Asymmetric Organocatalysis Hot Paper

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N-Heterocyclic Carbene Catalyzed Formal [3+2] Annulation Reaction of Enals: An Efficient Enantioselective Access to Spiro-Heterocycles**

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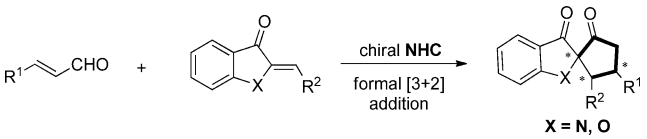
Abstract: *A highly enantioselective N-heterocyclic carbene (NHC) catalyzed formal [3+2] annulation of α,β-unsaturated aldehydes with azaaurones or aurone generating spiro-heterocycles has been developed. The protocol represents a unique NHC-activation-based approach to access spiro-heterocyclic derivatives bearing a quaternary stereogenic center with high optical purity (up to 95% ee).*

N-Heterocyclic carbene (NHC) catalysis has become well known for the development of unique transformations based on the umpolung of aldehydes.[1] In particular, the Bode group[2] and the Glorius group[3] have independently reported the NHC-catalyzed formal [3+2] annulation of enals with aldehydes via homoenolate intermediates affording γ-butyrolactones. Later, the NHC–homoenolate pathway was explored with various types of reactive electrophiles to prepare synthetically valuable cyclic[4–7] as well as acyclic[8] molecular scaffolds. The Nair group and the Bode group reported a formal [3+2] annulation of enals with cyclic dienones by a conjugate addition–cyclization sequence generating cyclopentanones.[9] Recently, the Scheidt group[10] and the Ye group[11] described the highly enantioselective formal [4+3] annulation of enals with *o*-quinone methides to access benzoxopinones. However, to the best of our knowledge, no highly enantioselective variant of the cyclopentanone annulation[9] to generate spiro-pseudoindoxyl moieties has been available.

The spiro-heterocyclic moiety constitutes the core structure of numerous natural alkaloids and pharmaceuticals exhibiting significant biological activities.[12] For example, brevianamide A, isolated as the major fluorescent metabolite from *Penicillium brevicompactum* by Birch and Wright,[13] was found to exhibit insecticidal activity.[14] In addition to its interesting biological activity, this unique structural motif contains a spirocyclic quaternary stereogenic carbon center at the C2 position of indole, a structural unit that has long challenged synthetic organic chemists.[15] Oxidative rearrangement of indole derivatives has been considered one of the most effective ways to construct the racemic spiro-pseudoindoxyl framework.[16] Despite extensive efforts, catalytic asymmetric syntheses of substituted spiro-heterocyclic derivatives by direct synthetic approaches are still rare.[11] Therefore, the development of a catalytic asymmetric synthesis of optically active spiro-pseudoindoxyl moieties has been a highly desirable yet challenging subject.

Based on the importance of the spiro-heterocycle synthesis and our interest in NHC chemistry, we envisioned that novel methods for spiro-heterocycles might be achieved by NHC-catalyzed annulation via an NHC-generated homoenolate (Scheme 1). Herein, we report our results on this NHC-catalyzed highly enantioselective formal [3+2] annulation of enals with azaaurones or aurone, thus providing an alternative route to valuable enantioenriched substituted spiro-heterocycles.



Scheme 1. The synthesis of spiro-heterocycles by the NHC-catalyzed annulation reaction.

We started the evaluation of our hypothesis by combining cinnamaldehyde (**1a**) with azaaurone[17] **2a** using azolium salt **4a** as the NHC precatalyst and DBU as the base in THF at 50 °C (Table 1, entry 1). To our delight, the reaction proceeded smoothly and afforded the desired product **3aa** in 18% yield with 23% *ee*. Encouraged by this result, we conducted a vigorous screening with different NHC catalysts, which displayed remarkable effects on the outcome of the reaction (entries 1–5). Gratifyingly, the desired spiro-pseudoindoxyl **3aa** could be obtained in 77% yield with 91% *ee* when the precatalyst **4d** was employed (entry 4). The NH variant of the azaaurone generated no product at all (entry 6). When 5 mol% catalyst was employed the yield and enantioselectivity were lower than with 10 mol% catalyst (entries 4 and 7). The use of other bases, such as NaOAc and Et_3N, resulted in no formation of the desired product (entries 8 and 9). Varying the solvents led to no improvement in the reaction performance and THF was proven to be the solvent of choice (entries 4 and 10–12). Naturally, the opposite configuration of **3aa** can be accessed in the same yield and enantioselectivity by using the opposite enantiomer of the NHC precatalyst **4d′**; in this way both spiro-pseudoindoxyl enantiomers can be

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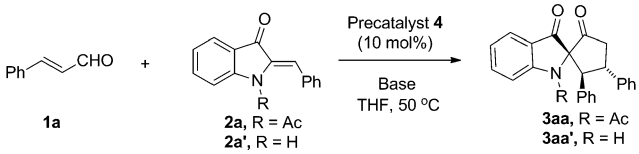
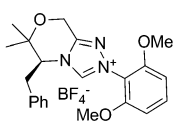
Table 1: Optimization of the reaction conditions.[a]

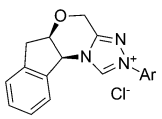


Entry	Precat.	Solv.	Base	Yield [%][b,c]	d.r.[d]	*ee* [%][e]
1	**4a**	THF	DBU	18	4:1	23
2	**4b**	THF	DBU	13	4:1	57
3	**4c**	THF	DBU	85	10:1	80
4	**4d**	THF	DBU	**77**	**12:1**	**91**
5	**4e**	THF	DBU	n.r.	–	–
6[f]	**4d**	THF	DBU	n.r.	–	–
7[g]	**4d**	THF	DBU	51	4:1	88
8	**4d**	THF	Et_3N	n.r.	–	–
9	**4d**	THF	NaOAc	n.r.	–	–
10	**4d**	toluene	DBU	35	4:1	70
11	**4d**	EtOAc	DBU	58	7:1	80
12	**4d**	CH_3CN	DBU	70	7:1	80
13[h]	**4d′**	**THF**	DBU	**75**	**12:1**	**91**

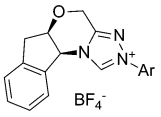
[a] Conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), chiral precatalyst (10 mol%), base (150 mol%), solvent (0.1 M in **2a**), 50 °C, 24 h. [b] Yield of the isolated product after column chromatography. [c] Combined yield of isolated diastereomers. [d] Determined by ^{1}H NMR spectroscopy. [e] The *ee* value was determined by HPLC using a chiral stationary phase. [f] **2a′** (1 equiv) was used. [g] 5 mol% of **4d** was used. [h] NHC precatalyst **4d′** (enantiomer of **4d**) was used and the enantiomer of **3aa** was obtained. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, n.r. = no reaction.



4a



4b: Ar = 2,6-$(MeO)_2C_6H_3$
4c: Ar= 2,6-$Et_2C_6H_3$



4d: Ar = 2,4,6-$Me_3C_6H_2$
4e: Ar = C_6F_5

prepared (entry 13). The relative and absolute configurations of **3aa** were assigned based on its single-crystal X-ray diffraction analysis (Figure 1).[18]

With the optimal reaction conditions in hand, we set out to explore the generality of the procedure in terms of substrates. As shown in Table 2, the annulation of azaaurone (**2a**) with

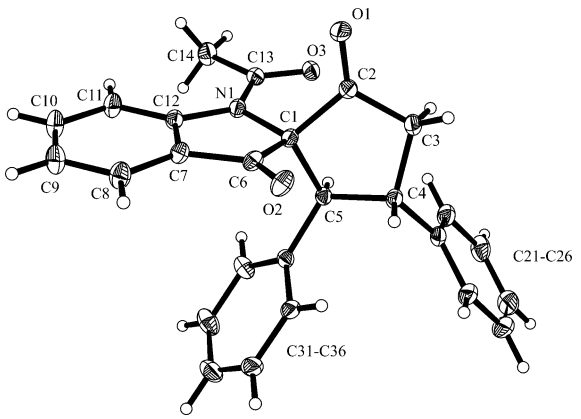
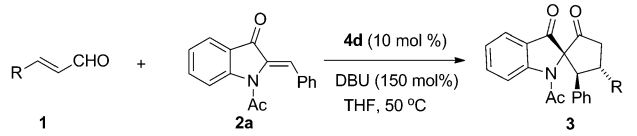
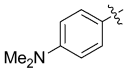


Figure 1. X-ray structure of compound **3aa** (thermal ellipsoids are shown at the 15% probability level).

Table 2: Scope of the α,β-unsaturated aldehydes.[a]



Entry	R	3	Yield [%][b,c]	d.r.[d]	*ee* [%][e]
1	C_6H_5	**3aa**	77	12:1	91
2	4-MeC_6H_4	**3ba**	70	14:1	92
3	4-$MeOC_6H_4$	**3ca**	74	17:1	92
4	2-furyl	**3da**	66	16:1	90
5		**3ea**	68 (61)[f]	7:1 (7:1)	92 (92)
6	4-ClC_6H_4	**3fa**	64	6:1	92
7	4-BrC_6H_4	**3ga**	58	4:1	94
8	4-FC_6H_4	**3ha**	80	3:1	91
9	3-ClC_6H_4	**3ia**	69	6:1	91
10	methyl	**3ja**	76	6:1	92
11	n-Pr	**3ka**	58	9:1	95

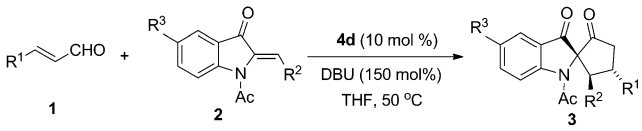
[a] Reactions performed with **1** (0.2 mmol) and **2a** (0.1 mmol), 24 h. [b] Yield of the isolated product after column chromatography. [c] Combined yield of isolated diastereomers. [d] Determined by ^{1}H NMR spectroscopy. [e] The *ee* value was determined by HPLC using a chiral stationary phase. [f] The reaction was performed on a 0.5 mmol scale.

a variety of α,β-unsaturated aldehydes **1**, including those bearing electron-withdrawing and -donating substituents was investigated under the optimized reaction conditions. High enantioselectivities ranging from 90% to 94% *ee* and synthetically useful diastereoselectivities were observed for all tested aldehydes (Table 2, entries 1–10). Electron-rich β-aryl enals could undergo smooth annulation reactions with 90-92% *ee* (entries 2–5). Electron-deficient β-aryl enals also facilitate the annulation with excellent stereoselectivities (entries 6–9). Notably, the extension of the protocol to alkyl-substituted enals was also successful and afforded annulation adducts **3ja** and **3ka** with high diastereo- and enantioselectivity (entries 10 and 11).

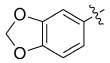
Investigation of the scope of the azaaurones **2** was carried out using α,β-unsaturated aldehyde **1a** as the reaction partner under the optimized conditions (Table 3). Substrates **2** containing a range of electron-donating and -withdrawing substituents on the phenyl ring react with α,β-unsaturated aldehyde **1a** to afford the corresponding annulation products **3ab–3al** with high diastereo- and enantioselectivities (up to >20:1 d.r. and 95% *ee*; Table 3, entries 1–10). Notably, the introduction of substituents to the indolin-3-one moiety was well tolerated and resulted in excellent levels of enantioselectivity (94% *ee*, entry 11). In addition, azaaurones having a cinnamyl substituent also worked well for the reaction, thus affording the desired spiro-heterocycles **3am** and **3jm** in moderate yields with excellent enantioselectivity (entries 12 and 13).

To test the synthetic utility of the present annulation of enals, we performed the reaction on a gram scale (5 mmol). Under the optimized reaction conditions, the formal [3+2] reaction proceeded smoothly and provided spiro-heterocycle **3ca** in 68% yield (1.44 g), 17:1 d.r. and 93% *ee* (Scheme 2).

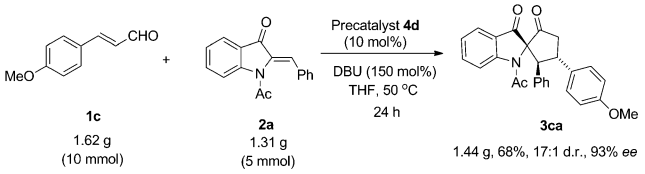
Table 3: Scope of the substituted azaaurones.[a]



1 2 3

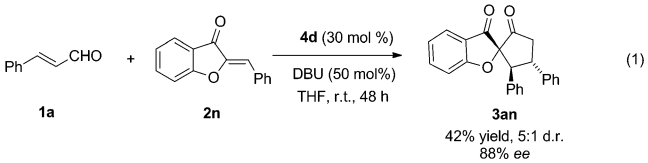
Entry	R^1	R^2	R^3	3	Yield [%][b,c]	d.r.[d]	*ee* [%][e]
1	Ph	4-BrC_6H_4	H	**3ab**	65	>20:1	95
2	Ph	4-ClC_6H_4	H	**3ac**	61	>20:1	93
3	Ph	4-FC_6H_4	H	**3ad**	83	10:1	94
4	Ph	4-CNC_6H_4	H	**3ae**	57	>20:1	90
5	Ph	3-ClC_6H_4	H	**3af**	61	10:1	93
6	Ph	4-$MeOC_6H_4$	H	**3ag**	62	12:1	92
7	Ph	4-MeC_6H_4	H	**3ah**	71	9:1	94
8	Ph	3-$MeOC_6H_4$	H	**3ai**	80	9:1	91
9[f]	Ph	2-furyl	H	**3aj**	51	3:1	90
10	Ph		H	**3ak**	82 (71)[g]	14:1 (12:1)	94 (94)
11	Ph	C_6H_5	Cl	**3al**	70	9:1	94
12	Ph		H	**3am**	48	3:1	91
13	Me		H	**3jm**	50	8:1	90

[a] Reactions performed with **1a** (0.2 mmol) and **2** (0.1 mmol), 24 h. [b] Yield of the isolated product after column chromatography. [c] Combined yield of isolated diastereomers. [d] Determined by ^{1}H NMR spectroscopy. [e] The *ee* value was determined by HPLC using a chiral stationary phase. [f] The starting material was used as an *E*/*Z* mixture (3:2). [g] The reaction was performed on a 0.5 mmol scale.



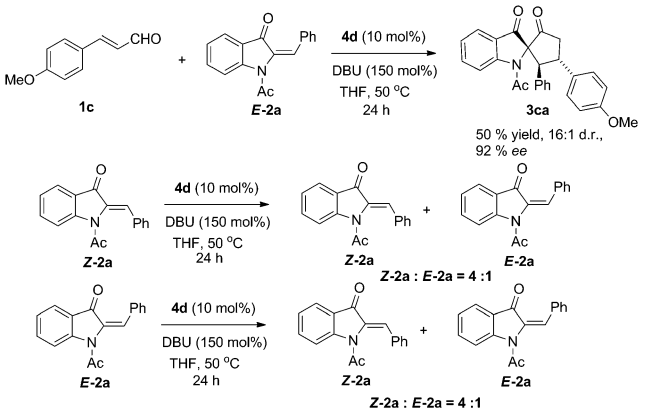
Scheme 2. Scale-up of the formal [3+2] reaction.

To further expand the usefulness of this transformation the formation of spiro-heterocycles from an aurone was also tested [Eq. (1)]. The reaction conditions for this formal [3+2] reaction were investigated again. We found that the reaction of aurone **2n** with 30 mol% of catalyst **4d** yielded **3an** with high enantioselectivity.



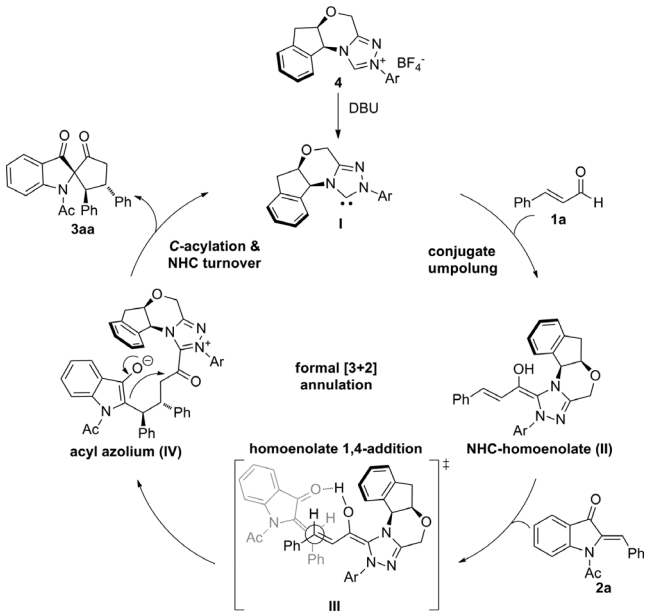
(1)

We next evaluated the effect of the configuration of azaaurone **2a** in the reaction with enal **1c** (Scheme 3). Under the optimized conditions, the same product **3ca** was formed in high enantioselectivity when ***E*-2a** was used in this annulation procedure. To advance the understanding of this phenomenon, a series of control experiments were carried out. Under the optimized conditions, in the absence of enal, ***Z*-2a** was converted to a mixture of azaaurones (***Z*:*E*** = 4:1). A parallel experiment using ***E*-2a** was independently carried out and generated a mixture with the same ratio of configurations (***Z*:*E*** = 4:1).[19] On the basis of the experimental study and the absolute configurations of the products, ***Z*-azaaurone** is most likely involved in the reaction.



Scheme 3. Effect of the configuration of the azaaruone.

The proposed catalytic cycle is illustrated in Scheme 4. First, the NHC organocatalyst **I** is generated by deprotonation of the precatalyst salt **4**. The addition of NHC organocatalyst **I** to the enal **1a** gives the NHC–homoenolate **II**, which forces the Michael addition from the back face and subsequent coordination through a hydrogen-bonding interaction presented in the intermediate **III**. Notably, the stereochemistry observed can be best explained by the proposed reaction model shown in the intermediate **III**. Following carbon–carbon bond formation, the tautomerization process occurs that gives rise to acyl azolium **IV**, which then presumably undergoes *C*-acylation to furnish the final product **3aa** and regenerates the NHC organocatalyst **I**.[1,9,20]



Scheme 4. Proposed mechanism.

It should be noted that the pathway for regeneration of the free NHC catalyst from an acyl azolium intermediate **IV** via *C*-acylation is very rare.

In conclusion, we have developed an asymmetric, NHC-catalyzed formal [3+2] annulation of α,β-unsaturated aldehydes with azaaurones or aurone. The desired products were obtained in moderate to good yields with excellent enantioselectivities. Furthermore, the protocol also represents a unique NHC-activation-based approach to access spiroheterocyclic derivatives bearing a quaternary stereogenic center with high optical purity; this structural unit is difficult to prepare by traditional strategies. The reaction proceeded probably through the conjugate addition of an NHC–homoenolate to the azaaurone or aurone, followed by *C*-acylation to regenerate the NHC catalyst and provide the spiroheterocyclic product. We expect this direct functionalization to offer alternative and concise strategies for the synthesis of indole-based alkaloids and pharmaceutical molecules.

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Keywords: asymmetric synthesis · enals · N-heterocyclic carbenes · organocatalysis · spiro-heterocycles

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Communications

Asymmetric Organocatalysis

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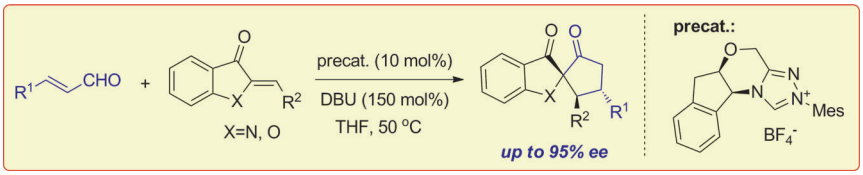
N-Heterocyclic Carbene Catalyzed Formal [3+2] Annulation Reaction of Enals: An Efficient Enantioselective Access to Spiro-Heterocycles



Ring, ring: A highly enantioselective formal [3+2] annulation of α,β-unsaturated aldehydes with azaaurones or aurone is catalyzed by an N-heterocyclic carbene (NHC) and generates spiro-heterocycles. The protocol represents a unique NHC activation-based approach to access spiro-heterocyclic derivatives bearing a quaternary stereogenic center with high optical purity.