Synthesis of Chiral Diazine and Pyridine Sulfoxides. Asymmetric Induction by Chiral Sulfoxides in an "Aromatic *Ortho*-Directed Metalation−Reaction with Electrophiles Sequence". Diazines. 24

P. Pollet, A. Turck, N. Plé, and G. Quéguiner*

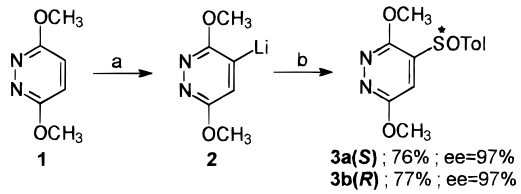
IRCOF-INSA, Laboratoire de Chimie Organique Fine et Hétérocyclique, UPRESA 6014, B.P. 08, 76131 Mont St Aignan Cedex, France

Received June 11, 1998

Ortho-directed metalation is a useful method to functionalize aromatic ring systems. We report here *ortho*-directed metalations in the π-deficient heterocyclic series (pyridazine, pyrimidine, and pyridine) using an aryl sulfoxide as a chiral *ortho*-directing group. In aliphatic series, many papers have described asymmetric induction on sp^3 carbon substituted by a chiral sulfoxide during a metalation and reaction with electrophiles process.[1−12] Very few publications have reported metalations of aromatic rings followed by asymmetric inductions during reaction of the lithio compound with a prochiral electrophile; de's in the range 10−83% have been obtained.[13−17] The only reference with sulfur derivatives is that of H. Takahashi[18] who obtained up to 82% de using chiral sulfonamides.

Our knowledge about sulfur derivatives as directing groups for metalations of diazines and our successful metalations of racemic sulfoxides[19,20] prompted us to study a *p*-tolylsulfinyl group as a chiral directing agent.

Scheme 1[a]



[a] Reagents: (a) LTMP (2.2 equiv), 30 min, −75 °C, THF; (b) (*S*)- or (*R*)-menthyl *p*-toluenesulfinate, −75 °C, 1 h 30 min.

Sulfoxides[21,22] have not been used previously as asymmetric directing groups for the enantioselective "*ortho*-directed metalation−reaction with electrophile sequence" in the aromatic series.

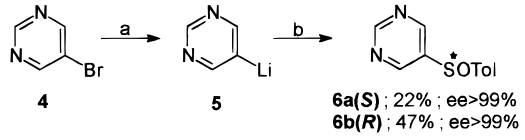
The synthesis of enantiomerically pure sulfinyl pyridazines was unknown. Asymmetric oxidations of 3-phenyl or 3-(methylthio)-6-methoxypyridazine and 2-phenyl- or -(methylthio)pyrazine by Sharpless or Kagan's method[23−31] and using oxaziridines[32−39] failed. On the other hand, Andersen's method[40−42] using organometallics and chiral menthyl *p*-toluenesulfinates, which are commercially available, gave excellent enantiomeric excesses after extensive studies (Schemes 1−3). Synthesis of products **3a** and **3b** (Scheme 1) could be achieved as follows. The preparation of **2** was carried out in the usual conditions. The second step from **2** to **3a** or **3b** was successful only if a reverse addition was used; i.e., the reaction mixture containing the lithium derivatives was poured into a solution of the menthyl *p*-toluenesulfinate in THF. Under these conditions, **3a** and **3b** were obtained

* To whom correspondence should be addressed. Phone + 33(0) 2 35 52 29 00. Fax: + 33(0) 2 35 52 29 62. E-mail: guy.queguiner@ircof.insa-rouen.fr.

(1) Baker, R. W.; Pocock, G. R.; Sargent, M. V.; Twiss, E. *Tetrahedron Asymmetry* **1993**, *4*, 2423.
(2) Durst, T.; Vian, R.; McClory, M. R. *J. Am. Chem. Soc.* **1971**, *93*, 3077.
(3) Lavielle, S.; Bory, S.; Moreau, B.; Luche, J.; Marquet, A. *J. Am. Chem. Soc.* **1978**, *100*, 1558.
(4) Wills, M.; Butlin, R. J.; Linney, I. D.; Gibson, W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3383.
(5) Cose, P. J.; Persad, A.; Simpkins, N. S. *Synlett* **1992**, 194.
(6) Cose, P. J.; Persad, A.; Simpkins, N. S. *Synlett* **1992**, 197.
(7) Arai, Y.; Masuda, T.; Masaki, Y.; Koizumi, T. *Heterocycles* **1994**, *38*, 1751.
(8) Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1989**, *30*, 7091.
(9) Shibutani, T.; Fujihara, H.; Furukawa, N. *Tetrahedron Lett.* **1991**, *32*, 2943.
(10) Heinisch, G.; Langer, T.; Tonnel, J. *Heterocycles* **1996**, *43*, 1057.
(11) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, 336.
(12) Amat, M.; Pshenichnyi, G.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron Asymmetry* **1996**, *7*, 3091.
(13) Meyers, A. I.; Hanagan, M. A.; Trefonas, L. M.; Baker, R. J. *Tetrahedron* **1983**, *39*, 1991.
(14) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271.
(15) Beak, P.; Tse, A.; Hawkins, Chen, C. W.; Mills, S. *Tetrahedron* **1984**, *39*, 1983.
(16) Eguchi, S.; Suzuki, T.; Okawa, T.; Matsushita, Y. *J. Org. Chem.* **1996**, *61*, 7316.
(17) Matsui, S.; Uejima, A.; Suzuki, Y.; Tanaka, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 701.
(18) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Chem. Pharm. Bull.* **1991**, *39*, 260.
(19) Turck, A.; Plé, N.; Pollet, P.; Mojovic, L.; Duflos, J.; Queguiner, G. *J. Heterocycl. Chem.* **1997**, *34*, 621.
(20) Turck, A.; Plé, N.; Pollet, P.; Queguiner, G. *J. Heterocycl. Chem.*, submitted.
(21) Walker, A. J. *Tetrahedron Asymmetry* **1992**, *3*, 961.
(22) Carreño, M. C.; Garcia Ruano, J. L.; Toledo, M. A.; Urbano, A. *Tetrahedron Asymmetry* **1997**, *8*, 913.
(23) Arai, Y.; Suzuki, A.; Masuda, T.; Masaki, Y.; Shiro, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2913.
(24) Girodier, L. G.; Rouessac, F. P. *Tetrahedron Asymmetry* **1994**, *5*, 1203.
(25) Hill, J. G.; Rossiter, B. E.; Sharpless, K. *J. Org. Chem.* **1983**, *48*, 3607.
(26) Kagan, H. B.; Dunach, E.; Nemecek, C.; Pitchen, P.; Samuel, O.; Zhao, S. *Pure Appl. Chem.* **1985**, *57*, 1911.
(27) DiFuria, F.; Modena, G.; Seraglia, R. *Synth. Commun.* **1984**, 325.
(28) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188.
(29) Brunel, J. M.; Diter, P.; Duetsch, M.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 8086.
(30) Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 1049.
(31) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135.
(32) Bulman Page, P. C.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Synlett* **1995**, 773.
(33) Davies, F. A.; McCauley, J. P., Jr.; Harakal, M. E. *J. Org. Chem.* **1984**, *49*, 1465.
(34) Davies, F. A.; Reddy, R. T.; Han, W.; Caroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428.
(35) Davies, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.
(36) Bullman Page, P. C.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Tetrahedron Asymmetry* **1995**, *6*, 2911.
(37) Davies, F. A.; McCauley, J. P., Jr.; Chattopadhyay, S.; Harakal, M. E.; Towson, J. C.; Watson, W. H.; Tavanaiepour, I. *J. Am. Chem. Soc.* **1987**, *109*, 3370.
(38) Davis, F. A.; Billmers, J. M.; Gosciniak, D. J.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 4240.
(39) Davies, F. A.; Jenkins, R., Jr.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, *52*, 5171.
(40) Andersen, K. K.; *J. Am. Chem. Soc.* **1964**, *2*, 1953.
(41) Girodier, L.; Maignan, C.; Rouessac, F. *Tetrahedron Asymmetry* **1992**, *3*, 857.
(42) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *4*, 5637.

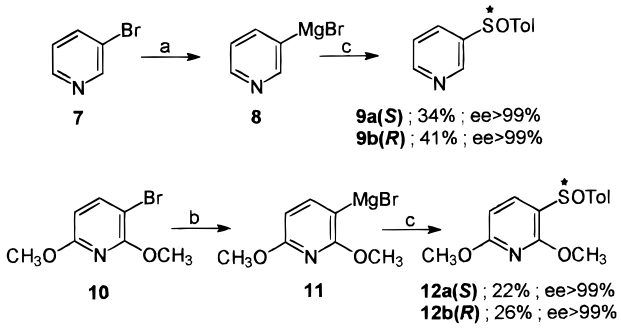
10.1021/jo981125d CCC: $18.00
Published on Web 05/18/1999

Scheme 2[a]



[a] Reagents: (a) BuLi (1.2 equiv), 5 min, −100 °C, THF; (b) (*S*)- or (*R*)-menthyl *p*-toluenesulfinate, −75 °C, 1 h 30 min.

Scheme 3[a]



[a] Reagents: (a) *i*-PrMgCl, 1 h, rt, THF; NEt_3, 5 min; (b) *n*-BuLi, 20 min, rt, THF; $MgCl_2$, 30 min; (c) (*S*)- or (*R*)-menthyl *p*-toluenesulfinate, −75 °C, 1 h 30 min.

in 76% and 77% yields, respectively, with a 97% ee (determined by HPLC). The lithiated pyrimidine **5** has been obtained by halogen/metal exchange.[43,44] The reaction with menthyl *p*-toluenesulfinate gave products **6a,b** in 22% and 47% yields, respectively, and in more than 99% ee (Scheme 2). Some pyridines such as 3-(*p*-tolylsulfinyl)pyridines[45](**9a**, **9b**) and 2,6-dimethoxy-4-(*p*-tolylsulfinyl)pyridines (**12a**, **12b**) were synthesized (Scheme 3).

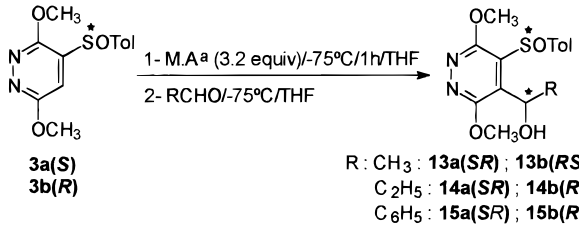
Starting from 3-bromopyridine derivatives (**7**, **10)**, the Grignard compounds (**8** and **11)** were obtained by exchange with isopropylmagnesium chloride. The reaction with menthyl *p*-toluenesulfinate was stereospecific. Products **9a,b** and **12a,b** were obtained in moderate yields but with more than 99% ee. When 3-lithiopyridine was used instead of the Grignard compound **8**, the yields were close but the ee decreased to 39% (**9a**) and 54% (**9b**).

With the chiral sulfoxides prepared, we could now use them as chiral *ortho*-directing groups. A preliminary study was necessary to optimize this metalation reaction. The best metalation reaction conditions were found to be 3.2 equiv of lithium 2,2,6,6-tetramethylpiperidide (LTMP) or lithium diisopropylamide (LDA) as metalating agents for 1 h at −75 °C, followed by reaction with various aldehydes at −75 °C (Scheme 4, Table 1).

These results indicated that the diastereoselectivity in these reactions was almost complete. The X-ray data allowed us to assign the absolute configuration of compounds **13** and **14**. It was found that the stereogenic carbon of the secondary alcohol of **13a** and **14b** had an opposite configuration to that of the sulfoxides, a (*R*) sulfoxide leading to the (*RS*) diastereoisomer. It was not possible to crystallize correctly the other products in order to perform X-ray analysis; however, it can be supposed that they have the same configuration (Schemes 4, 5).

(43) Gronowitz, S.; Roe, J. *Acta Chem. Scand.* **1965**, *19*, 1741.
(44) Boehner, B.; Forey, W.; Shurter, R.; Pissiotas, G. (Ciba-Geigy A.-G.) Eur. Pat. Appl. EP96, 004, 1983; *Chem. Abstr.* **1980**, *100*, 139152c.
(45) Imanishi, T.; Obika, S.; Nishiyama, T.; Nishimoto, M.; Hamano, Y.; Miyashita, K.; Iwata, C. *Chem. Pharm. Bull.* **1996**, *44*, 267.

Scheme 4[a]

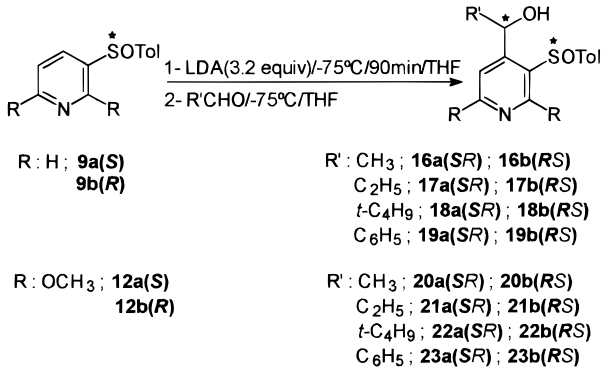


[a] M.A.: metalating agent.

Table 1. Metalation and Reaction with Aldehydes of 4-(*p*-Tolylsulfinyl)-3,6-dimethoxypyridazine 3a and 3b

R	products	metalating agent	de, %	yield, %
CH_3	**13a**	LDA	96	53
CH_3	**13a**	LTMP	96	76
CH_3	**13b**	LDA	98	63
CH_3	**13b**	LTMP	99	70
C_2H_5	**14a**	LDA	96	40
C_2H_5	**14a**	LTMP	95	35
C_2H_5	**14b**	LDA	97	30
C_2H_5	**14b**	LTMP	94	39
C_6H_5	**15a**	LDA	93	50
C_6H_5	**15a**	LTMP	95	68
C_6H_5	**15b**	LDA	93	30
C_6H_5	**15b**	LTMP	98	57

Scheme 5



The remarkable diastereoselectivity observed could be favored by the high steric hindrance in the molecule (**3a,b**). To test a less-hindered substrate, the same reaction was performed with pyrimidine (**6a,b)** and pyridine (**9a,b**). Numerous attempts to metalate 5-(*p*-tolylsulfinyl)pyrimidine (**6a,b**) have failed but the reaction worked with 3-(*p*-tolylsulfinyl)pyridine (**9a,b**). The best experimental conditions for the metalation of this pyridine substrate required the use of 3.2 equiv of LDA as metalating agent for 90 min at −75 °C (Scheme 5). The reaction with various electrophiles at −75 °C gave the results summarized in Table 2. All attempts to metalate these compounds with LTMP as metalating agent failed.

For pyridines **9a,b** (Table 2), diastereoselectivity was complete with benzaldehyde and 2,2-dimethylpropanal as electrophiles. Products **18a,b** and **19a,b** were obtained in low yields (25, 37, 13, and 18%, respectively) but with total diastereoselectivity (>99%). Unhindered aliphatic aldehydes such as acetaldehyde and propionaldehyde gave products **16a,b** and **17a,b** in low yields and low de's. In all cases, the yields were low, making the results with 3-(*p*-tolylsulfinyl)pyridine (**9a,b**) unsatisfactory. So we planned to use another substrate in the pyridine series which would give a more stable lithium derivative than

Table 2. Metalation and Reaction with Aldehydes of 3-(*p*-Tolylsulfinyl)pyridine 9a,b and 3-(*p*-tolylsulfinyl)-2,6-dimethoxypyridine 12a,b

starting material	R	products	de, %	yield, %
9a,b	CH_3	**16a,b**	14, 0[a]	27, 18
9a,b	C_2H_5	**17a,b**	26, 20	27, 18
9a,b	*t*-C_4H_9	**18a,b**	>99, >99	25, 37
9a,b	C_6H_5	**19a,b**	>99, >99	13, 18
12a,b	CH_3	**20a,b**	38, 36	75, 89
12a,b	C_2H_5	**21a,b**	28, 20	53, 73
12a,b	*t*-C_4H_9	**22a,b**	>99, >99	60, 63
12a,b	C_6H_5	**23a,b**	>99, >99	60, 77

[a] Diastereoisomers could not be separated on the chiracel OD column.

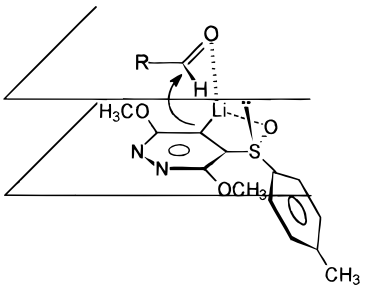


Figure 1.

9a,b and less steric hindrance at the C-4 position than pyridazines **3a,b**. So, 2,6-dimethoxy-3-(*p*-tolylsulfinyl)-pyridine (**12a,b**) was chosen (Scheme 5). A good de was obtained with hindered aldehydes as previously with compounds **9a,b**, and it can be noticed that yields were better (Table 2).

In summary, excellent diastereoselectivity was obtained with 3,6-dimethoxy-4-(*p*-tolylsulfinyl)pyridazine **3a,b** independently of the steric hindrance of the aldehyde. With pyridine sulfoxides **9a,b** and **12a,b**, the de's were high with hindered aldehydes and low with the less bulky aldehydes. These results can be explained by the geometry of the heterocyclic substrate which presents a convex and a concave face (Figure 1). The concave face being more crowded, the approach of the aldehyde took place on the less-hindered convex face leading to the S_C,R_S diastereoisomer. In the case of pyridinic substrate, the steric hindrance was lower and the unhindered aldehydes could approach by both faces leading to the two diastereoisomers.

Experimental Section

General Procedure for Synthesis of Sulfinate (3a,b; 9a,b; 12a,b). Into a 100 mL round-bottomed two-necked flask provided with thermometer and magnetic stirring bar and under an atmosphere of dry argon was placed dry THF (10 mL). After cooling to T_1 °C, metalating agent (2.2 mmol) was introduced. A solution of the substrate (1.0 mmol) dissolved in THF (5 mL) was added, and the reaction mixture was stirred for 1 h at T_1 °C. It was poured by double-needle over a solution of (*R* or *S*)-menthyl *p*-toluenesulfinate (2.2 mmol) in dry THF and under atmosphere of dry argon. The reaction mixture was stirred for 2 h at −75 °C. A saturated NH_4Cl solution (5 mL) was added. Neutralization was then carried out with a saturated $NaHCO_3$ solution (1 mL). The resulting mixture was concentrated and was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. Column chromatography on silica gel with ethyl acetate/light petroleum ether (3/7) as an eluent afforded pure product.

(*S*)-3,6-Dimethoxy-4-(*p*-tolylsulfinyl)pyridazine (3a). Metalating agent: LTMP; T_1 = −75 °C. Yield: 76%; mp 110 °C; ee = 97%. IR (KBr) 2953, 1013 cm^{-1}; HRMS *m*/*z* 278 (M^+), 229, 139; ^1H NMR (200 MHz, $CDCl_3$) δ 2.37 (s, 3H), 4.00 (s, 3H), 4.07 (s, 3H), 7.26 (d, 2H, J = 8.0 Hz), 7.59 (m, 3H). Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.17; H, 5.07; N, 10.08. Found: C, 56.20; H, 5.10; N, 10.11.

(*S*)-5-(*p*-Tolylsulfinyl)pyrimidine (6a). Into a 100 mL round-bottomed two-necked flask provided with a thermometer and magnetic stirring bar and under an atmosphere of dry argon was placed dry THF (10 mL). After cooling to −100 °C, *n*-butyllithium (1.6 M, 2.40 mL, 3.8 mmol) and then 5-bromopyrimidine **4** (0.50 g, 3.2 mmol) dissolved in dry THF (5 mL) were introduced. The reaction mixture was stirred for 10 min at −100 °C. (*R*)-Menthyl *p*-toluenesulfinate (2.40 g, 8.3 mmol) in dry THF (10 mL) was added, and stirring was continued for 4 h at −75 °C. The mixture was hydrolyzed with a saturated NH_4Cl solution (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. Column chromatography on silica gel with ethyl acetate as an eluent afforded **6a** as a white solid (47%, 0.65 g); mp 136 °C; ee > 99%; IR (KBr) 3026, 1053 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_2.43 (s, 3H), 7.36 (d, 2H, J = 8.0 Hz), 7.60 (d, 2H, J = 8.0 Hz), 8.90 (s, 2H), 9.27 (s, 1H). Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.60; H, 4.62; N, 12.85. Found: C, 60.82; H, 4.57; N, 12.67.

(*S*)-3-(*p*-Tolylsulfinyl)pyridine (9a). Metalating agent: *i*-PrMgBr; T_1 = rt. Yield: 34%; mp 56 °C; ee > 99%. IR (KBr) 3048, 2922, 1050 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.39 (s, 3H), 7.31 (d, 2H, J = 8.1 Hz), 7.38−7.45 (dd, 1H, J = 8.1 Hz, J = 4.8 Hz), 7.56 (d, 2H, J = 8.1 Hz), 7.96−8.02 (dt, 1H, J = 8.1 Hz, J = 1.8 Hz), 8.67 (dd, 1H, J = 4.8 Hz, J = 1.8 Hz), 8.77 (d, 1H, J = 1.8 Hz). Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 4.98; N, 6.37. Found: C, 66.39; H, 5.25; N, 6.22.

(*S*)-2,6-Dimethoxy-4-(*p*-tolylsulfinyl)pyridine (12a). Metalating agent: *n*-BuLi (1.6 M)/$MgCl_2$; T_1 = rt. Yield: 26%; mp 106−108 °C; ee > 99%. IR (KBr) 3025, 2950, 1041 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.92 (s, 3H), 3.96 (s, 3H), 6.45 (d, 1H, J = 8.2 Hz), 7.25 (d, 2H, J = 8.2 Hz), 7.58 (d, 2H, J = 8.2 Hz), 7.97 (d, 1H, J = 8.2 Hz). Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.70; H, 5.46; N, 5.06; S, 11.58. Found: C, 61.07; H, 5.48; N,4.89; S, 11.42.

General Procedure for Metalation with Electrophile Sequence. A solution of *n*-butyllithium (1.6 M or 2.5 M in hexane) was added to cold (−40 °C), stirred anhydrous THF (10 mL) under an atmosphere of dry argon. Diisopropylamine or 2,2,6,6-tetramethylpiperidine was introduced. The solution was warmed to 0 °C and kept for 20 min at this temperature. It was then cooled to −75 °C. A solution of the substrate to metalate dissolved in THF (5 mL) was added, and the mixture was stirred for t_1 at −75 °C, followed by reaction with the corresponding electrophile for a further t_2 (the volatility of acetaldehyde required a large excess). Hydrolysis was then carried out at −75 °C using a mixture of 35% aqueous HCl (1 mL), ethanol (4 mL), and THF (5 mL). The reaction solution was warmed to 0 °C, made slightly basic with a saturated $NaHCO_3$ solution, and was evaporated nearly to dryness. The residue was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography on silica gel.

(*S*)-3,6-Dimethoxy-5-(1-hydroxyethyl)-4-(*p*-tolylsulfinyl)-pyridazine (13a). Metalation of (*S*)-3,6-dimethoxy-4-(*p*-tolylsulfinyl)pyridazine **3a** (0.10 g, 0.4 mmol) according to the general procedure with *n*-butyllithium 1.6 M (0.72 mL, 1.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.19 mL, 1.2 mmol), t_1 = 60 min, followed by reaction with acetaldehyde (1.00 mL, 18.0 mmol), t_2 = 30 min, was carried out. Purification by column chromatography eluting with ethyl acetate/light petroleum ether (1/1) afforded **13a** as a pale yellow solid (76%, 88.2 mg); mp 146 °C; de = 96%. IR (KBr) 3300, 2979, 2948, 1028 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.66 (d, 3H, J = 6.7 Hz), 2.38 (s, 3H), 4.00 (s, 3H), 4.12 (s, 3H), 4.00−4.12 (m, 1H), 5.88 (q, 1H, J = 6.7 Hz), 7.29 (d, 2H, J = 8.2 Hz), 7.62 (d, 2H, J = 8.2 Hz). Anal. Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.95; H, 5.63; N, 8.70. Found: C, 55.63; H, 5.83; N, 8.62.

(*S*)-3,6-Dimethoxy-5-(1-hydroxypropyl)-4-(*p*-tolylsulfinyl)-pyridazine (14a). Metalation of (*S*)-3,6-dimethoxy-4-(*p*-tolylsulfinyl)pyridazine **3a** (0.10 g, 0.4 mmol) according to the general procedure with *n*-butyllithium 1.6 M (0.72 mL, 1.2 mmol) and

2,2,6,6-tetramethylpiperidine (0.19 mL, 1.2 mmol), $t_1 = 60$ min, followed by reaction with propionaldehyde (0.06 mL, 0.7 mmol), $t_2 = 60$ min, was carried out. Purification by column chromatography eluting with ethyl acetate/light petroleum ether (1/1) afforded **14a** as a white solid (40%, 46.8 mg); mp 134 °C; de = 96%. IR (KBr) 3319, 2940, 2870, 1029 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.08 (t, 3H, $J = 7.4$ Hz), 1.85−2.07 (m, 2H), 2.38 (s, 3H), 3.98 (s, 3H), 4.10 (s, 3H), 3.90−4.12 (m, 1H), 5.56−5.63 (m, 1H), 7.28 (d, 2H, $J = 8.6$ Hz), 7.61 (d, 2H, $J = 8.6$ Hz). Anal. Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.19; H, 6.00; N, 8.34. Found: C, 56.93; H, 6.28; N, 8.36.

(*S*)-3,6-Dimethoxy-5-(α-hydroxybenzyl)-4-(*p*-tolylsulfinyl)-pyridazine (15a). Metalation of (*S*)-3,6-dimethoxy-4-(*p*-tolylsulfinyl)pyridazine **3a** (0.10 g, 0.4 mmol) according to the general procedure with *n*-butyllithium 1.6 M (0.72 mL, 1.2 mmol) and diisopropylamine (0.16 mL, 1.2 mmol), $t_1 = 60$ min, followed by reaction with benzaldehyde (0.08 mL, 0.7 mmol), $t_2 = 60$ min, was carried out. Purification by column chromatography eluting with ethyl acetate/light petroleum ether/cyclohexane (1/1/1) afforded **15a** as a white solid (50%, 68.7 mg); mp 180 °C; de = 93%. IR (KBr) 3258, 3014, 2948, 1026 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.40 (s, 3H), 4.02−4.07 (m, 6H), 5.31 (m, 1H), 6.25 (m, 1H), 6.49 (s, 1H), 6.92 (s,1H), 7.08−7.33 (m, 8H), 7.75 (d, 1H). Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.56; H, 5.25; N, 7.29. Found: C, 62.93; H, 5.12; N, 7.09.

(*S*)-4-(1-Hydroxyethyl)-3-(*p*-tolylsulfinyl)pyridine (16a). Metalation of (*S*)-3-(*p*-tolylsulfinyl)pyridine **9a** (0.10 g, 0.5 mmol) according to the general procedure with *n*-butyllithium *2.5 M* (0.59 mL, 1.5 mmol) and diisopropylamine (0.21 mL, 1.5 mmol), $t_1 = 60$ min, followed by reaction with acetaldehyde (1.00 mL, 18.0 mmol), $t_2 = 60$ min, was carried out. Purification by column chromatography eluting with ethyl acetate afforded **16a** as an orange oil (27%, 32.2 mg); de = 14%. IR (KBr) 3344, 3052, 2974, 1045, 1013 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (d, 3H, $J =$ 6.4 Hz), 1.35 (d, 3H, $J = 6.4$ Hz), 2.38 (s, 3H), 4.10 (m, 1H), 5.19 (m, 1H), 7.27 (m, 2H), 7.40−7.52 (m, 3H), 8.58 (d, 1H), 8.64 (d, 1H), 8.81 (s, 1H), 8.90 (s, 1H). Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.43; H, 5.79; N, 5.37. Found: C, 64.58; H, 5.56, N, 5.21.

(*S*)-4-(1-Hydroxypropyl)-3-(*p*-tolylsulfinyl)pyridine (17a). Metalation of (*S*)-3-(*p*-tolylsulfinyl)pyridine **9a** (0.10 g, 0.5 mmol) according to the general procedure with *n*-butyllithium 2.5 M (0.74 mL, 1.5 mmol) and diisopropylamine (0.26 mL, 1.5 mmol), $t_1 = 60$ min, followed by reaction with propionaldehyde (0.07 mL, 0.6 mmol), $t_2 = 60$ min, was carried out. Purification by column chromatography eluting with ethyl acetate afforded **17a** as an orange oil (27%, 33.7 mg); de = 26%. IR (KBr) 3347, 2964, 2922, 1047 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, 3H, $J =$ 7.1 Hz), 1.60 (m, 2H), 2.37 (s, 3H), 3.90 (m, 1H), 4.15 (m, 1H), 4.93 (m, 1H), 7.27 (m, 2H), 7.39−7.47 (m, 3H), 8.55 (d, 1H, $J =$ 4.7 Hz), 8.57 (d, 1H, $J = 4.7$ Hz), 8.81 (s, 1H), 8.81 (s, 1H). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.51; H, 6.23; N, 5.09. Found: C, 65.31; H, 6.45; N, 5.07.

(*S*)-4-(1-Hydroxy-2-methylpropyl)-3-(*p*-tolylsulfinyl)pyridine (18a). Metalation of (*S*)-3-(*p*-tolylsulfinyl)pyridine **9a** (0.06 g, 0.3 mmol) according to the general procedure with *n*-butyllithium 1.6 M (0.58 mL, 0.9 mmol) and diisopropylamine (0.12 mL, 0.9 mmol), $t_1 = 60$ min, followed by reaction with 2,2-dimethympropanal (0.05 mL, 0.4 mmol), $t_2 = 60$ min, was carried out. Purification by column chromatography eluting with ethyl acetate afforded **18a** as a pale yellow solid (25%, 24.8 mg); mp: 158 °C; de > 99%. IR (KBr) 3171, 2919, 1046 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, 3H, $J = 7.1$ Hz), 1.60 (m, 2H), 2.37 (s, 3H), 3.90 (m, 1H), 4.15 (m, 1H), 4.93 (m, 1H), 7.27 (m, 2H), 7.39−7.47 (m, 3H), 8.55 (d, 1H, $J = 4.7$ Hz), 8.57 (d, 1H, $J = 4.7$ Hz), 8.81 (s, 1H), 8.81 (s, 1H). Anal. Calcd for $C_{17}H_{21}NO_2S$: C, 67.39; H, 6.98; N, 4.62. Found: C, 67.12; H, 7.10; N, 4.47.

(*S*)-4-(α-Hydroxybenzyl)-3-(*p*-tolylsulfinyl)pyridine (19a). Metalation of (*S*)-3-(*p*-tolylsulfinyl)pyridine **9a** (0.10 g, 0.5 mmol) according to the general procedure with *n*-butyllithium *2.5 M* (0.74 mL, 1.5 mmol) and diisopropylamine (0.26 mL, 1.5 mmol), $t_1 = 60$ min, followed by reaction with benzaldehyde (0.10 mL, 0.7 mmol), $t_2 = 60$ min, was carried out. Purification by column chromatography eluting with ethyl acetate afforded **19a** as a beige solid (13%,18.1 mg); mp 158 °C; de > 99%. IR (KBr) 3171, 2919, 1046 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.41 (s, 3H), 4.20 (m, 1H), 6.11 (s, 1H), 7.10 (d, 2H, $J = 8.0$ Hz),7.20 (m, 2H), 7.32 (m, 3H), 7.50 (d, 2H, $J = 8.0$ Hz), 8.60 (d, 1H, $J = 4.6$ Hz), 8.96 (s, 1H). Anal. Calcd for $C_{19}H_{17}NO_2S$: C, 70.65; H, 5.30; N, 4.34. Found: C, 70.92; H, 5.51; N, 4.03.

(*S*)-4-(1-Hydroxyethyl)-2,6-dimethoxy-3-(*p*-tolylsulfinyl)-pyridine (20a). Metalation of (*S*)-2,6-dimethoxy-3-(*p*-tolylsulfinyl)pyridine **12a** (0.10 g, 0.4 mmol) according to the general procedure with *n*-butyllithium 2.5 M (0.72 mL, 1.1 mmol) and diisopropylamine (0.15 mL, 1.1 mmol), $t_1 = 90$ min, followed by reaction with acetaldehyde (1.00 mL, 18.0 mmol), $t_2 = 30$ min, was carried out. Purification by column chromatography eluting with ethyl acetate/light petroleum ether (1/1) afforded **20a** as a yellow oil (75%, 87.3 mg); de = 38%. IR (KBr) 3360, 2925, 1060, 1012 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (d, 3H, $J = 6.1$ Hz), 1.50 (d, 3H, $J = 6.4$ Hz), 2.38 (s, 6H), 3.80 (s, 3H), 3.91 (s, 3H), 3.95.(s, 3H), 3.99 (s, 3H), 4.00 (m, 1H), 5.08 (m, 2H), 5.48 (q, 1H, $J = 6.4$ Hz), 6.48 (s, 1H), 6.58 (s, 1H), 7.23 (d, 2H, $J =$ 8.1 Hz), 7.25 (d, 2H, $J = 8.1$ Hz), 7.25 (d, 2H, $J = 8.2$ Hz), 7.47 (d, 2H, $J = 8.2$ Hz). Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.87; H, 5.97; N, 4.36; S, 9.99. Found: C, 60.02; H, 6.11; N,4.27; S, 10.20.

(*S*)-4-(1-Hydroxypropyl)-2,6-dimethoxy-3-(*p*-tolylsulfinyl)-pyridine (21a). Metalation of (*S*)-2,6-dimethoxy-3-(*p*-tolylsulfinyl)pyridine **12a** (0.10 g, 0.4 mmol) according to the general procedure with *n*-butyllithium 2.5 M (0.72 mL, 1.1 mmol) and diisopropylamine (0.15 mL, 1.1 mmol), $t_1 = 90$ min, followed by reaction with propionaldehyde (0.04 mL, 0.6 mmol), $t_2 = 60$ min, was carried out. Purification by column chromatography eluting with ethyl acetate/light petroleum ether (1/1) afforded **21a** as a yellow oil (53%, 63.7 mg); de = 28%. IR (KBr) 3362, 2925, 1060 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.78 (t, 3H, $J = 4.9$ Hz), 1.00 (t, 3H, $J = 4.9$ Hz), 1.53−1.73 (m, 2H), 1.71−1.78 (m, 2H), 2.37 (s, 3H), 2.38 (s, 3H), 3.78 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 4.00 (m, 1H), 4.67 (m, 1H), 4.87 (m, 1H), 5.21 (m, 1H), 6.45 (s, 1H), 6.54 (s, 1H), 7.23 (d, 2H, $J = 8.1$ Hz, H_{tol}), 7.24 (d, 2H, $J = 8.2$ Hz), 7.41 (d, 2H, $J = 8.2$ Hz), 7.47 (d, 2H, $J = 8.2$ Hz). Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.95; H, 6.32; N, 4.18. Found: C, 61.34; H, 6.54; N, 4.14.

(*S*)-4-(1-Hydroxy-2-methylpropyl)-2,6-dimethoxy-3-(*p*-tolylsulfinyl)pyridine (22a). Metalation of (*S*)-2,6-dimethoxy-3-(*p*-tolylsulfinyl)pyridine **12a** (0.10 g, 0.4 mmol) according to the general procedure with *n*-butyllithium 2.5 M (0.72 mL, 1.1 mmol) and diisopropylamine (0.15 mL, 1.1 mmol), $t_1 = 90$ min, followed by reaction with 2,2-dimethylpropanal (0.06 mL, 0.6 mmol), $t_2 = 60$ min, was carried out. Purification by column chromatography eluting with ethyl acetate/light petroleum ether (1/1) afforded **22a** as a pale yellow solid (58%, 75.4 mg); mp 110 °C dec; de > 99%. IR (KBr) 3250, 2935, 1064, 1015 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 9H), 2.33 (s, 3H), 3.70−3.80 (m, 1H), 3.71 (s, 3H), 3.86 (s, 3H), 5.27 (m, 1H), 6.54 (s, 1H), 7.14 (d, 2H), 7.39 (d, 2H). Anal. Calcd for $C_{19}H_{25}NO_4S$: C, 62.87; H, 6.94; N, 3.86; S, 8.83. Found: C, 63.01; H, 6.97; N, 3.74; S, 9.10.

(*S*)-4-(α-Hydroxybenzyl)-2,6-dimethoxy-3-(*p*-tolylsulfinyl)-pyridine (23a). Metalation of (*S*)-2,6-dimethoxy-3-(*p*-tolylsulfinyl)pyridine **12a** (0.10 g, 0.4 mmol) according to the general procedure with *n*-butyllithium 2.5 M (0.72 mL, 1.1 mmol) and diisopropylamine (0.15 mL, 1.1 mmol), $t_1 = 90$ min, followed by reaction with benzaldehyde (0.04 mL, 0.6 mmol), $t_2 = 60$ min, was carried out. Purification by column chromatography eluting with ethyl acetate/light petroleum ether (1/1) afforded **23a** as a pale yellow solid (60%, 81.6 mg); mp 134 °C; de > 99%. IR (KBr) 3250, 2935, 1064, 1015 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.88 (s, 3H), 4.02 (s, 3H), 5.42 (m, 1H), 5.90 (s, 1H), 6.11 (s, 1H), 7.03−7.08 (m, 2H), 7.23−7.30 (m, 5H), 7.51 (d, 2H, $J =$ 8.2 Hz). Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.80; H, 5.53; N, 3.66. Found: C, 65.74; H, 5.66; N, 3.65.

Supporting Information Available: Purification of materials and data for **3b**, **6b**, **9b**, **12b**, **13b**, **14b**, **15b**, **16b**, **17b**, **18b**, **19b**, **20b**, **21b**, **22b**, **23b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO981125D