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Chiral Spirooxindole–Butenolide Synthesis through Asymmetric N-Heterocyclic Carbene-Catalyzed Formal (3 + 2) Annulation of 3-Bromoenals and Isatins

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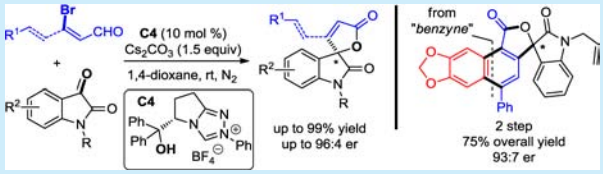
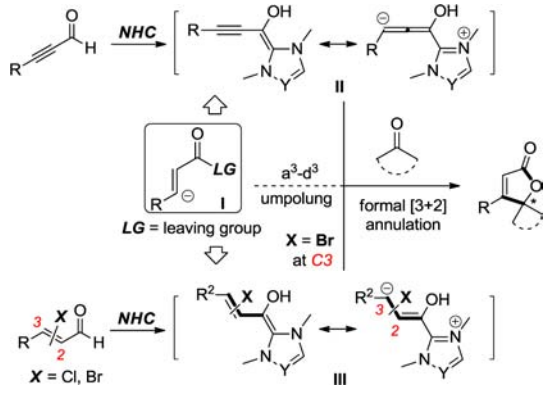
Supporting Information

ABSTRACT: By using an N-heterocyclic carbene catalyst bearing a hydroxyl moiety, the asymmetric formal (3 + 2) cyclization of aryl 3-bromoenals and isatins was achieved to produce a series of chiral spirooxindole–butenolides including an alkenyl-substituted compound, which underwent benzannulations with benzynes to form intriguing spirocyclic scaffolds.



The formal [3 + 2] annulation of the umpoled β-acylvinyl anionic synthon (**I**) with carbonyls constitutes a promising approach for the construction of butenolide scaffolds[1,2] because this reaction enables formation of the unsaturated five-membered ring and a stereogenic center in a single-step process, which remarkably possesses the ability to form spirocyclic frameworks with a butenolide moiety by using cyclic ketone substrates (Scheme 1, middle).[3]

Scheme 1. NHC-Catalyzed Formal [3 + 2] Annulation of Alkynals (Top) and 3-Bromoenals (Bottom) to Butenolides



Over the past decade, N-heterocyclic carbene (NHC)-catalyzed umpolung reactions of aldehydes have become a quickly growing field and have found a wide range of applications in synthetic chemistry.[4] Following the conceptual studies of NHC-homoenolate formation reported by the groups of Bode and Glorius,[5,6] two sorts of Breslow-type species,[7] **II** and **III**, have been exploited as potential β-acylvinyl anionic synthon equivalents. In 2006, Zeitler[8a] disclosed that the addition of NHCs to alkynyl aldehydes resulted in the generation of NHC-bound allenoate intermediates **II**, which would be protonated and allowed the formation of α,β-unsaturated acyl azoliums for further reactions with different nucleophiles.[8] Upon the nucleophilicity of species **II**,[9] the She group[9a] realized the formal [3 + 2] annulation between alkynals and β,γ-unsaturated α-ketoesters to butenolide products by NHC/Lewis acid catalysis[10] (Scheme 1, top). Independently, Snyder shed light on the potential application of the allenoate reactivity in a diastereoselective cycloisomerization to the securinega family of alkaloids.[9b] Very recently, Du and Lu reported the NHC/Lewis-acid-catalyzed annulation of alkynyl aldehydes and isatins to spirooxindoles in moderate to good yield.[9c] On the other hand, in 2010, we displayed that the combination of NHCs and β-haloenals provided access to 3-halogen-substituted homoenolates **III** (Scheme 1, bottom).[11] After the reaction with a variety of electrophiles and subsequent elimination of the halogen, a series of butenolides and analogues were obtained. Thereafter, the groups of Ye, Jiao, and Yao independently uncovered the formation of 2-halogen-substituted homoenolates, which were easily transformed into α,β-unsaturated acyl azoliums via tautomerization and halogen elimination and thereby facilitated a set of fascinating cascade reactions.[12]

Despite these advances, the development of efficient and highly enantioselective methods through the [3 + 2] annulation strategy involving the umpoled β-acylvinyl anionic synthon (**I**) for the synthesis of spirocyclic butenolide products has remained elusive.[13] We herein wish to report an asymmetric formal [3 + 2] annulation of aryl 3-bromoenals and isatins to furnish spirooxindole–butenolides in excellent yield with high enatioselectivity by hydrogen-bonding activation-assisted chiral NHC catalysis.[14]

We initiated our studies by examining the reaction of 3-bromoenal **1a** and *N*-allyl-substituted isatin **2a** in the presence of NHC precursors **C** and stoichiometric base (Table 1). Upon treatment with DBU (1.5 equiv), racemic spirooxindole–butenolide **3a** was isolated in 99% yield by using imidazolium salt **C1** as the NHC precursor (Table 1, entry 1). Therefore, a

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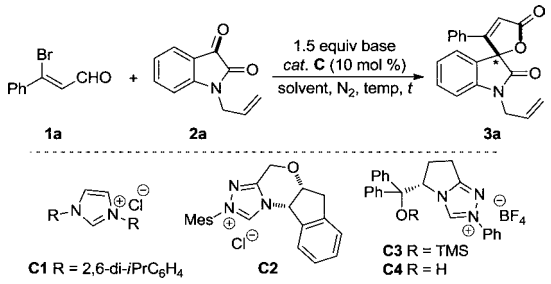
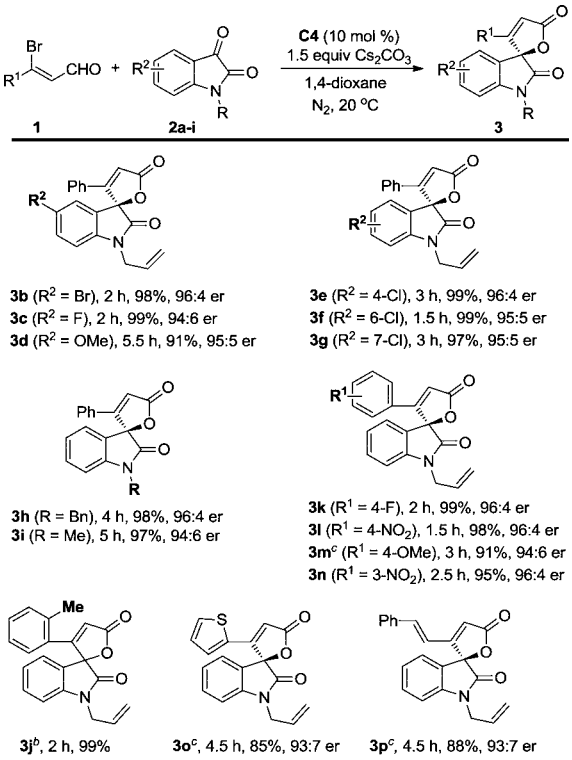
Table 1. Optimization of Reaction Conditions[a]



entry	C/base/solvent	temp (°C)	t (h)	yield (%)[b]	er[c]
1	**C1**/DBU/THF	0	1	99	
2	**C2**/DBU/THF	−78	1	95	50:50
3	**C3**/DBU/THF	0	24	NR	
4	**C4**/DBU/THF	0	24	NR	
5	**C3**/Cs_2CO_3/THF	0	24	trace	
6	**C4**/Cs_2CO_3/THF	0	12	90	95:5
7	**C4**/K_2CO_3/THF	0	48	47(45)[d]	95:5
8	**C4**/Li_2CO_3/THF	0	24	trace	
9	**C4**/Cs_2CO_3/THF	20	5	99	95:5
10	**C4**/Cs_2CO_3/dioxane	20	2.5	99	96:4
11	**C4**/Cs_2CO_3/DCM	20	10	98	95:5
12	**C4**/Cs_2CO_3/toluene	20	22	85	93:7
13	**C4**/Cs_2CO_3/DCM-*t*BuOH (10:1)	20	2	99	90:10

[a]Unless otherwise noted, reactions were conducted on a 0.2 mmol scale of **2a** with **1a** (0.4 mmol), catalyst **C** (10 mol %), and base (0.3 mmol) in solvent (4 mL) under N_2. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Recovery of **2a** is in parentheses.

Scheme 2. Scope of the Reaction[a]



[a]Unless otherwise noted, **1** (0.4 mmol), **2** (0.2 mmol), **C4** (10 mol %), and Cs_2CO_3 (0.3 mmol) in solvent (4 mL) under N_2. [b]**C1** as the catalyst. [c]Using 0.6 mmol of aldehydes at 40 °C. The yields are of the isolated products. The er value is determined by chiral HPLC analysis.

set of chiral azolium salts **C2**−**C4** was tested to carry out this reaction enantioselectively. Unfortunately, Rovis's triazolium catalyst **C2**,[15] a common chiral catalysts in typical NHC-homoenolate additions, was not suitable for this reaction and afforded **3a** as a racemic mixture even at −78 °C in 95% yield (Table 1, entry 2). Moreover, **C3** and its free hydroxyl counterpart **C4** could not yield any desired product with DBU as the base (Table 1, entries 3 and 4).[16] Switching DBU to Cs_2CO_3, while **C3** was still ineffective, the triazolium **C4** gave **3a** in 90% yield and 95:5 er at 0 °C after 12 h (Table 1, entries 5 and 6). Screening of inorganic bases revealed that Cs_2CO_3 was the best choice (Table 1, entries 6−8), suggesting that Cs^+ ions might play some distinct role arising from the inherent coordination ability to accelerate this reaction.[17] Performing the reaction at 20 °C or increasing the polarity of solvents could accelerate this conversion (Table 1, entries 9−12). Nevertheless, the use of protic solvents resulted in a diminished er, presumably due to erosion of the possible H-bonding between the substrates and the free hydroxyl moiety of the catalyst **C4** (Table 1, entry 11 vs 13).

With the optimized reaction conditions in hand, we explored the scope of this transformation (Scheme 2). The reaction of 3-bromoenal **1a** proceeded smoothly for a wide scope of N-substituted isatins **2** bearing a set of groups (−F, −Cl, −Br, and −OMe) at different positions (4-, 5-, 6-, and 7-positions) of the isatin scaffold and gave the corresponding products **3b**−**3g** in excellent yields and high enantioselectivities (94:6−96:4 er). Electron-rich isatin (R^2 = OMe) underwent the reaction slowly and required extended reaction times (5.5 h) to yield **3d** (91%, 95:5 er). Moreover, N-Bn- and N-Me-substituted isatins **2** were also suitable for the outlined reaction, producing the desired butenolides **3h** (96:4 er) and **3i** (94:6 er) in nearly quantitative yield.

On the other hand, as shown in Scheme 2, the reaction of isatin **2a** with a variety of aryl *β*-bromoenals **1** bearing either electron-withdrawing (−NO_2) or electron-donating groups (−OMe) at the *para*- or *meta*-position of benzene rings occurred smoothly to furnish products **3k**−**3n** in 91−99% yield and 94:6 to 96:4 er. Although *racemic* **3j** could be delivered in 99% yield by using the salt **C1**, enantioselective synthesis of **3j** was unsuccessful by chiral NHC catalyst **C4**, probably due to the steric hindrance of the methyl group at the *ortho*-position. It was found that the reaction rate of this process decreased with increasing electron richness of the aldehyde substrates, and elevated temperature (40 °C) was required to accomplish conversions to **3m**, **3o**, and **3p**, yet in high yields and stereoinduction. The absolute configuration of the produced stereocenter was unambiguously established by a single-crystal X-ray analysis of **3b** to be *R*. Notably, the optically pure product **3k** (>99.5:0.5 er) could be obtained through a single recrystallization from CH_2Cl_2/hexane in 83% yield. Nevertheless, alkyl-substituted bromoenals are not suitable substrates to form the corresponding chiral products.

A proposed reaction pathway for this annulation is depicted in Scheme 3. Initial addition of in situ generated NHC **I** to *β*-bromoenal **1a** and subsequent 1,2-H-migration would produce Breslow-type intermediate **II**.[18] Species **II** may undergo nucleophilic addition to the ketone moiety of **2** presumably through a postulated transition state of **III**, wherein the substrate **2** (R = Me, R^2 = H) could be activated and approached to the enolate with its *Si* face because of potential

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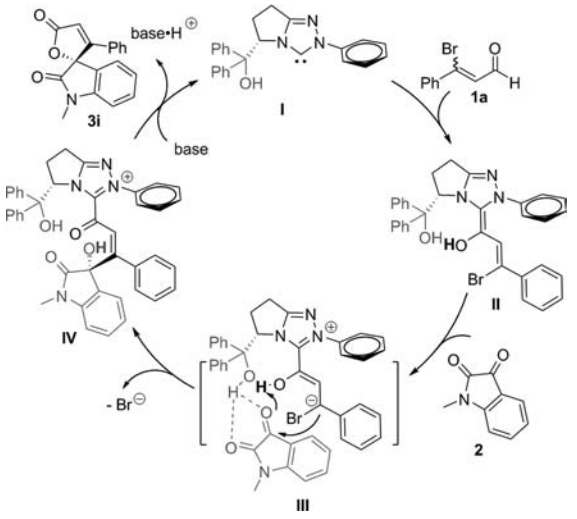
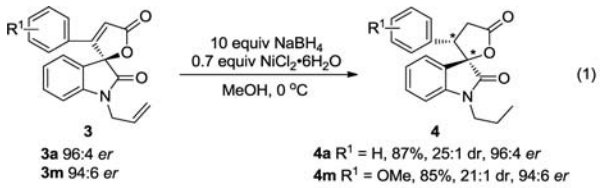
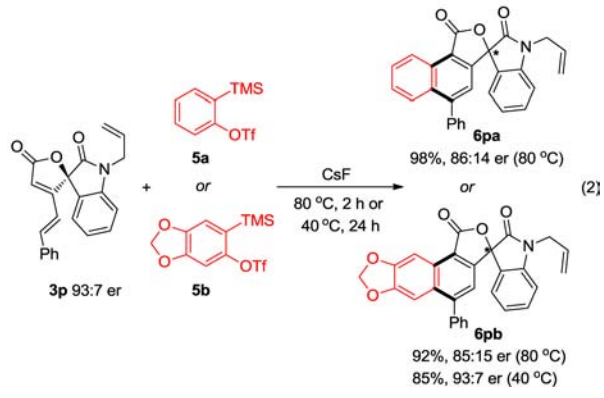
Scheme 3. Proposed Reaction Pathway



hydrogen bonds and $\pi-\pi$ stacking effects. Nevertheless, in view of the distinguished positive effect of cesium carbonate as the base, we assume that the Cs^+ ion may be involved in **III** as a Lewis acid to facilitate this conversion rather than a standby cation. Carbon−carbon bond formation followed by proton transfer would afford azolium **IV** along with the elimination of bromide anions. Finally, base-prompted O-acylation would occur to form the butenolide product **3i** and regenerate the NHC catalyst.

Treatment of *N*-allyl-substituted butenolides **3a** and **3m** with a $NaBH_4/NiCl_2$ system[19] afforded spirocyclic lactones **4a** and **4m** with almost complete transfer of chirality and excellent diastereoselectivities (>21:1 dr) in good yields (eq 1). On the





other hand, the reaction of alkenyl-substituted product **3p** with aryne precursors[20] **5a** and **5b** by CsF (4 equiv) at 80 °C directly furnished aromatic products **6pa** and **6pb** in 98 and 92% yield, respectively, despite a slightly diminished er, presumably via a spontaneous dehydro-aromatization of the intermediacy of Diels−Alder adducts.[21] In addition, decreasing the reaction temperature to 40 °C could give **6pb** in 93:7 er and 85% yield after 24 h (eq 2).

In conclusion, we have reported an asymmetric NHC-catalyzed formal [3 + 2] annulation of aryl 3-bromoenals and isatins, giving rise to a set of chiral spirooxindole−butenolides in excellent yield and high enantioselectivity. The resulting butenolides are of potential synthetic interest as they can be converted to various chiral spirocyclic scaffolds. This study extends the synthetic potentiality of functionalized homoenolate azoliums in asymmetric catalytic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic data of (*R*)-**3b** and (2*R*,3*S*)-**4a**; experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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