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Organocatalytic Asymmetric Formal [4 + 2] Cycloaddition for the Synthesis of Spiro[4-cyclohexanone-1,3′-oxindoline] Derivatives in High Optical Purity

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ABSTRACT

A bifunctional organocatalytic asymmetric formal [4 + 2] cycloaddition reaction of Nazarov reagents and methyleneindolinones afforded spiro[4-cyclohexanone-1,3′-oxindoline] derivatives with excellent enantioselectivity (up to 98% ee).

The spiro[4-cyclohexane-1,3′-oxindoline] structural motif is commonly present in a number of natural products as exemplified by gelsemium and marcfortine alkaloids.[1,2] It also comprises a core component of various biologically active compounds.[3] Recently, they have been found serving as antagonists of MDM2 interactions and hence hold great potential to be selective and potent anticancer agents.[4] In the past several years, significant advances have been achieved on the development of synthetic methods to access spirooxindole derivatives with a concomitant creation of an all-carbon quaternary stereogenic center in an enantioselective manner.[5] Overman pioneered an asymmetric intramolecular Heck reaction rendering the synthesis of spiro[pyrrolidin-3,3′-oxindole] derivatives with high enantiomeric purity.[6] Trost developed an elegant asymmetric alkylation reaction of an oxindole enolate enabling a concise synthesis of horsfiline.[7] Recently, Barbas and Melchiorre independently reported organocatalytic conjugate addition reactions of 3-substituted oxindoles to electronically deficient olefins creating an all-carbon stereogenic center with high levels of stereochemical control.[8] Chen and co-workers presented a

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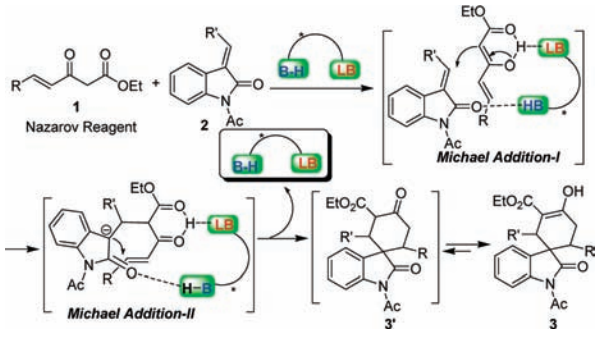
Mannich reaction of 3-substituted oxindoles to imines, yielding oxindole derivatives with high enanioselectivity.[9] Very recently, we disclosed a Brønsted acid catalyzed 1,3-dipolar addition of azomethine ylide to methyleneindolinones, leading to a structurally diverse synthesis of optically active spiro[pyrrolidin-3,3′-oxindole] derivatives.[10] In sharp contrast to the well-established approaches to access spiro-[pyrrolidin-3,3′-oxindole] derivatives,[5] however, so far only a single asymmetric catalytic entry currently available to spiro[4-cyclohexanone-1,3′-oxindoline] was very recently disclosed by Melchiorre and co-workers, consisting of an enamine-catalyzed cyclization reaction of enones with methyleneindolinones.[11] As our continuous efforts on seeking efficient enantioselective approach toward the construction of spirooxindole motif,[10] we will herein report a formal [4 + 2] cycloaddition reaction, providing spiro[4-cyclohexanone-1,3′-oxindoline] derivatives in excellent enantioselectivity.

Nazarov reagents of type **1** possess a nucleophilic acidic carbon and an electronically poor C−C double bond,[12] allowing for design of a cascade procedure to build up an all-carbon ring system by the use of organocatalysts.[13] Our initial idea for the catalytic synthesis of spiro[4-cyclohexanone-1,3′-oxindoline] including double conjugate addition reactions cascade is shown in Scheme 1. The reaction is

Scheme 1. General Strategy for the Cyclization of Methyleneindolinones with Nazarov Reagents by Bifunctional Catalysts



believed to commence with one conjugate addition of a Nazarov reagent to a methyleneindolinone, followed by the other conjugate addition of the carbon anion generated from the former conjugate addition, yielding a spiro[4-cyclohexanone-1,3′-oxindoline]. In principal, chiral BH-LB bifunctional organocatalyst[14] will afford an enantioselective cascade cyclization reaction.

Initially, we chose Takemoto type catalysts (Figure 1) to promote a model reaction of Nazarov reagent **1a** with (*E*)-

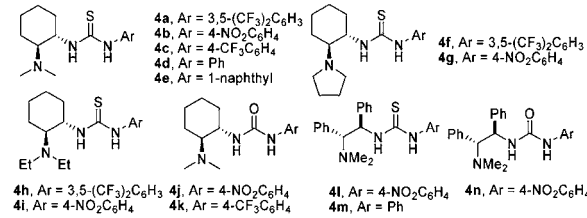
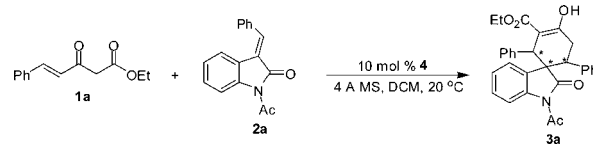


Figure 1. Organocatalysts evaluated in this study.

1-acetyl-3-benzylideneindolinone (**2a**) for the validation of our hypothesis because these catalysts possess Brønsted acidic and Lewis basic functionalities and have shown unique ability in catalyzing conjugate addition reactions.[15] Indeed, the reaction proceeded smoothly in the presence of 10 mol % of the catalysts under the assistance of 4 Å molecular sieves. In general, both the reaction conversion and stereoselectivity relied apparently on the electronic feature of the aryl substituent on the thiourea moiety. As can be seen from the reaction with **4a**−**e**, the catalysts with highly electronically poor aryl group basically delivered higher enantioselectivity and yields than those bearing electronically neutral substituents (entries 1−3 vs 4−5), indicating that the more acidic thiourea proton renders the reaction cleaner and more

Table 1. Evaluation of Organocatalysts[a]



entry	4	time (days)	yield (%)[b]	dr[c]	ee (%)[d]
1	**4a**	3	78	95/5	75
2	**4b**	3	91	95/5	85
3	**4c**	3	91	94/6	84
4	**4d**	5	56	95/5	71
5	**4e**	2	56	85/15	58
6	**4f**	3	87	95/5	70
7	**4g**	3	89	95/5	77
8	**4h**	7	6	90/10	67
9	**4i**	7	17	88/12	70
10	**4j**	3	90	95/5	91
11	**4k**	3	90	95/5	91
12	**4l**	5	25	95/5	80
13	**4m**	7	14	92/8	49
14	**4n**	5	60	97/3	94

[a] Reaction was performed in 0.1 mmol scale in DCM (0.5 mL) with 4 Å MS (100 mg) and the ratio of **2a**/**1a** is 1:2. [b] Isolated yield. [c] Measured by ^{1}HNMR. [d] Determined by HPLC.

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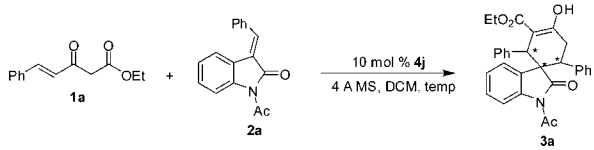
stereoseletive by engaging in the activation of either reaction component through hydrogen bonding interactions, as demonstrated in previous reports.[14,15] Finely tuning the substituent of the Lewis basic tertiary amine moiety did not provide further improvement in the catalytic activity and stereoselectivity (entries 6−9). Interestingly, a significant enhancement in the stereoselectivity was achieved by the use of urea surrogates as catalysts (entries 10 and 11). 1,2-Diphenylethane-1,2-diamine derived bifunctional catalysts showed less catalytic activity (entries 12−14), although **4n** afforded the highest levels of enantioselectivity (entry 14). In terms of the reaction conversion and stereoselectivity, **4j** and **4k** turned out to be the optimal catalysts (entries 10 and 11). However, **4j** is easier and cheaper to be prepared than **4k**. Thus, we chose **4j** as the catalyst for further investigations.

Then, we optimized the reaction conditions (Table 2). The reaction proceeded slower in toluene than dichloromethane

Table 2. Optimization of Reaction Conditions[a]



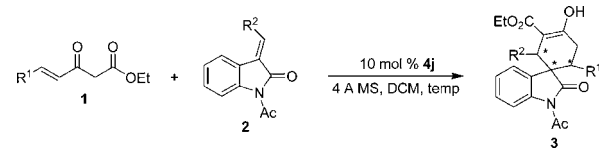
entry	ratio of **2a/1a**	time (days)	temp (°C)	yield (%)[b]	dr[c]	ee (%)[d]
1	1/2	3	20	70	99/1	90[e]
2	1/2	3	20	90	95/5	91
3	1/2	3	10	90	96/4	94
4	1/2	4	0	71	96/4	96
5	1/1.2	3	10	54	95/5	92
6	1/1.5	3	10	67	95/5	93
7	1.2/1	3	10	73	95/5	90
8	1.5/1	3	10	73	95/5	91
9	2/1	3	10	83	95/5	91

[a] Reaction was performed in 0.1 mmol scale in DCM (0.5 mL) with 4 Å MS (100 mg). [b] Isolated yield. [c] Measured by ^{1}HNMR. [d] Determined by HPLC. [e] In toluene.

but afforded comparable stereoselectivity (entries 1 and 2). Lowering the temperature led to a higher enantioselectivity (entries 2−4) but suffered from an eroded yield as demonstrated by a reaction conducted at 0 °C (entry 4). By tuning the stoichiometry of **2a** to **1a** we found that the use of 2 equiv of Nazarov reagent was necessary to ensure a cleaner reaction because decreasing the amount of **1a** led to a lower conversion (entries 3, 5, and 6). Although excess amounts of **2a** gave good yields, the enantioselectivity was sacrificed slightly (entries 7−9).

Having the optimized reaction conditions, we explored the generality of the protocol for different 3-substituted methyleneindolinones (Table 3). A wide range of 3-aryl methyleneindolinones were examined to react with Nazarov

Table 3. Generality for 3-Substituted Methyleneindolinones[a]



entry	**3**	R^1	R^2	yield (%)[b]	dr[c]	ee (%)[d]
1	**3b**	Ph	4-$MeOC_6H_4$	80	98:2	93
2	**3c**	Ph	4-MeC_6H_4	76	96:4	94
3	**3d**	Ph	4-ClC_6H_4	91	92:8	91
4	**3e**	Ph	4-BrC_6H_4	89	92:8	91
5	**3f**	Ph	4-$MeO_2CC_6H_4$	95	90:10	95
6	**3g**	Ph	3-ClC_6H_4	98	93:7	91
7	**3h**	Ph	2-ClC_6H_4	66	95:5	90
8	**3i**	Ph	3,4-$Cl_2C_6H_3$	91	89:11	88
9	**3j**	Ph	Ph	86	96:4	95
10	**3k**	Ph	2-naphthyl	90	95:5	93
11[e]	**3l**	Ph	COOEt	80	94:6	96
12[e]	**3m**	Ph	COOBn	80	94:6	97
13[e]	**3n**	Ph	COO^{t}Bu	93	94:6	97
14	**3o**	Ph	Pr	91	99:1	90
15	**3p**	Ph	*i*-Bu	94	99:1	93
16	**3q**	Pr	Ph	89	97:3	90
17	**3r**	4-$OMeC_6H_4$	Ph	78	95:5	94
18	**3t**	4-MeC_6H_4	Ph	86	96:4	93
19	**3u**	4-BrC_6H_4	Ph	97	95:5	93
20	**3v**	4-$NO_2C_6H_4$	Ph	91	96:4	93
21[e]	**3w**	OMe	COOEt	29	99:1	93

[a] Reaction was performed in 0.2 mmol scale in DCM (1 mL) with 4 Å MS (200 mg) at 10 °C and the ratio of **2**/**1** is 1:2. The reaction was performed for 2−7 days. [b] Isolated yield. [c] Measured by ^{1}HNMR. [d] Determined by HPLC. [e] Reaction was conducted at −30 °C.

reagent **1a** (entries 1−10). Basically, the reaction proceeded smoothly to give desired product in high yields. The electronic feature of aryl substituent has little effect on the enantioselectivity. As a result, monosubstituted benzaldehydes engaged in the cyclization reactions with excellent enantioselectivity ranging from 90 to 94% ee (entries 1−7). On the contrary, the diastereoselection was to some degree sensitive to electronic property of the substituent and benefited from the electron donating feature. For example, very high diastereomeric ratio of 98/2 was observed for (*E*)-1-acetyl-3-(4-methoxybenzylidene)indolinone, whereas (*E*)-methyl 4-((1-acetyl-2-oxoindolin-3-ylidene)methyl)benzoate only gave 90/10 dr (entry 1 vs 5). Interestingly, the methyleneindolinones having a much electron-deficient carbon−carbon double bond are much more reactive toward the Nazarov reagent and thus achieved clean cyclization reactions at −30 °C with high enantioselectivity (96−97% ee, entries 11−13). More significantly, 3-alkyl methyleneindolinones could be accommodated in the reaction in high yields and with excellent enantioselectivity (entries 14 and 15). Moreover, the current cyclization reaction was also operative for

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a variety of Nazarov reagents, including alkyl, aryl and methoxy substituted ones, providing high stereoselectivity (entries 16−21), but an incomplete reaction was found for the 3-methoxy methyleneindolinone (entry 21).

The capability of the reaction conditions in tolerating the substituent on the indolinone moiety of methyleneindolinones was finally investigated. As shown in Figure 2, the substitution at indolinone moiety with halogen was well tolerable in high yields and with high levels of stereochemical control. Importantly, the configuration of **5c** was assigned as 1*R*,2*S*,6*S* on the basis of the X-ray crystallography.[16]

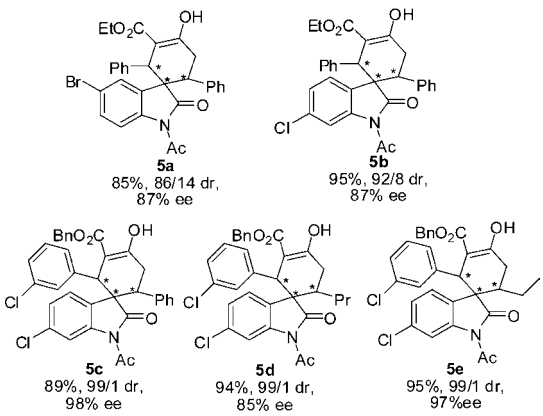
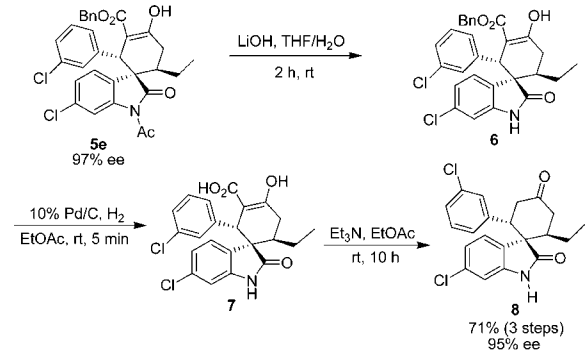


Figure 2. Generality for Substituent at the indolinone moiety. The reaction was performed in 0.2 mmol scale in DCM (1 mL) with 4 Å MS (200 mg) at 10 °C and the ratio of **2a**/**1a** is 1:2. Isolated yield. The dr was measured by ^{1}HNMR. The ee was determined by HPLC. The reaction was performed for 2−4 days. The reactions producing **5c** and **5e** were conducted at −20 °C.

To demonstrate the synthetic utility of the current reaction, a straightforward synthesis of spiro[cyclohexane-1,3′-indoline]-2′,4-dione derivatives, which have found applications in the discovery of antitumor agents, was established (Scheme 2).[4] The treatment of **5e** (97% ee) with a lithium hydroxide solution in a solvent mixture of THF and water readily accomplished a deprotection reaction to give **6**. The hydrogenation of **6** on Pd/C to remove the benzyl group and followed by a decarboxylation reaction with triethylamine provided **8** in 71% overall yield and 95% ee.

Scheme 2. Synthesis of a Spiro[cyclohexane-1,3′-indoline]-2′,4-dione



In summary, we have disclosed a highly enantioselective formal [4 + 2] cycloaddition reaction between methyleneindolinones and Nazarov Reagents catalyzed by Brønsted acid-Lewis base binfunctional organocatalysts. This reaction is accomplished via sequential double Michael addition reactions in which the bifunctional chiral catalyst activates each reaction component by hydrogen bonding interactions. This protocol holds great potential in the synthesis of biologically active spiro[cyclohexane-1,3′-indoline]-2′,4-dione derivatives in high enantiomeric purity.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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