

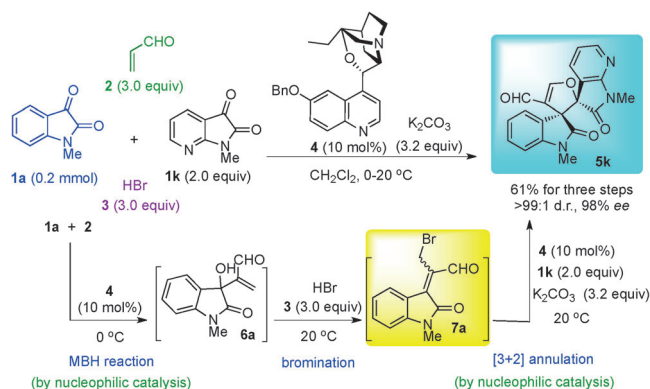
One-Pot Tandem Approach to Spirocyclic Oxindoles Featuring Adjacent Spiro-Stereocenters**

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The efficient synthesis of complex organic molecules having significant structural diversity from simple chemicals in an operationally simple and stereochemically controllable fashion, not only has important applications in the development of new biological probes and drugs, but represents a long-standing goal challenging organic chemists.^[1] The ever-increasing demand in chemistry biology and medicinal research for privileged scaffolds, which recapitulate the attractive features of bioactive compounds, requires the invention of new synthetic strategies to facilitate the construction of libraries of optically active compounds with polycyclic structures derived from the variation of the core structure of natural bioactive compounds.^[2] In contrast, protocols that allow efficient syntheses of spirocyclic compounds bearing all-carbon quaternary stereocenters are highly desirable,^[3] as the catalytic asymmetric construction of such centers is still a formidable task in organic synthesis.^[4]

The modular combination of organocatalytic reactions in a cascade has been established as a powerful strategy for building molecular complexity^[5] given the pioneering work of the groups of List, MacMillan, and Jørgensen.^[6] While a number of elegant organocatalytic tandem reactions have been reported,^[5,7] the development of conceptually new cascade reactions to realize biomimetic-like, intermolecular, tandem reactions is still very much in demand.^[5] Herein, we report a novel Morita–Baylis–Hillman (MBH) reaction/bromination/[3+2] annulation sequence, which consists of three intermolecular reactions and involves two distinct nucleophilic catalytic steps^[8] using the same tertiary amine catalyst (Scheme 1). Accordingly, a highly efficient and stereoselective protocol for the synthesis of bis(spirooxindole)s and spirocyclic oxindoles featuring two adjacent spiro-stereocenters is developed.

The [3+2] annulation of MBH adducts catalyzed by organocatalysts^[9,10] was pioneered by Lu et al.^[9a] and is



Scheme 1. One-pot organocatalyzed MBH/bromination/[3+2] annulation reaction sequence.

a fruitful strategy for the synthesis of functionalized cyclic compounds.^[9] Because the MBH reaction is facilitated by nucleophilic catalysis as well,^[11] we thus considered integrating both in the design of a new organocatalytic tandem reaction. However, the MBH adducts, α -methylene- β -hydroxycarbonyl compounds, are reluctant to participate in the [3+2] annulations.^[9] Therefore, further conversion of these MBH adducts into more-reactive dipole precursors seemed essential for the reaction design. The key in the derivation would be to minimize the formation of by-products and avoid the use of excess reagents, which may have a negative influence on the stereocontrol of the [3+2] annulation step. In this context, we envisioned that treatment of the MBH adducts with HBr would lead to the formation of the corresponding brominated MBH adducts which might be reactive enough to function as dipole precursors. In this way, only H₂O is produced as waste and the excess HBr can be readily neutralized by the base used in the next step.

The viability of the newly designed sequence depends on the development of a highly stereoselective catalytic asymmetric [3+2] annulation using halogenated MBH adducts, an annulation which has not been realized thus far, to the best of our knowledge. Despite notable achievements, all the known methods are based on the more reactive MBH carbonate adducts,^[9a,p] including the first intramolecular version reported by Tang, Zhou and co-workers,^[9j] and the leading intermolecular process reported by Tan, Barbas III and co-workers,^[9j] as well as the independent work from the group of Lu.^[9k] In addition, tetrasubstituted alkenes derived from MBH adducts have not been examined in asymmetric studies despite their potential in the construction of two adjacent spiro-stereocenters.

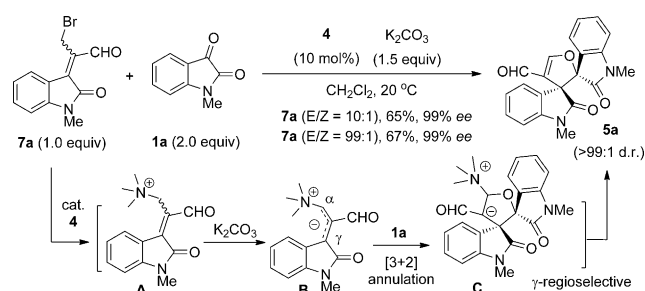
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[**] The financial support from the 973 program (2011CB808600), NSFC (21172075, 21222204), Ministry of Education (NCET-11-0147 and PCSIRT), and Program of SSCS (13XD1401600) is appreciated.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201307250>.

Since the synthesis of optically active dihydrofuran derivatives by [3+2] annulation of MBH adducts with carbonyl compounds was unprecedented,^[9o,p] we first tried to develop a highly stereoselective annulation of allyl bromides (**7**), featuring a tetrasubstituted alkene moiety and a synthetically versatile aldehyde group, with isatins (**1**) to furnish bis(spirooxindole)s (**5**). Some of our efforts resulted in the catalytic asymmetric synthesis of oxindoles having quaternary centers^[12a–j] and the exploration of acrolein-related MBH chemistry.^[12i–k] Structurally, bis(spirooxindole)s contain two linked oxindoles, a type of privileged scaffold in bioactive compounds.^[13] Current methods, which are all based on a Michael-addition-triggered sequence, for syntheses of optically active bis(spirooxindole)s are limited^[14] despite the many efforts focused on the asymmetric synthesis of spirocyclic oxindoles.^[15] To our delight, in the presence of 10 mol % of **4**,^[16] **7a** reacted with the isatin **1a** at 20 °C in CH₂Cl₂ to regioselectively give the bis(spirooxindole) **5a** in good yield with excellent d.r. and *ee* values (Scheme 2; for details, see Table S1 and S2 in the Supporting Information). The proposed intermediates (**A** and **C**) of this [3+2] annulation reaction were supported by ESI-MS studies (see the Supporting Information).

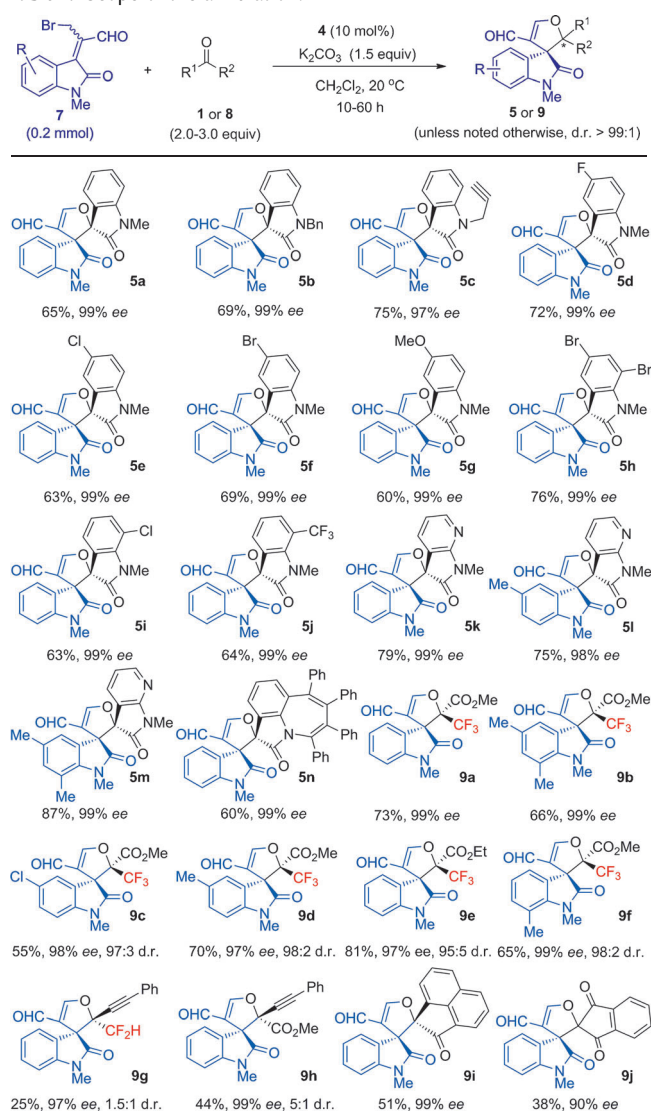


Scheme 2. Catalytic asymmetric γ -regioselective [3+2] annulation of MBH bromide **7a** and isatin **1a**.

Several interesting features are notable in this reaction. First, **5a**, obtained by the γ -regioselective annulation, features two side-by-side oxindole skeletons, which is distinct from those accessed by the existing methods.^[14] Second, the stereochemistry at the double bond of the olefin **7a** has little influence on the reaction outcome, as evidenced by the fact that using **7a** having different *E/Z* ratios afforded **5a** with the same stereochemical results (>99:1 d.r. and 99% *ee*).

The substrate scope was then evaluated using the optimized reaction conditions (Table 1). Generally, differently substituted isatins (**1**) worked well with the substrates **7** to give the bis(spirooxindole)s **5a–n** in good yields and excellent stereoselectivities. Remarkably, our reaction provides a new strategy for the catalytic asymmetric synthesis of stereogenic carbon centers bearing an α -CF₃ or α -CF₂H group, an area of considerable current research interest.^[17] Methyl and ethyl trifluoropyruvate (**8a** and **8b**, respectively) readily gave the trifluoromethylated spirocyclic oxindoles **9a–f** in reasonable yields with excellent *ee* and d.r. values. A α -CF₂H-substituted ynone reacted with **7a** to give **9g** in 97% *ee*, albeit with moderate yield and a low d.r. value. Gratifyingly,

Table 1: Scope of the annulation.^[a,b]



[a] For details, see the Supporting Information. [b] Yield of isolated product.

other types of activated ketones were also viable substrates, thus affording the products **9h–j** in acceptable yields and excellent selectivities (for full substrate scope, see Table S3 and S4). The relative and absolute configuration of **5h** and **9c** were determined by X-ray analysis.^[18]

Having established a highly stereoselective [3+2] annulation of the bromides **7** with activated ketones, we next examined the potential of the envisioned tandem reaction. The initial MBH reaction of **1a** and acrolein, catalyzed by 10 mol % of **4**, proceeded well in CH₂Cl₂ at 0 °C. After the consumption of **1a**, as shown by TLC analysis, the mixture was warmed to 20 °C and a combination of CH₃COBr and MeOH (1:1; a masked source of HBr) was added and the reaction stirred for 6–8 hours. Next, the dipolarophile (**1** or **8**) and 3.2 equivalents of K₂CO₃ were added. By using this one-pot sequential reaction, a variety of spirocyclic oxindoles were accessed in acceptable yields and excellent selectivities (Table 2), although the *ee* values of some products decreased

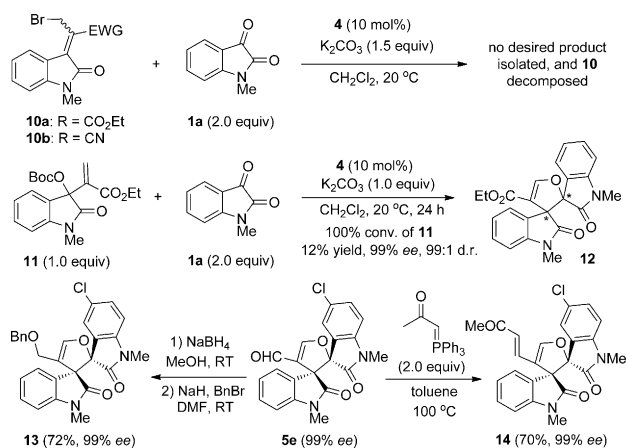
Table 2: One-pot tandem reaction.^[a]

Entry	Product	Yield [%] ^[b]	d.r.	ee [%]
1	5a	53	> 99:1	99
2	5b	63	> 99:1	97
3	5c	59	> 99:1	95
4	5d	53	> 99:1	98
5	5e	57	> 99:1	98
6	5f	60	> 99:1	98
7	5g	49	> 99:1	99
8	5h	60	> 99:1	99
9	5i	54	> 99:1	96
10	5j	74	> 99:1	99
11	5k	61	> 99:1	98
12	5n	41	> 99:1	99
13	9g	20	1.4:1.0	97
14	9h	30	5.0:1.0	99
15	9i	50	> 99:1	98
16	9j	31	—	90

[a] For details, see the Supporting Information. [b] Yield of the isolated product.

slightly as compared with those shown in Table 1 (for example, the *ee* value of **5c** fell from 97% to 95%). These results unambiguously demonstrate the synthetic utility of the MBH/bromination/[3+2] sequence for the construction of polycyclic compounds, thus suggesting that other dipolarophiles such as imines and electron-deficient olefins might also be potentially integrated into this reaction.

It is noteworthy that MBH adducts derived from acrolein are introduced to [3+2] annulation, as all previous researches focused on the utilization of MBH adducts derived from acrylonitrile, acrylate, and vinyl ketones.^[9,11] Noticeably, the newly developed substrates **7**, featuring a formyl group, was crucial for the reaction because the analogous bromides **10a** and **10b**, bearing an ester or a cyano group, respectively, decomposed under the same reaction conditions and failed to give the corresponding products (Scheme 3). In contrast, the carbonate **11**, the only type of oxindole-based dipoles to have been used in asymmetric reactions up to now, reacted with **1a** to give the product **12** in only 12% yield, even in the presence of extra base (no K_2CO_3 , no product **12** formation). Interestingly it was usually not necessary to use extra base in the [3+2] annulation of MBH carbonates.^[9] The oxindole-based MBH carbonates derived from acrylonitrile or acrolein, analogues of **11**, had not been previously reported and could not be prepared by the same method used for **11**. These results suggested that brominated MBH adducts derived from acrolein might provide a new synthetic opportunity for the asymmetric catalytic [3+2] annulation. In particular, the formyl group in the resulting product provided a convenient handle for further elaboration, as evidenced by the facile



Scheme 3. Control experiments and product elaboration.

conversion of the product **5e** into compounds **13** and **14** in good yields, without erosion in the *ee* values.

DFT calculations indicated that the [3+2] annulation of **7a** and **1a** proceeded by a concerted mechanism, and four transition states (TS) corresponding to the four possible diastereomers were identified (for details, see the Supporting Information). The optimized structures of the two most stable TSs leading to either the *S,S* or *R,R* enantiomer of **5a** are shown in Figure 1. In the orientation shown in TS-(*S,S*), the

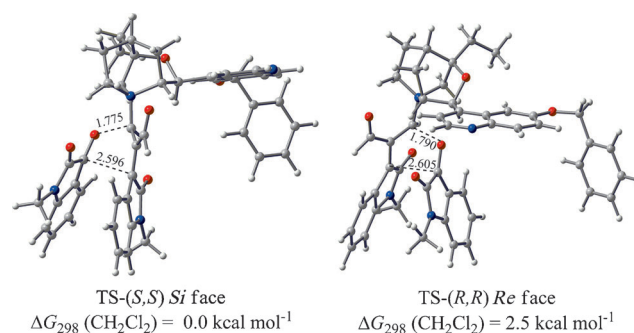


Figure 1. Optimized transition states leading to the *S,S* and *R,R* enantiomers of **5a**.

attack of the dipole from the *Si* face of **1a** to form (*S,S*)-**5a** was preferred, as it avoids the unfavorable interaction between the isatin and catalyst scaffold. The calculated Gibbs free-energy gap between TS-(*S,S*) and TS-(*R,R*) is 1.1 kcal mol⁻¹, which increases to 2.5 kcal mol⁻¹ after adding the solvent free energy. This result was in accordance with the experimental results.

In conclusion, we have developed a novel organocatalytic MBH/bromination/[3+2] annulation sequence, thus providing facile access to bis(spirooxindole)s and fluoroalkyl-substituted spirocyclic oxindoles featuring two adjacent spiro-stereocenters, and they are interesting targets for medicinal research. The key step is an unprecedented catalytic asymmetric [3+2] annulation of brominated MBH adducts, and it is also catalyzed by tertiary amine;^[9],m,19] [3+2] cycloaddition of MBH adducts typical rely on tertiary

phosphine catalysis.^[9] The scope of the newly developed [3+2] annulation, along with the exploration of the tandem reaction for the efficient synthesis of polycyclic compounds, are now in progress in our laboratory.

Received: August 18, 2013

Revised: September 27, 2013

Published online: November 7, 2013

Keywords: asymmetric catalysis · heterocycles · organocatalysis · spiro compounds · synthetic methods

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- [18] Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 949442 (**5h**), 950595 (**5k**), 949443 (**7a**), and 949444 (**9c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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