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Tertiary Amine-Catalyzed Chemoselective and Asymmetric [3 + 2] Annulation of Morita–Baylis–Hillman Carbonates of Isatins with Propargyl Sulfones

Jing Peng,[†] Xin Huang,[†] Lin Jiang,[†] Hai-Lei Cui,[†] and Ying-Chun Chen*[,†,‡]

Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry, Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, China, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China

ycchenhuaxi@yahoo.com.cn

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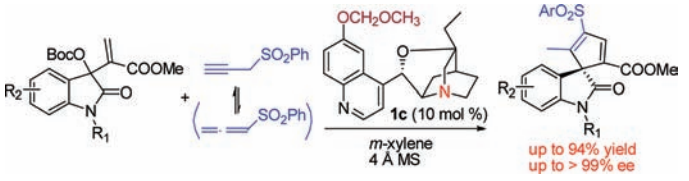
ABSTRACT



A chemo- and enantioselective [3 + 2] annulation of Morita–Baylis–Hillman carbonates of isatins with propargyl sulfones was catalyzed by a β-ICD *O*-MOM ether 1c, affording spirocyclic 2-oxindoles bearing an unusual cyclopentadiene motif in outstanding ee values (up to >99%). More electrophiles, such as *N*-phenylmaleimide, have been also utilized to deliver complex spirocyclic 2-oxindoles with good results.

The densely functionalized β-hydroxyl α-methylene carbonyl compounds, the so-called Morita–Baylis–Hillman (MBH) products, have attracted much attention in synthetic organic chemistry over the past decades.[1] As much effort has been devoted to the development of an enantioselective (aza) MBH reaction,[2] recently, there has been an increasing interest focused on the catalytic dynamic asymmetric transformations of racemic MBH products. In particular, great progress has been made in the asymmetric allylic alkylation of MBH carbonates or acetates catalyzed by either chiral Pd complexes[3] or organic tertiary phosphines and amines.[4,5] An asymmetric Michael addition–elimination pathway for MBH adducts has been also reported but with very limited examples.[6] On the other hand, Lu and others have presented a series of phosphine

[†] West China School of Pharmacy.
[‡] West China Hospital.

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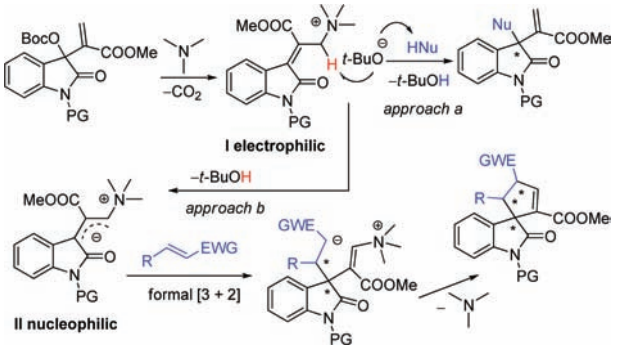
(or sulfide)-catalyzed [3 + 2], [3 + 4], or [3 + 6] annulation reactions of MBH derivatives via allylic *P* (or *S*)-ylide intermediates;[7] unfortunately, the asymmetric variants have been poorly developed,[8] except for a notable chiral bisphosphine-catalyzed [3 + 2] example presented by Barbas very recently.[9] Therefore, the development of a catalytic system that can realize the asymmetric annulations of MBH derivatives to construct enantioenriched carbo- or heterocycles would be highly desirable, especially with more air-stable Lewis basic amines.

Recently, we reported an electrophilic process to deliver 2-oxindoles bearing C3-quaternary stereocenters through asymmetric allylic alkylation of MBH carbonates of isatins (Scheme 1, *approach a*) by the catalysis of *β*-isocupreidine **1a** (*β*-ICD; see Table 1).[10] We envisioned that, as a result of the highly electron-withdrawing ability of the 2-oxindole motif, the vinylogous proton of the ammonium **I** would be easily removed by the *in situ* generated *tert*-butoxy anion *in the absence of an additional acidic reagent*, thus forming a nucleophilic *N*-ylide **II** (*approach b*).[11] Subsequently, an asymmetric [3 + 2] annulation to construct chiral five-membered spirocyclic 2-oxindoles, which have been witnessed in numerous biologically active materials,[12] would be achieved by the reaction with suitable activated unsaturated systems.[13] It should be noted that tertiary amines have been rarely applied in the transformations of MBH adducts via allylic *N*-ylides even in a racemic manner.[14]

Scheme 1. Tertiary Amine-Catalyzed Asymmetric Transformations of MBH Carbonates Derived from Isatins



Although the initial screenings in the DABCO-catalyzed reactions of MBH carbonate **2a** with a few activated olefins, such as methyl acrylate, vinyl phenyl sulfone, and chalcone, *etc*., resulted in no success at room temperature,[15] we were able to detect a spirocyclic 2-oxindole product **4a** incorporating a cyclopentadiene moiety when a propargyl phenyl sulfone **3a** was applied (***3a*** *easily isomerizes to allenyl phenyl sulfone by base catalysis, which should be the actual electrophile*),[16] albeit in very low yield (Table 1, entry 1). Hence the expected [3 + 2] annulation occurred, followed by a domino isomerization sequence to give the thermally more stable conjugated counterpart. Nevertheless, sulfone **3a** was consumed rapidly because of its self-dimerization and other side reactions by nucleophilic amine catalysis.[17,18] To our delight, we observed that chiral *β*-ICD **1a** exhibited a highly catalytic preference to [3 + 2] annulation pathway, though the yield was still unsatisfying due to the sluggish conversion, while the enantioselectivity was inspiring (entry 2).[19] The reaction could be slightly enhanced by adding 4 Å molecular sieves (entry 3). We reasoned that the acidic hydroxyl group of *β*-ICD **1a** would affect the deprotonation of intermediate **I** to generate active *N*-ylide **II**. Later it was very pleasing to find that the desired reaction could be greatly accelerated by the catalysis of *β*-isoquinidine **1b**,[20] and more importantly, excellent enantioselectivity was obtained (entry 4).[21] Subsequently, a few modified *β*-ICD derivatives **1c**–**1i** in consideration of steric and electronic features were further prepared and tested (entries 5–11), and the best results in regard to yield and ee were gained by applying a new *β*-ICD *O*-MOM ether **1c** as the catalyst (entry 5). It should be noted that the catalytic efficacy was dramatically decreased when *β*-ICD *O*-triflate **1e** and *β*-isocinchonine **1i** were used, indicating that the electron-rich characteristics of Lewis bases are significant to the catalysis (entries 7 and 11). In addition, the annulation could proceed smoothly at

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(18) Propargyl phenyl sulfone **3a** was also consumed rapidly in the presence of a tertiary phosphine such as Ph_3P.

(19) Simple quinidine or $(DHQD)_2AQN$ showed no catalytic activity, while quinidine *O*-Me or quinine *O*-Me ether afforded poor results (28%, 30% ee, or 36%, −46% ee, respectively).

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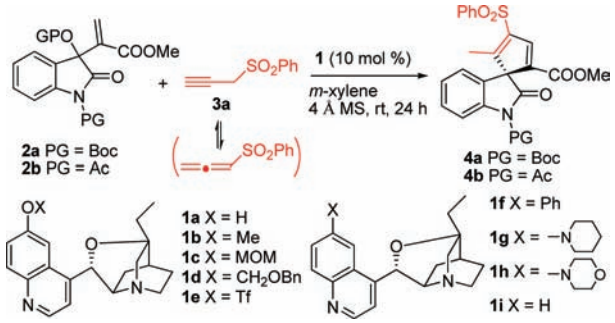
(21) Other solvents (toluene, $PhCF_3$, DCM, $CHCl_3$, and 1,4-dioxane) could be well tolerated (> 80% yield, 85–90% ee).

Table 1. Screening Studies of [3 + 2] Annulation of MBH Carbonate **2a** and Propargyl Phenyl Sulfone **3a**[a]



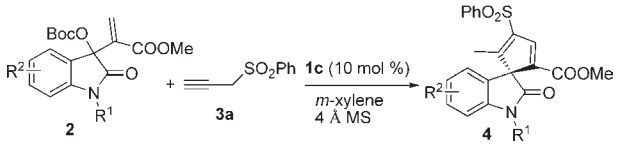
entry	cat.	yield[b] (%)	ee[c] (%)
1[d]	DABCO	<20	–
2[d]	**1a**	22	50
3	**1a**	40	50
4	**1b**	80	91
5	**1c**	82	94
6	**1d**	75	94
7	**1e**	40	45
8	**1f**	61	86
9	**1g**	62	91
10	**1h**	80	75
11	**1i**	63	7
12[e]	**1c**	84	99
13[f]	**1c**	34	94
14[e,g]	**1c**	72	99

[a] Unless otherwise noted, reactions were performed with 0.12 mmol of **2a**, 0.1 mmol of **3a**, 0.01 mmol of catalyst, and 4 Å MS (30 mg) in *m*-xylene (1 mL) at rt under aerobic conditions. [b] Yield of isolated product **4a**. [c] Determined by HPLC on a chiral stationary phase. [d] Without adding 4 Å MS. [e] At 0 °C. [f] **2b** was used, and the data were related to **4b**. [g] At 0.5 mmol scale.

0 °C, and the enantiomerically pure product **4a** was isolated in high yield (entry 12). MBH acetate **2b** exhibited a much lower reactivity with sulfone **3a** under the same conditions, probably because the CH_3CO_2 anion could not efficiently produce the reactive *N*-ylide on account of its decreased basicity (entry 13). Finally, we tested the reaction at a larger scale by the catalysis of **1c**. The same enantiopure product could be obtained with good yield (entry 14).

Consequently, we investigated a number of MBH carbonates **2** derived from diverse isatins with propargyl phenyl sulfone **3a** by the catalysis of β-ICD *O*-MOM ether **1c**. The results are summarized in Table 2. A *N*-methyl protected 2-oxindole substrate showed the similar reactivity and enantiocontrol in the annulation reaction (Table 2, entry 2). MBH carbonates bearing electron-donating substituents on the aryl ring exhibited better reactivity, and excellent yields and enantioselectivity were obtained (entries 3–5). On the other hand, a slower reaction rate was observed for 2-oxindole substrates with electron-withdrawing groups even at room temperature, but the ee values were still remarkable (entries 6–11). Nevertheless, the introduction of a *N*-methyl group in such a type of

Table 2. Substrate Scope in [3 + 2] Annulation of MBH Carbonates **2** and Propargyl Phenyl Sulfone **3a**[a]

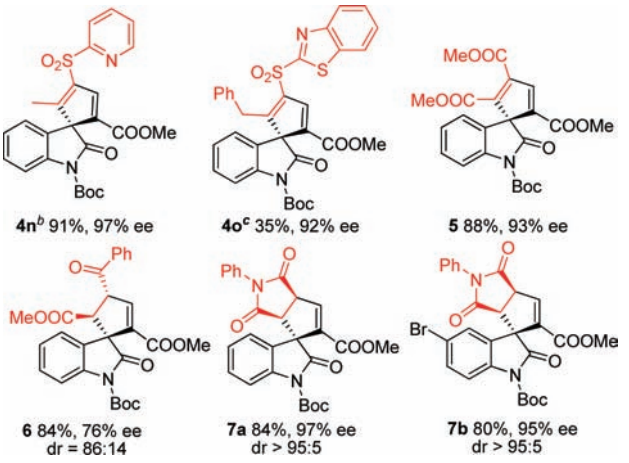


entry	R^1	R^2	temp (°C)	*t* (h)	yield[b] (%)	ee[c] (%)
1	Boc	H	0	24	**4a**, 84	99[d]
2	Me	H	0	24	**4c**, 87	98
3	Boc	5-Me	0	12	**4d**, 94	98
4	Boc	5-MeO	0	12	**4e**, 93	>99
5	Boc	5,7-Me_2	0	12	**4f**, 88	96
6	Boc	5-F	rt	24	**4g**, 72	95
7	Boc	5-Cl	rt	24	**4h**, 74	97
8	Boc	5-Br	rt	24	**4i**, 63	97
9	Boc	5-I	rt	24	**4j**, 81	97
10	Boc	5-CF_3O	rt	24	**4k**, 83	97
11	Boc	7-F	rt	24	**4l**, 71	91
12	Me	5-Br	0	12	**4m**, 82	96

[a] Reactions were performed with 0.12 mmol of **2**, 0.1 mmol of **3a**, 0.01 mmol of **1c**, and 4 Å MS (30 mg) in *m*-xylene (1 mL). [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] The absolute configuration of **4a** was determined by X-ray analysis; see the Supporting Information. The other products were assigned by analogy.

substrates could provide beneficial effects on the annulation process (entry 12 vs 8).

Scheme 2. More Expansions of [3 + 2] Annulations[a]



[a] Unless otherwise noted, reactions were performed with 0.12 mmol of MBH carbonate, 0.1 mmol of electrophile, 0.01 mmol of **1c**. and 4 Å MS (30 mg) in *m*-xylene (1 mL) at rt for 24 h. [b] At 0 °C for 12 h. [c] For 48 h.

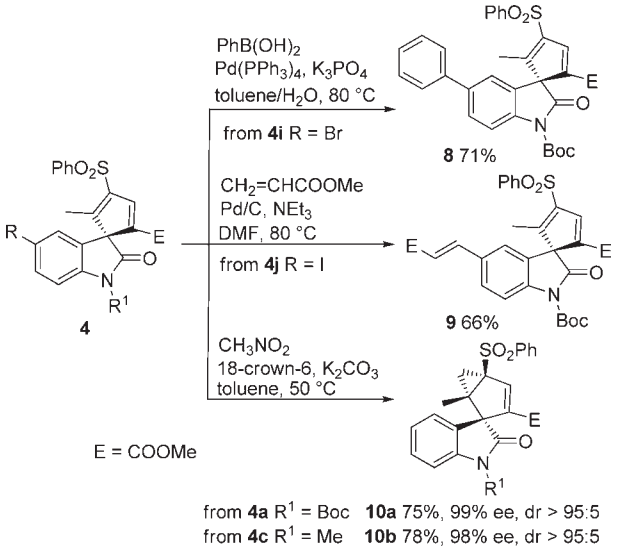
We explored more propargyl sulfones and other electrophiles in **1c**-catalyzed [3 + 2] annulations. A propargyl 2-pyridyl sulfone afforded excellent results (Scheme 2, **4n**). Nevertheless, the reaction became quite sluggish for a γ-substituted propargyl sulfone even bearing a more electron-withdrawing benzothiazol-2-yl group, while the

enantioselectivity was still satisfactory (**4o**). Dimethyl but-2-ynedioate reacted with MBH carbonate **2a** smoothly, and a multifunctional product **5** was produced in high yield and enantiopurity. On the other hand, some activated olefins have been tested for the synthesis of 2-oxindoles with a spiro cyclopentene structure.[9] The reaction of methyl (*E*)-4-oxo-4-phenyl-but-2-enoate and **2a** proceeded well at room temperature, but the diastereo- and enantioselectivity of adduct **6** were moderate. Importantly, *N*-phenylmaleimide could be efficiently utilized, and tetracyclic heterocycles **7a** and **7b** were prepared with remarkable dr and *ee* values. Nevertheless, other activated olefins, such as nitroolefins, did not provide the desired cycloadducts under current catalytic conditions and remain to be explored.

The multifunctional anulation adducts allow some synthetic transformations with high chemo- and regioselectivity. As outlined in Scheme 3, the Pd-catalyzed Suzuki or Heck reaction could be smoothly conducted with halo-substituted products **4i** or **4j**, thus delivering the further functionalized spirocyclic oxindoles **8** and **9**, respectively, without affecting the cyclopentadiene moiety. More importantly, we found that an α,β-unsaturated sulfone motif exhibits higher electrophilicity, and a [2 + 1] annulation occurred with remarkable diastereoselectivity by employing CH_3NO_2 as a nucleophilic methylene transfer reagent.[22] The fused cyclopropane derivatives **10a** and **10b** bearing three contiguous quaternary chiral centers were efficiently constructed with retained enantiopurity.[23]

In conclusion, we have developed the first highly chemo- and enantioselective [3 + 2] annulation of Morita–Baylis–Hillman carbonates of isatins with propargyl sulfones by the catalysis of a chiral tertiary amine β-ICD *O*-MOM ether (up to >99% ee). The reaction proceeds via formal dipolar cycloaddition of *in situ* generated allylic *N*-ylide and allenyl sulfone followed by a C=C bond isomerization sequence, giving an efficient protocol to construct spirocyclic 2-oxindoles incorporating an unusual cyclopentadiene motif. Moreover, the catalytic system has been expanded to the synthesis of spirocyclic 2-oxindoles with more structural diversity, which might be useful in medicinal chemistry. Currently studies are actively underway to investigate the catalytic and synthetic utilities reported in this work.

Scheme 3. Synthetic Transformations of Multifunctional Adducts



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Supporting Information Available. Experimental procedures, structural proofs, NMR spectra and HPLC chromatograms of the products, cif files of enantiopure **4a**, **7b**, and **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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