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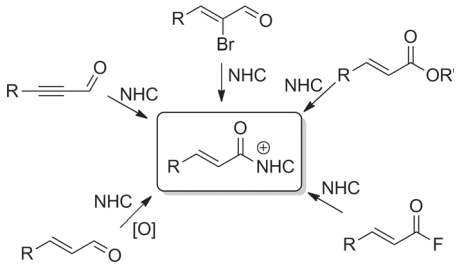
N-Heterocyclic Carbene-Catalyzed Enantioselective Annulation of Indolin-3-ones with Bromoenals

Qijian Ni, Xiaoxiao Song, Gerhard Raabe, and Dieter Enders*[a]

Abstract: *N*-Heterocyclic carbene-catalyzed reactions of indolin-3-ones with 2-bromoenals opened an asymmetric access to 3,4-dihydropyrano[3,2-*b*]indol-2(5*H*)-ones in good yields and with good to excellent enantioselectivities. This protocol tolerates a broad substrate scope. In addition, a possible mechanism for the annulation reaction is presented.

Over the past decade, *N*-heterocyclic carbene (NHC) catalysis opened an efficient and elegant access for the asymmetric synthesis of various chiral building blocks, which was made possible by its unique umpolung ability.[1] The classic NHC-catalyzed a^1-d^1-umpolung reactions, such as the benzoin condensation[2] and the Stetter reaction,[3] have been developed intensively. Since the pioneering reports by the groups of Glorius, Bode, and Rovis in 2004, homoenolate intermediates played an important role as new nucleophiles at the α or β position of aldehydes accessible for different electrophiles.[4] Recently, α,β-unsaturated acylazolium intermediates opened a new mode of reactions catalyzed by NHCs and they attracted great attention. Up to now, there are five kinds of precursors for the generation of α,β-unsaturated acylazoliums, such as ynals,[5] α,β-unsaturated acyl fluorides,[6] α,β-unsaturated esters,[6a,7] and stoichiometric oxidation of homoenolates[8] and α-functionalized enals,[9] which have been documented (Scheme 1).

With the development of these new approaches to α,β-unsaturated acylazolium intermediates, screening the nucleophiles was also essential. 1,3-Dicarbonyl compounds were recognized as the most common Michael donors to conduct 1,4-addition reactions followed by Claisen rearrangements and intramolecular acylations, which delivered dihydropyranones. Bode and co-workers have recently reported NHC-catalyzed annulations of α,β-unsaturated acylazoliums with stable enols such as naphthol[5c] and kojic acid.[5a] In addition, the NHC-catalyzed rearrangement of α,β-unsaturated enol esters to form dihydropyranones was demonstrated by Lupton and co-workers.[10] Very recently, Biju and co-workers have developed NHC-catalyzed reactions of enolizable aldehydes with α,β-unsaturated acylazoliums generated from 2-bromoenals.[9f] However, indolin-3-ones as a kind of C-/enol-O dinucleophiles were rarely employed in NHC-catalyzed reactions. To the best of our knowledge, only one recent paper reported the reaction of indolin-3-ones with ynals and enals combined with stoichiometric oxidants, thus leading to the formation of tricyclic indole-fused dihydropyranones.[5e] Based on the previous work, we now report the enantioselective NHC-catalyzed reaction of 2-bromoenals with indolin-3-ones, resulting in 3,4-dihydropyrano[3,2-*b*]indol-2-ones, which are regarded as common scaffolds in many biologically active natural products.[11]



Scheme 1. Formation of NHC-derived α,β-unsaturated acylazolium intermediates.

Initially, we investigated the optimal NHC catalysts for the model reaction of 1-acetylindolin-3-one (**1a**) with α-bromocinnamaldehyde (**2a**). The achiral precatalyst **A** promoted the reaction and gave the desired product in 13% yield in the presence of NaOAc (Table 1, entry 1). However, the precatalysts **B** and **E** did not yield the product under the same condition (Table 1, entries 2 and 5). Gratifyingly, good yields and *ee* values were obtained when the precatalysts **C** and **D** were used, and the former one proved to be superior in terms of yield and enantioselectivity (Table 1, entries 3 and 4). Further base screening (Table 1, entries 6–13) revealed that the use of inorganic or organic bases, such as K_3PO_4, NEt_3, DMAP, DIPEA, DPE, or TMEDA, resulted in good yields and good to excellent *ee* values of the desired product (Table 1, entries 6, 8, 10–13), except DBU, which led to no reaction (Table 1, entry 7), and DABCO producing only 15% yield (Table 1, entry 9). It is noteworthy that the base TMEDA obviously improved the *ee* value up to 92%. Based on these conditions, a number of solvents were screened next. Fortunately, 96% *ee* and 66% yield were ob-

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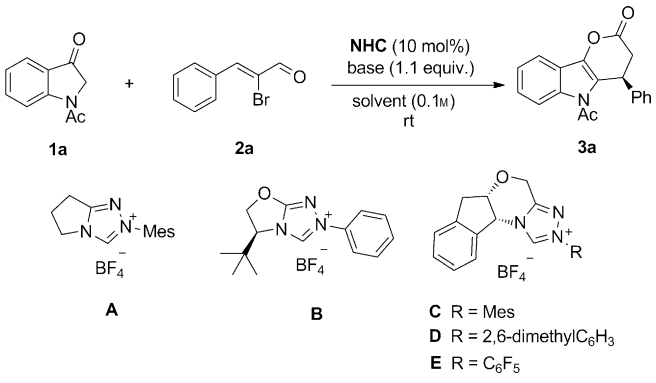
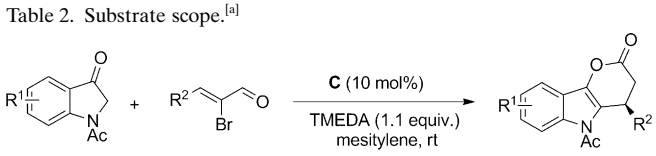
Table 1. Optimization of the reaction conditions.[a]



Entry	NHC	Solvent	Base	*t* [d]	Yield [%][b]	*ee* [%][c]
1	**A**	Toluene	NaOAc	2	13	0
2	**B**	Toluene	NaOAc	2	n.r.	–
3	**C**	Toluene	NaOAc	2	80	80
4	**D**	Toluene	NaOAc	2	63	77
5	**E**	Toluene	NaOAc	2	n.r.	–
6	**C**	Toluene	K_3PO_4	2	21	81
7	**C**	Toluene	DBU	2	n.r.	–
8	**C**	Toluene	DIPEA	2	75	80
9	**C**	Toluene	DABCO	2	15	90
10	**C**	Toluene	NEt_3	2	75	85
11	**C**	Toluene	DMAP	0.5	75	87
12	**C**	Toluene	DPE	1	67	89
13	**C**	Toluene	TMEDA	1	69	92
14	**C**	$CHCl_3$	TMEDA	1	64	83
15	**C**	THF	TMEDA	1	70	70
16	**C**	**Mesitylene**	**TMEDA**	**1**	**66**	**96**
17[d]	**C**	Mesitylene	TMEDA	1	30	96

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), NHC (10 mol%), base (1.1 equiv), solvent (2 mL), rt. [b] Yield of isolated product **3a** after column chromatography. [c] The *ee* value was determined by HPLC on a chiral stationary phase. [d] (*Z*)-2-iodocinnamaldehyde instead of **2a**. TMEDA = *N,N,N′,N′*-tetramethylethylenediamine, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DIPEA = *N,N*-diisopropylethylamine, DPE = 1,2-di(pyrrolidinyl)ethane, Mes = 2,4,6-trimethylphenyl, n.r. = no reaction.

Table 2. Substrate scope.[a]



3	R^1	R^2	Yield [%][b]	*ee* [%][c]
3a	H	Ph	68	92
3b	6-Cl	Ph	72	89
3c	6-F	Ph	62	93
3d	5-CF_3	Ph	67	67
3e	H	4-MeC_6H_4	66	93
3f	H	4-$MeOC_6H_4$	66	98
3g	H	2-MeO-5-Br-C_6H_3	70	94
3h	H	3-$MeOC_6H_4$	61	92
3i	H	4-ClC_6H_4	71	89
3j	H	3-ClC_6H_4	60	97
3k	H	4-FC_6H_4	68	93
3l	H	2-furyl	60	95

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), **C** (10 mol%), TMEDA (1.1 equiv), mesitylene (5 mL), rt. [b] Yield of isolated product **3** after column chromatography. [c] The *ee* value was determined by HPLC on a chiral stationary phase.

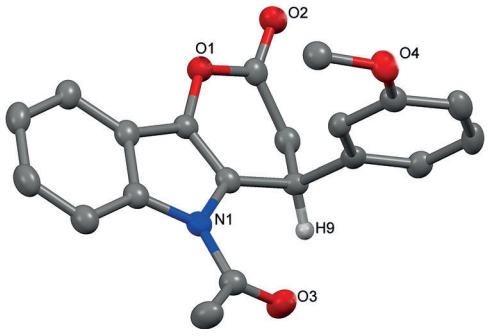


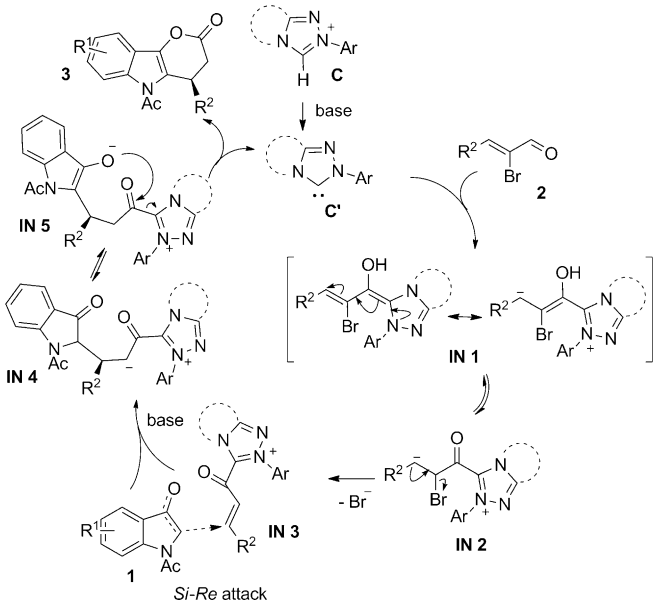
Figure 1. X-ray crystal structure of **3h**.

tained when mesitylene was used as solvent (Table 1, entry 16). Moreover, a switch of substrate **2** from **2a** to α-iodocinnamaldehyde led to an inferior yield (30%) but comparable *ee* value (96%) (Table 1, entry 17).

With the optimized conditions in hand, the substrate scope of the reaction was explored. Initially, we examined various substituted 1-acetylindolin-3-ones **1**. As shown in Table 2, indolinones bearing different substituents at the C6 position, such as 6-Cl or 6-F, gave the desired products in good yields and excellent *ee* values (Table 2, **3b** and **3c**). However, when R^1 is a 5-CF_3 group (Table 2, **3d**), only 67% *ee* was obtained. Next, a series of 2-bromoenals was tested for the reaction with **1a** in this protocol. Electron-donating or -withdrawing groups on the aromatic rings were well tolerated, delivering the dihydropyranoindol-2-ones in good yields and excellent enantioselectivities (Table 2, **3e–3k**). It is noteworthy that the (2)-furyl-substituted 2-bromoenal also underwent the transformation smoothly, yielding the product in 60% yield and with an *ee* value of 95% (Table 2, **3l**). Moreover, the absolute configuration of **3h** was unambiguously determined to be the *S*-configuration by X-ray crystal-structure analysis (Figure 1).[12] Further expanding the scope of the reaction revealed that this protocol required R^2 to be an aromatic substituent. Ethyl and *iso*-propyl substituents were also tested, but no products were obtained.

A plausible pathway for the annulation reaction is illustrated in Scheme 2. Initially, the nucleophilic addition of the NHC-catalyst **C′**, generated by the deprotonation of the triazolium salt **C**, to the bromoenal **2** affords the Breslow intermediate **IN1**,[13] which can be drawn as a mesomeric structure. Tautomerization and loss of bromide via **IN2** leads to the key α,β-unsaturated acylazolium **IN3**, which undergoes a Michael addition from the *Si* face of indolinone **1** attacking to the *Re* face of the α,β-unsaturated acylazolium due to the steric demand of the chiral NHC backbone. The subsequent lactonization yields the target product **3**, thereby releasing the NHC catalyst for further cycles.

In conclusion, we have developed an efficient NHC-catalyzed enantioselective annulation of indolin-3-ones with bro-



Scheme 2. Proposed reaction mechanism of the NHC-catalyzed annulation.

moenals to deliver dihydropyranoindol-2-ones in good yields and good to excellent *ee* values. The solvent mesitylene and the diamine base played important roles for the enantioselectivity. In addition, a wide range of substrates are tolerated under the optimized conditions.

Experimental Section

General Procedure for the Synthesis of 3,4-Dihydropyrano[3,2-b]indol-2-ones: To a dried and argon-filled Schlenk flask was added 1-acetylindolin-3-one (**1**) (0.5 mmol, 1.0 equiv), 2-bromocinnamaldehyde (**2**) (0.6 mmol, 1.2 equiv), triazolium salt **C** (0.05 mmol, 10 mol%), and TMEDA (0.55 mmol, 1.1 equiv) in mesitylene (5 mL). The mixture was stirred at room temperature and monitored by thin-layer chromatography until completion of the reaction. After work-up, the crude product was purified by column chromatography on silica gel (pentane/Et_2O 3:1) to afford the desired product **3** as a solid.

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Keywords: annulation · asymmetric synthesis · dihydropyranoindol-2-ones · *N*-heterocyclic carbenes · organocatalysis

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[12] CCDC 983351 contains the supplementary crystallographic data for the compound **3h** reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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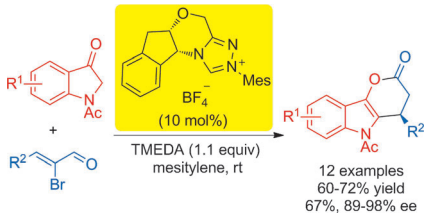

Asymmetric Synthesis

*Qijian Ni, Xiaoxiao Song, Gerhard Raabe, Dieter Enders** ____ ▮▮▮▮–▮▮▮▮

N-Heterocyclic Carbene-Catalyzed Enantioselective Annulation of Indolin-3-ones with Bromoenals