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Asymmetric (4 + 3) and (4 + 1) Annulations of Isatin-derived Morita–Baylis–Hillman Carbonates to Construct Diverse Chiral Heterocyclic Frameworks

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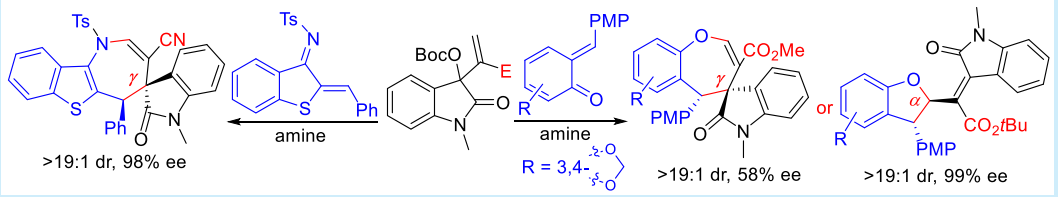
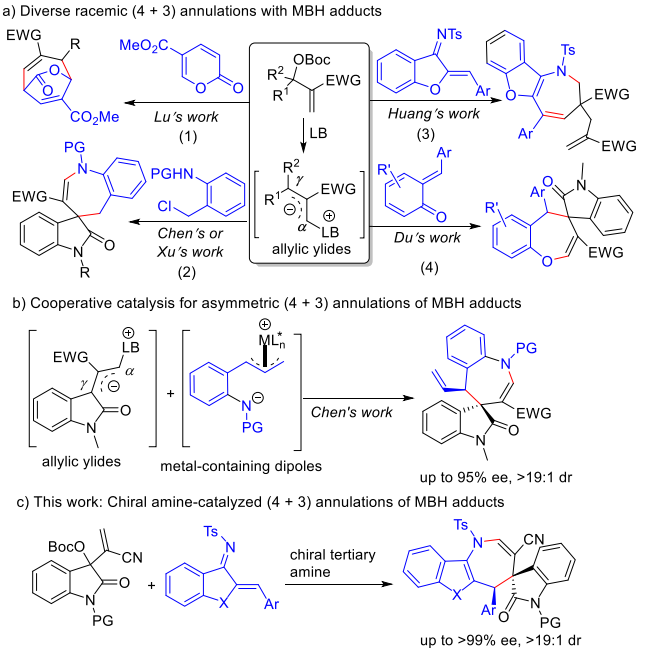


ABSTRACT: A chiral tertiary amine-catalyzed asymmetric γ-regioselective (4 + 3) annulation reaction of isatin-derived Morita–Baylis–Hillman carbonates and 1-azadienes was developed, delivering chiral azepane spirooxindoles with excellent stereoselectivity. In addition, by tuning the substituents of Morita–Baylis–Hillman carbonates, the switchable γ-(4 + 3) or α-(4 + 1) annulation reaction with *o*-quinone methides was observed to furnish benzo[*b*]oxepines or 2,3-dihydrobenzofurans, respectively, under similar catalytic conditions.

The seven-membered *N*-heterocyclic motif is a privileged scaffold in diverse bioactive natural products and pharmaceuticals,[1] and thus the development of effective protocols to construct these architectures has attracted growing interest for synthetic chemists.[2] Nevertheless, compared with five- or six-membered rings via classic [3 + 2] or [4 + 2] cycloadditions or (3 + 3) annulations, the formation of seven-membered hetero- or carbocycles, especially via asymmetric catalysis, is more challenging, as harsh conditions are usually required to overcome entropic and enthalpic penalties.[3] The asymmetric (4 + 3) annulation reaction has been regarded as one of the most efficient approaches to access these compounds, and highly reactive three-atom components are usually utilized. As a result, the current protocols mainly rely on employing active 1,3-poles, including nitrones,[4] azomethine imines,[5] in-situ-generated homoenolates[6] or acyl azoliums[7] via *N*-heterocyclic carbene (NHC) catalysis and palladium-trimethylenemethane (Pd-TMM) intermediates.[8]

The Morita–Baylis–Hillman (MBH) carbonates could generate zwitterionic allylic ylide species in the presence of Lewis base catalysts, acting as good three-atom synthons with suitable electrophilic reagents in various stereoselective (3 + *n*) annulation reactions.[9] In particular, the Lu group disclosed the first (4 + 3) reaction of benzaldehyde-derived MBH carbonates and methyl coumalate catalyzed by phosphines (Scheme 1a, 1).[10] Later, a few four-atom units, including 1-azadienes and *o*-quinone methides, were utilized to furnish different (4 + 3) annulations with MBH derivatives (Scheme 1a, 2–4).[11] Unfortunately, no asymmetric version has been

Scheme 1. Diverse (4 + 3) Annulations of MBH Carbonates



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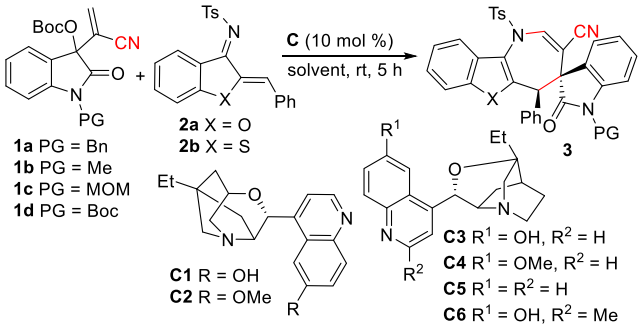
uncovered despite the significant progress in this field. Very recently, an asymmetric (4 + 3) annulation reaction with γ-regio-, chemo-, and stereoselectivity was disclosed by our group, in which two types of zwitterionic species were generated from MBH carbonates and functionalized allylic carbonates, respectively, under the cooperative catalysis of tertiary amines and chiral iridium complexes (Scheme 1b).[12] Nevertheless, the asymmetric version achieved by a single chiral Lewis base organocatalyst, as a more atom-economical and convenient approach, is still desirable. Here we report an asymmetric (4 + 3) annulation reaction between isatin-derived MBH carbonates and 1-azadienes under the catalysis of chiral tertiary amines, producing fused azepane spirooxindoles with excellent stereoselectivity (Scheme 1c).

Because 2-benzylenebenzofuran-3(2*H*)-one-based 1-azadiene **2a** has been successfully utilized as a four-atom partner in (4 + 3) annulation with a simple MBH carbonate,[11c,13] we first explored the assembly of **2a** and isatin-derived MBH carbonate **1a** under the catalysis of DABCO (10 mol %). As expected, the (4 + 3) annulation reaction proceeded efficiently in toluene at room temperature, and the γ-regioselective azepane product **3a** was obtained in an excellent yield with exclusive diastereoselectivity after 5 h (Table 1, entry 1). As a result, we explored the asymmetric version with chiral tertiary amines. Although a spectrum of catalytic parameters were explored, only moderate enantioselectivity for chiral **3a** was attained in a fair yield in $CHCl_3$ under the catalysis of α-IC **C1** (Table 1, entry 2).[14] Because a much higher reactivity was observed by using the 2-benzylenebenzo[*b*]thiophen-3(2*H*)-one-derived 1-azadiene **2b** (Table 1, entry 3),[15] we then explored the catalytic conditions for the assembly of MBH carbonate **1** and 1-azadiene **2b**. A few cinchona-derived tertiary amine catalysts were evaluated (Table 1, entries 4−7), indicating that β-ICD **C3** derived from quinidine provided the best enantioselectivity (Table 1, entry 5). Other solvents were briefly screened but with inferior data (Table 1, entries 8−11). The reaction proceeded smoothly at lower temperature, and less MBH carbonate **1a** was required (Table 1, entry 12). We further modified the substitution pattern of the MBH carbonate partner (Table 1, entries 13−15), and better enantioselectivity was gained when MBH carbonate **1b** or **1d** was used (Table 1, entries 13 and 15). In addition, adding 4 Å MS was slightly beneficial for enantioselectivity (Table 1, entry 16).[14] To improve the enantiocontrol, the 2′-methylated β-ICD **C6** was used for the reaction of MBH carbonates **1b** and **2b**, and an outstanding ee value was pleasingly achieved (Table 1, entry 17). Importantly, the annulation still proceeded effectively with 2 mol % **C6**, furnishing retained high yield and stereoselectivity at room temperature (Table 1, entry 18). The asymmetric reaction also took place on a larger scale, and similar excellent data were gained (Table 1, entry 19).

Consequently, the substrate scope and limitations of this γ-regioselective asymmetric (4 + 3) annulation reaction were investigated under the optimal catalytic conditions. As shown in Table 2, most reactions proceeded smoothly, affording the corresponding azepane spirooxindoles in high yields with excellent diastereo- and enantioselectivity. Specifically, the different N-substitutions of the MBH carbonates **1** had inappreciable effects on the reactions (Table 2, entries 1−4). In addition, the MBH carbonates **1** bearing electron-donating or -withdrawing groups on the aryl ring were well tolerated in the reactions with 1-azadiene **2b** (Table 2, entries 5−12). The MBH carbonate derived from 7-azaisatin also delivered good

Table 1. Screening Conditions of (4 + 3) Annulations of MBH Carbonates 1 and 1-Azadienes 2[a]



entry	C	1	solvent	yield (%)[b]	ee (%)[c]
1[d]	DABCO	1a	toluene	3a, 92	
2[d]	C1	1a	$CHCl_3$	3a, 43	−66
3	C1	1a	toluene	3b, 93	−40
4	C2	1a	toluene	3b, 84	−50
5	C3	1a	toluene	3b, 93	70
6	C4	1a	toluene	3b, 87	60
7	C5	1a	toluene	3b, 90	40
8	C3	1a	$PhCF_3$	3b, 90	65
9	C3	1a	$CHCl_3$	3b, 96	67
10	C3	1a	THF	3b, 96	50
11	C3	1a	CH_3CN	3b, 60	40
12[e,f]	C3	1a	toluene	3b, 95	70
13[e,f]	C3	1b	toluene	3c, 96	80
14[e,f]	C3	1c	toluene	3d, 95	70
15[e,f]	C3	1d	toluene	3e, 95	83
16[e,f,g]	C3	1b	toluene	3c, 95	82
17[e,f,g]	C6	1b	toluene	3c, 94	98
18[e,g,h]	**C6**	**1b**	**toluene**	**3c, 96**	**98**
19[e,g,h,i]	C6	1b	toluene	3c, 92	98

[a]Unless otherwise noted, the reaction was performed with MBH carbonate **1** (0.1 mmol, 2.0 equiv), 1-azadiene **2b** (0.05 mmol, 1.0 equiv), and **C** (10 mol %) in solvent (0.05 mL) at rt for 5 h. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase; dr >19:1 by ^{1}H NMR analysis. [d]**2a** was used. [e]MBH carbonate **1** (0.06 mmol, 1.2 equiv) was used. [f]At 5 °C for 12 h. [g]4 Å MS (20.0 mg) was added. [h]With **C** (2 mol %) at room temperature for 12 h. [i]On a 1.0 mmol scale.

data (Table 2, entry 13). On the contrary, a number of benzothiophene-derived 1-azadienes **2** bearing different substituents were explored in the reactions with MBH carbonate **1b** under the same catalytic conditions, and outstanding data were generally produced (Table 2, entries 14−22). It should be note that the MBH carbonate **4a** (Table 3, R^1 = H) derived from acrylate was inert in the reaction with 1-azadiene **2b** under identical conditions.[14]

In 2019, the Du group developed an efficient Lewis-base-catalyzed γ-regioselective (4 + 3) annulation reaction of *o*-quinone methides (*o*-QMs) and isatin-based MBH carbonates, and a series of valuable benzo[*b*]oxepine derivatives incorporating a spirooxindole motif were produced in moderate to excellent yields with good diastereoselectivity but without achieving any asymmetric success.[11d] Pleasingly, the asymmetric γ-regioselective (4 + 3) annulation reaction of MBH carbonates **4** from methyl acrylate and *o*-QMs **5** could be realized under our catalytic conditions. After screenings,[14] the chiral product **6a** was obtained in 83% yield with 77% ee under the catalysis of amine C2 (Table 3, entry 1). The substrate

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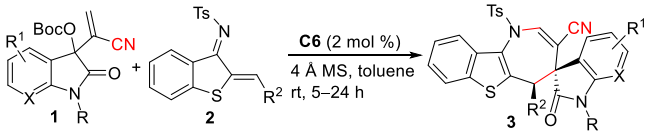
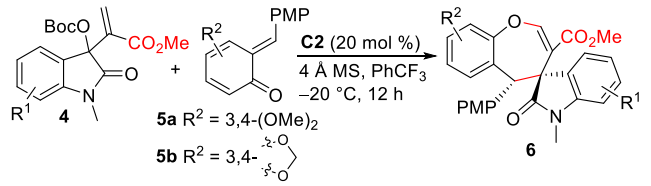
Table 2. Substrate Scope and Limitations of (4 + 3) Annulations for MBH Carbonates 1 and 1-Azadienes 2[a]



entry	R	R^1, R^2	yield (%)[b]	ee (%)[c]
1	Bn	H, Ph	**3b**, 94	>99
2	Me	H, Ph	**3c**, 95	98[d]
3	MOM	H, Ph	**3d**, 95	98
4	Boc	H, Ph	**3e**, 95	98
5	Bn	5-Me, Ph	**3f**, 96	98
6	Bn	5-MeO, Ph	**3g**, 89	92
7	Bn	5,7-Me_2, Ph	**3h**, 90	98
8	Bn	5-F, Ph	**3i**, 95	98
9	Bn	5-Cl, Ph	**3j**, 95	99
10	Bn	7-Cl, Ph	**3k**, 97	99
11	Bn	5-Br, Ph	**3l**, 94	92
12	Bn	5-I, Ph	**3m**, 96	98
13[e]	Me	H, Ph	**3n**, 97	98
14	Me	H, 4-FC_6H_4	**3o**, 97	97
15	Me	H, 4-ClC_6H_4	**3p**, 95	97
16	Me	H, 3-BrC_6H_4	**3q**, 97	97
17	Me	H, 4-BrC_6H_4	**3r**, 96	96
18	Me	H, 3-MeC_6H_4	**3s**, 93	98
19	Me	H, 4-MeC_6H_4	**3t**, 99	98
20	Me	H, 4-$MeOC_6H_4$	**3u**, 84	98
21	Me	H, 2-naphthyl	**3v**, 99	98
22	Me	H, 2-thienyl	**3w**, 96	>99

[a]Unless otherwise noted, the reactions were performed with MBH carbonate **1** (0.12 mmol, 1.2 equiv, X = CH), 1-azadiene **2** (0.1 mmol, 1.0 equiv), 4 Å MS (40.0 mg), and **C6** (2 mol %) in toluene (1.0 mL) at rt for 5−24 h. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase; dr >19:1 by ^{1}H NMR analysis. [d]Absolute configuration of enantiopure **3c** was determined by X-ray analysis. The other products were assigned by analogy. [e]X = N.

Table 3. Substrate Scope of γ-Regioselective (4 + 3) Annulations of MBH Carbonates 4 and *o*-QMs 5[a]



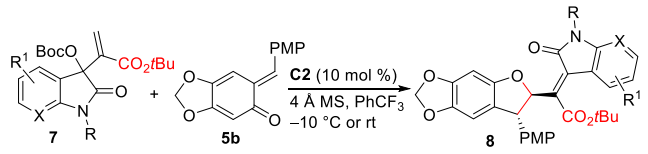
entry	R^1, **5**	yield (%)[b]	ee (%)[c]
1	H, **5a**	**6a**, 83	73
2	5-Me, **5a**	**6b**, 75	67
3	5-MeO, **5a**	**6c**, 70	66
4	5-Cl, **5a**	**6d**, 60 (32)	75 (98)[d]
5	5-I, **5a**	**6e**, 63 (39)	76 (98)[d]
6	7-F, **5a**	**6f**, 79	73
7[e]	H, **5b**	**6g**, 81	58

[a]Unless otherwise noted, the reactions were performed with MBH carbonate **4** (0.15 mmol, 1.5 equiv, added in two potions), *o*-QM **5** (0.1 mmol, 1.0 equiv), 4 Å MS (40.0 mg), and amine **C2** (20 mol %) in $PhCF_3$ (1.0 mL) at −20 °C for 12 h. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase; dr >19:1 by ^{1}H NMR analysis. [d]Data in parentheses were obtained after recrystallization. [e]At rt.

scope and limitations of the γ-regioselective (4 + 3) annulations were briefly explored, and an array of chiral oxepane spirooxindole frameworks **6** could be constructed in good yields with moderate enantioselectivity (Table 3, entries 2−7). In addition, the enantiopurity of the cycloadducts could be significantly improved after simple recrystallization (Table 3, entries 4 and 5, data in parentheses).

During the exploration for the substrate scope of the MBH carbonates **4**, it was found that the γ-regioselective (4 + 3) annulation pattern was dominantly switched to an α-regioselective (4 + 1) version by using the MBH carbonates **7** from *t*-butyl acrylate under the identical catalytic conditions.[16] To the best of our knowledge, this is the first example of the chiral tertiary amine-catalyzed asymmetric α-regioselective (4 + 1) annulation reaction of isatin-derived MBH carbonates.[17] The 2,3-dihydrobenzofuran **8a** having a tetrasubstituted alkene moiety was isolated in 77% yield with 98% ee catalyzed by amine **C2** in $PhCF_3$ (Table 4, entry 1),[14]

Table 4. Substrate Scope of α-Regioselective (4 + 1) Annulations for MBH Carbonates 7 and *o*-QM 5b[a]



entry	R	R^1	yield (%)[b]	ee (%)[c]
1	Me	H	**8a**, 71	99
2[d]	Bn	H	**8b**, 64	99
3[d]	Bn	5-MeO	**8c**, 58	95
4	Me	5-Me	**8d**, 73	>99
5	Me	5-F	**8e**, 61	95
6	Me	5-Cl	**8f**, 63	95
7[e]	Me	5-I	**8g**, 76 (67)	97 (97)[f]
8[d,g]	Bn	H	**8h**, 64	89

[a]Unless otherwise noted, the reactions were performed with MBH carbonate **7** (0.12 mmol, 1.2 equiv, X = CH), *o*-QM **5b** (0.1 mmol, 1.0 equiv), 4 Å MS (40.0 mg), and amine **C2** (10 mol %) in $PhCF_3$ (1.0 mL) at −10 °C or rt for 10−36 h. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase; dr >19:1 by ^{1}H NMR analysis. [d]MBH carbonate **7** (0.15 mmol, 1.5 equiv) was used. [e]Data in parentheses were obtained on a 1.0 mmol scale. [f]Absolute configuration of enantiopure **8g** was determined by X-ray analysis. The other products were assigned by analogy. [g]X = N.

indicating that the steric hindrance of the ester group of **7** plays a key role in achieving the switched regio- and chemoselectivity. As summarized in Table 4, an array of assemblies of MBH carbonates **7** and *o*-QM **5b** were explored, and the corresponding products **8b−h** were obtained in moderate yields with excellent enantioselectivity (Table 4, entries 2−8). In addition, high levels of stereoselectivity could also been attained on a larger scale, albeit in a slightly decreased yield (Table 4, entry 7, data in parentheses).

Product **3c** possessing multiple functional groups could undergo selective transformations. As illustrated in Scheme 2, the cyano group was smoothly hydrogenated and subsequently protected as an *N*-Boc derivative in the presence of Raney Ni and $(Boc)_2O$, giving the product **9** in a high yield with the retained ee value. Importantly, a highly diastereoselective 1,3-dipolar cycloaddition reaction of the crowded tetrasubstituted alkene moiety of compound **8g** could still be efficiently

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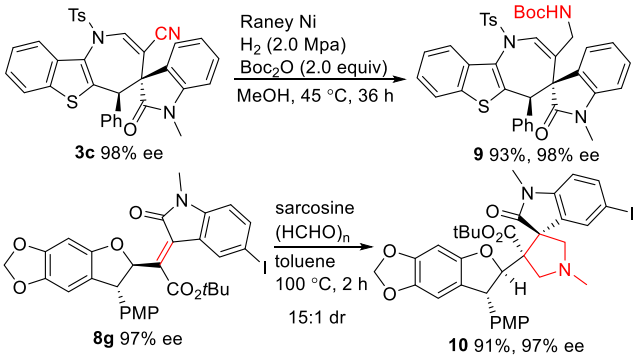
Scheme 2. Synthetic Transformations of Cycloadducts



conducted with sarcosine and paraformaldehyde,[18] furnishing the separable spirooxindole product **10** with four contiguous stereogenic centers in excellent yield.

In conclusion, we have developed a chiral tertiary amine-catalyzed asymmetric γ-regioselective (4 + 3) annulation reaction between isatin-derived MBH carbonates and 2-alkylenebenzo[*b*]thiophen-3(2*H*)-one-derived 1-azadienes. An array of chiral azepane spirooxindole frameworks were efficiently constructed in good yields with excellent diastereo- and enantioselectivity. Moreover, the asymmetric γ-regioselective (4 + 3) annulation reaction between MBH carbonates from acrylate and *o*-quinone methides was realized, and a switchable α-regioselective (4 + 1) annulation reaction was observed by simply tuning the ester group of MBH carbonates under similar catalytic conditions, producing oxepane spirooxindoles or 2,3-dihydrobenzofuran derivatives, respectively, with moderate to excellent stereocontrol. The investigation of the further applications of these heterocycles with structural diversity is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01283.

More screening conditions, complete experimental procedures and characterization of new products, NMR and HRMS spectra, HPLC chromatograms, and crystallographic information (PDF)

Accession Codes

CCDC 1996131−1996132 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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