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Organocatalyzed aza-Michael–Michael cascade reactions to construct spirooxindole tetrahydroquinolines with all-carbon chiral centers†

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An efficient organocatalytic aza-Michael–Michael cascade reaction for the asymmetric synthesis of highly functionalized spirooxindole tetrahydroquinolines has been reported through a formal [4+2] annulation strategy.

Spirooxindole scaffolds are the structural centerpieces of a large number of alkaloids and unnatural compounds which exhibit pronounced biological and medicinal activities.[1] In the past few years, a flourish of asymmetric reactions targeting the construction of highly strained chiral spirooxindole structures has been witnessed.[2] Among these interesting spiro structures, 3,3′-azacyclic-spirooxindoles are especially biologically useful demonstrated with the compounds in Fig. 1.[3] For example, quinazoline compounds alantrypinone (**1**) and serantrypinone (**2**) are endowed with anti-GABAergic insecticidal action.[3a] while compound (**3**) is a potent non-peptide MDM2 inhibitor.[3b] In addition, Spirotryprostatin A (**4**) has been found to have anti-mitoic properties.[3c,3d]

Due to their biological activities and physical properties, 3,3′-azacyclic-spirooxindoles have emerged as attractive synthetic targets among organic chemists, and a number of elegant strategies have been developed to construct these structural skeletons.[4] For example, Wang and coworkers reported an efficient method for the enantioselective synthesis of chiral 3,3′-pyrrolidonyl spirooxindoles catalysed by rosin-derived bifunctional thiourea catalysts.[5] Moreover, Gong *et al.* developed asymmetric 1,3-dipolar cycloadditions of methyleneindolinones with amino esters and aldehydes to construct these spiro compounds by using chiral phosphoric acids as catalysts.[6] Although there were numerous publications about constructing 3,3′-pyrrolidonyl spirooxindoles, an efficient method to build chiral spirocyclic oxindoles fused with piperidines or tetrahydroquinolines is still rare (Scheme 1). In 2010, Chen and coworkers tried to construct this motif *via* a three-component domino reaction,[7] however, the scope of the reaction is very limited and the chemical yield of the domino reaction is less than 40%. Therefore, development of novel efficient method to contruct these spiroheterocycles is still of high interest. Herein, we reported the organocatalytic aza-Michael–Michael reaction for the asymmetric construction of the spirooxindole tetrahydroquinolines derivatives. It is worth noting that to date no report concerning stereoselective construction of these kinds of spiro compounds has been developed.

Initially, methyleneindolinone **1a** was chose as a dipolarphile upon the consideration that the *tert*-butoxycarbonyl group on the nitrogen atom would act as a hydrogen acceptor.[8] Moreover, this strong electron-withdrawing group would reduce the energy of the lowest unoccupied molecular orbital and enhance the polarizability of the dipolarophiles.[6] On the basis of our recent progress in enantioselective organocatalysis using amino acid-derived bifunctional catalysts,[9] several amino acid-derived tertiary amine thiourea catalysts were screened to promote the reaction. However, the reaction between **1a** and *ortho*-amino-α,β-unsaturated ketones **2a** in toluene at room temperature was inefficient

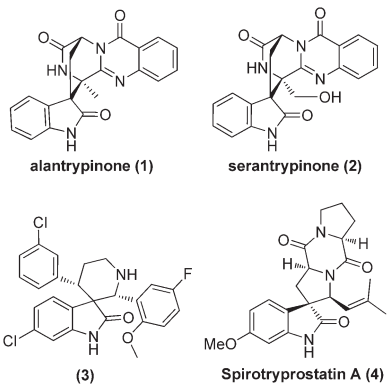

Fig. 1 3,3′-Azacyclic-spirooxindole-containing natural products and synthetic compounds.

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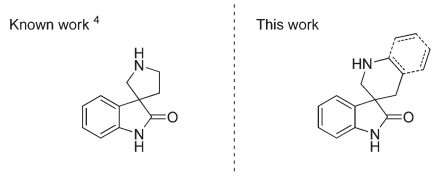


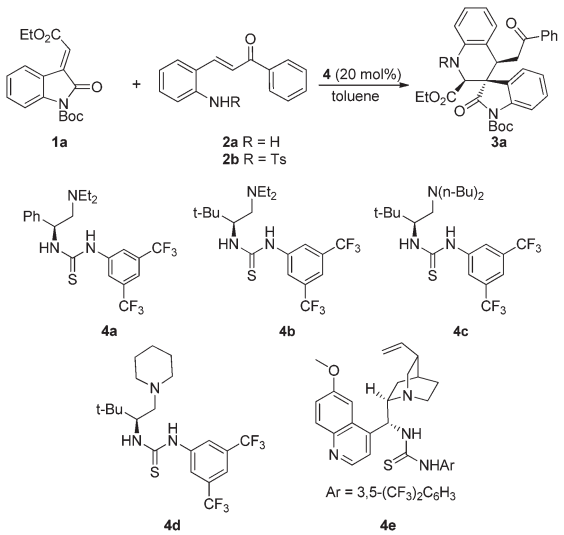
Scheme 1 Known studies on construction of 3,3′-pyrrolidonyl spirooxindole structural motif and spirooxindole tetrahydroquinoline reported herein.

with catalyst **4a**, giving the corresponding product with only 30% yield (Table 1, entry 1). This was probably because the pK_a of the arylamine is not low enough that it can not be efficiently activated by the tertiary amine of catalyst. In order to improve the reaction activities of the substrates, the *p*-methylbenzenesulfonyl (Ts) protected α,β-unsaturated ketones **2b** was synthesized. As we expected, the double Michael reactions of **1a** with **2b** provided the desired product smoothly in the presence of **4a–4c** with excellent yields and diastereoselectivities. Although poor enantioselectivity was observed with **4a**, this could be largely improved with the L-*tert*-leucine-derived catalyst **4b** and **4c**, providing the products with promising enantioselectivities (72 and 76% ee) (Table 1, entries 2–4). Subsequent evaluation of other solvents revealed that both THF and DCM had a deterious effect on the stereoselectivity (Table 1, entries 5–6). Lowering the reaction temperature to 0 °C did not facilitate to improve the enantioselectivity (Table 1, entry 7). A further designing of the catalysts showed that replacement of triethyl amine with cyclohexylamine improved the enantiomeric excess to 90% (Table 1, entries 8 and 11). Gratifyingly, adding 4 Å molecular sieves in the reaction further enhanced the yield (99%) of the product while stereoselectivity keep the same level (Table 1, entry 9). Additionally, lowering the catalyst loading to 10 mol% did not compress the yield and stereoselectivities (Table 1, entry 10). Therefore, the optimal conditions were found to be the use of 10 mol% of catalyst with 4 Å MS in toluene at room temperature.

With the optimal reaction conditions in hand, the scope of the reaction was then investigated and the results are shown in Table 2. Both electron-donating and electron-withdrawing substituents on the aromatic ring of methyleneindolinone were compatible with this reaction and the desired products were obtained with excellent chemical yields and stereoselectivities (**3b–3g**). Ester or ketone groups attached to the carbon–carbon double bond centers had little effect on the yields and stereoselectivities as well (**3h–3j**). Subsequent evaluation of the substituents on both arenes of the *ortho*-(*p*-methylbenzenesulfonamide)-α,β-unsaturated aromatic ketones **2** revealed that substrates with electron-withdrawing substituents provided products with a little lower yields (**3o–3q**) than that with electron-donating groups (**3l–3p**). Notably, the enantioselectivity of the reaction decreased seriously with α,β-unsaturated aliphatic ketone (**2r**). The absolute configuration of **3a** was unambiguously determined by using a single-crystal X-ray diffraction and all the other products can therefore be assigned by analogy.

In order to explore the mechanism of this reaction, we then synthesized methyleneindolinones with different substituents on the nitrogen atom (**1s**, **1t**; Scheme 2). These results showed that

Table 1 Optimization for the aza-Michael–Michael reaction[a]



Entry	R	Catalyst	Time [h]	Yield [%][b]	dr[c]	ee [%][d]
1	H	**4a**	24	30	—[e]	—[e]
2	Ts	**4a**	2	95	>20 : 1	0
3	Ts	**4b**	2	95	>20 : 1	76
4	Ts	**4c**	2	98	>20 : 1	72
5[f]	Ts	**4b**	6	92	>20 : 1	11
6[g]	Ts	**4b**	48	85	>20 : 1	66
7[h]	Ts	**4b**	24	85	>20 : 1	77
8	Ts	**4d**	8	97	>20 : 1	90
9[i]	Ts	**4d**	8	99	>20 : 1	90
10[j]	Ts	**4d**	8	97	>20 : 1	90
11	Ts	**4e**	0.5	90	>20 : 1	−27

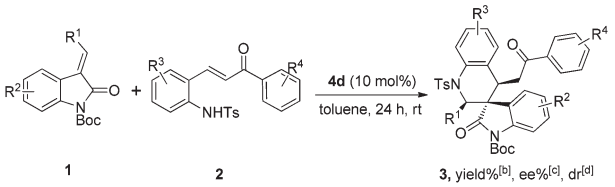
[a] Reaction conditions: **1a** (0.05 mmol, 1.0 equiv.), **2** (0.06 mmol, 1.2 equiv.) were used in toluene (1.0 mL) in the presence of **4** (20 mol%). [b] Isolated yields. [c] Determined by ^{1}H NMR analysis of crude product. [d] Determined by chiral HPLC analysis. [e] Not determined. [f] The reaction was carried out in THF. [g] The reaction was carried out in DCM. [h] The reaction was carried out at 0 °C. [i] 40 mg 4 Å MS was added. [j] The reaction was carried out with 10 mol% **4d** and 40 mg 4 Å MS.

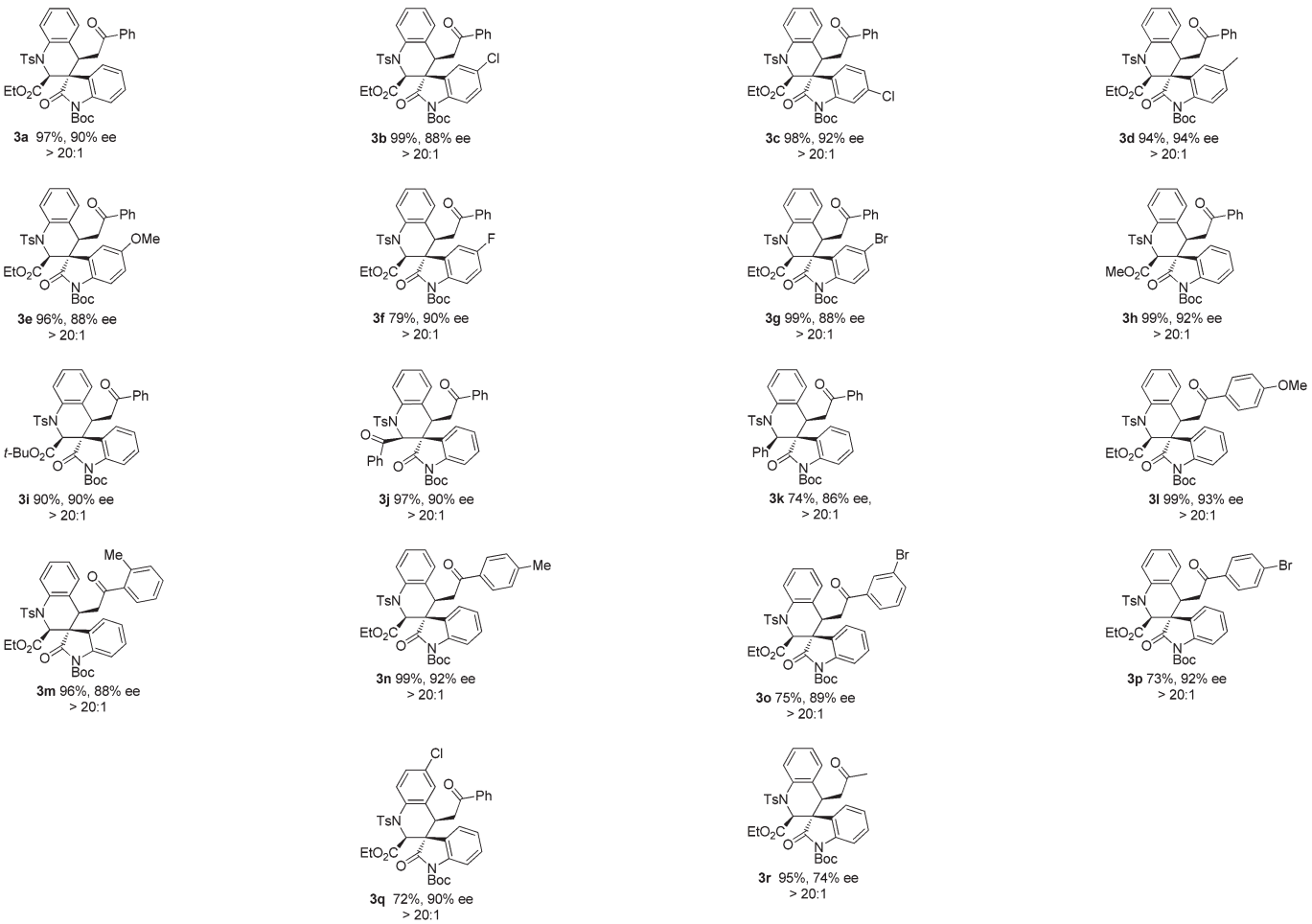
the protecting group substantially impacted the stereoselectivity of the reaction, which could be regarded as an evidence that *tert*-butoxycarbonyl group could indeed act as a good hydrogen acceptor.

On the basis of our experimental results and previous studies, we have proposed a plausible transition state to explain the stereochemistry of the aza-Michael–Michael reaction sequence. The electron-deficient methyleneindolinone is activated by hydrogen bonds between the carbonyl groups in the indolinone and the N–H bonds of the thiourea moiety, and the nucleophilicity of the *ortho*-(*p*-methylbenzenesulfonamide)-chalcones is enhanced by the tertiary amine of the catalyst. Then the back of Michael acceptor is approached by the incoming amine nucleophile. Subsequent nucleophilic attack of the nitrogen atom onto the electron-deficient double bond led to the formation of major stereoisomer (Fig. 2).

In summary, a novel and efficient amine acid-derived thiourea catalyzed asymmetric aza-Michael–Michael cascade reaction of

Table 2 Substrate scope studies[a]





[a] Reaction conditions: **1** (0.1 mmol, 1.0 equiv.), **2** (0.12 mmol, 1.2 equiv.), **4** (10 mol%), toluene (2.0 mL) with 4 Å MS (40 mg). [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR analysis of crude product.

various methyleneindolinones with *ortho*-(*p*-methylbenzenesulfonamide)-α,β-unsaturated ketones has been developed. This process provides a promising route for the enantioselective construction of polysubstituted spirooxindole tetrahydroquinolines structure with three consecutive stereogenic centers. The evaluation of the biological activity of the synthetic spirooxindoles and detailed mechanistic investigations of this novel aza-Michael–Michael cascade reaction are still underway in our laboratory.

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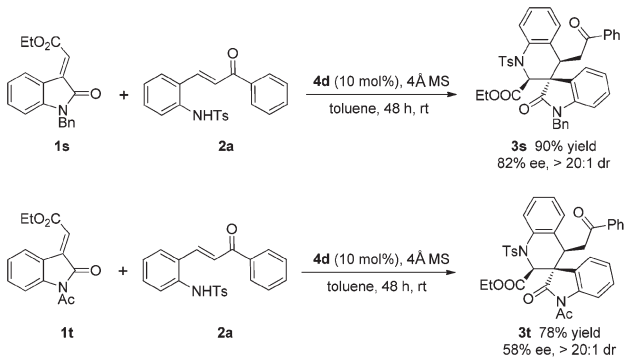

Scheme 2 Substrate scope with variation of substituents on the nitrogen atom of methyleneindolinones.

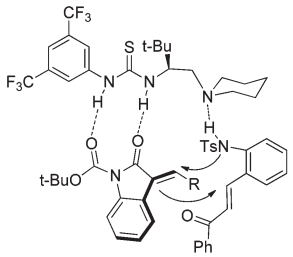

Fig. 2 Possible transition state.

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