1,4-Bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines in Synthesis. Highly Regio- and Stereoselective S_N1' and Alkylation Reactions

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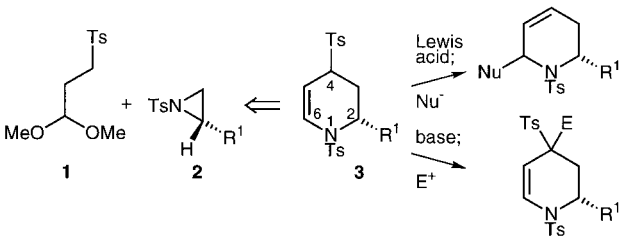
Abstract: Reaction of lithiated β-sulfonyl acetals with amino acid-derived *N*-tosylaziridines followed by acid-catalysed cyclisation gives enantiomerically pure 2-alkyl 1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines **3** in good yields. These heterocyclic substrates react efficiently and highly stereoselectively with a range of carbon nucleophiles under Lewis acidic conditions to give the 1,2,5,6-tetrahydropyridine products of S_N1' reaction, and undergo lithiation followed by completely stereoselective reaction at the 4-position with haloalkanes.

As part of our ongoing programme investigating the utility of sulfone-containing intermediates in heterocyclic synthesis,[1] we have been looking at the synthesis and reactions of 1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines **3**. It occurred to us that these would serve as useful, stereodefined templates for C–C bond forming reactions on account of the diverse reactivity of the sulfonyl group. Specifically, we envisaged two main types of reactivity. Firstly, it was anticipated that **3** would undergo ionisation on treatment with Lewis acids, giving conjugated iminium species which would react with carbon nucleophiles.[2] Secondly, we considered that lithiation and alkylation would take place at the 4-position[3] to give more substituted analogues of **3**. We reasoned that **3** would be readily available in enantiomerically pure form from the simple sulfonylacetal **1** and *N*-tosylaziridines **2** (Scheme 1).



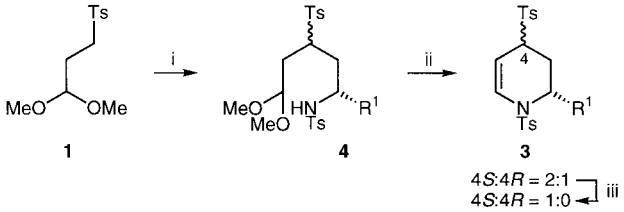
Scheme 1

Compound **1** was easily made according to the literature procedure,[4] or by a three-step sequence from acrolein and thiocresol.[5] Lithiation of **1** and reaction with **2**[6] gave the expected adducts **4** as diastereomeric mixtures. These were converted into **3** upon treatment with TMSI in MeCN (method A), or by brief exposure to a catalytic amount of concentrated sulfuric acid in CH_2Cl_2 (method B), although the former method generally gave higher yields. Tetrahydropyridines **3** prepared in this way were isolated typically as ca. 2:1 mixtures of 4*S* and 4*R* diastereomers; treatment with potassium *tert*-butoxide in *t*-BuOH–THF effected complete, quantitative conversion into the 4*S* compounds.[7] The syntheses of **3** are shown in Scheme 2 and Table 1.

We initially investigated reactions of **3** with Lewis acidic organometallic reagents possessing nucleophilic alkyl groups. Treatment of toluene solutions of **3** with trimethylaluminium at room temperature over 0.5-2 h gave in mostly excellent yields the products **5a-d** of S_N' reactions as single diastereomers. The 2,6-syn nature of these products was unambiguously established by n.O.e. studies,[8] and by X-ray crystallographic analysis;[9] Figure 1 shows the structure of **5b**.

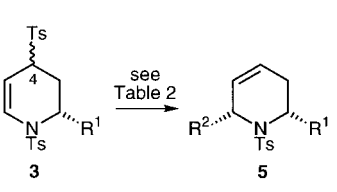
Table 1. Synthesis of tetrahydropyridines **3**

Entry	R^1	% yield of 4	% yield of 3	method
a	CH_2Ph	93	90	A
b	*i*-Pr	85	74	A
c	*i*-Bu	80	78	A
d	$CH_2OTBDPS$	74	50	A



Scheme 2. (i) *n*-BuLi (1.1 eq), THF–TMEDA (4:1, 0,2M), -78°C, add **2** (1 eq), -78°C→rt, then AcOH–THF (1 eq); (ii) TMSCl (6 eq), MeCN (0.1M), rt, 20 min (method A), or conc. H_2SO_4 (cat.), CH_2Cl_2 (0.2M), rt, 15 min (method B); (iii) **t**-BuOK (0.1 eq), *t*-BuOH (10 eq), THF

Reaction of **3** with diethylaluminium chloride similarly gave the ethyl analogues **5e-h** as single, syn diastereomers. Allylation could be effected by addition of $SnCl_4$ to dichloromethane solutions of **3** and allyltrimethylsilane at low temperature,[10] and a single example of an aldol-like transformation was carried out using the *tert*-butyldimethylsilyl (TBS) enol ether derived from pinacolone as the nucleophile in conjunction with $SnCl_4$, in a fashion analogous to the allyltrimethylsilane reactions. As with the products **5a-h** of the organometallic-mediated processes, compounds **5i-l** were formed exclusively as the 2,6-syn isomers. The Lewis acid-mediated reactions of **3** are summarised in Scheme 3 and Table 2.[11]



Scheme 3

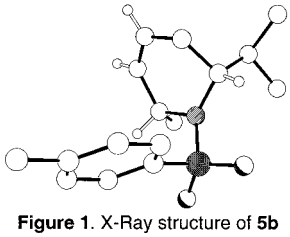


Figure 1. X-Ray structure of **5b**

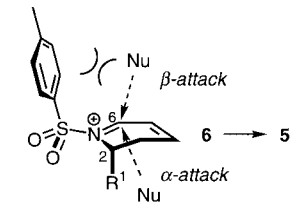
That the reactions proceeded via an S_N1' mechanism was shown by the complete stereoselectivity of the transformations, irrespective of the configuration at C-4 in **3**. Presumably, initial Lewis acid-assisted ionisation of **3** takes place to generate the conjugated iminium species **6**, which are intercepted exclusively from the α-face to give 2,6-syn **5**. That nucleophilic attack at the iminium centre takes place along the ostensibly more hindered axial, α-trajectory is striking, and may be a consequence of a stereoelectronic preference for a more chair-like transition-state.[12] Also, the X-ray crystal structure of **3a** (Figure 2)[9] shows the *N*-tosyl group oriented so as to minimise repulsive interactions with the axial C-2 substituent, and an analogous solution

Table 2. Lewis acid-mediated reactions of **3**

Entry	R^1 in 3	Lewis acid	Nuc	R^2 in 5	% yield of 5
a	CH_2Ph	Me_3Al (1.1 eq)[a]		Me	85
b	*i*-Pr	Me_3Al (2eq)		Me	80
c	*i*-Bu	Me_3Al (2 eq)		Me	99
d	CH_2OP[b]	Me_3Al (3 eq)		Me	66
e	CH_2Ph	Et_2AlCl (1.1 eq)		Et	86
f	*i*-Pr	Et_2AlCl (1.1 eq)		Et	99
g	*i*-Bu	Et_2AlCl (1.1 eq)		Et	99
h	CH_2OP[c]	Et_2AlCl (2.2 eq)		Et	70
i	CH_2Ph	$SnCl_4$[c]	$TMSCH_2CHCH_2$	CH_2CHCH_2	99
j	*i*-Pr	$SnCl_4$	$TMSCH_2CHCH_2$	CH_2CHCH_2	99
k	*i*-Bu	$SnCl_4$	$TMSCH_2CHCH_2$	CH_2CHCH_2	89
l	CH_2Ph	$SnCl_4$	$TBSOC(CH_2)t$-Bu	CH_2COt-Bu	99

For entries **a**-**h** reactions were carried out in PhMe; [b]P = $SiPh_2t$-Bu; [c]in entries **i**-**l** reactions were carried out in CH_2Cl_2; 2 eq of Lewis acid and nucleophile were used

conformation for intermediate **6** would render the α-face of C-6 sterically less encumbered (Scheme 4). Similar phenomena have been described for related, more highly oxygenated nitrogen heterocycles.[13]



Scheme 4

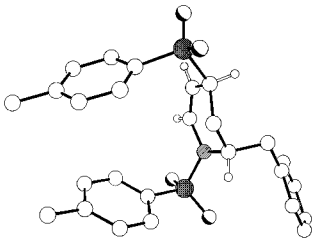
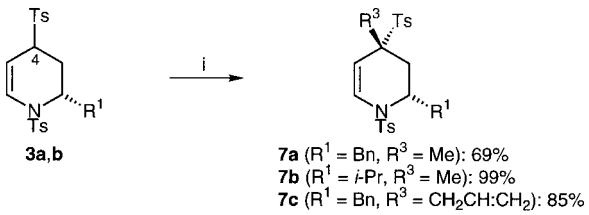
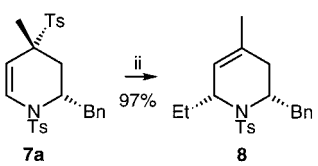


Figure 2. X-Ray structure of **3a**

The second part of our investigation was concerned with the generation and synthetic potential of nucleophilic species derived from **3**. Treatment of a THF solution of **3a** or **3b** with *n*-butyllithium at low temperature effected formation of an orange-red lithio-anion, which combined smoothly with iodomethane or 1-bromo-2-propene to give the products **7a**-**c** of exclusive 4-alkylation, α- to the sulfone group.[3] These reactions were completely selective for the 2,4-anti diastereomers, as shown by X-ray crystallographic analysis of **7b**[9] (Scheme 5, Figure 3). Like the parent compounds **3**, substrate **7a** reacted efficiently with diethylaluminium chloride in toluene, and gave the expected trialkyltetrahydropyridine **8** in almost quantitative yield.





7a

Scheme 5. (i) LDA (1.1 eq), THF–TMEDA (10:1, 0.05M), -78°C, 30 min, then add MeI (2.2 eq) or $BrCH_2CH:CH_2$ (1.1 eq), -78°C→rt, 1 h; (ii) Et_2AlCl (1.2 eq), PhMe (0.15M), rt, 1 h

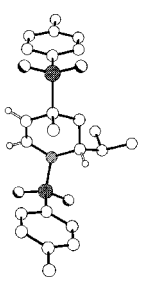
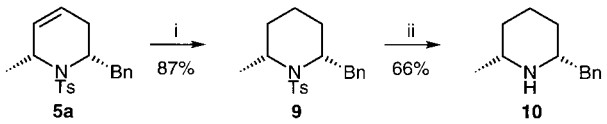


Figure 3. X-Ray structure of **7b**

The final part of this study was devoted to the identification of reaction conditions for the reduction of the C3–C4 double bond, and for removal of the *N*-tosyl group. After extensive experimentation, it was found that **5a** could be hydrogenated under one atmosphere of H_2 in the presence of Wilkinson's catalyst,[14] giving **9** in high yield. Several reagent systems, including H_2–Pd(C) and diimide failed to effect this transformation. We speculate that the low reactivity of the double bond is a consequence of its doubly-hindered nature, with the β-face encumbered by the *N*-tosyl group, and the α-face blocked by the axial C-6 substituent. Piperidine **9** was efficiently desulfonylated in high yield to give **10** by treatment with excess Na(Hg)[15] in boiling THF–MeOH (Scheme 6).



5a **9** **10**

Scheme 6. (i), H_2 (1 atm), $RhCl(PPh_3)_3$ (18 mol%), PhMe, rt, 72 h; (ii) 6% Na(Hg) (5 eq), 1:1 THF–MeOH (0.04M), reflux, 12 h

In summary, we have discovered that a new class of readily available, enantiomerically pure tetrahydropyridines enter into efficient and highly selective reactions with nucleophiles and electrophiles under Lewis acidic and basic conditions respectively.[16] The following paper describes the extension of this chemistry to the intramolecular mode, and shows that the novel cyclisation reactions uncovered have significant potential in the assembly of natural product skeletons.[17]

Acknowledgements

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References and Notes

1. Craig, D.; Ikin, N. J.; Mathews, N.; Smith, A. M. *Tetrahedron Lett.* **1995**, *36*, 7531-7534; Craig, D.; Tierney, J. P.; Williamson, C. *Tetrahedron Lett.* **1997**, *38*, 4153-4156.
2. Allylic and tertiary sulfones may be cleaved by oxaphilic Lewis acids: Trost, B. M.; Reza Ghadiri, M. *J. Am. Chem. Soc.* **1986**, *108*, 1098-1100, and references therein.
3. Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon: Oxford, 1993, pp 115-117.
4. Bonete, P.; Nájera, C. *Tetrahedron* **1995**, *51*, 2763-2776. All yields cited herein are of isolated, purified materials which gave satisfactory ^1H, ^{13}C nmr and ir spectra, and which showed low-resolution ms and either elemental combustion analysis or high-resolution ms characteristics in accord with the assigned structures.
5. Triethylamine-catalysed conjugate addition of thiocresol to acrolein was followed by acetalisation (trimethyl orthoformate, K-10 clay, CCl_4) and oxidation (CH_3CO_3H).
6. Berry, M. B.; Craig, D. *Synlett* **1992**, 41-44.
7. Treatment of **3a** with one equivalent of *t*-BuOK resulted in the high-yielding formation of 2-benzylpyridine. We are currently investigating the scope and limitations of this novel pyridine-forming reaction.
8. We thank Mr Dick Sheppard and Mr Paul Hammerton of this department for these determinations.
9. We thank Professor David J. Williams and Dr Andrew J. P. White of this department for these determinations.

Crystal data for **3a**: $C_{26}H_{27}NO_4S_2$, *M* = 481.6, monoclinic, space group $P2_1$ (no. 4), *a* = 12.744(3), *b* = 6.351(1), *c* = 15.802(3) Å β = 105.94(2)°, *V* = 1229.8(4) $Å^3$, *Z* = 2, D_c = 1.301 g cm^{-3}, μ(Cu-K_α) = 2.23 mm^{-1}, *F*(000) = 508. A clear platy needle of dimensions 0.30 x 0.22 x 0.05 mm was used. 2198 Independent reflections were measured on a Siemens P4/PC diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and all the non-hydrogen atoms were refined anisotropically by full-matrix least squares based on F^2 to give R_1 = 0.043, wR_2 = 0.106 for 1918 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 124°$] and 287 parameters. The absolute chirality was determined unambiguously by use of the Flack parameter which refined to a value of -0.01(3).

Crystal data for **5b**: $C_{16}H_{23}NO_2S$, *M* = 293.4, monoclinic, space group $P2_1$ (no. 4), *a* = 8.159(2), *b* = 13.565(3), *c* = 8.286(2) Å β = 115.27(2)°, *V* = 829.4(3) $Å^3$, *Z* = 2, D_c = 1.175 g cm^{-3}, μ(Cu-K_α) = 1.74 mm^{-1}, *F*(000) = 316. A clear plate of dimensions 0.50 x 0.40 x 0.20 mm was used. 1417 Independent reflections were measured on a Siemens P4/PC diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and all the non-hydrogen atoms were refined anisotropically by full-matrix least squares based on F^2 to give R_1 = 0.035, wR_2 = 0.092 for 1385 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 126°$] and 182 parameters. The absolute chirality was determined unambiguously by use of the Flack parameter which refined to a value of 0.09(4).

Crystal data for **7b**: $C_{23}H_{29}NO_4S_2$, *M* = 447.6, orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 8.699(2), *b* = 13.156(2), *c* = 20.317(3) Å, *V* = 2325.1(7) $Å^3$, *Z* = 4, D_c = 1.279 g cm^{-3}, μ(Cu-K_α) = 2.31 mm^{-1}, *F*(000) = 952. A clear columnal needle of dimensions 0.93 x 0.18 x 0.10 mm was used. 2157 Independent reflections were measured on a Siemens P4/PC diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and all the non-hydrogen atoms were refined anisotropically by full-matrix least squares based on F^2 to give R_1 = 0.051, wR_2 = 0.127 for 1699 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 126°$] and 272 parameters. The absolute chirality was determined unambiguously by use of the Flack parameter which refined to a value of 0.04(5).

All computations were carried out using the SHELXTL PC program system version 5.03. Atomic coordinates, bond lengths and angles, and thermal parameters for **3a**, **5b** and **7a** have been deposited at the Cambridge Crystallographic Data Centre.

10. For a review of electrophilic substitution reactions of allylsilanes, see: Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761-786; see also: Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1981**, *22*, 745-748.

11. Experimental procedure for preparation of **5a**.
To a stirred solution of 1,1-dimethoxy-3-(4-tolylsulfonyl)propane **1** (435 mg, 1.68 mmol, 1 eq) in THF (6.8 ml) and TMEDA (1.7 ml) at -78°C under N_2 was added *n*-BuLi (742 μl of a 2.5 M solution in hexanes, 1.85 mmol, 1.1 eq). After stirring for 20 min a solution of (*S*)-2-(phenylmethyl)-1-(4-tolylsulfonyl)aziridine **2a** (487 mg, 1.69 mmol, 1 eq) in THF (2 ml) was added via cannula. The reaction mixture was allowed to warm to rt, and after 30 min AcOH (1.85 ml of a 1M solution in THF, 1.85 mmol, 1.1 eq) was added. Simple extractive work-up (ether) and concentration under reduced pressure gave a pale yellow solid. Chromatography (SiO_2, 70% ether–petrol) yielded an isomeric mixture of *(5S)*-3-(4-tolylsulfonyl)-5-[(4-tolylsulfonyl)-amino]-1,1-dimethoxy-6-phenylhexane **4a** (0.85 g, 1.56 mmol, 93%) as a colourless solid.
To a solution of **4a** (204 mg, 0.374 mmol) and NaI (168 mg, 1.12 mmol, 3 eq) in MeCN (3.8 ml) at rt was added TMSCl (142 μl, 1.12 mmol, 3 eq). After 20 min the reaction was quenched with satd. aq. $NaHCO_3$ (2 ml) and diluted with water (2 ml). Simple extractive work-up (ether) including washing with aq $Na_2S_2O_3$, and concentration under reduced pressure followed by chromatography of the residue (SiO_2, 80% ether–petrol) yielded a 2:1 mixture of *S*)-1,4-bis(4-tolylsulfonyl)-2-benzyl-1,2,3,4-tetrahydropyridine **3a** (173 mg, 96%) as a colourless solid.
To a stirred solution of **3a** (112 mg, 0.23 mmol) in PhMe (3 ml) under N_2 at rt was added Me_3Al (232 μl of a 2M solution in hexanes, 0.46 mmol, 2 eq). After 30 min the reaction was quenched with satd. aq. $NaHCO_3$ (3 ml). Simple extractive work-up (ether) and removal of solvents under reduced pressure followed by chromatography (SiO_2, 70% ether–petrol) yielded (2*R*,6*R*)-2-methyl-6-benzyl-1-(4-tolylsulfonyl)-1,2,5,6-tetrahydropyridine **5a** (66 mg, 84%) as a colourless, oily solid; R_f 0.63 (70% ether–petrol); $[\alpha]_D^{26}$ +2.7 (*c* 1.3, CH_2Cl_2); ν_{max} (film) 3028, 2957, 2929, 2852, 1598, 1494, 1454, 1389, 1330, 1289, 1234, 1163, 1131, 1101, 982, 726, 702, 653 cm^{-1}; δ_H (300 MHz) 7.68 (2H, d, J 8.5 Hz, H-2 and H-6 of Ts), 7.28 (2H, d, J 8.5 Hz, H-3 and H-5 of Ts), 7.25-7.23 (3H, m, Ph), 7.20 (2H, t, J 7.5 Hz, Ph), 5.68-5.61 (2H, m, H-3 and H-4), 4.46-4.44 (1H, m, H-2 or H-6), 4.21-4.17 (1H, m, H-6 or H-2), 2.99 (1H, dd, J 13.0 and 3.5 Hz, C*H*$_2$Ph), 2.86 (1H, dd, J 13.0 and 11.5 Hz, C*H*$_2$Ph), 2.39 (3H, s, CH_3 of Ts), 1.76 (1H, dd, J 17.5 and 6.0 Hz, H-5), 1.64-1.60 (1H, m, H-5), 1.49 (3H, d, J 7.0 Hz, C-2 CH_3); δ_C (75 MHz) 143.0, 139.2, 138.3, 134.8, 129.7, 129.3, 128.6, 126.8, 126.5, 121.5, 52.3, 49.1, 41.8, 24.1, 24.0, 19.1; *m/z* (CI) 359 $[M+NH_4]^+$, 342 $[M+H]^+$, 274, 250 $[M-C_7H_7]^+$, 188, 96 (Found: $[M+H]^+$, 342.1515. $C_{20}H_{23}NO_2S$ requires $[M+H]^+$, 342.1528).

12. Toromanoff, E. *Tetrahedron* **1980**, *36*, 2809-2931.

13. Hopman, J. C. P.; van den Berg, E.; Ollero Ollero, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1995**, *36*, 4315-4318.

14. For leading references, see: Takaya, H.; Noyori, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 8, pp 443-444.

15. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477-3478.

16. We thank Dr Christopher J. Etheridge (Imperial College) for some exploratory experiments.

17. 2,3-Dihydro-4-pyridones have emerged as versatile intermediates for the enantiocontrolled synthesis of nitrogen heterocycles. See: Comins, D. L.; Joseph, S. P.; Hong, H.; Alawar, R. S.; Foti, C. J.; Zhang, Y. M.; Chen, X. H.; La Munyon, D. H.; Guerra-Weltzien, M. *Pure Appl. Chem.* **1997**, *69*, 477-481, and references therein.