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Spiro Compounds |*Hot Paper*|

Highly Stereoselective [4+2] and [3+2] Spiroannulations of 2-(2-Oxoindolin-3-ylidene)acetic Esters Catalyzed by Bifunctional Thioureas

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Abstract: A new Michael–Michael cascade reaction between 2-(2-oxoindolin-3-ylidene)acetic esters **1** and nitroenoates **2**, catalyzed by bifunctional thioureas, is investigated. The combination of the two Michael reactions results in a novel and facile [4+2] or [3+2] spiroannulation process, which is characterized by the following features: 1) two carbon–carbon bonds and four stereocenters, including a quaternary spiro carbon, are formed under mild conditions; 2) an unprecedented and stereochemically defined substitution pattern on the spirocarbocyclic unit is obtained; 3) the double-bond configuration of the donor–acceptor nitroenoate **2** determines the absolute configuration of the spiro center, whereas the remaining stereocenters are formed under control of the catalyst. The effect on the final stereochemical outcome of structural variations of each starting material, catalyst, and experimental conditions is analyzed in detail. In particular, the use of specifically designed chiral nitroenoates enables diverse polyfunctional spirocyclohexane derivatives containing six consecutive stereogenic centers to be constructed. To our knowledge, this is the first asymmetric organocatalytic strategy enabling both five- and six-membered β-nitro spirocarbocyclic oxindoles.

Introduction

The oxindole scaffold is present in the core structure of an impressive number of natural and synthetic bioactive compounds.[1] In particular, five- and six-membered spirocyclic oxindoles are considered privileged molecular structures associated with various compounds with potent pharmaceutical properties (Figure 1).[2] The considerable medicinal potential of the spirocyclic oxindole structural motif has led the scientific community to design innovative and efficient synthetic approaches,[3,4] exploiting either metal catalysts or organocatalysts. The greatest efforts were devoted to the asymmetric synthesis of the chiral backbone, often containing a sequence of stereocenters that includes the demanding quaternary spiro center at the 3-position of the oxindole ring. Domino reactions are particularly suited to address this challenge through an ordered sequence of C–C bond-forming reactions.[5] Indeed, organocascade processes have been recently employed in the enantioselective synthesis of spirocyclic oxindoles.[6] However, despite the considerable effort that has been made in this field, much work is needed to develop more flexible synthetic strategies, to expand structural and stereochemical diversity, and extend the functional pattern of spirocyclic oxindoles.

In this scenario lie the β-amino spirocarbocyclic oxindoles, which is a structural motif present in many bioactive indole alkaloids such as Gelsemine, Citrinadin A, and Marcfortine B (Figure 1), and related families of prenylated indole alkaloids,[7] including Paraherquamides,[8a,b] Sclerotiamide,[8c] Notoamides,[8d,e] Brevianamides,[8f,g] and Versicolamide B.[8e,h] Currently, the most used organocatalytic strategies that address amino-substituted spirooxindoles involve the introduction of a nitro group[9] as the amino group precursor. However, only a few examples of the organocatalyzed enantioselective synthesis of five- or six-membered β-nitro spirocarbocyclic oxindoles have been reported (Scheme 1, Eq. 1 and 2).[10–12] Moreover, the synthetic approach is almost invariably based on the use of nitroalkenes as Michael acceptors (Scheme 1, Eq. 1).[10] Only Kanger and co-workers developed a Michael–aldol cascade reaction employing nitroketones as donor/acceptor bifunctional synthons to generate β-nitro δ-hydroxy cyclopentane derivatives (Scheme 1, Eq. 2).[11] The limited number of approaches available for the synthesis of β-nitro spirocarbocyclic oxindoles mean that the development of innovative and efficient methodologies remains highly desirable.

As part of our ongoing studies on the asymmetric thiourea-catalyzed[13] conjugate addition of nitroalkanes to α,β-unsaturated systems,[14] we designed a new asymmetric Michael–Michael domino process involving multiple donor–acceptor reagents such as oxindoles **1** and nitro compounds **2**. A precisely defined sequence of C–C bond-forming reactions grants an ef-

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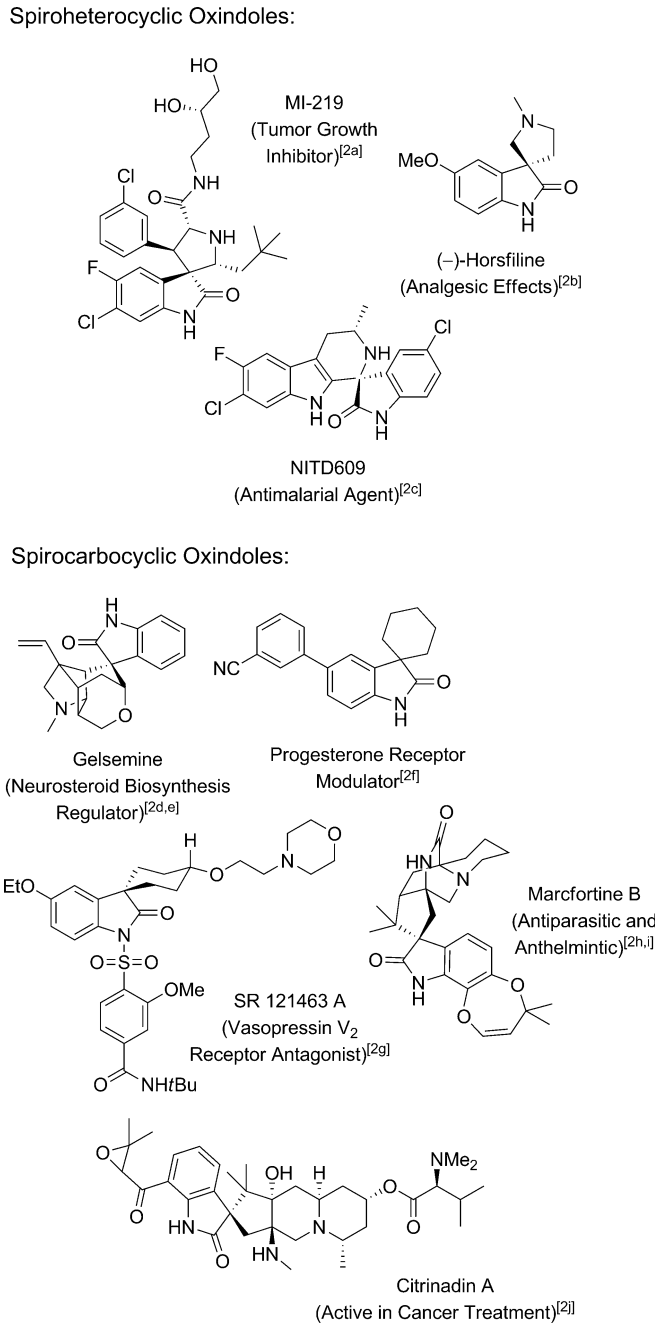


Figure 1. Natural and synthetic bioactive compounds containing a five- or six-membered spirocyclic oxindole core.

ficient spiroannulation methodology leading to β-nitro spirooxindoles **3** and **4** (Scheme 1, Eq. 3).

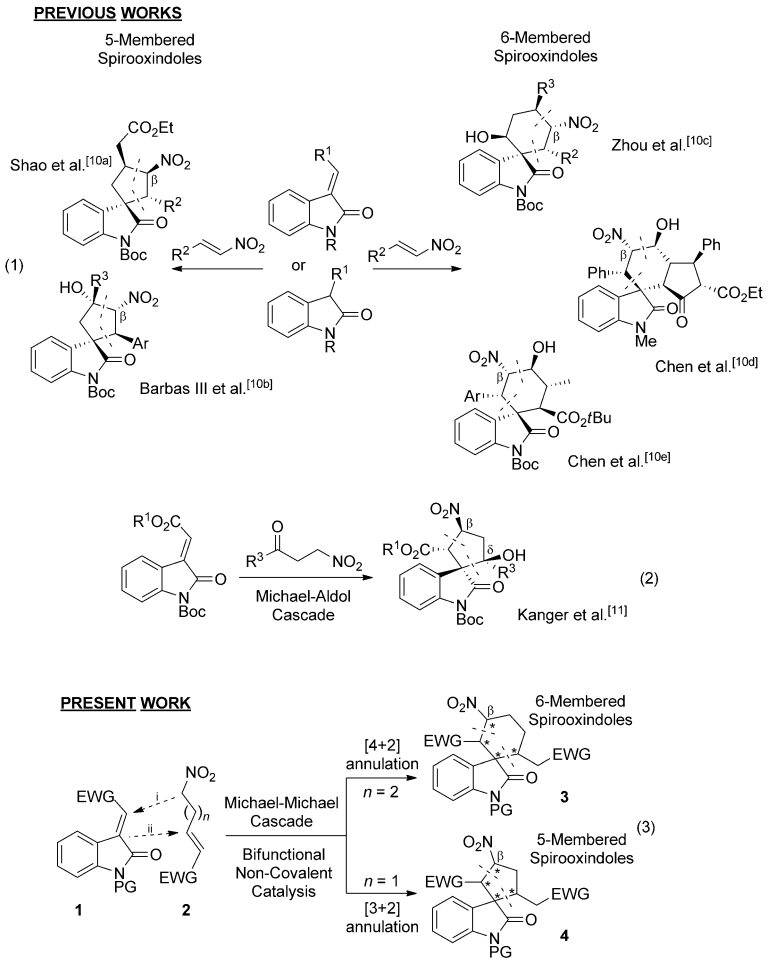
Results and Discussion

Synthesis of 1′-(*tert*-butyl) 2-ethyl 6-(2-ethoxy-2-oxoethyl)-3-nitro-2′-oxospiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate and analogues

Our preliminary investigations focused on the addition of nitroester (*E*)-**2a** to N-substituted (*E*)-ethyl 2-(2-oxoindolin-3-ylidene)acetates **1a**–**c** promoted by commercially available bifunctional Takemoto's catalyst **I**. The performance of the reaction depended strongly on the nature of the N-protecting group (Table 1, entries 1–3).

The *N*-Boc oxindole derivative **1c** afforded the desired six-membered β-nitro spirooxindole **3c** with high conversion (90%) as a single detectable diastereoisomer in 98% *ee* (Table 1, entry 3). However, *N*-benzyl oxindole **1b** showed both a lower reactivity (60% conversion after 7 days) and poorer enantioselectivity (75% *ee*, entry 2). Unprotected oxindole **1a** performed even less efficiently, yielding only acyclic intermediate **5a** (Table 1, entry 1). From a mechanistic point of view, the first step, namely the Michael addition of the nitronate derived from **2** to 3-ylidene oxindole **1**, afforded the *anti* acyclic adduct **5**, characterized by three new stereocenters. The absolute configurations of Cα and Cβ were controlled by the catalyst, whereas C3 was stereolabile under the adopted reaction conditions. As a consequence, **5** consisted of a 1:1 mixture of two C3 epimers. The second step involved the formation of a C3 enolate species of **5** and consequent intramolecular addition to the α,β-unsaturated ester, leading to a stereospecific [4+2] spiroannulation with well-defined configurations of the newly formed C3 and Cε stereocenters. The higher reactivity of the *N*-Boc adduct **5c** might be explained by considering that the acidity of C3-H is significantly affected by the nature of the N-protecting group (pK_a C3-H of *N*-acetyloxindole ≈ 13).[15] Thus, we carried out an optimization screening on **1c**, first testing the efficacy of catalysts **I**–**XII**. The best catalyst was the (1*R*,2*R*)-cyclohexane-1,2-diamine-based catalyst **I**, whereas all the Cinchona-derived bifunctional thioureas performed similarly. In particular, the vinyl substituent on the quinuclidine system (-R), the substituent on the quinoline ring (-R^1), and the group installed on the thiourea moiety (-R^2) were systematically varied, without appreciable changes in reactivity or stereoselectivity. The spirooxindole **3c** conversions ranged between 46 and 61% (7 days reaction time; Table 1, entries 4–11) and the stereocontrol was invariably high (95–97% *ee*) with all the catalysts except for **VII** and **IX**, which provided slightly worse results (86% *ee*; Table 1, entries 9 and 11). As expected, pseudo-enantiomeric catalysts (**II** and **V**) afforded opposite enantiomers (Table 1, entries 4 and 7). The crucial role in determining the enantioselectivity played by the thiourea moiety was confirmed by employing alkaloids **X** and **XI** (entries 12–13). Although a bifunctional system was still present, these catalysts exerted lower levels of stereocontrol (66–73% *ee*). Disappointingly, Jacobsen's thiourea **XII** proved to be less competent (Table 1, entry 14). Having established that the best performance in terms of both reaction rate and stereocontrol was obtained with catalyst **I**, we optimized the reaction conditions using Takemoto's catalyst. The effects of catalyst loading and solvent were investigated (see the Supporting Information) and the optimal conditions were elected as 10 mol% **I** and dichloromethane (CH_2Cl_2) as the reaction medium.

To expand the scope of the reaction, our protocol was applied to a variety of 3-ylidene oxindoles (**1c**–**p**); we were delighted to find that the process tolerated a range of substitution patterns (Table 2). The reactions proceeded smoothly when the oxindole aromatic ring was decorated with either



Scheme 1. Asymmetric organocatalytic syntheses of five- and six-membered β-nitro spirocarbocyclic oxindoles (EWG = electron-withdrawing group; PG = protecting group).

electron-withdrawing groups (EWG; Table 2, entries 2–4) or electron-donating groups (EDG; Table 2, entries 5–7), although both the yield and *ee* were affected by the position of the substituent (Table 2, entries 2 and 3 vs. entry 4). As a general trend, oxindoles substituted with an EWG reacted faster than those with an EDG group (Table 2, entries 2–4 vs. entries 5–7).

The ethyl ester could be smoothly replaced by a benzyl ester (74% yield and 96% *ee* in only 24 h, entry 8). We also investigated the replacement of the ester on the oxindole double bond with other electron-withdrawing groups. The insertion of an aromatic ketone (entry 9) provided a complex mixture of compounds, from which the desired product **3k** was isolated in very good *ee* (90%), but in very low yield (19%). The *para*-nitrophenyl derivative **1l** afforded the product in good yield but with poor stereocontrol (entry 10), whereas the cyano-substituted substrate **1m** showed both inadequate yield and *ee* (entry 11). As demonstrated for the addition of nitroalkanes to 3-ylidene oxindoles,[14a] the ester group on the indolinone exocyclic double bond is essential to force the domino process on a well-defined and stereochemically unambiguous reaction pathway.[16] According to the dual activation model,[17] the bifunctional organocatalyst can simultaneously activate both the Michael donor and the acceptor, and governs the nitroalkane approach to the 3-ylidene oxindole during the first step of the cascade reaction. The thiourea moiety reasonably coordinates the oxindole through multiple hydrogen bonds and the ester group participates in the catalyst–substrate interaction, enhancing the electrophile reactivity and ensuring a high enantioselectivity.

The relative configuration of the stereocenters in this series of products was unambiguously identified through X-ray crystallographic analysis of compound **3c**.[18] Here, a *trans* orientation between nitro and ester groups and a *cis* orientation between ester and Cε-chain were identified (Figure 2; see the Supporting Information for details).

We were also committed to the challenging construction of a second quaternary stereocenter at the Cα position, contiguous to the quaternary spiro carbon (C3). To this end, the protocol was applied to substrates **1n–p**, featuring a tetrasubstituted double bond. The reactivity

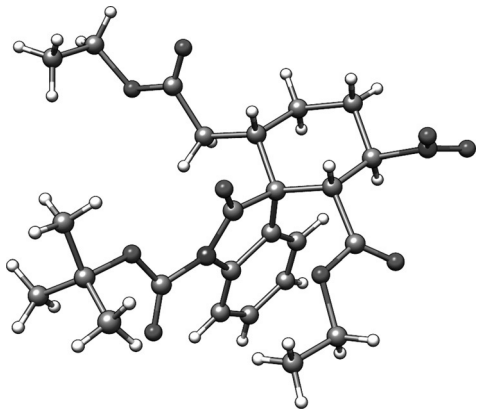
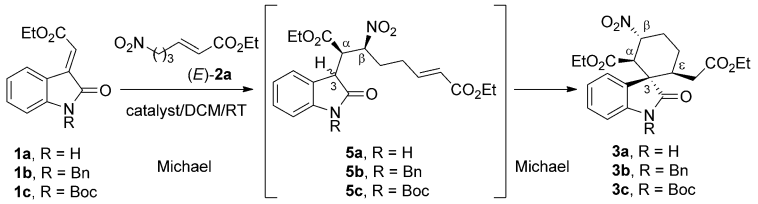
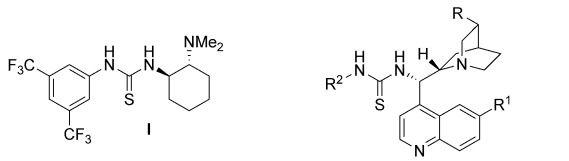


Figure 2. Determination of the relative stereochemistry of β-nitro cyclohexane spirooxindole **3c** through X-ray crystallographic analysis.

of these 3-ylidene oxindoles was much lower. The nitroalkane conjugate addition did not proceed at all on derivative **1p** (R^2 = NHBoc, R^3 = CO_2Me; entry 14), whereas two equivalents of nitro compound and 20 mol% of catalyst **I** were required to obtain the α-methylated product **3n** in acceptable yield (entries 12–13). However, the process retained an excellent stereo-

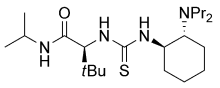
Table 1. N-Protecting groups and catalyst screening in the asymmetric Michael–Michael organocascade reaction between 3-ylidene oxindoles **1a–c** and nitroester (*E*)-**2a**.[a]



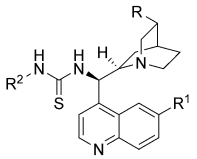


I

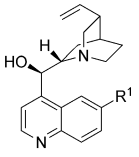
II, R = CH=CH$_2$, R^1 = H, R^2 = 3,5-(CF$_3$)$_2$Ph
III, R = CH$_2$CH$_3$, R^1 = H, R^2 = 3,5-(CF$_3$)$_2$Ph
IV, R = CH=CH$_2$, R^1 = OMe, R^2 = *t*Bu



XII



V, R = CH=CH$_2$, R^1 = H, R^2 = 3,5-(CF$_3$)$_2$Ph
VI, R = CH=CH$_2$, R^1 = OMe, R^2 = 3,5-(CF$_3$)$_2$Ph
VII, R = CH$_2$CH$_3$, R^1 = OMe, R^2 = 3,5-(CF$_3$)$_2$Ph
VIII, R = CH=CH$_2$, R^1 = H, R^2 = Ph
IX, R = CH=CH$_2$, R^1 = H, R^2 = CHPh$_2$



X, R^1 = OMe
XI, R^1 = H

Entry	Substrate	Cat.	*t* [d]	Product	Conversion [%][b]	*ee* [%][c]
1	**1a**	**I**	4	**3a**	trace	–
2	**1b**	**I**	7	**3b**	60	75
3	**1c**	**I**	3	**3c**	90	98
4	**1c**	**II**	7	**3c**	54	96[d]
5	**1c**	**III**	7	**3c**	60	96[d]
6	**1c**	**IV**	7	**3c**	46	95[d]
7	**1c**	**V**	7	**3c**	49	96
8	**1c**	**VI**	7	**3c**	54	97
9	**1c**	**VII**	7	**3c**	61	86
10	**1c**	**VIII**	7	**3c**	56	95
11	**1c**	**IX**	7	**3c**	47	86
12	**1c**	**X**	7	**3c**	52	66
13	**1c**	**XI**	7	**3c**	59	73
14	**1c**	**XII**	7	**3c**	60	63

[a] Reaction conditions: **1** (0.1 mmol), (*E*)-**2a** (0.12 mmol), catalyst (10 mol%), CH_2Cl_2 (0.15 mL), RT. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. Products **3b** and **3c** were detected as single diastereoisomers. [c] Determined by chiral stationary phase HPLC (CSP-HPLC) analysis of isolated product **3**. [d] Opposite enantiomer was formed.

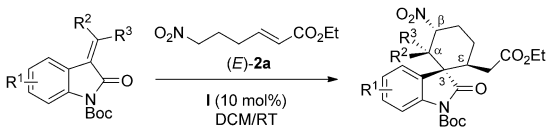
selectivity, allowing the isolation of spiroindolinone **3n**, characterized by two adjacent quaternary stereocenters, in 95% *ee*. A possible explanation for the low yield of **3n** might lie in the reactivity of the allylic position, which was already demonstrated for 3-ylidene oxindoles in the presence of bifunctional organocatalysts.[19] Under our reaction conditions, alkylidene indolinones **1n** and **1o** could undergo deprotonation[20] to an intermediate dienolate (Scheme 2), which was likely responsible for a variety of side reactions that decreased the yield of the desired spirocycle. Another interesting remark concerning substrates **1n** and **1o** is that the α-methyl spirooxindole **3n** was formed with high *ee* and the same absolute stereochemistry, regardless of the starting *Z*/*E* double bond configuration. ^{1}H NMR spectra showed that double-bond isomerization occurred when pure **1n** or **1o** was exposed to catalyst **I**,[21] likely via an intermediate dienolate (Scheme 2; see the Supporting Information for experimental details). The observed stereoconvergence suggested that only one of the two isomeric 3-ylidene-indolin-2-ones participated as acceptor to the first intermolecular Michael reaction with (*E*)-**2a**. Moreover, 1D NOESY experiments on product **3n** indicated the same relative stereochemistry previously observed for spirooxindole **3c**, leading us to hypothesize that the (*E*)-configured 3-ylidene indolinone **1n** was the reactive species.

The good results obtained with 3-ylidene oxindoles **1c–o** prompted us to explore different nitro compounds (Tables 3 and 4), with the aim of further increasing the structural and the stereochemical diversity of the β-nitro spirocyclohexane indolinones **3**.

We confirmed that replacement of the ethyl ester with a benzyl group was well tolerated (Table 3, entry 2). When we moved to (*E*)-**2c**, the α,β-unsaturated ketone triggered side reactions, affording a complex mixture of products (Table 3, entry 3). The use of the cyano derivative (*E*)-**2d** allowed the corresponding spirooxindole **3s** to be obtained in high yield and enantioselectivity, but with poor diastereocontrol (Table 3, entry 4). Lastly, focusing our efforts on the challenging construction of a fifth exocyclic stereocenter, we applied our protocol to the trisubstituted nitroenoate (*E*)-**2e** (Table 3, entry 5). The reactivity of this substrate was significantly lower (20 mol% catalyst loading was required for acceptable conversion), but the desired product **3t**, possessing five contiguous stereocenters, was formed with an excellent level of stereocontrol (96% *ee*).

Finally, we explored how the enoate geometry affected the stereocontrol of the spiroannulation process by using (*Z*)-configured α,β-unsaturated nitroesters **2a–e** (Table 4).

Table 2. Scope of the asymmetric organocatalytic synthesis of β-nitro spirocyclohexane indolinones **3** from 3-ylidene oxindoles.[a]

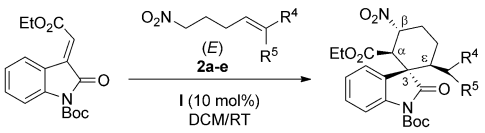


1c-p 3c-n

Entry	Substrate	$R^1/R^2/R^3$	*t* [d]	Product	Yield [%][b]	*ee* [%][c]
1	**1c**	H/CO_2Et/H	3	**3c**	73	98
2	**1d**	5-Cl/CO_2Et/H	2	**3d**	82	96
3	**1e**	6-Cl/CO_2Et/H	1	**3e**	63	97
4	**1f**	7-Cl/CO_2Et/H	2	**3f**	42	82
5	**1g**	5-Me/CO_2Et/H	5	**3g**	77	97
6	**1h**	5-OMe/CO_2Et/H	2	**3h**	76	95
7	**1i**	5-OCF_3/CO_2Et/H	3	**3i**	78	94
8	**1j**	H/CO_2Bn/H	1	**3j**	74	96
9	**1k**	H/COPh/H	1	**3k**	19	90
10	**1l**	H/*p*NO_2Ph/H	2	**3l**	83	55
11	**1m**	H/CN/H	1	**3m**	47	23
12[d]	**1n**	H/CO_2Et/Me	2	**3n**	40	95
13[d]	**1o**	H/Me/CO_2Et	2	**3n**	38	95
14	**1p**	H/NHBoc/CO_2Me	7	**3p**	–	–

[a] Reaction conditions: **1** (0.1 mmol), (*E*)-**2a** (0.12 mmol), catalyst **I** (10 mol%), CH_2Cl_2 (0.15 mL), RT. [b] Yield of isolated product after flash chromatography. [c] Determined by CSP-HPLC analysis of isolated product **3**. [d] (*E*)-**2a** (0.2 mmol), catalyst **I** (20 mol%).

Table 3. Scope of the asymmetric organocatalytic synthesis of β-nitro spirocyclohexane indolinones **3** from (*E*)-α,β-unsaturated nitroesters.[a]

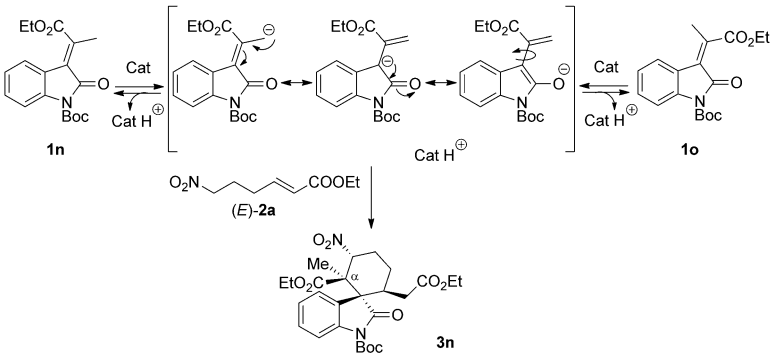


1c 3c, 3q-s

Entry	Substrate	R^4/R^5	*t* [d]	Product	Yield [%][b]	*ee* [%][c]
1	(*E*)-**2a**	CO_2Et/H	3	**3c**	73	98
2	(*E*)-**2b**	CO_2Bn/H	1	**3q**	65	>99
3	(*E*)-**2c**	COPh/H	1	**3r**	–[d]	–
4	(*E*)-**2d**	CN/H	2	**3s**	90	91[e]
5[f]	(*E*)-**2e**	CO_2Et/Me	4	**3t**[g]	40	96

[a] Reaction conditions: **1c** (0.1 mmol), **2** (0.12 mmol), catalyst **I** (10 mol%), CH_2Cl_2 (0.15 mL), RT. [b] Yield of isolated product after flash-chromatography. [c] Determined by CSP-HPLC analysis of isolated product. [d] A complex mixture of products was obtained. [e] Product **3s** was obtained as a mixture of four diastereoisomers (*dr* = 22:35:27:16). The reported *ee* concerns the major isomer. [f] Catalyst **I** (20 mol%). [g] ^{1}H NMR spectroscopic analysis indicated that the relative stereochemistry of **3t** was as shown in Table 4.

nary stereocenter is inverted. Considering the strong dependence of bioactivity on stereochemistry, the development of stereospecific processes that allow precisely defined stereoisomers to be synthesized from different *E*/*Z* isomeric starting materials, is clearly highly desirable.



Scheme 2. Stereoconvergent organocatalyzed formation of α-methyl spirooxindole **3n** starting from **1n** or **1o**.

As a final test, nitroester (*Z*)-**2e**, bearing a trisubstituted double bond, was also employed in the Michael–Michael [4+2] spiroannulation sequence (Table 4, entry 4). Analogously to the corresponding (*E*)-configured compound, (*Z*)-**2e** exhibited poor reactivity (35% yield), although spirocycle **3t**, containing five contiguous stereocenters, was obtained in 96% *ee*. Intriguingly, both (*Z*)-**2e** and (*E*)-**2e**

We were pleased to observe that the Michael–Michael spiroannulation took place easily with (*Z*)-**2a** and (*Z*)-**2b** (Table 4, entries 1 and 2), providing new diastereomeric β-nitro spirooxindoles **3u** and **3v** with excellent *ee* values. It is also worth mentioning the different reaction profile of the stereoisomers (*E*)- and (*Z*)-**2d**. Here, whereas the (*Z*)-α,β-unsaturated nitrile **2d** provided the corresponding product **3w** in high yield and excellent enantio- and diastereoselectivity (entry 3), the latter feature was not shared by (*E*)-α,β-unsaturated nitrile **2d** (Table 3, entry 4).[22] The relative stereochemistry of this series of products was unambiguously established through X-ray crystallographic analysis of **3u**[18] (Figure 3; see the Supporting Information for details).

It is very interesting to note that upon varying the nitroester double bond geometry, the configuration of the spiro quater-

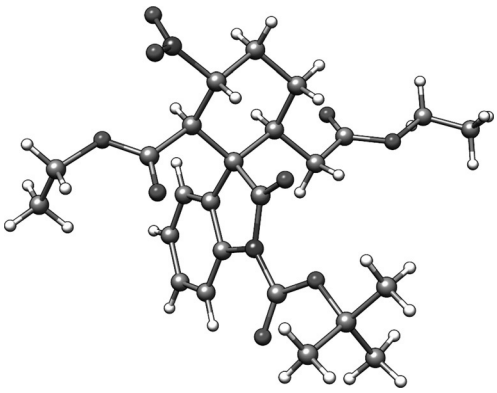
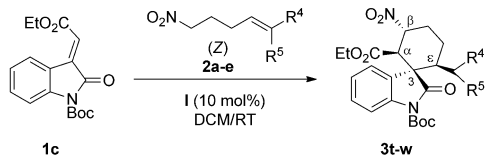


Figure 3. Determination of the relative stereochemistry of β-nitro cyclohexane spirooxindole **3u** through X-ray crystallographic analysis.

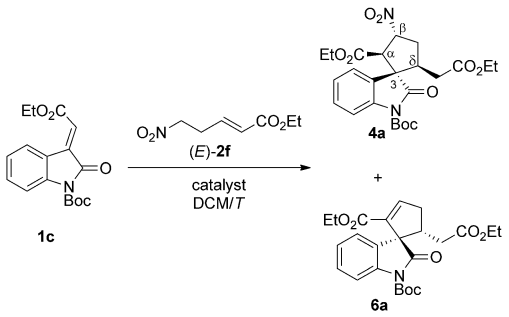
Table 4. Spiroannulation domino reaction using (*Z*)-α,β-unsaturated nitroesters.[a]



Entry	Substrate	R^4/R^5	*t* [d]	Product	Yield [%][b]	*ee* [%][c]
1	(*Z*)-**2a**	H/CO_2Et	1	**3u**	79	97
2	(*Z*)-**2b**	H/CO_2Bn	1	**3v**	75	98
3	(*Z*)-**2d**	H/CN	2	**3w**	83	95
4[d]	(*Z*)-**2e**	Me/CO_2Et	4	**3t**	35	96

[a] Reaction conditions: **1c** (0.1 mmol), **2** (0.12 mmol), catalyst **I** (10 mol%), CH_2Cl_2 (0.15 mL), RT. [b] Yield of isolated product after flash chromatography. [c] Determined by CSP-HPLC analysis of the isolated product. [d] Catalyst **I** (20 mol%).

Table 5. Optimization of the asymmetric Michael–Michael organocascade protocol for the synthesis of β-nitro spirocyclopentane indolinones **4**.[a]



Entry	Catalyst [mol%]	*T* [°C]	*t* [h]	Conv. [%][b]	d.r.[b,c]	*ee* **4a** [%][d]	*ee* **6a** [%][d]
1	**I** (10)	RT	5	80	60:40	99	92
2	**I** (5)	RT	72	82	60:40	99	96
3	**I** (10)	−10	48	53	65:35	>99	>99
4	**III** (10)	0	48	42	70:30	99[e]	99[e]
5	**V** (10)	0	48	58	70:30	99	92
6	**VI** (10)	0	48	59	80:20	97	94
7	**VII** (10)	0	48	90	80:20	93	–[f]
8	**VIII** (10)	0	48	75	80:20	99	99
9	**IX** (10)	0	48	90	85:15	98	–[f]
10	**IX** (10)	RT	5	90	85:15	98	–[f]

[a] Reaction conditions: **1c** (0.1 mmol), (*E*)-**2f** (0.12 mmol), CH_2Cl_2 (0.15 mL). [b] Determined by ^1H NMR spectroscopic analysis of the crude mixture. [c] Assuming that **6a** derived from a diastereoisomer of **4a**, we indicated also **4a**/**6a** ratio as d.r. [d] Determined by CSP-HPLC analysis. [e] Opposite enantiomer was formed. [f] The minor species was not **6a**, but a diastereoisomer of **4a**.

provided the same isomer **3t**. To explain this result, we hypothesized that the slow spirocyclization rate allowed catalyst **I** to isomerize the double bond, through deprotonation of the allylic position (see Scheme 2). Accordingly, it could be assumed that, despite the concomitant presence in solution of both (*Z*)-**2e** and (*E*)-**2e**, only one of them was directly involved in the final ring-closing step.[23]

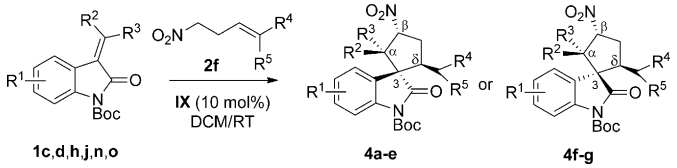
Synthesis of 1′-(*tert*-butyl) 2-ethyl 5-(2-ethoxy-2-oxoethyl)-3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2-dicarboxylate and analogues

To test the versatility of the newly proposed spiroannulating organocascade process, we decided to approach β-nitro spirocyclopentane indolinones **4** (Table 5) by using nitro compound **2f**, characterized by a shorter functionality span between the nitro and the enoate groups. When nitroester (*E*)-**2f** was subjected to the Michael–Michael organocascade sequence under the previously optimized reaction conditions (entry 1), to our delight, the spiroannulation to five-membered spirooxindole proceeded even faster than that to the corresponding six-membered analogue. However, two main products were isolated in a 60:40 ratio, a ratio that remained constant during the reaction progress, also for prolonged times. In particular, the most abundant β-nitro spirocyclopentane indolinone **4a** was accompanied by the spirocyclopentene oxindole **6a**, both provided with excellent enantiocontrol. We hypothesized that **6a**, derived from a minor diastereoisomer, formed during the cascade process through HNO_2 elimination.[24]

To optimize the β-nitro spirocyclopentane indolinone formation, we varied the catalyst loading (Table 5, entry 2) and the reaction temperature (entry 3), but noted only a moderate impact on the diastereoselectivity. Thus, we performed a brief catalyst screening (Table 5, entries 4–9). The best trade-off between reaction rate and stereoselectivity was achieved with catalyst **IX**, which gave **4a** with 90% conversion, 85:15 d.r. and 98% *ee* in 48 h at 0 °C (Table 5, entry 9) and in only 5 h at room temperature (entry 10). With these optimized conditions, we explored the scope of our route to β-nitro cyclopentane spirooxindoles (Table 6). The protocol proved to be efficient with both EWG- and EDG-substituted oxindoles **1** (Table 6, entries 2 and 3). Again, ethyl and benzyl esters could be successfully exchanged (Table 6, entry 4). We were intrigued by the construction of a quaternary stereocenter at the Cα position; therefore, 3-ylidene oxindoles **1n** and **1o** were subjected to the spiroannulation conditions (Table 6, entries 5 and 6). The observed stereoconvergent behavior of these two substrates was similar to that reported for six-membered spirooxindoles (see Table 2, entries 12 and 13). Starting from either (*E*)- or (*Z*)-configured 3-ylidene indolinone, the same spirocyclopentane oxindole **4e** was obtained (see Scheme 2). Interestingly, spirocyclic compound **4e**, featuring two consecutive all-carbon quaternary stereocenters, was produced with high stereocontrol (90:10 d.r., 94% *ee*).

Finally, the following analogies between the spironnulations with nitro compounds **2a**–**e**, on one hand, and **2f** were recorded: 1) (*Z*)-**2f** and (*E*)-**2f** reacted in a stereodivergent manner to provide β-nitro spirocyclopentane indolinones differing at the spiro carbon only (**4f**: 90:10 d.r., 99% *ee*; Table 6, entry 7). 2) Once again, the same reaction on 3-ylidene oxindoles **1n** and **1o** with (*Z*)-**2f** provided spirocyclopentane **4g**, the C3-epimer of **4e**, in low yield but with excellent stereocontrol (Table 6, entries 8 and 9). Thus, for five-membered spirooxindoles, it was also demonstrated that variation of the nitroest-

Table 6. Scope of the asymmetric organocatalytic synthesis of β-nitro spirocyclopentane indolinones **4** from 3-ylidene oxindoles and nitroesters.[a]



1c,d,h,j,n,o **4a-e** **4f-g**

Entry	**1** $R^1/R^2/R^3$	**2** R^4/R^5	*t* [h]	Product, yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1c** H/CO_2Et/H	(*E*)-**2f** CO_2Et/H	5	**4a**, 73	85:15	98
2	**1d** 5-Cl/CO_2Et/H	(*E*)-**2f** CO_2Et/H	8	**4b**, 57	90:10	>99
3	**1h** 5-OMe/CO_2Et/H	(*E*)-**2f** CO_2Et/H	8	**4c**, 65	90:10	98
4	**1j** H/CO_2Bn/H	(*E*)-**2f** CO_2Et/H	8	**4d**, 63	85:15	99
5[e]	**1n** H/CO_2Et/Me	(*E*)-**2f** CO_2Et/H	6	**4e**, 30	90:10	92
6[e]	**1o** H/Me/CO_2Et	(*E*)-**2f** CO_2Et/H	8	**4e**, 31	90:10	94
7[e]	**1c** H/CO_2Et/H	(*Z*)-**2f** H/CO_2Et	6	**4f**, 52	90:10	99
8[e]	**1n** H/CO_2Et/Me	(*Z*)-**2f** H/CO_2Et	4	**4g**, 36	90:10	99
9[e]	**1o** H/Me/CO_2Et	(*Z*)-**2f** H/CO_2Et	4	**4g**, 30	90:10	99

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), catalyst **IX** (10 mol%), CH_2Cl_2 (0.15 mL), RT. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [d] Determined by CSP-HPLC analysis of the isolated product. [e] With methylated 3-ylidene oxindoles **1n–o** or (*Z*)-**2f** as nitro compound, catalyst **I** provided the best results.

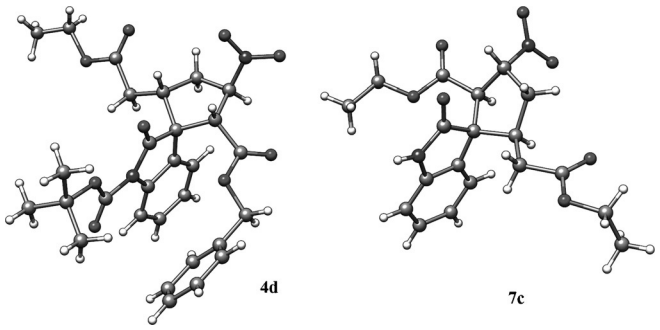


Figure 4. Determination of the relative (**7c**) and absolute (**4d**) stereochemistry of β-nitro cyclopentane spirooxindoles through X-ray crystallographic analysis.

er double bond geometry leads to inversion of configuration of the spiro quaternary stereocenter.

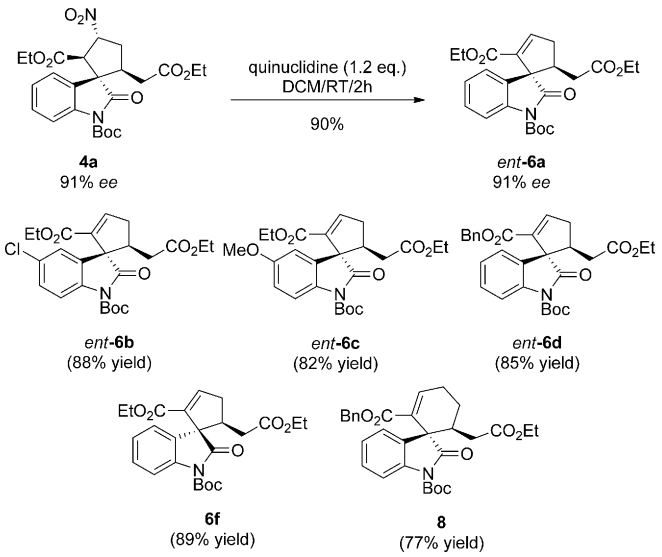
The relative and absolute stereochemistry of β-nitro cyclopentane spiroindolinones was unambiguously assessed by X-ray crystallographic analysis of **4d** and **7c** (Figure 4),[18] the latter derived from **4f** through Boc-removal (see Scheme 6 and the Supporting Information for experimental details).

Having optimized the asymmetric organocatalytic synthesis of β-nitro spirocyclopentane oxindoles **4**, we focused our attention on spirocyclopentene indolinones **6**. Quite recently, the synthesis of spirocyclic 2-oxindoles bearing a cyclopentene motif has attracted much attention, because this architecture is present in bioactive natural products[25a,b] and might be efficiently employed in the construction of drug candidates.[25c] Despite considerable synthetic effort,[26] relatively few enantioselective organocatalytic approaches have been reported[27] and the great majority exploit chiral tertiary phosphines as catalysts. Given that our Michael–Michael protocol provided the spirocyclopentene derivative **6a** (Table 5, entries 1–5) in considerable amounts, we tried to optimize the stereoselective formation of **6**. Thus, we exposed the enantioenriched spirocyclopentane **4a** to quinuclidine, and spirocyclopentene *ent*-**6a** was quantitatively obtained without erosion of the enantiomeric excess (Scheme 3).[28]

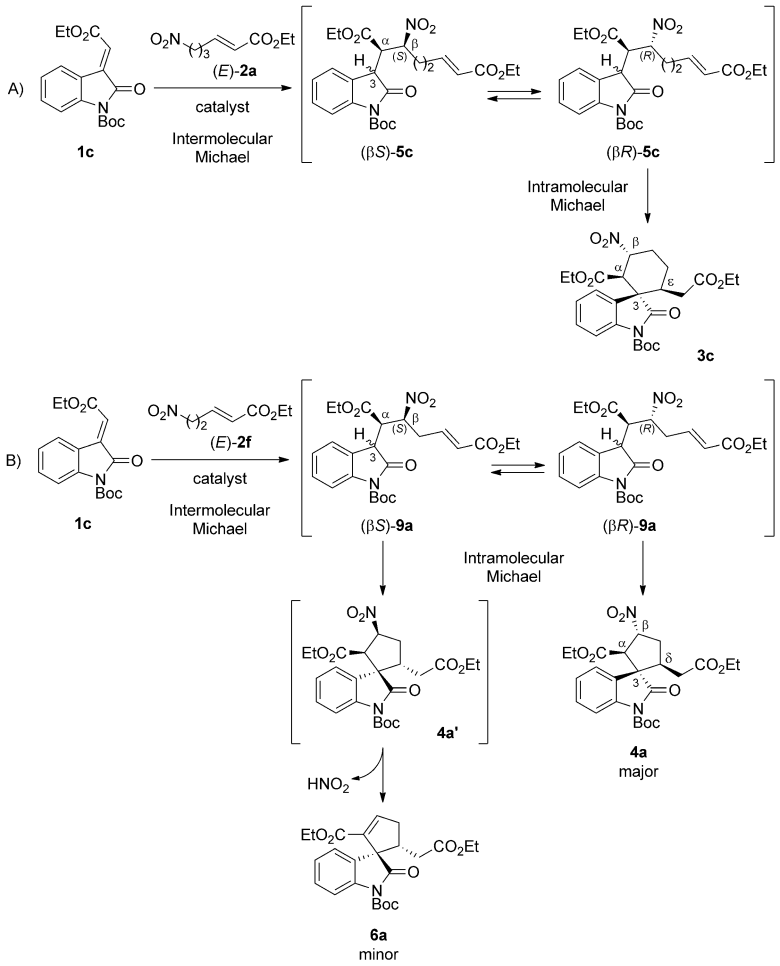
The same approach was exploited to synthesize a small library of cyclopentene spiroindolinones (Scheme 3), including **6f**, starting from the epimeric cyclopentane **4f**. The base-promoted HNO_2 elimination was also applied in the efficient synthesis of cyclohexene spiroindolinone[29] **8**, which was obtained in good yield (77%, with 2.5 equivalents of quinuclidine).[30]

Mechanistic hypotheses for the [4+2] and [3+2] spiroannulations

The observation that quinuclidine-promoted HNO_2 elimination from **4a–d** afforded *ent*-**6a–d** as enantiomers of the unsaturated spirocyclic compounds **6a–d** obtained in the organocatalyzed spiroannulation process (Table 5 and Table 6), required a deeper understanding of the reaction mechanism. For six-membered spirooxindoles (Scheme 4A), the ^{1}H NMR spectrum of the crude mixture recorded after three hours, showed very low amounts of both 3-ylidene oxindole **1c** and spirocyclohexane indolinone **3c**. The main component was the acyclic intermediate (β*S*)-**5c**, characterized by



Scheme 3. Base-promoted stereoselective synthesis of spirocyclopentene indolinones **6** and spirocyclohexene indolinone **8**.

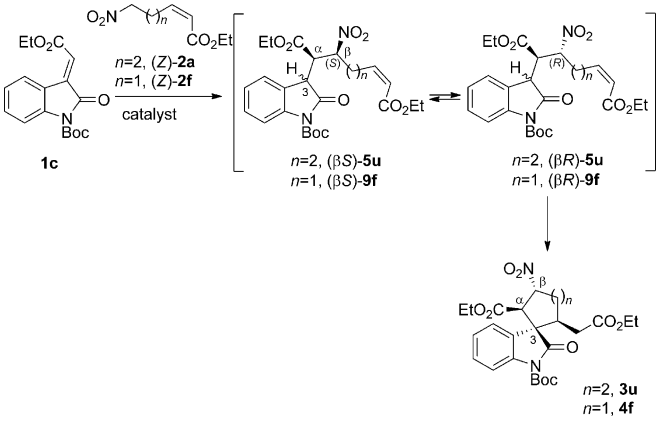


Scheme 4. Proposed mechanisms for the asymmetric organocatalytic [4+2] spiroannulation (**A**) and [3+2] spiroannulation (**B**) employing (*E*)-configured nitroenoates.

an α,β-*anti* relationship (see the Supporting Information). Given that X-ray crystallographic analysis assigned the α,β-*trans* relative configuration to spirocyclic product **3c**, we assume that the bifunctional organocatalyst first promotes Cβ epimerization, followed by selective spirocyclization of (β*R*)-**5c**, only (see the Supporting Information for further studies on the spiroannulations mechanism).

In the case of five-membered spirooxindoles (Scheme 4B), both the acyclic intermediates (β*S*)-**9a** and (β*R*)-**9a** are able to cyclize. In the presence of bifunctional organocatalyst **I**, (β*S*)-**9a** is formed more rapidly, then it equilibrates to (β*R*)-**9a**. The intramolecular Michael reaction on (β*R*)-**9a** is kinetically favored, forming spirocyclopentane **4a** as the major product. However, in contrast to six-membered rings, (β*S*)-**9a** also undergoes cyclization followed by loss of HNO_2 to generate spirocyclopentene **6a**. Both the epimerization and the spirocyclization rates depend on the structure of the catalyst, as suggested by the results reported in Table 5. From a stereochemical point of view, the two isomers **4a** and **4a**′ differ for all the absolute configurations other than Cα. The opposite C3–Cδ *trans* relationship was demonstrated by X-ray crystallographic analysis of **6d** (see the Supporting Information) and by the formation of *ent*-**6a** through base-promoted HNO_2 elimination from **4a** (Scheme 3). These findings lead us to conclude that the simple inversion of configuration at Cβ determines the inversion of both C3 and Cδ configurations during the ring-closure step.

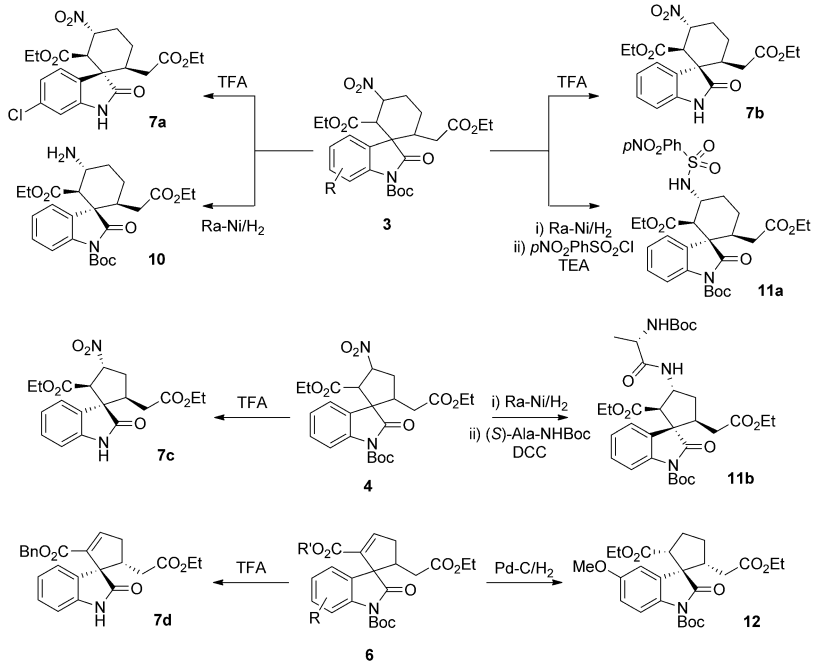
Concerning the spiroannulation sequences carried out with (*Z*)-configured nitroenoates, the reaction pathways to six- and five-membered spiroindolinones are more similar, with the cyclization of (β*R*)-acyclic intermediates being greatly favored in both cases (Scheme 5).



Scheme 5. Common mechanism proposed for the asymmetric organocatalytic [4+2] and [3+2] spiroannulations employing (*Z*)-configured nitroenoates.

Synthetic versatility and manipulations of 3-nitro-2′-oxospiro[cyclohexane-1,3′-indoline]-2-carboxylates, 3-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-2-carboxylates and 2′-oxospiro[cyclopentane-1,3′-indolin]-2-ene-2-carboxylates

We have hereto demonstrated how the newly proposed spiroannulation procedure opens an efficient and highly stereoselective route to a library of variably substituted and stereochemically diverse six- and five-membered β-nitro spirooxindoles. Now we show how versatile the functional groups present on these scaffolds are by subjecting them to further transformations (Scheme 6). First, spirocyclohexanes **3**, spirocyclopentanes **4**, and spirocyclopentenes

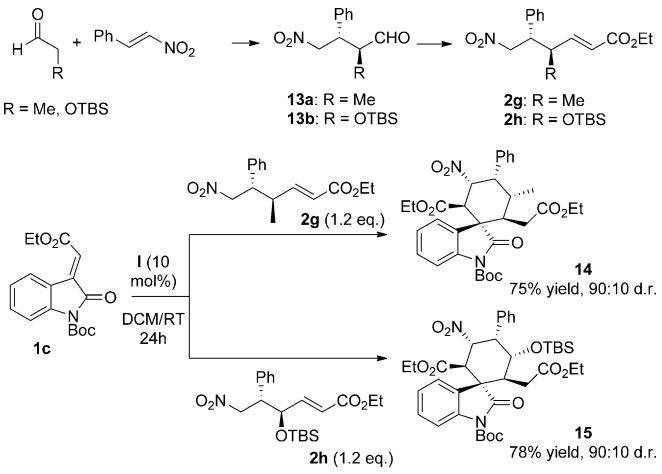


Scheme 6. Synthetic elaborations on the optically active spirocyclohexane (**3**), spirocyclopentane (**4**) and spirocyclopentene (**6**) oxindoles (see the Supporting Information for experimental details). TFA = trifluoroacetic acid, TEA = triethylamine, DCC = *N*,*N*′-dicyclohexylcarbodiimide.

6 could be easily deprotected to free-N spirooxindoles **7a–d**, as shown in Scheme 6. The β-nitro functionality can be quantitatively reduced to yield β-amino spiroindolinones **10**, which might be further elaborated, as shown in the synthesis of sulfonamide derivative **11a** and (*S*)-alanine-conjugated spirooxindole **11b**. Lastly, the stereoselective hydrogenation of cyclopentene **6c** provided spirocyclopentane oxindole **12** as a single stereoisomer.

Synthesis of 1′-(*tert*-butyl) 2-ethyl 6-(2-ethoxy-2-oxoethyl)-3-nitro-2′-oxo-4-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylates possessing six contiguous stereocenters

The last part of this study is dedicated to exploring the opportunity offered by optically active 2,3-disubstituted nitroenoates as Michael donor/acceptor synthons in our organocascade process, eventually leading to the construction of spirocyclohexane systems with six contiguous stereocenters. We report here the matched pair made up by chiral *anti* nitro compounds **2g** and **2h** (easily synthesized via nitro aldehydes **13**) and Takemoto's catalyst **I** (Scheme 7). When compounds **2g–h** were subjected to optimal cascade reaction conditions, two new β-nitro spirocyclohexane oxindoles (**14** and **15**) were achieved in high yields and with excellent stereoselectivity. We wish to stress that very few examples[31] of an asymmetric organocatalytic approach to fully substituted spirocyclohexane indolinones have been recorded, and that the peculiar stereochemical pattern characteristic of **14** and **15** has, to our knowledge, not been reported to date.



Scheme 7. Stereoselective synthesis of nitroenoates **2g** and **h** and Michael–Michael organocascade protocol applied to optically active nitro compounds (see the Supporting Information for the complete study on the use of chiral nitroesters).

Conclusion

Efficient and elegant syntheses of complex organic molecules with multiple stereogenic centers continue to be a primary challenge in both academia and the pharmaceutical industry. Catalytic asymmetric cascade reactions are remarkably attractive for the development of synthetic chemistry because of the high stereocontrol that is often achieved and because these approaches can avoid time-consuming and costly intermediate processes. With the aim of developing a novel synthetic approach to spirocarbocyclic oxindoles, we envisioned an innovative asymmetric [4+2] and [3+2] spiroannulation protocol, involving 2-(2-oxoindolin-3-ylidene)-acetic esters **1** and nitroenoates **2** as donor/acceptor synthons, catalyzed by thiourea-based bifunctional organocatalysts, through a double Michael sequence. Two carbon–carbon bonds and four stereocenters, including the spiro quaternary center, are formed by using almost equimolar amounts of reactants. A series of polyfunctional spirocyclohexane oxindoles **3** and spirocyclopentane oxindoles **4** were obtained in good yields, very good diastereocontrol, and excellent enantiocontrol under mild conditions. The new cascade process allowed us to address an unprecedented and stereochemically defined substitution pattern on the spirocarbocyclic unit. Careful sub-

strate optimization allowed us to rationalize how the configuration of the double bond of nitroenoate **2** acts as a switch that determines the absolute configuration of the spiro center, whereas the remaining stereocenters are formed under control of the catalyst. Defined diastereoselective conditions that can be used to generate different stereoisomeric spirocyclopentene oxindoles **6** have been identified, with the aim of approaching stereochemical diversity in a rational way. Further variations of the starting materials led us to obtain diverse polyfunctional spirocyclohexane derivatives such as **14** and **15**, containing six consecutive stereogenic centers. To our knowledge, this is the first asymmetric organocatalytic strategy enabling both five- and six-membered β-nitro spirocarbocyclic oxindoles, which are precursors of the corresponding β-amino analogues, the structural motif of which is present in many bioactive indole alkaloids.

Experimental Section

General procedure for the synthesis of spirocyclohexane oxindoles

Nitro compound **2** (0.12 mmol) was added to a solution of catalyst (10 mol%) and 3-ylidene oxindole **1** (0.1 mmol) in CH_2Cl_2 (0.15 mL). The reaction was stirred at RT for the reported time. The conversion was monitored by TLC and ^{1}H NMR analysis. The crude mixture was purified directly by flash chromatography on silica gel (cyclohexane/ethyl acetate, 9:1).

General procedure for the synthesis of spirocyclopentane oxindoles

Nitro compound **2** (0.12 mmol) was added to a solution of catalyst (10 mol%) and 3-ylidene oxindole **1** (0.1 mmol) in CH_2Cl_2 (0.15 mL). The reaction was stirred at the reported temperature for the reported time. The conversion was monitored by TLC and ^{1}H NMR analysis. The reactions carried out below RT were quenched at 0 °C with HCl (1 M), extracted with CH_2Cl_2, and concentrated under reduced pressure before the ^{1}H NMR spectroscopic analysis and/or the chromatographic purification. The reactions carried out at RT were purified directly by flash chromatography on silica gel (cyclohexane/ethyl acetate, 9:1 to 8:2).

Acknowledgements

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Keywords: asymmetric catalysis · domino reactions · Michael addition · organocatalysis · spiro compounds

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character exhibited by the intermediate deprotonated in the allylic position might give rise to side reactions, decreasing the yield of spirooxindole **3t**.

[24] To definitively exclude that **6a** derived from **4a** through catalyst-promoted HNO_2 elimination, we subjected isolated **4a** to catalyst **I** (10 mol%) in CH_2Cl_2 at room temperature for 21 h, without observing **6a** formation.

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