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N-Heterocyclic-Carbene-Catalyzed Reaction of α-Bromo-α,β-Unsaturated Aldehyde or α,β-Dibromoaldehyde with Isatins: An Efficient Synthesis of Spirocyclic Oxindole–Dihydropyranones

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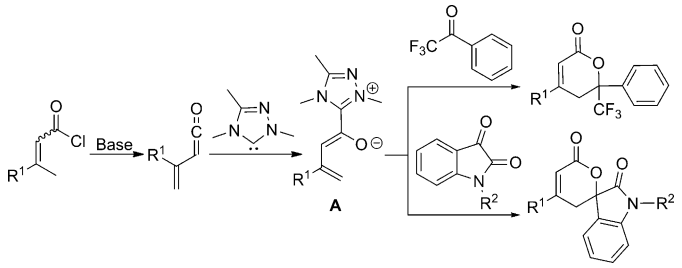
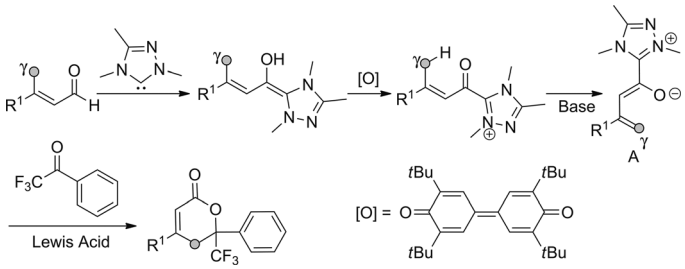
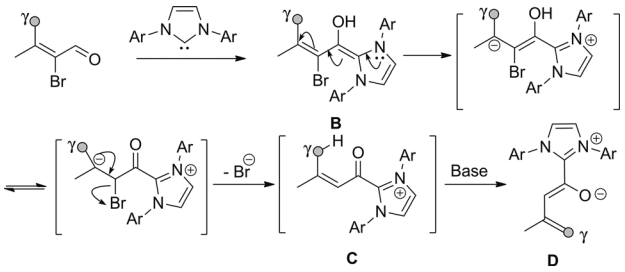
In past decades, extensive attentions have been paid to *N*-heterocyclic carbene (NHCs)-catalyzed umpolung reactions, for example, the benzoin condensation and the Stetter reaction, due to their broad applications in organic synthesis.[1] Some recent reports described the NHC-catalyzed redox-type transformations of α-functionalized aldehydes bearing reducible functionalities (internal redox reaction) or the oxidation of aldehyde in the presence of oxidants (external redox reaction).[1a,c,2] 5,6-Dihydropyran-2-one (α,β-unsaturated δ-lactone) is a privileged structure presented widely in natural products and synthesized biological molecules.[3] Its derivatives could be also used as versatile synthetic intermediates.[4] So many efforts have been devoted to the development of efficient approaches for its construction.[5] In 2011, Ye et al. disclosed a facile assembly of α,β-unsaturated δ-lactone from the formal [4+2] reaction of activated ketones, for example, trifluoromethyl ketones and isatins, and NHC-bonded vinyl enolate (**A**) generated from α,β-unsaturated β-methylacyl chloride under basic conditions (Scheme 1).[6] More recently, Chi et al. described an elegant way to yield the same intermediate **A** through the oxidation of enal bearing γ-H presented by NHC (Scheme 2).[7] Our previous communication showed that the reaction of 2-bromo-2-enal and NHCs could give the Breslow intermediate **B**, which would be transformed into intermediates **C** readily through an $a^3 \rightarrow d^3$ umpolung and debromination.[8a] We speculated that the deprotonation of the intermediate **C** at the γ-position would give an intermediate (**D**) similar to **A** effectively. The following reaction of **D** with activated ketones would give rise to α,β-unsaturated δ-lactones in the absence of external oxidants (Scheme 3). Among the most ubiquitous heterocycles in nature, indoles are common structural motifs in many biologically active molecules and pharmaceutical substances.[9] Also, the oxindole skeleton has attracted much attention in the field of medicinal chemistry



Scheme 1. NHC-bonded vinyl enolate generated from α,β-unsaturated β-methylacyl chloride.



Scheme 2. Formation of NHC-bonded vinyl enolate from oxidation of enal bearing γ-H.



Scheme 3. An envisaged pathway to generate NHC-bonded vinyl enolate from 2-bromo-2-enal with γ-H.

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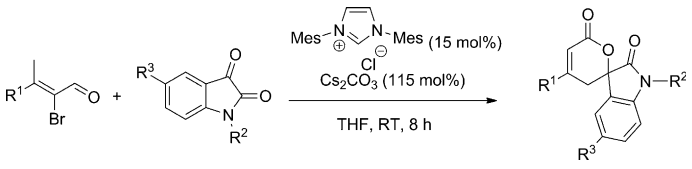
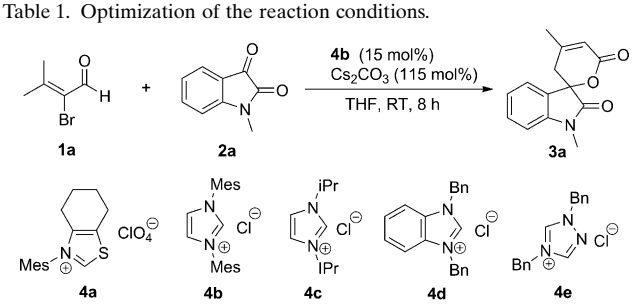
due to its biological significance and wide occurrence in natural products.[10] Its combination with pyran scaffolds should arouse great interest in synthetic and medicinal chemists.[11] Isatin derivatives are versatile building blocks to assemble the spirocyclic frameworks.[12] To continue our work on the NHC-catalyzed synthesis of dihydropyranones,[8a] herein we shall report our preliminary results of an NHC-catalyzed reaction of 2-bromo-2-enal bearing γ-H with isatins, which may afford spirocyclic oxindole-dihydropyranone derivatives with potential biological activities (Scheme 4).



Scheme 4. This work.

The influences of various NHCs, bases, solvents, and different temperatures on the reaction of **1** and **2a** were investigated to optimize the reaction conditions. As shown in Table 1, initially, we screened the precatalyst by using different imidazolium, thiazolium, and triazolium salts **4a**--**4e** and it was found that the best precatalyst for the synthesis of spirocyclic product **3a** was **4b** (Table 1, entry 2). After that, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Cs_2CO_3 and

Table 1. Optimization of the reaction conditions.



Mes = 2,4,6-$(CH_3)_3C_6H_2$ IPr = 2,6-$(CH_3CHCH_3)_2C_6H_3$

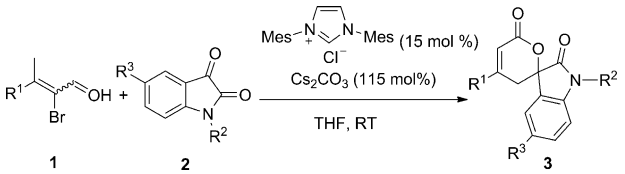
	Precat. [(mol%)]	Solvent	Base [(mol%)]	*T* [°C]	*t* [h]	Yield [%][a]
1	**4a** (20)	THF	Cs_2CO_3 (120)	25	24	N.R[b]
2	**4b** (20)	THF	Cs_2CO_3 (120)	25	8	86
3	**4c** (20)	THF	Cs_2CO_3 (120)	25	10	16
4	**4d** (20)	THF	Cs_2CO_3 (120)	25	24	N.R[b]
5	**4e** (20)	THF	Cs_2CO_3 (120)	25	12	11
6	**4b** (20)	THF	*t*BuOK (120)	25	24	8
7	**4b** (20)	THF	DBU (120)	25	18	23
8	**4b** (5)	THF	Cs_2CO_3 (105)	25	15	78
9	**4b** (10)	THF	Cs_2CO_3 (110)	25	12	85
10	**4b** (15)	THF	Cs_2CO_3 (115)	25	8	90
11	**4b** (15)	CH_2Cl_2	Cs_2CO_3 (115)	25	10	72
12	**4b** (15)	toluene	Cs_2CO_3 (115)	25	9	79
13	**4b** (15)	THF	Cs_2CO_3 (150)	0	22	80
14	**4b** (15)	THF	Cs_2CO_3 (110)	35	6	63
15	**4b** (15)	THF	Cs_2CO_3 (120)	40	4.5	35

[a] Yield of the isolated product. [b] No reaction.

*t*BuOK were tested to evaluate the scope of the base, and it was found that Cs_2CO_3 was the best among them, however *t*BuOK could only give a poor yield of the desired product (Table 1, entries 6 and 7). An investigation of the amount of catalyst and base required indicated that 15 mol% of **4b** along with 115 mol% of Cs_2CO_3 was optimal to the reaction. When the loading of the catalyst was decreased from 15 to 5 mol%, the yield of the desired product **3a** reduced (Table 1, entries 8–10); however, the use of 20 mol% of **4b** did not affect the yield notably (Table 1, entry 2). Subsequently, the solvent effect on the reaction was studied using **4b** (15 mol%) and Cs_2CO_3 (115 mol%), and THF was found to be the best solvent in terms of yield among THF, toluene, and CH_2Cl_2 (Table 1, entries 10–12). An optimization of the temperature revealed that 25 °C was preferable.

Under the optimized reaction conditions the reaction scope was then briefly explored (Table 2). In the course of the experiment, we found that electron-donating substitu-

Table 2. Synthesis of spirocyclic oxindole–dihydropyranones.

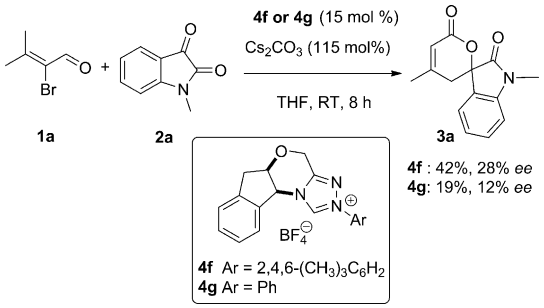


	R^1	R^2	R^3	Product	Yield [%][a]
1	Me	Me	H	**3a**	90
2	Me	Et	H	**3b**	87
3	Me	Me	OCF_3	**3c**	82
4	Me	Allyl	H	**3d**	86
5	Me	Me	Me	**3e**	89
6	Me	Et	Me	**3f**	90
7	Me	Bn	Me	**3g**	87
8	Me	Allyl	Me	**3h**	85
9	Me	Me	OMe	**3i**	93
10	Me	Et	OMe	**3j**	90
11	Me	Bn	OMe	**3k**	91
12	Me	Me	Cl	**3l**	84
13	Ph	Me	Me	**3m**	75

[a] Yield of the isolated product.

ents on the aromatic ring of isatins needed a longer reaction time, but which could provide a better yield of the product relative to those with electron-withdrawing substituents. In addition, different substituted groups on the N-atom of isatins influenced the reactivity and the product yield; when the methyl or ethyl group was replaced with allyl or benzyl group, the reaction rate and yield were both slightly decreased.

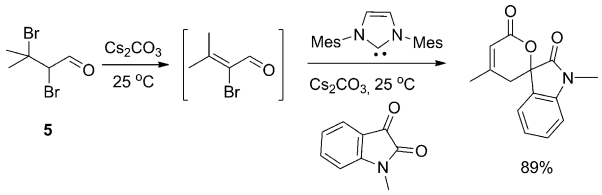
An initial exploration of stereoselective synthesis of the target compound **3** was performed due to the presence of a pseudo-quaternary carbon in the final product. Unfortunately, when chiral precatalysts **4f** was applied to the reaction, product **3a** was obtained in 42% yield and with an enantiomeric excess (*ee*) of 28%. In addition, the chemical yield and enantioselectivity became worse when precatalyst **4g**



Scheme 5. Asymmetric annulation catalyzed by chiral precatalysts.

was used (Scheme 5). It is clear that the level of chiral induction is not yet ideal. We are currently designing new catalysts to perfect this reaction from the standpoint of enantioselectivity.

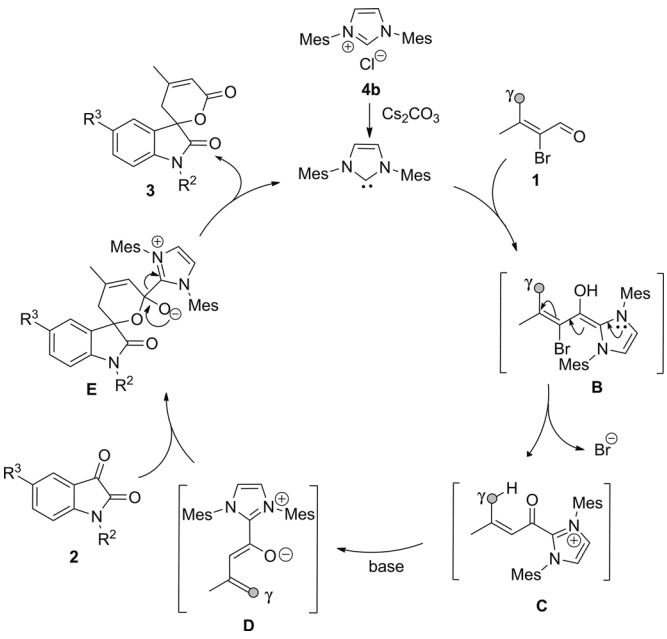
Our previous work demonstrated that α,β-dibromoaldehydes could readily give 2-bromo-2-enal under basic conditions through dehydrogenbromination.[8a] So 2,3-dibromo-3-methylbutanal **5** was used instead of 2-bromo-3-methylbut-2-enal and the reaction worked well to give the same desired product in a yield of 89% (Scheme 6).



Scheme 6. *N*-Heterocyclic-carbene-catalyzed reaction of α,β-dibromoaldehyde with isatin derivatives.

A postulated reaction pathway for the formation of spirocyclic product **3** is illustrated in Scheme 7. The Breslow intermediate **B**, generated by the reaction of 2-bromo-2-enal with the NHC, was transformed into **C** through $a^3 \rightarrow d^3$ umpolung and debromination. The acylazoliumion **C** was deprotonated at the γ-position to give the vinyl enolate **D** with the aid of base. Next, intermediate **D** reacted with isatins **2**, maybe through a procedure similar to the Diels–Alder reaction or a non-concerted nucleophilic addition reaction followed by an intramolecular cyclization to afford target product **3** and release the catalyst to complete the catalytic cycle.

In conclusion, we have developed an efficient NHC-catalyzed [4+2] annulation of α-bromo-α,β-unsaturated aldehydes or α,β-dibromoaldehyde bearing γ-H with isatin derivatives under mild reaction conditions to prepare spirocyclic oxindole–dihydropyranones. This approach is particularly attractive due to the concise construction, straightforward procedure, avoidance of external oxidants, and the potential utilization value of final products in molecular biology and pharmacy. This strategy also extends the scope of NHC-catalysis and provides a simple protocol for NHC-catalyzed hetero-Diels–Alder reactions.



Scheme 7. A proposed reaction mechanism.

Experimental Section

Typical procedure—NHC-catalyzed reaction of α-bromo-α,β-unsaturated aldehydes or α,β-dibromoaldehyde with isatin derivatives: Precatalyst **4b** (51 mg, 0.15 mmol) (or **4f** (63 mg, 0.15 mmol) or **4g** (57 mg, 0.15 mmol)) and Cs_2CO_3 (374 mg, for 2,3-dibromo-3-methylbutanal, 699 mg of Cs_2CO_3 was used) were weighed into an oven-dried 25 mL vial. THF (5 mL) was added to the mixture. The resulting mixture was stirred at room temperature for 5 min followed by the addition of a solution of 2-bromo-2-enal (or 2,3-dibromo-3-methylbutanal, 1 mmol), isatins **2** (1 mmol) in THF (5 mL). The mixture was stirred at room temperature until completion (monitored by TLC). After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, mixtures of ethyl acetate/petroleum ether, 1:1, v/v).

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Keywords: annulation · carbenes · redox reaction · spiro compounds · umpolung

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