

Article

Synthesis of 2,3-Dihydro-1H-azepine and 1H-Azepin-2(3H)-one Derivatives From Intramolecular Condensation between Stable Tertiary Enamides and Aldehydes

Wenju Zhu, Liang Zhao, and Mei-Xiang Wang

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b02021 • Publication Date (Web): 09 Nov 2015

Downloaded from <http://pubs.acs.org> on November 9, 2015

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



ACS Publications

Synthesis of 2,3-Dihydro-1*H*-azepine and 1*H*-Azepin-2(3*H*)-one Derivatives From Intramolecular Condensation between Stable Tertiary Enamides and Aldehydes

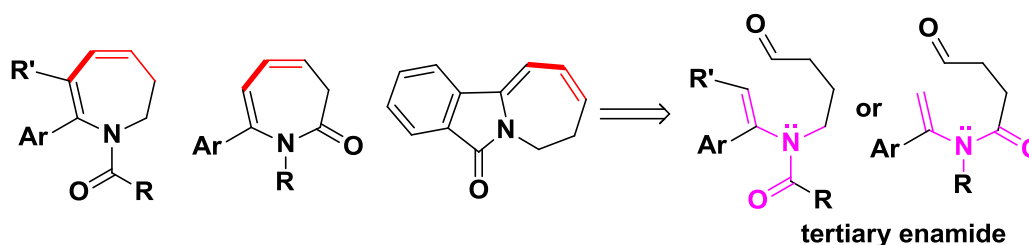
Wenju Zhu, Liang Zhao, Mei-Xiang Wang*

MOE Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology,

Department of Chemistry, Tsinghua University, Beijing, 100084, China

wangmx@mail.tsinghua.edu.cn

Abstract



A new strategy to construct 2,3-dihydro-1*H*-azepine and 1*H*-azepin-2(3*H*)-one heterocyclic rings is reported based on emerging tertiary enamide synthons. Under very mild conditions employing BBr_3 as a Lewis acid catalyst and P_2O_5 as an additive, tertiary enamides that contain a formyl group underwent highly efficient and scalable intramolecular cyclic condensation to afford diverse 2,3-dihydro-1*H*-azepine and 1*H*-azepin-2(3*H*)-one derivatives in 71% - 96% yields. The reaction proceeded most probably through a nucleophilic addition of enamides to aldehyde, deprotonation and dehydration cascade. Application of the method in the synthesis of dihydro-azepino[2,1-*a*]isoindol-5-ones, the core structure of naturally occurring lennoxamine, was also demonstrated.

Introduction

Azepines and especially their partially saturated structures occur frequently in natural products and synthetic pharmaceuticals (Figure 1). (-)-Balanol (**A**), for example, is an azepane containing metabolite from *Verticillium balanoids*.^{1,2} It shows potent ATP-competitive inhibitory activity³ and has served as a template for the development

of a number of analogues as antitumor agents.⁴ (\pm)-Chilenamine (**B**)⁵ and (\pm)-lennoxamine (**C**)⁶ are among a number of isoindolobenzazepine alkaloids isolated from Chilean *Berberis* species. On the other hand, 10-11-dihydro-5*H*-dibenzo[*b,f*]azepine compounds such as imipramine (**D**) and chlomidipramine (**E**) are inhibitors of monoamine transporters and are used clinically as antidepressant drugs.⁷ Recently, a series of substituted 7,8,9,10,11,11*a*-hexahydro-5*H*-azepino[2,1-*a*]isoindol-5-one derivatives including compound **F** have been shown to be novel and potent urotensin-II receptor antagonists.^{8,9} Because of the interesting conformational structures and wide applications in the synthesis of natural products and bioactive compounds of medicinal significance, studies on the construction of azepines and related structures have always attracted great attentions of organic and medicinal chemists. To access the seven-membered heterocyclic derivatives, both cyclization of linear precursors and ring transformation of a three- to six-membered ring reactant are predominant synthetic methods.^{10,11} Among various cyclization methods documented in literature, formation of a C-N bond through displacement reactions and formation of a C-C-double bond through olefin metathesis constitute the general and widely used strategies in synthesis. Despite the use of many pre-functionalized materials in cyclization reactions, construction of azepines and their derivatives with an *N*-vinyl component has not yet been reported.^{10a}

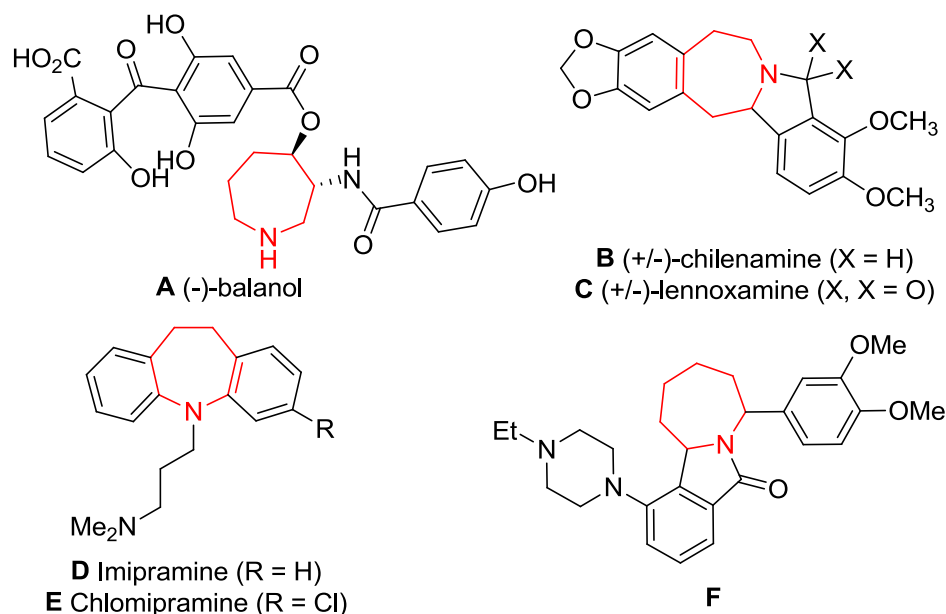


Figure 1. Representative examples of azepine ring-containing natural products and synthetic pharmaceuticals.

As the *N*-vinyl-bearing compounds, tertiary enamides are remarkable and useful chemical entities because of their easy availability, intriguing stability and reactivity.¹²⁻¹⁴ In comparison to conventional enamines, secondary and tertiary enamides have long been recognized as chemically stable species because of the electron-withdrawing effect of *N*-acyl group. In recent years, secondary enamides have been shown to act as aza-ene components to undergo aza-ene addition reactions with reactive enophiles.¹⁵ On contrary, no reactions occurred when tertiary enamides were employed instead of secondary enamides.¹⁵ However, based on the cross conjugation system within the molecules, we proposed a few years ago that the effective tuning of delocalization of lone pair electrons on nitrogen into the carbon-carbon double bond would reinvigorate the nucleophilic activity of enamides.¹² In line with this working hypothesis, enaminic reactions of tertiary enamides have been successfully established towards epoxides,¹⁶ carbonyls,¹⁷ imines¹⁸ and nitriliums,¹⁹ providing unique and powerful methods for the synthesis of diverse compounds including five-,^{16b,17a,b} six-^{16b,17c,18,19a,b} and eight-membered heterocycles.^{16a} To further explore the synthetic utility of this emerging type of synthons, we undertook the current study of intramolecular cyclization reaction of

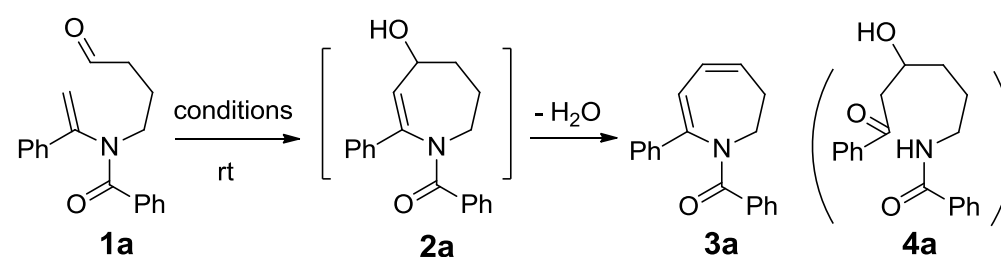
tertiary enamides with aldehydes, envisioning a novel strategy to construct seven-membered nitrogenous heterocycles. We report herein a highly efficient synthesis of 2,3-dihydro-1*H*-azepine and 1*H*-azepin-2(3*H*)-one derivatives. Facile constructions of ring-fused azepine structures that resemble novel and potent urotensin-II receptor antagonists **F** are also demonstrated.

Results and discussion

We have shown in our previous study that tertiary enamides are able to undergo intramolecular and intermolecular nucleophilic addition to aldehydes to form 4-hydroxy-1,2,3,4-tetrahydropyridine derivatives.^{17c} It was envisioned that the similar cyclization reaction of **1a** would afford hydroxylated 4,5,6,7-tetrahydro-1*H*-azepine compound, a key precursor to balanol analogs.¹⁻⁴ We thus first scrutinized the reaction of formyl-substituted tertiary enamide **1a**. As expected, tertiary enamide **1a** was stable under ambient conditions. No reaction was observed either in refluxing DCM. The cyclization reaction took place slowly when a Brønsted acid such as TfOH (30 mol%) was added. Surprisingly, instead of the addition product **2a**, a dehydration compound **3a** was obtained as the sole product in 24% yield. A number of Lewis acids were then screened as catalysts (30 mol %) in order to improve the conversion of reactant, the selective formation of adduct **2a** or dehydration product **3a**, and the chemical yield of product. As listed in Table 1, Lewis acids including iron, nickel, copper, zinc and indium salts were either catalytically inactive or detrimental to reaction leading to no product or an inseparable mixture, respectively (entries 4 – 11, Table 1). It should be noted that the use of FeCl₃ as a catalyst resulted in the formation of a ketone product **4a** (24% yield) in addition to **3a** (18% yield). The former compound is most probably derived from the hydrolysis of the cyclic iminium intermediate that was generated directly from enaminic addition of tertiary enamide to aldehyde functional group (*vide infra*). While AlCl₃ and Et₂AlCl were effective to catalyzed the reaction (entries 12 and 13), BCl₃ (entry 14, Table 1) and especially BBr₃ appeared to be more efficient catalysts. For example, with the loading of BBr₃ decreasing from 30 mol % to 3 mol% or even 1 mol %, the reaction proceeded rapidly to form **3a** in moderate yields.

Notably, solvent played a crucial role in this BBr_3 -catalyzed cyclization reaction (entries 17 and 19 – 21, Table 1). For instance, reaction was accelerated in acetonitrile giving a good yield of **3a** in 0.5 h whereas the reaction was completely inhibited in THF. It should be noted that in all cases using different Lewis acid catalysts, no 5-hydroxy-2,3,4,5-tetrahydro-1*H*-azepine **2a** was obtained. The outcomes were completely different from the synthesis of 4-hydroxy-1,2,3,4-tetrahydropyridine derivatives from analogous intramolecular reaction of tertiary enamides with aldehyde in which no dehydration reaction.^{17c} To account for the difference, we proposed that intermediate **2a**, due to conformational flexibility of seven-membered *N*-heterocycles, would adopt a conformational structure that favors considerably the dehydration reaction to afford a thermodynamically more stable conjugated diene product **3a**. Since the formation of **3a** involved a dehydration step, the released water may deactivate the Lewis acid catalyst causing incomplete conversion of the substrate. To circumvent this problem, drying agents were examined (entries 22 – 26, Table 1). Besides, the use of drying agents may also be beneficial to dehydration reaction. Pleasingly, the presence of a drying agent including CaCl_2 and P_2O_5 did improve the chemical yield in general. Finally, we found that a combination of BBr_3 (3 mol %) and P_2O_5 (20 equiv) in anhydrous DCM at ambient temperature worked optimally for the transformation of tertiary enamide **1a** into 1-benzoyl-7-phenyl-2,3-dihydro-1*H*-azepine **3a** (entry 27, Table 1).

Table 1. Development of Lewis Acid Catalyzed Cyclization Reaction of **1a**^a



Entry	Catalyst (mol %)	Additive (equiv)	Solvent	<i>t</i> (h)	3a (%) ^b
1	-	-	DCM	96	n.r. ^c
2	TfOH (30)	-	DCM	96	24
3	FeCl_3 (30)	-	DCM	10	18 + 4a (24)

4	Fe(OTf) ₃ (30)	-	DCM	96	- ^d
5	NiCl ₂ (30)	-	DCM	96	n.r. ^c
6	Ni(OTf) ₂ (30)	-	DCM	96	n.r. ^c
7	CuClO ₄ (30)	-	DCM	16	16
8	CuOTf (30)	-	DCM	96	n.r. ^c
9	ZnCl ₂ (30)	-	DCM	96	- ^d
10	Zn(OTf) ₂ (30)	-	DCM	96	n.r. ^c
11	In(OTf) ₃ (30)	-	DCM	96	n.r. ^c
12	AlCl ₃ (30)	-	DCM	96	66
13	Et ₂ AlCl (30)	-	DCM	96	41
14	BCl ₃ (30)	-	DCM	16	52
15	BBr ₃ (30)	-	DCM	1	68
16	BBr ₃ (5)	-	DCM	1	52
17	BBr ₃ (3)	-	DCM	1	57
18	BBr ₃ (1)	-	DCM	1	49
19	BBr ₃ (3)	-	Toluene	45	47
20	BBr ₃ (3)	-	THF	45	n.r. ^c
21	BBr ₃ (3)	-	CH ₃ CN	0.5	74
22	BBr ₃ (3)	MgSO ₄ (30)	CH ₃ CN	3.5	63
23	BBr ₃ (3)	SiO ₂ (30)	CH ₃ CN	0.5	78
24	BBr ₃ (3)	CaCl ₂ (30)	CH ₃ CN	3.5	82
25	BBr ₃ (3)	P ₂ O ₅ (30)	CH ₃ CN	0.5	88
26	BBr ₃ (3)	P ₂ O ₅ (10)	CH ₃ CN	1	83
27	BBr ₃ (3)	P ₂ O ₅ (20)	DCM	1	93

^a A mixture of tertiary enamide **1a** (0.3 mmol), catalyst and additive was stirred in dry solvent (15 mL) under argon protection. ^b Isolated yield. ^c No reaction. ^d A inseparable mixture was obtained.

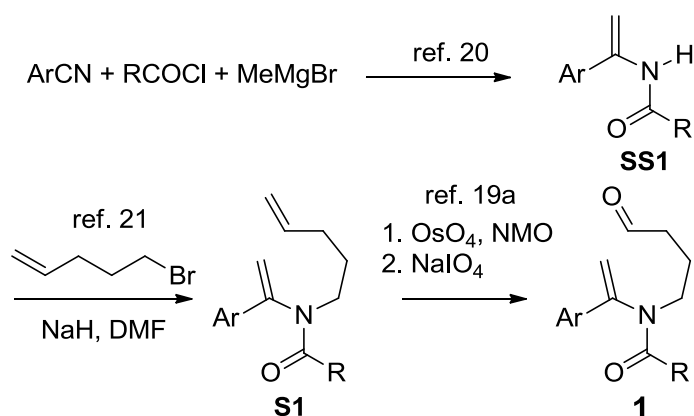
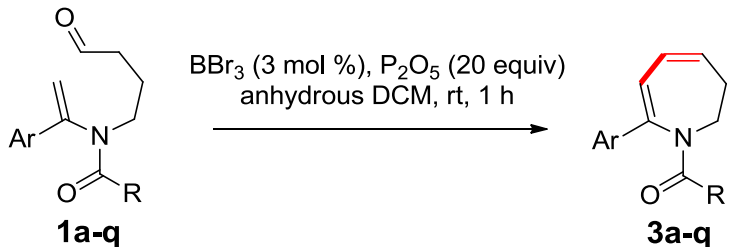


Figure 2. Preparation of substrates **1**.

To test the scope of BBr₃-catalyzed intramolecular condensation between tertiary enamides and aldehyde, a number of substrates were prepared from ozonolysis^{19a} of

the terminal olefin moiety of tertiary enamides **S1** that were synthesized according to a literature method^{20,21} (Figure 2). The results compiled in Table 2 show clearly that almost all substrates tested underwent cyclization reaction to furnish 2,3-dihydro-1*H*-azepine products. Various functional groups were tolerated by the catalytic system. For example, all *N*-aroyl-substituted tertiary enamides **1a-g**, irrespective of the electronic nature and the substitution pattern of a substituent on benzene ring, were transformed efficiently into the corresponding products **3a-g** in excellent yields (entries 1 – 7, Table 2). *N*-Benzyloxycarbonyl- and *N*-ethoxycarbonyl-bearing tertiary enamide substrates **1h** and **1i** underwent equally efficient reaction while the reaction of *N*-acetyl-containing reactant **1j** proceeded sluggishly (entries 8 – 10, Table 2). In these cases, slightly diminished chemical yields were obtained due to the formation of a polar and unidentified mixture as by-products. It is worth noting that the slow reaction rate of **1j** reflected low nucleophilicity of *N*-acetyl-substituted tertiary enamide. Different reaction velocity of tertiary enamides is indicative of the tuning effect of *N*-electron-withdrawing group on the nucleophilic activity of enamides. On the other hand, enamides having an aryl substituent on the α -position behaved as excellent substrates, and all reactants **1k-p** underwent similarly rapid cyclization reaction to produce high yield of products **3k-p** (entries 11 – 16, Table 2). The catalytic reaction was applicable to tertiary enamide that contains an α -heterocyclic substituent as well. 1-Benzoyl-7-(thiophen-2-yl)-2,3-dihydro-1*H*-azepine **3q** was thus prepared readily in 93% yield (entry 17, Table 2).

Table 2. Catalytic synthesis of 2,3-dihydro-1*H*-azepine derivatives **3a-q**

							
entry	Ar	R	3 (%) ^a	entry	Ar	R	3 (%) ^a

1 ^b	Ph	Ph	3a (93)	10 ^c	Ph	Me	3j (74)
2	Ph	4-MeOC ₆ H ₄	3b (92)	11	4-MeOC ₆ H ₄	Ph	3k (92)
3	Ph	3,4-(MeO) ₂ C ₆ H ₃	3c (95)	12	4-MeC ₆ H ₄	Ph	3l (82)
4	Ph	4-O ₂ NC ₆ H ₄	3d (96)	13	4-FC ₆ H ₄	Ph	3m (82)
5	Ph	4-ClC ₆ H ₄	3e (89)	14	4-ClC ₆ H ₄	Ph	3n (94)
6	Ph	4-BrC ₆ H ₄	3f (90)	15	4-BrC ₆ H ₄	Ph	3o (91)
7	Ph	2-BrC ₆ H ₄	3g (95)	16 ^d	2-BrC ₆ H ₄	Ph	3p (94)
8	Ph	BnO	3h (79)	17	2-thienyl	Ph	3q (93)
9	Ph	EtO	3i (71)				

^a Isolated yield. ^b **3a** (1.25 g, 91%) was obtained from a gram-scale reaction of **1a** (1.49 g, 5 mmol). ^c Reaction time was 20 h. ^d **3p** (1.19 g, 93%) was obtained from a gram-scale reaction of **1p** (1.35 g, 3.63 mmol).

The generality of the catalytic reaction was further demonstrated in the synthesis of 1-benzoyl-6-methyl-7-phenyl-2,3-dihydro-1*H*-azepine **3r** and 7,8-dihydro-5*H*-azepino[2,1-*a*]isoindol-5-one **3s**. In comparison to its disubstituted tertiary enamide analog **1a**, the trisubstituted tertiary enamide **1r** is less reactive. Nevertheless, in refluxing DCM it was converted smoothly into product **3s** in 12 h. In the case of isoindolin-1-one-derived enamide **1s**, BBr₃-catalyzed cyclization under very mild conditions provided efficiently a straightforward route to fused heterocyclic ring product **3s**, a compound that resembles the core structure of naturally occurring lennoxamine (Figure 3).

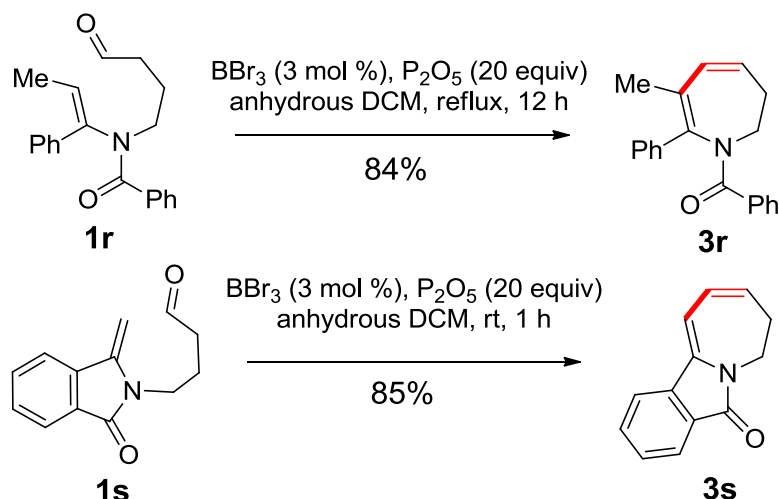


Figure 3. Synthesis of **3r** and **3s**.

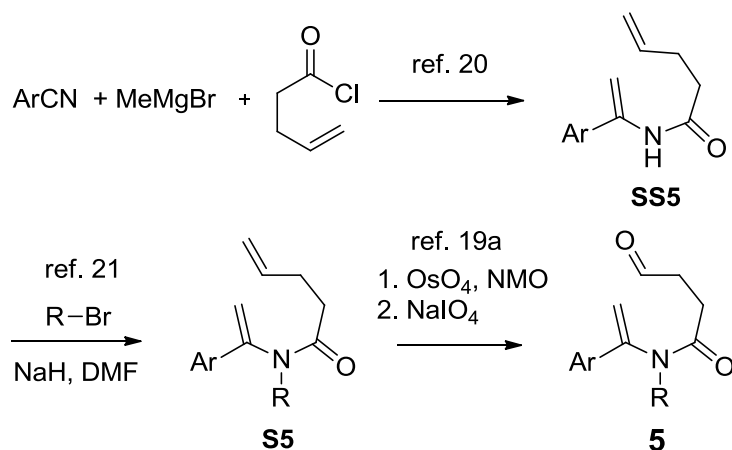


Figure 4. Preparation of substrates **5**.

Following the successful synthesis of various 2,3-dihydro-1*H*-azepine derivatives **3**, we then attempted the construction of 1*H*-azepin-2(3*H*)-one structure by means of BBr₃-catalyzed cyclic condensation reaction of tertiary enamides **5** (Table 3). The reactants **5** were readily obtained following the reported procedure^{19a,20,21} depicted in Figure 4. The shift of the carbonyl moiety of enamide from *exo*- to *endo*-position leads to marginal variation of nucleophilic reactivity. Enaminic addition of enamides to aldehyde proceeded equally well with tertiary enamides to form intermediates **6**. Although intermediates **6** were not stable and they underwent spontaneous dehydration reaction to form conjugated diene products **7**, in some cases the

consequent dehydration reaction of **6** appeared slower than that of **2**. For example, the intermediate **2** was never isolated from the reaction of **1**. In contrast, under the identical catalytic conditions, the intramolecular adduct **6b** was obtained in 44% yield along with the formation **7b** in 49% yield when the reaction was quenched within 20 min (*cf.* Experimental Section). Elongated reaction time (3 – 5 h) led to the production of **7** as the sole products in good yields (entries 1 – 3, Table 3). Intriguingly, tertiary enamides **5e** and **5f** underwent very efficient nucleophilic addition and the consecutive dehydration reaction, furnishing the corresponding products **7e** and **7f** in excellent yields.

Table 3. Synthesis of 1*H*-azepin-2(3*H*)-one derivatives **7a-f**

entry	Ar	R	<i>t</i> (h)	7 (%) ^a
1	Ph	Bn	5	7a (85)
2	Ph	4-BrC ₆ H ₄ CH ₂	5	7b (88)
3	Ph	4-MeOC ₆ H ₄ CH ₂	3	7c (87)
4	4-MeOC ₆ H ₄	Me	4	7e (84)
5	Ph	Me	1	7e (94)
6	4-ClC ₆ H ₄	Me	1	7f (94.5)

^a Isolated yield.

Structures of all 2,3-dihydro-1*H*-azepine and 1*H*-azepin-2(3*H*)-one products **3** and **7** were established on the basis of their spectroscopic data. To put the structures beyond any ambiguity, high quality single crystals of **3a** and **7b** were obtained from recrystallization and their X-ray molecular structures were determined (Figures 5 and 6). The variable temperature ¹H NMR spectra of these seven-membered nitrogenous

heterocycles are especially worth addressing. As illustrated in Figures 7 and 8, either compounds **3** and **7** did not give a complete set of proton signals below 60 °C. For instance, one of the methylenes within heterocycle of **3a** (H-6) exhibited a broad peak at *ca.* 2.7 ppm while the other (H-7) showed no proton signal (Figure 7). In the case of **7b**, the methylene within the ring (H-3) gave a very broad peak at *ca.* 3.0 ppm. No resonance signals corresponding to the methylene of benzyl group (H-8) was observed (Figure 8). The ¹H NMR spectra measured at the temperature lower than 60 °C indicated the existence of a mixture of conformers which undergo very slow inter-conversions in relative to ¹H NMR time scale due to the rigidity of partially saturated medium-sized heterocycles. Upon heating to 150 °C in DMSO-*d*₆, the *broadened and unobservable* proton signals emerged and all peaks became well-resolved because of the acceleration of inter-conversion of various conformers (Figures 7 and 8).

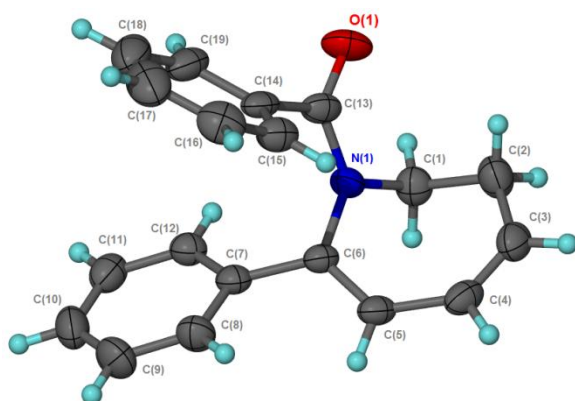


Figure 5. X-ray molecular structure of **3a**. The molecular structure is depicted in an ellipsoid style at 50% probability level.

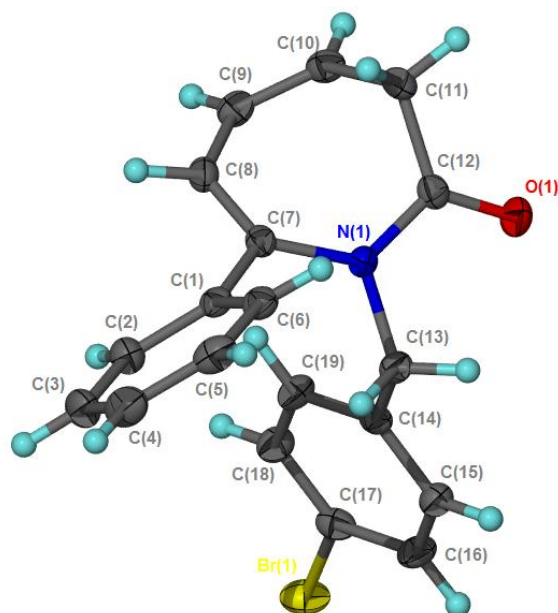


Figure 6. X-ray molecular structure of **7b**. The molecular structure is depicted in an ellipsoid style at 50% probability level.

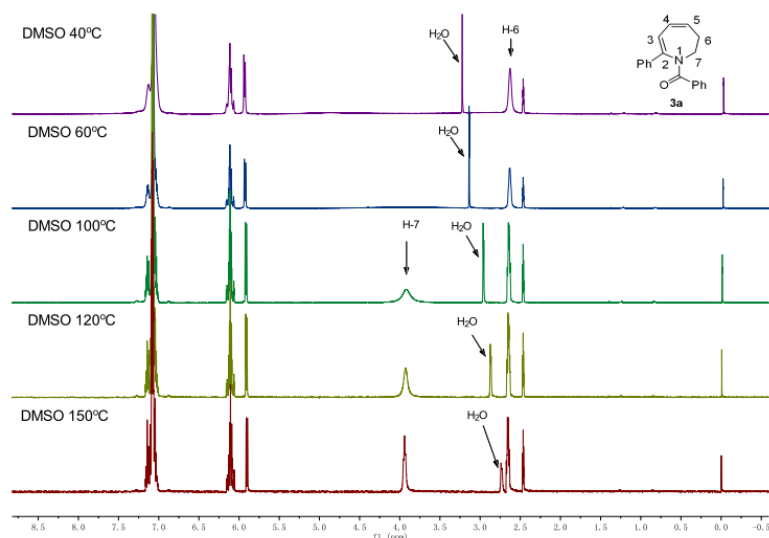


Figure 7. Variable temperature ¹H NMR spectra of **3a**. The signals at *ca.* 2.5 are protons of DMSO.

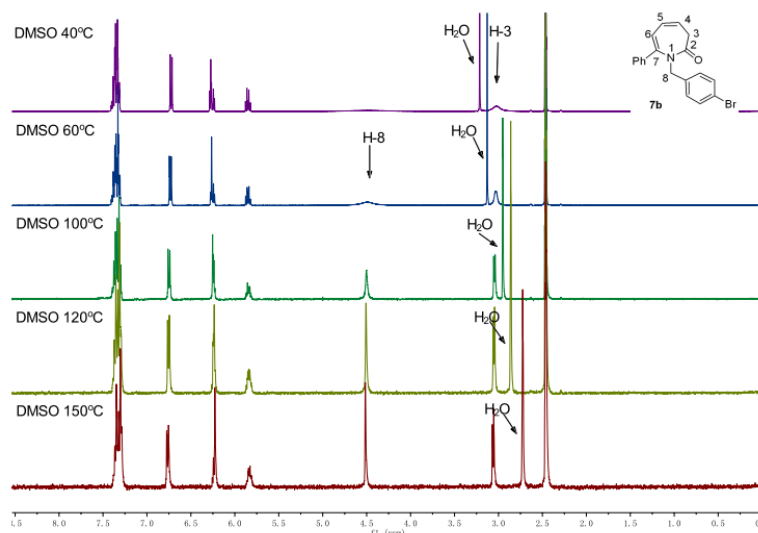


Figure 8. Variable temperature ^1H NMR spectra of **7b**. The signals at *ca.* 2.5 are protons of DMSO.

The outcomes of the BBr_3 -catalyzed cyclization of tertiary enamides **1** or **5** suggest a nucleophilic addition of enamides to aldehyde, deprotonation and dehydration cascade as delineated in Figure 9. It is important to address that the use of a Lewis acid catalyst with a single coordination site is imperative. The enamide substrates **1** and **5** can actually act as a bidentate or tridentate ligand to interact with transition metals. Competitive formation of stable chelating complexes with Lewis acids would therefore inhibit the designed enaminic reaction. It is also interesting to note that due to some subtle conformational differences between intermediates **2** and **6**, the former undergo very fast dehydration reaction to afford directly the intramolecular condensation products **3**. In the case of the later intermediate, however, dehydration reaction proceeds relatively slowly, allowing the isolation and characterization of **6b**. The heterocyclic iminium intermediates **B** or **B'** is also susceptible to nucleophilic agents because of its high electrophilic nature. The interception of **B** by water prior to deprotonation step results in the generation of ketone compound **4a**.

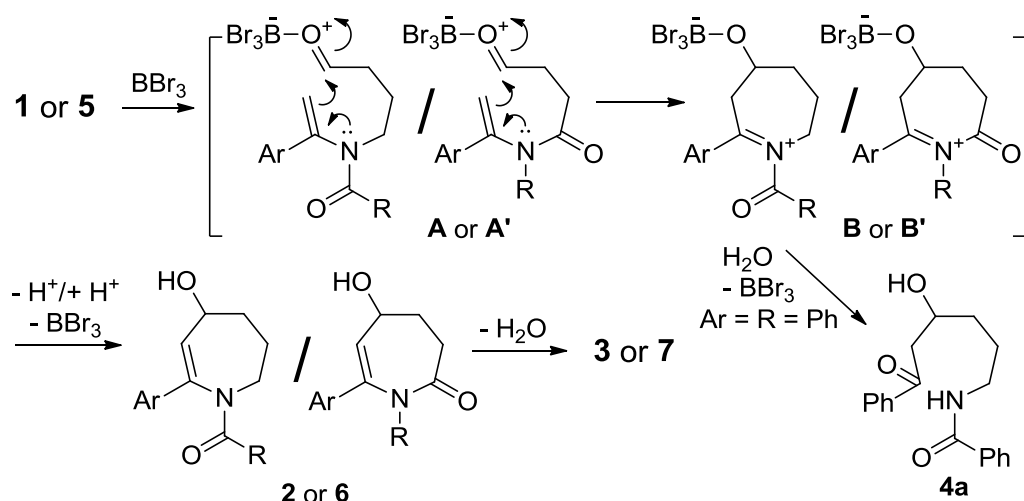
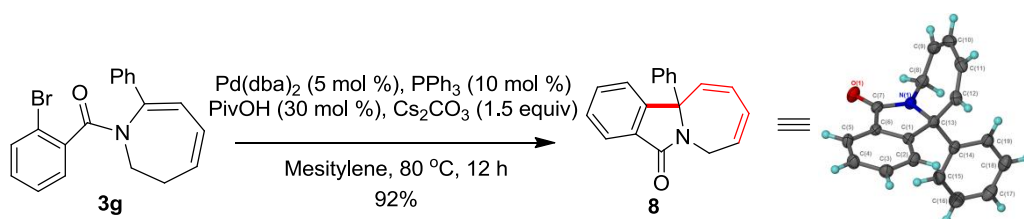


Figure 9. Plausible reaction mechanism.

The catalytic construction of 2,3-dihydro-1*H*-azepine and 1*H*-azepin-2(3*H*)-one structures from tertiary enamides is efficient and practically useful. The method can be easily scaled up to a gram scale. In the gram-scale synthesis, we were delighted to find out that more than a gram of the products **3a** (1.25 g, 91%) or **3p** (1.19 g, 93%) were prepared in 1 h starting from tertiary enamides **1a** (5 mmol) or **1p** (3.63 mmol) (entries 1 and 10, Table 2). The acquired 2,3-dihydro-1*H*-azepine and 1*H*-azepin-2(3*H*)-one derivatives are valuable in organic synthesis because they contain multiple transformable functional groups. Just to demonstrate their synthetic applications, we conducted the intramolecular Heck reaction of **3g** following a well-established procedure.²² Interestingly, despite several possible cross-coupling reaction pathways, compound **3g** underwent intramolecular coupling reaction between bromobenzene moiety and the α -carbon of tertiary enamide with concomitant shift of diene bonds to generate 11*a*-phenyl-7,11*a*-dihydro-5*H*-azepino[2,1-*a*]isoindol-5-one **8** (Scheme 1), a fused heterocyclic compound that is hard to prepare by other means.



Scheme 1. Synthesis of **8** and its X-ray molecular structure. The molecular structure of **8** is depicted in an ellipsoid style at 50% probability level.

Conclusion

In summary, we have established a new synthetic strategy to construct 2,3-dihydro-1*H*-azepine and 1*H*-azepin-2(3*H*)-one heterocyclic rings. Under very mild conditions employing BBr₃ as a Lewis acid catalyst and P₂O₅ as an additive, tertiary enamides underwent efficient and scalable intramolecular cyclic condensation to afford various 2,3-dihydro-1*H*-azepine and 1*H*-azepin-2(3*H*)-one derivatives in high yields. The reaction proceeds through a cascade involving nucleophilic addition of enamides to aldehyde, deprotonation and dehydration. The study along with our previous ones has demonstrated that tertiary enamides are powerful and versatile synthons in organic synthesis. Successful exploration of the reactions of stable tertiary enamides has provided unique and convenient routes to a variety of diverse five- to eight-membered heterocyclic compounds that are difficult to prepare using other means. The tandem reactions of tertiary enamides in the synthesis of complex alkaloids and analogs are being actively pursued in this laboratory and the results will be reported in due course.

Experimental Section

General procedure for the preparation of **1**.^{19a,20,21}

Step 1. The synthesis of secondary enamides was carried out following a literature method.²⁰ Under N₂ protection, methylmagnesium bromide (20 mL, 3.0M in ether, 60 mmol) was added to nitrile (60 mmol). After refluxing for 6 h, the mixture was cooled down to room temperature and ether (60 mL) was added. After cooling down to 0 °C, acyl chloride (60 mmol) was added dropwise. The resulting mixture was refluxed for 1 h. After solvent was evaporated in vacuo and the residue was mixed with ethanol (60 mL) and refluxed for another 1 h. Solvent was removed in vacuo and the residue was mixed with water (100 mL) and EtOAc (100 mL) and then extracted with EtOAc (3×60 mL). The combined organic phase was washed with water (30 mL), brine (30

mL), dried with anhydrous MgSO_4 . The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column to afford products **SS1**.

Step 2. Alkylation of secondary enamides was conducted following a reported procedure.²¹ To a solution of **SS1** (10 mmol) in DMF (50 mL) at 0 °C under argon protection was added NaH (600 mg, 60% in mineral oil, 15 mmol). After being stirred for 0.5 h, a solution of 5-bromopent-1-ene (12 mmol) in DMF (5 mL) was added dropwise, and the resulting mixture was kept stirring for another 5 h. The mixture was poured into ice-cold water (60 mL) and EtOAc (40 mL), and extracted with EtOAc (3×50 mL). The combined organic phase was washed with water (5×30 mL), brine (30 mL), dried with anhydrous MgSO_4 . The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column to give products **S1**.

Step 3. Oxidation of alkene into aldehyde was realized using a known method.^{19a} To a mixture of **S1** (6 mmol), 1,4-dioxane (40 mL) and water (20 mL) was added an aqueous solution of *N*-methylmorpholine-*N*-oxide (4.0 mL, 50% w/w) and OsO_4 (0.5 mL, 1% in water). After the mixture was stirred for 12 h, NaIO_4 (2.56 g, 12 mmol) was added. The reaction mixture was kept stirring at room temperature for 1 h before quenching with a saturated thiosulfate solution. The mixture was then extracted with EtOAc (3×50 mL). The combined organic phase was washed with saturated thiosulfate solution (3×30 mL), brine (30 mL), dried with anhydrous MgSO_4 . The solvent was evaporated in vacuo and the residue was purified by flash silica gel chromatography to afford the product. All substrates **1** were characterized by means of spectroscopic data.

N-(4-Oxobutyl)-N-(1-phenylvinyl)benzamide 1a (1.3 g, 68% yield): white solid, mp. 92-93 °C; R_f = 0.23 (EtOAc / petroleum ether = 1 / 4); ^1H NMR (400 MHz, CDCl_3) δ 9.76 (d, J = 1.0 Hz, 1H), 7.50 – 7.47 (m, 4H), 7.41 – 7.36 (m, 3H), 7.32 – 7.26 (m, 1H), 7.23 – 7.20 (m, 1H), 5.39 (s, 1H), 4.82 (s, 1H), 3.65 (s, 2H), 2.52 (t, J = 8 Hz, 2H), 2.02 – 1.94 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.5, 171.4, 147.1, 135.9, 135.8, 130.0, 129.0, 128.9, 127.8, 127.6, 126.3, 114.1, 46.2, 41.1, 20.0; IR (KBr, cm^{-1}) ν 1717, 1636. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_2$ ($\text{M} + \text{Na}$)⁺:

316.1308. Found: 316.1311.

4-Methoxy-N-(4-oxobutyl)-N-(1-phenylvinyl)benzamide 1b (1.16 g, 64% yield from 5.6 mmol of **S1b**): pale yellow oil; R_f = 0.14 (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, CDCl_3) δ 9.76 (d, J = 1.3 Hz, 1H), 7.51 – 7.48 (m, 4H), 7.40 – 7.38 (m, 3H), 6.73 – 6.71 (m, 2H), 5.40 (s, 1H), 4.81 (s, 1H), 3.76 (s, 3H), 3.61 (s, 2H), 2.50 (t, J = 8 Hz, 2H), 2.00 – 1.94 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.6, 171.0, 160.9, 147.5, 135.9, 129.8, 129.1, 128.9, 127.8, 126.3, 113.8, 113.0, 55.2, 46.3, 41.2, 20.0; IR (KBr, cm^{-1}) ν 1721, 1638, 1607. HRMS (ESI-ion trap) Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_3$ ($\text{M} + \text{Na}$) $^+$: 346.1414. Found: 346.1408.

3,4-Dimethoxy-N-(4-oxobutyl)-N-(1-phenylvinyl)benzamide 1c (380 mg, 47% yield from 2.28 mmol of **S1c**): white solid, mp. 86-87 $^\circ\text{C}$; R_f = 0.25 (EtOAc / petroleum ether = 1 / 2); ^1H NMR (400 MHz, CDCl_3) δ 9.76 (s, 1H), 7.51 – 7.49 (m, 2H), 7.40 – 7.34 (m, 3H), 7.14 (d, J = 8.3 Hz, 1H), 7.07 (s, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.42 (s, 1H), 4.85 (s, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 3.63 (br, 2H), 2.51 (t, J = 7.4 Hz, 2H), 2.03 – 1.96 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.5, 171.0, 150.5, 148.0, 147.4, 135.8, 129.0, 128.9, 127.9, 126.2, 121.1, 113.7, 111.3, 109.8, 55.8, 55.6, 46.5, 41.2, 20.0; IR (KBr, cm^{-1}) ν 1720, 1633. HRMS (ESI-ion trap) Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_4$ ($\text{M} + \text{Na}$) $^+$: 376.1519. Found: 376.1515.

4-Nitro-N-(4-oxobutyl)-N-(1-phenylvinyl)benzamide 1d (436 mg, 58% yield from 2.22 mmol of **S1d**): yellow solid, mp. 89-90 $^\circ\text{C}$; R_f = 0.12 (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, CDCl_3) δ 9.76 (d, J = 1.1 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 7.7 Hz, 2H), 7.42 – 7.36 (m, 5H), 5.43 (s, 1H), 4.87 (s, 1H), 3.67 (t, J = 7.1 Hz, 2H), 2.53 (t, J = 7.3 Hz, 2H), 2.01 – 1.94 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.1, 169.1, 148.2, 146.5, 141.9, 135.1, 129.4, 129.0, 128.3, 126.0, 123.0, 114.6, 46.4, 41.0, 19.8; IR (KBr, cm^{-1}) ν 1721, 1644, 1602, 1519. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$ ($\text{M} + \text{Na}$) $^+$: 361.1159. Found: 361.1150.

4-Chloro-N-(4-oxobutyl)-N-(1-phenylvinyl)benzamide 1e (1.12 g, 66% yield from 5.2 mmol of **S1e**): pale yellow oil; R_f = 0.12 (EtOAc / petroleum ether = 1 / 4);

¹H NMR (400 MHz, CDCl₃) δ 9.76 (d, *J* = 0.9 Hz, 1H), 7.46 – 7.36 (m, 7H), 7.19 – 7.17 (m, 2H), 5.41 (s, 1H), 4.83 (s, 1H), 3.63 (s, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 1.97 (t, *J* = 7.1 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 201.3, 170.3, 147.0, 136.0, 135.5, 134.1, 129.2, 129.1, 129.0, 128.0, 126.2, 114.2, 46.4, 41.1, 19.9; IR (KBr, cm⁻¹) ν 1723, 1643, 1596. HRMS (ESI-ion trap) Calcd for C₁₉H₁₈NO₂Cl (M + Na)⁺: 350.0918. Found: 350.0917.

4-Bromo-N-(4-oxobutyl)-N-(1-phenylvinyl)benzamide 1f (410 mg, 68% yield from 1.64 mmol of **S1f**): pale yellow oil; *R_f* = 0.2 (EtOAc / petroleum ether = 1 / 3); ¹H NMR (400 MHz, CDCl₃) δ 9.77 (s, 1H), 7.49 – 7.45 (m, 2H), 7.41 – 7.39 (m, 3H), 7.36 (s, 4H), 5.42 (s, 1H), 4.83 (s, 1H), 3.64 (s, 2H), 2.51 (t, *J* = 7.4 Hz, 2H), 1.99 – 1.95 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 201.4, 170.4, 147.0, 135.5, 134.7, 131.1, 129.3, 129.0, 126.3, 124.5, 114.4, 46.4, 41.2, 20.0; IR (KBr, cm⁻¹) ν 1722, 1641, 1399. HRMS (ESI-ion trap) Calcd for C₁₉H₁₈BrNO₂ (M + Na)⁺: 394.0413. Found: 394.0412.

2-Bromo-N-(4-oxobutyl)-N-(1-phenylvinyl)benzamide 1g (1.78 g, 68% yield from 7.0 mmol of **S1g**): white solid, mp. 84-85 °C; *R_f* = 0.19 (EtOAc / petroleum ether = 1 / 3); ¹H NMR (400 MHz, CDCl₃, 60 °C) δ 9.77 (s, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.30 (s, 5H), 7.02 (s, 3H), 5.33 (s, 1H), 5.27 (s, 1H), 3.72 (s, 2H), 2.57 (t, *J* = 6.8 Hz, 2H), 2.02 (t, *J* = 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 201.3, 169.0, 145.5, 138.3, 135.3, 132.5, 129.8, 128.9, 128.6, 126.7, 126.3, 125.8, 120.3, 113.3, 45.2, 40.8, 20.0; IR (KBr, cm⁻¹) ν 1720, 1644, 1627, 1402. HRMS (ESI-ion trap) Calcd for C₁₉H₁₈NBrO₂ (M + Na)⁺: 394.0413. Found: 394.0405.

Benzyl (4-oxobutyl)(1-phenylvinyl)carbamate 1h (660 mg, 44% yield from 4.6 mmol of **S1h**): white solid, mp. 95-96 °C; *R_f* = 0.67 (EtOAc / petroleum ether = 1 / 3); ¹H NMR (400 MHz, CDCl₃, 60 °C) δ 9.72 (s, 1H), 7.33 – 7.29 (m, 5H), 7.24 (d, *J* = 2.9 Hz, 3H), 7.11 (s, 2H), 5.55 (s, 1H), 5.18 (s, 1H), 5.08 (s, 2H), 3.52 (t, *J* = 7.3 Hz, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 1.96 – 1.92 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 201.1, 155.4, 145.7, 136.6, 136.1, 135.8, 128.3, 127.6, 127.3, 125.5, 111.8, 67.0, 47.9, 40.6, 20.7; IR (KBr, cm⁻¹) ν 1703, 1629. HRMS (ESI-ion trap) Calcd for C₂₀H₂₁NO₃ (M + Na)⁺: 346.1414. Found: 346.1412.

Ethyl (4-oxobutyl)(1-phenylvinyl)carbamate 1i (231 mg, 77% yield from 1.15 mmol of **S1i**): pale yellow oil; $R_f = 0.67$ (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, CDCl_3 , 60 $^\circ\text{C}$) δ 9.77 (d, $J = 1.36$ Hz, 1H), 7.36 – 7.30 (m, 5H), 5.54 (s, 1H), 5.18 (s, 1H), 4.09 (q, $J = 7.1$ Hz, 2H), 3.51 (t, $J = 6.8$ Hz, 2H), 2.50 – 2.46 (m, 2H), 1.99 – 1.92 (m, 2H), 1.10 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.2, 155.6, 145.8, 136.7, 128.3, 125.5, 111.6, 61.3, 47.6, 40.7, 20.7, 14.1; IR (KBr, cm^{-1}) ν 1701, 1629. HRMS (ESI-ion trap) Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_3$ ($\text{M} + \text{Na}$) $^+$: 322.1414. Found: 322.1411.

N-(4-Oxobutyl)-N-(1-phenylvinyl)acetamide 1j (1.54g, 61% yield from 10.9 mmol of **S1j**): pale yellow oil; $R_f = 0.26$ (EtOAc / petroleum ether = 1 / 1); ^1H NMR (400 MHz, CDCl_3) δ 9.68 (d, $J = 1.2$ Hz, 1H), 7.34 – 7.32 (m, 5H), 5.72 (s, 1H), 5.17 (s, 1H), 3.40 (t, $J = 7.3$ Hz, 2H), 2.41 (t, $J = 7.4$ Hz, 2H), 2.01 (s, 3H), 1.85 – 1.80 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.3, 170.7, 146.6, 134.9, 129.1, 128.8, 125.6, 113.8, 45.0, 40.9, 21.8, 20.2; IR (KBr, cm^{-1}) ν 1723, 1658, 1630, 1396. HRMS (ESI-ion trap) Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$ ($\text{M} + \text{Na}$) $^+$: 254.1152; Found: 254.1147.

N-(1-(4-Methoxyphenyl)vinyl)-N-(4-oxobutyl)benzamide 1k (1.09 g, 71% yield from 4.76 mmol of **S1k**): white solid, mp. 95-96 $^\circ\text{C}$; $R_f = 0.11$ (EtOAc / petroleum ether = 1 / 4); ^1H NMR (400 MHz, CDCl_3) 9.77 (d, $J = 1.4$ Hz, 1H), 7.51 – 7.49 (m, 2H), 7.43 – 7.41 (m, 2H), 7.31 – 7.22 (m, 3H), 6.94 – 6.91 (m, 2H), 5.28 (s, 1H), 4.72 (s, 1H), 3.85 (s, 3H), 3.65 (s, 2H), 2.52 (t, $J = 7.3$ Hz, 2H), 2.06 – 1.96 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.6, 171.4, 160.3, 146.6, 135.9, 129.9, 128.1, 127.8, 127.7, 127.5, 114.2, 112.5, 55.3, 46.1, 41.2, 20.0; IR (KBr, cm^{-1}) ν 1723, 1638, 1605. HRMS (ESI-ion trap) Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_3$ ($\text{M} + \text{Na}$) $^+$: 346.1414. Found: 346.1405.

N-(4-Oxobutyl)-N-(1-(p-tolyl)vinyl)benzamide 1l (1.19 g, 64.5% yield from 6.0 mmol of **S1l**): pale yellow oil; $R_f = 0.19$ (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, CDCl_3) δ 9.76 (d, $J = 1.4$ Hz, 1H), 7.51 – 7.49 (m, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.29 – 7.26 (m, 1H), 7.21 (t, $J = 7.3$ Hz, 4H), 5.34 (s, 1H), 4.75 (s, 1H), 3.63 (s, 2H), 2.50 (t, $J = 7.4$ Hz, 2H), 2.38 (s, 3H), 1.98 – 1.94 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.5, 171.4, 146.8, 139.2, 135.8, 132.8, 129.9, 129.6, 127.7, 127.5, 126.2,

113.5, 46.0, 41.1, 21.2, 20.0; IR (KBr, cm^{-1}) ν 1722, 1642, 1395. HRMS (ESI-ion trap) Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_2$ ($\text{M} + \text{Na}$) $^+$: 330.1465. Found: 330.1459.

N-(1-(4-Fluorophenyl)vinyl)-N-(4-oxobutyl)benzamide 1m (390 mg, 65% yield from 1.94 mmol of **S1m**): colorless oil; R_f = 0.11 (EtOAc / petroleum ether = 1 / 4); ^1H NMR (400 MHz, CDCl_3) δ 9.76 (s, 1H), 7.47 – 7.41 (m, 4H), 7.32 – 7.28 (m, 1H), 7.22 (t, J = 7.8 Hz, 2H), 7.06 (t, J = 8.7 Hz, 2H), 5.32 (s, 1H), 4.84 (s, 1H), 3.65 (t, J = 6.9 Hz, 2H), 2.52 (t, J = 7.3 Hz, 2H), 2.02 – 1.95 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.3, 171.3, 164.2, 161.7, 146.2, 135.7, 132.0, 132.0, 129.9, 128.0, 128.0, 127.7, 127.4, 115.9, 115.6, 113.5, 46.3, 41.0, 20.0; ^{19}F NMR (376 MHz, CDCl_3) δ -111.9; IR (KBr, cm^{-1}) ν 1722, 1644, 1601, 1507, 1391. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_2\text{F}$ ($\text{M} + \text{Na}$) $^+$: 334.1214. Found: 334.1207.

N-(1-(4-Chlorophenyl)vinyl)-N-(4-oxobutyl)benzamide 1n (994 mg, 62% yield from 4.9 mmol of **S1n**): colorless oil; R_f = 0.2 (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, CDCl_3) δ 9.77 (s, 1H), 7.44 (d, J = 7.3 Hz, 2H), 7.39 – 7.28 (m, 5H), 7.22 (t, J = 7.8 Hz, 2H), 5.37 (s, 1H), 4.86 (s, 1H), 3.63 (t, J = 6.8 Hz, 2H), 2.52 (t, J = 7.4, 2H), 2.01 – 1.93 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.3, 171.4, 146.3, 135.7, 135.0, 134.5, 130.1, 129.1, 127.9, 127.5, 127.5, 114.3, 46.4, 41.1, 20.0; IR (KBr, cm^{-1}) ν 1722, 1645, 1392. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_2\text{Cl}$ ($\text{M} + \text{Na}$) $^+$: 350.0918. Found: 350.0912.

N-(1-(4-Bromophenyl)vinyl)-N-(4-oxobutyl)benzamide 1o (944 mg, 72.5% yield from 3.5 mmol of **S1o**): colorless oil; R_f = 0.29 (EtOAc / petroleum ether = 1 / 2); ^1H NMR (400 MHz, CDCl_3) δ 9.77 (d, J = 1.2 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.45 – 7.43 (m, 2H), 7.34 – 7.29 (m, 3H), 7.24 – 7.21 (m, 2H), 5.39 (s, 1H), 4.86 (s, 1H), 3.63 (s, 2H), 2.52 (td, J = 7.3, 1.36 Hz, 2H), 2.01 – 1.94 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.3, 171.4, 146.3, 135.6, 134.9, 132.0, 130.1, 127.9, 127.8, 127.5, 123.2, 114.4, 46.4, 41.1, 20.0; IR (KBr, cm^{-1}) ν 1721, 1644, 1391. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{18}\text{BrNO}_2$ ($\text{M} + \text{Na}$) $^+$: 394.0413. Found: 394.0405.

N-(1-(2-Bromophenyl)vinyl)-N-(4-oxobutyl)benzamide 1p (1.39 g, 63% yield from 5.94 mmol of **S1p**): pale yellow oil; R_f = 0.26 (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, CDCl_3) δ 9.80 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.38 (dd, J = 8.2, 1.3 Hz, 2H), 7.27 – 7.24 (m, 1H), 7.21 – 7.17 (m, 2H), 7.12 – 7.00 (m, 3H), 5.26 (s, 1H), 5.16 (s, 1H), 3.76 (t, J = 7.3 Hz, 2H), 2.57 (d, J = 7.3 Hz, 2H), 2.14 – 2.07 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.5, 171.0, 147.2, 138.0, 136.7, 133.7, 131.0, 129.8, 129.4, 127.9, 127.4, 127.2, 121.5, 113.6, 49.4, 41.3, 21.0; IR (KBr, cm^{-1}) ν 1722, 1650, 1615, 1386. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_2\text{Br}$ ($\text{M} + \text{Na}$) $^+$: 394.0413. Found: 394.0408.

N-(4-Oxobutyl)-N-(1-(thiophen-2-yl)vinyl)benzamide 1q (1.21 g, 62% yield from 6.5 mmol of **S1q**): yellow solid, mp. 109-110 $^\circ\text{C}$; R_f = 0.19 (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, CDCl_3) δ 9.76 (s, 1H), 7.50 – 7.48 (m, 2H), 7.31 – 7.28 (m, 1H), 7.26 – 7.20 (m, 3H), 7.12 – 7.11 (m, 1H), 7.00 – 6.98 (m, 1H), 5.33 (s, 1H), 4.75 (s, 1H), 3.71 (s, 2H), 2.52 (t, J = 7.4 Hz, 2H), 2.03 – 1.97 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.4, 171.1, 141.6, 140.9, 135.7, 130.0, 127.8, 127.7, 127.4, 126.4, 125.8, 113.6, 46.6, 41.1, 20.2; IR (KBr, cm^{-1}) ν 1718, 1634. HRMS (ESI-ion trap) Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_2\text{S}$ ($\text{M} + \text{Na}$) $^+$: 322.0872. Found: 322.0865.

(E)-N-(4-Oxobutyl)-N-(1-phenylprop-1-en-1-yl)benzamide 1r (277 mg, 60% yield from 1.5 mmol of **S1r**): colorless oil; R_f = 0.19 (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, CDCl_3 , 60 $^\circ\text{C}$) δ 9.74 (s, 1H), 7.56 – 7.54 (m, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.41 – 7.37 (m, 2H), 7.34 – 7.28 (m, 2H), 7.18 (t, J = 7.7 Hz, 2H), 5.85 (q, J = 7.1 Hz, 1H), 4.12 – 4.04 (m, 1H), 3.11 – 3.04 (m, 1H), 2.49 – 2.37 (m, 2H), 2.08 – 2.02 (m, 1H), 1.92 – 1.84 (m, 1H), 1.45 (d, J = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.4, 171.0, 140.2, 136.5, 135.7, 130.2, 128.9, 128.3, 127.5, 126.0, 122.8, 46.5, 41.5, 19.9, 14.5; IR (KBr, cm^{-1}) ν 1722, 1637, 1446, 1399. HRMS (ESI-ion trap) Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_2$ ($\text{M} + \text{Na}$) $^+$: 330.1465. Found: 330.1459.

4-(1-Methylene-3-oxoisindolin-2-yl)butanal 1s (746 mg, 53% yield from 6.5 mmol of **S1s**): pale yellow oil; R_f = 0.16 (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, CDCl_3) δ 9.76 (d, J = 0.8 Hz, 1H), 7.78 (d, J = 7.3 Hz, 1H), 7.66 (d, J =

7.6 Hz, 1H), 7.55 (t, $J = 7.3$ Hz, 1H), 7.46 (t, $J = 7.8$ Hz, 1H), 5.20 (d, $J = 1.8$ Hz, 1H), 4.93 (d, $J = 1.8$ Hz, 1H), 3.79 (t, $J = 7.0$ Hz, 2H), 2.54 (t, $J = 7.0$ Hz, 2H), 2.03 – 1.94 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.2, 167.1, 141.4, 136.1, 131.9, 129.4, 129.0, 122.9, 119.8, 89.0, 40.8, 38.2, 20.5; IR (KBr, cm^{-1}) ν 1705, 1644, 1395. HRMS (ESI-ion trap) Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_2$ ($\text{M} + \text{Na}$) $^+$: 238.0839. Found: 238.0838.

Preparation of substrates 5. The aforementioned procedures for the synthesis of substrates **1** were followed for the preparation of **5**.^{19a,20,21}

N-Benzyl-4-oxo-N-(1-phenylvinyl)butanamide 5a (840 mg, 70% yield from 4.1 mmol of **S5a**): yellow solid, mp. 48-49 °C; $R_f = 0.59$ (EtOAc / petroleum ether = 1 / 1); ^1H NMR (400 MHz, CDCl_3) δ 9.83 (s, 1H), 7.48 – 7.47 (m, 2H), 7.44 – 7.38 (m, 3H), 7.28 – 7.25 (m, 5H), 5.67 (s, 1H), 4.96 (s, 1H), 4.66 (s, 2H), 2.81 (t, $J = 6.3$ Hz, 2H), 2.68 (t, $J = 6.3$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.9, 171.5, 145.7, 137.4, 135.1, 129.2, 128.9, 128.9, 128.3, 127.3, 125.9, 115.0, 50.1, 39.0, 26.5; IR (KBr, cm^{-1}) ν 1708, 1646, 1402. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_2$ ($\text{M} + \text{Na}$) $^+$: 316.1308. Found: 316.1308.

N-(4-Bromobenzyl)-4-oxo-N-(1-phenylvinyl)butanamide 5b (940 mg, 65% yield from 3.86 mmol of **S5b**): yellow solid, mp. 85-86 °C; $R_f = 0.59$ (EtOAc / petroleum ether = 1 / 1); ^1H NMR (400 MHz, CDCl_3) δ 9.82 (d, $J = 0.6$ Hz, 1H), 7.46 – 7.38 (m, 7H), 7.11 (d, $J = 7.2$ Hz, 2H), 5.67 (s, 1H), 4.94 (s, 1H), 4.57 (s, 2H), 2.81 (t, $J = 6.3$ Hz, 2H), 2.66 (t, $J = 6.1$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.8, 171.5, 145.5, 136.3, 134.8, 131.3, 130.6, 129.2, 128.9, 125.8, 121.2, 115.0, 49.3, 38.9, 26.3; IR (KBr, cm^{-1}) ν 1710, 1654, 1630, 1423. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_2\text{Br}$ ($\text{M} + \text{Na}$) $^+$: 394.0413. Found: 394.0405.

N-(4-Methoxybenzyl)-4-oxo-N-(1-phenylvinyl)butanamide 5c (780 mg, 78% yield from 3.1 mmol of **S5c**): white solid, mp. 80-81 °C; $R_f = 0.19$ (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, CDCl_3) δ 9.83 (s, 1H), 7.46 – 7.39 (m, 5H), 7.16 (d, $J = 8.4$ Hz, 2H), 6.80 (d, $J = 8.3$ Hz, 2H), 5.67 (s, 1H), 4.92 (s, 1H), 4.58 (s, 2H), 3.78 (d, $J = 0.9$ Hz, 3H), 2.80 (t, $J = 6.4$ Hz, 2H), 2.65 (t, $J = 6.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.0, 171.3, 158.9, 145.7, 135.3, 130.3, 130.0, 129.2, 129.0,

125.9, 114.9, 113.6, 55.2, 49.5, 39.1, 26.6; IR (KBr, cm^{-1}) ν 1709, 1651. HRMS (ESI-ion trap) Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_3$ ($\text{M} + \text{Na}$) $^{+}$: 346.1414. Found: 346.1413.

4-((1-(4-Methoxyphenyl)vinyl)(methyl)amino)butanal 5d (669 mg, 69% yield from 4.28 mmol of **S5d**): white solid, mp. 74-75 $^{\circ}\text{C}$; R_f = 0.11 (EtOAc / petroleum ether = 1 / 2); ^1H NMR (400 MHz, CDCl_3) δ 9.58 (s, 1H), 7.21 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H), 5.44 (s, 1H), 4.99 (s, 1H), 3.61 (s, 3H), 2.88 (s, 3H), 2.54 (t, J = 6.1 Hz, 2H), 2.43 (t, J = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.5, 170.9, 159.9, 147.2, 127.1, 126.6, 113.8, 110.2, 54.7, 38.4, 34.9, 25.8; IR (KBr, cm^{-1}) ν 1709, 1648. HRMS (ESI-ion trap) Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3$ ($\text{M} + \text{Na}$) $^{+}$: 270.1101. Found: 270.1098.

N-Methyl-4-oxo-N-(1-phenylvinyl)butanamide 5e (734 mg, 68% yield from 5.0 mmol of **S5e**): pale yellow oil; R_f = 0.19 (EtOAc / petroleum ether = 1 / 2); ^1H NMR (400 MHz, CDCl_3) δ 9.71 (s, 1H), 7.39 (d, J = 7.8 Hz, 2H), 7.35 – 7.29 (m, 3H), 5.68 (s, 1H), 5.24 (s, 1H), 3.02 (s, 3H), 2.68 (t, J = 6.3 Hz, 2H), 2.54 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.8, 171.3, 147.9, 134.9, 129.0, 128.7, 125.4, 112.6, 38.8, 35.3, 26.1; IR (KBr, cm^{-1}) ν 1718, 1658, 1387. HRMS (ESI-ion trap) Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2$ ($\text{M} + \text{Na}$) $^{+}$: 240.0995. Found: 240.0993.

4-((1-(4-Chlorophenyl)vinyl)(methyl)amino)butanal 5f (313 mg, 73 % yield from 1.8 mmol of **S5f**): pale yellow oil; R_f = 0.11 (EtOAc / petroleum ether = 1 / 2); ^1H NMR (400 MHz, CDCl_3) δ 9.69 (s, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 5.65 (s, 1H), 5.23 (s, 1H), 2.97 (s, 3H), 2.68 (t, J = 5.1, 2H), 2.50 (d, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.7, 171.2, 146.9, 134.8, 133.5, 128.9, 126.9, 113.2, 38.7, 35.2, 26.1; IR (KBr, cm^{-1}) ν 1715, 1633. HRMS (ESI-ion trap) Calcd for $\text{C}_{13}\text{H}_{14}\text{NO}_2\text{Cl}$ ($\text{M} + \text{Na}$) $^{+}$: 274.0605. Found: 274.0602.

General procedure for the synthesis of 3 and 7. Under argon protection, a solution of BBr_3 (9 μL , 3 mol %, 1.0 M in DCM) was added to a mixture of tertiary enamides **1** or **5** (0.30 mmol) and P_2O_5 (85 mg, 6 mmol) in DCM (15 mL). The resulting mixture was stirred at room temperature for a period of time (see Tables 2 and 3 and Figure 3). The reaction was quenched by adding a saturated NaHCO_3 aqueous solution (10 mL). The aqueous layer was extracted with DCM (3 \times 20 mL). The

combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give a crude mixture. Silica gel column chromatography (200 – 300 mesh) eluted with a mixture of ethyl acetate and petroleum (1 : 20 to 1 : 3) afforded pure product **3** or **7**. All products were fully characterized and their characterization data are listed below.

Phenyl(7-phenyl-2,3-dihydro-1H-azepin-1-yl)methanone 3a (77.1 mg, 93% yield): white solid, mp. 99-100 °C; R_f = 0.3 (EtOAc / petroleum ether = 1 / 5); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 150 °C) δ 7.24 – 7.10 (m, 10H), 6.22 – 6.14 (m, 2H), 5.98 (d, J = 6.4 Hz, 1H), 4.02 (s, 2H), 2.73 (dd, J = 8.2, 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 169.4, 145.2, 139.5, 137.9, 135.4, 130.7, 129.0, 128.5, 128.4, 128.0, 126.5, 124.0, 116.4, 46.3, 33.4; IR (KBr, cm^{-1}) ν 1643, 1629. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{17}\text{NO}$ ($\text{M} + \text{H}$) $^+$: 276.1383. Found: 276.1387. A high quality single crystal was obtained from recrystallization from a mixture of *n*-hexane and ethyl acetate.

(4-Methoxyphenyl)(7-phenyl-2,3-dihydro-1H-azepin-1-yl)methanone 3b (84 mg, 92% yield): white solid, mp. 139-140 °C; R_f = 0.5 (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 150 °C) δ 7.20 – 7.12 (m, 7H), 6.70 (d, J = 8.7 Hz, 2H), 6.17 (d, J = 5.0 Hz, 2H), 5.97 (d, J = 6.0 Hz, 1H), 4.01 (s, 2H), 3.73 (s, 3H), 2.71 (s, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 169.0, 161.3, 145.5, 139.5, 135.4, 130.1, 129.1, 128.6, 126.3, 124.1, 116.1, 113.8, 56.0, 46.5, 33.7; IR (KBr, cm^{-1}) ν 1648, 1265. HRMS (ESI-ion trap) Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2$ ($\text{M} + \text{Na}$) $^+$: 328.1308. Found: 328.1303.

(3,4-Dimethoxyphenyl)(7-phenyl-2,3-dihydro-1H-azepin-1-yl)methanone 3c (96 mg, 95% yield): white solid, mp. 92-93 °C, R_f = 0.19 (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 150 °C) δ 7.18 – 7.12 (m, 5H), 6.84 – 6.73 (m, 3H), 6.19 – 6.16 (m, 2H), 5.97 (d, J = 6.4 Hz, 1H), 4.01 (s, 2H), 3.73 (s, 3H), 3.66 (s, 3H), 2.71 (t, J = 2.1 Hz, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 169.1, 151.0, 148.5, 145.7, 139.5, 135.4, 130.2, 129.1, 128.6, 126.4, 124.0, 121.7, 115.9, 112.0, 111.3, 56.3, 56.2, 46.5, 33.7; IR (KBr, cm^{-1}) ν 1651, 1626. HRMS (ESI-ion trap) Calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_3$ ($\text{M} + \text{Na}$) $^+$: 358.1414. Found: 358.1407.

(4-Nitrophenyl)(7-phenyl-2,3-dihydro-1H-azepin-1-yl)methanone 3d (97 mg, 96% yield): yellow solid, mp. 93-94 °C; R_f = 0.41 (EtOAc / petroleum ether = 1 / 4); ^1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.95 (d, J = 8.68 Hz, 2H), 7.35 (d, J = 8.72 Hz, 2H), 7.16 (s, 5H), 6.26 – 6.16 (m, 2H), 6.05 (d, J = 6.9 Hz, 1H), 4.04 (s, 2H), 2.78 (d, J = 4.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 167.7, 148.4, 144.1, 143.9, 139.3, 135.9, 129.3, 129.2, 128.7, 126.7, 123.8, 123.8, 117.5, 46.4, 33.2; IR (KBr, cm^{-1}) ν 1652, 1521, 1352. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$: 321.1234. Found: 321.1228.

(4-Chlorophenyl)(7-phenyl-2,3-dihydro-1H-azepin-1-yl)methanone 3e (82 mg, 88% yield): white solid, mp. 142-143 °C; R_f = 0.45 (EtOAc / petroleum ether = 1 / 5); ^1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.19 – 7.16 (m, J = 4.1 Hz, 9H), 6.23 – 6.16 (m, 2H), 6.01 (t, J = 5.7 Hz, 1H), 4.01 (s, 2H), 2.73 (s, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 168.3, 144.8, 139.3, 136.7, 135.7, 135.4, 129.8, 129.2, 128.7, 128.6, 126.5, 123.9, 116.8, 46.4, 33.4; IR (KBr, cm^{-1}) ν 1652, 1384. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{16}\text{ClNO}$ ($\text{M} + \text{H}$) $^+$: 310.0993. Found: 310.0993.

(4-Bromophenyl)(7-phenyl-2,3-dihydro-1H-azepin-1-yl)methanone 3f (96 mg, 90% yield): white solid, mp. 139-140 °C; R_f = 0.35 (EtOAc / petroleum ether = 1 / 4); ^1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.33 (dd, J = 8.2, 1.8 Hz, 2H), 7.20 – 7.17 (m, 5H), 7.09 (dd, J = 8.7, 1.8 Hz, 2H), 6.23 – 6.13 (m, 2H), 6.01 (d, J = 6.0 Hz, 1H), 4.01 (s, 2H), 2.73 (d, J = 3.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6 , 150 °C) δ 168.4, 144.8, 139.3, 137.0, 135.7, 131.6, 130.0, 129.2, 128.8, 126.5, 124.2, 123.9, 116.9, 46.4, 33.4; IR (KBr, cm^{-1}) ν 1652. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{16}\text{BrNO}$ ($\text{M} + \text{Na}$) $^+$: 376.0308. Found: 376.0304.

(2-Bromophenyl)(7-phenyl-2,3-dihydro-1H-azepin-1-yl)methanone 3g (101 mg, 95% yield): white solid, mp. 84-85 °C; R_f = 0.39 (EtOAc / petroleum ether = 1 / 5); ^1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.33 (s, 1H), 7.17 (s, 5H), 7.09 (s, 2H), 6.90 (s, 1H), 6.19 – 6.08 (m, 2H), 5.88 (d, J = 6.4 Hz, 1H), 3.96 (s, 2H), 2.77 (s, 2H); ^{13}C NMR (100 MHz, DMSO- d_6 , 150 °C) δ 166.8, 143.4, 139.3, 138.5, 134.3, 132.4, 130.2, 128.9, 128.1, 127.6, 126.6, 125.9, 123.2, 119.4, 117.5, 45.9, 32.0; IR (KBr, cm^{-1}) ν

1645, 1629, 1596, 1391. HRMS (ESI-ion trap) Calcd for $C_{19}H_{16}BrNO$ ($M + Na$)⁺: 376.0308. Found: 376.0300.

Benzyl 7-phenyl-2,3-dihydro-1H-azepine-1-carboxylate 3h (72 mg, 79% yield): white solid, mp. 95-96 °C; R_f = 0.67 (EtOAc / petroleum ether = 1 / 3); 1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.42 (d, J = 7.8 Hz, 2H), 7.37 – 7.29 (m, 3H), 7.26 – 7.22 (m, 3H), 6.98 – 6.96 (m, 2H), 6.03 (t, J = 2.7 Hz, 2H), 6.00 – 5.99 (m, 1H), 4.96 (s, 2H), 3.76 (t, J = 5.7 Hz, 2H), 2.67 – 2.64 (m, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 154.4, 142.6, 139.5, 139.4, 135.7, 133.4, 128.4, 128.0, 127.7, 127.5, 127.2, 125.4, 122.9, 115.5, 67.3, 46.4, 32.5; IR (KBr, cm^{-1}) ν 1698. HRMS (ESI-ion trap) Calcd for $C_{20}H_{19}NO_2$ ($M + Na$)⁺: 328.1308. Found: 328.1305.

Ethyl 7-phenyl-2,3-dihydro-1H-azepine-1-carboxylate 3i (52 mg, 71% yield): colorless oil; R_f = 0.67 (EtOAc / petroleum ether = 1 / 3); 1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.42 – 7.30 (m, 5H), 6.03 – 6.02 (m, 2H), 5.95 – 5.94 (m, 1H), 3.92 (q, J = 7.0 Hz, 2H), 3.73 (t, J = 5.5 Hz, 2H), 2.65 – 2.62 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 153.9, 143.4, 139.5, 133.5, 128.5, 127.8, 125.6, 123.5, 115.5, 61.2, 46.6, 32.8, 14.2; IR (KBr, cm^{-1}) ν 2964, 1715, 1261. HRMS (ESI-ion trap) Calcd for $C_{15}H_{17}NO_2$ ($M + Na$)⁺: 266.1152. Found: 266.1150.

1-(7-Phenyl-2,3-dihydro-1H-azepin-1-yl)ethan-1-one 3j (63 mg, 74% yield): pale yellow oil; R_f = 0.50 (EtOAc / petroleum ether = 1 / 3); 1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.51 – 7.48 (m, 2H), 7.45 – 7.42 (m, 2H), 7.38 – 7.34 (m, 1H), 6.19 (d, J = 5.0 Hz, 1H), 6.07 (s, 2H), 3.74 (s, 2H), 2.66 (s, 2H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 169.3, 143.6, 139.3, 135.5, 130.0, 129.2, 126.2, 123.4, 118.2, 45.9, 32.4, 24.2; IR (KBr, cm^{-1}) ν 1665, 1386. HRMS (ESI-ion trap) Calcd for $C_{14}H_{15}NO$ ($M + Na$)⁺: 236.1046. Found: 236.1041.

(7-(4-Methoxyphenyl)-2,3-dihydro-1H-azepin-1-yl)(phenyl)methanone 3k (84 mg, 92% yield): white solid, mp. 129-130 °C; R_f = 0.36 (EtOAc / petroleum ether = 1 / 7); 1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.23 – 7.13 (m, 5H), 7.08 (d, J = 8.7 Hz, 2H), 6.71 (d, J = 8.7 Hz, 2H), 6.14 (d, J = 4.6 Hz, 2H), 5.88 (d, J = 5.0 Hz, 1H), 3.99 (s, 2H), 3.73 (s, 3H), 2.71 (s, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 169.4, 159.7, 145.0, 138.0, 134.4, 132.0, 130.7, 128.5, 127.9, 127.8, 124.1, 114.8, 114.5,

56.0, 46.4, 33.3; IR (KBr, cm^{-1}) ν 1643, 1388. HRMS (ESI-ion trap) Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2$ ($\text{M} + \text{Na}$) $^+$: 328.1308. Found: 328.1302.

Phenyl(7-(p-tolyl)-2,3-dihydro-1H-azepin-1-yl)methanone 3l (71 mg, 82% yield): white solid, mp. 129-130 $^{\circ}\text{C}$; R_f = 0.36 (EtOAc / petroleum ether = 1 / 7); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 150 $^{\circ}\text{C}$) δ 7.24 – 7.13 (m, 5H), 7.05 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 7.8 Hz, 2H), 6.19 – 6.12 (m, 2H), 5.94 (d, J = 5.5 Hz, 1H), 4.00 (s, 2H), 2.72 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 169.4, 145.3, 137.9, 136.6, 135.0, 130.7, 129.7, 128.4, 128.0, 126.3, 124.0, 115.7, 46.4, 33.4, 21.5; IR (KBr, cm^{-1}) ν 1643, 1385. HRMS (ESI-ion trap) Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}$ ($\text{M} + \text{Na}$) $^+$: 312.1359. Found: 312.1353.

(7-(4-Fluorophenyl)-2,3-dihydro-1H-azepin-1-yl)(phenyl)methanone 3m (79 mg, 90% yield): white solid, mp. 124-125 $^{\circ}\text{C}$; R_f = 0.50 (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 150 $^{\circ}\text{C}$) δ 7.26 – 7.23 (m, 1H), 7.19 – 7.16 (m, 6H), 6.95 – 6.89 (m, 2H), 6.22 – 6.15 (m, 2H), 5.94 (d, J = 6.4 Hz, 1H), 4.01 (s, 2H), 2.72 (d, J = 5.0 Hz, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 169.4, 163.5, 161.1, 144.2, 137.9, 136.1, 135.4, 130.8, 128.7, 128.6, 128.5, 127.9, 123.9, 116.4, 116.0, 115.8, 46.3, 33.4; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -114.1; IR (KBr, cm^{-1}) ν 1644, 1383. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{16}\text{NOF}$ ($\text{M} + \text{H}$) $^+$: 294.1289. Found: 294.1285.

(7-(4-Chlorophenyl)-2,3-dihydro-1H-azepin-1-yl)(phenyl)methanone 3n (87 mg, 94% yield): white solid, mp. 145-146 $^{\circ}\text{C}$; R_f = 0.49 (EtOAc / petroleum ether = 1 / 4); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 150 $^{\circ}\text{C}$) δ 7.25 (q, J = 4.4 Hz, 1H), 7.19 – 7.17 (m, 8H), 6.24 – 6.13 (m, 2H), 6.00 (d, J = 6.9 Hz, 1H), 4.00 (s, 2H), 2.73 (d, J = 4.1 Hz, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 169.3, 143.9, 138.4, 137.8, 136.0, 132.9, 130.9, 129.0, 128.2, 127.9, 123.9, 117.1, 46.2, 33.4; IR (KBr, cm^{-1}) ν 1649, 1382. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{16}\text{NOCl}$ ($\text{M} + \text{H}$) $^+$: 310.0993. Found: 310.0990.

(7-(4-Bromophenyl)-2,3-dihydro-1H-azepin-1-yl)(phenyl)methanone 3o (97 mg, 91% yield): white solid, mp. 137-138 $^{\circ}\text{C}$; R_f = 0.52 (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 150 $^{\circ}\text{C}$) δ 7.31 (d, J = 8.7 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.18 (d, J = 4.1 Hz, 3H), 7.10 (d, J = 8.2 Hz, 2H), 6.25 – 6.13 (m, 2H), 6.01 (d, J = 7.3 Hz, 1H), 3.99 (s, 2H), 2.72 (d, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$)

δ 169.3, 144.0, 138.8, 137.8, 136.1, 132.0, 130.9, 128.6, 128.5, 128.0, 123.9, 121.5, 117.1, 46.3, 33.4; IR (KBr, cm^{-1}) ν 1647, 1381. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{16}\text{NOBr}$ ($\text{M} + \text{H}$) $^{+}$: 354.0488. Found: 354.0482.

(7-(2-Bromophenyl)-2,3-dihydro-1H-azepin-1-yl)(phenyl)methanone 3p (101 mg, 94% yield): white solid, mp. 95-96 $^{\circ}\text{C}$; R_f = 0.29 (EtOAc / petroleum ether = 1 / 2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 150 $^{\circ}\text{C}$) δ 7.42 – 7.40 (m, 1H), 7.27 (t, J = 7.3 Hz, 1H), 7.19 (t, J = 7.3 Hz, 2H), 7.07 (d, J = 6.9 Hz, 2H), 7.03 – 7.00 (m, 2H), 6.87 – 6.85 (m, 1H), 6.25 – 6.22 (m, 1H), 6.16 – 6.11 (m, 1H), 5.77 (d, J = 7.3 Hz, 1H), 4.06 (t, J = 5.3 Hz, 2H), 2.72 (d, J = 4.1 Hz, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 169.2, 144.0, 139.9, 138.1, 136.1, 133.8, 133.0, 130.6, 130.0, 128.9, 128.0, 127.3, 123.7, 121.4, 119.5, 46.7, 33.7; IR (KBr, cm^{-1}) ν 1649, 1379. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{16}\text{NOBr}$ ($\text{M} + \text{H}$) $^{+}$: 354.0488. Found: 354.0482.

Phenyl(7-(thiophen-2-yl)-2,3-dihydro-1H-azepin-1-yl)methanone 3q (80 mg, 93% yield): white solid, mp. 117-118 $^{\circ}\text{C}$; R_f = 0.39 (EtOAc / petroleum ether = 1 / 5); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 150 $^{\circ}\text{C}$) δ 7.32 – 7.28 (m, 3H), 7.24 – 7.21 (m, 3H), 6.89 (t, J = 1.8 Hz, 1H), 6.82 – 6.80 (m, 1H), 6.22 – 6.10 (m, 2H), 6.04 (d, J = 6.9 Hz, 1H), 3.97 (s, 2H), 2.71 (d, J = 4.1 Hz, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 169.2, 143.5, 139.3, 137.7, 135.7, 130.9, 128.5, 128.5, 127.9, 127.0, 125.8, 123.6, 115.5, 46.3, 33.2; IR (KBr, cm^{-1}) ν 1642, 1386. HRMS (ESI-ion trap) Calcd for $\text{C}_{17}\text{H}_{15}\text{NOS}$ ($\text{M} + \text{Na}$) $^{+}$: 304.0767. Found: 304.0761.

(6-Methyl-7-phenyl-2,3-dihydro-1H-azepin-1-yl)(phenyl)methanone 3r (73 mg, 84% yield): white solid, mp. 112-113 $^{\circ}\text{C}$; R_f = 0.43 (EtOAc / petroleum ether = 1 / 4); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 150 $^{\circ}\text{C}$) δ 7.27 (t, J = 7.3 Hz, 1H), 7.16 (t, J = 7.6 Hz, 2H), 7.10 (s, 3H), 7.00 (d, J = 7.8 Hz, 2H), 6.86 (d, J = 5.0 Hz, 2H), 6.12 (s, 2H), 4.08 (s, 2H), 2.68 (s, 2H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 169.7, 140.2, 139.6, 138.4, 133.8, 130.3, 129.9, 129.4, 128.5, 128.3, 127.7, 127.5, 124.0, 48.4, 32.9, 21.2; IR (KBr, cm^{-1}) ν 1652, 1389. HRMS (ESI-ion trap) Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}$ ($\text{M} + \text{Na}$) $^{+}$: 312.1359. Found: 312.1354.

7,8-Dihydro-5H-azepino[2,1-*a*]isoindol-5-one 3s (51 mg, 85% yield): yellow oil; R_f = 0.50 (EtOAc / petroleum ether = 1 / 2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.95 –

7.93 (m, 1H), 7.76 (d, $J = 7.3$ Hz, 1H), 7.68 (t, $J = 7.3$ Hz, 1H), 7.54 (t, $J = 7.6$ Hz, 1H), 6.31 (q, $J = 2.6$ Hz, 1H), 6.16 – 6.15 (m, 2H), 3.94 (t, $J = 4.8$ Hz, 2H), 2.62 (d, $J = 4.1$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 166.0, 138.1, 137.7, 135.4, 133.1, 129.9, 128.6, 125.4, 123.7, 120.7, 104.2, 41.9, 30.3; IR (KBr, cm^{-1}) ν 1703, 1645. HRMS (ESI-ion trap) Calcd for $\text{C}_{13}\text{H}_{11}\text{NO}$ ($\text{M} + \text{H}$) $^+$: 198.0913. Found: 198.0913.

Formation of N-(4-hydroxy-6-oxo-6-phenylhexyl)benzamide 4a. Under the catalysis of FeCl_3 (30 mol %), **3a** was obtained in 18% yield. In addition, product **4a** (22.5 mg, 24% yield) was isolated as a white solid: mp. 95-96 $^\circ\text{C}$; $R_f = 0.21$ (EtOAc / petroleum ether = 3 / 2); ^1H NMR (400 MHz, CDCl_3) δ 8.02 – 7.86 (m, 2H), 7.78 (d, $J = 7.3$ Hz, 2H), 7.67 – 7.52 (m, 1H), 7.52 – 7.43 (m, 3H), 7.43 – 7.36 (m, 2H), 6.86 (s, 1H), 4.32 – 4.20 (m, 1H), 3.71 – 3.40 (m, 3H), 3.18 (dd, $J = 17.4, 2.7$ Hz, 1H), 3.06 (q, $J = 8.9$ Hz, 1H), 1.93 – 1.74 (m, 2H), 1.67 (q, $J = 7.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.0, 167.6, 136.5, 134.7, 133.7, 131.3, 128.7, 128.5, 128.1, 126.9, 67.6, 45.0, 39.9, 33.7, 25.7; IR (KBr, cm^{-1}) ν 3352, 1682, 1637, 1536. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_3$ ($\text{M} + \text{Na}$) $^+$: 334.1414. Found: 334.1409.

1-Benzyl-7-phenyl-1,3-dihydro-2H-azepin-2-one 7a (70 mg, 85% yield): colorless oil; $R_f = 0.31$ (EtOAc / petroleum ether = 1 / 4); ^1H NMR (400 MHz, DMSO- d_6 , 150 $^\circ\text{C}$) δ 7.45 – 7.35 (m, 5H), 7.23 – 7.20 (m, 3H), 6.89 (d, $J = 6.9$ Hz, 2H), 6.32-6.37 (m, 2H), 5.91 (q, $J = 7.8$ Hz, 1H), 4.64 (s, 2H), 3.14 (d, $J = 6.4$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 168.0, 143.8, 138.4, 129.7, 129.4, 129.0, 128.3, 128.2, 127.7, 127.6, 126.0, 121.4, 49.2, 37.8; IR (KBr, cm^{-1}) ν 1668. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{17}\text{NO}$ ($\text{M} + \text{H}$) $^+$: 276.1383. Found: 276.1384.

1-(4-Bromobenzyl)-7-phenyl-1,3-dihydro-2H-azepin-2-one 7b (93 mg, 88% yield): white solid, mp. 101-102 $^\circ\text{C}$; $R_f = 0.50$ (EtOAc / petroleum ether = 1 / 4); ^1H NMR (400 MHz, DMSO- d_6 , 150 $^\circ\text{C}$) δ 7.44 – 7.37 (m, 7H), 6.84 (d, $J = 8.2$ Hz, 2H), 6.33 – 6.30 (m, 2H), 5.92 – 5.89 (m, 1H), 4.60 (s, 2H), 3.14 (d, $J = 6.9$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 168.0, 143.6, 138.3, 137.8, 132.0, 129.9, 129.8, 129.5, 128.3, 128.2, 126.2, 121.5, 120.9, 48.7, 37.8; IR (KBr, cm^{-1}) ν 1668. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{17}\text{NOBr}$ ($\text{M} + \text{H}$) $^+$: 354.0488. Found: 354.0479. A high quality

single crystal was obtained from recrystallization from a mixture of *n*-hexane and ethyl acetate.

1-(4-Methoxybenzyl)-7-phenyl-1,3-dihydro-2H-azepin-2-one 7c (80 mg, 87% yield): colorless oil; $R_f = 0.23$ (EtOAc / petroleum ether = 1 / 4); ^1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.46 – 7.36 (m, 5H), 6.79 (q, $J = 7.8$ Hz, 4H), 6.30 – 6.27 (m, 2H), 5.92 – 5.89 (m, 1H), 4.57 (s, 2H), 3.76 (s, 3H), 3.12 (d, $J = 6.4$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 167.9, 159.1, 143.7, 138.5, 130.3, 129.7, 129.4, 129.1, 128.3, 128.2, 126.0, 121.4, 114.4, 55.9, 48.6, 37.9; IR (KBr, cm^{-1}) ν 1668, 1513. HRMS (ESI-ion trap) Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2$ ($\text{M} + \text{Na}$) $^+$: 328.1308. Found: 328.1305.

7-(4-Methoxyphenyl)-1-methyl-1,3-dihydro-2H-azepin-2-one 7d (58 mg, 84% yield): white solid, mp. 93-94 °C; $R_f = 0.60$ (EtOAc / petroleum ether = 1 / 1); ^1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.38 (dd, $J = 6.9, 1.8$ Hz, 2H), 7.02 (dd, $J = 6.6, 2.1$ Hz, 2H), 6.29 (q, $J = 4.6$ Hz, 1H), 6.21 (d, $J = 5.0$ Hz, 1H), 5.86 – 5.80 (m, 1H), 3.86 (s, 3H), 3.04 (d, $J = 6.4$ Hz, 2H), 2.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 168.0, 160.3, 144.7, 130.8, 129.5, 128.0, 125.2, 117.8, 115.1, 56.1, 37.8, 35.9; IR (KBr, cm^{-1}) ν 1655. HRMS (ESI-ion trap) Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$: 230.1176. Found: 230.1175.

1-Methyl-7-phenyl-1,3-dihydro-2H-azepin-2-one 7e (56 mg, 94% yield): colorless oil; $R_f = 0.37$ (EtOAc / petroleum ether = 1 / 2); ^1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.47 – 7.41 (m, 5H), 6.33 – 6.28 (m, 2H), 5.89 – 5.84 (m, 1H), 3.06 (d, $J = 6.4$ Hz, 2H), 2.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 168.0, 145.0, 138.5, 129.7, 129.4, 128.2, 128.0, 125.7, 118.9, 37.8, 35.9; IR (KBr, cm^{-1}) ν 1666. HRMS (ESI-ion trap) Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}$ ($\text{M} + \text{H}$) $^+$: 200.1070. Found: 200.1070.

7-(4-Chlorophenyl)-1-methyl-1,3-dihydro-2H-azepin-2-one 7f (66 mg, 95% yield): pale yellow oil; $R_f = 0.53$ (EtOAc / petroleum ether = 1 / 1); ^1H NMR (400 MHz, DMSO- d_6 , 150 °C) δ 7.52 – 7.43 (m, 4H), 6.33 – 6.30 (m, 2H), 5.91 – 5.85 (m, 1H), 3.05 (d, $J = 6.4$ Hz, 2H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 168.1, 143.7, 137.4, 133.9, 130.0, 129.7, 127.8, 126.1, 119.4, 37.8, 35.8; IR (KBr, cm^{-1}) ν 1666, 1510. HRMS (ESI-ion trap) Calcd for $\text{C}_{13}\text{H}_{12}\text{NOCl}$ ($\text{M} + \text{H}$) $^+$: 234.0680. Found: 234.0679.

Formation of 2-(4-bromobenzyl)-5-hydroxy-3-phenylcyclohept-3-en-1-one 6b.

Under the standard conditions for the synthesis of **7b**, the reaction was quenched at 20 min. **7b** was obtained in 49% yield. In addition, product **6b** (49 mg, 44% yield) was isolated as a pale yellow oil: $R_f = 0.15$ (EtOAc / petroleum ether = 1 / 3); ^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.39 (m, 3H), 7.35 – 7.34 (m, 2H), 7.33 – 7.32 (m, 2H), 7.01 (d, $J = 8.2$ Hz, 2H), 5.94 (d, $J = 5.5$ Hz, 1H), 5.18 (d, $J = 14.2$ Hz, 1H), 4.28 – 4.22 (m, 1H), 3.75 (d, $J = 14.2$ Hz, 1H), 2.72 – 2.64 (m, 1H), 2.62 – 2.52 (m, 1H), 2.41 – 2.36 (m, 1H), 2.29 (b, 1H), 2.08 – 2.00 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.5, 139.3, 136.1, 134.9, 131.4, 130.8, 129.0, 129.0, 128.3, 126.8, 121.6, 67.4, 46.5, 39.4, 32.3; IR (KBr, cm^{-1}) ν 3387, 1662, 1639, 1388. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{18}\text{BrNO}_2$ ($\text{M} + \text{H}$) $^+$: 372.0594. Found: 372.0596.

Synthesis of 8. In an oven-dried Schlenk tube (10 mL) were charged with **3g** (71 mg, 0.2 mmol), $[\text{Pd}(\text{dba})_2]$ (9.2 mg, 0.01 mmol), PPh_3 (5.2 mg, 0.02 mmol), PivOH (6.2 mg, 0.06 mmol), cesium carbonate (97.8 mg, 0.3 mol) and 1.2 mL of mesitylene. The reaction mixture was degassed and then heated at 80 $^\circ\text{C}$. After 12 h, the reaction mixture was cooled to room temperature, and the residue was purified by flash silica gel column chromatography to afford a white solid **8** (50.3 mg, 92% yield): mp. 146–147 $^\circ\text{C}$; $R_f = 0.21$ (EtOAc / petroleum ether = 1 / 5); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.78 (d, $J = 7.3$ Hz, 1H), 7.65 (t, $J = 7.6$ Hz, 1H), 7.57 (t, $J = 7.6$ Hz, 1H), 7.51 (d, $J = 7.3$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.38 – 7.31 (m, 1H), 7.12 (d, $J = 7.8$ Hz, 2H), 6.56 (d, $J = 11.4$ Hz, 1H), 6.18 – 5.97 (m, 2H), 5.97 – 5.82 (m, 1H), 4.71 (dd, $J = 18.8, 6.4$ Hz, 1H), 3.27 (d, $J = 18.8$ Hz, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 166.9, 149.4, 141.9, 133.7, 133.7, 133.2, 130.1, 130.1, 129.8, 129.2, 127.9, 125.5, 125.4, 124.0, 124.0, 73.8, 40.3; IR (KBr, cm^{-1}) ν 1681. HRMS (ESI-ion trap) Calcd for $\text{C}_{19}\text{H}_{15}\text{NO}$ ($\text{M} + \text{Na}$) $^+$: 296.1046. Found: 296.1042. A high quality single crystal was obtained from recrystallization from a mixture of *n*-hexane and ethyl acetate.

ASSOCIATED CONTENT**AUTHOR INFORMATION**

Corresponding Author

wangmx@mail.tsinghua.edu.cn

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank the National Natural Science Foundation of China (21320102002) and Postdoctoral Science Foundation of China (2014M560073) for financial Support.

Supporting Information. Preparation of starting materials **1** and **5**, ^1H and ^{13}C NMR spectra of all products, and X-ray structures of **3a**, **7b** and **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

REFERENCES

1. Kulanthaivel, P.; Hallock, Y.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B.; Katz, B.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 6452.
2. Ohshima, S.; Yanagisawa, M.; Katoh, A.; Fujii, T.; Sano, T.; Mastukuma, T.; Fujii, M.; Watanabe, K.; Yokose, K. *J. Antibiot.* **1994**, *47*, 639.
3. Setyawan, J.; Kiode, K.; Diller, T. C.; Bunnage, M. E.; Taylor, S. S.; Nicolaou, K. C.; Brunton, L. L. *Mol. Pharmacol.* **1999**, *56*, 370.
4. Breitenlechner, C. B.; Friebe, W. G.; Brunet, E.; Werner, G.; Graul, K.; Thomas, U.; Kunkele, K. P.; Shafer, W.; Gassel, M.; Bossemeyer, D.; Huber, R.; Engh, R. A.; Masjost, B. *J. Med. Chem.* **2005**, *48*, 163.
5. Valencia, E.; Weiss, I.; Firdous, S.; Freyer, A. J.; Shamma, M.; Urzúa, A.; Fajardo, V. *Tetrahedron* **1984**, *40*, 3597.
6. Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett.* **1984**, *25*, 599.

7. Andersen, J.; Kristensen, A. S.; Bang-Andersen, B.; Strømgaard, K. *Chem. Commun.* **2009**, 3699.
8. Kinney, W. A.; Luci, D. K.; Marynoff, B. E.; Ghosh, S.; Lawson, E. C. US Patent 20100029616 A1, 2010.
9. Luci, D. K.; Lawson, E. C.; Ghosh, S.; Kinney, W. A.; Smith, C. E.; Qi, J.; Wang, Y.; Minor, L. K. Marynoff, B. E. *Tetrahedron Lett.* **2009**, 50, 4958.
10. (a) Bremner, J. B.; Samosom, S. *Azepines and their fused ring derivatives*. in *Comprehensive Heterocyclic Chemistry III*, Eds. Katrizky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. Elsevier Science Ltd. 2008. Vol. 13, Chapter 13.01. (b) Le Count, D. *Azepines and their fused ring derivatives* in *Comprehensive Heterocyclic Chemistry*, Eds. Katrizky, A. R.; Rees, C. W.; Scriven, E. F. V. Elsevier Science Ltd. 1996. Vol. 9, Chapter 9.01. (c) Smalley, R. K. *Azepines* in *Comprehensive Heterocyclic Chemistry*, Eds. Katrizky, A. R.; Rees, C. W. Pergamon Press, 1984. Vol. 5, Chapter 5.16.
11. For recent examples of synthesis, see: (a) Sakya, S. M.; Flick, A. C.; Coe, J. W.; Gray, D. L.; Liang, S.; Ferri, F.; Van Ben Berg, M.; Pouwer, K. *Tetrahedron Lett.* **2012**, 53, 723. (b) Mehta, V. P.; Modha, S. G.; Ruijter, E.; Van Hecke, K.; Van Meervelt, L.; Pannecouque, C.; Balzarini, J.; Orru, R. V. A.; Van der Eycken, E. *Org. Lett.* **2011**, 76, 2828. (c) Yoshimatsu, M.; Tanaka, M.; Fujimura, Y.; Ito, Y.; Goto, Y.; Kobayashi, Y.; Wasada, H.; Hatae, N.; Tanabe, G.; Muraoka, O. *J. Org. Chem.* **2015**, 80, 9480. (d) Pellegrino, S.; Bonetti, A.; Clerici, F.; Contini, A.; Moretto, A.; Soave, R.; Gelmi, M. L. *J. Org. Chem.* **2015**, 80, 5507. (e) Zhou, M.-B.; Song, R.-J.; Wang, C.-Y.; Li, J.-H. *Angew. Chem. Int. Ed.* **2013**, 52, 10805. (f) Cini, E.; Bifulco, G.; Menchi, G.; Rodriguez, M.; Taddei, M. *Eur. J. Org. Chem.* **2012**, 2133. (g) Liu, H.; Li, X.; Chen, Z.; Hu, W.-X. *J. Org. Chem.* **2012**, 77, 5184.
12. Wang, M.-X. *Chem. Commun.* **2015**, 51, 6039.
13. Gopalaiah K.; Kagan, H. B. *Chem. Rev.* **2011**, 111, 4599.
14. Carbery, D. R. *Org. Biomol. Chem.* **2008**, 6, 3455.

15. (a) Matsubara R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292 and reference cited therein. (b) Bernadat G.; Masson, G. *Synlett* **2014**, 25, 2842 and reference cited therein.
16. (a) Yang, L.; Deng, G.; Wang, D.-X.; Huang, Z.-T.; Zhu, J.-P.; Wang, M.-X. *Org. Lett.* **2007**, *9*, 1387. (b) Yang, L.; Zheng, Q.-Y.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Org. Lett.* **2008**, *10*, 2461.
17. (a) Yang, L.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X.; *J. Am. Chem. Soc.* **2009**, *131*, 10390; (b) Yang, L.; Lei, C.-H.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Org. Lett.* **2010**, *12*, 3918. (c) Tong, S.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *Angew. Chem. Int. Ed.* **2012**, *51*, 4417.
18. Tong, S.; Yang, X.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *Tetrahedron* **2012**, *68*, 6492.
19. (a) Lei, C.-H.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *J. Am. Chem. Soc.* **2013**, *135*, 4708; (b) Lei, C.-H.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *Chem. Eur. J.* **2013**, *19*, 16981. (c) Lei, C.-H.; Zhao, L.; Wang, D.-X.; Zhu J.; Wang, M.-X. *Org. Chem. Front.* **2014**, *1*, 909.
20. (a) Padway, A.; Akiba, M.; Cohen, L. A.; MacDonald, J. G. *J. Org. Chem.* **1983**, *48*, 695. (b) Suen, Y. H.; Horeau, A.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1965**, *5*, 1454. (c) Kobayashi, K.; Matsumoto, K.; Nakamura, D.; Fukamachi, S.; Konishi, H. *Helv. Chim. Acta* **2010**, *93*, 1048.
21. Yang, L.; Tong, S.; Wang, D.-X.; Huang, Z.-T.; Zhu, J.; Wang, M.-X.; *Synlett*, **2011**, 927.
22. Saget, T.; Cramer, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 7865.