Organic Letters
Letter
pubs.acs.org/OrgLett

α-Regioselective Asymmetric [3 + 2] Annulations of Morita−Baylis−Hillman Carbonates with Cyclic 1-Azadienes and Mechanism Elucidation

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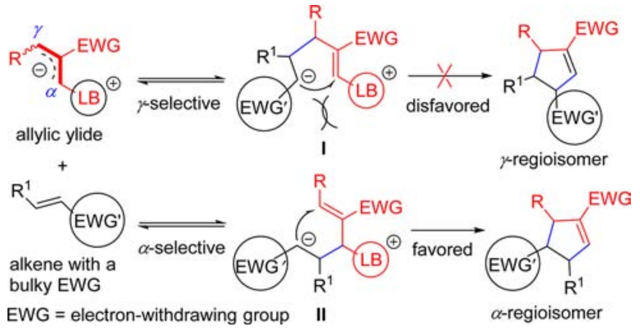
Ⓢ *Supporting Information*

ABSTRACT: An α-regio-, diastereo-, and enantioselective [3 + 2] annulation reaction of Morita−Baylis−Hillman carbonates of isatins and activated alkenes with a bulky electron-withdrawing 1,2-benzoisothiazole 1,1-dioxide or 1,2,3-benzoxathiazine 2,2-dioxide motif is reported, furnishing an array of spirooxindoles (>19:1 dr, up to >99% ee) catalyzed by cinchona-derived tertiary amines. Density functional theory calculation studies have been conducted to elucidate the originality of the α-regioselective annulations.

The Morita−Baylis−Hillman (MBH) adducts and their derivatives have been widely utilized as valuable synthons owing to their dense functionalities.[1] As readily accessible substrates, they also have been applied in asymmetric catalysis for the construction of chiral substances, especially under the catalysis of Lewis basic tertiary phosphines or amines.[2] In this respect, Lu first reported the [3 + 2] annulation pathway between MBH carbonates and activated alkenes through the in situ formation of zwitterionic allylic *P*-ylides.[3] As a consequence, MBH adducts have been serving as 1,3-dipole components in a range of [3 + 2] and other [3 + *n*] annulations, including the chiral versions, thus tremendously contributing to the construction of various carbo- or heterocycles.[4] While both α- and γ-carbons at allylic ylide species are negatively charged enabling nucleophilic addition, Zhou reported that, through density functional theory (DFT) calculations, the more negative charge at the more remote γ-carbon would favor the γ-regioselective [3 + 2] reactions.[5] Moreover, the steric hindrance of the bulky onium moiety at the α-position was considered as another factor for the regioselectivity. Therefore, in almost all reported cases of annulations with MBH carbonates, the formation of γ-regioselective isomers was preferable. Indeed, there are very few examples involving the α-regioselective annulation reactions of MBH carbonates,[6] and no asymmetric version has been accomplished yet.[7,8]

Although the previous reports suggest that the α-regioselective [3 + 2] annulations with MBH adducts are hard to accomplish, we envisaged that, in addition to the first potentially reversible addition step, the steric hindrance of the second cyclization step to furnish the ring systems might be applicable to control the regioselectivity. As outlined in Scheme 1, when an alkene with a bulky electron-withdrawing group is utilized, serious steric hindrance may be encountered in the substitution or addition−elimination step with γ-regioselective adduct **I**, as both the resulting carbanion and ammonium or phosphonium salt possess congested structures.[8] In contrast, although the initial α-regioselective addition step is not sterically and energetically preferred, the subsequent cyclization of zwitterionic intermediate **II** may have a lower energy barrier, thus making the entire catalytic cycle proceed more smoothly.

Scheme 1. Switching Regioselectivity in [3 + 2] Annulations of MBH Derivatives



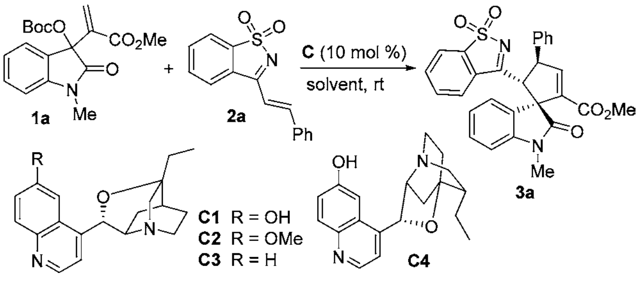
Recently, we reported that 3-styryl-1,2-benzoisothiazole 1,1-dioxide[9] **2a** could serve as a highly reactive 2π dienophile in asymmetric Diels−Alder cycloaddition with a 2,4-dienal via trienamine catalysis. This reaction exhibited abnormal *exo*-selectivity, which might be ascribed to the steric effect of the bulky electron-withdrawing 1,2-benzoisothiazole 1,1-dioxide

Received: January 20, 2016
Published: February 8, 2016

DOI: 10.1021/acs.orglett.6b00189

motif.[9a] Consequently, we investigated the reaction of MBH carbonate of isatin[10] **1a** and cyclic 1-azadiene **2a** under the catalysis of DABCO. Pleasingly, the reaction proceeded very smoothly in DCM at room temperature. The expected α-regioselective [3 + 2] product **3a** containing a spirocyclic oxindole skeleton[11] was obtained in a high yield with excellent diastereoselectivity (Table 1, entry 1). Ph_3P also efficiently catalyzed the same annulation reaction (entry 2). Inspired by this success, we next explored the asymmetric version with β-isocupreidine (β-ICD) **C1**.[12] The chiral product **3a** was produced in a high yield with remarkable enantioselectivity (entry 3). Chiral amines **C2** and **C3** without a free OH group delivered much poor results, indicating that the hydrogen-bonding interaction of OH group was crucial for both reactivity and enantiocontrol (entries 4 and 5). On the other hand, α-isocupreine (α-IC) **C4**,[13] the enantiocomplementary catalyst of **C1**, also promoted the annulation reaction in a high efficacy, and product **3a** with an opposite configuration was attained with outstanding data (entry 6). Other solvents could be tolerated catalyzed by amine **C1**, while inferior results were generally provided (entries 7–10). Importantly, the annulation proceeded smoothly with 5 mol % or even 2 mol % of **C1** with retained enantioselectivity, though a longer time was required (entries 11 and 12).

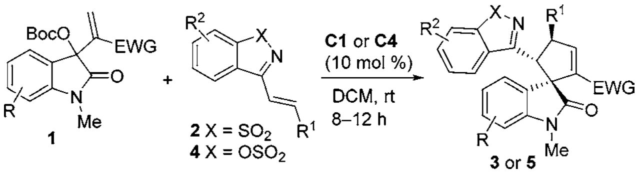
Table 1. Screening Studies of [3 + 2] Annulation of MBH Carbonate 1a and 1-Azadiene 2a[a]

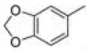


entry	cat.	solvent	time (h)	yield/%[b]	ee/%[c]
1	DABCO	DCM	12	90	
2	Ph_3P	DCM	8	86	
3	C1	DCM	8	94	98
4	C2	DCM	8	70	59
5	C3	DCM	8	76	13
6	C4	DCM	8	95	−98
7	C1	DCE	8	70	98
8	C1	toluene	8	42	95
9	C1	THF	8	66	92
10	C1	MeCN	8	50	92
11[e]	C1	DCM	12	92	98
12[f]	C1	DCM	36	84	98

[a] Unless noted otherwise, reactions were performed with MBH carbonate **1a** (0.12 mmol), 1-azadiene **2a** (0.1 mmol), and amine **C** (10 mol %) in solvent (1.0 mL) at rt. [b] Yield of isolated product. [c] By HPLC analysis on a chiral stationary phase; dr >19:1 by ^1H NMR analysis. [e] With 5 mol % of **C1**. [f] With 2 mol % of **C1**.

Table 2. Substrate Scope and Limitations[a]



entry	R	R^1, R^2	X	yield/%[b]	ee/%[c]
1	H	Ph, H	SO_2	**3a**, 94 (95)	98 (−98)
2	H	3-MeC_6H_4, H	SO_2	**3b**, 93	93
3	H	4-MeC_6H_4, H	SO_2	**3c**, 92	94
4	H	2-MeOC_6H_4, H	SO_2	**3d**, 93 (92)	90 (−91)
5	H	4-MeOC_6H_4, H	SO_2	**3e**, 98	91
6	H	 , H	SO_2	**3f**, 92	95
7	H	4-FC_6H_4, H	SO_2	**3g**, 89	98
8	H	2-ClC_6H_4, H	SO_2	**3h**, 91	99
9	H	4-$CF_3C_6H_4$, H	SO_2	**3i**, 81	95
10	H	3,4-$Cl_2C_6H_3$, H	SO_2	**3j**, 93 (91)	87 (−84)
11	H	1-naphthyl, H	SO_2	**3k**, 87 (83)	94 (−96)
12	H	2-naphthyl, H	SO_2	**3l**, 84 (87)	81 (−86)
13	H	2-furyl, H	SO_2	**3m**, 95	>99
14	H	Ph, 6-Br	SO_2	**3n**, 94	94
15	H	Ph, 5,7-Me_2	SO_2	**3o**, 84	96
16	H	2-styryl, H	SO_2	**3p**, 87	88
17	5-Me	Ph, H	SO_2	**3q**, 88	98
18	5-MeO	Ph, H	SO_2	**3r**, 95	>99
19	5,7-Me_2	Ph, H	SO_2	**3s**, 87	>99
20	5-F	Ph, H	SO_2	**3t**, 95 (93)	96 (−99)
21	5-Cl	Ph, H	SO_2	**3u**, 88	96
22	5-Br	Ph, H	SO_2	**3v**, 93	97
23	5-I	Ph, H	SO_2	**3w**, 82	95
24	5-CF_3O	Ph, H	SO_2	**3x**, 88 (89)	99 (−99)
25	7-F	Ph, H	SO_2	**3y**, 92 (92)	91 (−98)
26[d]	H	Ph, H	SO_2	**3z**, 93	94
27	H	Ph, H	OSO_2	**5a**, 93	95
28	H	Ph, 7-F	OSO_2	**5b**, 75	95
29	H	2-thienyl, H	OSO_2	**5c**, 81	99

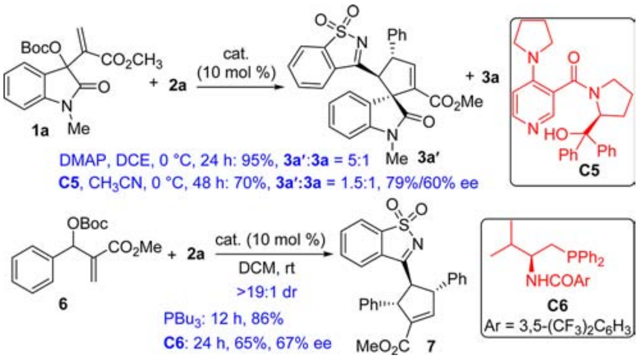
[a] Unless noted otherwise, reactions were performed with MBH carbonate **1** (0.12 mmol, EWG = CO_2Me) and 1-azadiene **2** or **4** (0.1 mmol), amine **C1** (10 mol %) in DCM (1.0 mL) at rt for 8–12 h. Data in parentheses obtained with amine **C4**. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase; dr >19:1 by ^1H NMR analysis. [d] EWG = CN.

With the optimized catalytic conditions in hand, we then investigated a variety of MBH carbonates of isatins and 3-vinyl-1,2-benzoisothiazole 1,1-dioxides under the catalysis of β-ICD **C1** (10 mol %). The results are summarized in Table 2. At first, a spectrum of 3-vinyl-1,2-benzoisothiazole 1,1-dioxides **2** bearing diversely substituted aryl, heteroaryl, or 2-styryl groups were explored in the reactions with MBH carbonate **1a**. All the reactions proceeded smoothly, and high yields with high to excellent enantioselectivity were generally obtained (Table 2, entries 1–16). Nevertheless, 1-azadienes carrying alkyl groups showed much lower reactivity. On the other hand, a number of

MBH carbonates with either electron-denoting or electron-withdrawing groups on the aryl ring also were well tolerated in the reactions with 1-azadiene **2a**, and outstanding data were generally produced (entries 17−25). In addition, MBH carbonate from isatin and acrylonitrile smoothly gave product **3z** with an excellent yield and enantiocontrol (entry 26). The analogous 4-styryl-1,2,3-benzoxathiazine 2,2-dioxides **4** exhibited the similar good reactivity with MBH carbonate **1a** under the same catalytic conditions, and annulation products **5a−c** were delivered with excellent ee values (entries 27−29). Moreover, a few substrates were studied by the catalysis of *α*-IC **C4**, and the corresponding products with an opposite configuration were efficiently furnished with high enantioselectivity (data in parentheses).

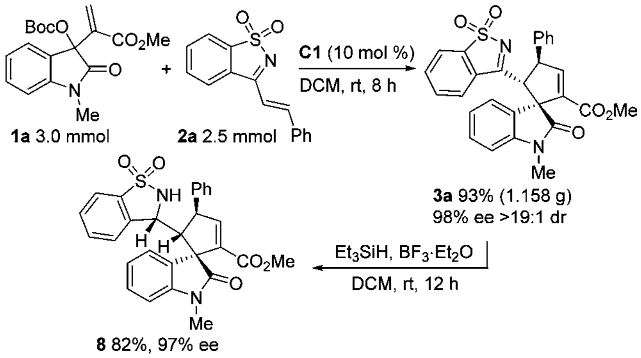
As previously reported,[8] DMAP also catalyzed a diastereodivergent annulation with **1a** and **2a**, giving **3a′** as the major product. Unfortunately, a number of chiral DMAP-type catalysts gave poor diastereoselectivity, and a moderate ee value was obtained for **3a′** with **C5**.[14] On the other hand, although both DABCO and Ph_3P failed to catalyze the annulation of simple MBH carbonate **6** from benzaldehyde and methyl acrylate with **2a**, Bu_3P exhibited high catalytic efficacy at room temperature, and the *α*-regioselective annulation adduct **7** was produced in a high yield, indicating that the selectivity was similarly controlled by the bulky electron-withdrawing group of **2a**. A bifunctional phosphine **C6** provided the chiral product **7** in a moderate yield and enantioselectivity (Scheme 2).[14]

Scheme 2. More *α*-Regioselective Annulation Explorations



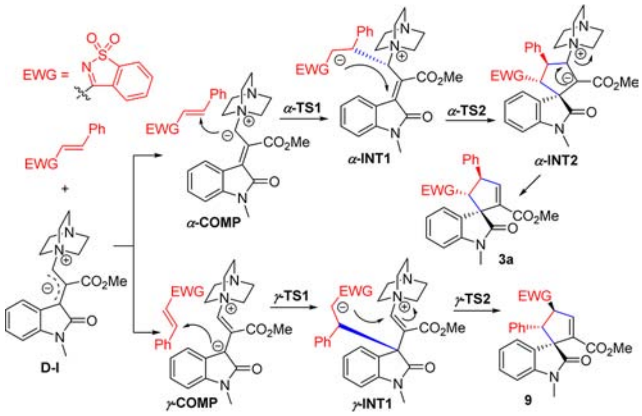
The reaction of **1a** and **2a** catalyzed by *β*-ICD **C1** proceeded effectively even on a gram scale, furnishing the highly enantioenriched product **3a** in an excellent yield. In addition, remarkable diastereoselectivity was achieved in the reduction of ketimine group with Et_3SiH and $BF_3{\cdot}Et_2O$, and product **8** with four chiral centers was obtained (Scheme 3).

Scheme 3. Synthetic Transformation of Product 3a



In order to gain more insight into the regioselective annulations, DFT calculations were performed to clarify the catalytic reaction of **1a** and **2a** with DABCO in DCM. Although a concerted [3 + 2] cycloaddition mechanism with MBH carbonate has been previously proposed,[5] in this case, we failed to identify any transition state (TS) supporting a concerted version. In contrast, the stepwise annulation TSs could be identified easily. Thus, both *α*- and *γ*-regioselective catalytic cycles to access products **3a** and **9**, respectively, were proposed in Scheme 4, and the computed potential energy surface for different approaches has been obtained accordingly (Figure 1).

Scheme 4. *α*- and *γ*-Regioselective Annulations Catalyzed by DABCO



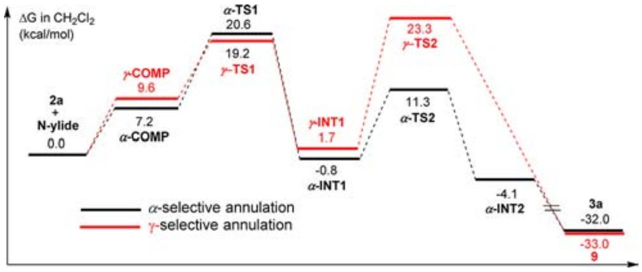


Figure 1. Computed potential energy surface of [3 + 2] annulation of **1a** and **2a** catalyzed by DABCO.

As shown in Figure 1, after the formation of complexes *α*- and *γ*-**COMP** between *N*-allylic ylide **D-I** and **2a**, the carbanion at *α*- or *γ*-position would attack the activated olefin to give *α*- or *γ*-**INT1**. The energy barrier of *α*-**TS1** in *α*-regioselective approach (13.4 kcal/mol) is a little higher (3.8 kcal/mol) than that of *γ*-**TS1** (9.6 kcal/mol) due to the steric hindrance from bulky ammonium ylide and phenyl ring, in accordance to the early observations that *γ*-regioselective annulations are generally preferable. Nevertheless, the following ring-closure step also would be crucial for controlling the actual selectivity. As expected, due to the steric hindrance from ammonium moiety and bulky 1,2-benzoisothiazole 1,1-dioxide skeleton, the energy barrier of *γ*-**TS2** in *γ*-regioselective approach (21.6 kcal/mol) is 9.5 kcal/mol higher than that of *α*-version (12.1 kcal/mol). Moreover, *γ*-**TS2** had the highest energy in the *γ*-regioselective annulation cycle, suggesting the reversible potential in the first addition step. Therefore, *α*-regioselective annulaiton would be theoretically more favorable in the reaction of **1a** and **2a** catalyzed by DABCO.[15]

In conclusion, we have developed an *α*-regioselective asymmetric [3 + 2] annulation reaction of MBH carbonates from isatins and 1-azadienes carrying a bulky 1,2-benzoisothiazole 1,1-dioxide or 1,2,3-benzoxathiazine 2,2-dioxide motif. A number of spirocyclic frameworks have been efficiently produced in high to excellent enantioselectivity (up to >99% ee) by the catalysis of cinchona-derived tertiary amines. DFT computational calculation studies verified that switching conventional γ-regioselective annulation to α-regioselective version significantly relied on the steric hindrance from ammonium salt and bulky electron-withdrawing group in the ring-closure process. This work and the mechanism elucidation would help design more regioselective annulation reactions with MBH derivatives, thus further expanding the application of these multifunctional materials. Additional results will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00189.

Complete experimental procedures and characterization of new products, NMR spectra, and HPLC chromatograms (PDF)

X-ray data for enantiopure product **8** (CIF)

X-ray data for racemic **3a′** (CIF)

X-ray data for racemic **7** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the NSFC (21125206, 21572135 and 21321061).

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(7) α-Regioselective products have been observed as the minor ones in an asymmetric [3 + 2] annulation reaction, while no ee values were reported. See ref 4c.

(8) Very recently, we reported α-regioselective divergent annulations of MBH carbonates of isatins with activated alkenes bearing a bulky 1*H*-indene-1,3(2*H*)-dione motif; see: Zhan, G.; Shi, M.-L.; He, Q.; Lin, W.-J.; Ouyang, Q.; Du, W.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2016**, *55*, 2147.

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(14) For more details, see the Supporting Information. The absolute configuration of chiral products **3a′** and **7** has not been assigned yet.

(15) Transition states involving asymmetric annulation of **1a** and **2a** catalyzed by bifunctional β-ICD have been investigated. For more details, see the Supporting Information.