Access to Spirooxindole-fused Cyclopentanes via Stereoselective Organocascade Reaction using Bifunctional Catalysis

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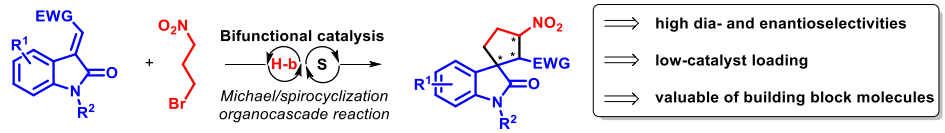
Supporting Information Placeholder



ABSTRACT: The present study reports an asymmetric organocascade reaction of oxindole-derived alkenes with 3-bromo-1-nitropropane efficiently catalyzed by the bifunctional catalyst. Spirooxindole-fused cyclopentanes were produced in moderate-to-good isolated yields (15-69%) with excellent stereochemical outcomes. The synthetic utility of the protocol was exemplified on a set of additional transformations of the corresponding spirooxidondole compounds.

INTRODUCTION

Nowadays, cascade reactions (or domino reactions)[1] represent a formidable challenge for modern synthetic chemistry.[2] Those reactions are generally described as multicomponent one-pot processes involving two or more transformations. That strategy offers many advantages over classical "stop-and-go" sequences, for example, in avoiding protecting groups or isolation of reaction intermediates. Besides operational efficiency (step and pot economy),[3] organocascade reactions showed significant advantages for constructing complex molecular frameworks with high selectivity levels (stereo-, chemo-). Not surprisingly, organocascade reactions were successfully used for the stereoselective preparation of valuable spirocycliclic compounds,[4] for example, the privileged scaffold - spirocyclic oxindole derivatives (spirooxindoles).[5] Spirooxindole structural motif appears as a part of various natural or synthetic compounds with remarkable biological activity, including medicinally relevant compounds (Figure 1).[6]

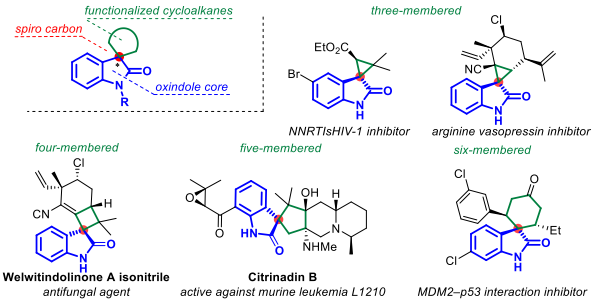
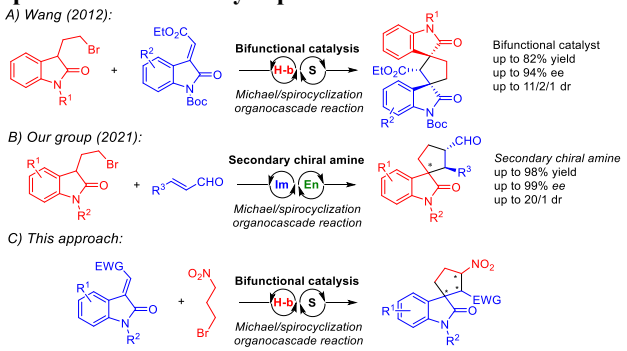


Figure 1. Selected biologically active spirooxindoles.

Organocascade reactions initiated by the Michael reaction are highly efficient for the construction of spirooxindole-fused derivatives,[7] using either oxindoles with nucleophilic C3 (Michael donors)[8-10] or electrophilic methyleneindolinones (Michael acceptors).[11,12] Interestingly, a combination of both types of starting materials was applied by Wang for the preparation of highly-rigid bispirooxindoles via Michael/spirocyclization reaction promoted by bifunctional organocatalyst (Scheme 1A).[13] Recently, our group described Michael/alkylation organocascade reaction of 3-(2-bromoethyl)oxindoles with α,β-unsaturated aldehydes efficiently catalyzed by chiral secondary amine producing valuable spirooxindole-fused cyclopentanes (Scheme 1B).[14]

Scheme 1. Examples of organocascade aproaches towards spirooxindole-fused cyclopentanes.

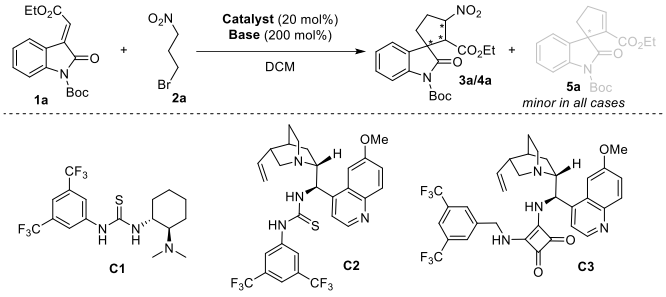


Considering the above, and in light of our ongoing interest in the enantioselective synthesis of spirocyclic compounds,[15] we envisioned the construction of novel spirooxindole-fused cyclopentane derivatives having up to three stereocenters via stereoselective organocascade Michael/spirocyclization reaction promoted by the bifunctional catalyst from 3-bromo-1-nitropropane and methyleneindolinones (Scheme 1C).

RESULTS AND DISCUSSIONS

To verify our designed strategy, we began our study by mixing easily accessible methyleneindolinone **1a** with 3-bromo-1-nitropropane (**2a**), bifunctional organocatalysts, and base (Table 1). To our delight, a reaction conducted with commercially available Takemoto catalyst (**C1**) and K_2CO_3 produced spirooxindole derivative **3a** as the main diastereomer. Moreover, compound **3a** was readily separable on silica and isolated in good yield (58%) with high enantioselectivity (99% *ee*, entry 1). Besides, we observed the formation of **5a** in traces as a product of base-induced HNO_2 elimination. Conversely, the diastereocontrol of the reactions catalyzed by Rawal´s and Soos´s catalysts was significantly diminished (entries 2 and 3). Apart from **C1**-**C3**, we tested other bifunctional organocatalysts (for details, please see the SI file), but no further improvement in reaction efficiency was observed. Interestingly, the reaction rate was significantly decreased when using Na_2CO_3 (entry 4) and $NaHCO_3$ (entry 5). Using organic bases, such as DIPEA (entry 6), significantly reduced diastereocontrol. Then, the effect of solvent on reaction efficiency and the stereochemical outcome was evaluated. Using polar aprotic solvents (ethyl acetate or MTBE) resulted in the highest reaction rates. On the other hand, diastereoselectivities of those reactions were significantly lowered (entries 7 and 8). The model reaction conducted in chloroform (entry 8) produced spirooxindole **3a** in high yield, with excellent stereochemical outcome. Additionally, we conducted the model reaction with reduced amount of 3-bromo-1-nitropropane (**2a**) and organocatalyst **C1** (1 mol%), producing **3a** with the same efficiency and stereocontrol (entry 11). For complete optimization studies, please, see the SI.

Table 1. Optimization studies of cascade reaction.



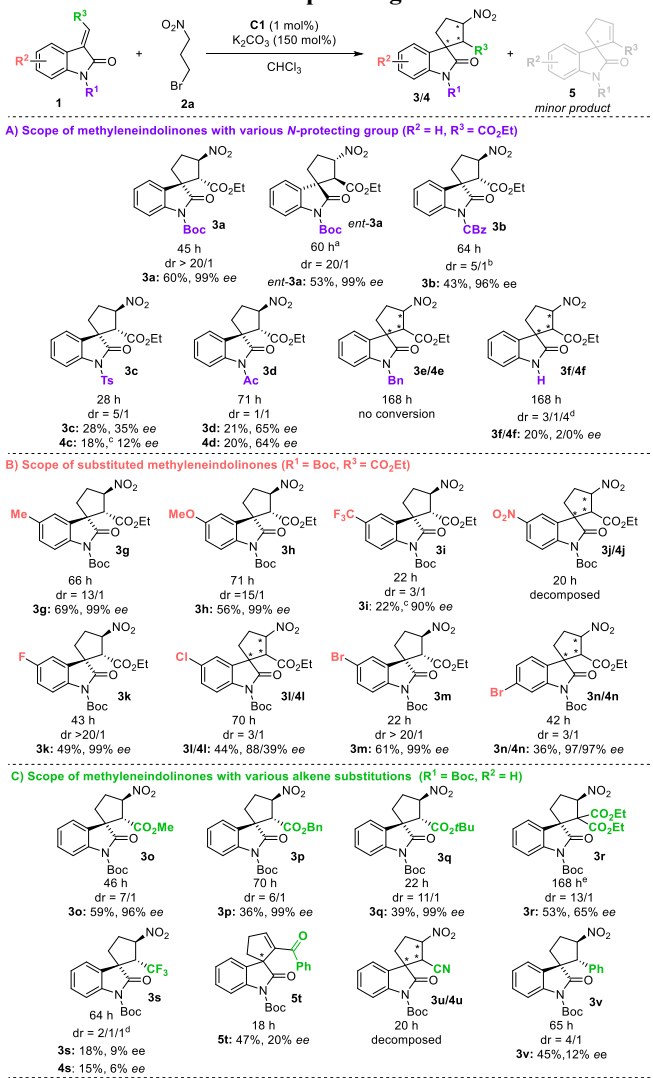
entry[a]	cat.	base	time (h)	dr[b]	yield[c] (%)	*ee*[d] (%)
1	**C1**	K_2CO_3	24	17/1	58	99
2	**C2**	K_2CO_3	24	3/1	39	92
3	**C3**	K_2CO_3	24	3/1	58	91
4	**C1**	Na_2CO_3	48	20/1	55	99
5	**C1**	$NaHCO_3$	168	20/1	32	99
6	**C1**	DIPEA	24	2/1	49	98
7[e]	**C1**	K_2CO_3	2	3/1	38	91
8[f]	**C1**	K_2CO_3	3	8/1	23	99
9[g]	**C1**	K_2CO_3	24	>20/1	59	99
10[h]	**C1**	K_2CO_3	18	>20/1	57	99
11[i]	**C1**	K_2CO_3	45	>20/1	64	99

[a] Reactions were conducted with **1a** (0.1 mmol), **2a** (0.2 mmol), corresponding base (0.2 mmol), and catalyst (20 mol%) in DCM (1.0 ml) at room temperature. [b] Determined by ^{1}H-NMR of the crude reaction mixture (**3a**/**4a**). [c] Isolated yield of **3a** after column chromatography. [d] Determined by chiral HPLC analysis. [e] EtOAc was used. [f] MTBE was used. [g] $CHCl_3$ was used. [h] Reaction was conducted with **1a** (0.10 mmol), **3a** (0.15 mmol), **C1** (20 mol%) in $CHCl_3$ (1.0 ml) at room temperature. [i] Reaction was conducted with **1a** (0.10 mmol), **3a** (0.15 mmol), **C1** (1 mol%) in $CHCl_3$ (1.0 ml) at room temperature.

After optimizing the reaction conditions, we began exploring the scope of the organocascade reaction by varying of *N*-protecting groups of methyleneindolinones **1** (Scheme 2A). We assessed the effect on reactivity and stereoselectivity of organocascade reactions using various *N*-protected methyleneindolinones. We identified oxycarbonyl-protecting groups as most effective in terms of stereocontrol; corresponding spirocyclic compounds **3a**,**b** were isolated in good yields (43-60%) with high stereoselectivity. On the other hand, organocascade reactions of other *N*-protected methyleneindolinones did not give products with acceptable yields and stereochemical outcomes. For example, the organocascade reaction of unprotected methyleneindolinone **1f** produced a mixture of products (**3f**/**4f**) with poor stereocontrol. Luckily, substrate **3f** can be prepared in high yield by TFA-mediated deprotection of the *N*-Boc protecting group of **3a** (for more details, please, see late-stage transformations). Subsequently, the scope of the developed organocascade reaction was investigated by varying substituted methyleneindolinones **1** (Scheme 2B). In general, spirooxindoles **3** were obtained in moderate-to-good yields with excellent stereoselectivity, when oxindole derivatives **1**

bearing electron-donating (**3g**, **3h**) and weakly electron-withdrawing groups (**3k**–**n**) on the oxindole aromatic ring were used. The reaction of methyleneindolinones bearing a strong electron-withdrawing group, such as the nitro group, led to a complex mixture or to the decomposition of starting material. Additionally, we studied the process using variously substituted alkene of methyleneindolinone derivatives **1**. Good efficiency of the developed method was shown in reactions of alkenes bearing various electron-withdrawing groups, especially in reactions of ester-derived alkenes producing spirocycles **3o-r** in moderate-to-good yields (36-59%) and excellent stereochemical outcomes. Remarkably, other electron-withdrawing groups did not show similar efficiency. For example, the reaction between ketone-derived alkene **1t** and **2a** produced only elimination product **5t** in moderate yield and low enantioselectivity.

Scheme 2. The substrate scope of organocascade reaction.



[a] *Ent*-**C1** was used. [b] Dr (**3**/**4**'). [c] NMR yield, for more infromations, see the SI. [d] Dr (**3**/**4**'/**4**). [e] Not full conversion of **1**.

The relative configuration of spirooxindole-fused cyclopentanes **3** was adopted on the basis of characteristic chemical shifts and *J* values of the cyclopentane ring (for details, please see the SI). In addition, the absolute configuration of **3a** was ascertained using X-ray diffraction analysis, and the configuration of **3a** was assigned as 2*R*, 9*R*, 10*R* (Figure 2, for details, see the SI).

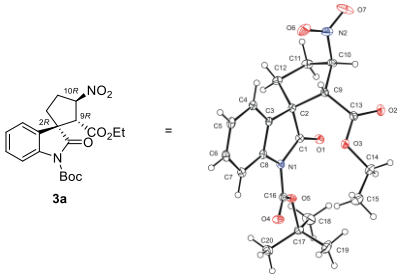


Figure 2. X-ray single-crystal structure of 3a, the displacement ellipsoids at 30% probability level.

On the basis of the absolute configuration of products and the previous report,[16] the transition state was proposed to rationalize the stereochemical outcome of the cascade process. The tertiary amine moiety of catalyst **C1** deprotonates an acidic proton of nitroalkane **2a**, generating the complex of nitronate non-covalently bounded to the tertiary amine. Simultaneously, the thiourea part of the catalyst activates methyleneindolinone **1a** prompting *Si*-face addition of nitronate to the electron-deficient alkene. Additionally, the sterical hindrance of *tert*-butyl moiety of the *N*-Boc group may increase the rigidity of the ternary complex, which seems crucial for high stereocontrol. That hypothesis is supported by lowered diasterocontrol, when methyleneindolinone **3b** with more planar *N*-CBz protecting group is used.

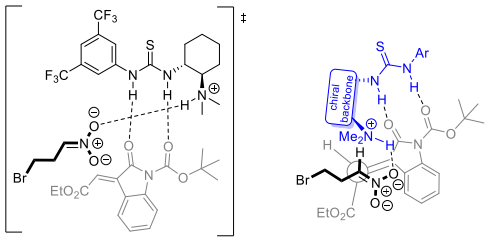
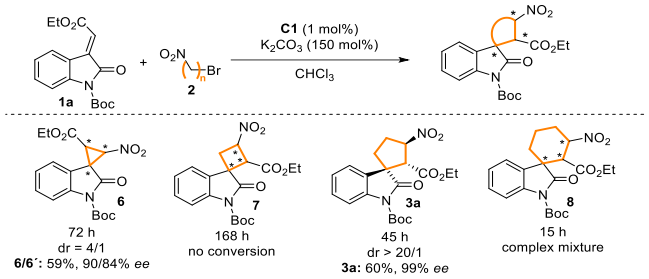


Figure 3. Proposed bifunctional activation and its Newmann representation.

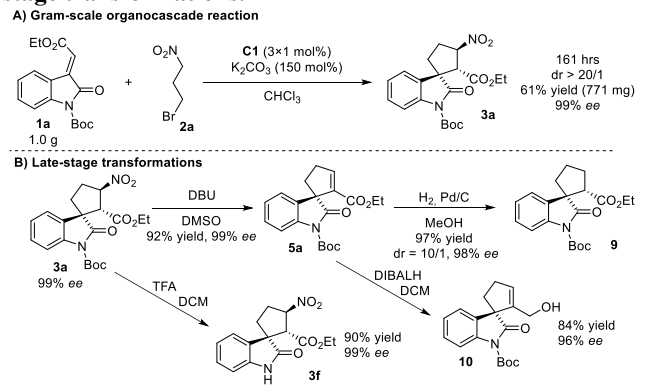
To expand the developed organocatalytic process toward the construction of spiro compounds containing 3-, 4-, and 6-membered rings (Scheme 3), 1-bromonitroalkanes **2** with various lengths of alkyl moiety were subjected to the reaction with methyleneindolinone **1a**. With respect to previously reported methods,[17] we isolated corresponding spirooxindole-fused cyclopropane **6** in good yield and stereochemical outcomes. Despite known examples of spirooxindole-fused cyclobutanes,[11b] we did not observe any conversion of starting methyleneindolinone **1a** in reaction with 1-bromo-2-nitroethane (**2c**). Interestingly, reaction of longer 1-bromo-2-nitrobutane produced unseparable complex mixture of products with major uncyclized products of the Michael reaction.

Scheme 3. Substrate scope with diverse bromonitroalkanes.



To demonstrate the synthetic utility of the developed organocascade reaction, we performed a reaction between **1a** and **2a** in gram scale, giving the product **3a** in 61% yield with retained stereochemical outcomes (99% *ee*, and dr >20/1, Scheme 4A). To reduce reaction time, the reaction was performed with a slightly higher amount of **C1** (3 mol%). As an example of late-stage transformations, spirooxindole **3a** was selectively converted to various derivatives (Scheme 4B). *N*-Boc protecting group was removed by treatment of **3a** with an excess of TFA. Rection provided the corresponding spirooxindole **3f** in excellent yield with retained enantioselectivity. Noteworthy, the sequence of the developed organocascade followed by *N*-deprotection is more appropriate compared to the direct organocascade reaction starting from **1f**. Next, DBU-mediated elimination of HNO_2 produced alkene **5a** in excellent yield with retained optical purity. Noteworthy, the double bond of alkene **5a** can be selectively reduced under catalytic hydrogenation conditions, producing cyclopentane derivative **9** with high diastereocontrol. The relative configuration of **9** was determined by 1D NOE NMR experiments (for more information, please, see the SI). Furthermore, ethyl ester **5a** can be chemoselectively reduced to corresponding allylic alcohol **9** by treatment with DIBALH. Spirocyclic allylic alcohol **10** may be used as a valuable building block for synthesizing valuable complex molecules.[18]

Scheme 4. Gram-scale organocascade reaction and late-stage transformations.



CONCLUSION

In summary, we have developed enantioselective organocascade Michael/spirocyclization reaction of readily available methyleneindolinone with 1-bromo-3-nitropropane. The reaction is efficiently catalyzed by a chiral bifuncitional catalyst, affording chiral spirooxindole-fused cyclopentanes in moderate-to-good yields and excellent stereochemical outcomes. The developed synthetic protocol is suitable for late-stage functionalizations, as shown by a set of additional transformations.

EXPERIMENTAL SECTION

Chemicals and solvents were purchased from commercial suppliers and purified using standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F_{254} were used, and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (AMC) or vanillin followed by heating. Column chromatography was performed using silica gel Fluka (40-63 μm) or SiliCycle-SiliaFlash P60 (particle size: 40-63 μm, pore diameter: 60 Å. ^{1}H, ^{13}C NMR, and ^{19}F spectra were recorded with Bruker AVANCE III 400. Chemical shifts for protons are given in δ relative to tetramethylsilane (TMS), and they are referenced to residual protium in the NMR solvent (chloroform-*d*: $\delta_H = 7.26$ ppm). Chemical shifts for carbon are referenced to the carbon of NMR solvent (chloroform-*d*: $\delta_C = 77.16$ ppm). The coupling constants *J* are given in hertz. IR DRIFT or ATR spectra were recorded with Nicolet AVATAR 370 FT-IR in cm^{-1}. Chiral HPLC was carried out using a LC20AD Shimadzu liquid chromatograph with SPD-M20A diode array detector with columns Daicel Chiralpak® IA, Daicel Chiralpak® IB, Daicel Chiralpak® AD, Daicel Chiralpak® ODH. Samples for measurement of chiral HPLC were prepared by dissolving of the corresponding sample in *n*-heptane/*i*-PrOH (8/2, *v*/*v*) mixture. Optical rotations were measured on AU-Tomatica polarimeter, Autopol III and specific optical rotations are given in concentrations *c* [g/100 ml]. Melting points were measured using a Büchi melting point B-545 apparatus. All melting points were measured in an open glass capillary, and all values are uncorrected. High-resolution mass spectra were recorded with a LCQ Fleet spectrometer. Samples for measurement of HRMS were prepared by dissolving of the corresponding sample in methanol.

Preparation of catalyst

Catalyst **C1** was purchased from commercial suppliers. *Ent*-**C1**, **C2**, **C3** are known and prepared according to previously reported procedures.[19]

Preparation of methyleneindolinones

Methyleneindolinone **1** are typically known (**1i** is new compound) and they were prepared according to previously reported procedures.[20]

tert-Butyl (E)-3-(2-ethoxy-2-oxoethylidene)-2-oxo-5-(trifluoromethyl)indoline-1-carboxylate (**1i**)

Ethyl 2-(triphenyl-λ^5-phosphaneylidene)acetate (142 mg, 0.41 mmol, 1.1 equiv.) was added in one portion to a stirred solution of 5-trifluoromethylisatin[21] (80 mg, 0.37 mmol, 1.0 equiv.) in THF (1 ml). The resulting mixture was stirred at room temperature for 3 hours. After the consumption of starting isatin (monitored by TLC), solvent was removed under reduced pressure. Crude product was purified by column chromatography (eluting with hexane/EtOAc = 3:1-1:1). The resulting heterocyclic alkene (quantitative yield) was used to the next step without other purification. Heterocyclic alkene (116 mg, 0.41 mmol, 1.0 equiv.) and di-*tert*-butyldicarbonate (98 mg, 0.45 mmol, 1.1 eq.) were added in one portion to a stirred solution of DMAP (3 mg, 0.02 mmol, 0.05 eq.) in THF (2 ml) at room temperature. The resulting mixture was stirred at room temperature for 14 hours. After

the consumption of starting alkene (monitored by TLC), reaction was quenched by adding water (5 ml) and diluted with EtOAc (5 ml). The organic phase was separated, and water phase was extracted with EtOAc (3 × 10 ml). Collected organic phases were washed with brine (1 × 10 ml) and dried over $MgSO_4$. After filtration of drying agent, solvents were removed under reduced pressure. The crude product was purified by column chromatography with toluene as an eluent.

Yellow amorphous solid. Yield = 49% (70 mg, over two steps). ^{1}H NMR (400 MHz, chloroform-*d*): δ 9.04 – 8.97 (m, 1H), 8.04 (dt, J = 8.7, 0.7 Hz, 1H), 7.69 (ddd, J = 8.6, 2.0, 0.8 Hz, 1H), 6.98 (s, 1H), 4.36 (q, J = 7.1 Hz, 2H), 1.65 (s, 9H), 1.38 (t, J = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.2, 165.1, 148.6, 144.3, 135.2, 129.6 (q, J = 3.8 Hz, 1C), 127.0 (q, J = 33.0 Hz, 1C), 125.7 (q, J = 4.0 Hz, 1C), 125.4, 124.0 (q, J = 272.1 Hz), 120.4, 115.2, 85.6, 61.9, 28.1 (3C), 14.2 ppm. ^{19}F NMR (376 MHz, chloroform-*d*): δ -62.27 (d, J = 0.9 Hz) ppm. IR (KBr): ν = 1765 (C=O, ester, amide), 1738 (C=O, ester, amide), 1711 (C=O, ester, amide), 1201 (C-CF_3) cm^{-1}. HRMS (ESI+) m/z: calcd. for $C_{18}H_{18}F_3NNaO_5$ $[M+Na]^+$: 408.1029, found: 408,1027.

Preparation of 1-bromonitrolalkanes

Alkane **2b** was purchased from commercial suppliers. **2d** is known and **2d** was prepared according to previously reported procedure.[22]

General procedure for Appel reaction (GP1)

NBS (1.3 eq.) and PPh_3 (1.3 eq.) were added portion-wise to a stirred solution of nitroalcohol (1.00 g, 9.51 mmol, 1.0 eq.) in DCM (0.3M solution of alcohol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour. After the full consumption of starting 3-nitropropan-1-ol (monitored by TLC), solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluting with hexane/EtOAc = 7:1).

*1-Bromo-3-nitropropane (***2a***)*

The title compound was synthesized according to general procedure GP1, using 3-nitropropan-1-ol[23] (1.00 g, 9.51 mmol).

Yellow oil. Yield = 50% (780 mg). ^{1}H NMR (400 MHz, chloroform-d): δ 4.59 (t, J = 6.5 Hz, 2H), 3.50 (t, J = 6.2 Hz, 2H), 2.54 (p, J = 6.4 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 73.3, 29.9, 28.7. ppm. GCMS (EI, 70 eV): t_R = 8.1 min, *m/z* (%): 89 (1), 72 (1), 57 (2), 42 (4), 41 (100), 39 (65), 27 (8). Our physical and spectroscopic data matched previously reported data.[24]

*1-Bromo-2-nitroethane (***2c***)*

The title compound was synthesized according to general procedure GP1, starting from 2-nitroethan-1-ol[25] (1030 mg, 11.3 mmol).

Light yellow liquid. Yield = 92% (1600 mg). ^{1}H NMR (400 MHz, chloroform-*d*): δ 4.77 (t, J = 6.4 Hz, 2H), 3.81 (t, J = 6.3 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 75.7, 23.8 ppm. GCMS (EI, 70 eV): t_R = 10.1 min, *m/z* (%): 89 (17), 75 (100), 59 (16), 47 (21), 31 (18). Our physical and spectroscopic data matched previously reported data.[24]

General procedure for Michael/alkylation cascade reaction (GP2)

The catalyst **C1** (0.4 mg, 0.001 mmol, 0.01 eq.) was added to a solution of the corresponding methyleneindolinone **1** (0.1 mmol, 1.0 eq.) in anhydrous chloroform (0.5 ml) at room temperature. Then, 1-bromnitroalkane **2** (0.15 mmol, 1.5 eq.) and potassium carbonate (20.7 mg, 0.15 mmol, 1.5 eq.) were added. The reaction was stirred at room temperature for the indicated time (TLC monitoring). With complete conversion of methyleneindolinone **1**, solvent was removed under reduced pressure. Crude product was purified by column chromatography.

Note: For racemic reactions, catalyst *rac*-**C1** was used.

*1'-(tert-Butyl) 2-ethyl (1R,2R,3R)-3-nitro-2'-oxospiro[cyclopentane-1,3'-indoline]-1',2-dicarboxylate (***3a, *ent*-3a***)*

The title compound was synthesized according to the GP2, using methyleneindolinone **1a** (31.8 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 45 hours. The products were purified by column chromatography (hexane/EtOAc - 10:1), the diastereomeric ratio of **3a**/**4a** > 20/1.

Ent-**3a** was prepared according to the modified GP2, using catalyst *ent*-C1 was used instead of **C1** and the same starting materials and purification method as **3a** (reaction time: 60 h). The diastereomeric ratio of *ent*-**3a**/*ent*-**4a** = 20/1.

White crystalline solid, crystals suitable for X-ray analysis were grown by the dissolution of **3a** in a minimal amount of boiling *i*-PrOH, followed by standing at r.t. overnight. Yield **3a** = 60% (24 mg). Yield *ent*-**3a** = 53% (21 mg). mp (**3a**) = 78 – 80 °C (*i*-PrOH). 99% *ee* for **3a**, 99% *ee* for *ent*-**3a**, the enantiomeric excesses of products **3a** and *ent*-**3a** was determined by HPLC using a Chiralpak® IA column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 210 nm): t_R = 4.4 min, t_R = 5.0 min. $[\alpha]_D^{20}$ (**3a**) = +9.2 (c = 0.4, $CHCl_3$). $[\alpha]_D^{20}$ (*ent*-**3a**) = -6.0 (c = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.88 – 7.81 (m, 1H), 7.42 – 7.29 (m, 2H), 7.28 – 7.20 (m, 1H), 5.69 (ddd, J = 9.5, 6.8, 3.6 Hz, 1H), 4.20 (d, J = 6.8 Hz, 1H), 4.09 (dq, J = 10.7, 7.1 Hz, 1H), 3.95 (dq, J = 10.8, 7.1 Hz, 1H), 3.08 – 2.89 (m, 1H), 2.47 – 2.21 (m, 3H), 1.64 (s, 9H), 1.06 (t, J = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 177.5, 168.5, 149.1, 139.8, 129.7, 129.1, 125.1, 122.0, 115.3, 87.6, 84.8, 62.0, 57.9, 56.7, 37.6, 31.2, 28.2 (3C), 13.7 ppm. IR (KBr): ν = 1759 (C=O, ester, amide), 1739 (C=O, ester, amide), 1549 (NO_2), 1350 (NO_2) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{20}H_{24}N_2NaO_7$ $[M+Na]^+$: 427.1476, found: 427.1474.

*Ethyl (1R,2R,3R)-3-nitro-2'-oxo-1'-(2-oxo-2-phenyl-1λ^2-ethyl)spiro[cyclopentane-1,3'-indoline]-2-carboxylate (***3b***)*

The title compounds was synthesized according to the GP2, using methyleneindolinone **1b** (33.3 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 64 hours. The product was purified by column chromatography (hexane/EtOAc - 3:1). The diastereomeric ratio of **3b**/**4b´** = 5/1.

Yellow oil. Yield = 43% (18 mg). 96% *ee*, the enantiomeric excess of product **3b** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 207 nm): t_R = 11.1 min, t_R = 12.9 min. $[\alpha]_D^{20}$ = +3.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.97 – 7.87 (m, 1H), 7.55 – 7.47 (m, 2H), 7.46 – 7.31 (m,

5H), 7.29 – 7.23 (m, 1H), 5.68 (ddd, *J* = 9.6, 6.9, 3.6 Hz, 1H), 5.51 – 5.39 (m, 2H), 4.22 (d, *J* = 6.9 Hz, 1H), 4.07 – 3.88 (m, 2H), 3.07 – 2.93 (m, 1H), 2.47 – 2.36 (m, 1H), 2.36 – 2.22 (m, 2H), 0.97 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 177.3, 168.4, 150.7, 139.4, 134.9, 129.6, 129.3, 128.8 (2C), 128.8, 128.5 (2C), 125.5, 122.1, 115.5, 87.6, 68.9, 62.2, 58.1, 56.7, 37.6, 31.2, 13.6 ppm. IR (KBr): ν 1765 (C=O, ester, amide), 1741 (C=O, ester, amide), 1724 (C=O, ester, amide), 1556 (NO_2), 1377 (NO_2) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{23}H_{22}N_2NaO_7$ $[M+Na+H_2O]^+$: 461.1319, found: 461.1327.

*Ethyl (1R,2R,3R)-3-nitro-2'-oxo-1'-tosylspiro[cyclopentane-1,3'-indoline]-2-carboxylate (***3c**/**4c***)*

The title compounds were synthesized according to the GP2, using methyleneindolinone **1c** (37.1 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 28 hours. The product was purified by column chromatography (hexane/EtOAc - 10:1). The diastereomeric ratio of **3c**/**4c** = 1/1. Products were obtained as inseparable mixture of **4c**/**5c** and pure **3c**.

*Ethyl (1R,2R,3R)-3-nitro-2'-oxo-1'-tosylspiro[cyclopentane-1,3'-indoline]-2-carboxylate (***3c***)*

Yellow oil. Yield = 28% (13 mg). 35% *ee*, the enantiomeric excess of product **3c** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 90:10, flow rate = 1.0 mL/min, λ = 207 nm): t_R = 10.6 min, t_R = 11.9 min. $[\alpha]_D^{20}$ = -2.3 (*c* = 0.7, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*): δ 8.00 – 7.91 (m, 3H), 7.41 – 7.29 (m, 4H), 7.23 (dd, *J* = 7.5, 1.0 Hz, 1H), 5.58 (ddd, *J* = 9.7, 7.0, 3.5 Hz, 1H), 4.13 (d, *J* = 7.0 Hz, 1H), 3.85 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.63 (dq, *J* = 10.6, 7.1 Hz, 1H), 2.90 (dddd, *J* = 14.0, 10.8, 9.6, 7.7 Hz, 1H), 2.42 (s, 3H), 2.40 – 2.03 (m, 3H), 0.91 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 177.3, 168.0, 145.8, 139.4, 135.0, 129.8 (2C), 129.6, 129.4, 128.3 (2C), 125.5, 122.4, 113.9, 87.1, 62.0, 57.6, 56.7, 37.2, 30.9, 21.8, 13.7 ppm. IR (KBr): ν = 1738 (C=O, ester, amide), 1552 (NO_2), 1371 (NO_2), 1336 (S=O, sulfonamide) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{22}H_{23}N_2O_7S$ $[M+H]^+$: 459.1220, found 459.1220.

*Ethyl-3-nitro-2'-oxo-1'-tosylspiro[cyclopentane-1,3'-indoline]-2-carboxylate (***4c***)*

Inseparable mixture **4c**/**5c** = 5/1. Yellow oil. NMR yield **4c** = 18%. 12/12% *ee* (**4c**/**5c**), the enantiomeric excess of product **4c** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 206 nm): t_R = 8.5 min, t_R = 9.0 min, the enantiomeric excess of product **5c** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 206 nm): t_R = 14.9 min, t_R = 20.4 min. $[\alpha]_D^{20}$ = +12.0 (*c* = 0.9, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*, **4c** − H′, **5c** − H): δ 8.03 (dd, *J* = 8.6, 2.0 Hz, 2H′), 8.01 (d, *J* = 6.6 Hz, 2H), 7.95 (dt, *J* = 8.2, 0.7 Hz, 1H′), 7.91 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.38 (d, *J* = 1.3 Hz, 1H), 7.35 (dd, *J* = 8.2, 1.2 Hz, 3H′), 7.33 – 7.28 (m, 2H), 7.18 – 7.11 (m, 1H + 1H′, *overlapped*), 7.11 – 7.08 (m, 1H), 7.02 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.99 (dd, *J* = 7.5, 1.4 Hz, 1H′), 5.58 (td, *J* = 8.8, 5.9 Hz, 1H′), 4.22 (d, *J* = 8.3 Hz, 1H′), 3.84 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.60 (dqd, *J* = 10.7, 7.1, 5.3 Hz, 1H′+1H, *overlapped*), 3.36 (dq, *J* = 10.7, 7.2 Hz, 1H′ + 1H, *overlapped*), 2.78 (dtd, *J* = 8.3, 5.9, 2.6 Hz, 1H), 2.74 – 2.65 (m, 1H′), 2.65 – 2.54 (m, 1H′+1H, *overlapped*), 2.53 – 2.45 (m, 1H′), 2.43 (s, 3H′), 2.40 (s, 3H), 2.22 – 2.13 (m, 1H), 1.95 (ddd, *J* = 13.2, 7.4, 4.7 Hz, 1H′), 0.83 (t, *J* = 7.1 Hz, 3H), 0.43 (t, *J* = 7.1 Hz, 3H′) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*, **4c** − C′, **5c** − C): δ 177.5 (1C), 176.3 (1C′), 167.8 (1C′), 162.4 (1C), 148.7 (1C′), 146.1 (1C′), 145.5 (1C), 139.0 (1C), 138.8 (1C′), 137.4 (1C), 135.5 (1C), 135.2 (1C′), 132.4 (1C), 129.9 (2C′ + 2C, *overlapped*), 129.8 (1C′), 129.7 (1C′), 129.2 (1C), 128.9 (1C), 128.2 (2C′ + 2C, *overlapped*), 125.2 (1C′), 125.0 (1C), 123.2 (1C′), 122.9 (1C), 113.9 (1C′), 113.5 (1C), 85.6 (1C′), 61.6 (1C′), 60.5 (1C), 57.0 (1C′), 56.4 (1C), 38.1 (1C), 37.3 (1C′), 32.2 (1C), 30.7 (1C′), 21.9 (1C′), 21.8 (1C), 13.8 (1C), 13.2 (1C′) ppm. IR (KBr): ν = 1761 (C=O, ester, amide), 1736 (C=O, ester, amide), 1550 (NO_2), 1373 (S=O, sulfonamide), 1317 (NO_2) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{22}H_{23}N_2O_7S$ $[M+H]^+$: 459.1220, found: 459.1216.

*Ethyl 1'-acetyl-3-nitro-2'-oxospiro[cyclopentane-1,3'-indoline]-2-carboxylate (***3d**/**4d***)*

The title compounds were synthesized according to the GP2, using methyleneindolinone **1d** (25.9 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 71 hours. The products were purified by column chromatography (hexane/EtOAc - 7:1), the diastereomeric ratio of **3d**/**4d** = 1/1.

*Ethyl (1R,2R,3R)-1'-acetyl-3-nitro-2'-oxospiro[cyclopentane-1,3'-indoline]-2-carboxylate (***3d***)*

Yellow oil. Yield = 21% (7 mg). 65% *ee*, the enantiomeric excess of product **3d** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 98:2, flow rate = 1.0 mL/min, λ = 204 nm): t_R = 17.2 min, t_R = 38.1 min. $[\alpha]_D^{20}$ = +6.8 (*c* = 0.4, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*): δ 8.24 (dt, *J* = 8.1, 0.8 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.32 – 7.26 (m, 1H), 5.66 (ddd, *J* = 9.5, 7.1, 3.8 Hz, 1H), 4.23 (d, *J* = 7.1 Hz, 1H), 4.11 – 3.91 (m, 2H), 3.05 – 2.83 (m, 1H), 2.64 (s, 3H), 2.51 – 2.18 (m, 3H), 1.06 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 180.0, 170.7, 168.5, 140.2, 129.4, 128.7, 125.9, 121.8, 116.9, 87.5, 62.2, 58.3, 56.7, 37.5, 31.2, 26.7, 13.8 ppm. IR (KBr): ν = 1739 (C=O, ester, amide), 1705 (C=O, ester, amide), 1552 (NO_2), 1273 (NO_2) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{17}H_{18}N_2NaO_6$ $[M+Na]^+$: 369.1057, found: 369.1052.

*Ethyl 1'-acetyl-3-nitro-2'-oxospiro[cyclopentane-1,3'-indoline]-2-carboxylate (***4d***)*

Yellow oil. Yield = 20% (7 mg). 64% *ee*, the enantiomeric excess of product **4d** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 98:2, flow rate = 1.0 mL/min, λ = 204 nm): t_R = 23.8 min, t_R = 49.2 min. $[\alpha]_D^{20}$ = +4.4 (*c* = 0.3, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*): δ 8.27 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.36 (ddd, *J* = 8.2, 7.6, 1.4 Hz, 1H), 7.19 (td, *J* = 7.6, 1.1 Hz, 1H), 7.07 (ddd, *J* = 7.6, 1.4, 0.6 Hz, 1H), 5.66 (ddd, *J* = 9.5, 8.4, 5.7 Hz, 1H), 4.32 (d, *J* = 8.4 Hz, 1H), 3.73 (qd, *J* = 7.2, 1.7 Hz, 2H), 2.81 (dtd, *J* = 13.9, 9.2, 7.5 Hz, 1H), 2.74 (s, 3H), 2.73 – 2.53 (m, 2H), 2.06 (ddd, *J* = 13.0, 7.6, 4.3 Hz, 1H), 0.70 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 178.8, 170.9, 167.9, 139.8, 129.6, 129.3, 125.6, 122.6, 117.0, 85.7, 61.8, 57.8, 56.8, 37.2, 30.8, 26.8, 13.5 ppm. IR (KBr): ν = 1759 (C=O, ester, amide), 1738 (C=O, ester, amide), 1699 (C=O, ester, amide), 1554 (NO_2), 1309 (NO_2) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{17}H_{19}N_2O_6$ $[M+H]^+$: 347.1243, found: 347.1540.

*Ethyl 3-nitro-2'-oxospiro[cyclopentane-1,3'-indoline]-2-carboxylate (***3f**/**4f**/**4f′***)*

The title compounds were synthesized according to the GP2, using methyleneindolinone **1f** (21.7 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 168 hours. The products were purified by column chromatography (hexane/EtOAc - 3:1). The diastereomeric ratio of **3f**/**4f**/**4f′** = 3/1/4. Products were obtained as inseparable mixture of diastereomers **3f**/**4f′** and diastereomer **4f** as inseparable mixture with inseparable byproduct.

Inseparable mixture of diastereomers (**3f**/**4f′**) = 1/1. Yellow oil. Combined yield (**3f**/**4f′**) = 20% (8 mg). 0/0% *ee*, the enantiomeric excess of product **3f** was determined by HPLC using a Chiralpak® IC column (*n*-heptane/*i*-PrOH - 90:10, flow rate = 1.0 mL/min, λ = 208 nm): t_R = 9.6 min, t_R = 12.6 min, the enantiomeric excess of product **4f′** was determined by HPLC using a Chiralpak® IC column (*n*-heptane/*i*-PrOH - 90:10, flow rate = 1.0 mL/min, λ = 207 nm): t_R = 13.6 min, t_R = 28.1 min. $[\alpha]_D^{20}$ = 0 (*c* = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*, **4f′** − H′, **3f** − H): δ 8.35 (br s, 1H′), 7.99 (br s, 1H), 7.35 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.29 – 7.21 (m, 1H′ + 1H, *overlapped*), 7.11 (td, *J* = 7.6, 1.0 Hz, 1H), 7.06 – 6.98 (m, 2H′), 6.92 (ddd, *J* = 9.5, 7.7, 0.8 Hz, 1H′+ 1H, *overlapped*), 5.76 – 5.63 (m, 1H′ + 1H, *overlapped*), 4.27 (d, *J* = 8.1 Hz, 1H′), 4.19 (d, *J* = 7.2 Hz, 1H), 4.10 – 3.95 (m, 2H), 3.83 (dq, *J* = 10.8, 7.1 Hz, 1H′), 3.74 (dq, *J* = 10.7, 7.1 Hz, 1H′), 3.06 – 2.94 (m, 1H), 2.81 – 2.62 (m, 2H′), 2.53 (dt, *J* = 13.1, 9.0 Hz, 1H′), 2.47 – 2.16 (m, 3H), 2.00 (ddd, *J* = 13.1, 7.3, 4.8 Hz, 1H′), 1.08 (t, *J* = 7.1 Hz, 3H), 0.72 (t, *J* = 7.1 Hz, 3H′) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*, **4f′** − C′, **3f** − C): δ 180.5 (1C), 179.4 (1C′), 168.7 (1C), 168.5 (1C′), 140.8 (1C), 140.6 (1C′), 131.2 (1C), 130.6 (1C′), 129.2 (1C′), 128.9 (1C), 123.5 (1C′), 123.2 (1C), 123.0 (1C′), 122.6 (1C), 110.2 (1C′), 110.0 (1C), 87.4 (1C), 86.1 (1C′), 61.9 (1C), 61.6 (1C′), 56.8 (1C), 56.5 (1C′), 36.5 (1C′+1C, *overlapped*), 30.9 (1C), 30.8 (1C′), 13.8 (1C), 13.5 (1C′) ppm, one *q*C′ and one *q*C was not found. IR (KBr): *v* = 3192 (N-H), 1734 (C=O, ester, amide), 1707 (C=O, ester, amide), 1552 (NO_2), 1342 (NO_2) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{15}H_{16}N_2NaO_5$ $[M+Na]^+$: 327.0951, found: 327.0948.

*1′-(tert-Butyl) 2-ethyl (1R,2R,3R)-5′-methyl-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (***3g***)*

The title compound was synthesized according to the GP2, using methyleneindolinone **1g** (33.1 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 66 hours. The product was purified by column chromatography (hexane/EtOAc - 10:1). The diastereomeric ratio of **3g**/**4g** = 13/1.

Yellow oil. Yield = 69% (29 mg). 99% *ee*, the enantiomeric excess of product **3g** was determined by HPLC using a Chiralpak® IA column (*n*-heptane/*i*-PrOH - 90:10, flow rate = 1.0 mL/min, λ = 204 nm): t_R = 4.9 min, t_R = 6.0 min. $[\alpha]_D^{20}$ = +19.9 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.71 (d, *J* = 8.3 Hz, 1H), 7.19 – 7.09 (m, 2H), 5.68 (ddd, *J* = 9.4, 6.8, 3.6 Hz, 1H), 4.18 (d, *J* = 6.8 Hz, 1H), 4.10 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.94 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.09 – 2.89 (m, 1H), 2.45 – 2.19 (m, 6H), 1.63 (s, 9H), 1.06 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 177.7, 168.5, 149.2, 137.4, 134.9, 129.6, 129.6, 122.6, 115.1, 87.6, 84.6, 62.0, 57.9, 56.7, 37.7, 31.2, 28.2 (3C), 21.3, 13.7 ppm. IR (KBr): *v* 1786 (C=O, ester, amide), 1757 (C=O, ester, amide), 1732 (C=O, ester, amide), 1552 (NO_2), 1369 (NO_2) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{21}H_{26}N_2NaO_7$ $[M+Na]^+$: 441.1632, found: 441.1626.

*1′-(tert-Butyl) 2-ethyl (1R,2R,3R)-5′-methoxy-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (***3h***)*

The title compound was synthesized according to the GP2, using methyleneindolinone **1h** (33.1 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 71 hours. The product was purified by column chromatography (hexane/EtOAc - 10:1). The diastereomeric ratio of **3h**/**4h** = 15/1.

Yellow oil. Yield = 56% (25 mg). 99% *ee*, the enantiomeric excess of product **3h** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 207 nm): t_R = 6.5 min, t_R = 8.6 min. $[\alpha]_D^{20}$ = +20.4 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.76 (d, *J* = 8.9 Hz, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.6 Hz, 1H), 5.69 (ddd, *J* = 10.1, 6.7, 3.7 Hz, 1H), 4.17 (d, *J* = 6.7 Hz, 1H), 4.10 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.95 (dq, *J* = 10.5, 7.1 Hz, 1H), 3.84 (s, 3H), 2.99 (dq, *J* = 14.4, 9.4 Hz, 1H), 2.39 (ddt, *J* = 14.6, 7.5, 4.0 Hz, 1H), 2.33 – 2.21 (m, 2H), 1.62 (s, 9H), 1.07 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 177.5, 168.4, 157.5, 149.2, 133.1, 130.9, 116.3, 113.7, 108.3, 87.6, 84.6, 62.0, 57.9, 57.0, 55.9, 37.7, 31.3, 28.2 (3C), 13.7 ppm. IR (KBr): *v* 1784 (C=O, ester, amide), 1755 (C=O, ester, amide), 1728 (C=O, ester, amide), 1552 (NO_2), 1369 (NO_2) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{21}H_{26}N_2NaO_8$ $[M+Na]^+$: 457.1581, found: 457.1584.

*1′-(tert-Butyl) 2-ethyl 3-nitro-2′-oxo-5′-(trifluoromethyl)spiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (***3i**/**4i***)*

The title compounds were synthesized according to the GP2, using methyleneindolinone **1i** (38.5 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 22 hours. the general procedure. The products were purified by column chromatography (hexane/EtOAc - 10:1), the diastereomeric ratio of **3i**/**4i** = 3/1. Products were obtained as inseparable mixture of diastereomers **3i**/**4i** with **5i**.

Inseparable mixture (**3i**/**4i**/**5i**) = 14/1/5. Yellow oil. NMR yield (**3i**) = 22%, 90% *ee* (**3i**) , the enantiomeric excess of product **3i** was determined by HPLC using a Chiralpak® IC column (*n*-heptane/*i*-PrOH - 98:2, flow rate = 1.0 mL/min, λ = 204 nm): t_R = 17.6 min, t_R = 36.2 min. $[\alpha]_D^{20}$ = -3.5 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*, **3i** − H″, **4i** − H′, **5i** − H): δ 8.06 (d, *J* = 8.6 Hz, 1H′), 8.02 – 7.96 (m, 1H′′+1H, *overlapped*), 7.63 (ddd, *J* = 8.5, 1.9, 0.9 Hz, 1H′′+1H′, *overlapped*), 7.62 – 7.59 (m, 1H′′), 7.57 (ddd, *J* = 8.6, 2.0, 0.9 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H′+1H, *overlapped*), 7.25 (q, *J* = 2.6 Hz, 1H), 5.73 – 5.66 (m, 1H′′), 5.63 (dd, *J* = 8.7, 6.4 Hz, 1H′), 4.58 (t, *J* = 6.5 Hz, 1H′), 4.34 (d, *J* = 8.4 Hz, 1H′), 4.24 (d, *J* = 6.8 Hz, 1H′′), 4.10 (dq, *J* = 10.8, 7.2 Hz, 1H′′), 4.04 – 3.91 (m, 1H′′+2H, *overlapped*), 3.77 (q, *J* = 7.1 Hz, 1H′), 3.11 – 2.94 (m, 1H′′), 2.88 (tdd, *J* = 6.6, 4.7, 3.3 Hz, 2H), 2.83 – 2.75 (m, 1H′), 2.76 – 2.66 (m, 1H+1H′, *overlapped*), 2.48 – 2.37 (m, 1H′′+1H′, *overlapped*), 2.37 – 2.23 (m, 2H′′), 2.12 – 2.00 (m, 1H′), 1.67 (s, 9H′), 1.65 (s, 9H), 1.64 (s, 9H′′), 1.08 (t, *J* = 7.1 Hz, 3H′′), 1.04 (d, *J* = 7.1 Hz, 3H), 0.76 (t, *J* = 7.1 Hz, 3H′) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*, **3i** − C″, **4i** − C′, **5i** − C): δ 177.1 (1C), 176.7 (1C″), 168.1 (1C″), 167.7 (1C), 162.4 (1C), 148.9, (1C″) 148.7 (1C), 142.7 (1C″), 137.4 (1C″), 133.0 (1C), 130.2 (1C″), 127.3 (q, *J* = 33.1 Hz, 1C″), 126.6 (q, *J* = 3.8 Hz, 1C″), 126.0 (q, *J* = 3.8 Hz, 1C), 123.9 (q, *J* = 272.1 Hz, 1C″), 119.3 (q, *J* = 3.6 Hz, 1C), 119.0

(q, J = 3.8 Hz, 1C″), 115.4 (1C″), 115.1 (1C), 87.2 (1C″ + 1C, *overlapped*), 85.4 (1C″), 62.2 (1C″), 60.8 (1C), 57.8 (1C″), 56.4 (1C), 38.0 (1C), 37.3 (1C″), 32.2 (1C), 31.0 (1C″), 28.1 (3C″ + 3C, *overlapped*), 13.7 (1C), 13.6 (1C″) ppm, four *qC* were not found. ^{19}F NMR (376 MHz, chloroform-*d*, **3i** − F″, **4i** − F′, **5i** − F): δ -61.83 (d, J = 0.8 Hz, 3F), -61.90 (d, J = 0.8 Hz, 3F″), -61.98 (s, 3F′) ppm. IR (KBr): ν = 1792 (C=O, ester, amide), 1766 (C=O, ester, amide), 1734 (C=O, ester, amide), 1556 (NO_2), 1371 (NO_2), 1120 (C-CF_3) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{20}H_{23}N_2NaO_7$ $[M+Na]^+$: 495.1350, found: 495.1357. *Note:* $^{13}C\{^1H\}$ NMR was determined for mixture **3i/5i**.

*1′-(tert-Butyl) 2-ethyl (1R,2R,3R)-5′-fluoro-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (***3k**)

The title compound was synthesized according to the GP2, using methyleneindolinone **1k** (33.5 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 43 hours. The product was purified by column chromatography (hexane/EtOAc - 10:1), the diastereomeric ratio of **3k**/**4k** > 20/1.

Yellow oil. Yield = 49% (21 mg). 99% *ee*, the enantiomeric excess of product **3k** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 207 nm): t_R = 5.8 min, t_R = 6.4 min. $[\alpha]_D^{20}$ = +5.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.84 (dd, J = 9.0, 4.5 Hz, 1H), 7.11 (dd, J = 7.6, 2.7 Hz, 1H), 7.04 (td, J = 8.9, 2.7 Hz, 1H), 5.68 (ddd, J = 9.5, 6.6, 3.5 Hz, 1H), 4.16 (d, J = 6.7 Hz, 1H), 4.10 (dq, J = 10.8, 7.2 Hz, 1H), 3.96 (dq, J = 10.7, 7.1 Hz, 1H), 3.07 – 2.91 (m, 1H), 2.47 – 2.35 (m, 1H), 2.32 – 2.22 (m, 2H), 1.63 (s, 9H), 1.07 (t, J = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 177.0, 168.2, 160.4 (d, J = 244.6 Hz, 1C), 149.1, 135.8 (d, J = 2.7 Hz, 1C), 131.5 (d, J = 7.9 Hz, 1C), 116.8 (d, J = 7.9 Hz, 1C), 115.7 (d, J = 22.7 Hz, 1C), 109.7 (d, J = 24.6 Hz, 1C), 87.5, 85.0, 62.2, 57.9, 56.9 (d, J = 1.9 Hz, 1C), 37.6, 31.3, 28.2 (3C), 13.7 ppm. ^{31}F NMR (376 MHz, $CDCl_3$): δ -116.68 (ddd, J = 9.0, 7.6, 4.6 Hz) ppm. IR (KBr): ν = 1788 (C=O, ester, amide), 1759 (C=O, ester, amide), 1732 (C=O, ester, amide), 1552 (NO_2), 1369 (NO_2), 1246 (C-F) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{20}H_{23}FN_2NaO_7$ $[M+Na]^+$: 445.1382, found: 445.1380.

*1′-(tert-Butyl) 2-ethyl 5′-chloro-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (***3l/4l***)*

The title compounds were synthesized according to the GP2, using methyleneindolinone **1l** (35.2 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 70 hours. The products were purified by column chromatography (hexane/EtOAc - 10:1). The diastereomeric ratio of **3l**/**4l** = 3/1.

Inseparable mixture of diastereomers **3l**/**4l** = 3/1. Yellow oil. Combined yield **3l**/**4l** = 44% (19 mg). 88/39% *ee* (**3l**/**4l**), the enantiomeric excess of product **3l** was determined by HPLC using a Chiralpak® IG column (*n*-heptane/*i*-PrOH - 90:10, flow rate = 1.0 mL/min, λ = 206 nm): t_R = 8.1 min, t_R = 11.7 min, the enantiomeric excess of product **4l** was determined by HPLC using a Chiralpak® IG column (*n*-heptane/*i*-PrOH - 90:10, flow rate = 1.0 mL/min, λ = 206 nm): t_R = 10.0 min, t_R = 10.8 min. $[\alpha]_D^{20}$ = +13.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*, **3l** − H′, **4l** − H): δ 7.88 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H′), 7.36 (d, J = 2.0 Hz, 1H′), 7.32 (ddd, J = 8.8, 2.2, 0.8 Hz, 1H′+1H, *overlapped*), 7.01 (d, J = 2.2 Hz, 1H), 5.67 (ddd, J = 9.4, 6.7, 3.5 Hz, 1H′), 5.64 – 5.57 (m, 1H), 4.32 (d, J = 8.4 Hz, 1H), 4.18 (d, J = 6.7 Hz, 1H′), 4.10 (dq, J = 10.7, 7.1 Hz, 1H′), 3.97 (dq, J = 10.8, 7.1 Hz, 1H′), 3.80 (qd, J = 7.1, 4.6 Hz, 2H), 3.49 – 3.39 (m, 1H), 3.05 – 2.93 (m, 1H′), 2.88 – 2.62 (m, 1H), 2.57 (dt, J = 13.2, 8.9 Hz, 1H), 2.47 – 2.35 (m, 1H′), 2.35 – 2.23 (m, 2H′), 2.05 – 1.97 (m, 1H), 1.65 (s, 9H), 1.62 (s, 9H′), 1.07 (t, J = 7.1 Hz, 3H′), 0.80 (t, J = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*, **3l** − C′, **4l** − C): δ 176.8 (1C′), 175.7 (1C), 168.2 (1C′), 167.9 (1C), 148.9 (1C′+1C, *overlapped*), 138.4 (1C′), 138.2 (1C), 131.4 (1C′), 130.8 (1C), 130.6 (1C′), 130.3 (1C), 129.4 (1C), 129.2 (1C′), 123.0 (1C), 122.5 (1C′), 116.8 (1C′+1C, *overlapped*), 87.4 (1C′+1C, *overlapped*), 85.5 (1C′), 85.4 (1C), 62.2 (1C′), 61.9 (1C), 57.9 (1C′), 57.6 (1C), 56.6 (1C′), 56.5 (1C), 37.5 (1C′), 37.1 (1C), 31.2 (1C′), 30.7 (1C), 28.2 (3C′+3C, *overlapped*) 13.7 (1C′), 13.5 (1C) ppm. IR (KBr): ν = 1790 (C=O, ester, amide), 1761 (C=O, ester, amide), 1732 (C=O, ester, amide), 1556 (NO_2), 1371 (NO_2), 752 (C-Cl) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{20}H_{23}ClN_2NaO_7$ $[M+Na]^+$: 461.1086, found: 461.1088.

*1′-(tert-Butyl) 2-ethyl (1R,2R,3R)-5′-bromo-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (***3m***)*

The title compound was synthesized according to the GP2, using methyleneindolinone **1m** (39.6 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 22 hours. The product was purified by column chromatography (hexane/EtOAc - 10:1). The diastereomeric ratio of **3m**/**4m** >20/1.

Yellow oil. Yield = 61% (29.3 mg). 99% *ee*, the enantiomeric excess of product **3m** was determined by HPLC using a Chiralpak® IA column (*n*-heptane/*i*-PrOH - 90:10, flow rate = 1.0 mL/min, λ = 205 nm): t_R = 5.1 min, t_R = 6.3 min. $[\alpha]_D^{20}$ = +24.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.76 (d, J = 8.5 Hz, 1H), 7.52 – 7.43 (m, 2H), 5.72 – 5.62 (m, 1H), 4.18 (d, J = 6.8 Hz, 1H), 4.10 (dq, J = 10.8, 7.1 Hz, 1H), 3.97 (dq, J = 10.7, 7.1 Hz, 1H), 3.07 – 2.90 (m, 1H), 2.47 – 2.20 (m, 3H), 1.62 (s, 9H), 1.08 (t, J = 7.2 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 176.7, 168.2, 148.9, 138.9, 132.1, 131.7, 125.3, 118.0, 117.0, 87.4, 85.2, 62.2, 57.9, 56.6, 37.5, 31.2, 28.2 (3C), 13.7 ppm. IR (KBr): ν 1790 (C=O, ester, amide), 1761 (C=O, ester, amide), 1730 (C=O, ester, amide), 1552 (NO_2), 1369 (NO_2), 538 (C-Br) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{20}H_{23}BrN_2NaO_7$ $[M+Na]^+$: 505.0580, found: 505.0577.

*1′-(tert-Butyl) 2-ethyl 6′-bromo-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (***3n**/**4n***)*

The title compounds were synthesized according to the GP2, using methyleneindolinone **1n** (39.6 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 42 hours. The products were purified by column chromatography (hexane/EtOAc - 10:1). The diastereomeric ratio of **3n**/**4n** = 3/1.

Inseparable mixture of diastereomers **3n**/**4n** = 4/1. Yellow oil. Combined yield **3n**/**4n** = 36% (17 mg). 97/97% *ee* (**3n**/**4n**), the enantiomeric excess of product **3n** was determined by HPLC using a Chiralpak® IA column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 208 nm): t_R = 4.4 min, t_R = 5.6 min, the enantiomeric excess of product **4n** was determined by HPLC using a Chiralpak® IA column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 208 nm):

t_R = 5.2 min, t_R = 6.2 min. $[\alpha]_D^{20}$ = +13.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*, **3n** − H′, **4n** − H): δ 8.15 (d, *J* = 1.8 Hz, 1H), 8.09 (d, *J* = 1.8 Hz, 1H′), 7.39 (dd, *J* = 8.0, 1.8 Hz, 1H′), 7.31 – 7.28 (m, 1H), 7.25 (d, *J* = 8.1 Hz, 1H′), 6.91 (d, *J* = 8.1 Hz, 1H), 5.67 (ddd, *J* = 9.4, 6.7, 3.5 Hz, 1H′), 5.59 (td, *J* = 8.8, 6.1 Hz, 1H), 4.30 (d, *J* = 8.4 Hz, 1H), 4.17 (d, *J* = 6.6 Hz, 1H′), 4.15 – 4.07 (m, 1H′), 3.97 (dq, *J* = 10.8, 7.1 Hz, 1H′), 3.79 (q, *J* = 7.1 Hz, 2H), 3.07 – 2.86 (m, 1H′), 2.79 – 2.63 (m, 2H), 2.56 (dt, *J* = 13.1, 8.9 Hz, 1H), 2.45 – 2.35 (m, 1H′), 2.31 – 2.22 (m, 2H′), 1.99 (ddd, *J* = 12.7, 7.4, 4.8 Hz, 1H), 1.66 (s, 9H), 1.63 (s, 9H′), 1.08 (t, *J* = 7.2 Hz, 3H′), 0.82 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*, **3n** − C′, **4n** − C): δ 176.9 (1C′), 175.8 (1C), 168.3 (1C′), 168.0 (1C), 148.9 (1C′ + 1C, *overlapped*), 140.9 (1C′), 140.7 (1C), 128.6 (1C), 128.1 (1C′), 128.0 (1C), 127.8 (1C′), 123.9 (1C), 123.3 (1C′), 123.2 (1C), 122.8 (1C′), 119.0 (1C), 118.9 (1C′), 87.5 (1C′+ 1C, *overlapped*), 85.5 (1C), 85.4 (1C′), 62.2 (1C′), 61.9 (1C), 57.8 (1C′), 57.5 (1C), 56.5 (1C′), 56.3 (1C), 37.5 (1C′), 37.1 (1C), 31.3 (1C′), 30.7 (1C), 28.2 (3C′ + 3C, *overlapped*), 13.8 (1C′), 13.5 (1C) ppm. IR (KBr): *v* = 1792 (C=O, ester, amide), 1763 (C=O, ester, amide), 1732 (C=O, ester, amide), 1552 (NO_2), 1369 (NO_2), 528 (C-Br) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{20}H_{23}BrN_2NaO_7$ $[M+Na]^+$: 505,0580; nalezeno: 505,0580.

*1′-(tert-Butyl) 2-methyl (1R,2R,3R)-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (**3o**)*

The title compound was synthesized according to the GP2, using methyleneindolinone **1o** (30.3 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 46 hours. The product was purified by column chromatography (hexane/EtOAc - 10:1). The diastereomeric ratio of **3o**/**4o** = 7/1.

Yellow oil. Yield = 59% (23 mg). 96% *ee*, the enantiomeric excess of product **3o** was determined by HPLC using a Chiralpak® IA column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 208 nm): t_R = 4.6 min, t_R = 5.2 min. $[\alpha]_D^{20}$ = +8.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.85 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.24 (td, *J* = 7.5, 1.1 Hz, 1H), 5.69 (ddd, *J* = 9.5, 6.9, 3.6 Hz, 1H), 4.24 (d, *J* = 6.9 Hz, 1H), 3.58 (s, 3H), 3.07 – 2.93 (m, 1H), 2.41 (ddt, *J* = 14.3, 7.4, 3.7 Hz, 1H), 2.35 – 2.21 (m, 2H), 1.64 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 177.6, 169.0, 149.1, 139.9, 129.4, 129.2, 125.2, 122.0, 115.5, 87.6, 84.8, 58.0, 56.7, 52.9, 37.5, 31.3, 28.2 (3C) ppm. IR (KBr): *v* 1763 (C=O, ester, amide), 1738 (C=O, ester, amide), 1724 (C=O, ester, amide), 1556 (NO_2), 1352 (NO_2) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{19}H_{22}N_2NaO_7$ $[M+Na]^+$: 413.1319; found: 413.1321.

*2-Benzyl 1′-(tert-butyl) (1R,2R,3R)-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (**3p**)*

The title compound was synthesized according to the GP2, using methyleneindolinone **1p** (37.9 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 70 hours. The product was purified by column chromatography (hexane/EtOAc - 10:1). The diastereomeric ratio of **3p**/**4p** = 6/1.

Yellow oil. Yield = 36% (17 mg). 99% *ee*, the enantiomeric excess of product **3p** was determined by HPLC using a Chiralpak® IA column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 210 nm): t_R = 4.7 min, t_R = 6.5 min. $[\alpha]_D^{20}$ = +7.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.76 (ddd, *J* = 8.1, 1.1, 0.6 Hz, 1H), 7.42 – 7.27 (m, 2H), 7.29 – 7.19 (m, 4H), 7.04 – 6.94 (m, 2H), 5.74 (ddd, *J* = 9.6, 6.9, 3.6 Hz, 1H), 5.06 – 4.91 (m, 2H), 4.28 (d, *J* = 7.0 Hz, 1H), 3.10 – 2.92 (m, 1H), 2.47 – 2.20 (m, 3H), 1.58 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 177.4, 168.3, 148.9, 139.8, 134.5, 129.3, 129.1, 128.6 (2C), 128.4, 127.7 (2C), 125.1, 122.0, 115.5, 87.5, 84.7, 67.7, 57.6, 56.8, 37.7, 31.0, 28.2 (3C) ppm. IR (KBr): *v* 1780 (C=O, ester, amide), 1730 (C=O, ester, amide), 1709 (C=O, ester, amide), 1543 (NO_2), 1369 (NO_2) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{25}H_{26}N_2NaO_7$ $[M+Na]^+$: 489.1632, found: 489.1630.

*di-tert-Butyl (1R,2R,3R)-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (**3q**)*

The title compound was synthesized according to the GP2, using methyleneindolinone **1q** (34.5 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 22 hours. The product was purified by column chromatography (hexane/EtOAc - 10:1), the diastereomeric ratio of **3q**/**4q** = 11/1.

Yellow oil. Yield = 39% (16 mg). 99% *ee*, the enantiomeric excess of product **3q** was determined by HPLC using a Chiralpak® IA column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 207 nm): t_R = 4.7 min, t_R = 6.5 min. $[\alpha]_D^{20}$ = +12.3 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.85 (dt, *J* = 8.2, 0.7 Hz, 1H), 7.38 (dt, *J* = 7.3, 0.9 Hz, 1H), 7.34 (td, *J* = 7.9, 1.5 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.1 Hz, 1H), 5.68 (ddd, *J* = 9.5, 6.6, 3.5 Hz, 1H), 4.10 (d, *J* = 6.6 Hz, 1H), 3.03 – 2.90 (m, 1H), 2.44 – 2.34 (m, 1H), 2.33 – 2.20 (m, 2H), 1.63 (s, 9H), 1.21 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 177.3, 167.5, 149.2, 139.8, 130.2, 128.9, 125.1, 122.0, 115.2, 87.7, 84.7, 83.2, 58.6, 56.9, 37.9, 31.1, 28.2 (3C), 27.6 (3C) ppm. IR (KBr): *v* 1782 (C=O, ester, amide), 1739 (C=O, ester, amide), 1726 (C=O, ester, amide), 1543 (NO_2), 1371 (NO_2) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{22}H_{28}N_2NaO_7$ $[M+Na]^+$: 455.1789, found: 455.1786.

*1′-(tert-Butyl) 2,2-diethyl 3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2,2-tricarboxylate (**3r**)*

The title compound was synthesized according to the GP2, using methyleneindolinone **1r** (38.9 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 168 hours (not full conversion of **1r** was observed). The product was purified by column chromatography (hexane/EtOAc - 10:1), the diastereomeric ratio of **3r**/**4r** = 13/1.

Yellow oil. Yield = 53% (25 mg). 65% *ee*, the enantiomeric excess of product **3r** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 205 nm): t_R = 4.8 min, t_R = 5.4 min. $[\alpha]_D^{20}$ = -26.0 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.15 (dd, *J* = 11.2, 7.8 Hz, 1H), 4.37 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.27 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.14 (dq, *J* = 11.2, 7.2 Hz, 1H), 4.01 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.01 – 2.91 (m, 1H), 2.90 – 2.80 (m, 1H), 2.69 (td, *J* = 12.7, 12.2, 7.3 Hz, 1H), 2.17 (ddd, *J* = 12.8, 9.2, 3.1 Hz, 1H), 1.62 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 177.5, 167.4, 166.7, 148.9, 140.3, 129.5, 127.0, 124.9, 123.4, 115.1, 88.3, 85.1, 68.2, 62.9, 62.4, 59.9, 34.4, 28.2 (3C), 27.7, 13.8, 13.4 ppm. IR (KBr): *v* 1786 (C=O, ester, amide), 1728 (C=O, ester, amide), 1552 (NO_2),

1346 (NO_2) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{23}H_{28}N_2NaO_9$ $[M+Na]^+$: 499.1687, found: 499.1683.

*tert-Butyl 3-nitro-2'-oxo-2-(trifluoromethyl)spiro[cyclopentane-1,3'-indoline]-1'-carboxylate (***3s**/**4s***)*

The title compounds were synthesized according to the GP2, using methyleneindolinone **1s** (31.3 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 64 hours. The products were purified by column chromatography (hexane/EtOAc - 10:1), the diastereomeric ratio of **3s**/**4s** = 2/1.

*tert-Butyl (1R,2R,3R)-3-nitro-2'-oxo-2-(trifluoromethyl)spiro[cyclopentane-1,3'-indoline]-1'-carboxylate (***3s***)*

Yellow oil. Yield = 18% (7 mg). 9% *ee*, the enantiomeric excess of product **3s** was determined by HPLC using a Chiralpak® IA column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 207 nm): t_R = 5.9 min, t_R = 7.6 min. $[\alpha]_D^{20}$ = -7.9 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.95 (d, *J* = 8.2 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.23 – 7.13 (m, 2H), 5.42 (td, *J* = 9.2, 4.4 Hz, 1H), 4.35 – 4.22 (m, 1H), 2.93 – 2.80 (m, 1H), 2.68 (ddd, *J* = 14.1, 7.8, 3.6 Hz, 1H), 2.61 (dt, *J* = 12.6, 9.8 Hz, 1H), 2.02 (ddd, *J* = 12.0, 7.5, 2.7 Hz, 1H), 1.66 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 175.1, 148.9, 139.2, 129.7, 126.9, 124.7, 124.6 (q, *J* = 279.3 Hz), 124.1, 115.8, 85.4, 84.9, 56.3 (q, *J* = 28.6 Hz), 55.8, 38.4, 31.6, 28.2 (3C) ppm. ^{19}F NMR (376 MHz, chloroform-*d*): δ -65.46 (d, *J* = 8.8 Hz) ppm. IR (KBr): *v* 1763 (C=O, ester, amide), 1732 (C=O, ester, amide), 1554 (NO_2), 1371 (NO_2), 1275 (C-CF_3) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{18}H_{19}F_3N_2NaO_5$ $[M+Na]^+$: 423.1138, found: 423.1126.

*tert-Butyl 3-nitro-2'-oxo-2-(trifluoromethyl)spiro[cyclopentane-1,3'-indoline]-1'-carboxylate (***4s***)*

Yellow oil. Yield = 15% (6 mg). 6% *ee*, the enantiomeric excess of product **4s** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 208 nm): t_R = 4.8 min, t_R = 6.1 min. $[\alpha]_D^{20} \sim 0$ (*c* = 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.27 (d, *J* = 14.9 Hz, 1H), 5.66 – 5.57 (m, 1H), 4.00 (p, *J* = 8.4 Hz, 1H), 3.26 – 3.14 (m, 1H), 2.47 – 2.35 (m, 2H), 2.28 (dd, *J* = 11.4, 8.3 Hz, 1H), 1.64 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 174.9, 148.9, 139.6, 129.8, 126.8, 125.4, 124.5 (q, J = 280.3 Hz), 122.1, 115.6, 85.3, 84.6, 56.9 (q, *J* = 28.6 Hz), 55.2, 37.3, 30.6, 28.2 (3C) ppm. ^{19}F NMR (376 MHz, chloroform-*d*): δ -65.34 (d, *J* = 8.4 Hz) ppm. IR (KBr): *v* 1790 (C=O, ester, amide), 1759 (C=O, ester, amide), 1732 (C=O, ester, amide), 1552 (NO_2), 1369 (NO_2), 1250 (C-CF_3) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{18}H_{19}F_3N_2NaO_5$ $[M+Na]^+$: 423.1138, found: 423.1141.

*tert-Butyl 2-benzoyl-2'-oxospiro[cyclopentane-1,3'-indolin]-2-ene-1'-carboxylate (***5t***)*

The title compounds were synthesized according to the GP2, using methyleneindolinone **1t** (34.9 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 18 hours. The products were purified by column chromatography (hexane/EtOAc - 10:1). Yellow oil. Yield = 47% (18 mg). 20% *ee*, the enantiomeric excess of product **5t** was determined by HPLC using a Chiralpak® IA column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 207 nm): t_R = 4.9 min, t_R = 6.6 min. $[\alpha]_D^{20}$ = 0 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.89 (dt, *J* = 8.1, 0.8 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.54 – 7.48 (m, 1H), 7.43 – 7.35 (m, 2H), 7.27 (ddd, *J* = 8.2, 6.7, 2.3 Hz, 1H), 7.13 – 7.04 (m, 2H), 6.94 (t, *J* = 2.6 Hz, 1H), 3.11 – 2.83 (m, 2H), 2.69 (ddd, *J* = 13.3, 8.9, 5.1 Hz, 1H), 2.28 (ddd, *J* = 13.3, 8.6, 6.1 Hz, 1H), 1.67 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 191.0, 177.7, 150.0, 149.7, 145.8, 140.1, 137.9, 132.5, 132.1, 129.1 (2C), 128.5, 128.4 (2C), 124.6, 121.9, 115.4, 84.2, 61.3, 37.7, 33.3, 28.3 (3C) ppm. IR (KBr): *v* 1778 (C=O, ester, amide) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{24}H_{23}NNaO_4$ $[M+Na]^+$: 412.1519, found: 412.1520.

*tert-Butyl 3-nitro-2'-oxo-2-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (***3v***)*

The title compound was synthesized according to the GP2, using methyleneindolinone **1v** (32.1 mg, 0.1 mmol), and 1-bromo-3-nitropropane (25.0 mg, 0.15 mmol), reaction time: 65 hours. The product was purified by column chromatography (hexane/EtOAc - 7:1). The diastereomeric ratio of **3v**/**4v** = 4/1.

Yellow oil. Yield = 45% (41 mg). 12% *ee*, the enantiomeric excess of product **3v** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 206 nm): t_R = 5.2 min, t_R = 5.9 min. $[\alpha]_D^{20}$ = +4.7 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.61 – 7.55 (m, 1H), 7.51 – 7.46 (m, 1H), 7.30 – 7.24 (m, 2H), 7.19 – 7.07 (m, 3H), 6.92 (dt, *J* = 8.6, 2.1 Hz, 2H), 5.99 – 5.91 (m, 1H), 4.09 (d, *J* = 10.5 Hz, 1H), 3.06 (dtd, *J* = 13.2, 8.9, 7.7 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.50 (ddd, *J* = 13.6, 10.6, 7.6 Hz, 1H), 2.40 (ddd, *J* = 13.5, 8.8, 4.3 Hz, 1H), 1.52 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 177.4, 148.6, 139.8, 132.5, 129.1, 128.6, 128.5 (2C), 128.4, 127.7 (2C), 125.0, 122.4, 115.1, 87.7, 84.4, 61.4, 60.1, 34.1, 29.9, 28.1 (3C) ppm. IR (KBr): *v* 1786 (C=O, amide), 1755 (C=O, amide), 1730 (C=O, amide), 1549 (NO_2), 1350 (NO_2) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{23}H_{24}N_2NaO_5$ $[M+Na]^+$: 431.1577, found: 431.1573.

*1'-(Tert-butyl) 2-ethyl 3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1',2-dicarboxylate (***6**/**6´***)*

The title compounds were synthesized according to the GP2, using methyleneindolinone **1a** (31.7 mg, 0.1 mmol), and commercially available bromonitromethane (21.0 mg, 0.15 mmol), reaction time: 72 hours. The products were purified by column chromatography (hexane/EtOAc - 8:1), the diastereomeric ratio (**6**/**6´**) = 4/1.

Inseparable mixture of diastereomers **6**/**6´** = 4/1. Light yellow oil. Combined yield **6**/**6´** = 59% (22 mg). 90/84% *ee* (**6**/**6´**), the enantiomeric excess of product **6** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 227 nm, *t* = 25 °C); t_R = 11.9 min, t_R = 16.8 min, the enantiomeric excess of product **6´** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 227 nm, *t* = 25 °C); t_R = 12.7 min, t_R = 24.0 min. $[\alpha]_D^{20}$ = +180.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*, diastereomer **6** − H′, diastereomer **6´** – H): δ 7.98 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.94 (dt, *J* = 8.3, 0.8 Hz, 1H´), 7.44 – 7.38 (m, 1H´+1H, *overlapped*), 7.29 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H), 7.22 – 7.17 (m, 2H´), 7.16 (dd, *J* = 2.5, 1.0 Hz, 1H), 5.30 (d, *J* = 6.2 Hz, 1H´), 5.27 (d, *J* = 6.3 Hz, 1H), 4.27 (qd, *J* = 7.1, 2.9

Hz, 2H′+1H, *overlapped*), 4.22 – 4.11 (m, 1H), 3.83 (d, *J* = 6.2 Hz, 1H′), 3.80 (d, *J* = 6.3 Hz, 1H), 1.63 (s, 9H′), 1.63 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H′), 1.24 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (chloroform-*d*, diastereomer **6** – C′, diastereomer **6′** – C) *δ* 168.3 (1C′), 167.4 (1C), 164.4 (1C), 163.0 (1C′), 148.7 (1C), 148.5 (1C′), 141.1 (1C′), 140.8 (1C), 130.3 (1C′), 130.1 (1C), 125.1 (1C′), 124.9 (1C), 122.4 (1C), 122.0 (1C′), 121.1 (1C), 120.2 (1C′), 115.7 (1C′), 115.6 (1C), 85.6 (1C′+1C, *overlapped*), 70.1 (1C′), 68.8 (1C), 62.8 (1C′+1C, *overlapped*), 40.1 (1C′), 39.4 (1C), 38.2 (1C), 35.9 (1C′), 28.2 (3C′+3C, *overlapped*), 14.1 (1C′+1C,*overlapped*) ppm. IR (ATR): ν 1793 (C=O, ester, amide), 1765 (C=O, ester, amide), 1736 (C=O, ester, amide), 1554 (NO_2), 1350 (NO_2) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{18}H_{20}N_2NaO_7$ $[M + Na]^+$, 399.1163; found, 399.1161.

Gram-scale organocascade reaction and late-stage transformations

*1′-(tert-Butyl) 2-ethyl (1R,2R,3R)-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (***3a***)*

The catalyst **C1** (12.4 mg, 0.001 mmol, 0.01 eq.) was added to a solution of the methyleneindolinone **1a** (1000.0 mg, 3.14 mmol, 1.0 equiv.) in anhydrous chloroform (16 ml) at room temperature. Then, 1-bromo-3-nitropropane (786 mg, 4.71 mmol, 1.5 eq.) and potassium carbonate (650 mg, 4.71 mmol, 1.5 eq.) were added. The reaction was stirred at room temperature 48 h. Then catalyst **C1** (12.4 mg, 0.001 mmol, 0.01 eq.) was added, addition of **C1** (12.4 mg, 0.001 mmol, 0.01 eq.) was repeated after next 48 h. With complete conversion of the methyleneindolinone **1a** (TLC monitored, reaction time: 161 hours) solvent was removed under reduced pressure. Crude product was purified by column chromatography (hexane/EtOAc - 10:1). The diastereomeric ratio of **3a**/**4a** > 20/1. Yield of **3a** = 61% (771 mg).

All analytical data matched the data of identical compounds prepared on a smaller scale.

*Ethyl (1R,2R,3R)-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-2-carboxylate (***3f***)*

TFA (38 µl, 0.5 mmol, 5.0 equiv.) was dropwise added (during 1 minute) to a stirred solution of spirocycle **3a** (40 mg, 0.1 mmol, 1.0 equiv., 99% *ee*) in anhydrous DCM (2.0 ml) at r.t. At this temperature, reaction mixture was stirred for 2 hours. After the full composition of starting material (monitored by TLC), reaction was quenched by careful addition of satured solution of $NaHCO_3$ (5 ml). Resulting mixture was diluted with DCM (5 ml). Organic phase was separated and the water phase was extracted with DCM (3 × 10 ml). Collected organic phases were washed with brine (1 × 10 ml) and dried over $MgSO_4$. After filtration of the drying agent, solvents were removed under reduced pressure. The crude product was purified by column chromatography with a mixture of hexane/EtOAc as an eluent (2:1).

Colorless oil. Yield = 90% (27 mg). 99% *ee*, the enantiomeric excess of product **3f** was determined by HPLC using a Chiralpak® IC column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 209 nm); t_R = 9.5 min, t_R = 12.2 min. $[\alpha]_D^{20}$ = +28.6 (*c* = 1.1, $CHCl_3$). ^1H NMR (600 MHz, chloroform-*d*): *δ* 8.28 (br s, 1H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 5.73 (ddd, *J* = 9.4, 7.2, 4.1 Hz, 1H), 4.18 (d, *J* = 7.2 Hz, 1H), 4.10 – 3.96 (m, 2H), 3.00 (dtd, *J* = 14.1, 10.1, 7.8 Hz, 1H), 2.46 – 2.37 (m, 1H), 2.32 (ddd, *J* = 13.4, 10.5, 8.8 Hz, 1H), 2.23 (ddd, *J* = 13.5, 7.8, 3.0 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 3H). ppm. $^{13}C\{^{1}H\}$ NMR (151 MHz, chloroform-*d*): *δ* 180.9, 168.7, 140.9, 131.2, 128.9, 123.2, 122.5, 110.1, 87.4, 61.9, 56.8, 56.5, 36.4, 30.9, 13.8 ppm. IR (ATR): *ν* 3159 (N-H, secondary amide), 1726 (C=O, ester, amide), 1701 (C=O, ester, amide), 1728 (C=O, ester, amide), 1545 (NO_2), 1360 (NO_2) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{15}H_{16}NO_3$ $[M+Na]^+$: 327.0951, found: 327.0956.

*1′-(Tert-butyl) 2-ethyl (S)-2′-oxospiro[cyclopentane-1,3′-indolin]-2-ene-1′,2-dicarboxylate (***5a***)*

DBU (30 µl, 0.2 mmol, 2.0 equiv.) was added in one portion to a stirred solution of spirocycle **3a** (40 mg, 0.1 mmol, 1.0 equiv., 99% *ee*) in DMSO (2.0 ml) at r.t. At this temperature, reaction mixture was stirred for 15 hours. After the full composition of starting material (monitored by TLC), reaction mixture was diluted with brine (10 ml). Resulting solution was extracted with EtOAc (3 × 10 ml). Collected organic phases were washed with brine (2 × 10 ml) and dried over $MgSO_4$. After filtration of the drying agent, solvents were removed under reduced pressure. The crude product was purified by column chromatography with a mixture of hexane/EtOAc as an eluent (7:1).

White semisolid. Yield = 92% (32 mg). 99% *ee*, the enantiomeric excess of product **5a** was determined by HPLC using a Chiralpak® IB column (*n*-heptane/*i*-PrOH - 99:2, flow rate = 1.0 mL/min, λ = 243 nm); t_R = 10.5 min, t_R = 14.7 min. $[\alpha]_D^{20}$ = -38.7 (*c* = 0.8, $CHCl_3$). ^1H NMR (600 MHz, chloroform-*d*): *δ* 7.84 (d, *J* = 8.2 Hz, 1H), 7.27 (td, *J* = 7.9, 1.6 Hz, 1H), 7.19 (t, *J* = 2.6 Hz, 1H), 7.10 (td, *J* = 7.5, 1.0 Hz, 1H), 7.06 (dd, *J* = 7.5, 1.5 Hz, 1H), 3.93 (qd, *J* = 7.2, 1.9 Hz, 2H), 2.92 – 2.76 (m, 2H), 2.67 (ddd, *J* = 13.4, 9.2, 6.4 Hz, 1H), 2.24 (ddd, *J* = 13.2, 8.3, 4.8 Hz, 1H), 1.64 (s, 9H), 1.01 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (151 MHz, chloroform-*d*): *δ* 177.9, 162.7, 149.5, 148.3, 139.5, 138.0, 132.4, 128.5, 124.6, 122.4, 115.0, 84.2, 60.6, 60.3, 38.2, 32.2, 28.2 (3C), 13.7 ppm. IR (ATR): *ν* 1793 (C=O, ester, amide), 1766 (C=O, ester, amide), 1707 (C=O, ester, amide) cm^{-1}. HRMS (ESI+) *m/z*: calcd. for $C_{20}H_{23}NNaO_5$ $[M+Na]^+$: 380.1468, found: 380.1469.

*1′-(tert-Butyl) 2-ethyl (1R,2S)-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate (***9***)*

Solution of spirocycle **5a** (18 mg, 0.05 mmol, 1.0 equiv., 99% *ee*) in MeOH (1.0 ml) was degassed (flask was evacuated and refilled with Ar three times) and Pd/C (10%, 10.6 mg, 0.2 equiv.) was added. The reaction flask was evacuated again and refilled with H_2 three times at r.t. Under hydrogen atmosphere (ballon), reaction mixture was stirred for 15 hours. After the full composition of starting material (monitored by TLC), reaction mixture was filtered through a short pad of Celite (washed was a minimal amount of MeOH. Resulting filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography with a mixture of hexane/EtOAc as an eluent (8:1). The diastereomeric ratio **9**/**9′** = 9/1.

Colorless oil. Yield = 97% (17 mg). 98% *ee*, the enantiomeric excess of product **9** was determined by HPLC using a Chiralpak® IC column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 208 nm); t_R = 7.6 min, t_R =13.9 min. $[\alpha]_D^{20} \sim 0$ (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*, only major diastereomer): *δ* 7.84 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.21 – 7.08 (m, 2H), 4.03 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.91 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.23 (dd, *J* = 10.7, 8.6

Hz, 1H), 2.57 – 2.42 (m, 1H), 2.37 – 2.17 (m, 3H), 2.01 – 1.88 (m, 2H), 1.63 (s, 9H), 1.06 (t, J = 7.1 Hz, 3H). ppm. $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d,* only major diastereomer): δ 178.5, 171.7, 149.6, 139.8, 132.9, 128.2, 124.6, 121.6, 115.0, 84.1, 60.9, 56.2, 55.8, 40.1, 28.9, 28.3 (3C), 24.2, 13.8 ppm. IR (ATR): ν 1790 (C=O, ester, amide), 1761 (C=O, ester, amide), 1724 (C=O, ester, amide) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{20}H_{25}NNaO_5$ $[M+Na]^+$: 382.1625, found: 382.1621.

*tert-Butyl (S)-2-(hydroxymethyl)-2'-oxospiro[cyclopentane-1,3'-indolin]-2-ene-1'-carboxylate (**10**)*

Solution of DIBALH (25 wt.% in toluene, 150 µl, 0.22 mmol, 2.2 equiv.) was dropwise added (during 3 minutes) to a stirred solution of spirocycle **5a** (36 mg, 0.1 mmol, 1.0 equiv., 99% *ee*) in anhydrous DCM (2.0 ml) at 0 °C (water/ice cooling bath). At this temperature, reaction mixture was stirred for 1 hour. After the full composition of starting material (monitored by TLC), reaction was quenched by careful addition of MeOH (1 ml) followed with Rochelle´s salt solution (5 ml). Resulting gelly solution was stirred before became to clear biphasic solution (aprox. 2 hours). Then organic phase was separated and water phase was extracted with DCM (3 × 10 ml). Collected organic phases were washed with brine (1 × 10 ml) and dried over $MgSO_4$. After filtration of the drying agent, solvents were removed under reduced pressure. The crude product was purified by column chromatography with a mixture of hexane/EtOAc as an eluent (3:1 to 2:1).

Colorless oil. Yield = 84% (27 mg). 96% *ee*, the enantiomeric excess of product **10** was determined by HPLC using a Chiralpak® IC column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 mL/min, λ = 240 nm); t_R = 8.0 min, t_R = 10.9 min. $[\alpha]_D^{20}$ = -117.7 (c = 0.3, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*): δ 7.98 – 7.61 (m, 1H), 7.26 – 7.14 (m, 2H), 6.99 (td, J = 7.5, 1.1 Hz, 1H), 5.75 (dd, J = 3.0, 1.5 Hz, 1H), 5.66 (s, 1H), 4.31 (d, J = 11.1 Hz, 1H), 3.89 (ddd, J = 7.4, 3.7, 1.9 Hz, 1H), 3.22 – 3.06 (m, 1H), 2.76 (ddd, J = 16.3, 8.7, 3.2 Hz, 1H), 2.41 – 2.23 (m, 2H), 1.60 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 149.5, 148.4, 128.6, 128.5, 124.7, 123.3, 122.5, 122.1, 114.9, 95.7, 64.9, 38.0, 37.5, 32.3, 28.6 (3C), 28.3 ppm. IR (ATR): ν 3408 (O-H, alcohol) 1705 (C=O, aldehyde, amide) cm^{-1}. HRMS (ESI+) *m*/*z*: calcd. for $C_{18}H_{23}NNaO_4$ $[M+Na]^+$: 340.1519, found: 340.1513.

Accession code

CCDC 2212693 contains the supplementary crystallographic data of this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_ request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Reaction conditions optimization, crystallographic data, copies of ^1H NMR, ^{13}C NMR, ^{19}F NMR, and copies chiral HPLC (PDF)

CIF file for compounds **3a** (CIF)

FAIR data, including the primary NMR FID files for all compounds (ZIP)

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Author Contributions

A.V., and V.D performed the synthesis of all compounds. S.P. performed selected NMR experiments. I.C. performed X-ray analysis. V.D., and J.V. wrote the manuscript. All authors have given approval to the final version of the manuscript.

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