Synthesis S. Mahajan et al. THIEME OPEN ACCESS Paper

Organocatalytic Asymmetric Domino Michael/Henry Reaction of Indolin-3-ones with *o*-Formyl-β-nitrostyrenes

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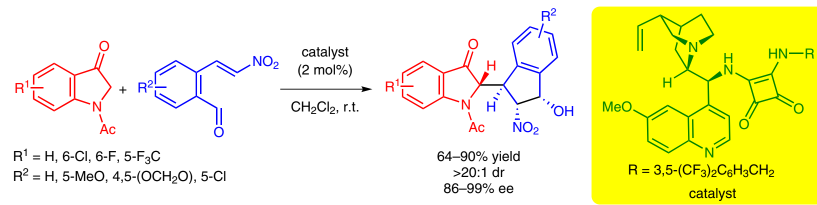


Received: 01.12.2014
Accepted: 02.12.2014
Published online: 05.01.2015
DOI: 10.1055/s-0034-1379943; Art ID: ss-2014-z0728-op

Abstract A highly diastereo- and enantioselective domino Michael/Henry reaction of 1-acetylindolin-3-ones with *o*-formyl-(*E*)-β-nitrostyrenes catalyzed by low loading of a quinine-derived amine-squaramide provides the corresponding indolin-3-one derivatives bearing four adjacent stereogenic centers in good to high yields and with excellent stereoselectivities.

Key words oxindole, indolin-3-one, domino reaction, squaramide, organocatalysis

The indolinone core is frequently found in a wide spectrum of synthetic and naturally occurring bioactive compounds.[1] Hence, over the last few years a tremendous advancement for their asymmetric synthesis has been witnessed. Especially, the enantioselective synthesis of indolin-2-one (i.e., 2-oxindole) derivatives is at the forefront.[2] However, the indolin-3-ones (3-oxindoles) bearing multiple stereogenic centers are also found in a wide range of biologically active natural products such as austamide (**A**),[3a] brevianamide A (**B**),[3b] fluorocurine (**C**),[3c] notoamide O (**D**),[3d] isatisine A (**E**),[3e,f] and cephalinone (**F**)[3g] (Figure 1). Thus, the development of new strategies for the asymmetric synthesis of indolin-3-one derivatives bearing several stereogenic centers would provide new entries to access the potentially bioactive oxindole derivatives. Recently, organocatalytic domino reactions emerged as a powerful strategy to introduce molecular complexity via the stereoselective construction of multiple stereogenic centers through several bond formations in one pot.[4]

Despite the common presence of the indolin-3-one core in natural products, the asymmetric synthesis of these characteristic heterocyclic core structures is less explored as compared to 2-oxindoles.[5–8] Recently, the asymmetric addition of indolin-3-ones to various acceptors emerged as

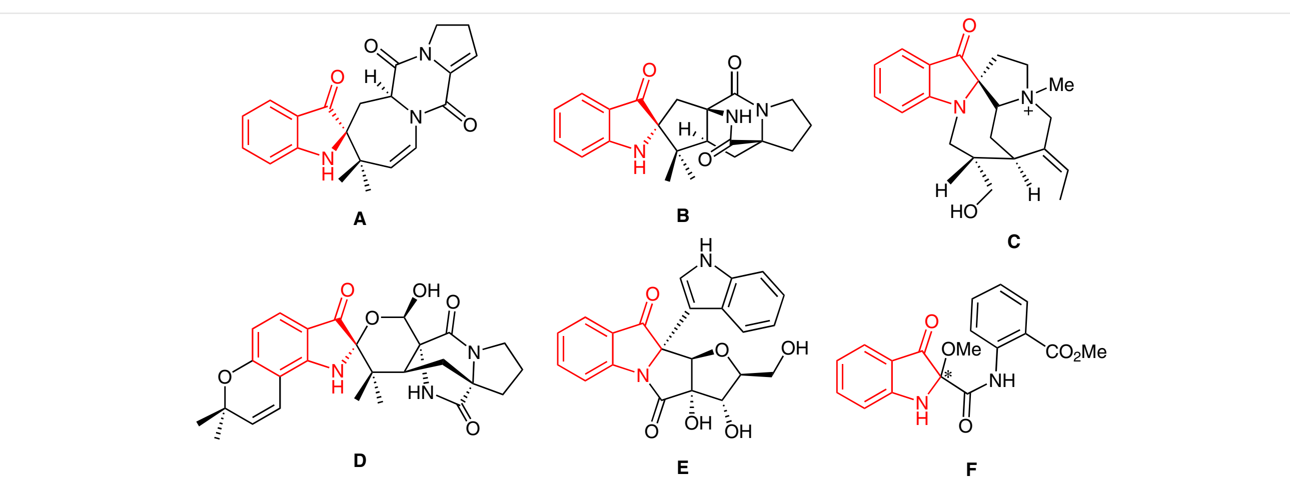
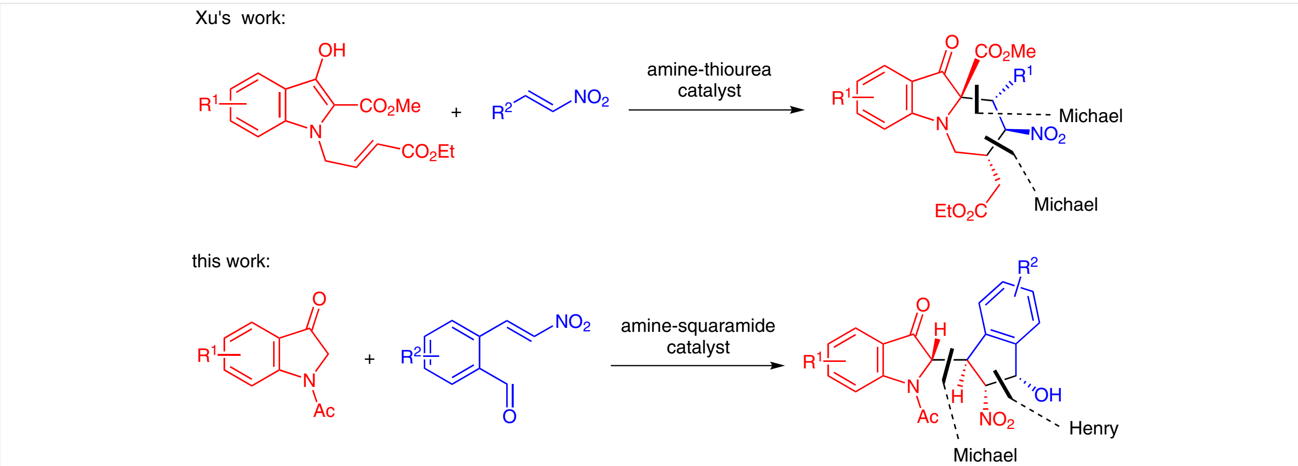


Figure 1 Representative examples of natural products bearing the indolin-3-one unit



Scheme 1 Indolin-3-one in organocatalytic asymmetric domino reactions

an efficient synthetic strategy for providing indolinone as well as indole derivatives.[6–8] However, the indolin-3-ones are less explored substrates in domino reactions.[7] Xu and co-workers have recently reported a thiourea-catalyzed asymmetric domino Michael/Michael reaction between the enol tautomer of indolin-3-ones and nitroolefins to yield functionalized N-fused piperidinoindoline derivatives (Scheme 1).[8] Owing to the wide occurrence of indoline derivatives in natural products and being aware of the catalytic potential of bifunctional amine-squaramide catalysts[9] for asymmetric domino reactions, we herein present an unprecedented squaramide-catalyzed domino Michael/Henry reaction of indolin-3-ones with *o*-formyl-(*E*)-β-nitrostyrenes.

Our group has recently found *o*-formyl-β-nitrostyrenes to be suitable substrates for organocatalytic domino Michael/Henry reactions with more common nucleophiles such as indoles,[10] 2-oxindoles,[9d] and β-dicarbonyl compounds,[9i] which give rise to substituted nitroindanol derivatives in an excellent level of stereoselectivity. We envisaged that 1-acetylindolin-3-ones can be used as nucleophiles to initiate a domino Michael/Henry reaction with *o*-formyl-β-nitrostyrenes to afford indolinone derivatives bearing four vicinal stereocenters. To accomplish this, the reaction of 1-acetylindolin-3-one (**1a**) with the *o*-formyl-(*E*)-β-nitrostyrene (**2a**) in the presence of various bifunctional hydrogen-bonding catalysts (Figure 2) in THF at room temperature was investigated (Table 1). Among the different catalysts screened, the amine-squaramide derived from quinine provided the desired adduct **3a** in 84% yield with 99% ee (Table 1, entry 1). The other squaramides **II**–**IV** also gave good yields of **3a**; however, the enantioselectivity was lower than that of catalyst **I** (entries 2–4). The squaramides **II** and **IV**, though, provided the opposite enantiomer of **3a**. The amine-thiourea **V** and the 6′-OH cinchona alkaloid **VI** led to inferior enantioselectivity than the squaramide cata-

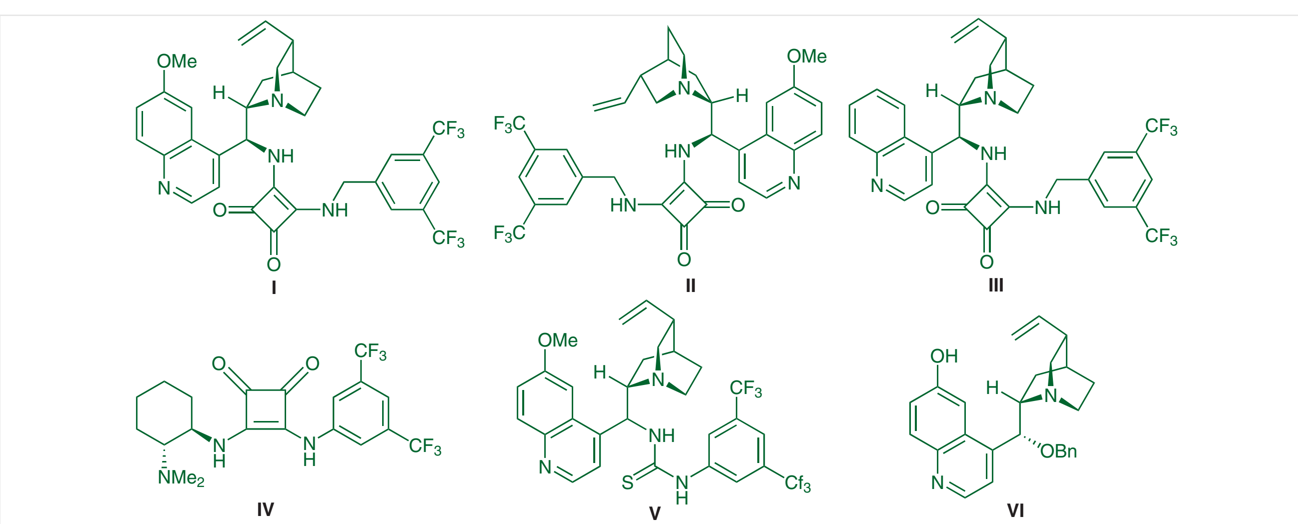
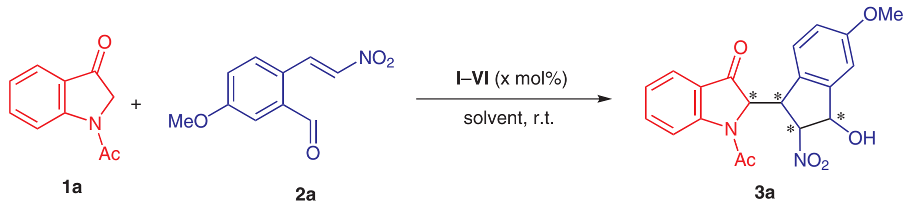


Figure 2 Organocatalysts used

Table 1 Catalyst Screening and Optimization[a]



Entry	Catalyst (x mol%)	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	**I** (2)	THF	20	84	99
2	**II** (2)	THF	20	86	–76[d]
3	**III** (2)	THF	24	78	92
4	**IV** (2)	THF	19	76	–48[d]
5	**V** (2)	THF	20	78	32
6	**VI** (2)	THF	21	64	34
7	**I** (2)	Et_2O	18	85	26
8	**I (2)**	**CH_2Cl_2**	**18**	**91**	**99**
9	**I** (2)	$CHCl_3$	18	82	99
10	**I** (2)	toluene	18	64	29
11	**I** (1)	CH_2Cl_2	24	87	97
12	**I** (0.5)	CH_2Cl_2	36	80	91

[a] Reaction conditions: 1-acetylindolin-3-one (**1a**; 0.2 mmol), *o*-formyl-(*E*)-β-nitrostyrene (**2a**; 0.24 mmol), and catalyst **I–VI** (x mol%) in solvent (0.5 mL) at r.t.
[b] Yield of isolated product after column chromatography.
[c] Enantioselectivity of the major diastereomer (>20:1 dr) determined by HPLC analysis on a chiral stationary phase.
[d] Negative sign indicates the ee of the opposite enantiomer.

lysts (entries 5, 6). Further optimization of the reaction conditions by screening different solvents (entries 7–10) revealed that dichloromethane as solvent affords the product **3a** in a maximum yield of 91% with 99% ee (entry 8). Lowering of the catalyst loading resulted in lower yields and enantioselectivities of **3a** (entries 11, 12). Thus, the best optimized conditions for this domino Michael/Henry reaction include 2 mol% of the catalyst **I** in CH_2Cl_2.

After optimization, the substrate scope was evaluated at a 0.4 mmol scale of 1-acetylindolin-3-ones **1** (Table 2). The *o*-formyl-β-nitrostyrenes bearing electron-donating **2a**,**b** and electron-withdrawing groups **2c** as well as an unsubstituted one **2d** reacted well with 1-acetylindolin-3-one (**1a**) to provide the desired products **3a**–**d** in good yields (68–89%) and with high enantioselectivities (86–99% ee). The 1-acetylindolin-3-ones **1b**–**d** bearing different substituents at the aromatic ring reacted also well under the optimized reaction conditions and afforded the corresponding products **3e**–**i** in 64–90% yield and with 92–99% ee.

The absolute configuration of the indolinone products **3a**–**i** could be assigned as 1*S*,2*R*,3*R*,4*S* via X-ray crystal structure analysis of the product **3a** (Figure 3).[11] The relative configuration of the indoline products **3** was further assigned by ^{1}H NOESY experiments.

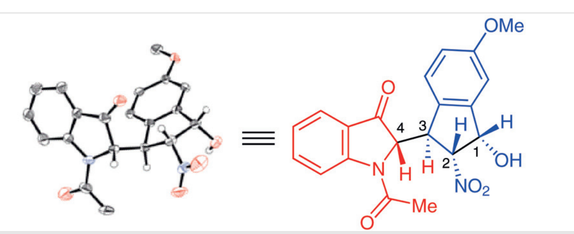
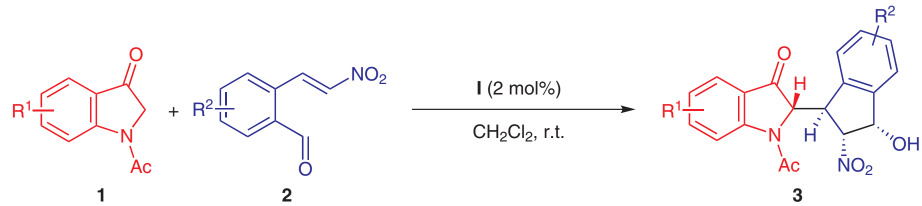


Figure 3 Determination of the absolute configuration of **3a** by the X-ray crystal structure analysis

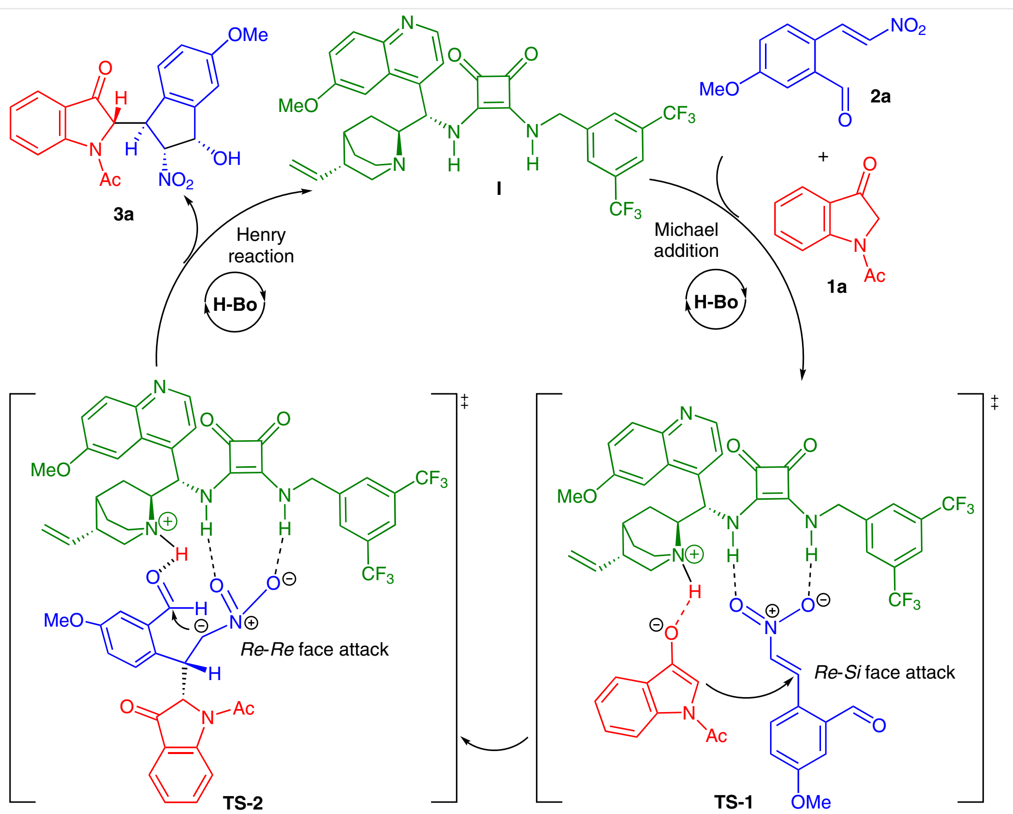
On the basis of the relative and absolute configuration of the products, the mechanism detailed in Scheme 2 is proposed for this domino Michael/Henry reaction. In the plausible transition state **TS-1**, the *o*-formyl-(*E*)-β-nitrostyrene is activated by the squaramide moiety through H-bonding with the nitro group and simultaneously an enolate is generated from the indolin-3-one by the quinuclidine nitrogen, thus facilitating a Michael addition from the *Re*-face of the indolinone to the *Si*-face of the nitroalkene. In **TS-2**, the protonated quinuclidine nitrogen then activates the aldehyde moiety of the *o*-formyl-β-nitrostyrene, which is attacked by the nitronate anion from the *Re*-face to afford the desired configuration of the indolinone product.

Table 2 Substrate Scope[a]



3	R^1	R^2	Time (h)	Yield (%)[b]	ee (%)[c]
a	H (**1a**)	5-MeO (**2a**)	24	89	99
b	H (**1a**)	4,5-(OCH_2O) (**2b**)	24	74	91
c	H (**1a**)	5-Cl (**2c**)	48	68	92
d	H (**1a**)	H (**2d**)	48	70	86
e	6-Cl (**1b**)	5-MeO (**2a**)	48	73	99
f	6-F (**1c**)	5-MeO (**2a**)	24	80	97
g	6-F (**1c**)	H (**2d**)	72	64	94
h	5-CF_3 (**1d**)	5-MeO (**2a**)	27	90	92
i	5-CF_3 (**1d**)	H (**2d**)	24	88	95

[a] Reaction conditions: 1-acetylindolin-3-one **1** (0.4 mmol), *o*-formyl-(*E*)-β-nitrostyrene **2** (0.48 mmol), and catalyst **I** (2 mol%) in CH_2Cl_2 (1.0 mL) at r.t.
[b] Yield of isolated product after column chromatography.
[c] Enantioselectivity of the major diastereomer (>20:1 dr) determined by HPLC analysis on a chiral stationary phase.



Scheme 2 Proposed reaction mechanism

In conclusion, we have developed an efficient asymmetric domino Michael/Henry reaction of indolin-3-ones with *o*-formyl-(*E*)-β-nitrostyrenes. A low loading of the bifunctional amine-squaramide catalyst provides the corresponding indolin-3-ones bearing four vicinal stereocenters in good yields and with excellent diastereo- and enantioselectivities.

All reactions were performed in oven-dried glassware. Analytical TLC was performed using SIL G-25 UV254 from Machery & Nagel and visualized with ultraviolet radiation at 254 nm. ^{1}H and ^{13}C NMR spectra were recorded in acetone-d_6 at r.t. on a Varian Innova 600 or a Varian Innova 400 instrument. Chemical shifts for ^{1}H NMR and ^{13}C NMR are reported in parts per million (ppm), with coupling constants given in hertz (Hz). Standard abbreviations were used to denote the signal multiplicities. The high-resolution mass spectra (HRMS) were acquired on a Finnigan MAT 95 and the ESI spectra on a ThermoFisher Scientific LTQ-Orbitrap XL. IR spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Elemental analyses were performed with a Vario EL elemental analyzer. Analytical HPLC was carried out either on a Hewlett-Packard 1050 series instrument or Agilent 1100 or a Thar SFC Waters Method Station II instrument using chiral stationary phases. Optical rotation values were measured on a Perkin-Elmer 241 polarimeter.

Unless specified, the starting materials and reagents were purchased directly from commercial suppliers and used without further purifications. All solvents used as reaction media were distilled before use. The 1-acetyl-3-indolinones **1a**–**d**[12] and the *o*-formyl-(*E*)-β-nitrostyrenes **2a**–**d**[9a,h,10] as well as the catalysts **I**–**VI**[13–15] were synthesized using the known literature procedures. For HPLC and SFC analysis, the opposite enantiomers of **3a**–**i** were synthesized by using the catalyst **II**.

Compounds 3a–i; General Procedure

In an oven dried round-bottomed flask, a solution of the squaramide catalyst **I** (2 mol%) and 1-acetylindolin-3-one **1** (0.4 mmol) in CH_2Cl_2 (1.0 mL) was stirred at r.t. After 5 min, the *o*-formyl-(*E*)-β-nitrostyrene **2** (0.48 mmol) was added and the stirring was continued until the complete consumption of the reactants was observed by TLC. Then the crude mixture was purified by flash chromatography on silica gel using a gradient of *n*-hexane–EtOAc (9:1 to 1:1) to afford the desired product **3**.

(*S*)-1-Acetyl-2-[(1′*S*,2′*R*,3′*R*)-2′,3′-dihydro-1′-hydroxy-6′-methoxy-2′-nitro-1′*H*-inden-3′-yl]indolin-3-one (3a)

Yield: 136 mg (89%); colorless solid; mp 190–192 °C; $[\alpha]_D^{24}$ +80.4 (*c* = 0.5, acetone).

HPLC: Chiralpak IA column; 214 nm, *n*-heptane–EtOH (7:3), 0.70 mL/min; t_R = 23.60 min (minor), t_R = 35.76 min (major); >20:1 dr, 99% ee.

IR (capillary): 3871, 3383, 2945, 2839, 2657, 2321, 2113, 1779, 1706, 1653, 1605, 1547, 1462, 1380, 1288, 1248, 1193, 1134, 1053, 1021, 924, 883, 817, 751 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.40 (br s, 1 H, ArH), 7.77–7.72 (m, 1 H, ArH), 7.44–7.42 (m, 1 H, ArH), 7.19–7.15 (m, 1 H, ArH), 6.87 (d, *J* = 2.5 Hz, 1 H, ArH), 6.78 (d, *J* = 8.5 Hz, 1 H, ArH), 6.54 (dd, *J* = 8.5, 2.5 Hz, 1 H, ArH), 6.14 (dd, *J* = 6.8, 5.0 Hz, 1 H, $CHNO_2$), 5.63–5.59 (m, 1 H, CHOH), 5.29 (d, *J* = 6.8 Hz, 1 H, CHO*H*), 5.18 (d, *J* = 4.0 Hz, 1 H, C*H*NAc), 4.96–4.94 (m, 1 H, C*H*$CHNO_2$), 3.69 (s, 3 H, OCH_3), 2.60 (s, 3 H, $COCH_3$).

^{13}C NMR (101 MHz, acetone-d_6): δ = 199.0, 170.0, 161.1, 155.1, 144.4, 138.2, 129.5, 126.3, 126.1, 124.8, 123.9, 118.8, 116.6, 110.5, 90.5, 75.0, 66.2, 55.6, 48.3, 24.6.

MS (ESI): *m*/*z* = 405.1 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{18}N_2O_6$ + Na: 405.1057; found: 405.1064.

(*S*)-1-Acetyl-2-[(5′*S*,6′*R*,7′*R*)-6′,7′-dihydro-5′-hydroxy-6′-nitro-5′*H*-indeno[5″,6″-*d*][1″3″dioxol-7′-yl]indolin-3-one (3b)

Yield: 117 mg (74%); colorless solid; mp 198–200 °C; $[\alpha]_D^{24}$ +45.6 (*c* = 0.25, acetone).

HPLC: Chiralpak WHELK-01 column; SFC: 220 nm, MeOH/CO_2, 150 bar, 4.00 mL/min; t_R = 8.21 min (minor), t_R = 9.16 min (major); >20:1 dr, 91% ee.

IR (capillary): 3862, 3628, 3392, 3097, 2949, 2696, 2496, 2298, 2105, 1980, 1910, 1717, 1658, 1546, 1466, 1380, 1280, 1213, 1142, 1090, 1025, 920, 886, 807, 752, 673 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 8.41 (br s, 1 H, ArH), 7.78–7.75 (m, 1 H, ArH), 7.50–7.48 (m, 1 H, ArH), 7.22–7.19 (m, 1 H, ArH), 6.77 (s, 1 H, ArH), 6.32 (s, 1 H, ArH), 6.14–6.12 (m, 1 H, $CHNO_2$), 5.85 (d, *J* = 21.4 Hz, 2 H, OCH_2O), 5.53–5.52 (m, 1 H, C*H*OH), 5.23 (d, *J* = 6.4 Hz, 1 H, CHO*H*), 5.17 (d, *J* = 3.9 Hz, 1 H, C*H*NAc), 4.94–4.92 (m, 1 H, C*H*CH-NO_2), 2.60 (s, 3 H, $COCH_3$).

^{13}C NMR (151 MHz, acetone-d_6): δ = 198.8, 170.1, 149.7, 149.1, 138.3, 136.2, 131.1, 126.1, 125.0, 124.1, 118.9, 106.0, 105.3, 102.5, 90.4, 83.6, 74.5, 66.1, 48.4, 24.6.

MS (ESI): *m*/*z* = 419.2 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{16}N_2O_7$ + Na: 419.0850; found: 419.0852.

(*S*)-1-Acetyl-2-[(1′*S*,2′*R*,3′*R*)-6′-chloro-2′,3′-dihydro-1′-hydroxy-2′-nitro-1′*H*-inden-3′-yl]indolin-3-one (3c)

Yield: 105 mg (68%); colorless solid; mp 136–138 °C; $[\alpha]_D^{24}$ +126.4 (*c* = 0.5, acetone).

HPLC: Chiralpak OJ-H column; SFC: 253 nm, MeOH/CO_2, 153 bar, 4.00 mL/min; t_R = 4.15 min (minor), t_R = 5.41 min (major); >20:1 dr, 92% ee.

IR (capillary): 3841, 3316, 3175, 2935, 2698, 2300, 2099, 1982, 1919, 1711, 1648, 1550, 1462, 1376, 1292, 1190, 1143, 1051, 911, 870, 820, 757, 679 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.35 (br s, 1 H, ArH), 7.76–7.72 (m, 1 H, ArH), 7.44–7.42 (m, 1 H, ArH), 7.34 (d, *J* = 1.8 Hz, 1 H, ArH), 7.19–7.15 (m, 1 H, ArH), 7.02 (dd, *J* = 8.2, 2.1 Hz, 1 H, ArH), 6.94 (d, *J* = 8.2 Hz, 1 H, ArH), 6.16 (dd, *J* = 6.9, 4.4 Hz, 1 H, $CHNO_2$), 5.72–5.68 (m, 1 H, C*H*OH), 5.55 (d, *J* = 6.7 Hz, 1 H, CHO*H*), 5.25 (d, *J* = 4.1 Hz, 1 H, C*H*NAc), 5.01–4.99 (m, 1 H, C*H*$CHNO_2$), 2.62 (s, 3 H, $COCH_3$).

^{13}C NMR (101 MHz, acetone-d_6): δ = 198.8, 170.0, 154.9, 145.3, 138.4, 136.9, 134.6, 129.8, 127.2, 126.2, 126.0, 124.9, 124.0, 118.8, 90.5, 74.7, 66.0, 48.8, 24.6.

MS (ESI): *m*/*z* = 409.1 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{15}ClN_2O_5$ + Na: 409.0562; found: 409.0564.

(*S*)-1-Acetyl-2-[(1′*S*,2′*R*,3′*R*)-2′,3′-dihydro-1′-hydroxy-2′-nitro-1′*H*-inden-3′-yl)]indolin-3-one (3d)

Yield: 98 mg (70%); colorless solid; mp 195–197 °C; $[\alpha]_D^{24}$ +87.2 (*c* = 0.5, acetone).

HPLC: Chiralpak OJ-H column; SFC: 213 nm, MeOH/CO_2, 151 bar, 4.00 mL/min; t_R = 2.95 min (minor), t_R = 4.14 min (major); >20:1 dr, 86% ee.

IR (capillary): 3846, 3344, 2927, 2684, 2494, 2295, 2096, 1928, 1712, 1548, 1456, 1372, 1293, 1033, 891, 752 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 8.42 (br s, 1 H, ArH), 7.77–7.74 (m, 1 H, ArH), 7.43–7.41 (m, 1 H, ArH), 7.34 (d, *J* = 7.6 Hz, 1 H, ArH), 7.19–7.16 (m, 2 H, ArH), 7.00–6.97 (m, 1 H, ArH), 6.89 (d, *J* = 7.0 Hz, 1 H, ArH), 6.17–6.15 (m, 1 H, $CHNO_2$), 5.67–5.65 (m, 1 H, C*H*OH), 5.33 (d, *J* = 6.8 Hz, 1 H, CHO*H*), 5.22 (d, *J* = 4.0 Hz, 1 H, C*H*NAc), 5.06–5.04 (m, 1 H, C*H*CHNO$_2$), 2.62 (s, 3 H, $COCH_3$).

^{13}C NMR (151 MHz, acetone-d_6): δ = 198.8, 170.0, 155.1, 142.8, 138.3, 138.0, 129.9, 129.3, 126.3, 126.1, 125.4, 124.8, 124.0, 118.9, 90.2, 74.9, 66.0, 48.8, 24.6.

MS (ESI): *m*/*z* = 375.1 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{16}N_2O_5$ + Na: 375.0951; found: 375.0964.

(*S*)-1-Acetyl-6-chloro-2-[(1′*S*,2′*R*,3′*R*)-2′,3′-dihydro-1′-hydroxy-6′-methoxy-2′-nitro-1′*H*-inden-3′-yl)]indolin-3-one (3e)

Yield: 121 mg (73%); colorless solid; mp 180–182 °C; $[\alpha]_D^{24}$ +170.4 (*c* = 0.25, acetone).

HPLC: Chiralpak OJ-H column; SFC: 230 nm, MeOH/CO_2, 150 bar, 4.00 mL/min; t_R = 2.14 min (minor), t_R = 3.81 min (major); >20:1 dr, 99% ee.

IR (capillary): 3860, 3645, 3221, 2935, 2696, 2495, 2305, 2107, 1899, 1708, 1647, 1601, 1550, 1429, 1378, 1300, 1260, 1134, 1061, 943, 887, 811, 733 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.51 (br s, 1 H, ArH), 7.43 (d, *J* = 8.2 Hz, 1 H, ArH), 7.20 (dd, *J* = 8.2, 1.8 Hz, 1 H, ArH), 6.88 (d, *J* = 2.5 Hz, 1 H, ArH), 6.80 (d, *J* = 8.6 Hz, 1 H, ArH), 6.60 (dd, *J* = 8.5, 2.5 Hz, 1 H, ArH), 6.13 (dd, *J* = 6.9, 4.9 Hz, 1 H, $CHNO_2$), 5.62–5.58 (m, 1 H, C*H*OH), 5.35 (d, *J* = 6.8 Hz, 1 H, CHO*H*), 5.26 (d, *J* = 3.9 Hz, 1 H, C*H*NAc), 4.95–4.93 (m, 1 H, C*H*CHNO$_2$), 3.70 (s, 3 H, OCH_3), 2.61 (s, 3 H, $COCH_3$).

^{13}C NMR (101 MHz, acetone-d_6): δ = 197.8, 170.4, 161.2, 144.4, 143.6, 129.2, 126.3, 125.3 (2 C), 125.2, 124.80, 119.0, 116.7, 110.6, 90.4, 74.9, 66.7, 55.6, 48.4, 24.4.

MS (ESI): *m*/*z* = 439.1 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{17}ClN_2O_6$ + Na: 439.0667; found: 439.0667.

(*S*)-1-Acetyl-6-fluoro-2-[(1′*S*,2′*R*,3′*R*)-2′,3′-dihydro-1′-hydroxy-6′-methoxy-2′-nitro-1′*H*-inden-3′-yl)]indolin-3-one (3f)

Yield: 160 mg (80%); grey solid; mp 193–195 °C; $[\alpha]_D^{24}$ +93.2 (*c* = 0.5, acetone).

HPLC: Chiralpak AS column; 230 nm, *n*-heptane–EtOH (7:3), 1.00 mL/min; t_R = 9.83 min (minor), t_R = 11.85 min (major); >20:1 dr, 97% ee.

IR (capillary): 3847, 3634, 3419, 2936, 2692, 2505, 2284, 2201, 2104, 1981, 1705, 1659, 1606, 1547, 1484, 1441, 1373, 1247, 1131, 1045, 968, 876, 818, 735, 662 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.18 (br s, 1 H, ArH), 7.50 (dd, *J* = 8.5, 5.9 Hz, 1 H, ArH), 6.96 (td, *J* = 8.7, 2.3 Hz, 1 H, ArH), 6.88 (d, *J* = 2.5 Hz, 1 H, ArH), 6.79 (d, *J* = 8.5 Hz, 1 H, ArH), 6.60 (dd, *J* = 8.5, 2.5 Hz, 1 H, ArH), 6.14 (dd, *J* = 6.9, 4.9 Hz, 1 H, $CHNO_2$), 5.61 (d, *J* = 4.5 Hz, 1 H, C*H*OH), 5.31–5.25 (m, 2 H, CHO*H*, C*H*NAc), 4.96–4.94 (m, 1 H, C*H*CH-NO$_2$), 3.70 (s, 3 H, OCH_3), 2.61 (s, 3 H, $COCH_3$).

^{13}C NMR (101 MHz, acetone-d_6): δ = 197.2, 170.3, 169.1, 161.2, 144.4, 129.2, 126.4, 126.3 (2 C), 122.8, 116.6, 112.8, 110.6, 106.2, 90.4, 74.9, 66.8, 55.6, 48.3, 24.4.

MS (ESI): *m*/*z* = 423.1 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{17}FN_2O_6$ + Na: 423.0963; found: 423.0973.

(*S*)-1-Acetyl-6-fluoro-2-[(1′*S*,2′*R*,3′*R*)-2′,3′-dihydro-1′-hydroxy-2′-nitro-1′*H*-inden-3′-yl]indolin-3-one (3g)

Yield: 94 mg (64%); colorless solid; mp 192–194 °C; $[\alpha]_D^{24}$ +59.6 (*c* = 0.5, acetone).

HPLC: Chiralpak OJ-H column; SFC: 230 nm, MeOH/CO_2, 152 bar, 4.00 mL/min; t_R = 2.3 min (minor), t_R = 3.09 min (major); >20:1 dr, 94% ee.

IR (capillary): 3853, 3281, 3089, 2940, 2663, 2466, 2286, 2201, 2103, 1982, 1665, 1605, 1551, 1442, 1376, 1251, 1178, 1094, 1014, 960, 876, 803, 754 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 8.18 (br s, 1 H, ArH), 7.49 (dd, *J* = 8.5, 5.9 Hz, 1 H, ArH), 7.35 (d, *J* = 7.5 Hz, 1 H, ArH), 7.21–7.19 (m, 1 H, ArH), 7.05–7.03 (m, 1 H, ArH), 6.97–6.90 (m, 2 H, ArH), 6.16 (dd, *J* = 6.5, 5.5 Hz, 1 H, $CHNO_2$), 5.66–5.64 (m, 1 H, C*H*OH), 5.38 (d, *J* = 6.8 Hz, 1 H, C*H*OH), 5.30 (d, *J* = 3.9 Hz, 1 H, C*H*NAc), 5.05–5.04 (m, 1 H, C*H*CH-NO$_2$), 2.63 (s, 3 H, $COCH_3$).

^{13}C NMR (101 MHz, acetone-d_6): δ = 197.0, 170.4, 169.2, 142.9, 137.8, 130.0, 129.4 (2 C), 126.4, 126.3, 125.4, 122.8, 112.8, 106.2, 90.0, 74.9, 66.62, 48.9, 24.4.

MS (ESI): *m*/*z* = 393.1 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{15}FN_2O_5$ + Na: 393.0857; found: 393.0859.

(*S*)-1-Acetyl-5-(trifluoromethyl)-2-[(1′*S*,2′*R*,3′*R*)-2′,3′-dihydro-1′-hydroxy-6′-methoxy-2′-nitro-1′*H*-inden-3′-yl]indolin-3-one (3h)

Yield: 162 mg (90%); grey solid; mp 107–109 °C; $[\alpha]_D^{24}$ +75.2 (*c* = 0.25, acetone).

HPLC: Chiralpak AD column; 230 nm, *n*-heptane–*i*-PrOH (7:3), 1.00 mL/min; t_R = 9.72 min (minor), t_R = 15.55 min (major); >20:1 dr, 92% ee.

IR (capillary): 3850, 3402, 2947, 2676, 2498, 2317, 2102, 1927, 1719, 1675, 1626, 1551, 1494, 1448, 1320, 1264, 1122, 1047, 920, 837, 757, 681 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.63 (d, *J* = 8.3 Hz, 1 H, ArH), 8.08–8.05 (m, 1 H, ArH), 7.70 (dd, *J* = 1.3, 0.7 Hz, 1 H, ArH), 6.89 (d, *J* = 2.4 Hz, 1 H, ArH), 6.79 (d, *J* = 8.5 Hz, 1 H, ArH), 6.56 (dd, *J* = 8.5, 2.5 Hz, 1 H, ArH), 6.14 (dd, *J* = 6.9, 4.8 Hz, 1 H, $CHNO_2$), 5.64–5.61 (m, 1 H, C*H*OH), 5.37–5.35 (m, 2 H, CHO*H*, C*H*NAc), 4.99–4.97 (m, 1 H, C*H*CHNO$_2$), 3.68 (s, 3 H, OCH_3), 2.65 (s, 3 H, $COCH_3$).

^{13}C NMR (101 MHz, acetone-d_6, major diastereomer): δ = 198.3, 170.6, 161.2, 157.2, 144.5, 134.8, 129.2, 126.2 (2 C), 126.1, 124.7, 121.1, 119.7, 116.7, 110.7, 90.5, 75.0, 67.0, 55.6, 48.4, 24.6.

MS (ESI): *m*/*z* = 449.1 [M]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{17}F_3N_2O_6$ + Na: 473.0931; found: 473.941.

(*S*)-1-Acetyl-5-(trifluoromethyl)-2-[(1′*S*,2′*R*,3′*R*)-2′,3′-dihydro-1′-hydroxy-2′-nitro-1′*H*-inden-3′-yl]indolin-3-one (3i)

Yield: 148 mg (88%); grey solid; mp 195–196 °C; $[\alpha]_D^{24}$ +80.2 (*c* = 0.5, acetone).

HPLC: Chiralpak OJ-H column; SFC: 254 nm, MeOH/CO_2, 148 bar, 4.00 mL/min; t_R = 2.05 min (minor), t_R = 3.24 min (major); >20:1 dr, 95% ee.

IR (capillary): 3861, 3400, 2947, 2665, 2515, 2299, 2095, 1938, 1719, 1667, 1549, 1373, 1320, 1269, 1216, 1129, 1049, 919, 844, 759, 679 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.63 (d, *J* = 8.2 Hz, 1 H, ArH), 8.07 (dd, *J* = 8.6, 1.8 Hz, 1 H, ArH), 7.69 (dd, *J* = 1.3, 0.7 Hz, 1 H, ArH), 7.36 (d, *J* = 7.2 Hz, 1 H, ArH), 7.21–7.18 (m, 1 H, ArH), 7.03–6.99 (m, 1 H, ArH), 6.91 (d, *J* = 7.6 Hz, 1 H, ArH), 6.15 (dd, *J* = 6.9, 5.0 Hz, 1 H, CH-NO_2), 5.69–5.65 (m, 1 H, CHOH), 5.40 (d, *J* = 4.0 Hz, 1 H, CHO*H*), 5.36 (d, *J* = 6.8 Hz, 1 H, CHNAc), 5.09–5.07 (m, 1 H, CHCHNO_2), 2.67 (s, 3 H, $COCH_3$).

^{13}C NMR (101 MHz, acetone-d_6): δ = 198.2, 170.6, 142.9, 137.7, 134.8, 130.0 (2 C), 129.5, 126.4 (2 C), 126.2, 126.1, 125.4 (2 C), 121.1, 119.7, 90.2, 75.0, 66.8, 49.0.

MS (ESI): *m*/*z* = 419.1 [M – H]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{15}F_3N_2O_5$ + Na: 443.0825; found: 443.0834.

Acknowledgment

We gratefully thank the European Research Council for funding this project with an ERC Advanced Grant 320493 'DOMINOCAT' and BASF SE for the donation of chemicals.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379943.

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