL) was added over a period of 1 h. After addition was complete, the reaction mixture was allowed to stir for 15 min at −78 °C.

**Flask 2. Preparation of Sodium Benzenethiolate**

Benzenethiol (0.13 g, 0.12 mL, 1.2 mmol, 1.2 equiv) was added to a suspension of NaH (50% in oil, 0.096 g, 2 mmol, 2 equiv) in THF (1 mL) at r.t., stirred for 15 min, and cooled to −78 °C.

**Flask 3. Preparation of the Ni(0) Catalyst**

To a solid mixture of nickel(0) catalyst \[Ni(C\(_3\)P\(_3\))\(_2\)Br\(_2\)] (0.074 g, 0.1 mmol, 10 mol%) and zinc powder (0.039 g, 0.6 mmol, 60 mol%) in THF (5 mL) was added over a period of 1 h. After addition was complete, the reaction mixture was stirred for 15 min at −78 °C. The residual signals of CH\(_2\)Cl\(_2\) (δ = 7.27, δ\(_C\) = 77.2) or C\(_6\)H\(_6\) (δ\(_C\) = 7.16, δ\(_C\) = 126.7) as the internal standard, unless otherwise specified. Coupling constants (J) are reported in Hz. A H NMR spectra refer to the number of protons attached to carbon as revealed by the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Signal assignments were based on COSY, HMOC and HMBC correlations. Ion mass/charge (m/z) ratios are reported as values in atomic mass units followed, in parenthesis, by the peak intensity relative to the base peak (100%). Mass spectra were recorded on samples judged to be ≥95% pure by \(^1\)H and \(^13\)C NMR spectroscopy.

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2-Heptyl-6-p-tolylsulfonyl-3,4-dihydro-2H-pyran (19b)
Colourless oil by Procedure A (83%).

IR (film): 1628 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\); \(\delta\) = 7.45 (2 H, d, \(J = 7.9\) Hz), 6.90 (2 H, d, \(J = 8.4\) Hz), 5.32–5.27 (1 H, m, C=C\(\cdot\)H), 3.68–3.58 (1 H, m, OCH), 2.03 (3 H, s, ArCH\(_3\)), 1.97–1.72 (2 H, m), 1.60–1.02 (14 H, m), 0.91 (3 H, t, \(J = 6.9\) Hz, CH\(_3\)).

\(^13\)C NMR (75 MHz, CD\(_2\)Cl\(_2\); \(\delta\) = 148.8 (C), 136.9 (C), 132.0 (C), 131.2 (2 CH), 130.2 (2 CH), 106.8 (CH), 78.4 (CH), 35.6 (CH\(_2\)), 32.6 (CH\(_2\)), 30.2 (CH\(_3\)), 30.0 (CH\(_2\)), 27.8 (CH\(_2\)), 26.0 (CH\(_2\)), 23.5 (CH\(_2\)), 22.8 (CH\(_3\)), 21.3 (CH\(_3\)), 14.7 (CH\(_3\)).

LRMS (ES\(^{+}\) mode): \(m/z\) = 305.2 (M\(^+\) + H).

HRMS (ES\(^{+}\) mode): \(m/z\) calcld for C\(_{19}\)H\(_{28}\)O\(_2\)S: C, 71.2; H, 8.81. Found: C, 71.2; H, 8.9.

Anal. Calcd for C\(_{19}\)H\(_{28}\)O\(_2\)S: C, 71.20; H, 8.81. Found: C, 71.2; H, 8.9.

6-Benzensulfanyl-2-(3-phenyl-1-propyl)-3,4-dihydro-2H-pyran (25)
Colourless oil by Procedure A (87%).

IR (film): 1628 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\); \(\delta\) = 7.76–7.71 (4 H, m), 7.49–7.45 (2 H, m), 7.24–7.18 (6 H, m), 7.07–7.00 (2 H, m), 6.94–6.88 (1 H, m), 5.30 (1 H, ddd, \(J = 4.6, 2.8, 0.8\) Hz), 3.63 (2 H, dd, \(J = 4.9, 3.1\) Hz, CH\(_2\)OSi), 1.85–1.65 (2 H, m, CH\(_2\)(CH\(_3\))), 1.51–1.36 (2 H, m), 1.11 (9 H, s, t-C\(_{2}\)H\(_5\)).

\(^13\)C NMR (75 MHz, CD\(_2\)Cl\(_2\); \(\delta\) = 147.6 (C), 136.4 (CH), 136.0 (C), 134.1 (2 C), 130.3 (2 CH), 129.5 (2 CH), 128.4 (4 CH) 126.7 (CH), 109.0 (CH), 78.9 (CH), 66.5 (CH\(_3\)), 27.3 (CH\(_2\)), 23.8 (CH\(_2\)), 22.4 (CH\(_3\)), 19.7 (C).

LRMS (ES\(^{+}\) mode): \(m/z\) = 483.1 (M\(^+\) + Na).

Anal. Calcd for C\(_{23}\)H\(_{29}\)O\(_3\)S: C, 73.00; H, 7.00. Found: C, 73.0; H, 7.15.

6-Benzenesulfanyl-2-(3-methoxyphenyl)-3,4-dihydro-2H-pyran (28)
White amorphous solid by Procedure A (85%); mp 66–67 °C (hexanes).

IR (film): 1630 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\); \(\delta\) = 7.53–7.49 (2 H, m), 7.10–6.90 (6 H, m), 5.29 (1 H, t, \(J = 3.6\) Hz, H\(_2\)C\(_{2}\)), 3.58–3.47 (1 H, m, OCH), 2.32 (2 H, t, \(J = 7.2\) Hz, CH\(_2\)Ph), 1.88–1.15 (8 H, m).

\(^13\)C NMR (75 MHz, CD\(_2\)Cl\(_2\); \(\delta\) = 147.8 (C), 142.8 (C), 135.8 (C), 130.1 (2 CH), 129.3 (2 CH), 129.0 (2 CH), 128.8 (2 CH), 126.9 (CH), 126.3 (CH), 108.1 (CH), 78.3 (CH), 36.1 (CH\(_2\)), 34.8 (CH\(_2\)), 27.5 (2 CH\(_2\)), 22.7 (CH\(_3\)).

LRMS (ES\(^{+}\) mode): \(m/z\) = 311.2 (M\(^+\) + H).

HRMS (ES\(^{+}\) mode): \(m/z\) calcld for C\(_{22}\)H\(_{23}\)O\(_3\)SNa: 333.1289; found: 333.1277.

6-Benzenesulfanyl-2-(3-methoxyphenyl)-3,4-dihydro-2H-pyran (28)
White amorphous solid by Procedure A (85%); mp 66–67 °C (hexanes).

IR (film): 1630 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\); \(\delta\) = 7.53–7.49 (2 H, m), 7.06–6.96 (3 H, m), 6.92–6.86 (2 H, m), 6.79 (1 H, d, \(J = 7.4\) Hz), 6.69 (1 H, ddd, \(J = 8.2, 2.6, 0.8\) Hz), 5.35 (1 H, dd, \(J = 4.6, 3.1\) Hz, H\(_2\)C\(_{2}\)), 4.64 (1 H, t, \(J = 6.3\) Hz, OCH), 3.26 (3 H, s, OCH\(_3\)), 1.96–1.82 (1 H, m), 1.78–1.62 (3 H, m).

\(^13\)C NMR (75 MHz, CD\(_2\)Cl\(_2\); \(\delta\) = 160.6 (C), 148.1 (C), 143.5 (C), 130.3 (2 CH), 129.9 (CH), 129.4 (2 CH), 127.0 (CH), 118.7 (CH), 114.0 (CH), 112.0 (CH), 108.7 (CH), 79.8 (CH), 55.0 (CH\(_2\)), 30.0 (CH\(_3\)), 23.0 (CH\(_3\)).

LRMS (ES\(^{+}\) mode): \(m/z\) = 321.0 (M\(^+\) + Na).

Anal. Calcd for C\(_{23}\)H\(_{23}\)O\(_3\)S: C, 72.45; H, 6.08. Found: C, 72.2; H, 6.0.
6-Benzoylphenyl-2,4-dimethyl-3,4-dihydro-2H-pyran (31)

Colourless oil by Procedure A (85%).

IR (film): 1622 cm⁻¹.

1H NMR (300 MHz, CDCl₃): 8 = 7.50–7.46 (2 H, m), 7.09–7.02 (2 H, m), 6.96–6.90 (1 H, m), 5.22 (1 H, t, J = 1.8 Hz, CH₃C=), 3.70 (1 H, d.q, J = 11.0, 6.3, 1.7 Hz, OCH), 2.13 (1 H, d, J = 17.8, 2.1 Hz, C=CH₂), 1.27 (1 H, dd, J = 13.4, 6.4 Hz, CH₂), 0.99 (3 H, d, J = 6.9 Hz, CH₃), 0.97–0.90 (1 H, m, CH₄), 0.76 (3 H, d, J = 6.9 Hz, CH₃ClH).

13C NMR (75 MHz, CDCl₃): 8 = 147.2 (C), 136.0 (C), 129.7 (2 CH), 129.4 (2 CH), 126.8 (CH), 114.9 (CH), 75.0 (CH), 38.9 (CH₂), 29.7 (CH₂), 21.4 (CH₃), 21.3 (CH₃).

LRMS (ES⁺ mode): m/z = 221 (M⁺ + H).


6-Benzoylphenyl-2-hexyl-3,4-dihydro-2H-pyran (19a) and 8-Phenylsulfonyl-3,4,5,6-tetrahydro-2H-oxocine (43); Procedure B Illustrating a Pd(0)-Catalysed Cross-Coupling of a Sodium Arenethiolate with an Enol Phosphate

Flask 1. Preparation of the Enol Phosphate: A solution of KHMDS (0.38 M in toluene, 3.7 mL, 1.4 equiv) in THF (3.4 mL) was cooled to –78 °C. A mixture of diphenylphosphoryl chloride (0.25 mL, 1.2 mmol, 1.2 equiv) and lactone 17 (0.198 g, 1 mmol, 1 equiv) in THF (5 mL) was added over a period of 1 h. The mixture was allowed to stir for 15 min at –78 °C.

Flask 2. Preparation of Sodium Benzenethiolate: In a second flask benzenethiol (0.13 g, 0.12 mL, 1.2 mmol, 1.2 equiv) was added to a suspension of NaH (50% in oil, 0.096 g, 2 mmol, 2 equiv) in THF (1 mL) at rt., stirred for 15 min and cooled to –78 °C.

The contents of flask 1 (the enol phosphate) was transferred to cannula to flask 2 (the sodium benzenethiolate) at –78 °C. LiCl (0.26 g, 6 mmol, 6 equiv) was added. The mixture was allowed to stir for 15 min and then refluxed until no trace of starting material remained by TLC. NaOH (5%, 30 mL) was added and the mixture was cooled to rt. The residue was purified by column chromatography on alumina (deactivated with 5% H₂O) eluting with hexanes containing 0.5% of Et₃N to give the title compound 19a (186 mg, 64%) as a colourless oil.

1H NMR (300 MHz, CDCl₃): 8 = 7.46–7.42 (2 H, m), 7.06–7.01 (2 H, m), 6.93 (1 H, m, 5.29 (1 H, d, J = 4.6, 3.1 Hz), 1.0 Hz, HC=CH₂), 3.65–3.56 (1 H, m, HCHO), 1.93–1.70 (2 H, m), 1.56–1.00 (14 H, m), 0.89 (3 H, t, J = 7.0 Hz).

13C NMR (75 MHz, CDCl₃): 8 = 147.9 (C), 135.9 (C), 130.1 (2 CH), 129.3 (2 CH), 126.8 (CH), 108.0 (CH), 78.4 (CH), 35.5 (CH₂), 32.5 (CH₃), 30.1 (CH₃), 29.9 (CH₂), 27.6 (CH₂), 25.8 (CH₂), 23.4 (CH₃), 22.7 (CH₂), 14.7 (CH₃).


Anal. Calcd for C₁₃H₁₇O₃S: C, 74.43; H, 9.02. Found: C, 74.3; H, 8.95.

43 Colourless oil by Procedure B (33%).

IR (film): 1630 cm⁻¹.

1H NMR (300 MHz, CDCl₃): 8 = 7.65–7.59 (2 H, m), 7.18–7.10 (2 H, m), 7.06–6.98 (1 H, m), 5.80 (1 H, t, J = 7.0 Hz, C=CH₂), 3.92–3.84 (2 H, m, OCH₂), 2.22–2.12 (2 H, m, CH₂C=CH₂), 1.58–1.44 (6 H, br. s).

13C NMR (75 MHz, CDCl₃): 8 = 147.6 (C), 135.4 (C), 130.3 (2 CH), 129.4 (2 CH), 126.8 (CH), 126.4 (CH), 71.5 (CH₂), 29.2 (CH₂), 27.9 (CH₂), 27.3 (CH₂), 26.9 (CH₃).

LRMS (El⁺ mode): m/z = 220.3 (M⁺, 10%), 111.1 (37), 83.2 (32), 69.1 (16), 55.1 (100).

HRMS (ES⁺ mode): m/z = calc'd for C₈₁H₂₁O⁰₃S, 221.1000; found, 221.1009.
6-Benzensulfinyl-1-2-prop-2-aryl-3,4-dihydro-2H-pyran (40); Procedure C Illustrating a Pd(0)-Catalysed Cross-Coupling of a Sodium Arenethiolate with an Enol Triflate

The enol triflate was prepared from lactone (154 mg, 1.00 mmol) in CH2Cl2 (2 mL). The reaction vessel was removed from the cooling bath and allowed to warm to r.t. The mixture was refluxed until no trace of starting material remained by TLC. NaOH (5%, 30 mL) was added and the mixture extracted with Et2O. The combined organic layers were dried (Na2SO4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel or alumina (deactivated with 5% H2O) eluting with hexanes–Et2O (0.5% of Et3N) gradient (4:1 to 1:1) to give the thioether (0.234 g, 95%) as a colourless oil.

Anal. Calcd for C18H26O2S: C, 70.54; H, 8.55. Found: C, 70.25; H, 8.6.

6-Benzensulfinyl-1-2-butyldiphenylsilyloxy-3,4-dihydro-2H-pyran (23)

Oxidation of the thioether (22) (0.64 mmol) gave sulfoxide (23) (0.204 g, 0.43 mmol, 67%) as a colourless oil. In another experiment, oxidation of the thioether (22) (0.45 mmol) gave sulfoxide (23) as a mixture of diastereoisomers (dr = 1:1, 0.124 g, 0.26 mmol) together with recovered thioether (22) (0.069 g). The yield of (23) based on recovered starting material was 91%.

IR (film): 1653, 1053 cm−1.

1H NMR (300 MHz, CDCl3): δ = 7.72–7.67 (2 H, m), 7.64–7.56 (4 H, m), 7.47–7.33 (9 H, m), 5.72 (1 H, dd, J = 7.6, 4.0 Hz, H2C=O), 4.06–3.91 (1 H, m, HCO), 3.69 (0.5 H, 2H, dd, J = 4.7, 1.9 Hz, CH2OSi) and 3.63 (0.5 H, 2H, dd, J = 5.1, 2.3 Hz, CH2OSi), 2.35–2.14 (2 H, m, CH2), 1.94–1.67 (2 H, m, CH2), 1.00 (0.5 × 9 H, s, t-C6H13) and 0.99 (0.5 × 9 H, s, t-C6H13).

13C NMR (75 MHz, CDCl3): δ = 156.2 and 155.9 (C), 142.8 and 142.7 (C), 136.0 (4 CH), 133.7 and 133.5 (2 C), 131.6 and 131.3 (CH), 130.2 (2 CH), 129.4 (CH), 126.1 (4 CH), 125.8 and 125.2 (2 CH), 104.0 and 103.9 (CH), 79.0 (CH), 65.6 and 65.4 (CH2), 27.2 (CH3), 24.0 and 23.9 (CH3), 20.7 and 20.6 (CH2), 19.6 (C).

LRMS (ES+ mode): m/z = 499 (M+ + Na).

Anal. Calcd for C20H22O2S: C, 72.85; H, 7.0. Found: C, 72.5; H, 7.0.

6-Benzensulfinyl-1-(3-phenylpropyl)-3,4-dihydro-2H-pyran (26)

Oxidation of the thioether (25) (0.37 mmol) gave sulfoxide (26) (mixture of diastereoisomers, dr = 1:1, 0.086 g, 70%) as a colourless oil.

IR (film): 1653, 1050 cm−1.

1H NMR (300 MHz, CDCl3): δ = 7.71–7.64 (2 H, m), 7.48–7.41 (3 H, m), 7.30–7.23 (2 H, m), 7.21–7.14 (1 H, m), 7.10–7.04 (2 H, m), 5.71–5.65 (1 H, m, J = 3.87–3.77 (1 H, m), 2.53–2.43 (2 H, m, CH2Ar), 2.25–2.15 (2 H, m, CH2=CH2), 1.87–1.74 (1 H, m, CH=CH), 1.65–1.35 (5 H, m).

13C NMR (75 MHz, CDCl3): δ = 155.6 and 155.5 (C), 142.4 and 142.2 (C), 142.0 and 142.0 (C), 131.0 and 130.9 (CH), 128.8 (2 CH), 128.3 (2 CH), 128.3 (2 CH), 125.8 (CH2), 125.2 and 124.9 (2 CH), 104.1 and 103.7 (CH), 78.4 and 78.2 (CH2), 35.4 and 35.4 (CH3), 33.7 and 33.6 (CH3), 27.0 and 26.9 (CH3), 26.6 and 26.5 (CH2), 20.4 (CH3).

LRMS (ES+ mode): m/z = 430.2 (M+ + Na).

Anal. Calcd for C22H22O2S2: C, 73.58; H, 6.79. Found: C, 73.65; H, 7.05.

6-Benzensulfinyl-1-(3-phenylpropyl)-3,4-dihydro-2H-pyran (29)

Oxidation of the thioether (28) (0.72 mmol) gave sulfoxide (29) (mixture of diastereoisomers, dr = 1:1:0.172 g, 76%) as a colourless oil.

IR (film): 1639, 1603, 1049 cm−1.

1H NMR (300 MHz, CDCl3): δ = 7.79–7.69 (2 H, m), 7.54–7.46 (3 H, m), 7.18 (1 H, d, J = 8.0, 2.8 Hz), 6.79 (1 H, dd, J = 8.5 Hz), 6.69–6.60 (2 H, m), 5.82–5.77 (1 H, m, C=CH2), 4.93 (0.5 H, dd, J = 9.6, 2.4 Hz, OCH2), 4.83 (0.5 H, dd, J = 10.2, 2.3 Hz, OCH2), 3.72 (0.5 × 3 H, s, OCH3), 3.71 (0.5 × 3 H, s, OCH3), 2.46–2.14 (2 H, m, CH2), 2.12–2.00 (1 H, m, CH=CH), 1.95–1.75 (1 H, m, CH=CH).

13C NMR (75 MHz, CDCl3): δ = 159.6 and 159.6 (C), 156.0 and 155.6 (C), 142.3 and 142.2 (C), 142.0 (C), 131.2 and 131.0 (CH), 129.4 (CH), 129.0 and 128.9 (2 CH), 125.4 and 124.9 (2 CH), 117.9 and 117.7 (CH), 113.5 and 113.4 (CH), 111.1 and 110.8 (CH),
2.87–2.76 (0.5 H, m), 2.69–2.42 (2 H, m)

\[ \text{HRMS (ES}^+\text{ mode): } m/z = 315.1 (M}^+ + H) \]


6-Benzonesulfinyl-2,4-dimethyl-3,4-dihydro-2H-pyran (32)

Oxidation of the thioether 31 (0.84 mmol) gave sulfoxide 32 (mixture of diastereoisomers, \( d_r = 1:1, 0.095 \text{ g}, 48\% \text{ along with } 0.048 \text{ g} \) of recovered starting material. The yield based on recovered starting material was 74%.

IR (film): 1644, 1583 cm⁻¹.

1H NMR (300 MHz, CDCl₃): \( \delta = 7.72–7.64 (2 \text{ H, m}), 7.52–7.44 (3 \text{ H, m}), 5.52 (1 \text{ H, apparent d, } J = 1.8 \text{ Hz, HCO}), 2.59–2.42 (1 \text{ H, m, C}=CH), 1.92–1.82 (1 \text{ H, m, CH₃}), 1.24–1.15 (1 \text{ H, m, CHH}), 1.22 (0.5 \times 3 \text{ H, d, } J = 5.8 \text{ Hz, CH₃}), 1.19 (0.5 \times 3 \text{ H, d, } J = 5.8 \text{ Hz, CH₃}), 1.07 (0.5 \times 3 \text{ H, d, } J = 3.0 \text{ Hz, CH₃}), 1.05 (0.5 \times 3 \text{ H, d, } J = 3.0 \text{ Hz, CH₃}). \]

13C NMR (75 MHz, CDCl₃): \( \delta = 133.7 \text{ (C)}, 131.9 \text{ (CH)}, 130.1 \text{ (CH)}, 129.5 \text{ (2 CH)}, 127.7 \text{ (CH)}, 126.3 \text{ (2 CH)}, 125.6 \text{ (CH)}, 119.8 \text{ (CH)}, 112.0 \text{ (CH)}, 30.5 \text{ (CH₂)}, 27.9 \text{ (CH)}. \]

LRMS (ES⁺ mode): \( m/z = 240.1 \text{ (M}^+ + H) \)


Oxidation of the thioether 34 (0.56 mmol) gave sulfoxide 35 (mixture of diastereoisomers, \( d_r = 1:1, 94\% \) as a colourless oil.

IR (film): 1658, 1053 cm⁻¹.

1H NMR (300 MHz, CDCl₃): \( \delta = 7.77–7.69 (2 \text{ H, m}), 7.54–7.48 (3 \text{ H, m}), 7.33–7.26 (2 \text{ H, m}), 7.24–7.14 (3 \text{ H, m}), 6.60 (1 \text{ H, dd}, J = 8.3, 3.8, 1.4 \text{ Hz, C}=CH), 4.24 (0.5 \text{ H, d}, J = 11.8, 8.8, 3.1 \text{ Hz, OCHH}), 4.17 (0.5 \text{ H, d}, J = 11.8, 5.4, 3.8 \text{ Hz, OCHH}), 3.74–3.64 (0.5 \text{ H, m, OCHH}), 3.30 (0.5 \text{ H, d}, J = 12.1, 9.8, 2.3 \text{ Hz, OCHH}), 2.87–2.76 (0.5 \text{ H, m}), 2.69–2.42 (2 \text{ H, m, CH₂}), 2.17–1.95 (2 \text{ H, m}). \]

13C NMR (75 MHz, CDCl₃): \( \delta = 215.4 \text{ (C)}, 142.0 \text{ (C)}, 131.0 \text{ (CH)}, 129.0 \text{ (2 CH)}, 125.2 \text{ (2 CH)}, 122.0 \text{ (CH)}, 76.7 \text{ (CH₂)}, 26.3 \text{ (CH₂)}, 26.0 \text{ (CH), 25.2(CH₂).} \]

HRMS (ES⁺ mode): \( m/z = 237.2 (M}^+ + H) \)


2-Benzonesulfinyl-4-phenyl-2,3,4,5-tetrahydrooxepine (35)

Oxidation of the thioether 34 (0.56 mmol) gave sulfoxide 35 (mixture of diastereoisomers, \( d_r = 1:1, 94\% \) as a colourless oil.

IR (film): 1665, 1054 cm⁻¹.

1H NMR (300 MHz, CDCl₃): \( \delta = 7.73–7.67 (2 \text{ H, m}), 7.52–7.46 (3 \text{ H, m}), 6.21 (1 \text{ H, t, } J = 6.1 \text{ Hz, CH₃}), 4.00–3.93 (2 \text{ H, dd, } J = 5.9, 3.6 \text{ Hz, OCH₃}), 2.33–2.25 (2 \text{ H, dd, } J = 11.8, 6.2 \text{ Hz, CH₂=C}, 1.84–1.60 (6 \text{ H, m}). \]

13C NMR (75 MHz, CDCl₃): \( \delta = 154.8 \text{ (CH)}, 142.5 \text{ (C), 131.1 (CH), 129.0 (2 CH), 125.2 (2 CH), 122.0 (CH), 76.7 (CH₂), 26.3 (CH₂), 26.0 (CH), 25.2(Ch).} \]

HRMS (ES⁺ mode): \( m/z = 237.2 (M}^+ + H) \)


2-Benzonesulfinyl-1-oxacyclohexadec-2-en (47)

Oxidation of the thioether 46 (0.28 mmol) gave sulfoxide 47 (0.085 g, 88%) as a colourless oil.

IR (film): 1652, 1637, 1050 cm⁻¹.

1H NMR (300 MHz, CDCl₃): \( \delta = 7.71–7.63 (2 \text{ H, m}), 7.54–7.44 (3 \text{ H, m}), 5.90 (1 \text{ H, t, } J = 7.9 \text{ Hz, CH₃}), 4.01–3.84 (2 \text{ H, m, OCH₂}), 2.26–2.14 (2 \text{ H, m, CH₃=CCH₃}), 1.63–1.99 (22 \text{ H, m}). \]

13C NMR (75 MHz, CDCl₃): \( \delta = 156.8 \text{ (C), 142.6 (C), 130.9 (CH), 129.0 (2 CH), 125.1 (2 CH), 121.3 (CH), 74.8 (CH₂), 29.7 (CH₂), 28.7 (CH₂), 27.6 (CH₂), 27.5 (CH₂), 26.7 (CH₂), 26.5 (CH₂), 26.1 (CH₂), 26.0 (CH₂), 25.4 (CH₂), 25.9 (CH), 24.0 (CH₀).} \]

The geometry of the alkene was determined by NOESY and NOE experiments.

LRMS (ES⁺ mode): \( m/z = 349.2 (M}^+ + H) \)


6-Heptyl-3,4-dihydro-2H-pyran (41)

Oxidation of the thioether 40 (0.30 mmol) gave sulfoxide 41 (mixture of diastereoisomers, \( d_r = 1:1, 0.055 \text{ g, 70}\% \) as a white solid with broad and variable mp. 6-Heptyl-3,4-dihydro-2H-pyran (41)

Synthesis of α-Lithiated Enol Ethers

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the combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified by column chromatography on alumina (deactivated with 5% H$_2$O) eluting with hexanes containing 0.5% of Et$_3$N to give the dihydropyran 48 (0.030 g, ca. 100%) as a colourless oil. The $^1$H and $^{13}$C NMR spectra were identical to those reported previously.\textsuperscript{22}

### 4-Phenyl-2,3,4,5-tetrahydrooxepine (51)

Sulfoxide–lithium exchange performed on sulfoxide 35 as described above gave the title compound 51 in ca. 100% yield.

IR (film): 1649 cm\(^{-1}\).

$^1$H NMR (300 MHz, C$_6$D$_6$): $\delta$ = 7.18–7.11 (2 H, m), 7.10–7.03 (1 H, m), 7.00–6.95 (2 H, m), 6.44 (1 H, dd, $J = 7.0$, 2.7 Hz, OCH$_3$), 4.61 (1 H, ddd, $J = 8.2$, 7.1, 2.9 Hz), 4.05 (1 H, ddd, $J = 12.2$, 7.4, 2.9 Hz), 3.52 (1 H, ddd, $J = 12.0$, 7.7, 3.1 Hz), 2.71 (1 H, tt, $J = 11.4$, 3.5 Hz). 2.36 (1 H, ddt, $J = 15.9$, 11.8, 2.8 Hz), 2.04 (1 H, dddd, 15.9, 8.2, 3.1, 1.8 Hz), 1.93–1.81 (1 H, m), 1.78–1.64 (1 H, m).

$^{13}$C NMR (75 MHz, C$_6$D$_6$): $\delta$ = 149.2 (CH), 147.7 (C), 129.0 (2 CH), 127.3 (2 CH), 126.7 (CH), 107.7 (CH), 71.3 (CH$_2$), 45.1 (CH), 39.9 (CH$_2$), 34.6 (CH$_2$).

HRMS (EI$^+$ mode): $m/z$ (%) = 175.3 (M$^+$ + H, 5%), 97.2 (M$^+$ – C$_6$H$_5$, 30).

HRMS (EI$^+$ mode): $m/z$ calcd for C$_{12}$H$_{14}$O, 174.1045; found, 174.1048.

Anal. Calcd for C$_{12}$H$_{14}$O: C, 82.72; H, 8.10. Found: C, 82.3; H, 8.35.

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### References

32. Sulfoxide–lithium exchange processes have recently been used to prepare glycosylolithiums: Carpintero, M.; Gómez, A. M.; López, J. C.; Valverde, S. Synlett 1996, 628.
33. For the generation of α-halo carbanions from aryl α-haloalkyl sulfoxides and aryl α-haloalkenyl sulfoxides by sulfoxide–metal exchange, see: Satoh, T.; Takano, K. Tetrahedron 1996, 52, 2349.
34. Lipton, M. F.; Sorenson, C. M.; Sadler, A. C.; Shapiro, R. H. J. Organometal. Chem. 1980, 186, 155.