Asymmetric Synthesis of Oxa-spirocyclic Indanones with Structural Complexity via an Organocatalytic Michael–Henry–Acetalization Cascade

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Abstract: The highly enantioselective preparation of drug-like oxa-spirocyclic indanone derivatives employing a multicomponent cascade reaction is described. This approach utilizes an organocatalytic Michael reaction followed by a Henry–acetalization sequence that yields the desired chiral spirocyclic backbone, bearing four contiguous stereogenic centers and multiple functional groups, in good yields and high stereoselectivities (up to 99% ee and 95:5 dr).

Key words: organocatalysis, chiral indanone, oxa-spirocycles, tandem reactions, asymmetric synthesis

Chiral indanone is a commonly occurring framework found in many natural products and pharmaceuticals.1 A range of biologically active compounds possessing this privileged scaffold are well documented.2 For instance, tripartin, a new dichlorinated indanone found in actinomycete bacteria, displays a potent and specific histone demethylase inhibiting effect.2a The natural indanone products, pterosin C and paucifloral F, were isolated from the aerial parts of Acrostichum aureum2b and the stem barks of Vatica pauciflora,2c respectively. The recent discovery of spiroindanone-based hybrid molecule and its analogues, which are able to decrease the intracellular level of Bcl-2 protein in leukemia cells,2d makes them potential leads for development as new anticancer agents (Figure 1). However, most biological studies of indanone and its congeners have concentrated on plant models. Consequently, relatively little is known about the potential benefits of these molecules to human health. Thus, optically active indanone analogues, particularly spiroindanone derivatives, have emerged as important synthetic targets due to their diverse architectures and potential medicinal utility.

In 2008, the groups of Yavari and Nair independently employed quinoline, dialkyl acetylenedicarboxylates and 1,3-indanedione to access spirocyclic molecules comprising of indanone and tetrahydropyrrolo[1,2-a]quinoline.3 In the same year, Li and co-workers described a tandem Knoevenagel–1,3-dipolar cycloaddition cascade for a four-component synthesis of five-membered aza-spiroacylic indanediones.4 Furthermore, Marini’s group5 reported an enantioselective one-pot synthesis of spiroindanones bearing an all-carbon chiral center at the C2 position by subjecting cyclic β-ketoesters and vinyl selenones to an organo-catalyzed Michael–cyclization sequence. Subsequently, Ramachary et al. presented the asymmetric synthesis of a spiroindane-1,3-dione skeleton incorporated with cyclohexane through a reflexive Michael reaction.6 Although most efficient methods available in the literature have focused on the synthesis of diversely structured spiroindanones bearing an all-carbon ring or nitrogen heterocycle at the C2 position, the enantioselective preparation of the corresponding oxa-spirocyclic indanones remains underdeveloped.7

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As part of our ongoing investigations aimed at stereoselectively assembling multiple substrates into synthetically important cyclic molecules, we envisaged a three-step organocatalytic relay cascade for the asymmetric synthesis of the oxa-spiroindanone scaffold. Mechanistically, the new protocol (Scheme 1) consists of an initial secondary amine catalyzed Michael addition of aldehyde 1 to the nitroalkene 2. The resulting intermediate 4 would then be poised to participate directly in the second catalytic cycle by serving as the donor in a base-promoted Henry reaction with the ninhydrin 5. Subsequent cyclization via an intramolecular acetalization of the carbonyl and hydroxy group of the tertiary alcohol intermediate forms the desired spiro-hemiacetal 6. Herein, we report the results of our experiments performed to demonstrate this domino reaction as an efficient method for the preparation of chiral oxa-spirocyclic indanones.

We selected propanal (1a), nitrostyrene (2a) and ninhydrin (5) as the model substrates to examine the feasibility of the designed process. The first Michael reaction proceeded in the presence of catalyst 3a (10 mol%) in acetonitrile at room temperature for three hours. An acetonitrile solution of ninhydrin (5) and triethylamine was added, resulting in successive Henry and acetalization reactions. To our gratification, the domino reaction proceeded smoothly to afford the desired product 6a. Direct oxidation of the hemiacetal with pyridinium chlorochromate (PCC) gave the corresponding more stable spirocyclic δ-lactone 7a in moderate yield and with good stereoselectivity.

Table 1 Optimization of the Catalytic Asymmetric Synthesis of Oxa-spirocyclic Indanone 7a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Base</th>
<th>Yield (%)</th>
<th>dr (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>MeCN</td>
<td>Et3N</td>
<td>41</td>
<td>78:22</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>MeCN</td>
<td>Et3N</td>
<td>35</td>
<td>80:20</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>MeCN</td>
<td>Et3N</td>
<td>25</td>
<td>78:22</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>MeCN</td>
<td>Et3N</td>
<td>30</td>
<td>85:15</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>3a</td>
<td>CH2Cl2</td>
<td>Et3N</td>
<td>43</td>
<td>80:20</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>3a</td>
<td>THF</td>
<td>Et3N</td>
<td>30</td>
<td>75:25</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>3a</td>
<td>toluene</td>
<td>Et3N</td>
<td>63</td>
<td>82:18</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>3a</td>
<td>toluene</td>
<td>K2CO3</td>
<td>54</td>
<td>75:25</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>3a</td>
<td>toluene</td>
<td>NaOH</td>
<td>48</td>
<td>80:20</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>3a</td>
<td>toluene</td>
<td>DBU</td>
<td>92</td>
<td>9:83</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>3a</td>
<td>toluene</td>
<td>DBU</td>
<td>43</td>
<td>90:10</td>
<td>90</td>
</tr>
</tbody>
</table>

Reactions were performed with 1a (0.4 mmol), 2a (0.30 mmol), 3 (10 mol%) and AcOH in solvent (2 mL) at r.t. for 3 h, after which 5 (0.2 mmol) and base (0.6 mmol) were added.

Yield of isolated pure diastereomer 7a.

Calculated from the yield of isolated 7a and its diastereomer.

Determined by chiral HPLC analysis.

H2O (0.4 mL) and TBAB (0.05 mmol) were added.

At 50 °C for 1 h.
tivity (Table 1, entry 1). Subsequently, several chiral secondary amine catalysts were tested. The triethylsilyloxy (O-TES) ether 3b provided an equally good enantiomeric excess, but without any improvement in the reactivity (Table 1, entry 2). High enantiocontrol was also achieved when catalyst 3c containing electron-withdrawing substituents, or 3d possessing bulkier groups were applied, but slower reaction rates were observed (Table 1, entries 3 and 4). With optimum catalyst 3a identified, we continued to screen solvents and other reaction parameters. It was found that the reaction medium had little influence on the reaction efficiency (Table 1, entries 5–7), and toluene proved to be the best choice. Importantly, further investigation revealed that a strong base was a crucial factor for improving the diastereoselectivity (Table 1, entries 8–10).

We propose that the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) promoted deprotonation of the diastereoisomer 6a′, and selective reprotonation of the resulting carbanion by chiral induction to furnish 6a could be responsible for the stereoconversion and high diastereomeric ratio (Table 1, entry 10). Good diastereoccontrol was also realized on raising the temperature, but a lower yield was obtained (Table 1, entry 11).

With optimized reaction conditions in hand, we next evaluated the generality of this methodology. As illustrated in Scheme 2, the reaction showed excellent functional group tolerance, and the respective polyfunctionalized oxa-spirocyclic products were obtained in moderate to good yields (up to 72% yield), with high enantio- and diastereoselectivities (up to 99% ee and 95:5 dr). For example, incorporation of one or two substituents on the aromatic ring of nitroalkene 2 had little effect on the efficiency and stereochemical outcome of this cyclization reaction. Moreover, both electron-withdrawing and electron-donating groups at ortho, meta, or para positions in substrates 2 were tolerated, affording the expected domino adducts 7b–g. Nitroolefins bearing β-heteroaromatic or alkyl groups could also be used to give the target products 7h–j, albeit with slightly lower yields and diastereomeric ratios. With respect to the nucleophilic aldehyde, both linear n-butanal and n-pentanal were shown to be compatible under our standard conditions (7k and 7l) in Scheme 2. 

\[ \text{Scheme 2} \quad \text{Investigation of the scope of the cascade reaction using the optimized conditions (see entry 10 and footnote a in Table 1). Yields are those of isolated pure diastereomers 7; enantiomeric excesses were determined by chiral HPLC analysis; diastereomeric ratios were calculated from the yields of isolated compounds 7 and their diastereomers.} \]

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addition to propanal. We also evaluated the use of the branched α,β-unsaturated aldehyde, 4-methylpent-2-enal via α-selective dienamine catalysis, which led to the formation of the desired allyl-substituted spiro-indanone 7m in a somewhat lower yield, but still with good levels of stereocontrol. The absolute configuration of 7b was determined to be 10S,11S,12R by X-ray crystallographic analysis (Figure 2). The absolute configurations of the other products were tentatively assigned by analogy.

![Figure 2 ORTEP drawing of compound 7b](image)

To further probe the usefulness of this organocatalytic domino reaction in diversity-oriented synthesis, other cyclic activated carbonyl substrates were screened (Scheme 3). We were pleased to find that the synthetically useful substrates, acenaphthenequinone and alloxan reacted smoothly under our experimental conditions to provide the corresponding cycloaddition products 8 and 9 in good yields and with excellent enantioselectivities.

![Scheme 3 Organocatalytic domino reactions with other activated carbonyl compounds](image)

More importantly, these oxaspirocyclic compounds can be easily converted into other important and valuable building blocks. As shown in Scheme 4, the hemiaminal 6a was dehydroxylated by treatment with triethylsilane and boron trifluoride–diethyl etherate, using dichloromethane as the solvent at −20 °C, to provide the chiral spirocyclic tetrahydropyran 10. Intriguingly, although the allylic product 6m has a crowded structure, the multiple functionalities allow simple transformation to access natural product mimics with greater molecular complexity.

![Scheme 4 Synthetic transformations to access different and valuable oxaspirocyclic scaffolds](image)

In conclusion, we have successfully developed an organocatalytic cascade reaction involving a Michael–Henry–acetalization relay for the asymmetric assembly of aldehydes, nitroolefins and ninyhydrin into six-membered oxaspiroindanones with structural and stereochemical complexity. The mild reaction conditions, short reaction times, and high tolerance of various functional groups makes this strategy an attractive method for the construction of enanto-enriched architectures. Currently, studies toward the application of this methodology for the synthesis of pharmaceutically important drug leads are ongoing.

All chemicals were used from Adams-beta without purification unless otherwise noted. NMR data was obtained for 1H at 400 MHz, and for 13C at 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in CDCl3 solution. ESI HRMS was recorded on a Waters SYNAPT G2.

**General Procedure for the Synthesis of Compounds 7a-m**

The reaction was carried out with aldehyde 1 (0.4 mmol) and nitroolefin 2 (0.3 mmol) in the presence of catalyst 3a (0.04 mmol) and AcOH (0.04 mmol) in toluene (2.0 mL) at r.t. for 3 h to afford the Michael adduct 4. When the reaction was complete, the toluene solution of ninyhydrin 5 (0.2 mmol) and DBU (0.6 mmol) was added in one pot. The reaction mixture was stirred at r.t. for the specified reaction time until the reaction was complete (monitored by TLC). Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (PE–EtOAc, 30:1) to give hemiacetal 6. To a solution of 6 in CH2Cl2 (2 mL) was added PCC (0.5 mmol). The mixture was stirred for 2 h at 50 °C. The solid was removed by filtration through Celite. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (PE–EtOAc, 20:1) to give spiroindanone δ-lactone 7.

**Typical Analytical Data**

7a was obtained as a white solid in 70% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 93% by HPLC on Chiralpak OD-H column (30% 2-ProH–n-hexane, 1 mL/min), UV 254 nm, t_{Rmax} = 11.05 min, t_{Rmin} = 12.11 min. Mp 167–168 °C; [α]D20 = −129.4 (c = 0.12 in CH2Cl2). 1H NMR (400 MHz, CDCl3): δ = 8.12–8.05 (m, 2 H), 7.58–7.44 (m, 2 H), 6.88–6.78 (m, 2 H), 6.68 (s, 1 H), 4.91 (s, 1 H), 3.96–3.80 (m, 2 H), 3.58–3.51 (m, 2 H), 2.16–2.02 (m, 1 H), 1.74–1.58 (m, 1 H), 1.43–1.31 (m, 1 H), 1.26–1.15 (m, 1 H), 0.86–0.78 (m, 3 H), 0.72–0.64 (m, 3 H), 0.59–0.51 (m, 3 H).

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8.01–7.94 (m, 2 H), 7.40–7.34 (m, 3 H), 7.27–7.26 (m, 2 H), 5.64 (d, J = 12.0 Hz, 1 H), 4.16 (t, J = 12.0 Hz, 1 H), 3.10–3.02 (m, 1 H), 1.39 (d, J = 6.8 Hz, 3 H). 13C NMR (100 MHz, CDCl3): δ = 192.31, 190.03, 169.62, 141.15, 140.18, 138.00, 137.48, 135.43, 129.51, 129.05, 127.77, 124.99, 124.72, 87.28, 46.58, 41.42, 14.74. HRMS (ESI) calcd for C20H15NO6+: 388.0797; found: 388.0795.

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