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

Suruchi Mahajan
Pankaj Chauhan
Charles C. J. Loh
Server Uzungelis
Gerhard Raabe
Dieter Enders*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
enders@rwth-aachen.de

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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.\(^3\)

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
an efficient synthetic strategy for providing indolinone as well as indole derivatives. However, the indolin-3-ones are less explored substrates in domino reactions. 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). Owing to the wide occurrence of indoline derivatives in natural products and being aware of the catalytic potential of bifunctional amine-squaramide catalysts for asymmetric domino reactions, we herein present an unprecedented squaramide-catalyzed domino Michael/Henry reaction of indolin-3-ones with \( \text{o-formyl-}(E)\)-\( \beta \)-nitrostyrenes.

Our group has recently found \( \text{o-formyl-}(E)\)-\( \beta \)-nitrostyrenes to be suitable substrates for organocatalytic domino Michael/Henry reactions with more common nucleophiles such as indoles, 2-oxindoles, and \( \beta \)-dicarbonyl compounds, 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 \( \text{o-formyl-}(E)\)-\( \beta \)-nitrostyrenes to afford indolinone derivatives bearing four vicinal stereocenters. To accomplish this, the reaction of 1-acetylindolin-3-one (1a) with the \( \text{o-formyl-}(E)\)-\( \beta \)-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-

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

![Scheme 1](image-url)

**Figure 2** Organocatalysts used

![Figure 2](image-url)
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$_2$Cl$_2$.

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 indoline products 3a–i could be assigned as 1S,2R,3R,4S via X-ray crystal structure analysis of the product 3a (Figure 3). 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 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 Scopea

<table>
<thead>
<tr>
<th></th>
<th>R¹</th>
<th>R²</th>
<th>Time (h)</th>
<th>Yield (%)b</th>
<th>ee (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>5-MeO (2a)</td>
<td>24</td>
<td>89</td>
<td>99</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>4,5-(OCH₂O) (2b)</td>
<td>24</td>
<td>74</td>
<td>91</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>5-Cl (2c)</td>
<td>48</td>
<td>68</td>
<td>92</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>H (2d)</td>
<td>48</td>
<td>70</td>
<td>86</td>
</tr>
<tr>
<td>e</td>
<td>6-Cl (1b)</td>
<td>5-MeO (2a)</td>
<td>48</td>
<td>73</td>
<td>99</td>
</tr>
<tr>
<td>f</td>
<td>6-F (1c)</td>
<td>5-MeO (2a)</td>
<td>24</td>
<td>80</td>
<td>97</td>
</tr>
<tr>
<td>g</td>
<td>6-F (1c)</td>
<td>H (2d)</td>
<td>72</td>
<td>64</td>
<td>94</td>
</tr>
<tr>
<td>h</td>
<td>5-CF₃ (1d)</td>
<td>5-MeO (2a)</td>
<td>27</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>i</td>
<td>5-CF₃ (1d)</td>
<td>H (2d)</td>
<td>24</td>
<td>88</td>
<td>95</td>
</tr>
</tbody>
</table>

* 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 CH₂Cl₂ (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 α-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 Macherey & Nagel and visualized with ultraviolet radiation at 254 nm. 1H and 13C NMR spectra were recorded in acetone-d6 at rt. on a Varian Inova 600 or a Varian Inova 400 instrument. Chemical shifts for 1H NMR and 13C 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 a Varian IIc. 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–d13 and the α-formyl-(E)-β-nitrostyrenes 2a–d14,10 as well as the catalysts 1–VI11,12 were synthesized using the known literature procedures. For HPLC and SFC analysis, 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-heptane–EtOH (7:3), 0.70 ml/min; tR = 23.60 min (minor), tR = 35.76 min (major); >20:1 dr, 99% ee.


In an oven dried round-bottomed flask, a solution of the squaramide catalyst I (2 mol%) and 1-acetylindolin-3-one (0.4 mmol) in CH2Cl2 (1.0 mL) was stirred at rt. After 5 min, the α-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-heptane–EtOAc (9:1 to 1:1) to afford the desired product 3.

(5)-1-Acetyl-2-[(5′S,6′R,7′R)-6′,7′-dihydro-5′-hydroxy-6′-methoxy-2′-nitro-1′H-inden-3′-yl]indolin-3-one (3a)

Yield: 136 mg (89%); colorless solid; mp 190–192 °C; [α]D24 +60.4 (c = 0.5, acetone).

IR (capillary): 3841, 3316, 3175, 2935, 2958, 2300, 2099, 1820, 1219, 1171, 1684, 1550, 1462, 1376, 1292, 1190, 1143, 1051, 911, 870, 820, 757, 679 cm–1.

(5)-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; [α]D +87.2 (c = 0.5, acetone).

HPLC: Chiralpak OJ-H column; SFC: 213 nm, MeOH/CO2 = 151 bar, 4.00 ml/min; tR = 2.95 min (minor), tR = 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.

1H NMR (600 MHz, acetone-δ): 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, CHNO₂), 5.67–5.65 (m, 1 H, CHO), 5.33 (d, J = 6.8 Hz, 1 H, CHO), 5.22 (d, J = 4.0 Hz, 1 H, CHCN), 5.06–5.04 (m, 1 H, CHCH₂O), 2.62 (s, 3 H, COCH₃).

13C NMR (151 MHz, acetone-δ): 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⁺].


(5)-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 (3g)

Yield: 94 mg (64%); colorless solid; mp 192–194 °C; [α]D +59.6 (c = 0.5, acetone).

HPLC: Chiralpak OJ-H column; SFC: 230 nm, MeOH/CO₂ = 152 bar, 4.00 ml/min; tR = 2.3 min (minor), tR = 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, 873, 803, 754 cm⁻¹.

1H NMR (600 MHz, acetone-δ): 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, CHNO₂), 5.66–5.64 (m, 1 H, CHOH), 5.38 (d, J = 6.8 Hz, 1 H, CHOH), 5.30 (d, J = 3.9 Hz, 1 H, CHCN), 5.05–5.04 (m, 1 H, CHCH₂O), 2.63 (s, 3 H, COCH₃).

13C NMR (101 MHz, acetone-δ): 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, 66.2, 48.9, 24.4.

MS (esi): m/z = 393.1 [M + Na⁺].


(5)-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; [α]D +75.2 (c = 0.25, acetone).

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

IR (capillary): 3850, 3402, 2947, 2676, 2498, 2317, 2102, 1927, 1719, 1675, 1526, 1551, 1494, 1448, 1320, 1264, 1122, 1047, 920, 837, 757, 681 cm⁻¹.

1H NMR (400 MHz, acetone-δ): 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 = 2.5 Hz, 1 H, ArH), 6.79 (d, J = 8.5 Hz, 1 H, ArH), 6.65 (dd, J = 8.5, 2.5 Hz, 1 H, ArH), 6.14 (dd, J = 6.9, 4.9 Hz, 1 H, CHNO₂), 5.64–5.61 (m, 1 H, CHOH), 5.37–5.35 (m, 2 H, CHOH, CHCN), 4.99–4.97 (m, 1 H, CHCH₂O), 3.68 (s, 3 H, OCH₃), 2.65 (s, 3 H, COCH₃).

13C NMR (101 MHz, acetone-δ): δ = 198.3, 170.6, 161.2, 157.2, 144.5, 134.8, 129.2, 126.2 (2 C), 126.1, 124.7, 127.1, 112.1, 119.7, 116.7, 110.7, 90.3, 75.0, 67.0, 55.0, 48.4, 24.6.

MS (esi): m/z = 449.1 [M⁺].

1H NMR (400 MHz, acetone-\textit{d}_6): \( \delta = 8.63 \) (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\textsubscript{2}), 5.69–5.65 (m, 1 H, CHO\textsubscript{H}), 5.49 (d, \( J = 4.0 \) Hz, 1 H, CHOH), 5.36 (d, \( J = 6.8 \) Hz, 1 H, CHNAc), 5.09–5.07 (m, 1 H, CHCH\textsubscript{NO\textsubscript{2}}), 2.67 (s, 3 H, COCH\textsubscript{3}).

13C NMR (101 MHz, acetone-\textit{d}_6): \( \delta = 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.

IR (capillary): 3861, 3400, 2947, 2665, 2515, 2299, 2095, 1938, 1719, 1674, 1647, 1549, 1373, 1269, 1216, 1129, 1049, 919, 844, 759, 679 cm\textsuperscript{-1}.

HRMS (ESI): \( m/z = 419.1 \) [M – H\textsuperscript{+}].

HRMS (ESI): \( m/z = [M + Na]^+ \) calcd for C\textsubscript{29}H\textsubscript{25}F\textsubscript{3}N\textsubscript{2}O\textsubscript{3} + Na: 443.0825; found: 443.0834.

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Supporting Information
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References


(11) CDCDC-1035962 (for 3a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from
the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk.


