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Highly enantioselective synthesis of functionalized azepino[1,2-*a*]indoles *via* NHC-catalyzed [3+4] annulation

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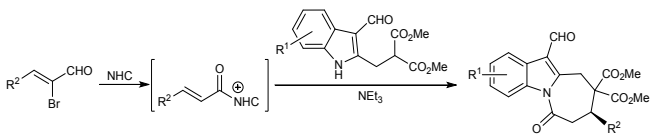
Enantioselective [3+4] annulation of 3-formylindol-2-methyl-malonates with 2-bromoenals catalyzed by NHCs is described to afford functionalized azepino[1,2-*a*]indoles in high yields with excellent enantioselectivities. This method, in which the 3-formyl group in indoles acts as a necessary mediated group, provided cycloaddition products under mild conditions.

The azepino[1,2-*a*]indole skeleton, which feature a fused seven-membered ring through the N1-C2 connection, is an important structural unit that occurs in several natural indole alkaloids.[1] In addition, many azepino[1,2-*a*]indoles exhibit attractive pharmacological activities including antiprotozoal properties,[2a] prostaglandin D2 receptor agonist,[2b] Hepatitis C NS5B inhibitors[2c-d] and anti-cytokine inhibitors.[2e] The development of efficient access through straightforward annulation reaction to form azepino[1,2-*a*]indoles has drawn extensive attention. Until now, some synthetic methods to this framework have been reported, such as olefin metatheses,[3] [2+5] cycloadditions,[4] radical cyclizations,[5] and transition-metal-catalyzed intramolecular cyclization cascade reactions.[6] However, the reported investigations have so far been limited to achiral or racemic derivatives.

Asymmetric syntheses that use *N*-heterocyclic carbenes (NHCs) as catalysts have been studied extensively and are an important method for asymmetric carbon-carbon bond formation.[7] The annulation reactions[8-11] have been applied for the synthesis of diverse chiral cyclic compounds. The asymmetric [3+4] annulations are efficient approaches for the synthesis of optically enriched seven-membered heterocyclic compounds. Among them, asymmetric synthesis of fused *ε*-lactones[12a-c, 12f] and spirocyclic oxindole-*ε*-lactones[12j] was demonstrated by several groups through NHC-catalyzed [3+4] annulations of enals, isatin-derived enals with *o*-quinone methides, *α*,*β*-unsaturated ketones, and *o*-hydroxyphenyl substituted *p*-quinone methides, respectively. In 2014, the group of Chi[12d] reported the stereoselective synthesis of dinitrogen-fused seven-membered heterocycles by NHC-catalyzed [3+4] cycloaddition of azomethine imines and enals. Glorius[12e] and our group[12i] independently disclosed the NHC-catalyzed [3+4] annulations to afford 1,2-diazepines. Enders *et al*.[12g] developed an enantioselective synthesis of spirobenzazepinones, spiro-1,2-diazepinones and spiro-1,2-oxazepinones through NHC-catalyzed [3+4] cycloaddition of isatin-derived enals with *in situ* formed aza-*o*-quinone methides, azoalkenes or nitrosoalkenes, respecttively. In 2017, enantioenriched N–H-free 1,5-benzothiazepines were synthesized by a formal [3+4] annulation of *α*,*β*-unsaturated acyl azoliums with 2-amino-benzenethiols[12h]. Additionally, NHC-catalyzed [3+4] annulation of α-bromoenals with aryl 1,2-diamines was developed for highly enantioselective synthesis of 4-aryl N-H-free 1,5-benzodiazepin-2-ones[12k-l]. Although asymmetric [3+4] annulations catalyzed by NHCs have been utilized to synthesize some seven-membered heterocycles, little effort has been focused on the enantioselective synthesis of azepino[1,2-*a*]indoles. Very recently, Chi and co-workers[12m] reported enantioselective synthesis of azepino[1,2-*a*]indoles by NHC and sulfinate co-catalyzed intermolecular Rauhut–Currier reaction between enals and nitrovinyl indoles. Therefore, it is of widespread interest to develop new entries to synthesize chiral azepino[1,2-*a*]indoles. As our group works on the NHC-catalyzed asymmetric reactions,[13] we aim to develop a straightforward [3+4] annulation method for synthesis of chiral azepino[1,2-*a*]indoles catalyzed by NHCs under mild conditions. As anticipated, the asymmetric [3+4] annulation of 2-((3-formyl-1*H*-indol-2-yl)methyl)malonate with 2-bromoenals proceeded smoothly (Scheme 1) and the desired



Scheme 1 NHC-Catalyzed enantioselective [3+4] annulation.

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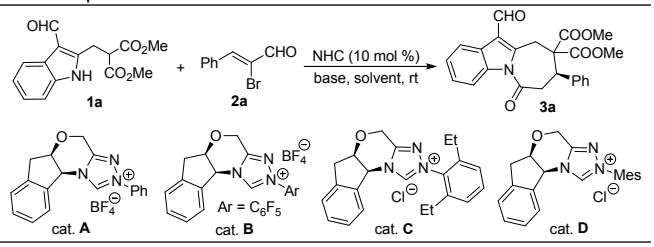
Electronic Supplementary Information (ESI) available: Crystallographic data, a detailed protocol, NMR and HPLC data of the synthesized compounds are provided. CCDC 1897738. See DOI: 10.1039/x0xx00000x

Table 1 Optimization of reaction conditions[a]



entry	catal.	base	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	**A**	NEt_3	toluene	24	21	85
2	**B**	NEt_3	toluene	24	–	–
3	**C**	NEt_3	toluene	24	26	93
4	**D**	NEt_3	toluene	24	34	92
5	**D**	Cs_2CO_3	toluene	48	–	–
6	**D**	DABCO	toluene	24	31	88
7	**D**	DMAP	toluene	24	19	94
8	**D**	DIPEA	toluene	24	24	94
9	**D**	NEt_3	DCM	24	55	98
10	**D**	NEt_3	THF	48	36	95
11	**D**	NEt_3	DCE	48	34	97
12	**D**	NEt_3	$CHCl_3$	48	56	97
13[d]	**D**	NEt_3	DCM	24	85	97
14[e]	**D**	NEt_3	DCM	24	88	98
15[f]	**D**	NEt_3	DCM	24	80	95
16[eg]	**D**	NEt_3	DCM	24	70	95
17[eh]	**D**	NEt_3	DCM	24	75	96

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol, 1 equiv), base (0.11 mmol, 1 equiv). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]**1a** (0.1 mmol), **2a** (0.13 mmol, 1.3 equiv), NEt_3 (0.143 mmol, 1.43 equiv). [e]**1a** (0.1 mmol), **2a** (0.14 mmol, 1.4 equiv), NEt_3 (0.154 mmol, 1.54 equiv). [f]**1a** (0.1 mmol), **2a** (0.15 mmol, 1.5 equiv), NEt_3 (0.165 mmol, 1.65 equiv). [g]50 mol % PhCOOH was added. [h]50 mol % LiCl was added.

azepino[1,2-*a*]indole products were obtained in high yield and excellent enantioselectivity.

We started our investigation with the reaction of dimethyl 2-((3-formyl-1*H*-indol-2-yl)methyl)malonate (**1a**) with (*Z*)-2-bromo-3-phenylacrylaldehyde (**2a**) in the presence of 10 mol % of NHC precatalyst and 1.1 equiv of NEt_3 in toluene (Table 1). The reaction using precatalyst **A** gave the desired [3+4] annulation product **3a** in 21% yield and 85% ee (entry 1). However, when precatalyst **B** was used under the same conditions, the product **3a** wasn't formed (entry 2). Additional studies found that chiral triazolium precatalyst **C** afforded **3a** with 26% yield and 93% ee (entry 3). The use of precatalyst **D** with *N*-mesityl substituent led to **3a** with 34% yield and 92% ee (entry 4). Subsequently, several bases were examined and the results showed that organic bases like DMAP and DIPEA gave compound **3a** with lower yields and slightly high ee values (entries 7–8). A switch of solvent from toluene to DCM resulted in a moderate yield (55%) and excellent ee (98%) (entry 9). Other solvents (THF, DCE) were screened, but the yield and enantioselectivity decreased (entries 10–11). In contrast, chloroform gave similar results for the asymmetric annulation (entry 12). To increase the yield of the reaction, the molar ratio of the substrates **1a** and **2a** were optimized (entries 13–15). The product **3a** was obtained in 88% yield and

Table 2 Substrates scope of the NHC-catalyzed [3+4] annulation[a]

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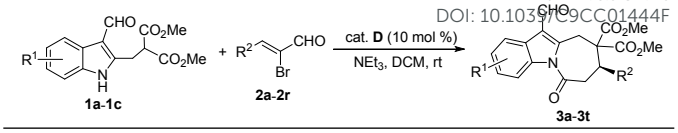


entry	R^1	R^2	time (h)	yield (%)[b]	ee (%)[c]
1	H (**1a**)	Ph (**2a**)	24	88 (**3a**)	98
2	H (**1a**)	2-BrC_6H_4 (**2b**)	24	84 (**3b**)	98
3	H (**1a**)	3-BrC_6H_4 (**2c**)	18	89 (**3c**)	91
4	H (**1a**)	4-BrC_6H_4 (**2d**)	12	91 (**3d**)	96
5[d]	H (**1a**)	4-MeC_6H_4 (**2e**)	24	89 (**3e**)	97
6	H (**1a**)	3-MeC_6H_4 (**2f**)	24	88 (**3f**)	96
7	H (**1a**)	3-ClC_6H_4 (**2g**)	12	90 (**3g**)	96
8	H (**1a**)	4-ClC_6H_4 (**2h**)	12	92 (**3h**)	96
9	H (**1a**)	4-FC_6H_4 (**2i**)	12	91 (**3i**)	97
10	H (**1a**)	3-FC_6H_4 (**2j**)	18	87 (**3j**)	96
11	H (**1a**)	4-$O_2NC_6H_4$ (**2k**)	24	85 (**3k**)	98
12	H (**1a**)	4-methyl formate (**2l**)	12	92 (**3l**)	99
13	H (**1a**)	1-naphthyl (**2m**)	12	91 (**3m**)	98
14	H (**1a**)	2-naphthyl (**2n**)	12	94 (**3n**)	>99
15	H (**1a**)	3,4-$Cl_2C_6H_3$ (**2o**)	12	90 (**3o**)	98
16	H (**1a**)	2-thienyl (**2p**)	18	89 (**3p**)	76
17	H (**1a**)	CH_3 (**2q**)	24	67 (**3q**)	93
18	H (**1a**)	Cy (**2r**)	24	12 (**3r**)	93
19	5-Cl (**1b**)	Ph (**2a**)	12	91 (**3s**)	98
20	5-CH_3 (**1c**)	Ph (**2a**)	18	87 (3t)	88

[a]Reaction conditions: **1** (0.1 mmol), **2** (0.14 mmol, 1.4 equiv), NEt_3 (0.154 mmol, 1.54 equiv), NHC **D** (0.01 mmol). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]The scale-up synthesis of compound **3e** was performed (**1a**, 1.73 mmol) and compound **3e** was obtained in 85% yield and 96% ee.

98% ee when 1.4 equiv of the 2-bromoenal **2a** was used (entry 14). Further screening of additives, such as $PhCO_2H$ and LiCl, failed to improve the yield (entries 16–17).

Having established the optimized conditions, the substrate scopes with regard to 2-bromoenals were investigated. As shown in Table 2, a range of 2-bromoenals **2a**–**2n** with both electron-withdrawing and electron-donating groups reacted smoothly with **1a** and products **3a**–**3n** were obtained in high yields and excellent enantioselectivities (entries 1–14). When the reaction of 2-bromoenal **2l** bearing methyl formate and **1a** was examined, product **3l** was obtained in excellent yield and enantioselectivity (entry 12). A switch of substituents from substituted phenyl groups to 1-naphthyl or 2-naphthyl groups, the asymmetric annulation conducted well and gave excellent yields and enantioselectivities (entries 13–14). In addition, 3,4-dichlorophenyl substituted 2-bromoenal **2o** was found to be readily participated in the asymmetric [3+4] annulation and afforded products **3o** with excellent yield and enantioselectivity (entry 15). However, 2-bromoenal with electron-riched heteroaromatic ring delivered the product **3p** in high yield and moderate enantioselectivity (entry 16). For (*Z*)-2-bromobut-2-enal (**2q**), product **3q** was formed in 67% yield and 93% ee (entry 17). Steric hindrance was proved obviously, and cyclohexyl substituted 2-bromoenal **2r** resulted in poor yield (entry 18). Finally, the asymmetric annulation of sub-

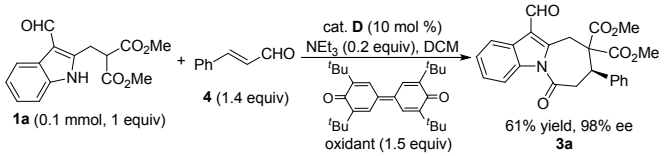
strates **1b–1c** with 2-bromoenal **2a** was evaluated. As expected, the desired product **3s** was obtained in 91% yield and 98% ee (entry 19). When 5-methyl substituted substrate **1c** was employed, the product **3t** was obtained in slightly lower yield and enantioselectivity (entry 20).

In order to further explore the scope of substrates, the enantioselective [3+4] annulations of **1a** with cinnamaldehyde, cinnamic acid, 3-phenylpropanoic acid were carried out, respectively. It is worth noting that compound **3a** could also be obtained by the annulation of **1a** with cinnamaldehyde (**4**) catalyzed by NHC precatalyst **D** in the presence of oxidant (Scheme 2). However, when carboxylic acids were used, the reactions did not occur. The cycloaddition product can readily undergo further transformation. Treatment of compound **3e** with $NaBH_4$ in THF at 0 °C, the reductive product **5** was afforded in 88% yield and 92% ee (Scheme 3).

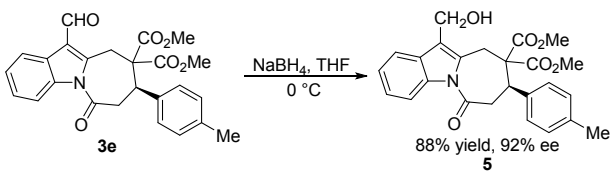
The absolute configuration of the product was determined to be (*R*)-**3d** by using X-ray crystal analysis (Figure 1). Other product configurations were assigned tentatively by analogy.

To understand the mechanism further, some control experiments were carried out (Scheme 4). Treatment of methyl 3-(3-formyl-1*H*-indol-2-yl)propanoate (**6**) with 2-bromoenal **2a** in the optimal conditions, the desired compound **7** wasn't formed (eqn. (1)). We next examined the reaction of dimethyl 2-((1*H*-indol-2-yl)methyl)malonate (**8**) with **2a** and product (*E*)-dimethyl 2-((1-cinnamoyl-1*H*-indol-2-yl)methyl)malonate (**9**) was afforded in 51% yield (eq. (2)). Furthermore, the reaction of substrates **1d** and **1e** with **2a** were tested, and the results showed that the desired products could not be formed (eqn (3)). The above results showed that the 3-formyl group in the indole moiety was required for this annulation.

On the basis of the above control experiments and relevant calculated results[14], a possible mechanism is proposed in Figure 2. Initially, NHC catalyst combines with 2-bromoenal **2** generated Breslow intermediate **I**. Subsequently, α,β-unsaturated acylazolium **II** is formed through tautomerization and debromination of intermediate **I**. Next, deprotonation and proton transfer of the substrate **1a** to the **1a'** in the presence of NEt_3 is possibly involved in this process. The Michael addition of **1a'** to intermediate **II** from the *re*-face (**III**) gives the enolate **IV**. Finally, the intermediate **IV** undergoes proton transfer, tautomerization and intramolecular lactamization to form the desired product **3** with release of the NHC catalyst.



Scheme 2. Application of cinnamaldehyde for synthesis of **3a**.



Scheme 3 Reduction reaction of compound **3e**.

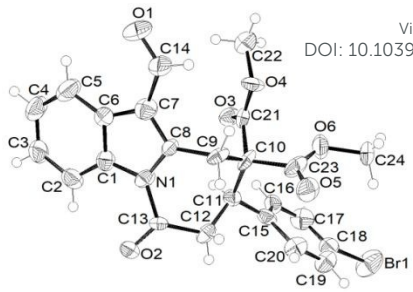
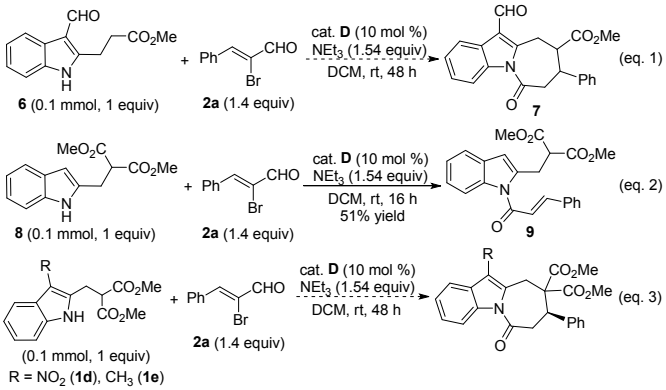


Figure 1 X-Ray crystallography of compound **3d**.



Scheme 4 Control experiments.

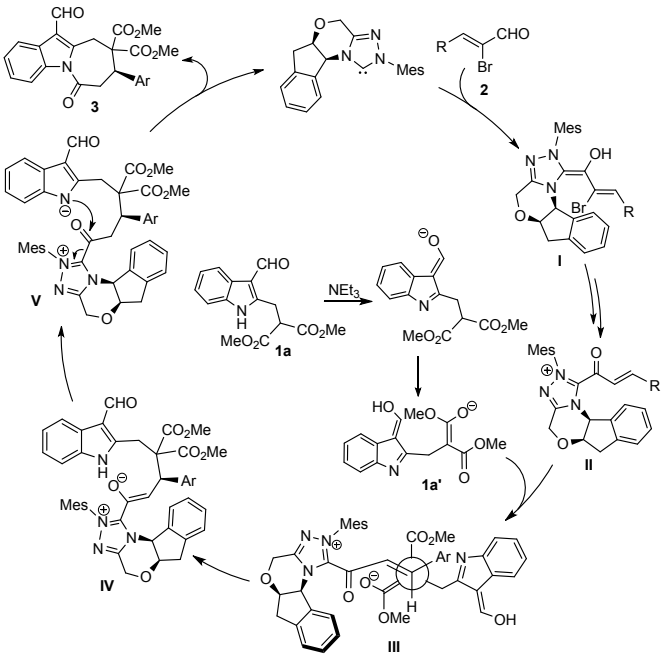


Figure 2 Possible catalytic cycle.

Conclusions

In summary, we have reported an efficiently enantioselective [3+4] annulation for the synthesis of functionalized azepino[1,2-*a*]indoles. The cycloaddition products were achieved in good yields with excellent enantioselectivities. Our studies suggest that the 3-formyl group in the indoles plays a

necessary mediated group for this [3+4] annulation. Future studies will aim to develop asymmetric [n+4] annulations.

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Conflicts of interest

There are no conflicts to declare.

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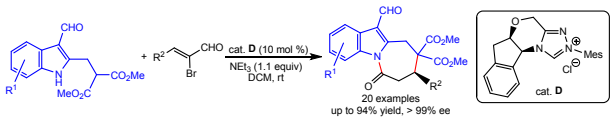

Enantioselective [3+4] annulation of 3-formylindol-2-methylmalonates with 2-bromoenals catalyzed by NHCs is described to efficient synthesis of functionalized azepino[1,2-*a*]indoles.