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Catalytic Asymmetric Construction of Spirocyclopentaneoxindoles by a Combined Ru-Catalyzed Cross-Metathesis/ Double Michael Addition Sequence

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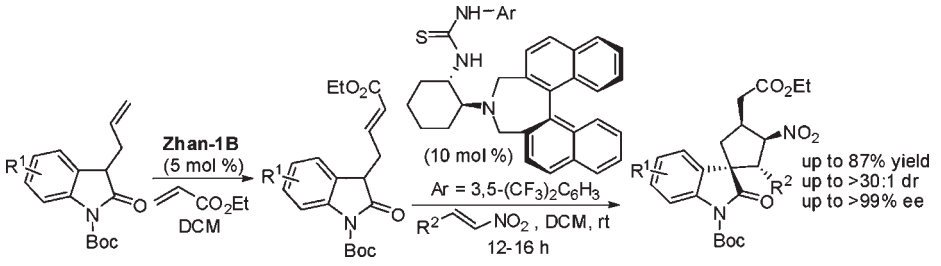
ABSTRACT



Biologically important and synthetically challenging spirocyclopentaneoxindoles with four contiguous stereocenters including one spiro-quaternary stereocenter have been constructed in good yields (72−87%) with excellent diastereoselectivity (16:1→30:1 dr) and enantioselectivity (93→99% ee) by a combined Ru-catalyzed cross-metathesis/organocatalyzed asymmetric double-Michael addition sequence.

The spirocyclic oxindole scaffold is featured in a large number of natural products and medicinally relevant compounds.[1−5] Thus, considerable efforts have been devoted toward the development of enantioselective methods to construct these spiroheterocyclic systems. Remarkable advances have been made on the enantioselective synthesis of pyrrolidinylspirooxindole compounds and analogues[1] as well as six-membered spirocyclic oxindole derivatives.[2] Quite recently, enantioselective syntheses of spirocyclic 2-oxindoles bearing a cyclopentene motif have also been developed via tertiary phosphine- or amine-catalyzed

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[3 + 2] cycloaddition reactions.[3] In contrast, the direct catalytic asymmetric construction of the spirocyclopentaneoxindole scaffold has remained an important challenge.

The 3-spirocyclopentane-2-oxindoles represent an important class of substructures that are widely encountered in a number of biologically active natural alkaloids[4] (Figure 1) and drug candidates.[5] However, the catalytic enantioselective synthesis of these molecules remain a daunting task. Generally, their asymmetric syntheses rely on chiral substrate-controlled methods.[4b−d] To the best of our knowledge, so far there are only two general reports concerning the catalytic enantioselective construction of spirocyclopentaneoxindole scaffolds. Trost and co-workers reported an elegant Pd-catalyzed asymmetric [3 + 2] cycloaddition of methyleneindolinones for the synthesis of spirocyclopentaneoxindoles.[6] During the course of our current work, Barbas and co-workers represented the only example of organocatalytic highly enantioselective synthesis of spirocyclopentaneoxindoles through cascade Michael−aldol reaction of activated methyleneindolinones.[7] This impressive cascade process led to bispirocyclic oxindole derivatives containing three quaternary stereocenters.

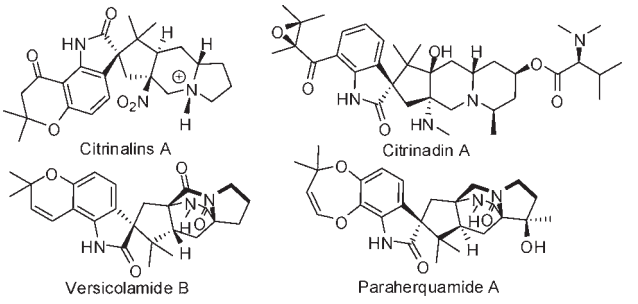
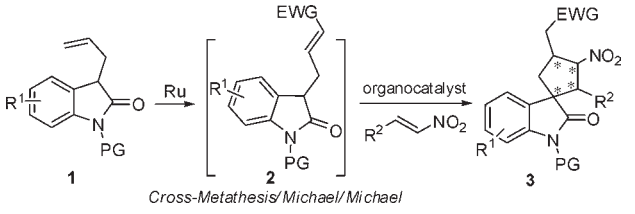


Figure 1. Representative natural products containing the spirocyclopentaneoxindole scaffold.

In view of their biological and pharmacological potentials as well as the challenges associated with their catalytic asymmetric syntheses, the development of a new strategy for the direct catalytic asymmetric synthesis of structurally diverse spirocyclopentaneoxindoles is highly desirable. In this context, we were intrigued in the development a new organocatalytic asymmetric method to construct spirocyclopentaneoxindole scaffold with novel structural and stereochemical diversity. We envisioned that the densely substituted 3-spirocyclopentane-2-oxindole skeletons **3** could be constructed through organocatalytic cascade double Michael addition reactions[8] between rationally designed new type of Michael donor−acceptor synthons **2**, bifunctional oxindoles,[9] and nitroolefins **3**[10] (Scheme 1). The bifunctional oxindoles **2** might be achieved through Ru-catalyzed cross-metathesis of easily available 3-allyloxindoles **1**.

Recently, we have developed a new class of bifunctional thiourea catalysts bearing central and axial chiral elements, which showed good performance in the catalytic asymmetric addition of 1,3-dicarbonyl compounds to nitroolefins.[11] Interestingly, we have found that this class of bifunctional thiourea catalysts could highly effectively catalyze designed cascade double-Michael addition with excellent diastereo- and enantioselectivity. As part of our interest in developing new catalysts for novel catalytic asymmetric reactions,[12] herein we report new results in the catalytic asymmetric construction of spirocyclopentaneoxindole scaffold.

Scheme 1. Strategy for Catalytic Asymmetric Construction of Spirocyclopentaneoxindole Scaffold



We initiated our studies by evaluating the model reaction involving a Ru-catalyzed cross-metathesis of

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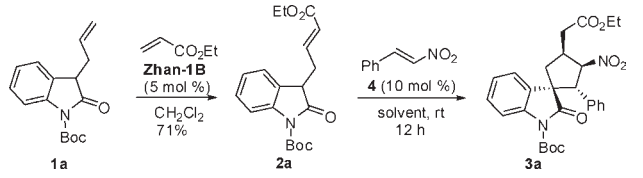
3-allyloxindole **1a** followed by an organocatalytic asymmetric double-Michael addition. Gratifyingly, the desired cross-metathesis reaction proceeded smoothly to afford the bifunctional oxindole **2a** in the presence of **Zhan-1B** catalyst (5 mol %) in dichloromethane.[13] With our bifunctional thiourea catalyst **4a** bearing central and axial chiral elements,[11] the expected asymmetric double Michael addition product **3a** was obtained in excellent stereoselectivity (25:1 dr, 99% ee) (Table 1, entry 1). To examine the effect of catalyst structure on the diastereo- and enantioselectivity, a series of other types of organocatalysts were also investigated (Figure 2). The cinchona alkaloid **4c**−**e**[14a−d] (entries 3−5) and α-amino acid-derived thiourea catalysts **4g**[14e,f] (entry 7) afforded unsatisfactory results. The bifunctional primary amine catalyst **4f**[8f] was also less effective (entry 6). Takemoto's catalyst **4h**[15] and Barbas's bulky catalyst **4i**[9c] proved to be promising (entries 8 and 13). These results indicated that the diamine scaffolds of the catalysts had a significant impact on both diastereo- and enantioselectivity, and notably the axial chiral binaphthyl moiety of our catalysts played an important role in the stereocontrol of the current reaction.

Table 1. Screening Studies of Ru-Catalyzed Cross-Metathesis/Organocatalyzed Michael/Michael Addition[a]



entry	cat.	solvent	yield[b] (%)	dr[c]	ee[d] (%)
1	**4a**	CH_2Cl_2	**86**	**25:1**	**99**
2	**4b**	CH_2Cl_2	80	10:1	−84
3	**4c**	CH_2Cl_2	70	6:1	3
4	**4d**	CH_2Cl_2	78	6:1	68
5	**4e**	CH_2Cl_2	82	5:1	60
6	**4f**	CH_2Cl_2	72	2.5:1	60
7	**4g**	CH_2Cl_2	80	50:1	41
8	**4h**	CH_2Cl_2	83	10:1	−88
9	**4h**	$CHCl_3$	91	10:1	−84
10	**4h**	toluene	90	6:1	−88
11	**4h**	*m*-xylene	84	7:1	−82
12	**4h**	THF	90	15:1	−28
13	**4i**	CH_2Cl_2	82	15:1	−90

[a] All double Michael reactions were performed with oxindole **2a** (0.1 mmol) with nitrostyrene (1.1 equiv) in the presence of 10 mol % of organocatalyst **4** in 0.5 mL of solvent at room temperature. [b] Isolated yields. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The ee of the major diastereoisomer was determined by HPLC analysis using a chiral stationary phase.

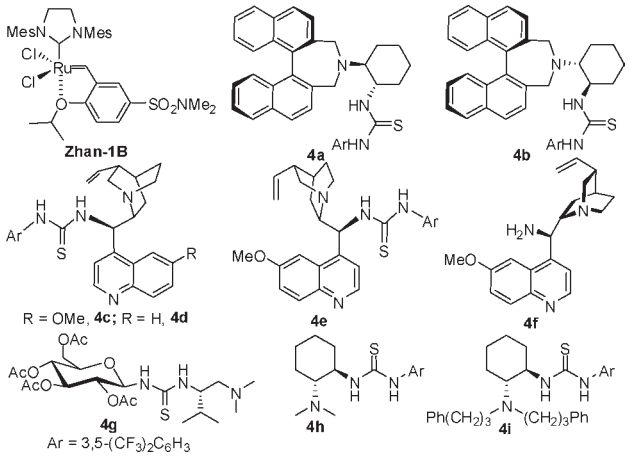
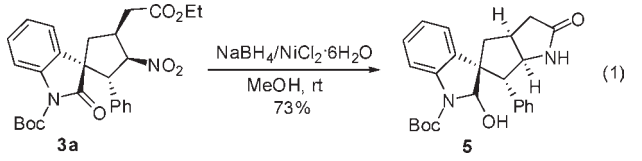


Figure 2. Catalysts evaluated in this study.

With the optimal reaction conditions established, the generality of the sequential catalytic asymmetric process was evaluated (Table 2). The desired sequential reactions proceeded smoothly to afford a variety of multifunctionalized spirocyclopentaneoxindoles containing the versatile nitro and ester groups in good yields with excellent diastereo- and enantioselectivity. The reactions tolerated different substituents in aromatic nitroolefins. The heteroaromatic nitroolefin was also a suitable substrate for the cascade process (entry 8). Notably, the reactions also worked well for the aliphatic nitroolefin (entries 10 and 11). The reaction with a β,β-disubstituted nitroolefin (*E*)-(1-nitroprop-1-en-2-yl)benzene did not occur. The substituted oxindole was also tested, giving the desired products in 82−84% yield with 25:1→30:1 dr and > 99% ee values (entries 9 and 10). The relative and absolute configurations of the sequential reaction products were assigned on the basis of X-ray crystal structural analysis of the product of **3i** (Figure 3; see the Supporting Information).



To demonstrate the synthetic utility of this sequential process further, the reaction product **3a** was transformed into an interesting tetracyclic molecule **5** possessing indoline,[16] pyrrolidin-2-one,[17] fused [5,5] bicyclic lactams[18],

(13) The reaction between **1a** and 1-phenylprop-2-en-1-one gave the cross-metathesis product **2a′** in very low yield.

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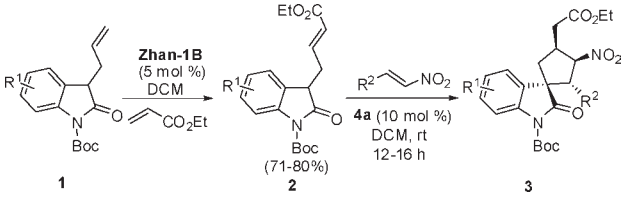
and spirocyclic components by reduction with $NaBH_4$/$NiCl_2 \cdot 6H_2O$ (eq 1). Because of the wide presence of these key moieties in numerous biologically active molecules, this would make the tetracyclic molecule **5** an attractive candidate for drug discovery.

Table 2. Ru-Catalyzed Cross-Metathesis/Organocatalyzed Asymmetric Michael/Michael Addition Sequence[a]



entry	R^1, R^2 (**3**)	yield[b] (%)	dr[c]	ee[d] (%)
1	H, Ph (**3a**)	86	25:1	99
2	H, 4-BrC_6H_4 (**3b**)	72	25:1	99
3	H, 4-$CF_3C_6H_4$ (**3c**)	73	30:1	>99
4	H, 3-$CF_3C_6H_4$ (**3d**)	76	25:1	96
5	H, 4-ClC_6H_4 (**3e**)	75	30:1	94
6	H, 4-$MeOC_6H_4$ (**3f**)	78	25:1	99
7	H, 4-MeC_6H_4 (**3g**)	75	25:1	93
8	H, 2-furyl (**3h**)	87	16:1	94
9	5-MeO, Ph (**3i**)	82	25:1	>99
10	5-MeO, *n*-C_7H_{15} (**3j**)	84	>30:1	>99
11	H, *n*-C_7H_{15} (**3k**)	87	>30:1	97

[a] The double Michael reactions were performed with **2** (0.1 mmol) and nitroolefins (1.1 equiv) in the presence of 10 mol % of organocatalyst **4a** in 0.5 mL of solvent. [b] Isolated yields. [c] Determined by ^1H NMR analysis. [d] The ee of major diastereoisomer determined by HPLC analysis using a chiral stationary phase.

In summary, through the design of a new type of Michael donor–acceptor oxindole synthon and the use of our recently developed bifunctional thiourea catalysts bearing central and axial chiral elements, we have developed a combined Ru-catalyzed cross-metathesis/organocatalyzed asymmetric double-Michael addition sequence[19] to construct biologically important and synthetically challenging spirocyclopentaneoxindoles with four contiguous stereocenters including one spiroquaternary stereocenter in good yields (72–87%) with excellent diastereoselectivity (16:1→30:1 dr) and enantioselectivity (93→99% ee). The multifunctional spirocyclopentaneoxindole molecules that are generated in the current catalytic asymmetric reaction are poised for use in medicinal chemistry and transformation into a variety of other potential candidates for drug discovery.

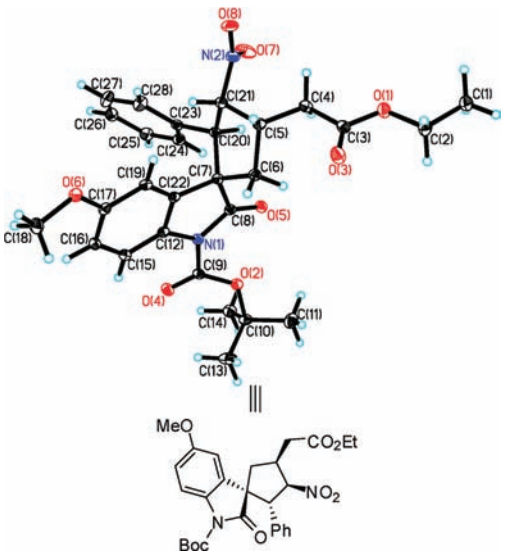


Figure 3. X-ray structure of **3i**.

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Supporting Information Available. Representative experimental procedure, compound characterization data, copies of spectra, and proposed reaction mechanism. This material is available free of charge via the Internet at http://pubs.acs.org.

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