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Diastereo- and enantioselective synthesis of densely functionalized cyclohexanones via double Michael addition of curcumins with nitroalkenes

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ABSTRACT

The asymmetric double Michael additions of curcumins to nitroalkenes to afford highly functionalized cyclohexanones have been carried out for the first time. A combination of a dihydrocinchonine-thiourea organocatalyst and K_2CO_3 was found to be the most effective in obtaining the desired cyclohexanones in good yield, diastereoselectivity and enantioselectivity.

1. Introduction

Curcumin is an active ingredient in turmeric which is widely used as a dietary spice and as a traditional medicine for the treatment of diabetes, jaundice, rheumatoid arthritis, and so on, in eastern countries.[1] In recent decades, studies on the biological activities of curcumin such as anti-oxidant,[2] anti-cancer,[3] anti-inflammatory,[4] anti-metastatic,[5] anti-HIV protease,[6] and anti-Alzheimer's[7] have received considerable attention. Recently, the metal complexes of the β-dicarbonyl moiety of the curcumins were also shown to exhibit numerous biological activities.[8] However, the poor solubility and bioavailability of curcumin prevented it from being used as a potent therapeutic agent. Therefore, the synthesis of analogs and derivatives of curcumin, which possess superior solubility and bioavailability is a challenge for organic and medicinal chemists. In this context, several cyclohexanone and heterocyclic curcumin analogs were synthesized and shown to exhibit a range of biological activities.[9]

Recently, we reported a highly diastereoselective synthesis of functionalized cyclohexanones and dihydrofurans via cascade double Michael and Michael–Feist–Benary reactions involving curcumins and nitroalkenes. (Scheme 1).[10,11] Subsequently, Ye et al. reported the addition of curcumins to nitroalkenes catalyzed by novel thiourea catalysts and isolated the single Michael adducts in good yields and enantioselectivities.[12] Very recently, Yan et al. exploited the multiple nucleophilic and electrophilic sites of curcumin in a domino Michael–Michael–oxa-Michael reaction of curcumins and isatylidene malononitriles for the synthesis of spirooxindoles. [13]

The synthesis of complex molecules, including natural products, containing multiple stereogenic centers via asymmetric domino/cascade reactions, often employing chiral organocatalysts, has also emerged as a fascinating area of research.[14] In particular, cascade [5+1] and [4+2] two-component double Michael reactions under asymmetric organocatalyzed conditions have been exploited to construct cyclohexanone scaffolds in excellent yields and selectivities.[15,16] However, the application of curcumin as a donor and acceptor in such transformations has received attention only recently.[10,11,13]

2. Results and discussion

In recent years, chiral bifunctional catalysts, containing a tertiary amine and a thiourea moiety, set the standard for asymmetric Michael additions of 1,3-dicarbonyl compounds to electron deficient alkenes. This is due to the exceptional ability of the catalyst to simultaneously activate both the substrates by aligning them in the proper orientation such that the reaction takes place in a highly stereoselective manner.[17] Therefore, we envisioned that the tertiary amine moiety in the quinuclidine ring would generate the enolate of curcumin by deprotonating the active methylene, whereas the thiourea moiety would activate the nitroalkene and/or stabilize the nitronate through multiple hydrogen bonding with the nitro group (Fig. 1).[18] The chiral backbone would provide enough rigidity to allow a double Michael addition to take place in a highly stereoselective manner to afford 4-nitrocyclohexanones. The synthesis of many biologically active compounds, such as neuramidase inhibitors, and natural products, such as (−)-aphanorphine alkaloids, (−)-epibatidine, and the antitumor antibiotic (−)-calcheamicinone, has been reported using 4-nitrocyclohexanone as the key starting compound.[19]

Following the rationale outlined in Figure 1,[18] we prepared various cinchona alkaloid derived thiourea catalysts **A**–**E** by reported procedures (Fig. 2).[20] We chose curcumin **1a** and nitroalkene **2a** as the model substrates for the optimization of the reaction conditions (Table 1). Initially, quinine-thiourea catalyst **A**, dihydroquinine-thiourea catalysts **B**–**C** (30 mol %), and the

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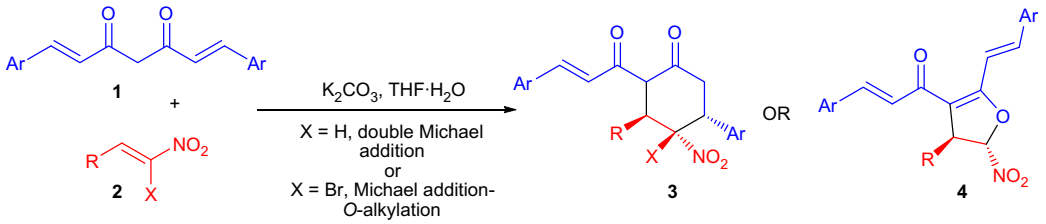


Scheme. 1.

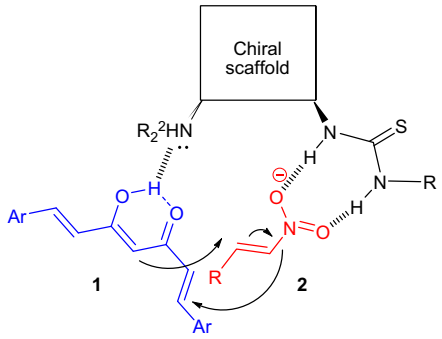


Figure 1. Proposed transition state model for the double Michael addition of curcumin **1** with nitroalkene **2**.

dihydrocinchonine-thiourea catalyst **D** were screened in THF as the solvent. This afforded the double Michael adduct **3a** in low to moderate yield and moderate to good selectivity (Table 1, entries 1–4). A slight improvement in selectivity was observed when dihydrocinchonine-thiourea catalyst **D** was used in chloroform (Table 1, entry 5). This prompted us to screen catalyst **D** in other solvents, such as dichloromethane, dichloroethane, and a mixture of solvents such as toluene–chloroform (1:1, Table 1, entries 6–8). Although the selectivity was high in dichloromethane, the yield remained below 50% (Table 1, entry 6). There was no reaction in the presence of proline-thiourea catalyst **E** in dichloromethane (Table 1, entry 9). The consistently low yield of the double Michael adduct **3a** encountered in the above reactions was due to incomplete conversion of the intermediate single Michael adduct, which was attributable to the poor nucleophilicity of the nitronate arising from the initial Michael addition. We felt that a stronger base would be necessary for the satisfactory completion of the second intramolecular Michael addition step. To this end, NaOAc was used as an additive to catalyst **D** in chloroform (Table 1, entry 10). Although this improved the yield and the diastereoselectivity, the enantioselectivity decreased dramatically (Table 1, entry 10). Finally, in order to ensure the complete conversion of curcumin **1a** into the double Michael adduct **3a**, the reaction was carried out in two steps as follows: the crude reaction mixture, after 3 days, was filtered through a short pad of silica gel to remove the unreacted nitroalkene **1a** and the resultant filtrate containing both the single and double Michael adducts was concentrated; the residue was treated with K_2CO_3 in THF/H_2O (7.5:1).[21] This led to the formation of the desired double Michael adduct **3a** in moderate yield and selectivity when THF was used as the solvent in the first step (entry 11); good yield (75%), and excellent diastereo- and enantioselectivity (dr 91:9 and ee 85%) were achieved when dichloromethane was used as solvent (Table 1, entry 12). A considerable decrease in the yield and a marginal decrease in the enantioselectivity were observed when the catalyst loading was reduced to 20 mol % (Table 1, entry 13).

The optimized conditions, that is, 30 mol % of catalyst **D** in CH_2Cl_2 followed by 0.8 equiv of K_2CO_3 in THF/H_2O (7.5:1), were employed for the reaction of curcumin **1a** with various nitroalkenes **2a**–**m** (Table 2). Nitroalkenes **2a**–**e** with a variety of electron donating substituents reacted with curcumin **1a** to afford the double Michael adducts **3a**–**e** in good yields (70–75%) and diastereoselectivities (80:20–91:9, Table 2, entries 1–5). However, no clear trend was observed in the enantioselectivities because nitroalkene **2c** with three methoxy groups on the aromatic ring and **2e** with a weakly activating Me group gave lower selectivities, 62% and 63%, respectively (entries 3 and 5), while other nitroalkenes **2a**, **2b**, and **2d** with 1–2 alkoxy groups afforded the double Michael adducts with better ee's (83–91%, Table 2, entries 1, 2 and 4). Parent nitrostyrene **2f** and nitroalkenes **2g**–**2i** with weakly deactivating aromatic substituents afforded the products in 60–73% yield, 77:23–88:12 de, and 72–86% ee (Table 2, entries 6–9). Finally, nitroalkenes **2j**–**2k** with a strong electron withdrawing nitro group and heteroaromatic nitroalkenes **2l**–**2m** gave the products in high yields (75–88%) and varying diastereoselectivities (50:50–90:10, Table 2, entries 10–13). While the ee was high with *o*-nitro-nitrostyrene **2j** (entry 10), moderate to good ee's were observed for the other nitroalkenes **2k**–**m** (Table 2, entries 11–13).

Having demonstrated the scope of nitroalkenes **2** in our asymmetric double Michael addition, we proceeded to explore the scope of curcumins **1** by reacting a representative nitroalkene **2a** with

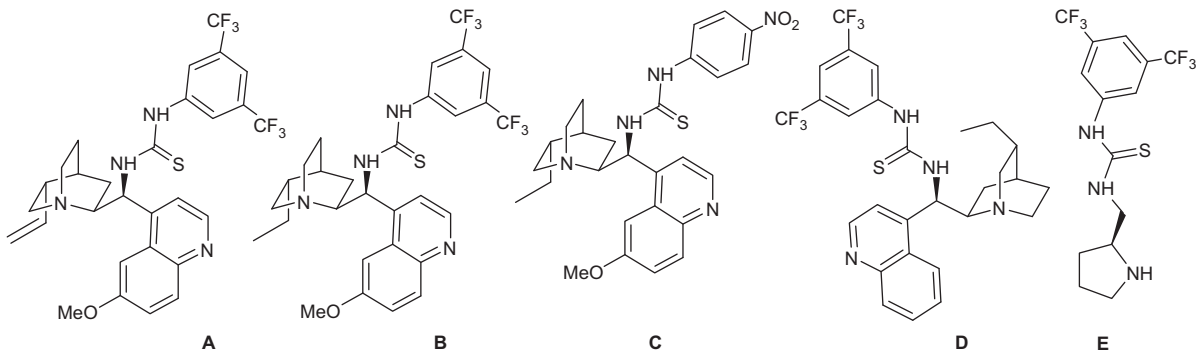
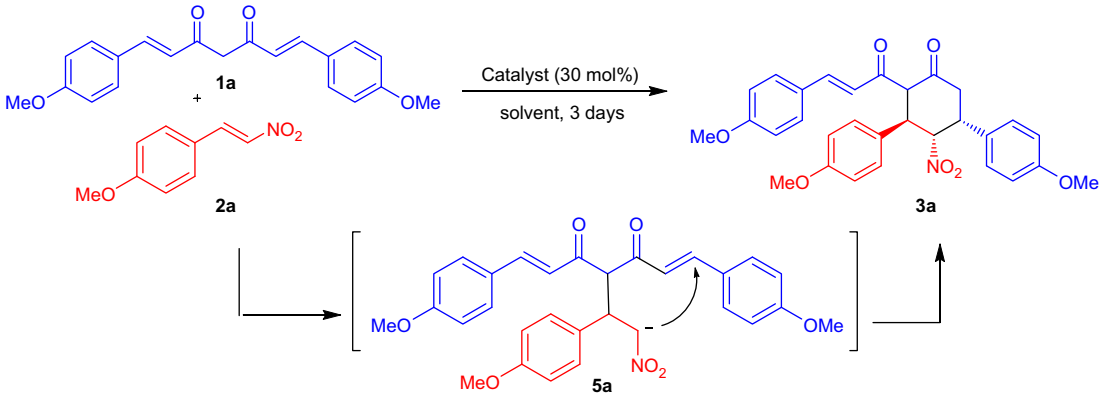


Figure 2. Catalysts screened for the double Michael addition of curcumin **1a** and nitroalkenes **2a**.

Table 1
Optimization of the enantioselective double Michael addition of curcumin **1a** to nitroalkene **2a** in the presence of thiourea catalysts **A**–**E**



Entry	Catalyst	Solvent	% Yield[a]	dr[b]	ee[c]
1	**A**	THF	33	80:18	(+)–70
2	**B**	THF	35	89:11	(+)–53
3	**C**	THF	40	77:23	(+)–79
4	**D**	THF	30	90:10	(−)–84
5	**D**	$CHCl_3$	45	85:15	(−)–85
6	**D**	CH_2Cl_2	40	94:06	(−)–85
7	**D**	CH_2Cl–CH_2Cl	38	79:21	(−)–35
8	**D**	Toluene–$CHCl_3$ (1:1)	47	67:33	(−)–50
9	**E**	CH_2Cl_2	–[d]	–	–
10	**D**	$CHCl_3$[e]	64	90:10	(−)–39
11	**D**	THF[f]	55	87:13	(−)–63
12	**D**	**CH_2Cl_2**[f]	**75**	**91:09**	(−)–**85**
13	**D**	CH_2Cl_2[f,g]	63	91:09	(−)–83

[a] Isolated yield after silica gel column chromatography.
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC.
[d] No reaction.
[e] 20 mol % NaOAc was used as an additive.
[f] After 3 days, the crude reaction mixture was treated with 0.8 equiv K_2CO_3 in THF/H_2O solvent system.
[g] 20 mol % of catalyst was used.

selected curcumins **1b**, **1f**, and **1l** (Table 3). In these cases, the yields, and the diastereo- and enantioselectivities were moderate.

3. Conclusion

The asymmetric double Michael addition of curcumins to nitroalkenes has been carried out for the first time. The products, 4-nitrocyclohexanones, were formed in most cases in good to high yields, excellent diastereoselectivities, and moderate to high enantioselectivities in the presence of a dihydrocinchonine-thiourea organocatalyst in conjunction with an achiral base, such as K_2CO_3. Our future work will include investigations of the synthetic and biological applications of these highly functionalized cyclohexanones.

4. Experimental

4.1. General

The melting points recorded are uncorrected. NMR spectra (^1H, ^1H decoupled ^{13}C) were recorded with TMS as the internal standard. The coupling constants (J values) are given in Hz. High resolution mass spectra were recorded at 60–70 eV under ESI Q-TOF conditions. Diastereoselectivities were determined by ^1H NMR and enantioselectivities by HPLC equipped with a PDA detector and chiral column. Specific rotations were measured for solutions of samples of known concentrations in $CHCl_3$ using a polarimeter equipped with a sodium vapor lamp. Nitroalkenes and curcumins were prepared following literature protocols.[22]

4.2. General procedure for the asymmetric double Michael addition of curcumin 1 to nitroalkenes 2

A solution of curcumin **1** (0.12 mmol, 1.0 equiv), nitroalkene **2** (0.18 mmol, 1.5 equiv), and catalyst **D** (22 mg, 0.036 mmol, 30 mol %) in dichloromethane (0.5 mL) was stirred at room temperature until curcumin **1** was completely consumed (monitored by TLC). The solvent was evaporated under reduced pressure and the excess nitroalkene **2** was removed by flash column chromatography using EtOAc–pet ether (5–50%, gradient elution) as eluent to obtain a mixture of **3** or **6** and the single Michael adduct. To this mixture in THF (1.5 mL) and H_2O (0.2 mL) was added K_2CO_3 (0.8 equiv, 14 mg) and the reaction mixture was stirred until the single Michael adduct was completely consumed. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography by eluting with EtOAc–pet ether (10–25%).

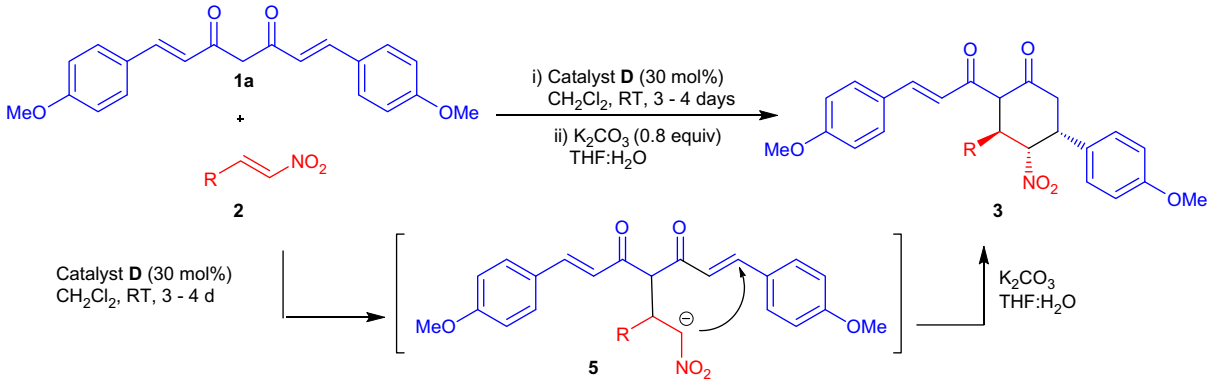
4.3. 3,5-Bis(4-methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl) acryloyl)-4-nitrocyclohexanone 3a[10]

$[\alpha]_D^{18} = -41.0$ (c 1.0, $CHCl_3$); HPLC: Chiralcel AD–H (pet ether/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 370 nm), t_R (major) = 19.0 min, t_R (minor) = 23.8 min; 85% ee.

4.4. 3-(3,4-Dimethoxyphenyl)-5-(4-methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryloyl)-4-nitro-cyclohexanone 3b[10]

$[\alpha]_D^{19} = -49.9$ (c 1.0, $CHCl_3$); HPLC: Chiralpak IA (pet ether/i-PrOH = 80/20, flow rate 0.5 mL/min, λ = 370 nm), t_R (major) = 28.3 min, t_R (minor) = 33.8 min; 83% ee.

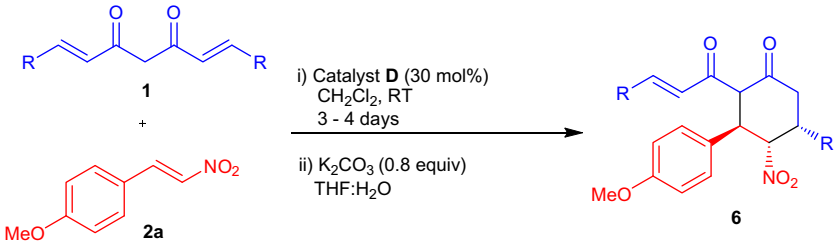
Table 2
Enantioselective double Michael addition of curcumin **1a** to nitroalkenes **2** in the presence of dihydrocinchonine-thiourea catalyst **D** and K_2CO_3



Entry	R	3	% Yield[a]	dr[b]	ee[c]
1	4-MeO-C_6H_4	**3a**	75	91:09	85
2	3,4-$(MeO)_2$-C_6H_3	**3b**	70	86:14	83
3	3,4,5-$(MeO)_3$-C_6H_3	**3c**	70	80:20	62
4	Benzo[*d*][1,3]dioxole	**3d**	70	89:11	91
5	4-Me-C_6H_4	**3e**	75	88:12	62
6	C_6H_5	**3f**	73	88:12	80
7	4-Cl-C_6H_4	**3g**	71	83:17	75
8	4-Br-C_6H_4	**3h**	60	87:13	86
9	3-Br-C_6H_4	**3i**	62	77:23	72
10	2-NO_2-C_6H_4	**3j**	80	81:19	89
11	3-NO_2-C_6H_4	**3k**	75	50:50	78
12	2-Furyl	**3l**	85	85:15	78
13	2-Thienyl	**3m**	88	90:10	69

[a] Isolated yield after silica gel column chromatography.
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC.

Table 3
Enantioselective double Michael addition of curcumins **1** to nitroalkene **2a** in the presence of dihydrocinchonine-thiourea catalyst **D** and K_2CO_3



Entry	R	6	Yield[a] (%)	dr[b]	ee[c]
1	3,4-$(MeO)_2$-C_6H_3	**6b**	58	70:30	34
2	C_6H_5	**6f**	55[d]	69:31	44
3	2-Furyl	**6l**	37[e]	80:20	60

[a] Isolated yield after silica gel column chromatography.
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC.
[d] 11 mg (20% yield) of single Michael adduct was isolated.
[e] 13 mg (22% yield) of single Michael adduct was isolated.

4.5. 5-(4-Methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryloyl)-4-nitro-3-(3,4,5-tri-methoxyphenyl)cyclohexanone 3c

Yellow crystalline solid: Yield 49 mg (70%); mp 200–202 °C; IR (KBr, cm^{-1}) 3437 (br, w), 2936 (w), 2835 (w), 1621 (w), 1592 (m), 1548 (m), 1513 (s), 1423 (m), 1256 (m), 1128 (m), 1032 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 2.87 (dd, J = 18.8, 6.5 Hz, 1H), 3.30 (dd, J = 18.8, 11.8 Hz, 1H), 3.47 (ddd, J = 11.8, 6.5, 2.2 Hz, 1H), 3.76 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 3.87 (s, 6H), 4.66 (d, J = 2.2 Hz, 1H), 5.04 (t, J = 2.2 Hz, 1H), 6.41 (d, J = 15.3 Hz, 1H), 6.56 (s, 2H), 6.82 (d, J = 8.6 Hz, 4H), 7.00 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 15.3 Hz, 1H), 17.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.4, 36.1, 45.3, 55.4, 55.5, 56.6, 61.0, 92.3, 104.3, 105.3, 114.4, 114.5, 117.4, 127.5, 128.4, 129.4, 130.3, 137.4, 137.8, 143.5, 154.1, 159.3, 161.9, 186.0, 187.6; MS (ES+) m/z (rel intensity) 578 ($[M+3]^+$, 12), 577 ($[M+2]^+$, 38), 576 ($[M+1]^+$, 100); HRMS (ES+) calcd

for $C_{32}H_{34}NO_9$ (MH^+) 576.2234, found 576.2218; $[\alpha]_D^{19} = -47.6$ (*c* 1.0, $CHCl_3$); HPLC: Chiralcel AD–H (pet ether/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 370 nm), t_R (major) = 22.2 min, t_R (minor) = 27.2 min; 62% ee.

4.6. 3-(Benzo[*d*][1,3]dioxol-5-yl)-5-(4-methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryloyl)-4-nitrocyclohexanone 3d[10]

$[\alpha]_D^{18} = -91.2$ (*c* 1.0, $CHCl_3$); HPLC: Chiralcel OD–H (pet ether/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 370 nm), t_R (major) = 36.3 min, t_R (minor) = 31.0 min; 91% ee.

4.7. 5-(4-Methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryloyl)-4-nitro-3-(*p*-tolyl)-cyclohexanone 3e

Yellow crystalline solid: Yield 46 mg (75%); mp 135–137 °C; IR (KBr, cm^{-1}) 3423 (br, w), 2956 (w), 2934 (w), 2841 (w), 1624 (w), 1601 (m), 1549 (s), 1513 (s), 1425 (m), 1256 (s), 1172 (s), 1032 (m), 830 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.85 (dd, *J* = 18.4, 6.2 Hz, 1H), 3.33 (dd, *J* = 18.4, 12.1 Hz, 1H), 3.43 (ddd, *J* = 12.1, 6.2, 2.0 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.70 (d, *J* = 2.0 Hz, 1H), 5.00 (t, *J* = 2.0 Hz, 1H), 6.40 (d, *J* = 15.3 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 7.5 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 7.19–7.29 (m, 6H), 7.66 (d, *J* = 15.3 Hz, 1H), 17.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 33.5, 35.6, 45.0, 55.4, 55.5, 92.4, 104.4, 114.5, 117.4, 127.6, 128.1, 128.4, 129.7, 130.3, 130.4, 138.1, 138.6, 143.3, 159.3, 161.8, 185.4, 188.1; MS (ES+) *m*/*z* (rel intensity) 502 ($[M+3]^+$, 7), 501 ($[M+2]^+$, 35), 500 (MH^+, 100); HRMS (ES+) calcd for $C_{30}H_{30}NO_6$ (MH^+) 500.2073, found 500.2071; $[\alpha]_D^{21} = -50.7$ (*c* 1.0, $CHCl_3$); HPLC: Chiralcel OD–H (pet ether/*i*-PrOH = 80/20, flow rate 0.5 mL/min, λ = 370 nm), t_R (major) = 32.4 min, t_R (minor) = 26.6 min; 62% ee.

4.8. 5-(4-Methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryoloyl)-4-nitro-3-phenylcyclohexanone 3f[10]

$[\alpha]_D^{21} = -55.3$ (*c* 1.0, $CHCl_3$); HPLC: Chiralpak IA (pet ether/*i*-PrOH = 90/10, flow rate 0.5 mL/min, λ = 370 nm), t_R (major) = 29.3 min, t_R (minor) = 23.6 min; 79% ee.

4.9. 3-(4-Chlorophenyl)-5-(4-methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryloyl)-4-nitrocyclohexanone 3g[10]

$[\alpha]_D^{21} = -104.2$ (*c* 1.0, $CHCl_3$); HPLC: Chiralcel OD–H (pet ether/*i*-PrOH = 80/20, flow rate 0.5 mL/min, λ = 370 nm), t_R (major) = 53.8 min, t_R (minor) = 42.0 min; 75% ee.

4.10. 3-(4-Bromophenyl)-5-(4-methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryloyl)-4-nitrocyclohexanone 3h

Yellow solid: Yield 42 mg (60%); mp 165–167 °C; IR (KBr, cm^{-1}) 3402 (br, m), 2929 (w), 1621 (m), 1602 (m), 1547 (m), 1512 (s), 1255 (vs), 1172 (s), 1031 (m), 827 (s), 738 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (dd, *J* = 17.3, 5.0 Hz, 1H), 3.29–3.41 (m, 2H), 3.76 (s, 3H), 3.81 (s, 3H), 4.72 (d, *J* = 2.2 Hz, 1H), 4.97 (t, *J* = 2.2 Hz, 1H), 6.34 (d, *J* = 15.3 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 15.3 Hz, 1H), 17.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 35.7, 44.6, 55.4, 55.5, 92.0, 103.8, 114.5, 114.6, 116.9, 122.4, 127.4, 128.4, 129.2, 130.0, 130.3, 132.8, 140.8, 143.9, 159.4, 162.0, 185.3, 188.1; MS (ES+) *m*/*z* (rel intensity) 567 ($[M+4]^+$, 30), 566 ($[M+3]^+$, 93), 565 ($[M+2]^+$, 28), 564 (MH^+, 100); HRMS (ES+) calcd for $C_{29}H_{27}NO_6Br$ (MH^+) 564.1022, found 564.1029; $[\alpha]_D^{21} = -112.3$ (*c* 1.0, $CHCl_3$); HPLC: Chiralcel OD–H (pet ether/*i*-PrOH = 80/10, flow rate 0.5 mL/min, λ = 370 nm), t_R (major) = 69.5 min, t_R (minor) = 54.8 min; 86% ee.

4.11. 3-(3-Bromophenyl)-5-(4-methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryloyl)-4-nitrocyclohexanone 3i

Yellow solid: Yield 43 mg (62%); mp 158–160 °C; IR (KBr, cm^{-1}) 3435 (br, s), 2923 (w), 2841 (w), 1624 (m), 1602 (s), 1547 (s), 1512 (s), 1424 (w), 1254 (m), 1172 (m), 1032 (m), 829 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (dd, *J* = 18.5, 6.2 Hz, 1H), 3.32 (dd, *J* = 18.5, 11.7 Hz, 1H), 3.39 (ddd, *J* = 11.7, 6.2, 2.3 Hz, 1H), 3.76 (s, 3H), 3.80 (s, 3H), 4.72 (d, *J* = 2.3 Hz, 1H), 5.00 (t, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 15.3 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.34–7.36 (m, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.56 (s, 1H), 7.68 (d, *J* = 15.3 Hz, 1H), 17.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6, 35.9, 44.7, 55.4, 55.6, 91.9, 103.8, 114.5, 114.6, 117.0, 123.8, 127.0, 127.4, 128.4, 129.2, 130.4, 131.2, 131.3, 131.6, 143.9, 144.2, 159.4, 162.0, 185.5, 188.0; MS (ES+) *m*/*z* (rel intensity) 567 ($[M+4]^+$, 6), 566 ($[M+3]^+$, 22), 565 ($[M+2]^+$, 8), 564 (MH^+, 21); HRMS (ES+) $C_{29}H_{27}NO_6Br$ (MH^+) 564.1022, found 564.1037; $[\alpha]_D^{19} = -79.4$ (*c* 1.0, $CHCl_3$); HPLC: Chiralpak IC (pet ether/*i*-PrOH = 80/20, flow rate 0.5 mL/min, λ = 370 nm), t_R (major) = 36.2 min, t_R (minor) = 42.5 min; 71% ee.

4.12. 5-(4-Methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryloyl)-4-nitro-3-(2-nitrophenyl)cyclohexanone 3j[10]

$[\alpha]_D^{19} = +5.4$ (*c* 1.0, $CHCl_3$); HPLC: Chiralcel AD–H (pet ether/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 370 nm), t_R (major) = 43.0 min, t_R (minor) = 24.4 min; 89% ee.

4.13. 5-(4-Methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryloyl)-4-nitro-3-(3-nitrophenyl)cyclohexanone 3k[10]

$[\alpha]_D^{19} = -18.6$ (*c* 1.0, $CHCl_3$); HPLC: Chiralcel AD–H (pet ether/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 370 nm), t_R (major) = 51.8 min, t_R (minor) = 57.1 min; 79% ee.

4.14. 3-(Furan-2-yl)-5-(4-methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryloyl)-4-nitrocyclohexanone 3l[10]

$[\alpha]_D^{19} = -71.5$ (*c* 1.0, $CHCl_3$); HPLC: Chiralcel OD–H (pet ether/*i*-PrOH = 80/20, flow rate 0.5 mL/min, λ = 370 nm), t_R (major) = 41.1 min, t_R (minor) = 36.2 min; 78% ee.

4.15. 5-(4-Methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)acryloyl)-4-nitro-3-(thiophen-2-yl)cyclohexanone 3m[10]

$[\alpha]_D^{18} = -77.4$ (*c* 1.0, $CHCl_3$); HPLC: Chiralcel OD–H (pet ether/*i*-PrOH = 80/20, flow rate 0.5 mL/min, λ = 370 nm), t_R (major) = 51.2 min, t_R (minor) = 33.9 min; 69% ee.

4.16. 5-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-2-((*E*)-3-(3,4-dimethoxyphenyl)acryloyl)-4-nitrocyclohexanone 6b[10]

$[\alpha]_D^{25} = -44.3$ (*c* 1.0, $CHCl_3$); HPLC: Chiralcel AD–Helen (pet ether/*i*-PrOH = 80/20, flow rate 0.5 mL/min, λ = 370 nm), t_R (major) = 42.1 min, t_R (minor) = 47.8 min; 34% ee.

4.17. 3-(4-Methoxyphenyl)-4-nitro-5-phenyl-2-((*E*)-3-phenylacryloyl)cyclohexanone 6f[10]

$[\alpha]_D^{25} = -40.3$ (*c* 1.0, $CHCl_3$); HPLC: Chiralcel AD–H (pet ether/*i*-PrOH = 85/15, flow rate 0.5 mL/min, λ = 370 nm), t_R (major) = 14.0 min, t_R (minor) = 21.1 min; 44% ee.

4.18. 5-(Furan-2-yl)-2-((*E*)-3-(furan-2-yl)-acryloyl)-3-(4-methoxyphenyl)-4-nitrocyclohexanone 6l[10]

$[\alpha]_D^{25} = -26.6$ (*c* 0.2, $CHCl_3$); HPLC: Chiralcel OD–H (pet ether/*i*-PrOH = 80/20, flow rate 0.5 mL/min, λ = 370 nm), t_R (major) = 18.9 min, t_R (minor) = 25.3 min; 60% ee.

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