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Double Spirocyclization of Arylidene-Δ²-Pyrrolin-4-Ones with 3-Isothiocyanato Oxindoles

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Abstract: Arylidene-Δ²-pyrrolin-4-ones undergo organocatalyzed double spirocyclization with 3-isothiocyanato 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 Δ²-pyrrolin-4-ones (pyrrolones) for the organocatalyzed construction of 3D-rich pyrroline-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].
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 (Δ²-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]).

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

**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-Δ2-pyrrolin-4-ones [71] 1 for the enantioselective construction of oxindole-thiopyrrolidinone-Δ2-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-1H-pyrrole-3-carboxylate (1a) and 3-isothiocyanato-1-methylindolin-2-one (2a) in THF yielded the corresponding racemic oxindole-thiopyrrolidineone-Δ2-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 (VIIb, 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).

| Solvent | Yield (%) | dr  | ee (%) |
|---------|-----------|-----|-------|
| toluene | 60        | 95:5| 79    |
| 1,4-dioxane | 46 | 93:7| 83    |
| Et2O   | 35        | 80:20| 75    |

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).

Having established the optimal reaction conditions (catalyst IXb, trifluorotoluene), the scope of the studied transformation was evaluated. For that purpose, several Δ²-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 Δ²-pyrrolin-4-ones 1a–g, the effect of electron-donating and electron-withdrawing substituents on the phenyl ring of the arylidene moiety, including thiophen-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 at longer reaction times. 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 (3R,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 (3R,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

### Table 1. Evaluation of organocatalyst IXb in bis-spiroheterocyclization of 5-arylidene-Δ²-pyrrolin-4-one 1a with 3-isothiocyanato oxindole 2a.\(^a\)

| Solvent         | Yield (%) | dr    | ee (%) |
|-----------------|-----------|-------|--------|
| toluene         | 60        | 95:5  | 79     |
| 1,4-dioxane     | 46        | 93:7  | 83     |
| Et₂O            | 35        | 80:20 | 75     |
| 1,2-dimethoxyethane | 49      | 95:5  | 78     |
| THF             | 55        | 94:6  | 82     |
| CH₂Cl₂          | 61        | 93:7  | 6      |
| PhCF₃           | 67        | 93:7  | 87     |
| acetone         | 44        | 94:6  | 87     |
| t-butyl methyl ketone | 41     | 95:5  | 87     |
| MeCN            | 30        | 79:21 | 52     |
| MeOH            | 34        | 86:14 | 36     |

\(^a\) 5-Arylidene-Δ²-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.
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 (3S,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 K₂CO₃ in acetone gave the S-methylated product 4 (Scheme 4).

According to the Grayson [72,73] proposal of stereochemistry 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](image)

Figure 2. Selected 5-arylidene-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylates 1 and 3-isothiocyanato oxindoles 2; color red—novel reported pyrrolones 1.
The absolute configuration \((3R,3'S,4'R)\) 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 \((3R,3'S,4'R)\) 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 \((7\% \text{ and } 14\%)\), and low to moderate enantioselectivities \((21\% \text{ and } 57\%) \text{ ee}\), 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 \((3S,3'R,4'S)\) was tentatively assigned to products \(3k\) and \(3l\) (Scheme 3).

Scheme 3. Synthesized bis-spiroheterocycles 3.

![Figure 3. Single crystal X-ray structure depicting product 3b. Thermal ellipsoids are shown at 50% probability.](image-url)
3. 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$_2$SO$_4$ 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 recorded 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 $\times$ 25 cm), CHIRALPAK AD-H (0.46 cm $\times$ 250 mm), CHIRALCEL AS-H (0.46 cm $\times$ 250 mm), and CHIRALCEL OD-H (0.46 cm $\times$ 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-1H-pyrrole-3-carboxylates 1 [71] and 3-isothiocyanatoxyindoles 2a and 2b [30,53,59] were prepared following the literature procedures. Organocatalysts Ia [70], II [69], IIa [70], IV [70], Vb [74], VIA [75], Vlb [76], VIa [77], VIIIb [76], IXa [78], IXb [79], IXc [80], Xb [81], Xa [19], and Xlb [78] were prepared following the literature procedures; organocatalysts VIIIb and XII were purchased from Sigma-Aldrich.

![Scheme 4. Follow-up methylation of compound 3a.](image)

![Scheme 5. Postulated transition state leading to the product 3a.](image)
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, \( \omega = 0.85 \)) 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\(_2\)O (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 \( \Delta^2 \)-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\(_2\)O 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-1H-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-\( \Delta^2 \)-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 \( \text{rac}-3 \) were combined and volatile components were evaporated in vacuo followed by HPLC analysis on chiral columns. Products \( \text{rac}-3 \) (compounds \( \text{rac}-3k-n \)), 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-\( \Delta^2 \)-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 \( \Delta^2 \)-pyrrolin-4-ones (pyrrololes), which are easily prepared from bulk chemicals [71], undergo stereoselective organocatalyzed double spiro-cyclization with 3-isothiocyanato 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 pyrrolole-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.

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References
1. Panda, S.S.; Mohapatra, P.P.; Jones, R.A.; Bachawala, P. Spirooxindoles as Potential Pharmacophores. *Mini Rev. Med. Chem.* 2017, 17, 1515–1536. [CrossRef] [PubMed]
2. Yu, B.; Yu, D.-Q.; Liu, H.-M. Spirooxindoles: Promising scaffolds for anticancer agents. *Eur. J. Med. Chem.* 2015, 97, 673–698. [CrossRef] [PubMed]
3. Zheng, Y.; Tice, C.M.; Singh, S.B. The use of spirocyclic scaffolds in drug discovery. *Bioorg. Med. Chem. Lett.* 2014, 24, 3673–3682. [CrossRef] [PubMed]
4. Galliford, C.V.; Scheidt, K.A. Pyrrolidinyl-spirooxindole natural products as inspirations for the development of potential therapeutic agents. *Angew. Chem. Int. Ed.* 2007, 46, 8748–8758. [CrossRef]
5. Zhao, Y.; Yu, S.; Sun, W.; Liu, L.; Lu, J.; McEachern, D.; Shargary, S.; Bernard, D.; Li, X.; Zhao, T.; et al. A Potent Small-Molecule Inhibitor of the MDM2-p53 Interaction (MI-888) Achieved Complete and Durable Tumor Regression in Mice. *J. Med. Chem.* 2013, 56, 5553–5561. [CrossRef] [PubMed]
6. Crosignani, S.; Page, P.; Missotten, M.; Colovray, V.; Cleva, C.; Arrighi, J.-F.; Atherall, J.; Macritchie, J.; Martin, T.; Humbert, Y.; et al. Discovery of a New Class of Potent, Selective, and Orally Bioavailable CRTH2 (DP2) Receptor Antagonists for the Treatment of Allergic Inflammatory Diseases. *J. Med. Chem.* 2008, 51, 2227–2243. [CrossRef] [PubMed]
7. Edmondson, S.; Danishefsky, S.J.; Sepp-Lorenzino, L.; Rosen, N. Total Synthesis of Spirotryprostatin A, Leading to the Discovery of Some Biologically Promising Analogs. *J. Am. Chem. Soc.* 1999, 121, 2147–2155. [CrossRef]
8. Yeung, B.K.S.; Zou, B.; Rottmann, M.; Lakshminarayana, S.B.; Ang, S.H.; Leong, S.Y.; Tan, J.; Wong, J.; Keller-Maerki, S.; Fischli, C.; et al. Spirotetrahydro β-Carbolines (Spiroindolones): A New Class of Potent and Orally Efficacious Compounds for the Treatment of Malaria. *J. Med. Chem.* 2010, 53, 5155–5164. [CrossRef]
9. Yu, Q.; Guo, P.; Jian, J.; Chen, Y.; Xu, J. Nine-step total synthesis of (-)-strychnofoline. *Chem. Commun.* 2018, 54, 1125–1128. [CrossRef]
10. Ye, N.; Chen, H.; Wold, E.A.; Shi, P.Y.; Zhou, J. Therapeutic Potential of Spirooxindoles as Antiviral Agents. *ACS Infect. Dis.* 2016, 2, 382–392. [CrossRef]
11. Torres, R.R. (Ed.) *Stereoselective Organocatalysis: Bond Formation Methodologies and Activation Modes*, 1st ed.; JohnWiley & Sons: Hoboken, NJ, USA, 2013.
12. Jakab, G.; Schreiner, P.R. Brønsted Acids: Chiral (Thio)urea Derivatives. In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, 1st ed.; Dalko, P.I., Ed.; Wiley-VCH: Weinheim, Germany, 2013; pp. 315–342.
13. Krištofíková, D.; Modrocká, V.; Mečiarová, M.; Šebesta, R. Green Asymmetric Organocatalysis. *ChemSusChem* 2020, 13, 2828–2858. [CrossRef]
14. Chanda, T.; Zhao, J.C.G. Recent Progress in Organocatalytic Asymmetric Domino Transformations. *Adv. Synth. Catal.* 2018, 360, 2–79. [CrossRef]
15. Held, F.E.; Tsogoeva, S.B. Asymmetric cycloaddition reactions catalyzed by bifunctional thiourea and squaramide organocatalysts: Recent advances. Catal. Sci. Technol. 2016, 6, 645–667. [CrossRef]

16. Holland, M.C.; Gilmour, R. Deconstructing Covalent Organocatalysis. Angew. Chem. Int. Ed. 2015, 54, 3862–3871. [CrossRef] [PubMed]

17. Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. Bifunctional Amine-Squaramides: Powerful Hydrogen-Bonding Organocatalysts for Asymmetric Domino/Cascade Reactions. Adv. Synth. Catal. 2015, 357, 253–281. [CrossRef]

18. Serdyuk, O.V.; Heckel, C.M.; Tsogoeva, S.B. Bifunctional primary amine-thioureas in asymmetric organocatalysis. Org. Biomol. Chem. 2013, 11, 7051–7071. [CrossRef]

19. Malerich, J.P.; Hagihara, K.; Rawal, V.H. Chiral Squaramide Derivatives are Excellent Hydrogen Bond Donor Organocatalysts. J. Am. Chem. Soc. 2008, 130, 14416–14417. [CrossRef]

20. Alem, J.; Parra, A.; Jiang, H.; Jørgensen, K.A. Squaramides: Bridging from Molecular Recognition to Bifunctional Organocatalysis. Chem. Eur. J. 2011, 17, 6890–6899. [CrossRef]

21. Enders, D.; Huttl, M.R.M.; Grondal, C.; Raabe, G. Control of four stereocentres in a triple cascade organocatalytic reaction. Nature 2006, 441, 861–863. [CrossRef]

22. Tan, F.; Cheng, H.-G. Recent advances in catalytic asymmetric cascade reactions of 3-isothiocyanato oxindoles for synthesis of spirooxindoles. Targets Heterocycl. Syst. 2017, 21, 158–180.

23. Mei, G.-J.; Shi, F. Catalytic asymmetric synthesis of spirooxindoles: Recent developments. Chem. Commun. 2018, 54, 6607–6621. [CrossRef]

24. Gasperi, T.; Miceli, M.; Campagne, J.-M.; Marcia de Figueiredo, R. Non-covalent organocatalyzed domino reactions involving oxindoles: Recent advances. Molecules 2017, 22, 1636. [CrossRef] [PubMed]

25. Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C.F. Organocatalytic Asymmetric Assembly Reactions: Synthesis of Spirooxindoles via Organocascade Strategies. ACS Catal. 2014, 4, 743–762. [CrossRef]

26. Zhang, C.-B.; Dou, P.-H.; You, Y.; Wang, Z.-H.; Zhou, M.-Q.; Xu, X.-Y.; Yuan, W.-C. Organocatalytic asymmetric [3+2]-cycloaddition of 3-isothiocyanato oxindoles with 1,3,5-trisubstituted-hexahydro-1,3,5-triazines to access spiroimidazolinethione-oxindoles. Tetrahedron 2019, 75, 130571. [CrossRef]

27. Gui, H.-Z.; Wei, Y.; Shi, M. Construction of spirothioureas having an amino quaternary stereogenic center via a [3+2] annulation of 3-isothiocyanato oxindoles with 2-aminoacrylates. Org. Biomol. Chem. 2018, 16, 9218–9222. [CrossRef]

28. Du, D.; Xu, Q.; Li, X.-G.; Shi, M. Construction of Spiroyclic Oxindoles through Regio- and Stereoselective [3+2] or [3+2][4+2] Cascade Reaction of α,β-Unsaturated Imines with 3-Isothiocyanato Oxindole. Chem. Eur. J. 2016, 22, 4733–4737. [CrossRef] [PubMed]

29. Bai, M.; Cui, B.-D.; Zuo, J.; Zhao, J.-Q.; You, Y.; Chen, Y.-Z.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. Quinine-catalyzed asymmetric domino Mannich-cyclization reactions of 3-isothiocyanato oxindoles with imines for the synthesis of spirocyclic oxindoles. Tetrahedron 2015, 71, 949–955. [CrossRef]

30. Cai, H.; Zhou, Y.; Zhang, D.; Xu, J.; Liu, H. A Mannich/cyclization cascade process for the asymmetric synthesis of spirothioimidazolidinethioneoxindoles. Chem. Commun. 2014, 50, 14771–14774. [CrossRef]

31. Zhang, C.-B.; Dou, P.-H.; Zhao, J.-Q.; Yuan, W.-C. Organocatalyzed asymmetric cascade Mannich/cyclization of 3-isothiocyanato oxindoles with cyclic ketimines for the synthesis of poly cyclic spirothioimidazolidinethionexindoles. Tetrahedron 2020, 76, 131116. [CrossRef]

32. Zhao, B.-L.; Du, D.-M. Asymmetric Synthesis of Spirooxindoles with Seven Stereocenters via Organocatalysed One-pot Three-component Sequential Cascade Reactions. Adv. Synth. Catal. 2019, 361, 3412–3419. [CrossRef]

33. Chen, S.; Wang, G.-L.; Xu, S.-W.; Tian, M.-Y.; Zhang, M.; Liu, X.-L.; Yuan, W.-C. Regio- and stereoselective [3+2] cycloaddition reaction: Access to isoxazole-dispirooxindoles featuring three contiguous stereocenters. Org. Biomol. Chem. 2019, 17, 6551–6556. [CrossRef] [PubMed]

34. Bai, M.; Chen, Y.-Z.; Cui, B.-D.; Xu, X.-Y.; Yuan, W.-C. Thiourea-catalyzed asymmetric domino Michael-cyclization reaction of 3-isothiocyanato oxindoles with β,γ-unsaturated α-keto esters for the synthesis of spirocyclic oxindoles. Tetrahedron 2019, 75, 2155–2161. [CrossRef]

35. Zhu, W.-R.; Chen, Q.; Lin, N.; Chen, K.-B.; Zhang, Z.-W.; Fang, G.; Weng, J.; Lu, G. Organocatalytic Michael/cyclization cascade reactions of 3-isothiocyanato oxindoles with 3-trifluoroethylidene oxindoles: An approach for the synthesis of 3’-trifluoromethyl substituted 3,2’-pyrrolidine-bispirooxindoles. Org. Chem. Front. 2018, 5, 1375–1380. [CrossRef]
36. Song, Y.-X.; Du, D.-M. Squaramide-Catalyzed Asymmetric Michael/Cyclization Cascade Reaction of Unsaturated Thiazolidinones and 3-Isothiocyanato Oxindoles: Synthesis of New Dispiro cyclic Heterocycles. *Synthesis* 2018, 50, 1535–1545.

37. Lin, N.; Long, X.-w.; Chen, Q.; Zhu, W.-r.; Wang, B.-c.; Chen, K.-b.; Jiang, C.-w.; Weng, J.; Lu, G. Highly efficient construction of chiral dispiro cyclic oxindole/thiobutyrolactam/chromalone complexes through Michael/cyclization cascade reactions with a resin-based squaramide catalyst. *Tetrahedron* 2018, 74, 3734–3741. [CrossRef]

38. Cao, Y.-M.; Shen, F.-F.; Zhang, F.-T.; Wang, R. Catalytic asymmetric Michael addition reaction of 3-isothiocyanato oxindoles with chalcones for synthesis of pyrrolidinyl spirooxindoles. *Adv. Synth. Catal.* 2016, 358, 2619–2630. [CrossRef]

39. Cui, B.-D.; Li, S.-W.; Zuo, J.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. Quinine-catalyzed asymmetric domino cyclization cascade reactions of unsaturated pyrazolones by a chiral tertiary amine thiourea catalyst. *Org. Lett.* 2013, 15, 1246–1249. [CrossRef] [PubMed]

40. Wu, C.; Jing, L.; Qin, D.; Yin, M.; He, Q. Organocatalytic asymmetric synthesis of trans-configured trispirooxindoles through a cascade Michael-cyclization reaction. *Tetrahedron Lett.* 2016, 57, 2857–2860. [CrossRef]

41. Kayal, S.; Mukherjee, S. Catalytic enantioselective cascade Michael/cyclization reaction of 3-isothiocyanato oxindoles with exocyclic α,β-unsaturated ketones en route to 3,2′-pyrrolidinyl bispireoxindoles. *Org. Biomol. Chem.* 2016, 14, 10175–10179. [CrossRef]

42. Chowdhury, R.; Kumar, M.; Ghosh, S.K. Organocatalyzed enantioselective Michael addition/cyclization cascade reaction of 3-isothiocyanato oxindoles with arylidene malonates. *Org. Biomol. Chem.* 2016, 14, 11250–11260. [CrossRef]

43. Cui, B.-D.; Li, S.-W.; Zuo, J.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. Quinine-catalysed asymmetric domino Michael-cyclization reaction for the synthesis of spirocyclic oxindoles bearing two spiro quaternary centers and three consecutive stereocenters. *ChemCatChem* 2014, 7, 3551–3556. [CrossRef] [PubMed]

44. Han, W.-Y.; Li, S.-W.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. 3-Isothiocyanato oxindoles serve as powerful and versatile precursors to structurally diverse dispiro cyclic thiopyrrolidineoxindoles through a cascade Michael/cyclization process with amino-thiocarbamate catalysts. *Chem. Eur. J.* 2013, 19, 5551–5556. [CrossRef]

45. Kayal, S.; Mukherjee, S. Catalytic Asymmetric Michael Addition/Cyclization Cascade Reaction of 3-Isothiocyanatooxindoles with Nitro Olefins. *Eur. J. Org. Chem.* 2013, 2071–2075. [CrossRef]

46. Wu, H.; Zhang, L.-L.; Chen, X.-Q.; Song, X.-Q.; Zhao, Y.-D.; Liu, Y.-Y. Highly Enantioselective Construction of Dispirobarbiturates. *Adv. Synth. Catal.* 2013, 1229–1238. [CrossRef]

47. Han, W.-Y.; Li, S.-W.; Zuo, J.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. Highly efficient construction of chiral dispiro cyclic oxindole/thiobutyrolactam/chromalone complexes through Michael/cyclization cascade reactions with a resin-based squaramide catalyst. *Tetrahedron* 2018, 74, 3734–3741. [CrossRef]

48. Cao, Y.-M.; Shen, F.-F.; Zhang, F.-T.; Wang, R. Catalytic asymmetric Michael addition/cyclization of isothiocyanato oxindoles: Highly efficient and versatile approach for the synthesis of 3,2′-pyrrolidinyl mono- and bi-spirooxindole frameworks. *Chem. Eur. J.* 2013, 19, 1184–1188. [CrossRef]
71. Grošelj, U.; Ciber, L.; Gnidovec, J.; Testen, Ž.; Požgan, F.; Štefane, B.; Tavčar, G.; Svete, J.; Ričko, S. Synthesis of Spiro-∆2-Pyrrolin-4-One Pseudo Enantiomers via an Organocatalyzed Sulfa-Michael/Aldol Domino Sequence. *Adv. Synth. Catal.* 2019, *361*, 5118–5126. [CrossRef]

72. Grayson, M.N. Mechanism and Origins of Stereoselectivity in the Cinchona Thiourea- and Squaramide-Catalyzed Asymmetric Michael Addition of Nitroalkanes to Enones. *J. Org. Chem.* 2017, *82*, 4396–4401. [CrossRef]

73. Ričko, S.; Izzo, J.A.; Jørgensen, K.A. Insights on the Pseudo-Enantiomeric Properties of Bifunctional Cinchona Alkaloid Squaramide-derived Organocatalyst. *Chem. Eur. J.* 2020. Accepted Author Manuscript. [CrossRef]

74. Ričko, S.; Požgan, F.; Štefane, B.; Svete, J.; Golobić, A.; Grošelj, U. Stereodivergent Synthesis of Camphor-Derived Diamines and Their Application as Thiourea Organocatalysts. *Molecules* 2020, *25*, 2978. [CrossRef]

75. Mailhol, D.; Duque, M.d.M.S.; Raimondi, W.; Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. Enantioselective Organocatalytic Michael Addition of Cyclobutanones to Nitroalkenes. *Adv. Synth. Catal.* 2012, *354*, 3523–3532. [CrossRef]

76. Konishi, H.; Lam, T.Y.; Malerich, J.P.; Rawal, V.H. Enantioselective α-Amination of 1,3-Dicarbonyl Compounds Using Squaramide Derivatives as Hydrogen Bonding Catalysts. *Org. Lett.* 2010, *12*, 2028–2031. [CrossRef] [PubMed]

77. Baran, R.; Veverková, E.; Škvorcová, A.; Šebesta, R. Enantioselective Michael addition of 1,3-dicarbonyl compounds to a nitroalkene catalyzed by chiral squaramides—A key step in the synthesis of pregabalin. *Org. Biomol. Chem.* 2013, *11*, 7705–7711. [CrossRef] [PubMed]

78. Yang, W.; Du, D.-M. Highly Enantioselective Michael Addition of Nitroalkanes to Chalcones Using Chiral Squaramides as Hydrogen Bonding Organocatalysts. *Org. Lett.* 2010, *12*, 5450–5453. [CrossRef]

79. Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J.M.; Odriozola, J.M.; Razkin, J.; Oiarbide, M.; et al. Enantioselective Construction of Tetrasubstituted Stereogenic Carbons through Brønsted Base Catalyzed Michael Reactions: α′-Hydroxy Enones as Key Enolate Equivalent. *J. Am. Chem. Soc.* 2014, *136*, 17869–17881. [CrossRef]

80. Zhao, B.-L.; Du, D.-M. Catalytic asymmetric conjugate addition of various α-mercaptoketones to α,β-unsaturated N-acylated oxazolidin-2-ones with bifunctional organocatalyst. *RSC Adv.* 2014, *4*, 27346–27353. [CrossRef]

81. Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. Highly Enantioselective Conjugate Addition of Nitromethane to Chalcones Using Bifunctional Cinchona Organocatalysts. *Org. Lett.* 2005, *7*, 1967–1969. [CrossRef]

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