ENANTIOSELECTIVE EPOXIDE RING OPENING CATALYZED BY BIS(TETRAHYDROISOQUINOLINE) *N,N′*-DIOXIDES

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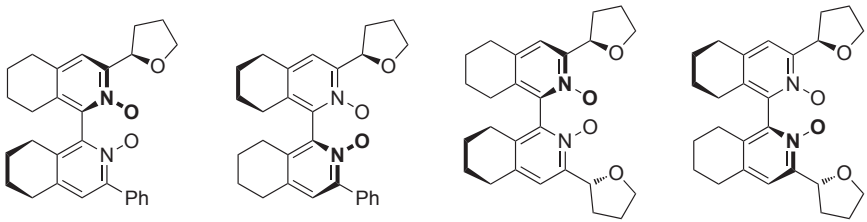
Dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday.

Four bis(tetrahydroisoquinoline) *N,N′*-dioxides were used as catalysts for the epoxide ring opening with tetrachlorosilane under various conditions. A strong solvent effect on asymmetric induction was observed for each of the used catalysts. The highest achieved asymmetric induction for the opening of *meso*-stilbene oxide was 69% ee. Regarding the cycloalkene oxides, 56% ee was obtained in the reaction with cyclooctene oxide.
Keywords: Asymmetric catalysis; Silanes; N ligands; Enantioselectivity.

Recently we have reported synthesis of several new Lewis basic compounds: bipyridine *N,N′*-dioxides that possess an axially chiral bis(tetrahydroisoquinoline) framework. Among them the best catalytic properties, in the terms of catalytic activity and asymmetric induction, were exhibited by the



(*R*,*R*$_{ax}$)-**1a** (*R*,*S*$_{ax}$)-**1b** (*R*,*R*$_{ax}$,*R*)-**2a** (*R*,*S*$_{ax}$,*R*)-**2b**

FIG. 1
Lewis basic bis(tetrahydroisoquinoline) *N,N′*-dioxides

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compounds bearing additional one or two chiral tetrahydrofurane moieties in 3- or 3,3′-position **1** and **2**, respectively (Fig. 1). These compounds were used as highly efficient catalysts for asymmetric allylation of aromatic and α,β-unsaturated aldehydes giving rise to products with high enantioselectivity (up to 99%)[1,2]. These results prompted us to use these chiral compounds as catalysts for another synthetically useful reaction: opening of the epoxide ring. Since epoxides represent a class of synthetically useful building blocks that after the ring opening can be transformed into a variety of compounds development of new catalytic and enantioselective methods for their cleavage is desirable. In this respect especially desirable is conversion of *meso*-epoxides into halohydrines generating two chiral centers.

Although numerous protocols for enantioselective epoxide opening has been developed, the one relying on the use of halosilanes has, since its discovery over 50 years ago[3], attracted considerable attention. The successful course of the reaction requires the presence of a Lewis basic catalyst that converts a halosilane (weakly Lewis acidic)[4] into strongly Lewis acidic extracoordinate silicon species[5] capable of breaking the carbon–oxygen bond in epoxides[6]. The group V compounds such as phosphines[7] and phosphorus based heterocycles[8], HMPA [9], phosphine oxides[10], etc. have been successfully used as catalysts for the epoxide ring opening. During the last decade it was demonstrated that chiral Lewis bases possessing one or two *N*-oxide moieties are especially active catalysts to bring about such a transformation in high yields and asymmetric induction. As typical examples may serve ferrocene-based planar chiral *N*-oxide[11], helical pyridine *N*-oxide[12], bis(isoquinoline) *N,N′*-dioxide[13], and chiral bipyridine *N*-oxide PINDOX[14].

RESULTS AND DISCUSSION

The catalysts **1** and **2** developed in this laboratory demonstrated high catalytic activity and asymmetric induction, it was logical consequence that we decided to test them in enantioselective ring opening of epoxides.

Since it was shown by us that the solvent effect played a significant role in enantioselective allylation by controlling the course of the reaction, the epoxide cleavage was initially studied in various solvents. Our first candidates for the catalytic ring opening of epoxide were two diastereoisomeric unsymmetrically substituted bis(tetrahydroisoquinoline) *N,N′*-dioxides **1a** and **1b** that exhibited superior properties in the enantioselective allylation of aldehydes[1e–1f]. The reaction of *meso*-stilbene oxide **3a** with $SiCl_4$ in the presence of Hünig's base (*i*-Pr_2NEt) to **4a** was chosen as a model reaction (Scheme 1). The obtained results clearly indicate that the solvent effect

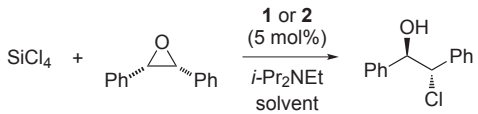
played the crucial role again (Table I). Using catalysts **1a**, the highest yields were obtained in electrophilic solvents such as dichloromethane (85%) and MeCN (99%) and also the highest asymmetric induction was achieved in dichloromethane, albeit of modest value (44%). In non-electrophilic solvents (THF, toluene, PhCl), longer reaction times (24 h) were required to obtain sensible yields of the products. It is worth mentioning that in toluene the opposite enantiomer was obtained as the major stereoisomer. In addition, inferior asymmetric induction was observed. Using **1b**, the yields were similar in dichloromethane, MeCN and THF. Interestingly, in toluene and PhCl, the reaction did not proceed at all and the starting epoxide was recovered unchanged. Obviously, the epoxide ring opening is favored in electrophilic solvents in terms of reactivity as well as asymmetric induction.

For comparison, the same reactions were carried out with two diastereoisomeric symmetrically substituted bis(tetrahydroisoquinoline) *N,N'*-di-

TABLE I
Solvent effect on asymmetric induction for the epoxide ring opening of *meso*-stilbene oxide **3a** to **4a** catalyzed by **1a** and **1b**

Solvent	(R,R_{ax})-**1a**[a]				(R,S_{ax})-**1b**[a]			
	t, h	*T*, °C	Yield, %	ee, %[b]	*t*, h	*T*, °C	Yield, %	ee, %[b]
CH_2Cl_2	12	–78	85	44	2	–78	74	26
MeCN	12	–40	99	22	1	–40	74	64
THF	24	–78	54	34	12	–78	60	30
Toluene	24	–78	71	16		–78	n.r.	
PhCl	24	–78	71	38		–78	n.r.	

[a] 5 mole %; [b] ee was determined from the corresponding Mosher acid esters.



SCHEME 1
Lewis base catalyzed reaction of tetrachlorosilane with *meso*-stilbene oxide **3a**

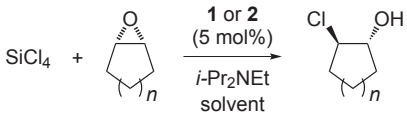
oxides **2a** and **2b**. The results are displayed in Table II. The reaction proceeded in all cases giving rise to product **4a**. Catalyst **2a** seemed to be more active then catalyst **2b**. In comparison with results presented in Table I, the best asymmetric induction with respect to the solvent used was surprisingly achieved in THF for both catalysts: 65% ee for **2a** and 69% for **2b**.

In the next stage, the cleavage of cyclopentene oxide **3b**, cyclohexene oxide **3c**, cycloheptene oxide **3d**, and cyclooctene oxide **3e** was carried out under the same reaction conditions (Scheme 2). On the bases of results displayed in Table I, the reactions were carried out with **1a** and **1b** in dichloromethane and MeCN only (Table III). Generally, the obtained results lucidly indicate that any prediction regarding the magnitude of asymmetric induction with respect to the solvent used, the cycloalkene oxide ring size, and the stereochemical features of the catalysts can not be easily envisioned. Although the highest asymmetric induction for **3b**, **3c**, and **3e** was achieved with **1b** in MeCN (43, 53 and 55% ee, respectively; Entries 2, 4 and 8), for

TABLE II
Solvent effect on asymmetric induction for the epoxide ring opening of *meso*-stilbene oxide **3a** to **4a** catalyzed by **2a** and **2b**

Solvent	(R,$R_{ax}R$)-**2a**[a]				(R,$S_{ax}R$)-**2b**[a]			
	t, h	*T*, °C	Yield, %	ee, %[b]	*t*, h	*T*, °C	Yield, %	ee, %[b]
CH_2Cl_2	6	–78	35	7	22	–78	81	53
MeCN	3	–40	86	15	22	–40	58	47
THF	22	–78	76	65	22	–78	74	69
Toluene	4	–78	41	23	22	–78	68	24
PhCl	1	–78	56	2	22	–78	86	15

[a] 5 mole %; [b] ee was determined from the corresponding Mosher acid esters.

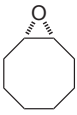


SCHEME 2
Lewis base catalyzed reaction of tetrachlorosilane with *meso*-cycloalkene oxides **3b–3e**

3d it was achieved with **1a** in CH_2Cl_2 (26% ee; Entry 5). However, regarding **3d** asymmetric induction of a similar value of 23 and 21% ee was obtained with **1b** in dichloromethane and MeCN (Entries 5 and 6). As for **3e** asymmetric induction of 45% ee was obtained with **1a** in dichloromethane (Entry 7). Interestingly, in some cases negligible enantioselectivity was observed (Entries 1, 3 and 4).

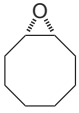
In comparison with catalysts **1**, the use of **2** resulted in inferior enantioselectivity (Table IV). It is worth noting that for **2a** as well as for **2b** increase of asymmetric induction was observed with increasing size of the cycloalkene oxide ring. The highest asymmetric induction with **2a** was observed in the case of cyclooctene oxide **3e** that yielded the corresponding chlorohydrine **4e** in 38% ee and for **2b** it was 29% ee (Entry 4). The lowest asymmetric induction was observed in the case of cyclopentene oxide **3b** that gave rise to the chlorohydrine **4b** with 8 and 10% ee, respectively (Entry 1).

TABLE III
The epoxide ring opening of **3b**–**3e** to **4b**–**4e** catalyzed by **1a** and **1b**

Entry	Epoxide		Solvent	(R,R_{ax})-**1a**[a]			(R,S_{ax})-**1b**[a]		
				t, h	Yield, %	ee, %[d]	t, h	Yield, %	ee, %[d]
1		**3b**	CH_2Cl_2[b]	5	33	<2		traces	<2
2			MeCN[c]	3	74	26	5	23	43
3		**3c**	CH_2Cl_2[b]		traces	<2		traces	<2
4			MeCN[c]	5	33	<2	5	30	53
5		**3d**	CH_2Cl_2[b]	5	46	26	5	38	23
6			MeCN[c]	3	30	3	12	40	21
7		**3e**	CH_2Cl_2[b]	24	41	45	12	24	26
8			MeCN[c]	24	35	27	12	52	55

[a] 5 mole %; [b] the reaction was carried out at –78 °C; [c] the reaction was carried out at –40 °C; [d] ee was determined from the corresponding Mosher acid esters.

TABLE IV
The epoxide ring opening of **3b–3e** to **4b–4e** catalyzed by **2a** and **2b**

Entry	Epoxide		Solvent	$(R,R_{ax}R)$-**2a**[a]			$(R,S_{ax}R)$-**2b**[a]		
				t, h	Yield, %	ee, %[c]	*t*, h	Yield, %	ee, %[c]
1		**3b**	THF[b]	3	44	8	2	78	10
2		**3c**	THF[b]	4	57	24	3	70	13
3		**3d**	THF[b]	22	55	28	22	59	26
4		**3e**	THF[b]	48	13	38	48	13	29

[a] 5 mole %; [b] the reactions were carried out at –78 °C; [c] ee was determined from the corresponding Mosher acid esters.

CONCLUSION

Despite the fact that both Lewis basic catalysts efficiently catalyzed the epoxide ring opening the overall enantioselectivity remained low: for *meso*-stilbene oxide **3a** it did not exceed 69% ee and for the *meso*-cycloalkene oxides the highest value was 55% ee. In analogy with the previously mentioned cases also here the solvent effect proved to crucially influence not only asymmetric induction but also catalytic activity. Although it has been shown that asymmetric induction in aldehyde allylation with trichloroallylsilane catalyzed by **1** and **2** depends on the reaction mechanism[1f,1g,1h], i.e. whether the reaction proceeds through cationic pentacoordinated silicon species (CH_2Cl_2, MeCN, etc.) or neutral six-coordinated silicon species (THF, PhCl, etc.)[15], no such clear-cut conclusion could be made here. Given the heterogeneity of the obtained results, it is difficult to draw any general rationale that would explain the relationship between the

catalyst used, its catalytic activity, the substrate structure, the solvent used, and magnitude of the asymmetric induction.

EXPERIMENTAL

General methods. All solvents unless otherwise stated were used as obtained. THF and toluene were distilled from sodium and benzophenone, dichloromethane from CaH_2 under argon. All other reagents were obtained from commercial sources. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian UNITY 300 MHz as solutions in $CDCl_3$. Chemical shifts (δ-scale) are given in ppm, coupling constants *J* in Hz. Fluka 60 silica gel was used for flash chromatography. TLC was performed on silica gel 60 F_{254}-coated aluminum sheets (Merck). All reactions were carried out under argon atmosphere using flasks.

General procedure for the opening of meso-epoxides. To a solution of a *meso*-epoxide (0.17 mmol) and bipyridine *N,N*-dioxides (*R,R*)-**1a** or (*S,R*)-**1b** (0.009 mmol, 4 mg) in CH_2Cl_2, MeCN, THF, toluene or chlorobenzene (2 ml), diisopropylethylamine (0.19 mmol, 33 µl, 25 mg) and silicon tetrachloride (0.19 mmol, 21 µl, 31 mg) were added at –78 °C (CH_2Cl_2, THF, toluene, and PhCl) or –40 °C (MeCN), and the reaction mixture was stirred for 1–48 h. TLC was used to monitor conversion of the reactants. The reaction mixture was quenched with 1 M KH_2PO_4 and the saturated aqueous solution of KF (1:1; 4 ml), then washed with saturated aqueous solution of $NaHCO_3$ (4 ml) and extracted with ether (3 × 5 ml). The combined organic fractions were dried over $MgSO_4$ and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (8:1 hexane/EtOAc) yielded the corresponding chlorohydrines. Enantiomeric purity was determined via Mosher's esters using ^{19}F NMR or ^1H NMR.

General procedure for the preparation of Mosher's esters. To a solution of chlorohydrine (0.04 mmol) and DMAP (0.2 mmol, 24 mg) in CH_2Cl_2 (2 ml), (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetic chloride (0.04 mmol, 10.1 mg) was added under argon at room temperature, and the reaction mixture was stirred overnight. Then the reaction was quenched with the saturated aqueous solution of NH_4Cl (5 ml), washed with the saturated aqueous solution of $NaHCO_3$ and extracted with ether (3 × 5 ml). The combined organic fractions were dried over $MgSO_4$, and volatiles were removed under reduced pressure. The crude product was used for determination of the diastereoisomeric ratio without further purification to avoid possible amplification of the ee.

2-Chloro-1,2-diphenylethanol (**4a**). ^1H NMR (300 MHz): 2.91 (s, 1 H), 4.76–4.85 (m, 2 H), 6.90–7.07 (m, 10 H). ^{13}C NMR (300 MHz): 70.5, 78.7, 127.0, 128.0, 128.1, 128.3, 128.5, 137.7, 138.8. The obtained values are in agreement with the reported data[8].

2-Chlorocyclopentanol (**4b**). ^1H NMR (300 MHz): 1.50–1.65 (m, 1 H), 1.75–1.85 (m, 3 H), 2.10–2.35 (m, 2 H), 2.37 (s, 1 H), 3.95–4.25 (m, 1 H), 4.20–4.30 (m, 1 H). ^{13}C NMR (300 MHz): 20.5, 31.2, 33.2, 65.6, 80.2. The signals of the corresponding Mosher acid esters were: ^{19}F NMR (300 MHZ): –71.62, –71.69. The obtained values are in agreement with the reported data[14].

2-Chlorocyclohexanol (**4c**). ^1H NMR (300 MHz): 1.40–1.23 (m, 3 H), 1.58–1.80 (m, 3 H), 2.08–2.14 (m, 1 H), 2.20–2.26 (m, 1 H), 2.53 (d, *J* = 2.1, 1 H), 3.55–3.48 (m, 1 H), 3.73 (ddd, *J* = 4.5, 9.3, 11.8, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$): 23.8, 25.4, 33.1, 35.0, 67.1, 75.0. The signals of the corresponding Mosher acid esters were: ^{19}F NMR (300 MHZ): –71.38, –71.76. The obtained values are in agreement with the reported data[14].

2-Chlorocycloheptanol (**4d**). ^{1}H NMR (300 MHz): 1.44–1.63 (m, 5 H), 1.69–1.80 (m, 2 H), 1.83–1.92 (m, 1 H), 1.94–2.0 (m, 1 H), 2.12–2.19 (m, 1 H), 2.48 (d, J = 1.9, 1 H), 3.64–3.70 (m, 1 H), 3.88 (ddd, J = 3.6, 8.7, 9.7, 1 H). ^{13}C NMR (300 MHz): 21.72, 23.46, 26.44, 31.98, 34.15, 71.13, 78.42. The signals of the corresponding Mosher acid esters were: ^{19}F NMR (300 MHZ): –71.38, –71.76. The obtained values are in agreement with the reported data[14].

2-Chlorocyclooctanol (**4e**). ^{1}H NMR (300 MHz): 1.39–1.84 (m, 9 H), 1.83–2.03 (m, 2 H), 2.15–2.23 (m, 1 H), 2.53 (s, 1 H), 3.82–3.87 (m, 1 H), 4.09 (ddd, J = 2.8, 7.4, 9.3, 1 H). ^{13}C NMR (300 MHz): 24.05, 24.83, 25.68, 25.73, 31.90, 32.31, 71.34, 76.24. The signals of the corresponding Mosher acid esters were: ^{19}F NMR (300 MHZ): –71.34, –71.88. The obtained values are in agreement with the reported data[14].

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