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氮杂环卡宾(NHC)催化[4＋3]环加成反应构建 4-氨基苯并环庚烯内酯

戴春波[a] 夏思奇[a] 陈晓玉 杨丽敏*
(杭州师范大学材料与化学化工学院 有机硅化学及材料技术教育部重点实验室 杭州 311121)

摘要 报道了 4-氨基苯并环庚烯内酯的合成方法, 在氮杂环卡宾的催化作用下, γ-氯醛与亚胺醌化合物经过[4＋3]环加成反应生成 4-氨基苯并环庚烯内酯, 产率良好, 且反应产物单一, 反应条件温和, 操作简便, 符合绿色化学原则. 为了探究氮杂环卡宾在该反应的位点选择性所起的作用, 利用密度泛函理论进行了理论研究, 研究表明形变力是导致位点选择差异性的主要原因.

关键词 氮杂环卡宾; 有机催化; [4＋3]环加成反应; 位点选择性; 4-氨基苯并环庚烯内酯

N-Heterocyclic Carbene (NHC)-Catalyzed [4＋3] Cycloaddition to Synthesize 4-Aminobenzoheptenolactons

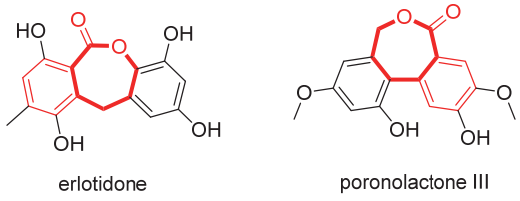
Dai, Chunbo† Xia, Siqi† Chen, Xiaoyu Yang, Limin*
(*Key Laboratory of Organosilicon Chemistry and Material Technology*, *Ministry of Education*, *College of Materials*, *Chemistry and Chemical Engineering*, *Hangzhou Normal University*, *Hangzhou 311121*)

Abstract A highly efficient N-heterocyclic carbene (NHC) catalyzed formal [3＋4] cycloaddition reaction of γ-chloroenal with iminoquinones has been developed, producing 4-aminobenzoheptenolactone derivatives in good yields. In order to explore the role of nitroheterocyclic carbene in the site selectivity of the reaction, a theoretical study was carried out using density functional theory. The study showed that the deformation force was the main reason for the difference in site selection.

Keywords N-heterocyclic carbene (NHC); organocatalysis; [4＋3] cycloaddition; site selectivity; 4-aminobenzoheptenolactone

1 Introduction

Benzoheptenolactones and its analogues are a very important class of seven membered lactones, which widely exist in natural products and drug molecules because of antifungal, antibacterial, anti-virus, and anti-tumor activities. For example, erlotidone is an effective kinase insert domain receptor (KDR) enzyme inhibitor, and poronolactone III[1] is a biologically active compound against arrhythmia (Figure 1). Due to its higher entropy barrier than five-membered and six-membered lactones,[2] the synthesis of heptenolactones with higher ring tension is full of challenges and has aroused great interest of chemists.[3] At present, there are relatively few methods to synthesize seven membered cyclolactones, the cycloaddition strategy[4] has been proved to be effective for the synthesis of seven membered cyclolactones and more flexible methods are required to synthesize hepteno lactones.[5]



erlotidone poronolactone III

Figure 1 Bioactive compounds containing benzoheptenolactone skeleton

In the past decade, the field of N-heterocyclic carbene (NHC) organocatalysis has been rapidly developed as a powerful strategy to construct cyclic compounds.[6] Since the pioneering work of Glorius[7] and Bode[8] on the NHC-catalyzed synthesis of γ-butyrolactone from enals, the strategy has been widely used in the construction of a variety of heterocycles,[9] such as five-membered lactones and six-membered lactones. For examples, NHC-catalyzed [3＋2] cycloaddition reactions of α,β-unsaturated aldehyde with

* Corresponding author. E-mail: myang@hznu.edu.cn
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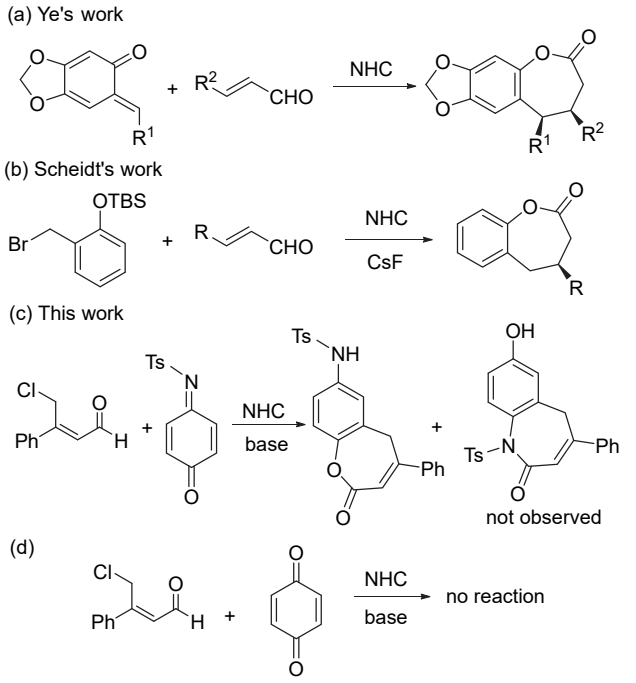
† 共同第一作者(These authors contributed equally to this work).

aldehyde/ketone afforded γ-lactones,[10] and [4＋2] cycloaddition reaction of γ-haloenals with isatains afforded δ-lactone.[11] Our ongoing interest in the NHC-catalyzed cycloaddition reactions inspired us to explore the synthesis of ε-lactones.[12] Ye group[13] reported the first synthesis of ε-lactones by NHC-catalyzed [4＋3] cycloaddition reaction of enoaldehyde and *o*-quinone formamide (Scheme 1, a). Subsequently, by employing a dual Lewis base and NHC catalyst, Scheidt group[14] reported an enantioselective formal [4＋3] fashion to access 2-benzoxopinones by NHC-bound homoenolate equivalents derived from α,β-unsaturated aldehydes combine with transient reactive *o*-quinone methides (Scheme 1, b). Herein, we reported a [4＋3] cycloaddition reaction of γ-chloroenal with iminoquinones to access benzoheptenolactones. In this [4＋3] cycloaddition reaction, the reaction proceeded smoothly to produce 4-aminobenzoheptenolactone instead of 4-hydroxylbenzoheptenolactam (Scheme 1, c). Meanwhile, the reaction between γ-chloroenal and benzoquinone was also tested, but no any 4-hydroxylbenzoheptenolactone product was obtained (Scheme 1, d).

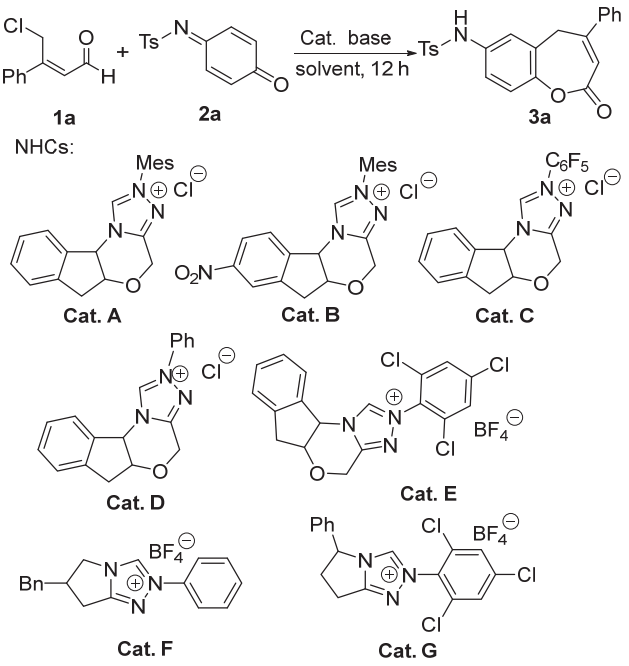


Scheme 1 Strategies for the synthesis of seven membered cyclolactones

2 Results and discussion

To examine the NHC-catalyzed [4＋3] cycloaddition reaction, we commenced our studies by readily prepared γ-chloroenal **1a** and iminoquinone **2a** with N-substituted triazolium salts using different kinds of bases and solvents (Table 1). In the presence of NHC **Cat. A** with triethylamine (TEA) as base in tetrahydrofuran (THF), the desired product 4-aminobenzoheptenolactone **3a** was provided in 30% yield (Table 1, Entry 1). Subsequently, **Cat. B** was employed with nitro substitution on phenyl ring, and the

Table 1 Optimization of the reaction conditions[a]



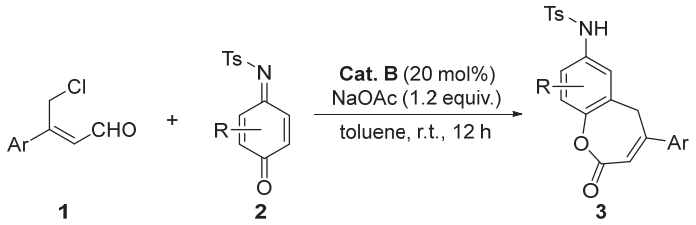
Entry	Solvent	Cat.	Base	*T*/℃	Yield[b]/%
1	THF	**Cat. A**	TEA	r.t	30
2	THF	**Cat. B**	TEA	r.t	35
3	THF	**Cat. C**	TEA	r.t	＜10
4	THF	**Cat. D**	TEA	r.t	Trace
5	THF	**Cat. E**	TEA	r.t	Trace
6	THF	**Cat. F**	TEA	r.t	Trace
7	THF	**Cat. G**	TEA	r.t	Trace
8	THF	**Cat. B**	DIPEA	r.t	Trace
9	THF	**Cat. B**	DABCO	r.t	Trace
10	THF	**Cat. B**	DMAP	r.t	Trace
11	THF	**Cat. B**	DBU	r.t	Trace
12	THF	**Cat. B**	Na_2CO_3	r.t	20
13	THF	**Cat. B**	NaOAc	r.t	40
14	THF	**Cat. B**	Cs_2CO_3	r.t	22
15	THF	**Cat. B**	$NaHCO_3$	r.t	＜10
16	THF	**Cat. B**	K_2CO_3	r.t	＜10
17	DCM	**Cat. B**	NaOAc	r.t	65
18	DCE	**Cat. B**	NaOAc	r.t	52
19	$CHCl_3$	**Cat. B**	NaOAc	r.t	56
20	Et_2O	**Cat. B**	NaOAc	r.t	64
21	Toluene	**Cat. B**	NaOAc	r.t	74
22	1,4-Dioxane	**Cat. B**	NaOAc	r.t	Trace
23	EA	**Cat. B**	NaOAc	r.t	50
24	MTBE	**Cat. B**	NaOAc	r.t	＜10
25	MeCN	**Cat. B**	NaOAc	r.t	＜10
26	Toluene	**Cat. B**	NaOAc	0	30
27	Toluene	**Cat. B**	NaOAc	30	70
28[c]	Toluene	**Cat. B**	NaOAc	r.t	51
29[d]	Toluene	**Cat. B**	NaOAc	r.t	70

[a] Unless otherwise stated, the reaction time was 12 h. **1a** (0.10 mmol, 1.0 equiv.), **2a** (0.10 mmol, 1.0 equiv.), base (0.12 mmol, 1.2 equiv.), 20 mol% catalyst, 1.5 mL of solvent. [b] Yields of isolated products. [c] The reaction time is 6 h. [d] The reaction time is 24 h.

yield was improved to 35%. When **Cat. D** with pentafluorophenyl group was employed, the yield of product 4-aminobenzoheptenolactone **3a** decreased significantly less than 10%. When **Cat. E** with 2,4,6-trichlorophenyl, **Cat. F** with Bn group, and **Cat. G** with phenyl group were used, the reaction could not proceed. Then by employing **Cat. B**, different organic bases, such as *N*,*N*-diisopropylethylamine (DIPEA), 1,4-diazabicyclo[2.2.2]octane (DABCO), 4-dimethylaminopyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were tested, only trace products were obtained (Table 1, Entries 8～11). When inorganic bases were employed, the reaction yields were significantly increased (Table 1, Entries 12～16). When NaOAc was used, the reaction yield reached 40% (Table 1, Entry 13). Finally, different solvents were screened in the presence of **Cat. B** and NaOAc. When dichloromethane (DCM) was used as solvent, the yield of 4-aminobenzoheptenolactone **3a** was 65% (Table 1, Entry 17). When dichloroethane (DCE), $CHCl_3$ and Et_2O were employed in the reaction, the yields decreased slightly (Table 1, Entries 18～20). While, methyl *tert*-butyl ether (MTBE), MeCN and 1,4-dioxane were not suitable for the reaction with significantly decreased yields (Table 1, Entries 23～25). Toluene was the best solvent for the reaction with the highest yield of 74% (Table 1, Entry 21). Different reaction temperatures and reaction times were also optimized catalyzed by **Cat. B** with toluene as solvent and NaOAc as base for the best reaction condition (Entries 26～29). It was found that the yield decreased a lot due to the lower reactivity of substrates at 0 ℃. When the reaction temperature increased to 30 ℃, it seemed no improvement on the reaction. When the reaction time was shortened to 6 h, the yield reduced a lot because the reaction was not completed. Prolonging reaction time did not increase the yield.

With the optimal reaction condition in hand, the substrate scope of the reaction between iminoquinone and *γ*-chloroenal was investigated. As illustrated in Table 2, a plethora of *γ*-chloroenals with diverse substitution phenyl ring were assessed with iminoquinone **2a**. For R^1 moiety, both electron-donating group (4-OMe) and electron-withdrawing group (4-CN) substituted phenyl rings were accommodated. The position of the substitution did not matter on the results. The thiophen-2-yl and naphthalen-2-yl substituted *γ*-chloroenals afforded 4-aminobenzoheptenolactones in good yields. In addition, in the optimal reaction conditions, the reactions of *γ*-chloroenals with different substituted iminoquinones were also investigated. The yield was decreased dramatically to 27% when employing the electron-with-

Table 2 Scope of *γ*-chloroaldehydes and iminoquinones



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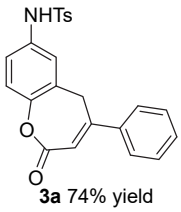
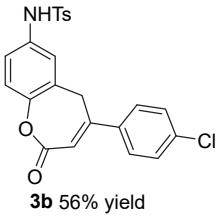
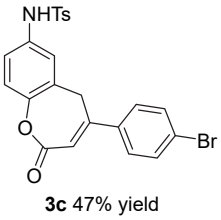


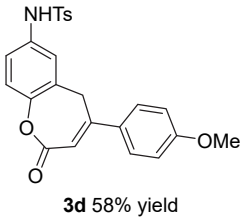
3a 74% yield



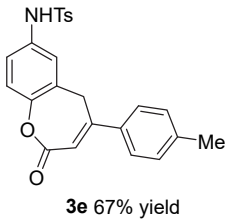
3b 56% yield



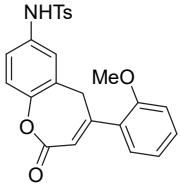
3c 47% yield



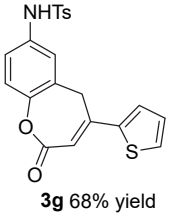
3d 58% yield



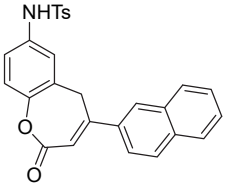
3e 67% yield



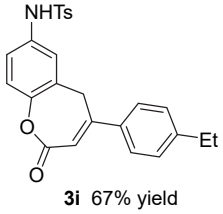
3f 67% yield



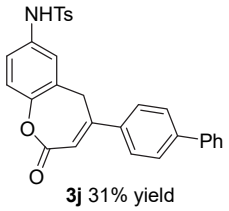
3g 68% yield



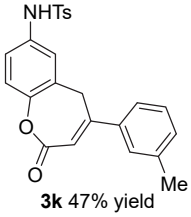
3h 58% yield



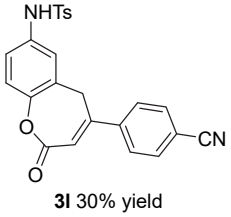
3i 67% yield



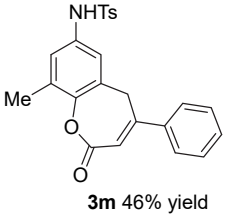
3j 31% yield



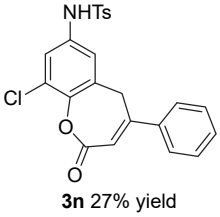
3k 47% yield



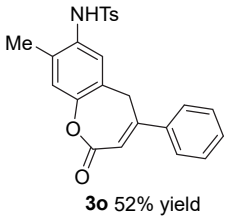
3l 30% yield



3m 46% yield



3n 27% yield

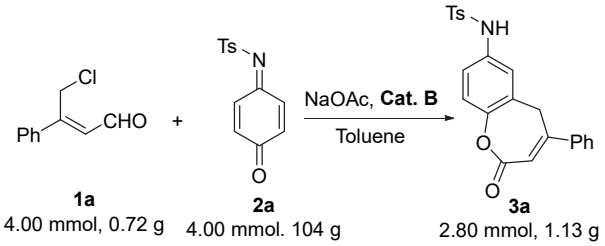


3o 52% yield

drawing group 3-Cl on iminoquinone. While introducing electron-donating groups such as 2-Me and 3-Me on iminoquinone, the yields were 52% and 46%, respectively.

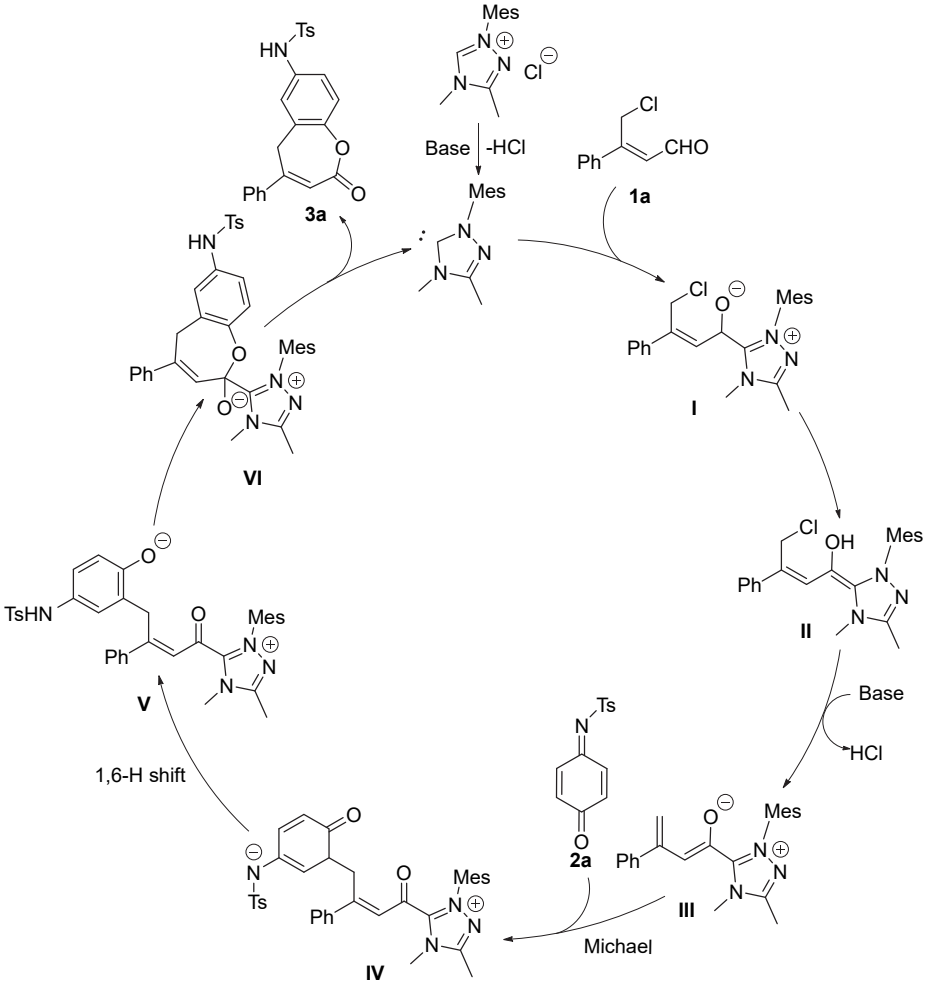
To demonstrate the practical nature of the present catalytic strategy, a gram-scale reaction preparation of compound **3a** was performed (Scheme 2). Under the standard reaction conditions, amplifying the model reaction to 4.00 mmol straightforwardly with *γ*-chloroenal **1a** (0.72 g, 4 mmol) and iminoquinone **2a** (1.04 g, 4 mmol) gave more than 1.00 g of **3a** without a loss of efficiency of 70% yield.

A plausible catalytic cycle for the [4+3] cycloaddition of iminoquinone and *γ*-chloroenal is outline in Scheme 3. Firstly, the nucleophilic addition of an NHC catalyst to *γ*-chloroenal **1a** followed by 1,2-H migration from carbon to oxygen gave a Breslow intermediate **II**. Then, the Breslow intermediate **II** underwent a tautomerization and C—Cl bond cleavage, an enolene-enone rearrangement along with a 1,5-H shift, and a capture of *γ*-proton by a base which provided vinyl enolate (diene) **III**. Finally, vinyl enolate **III** underwent a stepwise cycloaddition reaction with the iminoquinone derivative **2a** on *para*-carbon to quinone group and yielded 4-aminobenzoheptenolactone **3a** and released the NHC catalyst.



Scheme 2 Practicality of this reaction

To explore the origins of site selectivity, density functional theory (DFT) calculations were performed on the level of the B3LYP/6-311+G(d,p)/SMD (THF)//B3LYP/6-31G(d) with the Gaussian 16 package. Four transition structures were explored based on the optimized structures of vinyl enolate and iminoquinone **2a** (Figure 2).[13] **TSa**/**TSb** were formed by vinyl enolate intermediate approaching iminoquinone **2a** on the *re*-face and *si*-face on the *para*-carbon to quinone group. **TSc**/TSd were formed by vinyl enolate intermediate approaching iminoquinone **2a** on the *re*-face and *si*-face on the *para*-carbon to imine group. The activation energy for **TSa** is 18.5 kcal/mol with 9.3 kcal/mol distortion energy from iminoquinone, 13.3 kcal/mol distortion energy from vinyl enolate, and 4.1



Scheme 3 Possible reaction mechanism

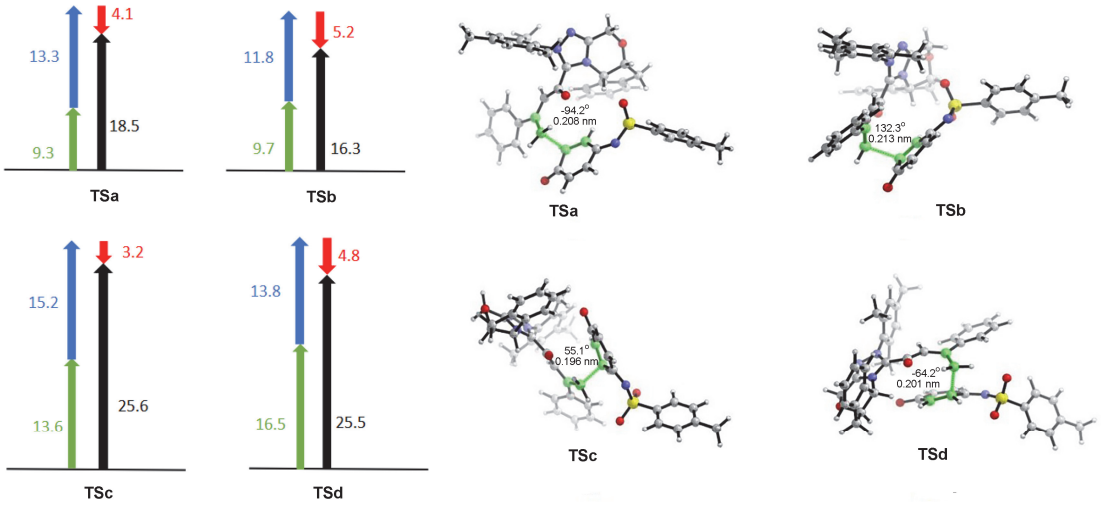


Figure 2 Graph of distortion, interaction and activation energies (kcal/mol) for transition states **TSa**, **TSb**, **TSc** and **TSd**
green: distortion energy of iminoquinone, blue: distortion energy of vinyl enolate, red: interaction energy, black: activation energy

kcal/mol interaction. While, the activation energy for **TSb** is 16.3 kcal/mol with 9.7 kcal/mol distortion energy from iminoquinone, 11.8 kcal/mol distortion energy from vinyl enolate, and 5.2 kcal/mol interaction. When the transition sate involved in imine part in iminoquinone **2a**, the activation energy for **TSc** is 25.6 kcal/mol with 13.6 kcal/mol distortion energy from iminoquinone, 15.2 kcal/mol distortion energy from vinyl enolate, and 3.2 kcal/mol interaction. The activation energy for **TSc** is 25.5 kcal/mol with 16.5 kcal/mol distortion energy from iminoquinone, 13.8 kcal/mol distortion energy from vinyl enolate, and 4.8 kcal/mol interaction. Thus, the activation energy for **TSb**, formed by vinyl enolate intermediate approaching iminoquinone **2a** on the *para*-carbon to quinone group, is more favorable than **TSd**, formed by vinyl enolate intermediate approaching iminoquinone **2a** on the *para*-carbon to imino group, by 9.2 kcal/mol. The site selectivity is also determined at this stage in accordance with experimental observations.

3 Conclusions

A highly efficient NHC catalyzed formal [3＋4] cycloaddition reaction of *γ*-chloroenal with iminoquinones has been developed, producing 4-aminobenzoheptenolactone derivatives in good yields (up to 74% yield). Based on computational investigation, the role of NHC on site selectivity is discussed.

4 Experimental section

4.1 General information

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate. Nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were recorded on a Bruker AMX 500 spectrophotometer ($CDCl_3$ as solvent, $SiMe_4$ as interal stand).

4.2 General synthesis of 4-aminobenzoheptenolactones

To an oven-dried 10 mL Schlenk bottle under argon were added *γ*-chloroenal **1a** (27.3 mg, 0.15 mmol), ethyl iminoquinone **2a** (39.2 mg, 0.15 mmol), **cat. A** (12.4 mg, 0.03 mmol) and 2.5 mL of toluene. Then NaOAc (14.8 mg, 0.18 mmol) was added at room temperature. The resulting solution was then stirred and the complete disappearance of the starting material was monitored by TLC. The solution was concentrated under reduced pressure and the residue was subjected to column chromatography using ethyl acetate (EA)/petroleumethe (PE) (*V*∶*V*=1∶4) as eluent to give the desired products **3a** as liquid. Compounds **3b**～**3o** were obtained as liquid using the same procedure.

4-Methyl-*N*-(2-oxo-4-phenyl-2,5-dihydrobenzo[*b*]oxepin-7-yl)benzenesulfonamide (**3a**): 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.60 (d, *J*=8.3 Hz, 2H), 7.46～7.44 (m, 5H), 7.19 (d, *J*=8.2 Hz, 2H), 7.12～7.06 (m, 2H), 6.90～6.85 (m 1H), 6.07 (s, 1H), 3.83 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ*: 162.80, 156.85, 147.89, 143.14, 137.70, 134.69, 132.78, 131.53, 129.10, 128.70, 127.97, 126.22, 125.33, 125.12, 121.11, 120.85, 120.64, 115.22, 34.06, 28.68, 20.53; HRMS (ESI) calcd for $C_{23}H_{20}NO_4S$ [M＋H$^+$] 406.1108, found 406.1100.

(4-(4-Chlorophenyl)-2-oxo-2,5-dihydrobenzo[*b*]oxepin-7-yl)-4-methylbenzenesulfonamide (**3b**): 56% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 10.52 (s, 1H), 7.79 (t, *J*=8.2 Hz, 4H), 7.63～7.58 (m, 2H), 7.45 (d, *J*=8.4 Hz, 2H), 7.36 (d, *J*=2.3 Hz, 2H), 7.29 (d, *J*=8.9 Hz, 1H), 7.25～7.21 (m, 1H), 3.51 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) *δ*: 167.92, 146.46, 143.87, 137.68, 137.07,

134.92, 133.89, 133.64, 130.25, 129.26, 128.47, 128.36, 127.19, 125.81, 122.14, 121.70, 121.39, 37.14, 21.44; HRMS (ESI) calcd for $C_{23}H_{19}ClNO_4S$ [M+H$^+$] 440.0718, found 440.0725.

(4-(4-Metheylphenyl)-2-oxo-2,5-dihydrobenzo[*b*]oxepin-7-yl)-4-methylbenzenesulfonamide (**3c**): 47% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.45 (s, 1H), 7.74 (d, J=8.3 Hz, 2H), 7.62 (d, J=8.2 Hz, 2H), 7.41 (d, J=8.0 Hz, 2H), 7.33 – 7.28 (m, 3H), 7.25～7.21 (m, 2H), 7.19～7.15 (m, 1H), 3.45 (s, 2H), 2.39 (s, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 167.99, 146.38, 143.85, 138.56, 137.09, 135.98, 135.12, 134.85, 130.24, 129.86, 128.62, 127.19, 126.55, 124.14, 122.05, 121.40, 121.37, 37.19, 21.43, 21.20; HRMS (ESI) calcd for $C_{23}H_{19}BrNO_4S$ [M+H$^+$] 484.0213, found 484.0220.

(4-(4-Bromophenyl)-2-oxo-2,5-dihydrobenzo[*b*]oxepin-7-yl)-4-methylbenzenesulfonamide (**3d**): 58% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.42 (s, 1H), 7.69 (d, J=8.3 Hz, 2H), 7.64 (s, 4H), 7.36 (d, J=8.0 Hz, 2H), 7.28～7.26 (m, 2H), 7.20 (d, J=8.9 Hz, 1H), 7.16～7.12 (m, 1H), 3.41 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 167.93, 146.46, 143.87, 138.06, 137.07, 134.92, 133.97, 132.18, 130.25, 128.75, 128.36, 127.19, 125.82, 122.30, 122.15, 121.72, 121.39, 37.09, 21.44; HRMS (ESI) calcd for $C_{24}H_{22}NO_5S$ [M+H$^+$] 436.1213, found 436.1203.

(4-(4-Methoxyphenyl)-2-oxo-2,5-dihydrobenzo[*b*]oxepin-7-yl)-4-methylbenzenesulfonamide (**3e**): 67% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.38 (s, 1H), 7.71～7.60 (m, 4H), 7.36 (d, J=7.5 Hz, 2H), 7.23 (s, 1H), 7.20～7.16 (m, 1H), 7.10 (d, J=8.5 Hz, 2H), 7.03～6.97 (m, 2H), 3.80 (d, J=1.6 Hz, 3H), 3.39 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 167.93, 146.46, 143.87, 138.06, 137.07, 134.92, 133.97, 132.18, 130.25, 128.75, 128.36, 127.19, 125.82, 122.30, 122.15, 121.72, 121.39, 37.09, 21.44; HRMS (ESI) calcd for $C_{24}H_{22}NO_4S$ [M+H$^+$] 442.1083, found 442.1074.

Methyl-*N*-(2-oxo-4-(thiophen-2-yl)-2,5-dihydrobenzo-[*b*]oxepin-7-yl)benzenesulfonamide (**3f**): 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61 (d, J=2.8 Hz, 2H), 7.59 (s, 1H), 7.42～7.40 (m, 1H), 7.25 (s, 1H), 7.19 (d, J=7.9 Hz, 2H), 7.11～7.07 (m, 2H), 6.85～6.82 (m, 1H), 6.56 (s, 1H), 6.14 (s, 1H), 3.80 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.14, 151.43, 148.94, 144.20, 139.59, 135.71, 133.71, 132.24, 129.73, 127.67, 127.25, 125.68, 125.24, 122.26, 121.90, 121.58, 114.17, 34.55, 21.57; HRMS (ESI) calcd for $C_{24}H_{22}NO_5S$ [M+H$^+$] 436.1213, found 436.1221.

Methyl-*N*-(2-oxo-4-(Naphthyl-2-yl)-2,5-dihydrobenzo-[*b*]oxepin-7-yl)benzenesulfonamide (**3g**): 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, J=1.4 Hz, 1H), 7.92～7.86 (m, 3H), 7.60～7.55 (m, 4H), 7.54～7.51 (m, 1H), 7.15～7.11 (m, 4H), 6.90～6.86 (m, 1H), 6.54 (s, 1H), 6.21 (s, 1H), 3.95 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 163.81, 157.68, 149.03, 144.17, 135.72, 133.84, 133.77, 133.00, 132.60, 129.69, 128.93, 128.66, 127.74, 127.53, 127.22, 127.09, 126.41, 123.41, 122.30, 122.05, 121.70, 116.44, 35.00, 21.45; HRMS (ESI) calcd for $C_{21}H_{18}NO_4S_2$ [M+H$^+$] 412.0672, found 412.0665.

(4-(2-Methoxyphenyl)-2-oxo-2,5-dihydrobenzo[*b*]oxepin-7-yl)-4-methylbenzenesulfonamide (**3h**): 58% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.34 (s, 1H), 7.65 (d, J=8.3 Hz, 2H), 7.45～7.41 (m, 1H), 7.33 (d, J=8.2 Hz, 2H), 7.17～7.15 (m, 1H), 7.14～7.10 (m, 2H), 7.06～7.03 (m, 2H), 6.99 (t, J=7.4 Hz, 1H), 5.88 (s, 1H), 3.83 (s, 3H), 3.67 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 163.58, 159.56, 156.88, 147.59, 143.85, 136.97, 135.35, 133.36, 131.65, 130.20, 129.53, 129.06, 127.13, 121.38, 121.32, 121.08, 119.86, 118.52, 112.10, 55.80, 35.70, 21.40; HRMS (ESI) calcd for $C_{27}H_{22}NO_4S$ [M+H$^+$] 456.1264, found 456.1275.

(4-(4-Ethylphenyl)-2-oxo-2,5-dihydrobenzo[*b*]oxepin-7-yl)-4-methylbenzenesulfonamide (**3i**): 67% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.40 (s, 1H), 7.69 (d, J=8.3 Hz, 2H), 7.59 (d, J=8.3 Hz, 2H), 7.36 (d, J=8.1 Hz, 2H), 7.29 (d, J=8.4 Hz, 2H), 7.24 (d, J=2.6 Hz, 1H), 7.21～7.16 (m, 2H), 7.13～7.11 (m, 1H), 3.41 (s, 2H), 2.66～2.62 (m, 2H), 2.34 (s, 3H), 1.19 (t, J=6.7 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 167.99, 146.39, 144.86, 143.86, 137.07, 136.26, 135.18, 134.83, 130.25, 130.11, 128.81, 128.69, 128.62, 127.19, 127.06, 126.65, 124.22, 122.06, 121.38, 37.22, 28.31, 21.43, 15.97; HRMS (ESI) calcd for $C_{25}H_{24}NO_4S$ [M+H$^+$] 434.1421, found 434.1433.

(4-Biphenyl)-2-oxo-2,5-dihydrobenzo[b]oxepin-7-yl)-4-methylbenzenesulfonamide (**3j**): 31% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.42 (s, 1H), 7.78 (d, J=4.2 Hz, 4H), 7.74～7.69 (m, 4H), 7.49 (t, J=7.7 Hz, 2H), 7.41～7.35 (m, 3H), 7.31～7.27 (m, 2H), 7.21 (d, J=8.9 Hz, 1H), 7.15～7.12 (m, 1H), 3.47 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 168.49, 146.73, 146.16, 143.88, 140.31, 137.74, 137.07, 134.54, 130.26, 129.50, 128.57, 128.14, 127.48, 127.25, 127.21, 127.11, 124.66, 122.08, 121.44, 117.42, 96.26, 37.40, 21.44; HRMS (ESI) calcd for $C_{29}H_{24}NO_4S$ [M+H$^+$] 482.1421, found 482.1412.

(4-(3-Methylphenyl)-2-oxo-2,5-dihydrobenzo[*b*]oxepin-7-yl)-4-methylbenzenesulfonamide (**3k**): 47% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.41 (s, 1H), 7.69 (d, J=8.3 Hz, 2H), 7.50 (s, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.37～7.31 (m, 3H), 7.26 (d, J=2.5 Hz, 1H), 7.22～7.17 (m, 3H), 7.14～7.11 (m, 1H), 3.41 (s, 2H), 2.36 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 168.03, 146.42, 143.86, 138.84, 138.52, 137.07, 135.32, 134.85, 130.25, 129.63, 129.17, 128.56, 127.23, 127.19, 124.87, 123.79, 122.08, 121.51, 121.38, 37.28, 21.50, 21.43; HRMS (ESI) calcd for $C_{24}H_{22}NO_4S$ [M+H$^+$] 420.1264, found 420.1252.

(4-(4-Cyanophenyl)-2-oxo-2,5-dihydrobenzo[*b*]oxepin-7-yl)-4-methylbenzenesulfonamide (**3l**): 30% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.05 (s, 1H), 7.99～7.97 (m, 2H), 7.91 (d, J=8.4 Hz, 2H), 7.69 (d, J=8.3 Hz, 2H), 7.43 (s, 1H), 7.36 (d, J=8.0 Hz, 2H), 7.31 (d, J=2.6 Hz, 1H), 7.22 (d, J=8.9 Hz, 1H), 7.18～7.14 (m, 1H), 3.49 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 193.08, 167.94, 146.60, 144.41, 143.90, 137.04, 136.09, 136.07, 134.95, 134.02, 130.42, 130.27, 128.23, 127.80, 127.31, 127.19, 122.24, 121.51, 40.49, 40.41, 40.32, 40.25,

40.16, 40.08, 39.99, 39.82, 39.65, 39.49, 37.01, 21.44; HRMS (ESI) calcd for $C_{24}H_{19}N_2O_4S$ [M+H$^+$] 431.1060, found 431.1051.

Methyl-*N*-(9-methyl-2-oxo-4-phenyl-2,5-dihydrobenzo-[*b*]oxepin-7-yl)benzenesulfonamide (**3m**): 46% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63 (d, J=8.3 Hz, 2H), 7.63 (d, J=8.3 Hz, 2H), 7.55～7.33 (m, 6H), 7.44～7.41 (m, 5H), 7.18 (d, J=8.0 Hz, 2H), 7.18 (d, J=8.0 Hz, 2H), 6.89 (s, 2H), 6.89 (s, 2H), 6.79 (d, J=2.3 Hz, 1H), 6.79 (d, J=2.3 Hz, 1H), 6.05 (s, 1H), 3.79 (s, 2H), 3.79 (s, 2H), 2.34 (s, 3H), 2.34 (s, 3H), 2.28 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 163.96, 158.13, 147.33, 144.07, 138.79, 135.81, 133.39, 132.60, 131.40, 130.05, 129.70, 128.96, 127.26, 126.36, 123.10, 119.13, 116.20, 35.15, 21.56, 16.59; HRMS (ESI) calcd for $C_{24}H_{22}NO_4S$ [M+H$^+$] 442.1083, found 442.1074.

(9-Chloro-2-oxo-4-phenyl-2,5-dihydrobenzo[*b*]oxepin-7-yl)-4-methylbenzenesulfonamide (**3n**): 27% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63 (d, J=8.3 Hz, 2H), 7.45～7.43 (m, 5H), 7.21 (d, J=8.1 Hz, 2H), 7.03～6.98 (m, 2H), 6.88 (s, 1H), 6.07 (s, 1H), 3.85 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 162.37, 157.81, 144.86, 144.50, 138.45, 135.49, 134.33, 134.22, 130.31, 129.89, 129.07, 127.23, 126.78, 126.36, 121.79, 119.54, 116.00, 35.26, 21.59; HRMS (ESI) calcd for $C_{23}H_{19}ClNO_4S$ [M+H$^+$] 440.0718, found 440.0710.

Methyl-*N*-(8-methyl-2-oxo-4-phenyl-2,5-dihydrobenzo-[*b*]oxepin-7-yl)benzenesulfonamide (**3o**): 52% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.56 (d, J=8.3 Hz, 2H), 7.49～7.44 (m, 5H), 7.25 (s, 1H), 7.16 (d, J=8.1 Hz, 2H), 6.99 (s, 1H), 6.40 (s, 1H), 6.07 (s, 1H), 3.83 (s, 2H), 2.36 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 163.98, 158.23, 149.18, 144.10, 138.83, 136.35, 132.28, 131.60, 130.10, 129.86, 129.70, 129.00, 127.11, 126.40, 124.88, 122.80, 116.17, 34.78, 21.58, 17.26; HRMS (ESI) calcd for $C_{24}H_{22}NO_4S$ [M+H$^+$] 420.1264, found 420.1273.

Supporting Information ^{1}H NMR and ^{13}C NMR spectra of compounds **3a**～**3o** and the cartesian coordinates. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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(Zhao, C.)

