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PAPER

Catalytic asymmetric Michael addition with curcumin derivative†

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Catalytic asymmetric Michael additions with curcumin derivatives were achieved by a new series of tertiary amine–thiourea organocatalysts to afford the Michael adducts in high yields and excellent enantioselectivities.

Introduction

Curcumin, obtained from the spice turmeric, has been used as a dietary spice and herbal medicine for centuries. Recently, the development of curcumin derivatives has drawn much attention because of their considerable biological activities including anti-malarial, anti-angiogenesis and anti-oxidant activities.[1] Besides, curcumin also acts as a selective cyclooxygenase-1 (COX-1) inhibitor, which plays an important role in inflammation and carcinogenesis.[2]

As one of the most important Michael additions in organic chemistry, the conjugate addition of nitroolefins has attracted much attention, which could be attributed to the construction of chiral building blocks.[3–4] In recent years, various nucleophiles, such as nitroalkanes,[5] malonate esters,[6] α,α-dicyanoolefins,[7] aldehydes[8] and ketones[9] have been developed for the Michael additions of nitroolefins. For asymmetric synthesis, organocatalysts have exhibited high catalytic activities and will hold tremendous potential in the future.[10] It is worthwhile to note that massive progress has been made in the development of tertiary amine–thiourea organocatalysts, which are an efficient tool for promoting the Michael addition of nitroolefins (Fig. 1, **1a–1d**).[11–14] Although chemists have made great effort towards the Michael addition of nitroolefins, the development of a new type of organocatalyst and search for new nucleophiles remain a great challenge. To the best of our knowledge, although enantioselective Michael addition reactions of 1,3-diketones to nitroolefins have been developed,[15] ***asymmetric enantioselective Michael addition reactions of curcumin to nitroolefins have not been reported so far***.[16] Herein we presented the enantioselective organocatalytic Michael additions of curcumin derivatives to nitroolefins with high yields and up to 97% ee value for the first time.

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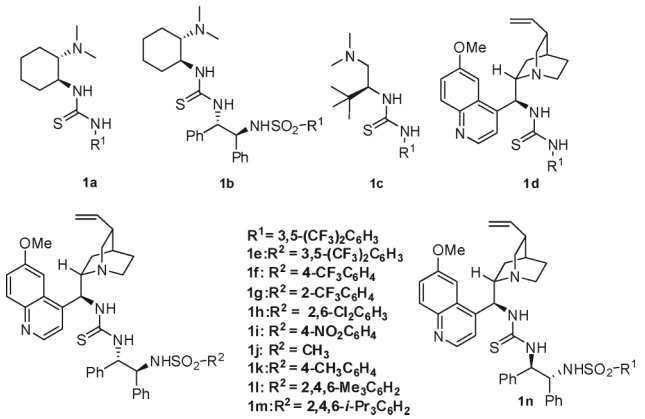


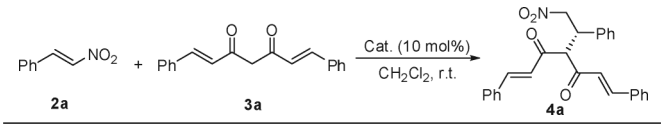
Fig. 1 Structure of tertiary amine–thiourea catalysts.

Results and discussion

We started our investigations using tertiary amine–thiourea organocatalysts (**1a–1d**) to promote the reaction and the representative results are summarized in Table 1. To our delight, the reaction of nitroolefin **2a** and curcumin derivative **3a** in the presence of 10 mol% of **1a–1d** afforded the Michael adduct **4a** in good conversions (78–87%) with good enantioselectivities (80–89%) after 5 h (entries 1–4). This outcome demonstrated that the Michael addition of nitroolefin **2a** and curcumin derivative **3a** could be efficiently catalyzed by the chiral tertiary amine–thiourea organocatalysts.

Encouraged by the promising results obtained, we designed and synthesized a new series of tertiary amine–thiourea organocatalysts, which consisted of 9-amino(9-deoxy)epiquinine and 1,2-diphenylethene-diamine moieties (Fig. 1, **1e–1n**). Then we explored these organocatalysts (**1e–1n**) for the Michael reaction. Gratifyingly, up to 95% conversion with 95% ee was obtained in the presence of 10 mol% of **1e**, which bears two CF_3 groups in the sulfonamide $NHSO_2R_2$ (entry 5). We next examined the catalytic activities of other organocatalysts (**1f–1n**), which had different substituents on the sulfonamide $NHSO_2R_2$. Further investigations revealed that the position and the number of CF_3 groups in the sulfonamide would influence the enantioselectivity. For example, 92% and 86% ee values were obtained in the presence of **1f**

Table 1 Catalyst screen for the Michael reaction between **2a** and **3a**



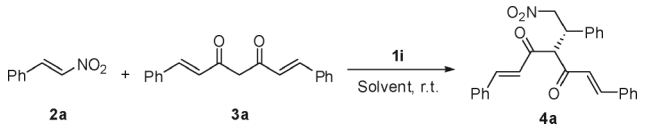
Entry[a]	Catalyst	Conv. (%)[b]	ee (%)[c]
1	**1a**	87	80
2	**1b**	78	81
3	**1c**	84	86
4	**1d**	86	89
5	**1e**	95	95
6	**1f**	93	92
7	**1g**	94	86
8	**1h**	94	96
9	**1i**	97	97
10	**1j**	95	90
11	**1k**	91	87
12	**1l**	91	96
13	**1m**	95	93
14	**1n**	88	51

[a] *Reaction conditions*: A mixture of **2a** (0.05 mmol), **3a** (0.075 mmol) and catalyst (10 mol%) in CH_2Cl_2 (0.3 mL) was stirred at room temperature for 5 h. [b] The conversion was determined by the crude ^{1}H NMR. [c] Determined by HPLC.

and **1g** (entry 6–7). The reaction proceeded to 94% conversion with 96% ee using 10 mol% of **1h**, which bears two chlorine groups on the aromatic ring (entry 8). It seemed that the strong electron-withdrawing group in the sulfonamide would be helpful to the enantioselective control. As we expected, the best results (97% conversion, 97% ee) were obtained if a nitro group was introduced to the aromatic ring (entry 9). However, when the electron-withdrawing group in the sulfonamide was replaced with an electron-donating one, the ee values decreased to 90% and 87% (entries 10–11) in the presence of **1j** ($R_2 = CH_3$) and **1k** ($R_2 = 4\text{-}CH_3C_6H_4$). When bulkier groups in the sulfonamide were introduced to the catalyst (**1l**, $R_2 = 2,4,6\text{-}Me_3C_6H_2$; **1m**, $R_2 = 2,4,6\text{-}i\text{-}Pr_3C_6H_2$), a slight decrease of conversion and enantioselectivity was induced (entries 12–13), which could be attributed to the steric block between the catalyst and the substrate. However, if the (*S*,*S*)-1,2-diphenyl-ethenediamine was replaced with the (*R*,*R*)-1,2-diphenyl-ethenediamine, **1n** instead of catalyst **1e**, the enantioselectivity decreased to 51% with 88% of conversion, but the configuration of the Michael adduct was not altered (entry 14). Therefore, it could be concluded that the (*S*,*S*)-1,2-diphenyl-ethenediamine would match 9-amino(9-deoxy)epiquinine and the configuration of the desired adduct was mainly determined by 9-amino(9-deoxy)epiquinine.

Having identified organocatalyst **1i** as the best choice in the catalyst family, the effect of solvent was consequently taken into account. Noticeably, **3a** was soluble in dichloromethane, partially soluble in toluene, $CHCl_3$ and insoluble in other solvents. As shown in Table 2, the reaction in toluene and $CHCl_3$ resulted in lower enantioselectivities (entries 2–3). As we know, low catalyst loading and fast reaction rate are vital goals in organocatalysis. Therefore, we next promoted the reaction in the presence of a lower catalyst loading. To our delight, good results could still be obtained when a lower catalyst loading was employed. In the presence of 5 mol% of **1i**, up to 97% conversion and 96% ee were obtained after 12 h (entry 4). Even when the catalyst loading was

Table 2 Solvent and catalyst loading screens for the Michael reaction between **2a** and **3a**



Entry[a]	Solvent	Time/h	Conv. (%)[b]	ee (%)[c]
1	CH_2Cl_2	5	97	97
2	Toluene	5	94	84
3	$CHCl_3$	5	93	81
4[d]	CH_2Cl_2	12	97	96
5[e]	CH_2Cl_2	12	92	92

[a] *Reaction conditions*: A mixture of **2a** (0.05 mmol), **3a** (0.075 mmol) and catalyst **1i** (10 mol%) in the solvent (0.3 mL) was stirred at room temperature for the time given in the table. [b] The conversion was determined by the crude ^{1}H NMR. [c] Determined by HPLC. [d] Catalyst (5 mol%). [e] Catalyst (2 mol%).

reduced to 2 mol%, 92% conversion and 92% ee were still achieved after 12 h (entry 5). These encouraging outcomes indicated that this type of organocatalyst (**1e–1n**) may have great potential in catalyzing the Michael addition of nitroolefins efficiently.

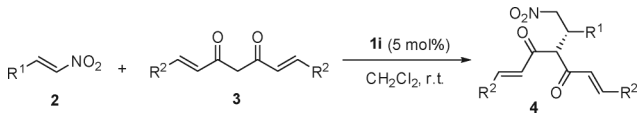
With the optimized reaction conditions in hand, the scope of the Michael reaction was investigated. As illustrated in Table 3, a wide range of aryl nitroolefins, which bear electron-rich and electron-deficient groups on the *o*-, *m*-, *p*-positions of benzene ring, reacted with curcumin derivative (**3a**) smoothly with high yields (73–96%) and excellent enantioselectivities (89–97%) (entries 1–13). Noticeably, the methodology was also applicable to heterocyclic nitroolefins. For example, up to 62% yield with 93% ee was obtained when (2-nitrovinyl)furan was used (entry 14). Moreover, alkyl nitroolefins also exhibited high reactivities. The Michael addition of curcumin derivative to nitropent-1-ene gave 82% yield with 92% ee (entry 15). While other alkyl nitroolefins, such as 3-methyl-1- nitrobut-1-ene, resulted in 72% yield with 84% ee (entry16). To our delight, the Michael additions of other curcumin derivatives (**3b–3e**) to nitroolefin also achieved good results (entries 17–20). High yields ranging from 72% to 82% with excellent enantioselectivities (90–96%) were observed correspondingly.

In order to determine the absolute configuration of the Michael addition adduct, enantiopure **4ea** was fortunately obtained. The absolute stereoconfiguration of **4ea** was determined to be *S* by X-ray crystal structural analysis (Fig. 2).[17] A plausible transition state was proposed to illustrate the stereochemical outcome of the Michael addition (Fig. 3). The curcumin derivative and nitroolefin were separately activated by the tertiary amine and thiourea through hydrogen bonding. This may direct the attack of the curcumin derivative toward one enantioface of the double bond. The sulfonamide group simultaneously blocks the other enantioface of the double bond through steric hindrance to give the *S* adduct with an excellent ee value.

Conclusions

In conclusion, catalytic asymmetric Michael additions with curcumin derivatives were achieved by a new series of tertiary amine–thiourea organocatalysts, which bear tertiary amine, thiourea and sulfonamide. It is noteworthy that the Michael additions of

Table 3 Enantioselective Michael reactions of nitroolefins **2** with curcumin derivatives **3** in the presence of **1i**



Entry[a]	R^1 (**2**)	R^2 (**3**)	*t*/h	Yield (%, **4**)[b]	ee (%)[c]
1	C_6H_5(**2a**)	C_6H_5(**3a**)	12	96(**4aa**)	96
2	2-ClC_6H_4(**2b**)	C_6H_5(**3a**)	72	86(**4ba**)	97
3	3-ClC_6H_4(**2c**)	C_6H_5(**3a**)	72	81(**4ca**)	93
4	4-ClC_6H_4(**2d**)	C_6H_5(**3a**)	72	74(**4da**)	90
5	3-BrC_6H_4(**2e**)	C_6H_5(**3a**)	18	81(**4ea**)	90
6	2-FC_6H_4(**2f**)	C_6H_5(**3a**)	18	85(**4fa**)	95
7	3-FC_6H_4(**2g**)	C_6H_5(**3a**)	72	76(**4ga**)	92
8	4-FC_6H_4(**2h**)	C_6H_5(**3a**)	72	93(**4ha**)	90
9	4-$MeOC_6H_4$(**2i**)	C_6H_5(**3a**)	24	82(**4ia**)	89
10	2,3-$(MeO)_2C_6H_3$(**2j**)	C_6H_5(**3a**)	24	92(**4ja**)	96
11	2,4-$(MeO)_2C_6H_3$(**2k**)	C_6H_5(**3a**)	24	73(**4ka**)	95
12	4-MeC_6H_4(**2l**)	C_6H_5(**3a**)	18	85(**4la**)	91
13	2-Naphthyl(**2m**)	C_6H_5(**3a**)	24	84(**4ma**)	90
14	2-Furanyl(**2n**)	C_6H_5(**3a**)	72	62(**4na**)	93
15	*n*-Pr(**2o**)	C_6H_5(**3a**)	48	82(**4oa**)	92
16[d,e]	*i*-Pr (**2p**)	C_6H_5(**3a**)	96	72(**4pa**)	84
17	C_6H_5(**2a**)	4-MeC_6H_4(**3b**)	144	78(**4ab**)	90
18[d]	C_6H_5 (**2a**)	4-ClC_6H_4(**3c**)	72	72(**4ac**)	92
19[d]	C_6H_5 (**2a**)	2-FC_6H_4(**3d**)	72	73(**4ad**)	96
20	C_6H_5(**2a**)	3-MeO-4-$AcOC_6H_3$(**3e**)	72	82(**4ae**)	92

[a] *Reaction conditions*: A mixture of **2** (0.15 mmol), **3** (0.225 mmol) and **1i** (5 mol%) in CH_2Cl_2 (0.9 mL) was stirred at room temperature for the time given in the table. [b] Isolated yield. [c] Determined by HPLC. [d] Catalyst (20 mol%). [e] The ratio of $E/Z = 25:1$.

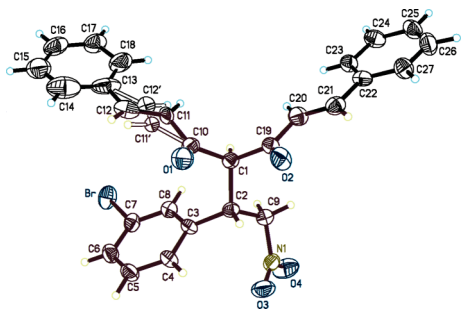


Fig. 2 X-Ray crystal structure of **4ea**.

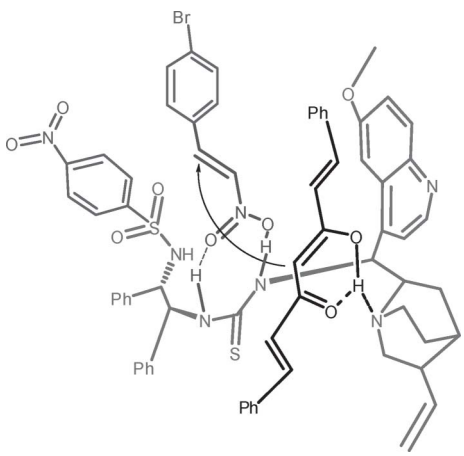


Fig. 3 Proposed catalytic transition state.

curcumin derivatives to nitroolefins have not been reported yet. This methodology could afford the required Michael adducts in high yields and excellent enantioselectivities with only 5 mol% catalyst loading. Besides, the Michael reaction has distinguished tolerance for aryl, heteroaryl and alkyl nitroolefins. Further research in this field are ongoing and the results will be presented in the future.

Experimental

General methods

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AV-400 spectrometer (400 MHz and 100 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ 7.26, $(CD_3)_2CO$: δ 2.05). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.16, $(CD_3)_2CO$: δ 29.87). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). Mass spectra (EI) were measured on a Waters Micromass GCT spectrometer. Mass spectra (ESI) were measured on a Waters Micromass LCT spectrometer. Optical rotations were measured on an Autopol III automatic polarimeter. High performance liquid chromatography (HPLC) was performed on an Agilent 1200 Series chromatography system using a Chiracel AS-H column (0.46 cm × 25 cm) as noted.

General procedure for the synthesis of organocatalysts

Reaction of (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine with 4-nitrobenzene-1-sulfonyl chloride. 4-Nitrobenzene-1-sulfonyl chloride (2.21 g, 10 mmol) in anhydrous THF (25 mL) was added dropwise to a solution of (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (2.12 g, 10 mmol), triethylamine (2.02 g, 20 mmol) and anhydrous THF (20 mL) with ice-cooling. The reaction mixture was warmed to room temperature and stirred for 12 h. TLC indicated the reaction was completed. The residue was purified by silica gel chromatography to afford the pure product as a white solid in 94% yield. Mp = 135–136 °C; $[\alpha]_D^{22}$ = 22.5 (*c* = 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.22–7.17 (m, 10H), 4.50 (d, *J* = 4.4 Hz, 1H), 4.22 (d, *J* = 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.3, 146.0, 141.1, 138.9, 128.6, 127.8, 127.7, 126.7, 126.3, 123.7, 63.2, 60.1. HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{20}H_{19}N_3O_4S$) requires *m*/*z* 398.1175, found *m*/*z* 398.1177.

Isothiocyanate formation. The product was prepared following the literature procedure.[12d] To a solution of 9-amino(9-deoxy)epihydroquinine (8.0 g, 24.7 mmol) and DCC (5.1g, 24.7 mmol) in dry THF (50 mL) at −10 °C was added CS_2 (10.7 g, 148.5 mmol) in one portion. The reaction mixture was warmed slowly to room temperature over a period of 3 h and then stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography to afford the pure product as a yellow solid in 80% yield.

Thiourea formation. To a solution of *N*-((1*S*,2*S*)-2-amino-1,2-diphenylethyl)-4-nitrobenzenesulfonamide (1.07 g, 2.7 mmol) in anhydrous THF (20 mL) was added 2-((*S*)-isothiocyanato(6-methoxyquinolin-4-yl)methyl)-8-vinyl-quinuclidine (1.0 g, 2.7 mmol) at room temperature. The solution was stirred overnight. TLC indicated completion of the reaction. The reaction mixture was concentrated under vacuum. The residue was purified by silica gel chromatography to afford the pure product **1i** as a yellow solid in 82% yield. Mp = 149–150 °C; $[\alpha]_D^{22}$ −7.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ (ppm) 8.77–8.76 (m, 1H), 8.06–7.94 (m, 4H), 7.69–7.67 (m, 2H), 7.53 (br, 1H), 7.45–7.43 (m, 1H), 7.10–6.93 (m, 10H), 5.83–5.72 (m, 2H), 4.99–4.88 (m, 2H), 4.77–4.75 (m, 1H), 4.05 (s, 3H), 3.31–3.18 (m, 3H), 2.69 (br, 2H), 2.30 (br, 1H), 2.06–2.05 (m, 2H), 1.69–1.58 (m, 3H), 1.41–1.35 (m, 1H), 1.03–0.99 (m, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ (ppm) 205.1, 170.1, 157.9, 149.4, 147.7, 146.9, 144.8, 141.6, 138.3, 138.1, 131.6, 128.2, 128.0, 127.9, 127.8, 127.5, 127.2, 123.6, 121.7, 113.9, 102.9, 102.8, 63.4, 59.7, 55.5, 55.4, 41.1, 39.5, 27.6, 27.4, 25.7, 20.1, 13.7. HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{41}H_{43}N_6O_5S_2$) requires *m*/*z* 763.2736, found *m*/*z* 763.2726.

General procedure for asymmetric Michael addition

To a solution of *trans*-β-substituted nitroolefins **2** (0.15 mmol) in dichloromethane (0.9 mL) were added curcumin derivates **3** (0.225 mmol) and catalyst **1i** (0.0075 mmol). The reaction mixture was stirred at room temperature for the time indicated in Table 3 and then the solvent was removed under vacuum. The residues were purified by silica gel chromatography to yield the desired addition products.

4-(2-Nitro-1-phenylethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4aa). The product was obtained in 96% yield, yellow solid. Mp = 138–140 °C; $[\alpha]_D^{22}$ −210.0 (*c* 0.99, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75 (d, *J* = 16.0 Hz, 1H), 7.58–7.56 (m, 2H), 7.51–7.46 (m, 3H), 7.44–7.35 (m, 7H), 7.32–7.29 (m, 2H), 7.27–7.23 (m, 2H), 6.95 (d, *J* = 16.0 Hz, 1H), 6.73 (d, *J* = 16.0 Hz, 1H), 4.82–4.72 (m, 3H), 4.60–4.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.9, 191.8, 146.3, 145.4, 136.2, 133.8, 133.7, 131.5, 131.2, 129.1, 128.9, 128.7, 128.3, 128.1, 123.7, 123.1, 78.3, 67.5, 42.9. HRMS (EI): exact mass calculated for M^+ ($C_{27}H_{23}NO_4$) requires *m*/*z* 425.1627, found *m*/*z* 425.1637. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 12.1 min (major), 15.9 min (minor), ee = 96%.

4-(1-(2-Chlorophenyl)-2-nitroethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4ba). The product was obtained in 86% yield, yellow oil. $[\alpha]_D^{22}$ −155.4 (*c* 0.99, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (d, *J* = 16.0 Hz, 1H), 7.58–7.54 (m, 3H), 7.51–7.49 (m, 2H), 7.45–7.37 (m, 7H), 7.31–7.29 (m, 1H), 7.23–7.17 (m, 2H), 6.90 (d, *J* = 16.0 Hz, 1H), 6.84 (d, *J* = 16.0 Hz, 1H), 5.11–5.93 (m, 3H), 4.87–4.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.9, 191.7, 146.2, 145.7, 134.0, 133.8, 133.7, 131.4, 131.2, 130.5, 129.4, 129.1, 129.0, 128.9, 128.8, 127.4, 124.4, 122.4, 76.5, 65.4, 53.4. HRMS (EI): exact mass calculated for M^+ ($C_{27}H_{22}NO_4Cl$) requires *m*/*z* 459.1237, found *m*/*z* 459.1252. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 12.4 min (major), 15.1 min (minor), ee = 97%.

4-(1-(3-Chlorophenyl)-2-nitroethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4ca). The product was obtained in 81% yield, yellow solid. Mp = 123–124 °C; $[\alpha]_D^{22}$ −193.6 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (d, *J* = 16.0 Hz, 1H), 7.59–7.55 (m, 2H), 7.51–7.48 (m, 3H), 7.45–7.36 (m, 6H), 7.31–7.29 (m, 1H), 7.24–7.22 (m, 2H), 7.19–7.17 (m, 1H), 6.94 (d, *J* = 16.0 Hz, 1H), 6.74 (m, *J* = 16.0 Hz, 1H), 4.81–4.69 (m, 3H), 4.57–4.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 191.5, 146.6, 145.9, 138.5, 134.8, 133.7, 133.6, 131.6, 131.4, 130.3, 129.1,129.0, 128.9, 128.7, 128.6, 128.4, 126.5, 123.5, 123.1, 77.8, 67.0, 42.6. HRMS (EI): exact mass calculated for M^+ ($C_{27}H_{22}NO_4Cl$) requires *m*/*z* 459.1237, found *m*/*z* 459.1239. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 11.8 min (major), 16.8 min (minor), ee = 93%.

4-(1-(4-Chlorophenyl)-2-nitroethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4da). The product was obtained in 74% yield, yellow solid. Mp = 149–150 °C; $[\alpha]_D^{22}$ −179.6 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.77 (d, *J* = 16.0 Hz, 1H), 7.59–7.57 (m, 2H), 7.54–7.48 (m, 3H), 7.45–7.37 (m, 7H), 7.31–7.29 (m, 1H), 7.24–7.22 (m, 2H), 6.94 (d, *J* = 16.0 Hz, 1H), 6.73 (d, *J* = 16.0 Hz, 1H), 4.79–4.66 (m, 3H), 4.58–4.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 191.5, 146.6, 145.9, 134.8, 134.2, 133.6, 131.6, 131.4, 129.5, 129.3, 129.1, 129.0, 128.9, 128.7, 123.5, 122.8, 78.1, 67.3, 42.4. HRMS (EI): exact mass calculated for M^+ ($C_{27}H_{22}NO_4Cl$) requires *m*/*z* 459.1237, found *m*/*z* 459.1250. The enantiomeric excess was determined by HPLC.

[AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 11.5 min (major), 15.3 min (minor), ee = 90%.

4-(1-(3-Bromophenyl)-2-nitroethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4ea). The product was obtained in 81% yield, yellow solid. Mp = 117–118 °C; $[\alpha]_D^{22}$ −187.2 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (d, *J* = 16.0 Hz, 1H), 7.59–7.55 (m, 2H), 7.51–7.47 (m, 4H), 7.45–7.36 (m, 7H), 7.23–7.15 (m, 2H), 6.94 (d, *J* = 16.0 Hz, 1H), 6.74 (d, *J* = 16.0 Hz, 1H), 4.81–4.68 (m, 3H), 4.56–4.50 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.5, 191.5, 146.6, 145.9, 138.8, 133.7, 133.6, 131.6, 131.5, 131.4, 131.3, 130.5, 129.1, 129.0, 128.9, 128.8, 126.9, 123.5, 123.1, 123.0, 77.8, 67.0, 42.5. HRMS (EI): exact mass calculated for M^+ ($C_{27}H_{22}NO_4Br$) requires *m*/*z* 503.0732, found *m*/*z* 503.0737. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 12.4 min (major), 17.2 min (minor), ee = 90%.

4-(1-(2-Fluorophenyl)-2-nitroethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4fa). The product was obtained in 85% yield, yellow solid. Mp = 136–137 °C; $[\alpha]_D^{22}$ −184.8 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.77 (d, *J* = 16.0 Hz, 1H), 7.58–7.49 (m, 5H), 7.46–7.37 (m, 6H), 7.27–7.21 (m, 2H), 7.08–7.01 (m, 2H), 6.93 (d, *J* = 16.0 Hz, 1H), 6.79 (d, *J* = 16.0 Hz, 1H), 4.91–4.76 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 191.7, 162.3, 159.8, 146.3, 145.7, 133.8, 133.7, 131.5, 131.3, 131.1, 131.0, 130.2, 130.1, 129.1, 129.0, 128.9, 128.7, 124.7, 123.8, 122.8, 116.2, 116.0, 76.7, 65.3, 38.6. HRMS (EI): exact mass calculated for M^+ ($C_{27}H_{22}NO_4F$) requires *m*/*z* 443.1533, found *m*/*z* 443.1538. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 13.7 min (major), 15.8 min (minor), ee = 95%.

4-(1-(3-Fluorophenyl)-2-nitroethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4ga). The product was obtained in 76% yield, yellow solid. Mp = 137–138 °C; $[\alpha]_D^{22}$ −126.4 (*c* 0.99, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.77 (d, *J* = 16.0 Hz, 1H), 7.59–7.48 (m, 5H), 7.45–7.36 (m, 6H), 7.27–7.24 (m, 1H), 7.09–7.01 (m, 2H), 6.96–6.92 (m, 2H), 6.75 (d, *J* = 16.0 Hz, 1H), 4.81–4.69 (m, 3H), 4.60–4.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 191.5, 164.1, 161.6, 146.6, 145.8, 138.9, 133.6, 131.6, 131.4, 130.7, 130.6, 129.1, 129.0, 128.9, 128.7, 123.9, 123.5, 123.0, 115.5, 115.4, 115.3, 115.2, 77.9, 67.1, 42.6. HRMS (EI): exact mass calculated for M^+ ($C_{27}H_{22}NO_4F$) requires *m*/*z* 443.1533, found *m*/*z* 443.1535. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 11.7 min (major), 17.1 min (minor), ee = 92%.

4-(1-(4-Fluorophenyl)-2-nitroethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4ha). The product was obtained in 93% yield, yellow solid. Mp = 92–93 °C; $[\alpha]_D^{22}$ −209.6 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.77 (d, *J* = 16.0 Hz, 1H), 7.5–7.47 (m, 5H), 7.45–7.36 (m, 6H), 7.26–7.29 (m, 2H), 7.01–6.93 (m, 3H), 6.75 (d, *J* = 16.0 Hz, 1H), 4.81–4.69 (m, 3H), 4.60–4.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.7, 191.7, 163.6, 161.1, 146.5, 145.7, 133.7, 132.1, 132.0, 131.5, 131.4, 129.9, 129.8, 129.1, 129.0, 128.9, 128.7, 123.6, 122.9, 116.1, 115.9, 78.3, 67.5, 42.3. HRMS (EI): exact mass calculated for M^+ ($C_{27}H_{22}NO_4F$) requires *m*/*z* 443.1533, found *m*/*z* 443.1534. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 11.4 min (major), 15.3 min (minor), ee = 90%.

4-(1-(4-Methoxyphenyl)-2-nitroethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4ia). The product was obtained in 82% yield, yellow solid. Mp = 126–127 °C; $[\alpha]_D^{23}$ −179.6 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (d, *J* = 16.0 Hz, 1H), 7.59–7.57 (m, 2H), 7.51–7.47 (m, 3H), 7.47–7.36 (m, 6H), 7.21–7.19 (m, 2H), 6.95 (d, *J* = 16.0 Hz, 1H), 6.82–6.80 (m, 2H), 6.74 (d, *J* = 16.0 Hz, 1H), 4.77–4.67 (m, 3H), 4.55–4.49 (m, 1H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.1, 192.0, 159.3, 146.2, 145.3, 133.8, 133.7, 131.4, 131.2, 129.3, 129.0, 128.9, 128.7, 127.9, 123.8, 123.0, 114.4, 78.5, 67.6, 55.1, 42.3. HRMS (EI): exact mass calculated for M^+ ($C_{28}H_{25}NO_5$) requires *m*/*z* 455.1733, found *m*/*z* 455.1740. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 15.4 min (major), 21.5 min (minor), ee = 89%.

4-(1-(2,3-Dimethoxyphenyl)-2-nitroethyl)-1,7-diphenyl-hepta-1,6-diene-3,5-dione (4ja). The product was obtained in 92% yield, yellow oil. $[\alpha]_D^{23}$ −179.2 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.67 (d, *J* = 16.0 Hz, 1H), 7.55–7.50 (m, 5H), 7.42–7.38 (m, 6H), 6.95–6.92 (m, 1H), 6.83–6.77 (m, 4H), 6.99–6.93 (m, 2H), 4.85–4.75 (m, 2H), 4.02 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.6, 192.6, 152.7, 147.2, 145.6, 145.1, 134.0, 133.8, 131.2, 131.0, 129.4, 129.0, 128.9, 128.8, 128.7, 124.7, 124.0, 123.5, 121.2, 112.6, 76.8, 65.1, 60.8, 55.6, 38.6. HRMS (EI): exact mass calculated for M^+ ($C_{29}H_{27}NO_6$) requires *m*/*z* 485.1838, found *m*/*z* 485.1833. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 12.4 min (major), 17.1 min (minor), ee = 96%.

4-(1-(2,4-Dimethoxyphenyl)-2-nitroethyl)-1,7-diphenyl-hepta-1,6-diene-3,5-dione (4ka). The product was obtained in 73% yield, yellow oil. $[\alpha]_D^{23}$ −96.8 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.74 (d, *J* = 16.0 Hz, 1H), 7.59–7.57 (m, 2H), 7.49–7.46 (m, 3H), 7.42–7.37 (m, 6H), 7.08 (m, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 16.0 Hz, 1H), 6.77 (d, *J* = 16.0 Hz, 1H), 6.40–6.35 (m, 2H), 4.99–4.88 (m, 2H), 4.74–4.67 (m, 2H), 3.86 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.5, 192.5, 160.8, 158.3, 145.6, 144.6, 134.1, 133.9, 131.5, 131.2, 131.0, 129.0, 128.9, 128.8, 128.6, 124.3, 123.2, 115.9, 104.6, 99.2, 76.9, 65.5, 55.5, 55.2, 39.4. HRMS (EI): exact mass calculated for M^+ ($C_{29}H_{27}NO_6$) requires *m*/*z* 485.1838, found *m*/*z* 485.1837. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 13.4 min (major), 17.5 min (minor), ee = 95%.

4-(2-Nitro-1-*p*-tolylethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4la). The product was obtained in 85% yield, yellow solid. Mp = 94–95 °C; $[\alpha]_D^{23}$ −202.8 (*c* 0.49, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75 (d, *J* = 16.0 Hz, 1H), 7.58–7.56 (m, 2H), 7.51–7.46 (m, 3H), 7.46–7.35 (m, 6H), 7.18–7.16 (m, 2H), 7.10–7.08 (m, 2H), 6.95 (d, *J* = 16.0 Hz, 1H), 6.74 (d, *J* = 16.0 Hz, 1H), 4.79–4.69 (m, 3H), 4.56–4.50 (m, 1H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.1, 191.9, 146.2, 145.3, 138.0, 133.8, 133.7, 133.1, 131.4, 131.2, 129.7, 129.0, 128.9, 128.7, 128.0, 123.8, 123.1, 78.4, 67.5, 42.7, 21.0. HRMS (EI): exact mass calculated for M^+ ($C_{28}H_{25}NO_4$) requires *m*/*z* 439.1784, found *m*/*z* 439.1789. The enantiomeric excess was determined by HPLC.

[AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 11.2 min (major), 15.1 min (minor), ee = 91%.

4-(1-(Naphthalen-1-yl)-2-nitroethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4ma). The product was obtained in 84% yield, yellow solid. Mp = 129–130 °C; $[\alpha]_D^{23}$ −166.8 (*c* 0.49, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.81–7.75 (m, 5H), 7.57–7.55 (m, 2H), 7.47–7.32 (m, 12H), 6.97 (d, *J* = 16.0 Hz, 1H), 6.75 (d, *J* = 16.0 Hz, 1H), 4.86–4.82 (m, 3H), 4.76–4.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 191.8, 149.6, 146.2, 145.5, 142.7, 133.8, 133.7, 131.4, 131.2, 129.1, 129.0, 128.8, 128.7, 124.1, 123.0, 110.7, 109.1, 75.9, 64.2, 36.9. HRMS (EI): exact mass calculated for M^+ ($C_{31}H_{25}NO_4$) requires *m/z* 475.1784, found *m/z* 475.1786. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 13.6 min (major), 18.9 min (minor), ee = 90%.

4-(1-(Furan-2-yl)-2-nitroethyl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4na). The product was obtained in 62% yield, yellow solid. Mp = 128–129 °C; $[\alpha]_D^{23}$ −192.8 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (d, *J* = 16.0 Hz, 1H), 7.60–7.52 (m, 5H), 7.44–7.39 (m, 7H), 6.88 (d, *J* = 16.0 Hz, 1H), 6.77 (d, *J* = 16.0 Hz, 1H), 6.25–6.22 (m, 2H), 4.87–4.78 (m, 3H), 4.69–4.63 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 191.8, 149.6, 146.2, 145.6, 142.7, 133.8, 133.7, 131.4, 131.2, 129.1, 129.0, 128.8, 128.7, 124.1, 123.0, 110.7, 109.0, 75.9, 64.2, 36.9. HRMS (EI): exact mass calculated for M^+ ($C_{25}H_{21}NO_5$) requires *m/z* 415.1420, found *m/z* 415.1428. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 8 : 1, 0.8 mL min^{-1}]: 24.7 min (major), 28.6 min (minor), ee = 93%.

4-(1-Nitropentan-2-yl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4oa). The product was obtained in 82% yield, yellow solid. Mp = 89–90 °C; $[\alpha]_D^{23}$ −129.0 (*c* 0.99, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75–7.71 (m, 2H), 7.60–7.58 (m, 4H), 7.43–7.40 (m, 6H), 6.94–6.86 (m, 2H), 4.67–4.55 (m, 2H), 4.50 (d, *J* = 9.2 Hz, 1H), 3.18–3.12 (m, 1H), 1.52–1.33 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.8, 193.3, 145.7, 145.6, 133.9, 133.8, 131.3, 131.2, 129.1, 129.0, 128.8, 124.6, 123.4, 76.1, 65.6, 36.9, 31.5, 29.7, 19.7, 13.8. HRMS (EI): exact mass calculated for M^+ ($C_{24}H_{25}NO_4$) requires *m/z* 391.1784, found *m/z* 391.1786. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 30 : 1, 0.8 mL min^{-1}]: 19.4 min (major), 21.1 min (minor), ee = 92%.

4-(3-Methyl-1-nitrobutan-2-yl)-1,7-diphenylhepta-1,6-diene-3,5-dione (4pa). The product was obtained in 72% yield, yellow solid. Mp = 151–152 °C; $[\alpha]_D^{23}$ = + 5.3 (*c* = 0.99, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.78 (d, *J* = 16.0 Hz, 1H), 7.56–7.54 (m, 2H), 7.42–7.27 (m, 10H), 6.82 (d, *J* = 16.0 Hz, 1H), 3.69–3.63 (m, 1H), 3.50–3.42 (m, 1H), 3.30–3.28 (m, 1H), 2.91–2.84 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.1, 179.7, 142.2, 137.9, 135.0, 130.3, 129.1, 129.0, 128.2, 128.0, 127.2, 119.0, 106.5, 87.2, 45.5, 37.1, 34.7, 34.6, 29.7, 21.2, 19.8. HRMS (EI): exact mass calculated for M^+ ($C_{24}H_{25}NO_4$) requires *m/z* 391.1784, found *m/z* 391.1786. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 8.4 min (major), 9.8 min (minor), ee = 84%.

4-(2-Nitro-1-phenylethyl)-1,7-dip-tolylhepta-1,6-diene-3,5-dione (4ab). The product was obtained in 78% yield, yellow solid. Mp = 147–148 °C; $[\alpha]_D^{23}$ −130.4 (*c* 0.99, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (d, *J* = 16.0 Hz, 1H), 7.49–7.45 (m, 3H), 7.38–7.36 (m, 2H), 7.29–7.28 (m, 4H), 7.22–7.16 (m, 5H), 6.90 (d, *J* = 16.0 Hz, 1H), 6.69 (d, *J* = 16.0 Hz, 1H), 4.80–4.68 (m, 3H), 4.59–4.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.0, 191.9, 146.3, 145.4, 142.2, 141.9, 136.4, 131.1, 131.0, 129.8, 129.7, 128.9, 128.7, 128.2, 128.1 ,122.8, 122.2, 78.3, 67.4, 43.0, 21.6, 21.5. HRMS (EI): exact mass calculated for M^+ ($C_{29}H_{27}NO_4$) requires *m/z* 453.1940, found *m/z* 453.1945. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 8 : 1, 0.8 mL min^{-1}]: 13.5 min (major), 20.9 min (minor), ee = 90%.

1,7-Bis(4-chlorophenyl)-4-(2-nitro-1-phenylethyl)hepta-1,6-diene-3,5-dione (4ac). The product was obtained in 72% yield, yellow solid. Mp = 143–144 °C; $[\alpha]_D^{23}$ −200.8 (*c* 0.49, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.69 (d, *J* = 16.0 Hz, 1H), 7.52–7.48 (m, 2H),7.43–7.34 (m, 10H), 7.30–7.28 (m, 2H), 6.90 (d, *J* = 16.0 Hz, 1H), 6.68 (d, *J* = 16.0 Hz, 1H), 4.75–4.68 (m, 3H), 4.57–4.51 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.7, 191.6, 144.8, 143.9, 137.6, 136.1, 132.2, 132.1, 130.0, 129.8, 129.4, 129.3, 129.1, 128.4, 128.1, 123.9, 123.2, 78.2, 67.7, 42.9. HRMS (EI): exact mass calculated for M^+ ($C_{27}H_{21}NO_4Cl_2$) requires *m/z* 493.0848, found *m/z* 493.0867. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 12.9 min (major), 24.1 min (minor), ee = 92%.

1,7-Bis(2-fluorophenyl)-4-(2-nitro-1-phenylethyl)hepta-1,6-diene-3,5-dione (4ad). The product was obtained in 73% yield, yellow solid. Mp = 121–122 °C; $[\alpha]_D^{23}$ −164.4 (*c* 0.49, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.88 (d, *J* = 16.0 Hz, 1H), 7.62–7.56 (m, 2H), 7.47–7.35 (m, 4H), 7.29–7.27 (m, 2H), 7.23–7.08 (m, 6H), 7.04 (d, *J* = 16.0 Hz, 1H), 6.82 (d, *J* = 16.0 Hz, 1H), 4.80–4.77 (m, 3H), 4.58–4.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.9, 191.9, 163.1, 163.0, 160.6, 160.4, 138.65; 138.62, 137.97; 137.95, 136.2, 132.93; 132.85, 132.67; 132.58, 129.6, 129.0, 128.3, 128.1, 126.12; 126.05, 125.64; 125.57, 124.65; 124.61, 124.56; 124.53, 122.0, 121.9, 116.47; 116.40, 116.25; 116.18, 78.1, 67.1, 43.0. HRMS (EI): exact mass calculated for M^+ ($C_{27}H_{21}NO_4F_2$) requires *m/z* 461.1439, found *m/z* 461.1440. The enantiomeric excess was determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 4 : 1, 0.8 mL min^{-1}]: 13.1 min (major), 15.9 min (minor), ee = 96%.

1,7-Bis(4-hydroxy-3-methoxyphenyl)-4-(2-nitro-1-phenylethyl)-hepta-1,6-diene-3,5-dione (4ae). The product was obtained in 82% yield, yellow solid. Mp = 85–86 °C; $[\alpha]_D^{23}$ −207.2 (*c* 0.99, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.69 (d, *J* = 16.0 Hz, 1H), 7.43 (d, *J* = 16.0 Hz, 1H), 7.30–7.24 (m, 4H), 7.18–7.00 (m, 7H), 7.86 (d, *J* = 16.0 Hz, 1H), 6.64 (d, *J* = 16.0 Hz, 1H), 4.79–4.70 (m, 3H), 4.58–4.52 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.8, 191.7, 168.6, 168.5, 151.5, 151.4, 145.6, 144.7, 142.4, 142.2, 136.1, 132.7, 132.6, 129.1, 128.3, 128.1, 123.9, 123.5, 123.4, 122.2, 121.9, 111.9, 111.8, 78.2, 67.3, 55.9, 53.4, 42.9, 29.6, 20.6. HRMS (EI): exact mass calculated for M^+ ($C_{33}H_{31}NO_{10}$) requires *m/z* 601.1948, found *m/z* 601.1949. The enantiomeric excess was

determined by HPLC. [AS-H column, 254 nm, Hexane : EtOH = 1 : 1, 0.5 mL min^{-1}]: 15.7 min (major), 22.1 min (minor), ee = 92%.

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