Asymmetric Weitz−Scheffer Epoxidation of Isoflavones with Hydroperoxides Mediated by Optically Active Phase-Transfer Catalysts

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The asymmetric Weitz−Scheffer epoxidation of the isoflavones **3**, mediated by the cinchonine- and cinchonidine-derived phase-transfer catalysts (PTCs) **1**, affords the enantiomerically enriched isoflavone epoxides **4** with ee values of up to 98% in nearly quantitative yields. With the appropriately configured PTC **1**, both enantiomers of the isoflavone epoxides may be obtained by using the commercially available cumyl hydroperoxide **2b** as oxidant. Methylation of the hydroxy functionality in the most effective PTC (**1b**) reduces significantly the enantioselectivity of the isoflavone epoxidation as illustrated for the substrate **3c**. This fact indicates the pivotal role of the hydroxy group for enantioselective control, which is rationalized in terms of a hydrogen-bonded aggregate between the ether−oxygen atom of isoflavone **3** and the phase-transfer catalyst **1**. The present attractive and convenient method should be useful for the preparation of optically active epoxides of the biologically relevant isoflavone structure.

Introduction

The asymmetric Weitz−Scheffer epoxidation is the most frequently employed method for the epoxidation of electron-poor olefins.[1] For the cinchona-derived phase-transfer catalysts, initially used by Wynberg,[2] the enantioselectivities were recently significantly improved by changes of the catalyst structure as well as the oxidant type.[3] Alternatives such as the Julia method,[4] which employs polyamino acids as asymmetric inductors, have also been quite successful and still receive attention.[5] Moreover, soluble copolymers of the amino acids[6] and a biphasic reaction procedure[7] have been developed for this purpose. In regard to metal catalysts with chiral ligands, diethylzinc in the presence of methylpseudoephedrine or polybinaphthol has been shown to be an effective means to achieve asymmetric epoxidation with molecular oxygen.[8] Lanthanide[9] and ytterbium binols[9a,10] with achiral hydroperoxides as oxygen donors offer high enantioselectivities in the Weitz−Scheffer epoxidation, whereas optically active hydroperoxides[11] and bases[12] have been used only recently as asymmetric inductors.

The asymmetric epoxidation of *s-trans*-fixed enones under Weitz−Scheffer conditions has yet been little studied.[13] Taylor[13a,b] used equimolar amounts of phase-transfer catalysts to prepare the manumycin class of natural products in up to 89% ee and has studied the epoxidation of quinones with optically active sugar hydroperoxides, which resulted in up to 82% ee.[11c] Colonna epoxidized substituted naphthoquinones with bovine serum albumin as asymmetric inductor and obtained an enantiomerically pure product in one case.[13c] TADDOL

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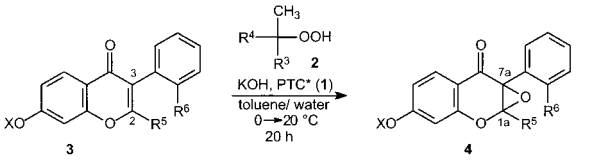
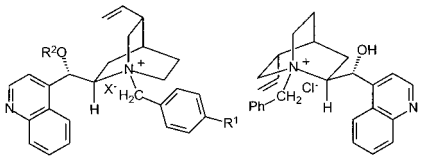
Scheme 1. Weitz−Scheffer Epoxidation of Isoflavones 3 by the Hydroperoxides 2 and the Optically Active Phase-Transfer Catalysts 1



2	R^3	R^4
a	Me	Me
b	C_6H_5	Me
c	C_6H_5	H
d	*p*-Cl-C_6H_4	H

3,4	X	R^5	R^6
a	Me	H	H
b	Me	Me	H
c	Me	Et	H
d	Me	*i*Pr	H
e	$MeSO_2$	H	OMe



1	R^1	R^2	X
a	H	H	Cl
b	CF_3	H	Br
c	CF_3	Me	Br

1d

hydroperoxide has been recently used by Seebach,[14] and 82% ee was obtained in the epoxidation of 3-methylcyclohexenone. Expectedly, the epoxidation of isoflavones with a sugar substituent on the benzo ring by dimethyldioxirane displayed no diastereoselectivity because the chiral inductor is too remote from the epoxidation site for effective stereocontrol.[15] However, the use of Jacobsen's manganese(salen) catalyst with dimethyldioxirane as oxygen source afforded isoflavone epoxides in enantioselectivities of up to 92% ee, but the epoxide yields were low (only up to 34%).[16]

A recent report[17] on the efficient synthesis of racemic isoflavone epoxides under Weitz−Scheffer conditions provided the incentive to develop an asymmetric method for the epoxidation of these natural compounds. For this purpose, the optically active cinchonine- and cinchonidine-derived phase-transfer catalysts **1** (Scheme 1) and the sterically demanding hydroperoxides **2a**,**b** were chosen, since the latter have previously proved to be more effective for enantioselective epoxidations than H_2O_2.[18] Should high enantioselectivities be achieved in these PTC epoxidations, the kinetic resolution of racemic hydroperoxides was to be attempted under these conditions. To date, no effective chemical method[19] is available to obtain enantiomerically pure hydroperoxides not derived from the chiral pool, such that the latter must be prepared by enzymatic kinetic resolution.[20]

Results

The isoflavones **3** and the corresponding racemic epoxides **4** were prepared according to literature methods.[17] The methylated phase-transfer catalyst **1d** (PTC) was made in analogy to a procedure for the allylated analogue.[21] A detailed procedure is given in the Experimental Section.

The results of the PTC (**1**)-mediated asymmetric epoxidation by the hydroperoxide **2** under Weitz−Scheffer conditions are given in Table 1 for the isoflavones **3**. When PTC **1a** and *tert*-butyl hydroperoxide **2a** (entry 1) were used with isoflavone **3c** as substrate, complete conversion to the epoxide **4c** was observed after 20 h, the latter was obtained quantitatively in an enantioselectivity of 70% ee in favor of the 1a*R*,7a*S* enantiomer. With cumyl hydroperoxide **2b** in place of **2a** under identical conditions, the same enantiomer (1a*R*,7a*S*) of the epoxide **4c** was formed in a somewhat higher ee value of 83% (entry 2). The enantioselectivity was increased to 90% ee (entry 3) when cumyl hydroperoxide **2b** was used together with the PTC **1b**. PTC **1c**, in which the hydroxy group of the commercially available PTC **1b** is methylated, afforded the 1a*R*,7a*S*-epoxide **4c** still quantitatively but with only 40% ee (entry 4).

For the most effective combination, that is, the catalyst PTC **1b** and cumyl hydroperoxide **2b**, the effect of the 2-alkyl substituent on the isoflavone ring was examined. To our gratification, the isoflavone **3a** was fully converted to the 1a*R*,7a*S*-epoxide **4a**, which was isolated in almost quantitative yield and an enantioselectivity of 98% ee (entry 5). When the amount of catalyst **1b** was lowered to 1 mol %, 95% of the isoflavone **3a** was converted to yield the corresponding epoxide **4a** with an ee value of 95% (entry 6). On further lowering of the catalyst amount to 0.1 mol %, the conversion dropped to 44% and an enantioselectivity of only 30% (entry 7) was observed. The 2-methyl derivative **3b** gave the 1a*R*,7a*S*-epoxide **4b** in 89% ee and 97% yield (entry 8) with PTC **1b** and cumyl hydroperoxide **2b**. The 2-isopropyl-substituted isoflavone **3d** was much less reactive under the same conditions (entry 9). Even after 3 d, only 15% of the isoflavone **3d** was converted to the 1a*R*,7a*S*-epoxide **4d** in an enantioselectivity of 53% ee.

Since under these optimized conditions excellent enantioselectivities were achieved for the 1a*R*,7a*S* -epoxides **4a** and **4c** (entries 5 and 3, respectively), the next objective was the preparation of the corresponding 1a*S*,7a*R* enantiomers of the epoxides **4**. With the commercially available cinchonidine-derived phase-transfer catalyst **1d**, whose configuration at the pertinent catalyst site is opposite to that of **1a**, the isoflavone **3a** was quantitatively oxidized to the desired 1a*S*,7a*R*-epoxide **4a** by cumyl hydroperoxide **2b** in 90% ee (entry 11). Under these conditions, the 1a*S*,7a*R*-**4c** epoxide was obtained in 64% ee and in quantitative yield from the isoflavone **3c** (entry 12).

The absolute configurations of the isoflavone epoxides **4a**,**e** were assigned by comparison with literature data.[16] The HPLC retention times and the sign of the α_D values (see the Supporting Information) are in good accord with those reported. The CD spectra and X-ray structures for both enantiomers of epoxide **4e**, obtained by the present procedure in an enantioselectivity of 80% ee (entry 10), have been reported previously[16] and have served as reference for the configurational assignment of the other derivatives. For the epoxides **4b**−**d**, the HPLC retention

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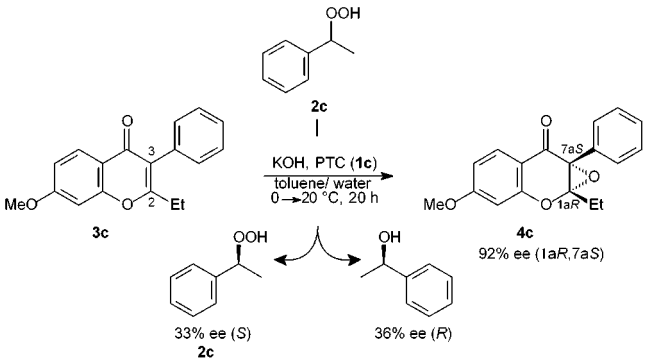
Table 1. Enantioselective Epoxidation of Isoflavones 3 with Cumyl Hydroperoxide 2b, Mediated by Phase-Transfer Catalysts 1[a]

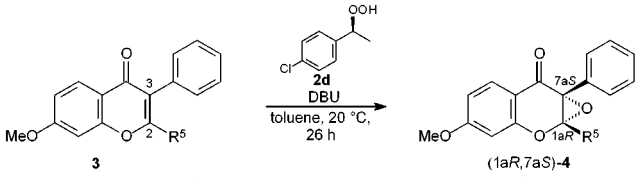
entry	PTC[b]	isoflavone	R^5	R^6	X	convn[c] (%)	yield (%)	ee[d] (%)
1[a]	**1a**	**3c**	Et	H	Me	100	99	70 [1a*R*,7a*S*]
2	**1a**	**3c**	Et	H	Me	100	99	83 [1a*R*,7a*S*]
3	**1b**	**3c**	Et	H	Me	100	91	90 [1a*R*,7a*S*]
4	**1c**	**3c**	Et	H	Me	100	95	40 [1a*R*,7a*S*]
5	**1b**	**3a**	H	H	Me	100	97	98 [1a*R*,7a*S*]
6[e]	**1b**	**3a**	H	H	Me	95	97	95 [1a*R*,7a*S*]
7[f]	**1b**	**3a**	H	H	Me	44	n.d.	30 [1a*R*,7a*S*]
8	**1b**	**3b**	Me	H	Me	100	97	89 [1a*R*,7a*S*]
9	**1b**	**3d**	*i*Pr	H	Me	15[g]	95	53 [1a*R*,7a*S*]
10	**1b**	**3e**	H	MeO	$MeSO_2$	100	84	80 [1a*R*,7a*S*]
11	**1d**	**3a**	H	H	Me	100	94	90 [1a*S*,7a*R*]
12	**1d**	**3c**	Et	H	Me	100	99	64 [1a*S*,7a*R*]

[a] 10 mol % of PTC and 1.5 equiv of cumyl hydroperoxide were used, except in entry 1 (*t*-BuOOH); reaction time 20 h, except entry 9 (see footnote g). [b] Structures are given in Scheme 1. [c] Determined by the areas under the characteristic signals in the ^{1}H NMR spectrum (error ± 5% of the stated values). [d] Determined by HPLC analysis on a Chiracel OD column, for which the conditions are given in the Supporting Information (error ± 3% of the stated values); the absolute configurations of the epoxide are given in brackets. [e] 1 mol % of PTC. [f] 0.1 mol % of PTC. [g] After 3 d of reaction time.

Scheme 2. Kinetic Resolution of 1-Phenylethyl Hydroperoxide 2c in the Epoxidation of Isoflavone 3c under Weitz−Scheffer Conditions



Scheme 3. Weitz−Scheffer Epoxidation of Isoflavones 3c,d with *S*-(−)-1-(*p*-Chlorophenyl)ethyl Hydroperoxide 2d and DBU as Base



Substrate	R^5	convn (%)[a]	Yield (%)	ee (%)[b]
3c	Et	90	91	45 [1a*R*,7a*S*]
3d	*i*Pr	42	99	37 [1a*R*,7a*S*]

[a] Determined by the areas under the characteristic signals in the ^{1}H NMR spectrum (error ± 5% of the stated values). [b] Determined by HPLC analysis on a Chiracel OD column, for which the conditions are given in the Supporting Information (error ± 3% of the stated values); the absolute configurations of the epoxide are shown in brackets.

times, α_D values, and CD spectral data are given in the Supporting Information. From these data, it is certain that the Weitz−Scheffer epoxidation with the PTCs **1a**−**c** affords the 1a*R*,7a*S*-epoxides **4** preferentially. The rigid structure of the isoflavone oxides **4** makes CD spectroscopy the tool of choice to assess the absolute configurations of such epoxides.

The high enantioselectivities (up to 98% ee) obtained in the epoxidation of the isoflavones **3** encouraged us to try the kinetic resolution of 1-phenylethyl hydroperoxide **2c**. Under Weitz−Scheffer conditions (Scheme 2), the *S*-(−)-enantiomer was obtained in only 33% ee from the racemic hydroperoxide **2c** and the corresponding *R*-(+)-alcohol in 36% ee, while the 1a*R*,7a*S*-epoxide **4c** was formed in 92% ee. The moderate kinetic resolution is in line with previous findings[18] and indicates that the steric interactions between the hydroperoxide and the phase-transfer catalyst are not strong enough for effective enantiodifferentiation in the transition state of the oxygen transfer.

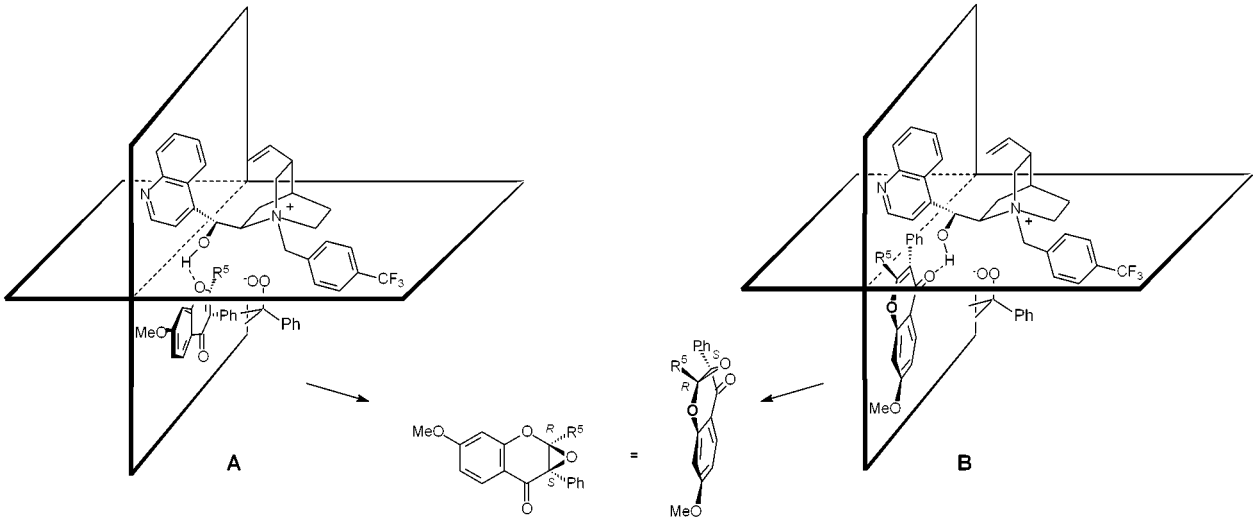
Similarily, when the optically active 1-(*p*-chlorophenyl)-ethyl hydroperoxide **2d** was used (Scheme 3), which had been found to be most effective in the asymmetric epoxidation of β-disubstituted olefins with DBU as base,[11] the isoflavone **3c** was converted within 26 h in 90% yield to the 1a*R*,7a*S*-epoxide **4c** but in only 45% ee (Scheme 3). Under these conditions, the efficiency of asymmetric epoxidation of isoflavones is much lower than in the corresponding case with PTC **1c** and cumyl hydroperoxide (Table 1, entry 3). For the isoflavone **3d**, the reactivity was considerably higher (42% conversion in 26 h) than with the PTC method (15% after 3 d; Table 1, entry 9); however, again an enantioselectivity of only 37% was observed with this method.

Discussion

The method presented herein, namely the phase-transfer-catalyzed epoxidation of isoflavones by hydroperoxides, is to date undoubtedly the most effective one to obtain optically active epoxides of these widespread natural products. It offers superior enantioselectivities and high chemical yields when compared to the previously reported method with Mn(salen) complexes.[16] By appropriate choice of the PTC configuration, both enantiomers of the isoflavone epoxides **4** are now available in nearly quantitative yield and excellent enantioselectivities, with commercially available hydroperoxides as oxidants. The high enantioselectivities not only offer new preparative perspectives for optically active epoxides derived from electron-poor olefins but also provide mechanistic insight into this asymmetric oxygen-transfer process.

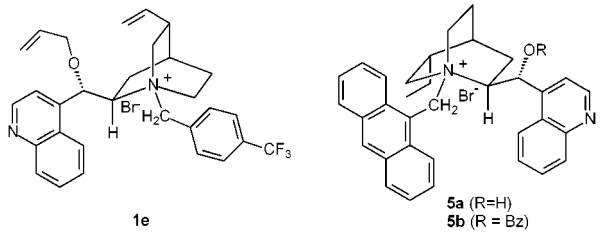
In this context, the present asymmetric Weitz−Scheffer epoxidation utilizes an achiral hydroperoxide **2**, an optically active PTC **1**, and the prochiral isoflavone **3**. Of these three components, the hydroperoxide excercises

Scheme 4. Hydrogen-Bonded Aggregates for the Phase-Transfer-Catalyzed Epoxidation of Isoflavones 3



only a minor influence on the control of the enantioselectivity, as revealed by the results when *tert*-butyl hydroperoxide (**2a**) (70% ee, Table 1, entry 1) was replaced by cumyl hydroperoxide (**2b**) (83% ee, Table 1, entry 2). Evidently, the hydroperoxide **2** is only weakly bound to the phase-transfer catalyst, as corroborated by the poor kinetic resolution of the racemic 1-phenylethyl hydroperoxide **2c** (Scheme 2). Thus, the dominating factor in the enantiofacial differentiation must be sought in the aggregation of the two remaining components, namely the isoflavone **3** and the PTC **1**.

The importance of the PTC structure on the enantiofacial differentiation is demonstrated by the inversion in the sense of the enantioselectivity that was obtained for isoflavone **3a** with oppositely configured PTC **1b** (entry 5) and PTC **1d** (entry 12). Thus, the favored enantiomer of the epoxide product is determined strictly by the configuration at the hydroxy-bearing site of the PTC. Indeed, the significance of the hydroxy functionality is revealed when PTC **1b** and its methyl derivative PTC **1c** are compared in the epoxidation of isoflavone **3c** (entries 3 and 4). The substantially lower ee value observed with PTC **1c** (40% ee) compared to PTC **1b** (90% ee) illustrates that the hydroxy group is necessary for effective enantiocontrol. This result is in contrast to those reported by Corey[3c] and Lygo,[3d] who have used the anthracyl-substituted PTCs **5** and found that the alkylation of the hydroxy functionality enhances the enantiofacial differentiation in the epoxidation of chalcone derivatives. However, also in the work of Shioiri and Arai,[3a,b] in which the allyl derivative **1e** and other



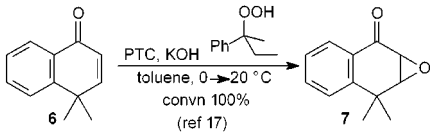
derivatives of the PTCs **1a**,**b**, have been thoroughly investigated, it was found that the free hydroxy functionality is essential for effective π-facial differentiation. In fact, Shioiri and Arai suggested hydrogen bonding between the enone substrate and the PTC to be a decisive factor in the enantiofacial control.[3b] Consequently, we suggest an aggregate for the oxygen-transfer step (Scheme 4) with hydrogen bonding between the isoflavone substrate and the hydroxy functionality of the PTC.

It must be emphasized that both aggregates **A** and **B** predict that for the PTC **1b** the (1a*R*,7a*S*)-configured epoxide results, but which arrangement is favored? A closer look at the substitution pattern of the various isoflavones **3** reveals that the aggregate **A** accounts best the observed ee values in Table 1. On the basis of B3LYP/6-31g* calculations,[22] the dihedral angle between the plane of the chromone ring and that of the phenyl group is 39° for isoflavone **3a** (see the Supporting Information). Moreover, the 3-phenyl group is expected to be larger than the 2-alkyl substituent of the enone functionality in the isoflavone and, thus, the arrangement in structure **A** should be sterically favored, since the phenyl group of the isoflavone points away from the stereocontrolling site of the PTC. This structure also offers a reason for the much reduced reactivity and enantioselectivity of the isopropyl-substituted isoflavone **3d**. Evidently, the larger isopropyl group interferes sterically in the aggregation process depicted in structure **A**, which in turn manifests itself in the lower reactivity and ee value (53%, entry 9).

A matter of mechanistic concern is that in the supposedly preferred aggregate **A** the hydrogen bonding is directed toward the endocyclic ether oxygen atom in the isoflavone rather than the exocyclic carbonyl oxygen atom as in aggregate **B**. In fact, we had previously reported that the *s-trans*-configured enone **6** (Scheme 5) is unselectively epoxidized in the PTC-mediated[18] Weitz−Schef-

(22) (a) Gaussian 98: Revision A.7: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A.; Gaussian, Inc., Pittsburgh, PA, 1998. (b) Becke, A. D. *Phys. Rev. A* **1988**, *39*, 3098−3100. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (d) Lee, G.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. (e) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627.

Scheme 5. Epoxidation of the *s-trans*-Fixed Enone 6 under PTC-Mediated Conditions.



PTC **1a**: 18% ee (-)-enantiomer
PTC **1d**: 8% ee (-)-enantiomer

fer reaction because coordination to the carbonyl group for the oxygen transfer is difficult.[11] Since the isoflavones **3** also possess a fixed *s-trans* configuration, one would expect the same difficulties here for the aggregate **B**. However, the endocyclic ether oxygen atom in the isoflavones **3** offers the required coordination site for the hydrogen bonding in structure **A** (Scheme 4). Thus, aggregate **A** accounts adequately for the high ee values observed in the epoxidation of the isoflavones **3**, but low ones with the enone **6** (Scheme 5),[18] since the latter provides no accessible coordination site for hydrogen bonding.

The comparison of the PTCs **1a** and **1d**, which possess opposite configurations at the pertinent catalyst site, further corroborate this mechanistic rationale. The epoxidation with PTC **1d** yields the opposite isoflavone epoxide enantiomer **4c** (1a*S*,7a*R*, 64% ee) versus PTC **1a** (1a*R*,7a*S*, 83% ee), whereas in the epoxidation of enone **6** both PTCs **1a**,**d** deliver the same enantiomer of the epoxide **7** in the low ee values of 18% (PTC **1a**) and 8% ee (PTC **1d**). The essential ether-oxygen coordination site for hydrogen bonding with the hydroxy group of the PTC, as is the case for the isoflavone **3** in aggregate **A**, is absent in enone **6** and only little enantiofacial control may be expected.

In summary, the asymmetric Weitz−Scheffer epoxidation of isoflavones **3** with the cinchonine- and cinchonidine-derived phase-transfer catalysts **1** and cumyl hydroperoxide **2b** as oxidant constitutes a highly enantioselective method that provides at will both enantiomers of epoxides **4** nearly quantitatively. The efficacious enantiocontrol is rationalized in terms of the hydrogen-bonded aggregate **A** between PTC **1** and isoflavone **3** during the asymmetric oxygen transfer. This expedient asymmetric method should be of synthetic value for the preparation of a wide range of optically active enone epoxides related to the isoflavone structure.

Experimental Section

General Aspects. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 (^{1}H: 200 MHz, ^{13}C: 50 MHz), a Bruker AC 250 (^{1}H: 250 MHz, ^{13}C: 63 MHz), or a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer, and the IR spectra were measured on a Perkin-Elmer 1600 FT-IR spectrophotometer. The HPLC analyses were carried out on chiral columns (Daicel CHIRALCEL OD) with a Kontron instrument, furnished with a spectrophotometer UVIKON 720 micro and a CHIRALYSER 1.6 from IBZ Messtechnik (Hannover, Germany). The optical rotations were determined on a Perkin-Elmer Polarimeter 241 MC. Mass spectra were carried out on a Finigan MAT8200; the exact mass was determined on a Finigan MAT90.

Solvents and commercially available chemicals were purified by standard procedures. PTCs **1a**,**b** and **1d** and hydroperoxides **2a**,**b** are commercially available. Cumyl hydroperoxide (**2b**) was used as technical grade (80%). Hydroperoxides **2c**,**d**[20] and isoflavones **3a**−**c**,**e**, as well as the correponding epoxides **4a**−**c**,**e**, were prepared according to the literature procedures.[16,17]

Preparation of the Starting Materials. PTC 1c.[23] To a solution of 500 mg (0.937 mmol) of PTC **1b** in 5 mL of CH_2Cl_2 at 0 °C were added 0.274 mL (5.00 mmol) of bromomethane (precooled to −78 °C) and 0.5 mL of a saturated aqueous NaOH solution. The flask was stoppered and stirred for 5 h at 25 °C. Water (5 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and evaporated on a rotary evaporator (20 °C, 20 mbar). The residual orange oil was stirred in 20 mL of Et_2O for 16 h, and the resulting yellow solid was collected and recrystallized from EtOH/Et_2O to yield 436 mg (85%) of a pale yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99−1.10 (m, 1 H), 1.61−2.01 (m, 4 H), 2.26−2.33 (m, 1 H), 2.45−2.51 (m, 1 H), 2.72−2.79 (m, 1 H), 3.36−3.62 (m, 2 H), 3.54 (s, 3 H), 4.13−4.18 (m, 1 H), 4.44−4.45 (m, 1 H), 4.79 (s br, 1 H), 5.20 (d, J = 17.2 Hz, 1 H), 5.28 (d, J = 10.4 Hz, 1 H), 5.40 (s br, 1 H), 5.86 (ddd, J = 17.2, 10.4, 7.1 Hz, 1 H), 5.98−6.01 (m, 1 H), 6.68−6.75 (m, 1 H), 7.61 (s br, 1 H), 7.69−7.76 (m, 3 H), 7.86−7.90 (m, 1 H), 8.09−8.16 (m, 3 H), 8.94−8.95 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1 (t), 23.4 (t), 27.0 (d), 37.8 (d), 54.9 (t), 55.8 (t), 57.2 (q), 60.6 (t), 66.3 (d), 77.2 (d), 118.4 (t) 119.4 (d), 122.1 (s), 125.0 (d), 126.0 (d), 128.9 (d), 129.9 (d), 130.2 (d), 131.1 (s), 132.6 (s), 134.7 (2xd), 134.9 (d), 139.0 (s), 148.5 (s), 149.4 (d). $C_{28}H_{30}BrF_3N_2O$ (547.5) HRMS (FAB, glycerine/PEG400 100:5 matrix): $[M - Br]^+$ calcd 467.2310, found 467.2310.

3-Isopropyl-7-hydroxyisoflavone. A 500-mL, round-bottom flask was charged with 2,4-dihydroxybenzoin (10.0 g, 45.6 mmol), isobutyric anhydride (55 mL), and isobutyryl chloride (30 mL) in 100 mL of toluene. Triethylamine (50 mL) was added, and the mixture was kept at reflux for 9 h. The hot solution was poured onto ice (200 g) and acidified with 7 M aqueous HCl (pH 1−2). The resulting colorless oil was collected by means of a pipet, and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 × 70 mL), dried ($MgSO_4$), and evaporated on a rotary evaporator (40 °C, 20 mbar). The residue was dissolved in methanol (200 mL) and heated with 20% NaOH solution (40 mL) for 15 min at reflux. After the reaction mixture was cooled in an ice bath, the precipitate was collected by filtration, washed with water (2 × 50 mL), and dried ($MgSO_4$). Recrystallization from methanol gave 10.0 g (70%) of 3-isopropyl-7-hydroxyisoflavone as a white powder, mp 273−275 °C. IR (KBr): ν (cm^{-1}) 3191, 2972, 1625, 1569, 1493, 1455, 1401, 1375, 1266, 1164, 1115, 988. ^{1}H NMR (200 MHz, DMSO): δ 1.29 (d, J = 6.8 Hz, 6 H), 2.98 (septet, J = 6.8 Hz, 1 H), 6.85−6.90 (m, 2 H), 7.29−7.34 (m, 2 H), 7.40−7.48 (m, 3 H), 8.05 (d, J = 9.2 Hz, 1 H). ^{13}C NMR (63 MHz, DMSO): δ 20.6 (q), 31.5 (d), 103.2 (d), 115.9 (d), 117.1 (s), 122.3 (s), 128.3 (d), 128.6 (d), 129.4 (d), 131.4 (d), 134.7 (s), 159.0 (s), 164.0 (s), 170.6 (s), 178.0 (s). $C_{18}H_{15}O$ (280.1) HRMS (CI): $[M - H]^+$ calcd 279.1021, found 279.1024.

3-Isopropyl-7-methoxyisoflavone (3d). To a solution of 4.07 g (14.9 mmol) of 3-isopropyl-7-hydroxyisoflavone and 4.47 mL (72.1 mmol) of methyl iodide in acetone was added 14.9 g (107 mmol) solid K_2CO_3 with magnetic stirring, and the mixture was heated for 5 h at reflux. The solid K_2CO_3 was removed by filtration, the solvent was evaporated (20 °C, 20 mbar), and the crude product was recrystallized from methanol to yield 2.76 g (63%) of 3-isopropyl-7-methoxyisoflavone (**3d**) as a white powder, mp 164−166 °C. IR (KBr): ν (cm^{-1}) 3054, 3015, 2981, 2932, 1636, 1608, 1440, 1258, 1168, 1017. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, J = 6.8 Hz, 6 H), 2.88 (septet, J = 6.8 Hz, 1 H), 3.84 (s, 3 H), 6.79 (d, J = 2.4 Hz, 1 H), 6.87 (dd, J = 8.8, 2.4 Hz, 1 H), 7.17−7.19 (m, 2 H), 7.28−7.37 (m, 3 H), 8.05 (d, J = 8.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2 (q), 31.0 (d), 55.8 (q), 99.8 (d), 114.1 (d), 117.4 (s), 121.8 (s), 127.6 (d), 128.4 (d), 128.4 (d), 130.3 (d), 133.3 (s), 157.7 (s), 163.9 (s), 169.4 (s), 176.7 (s). $C_{19}H_{18}O_3$ (294.1): calcd C 77.53 H 6.16, found C 77.44, H 6.31.

Preparation of the Epoxides. Representative Procedure for the Phase-Transfer-Catalyzed Epoxidation of

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3-Ethyl-7-methoxyisoflavone (3c).[17] To a magnetically stirred solution of the isoflavone **3c** (50.0 mg, 0.179 mmol) and cumyl hydroperoxide (51.0 mg of 80% purity, 0.269 mmol) at 0 °C was added the PTC **1b** (9.55 mg, 10 mol %). After 5 min of stirring, a 1.0 M aqueous solution of KOH (1 mL) was added at 0 °C, and stirring was continued for 20 h. Water (5 mL) was added, and the aqueous phase was extracted with ether (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and evaporated on a rotary evaporator (20 °C, 20 mbar). A sample was removed for HPLC and ^{1}H NMR analysis, the remaining crude product was dissolved in CH_2Cl_2 (10 mL), and the excess cumyl hydroperoxide was reduced with PPh_3 (TLC control with KI solution). The organic solvent was evaporated (20 °C, 20 mbar), and the residue was purified by flash chromatography on silica gel (1:9 ether−petroleum ether as eluent) to afford the epoxide **4c** in 91% yield and 90% ee as white needles, mp 92−93 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10 (t, J = 7.4 Hz, 3 H), 1.59−1.77 (m, 1 H), 1.85−2.03 (m, 1 H), 3.88 (s, 3 H), 6.56 (d, J = 2.4 Hz, 1 H), 6.72 (dd, J = 2.4, 8.8 Hz, 1 H), 6.34−7.52 (m, 5 H), 7.90 (d, J = 8.8 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 7.75 (q), 24.4 (t), 55.6 (q), 68.4 (s), 91.3 (s), 101.0 (d), 111.7 (d), 113.5 (s), 127.8 (d), 128.4 (d), 128.9 (d), 129.6 (d), 130.7 (s), 158.2 (s), 166.6 (s), 188.2 (s).

The ee values, yields and conversion, all in %, for the remaining epoxides **4** are given in Table 1 (see the main text). Epoxide (1a*R*,7a*S*)-**4d** was obtained in 97% ee after recrystallization from methanol.

Representative Procedure B for the Epoxidation of the 3-Ethyl-7-methoxyisoflavone 3c by the Optically Active Hydroperoxide 2d with DBU as a Base. To a solution of isoflavone **3c** (52.5 mg, 0.188 mmol) and optically active hydroperoxide *S*-(−)-**2d** (33.5 mg, 0.194 mmol) in 4 mL of dry toluene was added DBU (29.0 mg, 19.1 mmol) under a nitrogen atmosphere. The reaction mixture was stirred magnetically for 26 h at ca. 20 °C, poured into water (5 mL), and extracted with ether (3 × 6 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated (20 °C, 30 Torr). From the characteristic signals in the ^{1}H NMR spectrum, 90% conversion was determined. Purification by silica gel flash chromatography with 15:1 petroleum ether/ethyl ether mixture as eluent afforded 45.5 mg (91%) of (1a*R*,7a*S*)-isoflavone epoxide **4c** (45% ee). The spectral data are in accordance with those listed above.

The ee values, yields, and conversion, all in %, for isoflavone epoxide **4d** are given in Scheme 3.

3-Isopropyl-7-methoxyisoflavone Epoxide (4d). A 100-mL, round-bottom flask was charged with 250 mg (0.848 mmol) of 3-isopropyl-7-methoxyisoflavone (**3d**) in 20 mL of methanol at 0 °C, followed by 1 mL of 35% aqueous H_2O_2 (99.0 mmol) and 1 mL of 4 M aqueous NaOH solution (4.00 mmol). After 16 h of magnetic stirring at ca. 20 °C, 50 mL of water was added and the precipitate was collected by filtration and dried. Recrystallization from methanol yielded 220 mg (708 mmol, 84%) of pure epoxide as colorless cubes, mp 103−105 °C. IR (KBr): ν (cm^{-1}) = 3056, 2970, 1671, 1615, 1581, 1439, 1281, 1251, 1204, 1170, 1112, 937. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (d, J = 6.9 Hz, 3 H), 1.31 (d, J = 6.9 Hz, 3 H), 1.58 (septet, J = 6.9 Hz, 1 H), 3.89 (s, 3 H), 6.56 (d, J = 2.4 Hz, 1 H), 6.73 (dd, J = 2.4, 8.8 Hz, 1 H), 7.36−7.44 (m, 5 H), 7.89 (d, J = 8.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6 (q), 16.9 (q), 30.3 (d), 55.7 (q), 69.3 (s), 93.0 (s), 100.9 (d), 111.5 (d), 113.4 (s), 127.6 (d), 127.6 (d), 128.5 (d), 129.2(d), 130.3 (s), 157.7 (s), 166.0 (s), 188.0 (s). $C_{19}H_{18}O_4$ (310.1): calcd C 73.53, H 5.85, found C 73.57, H 5.99.

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Supporting Information Available: The experimental procedures for the kinetic resolution of **2c**, the chiral HPLC analysis, α_D values, and CD-spectral data for epoxides **4** as well as the computational results are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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