On the enantioselective olefin epoxidation by doubly bridged biphenyl azepine derivatives – mixed *tropos*/*atropos* chiral biaryls†

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Diastereomeric doubly bridged biphenyl azepines, *atropos* at 20 °C and *tropos* at 80 °C, are precursors to effective iminium organocatalysts that are employed in the enantioselective epoxidation of prochiral olefins (up to 85% ee).

Introduction

Axially chiral biaryls are extensively studied owing to their importance in natural product chemistry and as reagents or catalysts in synthetic methodology.[1] Atropisomeric compounds with large rotational barriers of enantiomerisation are generally utilised as these configurationally stable derivatives display well-defined and permanent stereochemical environments. This class of *atropos* molecules is mainly constituted by tetra-*ortho*-substituted biphenyls, and 2,2′-disubstituted binaphthyls in particular.

However, recent applications in the asymmetric catalysis have made use of enantiopure substances bearing configurationally labile biaryls.[2] This class of *tropos* derivatives is mainly constituted of cyclic di-*ortho*-substituted biphenyls. The benefit, in this case, is the occurrence of intramolecular discriminating interactions that control the sense of twist of the fluctuating biaryl resulting, possibly and directly, in a 'matched' diastereomeric situation.[3]

The frontier between these two classes of molecules has been defined by Oki.[4] *Atropos* molecules should be isolable as single enantiomers and must present a half-life of at least 1000 s. At 20 °C, the rotational isomerisation must present, at least, a free energy barrier ($\Delta G^{\neq}$) of 21.4 kcal mol^{-1}. Interestingly, most *tropos* and *atropos* derivatives display energy barriers much lower and higher than this threshold respectively. It is, for instance, the case for biphenyl **1** and binaphthyl **2** azepines (Fig. 1).[5] Their quaternary ammonium salts present values of 13.4 and 36.9 kcal mol^{-1} respectively.[6] At 20 °C, this corresponds to half-lives of 1.1 ms and 11.6 million years. Cyclic biphenyls and binaphthyls of type **1** and **2** are thus clearly highly configurationally labile and stable over a large temperature range respectively.[7] Their role as *tropos* and *atropos* moieties cannot be interchanged.

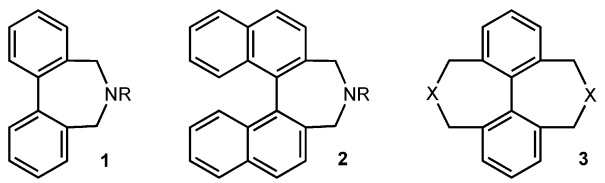

Fig. 1 Biphenyl **1** and binaphthyl **2** azepines; doubly bridged biphenyls **3**.

To benefit from the advantages of both approaches, a class of axially chiral biaryls that would display an *atropos* character at 20 °C and a *tropos* behaviour at slightly elevated temperature (>65 °C) was looked for. In other words, we searched for a family of biaryl derivatives that would possess free energy barriers of *ca.* 25 kcal mol^{-1} for the rotational isomerisation. Herein, we report that diastereomeric doubly bridged biphenyl azepines (DBBAs, Fig. 2) fit the case and show that these simple-to-make derivatives can be used in enantioselective organocatalysis.

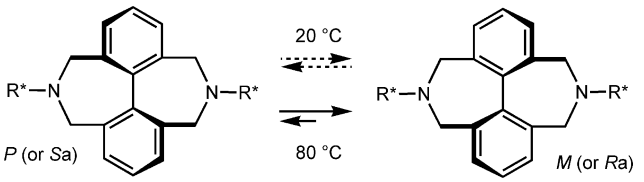

Fig. 2 Generic DBBA **4**, *atropos* and *tropos* at 20 and 80 °C respectively.

Results and discussion

D_2-symmetric core

Biphenyls bearing four identical substituents in positions 2, 2′, 6 and 6′ are achiral (provided there are no other substituents on the phenyl rings). However, biphenyl systems with two identical 2,6- and 2′,6′-bridges are chiral [Fig. 1, **3**: X = N, O, S, C(O), *etc.*], being exceptional in that they possess, instead of a plane of symmetry, three mutually perpendicular C_2 axes (D_2 point group).[8] The barrier to inversion between the *P* and *M* enantiomers (*S*a and *R*a) depends on the heteroatoms; values of 20 and 35 kcal mol^{-1} were measured for the dioxepin and dithiepin derivatives respectively.

In the particular case of DBBA **4** (Fig. 2), no such kinetic data could be found. However, good literature precedents indicated that these moieties were the ideal candidates.[9] Diastereomeric DBBAs were prepared previously by Zavada[9] by alkylation of 2,2′,6,6′-tetrakis(bromomethyl)biphenyl with enantiopure α-branched primary amines **a**, **b** and *ent*-**c** (Fig. 3). The resulting diastereomers were found to be *atropos* at room temperature and *tropos* at 80 °C; most of them were isolable by semi-preparative HPLC and/or crystallisation. Whereas kinetic stereocontrol was moderate

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† Electronic supplementary information (ESI) available: kinetic and thermodynamic ratios, CD spectra if isolated diastereomers, kinetics of isomerism for compounds **4c**–**e**, and determination of ee values of epoxides of olefins **7**–**9**. See DOI: 10.1039/b615797a

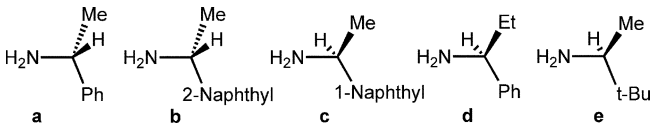


Fig. 3 Amines used the formation of DBBAs **4a**–**e**.

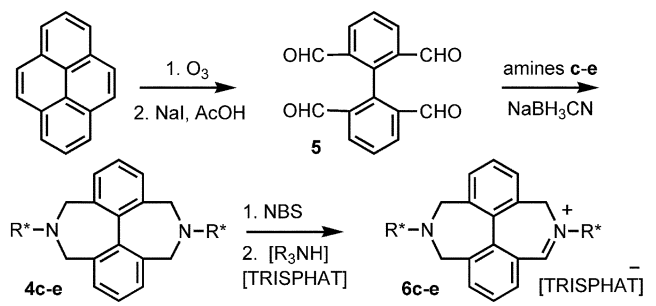
(dr up to 63 : 37, synthesis at 20 °C), thermodynamic selectivity was better as equilibration studies (80 °C) indicated that diastereomeric ratios up 82 : 18 could be achieved. Enantio- and diastereomerically pure derivatives of type **4** can thus be readily prepared.

Surprisingly, unlike derivatives **1** and **2**, compounds of type **4** have not been used in asymmetric synthesis despite the ease of preparation. It was thus decided to extend the chemistry of such diastereomeric DBBAs by finding chiral exocyclic appendages that would, after physical separation of the atropisomers, (i) allow a precise determination of the barrier of isomerisation and (ii) afford effective organocatalysts for enantioselective olefin epoxidation reactions.

Synthesis of diastereomeric doubly bridged biphenyl azepines (*P* and *M*)

In fact, recent studies have indicated that biphenyl and binaphthyl tertiary azepines bearing chiral exocyclic moieties are useful precursors to cyclic quaternary iminium salts; these unsaturated derivatives are effective catalysts for enantioselective epoxidation of unfunctionalised alkenes.[10,11] Care was thus taken to select, for the synthesis of the DBBA diastereomers, three enantiopure amines already tested as exocyclic auxiliaries in the above mentioned oxidation protocol. Along with amine **c**, we selected (*S*)-1-phenylpropylamine **d** and (*S*)-3,3-dimethylbutan-2-amine **e** (Fig. 3). Amine **e** is by far the best of the three auxiliaries in the *tropos* biphenyl series,[11d] and essentially as effective as L-acetonamine in the binaphthyl catalyst variant.[11b,e]

Synthesis of the derived DBBAs **4c**–**e** was realised in two steps (Scheme 1). After the ozonolysis of pyrene (O_3, then NaI, AcOH) giving biphenyl-2,2′,6,6′-tetracarbaldehyde **5** (55%),[12]



Scheme 1 Synthesis of DBBAs **4c**–**e** and iminium salts **6c**–**e**.

reductive amination in the presence of (*S*)-configurated amines **c**–**e**, $NaBH_3CN$ and AcOH afforded compounds **4c** (87%), **4d** (88%) and **4e** (100%) as mixtures of (*S*,*P*) and (*S*,*M*) atropisomers. Care was taken to measure the ratios between these species right after the synthesis (^{1}H NMR, HPLC) and verify, as observed by Zavada,[9] that no evolution occurred at 20 °C.[13] These ratios under kinetic control range from 52 : 48 to 70 : 30 (Table 1).

Kinetic and thermodynamic stereoinduction

Separation of the diastereomers was achieved by column chromatography on silica gel.[14] In all cases, the most predominant diastereomer after the synthesis eluted first and was readily isolated albeit in moderate yields (16–26%). Isolation of the second eluted (minor) diastereomer in analytically pure form was more problematic (due to the contamination by the first) and, in the case of **4d**, the use of semi-preparative HPLC was required. This separation was essential for the determination of the relative configuration of each diastereomer by circular dichroism (CD) following the guidelines established by Mislow[8a] and Sandström.[15] For amines **4c** and **4d**, the most (*i.e.* major) and least (*i.e.* minor) eluted diastereomers showed negative and positive Cotton effects around 255 nm, indicative of (*S*,*P*) and (*S*,*M*) configurations respectively; the situation is reversed for bisazepine **4e** (Table 1).

The diastereomeric ratios under thermodynamic control were then measured by heating separately each diastereomer for 20 h at 80 °C in benzene (Table 1). Under those conditions, a total equilibration was achieved starting from both diastereomers. In all cases, the kinetically favoured atropisomer is also thermodynamically preferred. Interestingly, bulky amine **e** does not afford the best diastereomeric excess after equilibration (71 : 29) as it is achieved with amines **c** and **d** (82 : 18 and 81 : 19).

Barrier of isomerisation

As mentioned earlier, precise values for the isomerisation barrier of DBBA were unknown in the literature. Diastereomerically pure samples of **4c**–**e** were heated at four different temperatures (60, 70, 80 and 90 °C) with a monitoring of the equilibration by analytical HPLC.[16] Kinetic constants were calculated at the four temperatures and the determination of all activation parameters realised (see ESI†, Table 1). $\Delta G^{\neq}$ values in accordance with our expectations (*ca.* 25 kcal mol^{-1}) were measured.

Synthesis of the iminium catalysts

With major (*S*,*P*)-**4c**, (*S*,*P*)-**4d**, (*S*,*M*)-**4e** and minor (*S*,*P*)-**4e** in hand, the synthesis of the mixed [azepine/azepinium] salts (**6**, Scheme 1) was realised in a one-pot process. Treatment with NBS in $CHCl_3$ at 20 °C afforded the unsaturated bromide salts in a matter of minutes. Then, ion exchange metathesis with

Table 1 Kinetic, thermodynamic data and activation parameters ($\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta G^{\neq}$) of the isomerisation barrier of DBBAs **4c**–**e**

	Amine	Major atropisomer[a]	Kinetic ratio[b]	Thermodynamic ratio[c]	$\Delta G^{\neq d,e}$	$\Delta H^{\neq d,e}$	$\Delta S^{\neq d,f}$
	4c	(*S*,*P*)	58 : 42	82 : 18	26.8	24.8	−6.6
	4d	(*S*,*P*)	52 : 48	81 : 19	25.9	18.1	−26.6
	4e	(*S*,*M*)	70 : 30	71 : 29	24.7	17.0	−26.2

[a] Kinetic and thermodynamic, configuration determined by CD. [b] At 20 °C. [c] At 80 °C (20 h, benzene). [d] T = 293 K. [e] Units: kcal mol^{-1}. [f] Units: cal mol^{-1} K^{-1}.

1.2 equiv. of ammonium TRISPHAT (Fig. 4) salt afforded, after chromatography (SiO_2, CH_2Cl_2), the final lipophilic salts (*S*,*P*)-**6c**, (*S*,*P*)-**6d**, (*S*,*M*)-**6e** and (*S*,*P*)-**6e** (79–92%, two steps).[17,18]

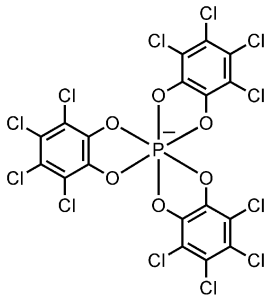


Fig. 4 TRISPHAT anion.

Enantioselective olefin epoxidation

Traditionally, iminium-catalyzed epoxidation reactions are performed in mixtures of CH_3CN and water. This combination is a good solvent for all reagents, the lipophilic olefins as well as the polar salts of iminium cations. However, using salts of type [**10c**–**e**][TRISPHAT] (Fig. 5), strict biphasic CH_2Cl_2/water conditions could be used and an enhancement of the selectivity

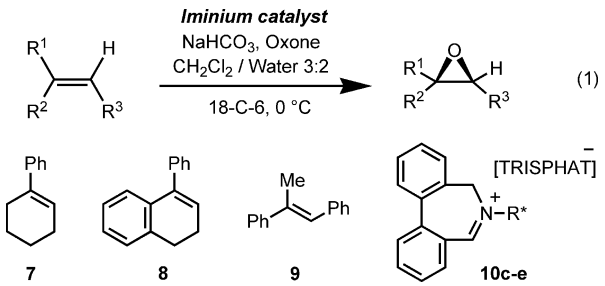


Fig. 5 Unfunctionalised olefins **7**–**9** and *tropos* catalysts **10c**–**e**.

of the epoxidation reactions as well as a good recovery of the epoxides was demonstrated.[19] Such epoxidation conditions [Oxone®, CH_2Cl_2/$NaHCO_3$/18-crown-6/H_2O, eqn (1) in Fig. 5] were therefore used and three different prochiral trisubstituted unfunctionalised alkenes (**7**–**9**, Fig. 5) were selected for the catalysis study.[20] The results are reported in Tables 2 and 3 for the diastereomeric (*S*,*M*)-**6e** and (*S*,*P*)-**6e**, and analogous (*S*,*P*)-**6c** and (*S*,*P*)-**6d** catalysts respectively. To measure the effect of the *atropos* backbone, the results are compared to those obtained with the *tropos* biphenyl iminium salts **10c**–**e** (Fig. 5).[11d]

Significantly, all [azepine/azepinium] salts derived from the major diastereomeric DBBAs behave as catalysts performing, in terms of ee, either as well as [Table 2, (*S*,*M*)-**6e**] or much better than [Table 3, (*S*,*P*)-**6c** and (*S*,*P*)-**6d**] their *tropos* iminium analogues **10c**–**e**; conversions being, however, globally lower.

If one compares the selectivity of the diastereomeric catalysts together – that is (*S*,*M*)-**6e** with (*S*,*P*)-**6e** (Table 2) – one observes different levels of stereoinduction with quite better ee with the (*S*,*M*)-configurated catalyst derived from the major atropisomer. Interestingly, an identical sense of induction is obtained for the non-racemic epoxides in all examples (included those of *tropos* **10e**). These two characteristics, appearance of 'matched'/'mismatched' distinction and the enantioselectivity of the epoxidation reaction being controlled by the exocyclic appendage rather than the configuration of the biaryl moiety are in sharp contrast to what is known with the *atropos* binaphthyl framework.[11b]

Maybe more importantly, the results detailed in Table 3 demonstrate that the central biaryl core can have a profound influence on the stereochemical outcome if the chiral exocyclic auxiliary fails to provide an effective stereoinduction. It is particularly evident if one compares the results of (*S*,*P*)-**6c** with **10c** and those of (*S*,*P*)-**6d** with **10d**: the *atropos* iminium cations lead to much better ee values, in particular in the case of olefin **8** (*e.g.* ee: **6c**: 67% *vs.* **10c**: 7% and **6d**: 85% *vs.* **10d**: 35%).

Table 2 Enantioselective epoxidation of olefins **7**–**9** using diastereomeric catalysts (*S*,*M*)-**6e** and (*S*,*P*)-**6e**; (*S*)-**10e** used as reference[a]

	Major (*S*,*M*)-**6e**			Minor (*S*,*P*)-**6e**			(*S*)-**10e** (reference)		
Alkene	ee[b]	Conv.	Conf.	ee[b]	Conv.	Conf.	ee[b]	Conv.	Conf.
7	76	56	(−)-(1*S*,2*S*)	—	—	—	66	68	(−)-(1*S*,2*S*)
8	76	80	(+)-(1*R*,2*S*)	49	76	(+)-(1*R*,2*S*)	80	100	(+)-(1*R*,2*S*)
9	59	61	(−)-(1*S*,2*S*)	41	75	(−)-(1*S*,2*S*)	46	75	(−)-(1*S*,2*S*)

[a] Conditions: 5 mol% of catalyst, 2.5 mol% 18-C-6, 1.1 equiv. Oxone®, 4.0 equiv. $NaHCO_3$, CH_2Cl_2–H_2O (3 : 2), 2 h, 0 °C. Average of at least two runs. [b] The enantiomeric excesses were determined by CSP-GC (**7**: Chiraldex Hydrodex β-3P) or CSP-HPLC (**8**,**9**: CHIRALCEL-ODH or CHIRALPAK®-IB, 0.5 mL min^{-1}, hexane–*i*-PrOH 95 : 5, $\lambda = 230$ nm); the conversions used an internal standard (naphthalene).

Table 3 Enantioselective epoxidation of olefins **7**–**9** using catalysts (*S*,*P*)-**6c**, (*S*,*P*)-**6d**; (*S*)-**10c** and (*S*)-**10d** used as references[a]

	Major (*S*,*P*)-**6c**			(*S*)-**10c** (reference)			Major (*S*,*P*)-**6d**			(*S*)-**10d** (reference)		
Alkene	ee[b]	Conv.	Conf.	ee[b]	Conv.	Conf.	ee[b]	Conv.	Conf.	ee[b]	Conv.	Conf.
7	58	26	(+)-(1*R*,2*R*)	3	86	(−)-(1*S*,2*S*)	71	82	(+)-(1*R*,2*R*)	26	86	(+)-(1*R*,2*R*)
8	67	69	(−)-(1*S*,2*R*)	7	100	(+)-(1*R*,2*S*)	85	60	(−)-(1*S*,2*R*)	35	92	(−)-(1*S*,2*R*)
9	49	44	(+)-(1*R*,2*R*)	8	66	(−)-(1*S*,2*S*)	55	51	(+)-(1*R*,2*R*)	6	53	(+)-(1*R*,2*R*)

[a] Conditions: 5 mol% of catalyst, 2.5 mol% 18-C-6, 1.1 equiv. Oxone®, 4.0 equiv. $NaHCO_3$, CH_2Cl_2–H_2O (3 : 2), 2 h, 0 °C. Average of at least two runs. [b] The enantiomeric excesses were determined by CSP-GC (**7**: Chiraldex Hydrodex β-3P) or CSP-HPLC (**8**,**9**: CHIRALCEL-ODH or CHIRALPAK®-IB, 0.5 mL min^{-1}, hexane–*i*-PrOH 95 : 5, $\lambda = 230$ nm); the conversions used an internal standard (naphthalene).

Conclusion

Although moderate yields of diastereomerically pure DBBAs can be obtained under kinetic control, the fact that the most useful (kinetic and thermodynamic) diastereomers can be favoured at elevated temperature renders this approach interesting as higher percentages of the useful catalyst precursors can then be afforded after equilibration. Interestingly, selective DBBA catalyst (*S*,*P*)-**6d** comes from chiral amine **d** that had so far shown no favourable disposition. Studies on further applications of doubly bridged biphenyls are currently underway in our group.

Experimental

General remarks

All reactions were carried out under dry N_2 by means of an inert gas/vacuum double manifold line and standard Schlenk techniques. Solvents were dried through a highly activated alumina column under a dry inert atmosphere prior to use. Compounds **10c**–**e** and [cinchonidinium][TRISPHAT] were prepared according to the reported procedures.[11d,17] Optical rotations were measured on a JASCO P-1030 polarimeter in a thermostated (20 °C) 10.0 cm long microcell with high pressure lamps of sodium or mercury and are reported as follows: $[\alpha]_D^{20}$ [c (g per 100 mL), solvent]. Melting points (mp) were measured in open capillary tubes on a Büchi B540 melting point apparatus and were uncorrected. IR spectra were recorded with a Perkin-Elmer 1650 FT-IR spectrometer using a diamond ATR Golden Gate sampling. NMR spectra were recorded on Bruker AMX-400 at room temperature. ^{1}H NMR chemical shifts are given in ppm relative to Me_4Si with the solvent resonance used as the internal standard. ^{13}C NMR (100 MHz): chemical shifts were given in ppm relative to Me_4Si, with the solvent resonance used as the internal standard. ^{31}P NMR (162 MHz) chemical shifts are given in ppm relative to H_3PO_4. Data were reported as follows: chemical shift (δ) in ppm on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, and m = multiplet), coupling constant (Hz), and integration. Electrospray mass spectra (ES-MS) were obtained on a Finnigan SSQ 7000 spectrometer and EI-MS spectra were obtained on a Varian CH4 or SM1 spectrometer; ionizing voltage 70 eV; *m*/*z* (intensity in %) by the Department of Mass Spectroscopy of the University of Geneva. Circular dichroism spectra were recorded on a JASCO J-715 polarimeter in a 1.0 cm quartz cell; λ are given in nm and molar circular dichroic absorptions ($\Delta\varepsilon$ in cm^2 mmol^{-1}). HPLC analyses were performed on an Agilent 1100 apparatus (binary pump, autosampler, column thermostat and diode array detector) using Chiralcel OD-H (0.46 × 25 cm) and Chiralpak IB (0.46 × 25 cm) columns. Chiral stationary phase (CSP) chromatography was performed on a Hewlett Packard 6890 GC chromatograph using a Hydrodex-β column (25 m × 0.25 m, H_2, 40 psi).

General procedure for the synthesis of bisazepines 4c–e

To a solution of biphenyl-2,2′,6,6′-tetracarboxaldehyde **5** (1.0 equiv.) in CH_3CN (6 mL per 0.1 g of aldehyde) was added the corresponding enantiopure amine **c** to **e** (2.2 equiv.). After 15 min of stirring, $NaBH_3CN$ (4 equiv.) was added and the reaction was stirred for 20 h before the addition of AcOH (*ca.* 10 equiv.). After 1 h, the reaction mixture was diluted with 2% MeOH/CH_2Cl_2 (40 mL), washed with 1M NaOH (until pH > 10), dried over Na_2SO_4 and concentrated under reduced pressure. To obtain analytically pure compounds, a filtration over basic alumina (eluent Et_2O) can be sometimes necessary to remove boron residues and any excess of starting amines.

Atropisomers 4c. Starting from 190 mg of biphenyl-2,2′,6,6′-tetracarboxaldehyde, compound **4c** was obtained as a mixture of two diastereomers [58 : 42 ratio (*S*,*P*)/(*S*,*M*), 340 mg, 87%] as a white solid. In a reaction starting from 506 mg of biphenyl-2,2′,6,6′-tetracarboxaldehyde, compound **4c** was obtained as a mixture of two diastereomers (600 mg, same ratio) with an unrepresentatively low yield (58%). It was nevertheless this batch that was used for the separation of the analytically pure diastereomers.

(*S*,*P*)-**4c**. This first eluted diastereomer was isolated by chromatography on basic alumina using toluene as eluent and obtained as a white solid (163 mg, 16%). Mp 101 °C; $[\alpha]_D^{20}$ −11.2 (*c* 0.20, CH_2Cl_2); CD (*c* 1.0 × 10^{-5} M, CH_2Cl_2) $\Delta\varepsilon$ (λ) −4.1 (255) cm^2 mmol^{-1}; ν_{max}/cm^{-1} 2971, 2791, 1594, 1509, 1450, 1372, 1225, 1112, 1068; δ_H(400 MHz; $CDCl_3$; Me_4Si) 8.40 (s, 2H), 7.6–7.8 (m, 6H), 7.3–7.45 (m, 6H), 7.0–7.25 (m, 6H), 4.29 (d, 2H, *J* = 6.3 Hz), 3.69 (d, 4H, *J* = 12.4 Hz), 3.06 (d, 4H, *J* = 12.1 Hz), 1.37 (d, 6H, *J* = 6,6 Hz): δ_C(100 MHz; $CDCl_3$; Me_4Si) 142.2, 140.5, 140.2, 138.0, 135.0, 134.4, 134.2, 131,3, 129.3, 129.2, 129.0, 128.9, 128.3, 127.8, 127.6, 127.4, 126.0, 125.8, 125.4, 124.1, 59.5, 53.5, 21.9; MS-ES (+) *m*/*z* (rel. intensity) 545.3 (100, M + 1), 391.3 (40, [M − $C_{12}H_{12}$] + 1), 357.3 (20), 277.5 (25), 237.5 (20, [M − 2 × $C_{12}H_{12}$] + 1).

(*S*,*M*)-**4c**. This second eluted diastereomer was isolated by chromatography on basic alumina using diethyl ether as eluent and obtained as a white solid (41 mg, 4%). Mp 118.0 °C; $[\alpha]_D^{20}$ +3.4 (*c* 0.23, CH_2Cl_2); CD (*c* 1.0 × 10^{-5} M, CH_2Cl_2) $\Delta\varepsilon$ (λ) 4.5 (255) cm^2 mmol^{-1}; ν_{max}/cm^{-1} 2975, 2793, 1595, 1507, 1452, 1372, 1224, 1111, 1068; δ_H(400 MHz; $CDCl_3$; Me_4Si) 8.39 (s, 2H), 8.0–7.0 (m, 18H), 4.27 (s, 2H), 3.74 (d, 4H, *J* = 12.4 Hz), 3.10 (d, 4H, *J* = 12.4 Hz), 1.75 (d, 6H, *J* = 6,1 Hz); δ_C(100 MHz; $CDCl_3$; Me_4Si) 139.3, 133.9, 133.2, 133.0, 130.5, 127.9, 127.7, 126.8, 126.7, 126.6, 126.4, 125.0, 124.8, 125.6, 124.4, 124.0, 123.1, 58.3, 52.0, 20.5; MS-ES (+) *m*/*z* (rel. intensity) 545.3 (100, M + 1), 391.3 (70, [M − $C_{12}H_{12}$] + 1), 237.5 (30, [M − 2 × $C_{12}H_{12}$] + 1).

Atropisomers 4d. Starting from 197 mg of biphenyl-2,2′,6,6′-tetracarboxaldehyde, compound **4d** was obtained as a mixture of two diastereomers [52 : 48 ratio (*S*,*P*)/(*S*,*M*), 310 mg, 88%] as a white foam.

(*S*,*P*)-**4d**. This first eluted diastereomer was obtained by selective precipitation in MeOH. The crude mixture containing the two diastereomers (310 mg) was dissolved in methanol (*ca.* 4 mL) and, after a few seconds, a white precipitate appeared. This precipitate was filtered, washed with cold methanol to give the desired diastereomer as a white powder (99 mg, 28%). R_f 0.21 (CH_2Cl_2); mp 100 °C; $[\alpha]_D^{20}$ −298.2 (*c* 0.39, MeOH); CD (*c* 1.0 × 10^{-5} M, MeOH) $\Delta\varepsilon$ (λ) −33.9 (255); ν_{max}/cm^{-1} 2961, 2797, 1730, 1492, 1453, 1353, 1261, 1083, 1024, 961; δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.44–7.23 (m, 16H), 3.76 (d, 4H, J_{AB} = 12.3 Hz), 3.36 (dd, 2H, *J* = 9.4 and 3.8 Hz), 3.06 (d, 4H, J_{AB} = 12.4 Hz), 1.96 (m, 2H), 1.68 (m, 2H), 0.61 (t, 6H, *J* = 7.3 Hz); δ_C(100 MHz; $CDCl_3$; Me_4Si) 128.9, 128.7, 128.2, 127.6, 127.1, 69.1, 52.9, 27.5, 10.6; MS-ES (+)

m/z (rel. intensity) 473.3 (100, M + 1), 355.1 (70, [M − C_9H_{12}] + 1), 277.3 (40), 237.1 (30, [M − 2 × C_9H_{12}] + 1).

(*S*,*M*)-**4d**. This second eluted diastereomer was isolated using a semi-preparative HPLC column (hexane–isopropanol 95 : 5). R_f 0.37 (benzene–diethyl ether 2 : 1); mp 89 °C; $[\alpha]_D^{20}$ +51.0 (*c* 0.39, MeOH); CD (*c* 1.0 × 10^{-5} M, MeOH) $\Delta\varepsilon$ (λ) 19.3 (255); ν_{max}/cm^{-1} 2965, 2789, 1631, 1598, 1451, 1356, 1220, 1100; δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.52–7.31 (m, 16H), 3.81 (d, 4H, J_{AB} = 12.4 Hz), 3.44 (dd, 2H, J = 9.6 and 3.5 Hz), 3.06 (d, 4H, J_{AB} = 12.4 Hz), 2.04 (m, 2H), 1.74 (m, 2H), 0.69 (t, 6H, J = 7.6 Hz); δ_C(100 MHz; $CDCl_3$; Me_4Si) 143.5, 140.3, 134.7, 129.0, 128.7, 128.3, 127.3, 126.9, 69.1, 53.0, 27.1, 10.3; MS-ES (+) m/z (rel. intensity) 473.3 (100, M), 355.1 (100, [M − C_9H_{12}] + 1), 237.3 (80, [M − 2 × C_9H_{12}] + 1).

Atropisomers 4e. Starting from 250 mg of biphenyl-2,2′,6,6′-tetracarboxaldehyde, compound **4e** was obtained as a mixture of two diastereomers [58 : 42 ratio (*S*,*M*)/(*S*,*P*), 380 mg, 100%].

(*S*,*M*)-**4e**. This first eluted diastereomer was isolated by chromatography on silica gel using benzene as eluent and obtained as a white solid (76 mg, 20%). R_f 0.91 (benzene–diethyl ether 1 : 1); mp 171–172 °C; $[\alpha]_D^{20}$ +256.0 (*c* 0.41, $CHCl_3$); CD (*c* 1.0 × 10^{-5} M, MeOH) $\Delta\varepsilon$ (λ) 16.4 (255); ν_{max}/cm^{-1} 2967, 2863, 1459, 1356, 1154, 1116; δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.35 (m, 6H), 3.65 (d, 4H, J_{AB} = 12.5 Hz), 3.48 (d, 4H, J_{AB} = 12.5 Hz), 2.53 (q, 2H, J = 7.0 Hz), 1.19 (d, 6H, J = 7.0 Hz), 0.99 (s, 18H); δ_C(100 MHz; $CDCl_3$; Me_4Si) 139.6, 136.4, 128.9, 128.0, 68.2, 54.1, 27.0, 11.6; MS-ES (+) m/z (rel. intensity) 405.7 (100, M + 1).

(*S*,*P*)-**4e**. This second eluted diastereomer was isolated by a preparative chromatography on basic alumina using pentane–*c*-hexane–ethyl acetate (50 : 50 : 1.2) as eluent and obtained as a pale yellow viscous oil (22.8 mg, 6%). R_f 0.18 (*c*-hexane); $[\alpha]_D^{20}$ −100.0 (*c* 0.41, $CHCl_3$); CD (*c* 1.0 × 10^{-5} M, MeOH) $\Delta\varepsilon$ (λ) −11.4 (255); ν_{max}/cm^{-1} 2949, 2902, 2865, 1637, 1480, 1548, 1355, 1154, 1114, 1074, 927; δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.35 (m, 6H), 3.56 (dd, 8H, J_{AB} = 12.0 Hz), 2.84 (q, 2H, J = 7.1 Hz), 1.19 (d, 6H, J = 7.0 Hz), 1.02 (s, 18H); δ_C(100 MHz; $CDCl_3$; Me_4Si) 139.6, 136.4, 128.1, 127.8, 69.8, 55.4, 27.4, 11.6; MS-ES (+) m/z (rel. intensity) 405.5 (100, M + 1), 321.5 (80, [M − C_6H_{14}] + 1), 237.1 (20, [M − 2 × C_6H_{14}] + 1).

General procedure for the synthesis of the iminium TRISPHAT salts 6c–e

In a 50 mL round-bottomed flask equipped with a magnetic stirring bar, diazepine **4c**–**e** (0.25 mmol, 1.0 equiv.) was dissolved in 5 mL of $CHCl_3$ and *N*-bromosuccinimide (0.32 mmol, 1.3 equiv.) was added to the solution. The mixture was stirred at room temperature for a few minutes (usually 5 min) then a solution of [cinchonidinium][Δ-TRISPHAT] (0.275 mmol, 1.1 equiv.) in a minimum amount of acetone was added. After 5 min of stirring at room temperature the solvents were removed under reduced pressure. The desired iminium salts **6c**–**e** were recovered after column chromatography (silica gel 60; CH_2Cl_2).

(*S*,*P*)-6c. Starting from (*S*,*P*)-**4c** (30 mg, 0.055 mmol), the desired compound was obtained as a yellow solid (65 mg, 90%). Mp 210.1 °C; $[\alpha]_D^{20}$ −1588 (*c* 0.10, MeOH); ν_{max}/cm^{-1} 2928, 1692, 1640, 1594, 1448, 1390, 1302, 1236, 991, 823, 670; δ_H(400 MHz; $CDCl_3$; Me_4Si) 10.5 (s, 1H), 8.4 (s, 1H), 8.3–6.5 (m, 20H), 5.45 (d, 1H, J = 7.6 Hz), 4.7 (d, 1H, J = 12.8 Hz), 4.3 (d, 1H, J = 6.2 Hz), 4.1 (d, 1H, J = 13.0 Hz), 3.8 (d, 1H, J = 12.2 Hz), 3.65 (d, 1H, J = 12.6 Hz), 3.0 (q, 2H, J = 12.2 Hz), 2.34 (d, 3H, J = 6.6 Hz), 1.45 (d, 3H, J = 6.4 Hz); δ_C(100 MHz; $CDCl_3$; Me_4Si) 170.0 (CH), 141.5 (C^{IV}, d, J = 6.4 Hz), 140.9 (C^{IV}), 137.9 (C^{IV}), 137.5 (CH), 136.4 (C^{IV}), 136.0 (C^{IV}), 134.4 (C^{IV}), 133.6 (C^{IV}), 133.0 (CH), 131.9 (CH), 131.8 (C^{IV}), 131.6 (CH), 130.9 (C^{IV}), 129.7 (CH), 129.1 (CH), 128.9 (CH), 127.9 (CH), 127.7 (CH), 127.3 (CH), 126.6 (C^{IV}), 126.5 (CH), 126.2 (CH), 126.0 (CH), 125.9 (CH), 125.7 (CH), 124.7 (CH), 123.1 (C^{IV}), 121.4 (CH), 114.2 (C^{IV}, d, J = 20.0 Hz), 68.1 (CH), 53.6 (CH_2), 53.1 (CH_2), 51.1 (CH_2), 29.7 (CH_2), 21.7 (CH), 18.6 (CH_3), 14.2 (CH_3); δ_P(162 MHz; $CDCl_3$; H_3PO_4) −80.99; MS-ES (+) m/z (rel. intensity) 575.3 (30), 543.7 (100, M^+), 389.3 (60, M − $C_{12}H_{12}$), 235.3 (10, M − 2 × $C_{12}H_{12}$); MS-ES (−) m/z (rel. intensity) 769.0 (100, TRISPHAT).

(*S*,*P*)-6d. Starting from (*S*,*P*)-**4d** (45 mg, 0.095 mmol), the desired compound was obtained as a yellow solid (100 mg, 85%). R_f 0.72 (CH_2Cl_2–MeOH 95 : 5, SiO_2); mp 200 °C (decomp.); $[\alpha]_D^{20}$ −3552 (*c* 0.12, MeOH); ν_{max}/cm^{-1} 2934, 1640, 1593, 1562, 1445, 1389, 1301, 1235, 990, 819, 718, 669; δ_H(400 MHz; $CDCl_3$; Me_4Si) 9.85 (s, 1H), 7.81–7.1 (m, 13H), 6.3 (d, 1H, J = 7.5 Hz), 5.9 (t, 1H, J = 7.2 Hz), 4.7 (d, 1H, J = 13.0 Hz), 4.3 (d, 1H, J = 13.2 Hz), 3.7 (dd, 2H, J = 25.0 and 37.9 Hz), 3.05 (t, 3H, J = 11.7 Hz), 2.55 (m, 3H), 2 (m, 1H), 1.65 (m, 2H), 1.15 (t, 3H, J = 7.2 Hz), 0.9 (m, 1H), 0.65 (t, 3H, J = 7.2 Hz); δ_C(100 MHz; $CDCl_3$; Me_4Si) 168.2 (CH), 142.7 (C^{IV}), 141.9 (C^{IV}), 141.5 (C^{IV}, d, J = 6.4 Hz), 138.4 (C^{IV}), 137.6 (CH), 136.5 (C^{IV}), 136.0 (C^{IV}), 133.4 (CH), 133.1 (C^{IV}), 132.8 (C^{IV}), 132.0 (CH), 130.4 (CH), 130.3 (CH), 129.3 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 127.0 (CH), 126.1 (C^{IV}), 123.0 (C^{IV}), 114.0 (C^{IV}, d, J = 20.0 Hz), 68.7 (CH), 53.2 (CH_2), 53.0 (CH_2), 51.6 (CH_2), 27.2 (CH_2), 25.2 (CH), 23.9 (CH_2), 11.0 (CH_3), 10.1 (CH_3); δ_P(162 MHz; $CDCl_3$; H_3PO_4) −80.97; MS-ES (−) m/z (rel. intensity) 768.5 (100, TRISPHAT); MS-ES (+) m/z (rel. intensity) 471.5 (100, M^+), 197.4 (20).

(*S*,*M*)-6e. Starting from (*S*,*M*)-**4e** (20.0 mg, 0.050 mmol), the desired compound was obtained as an orange solid (46 mg, 79%). R_f 0.42 (CH_2Cl_2, Al_2O_3 basic); mp 241.3 °C; $[\alpha]_D^{20}$ −329.6 (*c* 0.1, MeOH); ν_{max}/cm^{-1} 2959, 1634, 1591, 1559, 1446, 1388, 1302, 1235, 990, 819, 718, 669; δ_H(400 MHz; $CDCl_3$; Me_4Si) 8.80 (s, 1H), 7.82 (d, 1H, J = 7.8 Hz), 7.67–7.44 (m, 4H), 4.90 (d, 1H, J = 13.4 Hz), 4.12 (q, 1H, J = 6.8 Hz), 3.83 (d, 1H, J = 10.4 Hz), 3.79 (d, 1H, J = 9.0 Hz), 3.64 (d, 1H, J = 12.5 Hz), 3.51 (d, 1H, J = 11.9 Hz), 3.25 (d, 1H, J = 13.1 Hz), 2.63 (q, 1H, J = 7.0 Hz), 1.75 (d, 3H, J = 7.1 Hz), 1.22 (d, 3H, J = 7.0 Hz), 1.12 (s, 9H), 1.01 (s, 9H); δ_P(162 MHz; $CDCl_3$; H_3PO_4) −80.99; MS-ES (−) m/z (rel. intensity) 768.7 (100, TRISPHAT); MS-ES (+) m/z (rel. intensity) 403.5 (100, M^+), 197.5 (12).

(*S*,*P*)-6e. Starting from (*S*,*P*)-**4e** (13 mg, 0.032 mmol), the desired compound was obtained as a yellow solid (16.5 mg, 92%). R_f 0.65 (CH_2Cl_2–MeOH 9 : 1); mp 237.8 °C; $[\alpha]_D^{20}$ −134.0 (*c* 0.1, MeOH); ν_{max}/cm^{-1} 2963, 1633, 1591, 1559, 1447, 1389, 1302, 1260, 1235, 1096, 990, 819; δ_H(400 MHz; $CDCl_3$; Me_4Si) 9.28 (s, 1H), 7.91 (m, 1H), 7.78 (d, 1H, J = 7.5 Hz), 7.63 (m, 2H), 7.49 (d, 1H, J = 7.2 Hz), 7.31 (m, 1H), 4.83 (d, 1H, J = 13.3 Hz), 4.48 (d, 1H, J = 13.3 Hz) 4.21 (q, 1H, J = 7.0 Hz), 3.62 (m, 3H), 3.40 (d, 1H, J = 11.6 Hz), 2.91 (q, 1H, J = 7.1 Hz), 1.66 (d, 3H, J = 7.0 Hz), 1.21 (s, 9H), 1.04 (m, 12 H); δ_P(162 MHz; $CDCl_3$;

H_3PO_4) −80.81; MS-ES (+) *m/z* (rel. intensity) 319.3 (50, M − C_6H_{14}), 403.3 (100, M); MS-ES (−) *m/z* (rel. intensity) 768.8 (100, TRISPHAT).

Typical procedure for the biphasic enantioselective epoxidation procedure

In a 10 mL flask equipped with a magnetic stirring bar, $NaHCO_3$ (67.0 mg, 0.80 mmol, 4.0 equiv.) was added to 800 μL of water. Oxone® (132.0 mg, 0.21 mmol, 1.0 equiv.) was then added and the solution stirred for 2 min until effervescence subsided. 500 μL of a 0.4 mol L^{-1} solution of the alkene (0.20 mmol, 1.0 equiv.) and naphthalene (0.20 mmol, 1.0 equiv., internal reference) in CH_2Cl_2 was added and the resulting biphasic mixture was cooled to 0 °C with a cryostatic bath. The catalyst (10.0 μmol, 5 mol%) in CH_2Cl_2 (500 μL) was added, followed by a solution of 18-crown-6 (1.0 mg, 5.0 μmol, 2.5 mol%) in CH_2Cl_2 (200 μL). The reaction mixture was then stirred at room temperature for 2 h.

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