was added acetic anhydride (1 mL, 10.6 mmol) with stirring. The reaction mixture was allowed to reach room temperature and stirred for 2 h. Water (10 mL), ether (50 mL), and 10% HCl in water (30 mL) were added sequentially with vigorous stirring. The organic phase was separated and the aqueous phase extracted with ether (2 × 10 mL). The combined organic phases were washed with saturated brine, a saturated solution of $NaHCO_3$, and brine, dried, and concentrated. Purification by column chromatography gave **28** (1.33 g, 96% yield): $[\alpha]^{25}_D$ +12.1° (*c* 11.5, EtOH) (lit.[30] for the 3*S* isomer $[\alpha]^{18.5}_{546}$ −11.5°); ^{1}H NMR δ 0.81 (t, *J* = 7.3 Hz, 3 H), 1.46 (m, 2 H), 1.75 (m, 2 H), 1.96 (s, 3 H), 2.56 (m, 2 H), 4.80 (m, 1 H), 7.15 (m, 5 H); ^{13}C NMR δ 15.79 (q), 27.45 (q), 33.32 (t), 38.10 (t), 41.60 (t), 81.35 (d), 132.17 (d), 134.60 (d), 134.69 (d); IR ($CHCl_3$) (cm^{-1}) 3010, 2990, 2910, 1710, 1280; MS *m/z* (relative intensity) 206 (1), 146 (42), 117 (100), 104 (53), 91 (69); HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, obsd 206.1292.

(4*R*)-4-(Acetyloxy)hexanoic Acid (29). The oxidation reaction of **28** was performed on a 6.45-mmol (1.33 g) scale in accordance with the general procedure (large scale). After 2.5 h, the reaction was complete and the workup was carried out as described above (general procedure), providing **29** (0.81 g, 72% yield): $[\alpha]^{25}_D$ +0.93° (*c* 10.2, EtOH); ^{1}H NMR δ 0.86 (t, *J* = 7.2 Hz, 3 H), 1.55 (m, 2 H), 1.81 (m, 2 H), 2.02 (s, 3 H), 2.35 (t, *J* = 7.4 Hz, 2 H), 4.81 (m, 1 H), 9.1 (s, 1 H); ^{13}C NMR δ 9.55 (q), 21.12 (q), 26.99 (t), 28.47 (t), 30.15 (t), 74.58 (d), 171.25 (s), 179.14 (s); IR (film) (cm^{-1}) 3450, 3000, 2930, 1720, 1360, 1020, 940; MS *m/z* (relative intensity) 174 (1), 157 (1), 115 (16), 91 (2), 85 (100); HRMS calcd for $C_8H_{14}O_4$ 174.0892, obsd 174.0913.

(4*R*)-γ-Caprolactone (30). To a solution of the acid **29** (800 mg, 4.6 mmol) in ether (10 mL) was added a 30% NaOH aqueous solution saturated in brine (10 mL), and the mixture was vigorously stirred for 1 h at room temperature. The aqueous layer was separated, treated with concentrated HCl (10 mL), and stirred for 0.5 h. The reaction mixture was extracted with ether (3 × 10 mL). The combined organic phases were washed with saturated $NaHCO_3$ (10 mL) and brine, dried, and carefully concentrated to an oil, which was purified by bulb-to-bulb distillation, without vacuum, to obtain **30** (0.38 g, 73% yield): bp 215–225 °C; $[\alpha]^{25}_D$ +50.8° (*c* 1.3, MeOH) [lit.[23] $[\alpha]^{20}_D$ +53.2° (*c* 1.0, MeOH)]; ^{1}H NMR δ 1.01 (t, *J* = 7.0 Hz, 3 H), 2.09 (m, 6 H), 4.43 (m, 1 H); ^{13}C NMR δ 9.56 (q), 27.65 (t), 28.66 (t), 29.03 (t), 66.01 (nd), 177.55 (s); IR ($CHCl_3$) (cm^{-1}) 2990, 1740, 1420, 1150; MS *m/z* (relative intensity) 114 (2), 86 (17), 85 (100), 60 (92); HRMS calcd for $C_6H_{10}O_2$ 114.0681, obsd 114.0657.

(30) Hewitt, L. F.; Kenyon, J. *J. Chem. Soc.* **1925**, 1094.

Acknowledgment. This research was supported by a grant from the DGICYT (MEC of Spain), PB86-0322, and the U.S.–Spanish Joint Committee for Scientific and Technological Cooperation, CCA-8510/079. Special thanks are given to Professor K. Barry Sharpless for helpful discussions and encouragement. M.T.N. thanks the MEC of Spain for an FPI fellowship.

Registry No. 1, 125303-51-7; 2, 60121-03-1; 3, 125303-52-8; 4, 125303-53-9; 5, 20795-51-1; 6, 1117-74-4; 7, 38488-01-6; 8, 125303-54-0; 9, 91-57-6; 10, 88-99-3; 11, 125303-55-1; 12, 125303-56-2; 13, 125303-57-3; 14, 592-41-6; 15, 109-52-4; 16, 125303-58-4; 17, 125303-59-5; 18, 67935-45-9; 19, 125303-60-8; 20, 122-97-4; 21, 104-53-0; 22, 26429-97-0; 23, 75553-23-0; 24, 125303-61-9; 25, 115346-55-9; 26, 125303-62-0; 27, 105836-17-7; 28, 78571-82-1; 29, 78571-84-3; 30, 63357-95-9; $(MoO)_2P(O)$-CH_2CO_2Me, 5927-18-4.

Diastereoselective Additions of (*R*)-(+)-Methyl *p*-Tolyl Sulfoxide Anion to Imines. Asymmetric Synthesis of (*R*)-(+)-Tetrahydropalmatine[1]

Stephen G. Pyne* and Branko Dikic

Department of Chemistry, University of Wollongong, P.O. Box 1144, N.S.W. 2500, Australia

Received September 7, 1989

The addition of the lithium carbanion of methyl phenyl sulfoxide and (*R*)-(+)-methyl *p*-tolyl sulfoxide to imines having at least one aryl substituent, under kinetically controlled conditions, gives β-amino sulfoxides with good to modest diastereoselection. Under equilibrium controlled condition poor product diastereoselection results. The addition of these anions to 3,4-dihydro-6,7-dimethoxyisoquinoline is unique in that the most favorable product diastereoselection (92:8) is observed under equilibrium controlled conditions. Deuteration experiments suggest that equilibration occurs via a β-amino α-lithio sulfinyl carbanion through a retro-Michael addition then Michael addition reaction sequence. This methodology allows for the construction of (*R*)-(+)-tetrahydropalmatine in four efficient synthetic steps.

A prominent structural feature of a large number of alkaloids and pharmacologically active amines is a chiral carbon that has a nitrogen substituent. Several asymmetric synthetic method have been recently reported for the preparation of these types of compounds.[2] We have demonstrated that enantiomerically pure β-amino sulfoxides are versatile intermediates for chiral alkaloid synthesis.[3] Chiral β-amino sulfoxides can be conveniently prepared by either conjugate addition of amines to chiral vinyl sulfoxides[3,4] or from the addition of a chiral α-sulfinyl

(1) Chiral Sulfur Compounds. 11. For part 9 and 10, see refs 3c and 4f.

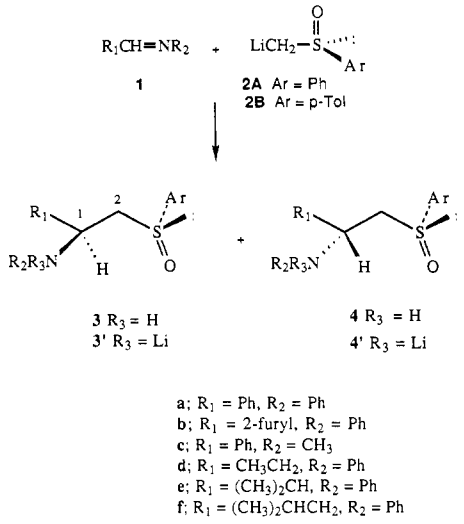
(2) (a) Gonzalez, M. A.; Meyers, A. I. *Tetrahedron Lett.* **1989**, *30*, 47–50. (b) Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 4859–4863. (c) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175–181. (d) Wanner, K. T.; Praschak, I. *Heterocycles* **1989**, *29*, 29–33. (e) Baird, P. D.; Blagg, J.; Davies, S. G.; Sutton, K. H. *Tetrahedron* **1988**, *44*, 171–186. (f) Czarnocki, Z.; MacLean, D. B.; Szarek, W. A. *Can. J. Chem.* **1987**, *65*, 2356–2361. (g) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117–7119.

(3) (a) Pyne, S. G.; Chapman, S. L. *J. Chem. Soc., Chem. Commun.* **1986**, 1688–1689. (b) Pyne, S. G. *Tetrahedron Lett.* **1987**, *28*, 4737–4740. (c) Pyne, S. G.; Bloem, P.; Chapman, S. L.; Dixon, C. E.; Griffith, R. *J. Org. Chem.* **1990**, *55*, 1086–1093.

(4) (a) Abbot, D. J.; Colonna, S.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1971**, 471. (b) Abbot, D. J.; Colonna, S.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. I* **1976**, 492–498. (c) Hansen, J. J.; Kjaer, A. *Acta. Chem. Scand., Ser B* **1974**, *28*, 418–424. (d) Pyne, S. G.; Griffith, R.; Edwards, M. *Tetrahedron Lett.* **1988**, *29*, 2089–2092. (e) Hirama, M.; Hioki, H.; Ito, S.; Kabuto, C. *Tetrahedron Lett.* **1988**, *29*, 3121–3124. (f) Pyne, S. G.; Bloem, P.; Griffith, R. *Tetrahedron*, in press.

0022-3263/90/1955-1932$02.50/0

Scheme I



a; R_1 = Ph, R_2 = Ph
b; R_1 = 2-furyl, R_2 = Ph
c; R_1 = Ph, R_2 = CH_3
d; R_1 = CH_3CH_2, R_2 = Ph
e; R_1 = $(CH_3)_2CH$, R_2 = Ph
f; R_1 = $(CH_3)_2CHCH_2$, R_2 = Ph

carbanion to an imine.[5] The diastereoeselectivity of the former method, however, is often modest,[3,4] while the latter process has not been fully developed. We now report the details of our initial investigation[5d] concerning the addition of the lithium carbanion of methyl phenyl sulfoxide (**2A**) and (*R*)-(+)-methyl *p*-tolyl sulfoxide (**2B**)[6a] to imines[7] and the application of this method to the asymmetric synthesis of (*R*)-(+)-tetrahydropalmatine.

Results

In contrast to the numerous reports on the addition of α-sulfinyl carbanions to aldehydes,[6] the addition of these carbanions to imines has received little attention,[5,8] In 1973, Tsuchihashi[5a] reported that the addition of the lithium carbanion of (*R*)-(+) methyl *p*-tolyl sulfoxide (**2B**) to *N*-benzylideneaniline **1a** at −10 to −20 °C was a highly diastereoselective process. The generality of this method, however, was not demonstrated. More recently Kagan[5b] reported the diastereoselective addition of the lithium carbanion of **2B** to **1a** and *N*-benzylidenealkylamines.

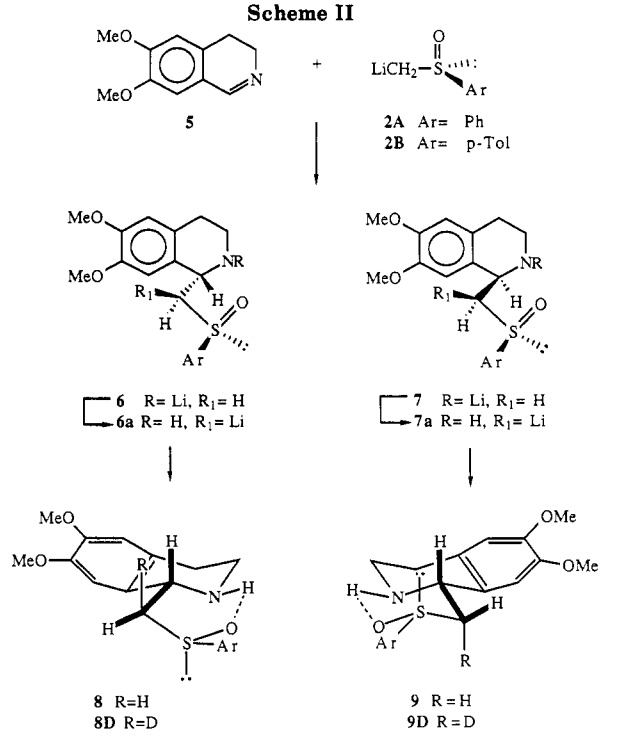
Our initial studies focused on the addition of the anion of racemic methyl phenyl sulfoxide (**2A**) to **1a** (Scheme I). The addition of **2A** to **1a** at −78 °C occurred smoothly over a period of 5 h, giving a mixture of the diastereoisomeric adducts **3a** and **4a** with modest diastereoselection (Table I). An identical product diastereoselection was realized when a solution of **2A** and **1a** was prepared at −78 °C and then held at −45 °C for 2 h or 0 °C for 5 min. Longer reaction times (0.5–12 h) at 0 °C resulted in very poor diastereoselection, suggesting that equilibration had occurred between the diastereoisomeric adducts **3'a** and **4'a**. A similar trend was observed when analogous reactions were performed with the anion of (*R*)-(+)-methyl

Table I. Reactions of 2 with Imines 1 or 5

entry	imine 1 or 5	anion	temp, °C; time, h	yield, %	diastreo-selctn 3:4 (8:9)[a]
1	**1a**	**2A**	−78; 5	96	82:18
2	**1a**	**2A**	−45; 2	95[a]	82:18
3	**1a**	**2A**	0; 5 min	95[a]	82:18
4	**1a**	**2A**	0; 1	95	58:42
5	**1a**	**2B**	0; 5 min	95	86:14
6	**1b**	**2A**	−45; 2	86	88:12
7	**1b**	**2A**	0; 2	94	76:24
8	**1b**	**2B**	0; 10 min	96	91:9
9	**1c**	**2A**	0; 2	86	88:12
10	**1c**	**2B**	0; 10 min	89	91:9
11	**1c**	**2B**	0; 12	89	51:49
12	**1d**	**2A**	−45; 2	85	79:21
13	**1d**	**2A**	0; 2	81	63:37
14	**1d**	**2B**	−45; 2	90	80:20
15	**1e**	**2B**	−45; 2	72	81:19
16	**1e**	**2B**	0; 2	62	66:44
17	**1f**	**2B**	−45; 2	78	81:19
18	**1f**	**2B**	0; 2	84	71:29
19	**5**	**2A**	−45; 2	64	(23:77)
20	**5**	**2A**	0; 12	85	(89:11)
21	**5**	**2B**	0; 12	92	(92:8)

[a] From ^1H NMR spectral analysis.

Scheme II



p-tolyl sulfoxide[6a] (**2B**) ($[\alpha]^{20}_D$ +168° (*c* 1.8, acetone)) and the imine **1a** or 2-furylmethylideneaniline **1b**. Kagan[5b] has also noted that the reaction temperature is a crucial variable in determining the product diastereoselection in these types of reactions.

N-Benzylidenemethylamine (**1c**) was found to be much less reactive than **1a** or **1b** toward addition of **2** and little reaction occurred at temperatures below −25 °C. When a solution of **1c** and **2** was prepared first at −78 °C and then allowed to warm slowly to 0 °C before being quenched at 0 °C after 10 min, a good product diastereoeselection (91:9) could be realized. However, extended reaction times (2–12 h) at 0 °C gave essentially an equal mixture of the two diastereomeric products **3c** and **4c** (Table I). The *N*-al-

(5) (a) Tsuchihashi, G. I.; Iriuchijam, S.; Maniwa, K. *Tetrahedron Lett.* **1973**, 3389–3392. (b) Ronan, B.; Marchalin, S.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 6101–6104. (c) Pyne, S. G.; Boche, G. *J. Org. Chem.* **1989**, *54*, 2663–2667. (d) Pyne, S. G.; Dikic, B. *J. Chem. Soc., Chem. Commun.* **1989**, 826–827. (e) Satoh, T.; Sato, T.; Oohara, T.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3973–3978.

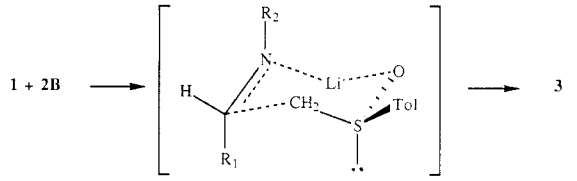
(6) (a) Solladie, G. *Synthesis* **1981**, 185–196. (b) References reported in ref. 5b.

(7) Prepared according to Tiollais: Tiollais, R. *Bull. Soc. Chim. Fr.* **1947**, 708–716.

(8) For the addition of racemic or achiral α-sulfinyl carbanions to imines, see: (a) Corey, E. J.; Chaykovsky, J. *J. Am. Chem. Soc.* **1965**, *87*, 1345–1353. (b) Nudelman, A.; Cram. D. J. *J. Org. Chem.* **1969**, *34*, 3659–3661. (c) Duhamel, L.; Duhamel, P.; Mancelle, N. *Bull. Soc. Chim. Fr.* **1974**, 331–337. (d) Ogura, K.; Furukawa, S.; Tsuchihashi, G. I. *Synthesis* **1976**, 202–204. (e) Satoh, T.; Oohara, T.; Yamakawa, K. *Tetrahedron Lett.* **1988**, *29*, 4093–4096.

(9) Brunet, E.; Carreno, M. C.; Gallego, M. T.; Ruano, J. L. G. *J. Chem. Soc., Perkin Trans II* **1983**, 937–942.

Scheme III



kylideneanilines **1d**, **1e**, and **1f** were more reactive toward 1,2 addition of **2** than **1c**. Addition occurred smoothly at −45 °C (2 h) to give a mixture (ca. 4:1, Table I) of the diastereomeric adducts **3d–f** and **4d–f** in good yields. Again a poorer ratio of the diastereomeric products **3d–f** and **4d–f** resulted when these reactions were allowed to warm to 0 °C for 2 h. Attempts to extend these reactions to nonaromatic imines were unsuccessful. For example, the reaction of **2** and *N*-pentylidenepentylamine at 0 °C gave a mixture of numerous products from which none of the desired adducts could be obtained analytically pure. Clearly aryl substituents on the imine that can stabilize incipient charge in the transition state are important to ensure high chemical reactivity in these reactions.

In contrast to **1c**, the addition of **2** to 3,4-dihydro-6,7-dimethoxyisoquinoline (**5**) occurred smoothly at −45 °C (Scheme II). Under these conditions a mixture of **8** and **9** was obtained in which the latter product was favored. At 0 °C, however, a high and much improved product diastereoselection was observed and **8** was the major diastereoisomeric product. A similar product diastereoselection was observed when a mixture of **5** and **2** was held at −45 °C for 2 h and then warmed to 0 °C (12 h).

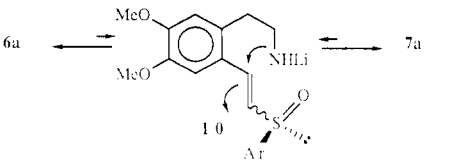
Discussion

The reactions of **2** with the imines **1a–f** show good to modest product diastereoselection under kinetically controlled conditions (−45 °C to 0 °C (10 min)); however, it is apparent that the initially formed diastereomeric adducts interconvert after extended reaction times at 0 °C. In general the product diastereoselection is poor under equilibrium control compared to that from kinetic control. The reaction of **5** with **2** is unique in that the most favorable product diastereoselection was observed under equilibrium controlled conditions.

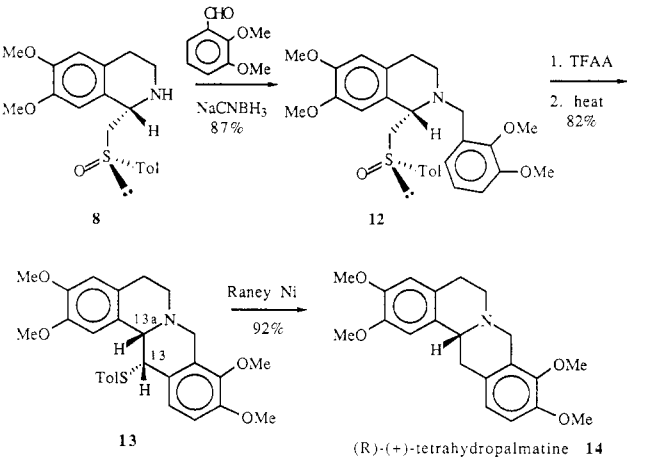
The relative stereochemistry of **3a–f** and **4a–f** was established by ^{1}H NMR spectroscopic analysis using **3a** and **4a** of known absolute stereochemistry as reference compounds. In general, the diastereotopic methylene protons H_2,H_2' in the *N*-phenyl compounds **3a,b,d–f** with the $1S,R_S$ absolute stereochemistry, have chemical shifts intermediate between the individual signals for these protons in $(1R,R_S)$-**4a,b,d–f**.

In **3a,b,d–f** the most downfield methylene proton shows a vicinal coupling of ca. 4 Hz while the other a vicinal coupling of ca. 8 Hz. A similar trend has been observed in the ^{1}H NMR spectrum of the diastereoisomers of racemic *N*-phenyl-2-(methylsulfinyl)-1-phenylethylamine.[9] The *N*-methyl diastereomeric compounds **3c** and **4d** show distinctly different ^{1}H NMR spectra than their *N*-phenyl counterparts. The ^{1}H NMR spectra of these compounds, however, show a good correlation with the ^{1}H NMR spectra reported for $(1R^*,R_S^*)$- and $(1R^*,S_S^*)$-1-phenyl-2-(methylsulfinyl)ethylamine, respectively.[10] We suggest the chair transition state (Scheme III) to account for the preference of the diastereomeric adducts **3b–f** over **4a–f** under kinetically controlled conditions.

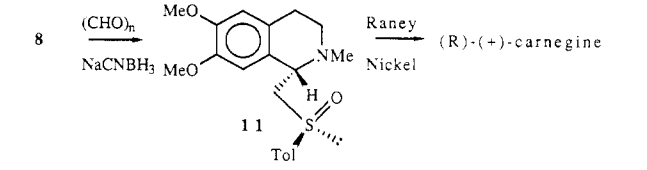
Scheme IV



Scheme V



The absolute stereochemistry of **8** was unequivocally determined by its conversion to (S,R_S)-(+)-**11** [mp 71 °C, lit.[3a] mp 70–72 °C, $[\alpha]^{23}_D$ +206° (*c* 1.1, $CHCl_3$)] by reductive methylation (92% yield).[11] We have previously converted **11** to (*R*)-(+)-carnegine by reductive desulfurization.[3a]



When the reaction mixture resulting from the treatment of **5** with **2A** at −45 °C for 2 h was quenched with D_2O, then quantitative and stereospecific (>95%) deuteration occurred, giving a mixture of the deuterated adducts **8D** and **9D**. These compounds must result from the deuteration of the α-sulfinyl carbanions **6a** and **7a**, respectively, which most likely arise via a proton-transfer mechanism from the initially formed adducts **6** and **7** (Scheme II). The stereochemistry of **8D** and **9D** is based upon literature precedent[6a] and ^{1}H NMR analysis (^{1}H NMR: **8D** (δ 4.59 (d, *J* = 3.1 Hz, H-1); **9D** (δ 4.38 (d, *J* = 3.8 Hz, H-1)), assuming that the intramolecular hydrogen-bonded forms of **8D** and **9D** are the major conformational isomers (Scheme II). We suggest that the interconversion of **6a** and **7a** occurs via a retro-Michael addition (β-elimination)–Michael addition reaction sequence (Scheme IV). The precise reason from the thermodynamic preference of **6a** over **7a**, however, is not clear.

To demonstrate the synthetic utility of this method, we have exploited **8** in an efficient synthesis of (*R*)-(+)-tetrahydropalmatine (**14**) in four synthetic steps using an intramolecular Pummerer reaction to build the required tetracyclic ring system as illustrated in Scheme V. Reductive alkylation of **8** (Ar = *p*-tolyl) with 2,3-dimethoxybenzaldehyde and sodium cyanoborohydride[12] smoothly afforded **12** in 87% yield, which upon exposure

(10) Brunet, E.; Gallego, M. T.; Ruano, J. L. G. *Tetrahedron* **1986**, *42*, 1423–1438.

(11) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673–1674.

(12) Borch, R. F.; Berstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.

to trifluoroacetic anhydride and then heating gave the tetracyclic sulfide **13** as a single diastereoisomer in 82% yield. The ^{1}H NMR spectra of **13** (δ 4.43, d, J = 2 Hz, H-14) is consistent with H-13 and H-13a having a cis relationship.[13] Reductive desulfurization of **13** with Raney nickel gave (R)-(+)-tetrahydropalmatine (**14**) (mp 138–139 °C, $[\alpha]^{20}_D$ +288.5 (c 2.0, EtOH), lit.[14] mp 142 °C, $[\alpha]_D$ +292° (EtOH)) that had identical spectral properties (^{1}H NMR,[15,16] ^{13}C NMR,[17] MS[15]) with that reported for the authentic material.

In conclusion, the stereochemistry of the products arising from the kinetically controlled addition of (R)-(+)-methyl p-tolyl sulfoxide anion to imines can be readily rationalized by assuming a chairlike transition state. This method allows for the construction of usefully functionalized enantiomerically pure isoquinolines that have potential for the asymmetric synthesis of a variety of alkaloids. Further applications of this methodology are currently under investigation.

Experimental Section[18]

Reaction of 2A or 2B with Imines: General Procedure. To a solution of diisopropylamine (121 mg, 1.2 mmol) in dry THF (3 mL) at 0 °C was added n-BuLi in hexane (1.1 mmol). After 10 min the solution was cooled to −78 °C and then a solution of (R)-(+)-methyl p-tolyl sulfoxide (1.0 mmol) in THF (2 mL) was added dropwise. After 1 h at −78 °C a solution of the imine **1** (1.3 mmol)[7] or **5**[19] (1 mmol) in THF (2 mL) was added. After 1 h, the solution was warmed slowly to the temperature specified in Table I, for the designated period of time. The reaction was then quenched rapidly by the addition of 10% K_2CO_3 (10 mL) and then extracted with $CHCl_3$ (2×). The combined extracts were dried ($MgSO_4$) and evaporated. The diastereoselection of these reactions was determined from ^{1}H NMR (400 MHz) analysis of the crude reaction product. Purification of the crude product by column chromatography on silica gel using ethyl acetate/hexane (or in the case of **8** and **9**, 5% methanol/ethyl acetate) as eluent gave the pure product. Yields are reported in Table I.

(R_S,1S)-N, 1-Diphenyl-2-(phenylsulfinyl)ethylamine (3a) and ((R_S,1R), 4A). 3a (Ar = p-tolyl): mp 200 °C (lit.[5a] mp 216–217 °C); IR (Nujol) 3310, 1030 cm^{-1}; ^{1}H NMR δ 7.49 (d, J = 8.2 Hz, 2 H), 7.3 (m, 7 H), 7.07 (m, 3 H), 6.67 (t, J = 7.3 Hz, 1 H), 6.53 (d, J = 7.6 Hz, 2 H), 5.28 (d, 1 H), 4.84 (t, 1 H), 3.16 (dd, J = 3.6, 13.7 Hz, 1 H), 3.06 (dd, J = 8.8, 13.7 Hz, 1 H), 2.39 (s, 3 H); ^{13}C NMR 146.6, 141.7, 141.4, 130.1, 129.0, 127.66, 127.65, 124.1, 118.0, 114.0, 64.1, 54.8, 21.4; MS 336 (51 M + H$^+$), 196 (100), 180 (22), 139 (22), 91 (22).

Anal. Calcd for $C_{21}H_{22}NOS$: C, 75.19; H, 6.31; N, 4.18. Found: C, 75.23; H, 6.43; N, 4.37.

4a (Ar = p-tolyl): ^{1}H NMR (in part) δ 5.12 (br s, 1 H), 4.90 (dd, J = 4.7, 9.8 Hz, 1 H), 3.26 (dd, J = 9.8, 13.5 Hz, 1 H), 2.94 (dd, J = 4.7, 13.5 Hz, 1 H), 2.38 (s, 3 H).

3a (Ar = Ph): mp 177–178 °C; IR (Nujol) 3320, 1030 cm^{-1}; ^{1}H NMR δ 7.68–7.05 (m, 12 H), 6.7–6.5 (m, 3 H), 5.28 (br s, 1 H), 4.85 (m, 1 H), 3.18 (dd, J = 3.7, 13.7 Hz, 1 H), 3.12 (dd, J = 8.7, 13.7 Hz, 1 H); ^{13}C NMR 131.1, 129.3, 129.0, 127.7, 126.3, 124.0, 118.0, 113.9, 64.1, 54.7; MS 322 (100, M + H$^+$), 196 (100), 182 (57), 104 (67), 93 (100).

Anal. Calcd for $C_{20}H_{19}NOS$: C, 74.36; H, 5.96; N, 4.36. Found: C, 73.15; H, 6.00; N, 4.36.

4a (Ar = Ph): ^{1}H NMR (in part) δ 3.28 (dd, J = 9.8, 13.6 Hz, 1 H), 2.98 (dd, J = 4.9, 13.6 Hz, 1 H).

3b (Ar = p-tolyl): mp 181 °C; ^{1}H NMR δ 7.52 (d, J = 8.1 Hz, 2 H), 7.32 (m, 3 H), 7.16 (t, J = 7.4 Hz, 2 H), 6.75 (t, J = 9.32 Hz, 1 H), 6.66 (d, J = 7.78 Hz, 2 H), 6.28 (m, 1 H), 5.05 (m, 1 H), 4.80 (m, 1 H), 3.26 (dd, J = 4.0, 13.3 Hz, 1 H), 3.20 (dd, J = 8.2, 13.3 Hz, 1 H), 2.41 (s, 3 H); ^{13}C NMR 153.2, 152.7, 146.8, 141.9, 130.1, 129.2, 124.1, 118.7, 114.2, 110.5, 107.4, 61.6, 49.0, 21.4; MS 186 (48, M − p-TolSO), 139 (41), 125 (72), 94 (100).

Anal. Calcd for $C_{19}H_{19}NO_2S$: C, 70.13; H, 5.88; N, 4.30. Found: C, 70.10; H, 5.94; N, 4.65.

3b (Ar = Ph): mp 176–177 °C; IR (Nujol) 3295, 1600, 1460, 1030 cm^{-1}; ^{1}H NMR δ 7.73–7.15 (m, 8 H), 6.82–6.25 (m, 5 H), 5.07 (m, 1 H), 4.70 (br s, 1 H), 3.28 (dd, J = 4.1, 13.3 Hz, 1 H), 3.22 (dd, J = 8.2, 13.4 Hz, 1 H), 2.41 (s, 3 H); ^{13}C NMR 153.3, 146.2, 143.6, 142.1, 131.1, 129.4, 129.3, 123.85, 118.6, 114.1, 110.5, 107.4, 61.6, 48.6; MS 312 (8, M + H$^+$), 219 (57), 185 (100), 125 (94), 93 (90).

Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.93; H, 5.71; N, 4.63.

4a (Ar = Ph): ^{1}H NMR (in part) δ 5.03 (t, J = 7.41 Hz, 1 H), 4.47 (br s, 1 H), 3.38 (dd, J = 7.3, 13.3 Hz, 1 H), 3.19 (dd, J = 7.2, 13.3 Hz, 1 H).

3c (Ar = p-tolyl): oil; IR (film) 3600–3200 (br), 3300 (sharp), 1035 cm^{-1}; ^{1}H NMR δ 7.52 (d, J = 8.2 Hz, 2 H), 7.27 (m, 7 H), 4.06 (dd, J = 3.4, 10.2 Hz, 1 H), 3.00 (dd, J = 10.2, 13.4 Hz, 1 H), 2.93 (dd, J = 3.4, 13.4 Hz, 1 H), 2.39 (s, 3 H), 2.31 (s, 3 H); ^{13}C NMR 141.2, 140.9, 140.6, 129.6, 128.3, 127.2, 126.6, 123.6, 65.0, 59.1, 33.8, 20.9; MS 274 (100, M + H$^+$), 148 (100), 134 (95), 118 (93), 106 (100); HRMS calcd for $C_{16}H_{20}NOS$ 274.1264, found 274.126.

4c (Ar = p-tolyl): ^{1}H NMR (in part) δ 3.22 (dd, J = 8.4, 13.1 Hz, 1 H), 2.81 (dd, J = 5.5, 13.1 Hz, 1 H), 2.39 (s, 3 H), 2.25 (s, 3 H).

3c (Ar = Ph): oil; IR (Nujol) 3700–3000 (br), 1650, 1050 cm^{-1}; ^{1}H NMR δ 7.63 (dd, J = 2.0, 7.3 Hz, 2 H), 7.50 (m, 3 H), 7.3 (m, 2 H), 7.26 (m, 2 H), 4.07 (dd, J = 3.4, 10.1 Hz, 1 H), 3.01 (dd, J = 10.1, 13.4 Hz, 1 H), 2.95 (dd, J = 3.5, 13.4 Hz, 1 H), 2.33 (s, 3 H); ^{13}C NMR 144.2, 141.4, 140.0, 129.3, 128.8, 127.8, 126.9, 123.9, 65.4, 59.3, 34.2; MS 260 (95, M + H$^+$), 134 (100), 125 (85), 120 (89), 91 (24).

3d (Ar = p-tolyl): mp 167 °C; IR (Nujol) 3330, 1030 cm^{-1}; ^{1}H NMR δ 7.52 (d, J = 8.1 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 7.16 (t, J = 7.5 Hz, 2 H), 6.70 (t, J = 7.3 Hz, 1 H), 6.64 (d, J = 7.8 Hz, 2 H), 3.89 (br, s, 2H), 2.98 (dd, J = 3.7, 13.3 Hz, 1 H), 2.79 (dd, J = 7.8, 13.3 Hz, 1 H), 2.41 (s, 3 H), 1.92–1.65 (m, 3 H), 0.96 (t, J = 7.5 Hz, 3 H); ^{13}C NMR 147.0, 141.5 (2 carbons), 130.0, 129.2, 123.9, 117.9, 113.8, 63.7, 51.1, 28.0, 21.3, 10.2; MS 288 (20, M + H$^+$), 148 (100), 134 (55), 125 (27), 118 (20), 91 (45), 77 (23); HRMS calcd for $C_{17}H_{22}NOS$ 288.1420, found 288.140.

Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.04; H, 7.36; N, 4.87. Found: C, 71.53; H, 7.49; N, 4.92.

4d (Ar = p-tolyl): ^{1}H NMR (in part) δ 3.13 (dd, J = 5.2, 13.4 Hz, 1 H).

3d (Ar = Ph): mp 119–120 °C; IR (Nujol) 3330, 1030 cm^{-1}; ^{1}H NMR δ 7.63 (dd, J = 2.2 7.6 Hz, 2 H), 7.51 (m, 3 H), 7.17 (t, J = 7.6 Hz, 2 H), 6.72 (t, J = 7.3 Hz, 1 H), 6.66 (d, J = 8.2 Hz, 2 H), 3.92 (br s, 1 H), 3.88 (br s, 1 H), 2.99 (dd, J = 3.5, 13.2 Hz, 1 H), 2.81 (dd, J = 7.9, 13.2 Hz, 1 H), 1.81–1.68 (m, 2 H), 0.98 (t, J = 7.3 Hz, 3 H); ^{13}C NMR 147.1, 131.0, 129.3, 123.9, 118.0, 113.8, 63.2, 51.2, 28.1, 10.3; MS 274 (21, M + H$^+$), 148 (100), 134 (37), 99 (90).

3e (Ar = p-tolyl): oil; ^{1}H NMR δ 7.55–6.5 (m, 9 H), 3.99 (m, 1 H), 2.99 (dd, J = 4.6, 13.3 Hz, 1 H), 2.78 (dd, J = 8.2, 13.3 Hz, 1 H), 2.40 (s, 3 H), 1.75 (m, 1 H), 1.6 (m, 2 H), 0.94 (d, J = 6.5 Hz, 3 H) 0.89 (d, J = 6.6 Hz, 3 H); ^{13}C NMR 147.0, 146.3, 141.4, 129.9, 129.3, 124.0, 117.7, 113.5, 113.1, 63.9, 48.0, 44.8, 24.9, 22.7, 22.3, 21.3; MS 316 (80, M + H$^+$), 176 (100), 162 (75), 133 (80) 119 (55), 106 (77); HRMS calcd for $C_{19}H_{26}NOS$ 316.1733, found 316.174.

4e (Ar = p-tolyl): ^{1}H NMR (in part) δ 3.87 (m, 1 H), 3.08 (dd, J = 4.3, 13.2 Hz, 1 H), 2.76 (dd, J ca. 8, 13.2 Hz, 1 H); ^{13}C NMR (in part) 62.7, 47.3, 44.5.

3f (Ar = p-tolyl): oil; ^{1}H NMR δ 7.60–7.05 (m, 6 H), 6.75–6.50 (m, 3 H), 3.60 (m, 1 H), 2.96 (dd, J = 3.0, 13.3 Hz, 1 H), 2.71 (dd, J = 9.9, 13.3 Hz, 1 H), 2.41 (s, 3 H), 2.05 (m, 1 H), 0.97 (d, J = 6.9 Hz, 3 H), 0.92 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (in part) 61.9,

(13) Yu, C. K.; MacLean, D. B.; Rodrigo, R. G. A.; Manski, R. H. F. *Can. J. Chem.* **1970**, *48*, 3673–3678.
(14) Späth, E.; Mosettig, E.; Tröthandl, O. *Chem. Ber.* **1923**, *56B*, 875–879.
(15) Chen. C. Y.; MacLean, D. B. *Can. J. Chem.* **1968**, *46*, 2501–2506.
(16) Yasuda, S.; Hirasawa, T.; Hanaoka, M. *Tetrahedron Lett.* **1987**, *28*, 2399–2402.
(17) Hughes, D. W.; Holland. H. L.; MacLean, D. B. *Can. J. Chem.* **1974**, *54*, 2252–2260.
(18) General procedures were as previously described.[4f,5b]
(19) Gray, A. P.; Archer, W. L.; Schlieper, D. C.; Cavallito, C. J. *J. Am. Chem. Soc.* **1955**, *77*, 3536–3541.

54.1, 32.0, 21.3, 18.5, 18.3; MS 302 (100, M + H$^+$), 162 (65), 139 (18), 119 (20), 106 (18); HRMS calcd for $C_{18}H_{24}NOS$ 302.1577, found 302.155.

4f (Ar = *p*-tolyl): ^{1}H NMR (in part) δ 3.89 (m, 1 H), 3.09 (dd, J = 7.7, 13.3 Hz, 1 H), 2.88 (dd, J = 5.8, 13.3 Hz, 1 H), 2.41 (s, 3 H), 2.15 (m, 1 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.90 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (in part) 59.8, 54.4, 30.7, 17.8.

(1*S*,*R*$_S$)-3,4-Dihydro-6,7-dimethoxy-1-[(*p*-tolylsulfinyl)methyl]isoquinoline (8) and ((1*R*,*R*$_S$) 9). **8 (Ar = *p*-tolyl)**: mp 124–125 °C; IR (Nujol) 3650–3310, 3265 (sharp), 1110, 1035 cm^{-1}; ^{1}H NMR δ 7.57 (d, J = 8 Hz, 2 H), 7.32 (d, J = 8 Hz, 2 H), 6.56 (s, 1 H), 6.45 (s, 1 H) 4.59 (dd, J = 2.9, 10.7 Hz, 1 H), 3.91 (s, 3 H), 3.77 (s, 3 H), 3.15 (m, H), 3.10 (dd, J = 3.1, 13.4 Hz, 1 H), 2.7 (m, 2 H), 2.40 (s, 3 H); ^{13}C NMR 147.8, 147.5, 141.1, 129.8, 128.2, 127.51, 123.7, 112.2, 109.3, 64.8, 55.9, 54.7, 49.8, 39.5, 28.8, 21.1; MS 346 (24, M + H$^+$), 205 (15), 192 (29), 154 (100), 136 (100).

9 (Ar = *p*-tolyl): ^{1}H NMR (in part) δ 6.57 (s, 1 H), 6.49 (s, 1 H), 4.38 (dd, J = 3.8, 9.2 Hz, 1 H).

(1*S,*R*$_S$*)-3,4-Dihydro-6,7-dimethoxy-1-[(phenylsulfinyl)methyl]isoquinoline. (8 (Ar = Ph))**: mp 170 °C; IR (Nujol) 3650–3100, 3380 (sharp), 1110, 1030 cm^{-1}; ^{1}H NMR δ 7.68 (dd, J = 1.5, 8.2 Hz, 2 H), 7.52 (m, 3 H), 6.56 (s, 1 H), 6.44 (s, 1 H), 4.60 (dd, J = 2.9, 10.7 Hz, 1 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 3.15 (m, 3 H), 3.06 (dd, J = 3.1, 13.4 Hz, 1 H), 2.71 (m, 2 H); ^{13}C NMR 147.8, 147.5, 144.3, 130.8, 129.3, 128.1, 127.5, 123.8, 112.1, 109.1, 64.9, 55.9, 55.8, 50.0, 39.5, 28.9; MS 322 (24, M + H$^+$), 205 (15), 192 (29), 154 (100), 136 (100).

Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.15; H, 6.65; N, 4.57.

(+)-(1*S*,*R*$_S$)-*N*-Methyl-3,4-dihydro-6,7-dimethoxy-1-[(*p*-tolylsulfinyl)methyl]isoquinoline (11). To a solution of **8** (Ar = *p*-tolyl, 198 mg, 0.6 mmol) in acetonitrile (2 mL) and aqueous formaldehyde (37%, 0.5 mL) was added sodium cyanoborohydride (50 mg, 0.8 mmol). After 20 min the pH of the solution was adjusted to neutral on wet pH paper by the addition of glacial acetic acid. After 6 h the mixture was concentrated by evaporated, treated with 2 M KOH (2 mL), and then extracted with chloroform. The combined extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate as eluent. The pure product (190 mg, 92%) had mp 71 °C, $[\alpha]^{23}_D$ +206° (c 1.1 ($CHCl_3$)) (lit.[3a] mp 70–72 °C, $[\alpha]^{23}_D$ +206° (c 1.1 ($CHCl_3$)) and spectral properties identical with an authentic sample.

(1*S*,*R*$_S$)-*N*-[(2,3-Dimethoxyphenyl)methyl]-3,4-dihydro-6,7-dimethoxy-1-[(*p*-tolylsulfinyl)methyl]isoquinoline (12). The titled compound was prepared from **9** (0.91 mmol) as described above for the preparation of **11** except that 2,3-dimethoxybenzaldehyde (1.5 mmol) was used in place of formaldehyde. Purification of the crude product by column chromatography on silica gel gave **12** (392 mg, 87%): oil; IR (film) 1520, 1460, 1260, 1040 cm^{-1}; ^{1}H NMR δ 7.52 (d, J = 8.1 Hz, 2 H), 7.28 (m, 3 H), 7.11 (t, J = 8.3 Hz, 1 H), 6.86 (d, J = 8.3 Hz, 1 H), 6.58 (s, 1 H), 6.57 (s, 1 H) 4.39 (dd, 1 H), 4.12 (d, J = 13.9 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.76 (d, J = 13.9 Hz, 1 H), 3.2–2.9 (m, 5 H), 2.40 (s, 3 H); ^{13}C NMR 152.6, 147.8, 147.7, 142.3, 140.9, 132.6, 129.8, 127.27, 126.7, 124.0, 123.8, 122.9, 112.0, 111.2, 110.5, 66.5, 61.0, 56.7, 56.0, 55.9, 55.7, 50.8, 41.3, 22.4, 21.3; MS 496 (88, M + H$^+$), 480 (75), 356 (100), 342 (60), 324 (60); HRMS calcd for $C_{28}H_{34}NO_5S$ 496.2154, found 496.212.

(+)-(13*S*,13a*S*)-5,8,13,13a-Tetrahydro-2,3,9,10-tetramethoxy-13-[(4-methylphenyl)thio]-6*H*-dibenzo[*a*,*g*]quinolizine (13). A solution of **12** (100 mg, 0.2 mmol) in chloroform (2.5 mL) at 0 °C was treated dropwise with trifluoroacetic anhydride (0.4 mmol). The mixture was heated at 95 °C in a sealed tube for 4 h. The mixture was then cooled, diluted with saturated sodium carbonate solution, and then extracted with ether (3×). The combined extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on alumina using ethyl acetate/hexane (1:1) and then ethanol as eluent. The desired product (81 mg, 82%) was obtained as an oil: $[\alpha]^{20}_D$ +148.3° (c 3.6, $CHCl_3$); IR (Nujol) 1600, 1515, 1490, 1460, 1375 cm^{-1}; ^{1}H NMR δ 7.07 (d, J = 8.1 Hz, 2 H), 6.98 (d, J = 7.9 Hz, 2 H), 6.73 (d, J = 8.4 Hz, 2 H), 6.68 (d, J = 7.9 Hz, 1 H), 6.67 (s, 1 H), 6.52 (s, 1 H) 4.43 (d, J = 2 Hz, 1 H), 4.30 (d, J = 16.2 Hz, 1 H), 3.99 (br s, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.71 (s, 3 H), 3.58 (d, J = 16.2 Hz, 1 H), 3.25 (m, 2 H), 2.65 (m, 2 H), 2.29 (s, 3 H); ^{13}C NMR (in part) 63.8, 60.0, 58.0, 55.8, 54.1, 51.1, 29.3, 21.0; MS 478 (25, M + H$^+$), 354 (100), 286 (14), 195 (50), 151 (39), 125 (89), 91 (47).

(*R*)-(+)-Tetrahydropalmatine (14). To a solution of **13** (70 mg) in ethanol (0.5 mL) was added Raney nickel (W2, ca. 200 mg), and the reaction mixture was stirred rapidly for 10 h. The mixture was then filtered through a pad of Celite and the ethanol was evaporated, giving a pale yellow solid (46 mg). Recrystallization from ethanol gave pure (*R*)-(+)-tetrahydropalmatine: mp 138–139 °C; $[\alpha]^{20}_D$ +288.5° (c 2, EtOH) (lit.[14] mp 142 °C, $[\alpha]^{20}_D$ +292.5° (EtOH)); ^{1}H NMR δ 6.89 (dd, J = 8.4 Hz, 1 H), 6.80 (dd, J = 8.4 Hz, 1 H), 6.73 (s, 1 H), 6.63 (s, 1 H), 4.29 (d, J = 15.8 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.86 (s, 6 H), 3.61 (d, J = 15.8 Hz, 1 H); ^{13}C NMR 150.0, 147.8, 145.0, 129.5, 128.3, 127.7, 126.8, 123.8, 111.7, 111.4, 109.1, 60.2, 59.4, 56.2, 56.0, 53.9, 51.5, 36.1, 29.0; MS 356 (58 M + H$^+$), 190 (33), 164 (77), 144 (100), 121 (36).

Acknowledgment. Financial support by the Australian Research Council is gratefully acknowledged.

Registry No. **1a**, 538-51-2; **1b**, 3237-23-8; **1c**, 622-29-7; **1d**, 7138-58-1; **1e**, 7020-77-1; **1f**, 4275-06-3; **2A** (Li = H), 4850-71-9; **2B** (Li = H), 1519-39-7; **3a** (Ar = Ph), 124687-72-5; **3a** (Ar = *p*-Tol), 50789-50-9; **3b** (Ar = Ph), 124687-75-8; **3b** (Ar = *p*-Tol), 124687-74-7; **3c** (Ar = Ph), 124687-81-6; **3c** (Ar = *p*-Tol), 121411-16-3; **3d** (Ar = Ph), 124687-84-9; **3d** (Ar = *p*-Tol), 124687-82-7; **3e** (Ar = *p*-Tol), 124687-85-0; **3f** (Ar = *p*-Tol), 124687-87-2; **4a** (Ar = Ph), 124687-73-6; **4a** (Ar = *p*-Tol), 121411-06-1; **4b** (Ar = Ph), 124687-76-9; **4b** (Ar = *p*-Tol), 124687-90-7; **4c** (Ar = Ph), 124687-91-8; **4c** (Ar = *p*-Tol), 121411-15-2; **4d** (Ar = Ph), 124687-92-9; **4d** (Ar = *p*-Tol), 124687-83-8; **4e** (Ar = *p*-Tol), 124687-86-1; **4f** (Ar = *p*-Tol), 124687-88-3; **5**, 3382-18-1; **8** (Ar = Ph), 124687-89-4; **8** (Ar = *p*-Tol), 124687-77-0; **9** (Ar = Ph), 124687-93-0; **9** (Ar = *p*-Tol), 124687-78-1; **11**, 109985-76-4; **12**, 124687-79-2; **13**, 124687-80-5; **14**, 3520-14-7; 2,3-dimethoxybenzaldehyde, 86-51-1.