Asymmetric oxidation of 2-(arylsulfenyl)pyrroles

Alison Thompson, Jose R. Garabatos-Perera, and H. Martin Gillis

Abstract: The asymmetric oxidation of prochiral 2-(arylsulfenyl)pyrroles has been investigated. A marked electronic effect within the substrate significantly influenced the degree of enantioselectivity obtained, with very high enantioselectivity being obtained for 5-(nitrobenzensulfenyl)pyrrole-2-carboxaldehydes using Ti(*i*-PrO)$_4$/(+)-(*R*,*R*)-DET/H_2O/CHP. This result bodes well for optimizing the asymmetric oxidation of other diaryl sulfides, substrates that have previously given only low enantiomeric excesses.

Key words: asymmetric oxidation, sulfide, sulfoxide, pyrrole.

Résumé : On a étudié l'oxydation asymétrique de 2-(arylsulfényl)pyrroles prochiraux. On a noté qu'un effet électronique marqué dans le substrat influence d'une façon significative le degré d'énantiosélectivité obtenu, la plus grande énantiosélectivité étant obtenue avec les 5-(nitrobenzènesulfényl)pyrrole-2-carboxaldéhydes en utilisant le Ti(*i*-PrO)$_4$/(+)-(*R*,*R*)-DET/H_2O/CHP. Les résultats obtenus sont de bon augure pour l'optimisation de l'oxydation asymétrique d'autres sulfures de diaryles, des substrats qui n'ont donné antérieurement que de très faibles excès énantiomériques.

Mots-clés : oxydation asymétrique, sulfure, sulfoxyde, pyrrole.

[Traduit par la Rédaction]

Introduction

The use of chiral sulfoxides as auxiliaries for the asymmetric synthesis of biologically important compounds has found many applications (1, 2). For example, the efficiency of sulfoxides has been demonstrated for controlling the stereoselectivities of alkylation reactions, Michael addition reactions, aldol reactions, cycloaddition reactions, and Pummerer rearrangements (3). Chiral sulfoxides are generally prepared using either organometallic reagents and resolved diastereomeric sulfinates (i.e., chiral sulfinyl transfer reagents) (2, 4–6) or via the asymmetric oxidation of prochiral sulfides (2, 7).

Synthetic strategies involving pyrroles often require the introduction of a deactivating electron-withdrawing group that reduces the electron-rich character of the pyrrole unit. As such, the nucleophilicity of the pyrrolic core may be controlled and undesirable side-reactions minimized (8). Whilst this control has commonly been achieved by the use of carboxylates at the 2-position, the use of a sulfenyl group to mask the 2-position, rather than protect through electron-withdrawal, has recently been demonstrated (9, 10). The utility of 2-(sulfenyl)pyrroles in acylation reactions, nitration reactions, and condensation reactions with various aldehydes, as well as the removal of the sulfenyl group using Raney nickel, highlights the sulfenyl group as a valuable masking/protecting group for pyrrolic compounds. With 2-(arylsulfenyl)pyrroles showing promise for the synthesis of functionalized pyrroles, 2-(arylsulfinyl)pyrroles (11) become of interest.

Chiral 2-(arylsulfinyl)pyrroles of high enantiomeric purity prepared by sulfinylation using diastereomerically pure menthyl arylsulfinates have attracted attention because of their use as removable chiral auxiliaries and as building blocks for macromolecular chemistry (4). While this method has been successfully applied for several 2-(arylsulfinyl)pyrroles (4, 5), it lacks generality because of the difficulty in obtaining a diverse set of diastereomerically pure menthyl aryl- or alkylsulfinates (2). Indeed, the preparation of diastereomerically pure menthyl arylsulfinates requires multiple recrystallizations, and, furthermore, menthyl alkylsulfinates (e.g., menthyl methanesulfinate) are typically oils, which thus prohibits recrystallization as a strategy by which to obtain diastereomerically pure material (12, 13). In this article, we report investigations towards an alternative approach to chiral 2-(arylsulfinyl)pyrroles involving the asymmetric oxidation of prochiral 2-(arylsulfenyl)pyrroles.

Although numerous methodologies have been reported for the asymmetric oxidation of sulfides to sulfoxides (2, 6, 14–16), so far, they have been largely limited to sulfides with two stereochemically different substitutents (i.e., aryl and alkyl). Substrates with similar groups such as dialkyl or diaryl generally lead to little or no asymmetric induction. For example, the asymmetric oxidation of methyl benzyl sulfide using a chiral titanium complex (17, 18), chiral oxaziridine (19), chiral metallo(salen) complex (20), or enzymatic methods (21, 22) gives the desired sulfoxide in modest–excellent yields (50%–97%), but with poor enantioselectivities (14%–58%). Even a recent example for the asymmetric oxidation of sulfides using hydrogen peroxide in water and a homochiral iron(III) catalyst focuses on the oxidation of methyl phenyl sulfide, with a somewhat reduced enantioselectivity being obtained for even ethyl phenyl sulfide (23). Similarly, a very recent novel

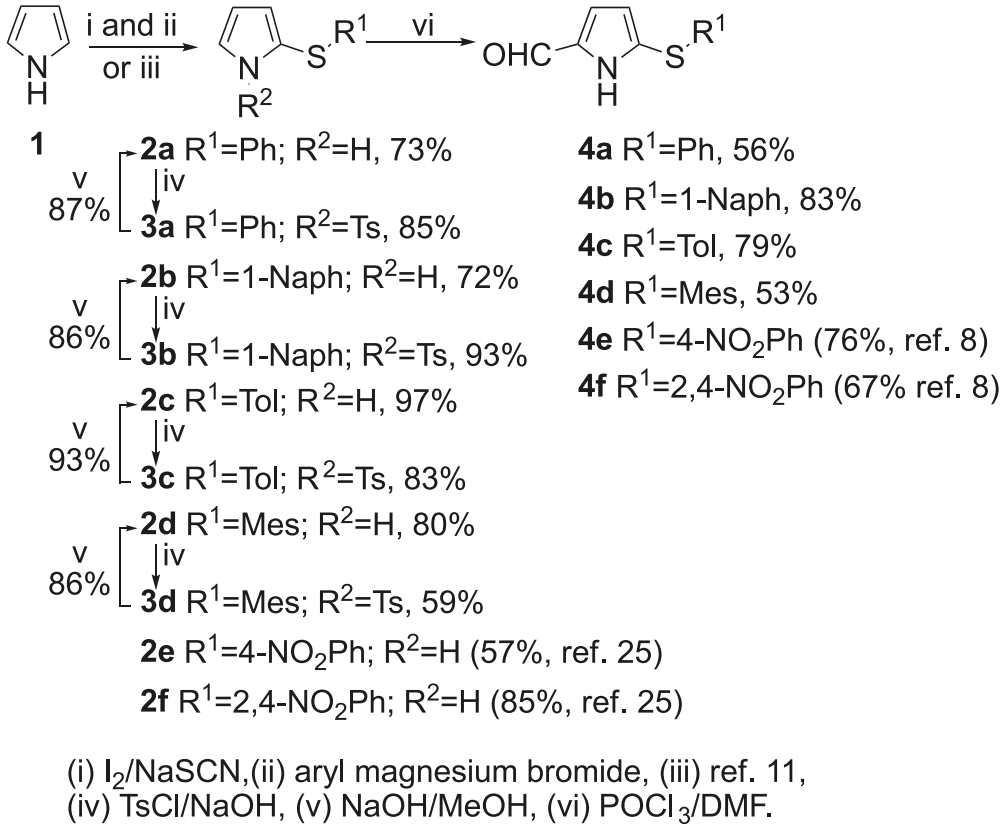
Received 3 December 2007. Accepted 19 February 2008. Published on the NRC Research Press Web site at canjchem.nrc.ca on 13 May 2008.

A. Thompson,[1] J.R. Garabatos-Perera, and H.M. Gillis. Department of Chemistry, Dalhousie University, Halifax, NS B3H 4J3, Canada.

[1]Corresponding author (e-mail: Alison.Thompson@dal.ca).

 doi:10.1139/V08-054

Scheme 1. Synthesis of 2-(arylsulfenyl)pyrroles.



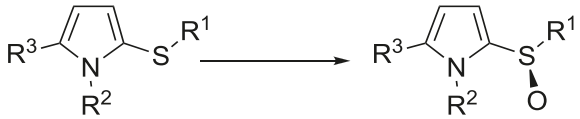
oxaziridinium salt, derived from cholesterol, gives good–excellent enantioselectivity for a variety of aryl alkyl sulfides, but no reports for diaryl sulfides are included (24).

Results and discussion

To probe their asymmetric oxidation, we prepared a series of 2-(arylsulfenyl)pyrroles with various substituents at the 2- and 5-positions. Following an established procedure for the preparation of 2-(phenylsulfenyl)pyrrole **2a** (10, 25) from 2-(thiocyanato)pyrroles (26–28) and phenylmagnesium bromide, a series of 2-(arylsulfenyl)pyrroles **2a**–**2d** were obtained in good yields by simply varying the Grignard reagent used (Scheme 1). We previously reported the preparation of **4e** and **4f** using Vilsmeier–Hack formylation conditions (9), and extension of this work for the 2-(arylsulfenyl)pyrroles **2a**–**2d** provided 5-(arylsulfenyl)pyrrole-2-carboxylaldehydes **4a**–**4d** in moderate to good yields. The excellent directing ability of the arylsulfenyl group for formylation at the vacant α-position emphasizes a general feature of sulfenyl masking groups. In our hands, 2-(arylsulfenyl)pyrroles **2a**–**2d** prepared via this route were found to be unstable to air (9) and were immediately protected as their corresponding *N*-tosyl derivatives **3a**–**3d** for ease of manipulation and storage (8). In all cases, the introduction of an electron-withdrawing group (tosyl or formyl) resulted in enhanced product stability.

With several prochiral 2-(arylsulfenyl)pyrroles available, we investigated their asymmetric oxidation (29–32) using chiral titanium complexes prepared from Ti(*i*-PrO)$_4$ and (+)-(*R*,*R*)-diethyl tartrate (DET), as described by Kagan (17, 33–38) and Modena (18). In our preliminary efforts, the asymmetric oxidation of 2-(phenylsulfenyl)pyrrole **2a** using *tert*-butyl hydroperoxide (TBHP) according to both the Kagan and Modena protocols resulted in essentially racemic sulfoxide **6a** (Table 1, entry 1), albeit in reasonable isolated yield. Under similar conditions, pyrroles **2e** and **2f**, bearing an electron-withdrawing group within the sulfenyl moiety, were oxidized using cumyl hydroperoxide (CHP) at –20 °C and 25 °C with a dramatic improvement of enantioselectivity (Table 1, entries 2 and 3 vs. entry 1). Interestingly, **2e**, bearing one nitro group, gave an enantioselectivity of 29% under these conditions, whereas **2e**, with two nitro groups, gave an enantioselectivity of 78%, and so decreasing the electron-density about the sulfide appeared to result in an increased enantioselectivity. However, the use of **3a** with an electron-withdrawing tosyl group on the pyrrolic nitrogen atom did not result in improved enantioselectivity, despite attempts under various conditions (Table 1, entry 4). Maintaining *N*-tosyl substitution, the introduction of the more sterically demanding naphthyl group within **3b**, rather than a phenyl or tolyl group within **3a** and **3c**, respectively, on the sulfenyl moiety did not significantly affect the oxidation reaction (Table 1, entries 5 and 6A). Furthermore, and significantly, other well-known methods for asymmetric sulfide oxidation resulted in poor yields and enantiopurities with 2-(*p*-tolylsulfenyl)pyrrole-*N*-tosylpyrrole **3c** (Table 1, entry 6; methods C–E). The poor enantioselectivities for **3c** serve to further emphasize that the preparation of enantiopure sulfoxides by the oxidation of diaryl sulfides is far from trivial.

Table 1. Asymmetric and racemic oxidation of 2-(arylsulfenyl)pyrroles.



Entry	Substrate	Product	R^1	R^2	R^3	Method[a]	Oxidant	Time (h)	Temperature (°C)	Isolated yield (%)	ee[b] (%)
1	**2a**	**6a**	Ph	H	H	A	TBHP	20	–20	72	0
						B	TBHP	20	–20	98	9
2	**2e**	**6e**	4-NO_2Ph	H	H	A	CHP	48	–20	80	29
3	**2f**	**6f**	2,4-NO_2Ph	H	H	A	CHP	20	25	87	78
4	**3a**	**5a**	Ph	Ts	H	A	CHP	20	–20	0	—
						A	CHP	20	25	77	8[c]
						B	TBHP	20	25	78	7
						F	*m*-CPBA	15 min	0	77	—
5	**3b**	**5b**	1-Naph	Ts	H	A	CHP	20	25	91	12[c]
						F	*m*-CPBA	2	25	72	—
6	**3c**	**5c**	Tol	Ts	H	A	CHP	20	–20	83	16[c]
						C	oxaziridine	48	25	11	31
						D	H_2O_2	48	25	6	0
						E	H_2O_2	48	25	0	—
						F	*m*-CPBA	2	25	45	—
7	**3d**	**5d**	Mes	Ts	H	A	CHP	20	–20	0	—
						A	CHP	48	25	37	27
8	**4a**	**7a**	Ph	H	CHO	A	TBHP	20	–20	62	69
						A	CHP	20	–20	79	54
						B	TBHP	20	–20	95	53
						B	CHP	20	–20	72	53
						B	CHP[d]	20	–20	70[e]	17
9	**4b**	**7b**	1-Naph	H	CHO	A	TBHP	20	–20	87	52
						A	CHP	20	–20	87	53
10	**4c**	**7c**	Tol	H	CHO	A	TBHP	20	–20	78	65
						A	CHP	20	–20	78	54
11	**4d**	**7d**	Mes	H	CHO	A	CHP	48	–20	93	48
12	**4e**	**7e**	4-NO_2Ph	H	CHO	**A**	CHP	48	–20	45	96
						F	*m*-CPBA	2	25	45	—
13	**4f**	**7f**	2,4-NO_2Ph	H	CHO	A	CHP	20	–20	0	—
						A	**CHP**	**20**	**25**	**85**	**98**
						F	*m*-CPBA	2	25	76	—

[a]Method A: Ti(*i*-PrO)$_4$/(+)-(*R*,*R*)-DET/H_2O/TBHP or CHP (1:2:1:2) in CH_2Cl_2. Method B: Ti(*i*-PrO)$_4$/(+)-(*R*,*R*)-DET/TBHP or CHP (1:4:2) in $ClCH_2CH_2Cl$. Method C: (+)-(1*S*)-(10-camphorsulfonyl)oxaziridine (1.05 equiv.) in CH_2Cl_2 (43). Method D: (–)-(*S*)-2-(*N*-3,5-diiodosalicyliden)amino-3,3-dimethyl-1-butanol/[$VO(acac)_2$]/H_2O_2 (1.5 equiv.) in CH_2Cl_2 (20, 44). Method E: chloroperoxidase/H_2O_2 (1.5 equiv.) in 20% acetonitrile and sodium citrate buffer (0.05 mol/L, pH 5) (45). Method F: *m*-CPBA (1.0 equiv.) in CH_2Cl_2.

[b]Determined by chiral HPLC analysis.

[c]Determined by chiral HPLC analysis of the corresponding tosyl deprotected **6c**.

[d]Kinetic resolution of *rac*-**7a** using 0.5 equiv. of CHP.

[e]Recovered **7a**.

Continuing the notion that the introduction of electron-withdrawing groups enhances the stereoselectivity of oxidation (Table 1, entries 2 and 3 cf. 1) the effect of the α-formyl substituent was investigated. Thus, 5-(arylsulfenyl)pyrrole-2-carboxylaldehydes **4a**–**4f** were oxidized in moderate–good yields using the Kagan and Modena protocols, and, in all cases, the enantioselectivities were enhanced (Table 1, entries 8–13) over attempts using analogous pyrroles lacking the formyl group. In particular, the asymmetric oxidation of **4e** and **4f** provided chiral sulfoxides **7e** and **7f**, respectively, in 45% yield (96% ee) and 85% yield (98% ee), respectively (Table 1, entries 12 and 13).

Our results regarding the asymmetric oxidation of 2-(arylsulfenyl)pyrroles possessing substitutents with varying electronic effects allow us to rationalize the effectiveness of the Kagan and Modena protocols for this transformation. Although the Kagan and Modena procedures have been widely used for the oxidation of many prochiral sulfides, the struc-

ture of the reagent responsible for the stereochemical course of the reaction is still unknown (39, 40). In some cases, additives and the preparation of the reagent are crucial in obtaining specific chiral sulfoxides with high enantiopurities and (or) yields (37, 41, 42). More seriously, prochiral sulfides with two sterically different substitutents are generally good substrates for asymmetric oxidation, whereas substrates with similar groups often give products with low enantiopurities. For example, Kagan and co-workers reported the asymmetric oxidation of aryl methyl sulfides using a chiral titanium complex prepared from Ti(*i*-PrO)$_4$/(+)-(*R*,*R*)-DET/H_2O/TBHP (1:2:1:1) to give chiral sulfoxides with good–excellent enantiopurities (i.e., phenyl, 89% ee; *p*-tolyl, 91% ee; *p*-methoxyphenyl, 86% ee; *p*-nitrophenyl, 77% ee); however, the asymmetric oxidation of alkyl methyl sulfides under the same conditions resulted in chiral sulfoxides with reduced enantiopurities (i.e., *n*-octyl, 71% ee, *t*-butyl, 53% ee; cyclohexyl, 54% ee; benzyl, 58% ee) (17). In the face of the poor enantioselectivities that have traditionally been obtained for the asymmetric oxidation of diaryl sulfides, the results from the present study suggest that there is an important electronic effect that can influence this transformation. Although the origin of enantioselectivity is speculative at this point, one factor that could temper the influence of an electronic effect is the substrate–reagent binding affinity. If the mechanism involves a reversible associative step and electron-rich substrates have high association constants, as would be expected, reactions involving electron-rich substrates would give lower enantioselectivities, since these substrates bind more strongly (i.e., high reactivity and less selective). For electron-poor substrates, low association constants would allow for the substrate to dissociate and reassociate before reaction occurs (i.e., low reactivity and more selective). The traditional model used to predict the stereochemical outcome of sulfide oxidation involves the differentiation of sterically different substituents, and electronic effects are not typically considered (17, 39, 40). On the contrary, the results of the study presented herein strongly suggest that electronic effects play an important role in the asymmetric oxidation of diaryl substrates.

Conclusions

We have demonstrated the asymmetric oxidation of 2-(arylsulfenyl)pyrroles using a chiral titanium complex. Our work suggests a strong electronic effect where the incorporation of electron-withdrawing groups to differentiate the two sulfenyl substituents results in an enhancement of enantioselectivity. This method is particularly well-suited for prochiral sulfides bearing two aryl groups and expands the scope of substrates suitable for the Kagan and Modena protocols to include prochiral 2-(arylsulfenyl)pyrroles. Our current research is directed towards the preparation of a range of enantiopure 2-(arylsulfinyl)pyrroles using alternative strategies.

Experimental section

Representative procedures

*2-(*p*-Tolylsulfenyl)pyrrole (2c)*

To a solution of *p*-tolylmagnesium bromide [prepared from *p*-bromotoluene (12.0 mL, 16.8 g, 100 mmol) and magnesium turnings (2.4 g, 100 mmol) in anhydrous THF (150 mL) at 0 °C under N_2], was added dropwise 2-(thiocyanato)pyrrole (4.9 g, 39 mmol) in anhydrous THF (150 mL). After stirring at 0 °C for 30 min, ice-cold water (~100 mL) was added. The mixture was diluted with EtOAc and washed with satd. aqueous NH_4Cl and brine, before being dried over $MgSO_4$ and concentrated to give crude 2-(*p*-tolylsulfenyl)pyrrole **2c**, which was purified using flash column chromatography (CH_2Cl_2 as eluent) to give the title compound **2c** (6.7 g, 38 mmol, 97%).

A solution of 2-(*p*-tolylsulfenyl)pyrrole-*N*-tosylpyrrole **3c** (0.52 g, 1.5 mmol) in 15% *v*/*v* 2 mol/L NaOH (5.5 mL, 11 mmol) in MeOH (35 mL) was heated to reflux for 2 h until no starting material remained (TLC analysis). The mixture was cooled to room temperature and diluted with EtOAc, washed with aqueous 0.1 mol/L NaOH (3×) and brine (3×) before being dried over $MgSO_4$ and then concentrated to give crude 2-(*p*-tolylsulfenyl)pyrrole **2c** (0.25 g, 1.4 mmol, 93%), which was used in the next reaction without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17 (1H, br s), 7.00–6.97 (2H, m), 6.93–6.91 (2H, m), 6.84–6.82 (1H, m), 6.53–6.52 (1H, m), 6.27–6.26 (1H, m), 2.24 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.5 (s), 135.5 (s), 129.9 (d × 2), 126.5 (d × 2), 121.8 (d), 118.4 (d), 116.4 (s), 110.4 (d), 21.0 (q). HRMS *m*/*z* calcd. for $C_{11}H_{11}NS$: 189.0612 (188.0534 for M – H); found: 188.0539 (ESI–).

*2-(*p*-Tolylsulfenyl)pyrrole-*N*-tosylpyrrole (3c)*

TsCl (8.1 g, 43 mmol) was added to a suspension of 2-(*p*-tolylsulfenyl)pyrrole **2c** (6.7 g, 35 mmol) and NaOH (5.6 g, 141 mmol) in 1,2-dichloroethane (130 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 12 h. Water was added, and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, and then concentrated to give crude 2-(*p*-tolylsulfenyl)pyrrole-*N*-tosylpyrrole **3c**, which was purified using flash column chromatography (50% CH_2Cl_2 in hexanes as eluent) to give the title compound **3c** (10.0 g, 29 mmol, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.73 (2H, d, *J* = 8.5 Hz), 7.61–7.59 (1H, m), 7.10 (2H, d, *J* = 8 Hz), 6.90 (2H, d, *J* = 8 Hz), 6.76 (2H, d, *J* = 8 Hz), 6.53–6.52 (1H, m), 6.33–6.31 (1H, m), 2.31 (3H, s), 2.24 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 145.1 (s), 135.7 (s), 135.5 (s), 134.1 (s), 129.68 (d × 2), 129.64 (d × 2), 128.2 (d × 2), 127.0 (d × 2), 126.6 (d), 125.8 (d), 121.0 (s), 111.8 (d), 21.7 (q), 21.1 (q). LRMS (EI): 343 ([M]$^+$, 100), 188 (73). HRMS *m*/*z* calcd. for $C_{18}H_{17}NO_2S_2$: 343.0701; found: 342.9792 (EI).

*5-(*p*-Tolylsulfenyl)pyrrole-2-carboxylaldehyde (4c)*

$POCl_3$ (0.28 mL, 0.47 g, 3.1 mmol) was added dropwise to DMF (0.24 mL, 0.23 g, 3.1 mmol) at 0 °C under N_2. The resulting mixture was heated to 100 °C and stirred for 15 min. After cooling to 0 °C, a solution of 2-(*p*-tolylsulfenyl)pyrrole **2c** (0.25 g, 1.4 mmol; 0.05 mol/L in

CH_2Cl_2) was slowly added and then heated at reflux for 1 h. The resulting mixture was cooled to 0 °C, and aqueous 1 mol/L AcONa (50 mL) was added. The resulting suspension was heated to reflux and stirred for 1 h. After cooling to room temperature, the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with satd. aqueous Na_2CO_3 (3×) and brine, before being dried over $MgSO_4$ and then concentrated to give crude 5-(*p*-tolylsulfenyl)pyrrole-2-carboxylaldehydes **4c** that was purified by flash column chromatography (CH_2Cl_2) to give the title compound **4c** (0.23 g, 1.1 mmol, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.62 (1H, br s), 9.38 (1H, s), 7.20 (2H, d, J = 8 Hz), 7.09 (2H, d, J = 8 Hz), 6.92–6.91 (1H, m), 6.40–6.30 (1H, m), 2.31 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.5 (d), 137.1 (s), 135.1 (s), 131.5 (s), 130.6 (d × 2), 130.4 (d × 3), 121.1 (s), 116.6 (d), 21.2 (q). HRMS *m*/*z* calcd. for $C_{12}H_{11}NOS$: 217.0561 (216.0483 for M – H); found: 216.0485 (ESI–).

*2-(*p*-Tolylsulfinyl)pyrrole-*N*-tosylpyrrole (5c)*

Racemic

50% wt% *m*-CPBA (0.22 g, 0.60 mmol) was added to a solution of 2-(*p*-tolylsulfenyl)-*N*-tosylpyrrole **3c** (0.20 g, 0.60 mmol) at room temperature for 2 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, and then concentrated to give crude 2-(*p*-tolylsulfinyl)pyrrole-*N*-tosylpyrrole **5c**, which was purified using flash column chromatography (10% ethyl acetate in CH_2Cl_2 as eluent) to give the title compound **5c** (0.092 g, 0.27 mmol, 45%).

Asymmetric

Ti(*i*-PrO)$_4$ (0.14 mL, 0.14 g, 0.50 mmol) was added dropwise to a solution of (+)-(*R*,*R*)-DET (0.17 mL, 0.20 g, 1.00 mmol) and 2-(*p*-tolylsulfenyl)pyrrole-*N*-tosylpyrrole **3c** (0.17 g, 0.50 mmol) in CH_2Cl_2 (2 mL) under argon at room temperature. After 5 min, water (9 μL, 0.50 mmol) was added, and stirring was continued at room temperature for 45 min. 80% wt% Cumylhydroperoxide (0.19 mL, 0.15 g, 1.00 mmol) was then added under argon at –20 °C, and stirring was continued for 20 h. Water was added, and the mixture was allowed to stir for 30 min at room temperature. The resulting mixture was diluted with CH_2Cl_2 and filtered through a pad of silica and eluted with ethyl acetate to give the crude product, which was purified using flash column chromatography (10% ethyl acetate in CH_2Cl_2 as eluent) to give the title 2-(*p*-tolylsulfinyl)pyrrole-*N*-tosylpyrrole **5c** (0.15 g, 40 mmol, 83%, 16% ee; determined by chiral HPLC analysis of the corresponding tosyl deprotected **6c**; see Supplementary Data).[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.81 (2H, d, J = 8.5 Hz), 7.61 (2H, d, J = 8 Hz), 7.33 (1H, m), 7.29–7.26 (4H, m), 6.62 (1H, dd, J = 2, 4 Hz), 6.31 (1H, dd, J = 3.5, 3.5 Hz), 2.40 (3H, s), 2.39 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 146.0 (s), 142.1 (s), 141.3 (s), 137.0 (s), 135.3 (s), 130.3 (d × 2), 129.9 (d × 2), 127.7 (d × 2), 126.4 (d), 126.0 (d × 2), 118.4 (d), 113.2 (d), 21.8 (q), 21.6 (q). HRMS *m*/*z* calcd. for $C_{18}H_{17}NO_3S_2$: 359.0650 (382.0548 for M + Na); found: 382.0542 (ESI+).

Acknowledgments

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) and AstraZeneca.

References

1. M.C. Carreno. Chem. Rev. **95**, 1717 (1995).
2. I. Fernandez and N. Khiar. Chem. Rev. **103**, 3651 (2003).
3. G. Hanquet, F. Colobert, S. Lanners, and G. Solladie. ARKIVOC, **7**, 328 (2003).
4. Y. Arai, T. Masuda, and Y. Masaki. J. Chem. Soc. Perkin Trans. 1, 2165 (1999).
5. K. Hiroi, I. Izawa, T. Takizawa, and K.-I. Kawai. Tetrahedron, **60**, 2155 (2004).
6. D.A. Evans, M.M. Faul, L. Colombo, J.J. Bisaha, J. Clardy, and D. Cherry. J. Am. Chem. Soc. **114**, 5977 (1992).
7. H.B. Kagan. Catalytic asymmetric synthesis. *Edited by* I. Ojima. Wiley-VCH, Inc., New York. 2000.
8. B. Jolicoeur, E.E. Chapman, A. Thompson, and W.D. Lubell. Tetrahedron, **62**, 11531 (2006).
9. J.R. Garabatos-Perera, B.H. Rotstein, and A. Thompson. J. Org. Chem. **72**, 7382 (2007).
10. P. Thamyongkit, A.D. Bhise, M. Taniguchi, and J.S. Lindsey. J. Org. Chem. **71**, 903 (2006).
11. A. Thompson, R.J. Butler, M.N. Grundy, A.B.E. Laltoo, K.N. Robertson, and T.S. Cameron. J. Org. Chem. **70**, 3753 (2005).
12. K.K. Andersen, B. Bujnicki, J. Drabowicz, M. Mikolajczyk, and J.B. O'Brien. J. Am. Chem. Soc. **49**, 4070 (1984).
13. K.K. Andersen, W. Gaffield, N.E. Papanikolaou, J.W. Foley, and R.I. Perkins. J. Am. Chem. Soc. **86**, 5637 (1964).
14. F.A. Davis, M.C. Weismiller, C.K. Murphy, R.T. Reddy, and B.-C. Chen. J. Org. Chem. **57**, 7274 (1992).
15. A. Gao, M. Wang, J. Shi, D. Wang, W. Tian, and L. Sun. Appl. Organomet. Chem. **20**, 830 (2006).
16. K. Matsumoto, T. Yamaguchi, and T. Katsuki. Chem. Commun. 1704, (2008).
17. P. Pitchen, E. Duiiach, M.N. Deshmukh, H.B. Kagan. J. Am. Chem. Soc. **106**, 8188 (1984).
18. F.D. Dufria, G. Modena, and R. Seraglia. Synthesis, 325 (1984).
19. F.A. Davis, R.T. Reddy, W. Han, and P.J. Carroll. J. Am. Chem. Soc. 114 (1992).
20. J. Legros and C. Bolm. Chem. Eur. J. 11 (2005).
21. S. Colonna, N. Gaggero, A. Manfredi, L. Casella, M. Gullotti, G. Carrea, and P. Pasta. Biochemistry, **29**, 10465 (1990).
22. S. Colonna, N. Gaggero, P. Pasta, and G. Ottolina. Chem. Commun. 2303 (1996).
23. H. Egami and T. Katsuki. J. Am. Chem. Soc. **129**, 8940 (2007).
24. R.E. del Rio, B. Wang, S. Achab, and L. Bohé. Org. Lett. **9**, 2265 (2007).
25. G. Campiani, V. Nacci, S. Bechelli, SM. Ciani, A. Garofalo, I. Fiorini, H. Wikstrom, P. Boer, Y. Liao, P.G. Tepper, A. Cagnotto, and T. Mennini. J. Med. Chem. **41**, 3763 (1998).
26. Caution: in our hands, 2-thiocyanatopyrrole decomposed very readily and was also extremely liable to pass through multiple layers of latex gloves to cause stains and discomfort of the skin.

[2] Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 3754. For more information on obtaining material, refer to cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

27. R.L.N. Harris. Aust. J. Chem. **25**, 985 (1972).
28. J.S. Yadav, B.V.S. Reddy, S. Shubashree, and K. Sadashiv. Tetrahedron Lett. **45**, 2951 (2004).
29. The asymmetric oxidation of prochiral sulfides presents the opportunity of coupling the initial asymmetric synthesis with a kinetic resolution. While the kinetic resolution of racemic **7a** using the Modena protocol (Table 1, entry 8; 30% conversion, 17% ee) revealed a small kinetic preference ($s = 3$), the results in Table 1 indicate that the enantioselectivity occurred predominantly via the initial asymmetric synthesis.
30. D.E. Ward, Y. Liu, and C.K. Rhee. Can. J. Chem. **72**, 1429 (1994).
31. T. Sugimoto, T. Kokubo, J. Miyazaki, S. Tanimoto, and M. Okano. Bioorg. Chem. **10**, 311 (1981).
32. Z. Dokuzovic, N.K. Roberts, J.F. Sawyer, J. Whelan, and B. Bosnich. J. Am. Chem. Soc. **108**, 2034 (1986).
33. H.B. Kagan, E. Dunach, C. Nemecek, P. Pitchen, O. Samuel, and S.-H. Zhao. Pure Appl. Chem. **57**, 1911 (1985).
34. C. Nemecek, E. Dunach, and H.B. Kagan. New J. Chem. **10**, 761 (1986).
35. J.M. Brunel and H.B. Kagan. Synlett, 404 (1996).
36. J.M. Brunel and H.B. Kagan. Bull. Soc. Chim. Fr. **133**, 1109 (1996).
37. J.M. Brunel, P. Diter, M. Duetsch, and H.B. Kagan. J. Org. Chem. **60**, 8086 (1995).
38. S.H. Zhao, O. Samuel, and H.B. Kagan. Org. Synth. **68**, 49 (1990).
39. P.G. Potvin and B.G. Fieldhouse. Tetrahedron: Asymmetry, **10**, 1661 (1999).
40. A. Massa, V. Mazza, and A. Scettri. Tetrahedron: Asymmetry, **16**, 2271 (2005).
41. M. Seenivasaperumal, H.-J. Federsel, A. Ertanc, and K. Szabo. J. Chem. Commun. 2187 (2007).
42. H. Cotton, T. Elebring, M. Larsson, L. Li, H. Sorensen, and S.V. Unge. Tetrahedron: Asymmetry, **11**, 3819 (2000).
43. F.A. Davis, J.C. Towson, M.C. Weismiller, S. Lal, and P.J. Carroll. J. Am. Chem. Soc. **110**, 8477 (1988).
44. C. Drago, L. Caggiano, and R.F.W. Jackson. Angew. Chem., Int. Ed. **44**, 7221 (2005).
45. H. Fu, H. Kondo, Y. Ichikawa, G.C. Look, and C.-H. Wong. J. Org. Chem. **57**, 7265 (1992).