Organic LETTERS

Letter

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Divergent Cyclization Reactions of Morita–Baylis–Hillman Carbonates of 2-Cyclohexenone and Isatylidene Malononitriles

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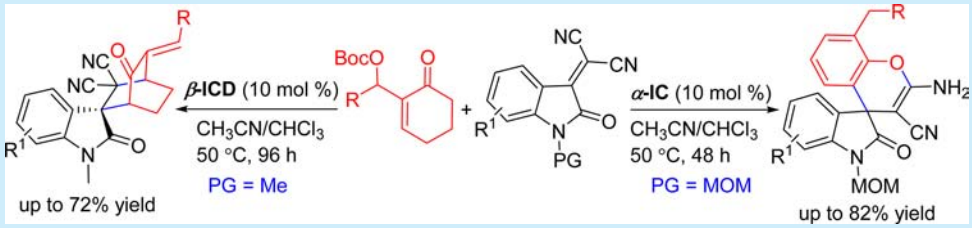
Supporting Information

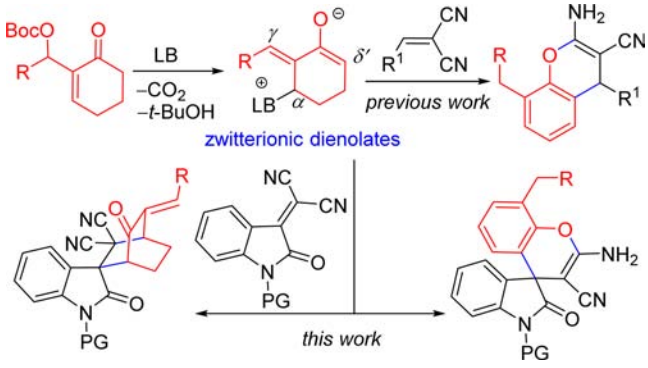


ABSTRACT: Zwitterionic dienolates generated from Morita–Baylis–Hillman carbonates of cyclohexen-2-one and a phenolic tertiary amine catalyst underwent divergent cyclization reactions with isatylidene malononitriles. A new [4 + 2] stepwise cyclization process was disclosed to deliver complex bridged spirooxindoles after the initial δ′-regioselective Rauhut–Currier-type reaction with *N*-methyl electrophiles by the catalysis of β-isocupreidine, while spirooxindoles incorporating an aromatic chromene motif were generated with *N*-MOM acceptors in the presence of α-isocupreine through different domino transformations.

Morita–Baylis–Hillman (MBH) alcohols and related derivatives represent synthetically useful reagents owing to their multifunctional characteristics.[1] A diversity of versatile transformations have been developed over the past decades, and they still attract research interest in modern organic chemistry.[2] In particular, great progress has been made in the field with MBH carbonates or acetates of simple acrylates or vinyl ketones under the catalysis of tertiary amines or phosphines, in both allylic alkylations[3] and various [3 + *n*] or other cyclization reactions.[4] Nevertheless, there are fewer studies on MBH derivatives from β-substituted activated alkenes, such as cyclohexen-2-one and cyclopenten-2-one, likely due to the decreased catalytic activity and reactivity of tertiary amines or phosphines toward such sterically hindered substances.[5]

Recently, we found that zwitterionic dienolates could be generated from MBH carbonates of cyclohexen-2-one in the presence of DABCO or β-isocupreidine (β-ICD), and a δ′-regioselective extended Rauhut–Currier-type reaction with alkylidene malononitriles occurred to furnish densely functionalized chromene derivatives after a domino cyclization and isomerization process, as illustrated in Scheme 1.[6] These results suggest that MBH carbonates of cyclohexen-2-one could provide more reaction feasibilities than those of simple acrylates. In our ongoing efforts to expand the application of such zwitterionic dienolates, here we would like to disclose a previously uncovered δ′,α-regioselective [4 + 2] cyclization pathway when assembling them with isatylidene malononitriles,[7] effectively constructing spirooxindoles bearing a bridged bicyclo[2.2.2]octane skeleton.[8] Interestingly, the analogous domino reaction to that of simple alkylidene manolonitriles also could be realized through tuning the *N*-protective group of isatylidene malononitriles and the tertiary amine catalyst, thus granting divergent strategies to access structurally different spirooxindoles with high molecular complexity from the similar substrate combinations (Scheme 1).

Scheme 1. Divergent Cyclization Pathways of MBH Carbonates of Cyclohexen-2-one and Isatylidene Malononitriles



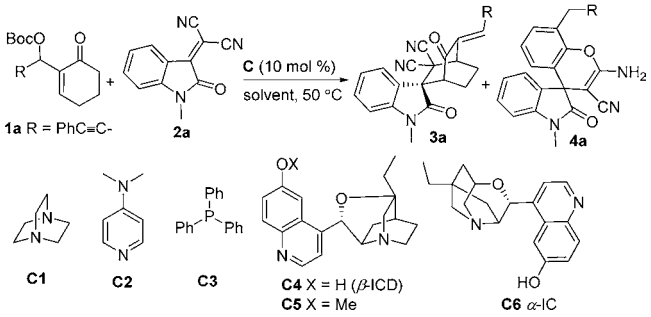
The initial studies on the reaction of MBH carbonate **1a** and *N*-methyl isatylidene malononitrile **2a** in CH_3CN were not

Received: July 26, 2015
Published: September 2, 2015

DOI: 10.1021/acs.orglett.5b02157
Org. Lett. 2015, 17, 4490–4493

successful by the catalysis of either DABCO **C1** or DMAP **C2**, and no major products could be isolated at 50 °C for 48 h (Table 1, entries 1 and 2). Almost no conversion occurred in

Table 1. Screening Conditions of Cyclization Reaction of MBH Carbonate 1a and Isatylidene Malononitrile 2a[a]



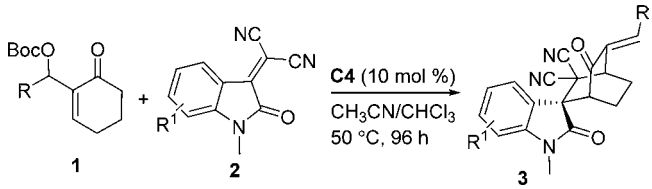
entry	cat.	solvent	t/h	yield/%[b]	ee/%[c]
1	**C1**	CH_3CN	48	–	–
2	**C2**	CH_3CN	48	–	–
3	**C3**	CH_3CN	48	NR	–
4	**C4**	CH_3CN	48	**3a**, 40	0
5	**C5**	CH_3CN	48	**3a**, 18	–
6	**C6**	CH_3CN	48	**3a**, 25; **4a**, 25	0; 11
7	**C4**	toluene	48	**3a**, <10	–
8	**C4**	THF	48	**3a**, <10	–
9	**C4**	$CHCl_3$	48	**3a**, <10	–
10	**C4**	mixture[d]	48	**3a**, 56	–
11	**C4**	mixture[d]	96	**3a**, 72; **4a**, <10	–

[a]Unless otherwise noted, reactions were performed with 0.1 mmol of **1a**, 0.12 mmol of **2a**, and 10 mol % of catalyst **C** in 1.0 mL of solvent at 50 °C. [b]Isolated yield. [c]Based on chiral HPLC analysis. [d]A mixture of $CH_3CN/CHCl_3$ (0.5/0.5 mL) was used.

the presence of Ph_3P (entry 3). To our gratification, β-isocupreidine (β-ICD, **C4**) exhibited better catalytic activity, and product **3a** could be isolated in 40% yield. In contrast to the previous report,[6] product **3a** was generated from a different [4 + 2] stepwise cyclization[9] after the initial δ′-regioselective Rauhut−Currier-type reaction with acceptor **2a**.[10] The resulted carboanion directly replaced the ammonium moiety to furnish a bridged bicyclo[2.2.2]octane structure in exclusive diastereoselectivity. Unfortunately, no enantioselectivity could be induced, probably because the δ′-site is very far from the chiral catalyst (entry 4).[6] A lower yield was obtained by using *O*-methyl β-ICD **C5** (entry 5). When α-isocupreine (α-IC, **C6**) was used, an aromatic chromene derivative **4a** was produced in accordance with the former reaction pathway,[6,11] along with the new [4 + 2] product **3a**, but both in low yields and with no or very poor enantiocontrol (entry 6).[12] Consequently, we investigated a few solvents under the catalysis of β-ICD **C4**, but giving very disappointing results (entries 7−9). As better solubility of acceptor **2a** was observed in $CHCl_3$, we explored the catalytic reaction in a mixture of CH_3CN and $CHCl_3$ and pleasingly found that a higher yield could be attained after 48 h (entry 10). Moreover, almost full conversion could be achieved by extending the reaction time to 96 h, and product **3a** was isolated in 72% yield. It should be noted that high chemoselectivity was observed under the optimized catalytic conditions, as the chromene derivative **4a** was formed in less than 10% yield (entry 11).

Consequently, we examined the substrate scope and limitations of the new [4 + 2] stepwise cyclizations for the construction of complex bridged spirooxindoles **3**. The results are summarized in Table 2. At first, a variety of MBH

Table 2. Scope of [4 + 2] Cyclization To Access Bridged Spirooxindoles[a]



entry	R	R^1	yield/%[b]
1	PhC≡C–	H	**3a**, 72
2	4-MeOPhC≡C–	H	**3b**, 65
3	4-ClPhC≡C–	H	**3c**, 62
4	PhCH=CH–	H	**3d**, 70
5	4-NO_2PhCH=CH–	H	**3e**, 52
6	Ph	H	**3f**, 48
7	4-MePh	H	**3g**, 39
8	PhC≡C–	5-MeO	**3h**, 69
9	PhC≡C–	5-Cl	**3i**, 61
10	PhCH=CH–	5-MeO	**3j**, 56
11	PhCH=CH–	5,7-Me_2	**3k**, 54
12	PhCH=CH–	5-F	**3l**, 59
13	PhCH=CH–	5-Cl	**3m**, 55
14	PhCH=CH–	5-Br	**3n**, 62
15	PhCH=CH–	7-F	**3o**, 55
16	Ph	5-MeO	**3p**, 42
17	Ph	5-Cl	**3q**, 33

[a]Reactions were performed with MBH carbonate **1** (0.1 mmol), isatylidene malononitrile **2** (0.12 mmol), and β-ICD **C4** (10 mol %) in $CH_3CN/CHCl_3$ (0.5/0.5 mL) at 50 °C for 96 h. [b]Isolated yield.

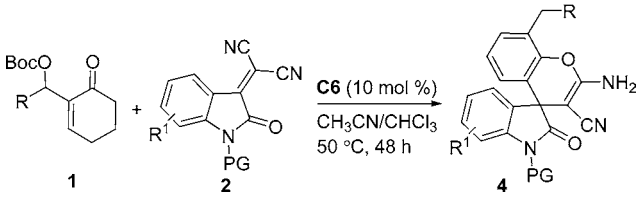
carbonates were explored in reactions with *N*-methyl isatylidene malononitrile **2a**. Similar moderate yields were obtained for MBH carbonates derived from cyclohexen-2-one and other aryl propiolaldehydes and cinnamaldehydes (Table 2, entries 1−5). Nevertheless, MBH carbonates from aryl aldehdyes exhibited lower reactivity, and only fair yields were attained under the same catalytic conditions (entries 6 and 7). In addition, the bridged products could not be produced by using MBH carbonates of aliphatic aldehydes. Moreover, MBH carbonates of cyclopenten-2-one also failed to participate in this type of [4 + 2] cyclization reaction.[5c] On the other hand, isatylidene malononitriles bearing various electron-donating or -withdrawing groups on the aryl ring could be well tolerated in reactions with phenylpropiolaldehyde or cinnamaldehyde-derived MBH carbonates, and the corresponding products **3h−3o** were generally furnished in modest yields (entries 8−15), while fair yields were still observed with benzaldehyde derived MBH carbonate (entries 16 and 17).

As the spirooxindole incorporating a chromene motif could be generated under the catalysis of α-IC **C6** albeit in a low yield, it would be intriguing that such an architecture could be produced more effectively. As a result, the divergent cyclization reactions would provide diverse spirooxindoles from the same set of starting materials. Since the cleaner reaction was observed with cinnamaldehyde-derived MBH carbonate, we further screened the reaction of such type of MBH carbonate and

DOI: 10.1021/acs.orglett.5b02157
Org. Lett. 2015, 17, 4490−4493

isatylidene malononitrile in a mixture of $CH_3CN/CHCl_3$ by the catalysis of α-IC **C6**. As summarized in Table 3, entry 1, it was

Table 3. Scope for the Synthesis of Chromene Derivatives[a]



entry	R	R^1	PG	yield/%[b]
1	PhCH=CH–	H	allyl	**4b**, 63
2	PhCH=CH–	H	Bn	**4c**, 80
3	PhCH=CH–	H	MOM	**4d**, 82
4	PhC≡C–	H	MOM	**4e**, 67
5	Ph	H	MOM	**4f**, 66
6	PhCH=CH–	5-MeO	MOM	**4g**, 81
7	PhCH=CH–	5,7-Me_2	MOM	**4h**, 80
8	PhCH=CH–	5-F	MOM	**4i**, 78
9	PhCH=CH–	5-Cl	MOM	**4j**, 77
10	PhCH=CH–	5-Br	MOM	**4k**, 65
11	PhCH=CH–	7-F	MOM	**4l**, 60

[a]Reactions were performed with MBH carbonate **1** (0.1 mmol), isatylidene malononitrile **2** (0.12 mmol), and α-IC **C6** (10 mol %) in $CH_3CN/CHCl_3$ (0.5/0.5 mL) at 50 °C for 48 h. [b]Isolated yield.

pleasing that the formation of chromene product **4b** could be greatly favored through simply replacing the *N*-methyl electrophile with a *N*-allyl one. Moreover, the yields could be further improved by using a *N*-benzyl or -MOM electrophile, respectively (entries 2 and 3).

With the optimized catalytic conditions in hand, we explored more MBH carbonates of cyclohexen-2-one and *N*-MOM isatylidene malononitriles. Both phenylpropiolaldehyde and benzaldehdye-derived carbonates also showed good reactivity with *N*-MOM isatylidene malononitrile, and the chromene products were obtained in moderate yields (Table 3, entries 4 and 5). On the other hand, a number of *N*-MOM electrophiles with diverse substitutions on the aryl ring were investigated in reactions with cinnamaldehyde-derived MBH carbonate, and the corresponding chromene derivatives were efficiently produced in modest to good yields (entries 6–11).

As illustrated in Figure 1, crystals suitable for X-ray diffraction analysis were smoothly obtained from both [4 + 2] product **3e** and chromene **4c**. Thus, the corresponding architectures from divergent cyclization reactions could be unambiguously assigned accordingly.

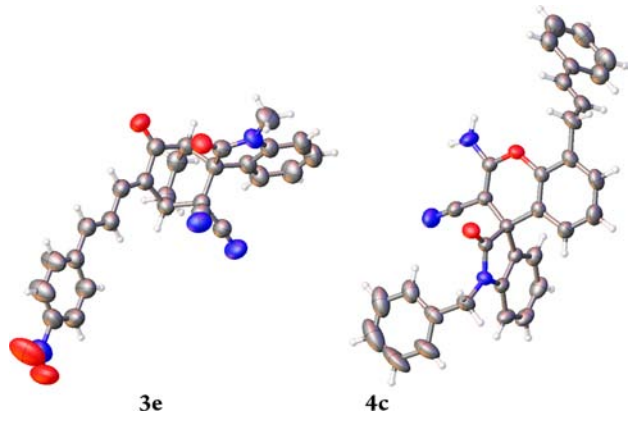
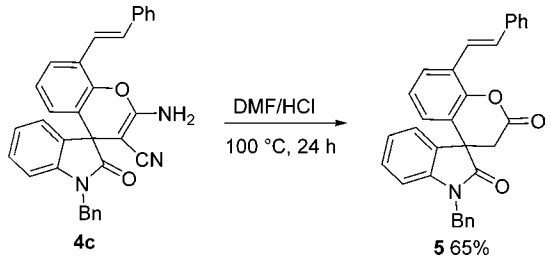


Figure 1. X-ray structures of [4 + 2] product **3e** and chromene **4c**.

Using the procedure reported previously,[6] a spirooxindole **5** incorporating a chroman-2-one motif could be produced from **4c** in a moderate yield, through acid-promoted hydrolysis and a subsequent decarboxylation reaction (Scheme 2).

Scheme 2. Transformation of Chromene Product 4c



In summary, we have explored the assembly of MBH carbonates of cyclohexen-2-one and isatylidene malononitriles catalyzed by phenolic tertiary amines derived from cinchona alkaloids. Divergent cyclization pathways have been realized after the initial δ'-regioselective Rauhut–Currier-type reaction of zwitterionic dienolates to acceptors, through tuning the *N*-protective group of acceptors and the amine catalyst. Spirooxindoles bearing a bridged bicyclo[2.2.2]octane skeleton and adjacent quaternary centers were obtained through a δ',α-regioselective [4 + 2] stepwise cyclization process, employing *N*-methyl isatylidene malononitriles as the acceptors and β-isocupreidine as the catalyst. Moreover, spirooxindoles incorporating a chromene motif were effectively produced with *N*-MOM electrophiles under the catalysis of α-isocupreine following a cyclization and isomerization sequence. Thus, the current work provides an efficient and straightforward protocol to access structurally diverse spirooxindoles with high molecular complexity from the same set of starting substrates. Currently the development of new reactions with zwitterionic dienolates of cyclic enones, including the asymmetric versions, is under investigation and 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.5b02157.

Complete experimental procedures and characterization of new products; NMR spectra (PDF)
Crystallographic file of racemic product **3e** (CIF)
Crystallographic file of racemic product **4c** (CIF)

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Author Contributions

§J.P. and G.Y.R. contributed equally.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.5b02157
Org. Lett. 2015, 17, 4490–4493

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the NSFC (21122056 and 21321061) and the Program for Changjiang Scholars and Innovative Research Team in University (IRT13031).

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(9) A similar regioselective [4 + 2] cyclization reaction with MBH alcohols of cyclopenten-2-one has been reported via a primary amine-based catalysis, but no reaction occurred with MBH alcohols of cyclohexen-2-one. See ref 5c.

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(12) Mass spectroscopy studies showed that the similar zwitterionic dienolate intermediate was generated between MBH carbonate **1a** and α-IC **C6**. See the Supporting Information.

DOI: 10.1021/acs.orglett.5b02157
Org. Lett. 2015, 17, 4490−4493