

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

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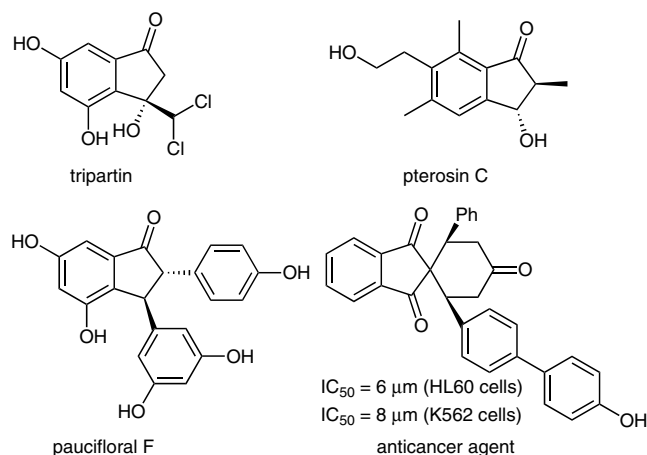
**Abstract:** The highly enantioselective preparation of drug-like oxa-spirocyclic indanone derivatives employing a multicomponent cascade reaction is described. This approach utilizes an organocatalytic Michael reaction followed by a Henry–acetalization sequence that yields the desired chiral spirocyclic 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.<sup>1</sup> A range of biologically active compounds possessing this privileged scaffold are well documented.<sup>2</sup> For instance, tripartin, a new dichlorinated indanone found in actinomycete bacteria, displays a potent and specific histone demethylase inhibiting effect.<sup>2a</sup> The natural indanone products, pterisin C and paucifloral F, were isolated from the aerial parts of *Acrostichum aureum*<sup>2b</sup> and the stem barks of *Vatica pauciflora*,<sup>2c</sup> 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,<sup>2d</sup> 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.<sup>3</sup> 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-spirocyclic

indanediones.<sup>4</sup> Furthermore, Marini's group<sup>5</sup> reported an enantioselective one-pot synthesis of spiroindanones bearing an all-carbon chiral center at the C2 position by subjecting cyclic  $\beta$ -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.<sup>6</sup> 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.<sup>7</sup>

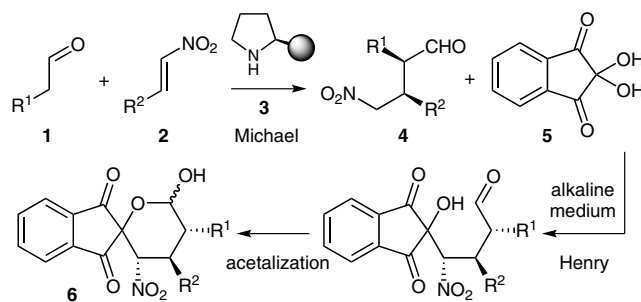


**Figure 1** Selected examples of biologically active indanones

The development of multicomponent organocatalytic tandem reactions for introducing multi-chiral centers has been hotly pursued.<sup>8</sup> A chiral  $\gamma$ -nitro aldehyde, easily prepared from the asymmetric direct Michael reaction of an aldehyde and a nitroalkene,<sup>9</sup> has been utilized successfully in subsequent domino transformations with enal,<sup>10</sup> imine<sup>11</sup> or saturated aldehyde<sup>12</sup> substrates for the synthesis of enantio-enriched monocyclic compounds. Nevertheless, very few examples demonstrate the analogous application with a ketone for the synthesis of a chiral spiro skeleton.

As part of our ongoing investigations aimed at stereoselectively assembling multiple substrates into synthetically important cyclic molecules,<sup>13</sup> 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.

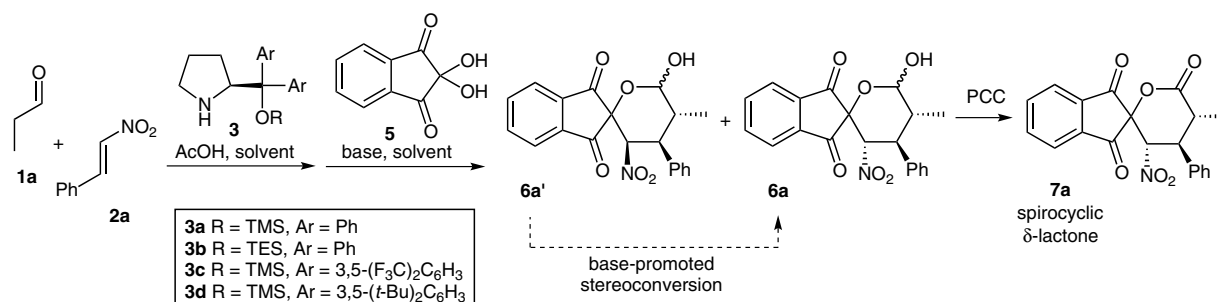
We selected propanal (**1a**), nitrostyrene (**2a**) and ninhydrin (**5**) as the model substrates to examine the feasibility of the designed process. The first Michael reaction proceeded in the presence of catalyst **3a** (10 mol%) in aceto-



**Scheme 1** Reaction design: the asymmetric synthesis of the oxa-spiroindanone scaffold through [2+2+2] cycloaddition

nitrile 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  $\delta$ -lactone **7a** in moderate yield and with good stereoselec-

**Table 1** Optimization of the Catalytic Asymmetric Synthesis of Oxa-spirocyclic Indanone **7a**<sup>a</sup>



Entry	Catalyst	Solvent	Base	Yield (%) <sup>b</sup>	dr <sup>c</sup>	ee (%) <sup>d</sup>
1	<b>3a</b>	MeCN	Et <sub>3</sub> N	41	78:22	91
2	<b>3b</b>	MeCN	Et <sub>3</sub> N	35	80:20	93
3	<b>3c</b>	MeCN	Et <sub>3</sub> N	25	78:22	93
4	<b>3d</b>	MeCN	Et <sub>3</sub> N	30	85:15	94
5	<b>3a</b>	CH <sub>2</sub> Cl <sub>2</sub>	Et <sub>3</sub> N	43	80:20	92
6	<b>3a</b>	THF	Et <sub>3</sub> N	30	75:25	90
7	<b>3a</b>	toluene	Et <sub>3</sub> N	63	82:18	94
8	<b>3a</b>	toluene	K <sub>2</sub> CO <sub>3</sub> <sup>e</sup>	54	75:25	92
9	<b>3a</b>	toluene	NaOH <sup>e</sup>	48	80:20	92
10	<b>3a</b>	toluene	DBU	70	92:8	93
11	<b>3a</b>	toluene	DBU <sup>f</sup>	43	90:10	90

<sup>a</sup> 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.

<sup>b</sup> Yield of isolated pure diastereomer **7a**.

<sup>c</sup> Calculated from the yield of isolated **7a** and its diastereomer.

<sup>d</sup> Determined by chiral HPLC analysis.

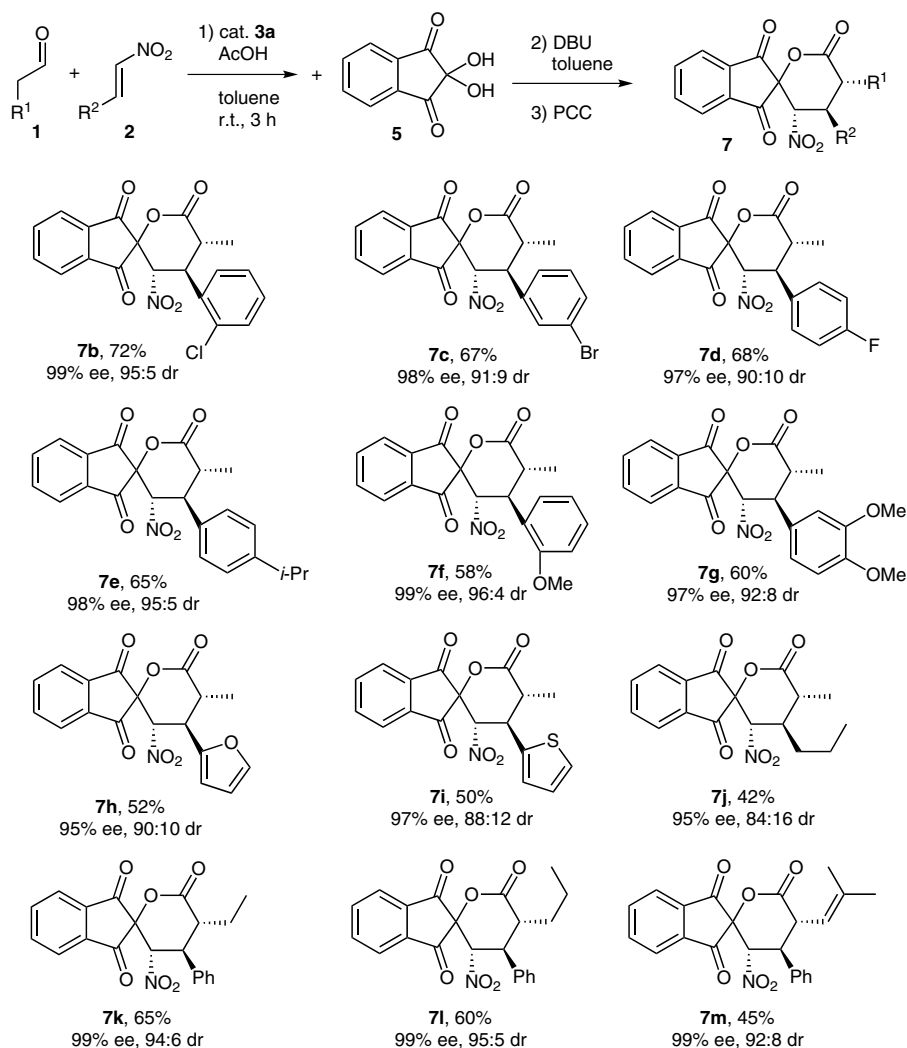
<sup>e</sup> H<sub>2</sub>O (0.4 mL) and TBAB (0.05 mmol) were added.

<sup>f</sup> 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 diastereocontrol 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.<sup>14</sup> 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  $\beta$ -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** 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

addition to propanal. We also evaluated the use of the branched  $\alpha,\beta$ -unsaturated aldehyde, 4-methylpent-2-enal via  $\alpha$ -selective dienamine catalysis,<sup>15</sup> 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 10*S*,11*S*,12*R* by X-ray crystallographic analysis (Figure 2).<sup>16</sup> The absolute configurations of the other products were tentatively assigned by analogy.

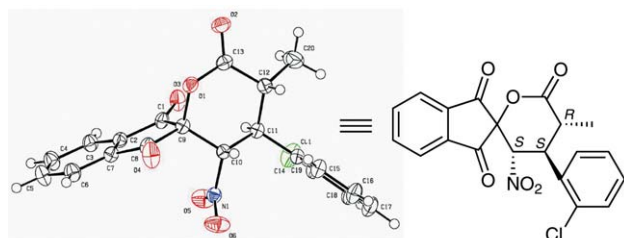
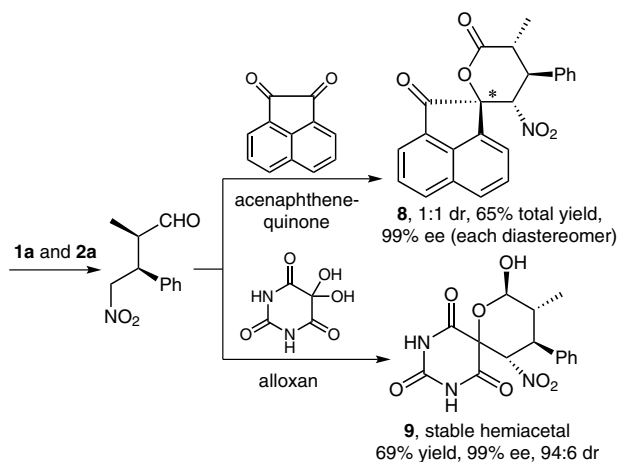


Figure 2 ORTEP drawing of compound **7b**

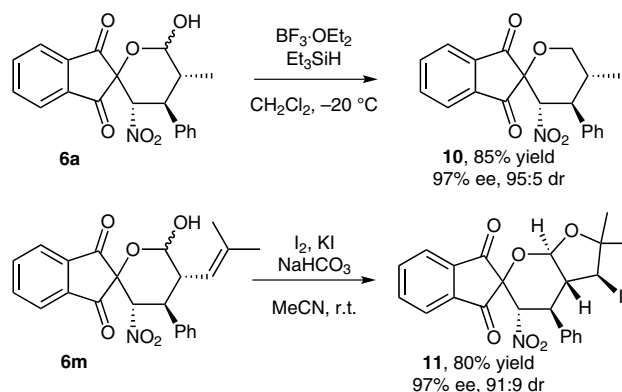
To further probe the usefulness of this organocatalytic domino reaction in diversity-oriented synthesis, other cyclic activated carbonyl substrates were screened (Scheme 3). We were pleased to find that the synthetically useful substrates, acenaphthenequinone and alloxan reacted smoothly under our experimental 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

More importantly, these oxa-spirocyclic 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  $-20^{\circ}\text{C}$ , 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.

The iodine-mediated cyclization reaction<sup>17</sup> of **6m** delivered the highly substituted hexahydrofuro[2,3-*b*]pyran **11**<sup>18</sup> with excellent stereocontrol.



Scheme 4 Synthetic transformations to access different and valuable oxa-spirocyclic scaffolds

In conclusion, we have successfully developed an organocatalytic cascade reaction involving a Michael–Henry–acetalization relay for the asymmetric assembly of aldehydes, nitroolefins and ninhydrin into six-membered oxa-spirocyclic indanones 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 enantio-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 Adamas-beta without purification unless otherwise noted. NMR data was obtained for  $^1\text{H}$  at 400 MHz, and for  $^{13}\text{C}$  at 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in  $\text{CDCl}_3$  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 ninhydrin **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, 10:1) to give hemiacetal **6**. To a solution of **6** in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added PCC (0.5 mmol). The mixture was stirred for 2 h at  $50^{\circ}\text{C}$ . The solid was removed by filtration through Celite. The filtrate was evaporated under reduced pressure and the residual was purified by column chromatography (PE–EtOAc, 20:1) to give spiroindanone  $\delta$ -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,  $t_{\text{R}}(\text{minor}) = 11.05$  min,  $t_{\text{R}}(\text{major}) = 12.11$  min. Mp  $167$ – $168^{\circ}\text{C}$ ;  $[\alpha]_{\text{D}}^{20} -129.4$  ( $c = 0.12$  in  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.12$ – $8.05$  (m, 2 H),

8.01–7.94 (m, 2 H), 7.40–7.34 (m, 3 H), 7.27–7.26 (m, 2 H), 5.64 (d,  $J = 12.4$  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).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 192.31, 190.03, 169.62, 141.15, 140.18, 138.00, 137.48, 135.43, 129.51, 129.05, 127.77, 124.99, 124.72, 87.28, 46.58, 41.42, 14.74$ . HRMS (ESI): calcd for  $\text{C}_{20}\text{H}_{15}\text{NO}_6 + \text{Na}$ : 388.0797; found: 388.0795.

## Acknowledgment

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## References and Notes

- (1) (a) Duarte, C. D.; Barreiro, E. J.; Fraga, C. A. *Mini-Rev. Med. Chem.* **2007**, *7*, 1108. (b) Lowe, J. A.; Hageman, D. L.; Drozda, S. E.; McLean, S.; Bryce, D. K.; Crawford, R. T.; Zorn, S.; Morrone, J.; Bordner, J. J. *Med. Chem.* **1994**, *37*, 3789. (c) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 4550.
- (2) (a) Kim, S.-H.; Kwon, S. H.; Park, S.-H.; Lee, J. K.; Bang, H.-S.; Nam, S.-J.; Kwon, H. C.; Shin, J.; Oh, D.-C. *Org. Lett.* **2013**, *15*, 1834. (b) Uddin, S. J.; Jason, T. L. H.; Beattie, K. D.; Grice, I. D.; Tiralongo, E. *J. Nat. Prod.* **2011**, *74*, 2010. (c) Ito, T.; Tanaka, T.; Linuma, M.; Nakaya, K.; Takahashi, Y.; Sawa, R.; Murata, J.; Darnaedi, D. *J. Nat. Prod.* **2004**, *67*, 932. (d) Pizzirani, D.; Roberti, M.; Grimaudo, S.; Cristina, A. D.; Pipitone, R. M.; Tolomeo, M.; Recanatini, M. *J. Med. Chem.* **2009**, *52*, 6936.
- (3) (a) Yavari, I.; Mirzaei, A.; Moradi, L.; Hosseini, N. *Tetrahedron Lett.* **2008**, *49*, 2355. (b) Nair, V.; Devipriya, S.; Suresh, E. *Synthesis* **2008**, 1065.
- (4) Li, M.; Yang, W.-L.; Wen, L.-R.; Li, F.-Q. *Eur. J. Org. Chem.* **2008**, 2751.
- (5) Sternativo, S.; Calandriello, A.; Costantino, F.; Testaferri, L.; Tiecco, M.; Marini, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 9382.
- (6) Ramachary, D. B.; Venkaiah, C.; Krishna, P. M. *Chem. Commun.* **2012**, 48, 2252.
- (7) For the diastereoselective synthesis of oxa-spirocyclic indanones, see: Lehmler, H.-J.; Nieger, M.; Breitmaier, E. *Synthesis* **1996**, 105.
- (8) (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134. (b) Enders, D.; Grondal, C.; Hüttel, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. (c) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.
- (9) (a) Betancort, J. M.; Barbas, C. F. III. *Org. Lett.* **2001**, *3*, 3737. (b) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611. (c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (d) List, B. *Tetrahedron* **2002**, *58*, 5573. (e) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212. (f) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123. (g) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.
- (10) (a) Enders, D.; Hüttel, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (b) Enders, D.; Hüttel, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 467.
- (11) (a) Han, B.; Xiao, Y.-C.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2009**, *11*, 4660. (b) Wang, Y.; Yu, D.-F.; Liu, Y.-Z.; Wei, H.; Luo, Y.-C.; Dixon, D. J.; Xu, P.-F. *Chem. Eur. J.* **2010**, *16*, 3922.
- (12) (a) Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 4922. (b) Uehara, H.; Imashiro, R.; Hernandez-Torres, G.; Barbas, C. F. III. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20672. (c) Ishikawa, H.; Sawano, S.; Yasui, Y.; Shibata, Y.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 3774.
- (13) (a) Wu, G.; Ouyang, L.; Liu, J.; Zeng, S.; Huang, W.; Han, B.; Wu, F.; He, G.; Xiang, M. *Mol. Diversity* **2013**, *17*, 271. (b) Huang, J.-R.; Dong, L.; Han, B.; Peng, C.; Chen, Y.-C. *Chem. Eur. J.* **2012**, *18*, 8896. (c) Dong, L.; Huang, J.-R.; Qu, C.; Zhang, Q.; Zhang, W.; Han, B.; Peng, C. *Org. Biomol. Chem.* **2013**, *11*, 6142.
- (14) **Compounds 7a–m; General Procedure**  
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, a solution of ninhydrin (**5**) (0.2 mmol) and DBU (0.6 mmol) in toluene (2.0 mL) was added. The mixture was stirred at r.t. for the requisite amount of time until the reaction was complete (monitored by TLC). The mixture was concentrated and the residue purified by flash chromatography on silica gel (PE–EtOAc, 10:1) to give hemiacetal **6**. To a solution of **6** in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added PCC (0.5 mmol) and the mixture 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 purified by column chromatography (PE–EtOAc, 20:1) to give spiroindanone  $\delta$ -lactone **7**.  
Oxa-spirocyclic indanone **7a** was obtained as a white solid in 70% yield over the two steps after flash chromatography. The enantiomeric excess was determined to be 93% by HPLC on a Chiralpak OD-H column (*i*-PrOH–*n*-hexane, 3:7, 1 mL/min); UV (254 nm),  $t_{\text{minor}} = 11.05$  min,  $t_{\text{major}} = 12.11$  min; mp 167–168 °C;  $[\alpha]_{\text{D}}^{20} -129.4$  (c 0.12,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.12$ – $8.05$  (m, 2 H), 8.01–7.94 (m, 2 H), 7.40–7.34 (m, 3 H), 7.27–7.26 (m, 2 H), 5.64 (d,  $J = 12.4$  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).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 192.31, 190.03, 169.62, 141.15, 140.18, 138.00, 137.48, 135.43, 129.51, 129.05, 127.77, 124.99, 124.72, 87.28, 46.58, 41.42, 14.74$ . HRMS (ESI):  $m/z$  [M + H] $^+$  calcd for  $\text{C}_{20}\text{H}_{15}\text{NO}_6 + \text{Na}$ : 388.0797; found: 388.0795.
- (15) For a comprehensive review on dienamine catalysis, see: Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865.
- (16) CCDC 919807 contains the supplementary crystallographic data for the structure in this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- (17) Bedford, S. B.; Bell, K. E.; Bennett, F.; Hayes, C. J.; Knight, D. W.; Shaw, D. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2143.
- (18) The hexahydrofuro[2,3-*b*]pyran derivatives are synthetically useful building blocks. For selected examples, see: (a) Drewes, S. E.; Horn, M. M.; Munro, O. Q.; Ramesar, N.; Ochse, M.; Bringmann, G.; Peters, K.; Peters, E.-M. *Phytochemistry* **1999**, *50*, 387. (b) Chen, X.-Z.; Wu, H.-F.; Li, G.-Y.; Lu, S.-M.; Li, B.-G.; Fang, D.-M.; Zhang, G.-L. *Helv. Chim. Acta* **2008**, *91*, 1072.

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