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

New 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, characterized by the following features: *i*) two carbon-carbon bonds and four stereocenters, including a quaternary spiro carbon, are formed under mild conditions; *ii*) an unprecedented and stereochemically defined substitution pattern onto the spirocarbocyclic unit is obtained; *iii)* the double bond configuration of the donor-acceptor nitroenoate **2** determines the absolute configuration of the spiro center, while the remaining stereocenters are formed under catalyst-control. The effect on the final stereochemical outcome of structural variations of each starting material, catalyst and experimental conditions is analyzed in depth. In particular, the use of specifically designed chiral nitroenoates enables diverse polyfunctional spirocyclohexane derivatives, containing six consecutive stereogenic centers. To the best of our knowledge, this is the first asymmetric organocatalytic strategy enabling both 5- and 6-membered β-nitro spirocarbocyclic oxindoles.

Introduction

The oxindole scaffold is present in the core structure of an impressive number of natural or synthetic bioactive compounds.[1] In particular, 5- and 6-membered spirocyclic oxindoles are considered privileged molecular structures associated with various and potent pharmaceutical properties (Figure 1).[2] The considerable medicinal potential of the spirocyclic oxindole structural motif 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 spirocenter 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 made in this field, much work is needed to develop more flexible synthetic strategies, to expand structural and stereochemical diversity, and the functional pattern of spirocyclic oxindoles.

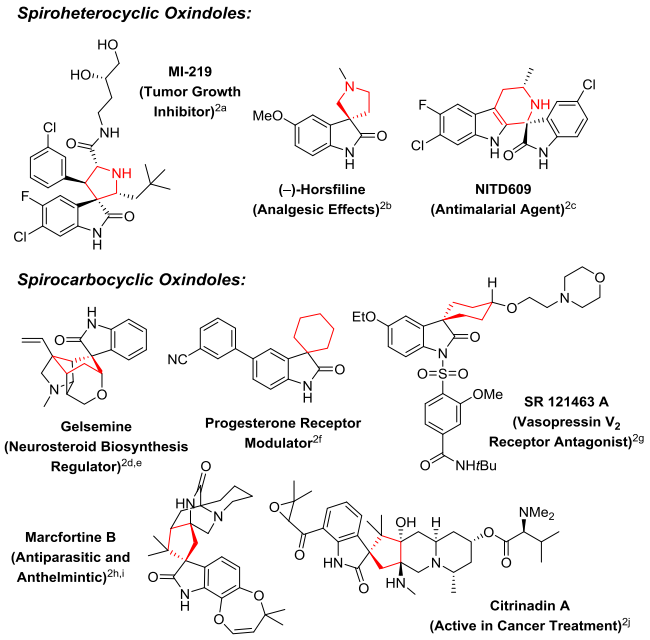

Figure 1. Natural and synthetic bioactive compounds containing a 5- or 6-membered spirocyclic oxindole core.

In this scenario lie the β-amino spirocarbocyclic oxindoles, a structural motif present in many bioactive indole alkaloids, such as Gelsemine, Citrinadin A, 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 few examples are present in the literature on the organocatalyzed enantioselective synthesis of 5- or 6-membered β-nitro spirocarbocyclic oxindoles (Scheme 1, Eq.s 1-2).[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

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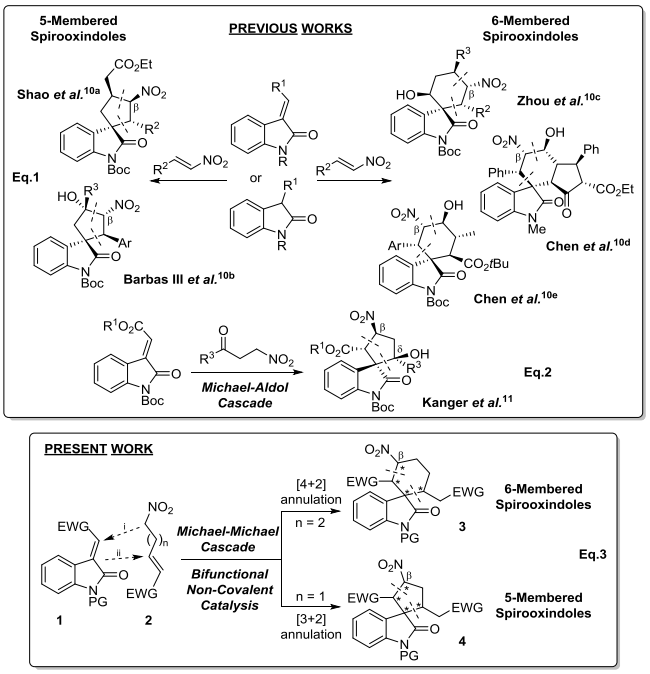
developed a Michael-Aldol cascade reaction employing nitroketones as donor/acceptor bifunctional synthons to generate β-nitro δ-hydroxy cyclopentane derivatives (Scheme 1, Eq. 2).[11] The limited approaches to the synthesis of β-nitro spirocarbocyclic oxindoles make the development of innovative and efficient methodologies still highly desirable.



Scheme 1. Asymmetric organocatalytic syntheses of 5- and 6-membered β-nitro spirocarbocyclic oxindoles (EWG = electron-withdrawing group; PG = protecting group).

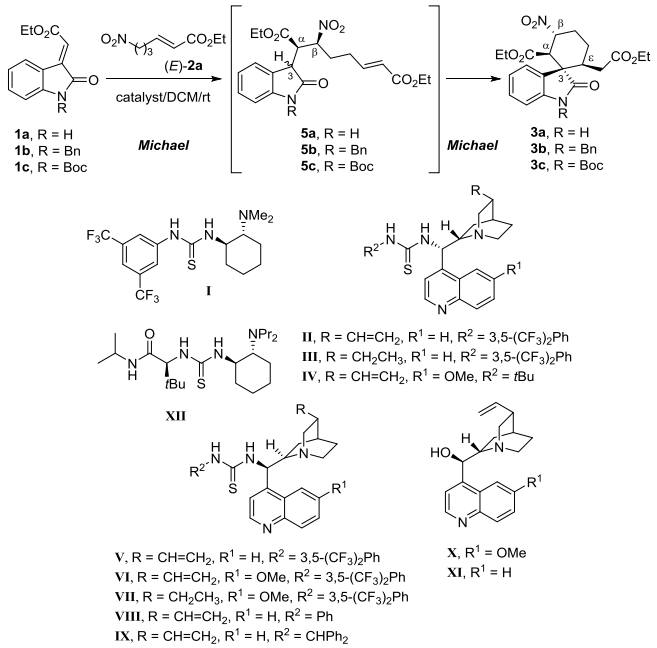
As part of our ongoing studies on the asymmetric thiourea-catalyzed[13] conjugate addition of nitroalkanes to α,β-unsaturated systems,[14] we designed a new asymmetric Michael-Michael domino process involving multiple donor-acceptor reagents such as oxindoles **1** and nitro compounds **2**. A precisely defined sequence of C-C bond-forming reactions grants an efficient 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 (3).

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

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



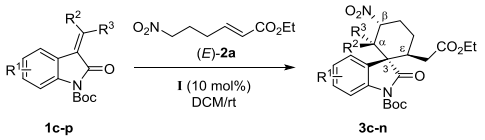
Entry	Substrate	Catalyst	Time [d]	Product	Conversion [%][b]	*ee* [%][c]
1	**1a**	**I**	4	**3a**	traces	-
2	**1b**	**I**	7	**3b**	60	75
3	**1c**	**I**	3	**3c**	90	98
4	**1c**	**II**	7	**3c**	54	96[d]
5	**1c**	**III**	7	**3c**	60	96[d]
6	**1c**	**IV**	7	**3c**	46	95[d]
7	**1c**	**V**	7	**3c**	49	96
8	**1c**	**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%), DCM (0.15 mL), rt. [b] Determined by ^{1}H NMR of the crude mixture. Products **3b** and **3c** were detected as single diastereoisomers. [c] Determined by chiral stationary phase HPLC (CSP-HPLC) of isolated product **3**. [d] Opposite enantiomer was formed. DCM = dichloromethane, rt = room temperature, d = days.

The *N*-Boc oxindole derivative **1c** afforded the desired 6-membered β-nitro spirooxindole **3c** with high conversion (90%) as a single detectable diastereoisomer in 98% *ee* (Table 1, entry 3). On the other hand, *N*-benzyl oxindole **1b** showed both a lower reactivity (60% conversion after 7 days) and poorer enantioselectivity (75% *ee*, entry 2). The unprotected oxindole **1a** performed even less efficiently, yielding only the acyclic intermediate **5a** (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, while 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 the 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 considering that the C3-H acidity is significantly affected by 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**, while 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 and stereoselectivity. The spirooxindole **3c** conversions ranged between 46% and 61% (7 days reaction time, entries 4-11) and the stereocontrol was invariably high (95-97% *ee*) with all the catalysts, except **VII** and **IX** providing slightly worse results (86% *ee*, entries 9 and 11). As expected, *pseudo*-enantiomeric catalysts (**II** and **V**) afforded opposite enantiomers (entries 4 and 7). The crucial role for the enantioselectivity played by the thiourea moiety was confirmed employing alkaloids **X** and **XI** (entries 12-13). Although a bifunctional system was still present, they exhibited a lower stereocontrol (66-73% *ee*). Disappointingly, the Jacobsen's thiourea **XII** proved to be less competent (entry 14). Having established that the best performances in terms of both reaction rate and stereocontrol were obtained with catalyst **I**, we optimized the reaction conditions using the Takemoto's catalyst. The effects of catalyst loading and solvent were investigated (see Supporting Information) and the optimal conditions were elected as 10 mol% of **I** and DCM as the reaction medium.

To expand the reaction scope, our protocol was applied to a variety of 3-ylidene oxindoles (**1c-p**) and we were delighted to find that the process well tolerated different substitution patterns (Table 2). The reactions smoothly proceeded when the oxindole aromatic ring was decorated with both electron-withdrawing (EWG) (entries 2-4) and electron-donating (EDG) (entries 5-7) groups, even if yield and *ee* were affected by the substituent position (cf. entries 2-3 with entry 4). As a general trend, EWG-substituted oxindoles reacted faster than EDG-substituted substrates (cf. entries 2-4 with entries 5-7).

Table 2. 3-Ylidene oxindoles scope of the asymmetric organocatalytic synthesis of β-nitro spirocyclohexane indolinones (**3**).[a]



1c-p **3c-n**

Entry	Substrate	$R^1/R^2/R^3$	Time [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%), DCM (0.15 mL), rt. [b] Yield of isolated product after flash-chromatography. [c] Determined by CSP-HPLC of isolated product **3**. [d] (*E*)-**2a** (0.2 mmol), catalyst **I** (20 mol%).

The ethyl ester could be smoothly replaced by a benzyl ester (74% yield and 96% *ee* in only 24 hours, 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*-nitro phenyl derivative **1l** afforded the product in good yield but poor stereocontrol (entry 10), whereas the cyano-substituted substrate **1m** showed both inadequate yield and *ee* (entry 11). As already 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 *via* multiple hydrogen bonds and the ester group

participates to 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 Supporting Information for details).

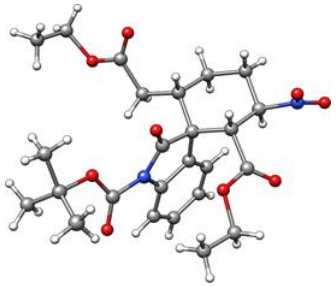
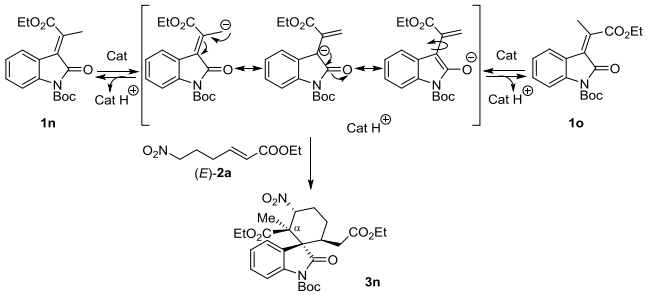


Figure 2. Determination of the relative stereochemistry of β-nitro cyclohexane spirooxindole **3c** *via* X-ray crystallographic analysis.

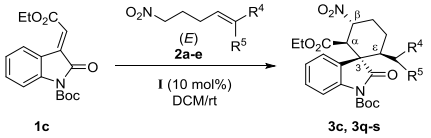
We were also committed to the challenging construction of a second quaternary stereocenter on the Cα position, contiguous to the quaternary spiro carbon (C3). To this purpose, the protocol was applied to substrates **1n-p** featuring a tetrasubstituted double bond. The reactivity of these 3-ylidene oxindoles was much lower. The nitroalkane conjugate addition did not proceed at all on the 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 stereoselectivity, 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, already demonstrated for 3-ylidene oxindoles in the presence of bifunctional organocatalysts.[19] In our reaction conditions, the alkylidene indolinones **1n** and **1o** could undergo deprotonation[20] to an intermediate dienolate (Scheme 2), which was likely responsible of a variety of side reactions that decreased the yield of the desired spirocycle. Another interesting remark concerning substrates **1n** and **1o** was 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 the double bond isomerization occurred when pure **1n** or **1o** was exposed to catalyst **I**,[21] likely *via* an intermediate dienolate, as shown in Scheme 2 (see 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** denoted 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.



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

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

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



Entry	Substrate	R^4/R^5	Time [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

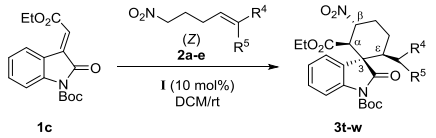
[a] Reaction conditions: **1c** (0.1 mmol), **2** (0.12 mmol), catalyst **I** (10 mol%), DCM (0.15 mL), rt. [b] Yield of isolated product after flash-chromatography. [c] Determined by CSP-HPLC of isolated product. [d] A complex mixture of products was obtained. [e] Product **3s** was obtained as a mixture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

We confirmed that the replacement of the ethyl ester with a benzyl analogous was well tolerated (entry 2). When we moved to (*E*)-**2c**, the α,β-unsaturated ketone triggered side reactions, affording a complex mixture of products (entry 3). The use of the cyano derivative (*E*)-**2d** allowed us to obtain the corresponding spirooxindole **3s** in high yield and enantioselectivity, but poor diastereocontrol (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**

(entry 5). The reactivity of this substrate was significantly lower (20 mol% of catalyst loading was required to get an 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 4. Spiroannulation domino reaction using (*Z*)-α,β-unsaturated nitroesters.[a]



Entry	Substrate	R^4/R^5	Time [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%), DCM (0.15 mL), rt. [b] Yield of isolated product after flash-chromatography. [c] Determined by CSP-HPLC of isolated product. [d] Catalyst **I** (20 mol%).

We were pleased to observe that the Michael-Michael spiroannulation took place easily with (*Z*)-**2a** and (*Z*)-**2b** (entries 1 and 2), providing new diastereomeric β-nitro spirooxindoles (**3u** and **3v**) in excellent *ee*s. It is also worth mentioning the different reaction profile of the stereoisomers (*E*)- and (*Z*)-**2d**. Here, while, the (*Z*)-α,β-unsaturated nitrile **2d** provided the corresponding product **3w** in high yield and excellent enantio- and diastereoselectivity (Table 4, entry 3), the last feature being 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 Supporting Information for details).

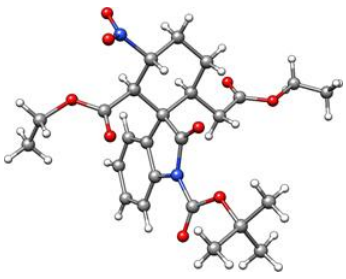


Figure 3. Determination of the relative stereochemistry of β-nitro cyclohexane spirooxindole **3u** *via* X-ray crystallographic analysis.

It is very interesting to note that, varying the nitroester double bond geometry, the spiro quaternary stereocenter inverts its configuration. Considering the strong dependence of bioactivity on stereochemistry, the development of stereospecific processes that allow to synthesize precisely defined stereoisomers from different *E*/*Z* isomeric starting materials, is always highly desirable.

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

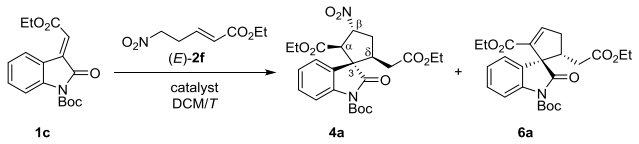
Synthesis of 1'-(*tert*-butyl) 2-ethyl 5-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclopentane-1,3'-indoline]-1',2-dicarboxylate and analogues (4).

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 5-membered spirooxindole proceeded even faster than that to the corresponding 6-membered analogue. However, two main products were isolated in a 60:40 ratio, a ratio that kept 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 *via* HNO_2 elimination.[24]

To optimize the β-nitro spirocyclopentane indolinone formation, we varied the catalyst loading (entry 2) and the reaction temperature (entry 3), recording only a moderate impact on the diastereoselectivity. Thus, we performed a quick catalysts screening (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 *dr* and 98% *ee* in 48 hours at 0 °C (entry 9) and only in 5 hours 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** (entries 2-3). Again, ethyl and benzyl esters could be successfully exchanged (entry 4). Since we were intrigued by the construction of a quaternary stereocenter at the Cα position, 3-ylidene oxindoles **1n** and **1o** were

subjected to the spiroannulation conditions (entries 5-6). The observed stereoconvergent behavior of these two substrates was similar to that reported for 6-membered spirooxindoles (see Table 2, entries 12-13). 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 *dr*, 94% *ee*).

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



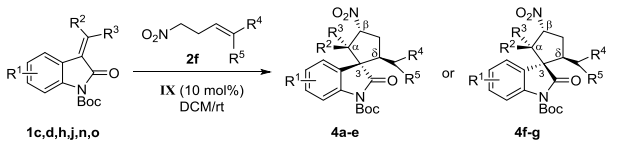
Entry	Catalyst [mol%]	*T* [°C]	Time [h]	Conversion [%][b]	*dr*[b,c]	*ee* **4a** [%][d]	*ee* **6a** [%][d]
1	**I** (10)	rt	5	80	60:40	99	92
2	**I** (5)	rt	72	82	60:40	99	96
3	**I** (10)	-10	48	53	65:35	>99	>99
4	**III** (10)	0	48	42	70:30	99[e]	99[e]
5	**V** (10)	0	48	58	70:30	99	92
6	**VI** (10)	0	48	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), DCM (0.15 mL). [b] Determined by ^{1}H NMR of the crude mixture. [c] Assuming that **6a** derived from a diastereoisomer of **4a**, we indicated also **4a**:**6a** ratio as *dr*. [d] Determined by CSP-HPLC. [e] Opposite enantiomer was formed. [f] The minor species was not **6a**, but a diastereoisomer of **4a**.

At last, the following analogies between the spironnulations with nitro compounds **2a-e**, on one hand, and **2f** were recorded: *i*) (*Z*)-**2f** and (*E*)-**2f** stereodiverged to provide β-nitro spirocyclopentane indolinones differing at the spiro carbon, only (**4f**: 90:10 *dr*, 99% *ee*, entry 7). *ii*) Once again, the same reaction on 3-ylidene oxindoles **1n** and **1o** with (*Z*)-**2f** provided the spirocyclopentane **4g**, epimer of **4e**, in low yield but excellent stereocontrol (entries 8-9). So, also for 5-membered spirooxindoles, it is demonstrated that the nitroester double bond geometry variation leads to the inversion of the spiro quaternary stereocenter configuration.

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 Supporting Information for experimental details).

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



Entry	**1** $R^1/R^2/R^3$	**2** R^4/R^5	Time [h]	Product, yield[b]	*dr*[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%), DCM (0.15 mL), rt. [b] Yield of isolated product. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by CSP-HPLC of isolated product. [e] With methylated 3-ylidene oxindoles **1n-o** or (*Z*)-**2f** as nitro compound, catalyst **I** provided the best results.

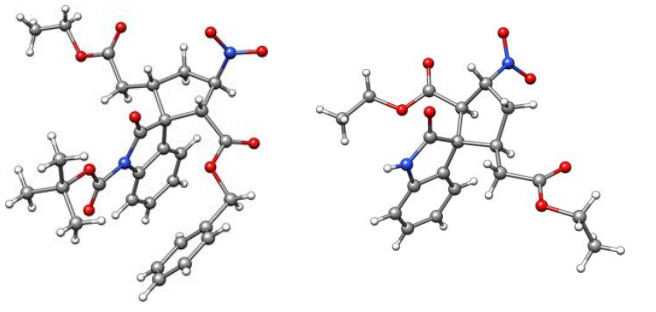
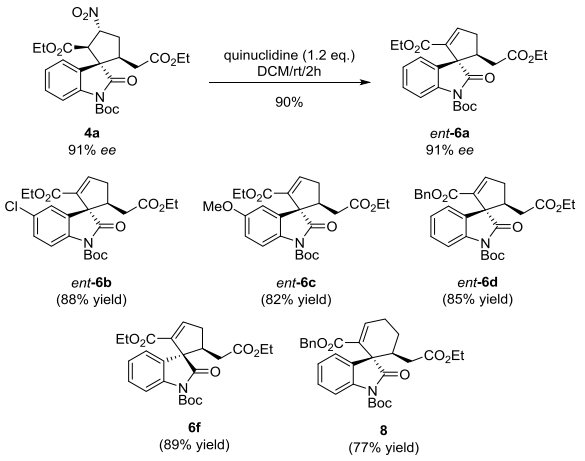


Figure 4. Determination of the relative (**7c**) and absolute (**4d**) stereochemistry of β-nitro cyclopentane spirooxindoles *via* X-ray crystallographic analysis.

Once 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 it might be efficiently employed in the construction of drug candidates.[25c] Despite a considerable synthetic effort has been made,[26] relatively few enantioselective organocatalytic approaches have been reported[27] and the great majority exploits chiral tertiary phosphines as catalysts. Since our Michael-Michael protocol provided the spirocyclopentene derivative **6a** (Table 5, entries 1-5) in a considerable extent, 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]

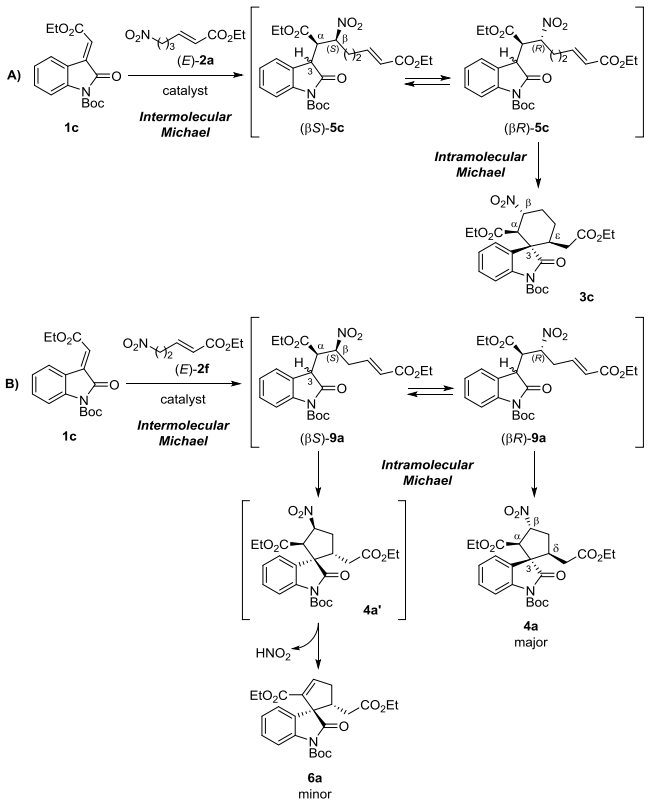


Scheme 3. Base-promoted stereoselective synthesis of spirocyclopentene indolinones **6** and spirocyclohexene indolinone **8**.

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

[4+2] and [3+2] spiroannulations mechanistic hypotheses.

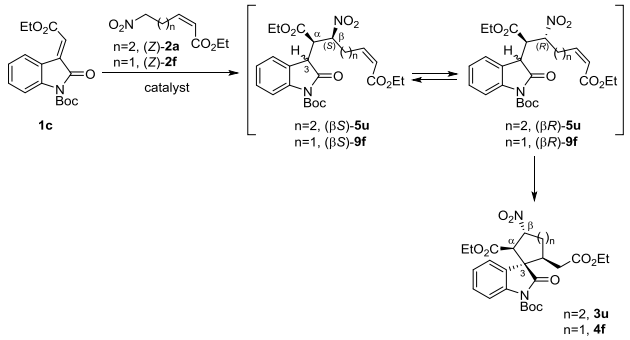
The observation that the quinuclidine-promoted HNO_2 elimination from **4a-d** afforded *ent*-**6a-d**, enantiomers of the unsaturated spirocyclic compounds **6a-d** obtained in the organocatalyzed spiroannulation process (Tables 5-6), required a deeper insight into the reaction mechanism. For 6-membered spirooxindoles (Scheme 4**A**), 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 an α,β-*anti* relationship (see Supporting Information). Since the X-ray crystallographic analysis assigned to spirocyclic product **3c** the α,β-*trans* relative configuration, we assume that the bifunctional organocatalyst first promotes the Cβ epimerization, followed by a selective spirocyclization of (β*R*)-**5c**, only (see Supporting Information for further studies on the spiroannulations mechanism).



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

On the other hand, in the case of 5-membered spirooxindoles (Scheme 4**B**), 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, being spirocyclopentane **4a** the major product. However, in contrast to 6-membered rings, (β*S*)-**9a** also undergoes cyclization followed by loss of HNO_2 to get spirocyclopentene **6a**. Both the epimerization and the spirocyclization rates depend on the catalyst structure, 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 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 6- and 5-membered spiroindolinones are more similar, the cyclization of (β*R*)-acyclic intermediates being greatly favored in both cases (Scheme 5).



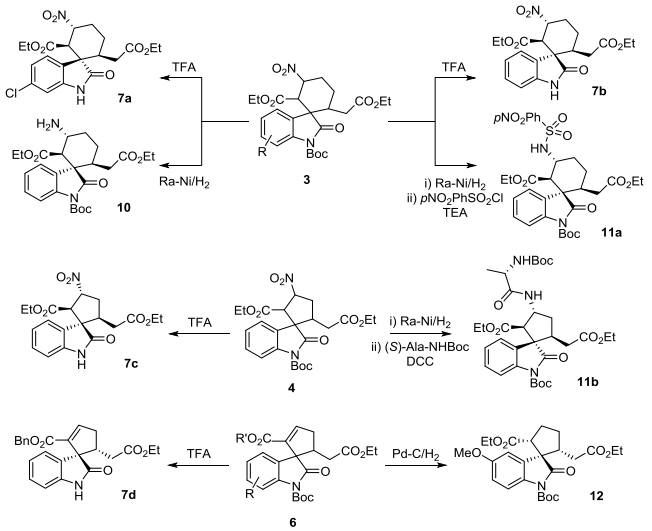
Scheme 5. Common mechanism proposed for the asymmetric organocatalytic [4+2] and [3+2] spiroannulations employing (*Z*)-configured nitroenoates.

Synthetic versatility and manipulations of 3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-2-carboxylates (3), 3-nitro-2'-oxospiro[cyclopentane-1,3'-indoline]-2-carboxylates (4) and 2'-oxospiro[cyclopentane-1,3'-indolin]-2-ene-2-carboxylates (6).

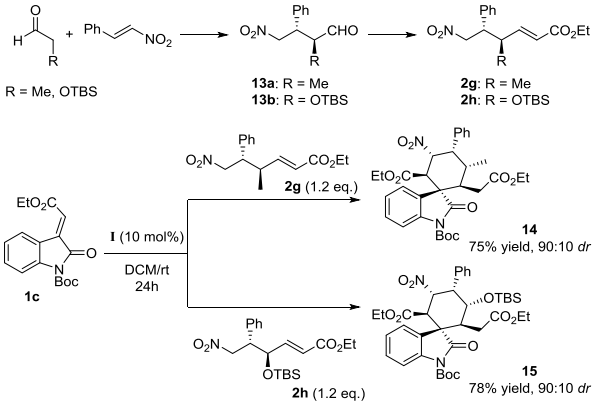
So far we have demonstrated how the newly proposed spiroannulation procedure opens an efficient and highly stereoselective route to a library of variably substituted and stereochemically diverse 6- and 5-membered β-nitro spirooxindoles. Now we show how versatile are the functional groups present on these scaffolds by subjecting them to further transformations (Scheme 6). First of all, spirocyclohexanes **3**, spirocyclopentanes **4** and spirocyclopentenes **6** can be easily deprotected to *N*-free 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 the spirocyclopentane oxindole **12** as 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 (14 and 15) possessing six contiguous stereocenters.

The last part of this study is dedicated to 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 asymmetric organocatalytic approach to fully substituted spirocyclohexane indolinones have been recorded in the literature, and that the peculiar stereochemical pattern characteristic of **14** and **15** has been never reported.



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



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

Conclusions

Efficient and elegant syntheses of complex organic molecules with multiple stereogenic centers continue to be a primary challenge in both the academia and the pharmaceutical industry. Catalytic asymmetric cascade reactions are remarkably

attractive in the forefront of synthetic chemistry for the high stereocontrol often achieved and since they avoid time-consuming and costly intermediate processes. With the aim to address a novel synthetic approach to spirocarbocyclic oxindoles, we developed 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 reactants. A series of polyfunctional spirocyclohexane oxindoles **3** and spirocyclopentane oxindoles **4** were obtained in good yields, very good diastereo-, and excellent enantiocontrol under mild conditions. The new cascade process allowed us to address an unprecedented and stereochemically defined substitution pattern onto the spirocarbocyclic unit. A careful substrate optimization led us to verify how the double bond configuration of nitroenoate **2** acts as a switch that determines the absolute configuration of the spiro center, while the remaining stereocenters are formed under catalyst-control. Defined diastereoselective conditions able to generate different stereoisomeric spirocyclopentene oxindoles **6** have been identified, with the aim to approach 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 the best of our knowledge, this is the first asymmetric organocatalytic strategy enabling both 5- and 6-membered β-nitro spirocarbocyclic oxindoles, precursors of the corresponding β-amino analogues, whose structural motif is present in many bioactive indole alkaloids.

Experimental Section

Typical procedure for the synthesis of spirocyclohexane oxindoles

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

Typical procedure for the synthesis of spirocyclopentane oxindoles

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

Acknowledgements

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Keywords: bifunctional thioureas •domino reactions • organocatalysis • oxindoles • spiro compounds

[1] For reviews on biologically active oxindole-containing compounds, see: a) V. Bhat, A. Dave, J. A. MacKay, V. H. Rawal, *Alkaloids*, San Diego, CA, United States, **2014**, pp. 65–160; b) S. Peddibhotla, *Curr. Bioact. Compd.* **2009**, *5*, 20–38; c) K. B. V. S. Suneel, L. Narasu, R. Gundla, R. Dayam, J. A. R. P. Sarma *Curr. Pharm. Des.* **2013**, *19*, 687–701; d) C. R. Prakash, P. Theivendren, S. Raja, *Pharmacol. Pharm.* **2012**, *3*, 62–71; e) A. D. Huters, E. D. Styduhar, N. K. Garg, *Angew. Chem. Int. Ed*. **2012**, *51*, 3758–3765; f) M. E. Sobhia, S. Paul, R. Shinde, M. Potluri, V. Gundam, A. Kaur, T. Haokip, *Expert Opin. Ther. Pat.* **2012**, *22*, 125–153; g) A. Millemaggi, R. J. K. Taylor, *Eur. J. Org. Chem*. **2010**, 4527–4547; h) K. L. Vine, L. Matesic, J. M. Locke, M. Ranson, D. Skropeta, *Anti-Cancer Agents Med.l Chem.* **2009**, *9*, 397–414.

[2] For examples of bioactive 5- and 6-membered spirocyclic oxindoles, see: a) S. Shangary, D. Qin, D. McEachern, M. Liu, R. S. Miller, S. Qiu, Z. Nikolovska-Coleska, K. Ding, G. Wang, J. Chen, D. Bernard, J. Zhang, Y. Lu, Q. Gu, R. B. Shah, K. J. Pienta, X. Ling, S. Kang, M. Guo, Y. Sun, D. Yang, S. Wang, *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 3933–3938; b) S. Hong, M. Jung, Y. Park, M. W. Ha, C. Park, M. Lee, H.-G. Park *Chem. Eur. J*. **2013**, *19*, 9599–9605; c) M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H.-P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler, T. T. Diagana, *Science* **2010**, *329*, 1175–1180; d) X. Zhou, T. Xiao, Y. Iwama, Y. Qin *Angew. Chem. Int. Ed*. **2012**, *51*, 4909–4912; e) S. Chirumbolo, *Frontiers in Neurology* **2011**, *2*, 1–2; f) A. Fensome, R. Bender, J. Cohen, M. A. Collins, V. A. Mackner, L. L. Miller, J. W. Ullrich, R. Winneker, J. Wrobel, P. Zhang, Z. Zhang, Y. Zhu, *Bioorg. Med. Chem. Lett*. **2002**, *12*, 3487–3490; g) H. Venkatesan, M. C. Davis, Y. Altas, J. P. Snyder, D. C. Liotta, *J. Org. Chem.* **2001**, *66*, 3653–3661; h) B. H. Lee, *Stud. Nat. Prod. Chem*. **2003**, *28*, 331–380 and references therein; i) B. M. Trost, D. A. Bringley, T. Zhang, N. Cramer, *J. Am. Chem. Soc*. **2013**, *135*, 16720–16735; j) Z. Bian, C. C. Marvin, S. F. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 10886–10889.

[3] For recent reviews on spiro-fused oxindoles synthesis, see: a) M. A. Borad, M. N. Bhoi, N. P. Prajapati, H. D. Patel, *Synth. Commun.* **2014**, *44*, 1043–1057; b) Y. Liu, H. Wang, J. Wan, *Asian J. Org. Chem.* **2013**, *2*, 374–386; c) P. Chauhan, S. S. Chimni, *Tetrahedron: Asymmetry* **2013**, *24*, 343–356; d) L. Honga, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023–1052; e) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev*., **2012**, *41*, 7247–7290; f) N. R. Ball-Jones, J. J. Badillo, A. K. Franz, *Org. Biomol. Chem*., **2012**, *10*, 5165–5181; g) G. S. Singh, Z. Y. Desta, *Chem. Rev*. **2012**, *112*, 6104–6155; h) J. E. M. N. Klein, R. J. K. Taylor, *Eur. J. Org. Chem*. **2011**, 6821–6841; i) J. S. Russel, *Top. Heterocycl. Chem.* **2010**, *26* (Heterocyclic Scaffolds II), 397–431; j) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal*. **2010**, *352*, 1381–1407; k) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, *18*, 3003–3025.

[4] For very recent examples of enantioselective catalytic synthesis of spirooxindoles, see: a) X.-N. Zhang, X. Dong, Y. Wei, M. Shi, *Tetrahedron* **2014**, *70*, 2838–2846; b) M. Takahashi, Y. Murata, F. Yagishita, M. Sakamoto, T. Sengoku, H. Yoda, *Chem. Eur. J*. **2014**, *20*, 11091–11100; c) T.-Z. Li, Y. Jiang, Y.-Q. Guan, F. Sha, X.-Y. Wu, *Chem. Commun*. **2014**, *50*, 10790–10792; d) F. Tan, L.-Q. Lu, Q.-Q. Yang, W. Guo, Q. Bian, J.-R. Chen, W.-J. Xiao, *Chem. Eur. J.* **2014**, *20*,

3415–3420; e) S. Kato, M. Kanai, S. Matsunaga, *Heterocycles* **2014**, *88*, 475–491; f) S. Zhao, J.-B. Lin, Y.-Y. Zhao, Y.-M. Liang, P.-F. Xu, *Org. Lett*. **2014**, *16*, 1802–1805; g) Z. Xiao, C. Yu, T. Li, X.-S. Wang, C. Yao, *Org. Lett*. **2014**, *16*, 3632–3635; h) H. Wu, Y.-M. Wang, *Chem. Eur. J*. **2014**, *20*, 5899–5904; i) F.-L. Hu, Y. Wei, M. Shi, *Adv. Synth. Catal*. **2014**, *356*, 736–742; j) B.-D. Cui, S.-W. Li, J. Zuo, Z.-J. Wu, X.-M. Zhang, W.-C. Yuan, *Tetrahedron* **2014**, *70*, 1895–1902; k) Y. Huang, C. Zheng, Z. Chai, G. Zhao, *Adv. Synth. Catal*. **2014**, *356*, 579–583; l) P.-Q. Chen, Y.-C. Xiao, C.-Z. Yuea, Y.-C. Chen, *Org. Chem. Front*. **2014**, *1*, 490–493.

[5] For selected reviews on domino reactions, see: a) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev*. **2014**, *114*, 2390–2431; b) P.-F. Xu, W. Wang, *Catalytic Cascade Reactions*, Wiley, VCH, Weinheim, **2014**; c) H. Pellissier, *Asymmetric Domino Reactions*, The Royal Society of Chemistry, Cambridge, UK, **2013**; d) A. Trabocchi, *Diversity-Oriented Synthesis*, Wiley, VCH, Weinheim, **2013**, pp. 135–176; e) H. Pellissier, *Chem. Rev*. **2013**, *113*, 442–524; f) J. Cossy, S. Arseniyadis, *Modern Tools for the Synthesis of Complex Bioactive Molecules*, Wiley, VCH, Weinheim, **2012**, pp. 271–334; g) L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Acc. Chem. Res*. **2012**, *45*, 1278–1293; h) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem*. **2010**, *2*, 167–178; i) K. C. Nicolaou, J. S. Chen, *Chem. Soc. Rev*. **2009**, *38*, 2993–3009; j) B. B. Toure, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439–4486; k) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley, VCH, Weinheim, **2006**.

[6] For reviews on the synthesis of spirooxindoles *via* organocascade reactions, see: a) D. Cheng , Y. Ishihara, B. Tan, C. F. Barbas III, *ACS Catal.* **2014**, *4*, 743–762. See also ref.s 3d,e. For very recent examples of enantioselective organocascade reactions, see: b) W. Sun, L. Hong, G. Zhu, Z. Wang, X. Wei, J. Ni, R. Wang, *Org. Lett*. **2014**, *16*, 544–547; c) Z. Zhou, X. Feng, X. Yin, Y.-C. Chen, *Org. Lett*. **2014**, *16*, 2370–2373; d) F.-F. Pan, W. Yu, Z.-H. Qi, C. Qiao, X.-W. Wang, *Synthesis* **2014**, *46*, 1143–1156; e) W. Guo, X. Wang, B. Zhang, S. Shen, X. Zhou, P. Wang, Y. Liu, C. Li, *Chem. Eur. J*. **2014**, *20*, 8545–8550; f) L.-Z. Ding, T.-S. Zhong, H. Wu, Y.-M. Wang, *Eur. J. Org. Chem*. **2014**, 5139–5143; g) R. Cesar da Silva, I. Chatterjee, E. Escudero-Adan, M. Weber Paixao, P. Melchiorre, *Asian J. Org. Chem*. **2014**, *3*, 466–469. See also ref.s 4c,h,j,k.

[7] For reviews on the synthesis and biosynthesis of prenylated indole alkaloids, see: a) T. Lindel, N. Marsch, S. K. Adla, *Top. Curr. Chem.* **2012**, *309*, 67–130; b) R. M. Williams, R. J. Cox, *Acc. Chem. Res*. **2003**, *36*, 127–139; c) R. M. Williams, E. M. Stocking, J. F. Sanz-Cervera, *Top. Curr. Chem*. **2000**, *209*, 97–173. For recent examples of prenylated indole alkaloids synthesis, see: d) E. V. Mercado-Marin, P. Garcia-Reynaga, S. Romminger, E. F. Pimenta, D. K. Romney, M. W. Lodewyk, D. E. Williams, R. J. Andersen, S. J. Miller, D. J. Tantillo, R. G. S. Berlinck, R. Sarpong, *Nature* **2014**, *509*, 318–324; e) S. W. Laws, J. R. Scheerer, *J. Org. Chem.* **2013**, *78*, 2422–2429; f) N. S. Simpkins, I. Pavlakos, M. D. Weller, L. Male, *Org. Biomol. Chem*., **2013**, *11*, 4957–4970.

[8] a) M. Yamazaki, E. Okuyama, M. Kobayashi, H. Inoue, *Tetrahedron Lett*. **1981**, *22*, 135–136; b) M. P. Lopez-Gresa, M. C. Gonzalez, L. Ciavatta, I. Ayala, P. Moya, J. Primo, *J. Agric. Food Chem*. **2006**, *54*, 2921–2925; c) A. C. Whyte, J. B. Gloer, D. T. Wicklow, P. F. Dowd, *J. Nat. Prod*. **1996**, *59*, 1093–1095; d) H. Kato, T. Yoshida, T. Tokue, Y. Nojiri, H. Hirota, T. Ohta, R. M. Williams, S. Tsukamoto, *Angew. Chem. Int. Ed*. **2007**, *46*, 2254–2256; e) S. Tsukamoto, T. Kawabata, H. Kato, T. J. Greshock, H. Hota, T. Ohta, R. M. Williams, *Org. Lett*. **2009**, *11*, 1297–1300; f) A. J. Birch, J. J. Wright, *J. Chem. Soc. Chem. Commun*. **1969**, 644–645; g) J. Coetzer, *Acta Crystallogr*. **1974**, *B30*, 2254–2256; h) T. J. Greshock, A. W. Grubbs, P. Jiao, D. T. Wicklow, J. B. Gloer, R. M. Williams, *Angew. Chem. Int. Ed*. **2008**, *47*, 3573–3577.

[9] For selected reviews on nitro compounds, see: a) R. Ballini, S. Gabrielli, A. Palmieri, *Eur. J. Org. Chem*. **2014**, 1805–1816; b) S. Lancianesi, A. Palmieri, M. Petrini, *Chem. Rev*. **2014**, *114*, 7108–7149; c) L. S. Aitken, N. R. Arezki, A. Dell'Isola, A. J. A. Cobb, *Synthesis* **2013**, *45*, 2627–2648; d) R. Ballini, N. Araujo, M. V. Gil, E. Roman, J. A. Serrano, *Chem. Rev*. **2013**, *113*, 3493–3515; e) A. Noble, J. C. Anderson, *Chem. Rev*. **2013**, *113*, 2887–2939; f) W. Yan, X. Shi, C. Zhong, *Asian J. Org. Chem*. **2013**, *2*, 904–914; g) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley, VCH, New York, **2001**.

[10] For asymmetric organocatalytic syntheses of β-nitro cyclopentane spirooxindoles, see: a) Y.-M. Li, X. Li, F.-Z. Peng, Z.-Q. Li, S.-T. Wu, Z.-W. Sun, H.-B. Zhang, Z.-H. Shao, *Org. Lett.* **2011**, *13*, 6200–6203; b) K. Albertshofer, B. Tan, C. F. Barbas III, *Org. Lett.* **2012**, *14*, 1834–1837. For asymmetric organocatalytic syntheses of β-nitro cyclohexane spirooxindoles, see: c) B. Zhou, Y. Yang, J. Shi, Z. Luo, Y. Li, *J. Org. Chem.* **2013**, *78*, 2897–2907; d) K. Jiang, Z.-J. Jia, X. Yin, L. Wu, Y.-C. Chen, *Org. Lett.* **2010**, *12*, 2766–2769; e) K. Jiang, Z.-J. Jia, S. Chen, L. Wu, Y.-C. Chen, *Chem. Eur. J.* **2010**, *16*, 2852–2856.

[11] A. Noole, K. Ilmarinen, I. Järving, M. Lopp, T. Kanger, *J. Org. Chem.* **2013**, *78*, 8117–8122.

[12] For examples of racemic synthesis of β-nitro carbocyclic spirooxindoles, see: a) S. Roy, M. Amireddy, K. Chen, *Tetrahedron* **2013**, *69*, 8751–8757; b) B. D. Chandler, J. T. Roland, Y. Li, E. J. Sorensen, *Org. Lett.* **2010**, *12*, 2746–2749.

[13] For selected reviews on bifunctional thiourea-based organocatalysts, see: a) O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva, *Org. Biomol. Chem*. **2013**, *11*, 7051–7071; b) Y. Xi, X. Shi, *Chem. Commun*. **2013**, *49*, 8583–8585; c) S. Narayanaperumal, D. G. Rivera, R. C. Silva, M. W. Paixao, *ChemCatChem* **2013**, *5*, 2756–2773; d) Y. Sohtome, K. Nagasawa, *Chem. Commun*. **2012**, *48*, 7777–7789; e) B. Pignataro, *New Strategies in Chemical Synthesis and Catalysis*, Wiley, VCH, Weinheim, **2012**, pp. 175-199; f) E. M. O. Yeboah, S. O. Yeboah, G. S. Singh, *Tetrahedron* **2011**, *67*, 1725–1762; g) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, *8*, 1229–1279; h) P. M. Pihko, *Hydrogen Bonding in Organic Synthesis*, Wiley, VCH, Weinheim, **2009**, pp. 141-351; i) S. J. Connon, *Synlett* **2009**, *3*, 354–376; j) S. J. Connon, *Chem. Commun*. **2008**, 2499–2510. For selected papers on the use of bifunctional Takemoto's organocatalyst, see: k) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; l) H. Miyabe, Y. Takemoto, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785–795.

[14] a) A. Quintavalla, F. Lanza, E. Montroni, M. Lombardo, C. Trombini, *J. Org. Chem*. **2013**, *78*, 12049–12064; b) A. Quintavalla, M. Lombardo, S. P. Sanap, C. Trombini, *Adv. Synth. Catal*. **2013**, *355*, 938–946; c) M. Chiarucci, M. Lombardo, C. Trombini, A. Quintavalla, *Adv. Synth. Catal*. **2012**, *354*, 364–370.

[15] a) F. G. Bordwell, H. E. Fried, *J. Org. Chem*. **1991**, *56*, 4218–4223; b) M. Ding, F. Zhou, Z.-Q. Qian, J. Zhou, *Org. Biomol. Chem*. **2010**, *8*, 2912–2914.

[16] Other authors noted that the ester moiety on the oxindole double bond was essential for a successful reaction outcome. See ref.s 11 and 26c.

[17] a) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc*. **2005**, *127*, 119–125; b) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem. Int. Ed*. **2005**, *44*, 105–108; c) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc*. **2006**, *128*, 13151–13160; d) B. Tan, Y. Lu, X. Zeng, P. J. Chua, G. Zhong, *Org. Lett*. **2010**, *12*, 2682–2685; e) T. Marcelli, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2011**, *1*, 142–152; f) J.-L. Zhu, Y. Zhang, C. Liu, A.-M. Zheng, W. Wang, *J. Org. Chem*. **2012**, *77*, 9813–9825.

[18] CCDC 1049663 (**3c**), CCDC 1049664 (**3u**), CCDC 1049665 (**4d**), CCDC 1049666 (**6d**) and CCDC 1049667 (**7c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] For examples of vinylogous reactions involving 3-ylidene oxindoles, see: a) Q. Chen, G. Wang, X. Jiang, Z. Xu, L. Lin, R. Wang, *Org. Lett*. **2014**, *16*, 1394–1397; b) B. Ranieri, A. Sartori, C. Curti, L. Battistini, G. Rassu, G. Pelosi, G. Casiraghi, F. Zanardi, *Org. Lett*. **2014**, *16*, 932–935; c) H. J. Lee, J. W. Lim, J. Yu, J. N. Kim, *Tetrahedron Lett*. **2014**, *55*, 1183–1187; d) G. Rassu, V. Zambrano, L. Pinna, C. Curti, L.

Battistini, A. Sartori, G. Pelosi, F. Zanardi, G. Casiraghi, *Adv. Synth. Catal*. **2013**, *355*, 1881–1886; e) G. Rassu, V. Zambrano, R. Tanca, A. Sartori, L. Battistini, F. Zanardi, C. Curti, G. Casiraghi, *Eur. J. Org. Chem*. **2012**, 466–470; f) C. Curti, G. Rassu, V. Zambrano, L. Pinna, G. Pelosi, A. Sartori, L. Battistini, F. Zanardi, G. Casiraghi, *Angew. Chem. Int. Ed*. **2012**, *51*, 6200–6204.

[20] The *N*-Boc protecting group might enhance the acidity of the β-methyl protons in substrates **1n-o**, thereby favouring the enolization. For *N*-carbamoyl group role in organocatalytic enantioselective reactions involving *N*-protected 3-ylidene oxindoles, see: a) Y. Shi, A. Lin, H. Mao, Z. Mao, W. Li, H. Hu, C. Zhu, Y. Cheng, *Chem. Eur. J*. **2013**, *19*, 1914–1918; b) F. Pesciaioli, P. Righi, A. Mazzanti, G. Bartoli, G. Bencivenni, *Chem. Eur. J*. **2011**, *17*, 2842–2845; c) B. Tan, G. Herna´ ndez-Torres, C. F. Barbas III, *J. Am. Chem. Soc*. **2011**, *133*, 12354–12357. See also ref.s 11, 18a,d,f.

[21] Setting the organocascade reaction on pure **1n** (*E*-isomer) or **1o** (*Z*-isomer), after few hours we observed the presence of both the isomers in the crude mixture (^{1}H NMR spectrum). This finding demonstrated that the starting material isomerization occurred in our reaction conditions and it was faster than the intermolecular Michael addition. For examples of *Z*/*E* isomerization of 3-ylidene oxindoles, see: a) T.-S. Jiang, R.-Y. Tang, X.-G. Zhang, X.-H. Li, J.-H. Li, *J. Org. Chem*. **2009**, *74*, 8834–8837; b) H. Ankati, S. K. Akubathini, S. Kamila, C. Mukherjee, S. R. D'Mello, E. R. Biehl, *Open Org. Chem. J*. **2009**, *3*, 1–10. See also ref.s 18a,c.

[22] The different diastereoselectivities obtained in the spirocyclization step employing (*Z*)- or (*E*)-configured α,β-unsaturated nitriles is difficult to be adequately rationalized. A significant role of the catalyst in coordinating cyano group cannot be excluded. For examples of thiourea-based organocatalysts coordinating nitriles, see: a) C.-L. Gu, L. Liu, Y. Sui, J.-L. Zhao, D. Wanga, Y.-J. Chen, *Tetrahedron: Asymmetry* **2007**, 18, 455–463; b) S. C. Pan, B. List, *Chem. Asian J.* **2008**, *3*, 430–437; c) P. Bernal, R. Fernández, J. M. Lassaletta, *Chem. Eur. J*. **2010**, *16*, 7714–7718; d) H. Xie, A. Song, X. Song, X. Zhang, W. Wang, *Tetrahedron Lett*. **2013**, *54*, 1409–1411; e) A. Martínez-Muñoz, D. Monge, E. Martín-Zamora, E. Marqués-López, E. Álvarez, R. Fernández, J. M. Lassaletta, *Org. Biomol. Chem.* **2013**, *11*, 8247–8255; f) Y.-D. Shaoa, S.-K. Tian, *Chem. Commun*. **2012**, *48*, 4899–4901.

[23] The trend of ^{1}H NMR signals suggested that nitroenoate **2e** reacted in *Z* configuration providing product **3t**. The possible nucleophilic 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 a catalyst-promoted HNO_2 elimination, we subjected isolated **4a** to catalyst **I** (10 mol%) in DCM at room temperature for 21 hours, without observing **6a** formation.

[25] a) P. R. Sebahar, R. M. Williams, *J. Am. Chem. Soc*. **2000**, *122*, 5666–5667; b) L. E. Overman, M. D. Rosen, *Angew. Chem. Int. Ed*. **2000**, *39*, 4596–4599; c) M. Pettersson, D. Knueppel, S. F. Martin, *Org. Lett*. **2007**, *9*, 4623–4626.

[26] For selected examples of racemic synthesis of cyclopentene spirooxindoles, see: a) Y. Han, Y.-J. Sheng, C.-G. Yan, *Org. Lett*. **2014**, *16*, 2654–2657; b) K. A. P. Lingam, P. Shanmugam, *Tetrahedron Lett*. **2013**, *54*, 4202–4206; c) F. Ji, M. Sun, M.-F. Lv, W.-B. Yi, C. Cai, *Synthesis* **2013**, *45*, 375–381; d) C. Hu, Q. Zhang, Y. Huang, *Chem. Asian J*. **2013**, *8*, 1981–1984; e) B. Yin, L. Huang, X. Wang, J. Liu, H. Jiang, *Adv. Synth. Catal*. **2013**, *355*, 370–376; f) K. Jiang, B. Tiwari, Y. R. Chi, *Org. Lett*. **2012**, *14*, 2382–2385; g) H.-P. Deng, Y. Wei, M. Shi, *Org. Lett*. **2011**, *13*, 3348–3351; h) X.-C. Zhang, S.-H. Cao, Y. Wei, M. Shi, *Chem. Commun*. **2011**, *47*, 1548–1550; i) S. Guo, R. Wang, J. Li, C. Li, H. Deng, X. Jia, *Synlett* **2011**, *15*, 2256–2258; j) X.-C. Zhang, S.-H. Cao, Y. Wei, M. Shi, *Org. Lett*. **2011**, *13*, 1142–1145; k) K. Selvakumar, V. Vaithiyanathana, P. Shanmugam, *Chem. Commun*. **2010**, *46*, 2826–2828.

[27] For enantioselective organocatalytic syntheses of cyclopentene spirooxindoles mediated by chiral tertiary phosphines, see: a) Y. Wang, L. Liu, T. Zhang, N.-J. Zhong, D. Wang, Y.-J. Chen, *J. Org. Chem*. **2012**, *77*, 4143–4147; b) F. Zhong, X. Han, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed*. **2011**, *50*, 7837–7841; c) B. Tan, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc*. **2011**, *133*, 4672–4675; d) A. Voituriez, N. Pinto, M. Neel, P. Retailleau, A. Marinetti, *Chem. Eur. J*. **2010**, *16*, 12541–12544. For the only example of enantioselective organocatalytic synthesis mediated by a chiral tertiary amine, see: e) J. Peng, X. Huang, L. Jiang, H.-L. Cui, Y.-C. Chen, *Org. Lett*. **2011**, *13*, 4584–4587. For the only example of enantioselective organocatalytic synthesis mediated by Hayashi's catalyst, see: f) K. Albertshofer, K. E. Anderson, C. F. Barbas III, *Org. Lett*. **2012**, *14*, 5968–5971.

[28] It could be assumed that quinuclidine was able to epimerize the Cβ stereocenter of **4a** generating a *trans* relative configuration between Cα-H and Cβ-NO_2, thus promoting the HNO_2 elimination. In the presence of the chiral organocatalyst this behavior might be disadvantaged or slowed by its more complex structure and steric hindrance.

[29] The organocatalytic asymmetric versions of cyclohexene spirooxindoles synthesis are rarely reported in the literature. See: a) X.-M. Shi, W.-P. Dong, L.-P. Zhu, X.-X. Jiang, R. Wang, *Adv. Synth. Catal*. **2013**, *355*, 3119–3123; b) K. L. Yao, H.-Y. Tao, G.-F. Qiu, X. Zhoua, C.-J. Wang, *Chem. Commun*. **2013**, *49*, 6078–6080; c) D. Qiana, J. Zhang, *Chem. Commun*. **2012**, *48*, 7082–7084; d) L.-L. Wang, L. Peng, J.-F. Bai, Q.-C. Huang, X.-Y. Xu, L.-X. Wang, *Chem. Commun.* **2010**, *46*, 8064–8066. See also ref. 20c.

[30] Surprisingly, the corresponding C3-Cε *cis* β-nitro spirocyclohexane, derived from (*Z*)-nitroenoate, did not eliminate HNO_2, even doubling the base amount.

[31] For the asymmetric organocatalytic syntheses of spirocyclohexane oxindoles bearing six adjacent stereocenters, see: a) I. Chatterjee, D. Bastida, P. Melchiorre, *Adv. Synth. Catal.* **2013**, *355*, 3124–3130. See also ref.s 10d,e. For a recent review on the enantioselective organocatalyzed synthesis of polysubstituted cyclohexanes, see: b) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* **2013**, *45*, 1909–1930.

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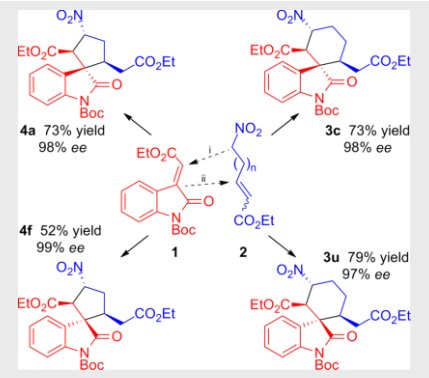
A new asymmetric spiroannulation protocol, catalyzed by bifunctional thioureas and involving 3-ylidene oxindoles **1** and nitroenoates **2**, is investigated. The double Michael sequence results in an unprecedented domino process, enabling both 5- and 6-membered β-nitro spirooxindoles. Four stereocenters are stereoselectively generated in a one-pot process where the double bond configuration of nitroenoate **2** determines the absolute configuration of the spiro center.



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New Stereospecific [4+2] and [3+2] Spiroannulations of 2-(2-Oxoindolin-3-Ylidene)Acetic Esters catalyzed by Bifunctional Thioureas