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Double Spirocyclization of Arylidene-Δ^2-Pyrrolin-4-Ones with 3-Isothiocyanato Oxindoles

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Abstract: Arylidene-Δ^2-pyrrolin-4-ones undergo organocatalyzed double spirocyclization with 3-isothiocianato oxindoles in a domino 1,4/1,2-addition sequence. The products contain three contiguous stereocenters (*ee* up to 98%, *dr* up to 99:1, 12 examples). The absolute configuration of the major diastereomer was determined by single crystal X-ray analysis. Along with heterocyclic Michael acceptors based on oxazolone, isoxazolone, thiazolidinone, pyrazolone, and pyrimidinedione, the reported results display the applicability of unsaturated Δ^2-pyrrolin-4-ones (pyrrolones) for the organocatalyzed construction of 3D-rich pyrrolone-containing heterocycles.

Keywords: organocatalysis; pyrrolones; spiroheterocyclization; 3-isothiocyanato oxindoles; cascade reaction; spiro compounds

1. Introduction

Spirooxindoles, containing various spiro rings attached at the C-3 position of the oxindole framework, represent a privileged core scaffold frequently encountered in natural and synthetic products exhibiting many different biological activities [1–4], as shown in Figure 1 [5–9]. Conformational rigidity of spirooxindoles provides an excellent strategy to enforce the desired conformation for a specific and strong ligand-protein binding [10].

Development of new catalytic methods for stereoselective construction of diverse spirooxindole frameworks, possessing both a variable pharmacophore and functional groups that enable follow-up transformations (i.e., the generation of compound libraries for the evaluation of their biological activities), represents an important ongoing challenge. In this context, organocatalysis has emerged as a powerful synthetic tool for the preparation of complex molecular architectures from simple starting materials, especially due to its operational simplicity, easily available catalysts, and benign reaction conditions [11–21]. 3-Isothiocyanato oxindoles, possessing both the nucleophilic and the electrophilic reaction site, represent a convenient building block for the cascade construction of diverse heterocyclic systems [22–25]. These transformations can be conducted under mild organocatalytic conditions in a highly stereoselective manner. Thus, various mono- and bis-spiroheterocycles and their fused analogues have been constructed featuring thioimidazolidinone-spirooxindoles [26–30], fused-thioimidazolidinone-spirooxindoles [31], thiopyrrolidinone-spirooxindoles [32–52], fused-thiopyrrolidinone-spirooxindoles [53–56], thiooxazolidinone-spirooxindoles [57–59], and thio-1,2,4-triazolidinone [60].

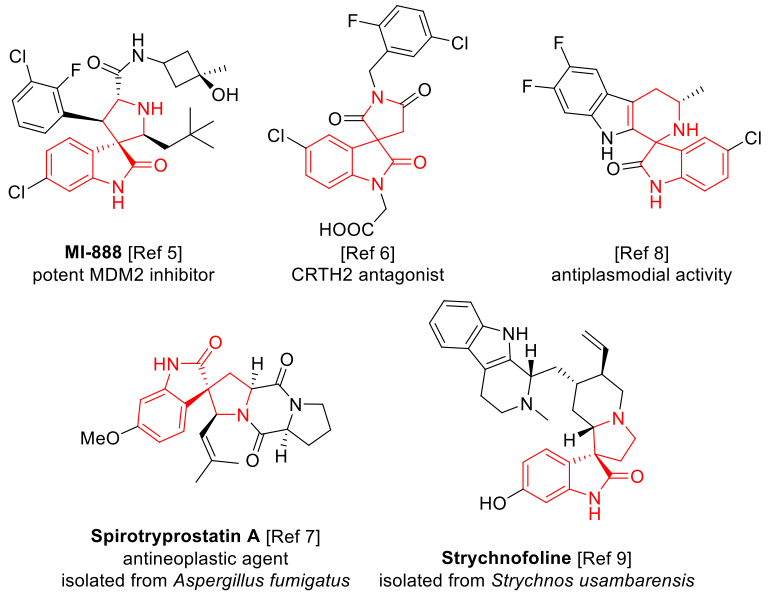
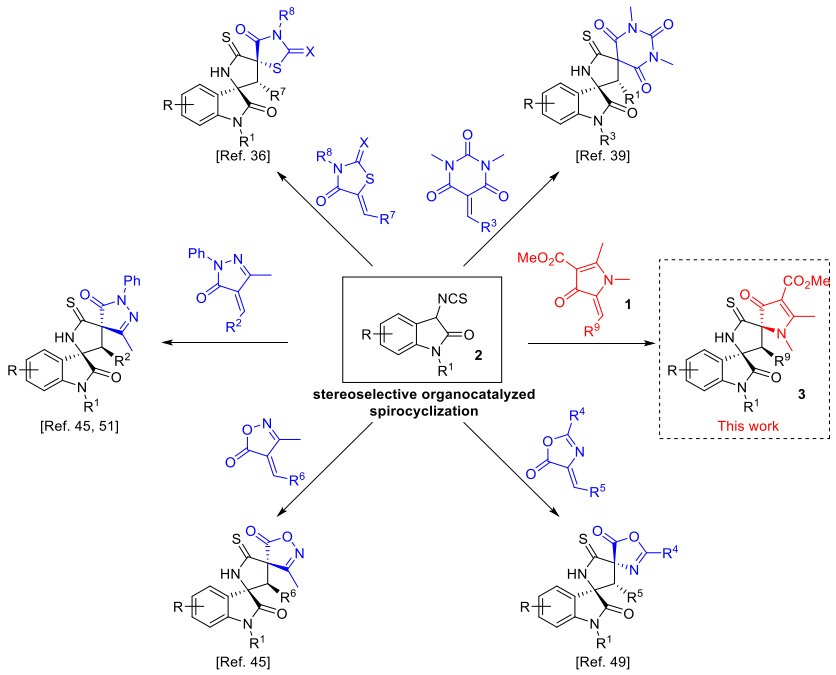


Figure 1. Selected biologically active compounds possessing a spirooxindole scaffold.

For the construction of bis-spiroheterocyclic thiopyrrolidinone-spirooxindoles with 3-isothiocyanato oxindoles, arylidene or (functionalized) alkylidene (hetero)cyclic Michael acceptors have been applied. Thereof, bicyclic systems are prevalent (i.e., indole, tetralone, and indanone-derived Michael acceptors) [33,35,37,38,40,41,46,47,52]. Among monocyclic heterocycles, Michael acceptors based on oxazolone [49], isoxazolone [45], thiazolidinone [36], pyrazolone [45,51], and pyrimidinedione (barbituric acid) [39] have been applied, with no reports on the application of pyrrolone-derived 1,4-acceptors (Scheme 1). The pyrrolone (Δ^2-pyrrolin-4-one) core is an interesting motif prominent in several natural products (Brevianamide A [61]), bioactive molecules (modulators of opioid receptors [62], antimalarials [63,64], HIV-1 protease inhibitors [65]), and phytopharmaceuticals (herbicides [66]).

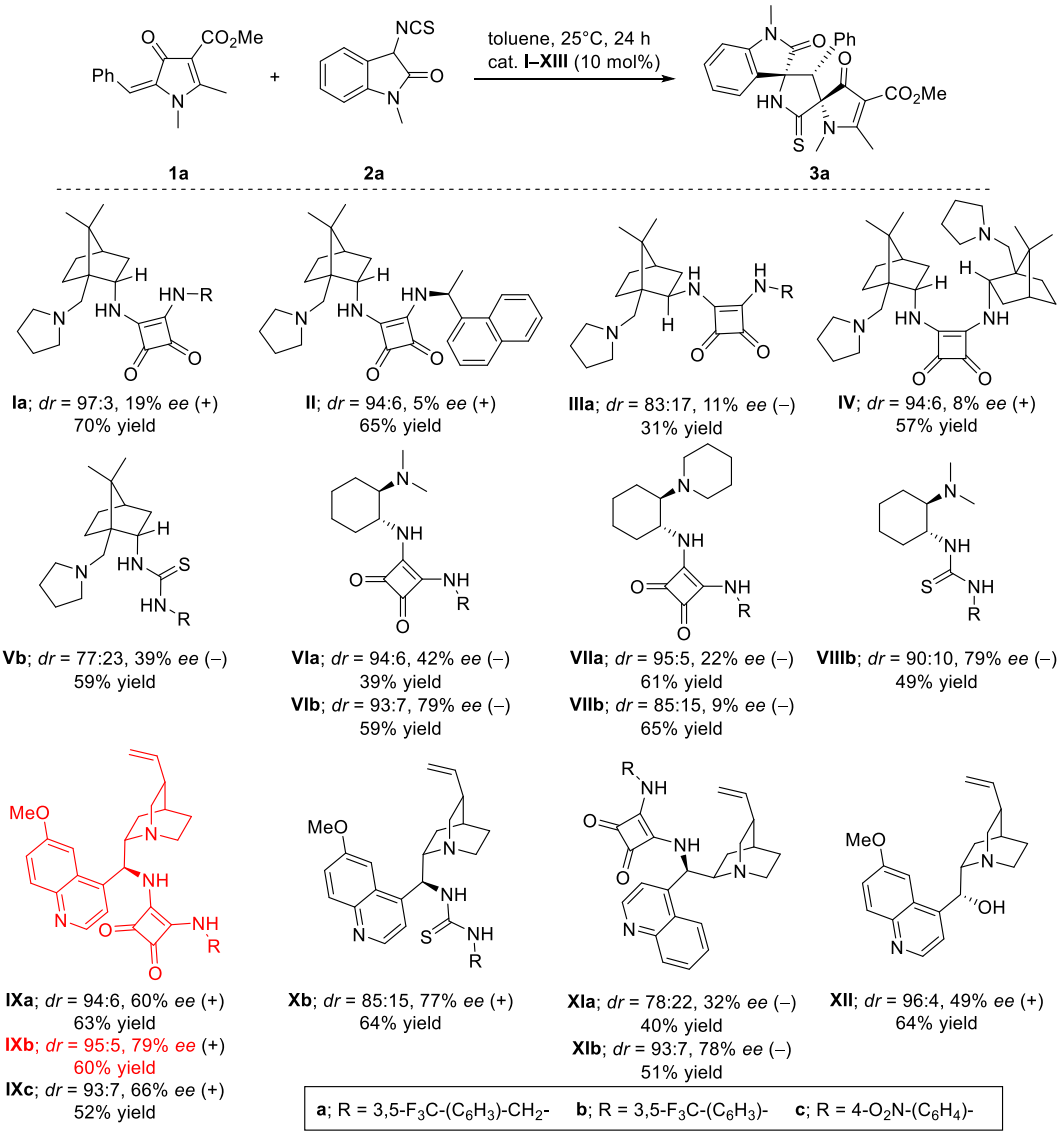


Scheme 1. Bis-spiroheterocyclic oxindoles containing oxazolone, thiazolidinone, pyrazolone, pyrimidinedione, and pyrrolone structural motifs.

In continuation of our research on the implementation of pyrrolone derivatives in asymmetric organocatalyzed transformations [67–70], we herein report a successful application of the arylidene-Δ^2-pyrrolin-4-ones [71] **1** for the enantioselective construction of oxindole-thiopyrolidinone-Δ^2-pyrrolin-4-one bis-spiroheterocycles **3** (Scheme 1).

2. Results and Discussion

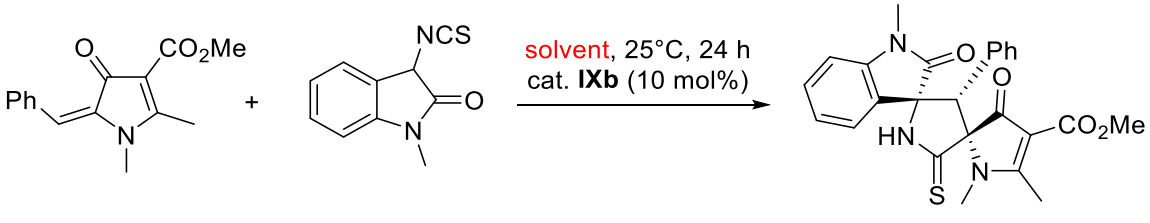
The DABCO-catalyzed reaction between methyl (*E*)-5-benzylidene- 1,2-dimethyl-4-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (**1a**) and 3-isothiocyanato-1-methylindolin-2- one (**2a**) in THF yielded the corresponding racemic oxindole-thiopyrrolidineone-Δ^2-pyrrolin-4-one ***rac*-3a**. The subsequent screening of the chiral noncovalent bifunctional organocatalysts **I-VII** based on camphor, cyclohexane-1,2-diamine, and quinuclidine in toluene at 25 °C is presented in Scheme 2. Several cyclohexane-1,2-diamine- and quinuclidine-based catalysts (**VIb**, **VIIIb**, **IXb**, **Xb**, **XIb**) containing either the thiourea or the squaramide H-bond donor and 3,5-bis(trifluoromethyl)phenyl group are compatible with the model reaction **1a** + **2a**→**3a** in both yields and stereoselectivity. Among the screened catalysts, the best results along with the cleanest reaction profile were obtained with the catalyst **IXb** (*dr* = 95:5, *ee* = 79%, 60% yield).



Scheme 2. Evaluation of organocatalysts **I-XII** in a model reaction **1a** + **2a**→**3a**.

With the optimal catalyst **IXb** in hand, solvent optimization for the reaction **1a** + **2a**→**3a** was performed (Table 1). Compared to toluene (Entry 1, 79% *ee*), the enantioselectivity decreased significantly in dichloromethane, acetonitrile, and methanol (Entries 6, 10, 11; up to 52% *ee*), while in ethereal solvents (Entries 2, 5, 9) and acetone (Entry 8), the enantioselectivity improved (82–87% *ee*). A drop of diastereoselectivity was observed in diethyl ether, acetonitrile, and methanol (Entries 3, 10, 11). In terms of yield, the conversion was lower in the majority of the tested solvents (Entries 2–6, 8–11). Trifluorotoluene (Entry 7) gave the cleanest reaction profile with practically unchanged diastereoselectivity, alongside the highest yield and enantioselectivity (*dr* = 93:7, *ee* = 87%, 67% yield).

Table 1. Evaluation of organocatalyst **IXb** in bis-spiroheterocyclization of 5-arylidene-Δ^2-pyrrolin-4-one **1a** with 3-isothiocyanatooxindole **2a**. [a]



1a **2a** **3a**

	Solvent	Yield (%)	*dr*	*ee* (%)
1	toluene	60	95:5	79
2	1,4-dioxane	46	93:7	83
3	Et_2O	35	80:20	75
4	1,2-dimethoxyethane	49	95:5	78
5	THF	55	94:6	82
6	CH_2Cl_2	61	93:7	6
7	$PhCF_3$	67	93:7	87
8	acetone	44	94:6	87
9	*t*-butyl methyl ketone	41	95:5	87
10	MeCN	30	79:21	52
11	MeOH	34	86:14	36

[a] 5-Arylidene-Δ^2-pyrrolin-4-one **1a** (0.1 mmol), 3-isothiocyanato oxindole **2a** (0.13 mmol), catalyst **IXb** (10 mol%), solvent (1 mL), 25 °C, 24 h; *ee* and *dr* determined by HPLC after flash column chromatography.

Having established the optimal reaction conditions (catalyst **IXb**, trifluorotoluene), the scope of the studied transformation was evaluated. For that purpose, several Δ^2-pyrrolin-4-ones **1** [71,72] and two 3-isothiocyanato oxindoles **2** [30,53,59] were applied (Figure 2). The results of the investigated scope are presented in Scheme 3. With the *N*-methyl-substituted Δ^2-pyrrolin-4-ones **1a**–**g**, the effect of electron-donating and electron-withdrawing substituents on the phenyl ring of the arylidene moiety, including tiophen-2-yl moiety, did not establish a clear trend; the products were isolated with good to excellent enantioselectivities (80–98% *ee*), diastereoselectivity above 75:25, and low to moderate yields (18–67%). Despite our best efforts, stereoisomers of the products ***rac*-3m**–**p**, derived from pyrrolones **1h**–**k** and unsubstituted 3-isothiocyanato oxindole **2a**, could not be separated on chiral HPLC columns (see the Supplementary Materials). The products **3f**–**j**, derived from 5-methyl substituted 3-isothiocyanato oxindole **2b**, compared with the products **3a**–**e**, derived from unsubstituted 3-isothiocyanato oxindole **2a**, were generally formed in slightly higher enantioselectivities though lower yields at longer reaction times.

The absolute configuration (3*R*,3′*S*,4′*R*) of the major stereoisomer of the product **3b** was determined by single crystal X-ray analysis (Figure 3) (see the Supplementary Materials). Consequently, the same absolute configuration (3*R*,3′*S*,4′*R*) was assigned to all the major diastereomers of products **3a**–**j**. The reaction of 3-isothiocyanato oxindoles **2a** and **2b** with *N*-unsubstituted pyrrolones **1l** and **1m** yielded the corresponding products **3k** and **3l** in low yields (7 and 14%), and low to moderate

enantioselectivities (21 and 57% *ee*), respectively. Based on previous observations, where enantiomeric products were obtained in the reaction of (*E*)- and (*Z*)-pyrrolones **1** with 2-mercaptoacetaldehyde [71], an enantiomeric relationship of (3*S*,3′*R*,4′*S*) was tentatively assigned to products **3k** and **3l** (Scheme 3).

The follow-up methylation of compound **3a** with iodomethane in the presence of K_2CO_3 in acetone gave the *S*-methylated product **4** (Scheme 4).

According to the Grayson [72,73] proposal of stereochemistry origin in squaramide-catalyzed asymmetric Michael addition reactions and the observed absolute configuration revealed by X-ray analysis of the major diastereomer of compound **3b** (cf. Figure 3), a plausible transition state (TS) leading to the product (as exemplified for the formation of product **3a**) can be postulated (Scheme 5). The protonated catalyst activates and coordinates the pyrrolone electrophile via the protonated quinuclidine moiety, while the squaramide functionality simultaneously orients and activates the nucleophile for the attack. The *Si* face of the nucleophile attacks the *Re* face of the electrophile, which is followed by the spiro-cyclisation yielding product **3a** (Scheme 5).

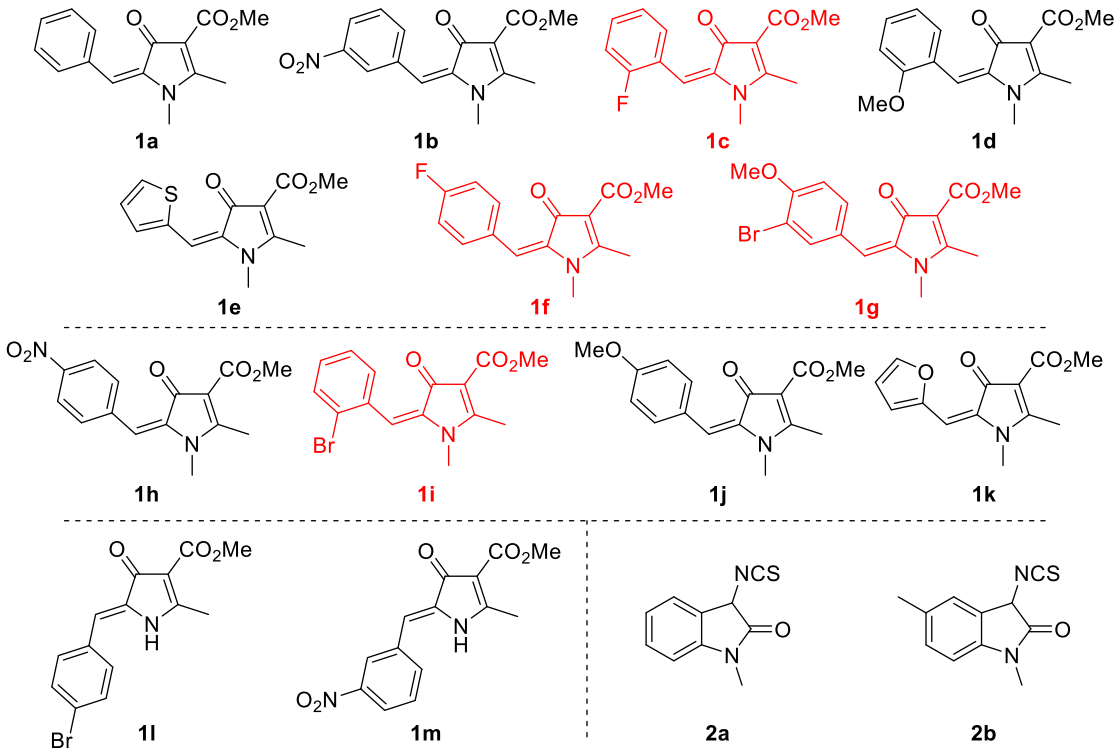
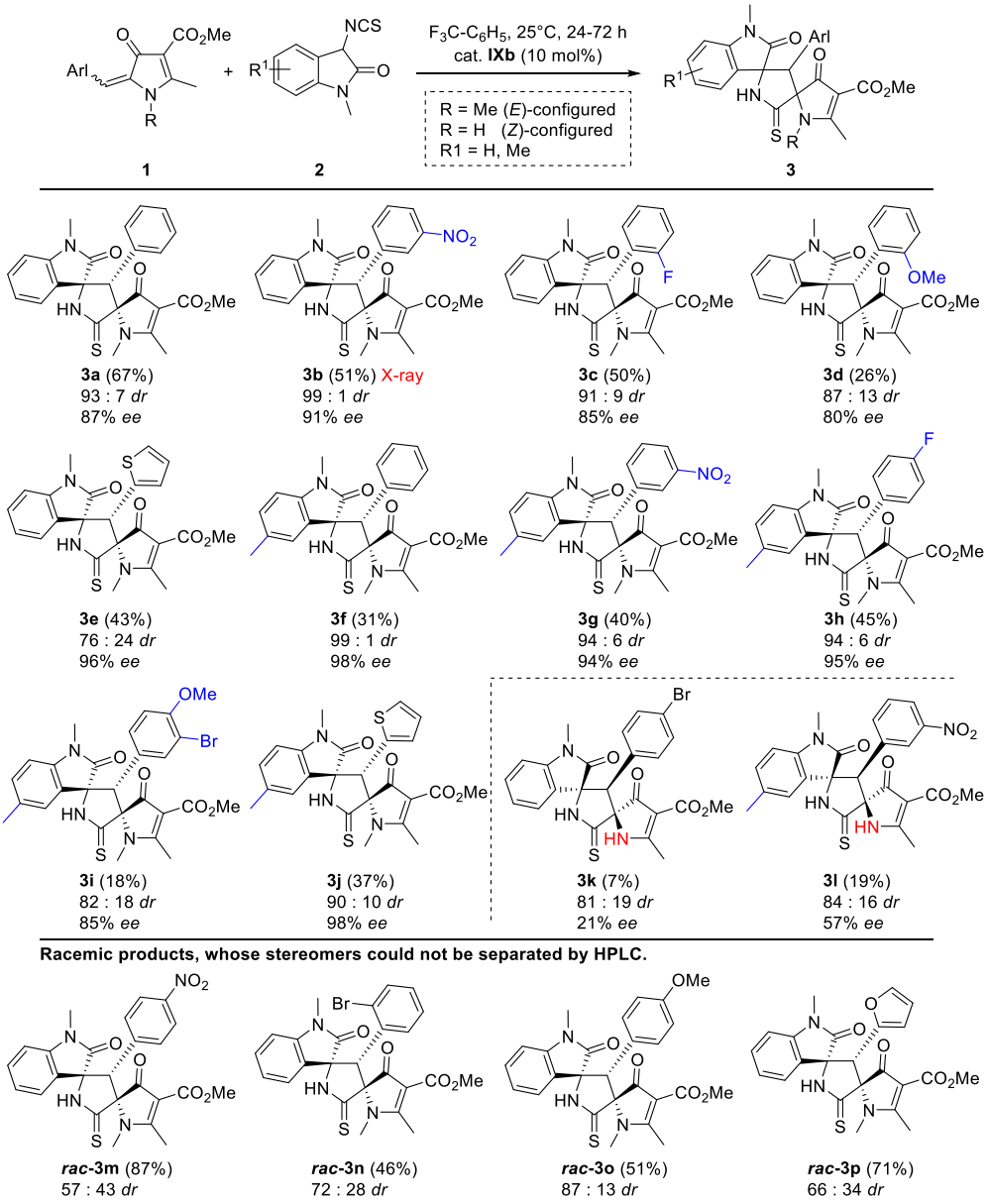


Figure 2. Selected 5-arylidene-2-methyl-4-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylates **1** and 3-isothiocyanato oxindoles **2**; color red—novel reported pyrrolones **1**.



Scheme 3. Synthesized bis-spiroheterocycles **3**.

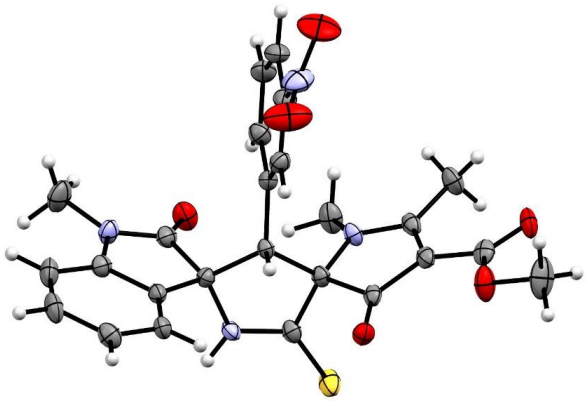
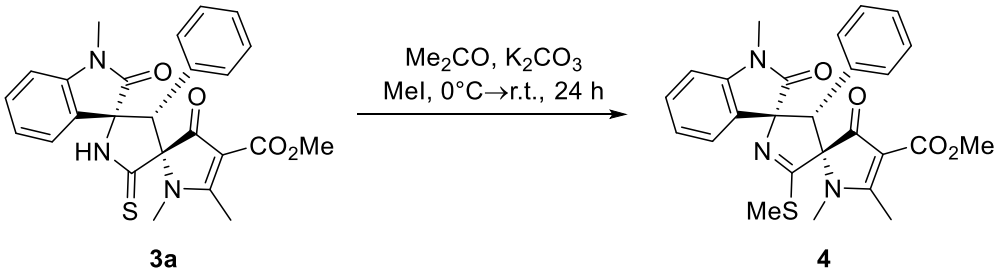
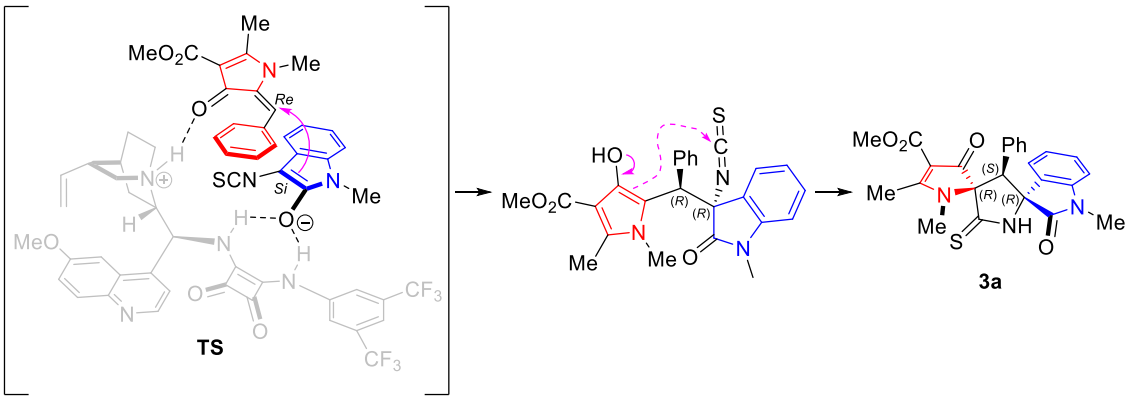


Figure 3. Single crystal X-ray structure depicting product **3b**. Thermal ellipsoids are shown at 50% probability.



Scheme 4. Follow-up methylation of compound **3a**.



Scheme 5. Postulated transition state leading to the product **3a**.

3. Materials and Methods

3.1. Materials and Methods, Syntheses, and Characterization

Solvents for chromatography and extractions were of technical grade. They were distilled prior to use. Technical grade anhydrous Na_2SO_4 was used for drying of extracts. Melting points were determined on a Kofler micro hot stage and an SRS OptiMelt MPA100-Automated Melting Point System (Stanford Research Systems, Sunnyvale, CA, USA). The NMR spectra were obtained on a Bruker UltraShield 500 plus (Bruker, Billerica, MA, USA) at 500 MHz for ^{1}H and 126 MHz for a ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS (Agilent Technologies, Santa Clara, CA, USA), and IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer (PerkinElmer, Waltham, MA, USA). Column chromatography (CC) was performed on silica gel (Silica gel 60, particle size: 0.035–0.070 mm (Sigma-Aldrich, St. Louis, MO, USA)). HPLC analyses were performed on an Agilent 1260 Infinity LC (Agilent Technologies, Santa Clara, CA, USA) using CHIRALPAK IA-3 (0.46 cm ø × 25 cm), CHIRALPAK AD-H (0.46 cm ø × 250 mm), CHIRALCEL AS-H (0.46 cm ø × 250 mm), and CHIRALCEL OD-H (0.46 cm ø × 250 mm) as chiral columns (CHIRAL TECHNOLOGIES, INC., West Chester, PA, USA). All the commercially available chemicals used were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Methyl 5-arylidene-2-methyl-4-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylates **1** [71] and 3-isothio cyanatooxindoles **2a** and **2b** [30,53,59] were prepared following the literature procedures.

Organocatalysts **Ia** [70], **II** [69], **IIIa** [70], **IV** [70], **Vb** [74], **VIa** [75], **VIb** [76], **VIIa** [77], **VIIb** [76], **IXa** [78], **IXb** [79], **IXc** [80], **Xb** [81], **XIa** [19], and **XIb** [78] were prepared following the literature procedures; organocatalysts **VIIIb** and **XII** were purchased from Sigma-Aldrich.

3.2. Synthesis of (E)-Methyl 5-Arylidene-1,2-Dimethyl-4-oxo-4,5-Dihydro-1H-Pyrrole-3-Carboxylate-General Procedure 1 (GP1)

To a solution of methyl (**Z**)-2-(2-chloroacetyl)-3-(methylamino)but-2-enoate (**E**) [71] (1 equivalent) in anhydrous EtOH at room temperature, KOH (1.05 equivalent, ω = 0.85) was added and the resulting reaction mixture was heated to 75 °C. After the disappearance of the starting material (ca. 45 min), according to the TLC analysis (mobile phase: EtOAc/MeOH = 4:1) (Figure S1), the mixture was cooled to room temperature. $KHSO_4$ (0.5 equivalent) was added, followed by the addition of H_2O (5 mL), and the mixture was stirred for 10 min at room temperature, followed by the addition of an aldehyde (1 equivalent). The mixture was heated to 75 °C and stirred until the disappearance of the Δ^2-pyrrolin-4-one intermediate **A** (ca. 30 min), according to the TLC analysis (mobile phase: EtOAc/MeOH = 4:1) (Figure S1). Afterwards, the solution was cooled to room temperature, followed by the slow addition of ice-cold water (ca. 100 mL) until the formation of the precipitate. The precipitate was collected by filtration, washed with ice-cold water, and dried under a high vacuum at 60 °C. Unless noted otherwise, the crude product was purified by recrystallization from MeOH/H_2O and dried under a high vacuum at 60 °C, which afforded the product **1** (compounds **1c**, **1f**, **1g**, **1i**) as a brightly colored solid. Other 5-arylidene-2-methyl-4-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylates were prepared following the literature procedures [71].

3.3. Organocatalyzed Bis-Spiroheterocyclization-Preparation of Racemic Mixtures-General Procedure 2 (GP2)

To a mixture of arylidene-Δ^2-pyrrolin-4-one **1** (0.1 mmol), 3-isothiocyanato oxindole **2** (0.13 mmol), and 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.01 mmol, 1.12 mg) under argon, anhydrous THF (1 mL) was added and the resulting reaction mixture was stirred at 25 °C for 24 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (Silica gel 60, mobile phase: EtOAc/petroleum ether = 2:1). Fractions containing the pure racemic product ***rac*-3** were combined and volatile components were evaporated in vacuo followed by HPLC analysis on chiral columns. Products ***rac*-3** (compounds ***rac*-3k-n**), that could not be separated on chiral columns, were fully characterized.

3.4. Organocatalyzed Stereoselective Bis-Spiroheterocyclization-General Procedure 3 (GP3)

To a mixture, arylidene-Δ^2-pyrrolin-4-one **1** (0.1 mmol), 3-isothiocyanato oxindole **2** (0.13 mmol), and organocatalyst **I-XII** (10 mol%) under argon, anhydrous solvent (1 mL) was added and the resulting reaction mixture was stirred at 25 °C for 24–72 h.

(i) For catalyst and solvent screening (model reaction **1a** + **2a**→**3a**), volatile components were evaporated in vacuo and the residue was purified by flash column chromatography to remove the catalyst (Silica gel 60, mobile phase: EtOAc/petroleum ether = 2:1). Fractions containing the product **3a** were combined and volatile components were evaporated in vacuo followed by determination of the enantiomeric excess and diastereomeric ratio by HPLC analysis.

(ii) For the reaction scope synthesis (reactions **1** + **2**→**3**; compounds **3a**–**l**), volatile components were evaporated in vacuo and the residue was purified by column chromatography (Silica gel 60, mobile phase: EtOAc/petroleum ether = 2:1). Fractions containing pure product **3** were combined and volatile components were evaporated in vacuo, followed by determination of the enantiomeric excess by HPLC analysis, determination of the diastereomeric ratio by ^{1}H-NMR, and full characterization.

4. Conclusions

We have shown that Michael acceptors based on Δ^2-pyrrolin-4-ones (pyrrolones), which are easily prepared from bulk chemicals [71], undergo stereoselective organocatalyzed double spiro-cyclization with 3-isothiocianato oxindoles. A library of 12 products containing three contiguous stereocenters (*ee* up to 98%, *dr* up to 99:1) has been synthesized and a follow-up transformation demonstrated. This research offers a new entry for the construction of 3D-rich pyrrolone-containing heterocycles.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/10/10/1211/s1, Synthesis and Characterization Data for Compounds **1** and **3**; HPLC data; Copies of ^{1}H- and ^{13}C-NMR spectra; Structure Determination by NMR-NOESY spectra (for compounds **1**); Copies of HRMS reports of Compounds **1** and **3**; Structure Determination by X-ray Diffraction Analysis, Figure S6: Ortep drawing of compound **3b**.

Author Contributions: For Conceptualization, U.G., S.R., J.S., F.P., and B.Š.; methodology, U.G. and S.R.; software, U.G., S.R., L.C., J.S., F.P., and B.Š.; validation, U.G., S.R., J.S., F.P., and B.Š.; formal analysis, U.G., Ž.T., H.B., and S.R.; investigation, S.R., Ž.T., L.C., and U.G.; resources, U.G., S.R. and J.S.; data curation, U.G., Ž.T., L.C., J.S., S.R., F.P., H.B., and B.Š.; writing—original draft preparation, U.G., S.R., J.S., F.P., and B.Š.; writing—review and editing, U.G., J.S., S.R., L.C., F.P., and B.Š.; visualization, U.G., B.Š., and J.S.; supervision, U.G.; project administration, U.G. and J.S.; funding acquisition, J.S., U.G., F.P., and B.Š. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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