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Formal [3+3] Annulation of Isatin-derived 2-Bromoenals with 1, 3-Dicarbonyl Compounds Enabled by Lewis Acid/N-Heterocyclic Carbene Cooperative Catalysis

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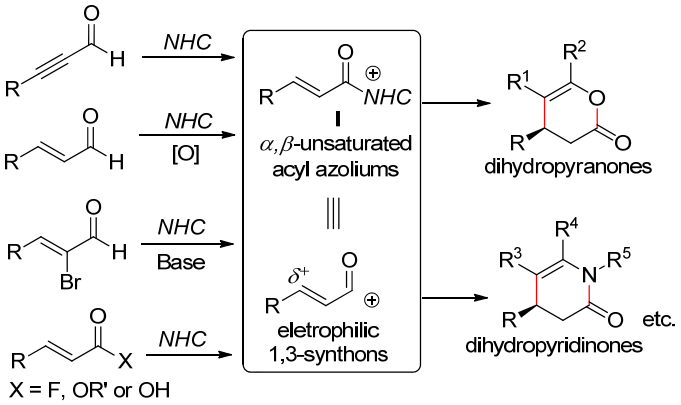
Abstract A series of novel isatin-derived 2-bromoenals were synthesized and applied for formal [3+3] annulation with 1,3-dicarbonyl compounds enabled by a NHC/Lewis acid cooperative catalysis strategy. This newly developed methodology offers rapid access to functionalized spirooxindole δ-lactones. The newly synthesized isatin-derived 2-bromoenals may be further used as potential electrophilic 1,3-synthons for diversity-oriented synthesis of spirooxindoles.

Over the past two decades, N-heterocyclic carbene (NHC)-catalyzed umpolung (polarity reversal) of aldehydes opened up a new and unique area of unconventional formation of carbon-carbon and carbon-heteroatom bonds *via* various reactive intermediates.[1] Among these intermediates, nucleophilic acyl anion intermediates[2] and homoenolate equivalents[3] generated with NHC catalysis have drawn immense attention. Recently, α,β-unsaturated acyl azoliums **I** have been used as novel and versatile electrophilic 1,3-synthons for the synthesis of various heterocyclic compounds like dihydropyranones and dihydropyridinones since its first discovery in 2006.[4] Up to now, α,β-unsaturated acyl azoliums **I** can be commonly generated from six types of precursors including ynals,[5] enals under external oxidative conditions,[5f, 6] 2-haloenals,[7] α,β-unsaturated esters[8] or acyl fluorides,[9] and *in situ* genereated mixed α,β-unsaturated anhydrides from their corresponding carboxylic acids[10] (Scheme 1).

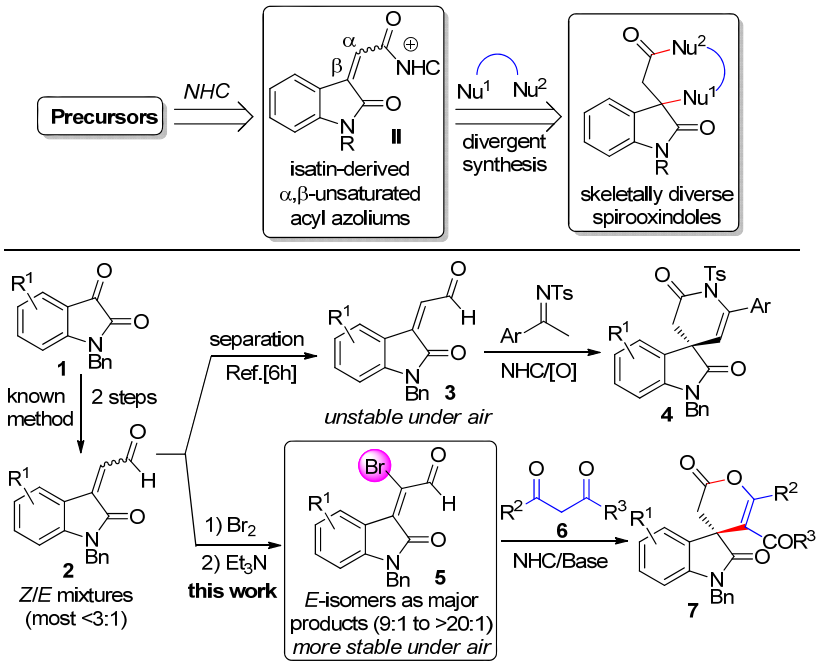


Scheme 1. Generation of α,β-unsaturated acyl azoliums from various precursors.

Spirooxindoles have emerged as attractive privileged structures and become important synthetic targets due to their prevalence in numerous natural products and synthetic compounds with diverse biological activities. However, the architecture of spirooxindole frameworks has always been a challenging endeavor for organic chemists because it often requires specific designed strategies to install the carbocyclic or heterocyclic moeities at the C3 position of the oxindole core to form a spiro quaternary carboncenter. Therefore, the development of simple and versatile substrates or synthetic approaches for diversity-oriented construction of spirooxindole skeletons is highly desirable.

As a continuation of our long-lasting goal to discover novel methodologies for rapid access to polycyclic indole derivatives,[3m, 5b, 5f, 7g, 11] we reasoned that isatin-derived α,β-unsaturated acyl azoliums **II** generated from diverse precursors under NHC catalysis can be utilized as versatile electrophilic 1,3-synthons to combine with different bisnucleophiles for divergent synthesis of skeletally diverse spirooxindoles (Scheme 2). During our research on the generation and applications of isatin-derived α,β-unsaturated acyl azoliums **II**, Zhong and co-workers[6h] very recently reported an oxidative NHC-catalyzed formal [3+3] annulation of imines with isatin-derived enals **3** for rapid access to spirooxindole **4** (Scheme 2). In this reaction, *Z*-isomers **3** are separated from the *Z*/*E* mixtures **2** which are prepared from substituted isatins **1** within 2 steps using known procedures. However, it is always difficult and timeconsuming to separate *Z*-isomers **3** from their *Z*/*E* mixtures **2** which are obtained with low stereoselectivity in most cases. On the other hand, enals **3** are

unstable under air, so they should be kept under an inert atmosphere and be used as soon as possible. Since α-bromoenals were reported to be more stable than their corresponding enals and were frequently used as α,β-unsaturated acyl azolium precursors, we tried to synthesize isatin-derived 2-bromoenals **5** *via* electrophilic addition of Br_2 to *Z*/*E* mixtures **2** followed by elimination with a base as a one-pot procedure. Gratifying, introduction of the bromine atom to the α-position of the enals **2** highly enhances the stereoselectivity which may be attributed to the steric effect of more hindered bromine atom. *E*-isomers **5** were formed as the major products (*E*/*Z* = 9:1 to >20:1) and proved to be more stable under air (Scheme 2). The pure *E*-isomers **5** can be easily obtained by recrystallization of the crude products. The structure and stereochemistry of *E*-isomers **5** were established by spectroscopic analysis and further confirmed by X-ray crystallography of **5d**. In order to test the reactivity of the isatin-derived 2-bromoenals **5**, 1,3-dicarbonyl compounds **6**, good 1,3-bisnucleophiles well-established for formal [3+3] annulations with α,β-unsaturated acyl azoliums **I**, were used to react with substrates **5** under NHC/base conditions to deliver desired spirooxindole *δ*-lactones **7** (Scheme 2). Herein, we wish to report the results.

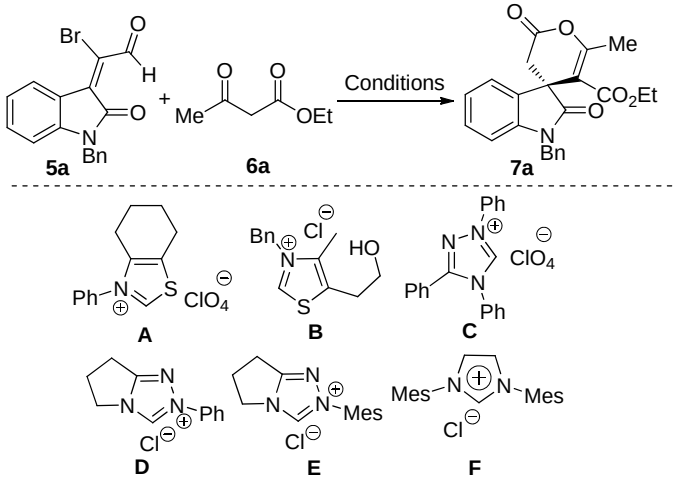


Scheme 2. Generation and applications of isatin-derived α,β-unsaturated acyl azoliums **II**.

We commenced the optimization studies using isatin-derived 2–bromoenal **5a** and ethyl acetoacetate **6a** as model substrates (Table 1). The initial screening of various

carbene precursors **A-F** was discourging as only precatalyst **F** afforded the desired product **7a** in less than 10% yield (entries 1-3). Further examination of a variety of bases and solvents using **F** as the precatalyst revealed that the yield was improved to 42% when the reaction was performed in 1,4-dioxane employing Cs_2CO_3 as a base (entry 12). In recent years, Lewis acids have proved to coordinate with the substrates effectively and thus facilitate the reactions resulting enhanced reaction yields as well as stereoselectivity.[6f, 6m, 11-12] Inspired by the findings, we tried several commonly used Lewis acids and found that LiCl could enhance the reaction yield to 63% (entry 15). Based on the above observations, the optimal reaction conditions were finally established as the reaction carried out in 1,4-dioxane using Cs_2CO_3 (1.5 equiv) as a base in the presence of 15 mol% of **F** and 1.1equiv of LiCl.

Table 1. Optimization of the reaction conditions [a]



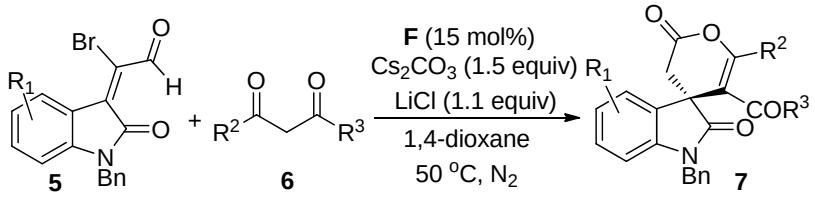
Entry	Catalyst	Base	Solvent	Additive	Yield[b]
1	**A**, **B**	DBU	THF	None	0
2	**C-E**	DBU	THF	None	trace
3	**F**	DBU	THF	None	<10
4	**F**	K_2CO_3	THF	None	23
5	**F**	Et_3N	THF	None	<10
6	**F**	DIPEA	THF	None	21
7	**F**	*t*BuOK	THF	None	16
8	**F**	Cs_2CO_3	THF	None	29
9	**F**	Cs_2CO_3	DCM	None	11
10	**F**	Cs_2CO_3	CH_3CN	None	trace
11	**F**	Cs_2CO_3	PhMe	None	<10
12	**F**	Cs_2CO_3	1,4-dioxane	None	42
13	**F**	Cs_2CO_3	1,4-dioxane	$Ti(OPr)_4$[c]	20
14	**F**	Cs_2CO_3	1,4-dioxane	$Yb(OTf)_3$[d]	28

15	**F**	**Cs_2CO_3**	**1,4-dioxane**	**LiCl** [c]	**63**

[a] All reactions were performed in a sealed tube on a 0.2 mmol scale with 1.0 equiv of **5a**, 2.0 equiv of **6a**, 15mol% of a carbene precursor, 1.5 equiv of a base and 200 mg of 4 Å MS in an anhydrous solvent (3 mL) at 50 °C for 2 h under N_2.
[b] Isolated yields based on **5a**.
[c] 1.1 equiv of a Lewis acid was used.
[d] 20 mol% of Lewis acid was used. DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene; Mes = 2,4,6-$(CH_3)_3C_6H_2$; DIPEA = *N*,*N*-diisopropylethylamine.

After establishing the optimal reaction conditions, we carried on to explore the scope of the reaction between various isatin-derived 2-bromoenals **5** with 1,3-dicarbonyl compounds **6** (Table 2). First, a variety of 1,3-dicarbonyl compounds were tested. The β-keto esters **6b-f** with diverse substituted phenyl group underwent efficient annulation to afford products **7b-f** in moderate to good yields (entries 2-6). The β-diketones **6g-i** were also found applicable to this reaction (entries 7-9). However, cyclohexane-1,3-dione **6j** did not work for this reaction (entry 10). Subsequently, isatin-derived 2-bromoenals **5** with diverse substituents on the phenyl ring were further examined using 1-phenylbutane-1,3-dione **6h** as the model substrate (entries 11-15). 2-Bromoenals **5b-f** with electron-donating and electron-withdrawing groups on the phenyl ring were well tolerated to the reaction. Particularly, substrate **5e** with 5-methyl group afforded the product **7m** in 95% yield (entry 14).

Table 2. The reaction scope[a]

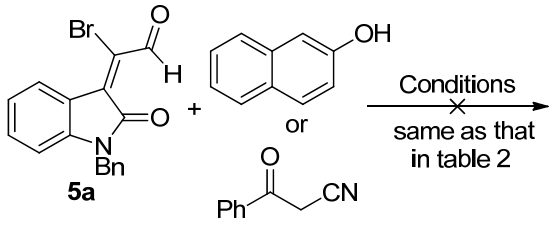


Entry	R^1, **5**	R^2, R^3, **6**	Products	Yield (%)[b]
1	H, **5a**	Me, OEt, **6a**	**7a**	63
2	H, **5a**	Ph, OEt, **6b**	**7b**	57
3	H, **5a**	(4-OMe)Ph, OEt, **6c**	**7c**	58
4	H, **5a**	Ph, OMe, **6d**	**7d**	80
5	H, **5a**	(4-Me)Ph, OMe, **6e**	**7e**	63
6	H, **5a**	(4-Cl)Ph, OMe, **6f**	**7f**	67
7	H, **5a**	Me, Me, **6g**	**7g**	54
8	H, **5a**	Ph, Me, **6h**	**7h**	80
9	H, **5a**	Ph, Ph, **6i**	**7i**	68
10	H, **5a**	cyclohexane-1,3-dione, **6j**		0
11	5-F, **5b**	Ph, Me, **6h**	**7j**	62

12	5-Cl, **5c**	Ph, Me, **6h**	**7k**	68
13	5-Br, **5d**	Ph, Me, **6h**	**7l**	45
14	5-Me, **5e**	Ph, Me, **6h**	**7m**	95
15	7-Cl, **5f**	Ph, Me, **6h**	**7n**	45

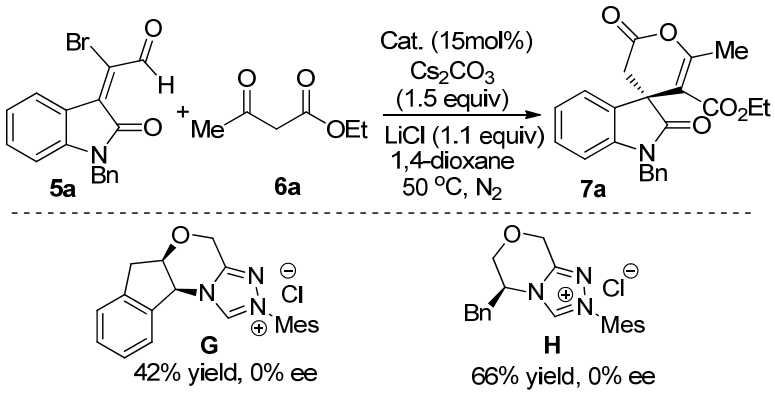
[a] All reactions were performed in a sealed tube on a 0.2 mmol scale with 1.0 equiv of **5**, 2.0 equiv of **6**, 15mol% of **F**, 1.5 equiv of Cs_2CO_3, 1.1 equiv of LiCl and 200 mg of 4 Å MS in an anhydrous 1,4-dioxane (3 mL) at 50 °C for 2 h under N_2.
[b] Isolated yields based on **5a**.

Since β-naphthol[5g] and enolizable carbonyl compounds[7c] have been successfully applied to the formal [3+3] annulations with α,β-unsaturated acyl azoliums **I**, we tested the feasibility of the annulation between **5a** with β-naphthol and 3-oxo-3-phenylpropanenitrile respectively (Scheme 3). Unfortunately, neither of the substrates was found applicable to this methodology.



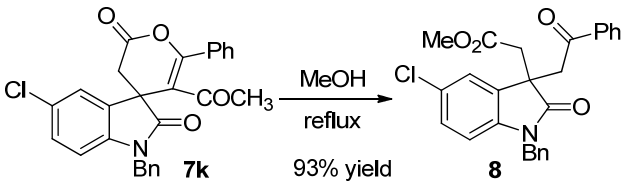
Scheme 3. The reactions of 2-bromoenal **5a** with β-naphthol or 3-oxo-3-phenylpropanenitrile.

A preliminary enantioselective study of the reaction was then carried out using chiral carbene precursors **G** and **H**. However, the desired product **7a** was obtained in moderate yields but 0% e.e. value for both cases (Scheme 4).



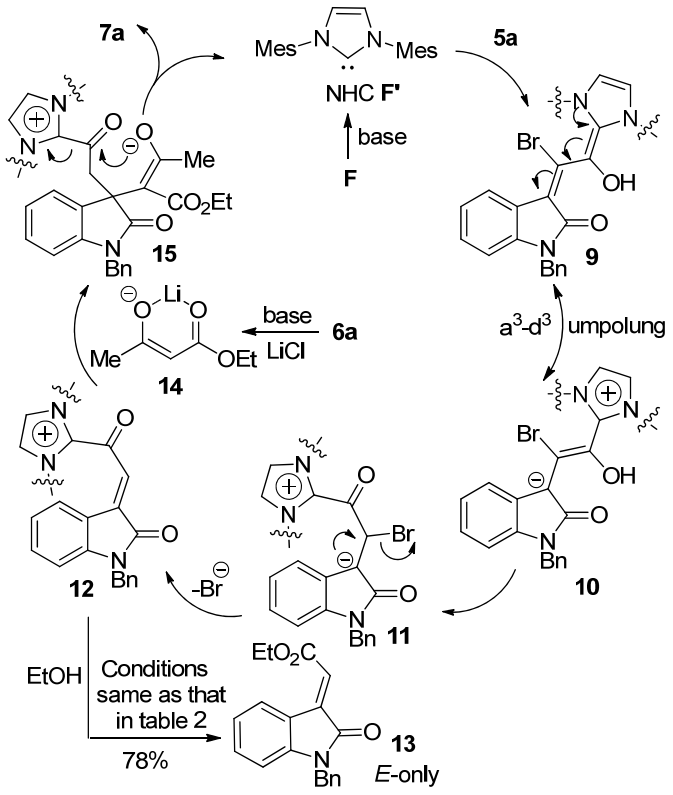
Scheme 4. Preliminary enantioselective studies.

The ring-opening reaction of the spirooxindole δ-lactones was also carried out (Scheme 5). Interesting, when compound **7k** was heated in MeOH, the ring-opening product **8** was obtained in 93% yield with the loss of an acetyl group.



Scheme 5. The ring-opening reaction of the product **7k**.

A plausible catalytic cycle is proposed in Scheme 6. The combination of isatin-derived 2-bromoenal **5a** with NHC **F'** generated upon deprotonation of carbene precursor **F** with a base affords Breslow intermediate **9**. The a^3-d^3 umpolung of **9** induces the formation of intermediate **10**, which is tautomerized to bromoacyl azolium **11**. The subsequent leaving of the bromide gives rise to the more stable (*E*)-isatin-derived α,β-unsaturated acyl azolium **12**. The stereochemistry of **12** was determined by trapping it with ethanol to only afford (*E*)-α,β-unsaturated ester **13** in 78% yield that is a known compound.[13] Notably, even if a *E*/*Z* (9:1) mixture of **5a** was applied to this reaction, only *E*-ester **13** was obtained in similar yield. Michael addition of carbon-centered nucleophile **14** derived from **6a** under base/LiCl conditions to acyl azolium **12** generates intermedate **15**, which is followed by intramolecular cyclization to afford spirooxindole *δ*-lactones **7a** and regenerate NHC **F'**.



Scheme 6. The proposed mechanism.

In summary, a cooperative NHC/Lewis acid-mediated formal [3+3] annulation of various isatin-derived 2-bromoenals **5** with 1,3-dicarbonyl compounds **6** is described. This protocol offers rapid access to functionalized spirooxindole δ-lactones **7**. The newly synthesized isatin-derived 2-bromoenals **5** can be utilized as promising versatile electrophilic 1,3-synthons for divergent construction of diverse spirooxindole skeletons. An enantioselective synthetic protocol from other precursors as well as further applications of isatin-derived 2-bromoenals to the synthesis of diverse spirooxindoles are currently undergoing in our laboratory.

Experimental section

General procedure for the synthesis of 5 from 2: To the solution of compounds **2** (263 mg, 1.0 mmol) in CH_2Cl_2 (3-4 mL) was added Br_2 (62 μL, 1.2 mmol). The resulting mixture was stirred at 5-10 ^oC for 15 mins followed by addition of Et_3N (235 μL, 1.7 mmol). The mixture was further stirred at 5-10 ^oC until the completion of the reaction as monitored by TLC. Then saturated sodium carbonate aqueous solution (20 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using hexane/EtOAc (3:1) as the eluent to afford products **5** as red solids.

General procedure for the synthesis of products 7: To an oven-dried 15 mL glass cylindrical pressure vessel was charged with 2-bromoenals **5** (0.2 mmol), 1,3-dicarbonyl compounds **6** (0.4 mmol), carbene precursor **F** (8 mg, 0.03 mmol), Cs_2CO_3 (98 mg, 0.3 mmol), LiCl (9.0 mg, 0.22 mmol) and 200 mg of 4 Å MS under N_2 atmosphere. Then anhydrous 1,4-dioxane (3 mL) was added and the vessel was immediately sealed tightly. The resulting mixture was stirred at 50 ^oC for 2 h. The mixture was cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel to using hexane/EtOAc (5:1) as the eluent afford products **7**.

Acknowledgements

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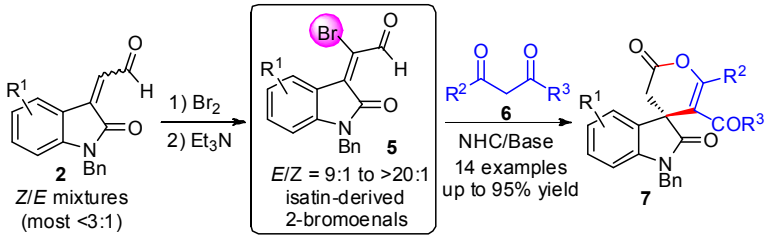

Several novel isatin-derived 2-bromoenals were applied for formal [3+3] annulation with 1,3-dicarbonyl compounds enabled by NHC/Lewis acid cooperative catalysis.