Organic LETTERS

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Asymmetric Synthesis of 3,3′-Spirooxindoles Fused with Cyclobutanes through Organocatalytic Formal [2 + 2] Cycloadditions under H-Bond-Directing Dienamine Activation

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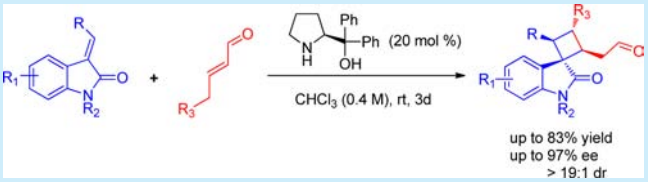
Supporting Information

ABSTRACT: The first organocatalytic asymmetric synthesis of a spirooxindole skeleton incorporated with a cyclobutane moiety has been successfully developed on the basis of H-bond-directing dienamine activation. Structurally complex spirocyclobutyl oxindoles, which possess four contiguous stereocenters, including one spiro quaternary center, were obtained in good yields (up to 83%) with excellent β,γ-regioselectivity (>19:1) and stereocontrol (up to >19:1 dr and 97% ee).



The cyclobutane skeleton constitutes the core structure of many naturally occurring and biologically important molecules[1] (Figure 1). For example, compound III[2] exhibits

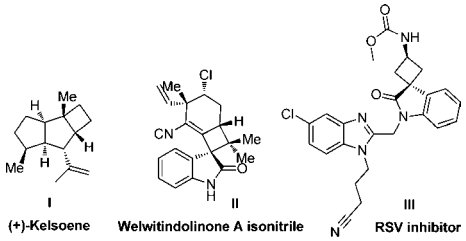


Figure 1. Examples of cyclobutane-containing natural products and synthetic bioactive compounds.

antiviral activity, in particular, having an inhibitory activity on the replication of the respiratory syncytial virus (RSV). Therefore, syntheses of structurally diversified cyclobutanes,[3] especially stereocontrolled ones, are highly valuable for bioactive evaluation in light of the principle of drug design. In addition, the opening of cyclobutane derivatives, driven by the relief of the ring strain, to construct more complex molecules is no doubt one of the most noteworthy synthetic transformations.[4] In this context, the last 10 years have witnessed rapid progress in the construction of chiral cyclobutane derivatives through [2 + 2] cycloadditions,[5] cyclization of acyclic precursors,[6] ring expansion of cyclopropanes,[7] and ring-contraction strategies.[8] More recently, Pd-catalyzed C−H activation and direct arylation of cyclobutanes provide an alternative approach.[9]

However, there are limited reports[10] on the catalytic enantioselective construction of enantioenriched cyclobutanes, not to mention organocatalytic variants. In 2007, Ishihara and co-workers[11] disclosed the first organocatalytic [2 + 2] cycloaddition of unactivated alkenes with α-acyloxyacroleins induced by chiral organoammonium salt. In 2012, Jørgensen[12] and Vicario groups[13] independently reported [2 + 2] cycloadditions of enals with nitroalkenes via dienamine activation.[14] More recently, the Xu group[15] developed an vinylogous Friedel−Crafts alkylation-initiated [2 + 2] cycloaddition through iminium−enamine activation of enals.

Spirooxindole scaffolds have recently become one of the most attractive topics for synthetic chemists because they are commonly present in numerous natural products as well as pharmaceutically active compounds. Accordingly, many kinds of impressive synthetic approaches have been developed for their syntheses over the past years, which mainly focused on the asymmetric construction of spirocyclic oxindoles bearing a five or six-membered ring system at the C3-position. Furthermore, asymmetric assembly of spirocyclic oxindoles fused with small size rings such as cyclopropanes,[16] β-lactones[17] and β-lactams[18] also be established via organocascade strategies. However, to the best of our knowledge, there have been no catalytic asymmetric reports of accessing optically enriched 3,3′-spirooxindoles bearing a cyclobutane moiety,[19] which possibly be ascribed to their unusual bonding and ring strain.

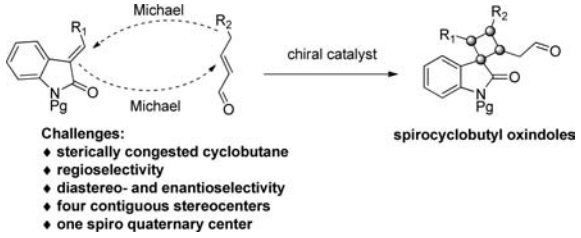
Considering the importance of chiral spirocyclobutyl oxindoles, and based on our persistent interest in the construction of spirooxindoles, herein we wish to present the first organocatalytic asymmetric [2 + 2] cycloaddition of methyleneindolinones with enals to provide structurally complex spirocyclobutyl oxindoles in good yields (up to 83%) with

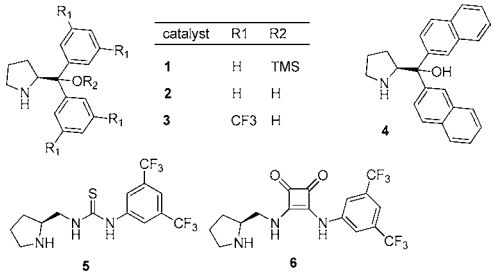
Received: November 10, 2014
Published: December 10, 2014

   dx.doi.org/10.1021/ol503266q | Org. Lett. 2014, 16, 6436−6439

excellent β,γ-regioselectivity (>19:1) and stereocontrol (up to >19:1 dr and 97% ee) (Scheme 1).

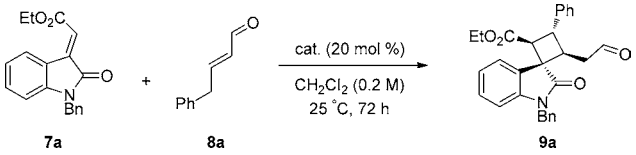
Scheme 1. Profile of Organocatalytic Asymmetric Construction of Spirocyclobutyl Oxindoles





Initially, we examined the reaction of methyleneindolinone **7a** (0.1 mmol) with dienamine activated α,β-unsaturated aldehyde **8a** (0.2 mmol) catalyzed by α,α-diphenylprolinol silyl ether **1** (0.02 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The desired [2 + 2] cycloadduct **9a** was isolated in 83% yield with excellent β,γ-regioselectivity (>19:1) and moderate stereoselectivity (dr 4:1, 50% ee; Table 1, entry 1). Surprisingly, the

Table 1. Evaluation of Catalysts[a]



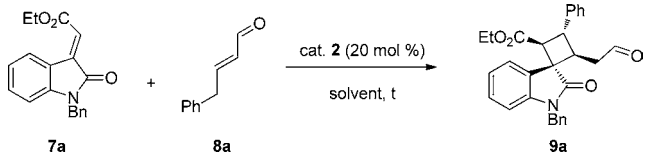
entry	cat.	yield[b] (%)	dr[c]	ee[d] (%)
1	**1**	83	4:1	50
2	**2**	73	12:1	97
3	**3**	51	11:1	94
4	**4**	64	12:1	97
5	**5**	51	3:1	73
6[e]	**6**	trace		

[a]Unless otherwise noted, reactions were performed by employing **7a** (0.1 mmol), **8a** (0.2 mmol), and the catalyst (0.02 mmol, 20 mol %) in CH_2Cl_2 (0.5 mL) at 25 °C for 3 days. [b]Isolated yield. [c]Determined by ^{1}HNMR spectroscopy. [d]Determined by chiral HPLC analysis of the corresponding Wittig olefination products. [e]3 equiv of DEA (*N*,*N*-diethylacetamide) applied.

α,α-diphenylprolinol[20] catalyst **2**, which combined H-bond directing activation and dienamine activation, resulted in significant improvement in stereocontrol (dr 12:1, 97% ee; Table 1, entry 2). Subsequently, a series of bifunctional catalysts were evaluated, and the readily accessible α,α-diphenylprolinol **2** was found to afford the best results. It was noteworthy that the thiourea-based catalyst **5** gave lower yield and stereoselectivity (51% yield, 3:1 dr and 73% ee; Table 1, entry 5). The catalyst **6** exhibited no catalytic activity (Table 1, entry 6).

To further optimize the reaction, a number of reaction parameters were investigated, and the results are listed in Table 2.

Table 2. Optimization of Reaction Conditions[a]



entry	solvent	temp (°C)	7a/8a ratio	yield[b] (%)	dr[c]	ee[d] (%)
1	CH_2Cl_2	25	1:2	73	12:1	97
2	$CHCl_3$	25	1:2	78	15:1	97
3	CH_2ClCH_2Cl	25	1:2	72	12:1	90
4	THF	25	1:2	57	10:1	93
5	Toluene	25	1:2	72	13:1	95
6	Et_2O	25	1:2	57	10:1	96
7	EtOAc	25	1:2	50	11:1	96
8	CH_3CN	25	1:2	77	4:1	94
9	$CHCl_3$	0	1:2	trace		
10	$CHCl_3$	40	1:2	82	8:1	92
11	$CHCl_3$	25	1:1	47	8:1	96
12	$CHCl_3$	25	2:1	54	9:1	96
13	$CHCl_3$	25	1:4	70	15:1	97
14[e]	$CHCl_3$	25	1:2	75	17:1	97
15[ef]	$CHCl_3$	25	1:2	51	19:1	97

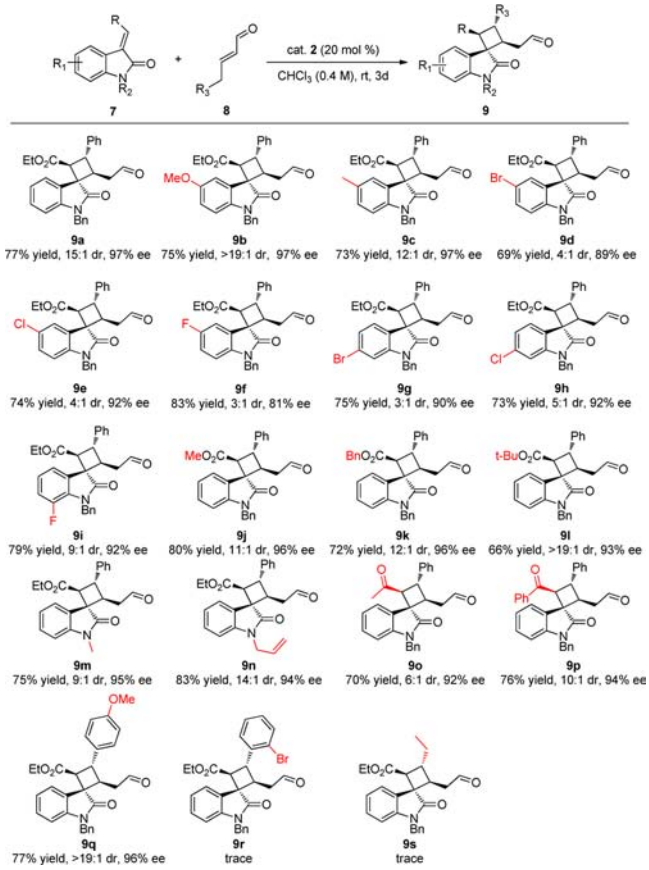
[a]Unless otherwise noted, reactions were performed by employing **7a** (0.1 mmol), **8a** (0.2 mmol), and **2** (0.02 mmol, 20 mol %) in solvent (0.5 mL) at 25 °C for 3 days. [b]Isolated yield. [c]Determined by ^{1}HNMR spectroscopy. [d]Determined by chiral HPLC analysis of the corresponding Wittig olefination products. [e]Performed at 0.4 M. [f]Performed at 10 mol % catalyst loading for 144 h.

A solvent survey showed that the reactions generally proceeded smoothly in chlorinated solvents and toluene, giving good yields (72−78%) and excellent stereoselectivities (>10:1 dr, 90−97% ee; Table 2, entries 1−3, 5), and $CHCl_3$ afforded slightly higher stereocontrol and yield. However, inferior results were observed in THF, Et_2O, and EtOAc without loss of stereocontrol (Table 2, entries 4, 6, 7). On the contrary, MeCN gave lower diastereoselectivity with good yield (Table 2, entry 8). Lowering or raising the temperature had clearly detrimental effects on the reaction in terms of yield and stereoselectivity (Table 2, entries 9 and 10). Tuning the mole ratio of **7a** to **8a** also offered no improvement (Table 2, entries 11−13). However, to our delight, the diastereoselectivity was slightly enhanced with the increase of reaction concentration (Table 2, entry 14). The reaction became tedious and gave moderate yield after the catalyst loading was lowered to 10 equiv % (Table 2, entry 15).

With the optimized reaction conditions in hand, we then investigated the generality of this formal [2 + 2] cycloaddition reaction. It was found that a wide range of methyleneindolinones were tolerated. A remarkable substituent effect on stereoselectivity was observed. The aromatic ring of methyleneindolinones bearing electron-donating groups provided the desired cycloadducts in good yields with excellent diastereoselectivities and enantioselectivities (**9a**−**c**, 73−77% yield, 97% ee, 12:1 to >19:1 dr), while the corresponding electron-withdrawing counterparts, regardless of the substituted position, gave good yields and moderate diastereoselectivities and slightly decreased

dx.doi.org/10.1021/ol503266q | *Org. Lett.* 2014, 16, 6436−6439

Table 3. Substrate Scope of Organocatalytic [2 + 2] Cycloadditions[a]

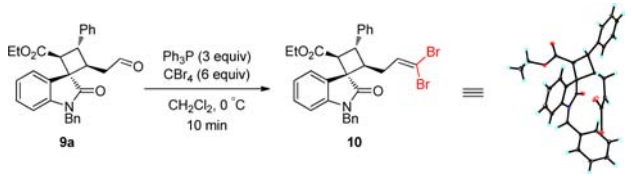


[a]Unless otherwise noted, reactions were performed by employing **7** (0.15 mmol), **8** (0.3 mmol), and **2** (0.03 mmol, 20 mol %) in $CHCl_3$ (0.38 mL) at rt for 3 days. See the Supporting Information for details.

enantioselectivities (**9d–i**, 69–83% yield, 3:1–9:1 dr, 81–92% ee). With the increase of steric hindrance of the ester group on methyleneindolinone, diastereocontrol was enhanced markedly with a slightly loss of reactivity and enantiocontrol (**9l vs 9j,k**; >19:1 dr, 66% yield, 93% ee). *N*-Methyl- and *N*-allylmethyleneindolinones (**7m,n**) were also effective to deliver spirocyclobutyl oxindoles with desirable results. Interestingly, when the ester group was replaced by acetyl or benzoyl, the reactions also proceeded smoothly with excellent stereocontrol (**9o,p**, 70–76% yield, 6:1–10:1 dr, 92–94% ee). In addition, we examined the α,β-unsaturated aldehyde scope. The reaction can not work well using γ-alkyl-substituted enal as partner, and only trace product was detected. However, γ-aryl-substituted enal incorporating a *para*-substituted electron-donating group provided an excellent outcome (**9q**, 77% yield, >19:1 dr, 96% ee). Disappointedly, the *ortho*-substituted enal **8r** gave trace product under the optimized conditions, possibly owing to sterically congestion.

Apparently, the formed highly functionalized products, along with an aldehyde moiety, were convenient for further transformations such as Wittig olefination and reduction to primary alcohol (see the Supporting Information). Furthermore, as shown in Scheme 2, the absolute configuration of the products was unambiguously established to be (1*S*,2*S*,3*R*,4*R*) by using single-crystal X-ray analysis of the corresponding Ramirez olefination products derived from **9a**. The stereochemistry of the other products in this work was assigned by analogy.

Scheme 2. Synthetic Transformation and Determination of the Absolute Configuration



In summary, the first organocatalytic formal [2 + 2] cycloaddition reaction of ethyleneindolinones with α,β-unsaturated aldehydes was developed successfully. This H-bond-directing dienamine-catalyzed process provided a straightforward approach to construct structurally complex spirocyclobutyl oxindoles in good yields (up to 83%) with excellent β,γ-regioselectivity (>19:1) and stereocontrol (up to >19:1 dr and 97% ee).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for the new compounds and X-ray crystallographic data for compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the financial support for this study from the National Natural Science Foundation of China (No. 21272230) and the Western Light Talent Culture Project.

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