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Advanced Synthesis & Catalysis

Synthesis of Spiro-Δ^2-Pyrrolin-4-One Pseudo Enantiomers *via* an Organocatalyzed Sulfa-Michael/Aldol Domino Sequence

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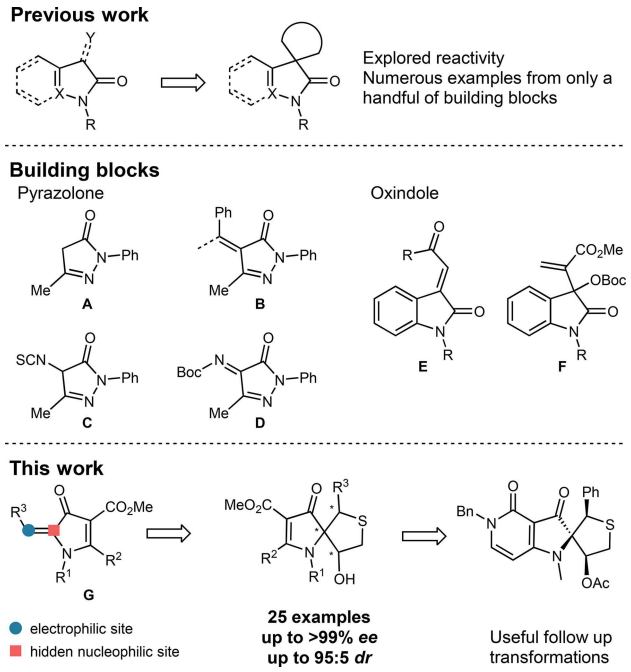
Abstract: Δ^2-Pyrrolin-4-ones undergo organocatalyzed sulfa-Michael/aldol domino spirocyclizations with mercaptoacetaldehyde dimer. The products contain three contiguous stereocenters (*ee* up to 99%, *dr* up to 95:5, 25 examples) and can be transformed into analogues of natural products. With the use of a single catalyst, the absolute configuration of the products were determined by the configuration of the exocyclic double bond of the starting material. These results point at the possibility of a widespread use of unsaturated Δ^2-pyrrolin-4-ones in various (organo)catalyzed (cascade) transformations for accessing libraries of 3D-rich pyrrolone-based (spiro)heterocycles.

Keywords: asymmetric catalysis; pyrrolin-4-one; organic catalysis; domino reaction; spiro compounds

Organocatalysis is a powerful synthetic tool for the preparation of complex molecular architectures from simple starting materials. This can largely be attributed to the development of the organocascade methodology, a process that involves two or more successive reactions initiated by an organocatalyst, where each subsequent reaction is the result of the functionality formed in the previous step.[1] Spirocyclic motif is an elegant structural element, ubiquitous in nature, that is still challenging to construct in an enantioselective manner. This difficulty arises from the need for precise stereocontrol during the formation of the carbon stereogenic center linking the two fused rings together. Another problem is related to the functional group incompatibility resulting in difficult post-modifications of spirocyclic systems, which limits the usefulness of the developed methodologies in the search of new lead compounds.[2] Over the years, several research groups overcame these obstacles by developing their own catalytic cascade sequences for the synthesis of various spirocyclic scaffolds.[1c,2,3] While highly elegant and efficient, they exploit the innate reactivity of only a handful of well-established building blocks. Majority of them are representatives of pyrazolones[3c,4] and oxindoles,[5] owing to their presence in natural products and pharmaceutical agents. Notably, pyrazolones **A** and especially their unsaturated variants **B**, unsaturated oxindoles **E** and isatin-derived MBH carbonates **F** are examples of important synthons, which can be transformed into diverse spirocyclic structures (Scheme 1).



Scheme 1. State-of-the-art in the area of asymmetric (cascade) transformations.

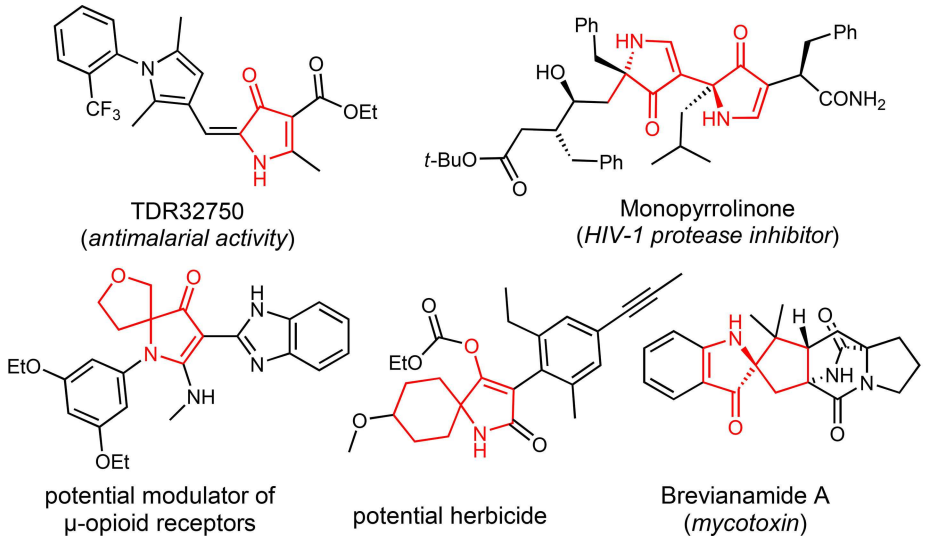


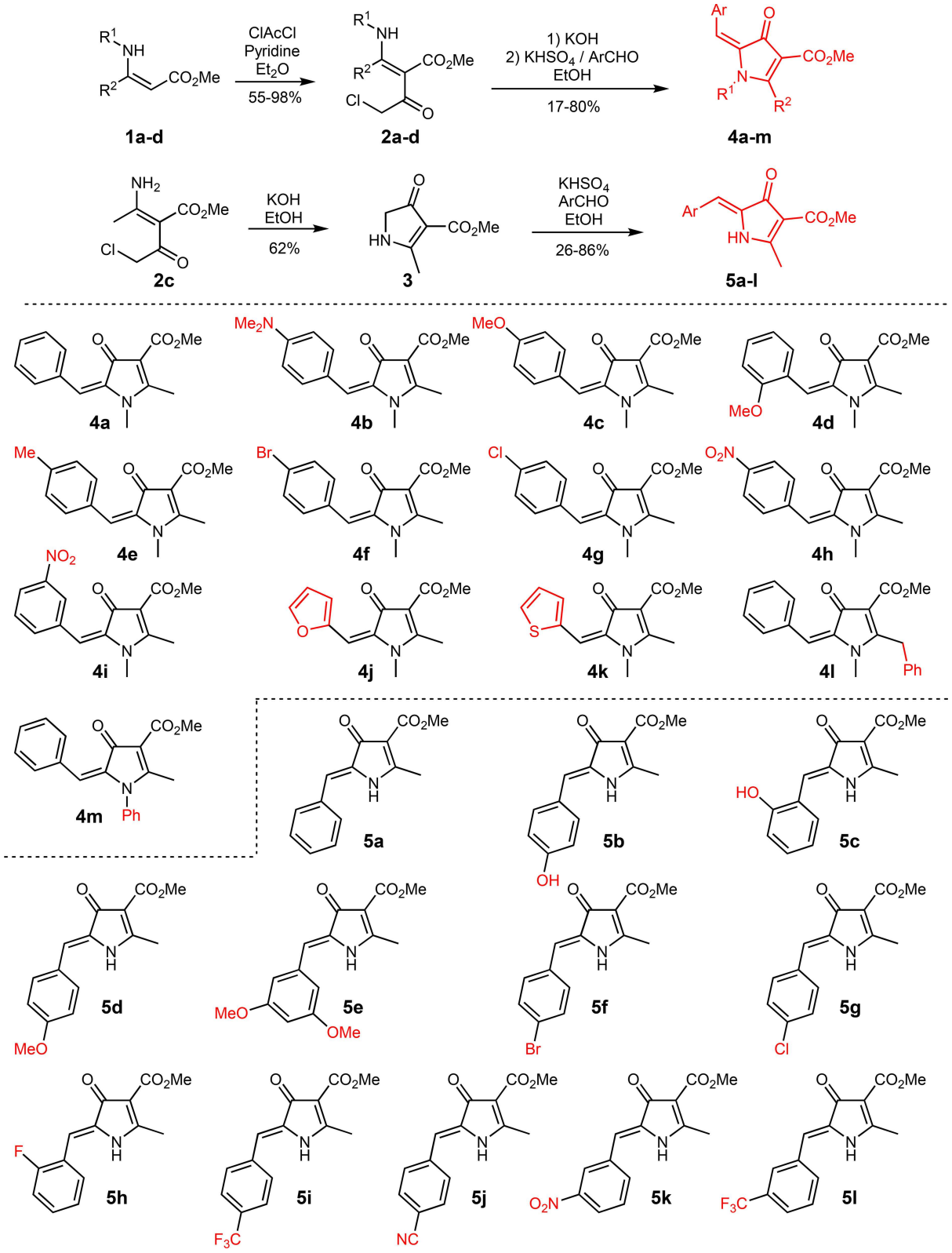
Figure 1. Biologically active compounds with the Δ^2-pyrrolin-4-one core.

The reason for their widespread use lies in the ease of sequential activation of multiple reactive sites of the substrate, either by metal or by organic catalyst.[6]

Nevertheless, the construction of new privileged building blocks is still challenging, because it requires the discovery of a structure that possesses the unique reactivity enabling its participation in cascade transformations. In this vein, Wang *et al.* prepared an isothiocyanate-derived pyrazolone **C** used for the synthesis of a new type of dispirotriheterocyclic pyrazolones.[7] Enders *et al.* were the first to prepare *N*-Boc-ketimine-derived pyrazolones[8] **D** and used them in aza-Friedel-Crafts/*N*,*O*-acetalization reaction furnishing furanonaphthopyrazolidinone derivatives[9] while Li *et al.* used them to construct trispirocyclic *N*, *O*-ketal tethered oxindoles and bisoxindoles.[10] Their versatility was also demonstrated in the synthesis of chiral non-spirocyclic indole derivatives[11] and β-amino silyl enol ethers.[12] Regarding oxindoles, Y. Zhou *et al.* recently prepared a somewhat specialized oxindole–chromone synthon which enabled access to optically active spirocyclic hexahydroxanthones[13] and chromanone-based spirocyclohexaneoxindoles.[14] Evidently, extensive research is now being directed towards the development of asymmetric transformations from novel building blocks, albeit using pyrazolones and oxindoles as the core scaffolds (Scheme 1).

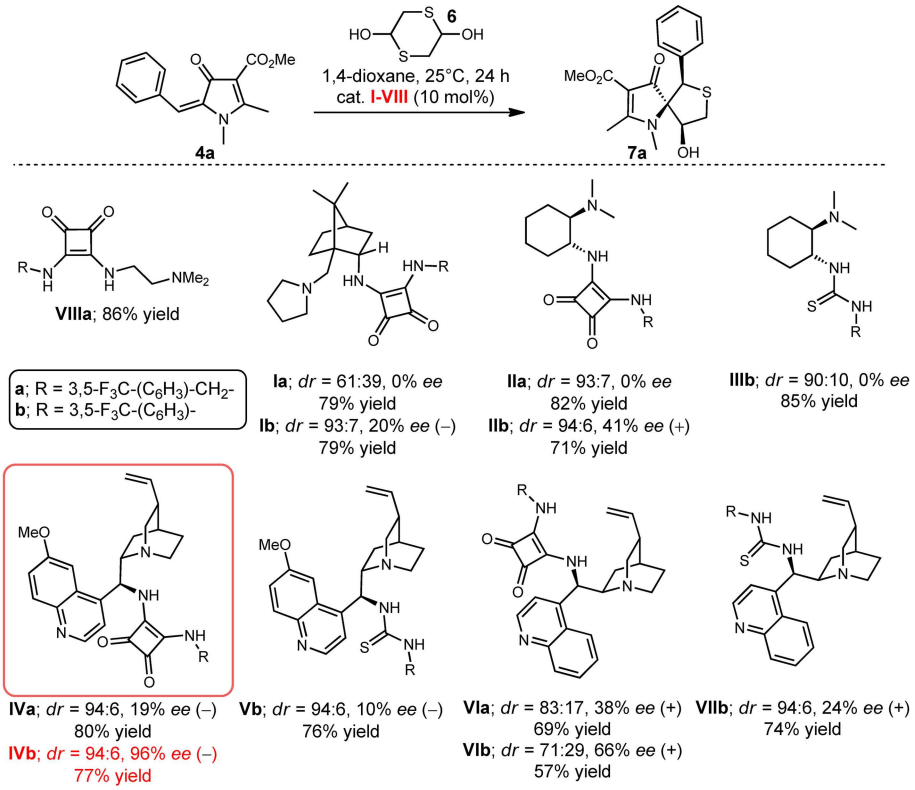
The Δ^2-pyrrolin-4-one core is an interesting motif prominent in several natural products (brevianamide A[15a]), bioactive molecules (modulators of opioid receptors,[15b] antimalarials,[15c,d] HIV-1 protease inhibitors[15e]) and phytopharmaceuticals (herbicides[15f]) (Figure 1). Although the first accounts concerning the spirocyclic derivatives of this scaffold head back all the way to 1958,[16] to the best of our knowledge, there exists no systematic report describing their preparation in optically pure form. Due to the wide representation and a general absence of non-racemic spiro-Δ^2-pyrrolin-4-one core libraries, a method enabling access of the aforementioned structures is highly desirable.

We predicted that with a proper catalytic system, arylidene-Δ^2-pyrrolin-4-ones of type **G** (Scheme 1) should participate in cascade reactions, yielding spirocyclic Δ^2-pyrrolin-4-ones. This would proceed *via* the initial Michael addition, which would liberate the nucleophilic active methylene functionality for the final ring closing. Inspired by this challenge, we decided to develop a scalable, operationally simple procedure for the preparation of synthons of type **G** and use them as a starting point in our continuous efforts to develop new asymmetric transformations.[17] While there are several reported procedures to access similar Δ^2-pyrrolin-4-ones systems, they were not convenient for our purpose because of the use of expensive reagents and excess metals,[18] unfavorable substitution patterns,[19] low yields, and undefined *E*/*Z* selectivity.[20] Arylidene-Δ^2-pyrrolin-4-ones were thus prepared following the procedure in Scheme 2. Firstly, aminocrotonates **1** were chloroacetylated to enaminones **2**. These were, in the case of *N*-substituted analogues (R^1 = Me or Ph), subjected to one-pot two step sequence *i.e.* a base-catalyzed cyclization followed by the acid-catalyzed condensation with a (hetero)aromatic aldehyde, thus affording the desired compounds **4a–m**. Base-catalyzed cyclization of *N*-unsubstituted enaminone **2a** furnished an air stable intermediate **3** in 62% yield, which upon condensation with aromatic aldehydes yielded the corresponding *N*-unsubstituted Δ^2-pyrrolin-4-ones **5a–l**. The obtained products **4**/**5** are air stabile brightly colored solids which precipitate out of the reaction mixture and are



Scheme 2. Synthesis of the arylidene-Δ^2-pyrrolin-4-ones **4a–m** and **5a–l**.

easily purified by recrystallization. As predicted, in the case of *N*-substituted analogues (R^2 = Me or Ph) only the *E*-configured alkenes **4** were formed while in the case of *N*-unsubstituted Δ^2-pyrrolin-4-ones the *Z*-



Scheme 3. Evaluation of organocatalysts **I**–**VIII**.

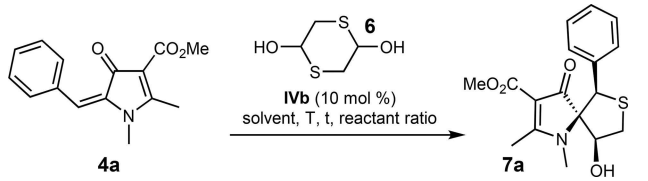
isomers **5** were obtained exclusively.[21] The configurational stability of the starting Δ^2-pyrrolin-4-ones could therefore easily be exploited for the stereoselective construction of pseudo-enantiomers using a single optimized organocatalyst (Scheme 2).

To determine if the prepared synthons **4** and **5** would participate in organocatalyzed domino transformations, 1,4-dithiane-2,5-diol (**6**) was chosen as the model reacting partner. While this dimer of 2-sulfanylacetaldehyde was highly reactive in sulfa-Michael/aldol domino sequences, yielding chiral spiro-tetrahydrothiophene rings, it gave only low to moderate enantiomeric excess in the presence of various chiral organocatalysts in the related reaction with the analogous unsaturated pyrazolones.[22] Firstly, a preliminary reaction between unsaturated pyrrolin-4-one **4a** and 1,4-dithiane-2,5-diol (**6**) in dioxane at 25 °C in the presence of an achiral bifunctional organocatalyst **VIIIa** was performed (Scheme 3). To our delight, the racemic spirocyclization product ***rac*-7a** was isolated in 86% yield as a mixture of two diastereoisomers after 24 h reaction time. Having shown that the unsaturated pyrrolin-4-one **4a** was a suitable reactant for the construction of spiro-pyrrolinone scaffolds, the effect of different chiral noncovalent bifunctional organocatalysts **I**–**VII** on the stereochemical outcome of the reaction was evaluated. The results are presented in Scheme 3. In general, higher *ee* values were obtained with squaramide-3,5-(CF_3)-aniline derived organocatalysts (**Ib**, **IIb**, **IVb**, **VIb**) with quinine derivatives (**IVb**, **VIb**) outperforming camphor[23] (**Ib**) and cyclohexane (**IIb**) analogues. Thiourea organocatalysts did not match their squaramide counterparts. The highest stereoselectivity (96% *ee*, *dr* = 94:6) was obtained with the catalyst **IVb** (Scheme 3).

With the optimal organocatalyst **IVb** in hand, we focused our attention on the optimization of the reaction conditions (Table 1). Somewhat expectedly, ethereal solvents and EtOAc gave very good *ee* values (81–93%), while polar or protic solvents exhibited low enantioselectivity. Reducing the catalyst loading (5 mol%, entry 13; 1 mol% entry 14,) or lowering (12 °C, entry 15) or raising (50 °C, entry 16) the temperature had no favorable effect on the stereochemical outcome of the reaction, while increasing the concentration of 1,4-dithiane-2,5-diol (**6**) (1.5 eq., entry 17) raised the enantioselectivity all the way up to 99% *ee*. With a shorter reaction time (2 h, entry 18) comparable yield (82%) with the same enantiomeric excess (99%) and a slightly lower diastereomeric ratio (*dr* = 90:10) was obtained. Prolonging the reaction time (48 h, entry 19) had no discernible effect on the yield and stereoselectivity.

Having established the optimal reaction conditions (Table 1, entry 17), we set out to determine the scope of the discovered transformation. Firstly, the effect of

Table 1. Optimization of the reaction conditions.



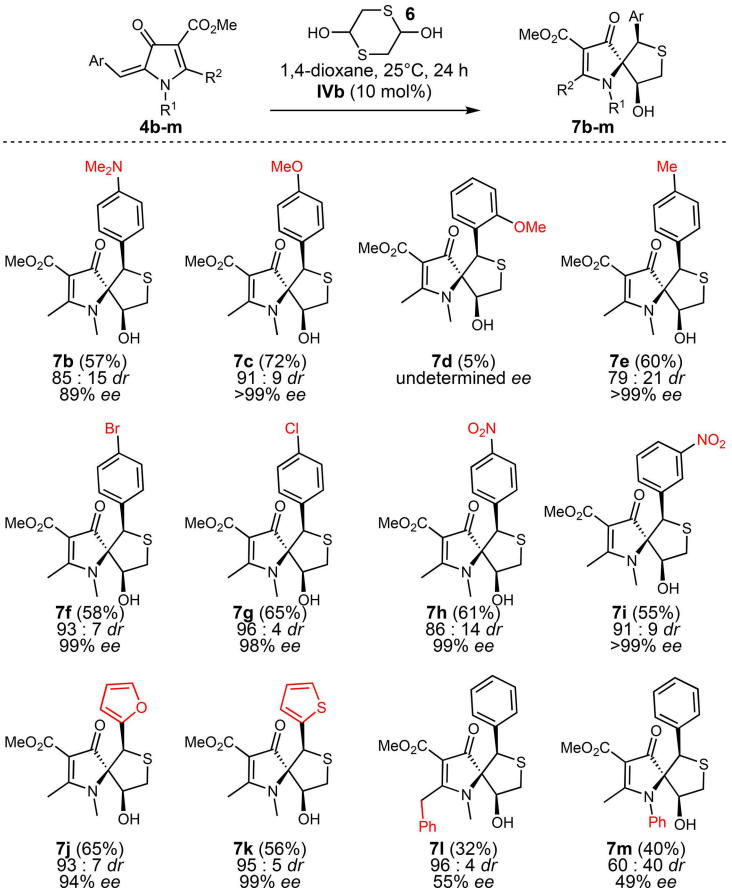
Entry[a]	Solvent	Yield[%]	*dr*	*ee*[%]
1	1,4-dioxane	72	94:6	96
2	toluene	75	95:5	71
3	Et_2O	88	95:5	82
4	1,2-dimetoxyethane	85	95:5	93
5	$CHCl_3$	75	93:7	79
6	EtOAc	69	94:6	84
7	THF	72	94:6	81
8	CH_2Cl_2	76	93:7	73
9	$PhCF_3$	82	94:6	48
10	acetone	86	93:7	51
11	MeOH	77	93:7	14
12	MeCN	69	89:11	12
13[b]	1,4-dioxane	65	93:7	95
14[c]	1,4-dioxane	59	64:36	88
15[d]	1,4-dioxane	63	88:12	81
16[e]	1,4-dioxane	82	93:7	92
17[f]	**1,4-dioxane**	**84**	**95:5**	**99**
18[f,g]	1,4-dioxane	82	90:10	99
19[f,h]	1,4-dioxane	86	95:5	99

[a] Pyrrol-4-one **4a** (0.1 mmol), 1,4-dithiane-2,5-diol (**6**) (0.07 mmol), catalyst **IVb** (10 mol%), solvent (1 mL), 25 °C, 24 h; conversion and *dr* determined by ^{1}H-NMR (DMSO); *ee* determined by HPLC.
[b] Catalyst **IVb** (5 mol%).
[c] Catalyst **IVb** (1 mol%).
[d] 12 °C.
[e] 50 °C.
[f] 1,4-Dithiane-2,5-diol (**6**) (0.15 mmol) used.
[g] 2 h reaction time.
[h] 48 h reaction time.

electron donating and electron withdrawing substituents on the phenyl ring of the arylidene moiety of the *N*-substituted Δ^2-pyrrolin-4-ones **4a–m** was evaluated. The results are presented in Scheme 4. In most cases, the products were isolated with excellent enantioselectivities (up to >99% *ee*), high diastereoselectivities (up to 91:9 *dr*), and typical yields between 55% and 72%. Product **7b**, with the dimethylamino group, was obtained with a slightly lower *ee* (89%), presumably due to the possible competing interference of the basic group with the organocatalyst (hydrogen bonding/deprotonation). The reaction with the *ortho*-OMe substituted Δ^2-pyrrolin-4-one **4d** proceeded sluggishly (yield <5%, t = 3 days) with the undetermined enantioselectivity, due to a complex mixture of products. Heteroaryl-substituted Δ^2-pyrrolin-4-ones **4j** and **4k** furnished products **7j** and **7k** in high enantiomeric purity (94% and 99% *ee*), high diastereomeric ratio (93:7 and 95:5), and in good yields (65% and 56%). On the other hand, the introduction of a benzyl group at the α-position of **4l** or a phenyl group at the ring nitrogen of **4m** turned out detrimental for the enantioselectivity of the corresponding spiro-heterocycles **7l** (55% *ee*) and **7m** (49% *ee*), arguably due to steric reasons. In light of these results, other bulkier groups were not investigated. In the case of *N*-unsubstituted Δ^2-pyrrolin-4-ones **5a–l** (Scheme 5), on average, higher yields with lower diastereoselectivities of the isolated products **8** were obtained compared to the *N*-Me substituted analogues **7**, while still retaining high enantioselectivity (up to >99%). Interestingly, in this series, the *ortho*-hydroxy substituted heterocycle **5c** gave the expected product **8c** with unchanged reactivity and only a slightly diminished *ee* value of 94%. The absolute configuration of the major stereoisomer of products **7a** and **8a** was determined by single crystal X-ray analysis of the corresponding acetoxy derivatives **10** and **9a**, respectively (Scheme 6). Consequently, the determined absolute configuration (5*S*,6*R*,9*S*) of the product **10** and (5*R*,6*S*,9*R*) of the product **9a** was tentatively assigned to all the major diastereomers of compounds **7a–m** and **8a–l**, respectively.

Analysis of the crystal structure revealed the pseudo-enantiomeric relationship between **7a** and **8a**. According to the observed configuration and DFT calculation studies by Grayson[24] a plausible transition state leading to the products **7a** and **8a** was postulated (Scheme 6). It is assumed that the catalyst **IVb** activates the electrophile **4a** or **5a** through hydrogen bonds provided by the protonated tertiary amine group. This activation proceeds irrespectively of the configuration or *N*-substitution of the starting alkene. In a similar manner, the mercaptoacetaldehyde nucleophile **6** is activated by the squaramide moiety through hydrogen bonding. The nucleophilic attack/Michael addition proceeds on the *Re* face of the *E*-alkene **4a** or on the *Si* face of the *Z*-alkene **5a**. The following intramolecular spirocyclization/aldol reaction yields the observed spirocyclic products **7a** and **8a** (Scheme 6). Gratifyingly, the catalyst of choice **IVb** can accommodate both the *E*- or the *Z*-configured arylidene-Δ^2-pyrrolin-4-ones furnishing products in high enantioselectivity. Furthermore, the configuration of the exocyclic C=C bond of **4** and **5** in conjunction with catalyst **IVb** dictates the absolute configuration of the spirocyclic products **7** and **8**, a very simple concept, though seldom applied in organocatalyzed transformations.

The synthetic utility of the discovered transformations **4a**→**7a** and **5a**→**8a** was demonstrated by performing these reactions on a gram scale. The reactions proceeded smoothly, yielding products with unchanged stereoselectivity (99% *ee*). Alcohols **7** and



Scheme 4. The scope of organocatalyzed spirocyclization of *N*-substituted Δ^2-pyrrolin-4-ones **4 b**–**m**.

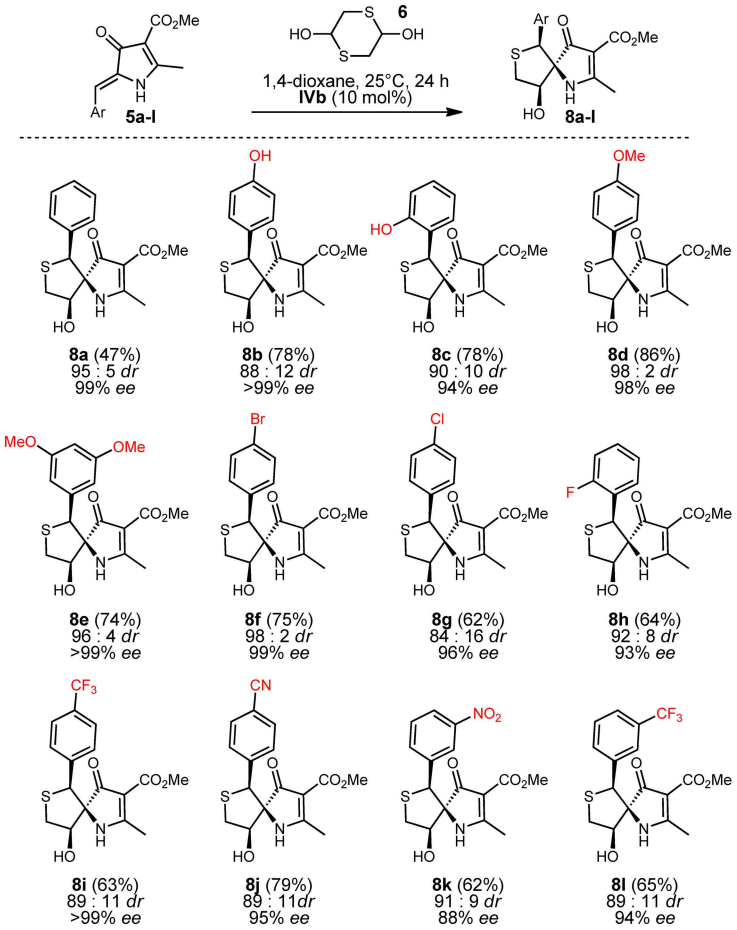
8 were routinely acetylated to the respective acetoxy derivatives **9** and **10** in order to determine the absolute configuration and for a reliable determination of enantiomeric excess in the case of compounds **8**.[21] Lastly, we set out to probe the reactivity of the active methyl group in the 2-position. Reacting compound **10** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) and further one-pot treatment of the enaminone intermediate with benzylamine furnished pyrrolo[3,2-*c*]pyridine spirocycle **12**, an analogue of Brevianamide A.[15a] Additionally, radical bromination of the methyl group of **9 a** furnished the dibromo derivative **11**, containing a potentially useful masked formyl group (Scheme 7).

In conclusion, an operationally simple procedure for the preparation of unsaturated-Δ^2-pyrrolin-4-ones was developed. The process allows for easy isolation of targeted heterocycles in multi-gram quantities. In the case of *N*-substituted heterocycles the products are isolated as pure *E*-isomers and in the case of *N*-unsubstituted Δ^2-pyrrolin-4-ones as pure *Z*-isomers. These heterocycles are easily transformed into the corresponding spirocyclic derivatives (25 examples) in high stereocontrol (*ee* up to >99%, *dr* up to 95:5) in good yields under organocatalyzed conditions. The absolute configuration of the product is dependent upon the applied organocatalyst, as well as the configuration of the exocyclic double bond in the starting material. These results point to the possibility of a widespread use of these building blocks in various (organo)catalyzed (cascade) transformations for accessing libraries of 3D-rich pyrrolone-based (spiro) heterocycles. Development of novel transformations of the reported heterocycles are already underway in our laboratories.

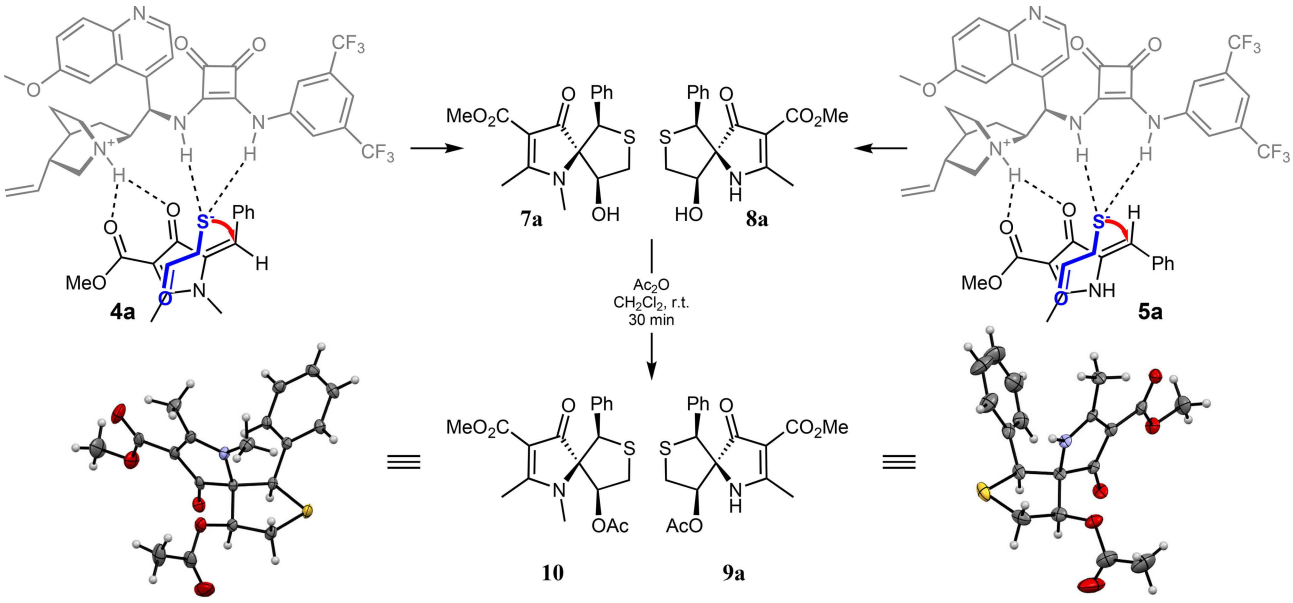
Experimental Section

Typical Procedure for Organocatalyzed Stereoselective Sulfa-Michael/aldol Domino Spiro Heterocyclization

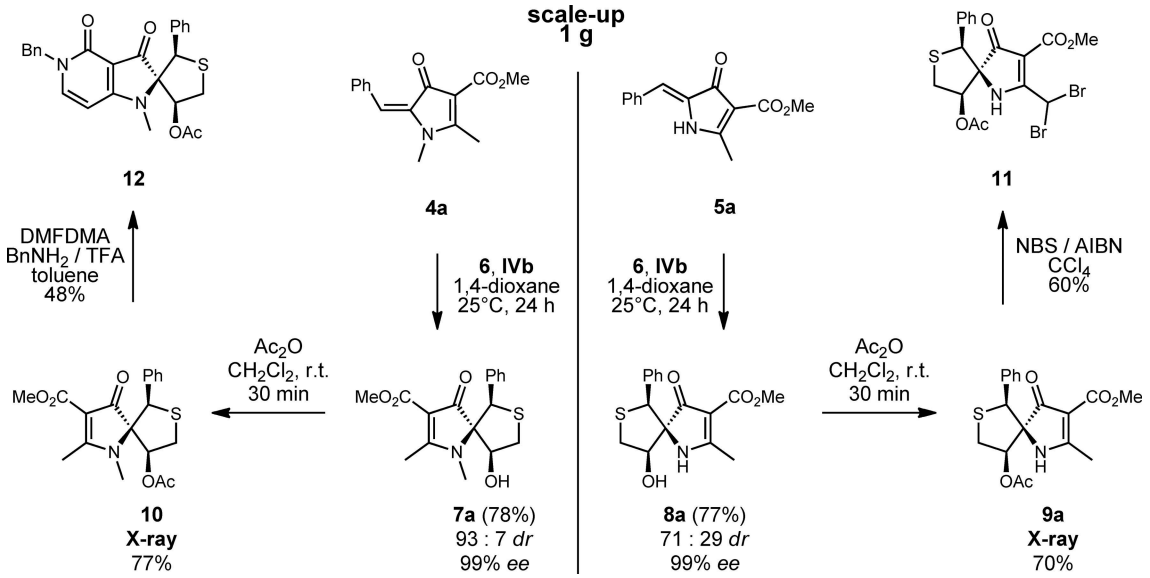
To a mixture of the organocatalyst **IVb** (0.01 mmol, 6.3 mg), methyl (*E*)-5-benzylidene-1,2-dimethyl-4-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (**4 a**) (0.1 mmol, 26 mg) and 1,4-dithiane-2,5-diol (**6**) (0.15 mmol, 23 mg) under Argon anhydrous dioxane (1 mL) was added and the resulting reaction mixture was stirred at 25 °C for 24 h. An aliquot of the reaction mixture was used to determine the reaction conversion and assess the diastereomeric ratio of the products by means of ^{1}H-NMR analysis. *dr* = 93:7. Volatile components were evaporated *in*



Scheme 5. The scope of organocatalyzed spirocyclization of *N*-unsubstituted Δ^2-pyrrolin-4-ones **5a–l**. Enantiomeric excess of compounds **8** was determined *via* their acetoxy derivatives **9**.[21]



Scheme 6. Proposed transition states for the formation of products **7a** and **8a** and X-ray structures of the corresponding acetates **10** and **9a**.



Scheme 7. Scale-up and follow-up transformations.

vacuo. The product **7a** was isolated by column chromatography (Silica gel 60, 1. EtOAc for the elution of nonpolar impurities; 2. EtOAc:MeOH = 4:1 for the elution of the product). Fractions containing the pure product **7a** were combined and volatile components evaporated *in vacuo*. Yield: 28 mg (0.084 mmol, 84%) of yellowish semisolid. HPLC: Chiralpak AD-H, *n*-Hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 254 nm. Major diastereomer: *t*R = 8.8 minutes (minor); 24.7 minutes (major) – 99% *ee*; minor diastereomer: *t*R = 11.9 minutes (minor); 22.0 minutes (major) – 71% *ee*.

Acknowledgements

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