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Catalyst-Controlled Switch in Chemo- and Diastereoselectivities: Annulations of Morita–Baylis–Hillman Carbonates from Isatins

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Abstract: *Regulating both the chemo- and diastereoselectivity, divergently, of a reaction is highly attractive but extremely challenging. Presented herein is a catalyst-controlled switch in the chemo- and diastereodivergent annulation reactions of Morita–Baylis–Hillman carbonates, derived from isatins and 2-alkylidene-1H-indene-1,3(2H)-diones, in exclusive α-regioselectivity. α-Isocupreine efficiently catalyzed [2+1] reactions to access cyclopropane derivatives, and the diastereodivergent [3+2] annulations were accomplished by employing either a chiral phosphine or a DMAP-type molecule. All reactions exhibited excellent chemoselectivities, and good to remarkable stereoselectivities were furnished, thus leading to a collection of compounds with skeletal and stereogenic diversity. Moreover, DFT computational calculations elucidated the catalyst-based switch in mechanism.*

The design and synthesis of structurally and stereochemically diverse compound collections is important for the discovery of probes and drug candidates, because the biological properties are intrinsically correlated to molecular structure. Therefore, synthetic chemists have paid a great deal of attention to the development of asymmetric reactions to construct libraries of chiral compounds having high molecular diversity.[1] On one hand, a number of examples have been presented to access structurally varied products in a chemo- or regiodivergent manner by employing different chiral catalysts or by tuning the catalytic conditions.[2] On the other hand, an array of elegant strategies to diversify the diastereochemical outcomes have also been reported.[3] An extremely challenging but ideal aspect of asymmetric catalysis is the ability to construct libraries of molecules, with both skeletal and stereogenic divergence, from identical starting materials under readily tunable catalytic conditions. As Trost pointed out: engineering a catalyst that completely overrides inherent regio- or chemoselectivity to give exclusively the desired product requires creativity and insight.[4] The concurrently achieving stereodivergence would further increase the difficulty.

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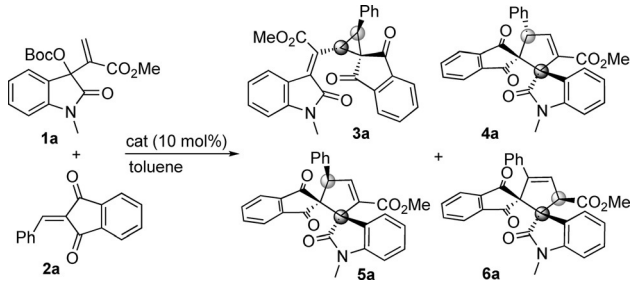
Morita–Baylis–Hillman (MBH) adducts and their derivatives are valuable building blocks in organic synthesis owing to their dense functionalities.[5] In this respect, Lu and coworkers first established interesting annulation pathways between MBH derivatives and various electrophiles, thus relying on the in situ formation of either zwitterionic allylic P or N ylides.[6] While MBH derivatives have widely served as 1,3-dipole synthons in asymmetric [3+2] reactions and other types of annulation reactions, almost all examples exhibited remote γ-regioselectivity. In addition, there are few reports on the realization of a switch in chemoselectivity from the same set of substrates in this field.[7] Moreover, a diastereodivergent annulation reaction with MBH adducts has not yet been accomplished. To address such deficiencies, herein we present annulation reactions of MBH carbonates, derived from isatins and 2-alkylidene-1*H*-indene-1,3(2*H*)-diones, with exclusive α-regioselectivity, wherein a switch in the chemo- and diastereoselectivities can be attained by employing different chiral Lewis base catalysts.

The initial reaction of the MBH carbonate **1a** and 2-benzylidene-1*H*-indene-1,3(2*H*)-dione[8] (**2a**) proceeded efficiently at room temperature in the presence of DABCO (10 mol%; Table 1, entry 1). An unusual [2+1] cyclopropane product[9] (**3a**) was cleanly obtained after 5 hours. The reaction exhibited exclusive diastereoselectivity, and the expected [3+2] annulation product was not observed. Ph_3P showed lower catalytic activity, but it delivered the α-regioselective [3+2] product **4a** in a moderate yield with high diastereoselectivity,[8] along with a few unidentified minor by-products (entry 2). Better catalysis was observed with Ph_2PMe, but results similar to those obtained with Ph_3P were obtained (entry 3). Interestingly, DMAP furnished the [3+2] product **5a**, thus demonstrating a switch in diastereoselectivity, in a good yield, and a minor unconjugated product (**6a**) was isolated with a moderate diastereoselectivity (entry 4). The yield of **6a** could be improved by simply extending the reaction time (entry 5), and almost complete conversion of **5a** into **6a** was observed by running the reaction at 50 °C for 24 hours (entry 6). In contrast, the DMAP-catalyzed reaction proceeded smoothly at 0 °C, and **5a** was produced in a high yield within 5 hours (entry 7).

Consequently, we investigated potential asymmetric versions under the catalysis of various chiral Lewis base catalysts. At first, α-isocupreine[10] (**C1** or α-IC; 10 mol%) was highly efficient for the reaction of **1a** and **2a** in toluene at ambient temperature, thus giving the desired [2+1] product **3a** in an excellent yield with high enantiomeric purity (Table 2, entry 1). The reaction proceeded well with 5 mol% of **C1**, though a longer reaction time was required (entry 2). Subsequently, different types of substrates were explored

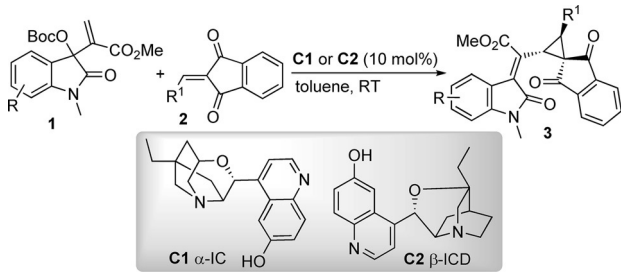
Table 1: Screening studies for annulation of **1a** and **2a**.[a]



Entry	Cat	*T* [°C]	*t* [h]	Yield [%][b]	d.r. [%][c]
1	DABCO	RT	5	**3a**, 82	>19:1
2[d]	Ph_3P	50	8	**4a**, 65	>19:1
3[d]	Ph_2PMe	RT	8	**4a**, 68	>19:1
4	DMAP	RT	12	**5a**, 70; **6a**, 21	>19:1; 4.8:1
5	DMAP	RT	24	**5a**, 45; **6a**, 42	>19:1; 4.8:1
6	DMAP	50	24	**5a**, <5; **6a**, 85	–; 4.5:1
7	DMAP	0	5	**5a**, 93; **6a**, <5	>19:1; –

[a] Unless otherwise noted, reactions were performed with 0.11 mmol of **1a**, 0.1 mmol of **2a**, 10 mol% of catalyst in 1.0 mL of toluene. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis. [d] With 20 mol% of catalyst. Boc = *tert*-butoxycarbonyl, DABCO = 1,4-diaza-bicyclo-[2.2.2]octane, DMAP = 4-dimethylaminopyridine.

Table 2: Substrate scope and limitations of [2+1] annulations.[a]



Entry	R	R^1	*t* [h]	Yield [%][b]	*ee* [%][c]
1	H	Ph	9 (9)	**3a**, 96 (95)	>99[d] (>−99)
2[e]	H	Ph	22	**3a**, 95	99
3	5-Cl	Ph	9	**3b**, 95	99
4	5-Br	Ph	9	**3c**, 94	98
5	7-F	Ph	10	**3d**, 94	97
6	5-NO_2	Ph	12	**3e**, 88	98
7	5-Me	Ph	9	**3f**, 97	98
8	5-MeO	Ph	9	**3g**, 98	>99
9	5,7-Me_2	Ph	9	**3h**, 95	97
10	H	2-ClC_6H_4	9 (9)	**3i**, 92 (90)	>99 (>−99)
11	H	4-ClC_6H_4	9	**3j**, 97	94
12	H	3-BrC_6H_4	9	**3k**, 97	99
13	H	4-MeC_6H_4	9	**3l**, 96	97
14	H	4-$MeOC_6H_4$	12	**3m**, 93	96
15	H	1-naphthyl	11	**3n**, 89	>99
16	H	2-naphthyl	12	**3o**, 91	>99
17	H	2-furyl	12	**3p**, 92	99
18	H	2-thienyl	12	**3q**, 90	>99
19[f]	H	*N*-Me-2-indolyl	12	**3r**, 87	>99
20[f]	H	2-styryl	12	**3s**, 82	>99
21[f]	H		12	**3t**, 83	98

[a] Unless noted otherwise, reactions were performed with MBH carbonate (**1**; 0.11 mmol), acceptor (**2**; 0.1 mmol), the catalyst **C1** (10 mol%) in toluene (1.0 mL) at RT. Data within parentheses were obtained with the catalyst **C2**. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase; d.r. >19:1 determined by ^{1}H NMR analysis. [d] The absolute configuration of **3a** was determined by X-ray analysis.[11] The other products were assigned by analogy. [e] With 5 mol% of **C1**. [f] At 50°C.

under the catalysis of **C1**. As summarized in Table 2, the scope was substantial, and high yields and stereoselectivities were generally obtained for substrates having various substitutions (entries 3–21). Nevertheless, the acceptors (**2**) with branched alkyl groups failed to give the cyclopropane products, probably because of the crowded structures. In contrast, optically pure **3a** and **3i**, having the opposite configuration, were obtained by using β-isocupreidine[10] (**C2** or β-ICD; entries 1 and 10; data within parentheses, respectively).

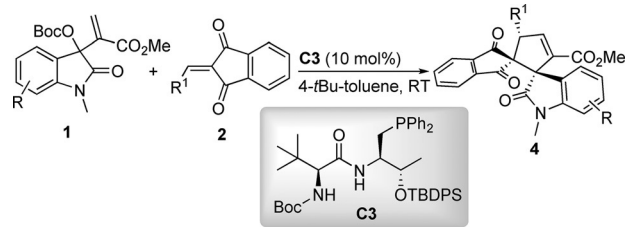
We next screened an array of chiral phosphines and reaction parameters to promote the asymmetric [3+2] annulations.[12] The bifunctional catalyst **C3**, developed by the group of Lu,[13] was optimal at a 10 mol% loading in 4-*tert*-butyltoluene. The desired [3+2] product **4a** was obtained after 24 hours at ambient temperature in an excellent yield and with a high *ee* value (Table 3, entry 1). As summarized, an array of MBH carbonates, derived from isatins and 2-alkylidene-1*H*-indene-1,3(2*H*)-diones, having a variety of aryl substitutions were well tolerated, thus giving the corresponding products in excellent yields and with good to high enantioselectivities (entries 2–13). At higher temperature, even alkyl-substituted electrophiles could be smoothly utilized (entries 14 and 15).

Interestingly, the bicyclic chiral phosphine **C4**, developed by the group of Kwon,[14] exhibited different diastereoselectivity compared with other chiral phosphines. The [3+2] product **5a** was obtained in a high yield and with remarkable stereoselectivity at 10°C by using 1,2-dichloroethane (DCE) and running the reaction for 36 hours (Table 4, entry 1). Importantly, a newly designed and more stable chiral DMAP-type compound,[12,15] **C5**, showed better catalytic activity, even at 0°C, thus affording the same chiral product with outstanding results after 24 hours (entry 1, data within parentheses). Therefore, we explored a number of substrates by using either **C4** or **C5** (entries 2–14). Excellent results were generally obtained, thus demonstrating the wide compatibility of both catalysts. **C5** was superior to **C4** in most cases, and was further verified for two acceptors having either an N-Me-2-indolyl or alkenyl group (entries 15 and 16).

As outlined in Scheme 1, the activated alkenes **7** and **9**, derived from cyclohexane-1,3-dione and Meldrum's acid, respectively, also exhibited high reactivity with **1a** in the presence of **C5**, thus producing the corresponding bis(spirocycle)s **8** and **10** in high yields and with excellent stereoselectivities.[16] In addition, after the asymmetric [3+2] annulation of **1a** and **2c** in DCE at 0°C, **C5** successfully promoted deconjugation to give **6j** by simply heating in THF at 50°C. The product **6j** was obtained in high yield, as well as enantio- and diastereoselectivity, thus further demonstrating the power of the current catalytic system to construct molecules with structural and stereochemical diversity.

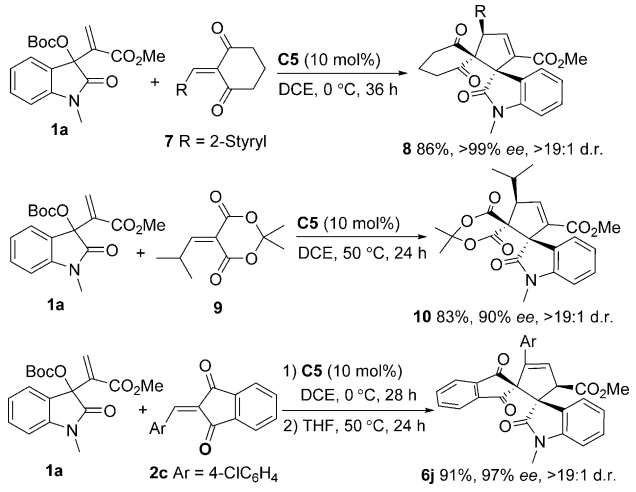
To rationalize the catalyst-controlled switch in annulations, density-functional theory (DFT) calculations were

Table 3: Substrate scope and limitations of [3+2] annulations to access **4**.[a]



Entry	R	R^1	*t* [h]	Yield [%][b]	*ee* [%][c]
1	H	Ph	24	**4a**, 93	87
2	5-Cl	Ph	28	**4b**, 92	85
3	5-Br	Ph	28	**4c**, 92	86
4	7-F	Ph	28	**4d**, 90	85
5	5-Me	Ph	24	**4f**, 95	85
6	5-MeO	Ph	24	**4g**, 93	86[d]
7	H	2-ClC_6H_4	20	**4i**, 91	89
8	H	4-ClC_6H_4	20	**4j**, 96	87
9	H	3-BrC_6H_4	24	**4k**, 95	79
10	H	4-MeC_6H_4	24	**4l**, 92	88
11[e]	H	4-$MeOC_6H_4$	10	**4m**, 80	94
12	H	1-naphthyl	30	**4n**, 86	92
13	H	2-naphthyl	25	**4o**, 89	81
14[e]	H	*c*Pentyl	12	**4u**, 83	85
15[e]	H	*c*Hexyl	12	**4v**, 80	82

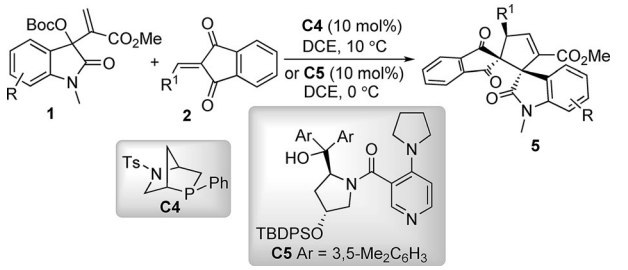
[a] Unless noted otherwise, reactions were performed with MBH carbonate (**1**; 0.11 mmol) and acceptor (**2**; 0.1 mmol), the catalyst **C3** (10 mol%) in toluene (1.0 mL) at RT. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase; d.r. > 19:1 determined by ^{1}H NMR analysis. [d] The absolute configuration of **4g** was determined by X-ray analysis.[11] The other products were assigned by analogy. [e] At 50 °C. TBDPS = *tert*-butyldiphenylsilyl.



Scheme 1. Additional substrates to explore products having structural diversity.

performed. The geometries of the intermediates and transition states (TSs) were optimized using the B3LYP functional together with the standard 6-31G(d) basis set, and the energies were calculated at the 6-31++G(d,p) level of theory (toluene as solvent).[12] We focused on the ring-closure step after the initial Michael addition of the ylide intermediate of **1a** to **2a**, a step which determines the final product

Table 4: Substrate scope and limitations of [3+2] annulations to access **5**.[a]



Entry	R	R^1	*t* [h]	Yield [%][b]	*ee* [%][c]
1	H	Ph	36 (24)	**5a**, 95 (98)	99 (99)
2	5-Cl	Ph	48 (28)	**5b**, 92 (95)	96 (>99)
3	5-Br	Ph	48 (28)	**5c**, 90 (93)	96 (>99)
4	7-F	Ph	48 (28)	**5d**, 89 (96)	96 (>99)
5	5-NO_2	Ph	48	**5e**, 94	94
6	5-Me	Ph	32 (24)	**5f**, 95 (97)	97 (93)
7	5-MeO	Ph	32 (24)	**5g**, 94 (95)	97 (95)
8	H	4-ClC_6H_4	28 (24)	**5j**, 90 (94)	97 (96)
9	H	3-BrC_6H_4	32 (24)	**5k**, 89 (92)	89 (96)
10	H	4-MeC_6H_4	32 (24)	**5l**, 92 (98)	97 (>99)
11	H	4-$MeOC_6H_4$	36 (28)	**5m**, 93 (96)	97 (>99)
12	H	2-naphthyl	36 (28)	**5o**, 88 (94)	94 (91)
13	H	2-furyl	36	**5p**, 89	90[d]
14	H	2-thienyl	36 (24)	**5q**, 83 (93)	89 (>99)
15	H	*N*-Me-2-indolyl	24 (36)	**5r**, – (93)	– (74)
16	H		24 (36)	**5t**, – (95)	– (70)

[a] Unless noted otherwise, reactions were performed with MBH carbonate (**1**; 0.11 mmol), acceptor (**2**; 0.1 mmol), the catalyst **C4** (10 mol%) in DCE (1.0 mL) at 10 °C. Data within parentheses were obtained with the catalyst **C5** at 0 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase; d.r. > 19:1 by ^{1}H NMR analysis. [d] The absolute configuration of **5p** was determined by X-ray analysis.[11] The other products were assigned by analogy. DCE = 1,2-dichloroethane, Ts = 4-toluenesulfonyl.

(Figure 1). In the reaction catalyzed by DABCO, the newly formed carbanion could attack the α-position through an S_N2 process via **TS2-A** to produce **3a**. In contrast, a sequential Michael addition could occur via **TS2-B**, thus generating **4a**. The energy barrier of **TS2-B** is 19.7 kcal mol^{-1} higher than that of **TS2-A**, thus indicating that the [3+2] process is unfavorable. The calculation is consistent with the experimental results in entry 1 of Table 1. Since the reaction catalyzed by DMAP also involved an N-ylide intermediate, the annulation selectivity was compared. Interestingly, the energy of **TS2-C**, which could lead to **5a**, is 4.2 kcal mol^{-1} lower than that of **TS2-D** which leads to **3a**, thus suggesting that the [3+2] pathway was favorable for the DMAP-catalyzed annulation reaction. Moreover, as shown in **TS2-B**, the distances between H^1 and H^2, and H^3 and H^4 are 1.91 Å and 1.98 Å, respectively, whereas the distance between C^1 and N^1 is 1.65 Å, which is much longer than that of normal C–N bond (1.53 Å in **TS2-C**). Therefore, the steric hindrance from DABCO in the [3+2] pathway is the main contribution to the switch in selectivity to the [2+1] reaction.[17] In contrast, we also studied the switch in diastereoselectivity observed with DMAP and PPh_3. As illustrated, **TS2-E** is the more feasible TS leading to **4a**, and its energy is 9.2 kcal mol^{-1} higher than

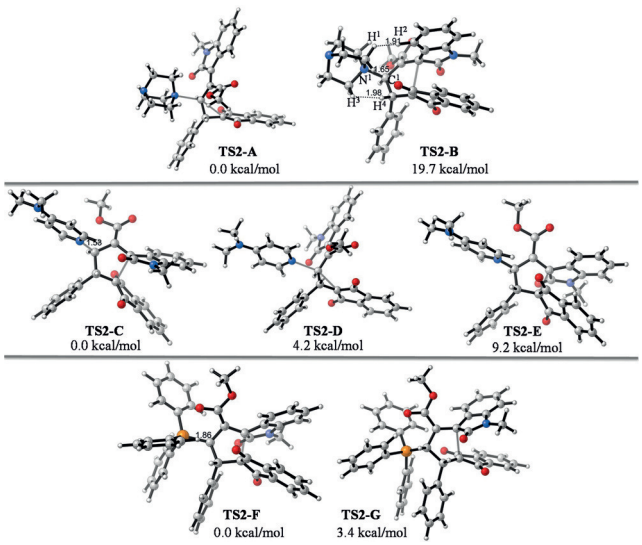


Figure 1. Optimized structures and Gibbs free energies of **TS2-A** to **TS2-G**. The bond distances of the optimized structures are in Å.

that of **TS2-C**, which leads to **5a**. For the reaction catalyzed by Ph_3P, **TS2-F** and **TS2-G** were calculated as reasonable TSs to produce **4a** and **5a**, respectively. The energy of **TS2-F** to produce **4a** is 3.4 kcal mol^{-1} lower than that of **TS2-G**, meaning that **4a** would be the main product in the Ph_3P-catalyzed reaction. The steric hindrance of Ph_3P may be the main factor leading to the diastereoselectivity, as Ph_3P and Ph in **TS2-G**, located at the same side of C–C bond, result in steric interactions. In accordance with the experimental results, use of the less congested **C4** produced **5a** when using DMAP as the catalyst.

In conclusion, we have investigated the asymmetric annulation reactions of Morita–Baylis–Hillman carbonates, derived from isatins and 2-alkylidene-1*H*-indene-1,3(2*H*)-diones, catalyzed by various chiral Lewis bases, thus leading to a switch in chemo- and diastereoselectivity. While [2+1] reactions catalyzed by chiral tertiary amines, derived from cinchona alkaloids, produced densely substituted cyclopropanes, diastereodivergent [3+2] annulations to generate bis(spirocycl)ic oxindoles were successfully realized by employing either a chiral phosphine or a DMAP-type catalyst. All reactions exhibited exclusive α-regioselectivity and excellent chemoselectivity, and good to outstanding stereoselectivity, thus furnishing a collection of complex compounds having structural and stereogenic diversity. Moreover, DFT calculations elucidated the catalyst-based switch in the annulation mechanism, and should thus be helpful for developing other asymmetric annulation reactions with MBH derivatives. Additional results will be reported in due course.

Acknowledgments

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Keywords: annulations · density-functional calculations · diastereoselectivity · heterocycles · organocatalysis

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