CHEMISTRY
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Authors: Ding Du, Jing Cao, Chao Fang, Kewen Sun, Jindong Zhu, and Tao Lu

To be cited as: *Chem. Eur. J.* 10.1002/chem.201705050

Link to VoR: http://dx.doi.org/10.1002/chem.201705050

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Direct and Enantioselective Synthesis of N-*H*-Free 1,5-Benzodiazepin-2-ones *via* NHC-Catalyzed [3+4] Annulation Reaction

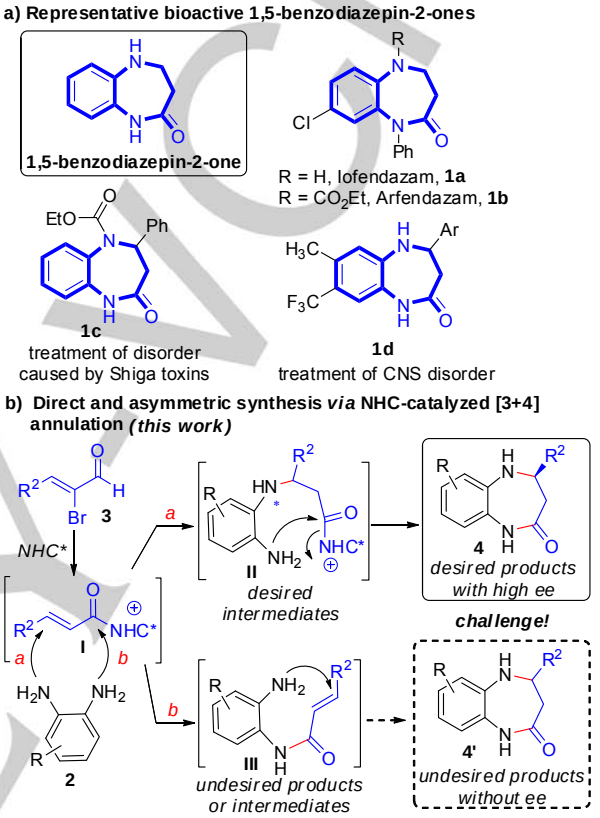
Chao Fang, Jing Cao, Kewen Sun, Jindong Zhu, Tao Lu,* and Ding Du*

Abstract: An NHC-catalyzed formal [3+4] annulation of α,β-unsaturated acylazoliums with protecting group-free aryl 1,2-diamines was developed for a direct and highly enantioselective synthesis of 4-aryl N-*H*-free 1,5-benzodiazepin-2-ones. This methodology offers an efficient and rapid access to a wide range of enantioenriched target compounds from easily accessible starting materials. The protocol is also scalable and the desired products can easily undergo subsequent N-functionalization to afford diverse N-substituted derivatives. Additionally, a mechanism was proposed to explain the high enantioselectivity in this process.

Introduction

The 1,5-benzodiazepin-2-one heterocyclic motif is a privileged structure frequently found in numerous natural products and synthetic compounds with diverse biological activities (Scheme 1a).[1] Among these 1,5-benzodiazepin-2-ones, 4-aryl-substituted derivatives have evoked considerable interest owing to their pronounced pharmacological activities, and great attention has been laid on their synthesis[2] and biological study.[3] However, enantioselective synthesis of 4-substituted 1,5-benzodiazepinones remains challenging and less investigated. So far, there are only three documented synthetic methods that utilized asymmetric hydrogenation or hydrosilylation of cyclic imine precursors to generate N-protected derivatives reported by Rueping[4] and Zhang[5] respectively. There are more or less some limitations for these methods such as preparation of the cyclic imines in advance, use of a transition metal catalyst or stoichiometric amount of a reductant, and the formation of N-protected products which inevitably require N-deprotection process for further N-functionalization. Thus, the development of direct and efficient synthetic strategies to access enantioenriched N-*H* free 1,5-benzodiazepin-2-ones from easily accessible starting materials is highly desirable.

Over the last decade, N-heterocyclic carbene (NHC) catalysis has emerged as a powerful tool to enable a variety of unconventional chemical transformations.[6] Among these transformations, the architecture of seven-membered ring systems *via* the formal [3+4] annulation of diverse NHC-bound intermediates is most intriguing and more challenging since it usually requires specific substrates and design strategies. On one hand, the groups of Ye,[7] Scheidt[8] and Zhao[9] developed NHC-catalyzed a^3-d^3 umpolung [3+4] annulations of enals with diverse electrophiles for the synthesis of functionalized ε-lactones, while Glorius[10] and Enders[11] recently developed



Scheme 1. Representative bioactive 1,5-benzodiazepin-2-ones and their asymmetric synthesis

three strategies for the asymmetric synthesis of N-containing seven-membered rings *via* NHC-catalyzed a^3-d^3 umpolung [3+4] annulation of enals or isatin-derived enals. On the other hand, Chi[12] reported an elegant work concerning NHC-catalyzed formal [3+4] annulation of enals with azomethine imines *via* an oxidative γ-activation strategy. α,β-Unsaturated acylazolium **I**[6] is an important class of NHC-bound intermediate that has been intensively studied in recent years (Scheme 1b). Notwithstanding, the formal [3+4] annulations of α,β-unsaturated acylazoliums with 1,4-bisnucleophiles were less investigated. There are only two [3+4] annulation examples [13] that utilized sulfur-centered and carbon-centered nucleophiles respectively for the β-functionalization of α,β-unsaturated acylazoliums. To date, the employment of nitrogen-centered nucleophiles for β-functionalization of α,β-unsaturated acylazoliums in [3+4] annulations has not yet been explored, although N-protected hydrazides have been previously used as nitrogen-centered nucleophiles for the β-functionalization of α,β-unsaturated acylazoliums in a [3+2] annulation by Chi's group.[14] In continuation of our studies on the exploration of NHC-catalyzed

[a] *State Key Laboratory of Natural Medicines, Department of Organic Chemistry, China Pharmaceutical University, Nanjing, 210009, P. R. China.*
Email: lut163@163.com (T. Lu) and ddmn9999@cpu.edu.cn (D. Du)

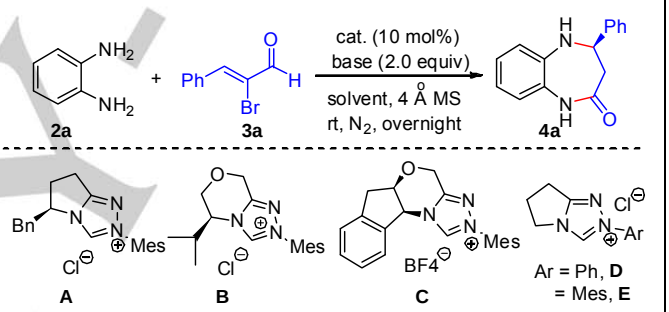
[3+m] annulations,[13b, 15] we hypothesized that it might be possible to realize a formal [3+4] annulation of α,β-unsaturated acylazoliums with readily accessible substituted aryl 1,2-diamines for the direct synthesis of enantioenriched N-*H* free 1,5-benzodiazepin-2-ones **4** that can easily undergo subsequent N-functionalization (Scheme 1b). However, there are two competing reaction pathways when 2-bromoenals **3**[15e, 16] and aryl 1,2-diamines **2** are used as the substrates with NHC catalysis. Besides the desired pathway (path a) *via* intermediate **II**, another pathway (path b) could also take place to form **III** as the final products or as the intermediates that may further undergo intramolecular conjugate addition to afford the undesired racemic products **4'**. Therefore, it is a challenge to achieve a highly chemoselective and enantioselective [3+4] annulation in this process. Fortunately, the desired 1,5-benzodiazepin-2-ones **4** were obtained in moderate to high yields with high chemoselectivity and enantioselectivity when the reactions were carried out in the presence of a chrial NHC precursor. Herein, we report an unprecedented asymmetric formal [3+4] annulation of aryl 1,2-diamines with α,β-unsaturated acylazoliums derived from 2-bromoenals. In this reaction, protecting group-free aryl amines that were rarely used as nucleophiles in C(sp^3)-N bond formation[17] with NHC catalysis were successfully installed at the β-carbon of 2-bromoenals in a highly enantioselective manner.Therefore, the obtained products avoid the N-deprotection process and thus can be used directly for subsequently diverse N-functionalization.

Results and Discussion

We started our investigations on the model reaction of commercially available benzene-1,2-diamine **2a** with (*Z*)-2-bromoenal **3a** (Table 1). Initially, the efficiency of three commonly chiral NHC precursors **A**-**C** was examined using NaOAc as the base and PhMe as the solvent (entries 1-3). All these catalysts especially **B** and **C** show high catalytic efficiency that the desired 1,5-benzodiazepin-2-one product **4a** was obtained in high yields and enantioselectivity. Further screening of the solvents and bases in the presence of catalyst **C** (entries 4-8) reveals that NaOAc and 1,2-dichloromethane (DCM) are the optimal base and solvent, respectively, affording product **4a** in 96% yield with 97% ee (entry 5). However, lowering the catalyst loading to 5 mol% led to a decreased yield but with a maintained ee value (entry 9). Therefore, the conditions shown in entry 5 were selected as the optimal one used for further scope exploration. Additionally, this transformation still works in the presence of achiral NHC precursor **D** or **E** but resulting in relatively lower yields (entries 10 and 11).

With the optimized conditions in hand, we moved our attention to explore the reaction scope initially through variation of the (*Z*)-2-bromoenals **3** (Table 2). It was found that a variety of 2-bromoenals with diverse substituents at different positions of the phenyl ring were well tolerated to this protocol and the corresponding products **4b-p** were obtained in moderate to high yields and excellent enantioselectivity. It seems that the steric effect of the substituents on the phenyl ring has certain influence on the reaction yields since 2-bromoenals with bigger substituents like OMe and Br at 2-position of phenyl ring afforded the desired products **4c**, **4d** and **4i** in lower yields but still with high ee values. Additionally, 1-or 2-naphthyl- and 2-heteroaromatic-substituted 2-bromoenals were also suitable for this transformation, affording the desired products **4q-u** in 48-96% yields with 90-98.6% ee. Unfortunately, this protocol was not applicable for the synthesis of 4-alkyl-substituted 1,5-benzodiazepin-2-one like **4v**. Subsequently, the generality of this protocol was evaluated by employing diversely substituted symmetric aryl 1,2-diamines. 4,5-Dihalogen- and 4,5-dimethyl-substituted benzene 1,2-diamines were first examined through their reactions with bromoenal **3a**. These reactions worked equally well to afford products **4aa-ad** in high yields with high enantioselectivity. The reaction of naphthalene-2,3-diamine also gave the desired product **4ae** in 87% yield with 98.2% ee. Unfortunately, when we tested the reactions of alkyl 1,2-diamines such as *cis*-cyclohexane-1,2-diamine and ethane-1,2-diamine, the desired products **4w** and **4x** were not obtained.

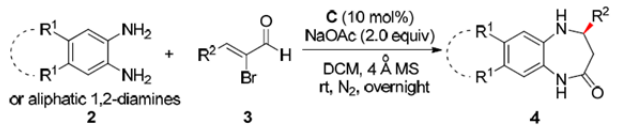
Table 1. Optimization of the reaction conditions[a]

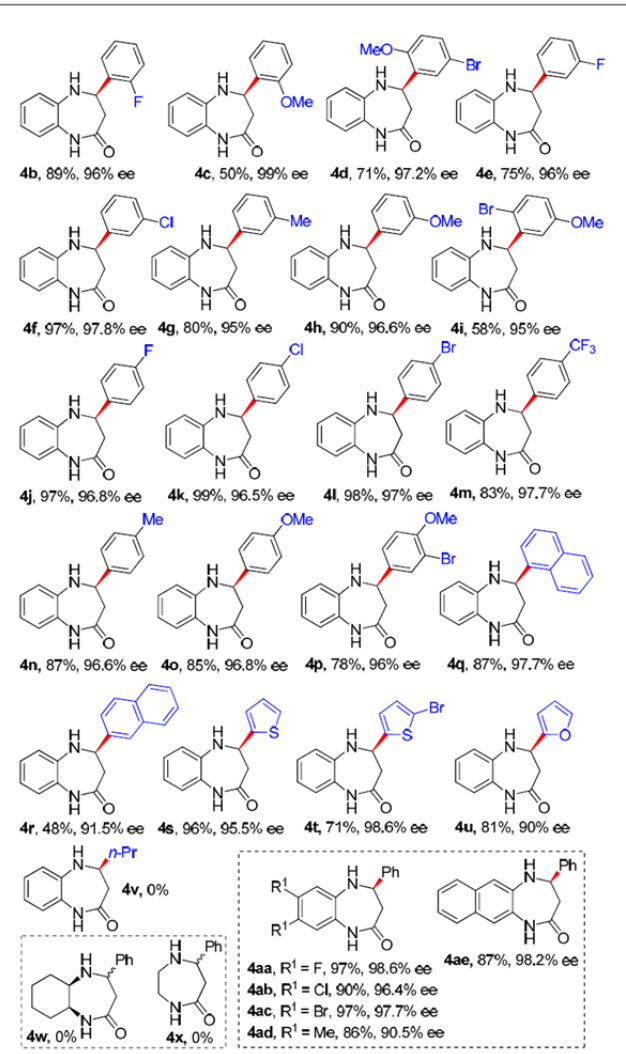


entry	cat.	base	solvent	yield (%)[b]	ee (%)[c]
1	**A**	NaOAc	PhMe	92	79
2	**B**	NaOAc	PhMe	91	96
3	**C**	NaOAc	PhMe	90	97
4	**C**	NaOAc	THF	41	98
5	**C**	NaOAc	DCM	96	97
6	**C**	K_2CO_3	DCM	<10	-
7	**C**	Cs_2CO_3	DCM	65	95
8	**C**	DIPEA	DCM	<10	-
9[d]	**C**	NaOAc	DCM	74	95
10	**D**	NaOAc	DCM	41	-
11	**E**	NaOAc	DCM	44	-

[a] Unless otherwise noted, all reactions were carried out with **2a** (0.2 mmol), **3a** (0.3 mmol), a base (0.4 mmol) and 200 mg of 4Å molecular sieves (MS) in an anhydrous solvent (3 mL) under N_2 at room temperature (rt). [b] Isolated yields based on **2a**. [c] Ee values were determined *via* HPLC analysis. [d] 5 mol% of **C** was used. Mes = 2,4,6-$(CH_3)_3C_6H_2$; DIPEA = *N*,*N*-diisopropylethylamine

Table 2. The reaction scope of 2-bromoenals with symmetric 1,2-diamines[a]

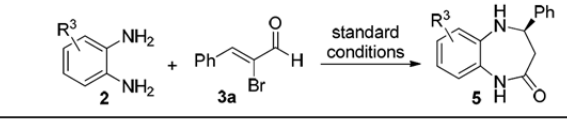


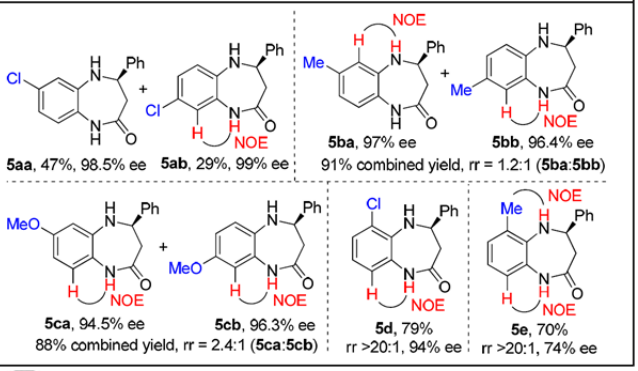


[a] Unless otherwise noted, all reactions were carried out with **2** (0.2 mmol), **3** (0.3 mmol), NaOAc (0.4 mmol) and 200 mg of 4Å MS in anhydrous DCM (3 mL) under N_2 at rt. All yields are isolated yields based on **2**. Ee values were determined *via* HPLC analysis.

Furthermore, the reactivity of several unsymmetrical benzene-1,2-diamines were also tested (Table 3). The reaction of 4-chlorobenzene-1,2-diamine afforded two regioisomers **5aa** and **5ab** in 47% and 29% yields, respectively. Both regioisomers were obtained in excellent enantioselectivity. The reaction of 4-methyl and 4-methoxy benzene-1,2-diamines both afforded two regioisomers with 1.2:1 rr and 2.4:1 rr, respectively, which cannot be separated by column chromatography. Although the regioselectivity of these cases is poor, the combined yields are high and ee values are excellent for each isomer. It is interesting that the reactions of 3-chloro and 3-methyl benzene-1,2-diamines gave the desired products **5d** and **5e** both in excellent regioselectivity. However, product **5e** was obtained with lower enantioselectivity. The structures of these regioisomers were established by analysis of their NOESY spectra since the hydrogen of N-*H* has interaction in space with the hydrogen or the methyl group on the benzene ring.

Table 3. The reaction scope of unsymmetrical benzene-1,2-diamines

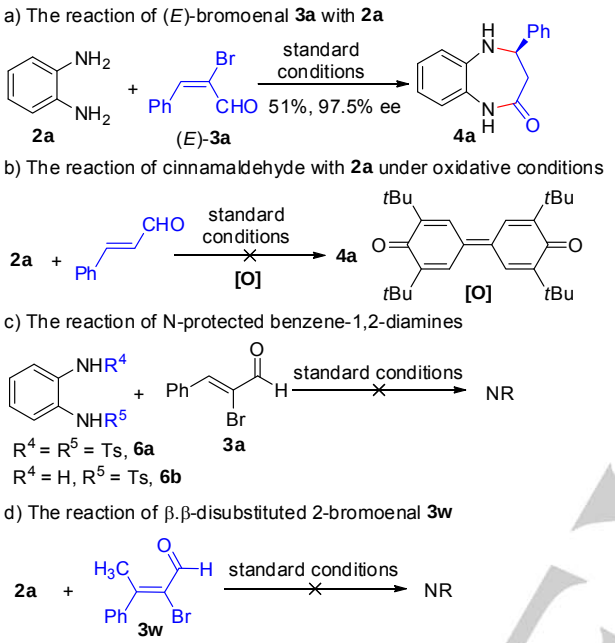




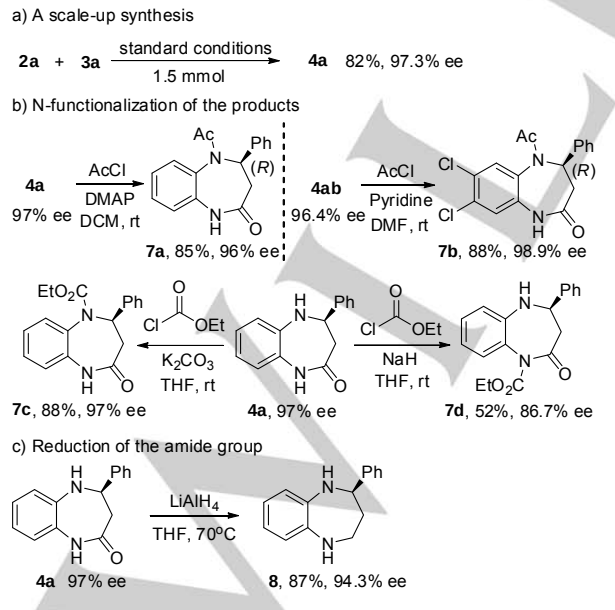
Subsequently, a control study of the stereochemistry of the 2-bromoenal substrate and further reaction scope exploration were carried out (Scheme 2). First, the reactivity of (*E*)-2-bromoenal **3a** under standard conditions was tested. The stereochemistry of 2-bromoenals proved to have great impact on the reaction yield since the reaction between (*E*)-**3a** and **2a** afforded product **4a** in a significantly decreased yield but with maintained enantioselectivity compared to that of (*Z*)-**3a** (Scheme 2a). Since α,β-unsaturated acylazolium **I** can be also generated from enals with NHCs under oxidative conditions,[6] the reaction of **2a** with cinnamaldehyde under NHC/oxidative conditions was test, but failed to afford the target product **4a** (Scheme 2b). Then, the reactivity of N-protected bis-secondary amine **6a** and mono-secondary amine **6b** were examined under the standard conditions, however, both substrates were not suitable to this protocol (Scheme 2c). Last, the reaction of β,β-disubstituted 2-bromoenal **3w** was examined but did not work (Scheme 2d).

To further explore the synthetic utility of this protocol, a scale-up synthesis of this protocol and derivatization of the products were carried out (Scheme 3). With a 1.5 mmol scale under standard conditions, product **4a** was obtained in a slightly decreased yield with maintained enantioselectivity (Scheme 3a). As the N-*H* free 1,5-benzodiazepin-2-ones can easily undergo N-functionalization, we then carried out some typical acylation reactions of **4a** and **4ab** (Scheme 3b). The N-acylation of **4a** and **4ab** afforded compounds **7a** and **7b** respectively in high yields and maintained ee values. Since the (*S*)-enantiomers of **7a** and **7b** are known compounds, the absolute configuration of **7a** and **7b** was assigned as (*R*) by comparing the optical rotation with the literature value of their (*S*)-enantiomers.[4] Therefore, the absolute configuration of products **4** and **5** was established as

(*R*). The reaction between **4a** and ethyl carbonochloridate with different bases gave different N-substituted products. The reaction using K_2CO_3 as a base afforded product **7c** as the enantiomeric variant of compound **1c** in a high yield with maintained enantioselectivity, while the reaction using NaH as a base afforded product **7d** in a moderate yield with somewhat decreased enantioselectivity. Last, the reduction of the amide group of **4a** with $LiAlH_4$ was carried out to give desired product **8** in 87% yield with 94.3% ee.

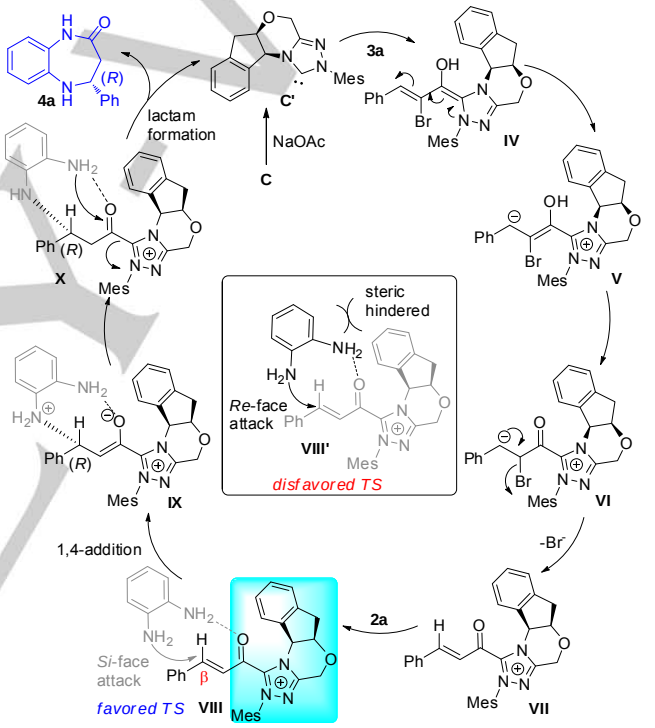


Scheme 2. Further reaction scope exploration.



Scheme 3. A scale-up synthesis and derivatization of the products.

A plausible mechanism for this transformation is proposed in Scheme 4. The reaction is initiated by a combination of (*Z*)-2-bromoenal **3a** with NHC **C'** generated upon deprotonation of carbene precursor **C** with NaOAc affording the Breslow intermediate **IV**. The a^3-d^3 umpolung of **IV** induces the formation of intermediate **V** that is tautomerized to 2-bromoacylazolium **VI**. The subsequent loss of the bromide produces the more stable (*E*)-α,β-unsaturated acylazolium **VII**. Possible H-bonding between amino group of **2a** and the carbonyl group of **VII** gives the favored transition state (TS) **VIII** that may play a significant role in controlling the enantioselectivity. TS **VIII'** is disfavored due to the steric conflict between the benzene ring of **2a** and the big chiral group of **VII**. The subsequent *Si*-face attack of the amino group to the β-carbon affords intermediate **IX** that undergoes sequential tautomerization and lactam formation to produce product (*R*)-**4a** in a highly enantioselective manner.



Scheme 4. Proposed mechanism.

Conclusions

In conclusion, we have demonstrated an NHC-catalyzed formal [3+4] annulation of α,β-unsaturated acylazoliums with aryl 1,2-diamines. This protocol offers a direct and rapid access to a wide range of enantioenriched N-H-free 4-aryl-substituted 1,5-benzodiazepin-2-ones from easily accessible starting materials. Moreover, this protocol is scalable for the synthesis of the target compounds that can easily undergo subsequent N-functionalization to give diverse N-substituted derivatives such as the enantiomeric variant of compound **1c** used for treating disorder caused by Shiga toxins.[1c] Further investigation and application of α,β-unsaturated acylazoliums in the construction

of diverse heterocyclic systems are currently underway in our laboratory.

Experimental Section

General experimental procedure for the synthesis of products 4 and 5

To an oven-dried 25 mL two-neck bound-bottom flask was charged with substituted aryl-1,2-diamines **2** (0.2 mmol), 2-bromoenals **3** (0.3 mmol), carbene precursor **C** (8.4 mg, 0.02 mmol), NaOAc (33 mg. 0.4 mmol), and 200 mg of 4 Å MS under N_2 atmosphere. Then anhydrous DCM (3 mL) was added and the resulting mixture was stirred overnight at rt under N_2. Then, the mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by chromatography on silica gel using hexane/EtOAc (3:1) as eluent to afford the products **4** or **5**.

Typical characterization of **4b**: Semi-solid, 46 mg, 89% yield, 96% ee. $[\alpha]_D^{RT}$ = +11.8 (c = 0.144 in CH_2Cl_2). HPLC DAICEL CHIRALCEL IF, *n*-hexane/2-propanol = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, retention time: 8.55 min (major), 12.44 min (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (brs, 1H), 7.59 (td, *J* = 7.6, 1.7 Hz, 1H), 7.30-7.22 (m, 1H), 7.15-7.00 (m, 3H), 6.97-6.88 (m, 2H), 6.83 (d, *J* = 7.5 Hz, 1H), 5.40 (dd, *J* = 7.0, 5.5 Hz, 1H), 3.82 (brs, 1H), 2.94-2.78 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 159.5 (d, *J* = 245 Hz), 138.4, 130.5 (d, *J* = 12.8 Hz), 129.4 (d, *J* = 8.1 Hz), 128.1, 127.6 (d, *J* = 4.0 Hz), 125.9, 124.4 (d, *J* = 3.3 Hz), 122.4, 121.6, 121.1, 115.6 (d, *J* = 21.5 Hz), 56.3 (d, *J* = 3.0 Hz), 39.8. HRMS (ESI) calcd for $C_{15}H_{13}FN_2O$: 256.1012, found: 256.1016.

Acknowledgements

This work is funded by the National Natural Science Foundation of China (No. 21572270), the Qing Lan Project of Jiangsu Province, and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

Keywords: benzodiazepinone •carbene • [3+4] annulation • asymmetric synthesis • α,β-unsaturated acylazolium

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10.1002/chem.201705050

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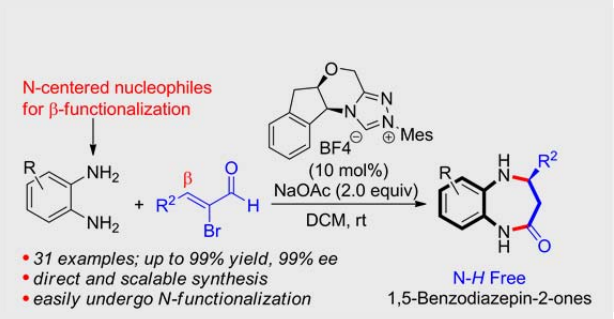

*Author(s), Corresponding Author(s)**

Page No. – Page No.

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