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Core Structure-Based Design of Organocatalytic [3+2]-Cycloaddition Reactions: Highly Efficient and Stereocontrolled Syntheses of 3,3′-Pyrrolidonyl Spirooxindoles

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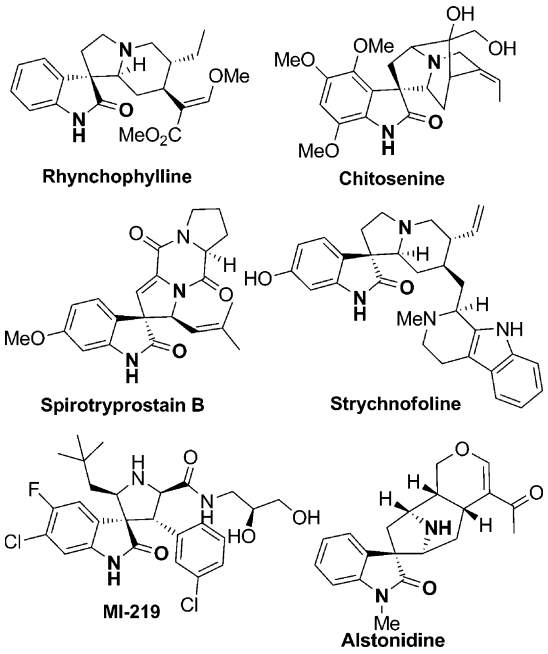
A spirocyclic oxindole core is the structural centerpiece of a wide variety of natural and synthetic compounds that exhibit diverse biological activities.[1] Consequently, approaches towards the efficient asymmetric synthesis of these molecules have received considerable attention.[2,3] As part of a program to address this family of molecules with organocatalysis, we have recently reported strategies based on oxindoles that provide rapid access to bispirooxindoles,[3a] spirocyclopenteneoxindoles,[3b] and carbazolespirooxindoles.[3c] While these approaches have met with some success, these efforts do not address the 3,3′-pyrrolidonyl spirooxindole motif[4] common to many bioactive molecules from this family of molecules (Scheme 1). Thus, an enantioselective catalytic approach for the direct construction of 3,3′-pyrrolidonyl spirooxindole skeletons is a significant unmet challenge.

To address this challenge, we sought to design an organocatalytic[5] domino reaction[6] that would ideally involve the reaction of two simple and readily accessible starting materials. Given the recent success of α-isothiocyanato derivatives as nucleophiles in organocatalytic aldol and Mannich reactions,[7] we envisioned that [3+2]-cycloaddition reactions between α-isothiocyanato imides and methyleneindolinones would yield the desired 3,3′-pyrrolidonyl spirooxindole skeletons in a highly stereoselective transformation (see Scheme 3). Given the pioneering studies of Deng and coworkers on cinchona alkaloid catalysis[8] and our own findings that this class of catalysts works efficiently in oxindole-based reactions,[3a,9] we focused our attention on this class of organocatalysts (Scheme 2). Herein, we present organocatalytic asymmetric [3+2]-cycloaddition reactions between isothiocyanato imide and methyleneindolinones that provide 3,3′-pyrrolidonyl spirooxindoles in good yields with high diastereo- and enantio-purity.[10]



Scheme 1. Examples of natural and synthetic bioactive compounds containing a 3,3′-pyrrolidonyl spirooxindole structural motif.

We initiated our studies by evaluating the reaction between isothiocyanato imide **1a** and methyleneindolinone **2a** using quinine as the catalyst in dichloromethane at room temperature (Scheme 3). We found that the reaction proceeded smoothly and afforded the desired product in high yield, albeit with poor diastereoselectivity (3:2).[11] Although high enantioselectivities (up to 97% *ee*) were attained with the thiourea catalysts of Scheme 2, the diastereoselectivities were consistently poor despite optimization studies with re-

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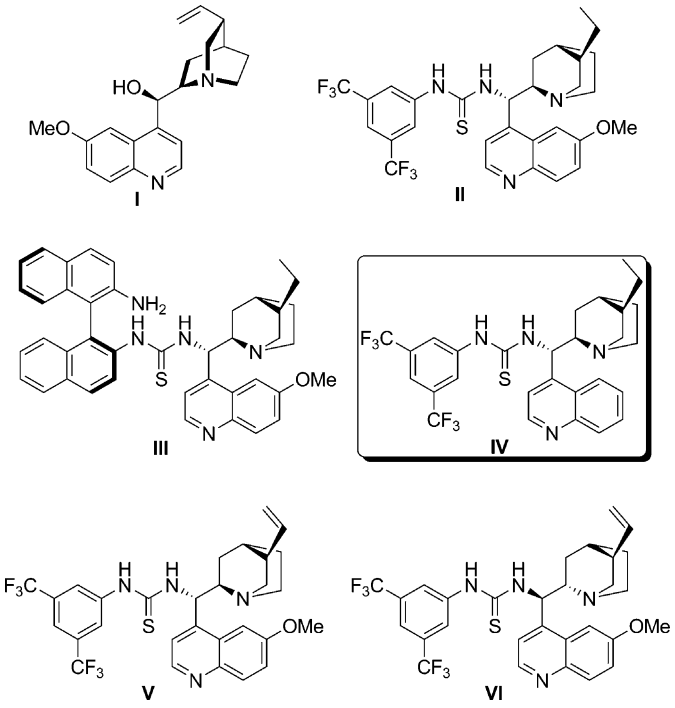
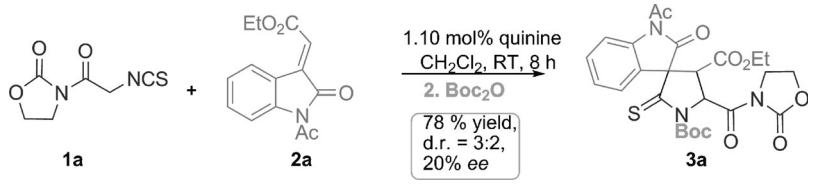


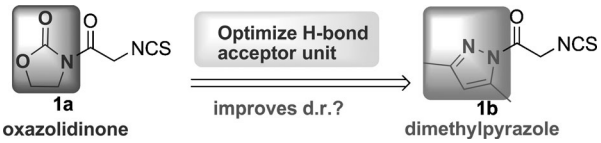
Scheme 2. Structures of cinchona alkaloid derived organocatalysts studied.

spect to solvent, catalyst, and temperature (see the Supporting Information).



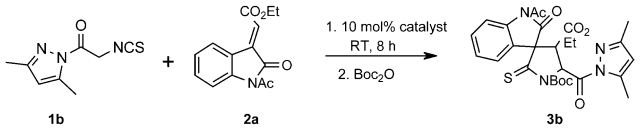
Scheme 3. Initial test of [3+2]-cycloaddition reaction catalyzed by quinine.

To solve this problem, we turned our attention towards modification of isothiocyanato imide **1a** with the aim of increasing its potential to hydrogen bond with our catalysts by providing it with another acceptor site that might aid in stereochemically fixing the reactive enolate and consequently guiding the stereochemical outcome of the reaction. We were inspired to attempt this based on a report by Sibi and Itoh in which it was shown that the 3,5-dimethyl pyrazole template plays a crucial role in providing H-bond acceptor sites with a thiourea catalyst in an organocatalytic Michael reaction.[12] We therefore designed the novel isothiocyanato imide **1b** to react with **2a** using quinine **I** as the catalyst with the expectation of improved diastereoselectivity (Scheme 4). Indeed, the [3+2]-cycloaddition reaction proceeded smoothly and provided the desired product with virtually complete diastereoselectivity. As noted in Table 1, the thiourea functionality within the catalyst is the key for this



Scheme 4. Key strategy for improvement of diastereoselectivity.

Table 1. Screen of reaction conditions.[a]

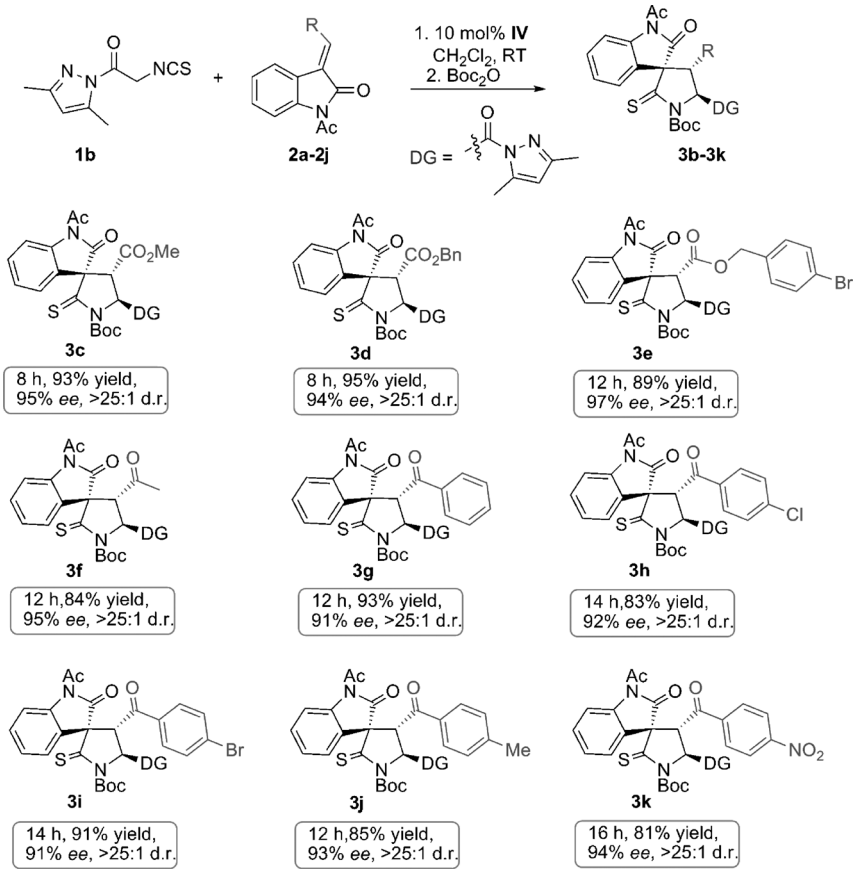


Entry	Catalyst	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**I**	CH_2Cl_2	71	10:1	5
2	**II**	CH_2Cl_2	91	>25:1	97
3[e]	**III**	CH_2Cl_2	94	>25:1	97
4	**IV**	CH_2Cl_2	94	>25:1	97
5	**V**	CH_2Cl_2	93	>25:1	97
6	**VI**	CH_2Cl_2	91	>25:1	−92
7	**IV**	toluene	83	>25:1	98
8	**IV**	Et_2O	87	>25:1	95
9[f]	**IV**	CH_2Cl_2	93	>25:1	97

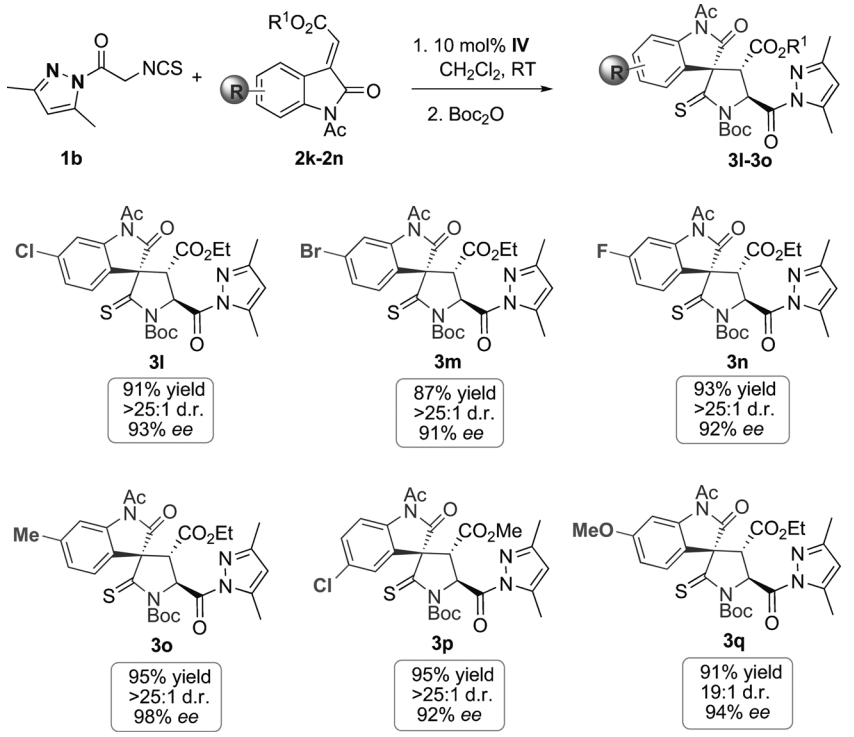
[a] Unless otherwise specified, all reactions were carried out using α-isothiocyanato imide **1b** (0.1 mmol, 1 equiv) and methyleneindolinone **2a** (0.1 mmol, 1 equiv) with 10 mol% of catalyst at 23 °C. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy and chiral-phase HPLC. [d] determined by chiral-phase HPLC analysis. [e] Reaction took 16 h to complete. [f] Reaction was conducted at 0 °C for 18 h.

reaction and provided largely diastereo- and enantiopure product (Table 1, entries 2–9). Of note is our newly designed catalyst **III** (see Scheme 2),[3a] which does not include a strong electron-withdrawing group (CF_3). This catalyst was as efficient as those containing the CF_3 group despite a predicted weaker acidity of its thiourea group (Table 1, entry 3). Solvent screening showed that the reaction was efficient in many solvents. Furthermore, use of the quinidine thiourea derivative **VI** as catalyst provided access to the opposite enantiomer of our products with excellent chemical and optical yields (Table 1, entry 6).

In our exploratory effort, this new methodology provided access to a range of multi-substituted spirocyclic oxindole derivatives and served as an expedient approach for the preparation of a range of substituted spirocyclo oxindoles containing three chiral centers in excellent enantiomeric excesses (91–98% *ee*) and almost complete diastereoselectivities (>25:1 d.r. in all cases) (Scheme 5). The **IV**-promoted [3+2]-cycloaddition reaction proceeded with a variety of methyleneindolinone derivatives bearing various substituents at the carbon–carbon double bond such as esters and ketones. Notably, minimal impact on efficiencies, enantioselectivities, and diastereoselectivities were observed regard-



Scheme 5. Generality of organocatalytic [3+2]-cycloaddition reactions.



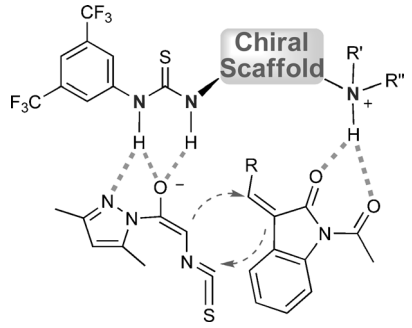
Scheme 6. Further exploration of the effects of indolinone substituents.

less of the electronic nature and bulkiness of the substituents (Scheme 5, **3g**–**3k**). The current system does have limitations: Phenyl-substituted methyleneindolinone was virtually unreactive, while the cyano(CN)-substituted methyleneindolinone provided product with low diastereoselectivity.

Further exploration of the substrate scope was focused on the indolinone moiety (Scheme 6). Substituents with a range of electronic properties were tolerated, and product yields ranged from 86% to 95% with excellent stereoselectivities (91–98% *ee*; >25:1 d.r.). The presence of chlorine or fluorine on the indolinone moiety is important for pharmacological activity for some molecules of this type.[13]

Our findings together with the dual activation model proposed by Takemoto and coworkers,[14] and the theoretical calculation studies by Papai[15a] and Zhong[15b] and their coworkers, allow us to suggest that the two substrates involved in the reaction are activated simultaneously by the catalyst as shown in Scheme 7. The acetyl-protecting group is crucial to high enantioselectivity, as seen from the low enantioselectivity (55% *ee*) obtained when a *tert*-butoxycarbonyl (Boc) protecting group was utilized (Scheme 8). The absolute configurations of **3b** and **3g** determined by X-ray analysis (see Figure 1[16] and the Supporting Information, respectively) are in accordance with that predicted by the catalytic model.

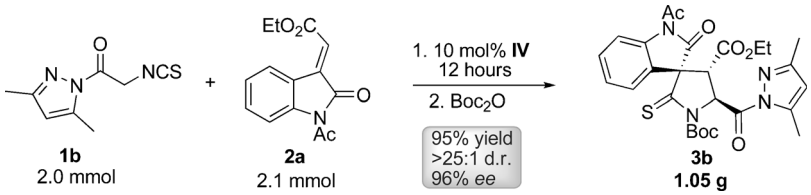
While we introduced the pyrazole group into the isothiocyanato imide to facilitate stereochemical control, the pyrozole group provides other advantages to our approach. Its intrinsic reactivity can be exploited in subsequent reactions that serve to further diversify our prod-



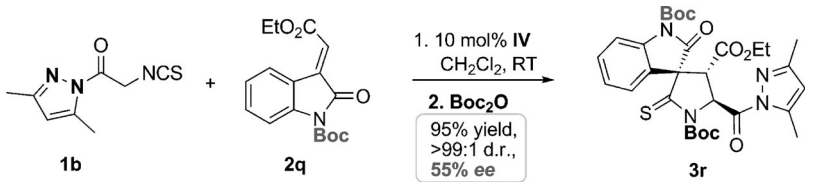
Scheme 7. Proposed mode of activation of substrates.

ucts, since the pyrazole moiety can be easily displaced by nucleophiles such as alcohols and amines. Furthermore, the thiolactam can be converted into the corresponding lactam, desulfurized, or subjected to sulfur contraction to obtain fully substituted spiropyrrolidine oxindole derivatives.[17] To further demonstrate the structural diversity of the products, some transformations into other spirooxindoles were investigated (Scheme 9). In support of the utility of our reaction, when the reaction was carried out on a gram scale, there was no change in reactivity or stereoselectivity (Scheme 10).

In summary, we have developed an efficient organocatalytic [3+2]-cycloaddition reaction for the direct construction the 3,3′-pyrrolidonyl spirooxindole motif common to many bioactive molecules through the rational design of α-isothiocyanato imides as dienophiles. Stereochemically complex products were obtained in excellent chemical and optical yield allowing us to set three contiguous stereocenters, including one all-carbon spiro quaternary center, in the products. This straightforward process makes use of simple starting materials and proceeds under mild conditions and will be useful in medicinal chemistry and diversity-oriented synthesis.



Scheme 10. Preparative-scale experiment.



Scheme 8. Control experiment in support of mechanism.

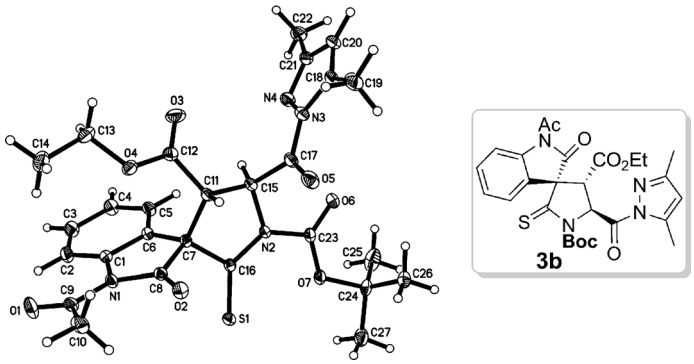


Figure 1. X-ray crystal structure of compound **3b**.[16]

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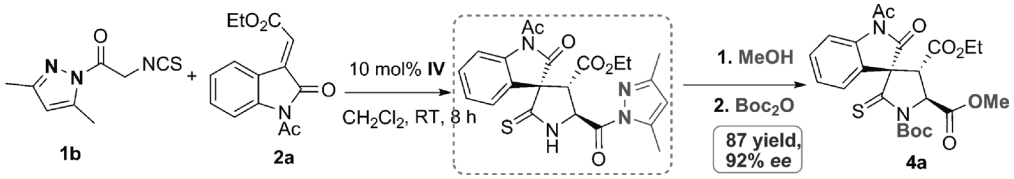
Keywords: 3,3′-pyrrolidonyl spirooxindoles · cycloaddition · methyleneindolinones · organocatalysis · spiro compounds



Scheme 9. Transformation of the pyrazole functionality.

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