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N-Heterocyclic Carbene-Catalyzed Homoenolate Additions with *N*-Aryl Ketimines as Electrophiles: Efficient Synthesis of Spirocyclic γ-Lactam Oxindoles

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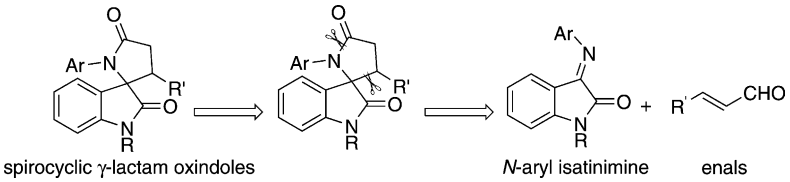
The indole unit is a ubiquitous skeleton in pharmaceuticals and bioactive natural products.[1] Among these, spirocyclic oxindole frameworks are present in a large number of bioactive, naturally occurring alkaloids and medicinally relevant compounds (Figure 1).[2,3] Consequently, numerous synthetic methods to construct these fascinating architectures have been established.[2,3] Alternatively, the spirocyclic γ-lactam oxindoles could be simply constructed by the *N*-heterocyclic carbene catalyzed conjugate umpolung reaction of α,β-unsaturated aldehydes with isatinimines as electrophiles (Scheme 1).



Scheme 1. Retrosynthetic analysis of spirocyclic γ-lactam oxindoles.

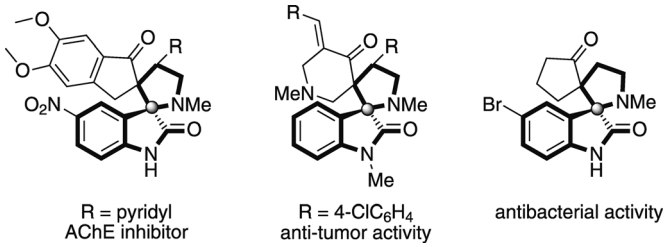


Figure 1. Examples of synthetic, bioactive compounds containing spirocyclic oxindole frameworks. AChE = acetylcholinesterase inhibitor.

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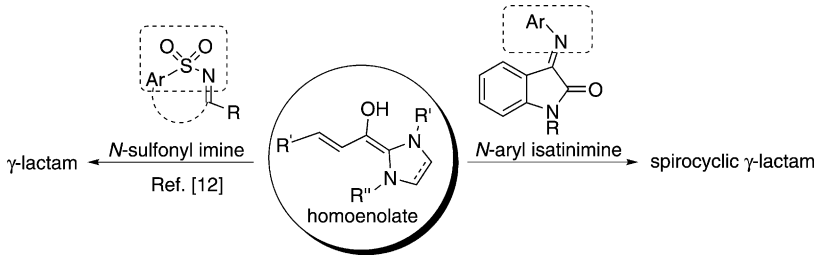
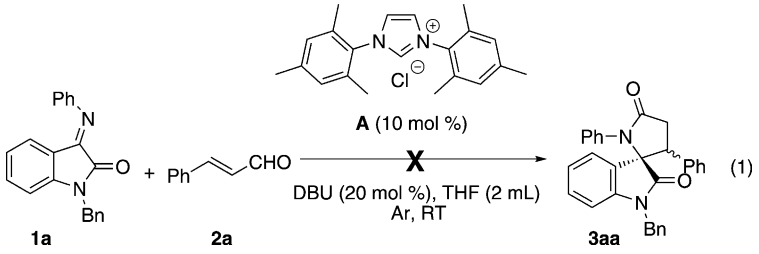
Over the past few years, there has been significant growth in the field of *N*-heterocyclic carbene (NHC) catalysis due to the unique umpolung ability of these compounds, which provides unconventional access to various target molecules.[4] The classic NHC-catalyzed a^1–d^1 umpolung reactions of aldehydes,[5] such as the benzoin condensation and the Stetter reaction, are generally thought to proceed via nucleophilic Breslow intermediates, which are generated by the addition of NHCs to aldehydes.[6,7] In recent years, umpolung reactions involving the use of enals have been reported independently by the groups of Glorius[8] and Bode.[9] Since then, a number of electrophiles for the synthesis of γ-butyrolactones have been found to be suitable acceptors for the homoenolate species, including aldehydes and ketones.[10,11] In contrast, the use of imines as electrophiles for the synthesis of γ-butyrolactams is limited and challenging; this is possibly due to decomposition of the imine and the potential reaction between NHC catalysts and imines leading to stable adducts that inhibit this catalytic reaction.[12] More recently, Bode's and Scheidt's groups have made significant progress towards the NHC-catalyzed addition of enals to imine electrophiles. However, the imine electrophiles are still limited to aromatic aldehyde-derived *N*-sulfonyl imines,[12] azomethine imines,[13] and *N*-phenyl nitrones.[14] *N*-Alkyl and *N*-aryl imines are unreactive, leading to lactone dimers of the starting enals. By using a Brønsted acid as the cooperative catalyst, Rovis and co-workers demonstrated the umpolung reaction of enals to *N*-aryl aldimine electrophiles.[15] Thus new types of electrophiles are highly desirable and would further widen the versatility of the reaction. Herein, we describe the first application of *N*-aryl ketimines as the electrophiles in NHC-catalyzed homoenolate additions, which provides a simple and efficient approach to spirocyclic γ-lactam oxindoles (Scheme 2).

Considering our interest in the construction and modification of the indole structure,[16] we investigated the possibility for the direct synthesis of a spirocyclic oxindole by the



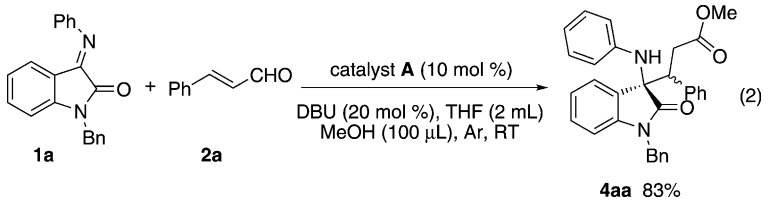
Scheme 2. Imines as the electrophiles for homoenolate addition.

NHC-catalyzed conjugate umpolung strategy (Scheme 1). We envisioned that *N*-aryl isatinimines, which have a different reaction activity to ordinary *N*-aryl ketimines,[17] could be electrophiles for homoenolate addition. Initially, the reaction of *N*-aryl isatinimine **1a** with *trans*-cinnamaldehyde (**2a**) in the presence of imidazolium salt **A** and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in THF was investigated [Eq. (1), Bn = benzyl]. Unfortunately, the desired product **3aa** was not detected, and only starting materials were recovered. We hypothesized that this outcome is a result of the steric hindrance of the Ph–NH group of the intermediate imidazolium species **III** (see the mechanism described later), which can not undergo further intramolecular acylation to generate the desired spirocyclic γ-lactam oxindole product, **3aa**.



Considering that the use of an appropriate, nucleophilic co-catalyst for a relay catalysis, such as those employed in acylation reactions described concurrently by the groups of Rovis[18] and Bode,[19] may provide a possible route for the amide bond formation, we next screened various nucleophilic co-catalysts. To our delight, the desired spirocyclic γ-lactam oxindole **3aa** was obtained in 12–13% yields by using imidazole or benzimidazole as the co-catalyst (see the Supporting Information; Table S1, entries 2 and 3). Other additives, such as 1-hydroxy-7-azabenzotriazole (HOAt), 1-hydroxybenzotriazole (HOBt), or 4-dimethylaminopyridine (DMAP), were ineffective in this reaction (see Table S1, entries 5–7). Interestingly, γ-amino acid ester **4aa** was obtained in 83% yield when MeOH (100 μL) was added to the above reaction [Eq. (2)]. After subsequent exposure of the isolated γ-amino acid ester **4aa** to a 1 M solution of aqueous HCl in methanol, the target product **3aa** was generated, and its structure was confirmed by single-crystal X-ray analysis (Figure 2). Notably, these two reaction steps can be performed in a one-pot process starting with the enal, making the transformation more convenient.

Encouraged by this result, the reaction conditions for a one-pot process were optimized (Table 1). The NHCs



were first screened, and in the presence of imidazolium salt **A** (10 mol%) and DBU (20 mol%) the desired product **3aa** was obtained in 80% yield without diastereoselectivity (Table 1, entry 1). NHC catalysts **B**–**H** performed less effectively (Table 1, entries 2–8). Different solvents then were tested. The results showed that toluene and chlorobenzene promoted diastereoselectivity (1:4 and 1:8, respectively) but with low yields (Table 1, entries 11 and 12; see also Table S2, entries 7–8 in the Supporting Information). Subsequently, various organic and inorganic bases were surveyed in toluene. K_2CO_3 gave promising results based on the yield and diastereoselectivity (Table 1, entry 15; see also Table S3, entry 5 in the Supporting Information). After further optimization, including the examination of mixed solvents and the concentration of the reaction, the best results were obtained when the reaction was conducted in 4 mL dioxane/toluene

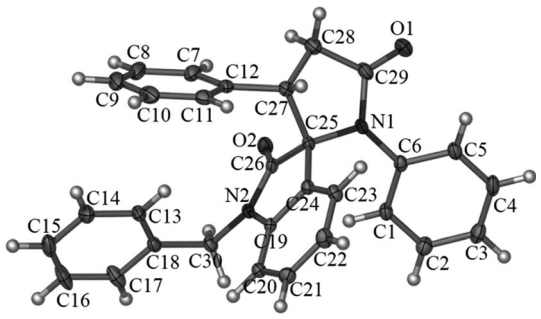
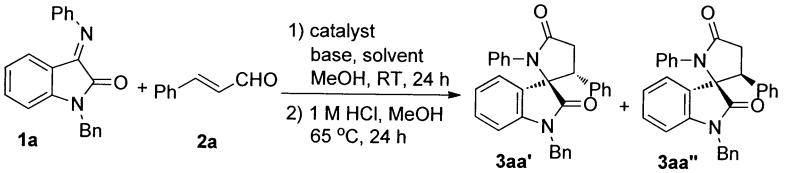
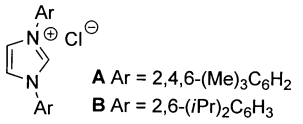
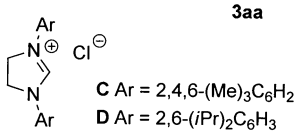


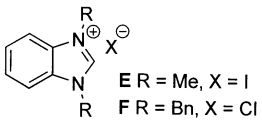
Figure 2. The X-ray crystal structure of **3aa**.

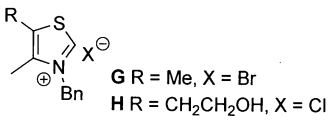
Table 1. Optimization of reaction conditions for the NHC-catalyzed, one-pot synthesis of spirocyclic γ-lactam oxindoles.[a]











Entry	Catalyst	Solvent	Base	Yield [%][b]	d.r.[c]
1	A	THF	DBU	80	1:1
2	B	THF	DBU	25	1:1
3	C	THF	DBU	32	2:1
4	D	THF	DBU	trace	–
5	E	THF	DBU	27	1:1
6	F	THF	DBU	16	1:1
7	G	THF	DBU	6	1:1
8	H	THF	DBU	10	1:1
9	A	CH_2Cl_2	DBU	20	1:2
10	A	dioxane	DBU	67	1:2
11	A	toluene	DBU	54	1:4
12	A	C_6H_5Cl	DBU	19	1:8
13	A	toluene	Et_3N	20	1:5
14	A	toluene	iPr_2NEt	15	1:5
15	A	toluene	K_2CO_3	64	1:4
16	A	toluene	Cs_2CO_3	54	1:4
17	**A**	**dioxane/toluene (1:1)**	**K_2CO_3**	**78**	**1:4[d]**
18	A	dioxane/C_6H_5Cl (1:1)	K_2CO_3	70	1:3

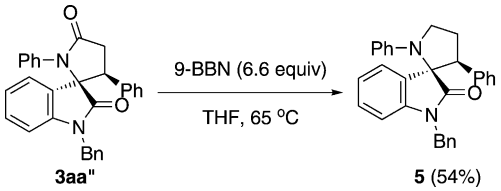
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.02 mmol), base (0.04 mmol), and MeOH (100 μL) were dissolved in the solvent (4.0 mL) and stirred under Ar at RT for 24 h. Then MeOH (2.0 mL) and 1 M HCl (2.0 mL) were added and the reaction was stirred at 65 °C for an additional 24 h. [b] Isolated yields. [c] The d.r. was determined by ^{1}H NMR analysis of the crude products (d.r. **3aa′**/**3aa″**). [d] Structure was determined by X-ray crystal-structure analysis.

(1:1; Table 1, entry 17; see also Table S4, entry 11, and Table S5, entry 4 in the Supporting Information).

With the optimized conditions in hand, the scope of this reaction with regard to *N*-aryl isatinimines was then investigated (Table 2). The *N*-aryl isatinimines derived from anilines and containing an electron-rich or electron-deficient group proceeded efficiently and afforded the products **3aa**–**3ha** in excellent yields (73–91 %) and with good diastereoselectivity (Table 2). Moreover, electron-withdrawing and electron-donating substituents at the 5 or 7 positions of the benzene ring of *N*-aryl isatinimines provided good yields (**3ia**–**3la**; Table 2). Different protecting groups on the nitrogen of the oxindole backbone were also examined. Various protecting groups, such as benzyl, methyl, diphenyl methylene, allyl, *para*-methoxybenzyl, and methoxymethyl groups, were tolerated, affording the products with good to excellent yields (**3ma**–**3qa**, 69–88 %; Table 2).

We then examined the scope of the reaction towards α,β-unsaturated aldehydes (Table 2). Electron-rich and electron-deficient cinnamaldehydes performed well in this transformation, leading to the desired spirocyclic γ-lactam oxindoles **3aa**–**3ag** in good yields (82–88 %; Table 2). Moreover, thiophene- and naphthalene-derived enals underwent this transformation smoothly to generate the desired products in moderate yields (**3ah**: 53 %, and **3ai**: 71 %, respectively). It is worth noting that alkenyl- and alkyl-substituted enals were also smoothly converted into the corresponding products (see examples **3aj** and **3ak**, Table 2). Furthermore, when acrolein was employed as the substrate, spirocyclic γ-lactam oxindole **3al** was obtained in 35 % yield (Table 2).

When the reaction was carried out on a preparative scale (3.0 mmol), there was no change in yield or diastereoselectivity (81 %, d.r. 1:4; see the Supporting Information). For the further application of these products, the spirocyclic γ-lactam oxindoles, such as **3aa″**, were easily reduced by 9-borabicyclo[3.3.1]nonane (9-BBN) to afford the corresponding spirocyclic oxindole **5** in 54 % yield [Eq. (3)].[20] This spirocyclic oxindole scaffold is present in many synthetic compounds exhibiting important biological activities.[3d–i]

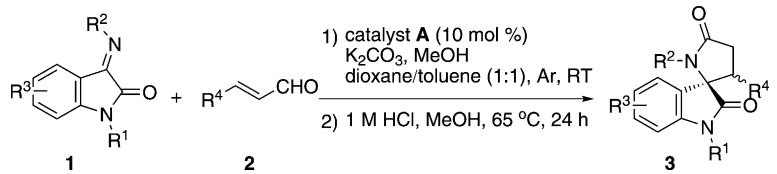


(3)

An enantioselective variant of this methodology would be useful, but highlights the established challenges of asymmetric addition to *N*-aryl ketimines. A range of chiral NHC catalysts were investigated for the asymmetric reaction (Table 3, see also the Supporting Information). The results show that **I2** is an effective catalyst for this asymmetric transformation, giving **3aa** in 80 % yield with 1:6 d.r. (**3aa′**/**3aa″**), and **3aa″** with an enantiomeric ratio of 87:13 (e.r.; Table 3, entry 2). Moreover, the opposite enantioselectivity (e.r.) could be induced by catalyst **J1** (e.r. 14:86, Table 3, entry 6). Significantly, the e.r. values were improved to 99:1 and 2.5:97.5, respectively, by fast recrystallization with acetone–hexane. Importantly, the use of catalyst **K** dramatically improved the diastereoselectivity (Table 3, entries 8 and 9).

A plausible mechanism for this reaction is illustrated in Scheme 3.[9–11] An NHC is generated by the deprotonation of an imidazolium salt in the presence of K_2CO_3. Addition of the NHC to α,β-unsaturated aldehydes **2** affords the Breslow intermediates **I** after addition and rearrangement, which serve as homoenolate equivalents. The homoenolate intermediates **I** attack the electrophilic *N*-aryl isatinimines **1** to produce the intermediates **II**. Tautomerization of the intermediates **II** generate the intermediates **III**. Subsequently,

Table 2. The reaction scope of the NHC-catalyzed, one-pot synthesis of spirocyclic γ-lactam oxindoles.[a–c]



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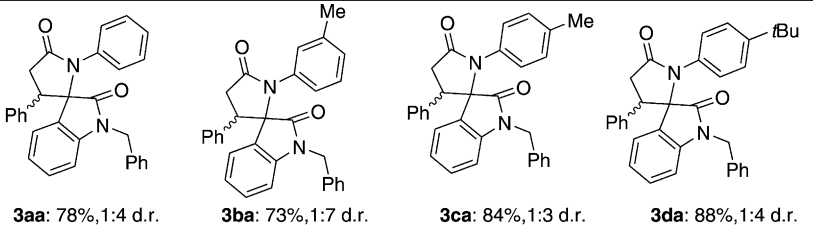
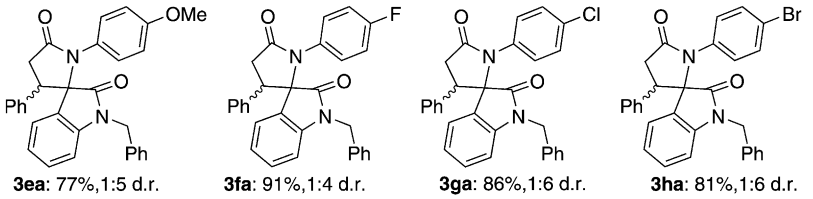
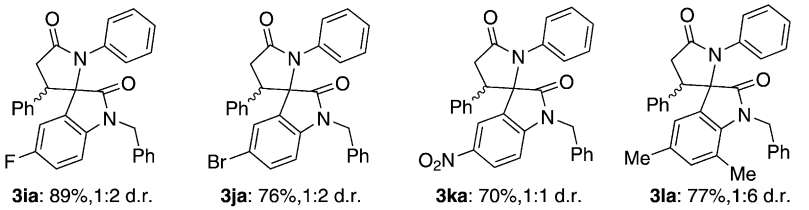


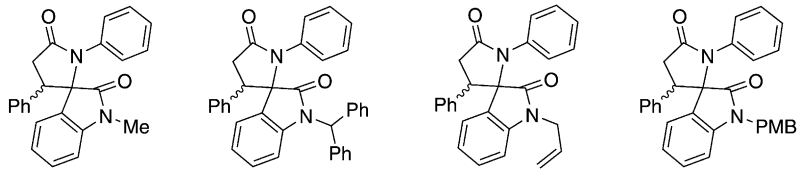
3aa: 78%,1:4 d.r. **3ba**: 73%,1:7 d.r. **3ca**: 84%,1:3 d.r. **3da**: 88%,1:4 d.r.



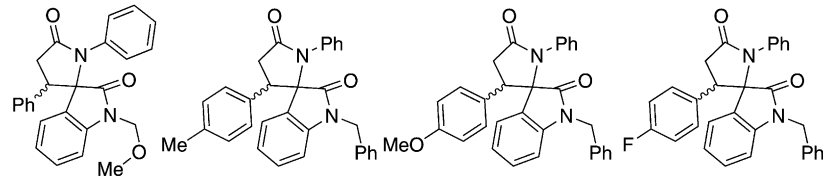
3ea: 77%,1:5 d.r. **3fa**: 91%,1:4 d.r. **3ga**: 86%,1:6 d.r. **3ha**: 81%,1:6 d.r.



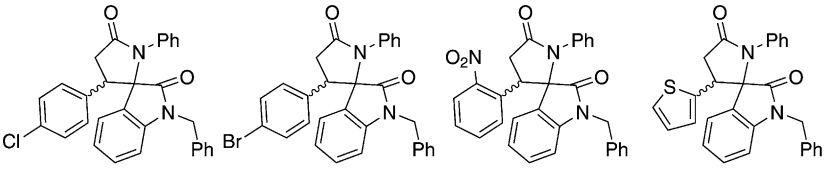
3ia: 89%,1:2 d.r. **3ja**: 76%,1:2 d.r. **3ka**: 70%,1:1 d.r. **3la**: 77%,1:6 d.r.



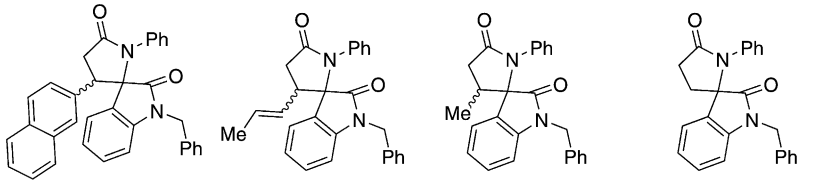
3ma: 88%,1:4 d.r. **3na**: 69%,1:6 d.r. **3oa**: 76%,1:6 d.r. **3pa**: 80%,1:4 d.r.



3qa: 87%,1:3 d.r. **3ab**: 88%,1:3 d.r. **3ac**: 87%,1:2 d.r. **3ad**: 82%,1:4 d.r.



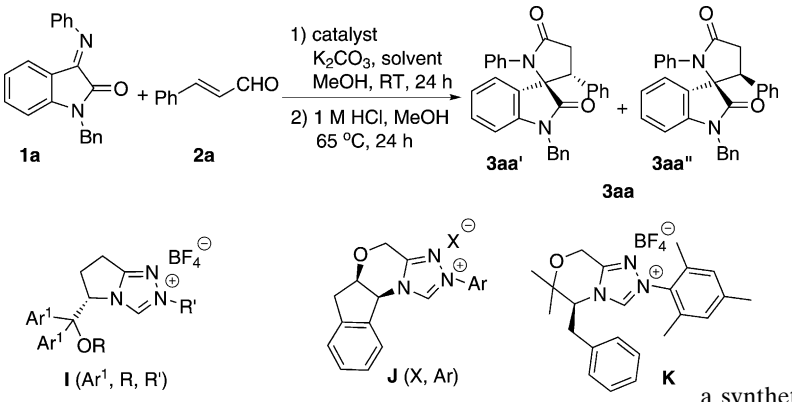
3ae: 85%,1:4 d.r. **3af**: 84%,1:4 d.r. **3ag**: 82%,1:4 d.r. **3ah**: 53%,1:5 d.r.



3ai: 71%,1:6 d.r. **3aj**: 61%,1:2 d.r. **3ak**: 79%,1:2 d.r.[d] **3al**: 35%[e]

[a] Reaction conditions: see Table 1, entry 17. [b] Isolated yields. [c] The d.r. was determined by ^{1}H NMR analysis of the crude products (d.r. **3′**/**3″**). [d] DBU was used as the base, and the reaction was stirred for 24 h in the first step. [e] Compound **2** (0.6 mmol), catalyst **A** (20 mol %) and K_2CO_3 (40 mol %) were employed, and the reaction was stirred for 24 h in the first step. PMB = *para*-methoxybenzyl.

Table 3. Enantioselective studies of this methodology.[a]



Entry	Catalyst	*T* [°C]	Yield [%][b]	d.r.[c]	e.r. (**3aa**″)[d]
1	**I1**	RT	NR		
2	**I2**	**RT**	**80**	**1:6**	**87:13 (99:1)[g]**
3	**I3**	RT	trace		
4	**I4**	0	56	1:5	86:14
5	**I5**	RT	trace		
6	**J1**	0	77	1:8	14:86 (2.5:97.5)[g]
7	**J2**	RT	82	1:3	48.5:51.5
8[e]	**K**	**0**	**88**	**1:15**	**35:65**
9[f]	**K**	0	38	**1:19**	35.5:64.5

[a] Reaction conditions: see Table 1, entry 17. [b] Isolated yields. [c] The ratio was determined by ^{1}HNMR analysis of the crude products (d.r. **3aa**′/**3aa**″). [d] The e.r. value was determined by chiral HPLC analysis. [e] THF was used as the solvent. [f] 4 Å MS were added (200 mg). [g] The e.r. values in parentheses were measured after fast recrystallization with acetone–hexane (see the Supporting Information). TBS = *tert*-butyldimethylsilyl, Mes = mesitylene.

the γ-amino acid esters **4** are produced by protonation and attack of MeOH[111,12b] with the reformation of the NHC to complete the catalytic cycle. Finally, the target products **3** can be obtained by acid hydrolysis of the γ-amino acid esters **4**.

In summary, we have demonstrated that *N*-aryl isatinimines can be used as stable and useful electrophiles in the NHC-catalyzed addition of enals to imines, and have developed an efficient one-pot protocol for the synthesis of spirocyclic γ-lactam oxindoles **3** (which are ubiquitous structural units in a number of biologically active compounds) by a synthetically challenging addition of homoenloate equivalents to *N*-aryl isatinimines and subsequent acid hydrolysis. The possibility of a catalytic enantioselective process is also shown. Further studies on the scope, asymmetric catalysis, and synthetic applications of this reaction are ongoing in our laboratory

Acknowledgements

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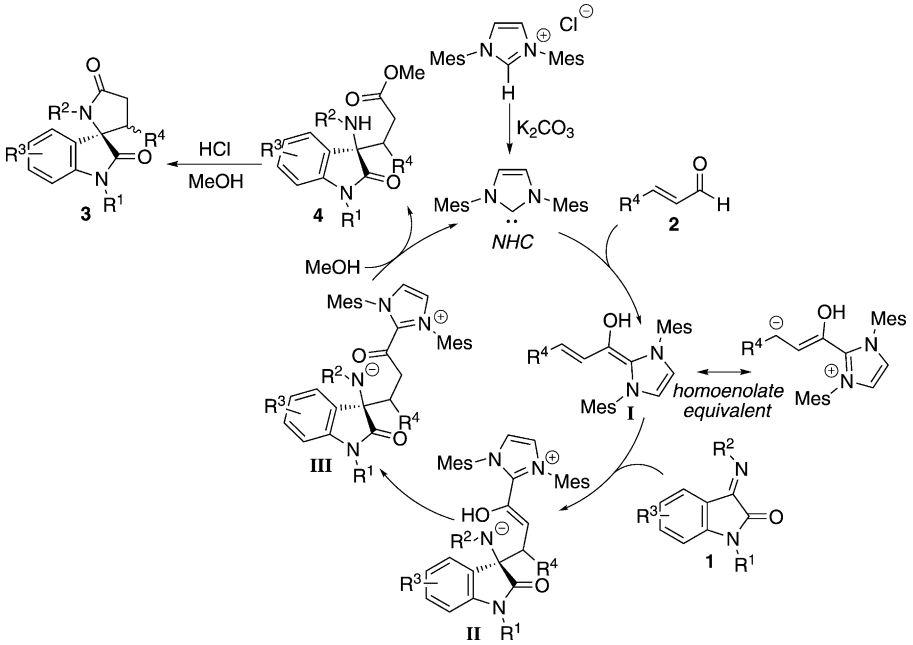
Keywords: carbenes · lactams · organocatalysis · spiro compounds · umpolung



Scheme 3. Proposed mechanism for the transformation. Mes = mesitylene.

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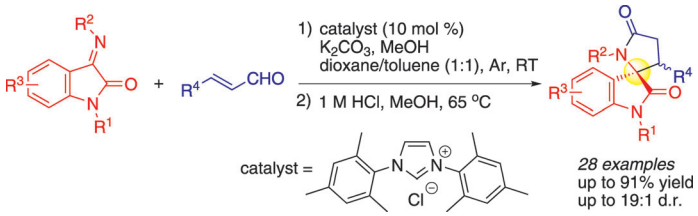

In pole position: A simple and efficient approach to spirocyclic γ-lactam oxindoles by the *N*-heterocyclic carbene catalyzed addition of homoenloate equivalents to *N*-aryl isatinimines has been developed (see scheme). The use of *N*-aryl isatinimines as electrophiles in the NHC-catalyzed umpolung reaction of α,β-unsaturated aldehydes is demonstrated for the first time.

Heterocyclic Carbenes

B. Zhang, P. Feng, L.-H. Sun, Y. Cui, S. Ye, N. Jiao**..... ▮▮▮▮–▮▮▮▮

_N_-Heterocyclic Carbene-Catalyzed Homoenolate Additions with _N_-Aryl Ketimines as Electrophiles: Efficient Synthesis of Spirocyclic γ-Lactam Oxindoles