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Chemistry of sulfones: synthesis of a new chiral nucleophilic catalyst

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Abstract—A chiral pyrrolidinopyridine was synthesized by using Buchwald methodology. The sulfone was used to add a benzyl group, which positioned a phenyl near the reacting position.

1. Introduction

Compounds such as 4-(dimethylamino)pyridine (DMAP)[1] and 4-(pyrrolidino)-pyridine (PPY) are potent nucleophilic acylation catalysts, which have been well known for a long period of time.[1] In recent years, there has been an enormous effort to develop compounds that could be used as catalysts for enantioselective acyl transfer reactions.[2] Some of the resulting derivatives are shown in Figure 1.

I is an axially chiral DMAP variant developed by Spivey et al.,[3] **II** is the planar chiral DMAP analogue reported by Fu et al.[4] and **III** is Fuji's chiral PPY derivative, which has been used in the non-enzymatic kinetic resolution of racemic alcohols through an 'induced fit' process.[5] Recently, Vedejs et al. described compound **IV** for acyl transfer,[6] while Connon et al.[7] reported **V** for the kinetic resolution of *sec*-alcohols. Other analogues of PPY have been reported by Spivey et al.[8] and Kotsuki et al.,[9] and have been used as chiral nucleophilic catalysts. Recently, we described the synthesis of pyrrolidine **4** (Fig. 2) starting from epoxide **1**, through the vinylsulfone **3**.[10] We also reported a facile procedure for the synthesis of compound **3**, starting from 2,3-*O*-*iso*-propylidene-D-erythronolactol **2**, on a large scale.[11]

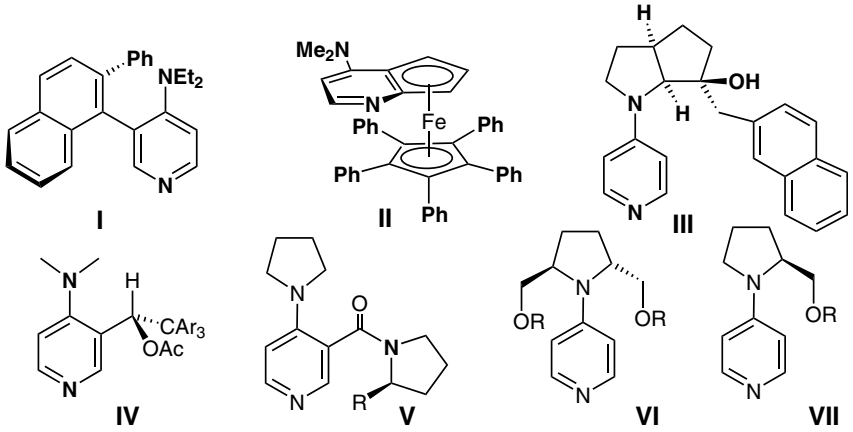

Figure 1.

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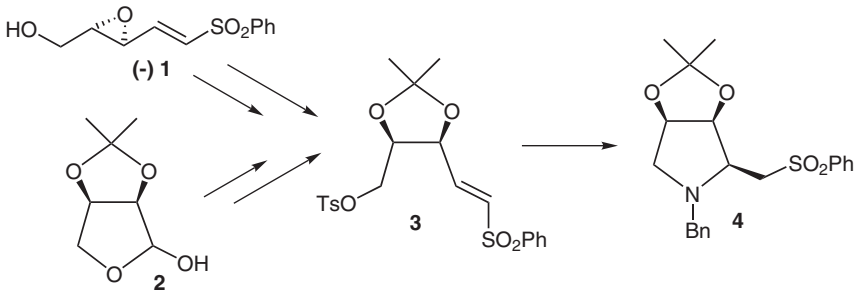
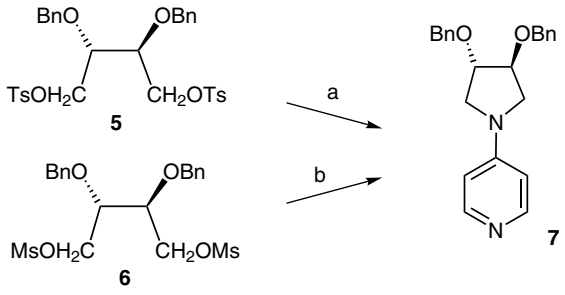


Figure 2.

Having access to gram quantities of vinylsulfone **3** and pyrrolidine **4**, we decided to use them in the synthesis of PPY analogues (Fig. 2).

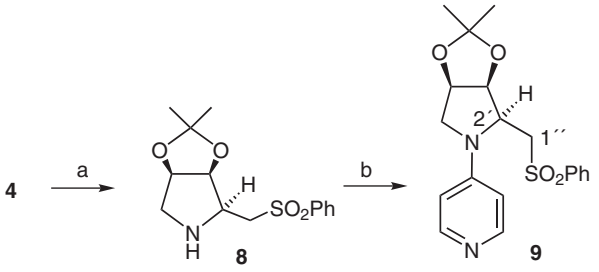
2. Results and discussion

Initially, we decided to use the traditional methodology of the displacement of a mesylate or tosylate. Thus, compounds **5** and **6** were synthesized as previously described by starting from L-(+)-DET.[12] Pyrrolidine formation took place in low yield in both cases, but permitted us to have enough compound to test compound **7** as a nucleophilic catalyst (Scheme 1).



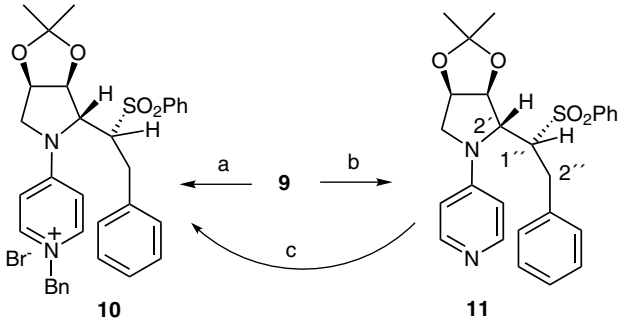
Scheme 1. Reagents and conditions: (a) 4-Aminopyridine, NaH, THF, reflux, 10%; (b) 4-aminopyridine, NaH, THF, reflux, 20%.

In a previous paper, we described a simple way of obtaining pyrrolidine **4** from vinyl sulfones **3**, using benzylamine in refluxing methanol.[10,11] In contrast, all attempts to use this methodology with 4-aminopyridine and vinylsulfone **3** failed to give any of the desired product. Therefore, we decided to use the coupling of a pyrrolidine to a pyridine. Sulfone **4** was deprotected under the usual conditions to give pyrrolidine **8** in 95% yield. Coupling of this sulfone with 4-chloropyridine in the presence of caesium carbonate in DMF,[13] or under a number of other conditions,[14] also failed to produce the PPY analogue we sought. Finally, we turned our attention to the use of coupling with a palladium catalyst under Buchwald conditions.[14] When pyrrolidine **8** was treated with 4-bromopyridine in the presence of a palladium catalyst, pyrrolidinopyridine **9** was obtained in 60% yield. Compound **9** was expected to behave as a nucleophilic catalyst, although the stereogenic centre is not near the active one and therefore would not be expected to produce much asymmetric induction (Scheme 2).



Scheme 2. Reagents and conditions: (a) H_2, Pd/C, MeOH, 95%; (b) 4-bromopyridine, $Pd_2(dba)_3$, Cs_2CO_3, BINAP, toluene, 80 °C, 2 days 60%.

In order to extend the influence of the chirality in the molecule, to the catalytically active centre, we decided to exploit the reactivity of the sulfone and introduce a benzyl group, using the usual conditions. Due to the nucleophilicity of the pyridine nitrogen, it was necessary to use a less than stoichiometric quantity of the electrophile (Scheme 3). When 1.2 equiv of the benzyl bromide was used, compound **10** was obtained in reasonable yield, whereas when only 0.5 equiv of benzyl bromide was employed, compound **11** could be isolated in a 40% yield (Scheme 3). Compound **11** can be transformed into **10** in excellent yield, by treatment with 1 equiv of benzyl bromide.



Scheme 3. Reagents and conditions: (a) (1) *n*-BuLi, THF, −78 °C, (2) BnBr 1.2 equiv, THF, 50%; (b) (1) *n*-BuLi, THF, −78 °C, (2) BnBr 0.5 equiv, THF, 40%; (c) BnBr 1.0 equiv, THF, rt, 90%.

NMR studies indicated that a change in the stereochemistry of C-2′ had occurred. In order to corroborate this, compound **10** was crystallized in hexane/$CHCl_3$, 1/9, meaning that its structure could be established by

X-ray crystallography.[15] An ORTEP view of this compound as observed in the crystal structure is shown in Figure 3, with 3/2 molecules of $CHCl_3$ omitted for clarity. As can be seen, there is a change in the configuration at C-2′ of the pyrrolidine.

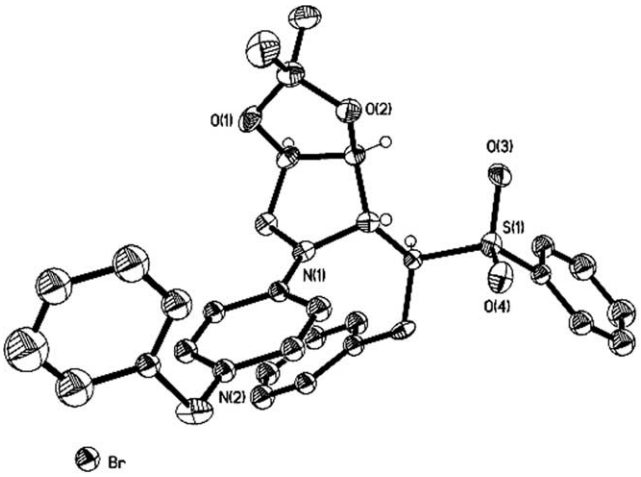


Figure 3. ORTEP view of **10**.

This inversion of stereochemistry can be explained by the opening and re-closing of the pyrrolidine ring, but it was not immediately clear whether the stereochemical control observed was due to thermodynamic or kinetic effects, or both. As a result, we built a model of the two stereoisomers of **9** (using maestro v.7.0.113) and carried out a conformational exploration using the mixed torsional search with low mode sampling available in macromodel v.9.0.016 with the MMFF94s forcefield and a limit of 5000 iterations of TNCG minimization, with all other parameters set to default values. Under these conditions, **9** appeared slightly *more* stable than its epimer at C-2′ (361.1 vs 369.0 kJ/mol). In view of the availability of the oxygen atoms of the dioxolane ring on the top face of the molecule, it seems likely that many of the possible anionic species would also be expected to show a preference of the stereochemistry at C-2′ of **9** rather than that found in the products **10** and **11**. Even allowing for solvent effects and errors in the forcefield, it seems unlikely that the small calculated preference in favour of the (*S*)-stereochemistry would be converted into a decisive preference for the observed (*R*)-product. Therefore, we studied all four possible diastereomers of **11**, taking into account the stereogenic centres C-2′ and C-1″ and using the same methodology as before. Compound **11**, with (*R*,*R*)-stereochemistry at C-2′ and at C-1″, was only the second lowest in energy (418.5 kJ/mol for the lowest-energy conformer found), with the (*S*,*S*)-stereoisomer 8.5 kJ/mol lower in energy in its lowest-energy conformation. However, it is worth noting that within a 50 kJ/mol 'window' above the lowest-energy conformation found, 30 conformations of **11** were found compared to only 6 for the (*S*,*S*)-stereoisomer, consistent with a far more cluttered environment for the entire C-2′ substituent in the latter compound. We therefore consider it likely that the stereocontrol in this reaction is produced principally by a kinetic effect, in which the more exposed (*R*)-enantiomer at C-2′, once formed by the ring-opening and ring-closing sequence, is rapidly quenched from the less hindered face of the anion to give (*R*,*R*)-product **11**.

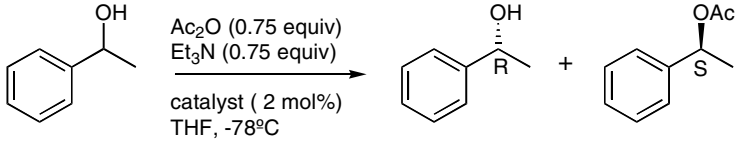
The kinetic resolution of **7**, **9** and **11** was briefly tested using 1-phenylethanol, with the results shown in Table 1.

The modest enantiomeric excess obtained for **11** is consistent with the lowest-energy conformation found for it (Fig. 4), which is representative of the low-energy conformations as a whole, with the benzyl group below the pyridine ring, but still somewhat distant from the catalytic centre. Nonetheless, we believe that our results are encouraging and that it will be possible, by appropriate modifications to this structure (such as using larger aromatic rings than phenyl), to achieve higher enantiomeric excesses.

3. Conclusion

Herein, we have reported the synthesis of a new pyrrolidinopyridine chiral catalyst that opens the way for a new series of nucleophilic catalysts.

Table 1. Kinetic resolution of 1-phenylethanol using different catalysts



Catalyst	*T*/min	*C*[a] (%)	(*R*)-Al ee[b] (%)	(*S*)-Ac ee[c] (%)	*s*
(+)-**7**	120	57.0	0.8	18.0	1.77
(+)-**7**	520	62.0	1.8	22.0	2.14
(+)-**9**	120	8.6	6.9	23.0	1.63
(+)-**9**	520	21.3	4.1	16.0	1.44
(+)-**11**	120	28.0	1.2	18.0	1.54
(+)-**11**	520	40.0	2.5	12.0	1.37

[a] Conversion by (HPLC) mass balance.
[b] By using HPLC using a Chiralcel OD column.
[c] (*R*)-Alcohol and (*S*)-acetate obtained as major enantiomers.

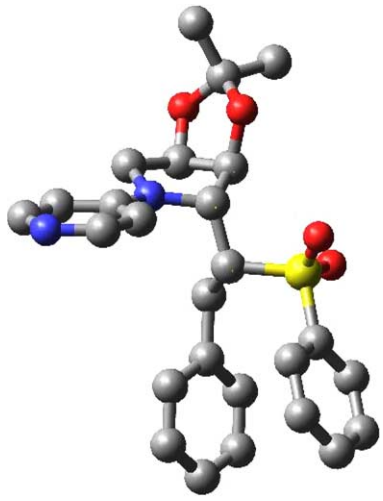


Figure 4.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased in the highest purity commercially available and used without further purification. Melting points were determined with a Kofler hot stage melting point apparatus and are uncorrected. IR spectra were recorded on a BOMEM 100 FT IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were performed in deuterochloroform and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^{1}H and ^{13}C, respectively, in a Bruker WP-200 SY and a BRUKER DRX 400 MHz. Chemical shifts are reported in δ, parts per million and coupling constants (J) given in Hertz. MS were performed in a VG-TS 250 spectrometer at 70 eV ionizing voltage. Mass spectra are presented as m/z (% rel. int.). HRMS were recorded in a VG Platform spectrometer using electronic impact (EI) or fast atom bombardment (FAB) technique. Optical rotations were determined in a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether, THF and benzene were distilled from sodium, and pyridine and dichloromethane were distilled under argon from CaH_2.

4.1.1. (2*S*,3*S*)-2,3-Bis(phenylmethoxy)-1,4-bis[[(4-methylphenyl)sulfonyl]oxy]butane, 5. To a stirred solution of 500 mg (1.65 mmol) of (2*S*,3*S*)-2,3-bis(phenylmethoxy)-1,4-butanediol in 8 mL of pyridine at −5 °C was added 943 mg (4.95 mmol) of tosyl chloride in one portion. After all the chloride had dissolved, the reaction mixture was allowed to stand at 0 °C for 15 h. The reaction mixture was then diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with 1 M HCl and saturated NaCl and then dried over Na_2SO_4. Concentration followed by chromatography (*n*-hexane–EtOAc, 8:2) gave **5** (908 mg, 90%). $[\alpha]_D^{20} = +14.6$ (c 0.3, $CHCl_3$), IR (film) ν (cm^{-1}): 3050, 2930, 1600, 1462, 1375, 1188, 1100, 938, 825; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 7.27 (10H, m, Ar), 4.45 (4H, d, $J = 11.4$ Hz, 2CH_2-Ph), 3.95–4.12 (4H, m, 2CH_2-O), 3.62–3.78 (2H, m, 2CH-O), 2.43 (6H, s, CH_3-Ph-SO_2); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 144.9 (Tos-*meta*), 137.4 (2C-*ipso*), 130.2 (Tos-*ipso*), 130.2 (Tos-*ortho*), 128.7 (4CH-*meta*), 128.3 (4CH-*ortho*), 127.9 (2CH-*para*), 75.6 (CH-2 and CH-3), 73.5 (2Ph-CH_2O), 68.8 (CH_2-1 and CH_2-4), 21.9 (2CH_3); EIMS m/z (%) 610 (M^++1, 100), 154 (55), 136 (50), 107 (25), 80 (45), HRMS (EI) m/z calcd for $C_{32}H_{34}O_8S_2$ 610.7246, found 610.7396 (M^++1).

4.1.2. (2*S*,3*S*)-2,3-Bis(phenylmethoxy)-1,4-bis(methylsulfonyloxy)butane, 6. To a solution of 500 mg (1.65 mmol) of (2*S*,3*S*)-2,3-bis(phenylmethoxy)-1,4-butanediol in 8 mL of CH_2Cl_2 was added 0.91 mL (6.60 mmol) of Et_3N. After this, 4.95 mL (0.38 mmol) of MsCl was added dropwise at 0 °C. The reaction mixture was stirred for 1 h and then diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and dried over Na_2SO_4. After concentration and chromatography (*n*-hexane–EtOAc, 8:2) gave **6** (603 mg, 85%). $[\alpha]_D^{20} = +17.9$ (c 0.5, $CHCl_3$), IR (film) ν (cm^{-1}): 2934, 2849, 1453, 1360, 1174, 1054, 808; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 7.32 (10H, m, Ar), 4.45 (4H, d, $J = 11.2$ Hz, 2CH_2-Ph), 4.21–4.42 (4H, m, 2CH_2-O), 3.78–3.85 (2H, m, 2CH-O), 2.93 (6H, s, 2CH_3-SO_2); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 137.3 (2C-*ipso*), 128.8 (4CH-*meta*), 128.5 (4CH-*ortho*), 127.9 (2CH-*para*), 75.9 (CH-2 and CH-3), 73.6 (2Ph-CH_2O), 68.4 (CH_2-1 and CH_2-4), 37.6 (2CH_3-SO_2); EIMS m/z (%) 458 (M^++1, 100), 154 (55), 126 (50), 90 (25), 80 (45), HRMS (EI) m/z calcd for $C_{20}H_{26}O_8S_2$ 458.1103, found 458.1069 (M^++1).

4.1.3. (3′*S*,4′*S*)-4-[(3′,4′)-Bis(benzyloxy)pyrrolidin-1′-yl]-pyridine, 7. A solution of 280 mg (2.98 mmol) of 4-aminopyridine in 18 mL of THF was added dropwise to a suspension of 238 mg (5.96 mmol) of NaH, which had been previously washed with *n*-hexane. The reaction mixture was stirred for 3 h and 4-aminopyridine was deprotonated, after which 908 mg (1.49 mmol) of tosylate **5** was added and the reaction mixture then heated under reflux for 3 days. The excess hydride was destroyed by the slow addition of 3 mL of NH_4OH (1 M). The reaction was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, brine and dried over Na_2SO_4. After concentration and chromatography (CH_2Cl_2–MeOH 9:1), 57 mg of **7** (10%) was obtained. $[\alpha]_D^{20} = +8.9$ (c 1.2, $CHCl_3$), IR (film) ν (cm^{-1}): 2913, 1875, 1615, 1561, 1462, 1107; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 8.19 (2H, d, $J = 6.4$ Hz, H-1 py, H-5 py), 7.32 (10H, m, Ar), 6.42 (2H, d, $J = 6.4$ Hz, H-2 py, H-4 py), 4.58 (4H, s, 2CH_2-Ph), 4.21 (2H, d, $J = 4.0$ Hz, 2CH-O), 3.60 (2H, dd, $J = 11.8$ Hz and $J = 4.0$ Hz, 2CH_2-N, H_A), 3.44 (2H, d, $J = 11.8$ Hz, 2CH_2-N, H_B); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 159.0 (C-py), 142.4 (CH-2 py and CH-4 py), 129.7 (2C-*ipso*), 128.9 (4CH-*meta*), 128.5 (4CH-*ortho*), 128.1 (2CH-*para*), 109.1 (CH-1 py and CH-5 py), 79.8 (CH-2 and CH-3), 71.9 (2Ph-CH_2O), 51.8 (CH_2-1 and CH_2-4); EIMS m/z (%) 360 (M^++1, 100), 115 (52), 105 (48), 175 (29), 203 (34), 256 (32), 313 (9),

371 (22). HRMS (EI) *m/z* calcd for $C_{23}H_{24}O_2N_2$ 360.4489, found 360.4838 (M^++1).

4.1.4. (3′*S*,4′*S*)-4-[(3′,4′)-Bis(benzyloxy)pyrrolidin-1′-yl]-pyridine, 7. A solution of 263 mg (2.80 mmol) of 4-aminopyridine in 17 mL of THF was added dropwise to a suspension of 224 mg (5.60 mmol) of NaH, which had previously been washed with *n*-hexane. The reaction mixture was stirred for 3 h and 4-aminopyridine was then deprotonated, after which 603 mg (1.40 mmol) of mesylate **6** was added and the reaction mixture heated under reflux for 3 days. The excess hydride was destroyed by the slow addition of 2 mL of NH_4OH (1 M). The reaction was then extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, brine and dried with Na_2SO_4. After concentration and chromatography (CH_2Cl_2–MeOH 9:1), 101 mg of **7** (20%) was obtained.

4.1.5. (2*S*,3*S*,4*R*)-2-Benzenesulfonylmethyl-3,4-isopropylidenedioxypyrrolidine, 8. A mixture of 500 mg (1.11 mmol) of compound **4** and a catalytic amount of Pd/C in 5 mL of MeOH was degassed and then hydrogenated under 3.5 atm of H_2 for 24 h. The reaction was filtered over Celite and concentrated to afford 313 mg of compound **8** (95%). $[\alpha]_D^{20} = -26.0$ (*c* 0.1, $CHCl_3$), IR (film) *v* (cm^{-1}): 3000, 2936, 1447, 1381, 1308, 1148, 1086, 650; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 7.95–7.50 (5H, m, Ar), 4.67 (1H, dd, $J = 4.0$ Hz and $J = 5.3$ Hz, H-4), 4.54 (1H, dd, $J = 4.2$ Hz and $J = 5.3$ Hz, H-3), 3.57 (1H, dd, $J = 5.0$ Hz and $J = 14.0$ Hz, H-$1'_A$), 3.36 (1H, dd, $J = 7.0$ Hz and $J = 14.0$ Hz, H-$1'_B$), 3.32 (1H, m, H-2), 3.13 (1H, d, $J = 12.7$ Hz, H-5_A), 2.69 (1H, dd, $J = 4.0$ Hz and $J = 12.7$ Hz, H-5_B), 2.20 (1H, s, H-1), 1.41 (3H, s, acetonide), 1.25 (3H, s, acetonide); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 139.7 (C-*ipso*), 133.7 (CH-*para*), 129.2 (2CH-*meta*), 127.2 (2CH-*ortho*), 111.1 (C-acetonide), 81.0 (CH-3), 80.8 (CH-4), 57.1 (CH-2), 55.9 (CH_2-1′), 52.6 (CH_2-5), 25.7 (CH_3-acetonide), 24.0 (CH_3-acetonide); EIMS *m/z* (%) 298 (M^++1,100), 154 (55), 136 (50), 107 (25), 80 (45), HRMS (EI) *m/z* calcd for $C_{14}H_{19}NO_4S$ 298.1068, found 298.1128 (M^++1).

4.1.6. (2′*S*,3′*S*,4′*R*)-4-(2′-Benzenesulfonylmethyl-3′,4′-isopropylidenedioxypyrrolidin-1′-yl)pyridine, 9. To a solution of 313 mg (1.05 mmol) of compound **8** in 10.5 mL of toluene were added 408 mg (2.10 mmol) of 4-bromopyridine, 46 mg (0.05 mmol) of $Pd_2(dba)_3$, 1.37 g (4.20 mmol) of Cs_2CO_3 and 131 mg (0.21 mmol) of BINAP. The reaction mixture was bubbled under an argon atmosphere for 5 min and then heated at 80 °C for 2 days. Afterwards, the reaction was diluted with 2 mL of NH_4OH (1 M) and extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and saturated NaCl and then dried over Na_2SO_4. Column chromatography (CH_2Cl_2–MeOH–NH_3 98:1:1) afforded 236 mg (60%) of compound **9**. $[\alpha]_D^{20} = -13.6$ (*c* 0.8, $CHCl_3$), IR (film) *v* (cm^{-1}): 3405, 1595, 1531, 1388, 1302, 1154, 1085; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 8.26 (2H, br s, H-2 py and H-6 py), 7.98 (2H, m, H*ortho*-SO_2Ph), 7.70 (2H, m, H*para*-SO_2Ph), 7.60 (2H, m, H*meta*-SO_2Ph), 6.52 (2H, d, $J = 5.6$ Hz, H-3 py and H-5 py), 4.85 (1H, m, H-4), 4.78 (1H, t, $J = 6.4$ Hz, H-3′), 4.45 (1H, dd, $J = 6.4$ Hz and $J = 8.5$ Hz, H-2′), 3.90 (1H, dd, $J = 9.6$ Hz and $J = 14.3$ Hz, H-$1''_A$), 3.57 (1H, dd, $J = 6.9$ Hz and $J = 11.0$ Hz, H-$5'_A$), 3.47 (1H, dd, $J = 3.7$ Hz and $J = 11.0$ Hz, H-$5'_B$), 3.33 (1H, d, $J = 14.3$ Hz, H-$1''_B$), 1.49 (3H, s, acetonide), 1.31 (3H, s, acetonide); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 151.6 (C-py), 148.6 (CH-2 py and CH-6 py), 139.5 (C-*ipso*SO_2Ph), 134.0 (CH-*para*SO_2Ph), 129.3 (2CH-*meta*SO_2Ph), 128.2 (2CH-*ortho*SO_2Ph), 113.1 (C-acetonide), 108.7 (CH-3 py and CH-5 py), 78.9 (CH-3), 77.6 (CH-4), 55.4 (CH-2′), 53.3 (CH_2-5), 52.8 (CH-1″), 26.6 (CH_3-acetonide), 25.0 (CH_3-acetonide); EIMS *m/z* (%) 374 (M^++1, 100), 154 (98), 375 (39), 107 (36), 77 (30), 307 (18), HRMS (EI) *m/z* calcd for $C_{19}H_{22}N_2O_4S$ 374.1113, found 374.1128 (M^++1).

4.1.7. (2′*R*,3′*S*,4′*R*,1″*R*)-4-[2′-(1″-Benzenesulfonyl-2″-phenylethyl)-3′,4′-isopropylidenedioxypyrrolidin-1-yl]*N*-benzylpyridinium bromide, 10. To a solution of 118 mg (0.32 mmol) of compound **9** in 3 mL THF at −78 °C was added 0.24 mL (0.38 mmol) of *n*-BuLi and the mixture stirred for 15 min. Afterwards, 31 μL (0.38 mmol) of BnBr was added and the reaction mixture allowed to warm to room temperature. Then, 1 mL of saturated aqueous NH_4Cl solution was added. The mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. After concentration and chromatography (CH_2Cl_2–MeOH 9:1), 73 mg of **10** (50%) was obtained. $[\alpha]_D^{20} = -22.2$ (*c* 0.6, MeOH), IR (film) *v* (cm^{-1}): 2945, 1830, 1555, 1531, 1220, 1100, 980; ^1H NMR (CD_3OD, 200 MHz) δ (ppm): 8.25 (2H, dd, $J = 7.4$ Hz and 9.8 Hz, H-2 py, H-6 py), 7.85 (2H, m, H*ortho*-SO_2Ph), 7.45–7.13 (14H, m, Ar), 6.72 (1H, dd, $J = 7.4$ Hz and $J = 2.9$ Hz, H-5 py), 6.20 (1H, dd, $J = 9.8$ Hz and $J = 2.9$ Hz, H-3 py), 5.51 (1H, d, $J = 5.8$ Hz, H-3′), 5.39 (2H, s, N-CH_2-Ar), 5.10 (1H, t, $J = 5.8$ Hz, H-4′), 4.45 (1H, d, $J = 2.3$ Hz, H-2′), 4.10 (1H, m, H-1″), 3.90 (1H, dd, $J = 11.2$ Hz and $J = 5.8$ Hz, H-5_A), 3.80 (1H, d, $J = 11.2$ Hz, H-5_B), 3.21 (1H, dd, $J = 2.6$ Hz and $J = 14.2$ Hz, H-$2''_A$), 2.98 (1H, dd, $J = 11.5$ Hz and $J = 14.2$ Hz, H-$2''_B$), 1.36 (3H, s, acetonide), 1.30 (3H, s, acetonide); ^{13}C NMR (CD_3OD, 50.3 MHz): 155.3 (C-py), 143.7 (CH-1 py and CH-5 py), 139.3 (C-*ipso*Ar_1), 136.6 (C-*ipso*SO_2Ph), 135.7 (C-*ipso*Ar_2), 135.4 (CH-*para*SO_2Ph), 130.6 (2CH-*meta*SO_2Ph), 130.5 (2CH-*para*Ar_1 and Ar_2), 130.3 (2CH-*ortho*Ar_1), 130.0 (2CH-*ortho*Ar_2), 129.3 (2CH-*meta*Ar_1), 129.0 (2CH-*meta*Ar_2), 128.4 (2CH-*ortho*SO_2Ph), 113.2 (CH-4 py), 111.1 (CH-2 py), 108.7 (C-acetonide), 82.3 (CH-3), 79.3 (CH-4′), 66.4 (CH-2′), 64.0 (CH-1″), 62.0 (N-CH_2-Ar_2), 57.3 (CH_2-5′), 33.6 (CH_2-2″), 26.8 (CH_3-acetonide), 24.7 (CH_3-acetonide).

4.1.8. (2′*R*,3′*S*,4′*R*,1″*R*)-4-[2′-(1″-Benzenesulfonyl-2″-phenylethyl)-3′,4′-isopropylidenedioxypyrrolidin-1-yl]pyridine, 11. To a solution of 118 mg (0.32 mmol) of compound **9** in 3 mL of THF at −78 °C was added 0.24 mL (0.38 mmol) of *n*-BuLi and the mixture stirred for 15 min. Afterwards, 13 μL (0.16 mmol) of BnBr was added and the reaction mixture allowed to warm to room temperature. Then, 1 mL of saturated aqueous NH_4Cl solution was added. The mixture was extracted

with EtOAc. The organic layer was washed with H_2O and brine, and dried with Na_2SO_4. After concentration and chromatography (CH_2Cl_2–MeOH 95:5), 59 mg of **11** (40%) was obtained. $[\alpha]_D^{20} = -28.3$ (*c* 0.9, $CHCl_3$), IR (film) ν (cm^{-1}): 2975, 1850, 1695, 1541, 1320, 1100, 980; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 8.04 (2H, br s, H-2 py, H-6 py), 7.76 (2H, m, H*ortho*-SO_2Ph), 7.70 (2H, m, H*para*-SO_2Ph), 7.58 (2H, m, H*meta*-SO_2Ph), 5.83 (2H, br s, H-3 py, H-5 py), 5.66 (1H, d, $J = 6.1$ Hz, H-3′), 5.17 (1H, t, $J = 6.1$ Hz, H-4′), 4.31 (1H, d, $J = 1.9$ Hz, H-2′), 4.04 (1H, dd, $J = 11.4$ Hz and $J = 5.80$ Hz, H-$5'_A$), 3.53 (2H, m, H-$5'_B$ and H-1″), 3.15 (1H, dd, $J = 2.5$ Hz and $J = 14.2$ Hz, H-$2''_A$), 2.93 (1H, dd, $J = 11.5$ Hz and $J = 14.2$ Hz, H-$2''_B$), 1.43 (3H, s, acetonide), 1.40 (3H, s, acetonide); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 143.8 (CH-2 py and CH-6 py), 138.2 (C-py), 135.3 (C-*ipso*SO_2Ph), 134.4 (CH-*para*-SO_2Ph), 129.7 (2CH-*meta*SO_2Ph), 129.3 (2CH-*ortho*), 129.1 (2CH-*meta*), 128.0 (2CH-*para*), 127.9 (2CH-*ortho*-SO_2Ph), 112.5 (C-acetonide), 108.6 (CH-3 py), 107.5 (CH-5 py), 80.2 (CH-3′), 78.6 (CH-4′), 64.5 (CH-2′), 63.6 (CH-1″), 55.8 (CH_2-5′), 33.6 (CH_2-2″), 26.9 (CH_3-acetonide), 24.9 (CH_3-acetonide); EIMS *m*/*z* (%) 465 (M^++1, 100), 154 (100), 136 (75), 91 (55), 307 (14), 413 (5), HRMS (EI) *m*/*z* calcd for $C_{26}H_{28}N_2O_4S$ 464.1770, found 464.1803 (M^++1).

4.1.9. A representative procedure for catalytic kinetic resolution of 1-phenylethanol, using catalyst (+)-9 as example. To a solution of catalyst (+)-**9** (7.0 mg, 0.02 mmol) and 1-phenylethanol (0.12 mL, 1.0 mmol) in THF (1 mL) was added Et_3N (0.1 mL, 0.75 mmol) and the reaction cooled to −78 °C. Ac_2O (0.71 mL, 0.75 mmol) was then added with vigorous stirring. After 120 min, approx 0.5 mL of the reaction mixture was removed via syringe and added to MeOH (1 mL). After 10 min, the solvent was removed in vacuo and the crude material passed through a short plug of silica to remove the catalyst. After 520 min, MeOH (2 mL) was added to the reaction mixture and warmed to room temperature. After 15 min, the solvent was removed in vacuo and the crude material passed through silica. The ees of both the alcohol and the acetate were determined for both aliquots by analytical chiral HPLC (Chiralcel OD column, 0.46 × 25 cm, 18 °C, hexanes–isopropanol, 85:15, 0.45 mL min^{-1}): R_t [(*R*)-acetate] 10.3 min; R_t [(*S*)-acetate] 10.7 min; R_t [(*R*)-alcohol] 12.5 min; R_t [(*S*)-alcohol] 13.7 min.

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15. A single crystal of compound **10** was subjected to X-ray diffraction studies on a Seifert 3003 SC four-circle diffractometer (CuK_α radiation, graphite monochromator) at 293(2) K. Crystal data for **10**: $C_{33}H_{37}N_2O_4S$, 3/2$CHCl_3$, Br^-, $M = 816.67$, triclinic, space group *P*1 (no 1), $a = 9.794(2)$ Å, $b = 10.351(2)$ Å, $c = 11.030(2)$ Å, $\alpha = 83.63(3)°$, $\beta = 74.32(3)°$, $\gamma = 67.49(3)°$, $V = 994.5(3)$ $Å^3$, $Z = 1$, $D_c = 1.364$ Mg/m^3, $m = (Cu\text{-}K_\alpha) = 4.981$ mm^{-1}, $F(000) = 418$. 2954 reflections were collected, of which 2404 were considered to be observed with $I > 2\sigma(I)$. The structure was determined by direct methods using the SHELXTL™ suite of programs. Many problems involve the crystal structure refinement of this compound, all of which are derived from the small size and bad quality of the crystals. The poorness of the spectra forced the refinement as rigid body of most part of the molecules. Hydrogen atoms were placed in calculated positions. Full-matrix least squares refinement based on F^2 with anisotropic thermal parameters for the non-hydrogen atoms led to agreement factors $R_1 = 0.1060$ and $wR_2 = 0.2639$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary material no. CCDC-271242.