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Highly Enantioselective [3 + 2]-Annulation of Isatin-Derived Morita–Baylis–Hillman Adducts with Cyclic Sulfonimines

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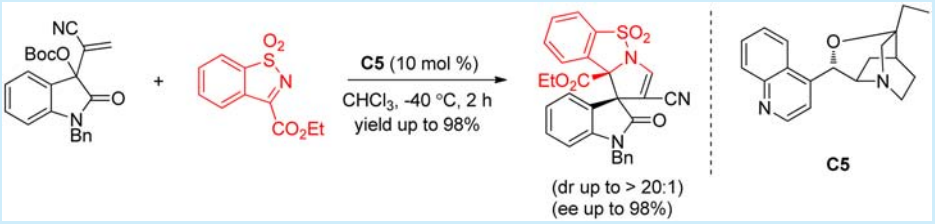
Supporting Information



ABSTRACT: An organocatalytic [3 + 2]-annulation between isatin-derived Morita–Baylis–Hillman adducts and cyclic sulfonimines has been developed in high yields with excellent enantio- and diastereoselectivities via an allylic nitrogen-ylide intermediate. The reaction provides access to heavily substituted aza-spirooxindole derivatives, which also contain ring fused cyclic sultams.

Due to the important structural motif and biological activities of aza-spirooxindoles **A**, many literature reports have focused on the asymmetric synthesis of these compounds.[1] On the other hand, the chiral cyclic sultams **B** and sulfamidates exhibit a broad spectrum of biological activities[2] and serve as chiral auxiliaries.[3] The construction of the molecule **C** bearing both structural units is very attractive and interesting (Figure 1). It has been suggested that the

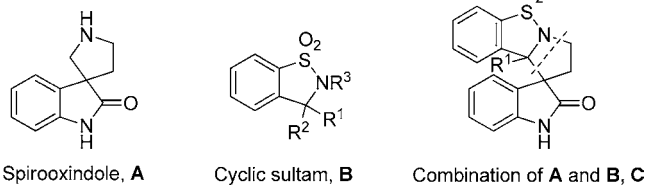


Figure 1. Biological structures containing aza-spirooxindoles and cyclic sultams.

construction of an aza-five-membered ring would be realized through [3 + 2]-cycloaddition of a 1,3-dipole with imine compounds, which was considered a powerful and efficient approach to access azacyclopentanes.

As is known, the cinchona alkaloids and their derivatives have been widely used as efficient tertiary-amine catalysts in many enantioselective reactions.[4] Meanwhile, Morita–Baylis–Hillman (MBH) adducts, owing to their dense functionalities, have been illustrated as valuable synthons and starting materials in the synthesis of many biologically active molecules and natural products.[5] As powerful precursors of 1,3-dipoles, MBH adducts have been extensively utilized in the construction of multifunctional cyclic compounds under nucleophilic tertiary-phosphine or tertiary-amine organocatalysis via allylic phosphorus and nitrogen ylide intermediates.[6] Since Lu and co-workers[7] reported the seminal phosphine-catalyzed [3 + 2]-annulation of MBH carbonates with maleimides, the annulations of MBH adducts with various dipolarophiles through allylic phosphorus ylide have achieved great progress in the past decades.[8] However, up to now, there have been limited reports on the use of cinchona alkaloids as chiral tertiary-amine catalysts to perform annulations through an allylic nitrogen ylide intermediate.[9] Recently, our group[9a] and Zhou's group,[9b] respectively, reported a [3 + 2]-annulation of MBH adducts with carbonyl compounds via an allylic nitrogen ylide intermediate in which cinchona alkaloids as a chiral tertiary-amine catalyst efficiently effected stereocontrol and avoided generation of the olefination products.[10] Due to the stability and easily modified property of chiral tertiary-amine catalyst, we wondered whether the strategy could be employed in asymmetric [3 + 2]-annulations of MBH adducts with imines. Although achiral tertiary-phosphine catalyzed [3 + 2]-annulation of MBH adducts with imines could proceed smoothly, all the products were racemic mixtures.[11] Ma and co-workers[11b] attempted to extend this annulation to being enantioselective by using chiral bisphosphine catalysts, but the results were not significant (up to 54% ee). Herein, we would like to report an asymmetric [3 + 2]-annulation of isatin-derived MBH carbonates with cyclic sulfonimine under cyclic cinchona alkaloid catalysis to afford chiral aza-spirooxindoles

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containing two newly created adjacent quaternary centers with high enantioselectivities.

In initial attempts, the [3 + 2]-annulation of MBH carbonate **1a** with cyclic sulfonimine **2a** in the presence of 10 mol % β-isocupreidine (β-ICD, catalyst **C1**) was carried out in chloroform at −40 °C for 2 h (Figure 2) (Table 1, entry 1).

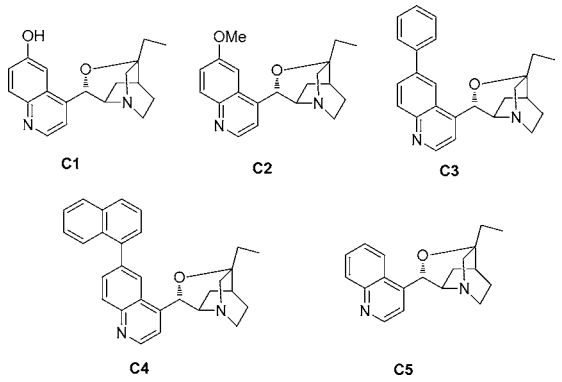
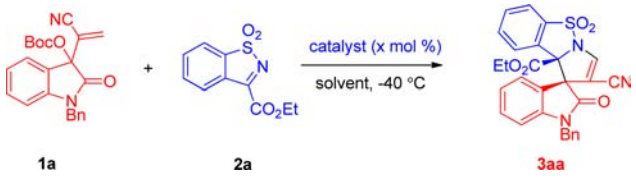


Figure 2. Chiral tertiary-amine catalysts.

Table 1. Screening of Catalysts and Solvents for Enantioselective [3 + 2]-Annulation of 1a with 2a[a]



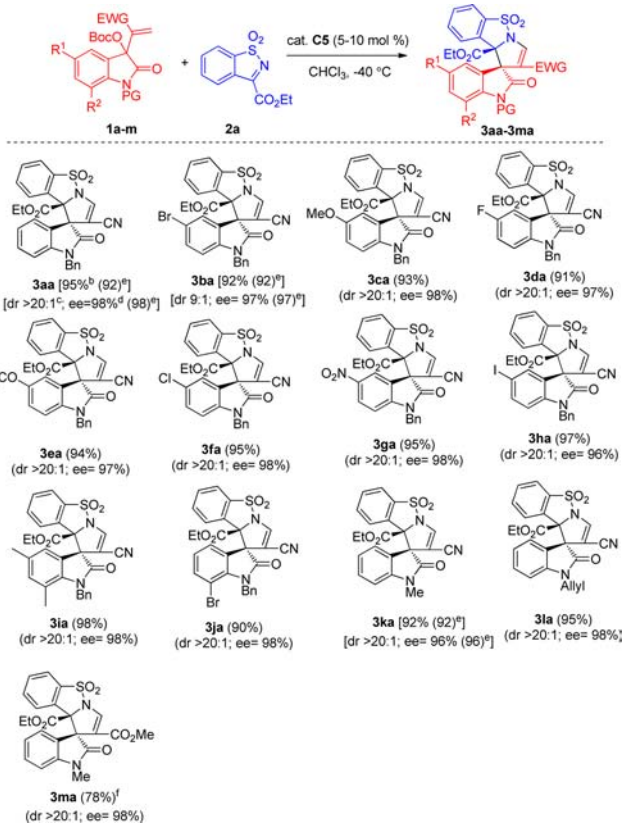
entry	catalyst (mol %)	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**C1** (10)	$CHCl_3$	2	trace	—	—
2	**C2** (10)	$CHCl_3$	2	91	>20:1	93
3	**C3** (10)	$CHCl_3$	2	92	>20:1	92
4	**C4** (10)	$CHCl_3$	2	90	>20:1	93
5	**C5** (10)	$CHCl_3$	2	95	>20:1	98
6	**C5** (10)	CH_2Cl_2	2	94	>20:1	97
7	**C5** (10)	toluene	2	95	>20:1	94
8	**C5** (10)	THF	4	85	>20:1	90
9	**C5** (10)	CH_3CO_2Et	1	95	>20:1	91
10	**C5** (5)	$CHCl_3$	5	92	>20:1	98
11	**C5** (1)	$CHCl_3$	20	91	>20:1	97

[a]The reaction was conducted with **1a** (0.11 mmol) and **2a** (0.1 mmol) in solvent (1.0 mL) at −40 °C in the presence of catalyst. [b]Isolated yields of diastereoisomer mixture. [c]The dr was determined by ^{1}H NMR spectroscopy. [d]The ee value was determined by chiral HPLC.

Unfortunately, only a trace amount of the [3 + 2]-annulation product was detected. To our delight, when OH of **C1** was changed to OMe and catalyst **C2** was employed in the reaction of **1a** with **2a** under the same conditions, the annulation product **3aa** was obtained in 91% yield with >20:1 dr and 93% ee (Table 1, entry 2). For catalyst **C3** with a phenyl group at the C-6′ position, an increase of the ee value of **3aa** was not observed (Table 1, entry 3). Moreover, if the phenyl group at C-6′ was replaced by a bulkier naphthyl group, in the case of catalyst **C4**, the yield and enantioselectivity of the reaction of **1a** with **2a** remained identical (Table 1, entry 4). However, by using the easily available catalyst **C5** without any substituent at the C-6′ position, it was found that the yield of corresponding product **3aa** was increased to 95% with >20:1 dr and 98% ee (Table 1, entry 5). If the catalyst loading was decreased to 5 or even 1 mol %, the yields of **3aa** could still remain >90% but the reaction time was prolonged to 5 or 20 h (Table 1, entries 10−11). Then the solvent effect was also examined. When the solvent was changed to dichloromethane (CH_2Cl_2), toluene, tetrahydrofuran (THF), and ethyl acetate, no better results were achieved (Table 1, entries 6−9). Therefore, the best results were obtained in $CHCl_3$ at −40 °C in the presence of catalyst **C5**.

Under the optimized reaction conditions, the scope of MBH carbonates **1** derived from isatin in the reaction with cyclic sulfonimine **2a** was investigated. The results are summarized in Scheme 1. In general, the MBH adducts bearing both electron-withdrawing and -donating substituents on the C5 and/or C7 positions afforded the corresponding [3 + 2]-annulation products **3aa**−**3ja** in both excellent yields (91−98%) and diastereoselectivities (up to >20:1) with excellent enantioselectivities (96−98% ee), except for the MBH carbonate with Br at the C5 position forming the product **3ba** with 9:1 dr. In addition, when the protective groups (PGs) on nitrogen were methyl and allyl, the annulation products **3ka** and **3la** were also obtained respectively with excellent results. It is worth mentioning that the MBH carbonate derived from isatin and

Scheme 1. Enantioselective [3 + 2]-Annulation of MBH Carbonates 1a−m with Cyclic Sulfonimine 2a[a]



[a]The reaction was conducted with **1a** (0.11 mmol) and **2a** (0.1 mmol) in solvent (1.0 mL) at −40 °C in the presence of 10 mol % catalyst for 2 h. [b]Isolated yields of diastereoisomer mixture. [c]The dr was determined by ^{1}H NMR spectroscopy. [d]The ee value was determined by chiral HPLC. [e]In parentheses, 5 mol % catalyst, 5 h. [f]The reaction was performed at room temperature for 20 h.

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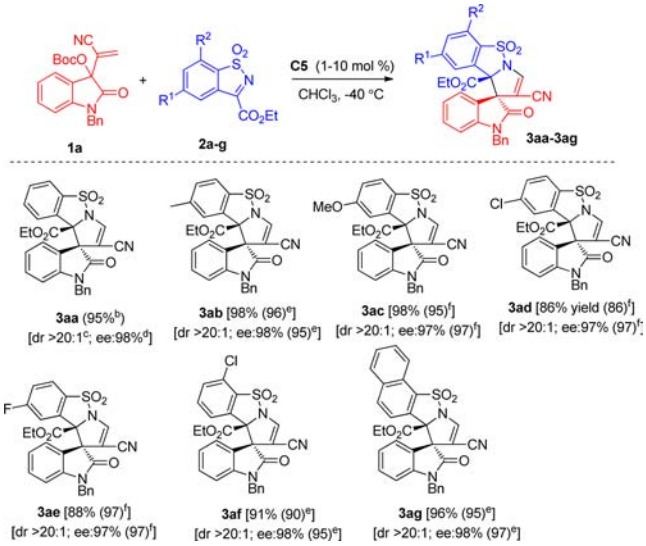
methyl acrylate also provided the annulation product **3ma** in 78% yield with >20:1 dr and 98% ee.

The [3 + 2]-annulations of MBH adduct **1a** with various cyclic sulfonimine **2** under tertiary-amine **C5** catalysis were also examined. The results are summarized in Scheme 2. When the

Scheme 2. Enantioselective [3 + 2]-Annulation of MBH Carbonate 1a with Cyclic Sulfonimines 2a−g[a]

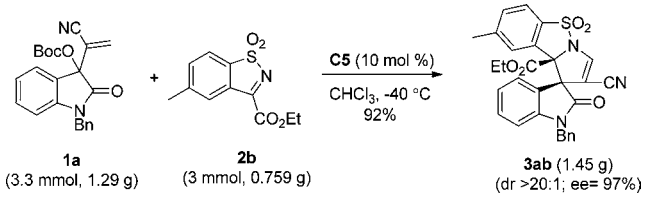


[a]The reaction was conducted with **1a** (0.11 mmol) and **2a** (0.1 mmol) in solvent (1.0 mL) at −40 °C in the presence of 10 mol % catalyst for 2 h. [b]Isolated yields of diastereoisomer mixture. [c]The dr was determined by ^{1}H NMR spectroscopy. [d]The ee value was determined by chiral HPLC. [e]In parentheses, 1 mol % catalyst loading for 24 h. [f]In parentheses, 5 mol % catalyst loading for 5 h.

substituents were electron-donating groups on the phenyl ring, the annulation products (**3aa−3ac**) were obtained in high yield (96−98%) with both excellent diastereoselectivities (up to >20:1) and enantioselectivities (97−98% ee). However, when cyclic sulfonimines bearing the electron-withdrawing substituents on the phenyl ring were employed, the yields of annulation products **3ad−3af** slightly decreased to 86−91% without any loss of stereoselectivities. For naphtho-cyclized sulfonimine, product **3ag** was gained with excellent results either. When the ester group of the cyclic imine was replaced by a phenyl group, no cycloaddition product was obtained. Meanwhile, when the catalyst loading was decreased to 5 or 1 mol %, the corresponding products could also be obtained with similar results.

To evaluate the practicality of this [3 + 2]-cycloaddition, a gram-scale reaction of **1a** and **2b** was carried out. As shown in Scheme 3, product **3ab** was obtained in 92% yield with >20:1 dr and 97% ee under a 10 mol % catalyst loading.

Scheme 3. Gram-Scale Reaction of 1a with 2b



On the basis of the above experimental data and literature reports,[8] a plausible reaction mechanism was proposed in Figure 3. The reaction was initiated through the attack of a

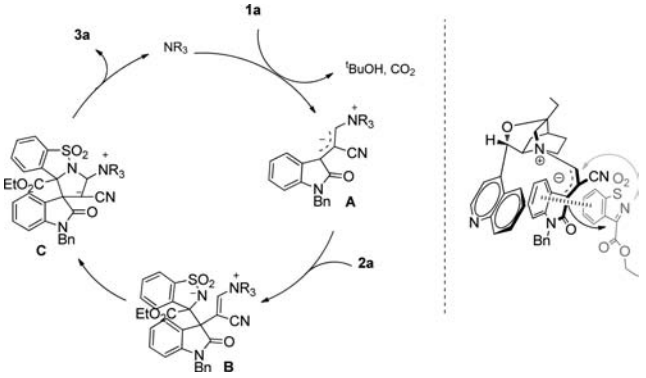


Figure 3. Proposed catalytic cycle and transition state.

cinchona alkaloid ($\mathbf{NR_3}$) to the MBH carbonate **1a** to afford the allylic nitrogen-ylide **A**. Then cyclic sulfonimine **2a** reacted with ylide **A** to generate intermediate **B**. Subsequent intramolecular aza-Michael addition provided the intermediate **C**, which could eliminate the catalyst to furnish the annulation product **3a** and completed the catalytic cycle. The configuration of two newly created chiral centers in product **3ja** was determined by X-ray analysis (Figure 4).[12] A plausible transition state for stereochemistry control was proposed in Figure 3.

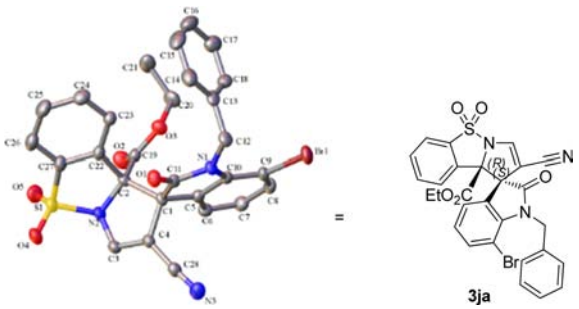


Figure 4. X-ray analysis of **3ja**.

In summary, we have demonstrated an organocatalytic and enantioselective [3 + 2]-annulation between isatin-derived Morita−Baylis−Hillman adducts and cyclic sulfonimines. The reaction efficiently and powerfully constructed the highly functionalized oxindole-fused spirotetrahydropyrrole frameworks in high yields with excellent enantio- and diastereoselectivities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and ^{1}H NMR, ^{13}C NMR, and HPLC spectra for new products. 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.

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(12) For details, see the Supporting Information. CCDC deposition number: 1030254

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