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Catalytic Enantioselective Aza-Benzoin Reactions of Aldehydes with 2*H*-Azirines

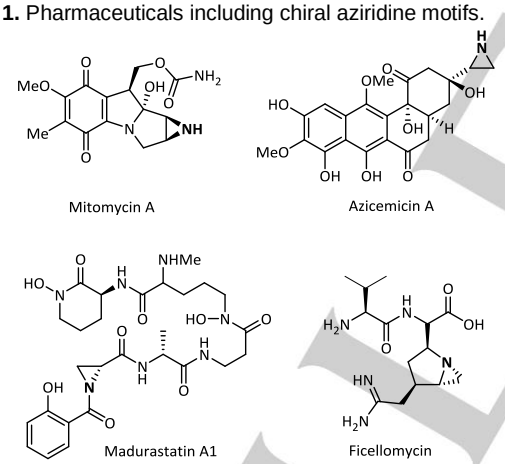
Qiupeng Peng, Donghui Guo, Jianbo Bie and Jian Wang*

Dedication ((optional)

Abstract: *The unprecedented enantioselective aza-benzoin reaction of aldehydes with 2H-azirines was developed by utilizing chiral N-heterocyclic carbene as catalyst. A wide range of corresponding aziridines can be obtained in good yields with high enantioselectivities. The obtained optically active aziridines as useful synthons should be useful in the synthesis of other valuable molecules.*

Owing to their inherent ring strain and medicinal property, aziridines are widely explored during the preparation of nitrogen containing complex molecules, natural products, and pharmaceuticals.[1] In biology, aziridine alkaloids have been known to play a seminal role in the secondary metabolism of some microorganisms and plants.[2] Moreover, aziridines in natural as well as synthetic molecules already exhibit a broad range of biological functions against pathogenic bacteria, microorganisms and cancer cell lines, strongly indicating that the aziridine core is essential to achieve such bioactivities.[3] As shown in Figure 1, Mitomycin A,[4a, 4b] Azicemicin B,[4c, 4d] Madurastatin A1[4e] and Ficellomycin [4f] have been identified as important pharmaceuticals.

Figure 1. Pharmaceuticals including chiral aziridine motifs.



Building upon the structure importance of aziridines, chemists devoted many efforts to the assembly of such scaffolds. In contrast to the broad applications of aziridines, synthetic protocol is rarely described. As shown in Scheme 1a, three general approaches were established.[5]

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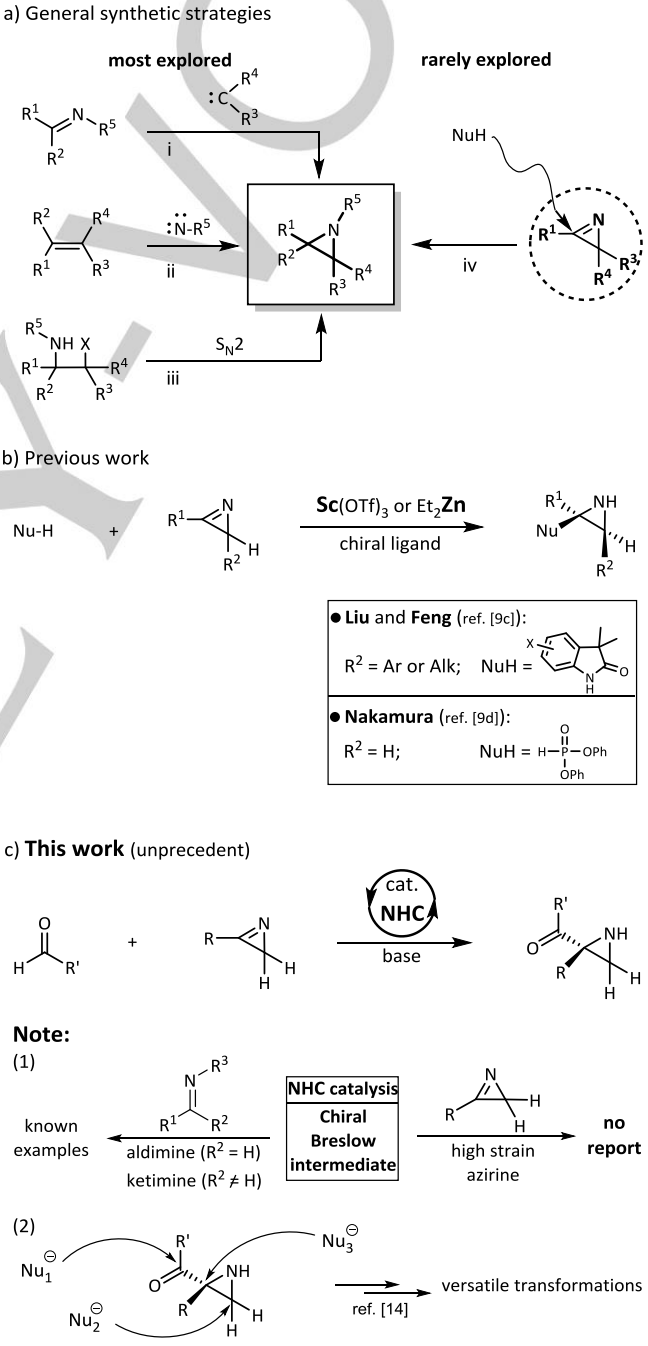
[**] Supporting information for this article is available on the WWW under http://dx.doi.org

Scheme 1. Asymmetric synthesis of chiral aziridines.



i) asymmetric aziridination via carbene addition to imines (Scheme 1a-i); ii) enantioselective aziridination via nitrene transfer to alkenes (Scheme 1a-ii); iii) chiral aziridination via stereoselective intramolecular S_N2 reaction of α-halo-β-amines (Scheme 1a-iii). In brief, above methods belong to ring

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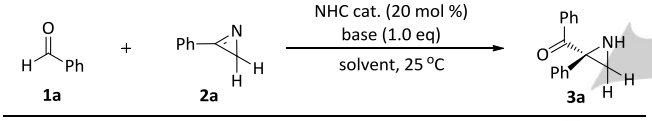
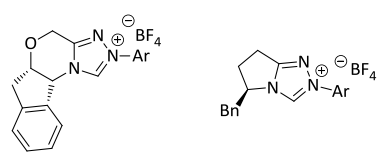
construction strategy. Recently, a promising strategy by using highly strained aza-three-membered cycles as substrates,[6] has attracted considerable attention of synthetic chemists to produce achiral aziridines. In this design, 2*H*-azirines[7] are selected and employed as the specific building blocks. Despite these successful examples, the catalytic enantioselective synthesis of chiral aziridines is still rarely explored.[8] Until 2002, Somfai and co-workers reported the first enantioselective reaction of 2*H*-azirines and Grignard reagents. However, this reaction employed a stoichiometric amount of (–)-sparteine and the generated products indicated with low *ee* values.[9a] Later on, the Zhang group reported an improved example of chiral imidodiphosphoric acid-catalyzed enantioselective reaction of 2*H*-azirines with pyrazoles, affording aziridines with moderate to high enantioselectivities.[9b] Simultaneously, Liu and Feng *et al.* reported a highly enantioselective imine amidation to assemble chiral aziridines by utilizing a novel chiral *N*,*N'*-dioxide/Sc^{III} catalyst.[9c] Shortly after, Nakamura and co-workers reported a chiral bis(imidazoline)/Zn(II)-catalyzed nucleophilic addition of phosphites to 2*H*-azirines, generating aziridines in good yields with high to excellent enantioselectivities.[9d] While pioneering works are influential, practical applications of these protocols are always affected by their scope to a certain extent. [10] And also, the model of stereocontrol for the assembly of chiral aziridine derivatives is still in its infancy. Therefore, new and efficient synthetic strategies are strongly recommended to complement existing protocols.

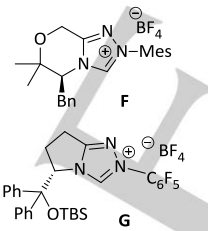
Table 1. Optimization of the reaction conditions.[a]





A: Ar = Mes
B: Ar = 2,4,6-$(Cl)_3C_6H_2$

C: Ar = Mes
D: Ar = 2,4,6-$(Cl)_3C_6H_2$
E: Ar = C_6F_5



F

G

Entry	NHC cat.	Base	Solvent	*ee* [%][b]	Yield [%][c]
1	**A**	Cs_2CO_3	THF	-	< 5
2	**B**	Cs_2CO_3	THF	78[g]	9
3	**C**	Cs_2CO_3	THF	97	29
4	**D**	Cs_2CO_3	THF	94	41
5	**E**	Cs_2CO_3	THF	-	< 5
6	**F**	Cs_2CO_3	THF	-	< 5
7	**G**	Cs_2CO_3	THF	-	< 5
8	**D**	Cs_2CO_3	MeCN	-	< 5
9	**D**	Cs_2CO_3	DCM	-	< 5
10	**D**	Cs_2CO_3	MTBE	95	65
11	**D**	KOAc	MTBE	94	33
12	**D**	$KHCO_3$	MTBE	-	< 5
13	**D**	DBU	MTBE	-	< 5
14[d]	**D**	Cs_2CO_3	MTBE	94	70
15[e]	**D**	Cs_2CO_3	MTBE	95	78
16[e, f]	**D**	Cs_2CO_3	MTBE	94	72

[a] Reaction conditions: **1a** (0.26 mmol), **2a** (0.20 mmol), NHC cat. (20 mol %), base (0.20 mmol), THF (3.0 mL), 25 ℃, argon atmosphere, 24 h. [b] The enantiomeric excesses (*ee*) were determined by HPLC with a chiral stationary phase. [c] Yield of isolated product. [d] MTBE (2 mL), MTBE = methyl *tert*-butyl ether. [e] MTBE (1.5 mL). [f] 15 mol % cat. **D**, 30 h. [g] Opposite enantiomer was obtained

Inspired by the nucleophilicity of Breslow intermediate,[11] we herein became intrigued by the possibility of achieving the *N*-heterocyclic carbenes (NHCs)-catalyzed aza-benzoin reaction via using ring strained 2*H*-azirines as substrates (Scheme 1c). In recent years, NHC-catalyzed umpolung reaction [12] of aldehydes has enabled numerous attractive reactions, thus leading to various accomplishments of challenging bond connections. Within this context, catalytic aza-benzoin reactions have received an impressive progress (Scheme 1c).[13] Despite the discovery of Breslow intermediate very early, the first asymmetic aza-benzoin reaction of aryl aldehydes with benzoyl aldimines was reported by Miller and coworkers until 2005.[13d] Recently, an elegant enantioselective NHC-catalyzed aza-benzoin reaction of *N*-Boc protected aldimines was reported by Rovis et al., using aliphatic aldehydes as reaction partners.[13k] Soon after, catalytic enantioselective aza-benzoin reaction of ketimines also received breakthroughs. The groups of Ye[13o] and Chi[13q] demonstrated the NHC-catalyzed asymmetric aza-benzoin reaction of aldehydes with activated ketimines (e.g. trifluoromethyl ketimines, isatin-derived ketimines) is also feasible. Most recently, Enders and coworkers disclosed a unique NHC-catalyzed homo-Mannich reaction of isatin-derived ketimines via the use of the β-carbon nucleophility of enals.[13r] To the best of our knowledge, the enantioselective aza-benzoin reaction of 2*H*-azirines with aldehydes catalyzed by NHC has not yet been reported by far. On the other hand, obtained chiral aziridine products are also useful building synthons for further valuable transformations in the presence of versatile nucleophiles[14] (Scheme 1c).

We commenced our study with the model reaction of benzaldehyde **1a** with 3-phenyl-2*H*-azirine **2a**. Key results are briefly summarized in Table 1. Given the importance of structural diversification on the success of a given catalytic transformation, examining a wide variety of catalyst structures is essential. A number of chiral triazolium catalysts **A**–**G** were screened initially. When the widely explored indanol-derived triazolium **A**[15] was used as catalyst, only a trace amount of product **3a** was formed (Table 1, entry 1). Although triazolium catalyst **B**[15] with *N*-2,4,6-$(Cl)_3C_6H_2$ substituent afforded **3a** with a moderate *ee*, only albeit a low yield (Table 1, entry 2). To further understand the importance of catalyst scaffold, a morpholinone-derived triazolium catalyst **F** was tested and showed no catalytic activity (Table 1, entry 6). In contrast, *L*-phenylalanine-derived catalyst **C**[16] afforded product **3a** in 29% yield with 97% *ee* (Table 1, entry 3). It was found that catalyst **E**[16] with an *N*-C_6F_5 side chain, or catalyst **G**[17] with a bulky *tert*-butyldimethylsilyl (TBS) side chain, also showed no catalytic activity (Table 1, entry 5 and 7, < 5% yield). Gratifyingly, an enhanced result was achieved in the presence of *L*-phenylalanine-derived triazolium catalyst **D** with an *N*-2,4,6-$(Cl)_3C_6H_2$ substituent (Table 1, entry 4, 94% *ee*, 41% yield). To further improve the catalytic performance, solvent, base, catalyst loading, and reaction concentration were next evaluated. We were pleased to find that catalyst **D** (15 mol %) in combination with Cs_2CO_3 (1.0 equiv) in methyl *tert*-butyl ether (MTBE, [M] = 0.13 mol/L) provides the desired product **3a** in a good yield with excellent enantioselectivity (Table 1, entry 16, 72%, 94% *ee*, 30 h).

With the optimized reaction conditions in hand, the scope of the aldehydes was investigated (Table 2). First, screened aromatic aldehydes bearing an electron-withdrawing group (e.g. CN, CF_3, or Ph), were compatible with the optimal conditions, resulting in the corresponding aziridines in good yields with excellent *ee* values (**3d–f**). It is noteworthy that halides (e.g. F, Cl, and Br) in position 2, 3 or 4 were also tolerated, and the corresponding products (**3b**, **3c**, **3h**, **3i** and **3j**, respectively) could undergo further functionalization via cross-coupling to assemble more elaborate structures. Second, electron-rich aldehydes was also suitable and provided the aziridine derivatives (**3g** and **3k)** in high yields with excellent enantioselectivities. The 2-naphthalenecarboxaldehyde can participate in the reaction to give **3l** in excellent

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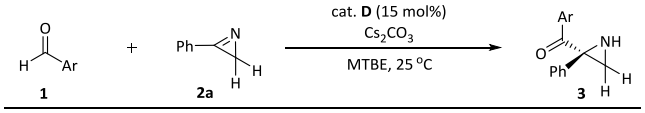
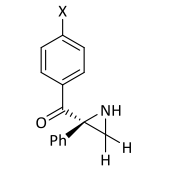
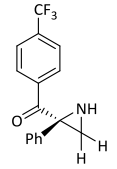
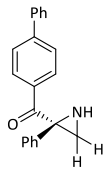
enantioselectivity. In addition, a number of heteroaromatic aldehydes successfully furnished the desired products **3m**–**t** in good conversions and with excellent *ee* values. Unfortunately, an aliphatic aldehyde such as butyraldehyde failed to participate in the reaction (not shown). In sharp cotrast to aromatic aldehydes, aliphatic aldehydes are known to be much less reactive in NHC-catalyzed aza-benzoin reactions.[13]

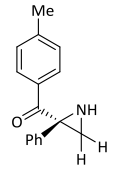
Table 2. Scope of aldehydes.[a,b]

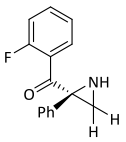


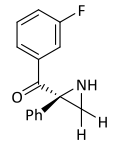

3a: X = H, 72%, 95% *ee*
3b: X = Cl, 95%, 96% *ee*
3c: X = Br, 90%, 96% *ee*
3d: X = CN, 87%, 97% *ee*

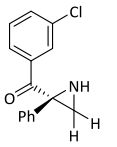

3e: 90%, 95% *ee*

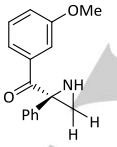

3f: 79%, 98% *ee*

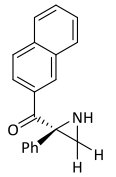

3g: 68%, 95% *ee*

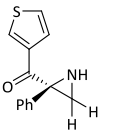

3h: 84%, 98% *ee*

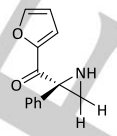

3i: 88%, 95% *ee*

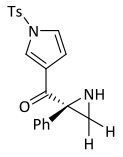

3j: 96%, 97% *ee*

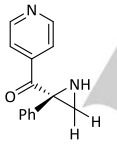

3k: 85%, 94% *ee*

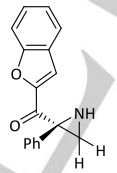

3l: 84%, 97% *ee*

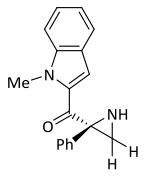

3m: 61%, 88% *ee*

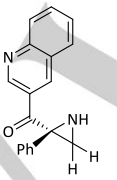

3n: 95%, 89% *ee*[c]

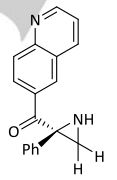

3o: 88%, 87% *ee*[c]


3p: 57%, 98% *ee*


3q: 91%, 93% *ee*[c]


3r: 89%, 70% *ee*

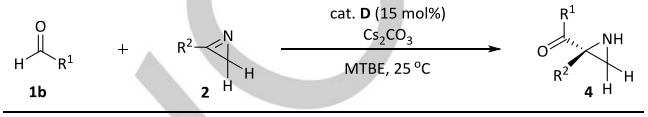

3s: 97%, 95% *ee*

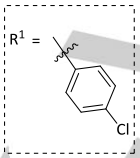

3t: 84%, 95% *ee*

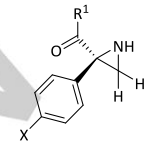
[a] Reaction conditions: **1** (0.26 mmol), **2a** (0.20 mmol), cat. **D** (15 mol %), Cs_2CO_3 (0.20 mmol), MTBE (1.5 mL), 25 ℃, argon atmosphere, 18-60 h. [b] Yield of isolated product. [c] cat. **C** (15 mol %) used.

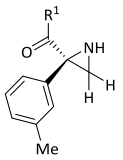
Further investigation on the scope of 2*H*-azirines was conducted (Table 3). The steric and electronic effects on the aromatic ring of azirines were evaluated by systematically varying substituent patterns. When examined substrates have either electron-withdrawing or electron-donating groups at 2-, 3-, or 4-substituted positions on the phenyl rings, good yields and high *ee* values were regularly observed (**4a–g**). Azirines having a naphthyl motif or a heteroaryl group, also afforded desired chiral aziridine derivatives **4h**–**k** in 81–87% yield with 93–94% *ee*. When a benzyl group replaced the aromatic ring in azirine, high *ee* could still be achieved (**4l**). When azirine has an alkyl substituent, the reaction showed a relatively low activity, but still provided high enantioselectivity (**4m**). Notably, azirine bearing an alkenyl group, was also successful in yielding the corresponding product **4n** in high enantioselectivity. The absolute configuration of **3f** was determined to be (*R*) by X-ray crystallography (Table 2), and other products were assigned by analogy. [18, 19]

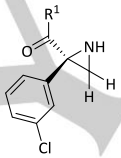
Table 3. Scope of 2-*H*-azirines.[a,b]

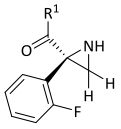


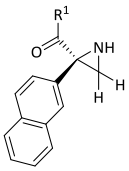


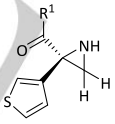

4a: X = Me, 92%, 93% *ee*
4b: X = OMe, 90%, 92% *ee*
4c: X = F, 90%, 96% *ee*
4c: X = Cl, 88%, 96% *ee*

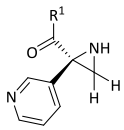

4e: 85%, 96% *ee*

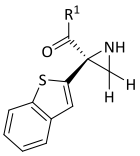

4f: 93%, 98% *ee*

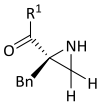

4g: 82%, 97% *ee*

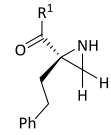

4h: 81%, 94% *ee*

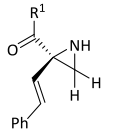

4i: 80%, 95% *ee*


4j: 86%, 97% *ee*[c]


4k: 87%, 94% *ee*

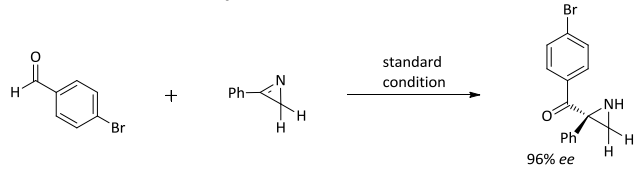

4l: 63%, 91% *ee*


4m: 48%, 91% *ee*


4n: 60%, 85% *ee*

[a] Reaction conditions: **1b** (0.26 mmol), **2** (0.20 mmol), cat. **D** (15 mol %), Cs_2CO_3 (0.20 mmol), MTBE (1.5 mL), 25 ℃, argon atmosphere, 18–60 h. [b] Yield of isolated product. [c] cat. **C** (15 mol %) used.

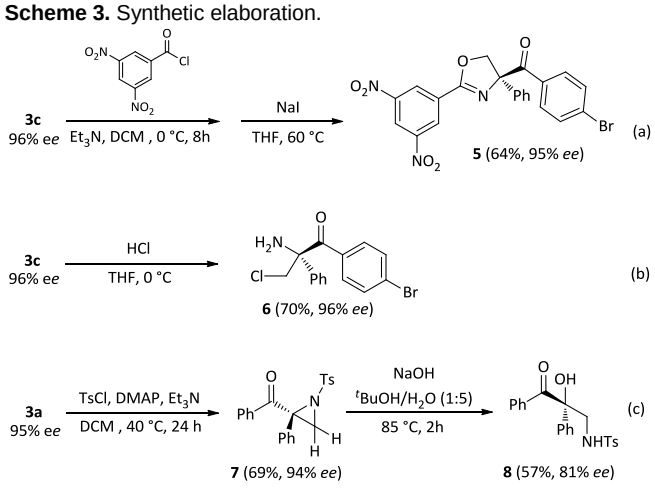
Scheme 2. Gram scale synthesis.



A gram-scale synthesis (4 mmol) was conducted under standard condition and **3c** was afforded in excellent yield and *ee* (Scheme 2). As literature reported, the synthetic elaboration of aziridines has been well explored.[14] On the basis of known

procedure,[20] **3c** was successfully converted to chiral oxazoline **5**, which could further yield chiral amino-alcohols (Scheme 3a). The reaction of **3c** with hydrogen chloride in THF gave β-chloro-α-aminoketone **6** in good yield (Scheme 3b).[21] On the other hand, the transformation of tosylated aziridine intermediate **7** prepared from **3a** could further allow generating β-amino-α-hydroxyketone **8** (Scheme 3c).[22]

Scheme 3. Synthetic elaboration.



In summary, we have successfully developed a new NHC-catalyzed aza-benzoin reaction of aldehydes with 2*H*-azirines, paving an avenue for synthetic chemists to build various chiral aziridines in high yields with excellent enantioselectivities. This new protocol allows the rapid assembly of optically active aziridines from simple and readily available starting materials under mild conditions. Further investigations on 2*H*-azirines as starting materials in asymmetric synthesis, as well as a detailed mechanistic study, are currently underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aza-benzoin • 2*H*-azirine • aziridine • *N*-hetereocyclic carbene • asymmetric catalysis

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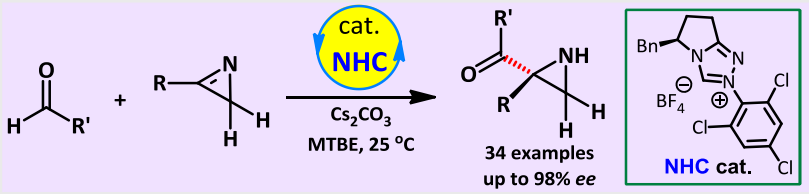

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