有机化学 DOI: 10.6023/cjoc202212002 研究论文
Chinese Journal of Organic Chemistry ARTICLE

烯胺酮平台构建转化生物质产品 Cyrene 为增值化合物

黄丽珠[a] 刘云云*,[a] 万结平*,[a,b]
([a]江西师范大学化学化工学院 国家单糖化学合成工程技术研究中心 南昌 330022)
([b]南京林业大学林产化学与材料国际创新高地 南京 210037)

摘要 发展了在二氢左旋葡萄糖酮(Cyrene, 昔兰尼)的酮 α-位烯胺化构建烯胺昔兰尼(EC)的方法, 有效地构建烯胺 Cyrene 作为平台合成子为将生物质产品 Cyrene 转化为增值化学品开辟了广阔的空间. 在此研究中, 实现了将烯胺昔兰尼向多种不同的手性有机衍生物, 包括 NH-/*N*,*N*-双取代结构的烯胺昔兰尼, 氰基烯-和烯基磷修饰的昔兰尼, 呋喃稠环结构的昔兰尼以及 2,2-二氟二氢呋喃稠合的昔兰尼的转化.
关键词 昔兰尼; 生物质产品; 烯胺化; 平台; 增值

Engineering Biomass Feedstock Cyrene to Value-Added Compounds by Enaminone Platform Construction

Huang, Lizhu[a] Liu, Yunyun*,[a] Wan, Jieping*,[a,b]
([a] *National Engineering Research Center for Carbohydrate Synthesis, College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022*)
([b] *International Innovation Center for Forest Chemicals and Materials, Nanjing Forestry University, Nanjing 210037*)

Abstract The enamination of Cyrene in the ketone α-site leading to the enamino Cyrene (EC) has been developed. The practical preparation of EC as a platform synthon opens broad space of chemical transformation for Cyrene biomass feedstock in the synthesis of diverse value-added chemicals. In the present work, the transformation of the EC for the synthesis of many different chiral organic derivatives, including NH-/*N*,*N*-disubstituted ECs, the cyanoalkenyl- and vinyl phosphine oxide-elaborated Cyrene, Cyrene fused furan, and 2,2-difluorodihydrofuran fused Cyrene, has been realized.
Keywords Cyrene; biomass feedstock; enamination; platform; value-added

1 Introduction

Cyrene, also known as dihydrolevoglucosenone, is a biomass chemical derived from cellulose and various other biomass with typical two-step procedure of levoglucosenone formation and its hydrogenation (Figure 1).[1] Besides the internal advantages associated with the biorenewable sources and the highly green production procedures, the Cyrene itself has received extensive attention for its very low toxicity [lower than the hazard standards in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS)[2]] and similar physical properties with useful dipolar solvents such as *N*,*N*-dimethylformamide (DMF) and NMP *etc*.[3] The sustainability and special physical property of Cyrene have thus attracted extensive interest in the solvent replacement chemistry by acting green medium of organic synthesis. Over the past decade, Cyrene has been identified as practical medium in a variety of different chemical processes[4] and a series of organic reactions, including the nucleophilic reactions,[5] carbon dioxide reduction,[6] cross coupling reactions,[7] alkenyl ester dimerization,[8] reduction of α-ketoester,[9] as well as multicomponent heterocycle construction.[10]

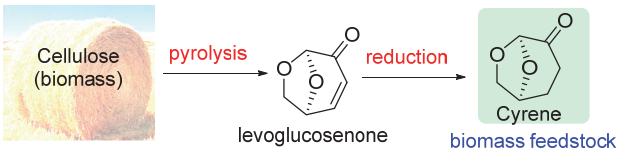


Figure 1 General production of Cyrene from cellulose

Alongside the utilization as green reaction medium, the transformation of Cyrene to other useful chemical products is also inarguably an issue of strategic importance. For

* Corresponding authors. E-mail: chemliuyunyun@jxnu.edu.cn; wanjieping@jxnu.edu.cn
Received December 3, 2022; revised January 6, 2023; published online January 18, 2023.
Project supported by the National Natural Science Foundation of China (No. 22161022).
国家自然科学基金(No. 22161022)资助项目.

example, Cyrene can be polymerized to different polymers,[11] hydrolysed to *gem*-diols,[12] transformed into ester by the Baeyer-Villiger oxidation,[13] reduced to alcohol by the hydrogenation on the carbonyl group,[14] and undertake other reactions such as aldol condensation[15] and Beckman rearrangement.[16] Regardless the known advances, it is clear that the overall availability of the methods for Cyrene transformation is yet rather scarce, which restricts the adequate utilization of this biomass feedstock. Therefore, developing new tactics, especially tactics with broad space of chemical transformation is currently a critical issue in exploring the value of Cyrene.

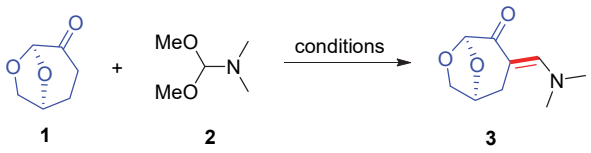
Over the last decade, the extensive efforts in the research of enaminones have disclosed the powerful application potential of the enaminone building block in organic synthesis. The enriched transformation pathways in the vinyl C—H bonds, the C=C double bond, the carbonyl, the C—N bond, as well as the flexible combination of conversion in different reactive sites of enaminones have demonstrated their exceptionally excellent application in organic synthesis.[17] Inarguably, transforming Cyrene in its enaminone derivative would significantly expand the space of utilization for this biomass derived chemical, and reasonably provides a powerful tool for engineering Cyrene to diverse value-added compounds.

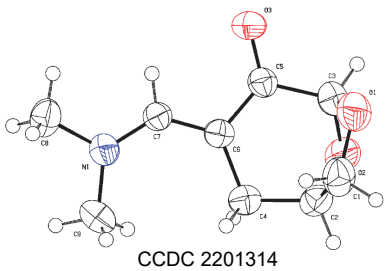
2 Results and discussion

To begin the study, the reaction of Cyrene **1** with DMF-DMA (*N*,*N*-dimethylformamide dimethyl acetal) **2** was first conducted by using different solvents as reaction medium. For the sake of developing conditions proper for scale-up synthesis, the reaction was run at 1 mmol scale. Generally, nonpolar media such as *p*-xylene and toluene, or low polar tetrahydrofuran (THF) could be used to provide the Cyrene derived enaminone **3** (Entries 1～3, Table 1). On the other hand, most highly 62 polar solvents such as DMF, ethyl lactate (EL), alcohols, dimethyl sulfoxide (DMSO), acetone, dioxane, *N*-methyl pyrrolidone (NMP) and acetonitrile were found to be inapplicable for this titled transformation (Entries 4～12, Table 1). Additionally, by fixing toluene as the selected medium, other parameters were optimized for further improving the result. The reaction with different stirring time proved that 4 hours of stirring gave the best result (Entries 13～15, Table 1). On the other hand, the comparison of the results at different temperatures showed that either lowering or heightening the reaction temperature led to decrease in the yield of product **3** (Entries 16～18, Table 1). The single crystal analysis provided confirmatory information for the structure of **3**.[18]

Upon establishing the practical conditions for the synthesis of EC **3**, the efforts in disclosing the synthetic application of this biomass derived scaffold were then made. One applicable transformation is the transamination of the tertiary enamine structure in **3** by reacting with a primary or secondary amine. The resultant product of product **5** could expand the synthetic application of such enamino Cyrene

Table 1 Synthesis of *N*,*N*-dimethylenamino Cyrene in different media[a]





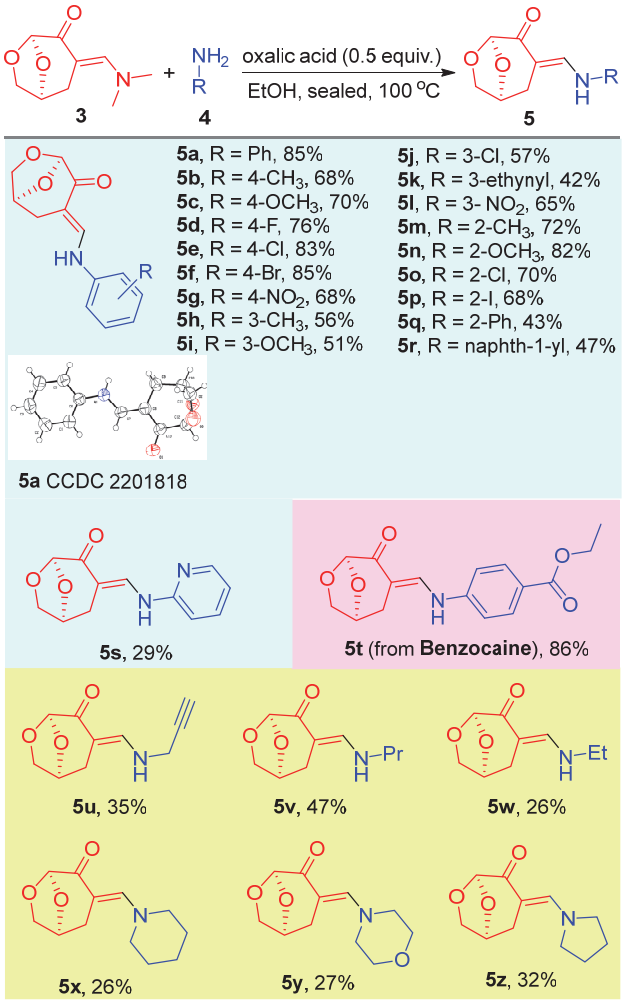
CCDC 2201314

Entry	Solvent	Time/h	*T*/℃	Yield[b]/%
1	*p*-Xylene	6	100	32
2	Toluene	6	100	84
3	THF	6	100	66
4	DMF	6	100	n.r
5	EL	6	100	n.r
6	EtOH	6	100	n.r
7	*i*-PrOH	6	100	n.r
8	DMSO	6	100	n.r
9	Acetone	6	100	n.r
10	1,4-Dioxane	6	100	n.r
11	NMP	6	100	n.r
12	MeCN	6	100	n.r
13	Toluene	5	100	87
14	Toluene	4	100	89
15	Toluene	3	100	56
16	Toluene	4	110	77
17	Toluene	4	90	83
18	Toluene	4	80	53

[a] General conditions: Cyrene **1** (2 mmol), DMF-DMA **2** (3 mmol), in 3 mL of solvent and heating at 100 ℃ or reflux. [b] Isolated yield.

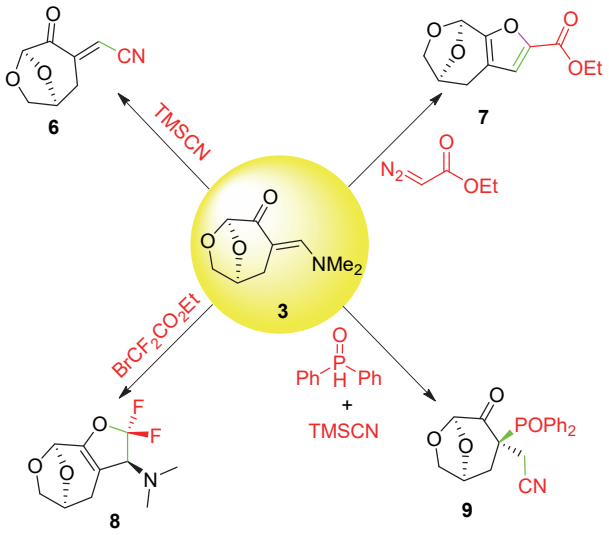
(EC) in theory by introducing the additional NH group. To ensure the practical transformation, systematical optimization on the reaction conditions was carried out. To our delight, the simple oxalic acid was found as a highly practical promoter allowing the synthesis of **5a** with excellent yield (85% yield) and *Z*-selectivity by simply heating in EtOH.[18] The catalytic method also displayed excellent tolerance to the synthesis of NH-based EC via the reactions of EC **3** with diverse primary and secondary amines (**5a**～**5z**, Scheme 1). The reaction with aromatic primary amines gave generally good to excellent yields. The reaction using *m*-substituted anilines (**5h**～**5l**, Scheme 1) gave products with lower yields. In addition, the anilines with bulky *o*-substituent (**5p**～**5q**, Scheme 1), naphtha-1-yl (**5r**, Scheme 1) and pyridin-2-yl amine (**5s**, Scheme 1) also gave low yield. Notably, the clinical medicine Benzocaine reacted with EC to provide the Cyrene decorated Benzocaine **3t** with excellent yield. In addition, alkyl primary amines (**3u**～**3w**,

Scheme 1) and secondary amines (**3x**～**3z**, Scheme 1) could also be used for the synthesis of correspond enamino functionalized Cyrenes with fair to moderate yield. A few other amines or ammonium such as diphenyl amine, benzylamine or ammonium acetate did not react with **3** to provide corresponding ECs via such transamination. The unconventional stereoselectivity in the formation of *Z*-NH-enaminones **5** might be ascribed to the stronger hydrogen bond effect between the NH group and the C(sp^3)—O atoms in the oxygen cycle.



Scheme 1 Synthesis of diverse ECs by C—N bond transamination

In order to further explore the synthetic application of EC **3** to other types of organic compounds, following the recently disclosed transformation modes, the reactions using different reaction partners were conducted under proper reaction conditions. Several new chiral products were outlined in Scheme 2, including the cyanovinyl Cyrene **6**, furan fused Cyrene **7**, 2,2-difluorinated dihydrofuran fused Cyrene **8** as well as cyanomethyl and phosphoryl difunctionalized Cyrene **9**.[19] These results further documented the promise of the EC scaffold **3** in the synthesis of structurally diverse chiral molecules based on the versatile transformations of enaminone.



Scheme 2 Synthesis of different chiral compounds with EC **3**

3 Conclusions

In conclusion, we have disclosed a new tactic for the Cyrene biomass feedstock transformation by building enaminone platform, which open significantly broader space of Cyrene transformation to diversity- and value-added chemical products. The primary investigation has verified in part the application of this newly prepared EC in the synthesis of many different chiral Cyrene derivatives via transamination, C—N bond cyanation, annulation and trifunctionalization *etc*. Further works on developing transformation of the EC to diverse and valuable molecules are presently on going in our group.

4 Experimental section

4.1 General experimental information

All chemicals were obtained from commercial sources. Reagents were used directly as obtained without further purification. Solvents have been treated following standard processes before use.

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer. The frequencies for ^{1}H NMR and ^{13}C NMR test are 400 and 100 MHz, respectively. The chemical shifts were reported with TMS as internal standard. Melting points were tested on a X-4A instrument without correcting temperature. The HRMS were obtained on a TripleTOF 6600 mass spectrometer under ESI model equipped with time of flight (TOF) analyzer.

4.2 Procedure for the synthesis of 3

To a 50 mL round-bottom flask were charged with Cyrene **1** (2 mmol), DMF-DMA **2** (3 mmol) and xylene (3 mL). Then, the mixture was stirred at 100 ℃ with oil bath heating for 4 h. Before being cooled down to room temperature, petroleum ether (50 mL) was added dropwise into the mixture while stirring. The precipitates were formed and collected by filtration, and washed with petroleum ether to

give the pure product **3**.

(1*S*,5*R*,*E*)-3-((Dimethylamino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**3b**): Yield 326.3 mg (89% yield). Yellow solid, m.p. 168～170 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 (s, 1H), 5.17 (s, 1H), 4.77 (t, J=5.4 Hz, 1H), 3.90 (t, J=6.0 Hz, 1H), 3.78 (d, J=7.0 Hz, 1H), 3.25 (dd, J=14.6, 5.1Hz, 1H), 3.11 (s, 6H), 2.63 (d, J=14.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.5, 151.9, 101.3, 93.9, 72.3, 68.1, 43.0, 30.9. HRMS (ESI-TOF) calcd for $C_9H_{14}NO_3$ $[M+H]^+$ 184.0968, found 184.0975.

4.3 General procedure for the synthesis of enaminocyrenes 5

In a 10 mL sealed tube were charged with EC **3** (0.3 mmol), amine **4** (0.6 mmol), oxalic acid (0.15 mmol), and ethanol (2 mL). The tube was then sealed with Teflon cap and stirred at 100 ℃ for 7 h with oil bath heating. Upon completion of the reaction, the vessel was allowed to cool down to room temperature. The products **5** were then purified by either methods A or B as noted below.

Method A (**5a**～**5f**, **5h**, **5k**, **5s**～**5t**): The reaction mixture was mixed with ethyl acetate (10 mL), and the resulting mixture solution was washed with water (10 mL×3). The organic phase was dried over anhydrous Na_2SO_4 and filtrated. The solution was evaporated under reduced pressure to remove the solvent, and the resulting filter residue was dissolved in 2 mL of $CHCl_2$. Petroleum ether (20 mL) was then added, and the pure products were precipitated thereby.

Method B (**5g**, **5i**～**5j**, **5l**～**5r**, **5u**～**5z**): The mixture was transferred into a round bottom flask and evaporated under reduced pressure to remove the solvent. The residue was then subjected to flash column chromatography by using mixed petroleum ether (PE) and ethyl acetate (EA) (V∶V=0.5∶1～8∶1) as eluent to afford pure products.

(1*S*,5*R*,*E*)-3-((Phenylamino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5a**): Yield 59.1 mg (85% yield). Yellow solid, m.p. 235～237 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.16 (d, J=13.6 Hz, 1H), 7.96 (d, J=13.4 Hz, 1H), 7.32 (t, J=7.6 Hz, 2H), 7.27～7.19 (m, 2H), 7.01 (t, J=7.4 Hz, 1H), 5.09 (s, 1H), 4.96 (t, J=5.4 Hz, 1H), 3.82 (t, J=6.6 Hz, 1H), 3.72 (d, J=7.4 Hz, 1H), 2.85 (dd, J=16.2, 5.4 Hz, 1H), 2.50 (d, J=7.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ: 188.4, 141.7, 139.9, 130.0, 123.0, 116.5, 100.9, 100.7, 72.0, 68.7, 29.9. HRMS (ESI-TOF) calcd for $C_{13}H_{14}NO_3$ $[M+H]^+$ 232.0968, found 232.0973.

(1*S*,5*R*,*E*)-3-((*p*-Tolylamino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5b**): Yield 50.2 mg (68% yield). Yellow solid, m.p. 235～237 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.13 (d, J=13.6 Hz, 1H), 7.92 (d, J=13.8 Hz, 1H), 7.12 (s, 4H), 5.07 (s, 1H), 4.95 (t, J=5.4 Hz, 1H), 3.81 (t, J=7.2 Hz, 1H), 3.71 (dd, J=7.4, 1.6 Hz, 1H), 2.83 (dd, J=16.0, 5.6 Hz, 1H), 2.42 (dd, J=15.4, 7.6 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.1, 140.2, 139.3, 132.1, 130.4, 116.6, 100.7, 100.2, 72.0, 68.7, 29.9, 20.7. HRMS (ESI-TOF) calcd for $C_{14}H_{16}NO_3$ $[M+H]^+$ 246.1125, found 246.1126.

(1*S*,5*R*,*E*)-3-(((4-Methoxyphenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5c**): Yield 54.8 mg (70% yield). White solid, m.p. 229～231 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.10 (d, J=13.8 Hz, 1H), 7.88 (d, J=14.0 Hz, 1H), 7.19～7.14 (m, 2H), 6.93～6.88 (m, 2H), 5.07 (s, 1H), 4.95 (t, J=5.4 Hz, 1H), 3.81 (t, J=5.8 Hz, 1H), 3.72 (s, 4H), 2.82 (dd, J=16.0, 5.6 Hz, 1H), 2.41 (d, J=16.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.0, 155.7, 140.8, 135.2, 118.1, 115.2, 100.7, 99.6, 72.0, 68.7, 55.7, 29.8. HRMS (ESI-TOF) calcd for $C_{14}H_{16}NO_4$ $[M+H]^+$ 262.1074, found 262.1079.

(1*S*,5*R*,*E*)-3-(((4-Fluorophenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5d**): Yield 57.1 mg (76% yield). White solid, m.p. 231～233 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.19 (d, J=13.6 Hz, 1H), 7.90 (d, J=13.6 Hz, 1H), 7.28～7.23 (m, 2H), 7.19～7.12 (m, 2H), 5.10 (s, 1H), 4.97 (t, J=5.4 Hz, 1H), 3.85～3.79 (m, 1H), 3.73 (d, J=7.4 Hz, 1H), 2.84 (dd, J=16.1, 5.4 Hz, 1H), 2.45 (d, J=16.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.3, 158.43 (d, J=238.0 Hz), 140.3, 138.3 (d, J=2.4 Hz), 118.18 (d, J=8.0 Hz), 116.55 (d, J=22.6 Hz), 100.8, 100.6, 72.0, 68.7, 29.9. HRMS (ESI-TOF) calcd for $C_{13}H_{13}FNO_3$ $[M+H]^+$ 250.0874, found 250.0878.

(1*S*,5*R*,*E*)-3-(((4-Chlorophenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5e**): Yield 66.0 mg (83% yield). Green solid, m.p. 254～256 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.22 (d, J=13.4 Hz, 1H), 7.91 (d, J=13.4 Hz, 1H), 7.34 (d, J=8.8 Hz, 2H), 7.24 (d, J=9.0 Hz, 2H), 5.11 (s, 1H), 4.97 (t, J=5.4 Hz, 1H), 3.85～3.78 (m, 1H), 3.73 (d, J=7.2 Hz, 1H), 2.85 (dd, J=16.2, 5.8 Hz, 1H), 2.46 (d, J=16.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.4, 140.7, 139.4, 129.7, 126.6, 118.0, 101.6, 100.6, 72.0, 68.7, 29.9. HRMS (ESI-TOF) calcd for $C_{13}H_{13}ClNO_3$ $[M+H]^+$ 266.0578, found 266.0586.

(1*S*,5*R*,*E*)-3-(((4-Bromophenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5f**): Yield 78.9 mg (85% yield). Yellow solid, m.p. 273～275 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.23 (d, J=13.4 Hz, 1H), 7.90 (d, J=13.4 Hz, 1H), 7.47 (d, J=8.6 Hz, 2H), 7.20 (d, J=8.6 Hz, 2H), 5.10 (s, 1H), 4.97 (t, J=5.4 Hz, 1H), 3.81 (t, J=6.8 Hz, 1H), 3.73 (d, J=7.4 Hz, 1H), 2.83 (dd, J=16.4, 5.4 Hz, 1H), 2.46 (d, J=16.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.4, 141.2, 139.2, 132.6, 118.5, 114.5, 101.7, 100.6, 72.0, 68.7, 29.9. HRMS (ESI-TOF) calcd for $C_{13}H_{13}BrNO_3$ $[M+H]^+$ 310.0073, found 310.0079.

(1*S*,5*R*,*E*)-3-(((4-Nitrophenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5g**): Eluent: V_{PE}∶V_{EA}=4∶1. Yield 56.6 mg (68% yield). Yellow solid, m.p. 220～222 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.66 (d, J=12.4 Hz, 1H), 8.18 (d, J=9.2 Hz, 2H), 7.97 (d, J=12.0 Hz, 1H), 7.43 (d, J=9.2 Hz, 2H), 5.16 (s, 1H), 5.00 (t, J=5.4 Hz, 1H), 3.85～3.80 (m, 1H), 3.77 (d, J=7.0 Hz, 1H), 2.90 (dd, J=16.2, 5.0 Hz, 1H), 2.57 (d, J=16.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.9, 147.8, 141.7, 137.5, 126.1, 116.0, 105.3, 100.4, 72.0, 68.7, 30.1. HRMS (ESI-TOF) calcd for $C_{13}H_{13}N_2O_5$ $[M+H]^+$ 277.0819, found 277.0827.

(1*S*,5*R*,*E*)-3-((*m*-Tolylamino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5h**): Yield 41.4 mg (56% yield). White solid, m.p. 188～190 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.12 (d, J=13.6 Hz, 1H), 7.95 (d, J=13.6 Hz, 1H), 7.19 (t, J=7.8 Hz, 1H), 7.05 (s, 1H), 7.01 (d, J=8.0 Hz, 1H), 6.83 (d, J=7.4 Hz, 1H), 5.09 (s, 1H), 4.96 (t, J=5.4 Hz, 1H), 3.81 (t, J=6.4 Hz, 1H), 3.72 (d, J=7.2 Hz, 1H), 2.83 (dd, J=16.4, 5.2 Hz, 1H), 2.45 (d, J=16.0 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.3, 141.7, 139.9, 139.4, 129.8, 123.8, 116.9, 113.9, 100.7, 72.0, 68.7, 29.9, 21.6. HRMS (ESI-TOF) calcd for $C_{14}H_{16}NO_3$ $[M+H]^+$ 246.1125, found 246.1129.

(1*S*,5*R*,*E*)-3-(((3-Methoxyphenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5i**): Eluent: V_{PE}∶V_{EA}=2∶1. Yield 40.1 mg (51% yield). White solid, m.p. 160～162 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.14 (d, J=13.6 Hz, 1H), 7.93 (d, J=13.6 Hz, 1H), 7.21 (t, J=8.0 Hz, 1H), 6.83～6.75 (m, 2H), 6.59 (d, J=8.6 Hz, 1H), 5.09 (s, 1H), 4.97 (t, J=5.4 Hz, 1H), 3.81 (t, J=6.6 Hz, 1H), 3.75 (s, 3H), 3.73～3.68 (m, 1H), 2.84 (dd, J=16.0, 5.4 Hz, 1H), 2.45 (d, J=16.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.3, 160.7, 143.0, 139.7, 130.9, 108.8, 108.5, 102.4, 101.0, 100.6, 72.0, 68.7, 55.5, 29.9. HRMS (ESI-TOF) calcd for $C_{14}H_{16}NO_4$ $[M+H]^+$ 262.1074, found 262.1079.

(1*S*,5*R*,*E*)-3-(((3-Chlorophenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5j**): Eluent: V_{PE}∶V_{EA}=4∶1. Yield 45.7 mg (57% yield). White solid, m.p. 189～191 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.22 (d, J=13.0 Hz, 1H), 7.92 (d, J=13.0 Hz, 1H), 7.36～7.27 (m, 2H), 7.21 (d, J=8.4 Hz, 1H), 7.03 (d, J=8.0 Hz, 1H), 5.11 (s, 1H), 4.98 (t, J=6.0 Hz, 1H), 3.85～3.78 (m, 1H), 3.77～3.70 (m, 1H), 2.85 (d, J=15.6 Hz, 1H), 2.47 (d, J=16.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.5, 143.3, 139.1, 134.4, 131.6, 122.5, 116.3, 114.8, 102.2, 100.6, 72.0, 68.7, 29.9. HRMS (ESI-TOF) calcd for $C_{13}H_{13}ClNO_3$ $[M+H]^+$ 266.0578, found 266.0587.

(1*S*,5*R*,*E*)-3-(((3-Ethynylphenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5k**): Yield 32.2 mg (42% yield). White solid, m.p. 222～224 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.19 (d, J=13.2 Hz, 1H), 7.93 (d, J=13.2 Hz, 1H), 7.31 (s, 3H), 7.10 (s, 1H), 5.11 (s, 1H), 4.97 (s, 1H), 4.30～4.14 (m, 1H), 3.77 (d, J=30.2 Hz, 2H), 2.84 (d, J=16.0 Hz, 1H), 2.46 (d, J=17.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.4, 142.0, 139.3, 130.4, 126.1, 123.2, 119.5, 116.9, 101.7, 100.6, 83.6, 81.3, 72.0, 68.7, 29.9. HRMS (ESI-TOF) calcd for $C_{15}H_{14}NO_3$ $[M+H]^+$ 256.0968, found 256.0977.

(1*S*,5*R*,*E*)-3-(((3-Nitrophenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5l**): Eluent: V_{PE}∶V_{EA}=3∶1. Yield 54.2 mg (65% yield). Yellow solid, m.p. 200～202 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.47 (d, J=13.2 Hz, 1H), 8.06～8.02 (m, 1H), 7.98 (d, J=13.2 Hz, 1H), 7.80 (d, J=8.0 Hz, 1H), 7.70 (d, J=8.2 Hz, 1H), 7.57 (t, J=8.2 Hz, 1H), 5.15 (s, 1H), 5.01 (t, J=5.4 Hz, 1H), 3.87～3.80 (m, 1H), 3.76 (d, J=7.4 Hz, 1H), 2.88 (dd, J=16.4, 5.6 Hz, 1H), 2.51 (d, J=12.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.7, 149.0, 143.1, 138.6, 131.3, 121.8, 116.8, 111.1, 103.0, 100.5, 72.0, 68.7, 29.9. HRMS (ESI-TOF) calcd for $C_{13}H_{13}N_2O_5$ $[M+H]^+$ 277.0819, found 277.0822.

(1*S*,5*R*,*E*)-3-((*o*-Tolylamino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5m**): Eluent: V_{PE}∶V_{EA}=8∶1. Yield 52.9 mg (72% yield). Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, J=12.2 Hz, 1H), 7.19 (d, J=7.8 Hz, 2H), 7.10 (d, J=8.2 Hz, 1H), 7.00 (t, J=7.6 Hz, 1H), 5.24 (s, 1H), 4.85 (t, J=5.6 Hz, 1H), 3.97 (t, J=7.0 Hz, 1H), 3.82 (d, J=7.2 Hz, 1H), 3.13 (d, J=14.4 Hz, 1H), 2.39 (s, 1H), 2.35 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.3, 145.8, 138.4, 131.2, 127.2, 126.3, 123.6, 113.5, 100.6, 96.6, 72.8, 68.2, 31.1, 17.6. HRMS (ESI-TOF) calcd for $C_{14}H_{16}NO_3$ $[M+H]^+$ 246.1125, found 246.1131.

(1*S*,5*R*,*E*)-3-(((2-Methoxyphenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5n**): Eluent: V_{PE}∶V_{EA}=4∶1. Yield 64.3 mg (82% yield). Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, J=12.6 Hz, 1H), 7.10 (d, J=7.8 Hz, 1H), 7.05～6.86 (m, 4H), 5.23 (s, 1H), 4.83 (t, J=5.4 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 1H), 3.81 (d, J=7.2 Hz, 1H), 3.13 (dd, J=14.8, 4.6 Hz, 1H), 2.37 (d, J=15.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.0, 148.3, 144.3, 129.5, 123.6, 121.0, 112.9, 111.1, 100.7, 96.6, 72.9, 68.2 55.9, 31.3. HRMS (ESI-TOF) calcd for $C_{14}H_{16}NO_4$ $[M+H]^+$ 262.1074, found 262.1084.

(1*S*,5*R*,*E*)-3-(((2-Chlorophenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5o**): Eluent: V_{PE}∶V_{EA}=4∶1. Yield 55.8 mg (70% yield). Yellow liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.87 (d, J=12.0 Hz, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.36 (t, J=7.6 Hz, 1H), 7.06 (t, J=7.4 Hz, 1H), 5.16 (s, 1H), 4.91 (t, J=5.4 Hz, 1H), 3.83 (t, J=6.4 Hz, 1H), 3.76 (d, J=6.4 Hz, 1H), 2.98 (dd, J=15.2, 4.8 Hz, 1H), 2.47 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 191.3, 145.1, 137.0, 130.3, 129.0, 124.2, 121.0, 115.5, 100.0, 99.2, 72.8, 68.2, 30.9. HRMS (ESI-TOF) calcd for $C_{13}H_{13}ClNO_3$ $[M+H]^+$ 266.0578, found 266.0587.

(1*S*,5*R*,*E*)-3-(((2-Iodophenyl)amino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5p**): Eluent: V_{PE}∶V_{EA}=4∶1. Yield 73.2 mg (68% yield). Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (dd, J=7.8, 1.4 Hz, 1H), 7.25 (t, J=8.4 Hz, 1H), 7.15 (d, J=11.8 Hz, 1H), 7.01 (d, J=8.2 Hz, 1H), 6.71 (t, J=7.6 Hz, 1H), 5.19 (s, 1H), 4.78 (t, J=5.4 Hz, 1H), 3.89 (t, J=6.6 Hz, 1H), 3.76 (d, J=6.8 Hz, 1H), 3.06 (dd, J=15.0, 4.6 Hz, 1H), 2.32 (d, J=15.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.6, 144.1, 140.1, 129.4, 124.8, 114.3, 100.6, 98.1, 88.0, 72.8, 68.3, 31.4. HRMS (ESI-TOF) calcd for $C_{13}H_{13}INO_3$ $[M+H]^+$ 357.9935, found 357.9941.

(1*S*,5*R*,*E*)-3-(([1,1'-Biphenyl]-2-ylamino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5q**): Eluent: V_{PE}∶V_{EA}=4∶1. Yield 39.7 mg (43% yield). Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (d, J=7.6 Hz, 2H), 7.45 (d, J=7.2 Hz, 1H), 7.40 (d, J=7.0 Hz, 2H), 7.33 (t, J=7.2 Hz, 1H), 7.28 (d, J=4.4 Hz, 1H), 7.24 (d, J=8.4 Hz, 1H), 7.19 (d, J=8.4 Hz, 1H), 7.12 (t, J=7.4 Hz, 1H), 5.11 (s,

1H), 4.77 (t, J=4.8 Hz, 1H), 3.88 (t, J=6.0 Hz, 1H), 3.75 (d, J=7.2 Hz, 1H), 3.05 (dd, J=14.8, 4.6 Hz, 1H), 2.30 (d, J=14.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.9, 144.9, 137.6, 137.5, 131.3, 129.2, 129.1, 128.7, 128.2, 123.6, 114.2, 100.5, 97.0, 72.8, 68.2, 31.4. HRMS (ESI-TOF) calcd for $C_{19}H_{18}NO_3$ $[M+H]^+$ 308.1281, found 308.1287.

(1*S*,5*R*,*E*)-3-((Naphthalen-1-ylamino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5r**): Eluent: V_{PE} ∶ V_{EA}=4∶1. Yield 40.0 mg (47% yield). Yellow solid, m.p. 164～166 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, J=8.2 Hz, 1H), 7.84 (d, J=7.8 Hz, 1H), 7.62～7.50 (m, 3H), 7.49～7.39 (m, 2H), 7.20 (d, J=7.4 Hz, 1H), 5.30 (s, 1H), 4.86 (t, J=5.2 Hz, 1H), 3.97 (t, J=6.4 Hz, 1H), 3.85 (d, J=7.2 Hz, 1H), 3.16 (dd, J=14.8, 4.8 Hz, 1H), 2.41 (d, J=14.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.7, 146.8, 136.1, 134.3, 128.5, 126.8, 126.7, 125.7, 124.7, 124.3, 120.8, 110.9, 100.7, 97.4, 72.9, 68.3, 31.2. HRMS (ESI-TOF) calcd for $C_{17}H_{16}NO_3$ $[M+H]^+$ 282.1125, found 282.1131.

(1*S*,5*R*,*E*)-3-((Pyridin-2-ylamino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5s**): Yield 20.3 mg (29% yield). Yellow solid, m.p. 221～223 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.68 (d, J=12.8 Hz, 1H), 8.60 (d, J=12.6 Hz, 1H), 8.26 (d, J=4.0 Hz, 1H), 7.74～7.67 (m, 1H), 7.10 (d, J=8.2 Hz, 1H), 7.01～6.97 (m, 1H), 5.11 (s, 1H), 4.98 (t, J=5.4 Hz, 1H), 3.82 (t, J=6.8 Hz, 1H), 3.74 (d, J=7.2 Hz, 1H), 2.87 (dd, J=16.4, 5.2 Hz, 1H), 2.54～2.51 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 189.1, 152.9, 148.5, 138.9, 137.5, 118.4, 112.0, 102.4, 100.6, 72.0, 68.7 , 30.0. HRMS (ESI-TOF) calcd for $C_{12}H_{13}N_2O_3$ $[M+H]^+$ 233.0921, found 233.0927.

Ethyl 4-(((*E*)-((1*S*, 5*R*)-4-*oxo*-6,8-dioxabicyclo[3.2.1]-octan-3-ylidene)methyl)amino)benzoate (**5t**): Yield 78.1 mg (86% yield). Yellow solid, m.p. 273～275 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.45 (d, J=13.0 Hz, 1H), 7.98 (d, J=13.0 Hz, 1H), 7.89 (d, J=8.8 Hz, 2H), 7.33 (d, J=8.8 Hz, 2H), 5.13 (s, 1H), 4.98 (t, J=5.4 Hz, 1H), 4.27 (q, J=7.2 Hz, 2H), 3.82 (t, J=7.0 Hz, 1H), 3.74 (d, J=7.2 Hz, 1H), 2.87 (dd, J=16.4, 5.4 Hz, 1H), 2.54 (s, 1H), 1.31 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.7, 165.8, 145.9, 138.3, 131.4, 123.6, 115.8, 103.3, 100.5, 72.0, 68.7, 60.8, 30.0, 14.7. HRMS (ESI-TOF) calcd for $C_{16}H_{18}NO_5$ $[M+H]^+$ 304.1179, found 304.1189.

(1*S*,5*R*,*E*)-3-((Prop-2-yn-1-ylamino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5u**): Eluent: V_{PE} ∶ V_{EA}=1∶1. Yield 20.5 mg (35% yield). White solid, m.p. 115～117 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.54 (d, J=13.8 Hz, 1H), 7.50～7.39 (m, 1H), 4.98 (s, 1H), 4.87 (t, J=5.4 Hz, 1H), 4.08～4.04 (m, 2H), 3.76 (t, J=6.6 Hz, 1H), 3.62 (d, J=7.2 Hz, 1H), 2.60 (dd, J=15.6, 5.4 Hz, 1H), 2.12 (d, J=15.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 187.1, 148.8, 100.8, 96.3, 81.3, 75.7, 72.0, 68.7, 36.9, 29.4. HRMS (ESI-TOF) calcd for $C_{10}H_{12}NO_3$ $[M+H]^+$ 194.0812, found 194.0818.

(1*S*,5*R*,*E*)-3-((Propylamino)methylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5v**): Eluent: V_{PE} ∶ V_{EA}=5∶1. Yield 27.8 mg (47% yield). White solid, m.p. 106～108 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.85 (s, 1H), 6.74 (d, J=12.8 Hz, 1H), 5.15 (s, 1H), 4.78 (t, J=5.4 Hz, 1H), 3.91 (t, J=6.6 Hz, 1H), 3.75 (d, J=7.0 Hz, 1H), 3.18 (q, J=6.8 Hz, 2H), 2.98 (dd, J=14.2, 4.6 Hz, 1H), 2.18 (d, J=14.2 Hz, 1H), 1.65～1.54 (m, 2H), 0.94 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.6, 155.6, 100.8, 91.8, 72.8, 68.1, 51.1, 30.9, 24.3, 11.1. HRMS (ESI-TOF) calcd for $C_{10}H_{16}NO_3$ $[M+H]^+$ 198.1125, found 198.1132.

(1*S*,5*R*,*E*)-3-((Ethylamino)methylene)-6,8-dioxabicyclo-[3.2.1]octan-4-one (**5w**): Eluent: V_{PE} ∶ V_{EA}=5∶1. Yield 14.5 mg (26% yield); White solid, m.p. 96～98 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.81 (s, 1H), 6.75 (d, J=12.8 Hz, 1H), 5.16 (s, 1H), 4.78 (t, J=5.2 Hz, 1H), 3.91 (t, J=6.6 Hz, 1H), 3.75 (d, J=7.0 Hz, 1H), 3.34～3.23 (m, 2H), 2.98 (dd, J=14.6, 4.6 Hz, 1H), 2.18 (d, J=14.2 Hz, 1H), 1.24 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.6, 155.0, 100.8, 91.9, 72.9, 68.1, 43.9, 30.9, 16.3. HRMS (ESI-TOF) calcd for $C_9H_{14}NO_3$ $[M+H]^+$ 184.0968, found 184.0972.

(1*S*,5*R*,*E*)-3-(Piperidin-1-ylmethylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5x**): Eluent: V_{PE} ∶ V_{EA}=1∶1. Yield 17.6 mg (26% yield). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (s, 1H), 5.21 (s, 1H), 4.77 (t, J=5.6 Hz, 1H), 3.92 (t, J=6.6 Hz, 1H), 3.78 (d, J=7.0 Hz, 1H), 3.47 (t, J=5.4 Hz, 4H), 3.19 (dd, J=14.2, 5.2 Hz, 1H), 2.45 (d, J=14.2 Hz, 1H), 1.69～1.60 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.7, 150.2, 101.4, 92.8, 72.2, 68.3, 31.7, 26.5, 23.9. HRMS (ESI-TOF) calcd for $C_{12}H_{18}NO_3$ $[M+H]^+$ 224.1281, found 224.1284.

(1*S*,5*R*,*E*)-3-(Morpholinomethylene)-6,8-dioxabicyclo-[3.2.1]octan-4-one (**5y**): Eluent: V_{PE} ∶ V_{EA}=1∶1. Yield 18.3 mg (27% yield). White solid, m.p. 147～149 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 (s, 1H), 5.21 (s, 1H), 4.78 (t, J=4.8 Hz, 1H), 3.92 (t, J=6.4 Hz, 1H), 3.78 (d, J=7.4 Hz, 1H), 3.76～3.68 (m, 4H), 3.56～3.47 (m, 4H), 3.17 (dd, J=14.6, 5.2 Hz, 1H), 2.47 (d, J=14.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.9, 149.5, 101.3, 94.6, 77.4, 77.0, 76.7, 72.1, 68.3, 66.7, 51.1, 31.4. HRMS (ESI-TOF) calcd for $C_{11}H_{16}NO_4$ $[M+H]^+$ 226.1074, found 226.1079.

(1*S*,5*R*,*E*)-3-(Pyrrolidin-1-ylmethylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**5z**): Eluent: V_{PE} ∶ V_{EA}=1∶2. Yield 20.1 mg (32% yield). White solid, m.p. 148～150 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (s, 1H), 5.20 (s, 1H), 4.76 (t, J=5.6 Hz, 1H), 3.92 (t, J=6.6 Hz, 1H), 3.78 (d, J=7.0 Hz, 1H), 3.66～3.53 (m, 4H), 3.26 (dd, J=14.8, 5.0 Hz, 1H), 2.67 (d, J=14.6 Hz, 1H), 1.98～1.85 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.6, 148.5, 101.4, 94.6, 72.4, 68.2, 30.6, 25.4. HRMS (ESI-TOF) calcd for $C_{11}H_{16}NO_3$ $[M+H]^+$ 210.1125, found 210.1128.

4.4 Procedure for the synthesis of **6**

In a 10 mL sealed tube were charged with enaminone **3** (0.3 mmol), TMSCN (cyanotrimethylsilane) (0.6 mmol), I_2 (0.045 mmol), oxalic acid (0.6 mmol) and CH_3OH (2 mL). The tube was then sealed with Teflon cap and stirred at 50 ℃ for 24 h with oil bath heating. Upon completion

(thin-layer chromatography, TLC), the vessel was allowed to cool down to room temperature. The mixture was diluted with ethyl acetate. The solution was directly transferred into a round bottom flask for rotary evaporation. After removing the solvent at reduced temperature, the resulting residue was subjected to flash silica gel column chromatography to provide the pure product with the elution of mixed petroleum ether/ethyl acetate (V∶V=5∶1).

(*E*)-2-((1*S*,5*R*)-4-*oxo*-6,8-Dioxabicyclo[3.2.1]octan-3-ylidene)acetonitrile (**6**): Yield 18.8 mg (38% yield). Colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.43～6.37 (m, 1H), 5.38 (s, 1H), 4.93 (t, J=5.4 Hz, 1H), 4.01～3.95 (m, 1H), 3.89 (d, J=7.6 Hz, 1H), 3.30～3.22 (m, 1H), 3.06 (d, J=18.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 185.0, 149.8, 114.9, 107.6, 100.0, 72.2, 68.7, 35.2. HRMS (ESI-TOF) calcd for $C_8H_8NO_3$ $[M+H]^+$ 166.0499, found 166.0488.

4.5 Procedure for the synthesis of **7**

A mixture of enaminone **3** (0.5 mmol), ethyl diazoacetate (1.1 mmol) and $In(OTf)_3$ (0.025) in DCE (3 mL) was stirred on an oil bath at reflux for 6 h. Upon completion, the mixture was directly employed to reduced pressure to remove the solvent, and the residue was employed to silica gel column chromatography with the elution of mixed petroleum ether and ethyl acetate (V∶V=8∶1) to provide pure product.

Ethyl (5*S*,8*R*)-4,5,6,8-tetrahydro-5,8-epoxyfuro[2,3-*c*]-oxepine-2-carboxylate (**7**): Yield 46.2 mg (41% yield). Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04 (s, 1H), 6.07 (s, 1H), 4.89～4.85 (m, 1H), 4.36 (q, J=7.1 Hz, 2H), 4.09～4.03 (m, 1H), 3.61 (dd, J=7.7, 2.2 Hz, 1H), 3.19～3.16 (m, 1H), 2.38 (dd, J=16.1, 1.0 Hz, 1H), 1.37 (t, J=7.1Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 185.3, 158.7, 153.7, 117.9, 114.9, 94.7, 72.2, 68.0, 61.0, 29.3, 14.3. HRMS (ESI-TOF) calcd for $C_{11}H_{13}N_5$ $[M+H]^+$ 225.0757, found 225.0772.

4.6 Procedure for the synthesis of **8**

In a 25 mL sealed tube were added enaminone **3** (0.3 mmol), $BrCF_2COOEt$ (0.75 mmol), Na_2CO_3 (0.3 mmol) and MeCN (3 mL). After sealing the tube with Teflon cap, the mixture was stirred at 130 ℃ with oil bath heating for 10 h. After being cooled down to room temperature, the mixture was transferred into the round bottom flask, and solvent was removed at reduced pressure. The residue obtained therein was subjected to flash silica gel column chromatography to provide the pure product with the elution of mixed petroleum ether and ethyl acetate (V∶V=1∶1).

(3*S*,5*S*,8*R*)-2,2-Difluoro-*N*,*N*-dimethyl-2,3,4,5,6,8-hexahydro-5,8-epoxyfuro[2,3-*c*]oxepin-3-amine (**8**): Yield 45.0 mg (64% yield). Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.55 (d, J=12.5 Hz, 1H), 4.85～4.77 (m, 1H), 4.12～4.01 (m, 1H), 3.97～3.85 (m, 1H), 3.74～3.69 (m, 1H), 2.79 (d, J=16.8 Hz, 1H), 2.45 (s, 6H), 1.97 (dd, J=16.7, 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.9 (dd, J=35.6, 3.5 Hz), 135.1～129.2 (m), 105.0 (ddd, J=30.3, 4.0, 1.9 Hz), 93.6 (d, J=18.4 Hz), 72.1 (d, J=11.7 Hz), 71.6～70.7 (m), 68.6 (d, J=19.7 Hz), 40.3 (d, J=3.3 Hz), 29.5 (d, J=24.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −60.43 (dd, J=149.0, 103.2 Hz), −82.29 (dd, J=424.9, 149.0 Hz). HRMS (ESI-TOF) calcd for $C_{10}H_{14}F_2NO_3$ $[M+H]^+$ 234.0936, found 234.0956.

4.7 Procedure for the synthesis of **9**

Enaminone **3** (0.3 mmol), diphenyl phosphine oxide (0.4 mmol) and TMSCN (0.6 mmol) were dissolved in MeCN (1 mL) in a 25 mL round-bottom flask. Subsequently, tetrabutyl ammonium hydroxide (TBAH) (0.06 mmol) was added. The resulting mixture was heated up to 50 ℃ with oil bath and stirred at the same temperature for 12 h (TLC). After cooling down to room temperature, the mixture was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography by using mixed petroleum ether and ethyl acetate (V∶V=3∶1) as eluent.

2-((1*S*,3*S*,5*R*)-3-(Diphenylphosphoryl)-4-*oxo*-6,8-dioxabicyclo[3.2.1]octan-3-yl)acetonitrile (**9**): Yield 68.4 mg (62% yield). Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89～7.78 (m, 4H), 7.58 (t, J=7.3 Hz, 2H), 7.53～7.46 (m, 4H), 5.76 (t, J=2.3 Hz, 1H), 5.47～5.43 (m, 1H), 4.92～4.88 (m, 1H), 4.72 (t, J=4.3 Hz, 1H), 3.85～3.77 (m, 2H), 2.98 (dd, J=15.5, 1.5 Hz, 1H), 2.76～2.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.5 (d, J=5.0 Hz), 132.9, 131.6 (d, J=10.5 Hz), 131.4 (d, J=10.4 Hz), 128.9 (d, J=13.4 Hz), 115.6, 101.4 (d, J=2.2 Hz), 98.6, 74.3 (d, J=5.5 Hz), 73.3, 69.0, 37.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 34.6. HRMS (ESI-TOF) calcd for $C_{20}H_{19}NO_4P$ $[M+H]^+$ 368.1046, found 368.1047.

Supporting Information Full data for the optimization toward **5a**, and the NMR spectra of all products. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

References

[1] (a) Sherwood, J.; De bruyn, M.; Constantinou, A.; Moity, L.; McElroy, C. R.; Farmer, T. J.; Duncan, T.; Raverty, W.; Hunt, A. J.; Clark, J. H. *Chem. Commun.* **2014**, *50*, 9650.
(b) Craythorne, S. J.; Anderson, K.; Lorenzini, F.; McCausland, C.; Smith, E. F.; Licence, P.; Marr, A. C.; Marr, P. C. *Chem.-Eur. J.* **2009**, *15*, 7094.
(c) De bruyn, M.; Fan, J.; Budarin, V. L.; Macquarrie, D. J.; Gomez, L. D.; Simister, R.; Farmer, T. J.; Raverty, W. D.; McQueen-Mason, S. J.; Clark, J. H. *Energy Environ. Sci.* **2016**, *9*, 2571.
(d) Miura, M.; Kaga, H.; Yoshida, T.; Ando, K. *J. Wood Sci.* **2001**, *47*, 502.
(e) Sui, X.-W.; Wang, Z.; Liao, B.; Zhang, Y.; Guo, Q.-X. *Bioresour. Technol.* **2012**, *103*, 466.

[2] See also information in Merck product introduction: https://www.merckgroup.com/en/research/science-space/envisioning-tomorrow/scarcity-of-resources/cyrene.html.

[3] Camp, J. E. *ChemSusChem* **2018**, *11*, 3048.

[4] (a) Duval, A.; Avérous, L. *Green Chem.* **2022**, *24*, 338.
(b) Meng, X.; Pu, Y.; Li, M.; Ragauskas, A. J. *Green Chem.* **2020**, *22*, 2862.
(c) Marathianos, A.; Liarou, E.; Hancox, E.; Grace, J. L.; Lester, D. W.; Haddleton, D. M. *Green Chem.* **2020**, *22*, 5833.
(d) Gao, F.; Bai, R.; Ferlin, F.; Vaccaro, L.; Li, M.; Gu, Y. *Green*

Chem. **2020**, *22*, 6240.
(e) Brouwer, T.; Schuur, B. *ACS Sustainable Chem. Eng.* **2020**, *8*, 14807.
[5] (a) Bousfield, T. W.; Pearce, K. P. R.; Nyamini, S. B.; Angelis-Dimakis, A.; Camp, J. E. *Green Chem*. **2019**, *21*, 3675.
(b) Mistry, L.; Mapesa, K.; Bousfield, T. W.; Jason, E. C. *Green Chem*. **2017**, *19*, 2123
[6] Yu, H.; Yu, D.; Xue, Z.; Zhang, B.; Mu, T. *Chem. Eng. J.* **2022**, *431*, 133397.
[7] (a) Wilson, K. L.; Kennedy, A. R.; Murray, J.; Greatrex, B.; Jamieson, C.; Watson, A. J. B. *Beilstein J. Org. Chem.* **2016**, *12*, 2005.
(b) Wilson, K. L.; Murray, J.; Jamieson, C.; Watson, A. J. B. *Synlett* **2018**, *29*, 650.
[8] Mention, M. M.; Flourat, A. L.; Peyrot, C.; Allais, F. *Green Chem.* **2020**, *22*, 2077.
[9] Gonzalo, G. *Biocatal. Biotransfor.* **2022**, *40*, 252.
[10] Tamargo, R. J. I.; Rubio, P. Y. M.; Mohandoss, S.; Shim, J.-J.; Lee, Y. R. *ChemSusChem* **2021**, *14*, 2133.
[11] Ray, P.; Hughes, T.; Smith, C.; Hibbert, M.; Saito, K.; Simon, G. P. *Polym. Chem.* **2019**, *10*, 3334.
(b) Diot-Néant, F.; Mouterde, L.; Fadlallah, S.; Miller, S. A.; Allais, F. *ChemSusChem* **2020**, *13*, 2613.
[12] De bruyn, M.; Budarin, V. L.; Misefari, A.; Shimizu, S.; Fish, H.; Cockett, M.; Hunt, A. J.; Hofsteffter, H.; Weckhuysen, B. M.; Clark, J. H.; Macquarrie, D. J. *ACS Sustainable Chem. Eng.* **2019**, *7*, 7878.
[13] Bonneau G.; Peru, A. A. M.; Flourat, A. L.; Allais, F. *Green Chem*. **2018**, *20*, 2455.
[14] Krishna, S. H.; McClelland, D. J.; Rashke, Q. A.; Dumesic, J. A.; Huber, G. W. *Green Chem*. **2017**, *19*, 1278.
[15] Hughes, L.; McElroy, C. R.; Whitwood, A. C.; Hunt. A. J. *Green Chem.* **2018**, *20*, 4423.
[16] Alhifthi, A.; Harris, B. L.; Goerigk, L.; White, J. M.; Williams, S. J. *Org. Biomol. Chem.* **2017**, *15*, 10105.
[17] (a) Wang, Z.; Zhao, B.; Liu, Y.; Wan, J.-P. *Adv. Synth. Catal.* **2022**, *364*, 1508.
(b) Zheng, X.; Liu, Y.; Wan, J.-P. *Chin. J. Org. Chem.* **2021**, *41*, 2700.
(c) Guo, H.; Liu, Y.; Wen, C.; Wan, J.-P. *Green Chem*. **2022**, *24*, 5058.
(c) Fu, L.; Xu, W.; Pu, M.; Wu, Y-D.; Liu, Y.; Wan, J.-P. *Org. Lett.* **2022**, *24*, 3003.
(d) Guo, Y.; Liu, Y.; Wan, J.-P. *Chin. Chem. Lett.* **2022**, *33*, 855.
(d) Yu, Q.; Liu, Y.; Wan, J.-P. *Chin. Chem. Lett.* **2021**, *32*, 3514.
(e) Duan, X.; Li, H.; Li, W.; Wang, J.; Liu, N. *ChemistrySelect* **2021**, *6*, 6478.
(f) Zhang, B.; Fu, Z.; Yang, H.; Liu, D.; Sun, Y.; Xu, Y.; Yu, F.; Yan, S. *Adv. Synth. Catal.* **2022**, *364*, 1602.
(g) Fu, R.; Liu, Y.; Wu, T.; Zhang, X.; Zhu, Y.; Luo, J.; Zhang, Z.; Jiang, Y. *Chem. Commun.* **2022**, *58*, 3525.
(h) Wu, Y.; Du, J.; Hao, W.; Jiang, B. *Chin. J. Org. Chem.* **2021**, *41*, 1563 (in Chinese).
(吴亚男, 杜建宇, 郝文娟, 姜波, 有机化学, **2021**, *41*, 1563.)
(i) Xie, Y.-Y.; Wang, Y.-C.; Qu, H.-E.; Tan, X.-C.; Wang, H.-S.; Pan, Y.-M. *Adv. Synth. Catal.* **2014**, *356*, 3347.
[18] CCDC 2201314 and 2201818 contain the crystallographic data associated with this work.
[19] The relative configuration of the chiral centres in products **8** and **9** were assigned by NOE NMR analysis.

(Lu, Y.)

