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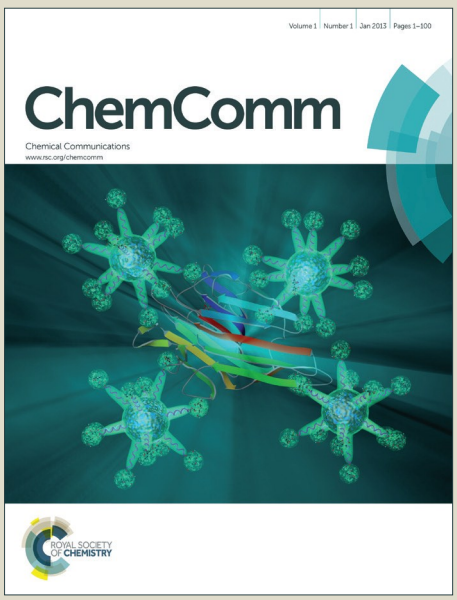

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Asymmetric synthesis of 3,3'-pyrrolidinyl-dispirooxindoles via a one-pot organocatalytic Mannich/deprotection/aza-Michael sequence †

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A highly stereoselective synthesis of functionalized 3,3'-pyrrolidinyl-dispirooxindole derivatives with three stereogenic centers, including two contiguous spiro-stereocenters, has been achieved through an organocatalytic Mannich/Boc-deprotection /aza-Michael sequence. Employing the commercially available $(DHQD)_2PHAL$ as the catalyst, the scalable reaction occurs with good yields and excellent stereoselectivities, providing a short entry into a series of 3,3'-pyrrolidinyl-dispirooxindoles of potentially medical value.

The 3,3'-pyrrolidinyl-spirooxindole skeleton is a privileged structural unit, which frequently appears not only in a plethora of complex bioactive oxindole alkaloids but also in several pharmaceuticals.[1] For instance, spirotryprostatin A (**1**), isolated from *Aspergillus fumigates*, exhibits anticancer activity.[2] Spirooxindole derivative MI-888 (**2**) is an efficacious MDM2 inhibitor (Figure 1, top).[3] Their potential pharmaceutical values, combined with their synthetic challenges, have attracted great attention in the chemical community and as a consequence numerous synthetic methods to assemble this type of spirooxindole compounds have been developed.[4] In addition, some 3,3'-pyrrolidinyl-dispirooxindole compounds have also been demonstrated to show promising bioactivities, including anti-microbial (**3**)[5] and anticancer (**4**)[6] properties. Compared to the compounds with the skeleton A, the 3,3'-pyrrolidinyl-dispirooxindole derivatives have more complex structures. These types of compounds bearing two vicinal spiro-stereocenters consist of two oxindole moieties and a pyrrolidinyl core (Figure 1, bottom).

Several synthetic methods have been reported on how to obtain these bis-spirooxindole derivatives despite the fact that the one-step assembly of two contiguous spiro-stereocenters is a formidable task in modern organic synthesis.[7] Almost all published approaches are based on chiral starting materials[8] or directed toward the synthesis of the racemates.[9] To the best of our knowledge, only one case of a catalytic asymmetric synthesis was reported. Recently, Shi and co-workers disclosed an elegant

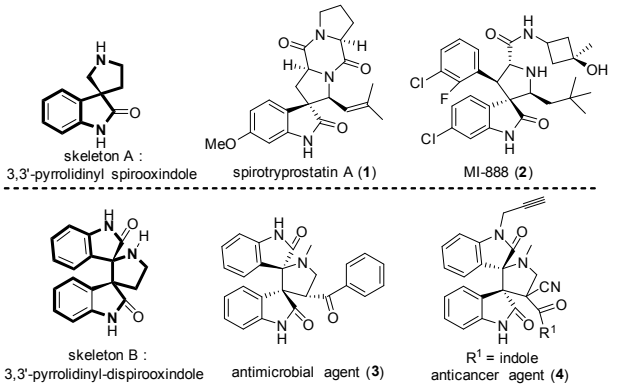

Fig.1 Biologically active 3,3'-pyrrolidinyl-(di)spirooxindole derivatives

approach to the enantioselective construction of the skeleton B via a chiral phosphoric acid catalyzed 1,3-dipolar cycloaddition between isatin-derived azomethine ylides and methyleneindolinones.[10] However, it is still highly desirable to develop a concise and stereoselective protocol to construct the 3,3'-pyrrolidinyl-dispirooxindole framework from readily available starting materials, especially under mild organocatalytic conditions.

Since the turn of the millennium, organocatalysis developed rapidly and is now considered as a third pillar of asymmetric synthesis beside metal and biocatalysis.[11] Within this research field organocatalytic domino and one-pot reactions have been shown to be powerful tools in organic synthesis,[12] which provide access to structurally complex molecules with relatively simple procedures.[13] As a continuation of our ongoing efforts towards developing novel organocatalytic domino reactions,[14] we envisioned that the

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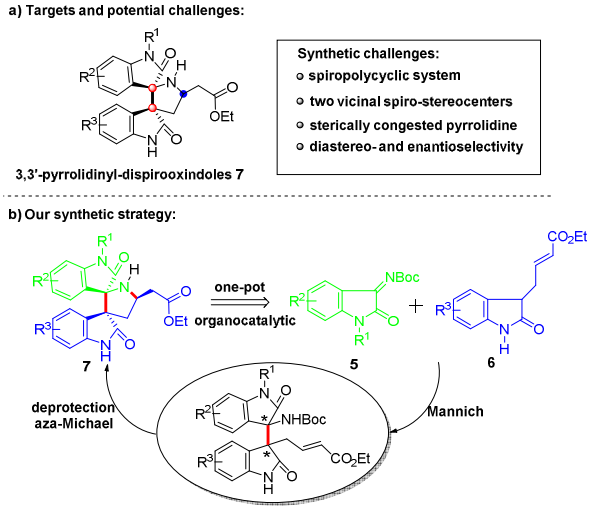
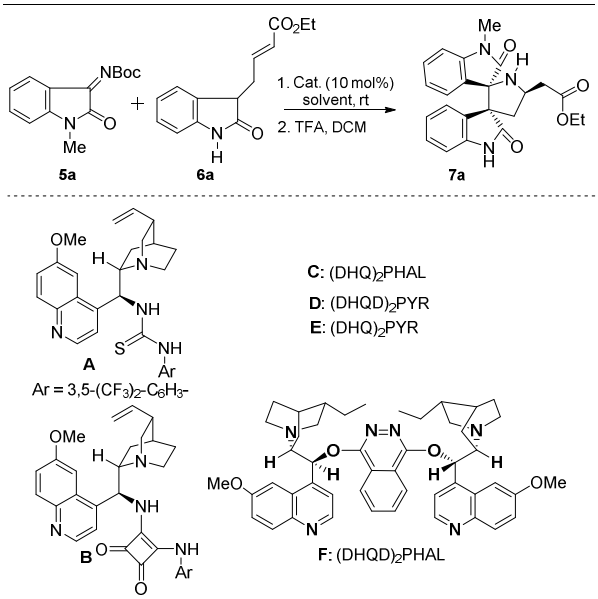
† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data (NMR,IR,MS,HPLC) and CDDC 1440552. See DOI: 10.1039/x0xx00000x

assembly of 3,3'-pyrrolidinyl-dispirooxindoles **7** could be realized through the union of N-Boc-protected isatin-derived ketimines **5**[15] and the donor-Michael acceptor synthons **6**[16] via a one-pot reaction, including a Mannich reaction and a Boc-deprotection/aza-Michael sequence (Scheme 1, b). Moreover, this transformation might be rendered enantioselective by using an appropriate chiral organocatalyst providing a convenient access to enantioenriched 3,3'-pyrrolidinyl-dispirooxindole derivatives **7**. For this proposed reaction, however, some potential challenges had to be addressed, such as 1) the construction of highly congested pyrrolidines bearing several stereogenic centers including two vicinal spiro-stereocenters, 2) the diastereo- and enantioselectivity of this one-pot reaction (Scheme 1, a).



Scheme 1 Strategy for the 3,3'-pyrrolidinyl-dispirooxindole synthesis.

Table 1 Catalyst screening and optimization studies[a]



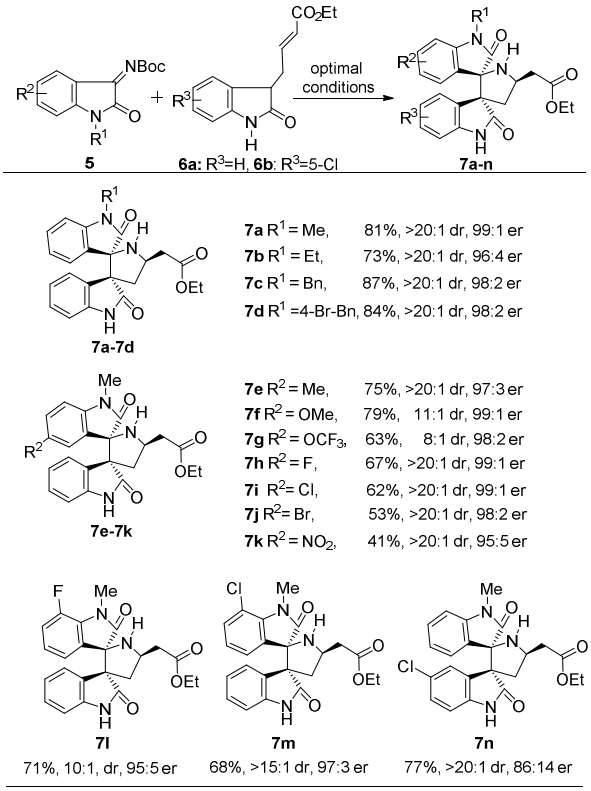
Entry	Cat.	Solvent	Yield (%)[b]	d.r.[c]	e.r.[d]
1	**A**	toluene	31	>20:1	58:42
2	**B**	toluene	trace	-	-
3	**C**	toluene	85	>20:1	5:95
4	**D**	toluene	69	>20:1	97:3
5	**E**	toluene	79	>20:1	4:96
6	**F**	toluene	87	>20:1	97:3
7	**F**	**MTBE**	**82**	**>20:1**	**99:1**
8	**F**	$CHCl_3$	63	>20:1	92:8

[a] All reactions were conducted with 0.21 mmol of **5a** (1.05 equiv), 0.2 mmol of **6a** (1.0 equiv) and 10 mol % of catalyst in a solvent (2.0 mL) at room temperature for 12 h. After evaporation of the solvent, DCM (2.0 mL) and TFA (0.4 mL) were added. [b] Yield of isolated compound **7a** after chromatography. [c] d.r. determined by ^{1}H NMR. [d] The e.r. values were determined by HPLC on a chiral stationary phase.

To test the feasibility of this planned reaction, we chose the readily available N-Boc ketimine **5a** and the 3-substituted oxindole **6a** as the model substrates to carry out the screening of reaction conditions (Table 1). First, the bifunctional thiourea catalyst **A** was examined. To our delight, the proposed reaction sequence proceeded readily and delivered the desired product **7a** with high diastereoselectivity, albeit in low yield and with poor enantioselectivity (Table1, entry 1). When the squaramide catalyst **B** was used, an inferior result was observed and only trace amounts of product **7a** were obtained (Table 1, entry 2). Considering previous reports using Sharpless ligands in the functionalization of 3-substituted oxindoles[17], we speculated that the Sharpless ligands might play a positive role for this transformation based on its attractive aromatic interaction. As expected, the yield and the enantioselectivity of this reaction improved remarkably when the Sharpless ligand $(DHQ)_2PHAL$ **C** was employed (Table 1, entry 3). Further catalyst screening showed that $(DHQD)_2PHAL$ **F** exhibited better stereocontrol capacity (up to 97:3 er) than catalysts **D** and **E** (Table 1, entries 5-6). Finally, the effect of the solvent was investigated and MTBE proved to be the best choice in terms of efficiency and stereoselectivity (Table 1, entry 7).

With the optimal conditions established (Table 1, entry 7), the substrate scope of the new one-pot protocol was explored and the results are shown in Table 2. Initially, we examined the generality of the N-Boc ketimine component. A wide range of ketimines underwent this one-pot sequence to afford the desired 3,3'-pyrrolidinyl-dispirooxindoles (Table 2, **7a-m**) in 41-87% yield with good to excellent diastereoselectivities and excellent enantioselectivities (up to 99:1 er). First, the effort of the substituent on the oxindole nitrogen atom was investigated. We found that common groups such as methyl, ethyl, benzyl and 4-bromobenzyl are well tolerated and the corresponding enantioenriched products (Table 2, **7a-d**) can be obtained in high yields. Next we evaluated the different substituents on the aromatic ring of **5**. The substrates containing both electron-donating groups (5-Me, 5-OMe, 5-CF_3O) and electron-withdrawing groups (5-F, 5-Cl, 5-Br, 5-NO_2, 7-F, 7-Cl) reacted smoothly with **6a** under optimized conditions, furnishing the desired products (Table

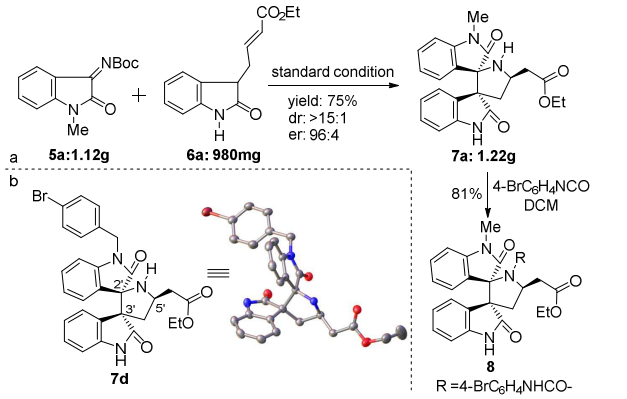
Table 2 Substrate scope of the reaction[a]



[a] Unless otherwise noted, the reactions were conducted with 0.42 mmol of **5** (1.05 equiv), 0.40 mmol of **6** (1.0 equiv) and 10 mol % of catalyst **F** in MTBE (4.0 mL) at room temperature for 12 h. Upon evaporation of the solvent, DCM (4.0 mL) and TFA (0.8 mL) were added. Yields are those of the isolated products **7a-n** after column chromatography. The diastereomeric ratio was determined by ^{1}H NMR and the enantiomeric ratio by HPLC on a chiral stationary phase.

2, **7e-m**) in 41-79% yield and with high stereoselectivities. In addition, when the oxindole **6b** was used, this reaction also readily under optimized conditions, furnishing the desired products (Table 2, **7e-m**) in 41-79% yield and with high stereoselectivities. In addition, when the oxindole **6b** was used, this reaction also readily took place to give the 3,3'-pyrrolidinyl-dispirooxindole **7n** in 77% yield and 86:14 e.r. (Table 2, **7n**).

To show the practical utility of this Mannich/Boc-deprotection/aza-Michael sequence, a gram scale reaction was carried out using the optimal conditions and the desired 3,3'-pyrrolidinyl-dispirooxindole **7a** could be isolated in 75% yield, >15:1 d.r., 96:4 e.r. (Scheme 2a). In addition, compound **7a** reacted with 4-bromophenyl isocyanate, delivering the urea derivative **8** in good yield. As shown in Scheme 2b, the absolute configuration of compound **7d** was determined unambiguously as (2'*R*), (3'*R*) and (5'*R*) based on the X-ray structure of **7d** and the configurations of other title compounds were assigned as (2'*R*,3'*R*, 5'*R*) by analogy (Scheme 2a).



Scheme 2 Gram-scale one-pot synthesis of dispirooxindole **7a** and X-ray crystal structure of **7d**.

In conclusion, the highly stereoselective construction of a new series of 3,3'-pyrrolidinyl-dispirooxindoles with potential biological activity has been achieved via a novel organocatalytic Mannich/Boc-deprotection/aza-Michael sequence. With this new protocol a variety of 3,3'-pyrrolidinyl-dispirooxindole derivatives, bearing two vicinal spiro-stereocenters, can be easily accessed in good yields with good to excellent diastereo- and enantioselectivities. This one-pot sequence can be scaled up without any loss of its efficiency and stereoselectivity.

We thank the European Research Council (ERC Advanced Grant 320493 "DOMINOCAT") for financial support and the BASF SE for the donation of chemicals.

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