Asymmetric epoxidation of 2-arylidene-1,3-diketones: facile access to synthetically useful epoxides†

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In this article the first enantioselective epoxidation reaction of acyclic and cyclic 2-arylidene-1,3-diketones is reported. Easily accessible or commercially available α,α-diaryl prolinols as the organocatalysts in the presence of *tert*-butyl hydroperoxide (TBHP) provide the corresponding epoxides in high to excellent yield (up to 99%) and up to 85% ee (ee >90% after crystallisation). These epoxides are pharmaceutically important building blocks and intermediates for the synthesis of densely functionalised epoxide derivatives.

Introduction

The asymmetric epoxidation of alkenes is a reaction of considerable interest, whose products represent versatile synthons, natural compounds and pharmaceuticals.[1] Although several functionalised and unfunctionalised alkenes can be epoxidized in a highly enantioselective manner, either using metal-catalysed[2] or organocatalytic systems,[3] expanding the scope of alkenes susceptible of asymmetric epoxidation would be highly desirable. In the context of electron-poor olefins, notable results have been recently achieved in the nucleophilic enantioselective epoxidation of challenging compounds such as α,β-unsaturated aldehydes[4] and cyclic[5] enones employing secondary and primary amines as organocatalysts.

Readily accessible α,α-diarylprolinols were demonstrated to be useful promoters in a variety of asymmetric reactions involving carbon–carbon and carbon–heteroatom bond formation.[6] We reported that commercially available compounds **1a** and **1b** catalyse the asymmetric epoxidation of α,β-unsaturated ketones[7] and the β-peroxidation of nitroalkenes with good to high levels of asymmetric induction (Fig. 1).[8] These catalysts are thought to synergistically activate the oxidant (TBHP) and the electrophile by means of general base and acid catalysis provided by the amino and hydroxyl groups, respectively.

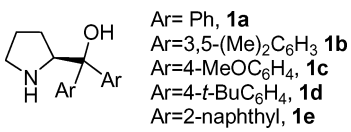

Fig. 1 α,α-Diarylprolinols employed as promoters in asymmetric oxidations.

On the basis of our interest in the area of asymmetric epoxidations and the observation of the lack of methodologies for the enantioselective epoxidation of trisubstituted electron-poor olefins,[9] we embarked on a study concerning the development of an asymmetric version for the epoxidation of 2-arylidene-1,3-diketones **2**. Herein, the first asymmetric epoxidation of 2-arylidene-1,3-diketones **2**, employing diaryl prolinols **1**[10]/TBHP system is reported (Scheme 1).

Scheme 1 Asymmetric organocatalytic epoxidation of alkenes **2**.

Results and discussion

Preliminary considerations were taken into the suitability of an organocatalytic activation for the nucleophilic asymmetric epoxidation of alkenes **2**. The generation of iminium ions, by condensation of compounds **2** with chiral secondary or primary amines, able to undergo 1,4-conjugate addition by a hydroperoxide derivative, was discarded on the basis of the sterically congested nature and low reactivity of the aryloyl groups.[11] Intrinsically higher reactivity of electron-poor alkenes **2** towards epoxidation *via* noncovalent dual activation provided by **1**/TBHP system, would be easily expected compared to α,β-enones. However, in both activation strategies, the control of the prochiral faces was supposed to not be trivial in view of the identical substitution at α-position of alkenes **2**.

Our study commenced with screening catalysts **1** at 20% mol loading, under different reaction conditions, in the epoxidation of model compound **2a** (R = Ar = Ph, Table 1). Interestingly, under previously optimized conditions, established for the epoxidation of α,β-enones using promoter **1a**,[7a] epoxide **3a** was isolated in good yield and 50% ee (entry 1). The reaction carried out in alternative non-polar solvents proceeded sluggishly (entries 2–5). Screening of catalysts **1b–e** in hexane revealed comparable efficiencies with respect to compound **1a** (entries 6–9), except in the case of promoter **1c**, which furnished the epoxide in excellent yield and 67% ee (entry 7). The use of cumyl hydroperoxide (CMHP) as oxidant was detrimental in all respects (entry 10). Although an improvement in the asymmetric induction was observed when

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Table 1 Optimization study for the epoxidation of **2a** with **1**/TBHP system at room temperature[a]

Entry	Catalyst	Solvent	*t*/h	Yield (%)[b]	ee (%)[c]
1	**1a**	Hexane	24	80	50
2	**1a**	Methylcyclohexane	24	78	48
3	**1a**	Toluene	22	14	44
4	**1a**	*p*-Xylene	23	13	48
5	**1a**	*m*-Xylene	23	14	48
6	**1b**	Hexane	16	98	41
7	**1c**	Hexane	19	99	67
8	**1d**	Hexane	46	85	46
9	**1e**	Hexane	32	80	44
10[d]	**1c**	Hexane	16	85	55
11[e]	**1c**	Hexane	75	36	74
12[e]	**1c**	Hexane/*p*-xylene 3 : 1	72	85	83
13[f]	**1c**	Hexane/*p*-xylene 3 : 1	89	74	74
14[e,g]	**1c**	Hexane/*p*-xylene 3 : 1	97	83	85

[a] Reaction conditions: **2a** (0.2 mmol)/TBHP (0.24 mmol)/**1** (0.04 mmol) in 1 mL of solvent. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] CMHP was used as oxidant. [e] At −18 °C. [f] At −30 °C. [g] 2 mL of solvent were used.

performing the epoxidation at −18 °C with organocatalyst **1c** and TBHP, the product was isolated in low yield, likely ascribed to a scarce solubility of the alkene under these conditions (entry 11). Pleasingly, hexane/*p*-xylene 3 : 1 mixture helped to significantly improve the yield and asymmetric induction to 85% and 83% ee, respectively (entry 12). Lowering the reaction temperature was not useful (entry 13), while under higher dilution a slight increase of the ee was achieved (entry 14).

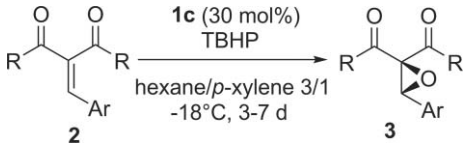
The absolute configuration of epoxide **3a** has been established by means of DFT calculations of two different chiroptical properties, *i.e.* optical rotation (OR) and vibrational circular dichroism (VCD).[12] Comparison of the experimental OR measurement and VCD spectra with the predicted properties of compound **3a** led to the assignment of *R* absolute configuration of the preferentially obtained enantiomer.

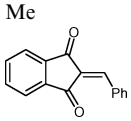
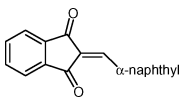
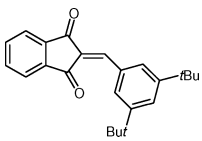
With optimized conditions in our hands, the scope and limitations of this enantioselective epoxidation protocol with regard to alkenes **2** was investigated (Table 2).

As highlighted in Table 2, a variety of electron-donating or withdrawing groups can be introduced in the β-phenyl ring of 2-arylidene-1,3-diketones **2** (entries 1–8) affording the epoxides in high yield and good to high levels of enantioselectivity. Substitution on the phenyl rings at the 1,3 positions is also tolerated (entry 9), whereas somewhat lower enantiocontrol was observed with the aliphatic 1,3-diketone (entry 10). Cyclic and less sterically demanding alkenes **2k–m**, derived from 1,3-indandione, were also checked under slightly different conditions, which required the employment of commercially available catalyst **1e** and CMHP in hexane/*p*-xylene 1 : 1 mixture (entries 11–13). Spiro-epoxides[13] **3k–m** were isolated in excellent yield and up to 80% ee.

The epoxides are solid and pleasingly a single crystallisation gave highly enantioenriched compounds in good yields (entries 1, 3, 7, 11, Table 2). Racemic epoxides, featuring the indandione motif, such as **3k–m**, were used as starting materials to prepare the first potent inhibitors series of the human papillomavirus HPV11[14] E1–E2 protein–protein interaction.[15] It has been recently demonstrated, *via* a diastereoselective approach and HPLC separations, that one enantiomer of the final product is the active

Table 2 Asymmetric epoxidation of 2-arylidene-1,3-diketones **2** by **1c**/TBHP system[a]



Entry	R	Ar	3	Yield (%)[b]	ee (%)[c]
1	Ph	Ph	**3a**	99 (86)	85 (95)
2	Ph	*m*,*p*-$(Me)_2C_6H_3$	**3b**	81	85
3	Ph	*p*-ClC_6H_4	**3c**	97 (65)	81 (94)
4	Ph	*p*-$MeOC_6H_4$	**3d**	61	77
5	Ph	*m*-$MeOC_6H_4$	**3e**	75	81
6	Ph	*p*-$CF_3C_6H_4$	**3f**	92	80
7	Ph	*p*-*t*BuC_6H_4	**3g**	90 (80)	85 (99)
8	Ph	β-naphthyl	**3h**	74	78
9	*p*-$MeOC_6H_4$	*p*-$CF_3C_6H_4$	**3i**	76	76
10	Me	Ph	**3j**	90	57
11[d]			**3k**	95 (68)	64 (91)
12[d,e]			**3l**	99	74
13[d]			**3m**	99	80

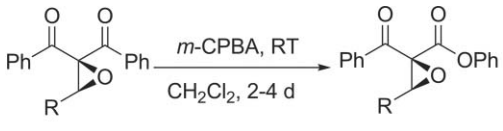
[a] Reaction conditions: **2** (0.2 mmol)/TBHP (0.24 mmol)/**1c** (0.06 mmol) in 2 mL of solvent. [b] Yield of isolated product. In parenthesis yield after crystallisation. [c] Determined by chiral HPLC analysis. In parenthesis ee after crystallisation. [d] Reaction conditions: **2** (0.2 mmol)/CMHP (0.24 mmol)/**1e** (0.06 mmol) in 2 mL of solvent (hexane/*p*-xylene 1 : 1). [e] TBHP was used as oxidant.

inhibitor,[16] thus indicating the requirement of synthetic routes to enantioenriched indandione-based epoxides.

Considering our previously postulated mode of action of the **1**/TBHP system,[6] the stereochemical outcome of the reaction might be explained invoking the establishment of a network of intermolecular hydrogen-bonding interactions between the two carbonyl groups with the ammonium ion in the transition state **TS** (Fig. 2).

The preferential attack of the alkylperoxy anion to the *re*-face of the carbon–carbon double bond would give the *R*-epoxide **3**.

To further demonstrate the synthetic utility of epoxides **3**, transformation of **3a**,**c** into esters was investigated (Scheme 2).



Scheme 2 Baeyer–Villiger oxidation of epoxides **3** to ketoesters **4**.

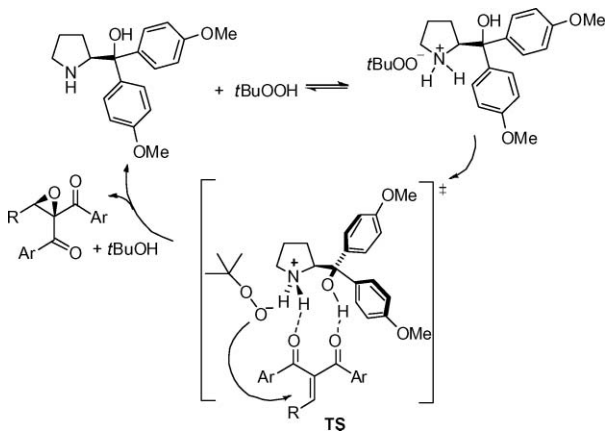


Fig. 2 Postulated catalytic cycle for the epoxidation.

The generation of the ketoesters **4a**,**c** was successfully accomplished by Baeyer–Villiger oxidation. Remarkably, the reaction proceeded with the regioselective oxidative cleavage, occurring preferentially at one benzoyl moiety, which furnished the epoxides in high diastereocontrol and without erosion of the enantioselectivity. It has to be noted that a quaternary centre is stereoselectively formed during the Baeyer–Villiger oxidation.[17] The asymmetric epoxidation of 2-arylidene-1,3-diketones followed by Baeyer–Villiger oxidation constitutes a facile entry to a class of diversely functionalised epoxides **4**, very difficult to synthesize by alternative strategies.[18]

Conclusions

In conclusion, we have described the first asymmetric epoxidation of challenging trisubstituted alkenes such as acyclic and cyclic 2-arylidene-1,3-diketones. A simple α,α-diaryl prolinol/TBHP system enables the formation of the epoxides in high to excellent yields and synthetically useful level of enantioselectivity. A single crystallisation efficiently furnishes products in high optical purity. These epoxides are pharmaceutically important synthons and can be transformed to densely functionalised epoxide derivatives. Further investigation to enlarge the scope of electron-poor trisubstituted alkenes susceptible of asymmetric epoxidation by **1**/TBHP system is under way.

Experimental section

General remarks

All reactions requiring dry or inert conditions were conducted in flame dried glassware under a positive pressure of nitrogen. THF was freshly distilled before use from $LiAlH_4$. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualised by UV light or by phosphomolybdic acid/ethanol spray test. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer at room temperature in $CDCl_3$ as solvent. Chemical shifts for protons are reported using residual $CHCl_3$ as internal reference ($\delta = 7.26$ ppm). Carbon spectra were referenced to the shift of the ^{13}C signal of $CDCl_3$ ($\delta = 77.0$ ppm). Optical rotations were performed on a Jasco Dip-1000 digital polarimeter using the Na lamp in cells of 10 cm path length. Concentrations are given in units of g/100mL. FTIR spectra were recorded as thin films on KBr plates using Bruker Vector 22 spectrometer and absorption maxima are reported in wavenumber (cm^{-1}). ESI-MS was performed using a Bio-Q triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray ion source. Melting points were measured on a digital Electrothermal 9100 apparatus and are uncorrected. Petrol ether (PE) refers to light petroleum ether. Anhydrous *p*-xylene and toluene were purchased from Aldrich. Catalysts **1a**, **1b** and **1e**, TBHP (5–6 M decane solution) and cumene hydroperoxide (technical grade, 80%) are commercially available reagents. They were purchased from Aldrich and used as received. Commercial *m*-CPBA (77% grade) was dissolved in CH_2Cl_2 and dried over Na_2SO_4, then crystallised by PE–Et_2O mixture at –20 °C. Catalysts **1c** and **1d** were prepared according to the literature.[19] Compounds **2a–m** were prepared according to general procedures reported in the literature.[20] Enantiomeric excess of epoxides were determined by HPLC (Waters-Breeze 2487, dual absorbance detector and 1525 Binary HPLC Pump) using Daicel Chiralpack AD-H, AS-H and Daicel Chiralcel OD-H columns. Absolute configurations of epoxides **3** were assigned as *R* by analogy.

General procedure for synthesis of racemic epoxides

A sample vial was charged with alkene (0.20 mmol), racemic 2-piperidinemethanol (23.0 mg, 0.20 mmol) and n-hexane–toluene 3 : 1 v/v (or 1 : 1 v/v) (2 mL). TBHP (5–6 M decane solution, 44 μL, 0.24 mmol) was added to the solution at room temperature. Stirring was maintained until the alkene was consumed (1–3 days) as monitored by TLC. The crude reaction mixture was directly purified by flash chromatography on silica gel eluting with mixtures of PE and PE–diethyl ether 98 : 2 (or PE–diethyl ether 90 : 10 to pure $CHCl_3$) affording epoxides in 48–95% yield.

General experimental procedure for the enantioselective epoxidation of alkene 2a–j

A sample vial was charged with alkene (0.20 mmol), catalyst **1c** (18.8 mg, 0.060 mmol) and n-hexane–*p*-xylene 3 : 1 v/v (2.0 mL). TBHP (5–6 M decane solution, 44 μL, 0.24 mmol) was then added to the stirred solution at –18 °C. The reaction was monitored by TLC (PE–diethyl ether 80 : 20 as eluent). The solvent was removed under reduced pressure and the crude reaction mixture was directly purified by flash chromatography on silica gel eluting with mixtures of PE and PE–diethyl ether 98 : 2 to provide the epoxide. Crystallisation solvents used: mixtures of n-hexane–EtOH.

General experimental procedure for the enantioselective epoxidation of alkene 2k–m

A sample vial was charged with alkene (0.20 mmol), catalyst **1e** (21.2 mg, 0.060 mmol) and n-hexane–*p*-xylene 1 : 1 v/v (2.0 mL). CMHP (44 μL, 0.24 mmol) was then added to the stirred solution at –18 °C. The reaction was monitored by TLC (PE–diethyl ether 70 : 30 as eluent). The solvent was removed under reduced pressure and the crude reaction mixture was directly purified by flash chromatography on silica gel eluting with mixtures of PE–diethyl ether 90 : 10 to pure $CHCl_3$ to provide the epoxide.

(3*R*)-(3-Phenyloxirane-2,2-diyl)bis(phenylmethanone) (3a). Isolated yield 86%. White solid m.p. 126–128 °C; $[\alpha]_D^{29} = +66.0$ (*c* 0.30, $CHCl_3$), ee 95%. ν_{max} (KBr)/cm^{-1} 3069, 1683, 1599, 1260, 1026, 698. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.3 Hz), 7.97 (dd, 2H, J_1 = 8.1 Hz, J_2 = 1.0 Hz), 7.57 (td, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.48-7.43 (m, 3H), 7.37-7.31 (m, 4H), 7.28-7.19 (m, 3H), 4.72 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.9, 190.9, 134.5, 134.4, 134.1, 132.2, 130.0, 129.6, 128.8, 128.7, 128.4, 128.3, 126.2, 73.9, 62.6. MS (ESI): 351.59 [(M+Na$^+$, 100%)]. HPLC analysis with Chiralpak AS-H column, 70 : 30 hexane–2-propanol, 0.2 mL min^{-1}, detection at 254 nm; t_R = 32.9 min (minor), enantiomer t_R = 34.4 min (major).

(3*R*)-[3-(3,4-Dimethylphenyl)oxirane-2,2-diyl]bis(phenylmethanone) (3b). Isolated yield 81%. White solid m.p. 147–149 °C; $[\alpha]_D^{29}$ = +48.1 (*c* 0.36, $CHCl_3$), ee 85%. ν_{max} (KBr)/cm^{-1} 3069, 1680, 1597, 1260, 1026, 698. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.97 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.59 (t, 1H, J = 7.4 Hz), 7.51-7.46 (m, 3H), 7.39-7.35 (m, 2H), 7.10-7.01 (m, 3H), 4.63 (s, 1H), 2.17 (s, 3H), 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.1, 191.2, 137.5, 136.7, 134.8, 134.3, 134.2, 134.1, 130.1, 129.7, 128.7, 128.5, 127.5, 123.7, 74.0, 62.9, 19.7, 19.5. MS (ESI): 379.63 [(M+Na$^+$, 100%)]. HPLC analysis with Chiralpak AS-H column, 70 : 30 hexane–EtOH, 0.2 mL min^{-1}, detection at 254 nm; t_R = 30.3 min (minor), t_R = 32.0 min (major).

(3*R*)-[3-(4-Chlorophenyl)oxirane-2,2-diyl]bis(phenylmethanone) (3c). Isolated yield 65%. White solid m.p. 93–95 °C; $[\alpha]_D^{27} = +86.8$ (*c* 0.22, $CHCl_3$), ee 94%. ν_{max} (KBr)/cm^{-1} 3068, 1680, 1598, 1322, 1126, 1018, 717. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.94 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.60 (t, 1H, J = 7.4 Hz), 7.52-7.46 (m, 3H), 7.39-7.35 (m, 2H), 7.29-7.23 (m, 4H), 4.69 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.7, 190.7 134.8, 134.5, 134.4, 134.0, 130.8, 130.0, 129.6, 128.8, 128.7, 128.6, 127.7, 73.8, 61.9. MS (ESI): 385.48 [(M+Na$^+$, 100%)] 387.51 [(M+Na$^+$, 25%)]. HPLC analysis with Chiralpak AS-H column, 86 : 14 hexane–2-propanol, 0.3 mL min^{-1}, detection at 254 nm; t_R = 25.8 min (minor), t_R = 34.3 min (major).

(3*R*)-[3-(4-Methoxyphenyl)oxirane-2,2-diyl]bis(phenylmethanone) (3d). Isolated yield 61%. Pale yellow solid m.p. 115–118 °C; $[\alpha]_D^{23}$ = +19.2 (*c* 0.25, $CHCl_3$), ee 77%. ν_{max} (KBr)/cm^{-1} 2934, 2838, 1678, 1393, 1254, 1174, 1031, 690, 714. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.96 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.60 (t, 1H, J = 7.4 Hz), 7.51-7.46 (m, 3H), 7.37 (t, 2H, J = 7.4 Hz), 7.27 (dd, 2H, J_1 = 7.4 Hz, J_2 = 1.2 Hz), 6.79 (d, 2H, J = 8.7 Hz), 4.65 (s, 1H), 3.73 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.1, 191.3, 160.0, 134.7, 134.4, 134.2, 130.0, 129.7, 128.7, 128.5, 127.7, 124.2, 113.9, 74.1, 62.7, 55.1. MS (ESI): 381.58 [M+Na$^+$, 100%)] 397.55 [M+K$^+$, 25%)]. HPLC analysis with Chiralpak AD-H column, 85 : 15 hexane–2-propanol, 0.5 mL min^{-1}, detection at 254 nm; t_R = 39.0 min (minor), t_R = 35.5 min (major).

(3*R*)-[3-(3-Methoxyphenyl)oxirane-2,2-diyl]bis(phenylmethanone) (3e). Isolated yield 75%. Pale yellow solid m.p. 108–110 °C; $[\alpha]_D^{26}$ = +56.4 (*c* 0.32, $CHCl_3$), ee 81%. ν_{max} (KBr)/cm^{-1} 2934, 1678, 1391, 1254, 1175, 1030, 691. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, 2H, J = 7.6 Hz), 7.97 (d, 2H, J = 7.6 Hz), 7.59 (t, 1H, J = 7.3 Hz), 7.50-7.46 (m, 3H), 7.36 (t, 2H, J = 7.8 Hz), 7.17 (t, 1H, J = 7.8 Hz), 6.97 (d, 1H, J = 7.6 Hz), 6.85 (s, 1H), 6.77 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.5 Hz), 4.67 (s, 1H), 3.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.0, 191.1, 159.6, 134.7, 134.4, 134.2, 133.9, 130.1, 129.7, 129.5, 128.8, 128.5, 118.9, 115.2, 111.0, 73.9, 62.6, 55.1. MS (ESI): 381.63 [M+Na$^+$, 100%)]. HPLC analysis with Chiralpak AD-H column, 85 : 15 hexane–2-propanol, 0.5 mL min^{-1}, detection at 254 nm; t_R = 28.6 min (minor), t_R = 27.4 min (major).

(3*R*)-[3-(4-(Trifluoromethyl)phenyl)oxirane-2,2-diyl]bis(phenylmethanone) (3f). Isolated yield 92%. White solid m.p. 126–128 °C; $[\alpha]_D^{28}$ = +57.2 (*c* 0.26, $CHCl_3$), ee 80%. ν_{max} (KBr)/cm^{-1} 3068, 1681, 1598, 1325, 1128, 1018, 717. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (dd, 2H, J_1 = 7.3 Hz, J_2 = 1.0 Hz), 7.94 (dd, 2H, J_1 = 7.3 Hz, J_2 = 1.0 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.55-7.47 (m, 7H), 7.37 (t, 1H, J = 7.8 Hz), 4.76 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.5, 190.6, 136.4, 134.6, 134.5, 134.1, 130.0, 129.6, 128.9, 128.7, 126.8, 125.4, 73.8, 61.8. MS (ESI): 419.49 [(M+Na$^+$, 100%)]. HPLC analysis with Chiralpak AS-H column, 86 : 14 hexane–2-propanol, 0.3 mL min^{-1}, detection at 254 nm; t_R = 21.7 min (minor), t_R = 31.2 min (major).

(3*R*)-[3-(4-*tert*-Butylphenyl)oxirane-2,2-diyl]bis(phenylmethanone) (3g). Isolated yield 80%. White solid m.p. 167–169 °C; $[\alpha]_D^{27}$ = +51.8 (*c* 0.37, $CHCl_3$), ee 99%. ν_{max} (KBr)/cm^{-1} 3069, 1681, 1600, 1260, 1027, 698. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.4 Hz), 7.95 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.3 Hz), 7.59-7.55 (m, 1H), 7.49-7.44 (m, 3H), 7.36-7.33 (m, 2H), 7.29-7.24 (m, 4H), 4.65 (s, 1H), 1.22 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.2, 191.3, 151.9, 134.8, 134.4, 134.2, 134.0, 130.1, 129.7, 129.2, 128.7, 128.5, 126.2, 125.4, 74.0, 62.8, 34.6, 31.1. MS (ESI): 407.61 [(M+Na$^+$, 100%)]. HPLC analysis with Chiralpak AS-H column, 70 : 30 hexane–EtOH, 0.2 mL min^{-1}, detection at 254 nm; t_R = 24.1 min (minor), t_R = 25.6 min (major).

(3*R*)-[3-(Naphthalen-2-yl)oxirane-2,2-diyl]bis(phenylmethanone) (3h). Isolated yield 74%. White solid m.p. 124–125 °C; $[\alpha]_D^{27}$ = +57.1 (*c* 0.38, $CHCl_3$), ee 78%. ν_{max} (KBr)/cm^{-1} 3069, 2934, 1681, 1598, 1260, 1025, 698. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.4 Hz), 7.97 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.3 Hz), 7.87 (s, 1H), 7.81-7.79 (m, 1H), 7.76-7.73 (m, 2H), 7.62-7.59 (m, 1H), 7.52-7.43 (m, 6H), 7.35-7.31 (m, 2H), 4.87 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.0, 191.0, 134.7, 134.5, 134.2, 133.4, 132.8, 132.4, 130.1, 129.7, 128.8, 128.5, 128.3, 128.3, 128.1, 127.7, 126.5, 126.4, 126.2, 123.4, 74.2, 62.9. MS (ESI): 401.71 [(M+Na$^+$, 100%)]. HPLC analysis with Chiralpak AS-H column, 70 : 30 hexane–2-propanol, 0.5 mL min^{-1}, detection at 254 nm; t_R = 15.0 min (minor), t_R = 16.7 min (major).

[(3-(4-(Trifluoromethyl)phenyl)oxirane-2,2-diyl]bis[(4-methoxyphenyl)methanone] (3i). Isolated yield 76%. Pale yellow solid m.p. 122–125 °C; $[\alpha]_D^{29}$ = –2.0 (*c* 0.30, $CHCl_3$), ee 76%. ν_{max} (KBr)/cm^{-1} 2935, 2844, 1669, 1601, 1325, 1262, 1068, 1027, 702. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (d, 2H, J = 9.0 Hz), 7.96 (dd, 2H, J_1 = 6.9 Hz, J_2 = 2.0 Hz), 7.52 (d, 2H, J = 8.4 Hz), 7.47 (d, 2H, J = 8.4 Hz), 6.94 (d, 2H, J = 9.0 Hz), 6.82 (d, 2H, J = 9.0 Hz), 4.70 (s, 1H), 3.86 (s, 3H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.9, 188.9, 164.7, 164.5, 136.8, 132.7, 132.2, 127.2 (q), 126.8, 125.3, 114.1, 113.9, 74.0, 61.6, 55.5, 55.4. MS (ESI): 479.48 [(M+Na$^+$, 100%)]. HPLC analysis with Chiralcel OD-H

column, 83 : 17 hexane–2-propanol, 0.3 mL min^{-1}, detection at 254 nm; t_R = 42.1 min (minor), t_R = 44.3 min (major).

1,1′-(3-Phenyloxirane-2,2-diyl)diethanone (3j). Isolated yield 90%. Yellow oil; $[\alpha]_D^{26}$ = −12.8 (*c* 0.35, $CHCl_3$), ee 57%. ν_{max} (KBr)/cm^{-1} 2925, 2853, 1729, 1710, 1362, 1252, 1102, 763, 700. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.33 (m, 3H), 7.28-7.21 (m, 2H), 4.39 (s, 1H), 2.27 (s, 3H), 1.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.7, 199.4, 131.7, 129.2, 128.7, 128.3, 126.1, 71.6, 61.9, 29.8, 25.2. MS (ESI): 227.46 [(M+Na$^+$, 100%)]. HPLC analysis with Chiralpak AS-H column, 70 : 30 hexane–2-propanol, 0.2 mL min^{-1}, detection at 220 nm; t_R = 35.8 min (minor), t_R = 32.0 min (major).

3′-Phenylspiro[indene-2,2′-oxirane]-1,3-dione (3k). Isolated yield 68%. White solid 140–143 °C; $[\alpha]_D^{28}$ = +392.7 (*c* 0.3, $CHCl_3$), ee 91%. ν_{max} (KBr)/cm^{-1} 2964, 1720, 1360, 1101, 703. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04-8.02 (m, 1H), 7.91-7.87 (m, 3H), 7.61-7.59 (m, 2H), 7.40-7.38 (m, 3H), 4.74 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.0, 191.1, 141.8, 140.4, 136.3, 136.0, 131.2, 129.5, 128.0, 127.4, 123.2, 67.9, 64.0. MS (ESI): 289.51 [(M+K$^+$, 100%)] 273.54 [(M+Na$^+$, 16%)]. HPLC analysis with Chiralpak AS-H column, 80 : 20 hexane–2-propanol, 0.8 mL min^{-1}, detection at 254 nm; t_R = 23.1 min (minor), t_R = 16.4 min (major).

3′-(Naphthalen-1-yl)spiro[indene-2,2′-oxirane]-1,3-dione (3l). Isolated yield 99%. Yellow solid m.p. 135–138 °C; $[\alpha]_D^{29}$ = +39.4 (*c* 0.3, $CHCl_3$), ee 74%. ν_{max} (KBr)/cm^{-1} 2970, 1719, 1366, 1099, 698. ^{1}H-NMR (CDCl3, 400 MHz): δ 8.11 (d, 2H, *J* = 7.6 Hz), 7.95-7.82 (m, 5H), 7.77 (d, 2H, *J* = 7.5 Hz), 7.64-7.58 (m, 2H), 7.45 (t, 1H, J = 7.2), 7.37 (t, 1H, J = 7.2), 5.29 (s, 1H). ^{13}C-NMR (CDCl3, 100 MHz): δ 193.3, 190.6, 141.6, 136.4, 136.0, 133.1, 130.8, 129.6, 129.1, 127.0, 126.7, 125.8, 125.6, 125.1, 123.3, 121.7, 65.8, 63.5. MS (ESI): 283.52 [(M-OH, 100%)] 323.55 [(M+Na+, 25%)]. HPLC analysis with Chiralpak AS-H column, 70 : 30 hexane–2-propanol, 0.5 mL min^{-1}, detection at 254 nm; t_R = 15.0 min (minor), t_R = 16.7 min (major).

[3′-(3,5-Di-*tert*-butylphenyl)spiro[indene-2,2′-oxirane]-1,3-dione (3m). Isolated yield 99%. Yellow gum; $[\alpha]_D^{28}$ = +74.4 (*c* 0.36, $CHCl_3$), ee 80%. ν_{max} (KBr)/cm^{-1} 2964, 1720, 1360, 1101, 703. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04-8.02 (m, 1H), 7.91-7.87 (m, 3H), 7.61-7.59 (m, 2H), 7.40-7.38 (m, 3H), 4.74 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.3, 191.1, 150.4, 142.1, 140.4, 136.2, 135.8, 130.3, 123.5, 123.2, 123.1, 122.0, 69.2, 64.5, 34.9, 31.4. MS (ESI): 307.62 [(M-*t*Bu, 100%)] 363.67 [(M+H$^+$, 17%)]. HPLC analysis with Chiralpak AS-H column, 90 : 10 hexane–2-propanol, 0.8 mL min^{-1}, detection at 254 nm; t_R = 8.6 min (minor), t_R = 6.2 min (major).

General procedure for Baeyer–Villiger oxidation of epoxides 3a and 3c

A sample vial was charged with the epoxide (0.20 mmol), crystallised *m*-CPBA (207 mg, 1.20 mmol) and CH_2Cl_2 (1 mL). The mixture was stirred at room temperature and reaction monitored by TLC. The reaction was quenched with saturated sodium bisulfite solution and extracted with $CHCl_3$. The organic phase was extracted with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated under reduced pressure. Purification by flash chromatography on silica gel with mixtures of PE/diethyl ether (98/2 to 90/10) afforded esters **4a** and **4c**.

Phenyl 2-benzoyl-3-phenyloxirane-2-carboxylate (4a). Isolated yield 75%. White solid; $[\alpha]_D^{26}$ = +50.6 (*c* 0.6, $CHCl_3$), dr 90 : 10, ee 99%. ν_{max} (KBr)/cm^{-1} 2925, 1762, 1689, 1491, 1451, 1226, 1198, 1023, 695. ^{1}H NMR ($CDCl_3$, 400 MHz) (major diastereoisomer): δ 7.95 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.3 Hz), 7.58 (t, 1H, *J* = 7.4 Hz), 7.45 (t, 2H, *J* = 7.8 Hz), 7.37-7.33 (m, 2H), 7.28-7.22 (m, 6H), 7.03 (d, 2H, *J* = 7.8 Hz), 4.89 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) (major diastereoisomer): δ 189.3, 165.2, 150.0, 135.3, 134.1, 131.8, 130.1, 129.5, 129.2, 128.9, 128.7, 128.5, 126.5, 126.4, 120.9, 65.8, 63.5. MS (ESI): 367.62 [(M+Na$^+$, 100%)]. HPLC analysis with Chiralpak AS-H column, 80 : 20 hexane–2-propanol, 0.6 mL min^{-1}, detection at 220 nm; major diastereoisomer: t_R = 19.6 min (minor), t_R = 13.3 min (major); minor diastereoisomer: t_R = 15.9 min (minor), t_R = 17.4 min (major).

Phenyl 2-benzoyl-3-(4-chlorophenyl)oxirane-2-carboxylate (4c). Isolated yield 65%. White solid; dr 85 : 15, ee 94%. ν_{max} (KBr)/cm^{-1} 2930, 1770, 1695, 1499, 1455, 1226, 1198, 1025, 697. ^{1}H NMR ($CDCl_3$, 400 MHz) (major diastereoisomer): δ 7.96 (dd, 2H, J_1 = 8.4 Hz, J_2 = 1.1 Hz), 7.64-7.60 (m, 1H), 7.52-7.46 (m, 3H), 7.42-7.35 (m, 3H), 7.30-7.27 (m, 1H), 7.25-7.22 (m, 4H), 7.04 (d, *J* = 8.1 Hz), 4.87 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) (major diastereoisomer): δ 189.1, 164.9, 150.0, 135.2, 135.1, 134.3, 134.2, 133.7, 130.4, 130.1, 129.5, 129.2, 128.8, 128.6, 128.5, 128.4, 128.0, 127.8, 126.6, 120.8, 65.8, 62.8. MS (ESI): 401.68 [(M+Na$^+$, 100%)]. HPLC analysis with Chiralpak AS-H column, 80 : 20 hexane–2-propanol, 0.6 mL min^{-1}, detection at 220 nm; major diastereoisomer: t_R = 20.2 min (minor), t_R = 14.5 min (major); minor diastereoisomer: t_R = 17.8 min (minor), t_R = 18.9 min (major).

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