JOC The Journal of Organic Chemistry

Article

Redox Property of Enamines

Yao Li, Dehong Wang, Long Zhang, and Sanzhong Luo

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02003 • Publication Date (Web): 23 Aug 2019

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

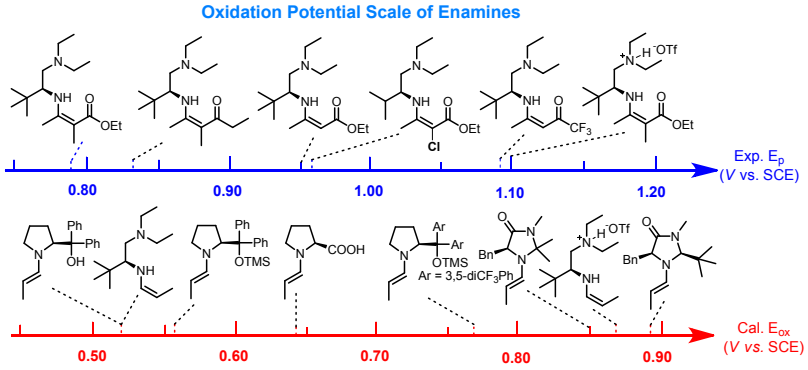
Redox Property of Enamines

Yao Li,[†,§] Dehong Wang,[‡,§] Long Zhang, [†,‡] and Sanzhong Luo*[,†,‡]

[†] *Center of Basic Molecular Science (CBMS), Department of Chemistry, Tsinghua University, Beijing 100084, China*

[‡] *Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China*

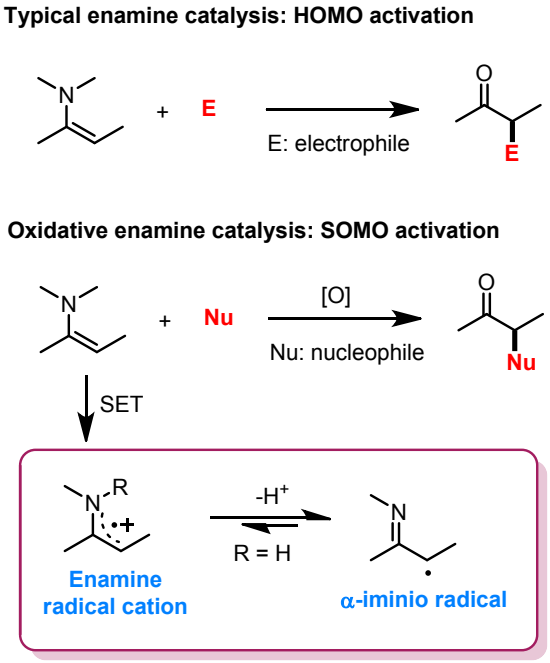
E-mail: luosz@tsinghua.edu.cn



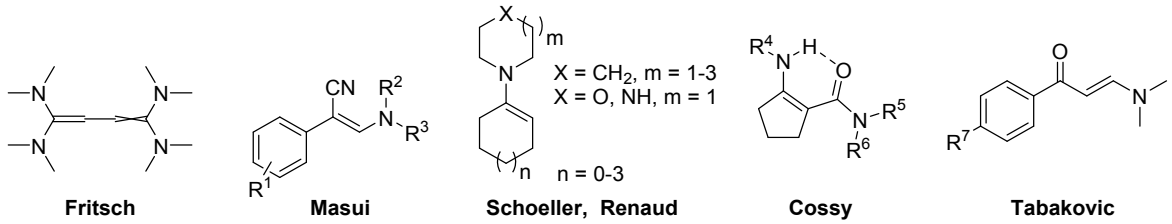
ABSTRACT: Enamines are electron-rich compounds bearing intriguing redox properties. Herein, a series of secondary enamines condensed from primary amine and β-ketocarbonyls were synthesized and their electrochemical oxidation properties were systematically studied by cyclic voltammetry. Furthermore, theoretical calculation of oxidation potentials of enamines, particularly those catalytic intermediates, was also conducted to further broaden the scope investigated. Possible structural factors on oxidation as well as the nature of the resulted radical cation intermediates were revealed and discussed. Correlation of redox potentials with molecular properties such as HUMO energies, NPA charge were explored, and there appears no simple linear correlation. On the other hand, a good correlation with Mayr's nucleophilicity parameter *N* was noted among a range of catalytically relevant enamines. Spin population analysis disclosed that enamine radical cations mainly exhibit carbon-center free radical feature. Taking experimental and computation data together, a comprehensive picture about the redox property of enamines is presented, which would provide guidance in the development of oxidative enamine catalysis and transformations.

INTRODUCTION

Enamines chemistry is a classical yet fundamental tool in carbonyl transformations. In the field of organocatalysis, enamine has been extensively explored as a nucleophilic intermediate, known as HOMO-enhancing enamine activation (Scheme 1).[1] On the other hand, the redox property of enamine, especially their single-electron oxidation *via* chemical or electrochemical or photo process,[2] is also quite intriguing. Such processes lead to open shell enamine intermediates such as enamine radical cation (Scheme 1), also known as SOMO activation, [2s,3] or α-iminio radical from secondary enamine,[2c] which lay the basis for a plethora of oxidative enamine transformations beyond the classical HOMO-activation pathway.[3a,4] Hence, redox properties of enamine are highly desirable in the pursuit of oxidation enamine transformations. Unfortunately, unlike the well-investigated nucleophilicity of enamines,[5] information on the redox properties are only sparsely available and has not been systematically investigated, particularly in the context of enamine catalysis (Scheme 2).[6] Half a century ago, Fritsch *et al.* investigated the electrolytic oxidations of *N*,*N*-dimethylaminoalkenes.[6a,6b] Besides, factors affecting the lifetimes of the cation radicals were also discussed.[6b] In 1984, Masui *et al.* explored the electrochemical properties of 2-cyano-2-phenylvinylamines and reported the anodic dimerization of these enamines.[6c] A few years later, Schoeller *et al.* and Renaud *et al.*[6d,6e] studied the redox properties of enamines derived from cyclic ketones and cyclic amines and irreversible oxidation processes were found. In 1995, Cossy *et al.*[6f] investigated the redox properties of several types of amidoenamines bearing unsaturated groups, i.e. allyl, propargyl, in an attempt to achieve electrochemical cyclization. In the same year, Tabaković disclosed anodic oxidation of enaminones and the dimerization of corresponding radical cations.[6g]



Scheme 1. Aminocatalytic mode.



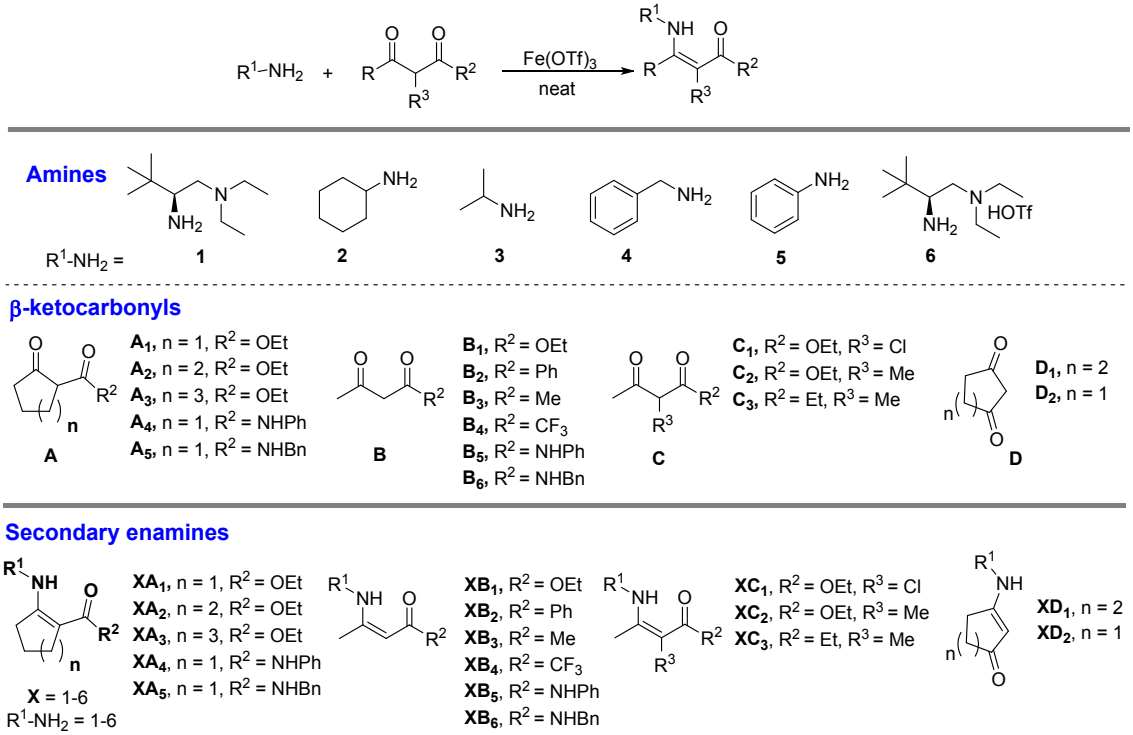
Scheme 2. Previous systematical studies of enamines' redox properties.

Herein, we wish to present our systematic studies on the redox property of enamines using both experimental and computational approaches. Stabilized enamines such as secondary enamines derived from β-ketocarbonyls were synthesized and analyzed by cyclic voltammetry (CV). The obtained experimental data were then served as bench mark on which DFT calculations on those catalytically interesting enamine intermediates could be formulated. Taken together, we aim to provide a coherent picture of one-electron oxidation chemistry of enamines. We also discussed the possible structural effect on redox properties as well as the structure of the resulted enamine radical cation intermediates.

EXPERIMENTAL METHODS

1. **Synthesis and characterization of enamines**

All secondary enamines were synthesized from corresponding primary amines (**1-6**) with β-ketocarbonyls (**A-D**) using the protocol described in literature (Scheme 3).[7]



Scheme 3. Secondary enamines investigated in electrochemical study.

2. **Cyclic voltammetric details**

We evaluated the redox properties of the enamines by cyclic voltammetry. Our setup comprised of an undivided cell, a glassy carbon working electrode (3mm diameter), a platinum wire counter electrode, and a saturated Ag/AgCl reference electrode. Each cyclic voltammogram (CV) was measured at a sweep rate of 100 mV/s. Measurements were carried out with 0.01 M enamines in dry CH_3CN using Bu_4NPF_6 (0.10 M) as the supporting electrolyte.

CALCULATION METHODS

Theoretical approaches have been found to give a precise prediction of electrochemistry properties in solution,[8] we also explored similar methods to predict the oxidation potentials of

enamines by using Gaussian09.[9] After benchmarked several conventional functions,[10] we found that Truhlar's M06-2X hybrid functional provided accurate predictions of oxidation potentials.[11] Geometry optimizations and frequency computations were performed at the M06-2X/6-311G(d,p) level of theory, in conjunction with the IEF-PCM model to account for the solvation effects of acetonitrile.[12] The calculated oxidation potentials were scaled to saturated calomel electrode (SCE).[13] Free energies include unscaled zero-point vibrational energies. Low frequencies (<100 cm^{-1}) were corrected in the vibrational component of the entropy using a free rotor approximation according to the method of Grimme *et al.*, since entropy associated with these loose vibrational modes was the most prone to computational error.[14] The quasi-harmonic oscillator corrections were obtained using the GoodVibes.[15] The Natural Bond Orbital (NBO) analysis was conducted at the same level of geometry optimization using NBO package build-in Gaussian 09.[16]

RESULTS AND DISCUSSION

1. Cyclic voltammetric investigations of stabilized secondary enamines

Irreversible oxidation peaks were observed in the CVs of each enamine species, and typical examples (**$1A_1$-$6A_1$**) are shown in Figure 1. The voltammograms of all investigated enamines show well defined anodic current maxima, but no corresponding cathodic wave on the reverse scan, even at rate up to 50 V/s (the second oxidation peak of **$1A_1$** may be attributed to the oxidation of tertiary amine moiety). The irreversibility is likely ascribed to the highly unstable cation radical generated by one-electron oxidation on anode. Due to the irreversibility electro-oxidation, the anodic peak potentials were selected for comparison. The reported oxidation peak potentials are converted from Ag/AgCl as reference electrode into saturated calomel electrode (SCE).[17] A summary of the oxidation peak potentials (E_p) is presented in Table 1 and an E_p scale-map of these enamines is given in Figure 2. The peak potentials of the enamines investigated vary greatly from the lowest 0.68 V to the highest 1.87 V which highly depend on the structures of the enamines as indicated in Table 1.

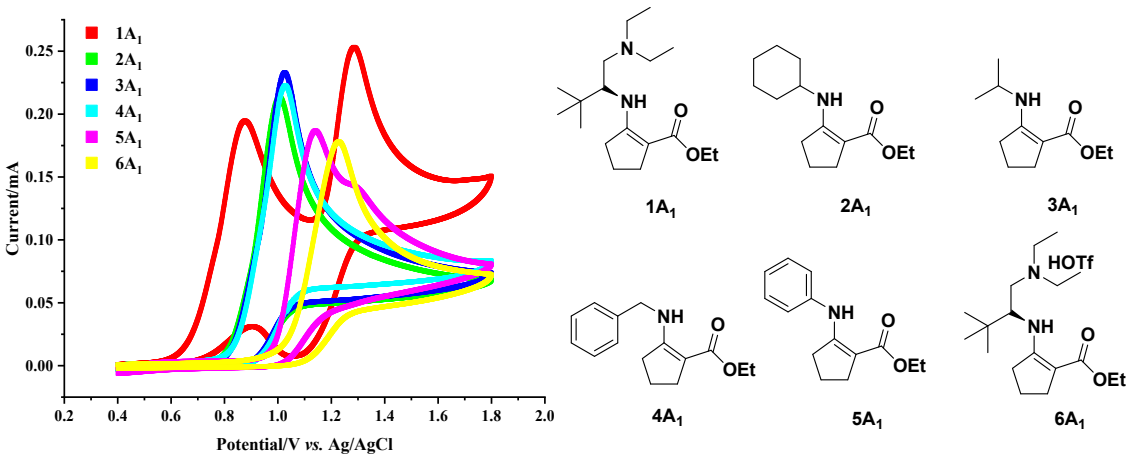
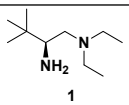
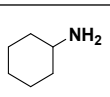
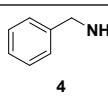
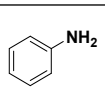
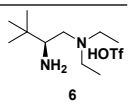
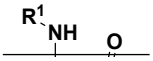
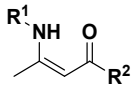
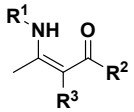
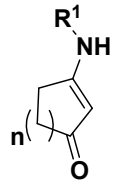


Figure 1. CVs of representative secondary enamines **1A$_1$-6A$_1$** (0.01 M in acetonitrile-0.1 M Bu_4NPF_6, sweep rate *v* 100 mV/s, 3 mm diameter glassy carbon electrode).

As can be seen in Table 1, both the primary amines and the carbonyls showed significant influences on the oxidative potential of enamines. With cyclic β-ketone amide **A$_5$**, the corresponding E_p increased from 0.68 V to 0.98 V when varying the primary amine from **1** to **6** (Table 1, **1A$_5$-6A$_5$**). The enamine derived from other carbonyls showed similar trends (Table 1). Generally, the enamine based on aliphatic amines give smaller E_p values than those with aromatic amines. The primary tertiary diamine derived enamines always give the lowest oxidative peak potentials (Table 1, **1A-1C**), due to the intramolecular electron-donating effect of the vicinal tertiary amines, which could significantly stabilize the *in-situ* formed radical cations after one-electron oxidation. Instead, the protonation of this tertiary amine moiety could completely destroy this stabilization effect and the corresponding E_p raised to a much higher level (Table 1, **6A-6C**).

Table 1. Oxidation peak potentials of secondary enamines in acetonitrile (E_p/V *vs.* SCE)

	R^1-NH$_2$ =	 1	 2	 3	 4	 5	 6						
	n = 1, R^2 = OEt	**1A$_1$**	0.85	**2A$_1$**	0.97	**3A$_1$**	0.99	**4A$_1$**	1.00	**5A$_1$**	1.11	**6A$_1$**	1.20

	n = 2, R^2 = OEt	**1A$_2$**	0.80	**2A$_2$**	0.95	**3A$_2$**	0.90	**4A$_2$**	1.02	**5A$_2$**	1.06	**6A$_2$**	1.15
	n = 3, R^2 = OEt	**1A$_3$**	0.79	**2A$_3$**	0.86	**3A$_3$**	0.86	**4A$_3$**	0.93	**5A$_3$**	1.02	**6A$_3$**	1.10
	n = 1, R^2 = NHPh	**1A$_4$**	0.73	**2A$_4$**	0.80	**3A$_4$**	0.81	**4A$_4$**	0.86	**5A$_4$**	0.89	**6A$_4$**	1.08
	n = 1, R^2 = NHBn	**1A$_5$**	0.68	**2A$_5$**	0.76	**3A$_5$**	0.77	**4A$_5$**	0.83	**5A$_5$**	0.86	**6A$_5$**	0.98
	R^2 = OEt	**1B$_1$**	0.95	**2B$_1$**	1.16	**3B$_1$**	1.17	**4B$_1$**	1.19	**5B$_1$**	1.34	**6B$_1$**	1.41
	R^2 = Ph	**1B$_2$**	0.97	**2B$_2$**	1.28	**3B$_2$**	1.30	**4B$_2$**	1.16	**5B$_2$**	1.34	**6B$_2$**	1.46
	R^2 = Me	**1B$_3$**	0.95	**2B$_3$**	1.21	**3B$_3$**	1.24	**4B$_3$**	1.27	**5B$_3$**	1.40	**6B$_3$**	1.43
	R^2 = CF_3	**1B$_4$**	1.09	**2B$_4$**	1.64	**3B$_4$**	1.63	**4B$_4$**	1.68	**5B$_4$**	1.72	**6B$_4$**	1.87
	R^2 = NHPh	/[a]		**2B$_5$**	0.92	**3B$_5$**	1.00	**4B$_5$**	0.97	/		/	
	R^2 = NHBn	/		**2B$_6$**	0.92	/		**4B$_6$**	0.96	/		/	
	R^2 = OEt, R^3 = Cl	**1C$_1$**	0.96	**2C$_1$**	1.11	**3C$_1$**	1.13	**4C$_1$**	1.16	**5C$_1$**	1.22	**6C$_1$**	1.37
	R^2 = OEt, R^3 = Me	**1C$_2$**	0.79	**2C$_2$**	0.86	**3C$_2$**	0.87	**4C$_2$**	0.93	/		**6C$_2$**	1.10
	R^2 = Et, R^3 = Me	**1C$_3$**	0.83	**2C$_3$**	0.87	**3C$_3$**	0.88	**4C$_3$**	0.93	/		**6C$_3$**	1.10
	n = 2	/		**2D$_1$**	1.20	**3D$_1$**	1.22	**4D$_1$**	1.31	**5D$_1$**	1.35	/	
	n = 1	/		**2D$_2$**	1.33	/		**4D$_2$**	1.46	**5D$_2$**	1.42	/	

[a] "/"indicates the corresponding enamines are not available.

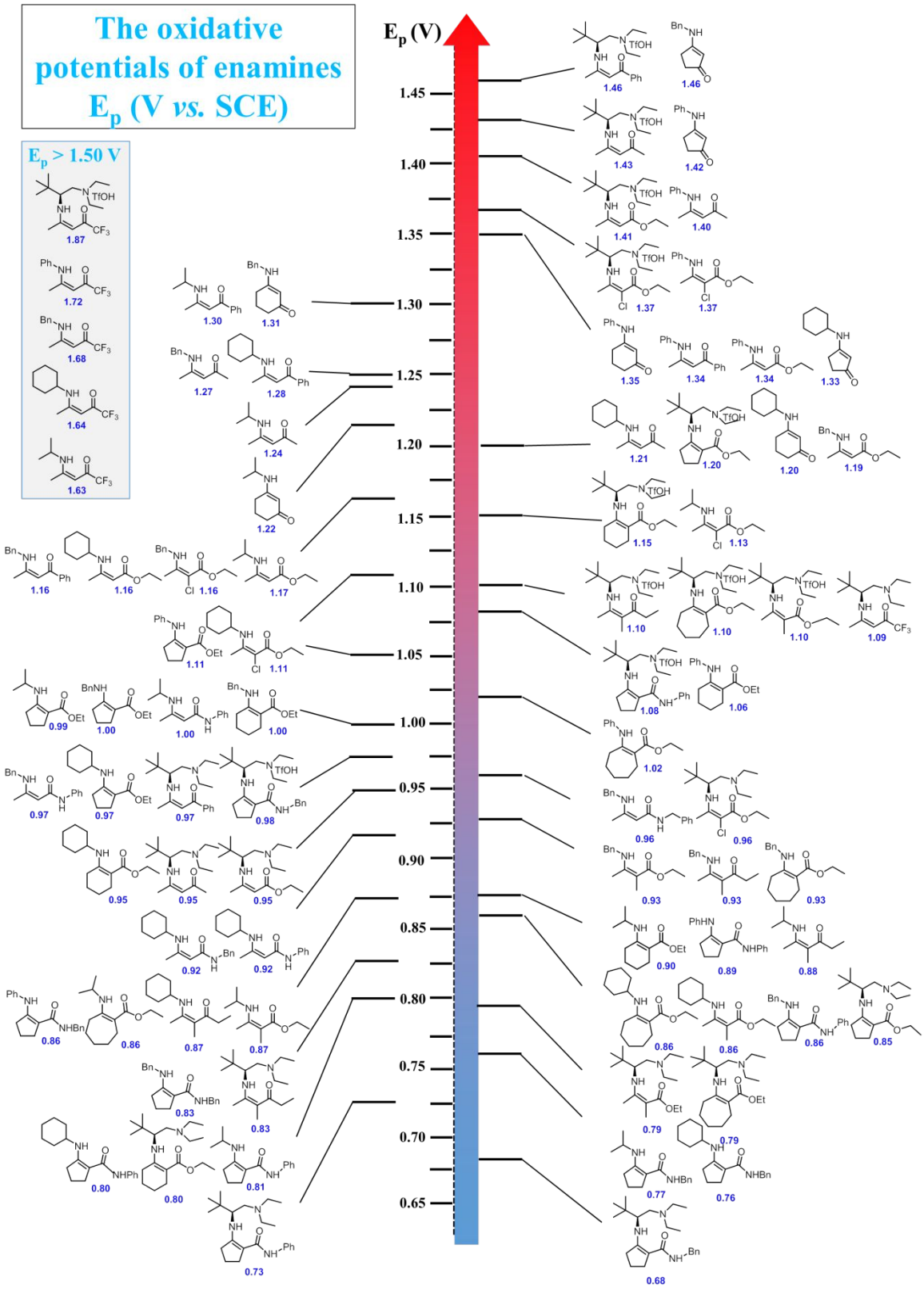


Figure 2. Oxidation peak potentials scale of secondary enamines in acetonitrile.

The structure of the carbonyl moiety also contributed significantly to the oxidative potentials. Generally, the enamines derived from α-alkyl substituted β-ketocarbonyls showed lower E_p values than the unsubstituted ones (Table 1, **1C$_2$-6C$_2$** *vs.* **1B$_1$-6B$_1$**, Figure 3, A). The α-chloro substituted enamines also exhibited minor yet noticeable more negative E_p in comparison with those unsubstituted ones (Table 1, **2C$_1$-6C$_1$** *vs.* **2B$_1$-6B$_1$**), which highlights the contribution of α-substituents on stabilizing the corresponding enamine radical cations. The enamines with β-ketoesters give higher E_p values than that with β-ketoamides (Table 1, **1A$_1$-6A$_1$** *vs.* **1A$_4$-6A$_4$, 1A$_5$-6A$_5$**; **2B$_5$-2B$_6$** *vs.* **2B$_1$** and **4B$_5$-4B$_6$** *vs.* 4**B$_1$**). Further increasing the electron-withdrawing nature of the carbonyls caused significant increase in E_ps (Table 1, **1B$_2$-6B$_2$**, **1B$_4$-6B$_4$** and Figure 3, B).

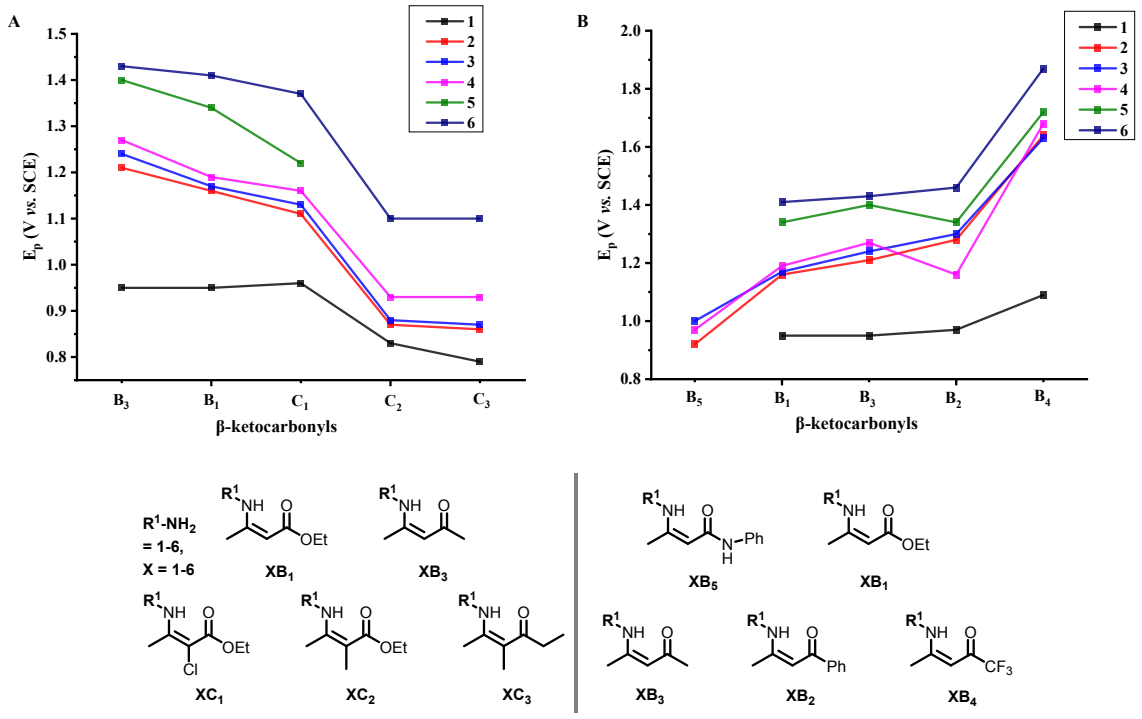


Figure 3. The influence of substituents of β-ketocarbonyls on the oxidation peak potentials.

We also observed a ring size effect of the ketone esters on the E_p of enamines. As can be seen in Figure 3, the oxidation peak potentials are mainly in the order **XA$_3$** < **XA$_2$** < **XA$_1$** (**X = 1-6**), which means larger rings generally possess lower E_p values, with only one observed exception (Figure 4, **4A$_2$** *vs.* **4A$_1$**).

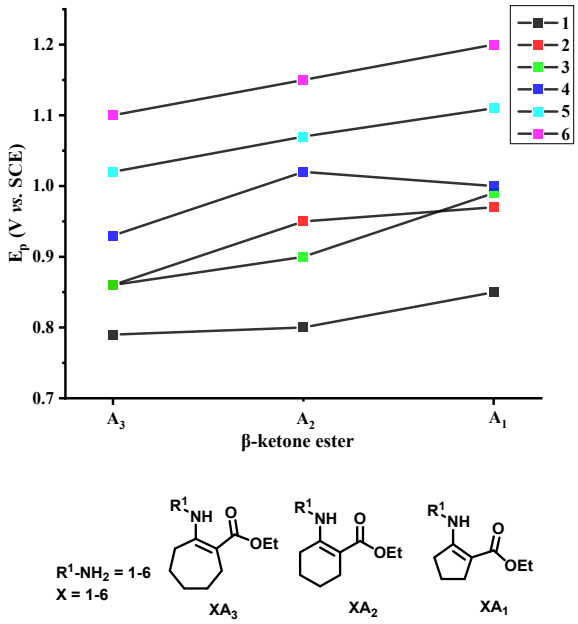


Figure 4. The influence of ring size on the oxidation peak potentials.

2. DFT Calculations studies

Besides the redox potentials of secondary enamines examined above, the E_p evaluation of other types of enamines are also urgently needed, especially for those enamines derived from simple aldehydes and ketones. However, it was very difficult to experimentally determine the reliable oxidation potentials of these enamines as they are generally unstable and cannot be isolated in the context of aminocatalysis. Since theory calculation have been found to give a precise prediction of electrochemistry properties in solution,[8] we carried out quantum chemical calculations to further broaden the enamine scope investigated. We first calculated oxidation potentials of simple enamines (deriving from pyrrolidine, morpholine and cyclohexanone) and benchmarked with the experimental data (Table S1).[6d] On this basis, the most accurate calculation method was reached and a very good linear correlation was found between the experimental oxidation peak potentials (of the known enamines our synthetic enamines deriving from β-ketocarbonyls) and calculated oxidation potentials (Figure 5 and Table S2).[17] This correlation indicated that the method is applicable for both secondary

enamines and tertiary enamines. With this method in hand, we started to investigate other types of enamines.

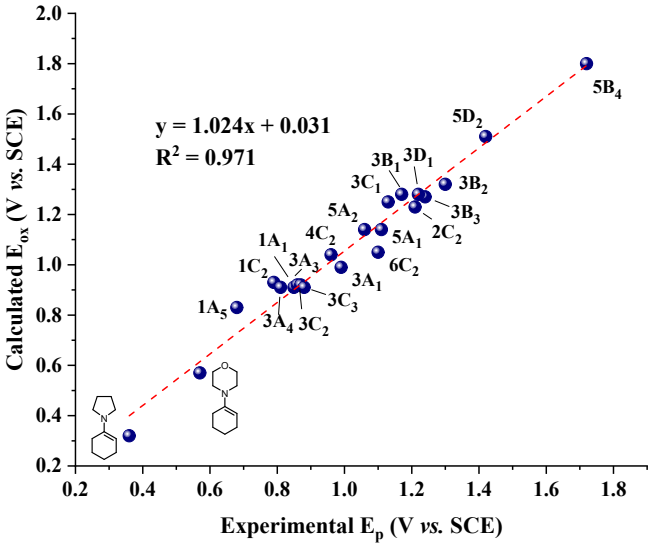


Figure 5. Correlation of experimental E_p and calculated E_{ox}.

The enamines deriving from various amines **(1-17)** and aldehydes or ketones **(E-J)** were evaluated (Figure 6). Besides those primary amines mentioned above, prevalent chiral aminocatalysts (**7-8, 11-17**) as well as the model cyclic amines (**9** and **10**) were also selected for evaluation (Figure 6).

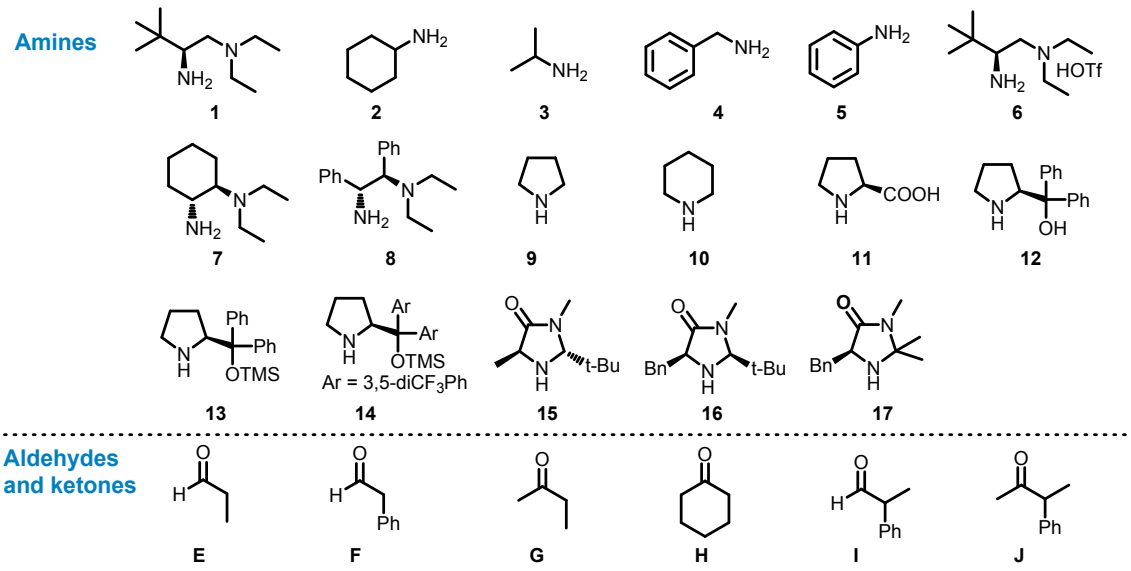


Figure 6. Enamines precursors investigated in DFT calculations.

2.1 **Enamine geometry**

Unlike secondary enamines of β-ketocarbonyls, which are stabilized by intramolecular H-bonding and have relatively rigid conformation, most enamines are conformationally flexible. To obtain a more reliable prediction of oxidation potentials, we first explored the *Z/E* configurations of enamines. It has been reported in the literatures that tertiary enamines from simple aldehydes (**E** and **F**) favor *E*-configured double bonds,[18a-e] while for secondary enamines (e.g. those from **E** and **G**), Z-configured double bond are generally favored.[18f-i] Our calculations for enamines deriving simple aldehydes and ketones (**E-G**) are in good agreement with previous reports[18] and the relative free energies between *Z*-enamines and *E*-enamines are briefly illustrated in Figure 7 (for details, see Table S3). It should be noted that *Z*-type enamines are more favored with chiral primary amine catalyst such as primary-tertiary diamines **1**, **6**, **7** and **8**. For 2-phenylacetaldehyde, both primary amine and secondary amine significantly prefer *E*-enamine geometry, likely a result of phenyl conjugation effect. For α-branched aldehyde and ketones (**G** and **I**), no obvious trend was observed but primary amine catalysts tend to form *E*-enamine with **I** and **J**.

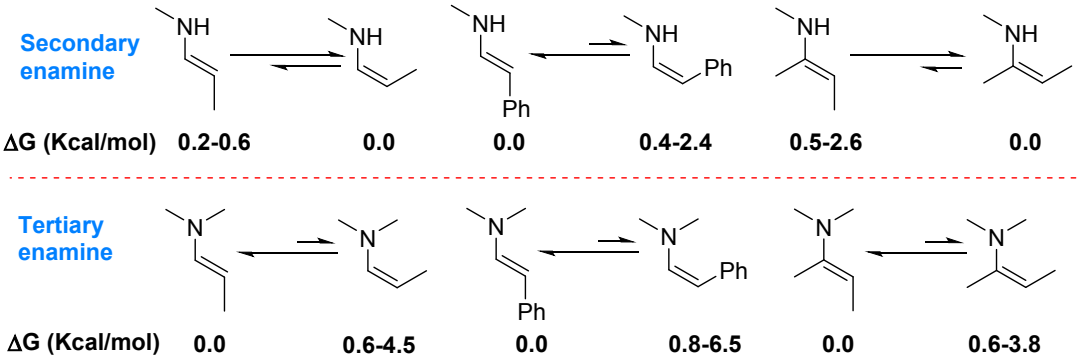


Figure 7. Calculated relative free energies of *Z/E*-enamines.

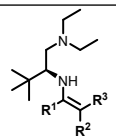
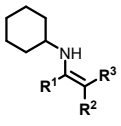
2.2 Calculated oxidation potentials of enamine intermediates

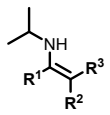
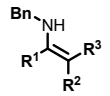
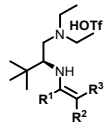
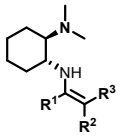
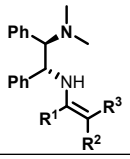
We have evaluated oxidation potentials of both *Z*-configured and *E*-configured enamines deriving from **E**, **F, G**, **I** and **J**. Compared with enamines in stable configurations, the oxidation potentials of enamines in unstable configurations can be higher or lower. The oxidation potentials of enamines in their relative stable configurations (Figure 7) were shown in Table 2 (for oxidation potentials of enamines in less stable configurations, see Table S3).

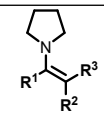
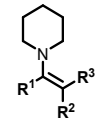
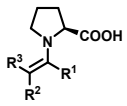
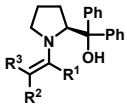
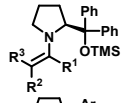
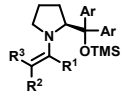
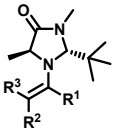
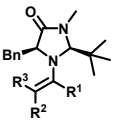
As shown in Table 2, the calculated oxidation potentials of the enamines vary greatly from the lowest 0.22 V to the highest 0.90 V. The oxidation potentials of enamines deriving from simple aldehydes or ketones are significantly lower than those derived from β-ketocarbonyls. The electronic effect of the carbonyl group showed a significant effect on the oxidative potentials of these enamines. For example, the oxidation potentials with butanone **G** are generally lower than those derived from its aldehyde analogue propionaldehyde **E** (Table 2, **1G-17G** *vs.* **1E-17E**), and enamines derived from α-branch aldehydes are easier to be oxidized than those with simple aldehydes (**E-F**) (Table 2, **1I-17I** *vs.* **1E-17E** and **1F-17F**).

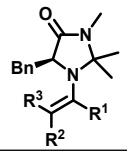
The nature of amine also showed significant influence on the oxidative potentials. The enamines based on aliphatic primary amines (**2-3**) were of lower oxidation potentials than those with aromatic primary amines (**4-5**). And the enamines deriving from primary tertiary diamines **1** or **7** demonstrated relative lower oxidation potentials comparing with those deriving from other primary amines. The protonation of tertiary amine moiety caused significant increase in the oxidation potentials (*ca.* 200-300 mv). For enamines with conventional chiral secondary amines, MacMillan catalysts **(15-17)** show higher oxidation potentials than proline-derived catalysts (**11-14**). Enamines derived from prolinol **12** are usually easier to be oxidized than those derived from prolinol silyl ether **13**. Enamines derived from the electron-deficient prolinol silyl ether **14** showed much higher oxidation potentials, which were even higher than proline **11**, probably due to the negative hyperconjugation effect. [5c,19-20] This result indicated that remote electronic effects may also have an impact on redox properties of enamines.

Table 2. Calculated oxidation potentials of enamines in acetonitrile (E_{ox}/V *vs.* SCE).[a]

Secondary enamines	R^1= H, R^2 = H, R^3 = Me	R^1= H, R^2 = Ph, R^3 = H	R^1= Me, R^2 = H, R^3 = Me	R^1, R^2 = -$(CH_2)_4$-, R^3 = H	R^1= H, R^2 = Ph, R^3 = Me	R^1= Me, R^2 = Ph, R^3 = Me
	**1E** 0.52	**1F** 0.51	**1G** 0.48	**1H** 0.39	**1I** 0.41[b]	**1J** 0.35[c]
	**2E** 0.62[b]	**2F** 0.64	**2G** 0.52	**2H** 0.47	**2I** 0.54[b]	**2J** 0.45[b]

	**3E**	0.60	**3F**	0.54	**3G**	0.44	**3H**	0.40	**3I**	0.47[b]	**3J**	0.36[c]
	**4E**	0.75	**4F**	0.73	**4G**	0.65	**4H**	0.70	**4I**	0.63[b]	**4J**	0.55[c]
	**5E**	0.84[b]	**5F**	0.82	**5G**	0.80	**5H**	0.78	**5I**	0.76[b]	**5J**	0.68[c]
	**6E**	0.87	**6F**	0.76	**6G**	0.79	**6H**	0.74	**6I**	0.73[b]	**6J**	0.71[b]
	**7E**	0.59	**7F**	0.53	**7G**	0.46	**7H**	0.39	**7I**	0.44[b]	**7J**	0.36[b]
	**8E**	0.72	**8F**	0.60	**8G**	0.54	**8H**	0.47	**8I**	0.57[b]	**8J**	0.42[b]

Tertiary enamines	R^1= H, R^2 = Me, R^3 = H	R^1= H, R^2 = Ph, R^3 = H	R^1= Me, R^2 = Me, R^3 = H	R^1, R^2 = -$(CH_2)_4$-, R^3 = H	R^1= H, R^2 = Ph, R^3 = Me	R^1= Me, R^2 = Ph, R^3 = Me
	**9E** 0.45	**9F** 0.51	**9G** 0.31	**9H** 0.32	**9I** 0.42[c]	**9J** 0.22[c]
	**10E** 0.53	**10F** 0.53	**10G** 0.49	**10H** 0.49	**10I** 0.40[c]	**10J** 0.36[c]
	**11E** 0.64	**11F** 0.64	**11G** 0.55	**11H** 0.52	**11I** 0.61[c]	**11J** 0.49[c]
	**12E** 0.52	**12F** 0.55	**12G** 0.42	**12H** 0.43	**12I** 0.48[b]	**12J** 0.47[b]
	**13E** 0.56	**13F** 0.60	**13G** 0.36	**13H** 0.45	**13I** 0.55[c]	**13J** 0.38[b]
	**14E** 0.77	**14F** 0.77	**14G** 0.61	**14H** 0.62	**14I** 0.68[b]	**14J** 0.57[b]
	**15E** 0.84	**15F** 0.82	**15G** 0.80	**15H** 0.81	**15I** 0.78[b]	**15J** 0.82[b]
	**16E** 0.89	**16F** 0.84	**16G** 0.89	**16H** 0.90	**16I** 0.82[c]	**16J** 0.87[c]

	**17E**	0.85	**17F**	0.79	**17G**	0.75	**17H**	0.75	**17I**	0.75[c]	**17J**	0.87[b]

[a] Unless otherwise noted, the reported oxidation potentials correspond to enamines' configurations drawn in column. [b] *E*-configured enamine. [c] *Z*-configured enamine.

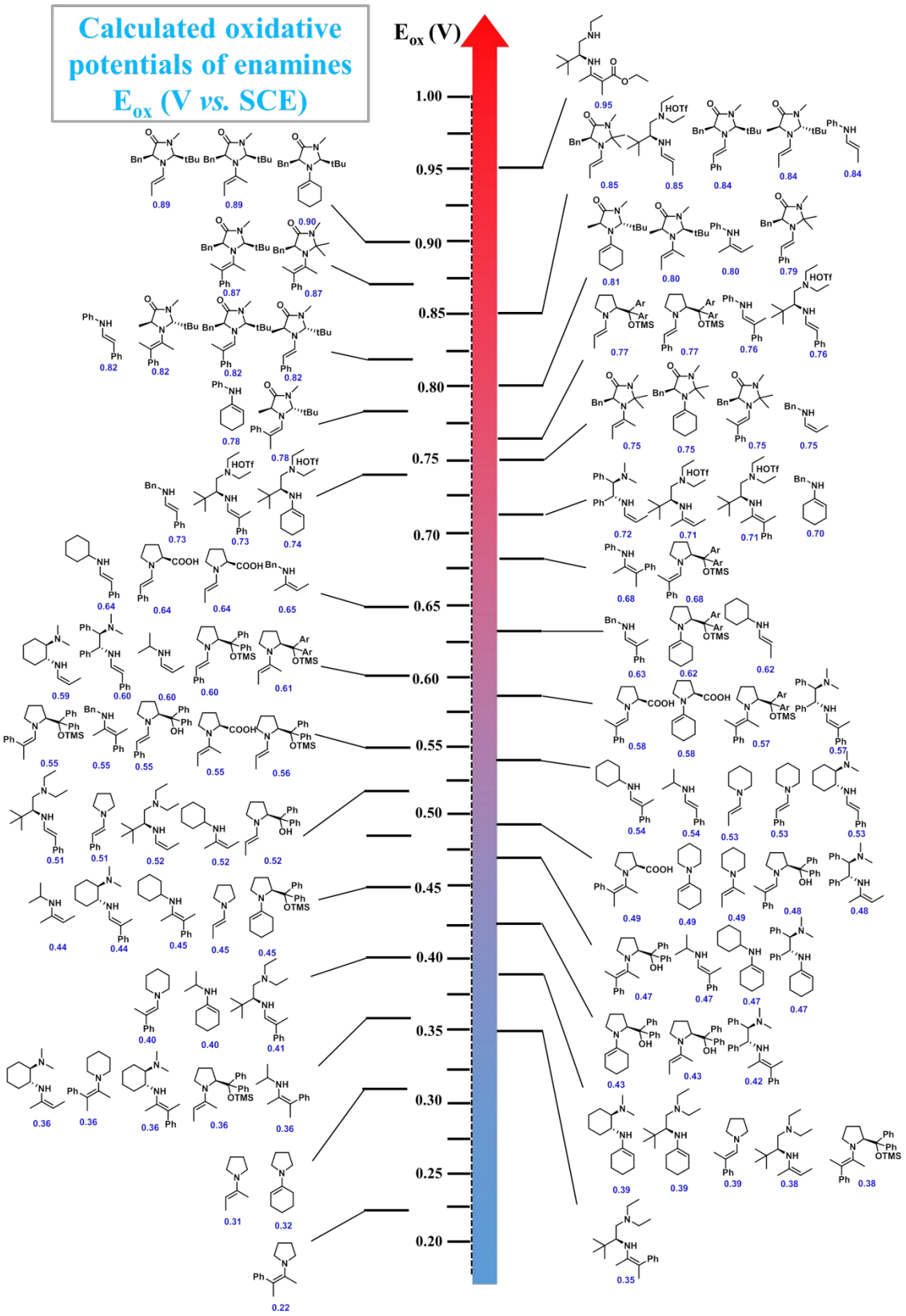


Figure 8. Calculated oxidation potentials scale of enamines in acetonitrile.

To obtain a better comparison, we constructed a calculated oxidation potentials scale for those catalytic enamines in Figure 8.

2.3 Correlation of calculated oxidation potentials with molecular properties

Previous work showed that there were certain connections between Hammett substituent constants, ionization potentials, electron affinities, HOMO and LUMO energies and the redox potentials.[21] Therefore, the relationship between the molecular properties and oxidation potentials were then explored. Initially, the relationships between HOMO energies and oxidation potentials of enamines deriving from propionaldehyde (**E**) and various amines (**1-17**) were investigated. Unfortunately, poor correlation was found (Figure 9, A, labeled in red square, $R^2 = 0.22$). Changing enamines to **1I-17I** gave a moderate correlation (Figure 9, A, labeled as black triangle, $R^2 = 0.49$). Enamines derived from the same amine (**1**) and different carbonyl compounds (**E-J**) were also examined and no overall correlation with their HOMO energies could be found. When limited to only ketones (**G**, **H** and **J**), a clear trend was noted (Figure 9, B, labeled in red triangle, $R^2 = 0.97$).

We next tried to reduce variations in structures and simple enamines deriving from pyrrolidine and cyclic ketones were investigated. A good linear correlation ($R^2 = 0.87$) was found between the HOMO energies of enamines and oxidation potentials (Figure 10, A). Further expanding the scope of to include acyclic ketones (**9P** and **9G**, as red dots) also gave good correlation ($R^2 = 0.89$). It seems that enamines with small rings display higher oxidation potentials than those with larger ring (Figure 10), which is consistent with our experimental data of cyclic ketoesters.

Since the oxidation of enamines mainly involve the loss of electron from nitrogen atom, we suspected that the oxidation potentials may have certain connections with the electronic density of nitrogen atom of enamines. To verify the hypothesis, the Natural Population Analysis (NPA) charges of enamines were evaluated.[16] A good linear correlation was found between the calculated oxidation potentials and NPA charge of nitrogen atom for enamines (**9H** and **9K-9O**) (Figure 10, B). The result was slightly better than using HOMO energies for this series of enamines ($R^2 = 0.93$). But expanding the scopes to include acyclic ketones (**9P** and **9G**, as red stars) resulted in a worse correlation (R^2 =

0.87).

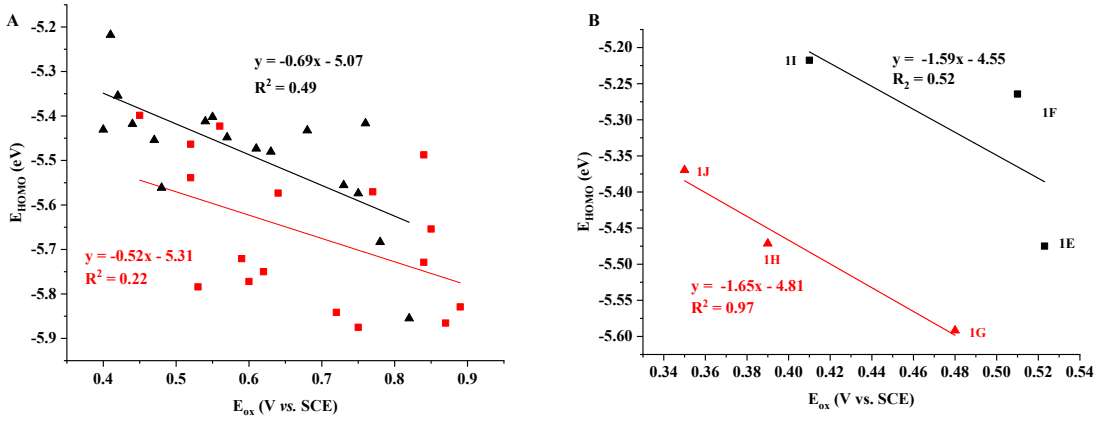
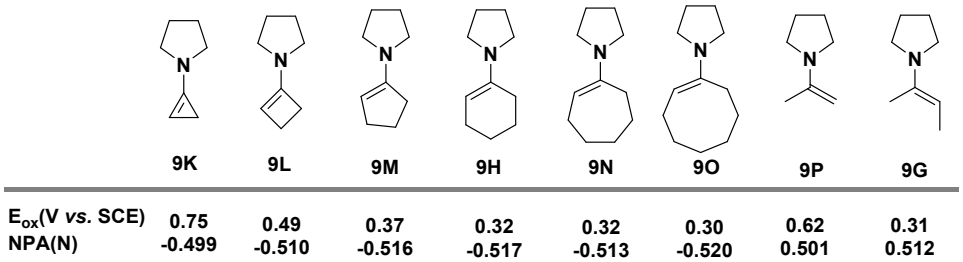


Figure 9. A) Correlation between HOMO energies and calculated oxidation potentials of enamines **1E-17E** and **1I-17I**. B) Correlation between HOMO energies and calculated oxidation potentials of enamines (**1E-1J**)



	9K	9L	9M	9H	9N	9O	9P	9G
E_{ox}(V *vs.* SCE)	0.75	0.49	0.37	0.32	0.32	0.30	0.62	0.31
NPA(N)	-0.499	-0.510	-0.516	-0.517	-0.513	-0.520	0.501	0.512

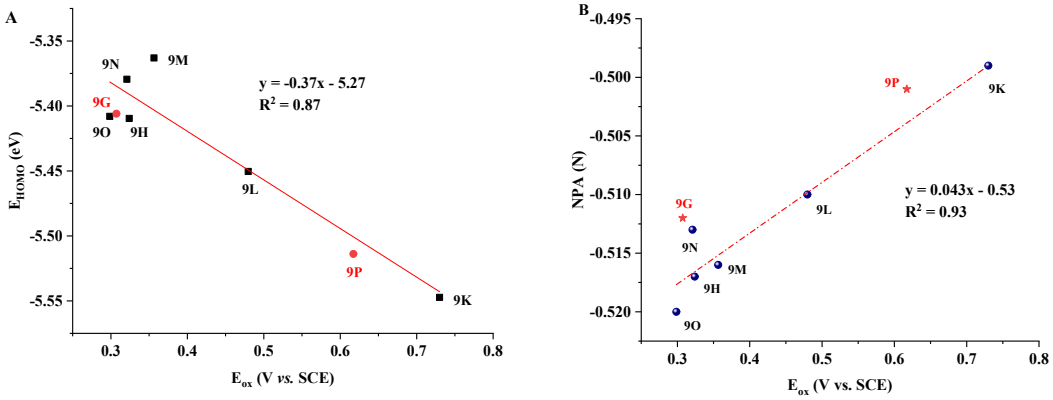


Figure 10. Correlation between calculated oxidation potentials and HOMO energies/NPA charges of nitrogen atom for pyrrolidine derived enamines.

2.4 Spin density and spin density distributions of enamine radical cation

To further gain insight into the nature of radical cations of enamine, an active single electron-oxidation intermediate, spin population analysis was conducted. Two spin population methods, Mulliken spin population and Becke spin population, were used and the results are similar.[25] The analysis of enamine radical cation **1C$_2$** and **9E** showed that the single electron is mainly located at the α-C-center and N-center free radical is less populated (Figure 11), which is in consistence with the previous calculated results of radical cation of enamine reported by Houk and MacMillan.[26] The spin analysis of enamines derived from other amines and carbonyls also gave the same results. Although the term 'enamine radical cation' has been widely used, our calculation indicated that it is mainly a carbon radical plus an iminium cation, which is also consistent with the previous electron spin resonance (ESR) studies reported by Fritsch *et al.* In this study, it was shown that unpaired electrons tend to polarize away from the dimethylamino groups in monocationic radicals.[6b]

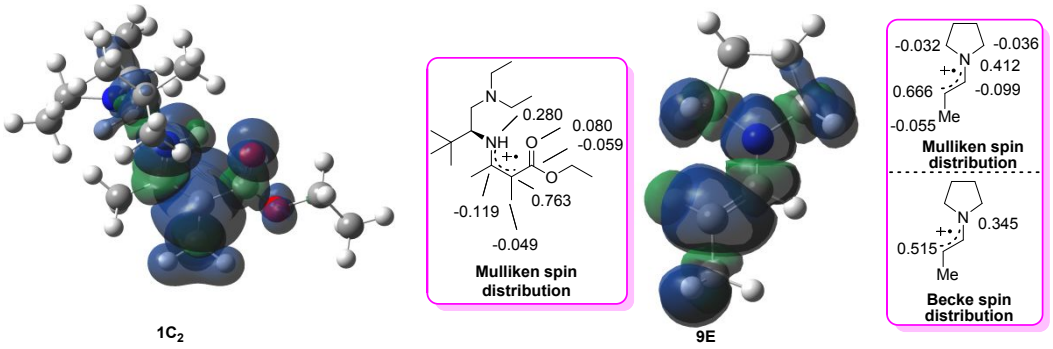


Figure 11. Spin density plot and spin density distributions of enamine radical cation **1C$_2$** and **9E**.

Recently, we have reported the oxidative enamine catalysis *via* α-imino radical by the primary -tertiary diamine catalyst.[2c] This strategy was further utilized to achieve oxidative enamine functionalization.[2e-f] Due to the strong acidity of radical cations in **1C$_2$**,[27] the intramolecular proton transfer from enamine nitrogen to tertiary amine nitrogen is significantly favored (Figure 12) leading to the formation of α-imino radical. In this equilibration, spin population is slightly shifted toward α-carbon in α-imino radical. Similar equilibration toward α-imino radical has also been observed with aldehyde enamine radical cation **1I** in both its *E*- and *Z*- isomer. Thus, for single-electron oxidation of secondary enamines, especially for those deriving from primary-tertiary diamines, α-iminio radical

may be the actual reactive intermediate.[2c,2e-f]

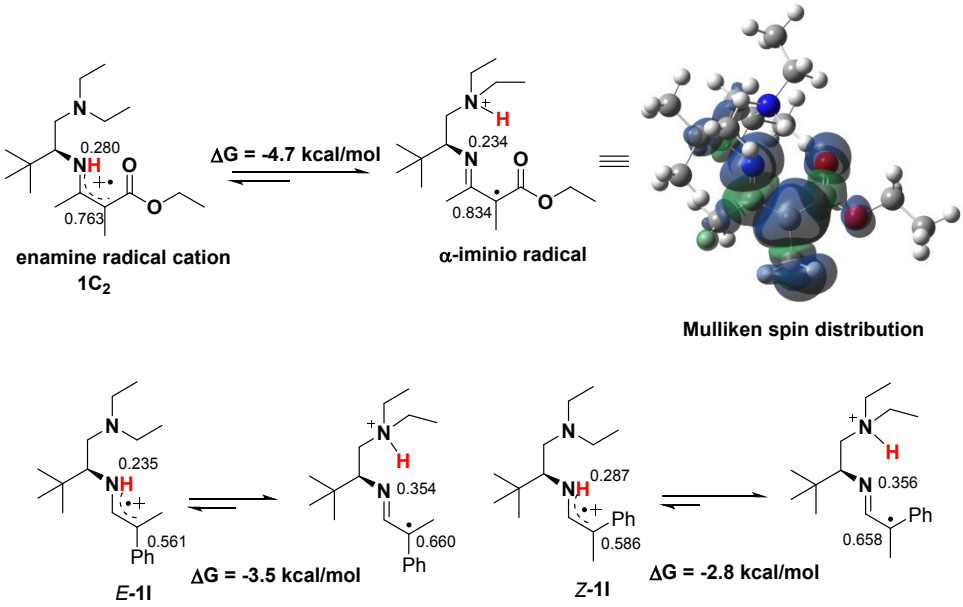


Figure 12. Free energy differences and spin density distributions of enamine radical cation **1C**/**1I** and their related α-iminio radicals.

2.5 **Application in organocatalysis**

Our experimental and calculated oxidation potentials for enamines could be used to explain the previous results in enamines oxidation transformations. For example, Macmillan's catalysts derived enamines have relative higher oxidation potentials (E_{ox}(**15E**) = 0.84 V, E_{ox}(**16E**) = 0.89 V *vs*. SCE in MeCN). That's why strong oxidant, such as ceric ammonium nitrate (CAN) (E_p [Ce(IV)/(III)] = 0.68 V *vs*. Fc^+/Fc in MeCN[28a]) and [Fe(phen)$_3$] • (PF_6)$_3$ ($E_{1/2}$ [Fe(III)/(II)] = 1.10 V *vs*. SCE in MeCN[28b]), were used in SOMO catalysis.[3] For direct β-alkylation of aldehydes reported by Macmillan,[29] photocatalyst Ir(ppy)$_3$ ($E_{1/2}$ [Ir^*(III)/(II)] = 0.31 V *vs.* SCE in MeCN[30a]) gave very low yield (7%), while Ru(bpy)$_3$Cl$_2$ ($E_{1/2}$ [Ru^*(III)/(II)] = 0.77 V *vs.* SCE in MeCN[30b]) and Ir(ppy)$_2$(dtbbpy)PF_6 ($E_{1/2}$ [Ir^*(III)/(II)] = 0.66 V *vs.* SCE in MeCN[30c]) gave moderate yield (50% and 52%, respectively) under the similar condition. These results can be rationalized by the calculated oxidation potentials of enamine **9E** (E_{ox}(**9E**) = 0.45 V *vs*. SCE in MeCN), which indicted that oxidation of enamine similar to **9E** by excited-state Ir(ppy)$_3$ should be unfavored and oxidation of enamine by excited-state

$Ru(bpy)_3Cl_2$ and excited-state $Ir(ppy)_2(dtbbpy)PF_6$ should be favored. Besides application in explaining previous results, we hope that enamines oxidation potentials will be helpful for mechanism consideration in enamines oxidation transformations.

Mayr and coworkers recently developed a nucleophilicity (*N*) scale for a series of enamine intermediates. [22] Previously, it has also been shown that oxidation potential could serve as a measure of the reactivity of nucleophiles. [23] In this study, we evaluated the correlation of calculated oxidation potentials with experimental nucleophilicity of enamines. It was found that the calculated oxidation potentials of enamines are in good consistence (Figure 13 A, $R^2 = 0.87$) with Mayr's nucleophilicity parameters *N* in acetonitrile.[5] The oxidation potentials also exhibited a good correlation with log k_2 (Figure 13 B, $R^2 = 0.86$), which are calculated by the Mayr-Patz equation (log k_2 (20 ºC)= $s_N(N + E)$) for the reactions of enamines with $(Me_2N\text{-}C_6H_4)_2CH^+$ (E = -7.02).[24] The above correlations, which cover more than eleven orders of magnitude, indicated that the oxidation potentials of enamines would also provide a guide for their nucleophilic reactivities.

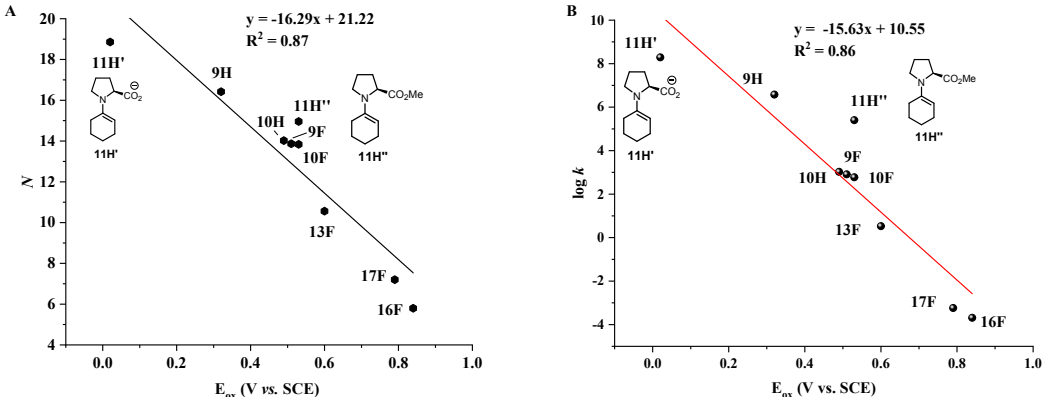


Figure 13. Correlation of calculated oxidation potentials with nucleophilicity parameters *N* and logarithm of rate constants (log k_2).

CONCLUSIONS

In summary, a broad series of secondary enamines, including those prepared from primary amines and β-ketoesters, β-ketoamides or 1,3-diketones, were synthesized and their redox properties were systematically investigated by cyclic voltammetry. All of the synthetic enamines showed

irreversible oxidation process. The electronic nature as well as the ring size of enamines showed significant effects on E_p values. Accurate DFT calculations were then performed to predict the oxidation potentials of a series of unstable and catalytically relevant enamines. The calculations provided effective supplement to the experimental oxidation potentials. Spin population analysis indicated that the resulted enamine radical cations mainly display C-center free radical property. Our calculations indicated that α-iminio radical may be the actual reactive intermediate in single-electron oxidation of primary-tertiary diamines derived secondary enamines. These electrochemical studies and theoretical calculations would provide guidance in exploring oxidative enamine transformations and aminocatalysis.

EXPERIMENTAL SECTION

General information. ^{1}H NMR and ^{13}C NMR spectra were measured on Bruker spectrometers (at 400 and 500 MHz for ^{1}H NMR, 101 and 126 MHz for ^{13}C NMR). Tetramethylsilane (TMS) served as the internal standard for ^{1}H NMR, and $CDCl_3$/DMSO-d_6 served as the internal standard for ^{13}C NMR. The following abbreviations were used to express the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. IR spectra were recorded on a Thermo Fischer Nicolet 6700 FT-IR spectrometer and are reported in terms of frequency absorption (cm^{-1}). HRMS was obtained using electrospray ionization (ESI) mass spectrometer, and the mass analyzer of the HRMS was orbitrap. Cyclic voltammograms were collected with a Shanghai Chenhua CH1600D potentiostat. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates.

Materials. Chiral primary amine **1**[31] and β-ketocarbonyls $\mathbf{A_3}$,[32a] $\mathbf{A_4}$,[32b] $\mathbf{A_5}$,[32b] $\mathbf{C_3}$[32c] were prepared according to the literature.

General procedure for synthesis of secondary enamines. All secondary enamines were synthesized according to procedure reported in the literature.[7] $Fe(OTf)_3$ (0.1 mmol, 50.2 mg) was added to a mixture of primary amines (10 mmol) and β-ketocarbonyls compounds (11 mmol) in a 25 mL round-bottom flask and the mixtures were allowed to stir at ambient temperature. The completion

of the reaction was monitored by TLC. The pure enamines were obtained by passing them directly through alkaline alumina column chromatography using hexanes/ethyl acetate. Some Enamines **2X**-**5X** (X = A-D) are known compounds that have been reported in literature.[33-38]

Ethyl (S)-2-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)cyclopent-1-ene-1-carboxylate ***(1A$_1$)***. This compound was prepared according to the general procedure using (*S*)-N^1,N^1-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and ethyl 2-oxocyclopentane-1-carboxylate (11 mmol, 1.72 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 62% yield (1.92 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 4.23 – 4.06 (m, 2H), 3.06 – 2.85 (m, 1H), 2.77 – 2.58 (m, 2H), 2.56 – 2.32 (m, 7H), 2.27 (dd, *J* = 13.7, 9.7 Hz, 1H), 1.79 (dd, *J* = 14.3, 6.9 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.00 – 0.88 (m, 15H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.7, 166.4, 91.0, 63.8, 58.2, 55.7, 48.0, 34.6, 32.7, 29.1, 26.7, 21.2, 14.8, 12.3. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{35}N_2O_2^+$ 311.2693, found 311.2694. IR (KBr, cm^{-1}): 2965, 2868, 1654, 1602, 1465, 1264, 1096.

Ethyl (S)-2-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)cyclohex-1-ene-1-carboxylate ***(1A$_2$)***.[33a] This compound was prepared according to the general procedure using (*S*)-N^1,N^1-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and ethyl 2-oxocyclohexane-1-carboxylate (11 mmol, 1.87 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 69% yield (2.23 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, *J* = 10.7 Hz, 1H), 4.18 – 4.00 (m, 2H), 3.31 – 3.03 (m, 1H), 2.62 (dd, *J* = 13.6, 2.2 Hz, 1H), 2.59 – 2.44 (m, 3H), 2.39 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.32 – 2.24 (m, 3H), 2.24 – 2.11 (m, 1H), 1.67 – 1.48 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.02 – 0.89 (m, 15H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.0, 160.9, 87.6, 60.2, 58.3, 56.4, 48.0, 34.7, 26.9, 26.8, 24.1, 23.1, 22.6, 14.7, 12.4. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{19}H_{37}N_2O_2^+$ 325.2850, found 325.2849. IR (KBr, cm^{-1}): 2967, 2933, 2868, 1644, 1600, 1455, 1234, 1095, 1065.

Ethyl (S)-2-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)cyclohept-1-ene-1-carboxylate ***(1A$_3$)***. This compound was prepared according to the general procedure using (*S*)-N^1,N^1-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and ethyl

2-oxocycloheptane-1-carboxylate (11 mmol, 2.02 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 72% yield (2.44 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, *J* = 10.1 Hz, 1H), 4.14 – 4.05 (m, 2H), 3.21 (td, *J* = 10.2, 2.1 Hz, 1H), 2.64 (dd, *J* = 13.7, 2.1 Hz, 1H), 2.57 – 2.36 (m, 8H), 2.29 (dd, *J* = 13.7, 9.4 Hz, 1H), 1.79 – 1.60 (m, 4H), 1.61 – 1.49 (m, 1H), 1.49 – 1.40 (m, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.99 – 0.90 (m, 15H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.7, 168.6, 92.5, 61.8, 58.4, 56.0, 48.0, 34.6, 31.7, 28.8, 28.8, 26.9, 26.0, 25.5, 14.8, 12.1. HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ calcd for $C_{20}H_{39}N_2O_2^+$ 339.3006, found 339.3005. IR (KBr, cm^{-1}): 2968, 2923, 2848, 1635, 1600, 1467, 1254, 1204, 1140, 1097, 1050.

(S)-2-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)-N-phenylcyclopent-1-ene-1-carboxamide ***(1A$_4$)***. This compound was prepared according to the general procedure using (*S*)-*N*^{1},*N*^{1}-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and 2-oxo-*N*-phenylcyclopentane-1-carboxamide (11 mmol, 2.24 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as colorless oil in 65% yield (2.33 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 11.0 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.37 – 7.19 (m, 2H), 7.07 – 6.84 (m, 1H), 6.56 (s, 1H), 3.01 – 2.84 (m, 1H), 2.76 (dt, *J* = 15.8, 7.7 Hz, 1H), 2.67 – 2.56 (m, 3H), 2.48 (dddt, *J* = 19.9, 14.1, 12.9, 7.1 Hz, 5H), 2.31 (dd, *J* = 13.7, 9.6 Hz, 1H), 1.96 – 1.85 (m, 2H), 1.01 – 0.89 (m, 15H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.0, 165.2, 139.3, 128.8, 122.6, 119.7, 92.1, 64.1, 55.9, 48.0, 34.6, 32.6, 29.5, 26.8, 20.9, 12.3. HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ calcd for $C_{22}H_{36}N_3O^+$ 358.2853, found 358.2855. IR (KBr, cm^{-1}): 3336, 2964, 2868, 1636, 1594, 1517, 1310, 1236.

(S)-N-benzyl-2-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)cyclopent-1-ene-1-carboxamide ***(1A$_5$)***. This compound was prepared according to the general procedure using (*S*)-*N*^{1},*N*^{1}-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and *N*-benzyl-2-oxocyclopentane-1-carboxamide (11 mmol, 2.39 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as colorless oil in 62% yield (2.32 g). Colorless oil, 2.32 g, 62% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 11.1 Hz, 1H), 7.34 – 7.28 (m, 4H), 7.25 – 7.21 (m, 1H), 5.05 (t, *J* = 5.4 Hz, 1H), 4.51 (ddd, *J* = 84.6, 14.9, 5.8 Hz,

2H), 2.99 – 2.85 (m, 1H), 2.72 (dt, *J* = 15.8, 7.8 Hz, 1H), 2.63 (dd, *J* = 13.7, 2.2 Hz, 1H), 2.56 – 2.39 (m, 7H), 2.30 (dd, *J* = 13.7, 9.6 Hz, 1H), 1.91 – 1.80 (m, 2H), 1.01 – 0.91 (m, 15H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 168.9, 163.6, 139.9, 128.5, 127.6, 127.0, 91.8, 63.7, 56.0, 48.0, 42.8, 34.7, 32.4, 29.3, 26.8, 20.9, 12.3. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{23}H_{38}N_3O^+$ 372.3009, found 372.3007. IR (KBr, cm^{-1}): 3342, 2964, 2868, 1628, 1589, 1517, 1270, 698.

*Ethyl (S,Z)-3-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)but-2-enoate (**1B$_1$**).* This compound was prepared according to the general procedure using (*S*)-N^1,N^1-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and ethyl 3-oxobutanoate (11 mmol, 1.43 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 69% yield (1.96 g). ^1H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, *J* = 8.9 Hz, 1H), 4.37 (s, 1H), 4.14 – 4.01 (m, 2H), 3.19 – 3.03 (m, 1H), 2.61 (dd, *J* = 13.7, 2.1 Hz, 1H), 2.52 (tt, *J* = 14.4, 7.2 Hz, 2H), 2.40 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.30 (dd, *J* = 13.7, 9.8 Hz, 1H), 1.94 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.00 – 0.93 (m, 15H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 170.8, 163.1, 80.9, 61.8, 58.0, 55.8, 48.1, 34.5, 26.7, 20.1, 14.7, 12.3. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{16}H_{33}N_2O_2^+$ 285.2537, found 285.2539. IR (KBr, cm^{-1}): 2967, 2871, 1647, 1609, 1263, 1173, 1107, 784.

*(S,Z)-3-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)-1-phenylbut-2-en-1-one (**1B$_2$**).* This compound was prepared according to the general procedure using (*S*)-N^1,N^1-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and 1-phenylbutane-1,3-dione (11 mmol, 1.78 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 67% yield (2.12 g). ^1H NMR (500 MHz, $CDCl_3$) δ 11.87 (d, *J* = 10.3 Hz, 1H), 8.03 – 7.76 (m, 2H), 7.48 – 7.32 (m, 3H), 5.64 (s, 1H), 3.29 (td, *J* = 10.5, 2.0 Hz, 1H), 2.70 (dd, *J* = 13.8, 2.0 Hz, 1H), 2.55 (tt, *J* = 14.3, 7.2 Hz, 2H), 2.43 (qd, *J* = 7.0, 5.1 Hz, 3H), 2.14 (s, 3H), 1.04 (s, 9H), 0.98 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 186.8, 166.0, 140.8, 130.1, 128.1, 126.9, 91.6, 62.9, 55.9, 48.2, 34.3, 26.8, 20.1, 12.3. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{20}H_{32}N_2O^+$ 316.2515, found 316.2517. IR (KBr, cm^{-1}): 2966, 1599, 1556, 1326, 1297, 1086, 1064, 731.

*(S,Z)-4-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)pent-3-en-2-one (**1B$_3$**).* This compound was prepared according to the general procedure using (*S*)-*N*^{1},*N*^{1}-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and pentane-2,4-dione (11 mmol, 1.10 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 61% yield (1.55 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.28 (d, *J* = 9.7 Hz, 1H), 4.90 (s, 1H), 3.17 (td, *J* = 10.5, 2.0 Hz, 1H), 2.61 (dd, *J* = 13.8, 2.1 Hz, 1H), 2.51 (tt, *J* = 14.4, 7.2 Hz, 2H), 2.45 – 2.28 (m, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 0.99 – 0.91 (m, 15H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.8, 164.4, 94.5, 62.4, 55.8, 48.1, 34.2, 28.6, 26.6, 19.5, 12.3. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{15}H_{31}N_2O^+$ 255.2431, found 255.2435. IR (KBr, cm^{-1}): 2966, 2873, 1608, 1582, 1310, 1191, 733.

*(S,Z)-4-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)-1,1,1-trifluoropent-3-en-2-one (**1B$_4$**).* This compound was prepared according to the general procedure using (*S*)-*N*^{1},*N*^{1}-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and 1,1,1-trifluoropentane-2,4-dione (11 mmol, 1.69 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 70% yield (2.16 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.56 (s, 1H), 5.29 (s, 1H), 3.31 (td, *J* = 10.4, 2.0 Hz, 1H), 2.67 (dd, *J* = 13.9, 2.0 Hz, 1H), 2.60 – 2.49 (m, 2H), 2.39 (ddd, *J* = 13.6, 9.7, 6.7 Hz, 3H), 2.14 (s, 3H), 1.01 (s, 9H), 0.95 (t, *J* = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.6 (q, *J* = 32.6 Hz), 170.4, 118.0 (q, *J* = 288.0 Hz), 89.1, 63.8, 55.5, 48.2, 33.9, 26.5, 19.9, 12.2. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{15}H_{28}F_3N_2O^+$ 309.2148, found 309.2145. IR (KBr, cm^{-1}): 2969, 2873, 1596, 1262, 1181, 1137, 1086, 1100.

*Ethyl (S,E)-2-chloro-3-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)but-2-enoate (**1C$_1$**).* This compound was prepared according to the general procedure using (*S*)-*N*^{1},*N*^{1}-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and ethyl 2-chloro-3-oxobutanoate (11 mmol, 1.81 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 58% yield (1.85 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (d, *J* = 10.2 Hz, 1H), 4.29 – 4.11 (m, 2H), 3.20 (td, *J* = 10.3, 2.1 Hz, 1H), 2.68 –

2.58 (m, 1H), 2.55 – 2.46 (m, 2H), 2.38 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.29 (dd, *J* = 13.7, 9.9 Hz, 1H), 2.21 (s, 3H), 1.31 (td, *J* = 7.1, 3.9 Hz, 3H), 0.99 – 0.91 (m, 15H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 167.7, 161.5, 90.8, 63.0, 59.9, 55.8, 48.0, 34.4, 26.7, 17.3, 14.6, 12.2. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{16}H_{32}ClN_2O_2^+$ 319.2147, found 319.2149. IR (KBr, cm^{-1}): 2968, 2871, 1636, 1597, 1448, 1258, 1074, 770.

*Ethyl (S,Z)-3-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)-2-methylbut-2-enoate (**1C$_2$**).*[33b] This compound was prepared according to the general procedure using (*S*)-*N*^{1},*N*^{1}-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and ethyl 2-methyl-3-oxobutanoate (11 mmol, 1.59 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 66% yield (1.97 g). ^1H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, *J* = 10.4 Hz, 1H), 4.16 – 4.01 (m, 2H), 3.19 (td, *J* = 10.6, 2.2 Hz, 1H), 2.62 (dd, *J* = 13.6, 2.2 Hz, 1H), 2.50 (tt, *J* = 14.3, 7.2 Hz, 2H), 2.45 – 2.35 (m, 2H), 2.29 (dd, *J* = 13.6, 9.6 Hz, 1H), 1.98 (s, 3H), 1.80 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.98 – 0.92 (m, 15H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 171.2, 161.1, 84.8, 61.7, 58.4, 56.1, 48.0, 34.7, 26.8, 16.0, 14.7, 12.9, 12.2. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{35}N_2O_2^+$ 299.2693, found 299.2691. IR (KBr, cm^{-1}): 2968, 2871, 1640, 1602, 1465, 1256, 1099, 782.

*(S,Z)-5-((1-(diethylamino)-3,3-dimethylbutan-2-yl)amino)-4-methylhex-4-en-3-one (**1C$_3$**).* This compound was prepared according to the general procedure using (*S*)-*N*^{1},*N*^{1}-diethyl-3,3-dimethylbutane-1,2-diamine (10 mmol, 1.72 g) and 3-methylhexane-2,4-dione (11 mmol, 1.41 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 63% yield (1.78 g). ^1H NMR (500 MHz, $CDCl_3$) δ 12.47 (d, *J* = 9.8 Hz, 1H), 3.27 (td, *J* = 10.1, 2.2 Hz, 1H), 2.63 (dd, *J* = 13.7, 2.2 Hz, 1H), 2.53 – 2.43 (m, 2H), 2.43 – 2.34 (m, 2H), 2.33 – 2.25 (m, 1H), 2.00 (s, 3H), 1.85 (s, 3H), 1.10 (t, *J* = 7.4 Hz, 3H), 0.96 (s, 9H), 0.92 (t, *J* = 7.1 Hz, 6H) (enamine). 3.20 (td, *J* = 9.9, 2.2 Hz, 1H), 2.12 (s, 3H), 1.85 (s, 3H), 0.97 (s, 9H) (imine). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 196.6, 163.4, 96.4, 62.4, 56.2, 48.0, 34.4, 32.9, 26.8, 15.8, 14.4, 12.2, 9.7 (enamine).$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 193.6, 168.6, 95.9, 62.5, 56.6, 48.1, 34.2, 28.3, 21.6, 14.3, 12.1, 11.7 (imine). HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for

$C_{17}H_{35}N_2O^+$ 283.2744, found 283.2742. IR (KBr, cm^{-1}): 2967, 2871, 1596, 1466, 1233, 1083, 830.

*Ethyl 2-(cyclohexylamino)cyclopent-1-ene-1-carboxylate (**2A$_1$**).*[34a,b] This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and ethyl 2-oxocyclopentane-1-carboxylate (11 mmol, 1.72 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 72% yield (1.71 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.17 (qd, *J* = 9.5, 4.7 Hz, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.53 – 2.47 (m, 2H), 1.91 – 1.79 (m, 4H), 1.79 – 1.69 (m, 2H), 1.63 – 1.51 (m, 1H), 1.38 – 1.16 (m, 8H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.5, 163.9, 92.0, 58.3, 53.3, 34.6, 31.9, 28.9, 25.4, 24.8, 21.1, 14.8.

*Ethyl 2-(cyclohexylamino)cyclohex-1-ene-1-carboxylate (**2A$_2$**).*[34c] This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and ethyl 2-oxocyclohexane-1-carboxylate (11 mmol, 1.87 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 70% yield (1.76 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, *J* = 8.5 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.44 – 3.18 (m, 1H), 2.34 (t, *J* = 6.3 Hz, 2H), 2.27 (t, *J* = 6.2 Hz, 2H), 1.85 (d, *J* = 10.6 Hz, 2H), 1.80 – 1.70 (m, 2H), 1.65 (dt, *J* = 12.2, 6.3 Hz, 2H), 1.56 (ddd, *J* = 11.3, 7.8, 4.0 Hz, 3H), 1.37 – 1.17 (m, 8H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 158.7, 88.9, 58.6, 50.3, 34.6, 26.9, 26.3, 25.6, 24.9, 23.9, 22.8, 22.4, 14.7.

*Ethyl 2-(cyclohexylamino)cyclohept-1-ene-1-carboxylate (**2A$_3$**).* This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and ethyl 2-oxocycloheptane-1-carboxylate (11 mmol, 2.03 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 68% yield (1.80 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, *J* = 6.8 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.34 (dd, *J* = 7.9, 3.9 Hz, 1H), 2.48 (dd, *J* = 10.7, 5.0 Hz, 4H), 1.86 (dd, *J* = 8.8, 4.4 Hz, 2H), 1.72 (ddd, *J* = 14.8, 11.8, 7.5 Hz, 4H), 1.58 (dt, *J* = 10.2, 5.0 Hz, 3H), 1.51 – 1.39 (m, 2H), 1.37 – 1.14 (m, 8H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.7, 166.8, 93.4, 58.5, 51.5, 34.8, 31.9, 28.8, 28.5, 25.8, 25.5, 24.7, 14.8. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{16}H_{28}NO_2^+$ 266.2115, found 266.2113. IR (KBr, cm^{-1}): 2978, 2926, 2851, 1639, 1593, 1451, 1251, 1203, 1097, 1048, 786.

*2-(cyclohexylamino)-N-phenylcyclopent-1-ene-1-carboxamide (**2A$_4$**).* This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and 2-oxo-N-phenylcyclopentane-1-carboxamide (11 mmol, 2.24 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as white solid in 55% yield (1.56 g). Mp 126-127 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.36 – 7.20 (m, 2H), 7.01 (td, *J* = 7.4, 1.1 Hz, 1H), 6.59 (s, 1H), 3.24 – 3.02 (m, 1H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 1.92 (ddd, *J* = 24.1, 11.9, 4.9 Hz, 4H), 1.76 (d, *J* = 9.3 Hz, 2H), 1.58 (d, *J* = 9.9 Hz, 1H), 1.35 – 1.11 (m, 5H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.0, 163.0, 139.0, 128.8, 122.9, 119.0, 92.9, 53.5, 34.8, 31.8, 29.3, 25.4, 25.0, 20.9. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{25}N_2O^+$ 285.1961, found 285.1957. IR (KBr, cm^{-1}): 2928, 2851, 1637, 1593, 1516, 1429, 1309, 1235, 1074, 749.

*N-benzyl-2-(cyclohexylamino)cyclopent-1-ene-1-carboxamide (**2A$_5$**).* This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and *N*-benzyl-2-oxocyclopentane-1-carboxamide (11 mmol, 2.39 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as yellowish solid in 61% yield (1.82 g). Mp 105-108 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 9.0 Hz, 1H), 7.36 – 7.28 (m, 4H), 7.28 – 7.21 (m, 1H), 5.12 (s, 1H), 4.50 (d, *J* = 5.8 Hz, 2H), 3.13 (qd, *J* = 9.5, 4.7 Hz, 1H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.47 – 2.35 (m, 2H), 1.87 (dt, *J* = 14.5, 7.4 Hz, 4H), 1.75 (dd, *J* = 8.7, 4.1 Hz, 2H), 1.61 – 1.49 (m, 1H), 1.37 – 1.11 (m, 5H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.7, 161.2, 139.7, 128.6, 127.7, 127.1, 92.7, 53.2, 42.8, 34.8, 31.7, 29.1, 25.5, 24.9, 20.9. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{19}H_{27}N_2O^+$ 299.2118, found 299.2112. IR (KBr, cm^{-1}): 2928, 2851, 1629, 1588, 1513, 1451, 1282, 1243, 698.

*Ethyl (Z)-3-(cyclohexylamino)but-2-enoate (**2B$_1$**).*[34d] This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and ethyl 3-oxobutanoate (11 mmol, 1.43 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish oil in 82% yield (1.73 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 6.7 Hz, 1H), 4.36 (s, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.38 – 3.17 (m, 1H), 1.91 (s, 3H), 1.84 (dd, J = 9.8, 3.5 Hz,

2H), 1.73 (dd, J = 9.5, 2.9 Hz, 2H), 1.61 – 1.49 (m, 1H), 1.33 – 1.13 (m, 8H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.6, 160.8, 81.7, 58.1, 51.4, 34.3, 25.4, 24.7, 19.2, 14.7.

(Z)-3-(cyclohexylamino)-1-phenylbut-2-en-1-one (***2B₂***).[34e] This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and 1-phenylbutane-1,3-dione (11 mmol, 1.78 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish oil in 65% yield (1.58 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.58 (d, *J* = 6.0 Hz, 1H), 7.99 – 7.63 (m, 2H), 7.47 – 7.31 (m, 3H), 5.62 (s, 1H), 3.57 – 3.30 (m, 1H), 2.09 (s, 3H), 1.92 (dd, *J* = 9.2, 4.0 Hz, 2H), 1.86 – 1.77 (m, 2H), 1.64 – 1.56 (m, 1H), 1.48 – 1.13 (m, 5H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 187.3, 163.6, 140.6, 130.3, 128.1, 126.8, 91.8, 51.9, 33.8, 25.3, 24.5, 19.2. IR (KBr, cm^{-1}): 2930, 2853, 1600, 1550, 1322, 1292, 734.

(Z)-4-(cyclohexylamino)pent-3-en-2-one (***2B₃***).[34f] This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and pentane-2,4-dione (11 mmol, 1.10 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish oil in 83% yield (1.50 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (s, 1H), 4.91 (s, 1H), 3.36 (ddd, *J* = 13.1, 8.8, 4.0 Hz, 1H), 1.99 (s, 3H), 1.94 (s, 3H), 1.91 – 1.82 (m, 2H), 1.77 (dd, *J* = 12.6, 7.9 Hz, 2H), 1.62 – 1.50 (m, 1H), 1.42 – 1.21 (m, 5H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 194.4, 161.8, 94.9, 51.5, 33.8, 28.7, 25.3, 24.4, 18.6.

(Z)-4-(cyclohexylamino)-1,1,1-trifluoropent-3-en-2-one (***2B₄***).[34g] This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and 1,1,1-trifluoropentane-2,4-dione (11 mmol, 1.69 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish solid in 73% yield (1.72 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.31 (s, 1H), 5.28 (s, 1H), 3.51 (qd, *J* = 9.2, 4.5 Hz, 1H), 2.10 (s, 3H), 1.95 – 1.87 (m, 2H), 1.84 – 1.76 (m, 2H), 1.66 – 1.57 (m, 1H), 1.48 – 1.20 (m, 5H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 175.0 (q, *J* = 32.4 Hz), 168.0, 117.8 (q, *J* = 288.0 Hz), 89.2, 52.6, 33.2, 25.1, 24.1, 19.0. IR (KBr, cm^{-1}): 2936, 2859, 1616, 1589, 1252, 1184, 1135, 726.

(Z)-3-(cyclohexylamino)-N-phenylbut-2-enamide (***2B₅***). This compound was prepared according

to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and 3-oxo-*N*-phenylbutanamide (11 mmol, 1.95 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as yellowish solid in 70% yield (1.81 g). Mp 136-139 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, J = 8.5 Hz, 1H), 7.42 (dd, J = 8.5, 0.9 Hz, 2H), 7.34 – 7.20 (m, 2H), 7.13 – 6.88 (m, 1H), 6.58 (s, 1H), 4.35 (s, 1H), 3.28 (dd, J = 9.1, 4.0 Hz, 1H), 1.94 (s, 3H), 1.88 (dt, J = 8.6, 4.4 Hz, 2H), 1.76 (d, J = 4.0 Hz, 2H), 1.59 (d, J = 12.3 Hz, 1H), 1.38 – 1.14 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.1, 159.4, 139.3, 128.8, 122.7, 119.8, 84.3, 77.4, 77.0, 76.7, 51.6, 34.5, 25.4, 24.9, 19.4. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{16}H_{23}N_2O^+$ 259.1805, found 259.1800. IR (KBr, cm^{-1}): 2929, 2851, 1593, 1531, 1498, 1434, 1311, 751.

*(Z)-N-benzyl-3-(cyclohexylamino)but-2-enamide (**2B$_6$**).* This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and *N*-benzyl-3-oxobutanamide (11 mmol, 2.10 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as yellowish solid in 66% yield (1.80 g). Mp 115-117 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.33 – 7.27 (m, 4H), 7.26 – 7.21 (m, 1H), 5.06 (s, 1H), 4.43 (d, *J* = 5.7 Hz, 2H), 4.24 (s, 1H), 3.34 – 3.16 (m, 1H), 1.90 (s, 3H), 1.86 (dd, *J* = 8.3, 4.8 Hz, 2H), 1.76 (dd, *J* = 12.4, 3.6 Hz, 2H), 1.62 – 1.51 (m, 1H), 1.37 – 1.13 (m, 5H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.7, 158.0, 139.7, 128.5, 127.6, 127.1, 83.9, 51.4, 42.8, 34.5, 25.5, 24.9, 19.3. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{25}N_2O^+$ 273.1961, found 273.1955. IR (KBr, cm^{-1}): 2928, 2850, 1624, 1597, 1533, 1481, 1449, 1283, 1241, 697.

*Ethyl (E)-2-chloro-3-(cyclohexylamino)but-2-enoate (**2C$_1$**).*[34h] This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and ethyl 2-chloro-3-oxobutanoate (11 mmol, 1.81 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish oil in 72% yield (1.77 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, *J* = 7.8 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.36 (dt, *J* = 9.0, 4.4 Hz, 1H), 2.19 (s, 3H), 1.93 – 1.83 (m, 2H), 1.81 – 1.70 (m, 2H), 1.64 – 1.55 (m, 1H), 1.39 – 1.18 (m, 8H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.6, 159.2, 88.4, 60.1, 52.6, 34.3, 25.5, 24.7, 16.6, 14.7. IR (KBr, cm^{-1}): 2933, 2855, 1639, 1593, 1513, 1451, 1259, 1151, 1070, 767.

*Ethyl (Z)-3-(cyclohexylamino)-2-methylbut-2-enoate (**2C$_2$**).* This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and ethyl 2-methyl-3-oxobutanoate (11 mmol, 1.59 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 77% yield (1.74 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, *J* = 6.7 Hz, 1H), 4.19 (dt, *J* = 7.1, 4.8 Hz, 2H), 3.46 – 3.27 (m, 1H), 2.19 (s, 3H), 1.89 (t, *J* = 10.8 Hz, 2H), 1.81 – 1.68 (m, 2H), 1.65 – 1.52 (m, 1H), 1.40 – 1.19 (m, 8H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.5, 159.1, 88.3, 60.0, 52.5, 34.1, 25.4, 24.5, 16.5, 14.6. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{13}H_{24}NO_2^+$ 226.1802, found 226.1798. IR (KBr, cm^{-1}): 2976, 2930, 2854, 1644, 1597, 1449, 1451, 1255, 1240, 1097, 778.

*(Z)-5-(cyclohexylamino)-4-methylhex-4-en-3-one (**2C$_3$**).* This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and 3-methylhexane-2,4-dione (11 mmol, 1.41 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 63% yield (1.32 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.18 (s, 1H), 3.39 (qd, *J* = 9.2, 4.5 Hz, 1H), 2.43 (q, *J* = 7.4 Hz, 2H), 1.99 (s, 3H), 1.92 – 1.84 (m, 2H), 1.82 (s, 3H), 1.80 – 1.72 (m, 2H), 1.58 (ddd, *J* = 9.7, 5.3, 2.2 Hz, 1H), 1.41 – 1.18 (m, 5H), 1.10 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 197.1, 160.9, 97.1, 51.9, 34.1, 32.8, 25.4, 24.6, 15.2, 14.0, 9.3. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{13}H_{24}NO^+$ 210.1852, found 210.1850. IR (KBr, cm^{-1}): 2930, 2853, 1596, 1572, 1449, 1224, 995, 814.

*3-(cyclohexylamino)cyclohex-2-en-1-one (**2D$_1$**).*[34i] This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and cyclohexane-1,3-dione (11 mmol, 1.23 g). Purification by alkaline alumina column chromatography (20% EtOAc/hexanes) provided the compound as yellow solid in 76% yield (1.47 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (s, 1H), 5.23 (s, 1H), 3.35 – 3.13 (m, 1H), 2.40 (t, *J* = 6.2 Hz, 2H), 2.34 (t, *J* = 6.4 Hz, 2H), 2.03 – 1.90 (m, 4H), 1.80 – 1.71 (m, 2H), 1.70 – 1.60 (m, 1H), 1.38 – 1.14 (m, 5H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 196.3, 164.5, 96.4, 51.8, 35.7, 32.3, 30.1, 25.4, 24.7, 21.9.

*3-(cyclohexylamino)cyclopent-2-en-1-one (**2D$_2$**).* This compound was prepared according to the general procedure using cyclohexanamine (10 mmol, 0.99 g) and cyclopentane-1,3-dione (11 mmol,

1.08 g). Purification by alkaline alumina column chromatography (20% EtOAc/hexanes) provided the compound as yellow solid in 79% yield (1.42 g). Mp 153-156 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (s, 1H), 5.02 (s, 1H), 3.20 (s, 1H), 2.56 (s, 2H), 2.47 – 2.31 (m, 2H), 2.00 (d, *J* = 9.8 Hz, 2H), 1.76 (dd, *J* = 9.6, 3.5 Hz, 2H), 1.65 (dd, *J* = 8.9, 3.8 Hz, 1H), 1.42 – 1.29 (m, 2H), 1.29 – 1.11 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 204.4, 175.0, 99.2, 53.9, 33.5, 32.4, 28.4, 25.4, 24.6. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{11}H_{18}NO^+$ 180.1383, found 180.1381. IR ($CHCl_3$, cm^{-1}): 3238, 2928, 2857, 1645, 1551, 1214, 744.

*Ethyl 2-(isopropylamino)cyclopent-1-ene-1-carboxylate (**3A$_1$**)*.[34a] This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and ethyl 2-oxocyclopentane-1-carboxylate (11 mmol, 1.71 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 70% yield (1.38 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.55 (ddt, *J* = 12.9, 9.1, 6.4 Hz, 1H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.53 – 2.41 (m, 2H), 1.82 (dt, *J* = 14.7, 7.5 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.6, 163.9, 92.1, 58.3, 46.3, 31.9, 28.9, 24.4, 21.1, 14.8.

*Ethyl 2-(isopropylamino)cyclohex-1-ene-1-carboxylate (**3A$_2$**)*.[34b] This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and ethyl 2-oxocyclohexane-1-carboxylate (11 mmol, 1.87 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 74% yield (1.56 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 7.3 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.80 – 3.60 (m, 1H), 2.35 (t, *J* = 6.3 Hz, 2H), 2.27 (t, *J* = 6.2 Hz, 2H), 1.70 – 1.60 (m, 2H), 1.56 (qd, *J* = 6.0, 3.7 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 158.7, 89.0, 58.5, 43.2, 26.2, 24.4, 23.8, 22.8, 22.4, 14.7.

*Ethyl 2-(isopropylamino)cyclohept-1-ene-1-carboxylate (**3A$_3$**)*. This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and ethyl 2-oxocycloheptane-1-carboxylate (11 mmol, 2.03 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 67% yield (1.51 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (d, *J* = 4.7 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.73 (tt, *J* = 12.8, 6.4 Hz, 1H), 2.58 – 2.38 (m, 4H), 1.71 (dt, *J* = 11.8, 5.9 Hz, 2H), 1.65 – 1.55 (m, 3H), 1.46 (dt, *J* = 11.6, 5.9 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.7, 166.8, 93.6, 58.6, 44.4, 31.9, 28.8, 28.5, 25.8, 25.7, 24.6, 14.8. HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ calcd for $C_{13}H_{24}NO_2^+$: 226.1802, found 226.1797. IR (KBr, cm^{-1}): 2974, 2922, 2849, 1639, 1593, 1250, 1204, 1121, 1054, 786.

2-(isopropylamino)-N-phenylcyclopent-1-ene-1-carboxamide ***(3A$_4$)***.[35a] This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and 2-oxo-*N*-phenylcyclopentane-1-carboxamide (11 mmol, 2.24 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as white solid in 81% yield (1.98 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.39 (m, 2H), 7.36 – 7.21 (m, 2H), 7.01 (dd, *J* = 10.6, 4.2 Hz, 1H), 6.60 (s, 1H), 3.55 (ddt, *J* = 12.9, 9.2, 6.4 Hz, 1H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.60 – 2.55 (m, 2H), 1.99 – 1.88 (m, 2H), 1.20 (d, *J* = 6.4 Hz,6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.0, 162.8, 139.0, 128.8, 122.9, 119.8, 93.0, 46.3, 31.8, 29.2, 24.5, 20.9.

N-benzyl-2-(isopropylamino)cyclopent-1-ene-1-carboxamide ***(3A$_5$)***. This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and *N*-benzyl-2-oxocyclopentane-1-carboxamide (11 mmol, 2.39 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as white solid in 76% yield (1.96 g). Mp 122-125 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 1H), 7.36 – 7.28 (m, 4H), 7.27 – 7.20 (m, 1H), 5.13 (s, 1H), 4.49 (d, *J* = 5.8 Hz, 2H), 3.52 (ddt, *J* = 12.9, 9.2, 6.4 Hz, 1H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.42 (dd, *J* = 7.7, 6.6 Hz, 2H), 1.87 (dt, *J* = 10.7, 7.4 Hz, 2H), 1.19 (d, *J* = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.7, 161.1, 139.7, 128.6, 127.7, 127.1, 92.9, 46.1, 42.8, 31.7, 29.1, 24.5, 20.9. HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ calcd for $C_{16}H_{23}N_2O^+$ 259.1805, found 259.1800. IR (KBr, cm^{-1}): 2964, 2923, 2839, 1624, 1578, 1518, 1288, 1187.

Ethyl (Z)-3-(isopropylamino)but-2-enoate ***(3B$_1$)***.[35b] This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and ethyl 3-oxobutanoate (11 mmol, 1.43 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the

compound as colorless oil in 65% yield (1.11 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 4.39 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.76 – 3.60 (m, 1H), 1.94 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.6, 160.8, 81.8, 58.2, 44.4, 24.1, 19.2, 14.7.

*(Z)-3-(isopropylamino)-1-phenylbut-2-en-1-one (**3B$_2$**).*[35c] This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and 1-phenylbutane-1,3-dione (11 mmol, 1.78 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish oil in 78% yield (1.58 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.45 (s, 1H), 7.86 (ddd, *J* = 5.6, 4.3, 2.5 Hz, 2H), 7.45 – 7.31 (m, 3H), 5.62 (s, 1H), 3.91 – 3.72 (m, 1H), 2.09 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 187.4, 163.6, 140.5, 130.3, 128.1, 126.8, 91.7, 45.0, 23.8, 19.2.

*(Z)-4-(isopropylamino)pent-3-en-2-one (**3B$_3$**).*[35d] This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and pentane-2,4-dione (11 mmol, 1.10 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 72% yield (1.02 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), 4.91 (s, 1H), 3.71 (ddt, *J* = 12.9, 8.9, 6.4 Hz, 1H), 1.99 (s, 3H), 1.95 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 194.5, 161.8, 94.9, 44.6, 28.8, 23.8, 18.6.

*(Z)-1,1,1-trifluoro-4-(isopropylamino)pent-3-en-2-one (**3B$_4$**).*[35c] This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and 1,1,1-trifluoropentane-2,4-dione (11 mmol, 1.69 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 63% yield (1.23 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.18 (s, 1H), 5.27 (s, 1H), 3.84 (ddt, *J* = 12.9, 8.8, 6.5 Hz, 1H), 2.11 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 175.1 (q, *J* = 32.4 Hz), 168.1, 117.8 (q, *J* = 288.2 Hz), 89.1, 45.9, 23.3, 19.0.

*(Z)-3-(isopropylamino)-N-phenylbut-2-enamide (**3B$_5$**).* This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and 3-oxo-*N*-phenylbutanamide (11 mmol, 1.95 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as white solid in 69% yield (1.51 g). Mp 135-138 ˚C. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 9.15 (d, *J* = 7.3 Hz, 1H), 7.42 (dd, *J* = 8.5, 0.9 Hz, 2H), 7.32 – 7.20 (m, 2H), 7.06 – 6.93 (m, 1H), 6.58 (s, 1H), 4.36 (s, 1H), 3.80 – 3.53 (m, 1H), 1.94 (s, 3H), 1.22 (d, *J* = 6.4 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.1, 159.4, 139.2, 128.8, 122.8, 119.8, 84.4, 44.4, 24.2, 19.4. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{13}H_{19}N_2O^+$ 219.1492, found 219.1486. IR (KBr, cm^{-1}): 2969, 2927, 1632, 1592, 1529, 1497, 1434, 1311, 1163.

*Ethyl (E)-2-chloro-3-(isopropylamino)but-2-enoate (**3C$_1$**).*[35e] This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and ethyl 2-chloro-3-oxobutanoate (11 mmol, 1.81 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 82% yield (1.69 g). ^1H NMR (500 MHz, $CDCl_3$) δ 9.09 (s, 1H), 4.19 (qd, *J* = 7.1, 4.5 Hz, 2H), 3.72 (ddt, *J* = 12.8, 8.3, 6.4 Hz, 1H), 2.20 (s, 3H), 1.31 (dt, *J* = 9.2, 7.1 Hz, 3H), 1.23 (d, *J* = 6.4 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 167.5, 159.1, 88.3, 60.0, 45.5, 24.0, 16.5, 14.6.

*Ethyl (Z)-3-(isopropylamino)-2-methylbut-2-enoate (**3C$_2$**).* This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and ethyl 2-methyl-3-oxobutanoate (11 mmol, 1.59 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 77% yield (1.43 g). ^1H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.69 (ddt, *J* = 12.8, 8.3, 6.4 Hz, 1H), 1.98 (s, 3H), 1.77 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 6.4 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.0, 158.8, 86.2, 58.6, 44.5, 24.3, 24.3, 15.3, 14.7, 12.6. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{10}H_{20}NO_2^+$ 186.1489, found 186.1487. IR (KBr, cm^{-1}): 2978, 2930, 1644, 1598, 1453, 1235, 1098, 779.

*(Z)-5-(isopropylamino)-4-methylhex-4-en-3-one (**3C$_3$**).* This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and 3-methylhexane-2,4-dione (11 mmol, 1.41 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 78% yield (1.32 g). ^1H NMR (500 MHz, $CDCl_3$) δ 12.08 (s, 1H), 3.84 – 3.59 (m, 1H), 2.43 (q, *J* = 7.4 Hz, 2H), 2.00 (s, 3H), 1.82 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 6H), 1.09 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 197.2, 160.9, 97.1, 44.7, 32.7, 24.0, 15.2,

13.9, 9.2. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{10}H_{20}NO^+$ 170.1539, found 170.1534. IR (KBr, cm^{-1}): 2970, 2932, 2878, 1600, 1570, 1231, 1159, 1000, 814.

*3-(isopropylamino)cyclohex-2-en-1-one (**3D$_1$**)*.[35f] This compound was prepared according to the general procedure using isopropylamine (10 mmol, 0.59 g) and cyclohexane-1,3-dione (11 mmol, 1.23 g). Purification by alkaline alumina column chromatography (20% EtOAc/hexanes) provided the compound as yellow solid in 83% yield (1.27 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (s, 1H), 4.52 (s, 1H), 3.59 (dq, *J* = 13.1, 6.5 Hz, 1H), 2.31 (t, *J* = 6.4 Hz, 4H), 2.09 – 1.88 (m, 2H), 1.20 (d, *J* = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.2, 163.1, 97.1, 44.1, 36.4, 30.1, 22.2, 22.0.

*Ethyl 2-(benzylamino)cyclopent-1-ene-1-carboxylate (**4A$_1$**)*.[34a] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and ethyl 2-oxocyclopentane-1-carboxylate (11 mmol, 1.72 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 84% yield (2.06 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.43 – 7.28 (m, 2H), 7.25 (ddd, *J* = 6.9, 4.4, 2.7 Hz, 3H), 4.39 (d, *J* = 6.5 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.65 – 2.41 (m,4H), 1.81 (dt, *J* = 14.8, 7.5 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.6, 164.6, 139.3, 128.7, 127.3, 126.8, 93.5, 58.5, 48.4, 32.1, 29.2, 20.9, 14.8.

*Ethyl 2-(benzylamino)cyclohex-1-ene-1-carboxylate (**4A$_2$**)*.[34a] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and ethyl 2-oxocyclohexane-1-carboxylate (11 mmol, 1.87 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 70% yield (1.82 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.35 – 7.29 (m, 2H), 7.24 (dd, *J* = 12.4, 6.8 Hz, 3H), 4.38 (d, *J* = 6.2 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.29 (t, *J* = 6.1 Hz, 4H), 1.69 – 1.51 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 159.4, 139.6, 128.7, 127.1, 126.8, 90.6, 58.7, 46.1, 26.9, 26.3, 23.9, 22.7, 22.3, 14.7.

*Ethyl 2-(benzylamino)cyclohept-1-ene-1-carboxylate (**4A$_3$**)*.[36a] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and ethyl 2-oxocycloheptane-1-carboxylate (11 mmol, 2.03 g). Purification by alkaline alumina column

chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 68% yield (1.86 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.37 – 7.29 (m, 2H), 7.29 – 7.18 (m, 3H), 4.44 (d, *J* = 6.2 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.54 – 2.47 (m, 2H), 2.47 – 2.39 (m, 2H), 1.66 (dt, *J* = 11.9, 5.9 Hz, 2H), 1.53 – 1.37 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.7, 167.3, 139.8, 128.6, 127.1, 126.8, 95.4, 58.8, 46.9, 31.8, 28.8, 28.4, 25.9, 25.0, 14.7. IR (KBr, cm^{-1}): 2978, 2922, 2849, 1636, 1597, 1452, 1240, 1139, 1066, 786.

*2-(benzylamino)-N-phenylcyclopent-1-ene-1-carboxamide (**4A$_4$**).*[34a] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and 2-oxo-*N*-phenylcyclopentane-1-carboxamide (11 mmol, 2.24 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as white solid in 68% yield (1.99 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.57 – 7.44 (m, 2H), 7.42 – 7.15 (m, 7H), 7.12 – 6.89 (m, 1H), 6.65 (s, 1H), 4.39 (d, *J* = 6.6 Hz, 2H), 2.59 (dd, *J* = 14.6, 7.2 Hz, 4H), 1.96 – 1.83 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.0, 163.6, 139.4, 138.9, 128.9, 128.7, 127.2, 126.9, 123.1, 119.8, 94.5, 48.4, 32.0, 29.4, 20.7.

*N-benzyl-2-(benzylamino)cyclopent-1-ene-1-carboxamide (**4A$_5$**).*[34a] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and *N*-benzyl-2-oxocyclopentane-1-carboxamide (11 mmol, 2.39 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as yellowish oil in 68% yield (2.08 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.36 – 7.29 (m,6H), 7.25 (ddd, *J* = 13.6, 12.0, 7.2 Hz, 4H), 5.22 (s, 1H), 4.49 (d, *J* = 5.8 Hz, 2H), 4.36 (d, *J* = 6.5 Hz, 2H), 2.53 (t, *J* = 7.6 Hz, 2H), 2.50 – 2.35 (m, 2H), 1.84 (dt, *J* = 14.8, 7.5 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.7, 161.8, 139.8, 139.6, 128.6, 128.6, 127.7, 127.2, 127.1, 126.9, 94.3, 48.3, 42.9, 31.9, 29.3, 20.7.

*Ethyl (Z)-3-(benzylamino)but-2-enoate (**4B$_1$**).*[36b] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and ethyl 3-oxobutanoate (11 mmol, 1.43 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 76% yield (1.67 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.39 – 7.30 (m, 1H), 7.27 – 7.22 (m, 1H), 4.53 (s, 1H), 4.42 (d, J = 6.4 Hz, 1H), 4.10 (q, J = 7.1 Hz, 1H), 1.91

(s, 1H), 1.25 (t, J = 7.1 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.6, 161.8, 138.8, 128.8, 127.3, 126.7, 83.2, 58.4, 46.8, 19.4, 14.6.

*(Z)-3-(benzylamino)-1-phenylbut-2-en-1-one (**4B$_2$**)*.[36c] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and 1-phenylbutane-1,3-dione (11 mmol, 1.78 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish solid in 74% yield (1.86 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.75 (s, 1H), 7.92 – 7.78 (m, 2H), 7.44 – 7.36 (m, 3H), 7.37 – 7.33 (m, 2H), 7.33 – 7.26 (m, 3H), 5.75 (s, 1H), 4.54 (d, *J* = 6.3 Hz, 2H), 2.07 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 188.1, 164.9, 140.3, 137.8, 130.6, 128.9, 128.2, 127.6, 127.0, 126.9, 92.6, 47.1, 19.6.

*(Z)-4-(benzylamino)pent-3-en-2-one (**4B$_3$**)*.[36c] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and pentane-2,4-dione (11 mmol, 1.10 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish oil in 71% yield (1.34 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.17 (s, 1H), 7.37 – 7.28 (m, 2H), 7.26 (dd, *J* = 8.7, 7.6 Hz, 3H), 5.04 (s, 1H), 4.45 (d, *J* = 6.4 Hz, 2H), 2.03 (s, 3H), 1.91 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 195.4, 163.1, 138.1, 128.8, 127.4, 126.7, 95.9, 46.7, 28.9, 18.9.

*(Z)-4-(benzylamino)-1,1,1-trifluoropent-3-en-2-one (**4B$_4$**)*.[36d] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and 1,1,1-trifluoropentane-2,4-dione (11 mmol, 1.69 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish solid in 64% yield (1.56 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.43 (s, 1H), 7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 1H), 7.27 (dd, *J* = 4.2, 3.6 Hz,2H), 5.40 (s, 1H), 4.56 (d, *J* = 6.2 Hz, 2H), 2.10 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 176.0 (q, *J* = 32.7 Hz), 169.6, 136.0, 129.1, 128.1, 127.0, 117.6 (q, *J* = 288.2 Hz), 89.9, 47.6, 19.5.

*(Z)-3-(benzylamino)-N-phenylbut-2-enamide (**4B$_5$**)*.[36e] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and 3-oxo-*N*-phenylbutanamide (11 mmol, 1.95 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes)

provided the compound as white solid in 68% yield (1.81 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.26 (dd, *J* = 17.2, 8.3 Hz, 6H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.62 (s, 1H), 4.49 (s, 1H), 4.43 (d, *J* = 6.4 Hz, 2H), 1.91 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.0, 160.5, 139.1, 128.9, 128.7, 127.2, 126.7, 123.0, 119.8, 85.7, 46.7, 19.5.

*(Z)-N-benzyl-3-(benzylamino)but-2-enamide (**4B$_6$**).*[36f] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and *N*-benzyl-3-oxobutanamide (11 mmol, 2.10 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as yellowish solid in 66% yield (1.85 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.38 – 7.24 (m, 10H), 5.18 (s, 1H), 4.47 (d, *J* = 5.7 Hz, 2H), 4.43 (d, *J* = 6.5 Hz, 2H), 4.40 (s, 1H), 1.89 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.6, 158.9, 139.6, 139.4, 128.7, 128.6, 127.6, 127.1, 127.0, 126.8, 85.4, 46.7, 42.9, 19.4.

*Ethyl (E)-3-(benzylamino)-2-chlorobut-2-enoate (**4C$_1$**).*[35e] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and ethyl 2-chloro-3-oxobutanoate (11 mmol, 1.81 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 68% yield (1.73 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.41 – 7.31 (m, 2H), 7.30 – 7.18 (m, 3H), 4.46 (t, *J* = 5.0 Hz, 2H), 4.25 – 4.06 (m, 2H), 2.16 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.5, 159.9, 138.2, 128.9, 127.6, 126.8, 89.6, 60.3, 47.7, 16.7, 14.5.

*Ethyl (Z)-3-(benzylamino)-2-methylbut-2-enoate (**4C$_2$**).*[34a] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and ethyl 2-methyl-3-oxobutanoate (11 mmol, 1.59 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 60% yield (1.40 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.33 – 7.29 (m, 2H), 7.24 (dd, J = 13.0, 7.2 Hz, 3H), 4.42 (d, J = 6.2 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 1.92 (s, 3H), 1.80 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.1, 159.4, 139.5, 128.7, 127.1, 126.7, 87.8, 58.8, 47.2, 15.4, 14.7, 12.8.

*(Z)-5-(benzylamino)-4-methylhex-4-en-3-one (**4C$_3$**).*[34a] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and 3-methylhexane-2,4-dione (11 mmol,

1.41 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 50% yield (1.09 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.29 (s, 1H), 7.37 – 7.29 (m, 2H), 7.28 – 7.20 (m, 3H), 4.46 (d, *J* = 6.1 Hz, 2H), 2.46 (q, *J* = 7.4 Hz, 2H), 1.95 (s, 3H), 1.85 (s, 3H), 1.10 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 198.4, 161.7, 138.7, 128.8, 127.3, 126.9, 98.3, 47.2, 33.0, 15.4, 14.1, 9.2.

*3-(benzylamino)cyclohex-2-en-1-one (**4D$_1$**)*.[36b] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and cyclohexane-1,3-dione (11 mmol, 1.23 g). Purification by alkaline alumina column chromatography (20% EtOAc/hexanes) provided the compound as yellowish solid in 78% yield (1.57 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.23 (m, 5H), 5.19 (s, 1H), 4.86 (s, 1H), 4.23 (d, *J* = 5.1 Hz, 2H), 2.37 (t, *J* = 6.2 Hz, 2H), 2.32 (t, *J* = 6.5 Hz, 2H), 2.03 – 1.94 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.4, 163.8, 136.8, 128.9, 128.0, 127.9, 97.7, 47.3, 36.5, 29.8, 22.0.

*3-(benzylamino)cyclopent-2-en-1-one (**4D$_2$**)*.[36g] This compound was prepared according to the general procedure using benzylamine (10 mmol, 1.07 g) and cyclopentane-1,3-dione (11 mmol, 1.08 g). Purification by alkaline alumina column chromatography (20% EtOAc/hexanes) provided the compound as yellow solid in 83% yield (1.55 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.19 (m, 5H), 6.17 (s, 1H), 5.02 (s, 1H), 4.29 (d, *J* = 5.0 Hz, 2H), 2.66 – 2.50 (m, 2H), 2.34 (dd, *J* = 6.7, 4.1 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 204.8, 176.7, 136.8, 128.9, 127.9, 127.6, 99.8, 49.2, 33.8, 28.1.

*Ethyl 2-(phenylamino)cyclopent-1-ene-1-carboxylate (**5A$_1$**)*.[34a] This compound was prepared according to the general procedure using aniline (10 mmol, 0.93 g) and ethyl 2-oxocyclopentane-1-carboxylate (11 mmol, 1.72 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 60% yield (1.39 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.27 (ddd, *J* = 9.4, 4.7, 2.2 Hz, 2H), 7.12 – 6.95 (m, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.57 (ddd, *J* = 6.0, 2.0, 1.0 Hz, 2H), 1.87 (dt, *J* = 14.7, 7.4 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.5, 160.5, 140.7, 129.2, 123.1, 120.8, 97.7, 59.0, 33.7, 28.8, 21.8, 14.7.

*Ethyl 2-(phenylamino)cyclohex-1-ene-1-carboxylate (**5A$_2$**)*.[37a] This compound was prepared

according to the general procedure using aniline (10 mmol, 0.93 g) and ethyl 2-oxocyclohexane-1-carboxylate (11 mmol, 1.87 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 65% yield (1.59 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 7.28 (dd, *J* = 13.3, 5.4 Hz, 2H), 7.15 – 7.02 (m, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.35 (q, *J* = 5.3 Hz, 4H), 1.71 – 1.54 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 156.6, 139.9, 128.9, 124.9, 124.2, 93.1, 59.1, 28.2, 23.9, 22.7, 22.3, 14.6.

*Ethyl 2-(phenylamino)cyclohept-1-ene-1-carboxylate (**5A$_3$**)*.[37b] This compound was prepared according to the general procedure using aniline (10 mmol, 0.93 g) and ethyl 2-oxocycloheptane-1-carboxylate (11 mmol, 2.03 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as colorless oil in 66% yield (1.71 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.90 (s, 1H), 7.29 (dd, *J* = 10.7, 5.0 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.7 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.67 – 2.38 (m, 4H), 1.75 (dt, *J* = 11.7, 5.9 Hz, 2H), 1.69 – 1.60 (m, 2H), 1.57 – 1.47 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.7, 163.4, 140.2, 129.0, 124.5, 124.2, 99.1, 59.2, 31.9, 29.9, 27.9, 26.2, 26.1, 14.6. IR (KBr, cm^{-1}): 2979, 2922, 2849, 1643, 1593, 1499, 1250, 1211, 1049, 786.

*N-phenyl-2-(phenylamino)cyclopent-1-ene-1-carboxamide (**5A$_4$**)*.[37c] This compound was prepared according to the general procedure using aniline (10 mmol, 0.93 g) and 2-oxo-*N*-phenylcyclopentane-1-carboxamide (11 mmol, 2.24 g). Purification by alkaline alumina column chromatography (30% EtOAc/hexanes) provided the compound as yellowish solid in 76% yield (2.11 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.45 (s, 1H), 7.61 – 7.43 (m, 2H), 7.37 – 7.29 (m, 2H), 7.29 – 7.22 (m, 2H), 7.11 – 7.03 (m, 3H), 7.01 (ddd, *J* = 8.5, 2.1, 1.1 Hz, 1H), 6.79 (s, 1H), 2.87 (t, *J* = 7.5 Hz, 2H), 2.64 (dd, *J* = 7.8, 6.5 Hz, 2H), 1.98 (dt, *J* = 14.5, 7.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.8, 159.4, 140.9, 138.5, 129.2, 129.0, 123.6, 122.9, 120.7, 120.1, 98.3, 33.6, 29.0, 21.6.

*N-benzyl-2-(phenylamino)cyclopent-1-ene-1-carboxamide (**5A$_5$**)*. This compound was prepared according to the general procedure using aniline (10 mmol, 0.93 g) and *N*-benzyl-2-oxocyclopentane-1-carboxamide (11 mmol, 2.39 g). Purification by alkaline alumina

column chromatography (30% EtOAc/hexanes) provided the compound as yellowish solid in 73% yield (2.13 g). Mp 118-120 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.38 – 7.31 (m, 4H), 7.31 – 7.21 (m, 3H), 7.03 (dd, *J* = 8.5, 0.9 Hz, 2H), 7.01 – 6.95 (m, 1H), 5.38 (s, 1H), 4.54 (d, *J* = 5.8 Hz, 2H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.48 (dd, *J* = 7.7, 6.6 Hz, 2H), 1.94 (dd, *J* = 14.7, 7.3 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.5, 157.6, 141.3, 139.2, 129.1, 128.7, 127.7, 127.3, 122.4, 120.4, 98.3, 43.0, 33.5, 28.8, 21.6. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{19}H_{21}N_2O^+$ 293.1648, found 293.1643. IR (KBr, cm^{-1}): 2920, 2848, 1625, 1597, 1497, 1270.

*Ethyl (Z)-3-(phenylamino)but-2-enoate (**5B$_1$**).*[34d,36b] This compound was prepared according to the general procedure using aniline (10 mmol, 0.93 g) and ethyl 3-oxobutanoate (11 mmol, 1.43 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellow oil in 82% yield (1.68 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.37 – 7.27 (m, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 2H), 4.69 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 1.99 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.4, 158.9, 139.4, 129.1, 124.9, 124.4, 86.1, 58.8, 20.3, 14.6.

*(Z)-1-phenyl-3-(phenylamino)but-2-en-1-one (**5B$_2$**).*[37d] This compound was prepared according to the general procedure using aniline (10 mmol, 0.93 g) and 1-phenylbutane-1,3-dione (11 mmol, 1.78 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish solid in 80% yield (1.90 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.10 (s, 1H), 8.05 – 7.74 (m, 2H), 7.49 – 7.40 (m, 3H), 7.40 – 7.31 (m, 2H), 7.28 – 7.14 (m, 3H), 5.90 (s, 1H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 188.7, 162.2, 140.0, 138.7, 130.9, 129.2, 128.3, 127.1, 125.8, 124.8, 94.3, 20.5.

*(Z)-4-(phenylamino)pent-3-en-2-one (**5B$_3$**).*[36c] This compound was prepared according to the general procedure using aniline (10 mmol, 0.93 g) and pentane-2,4-dione (11 mmol, 1.10 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as white solid in 78% yield (1.37 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.48 (s, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H), 7.10 (d, J = 7.5 Hz, 2H), 5.19 (s, 1H), 2.10 (s, 3H), 1.99 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 196.2, 160.2, 138.8, 129.1, 125.6, 124.8, 97.6, 29.2, 19.9.

*(Z)-1,1,1-trifluoro-4-(phenylamino)pent-3-en-2-one (**5B$_4$**)*.[36d] This compound was prepared according to the general procedure using aniline (10 mmol, 0.93 g) and 1,1,1-trifluoropentane-2,4-dione (11 mmol, 1.69 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish solid in 69% yield (1.58 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.60 (s, 1H), 7.50 – 7.38 (m, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.23 – 7.07 (m, 2H), 5.55 (s, 1H), 2.12 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.6 (q, *J* = 33.0 Hz), 167.9, 137.0, 129.5, 127.5, 125.3, 117.5 (q, *J* = 288.5 Hz), 90.9, 20.3.

*Ethyl (E)-2-chloro-3-(phenylamino)but-2-enoate (**5C$_1$**)*.[38a] This compound was prepared according to the general procedure using aniline (10 mmol, 0.93 g) and ethyl 2-chloro-3-oxobutanoate (11 mmol, 1.81 g). Purification by alkaline alumina column chromatography (10% EtOAc/hexanes) provided the compound as yellowish solid in 72% yield (1.73 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.73 (s, 1H), 7.34 (dd, *J* = 13.0, 4.9 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 9.1 Hz, 2H), 4.42 – 4.19 (m, 2H), 2.19 (s, 3H), 1.41 – 1.27 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.3, 157.0, 139.1, 129.2, 125.6, 125.1, 92.6, 60.7, 18.4, 14.5.

*3-(phenylamino)cyclohex-2-en-1-one (**5D$_1$**)*.[38b] This compound was prepared according to the general procedure using aniline (10 mmol, 0.93 g) and cyclohexane-1,3-dione (11 mmol, 1.23 g). Purification by alkaline alumina column chromatography (20% EtOAc/hexanes) provided the compound as yellow solid in 76% yield (1.42 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 8.3 Hz, 3H), 6.82 (s, 1H), 5.56 (s, 1H), 2.50 (t, *J* = 6.2 Hz, 2H), 2.34 (t, *J* = 6.5 Hz, 2H), 2.07 – 1.94 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.4, 162.4, 138.2, 129.3, 125.5, 124.0, 99.7, 36.5, 29.7, 21.9.

*3-(phenylamino)cyclopent-2-en-1-one (**5D$_2$**)*.[38c] This compound was prepared according to the general procedure using aniline (10 mmol, 0.93 g) and cyclopentane-1,3-dione (11 mmol, 1.08 g). Purification by alkaline alumina column chromatography (20% EtOAc/hexanes) provided the compound as yellow solid in 83% yield (1.44 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.59 (s, 1H), 7.40 – 7.31 (m, 2H), 7.24 – 7.18 (m, 2H), 7.12 – 7.04 (m, 1H), 5.41 (s, 1H), 2.76 – 2.69 (m, 2H), 2.25 – 2.20 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 204.5, 172.3, 141.0, 129.8, 123.9, 120.5, 101.4,

33.3, 29.0.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra for all new compounds, CV Plots, computational data (PDF), and Cartesian coordinates of all structures (PDF).

AUTHOR INFORMATION

Author Contributions

§ These authors contributed equally.

Corresponding Author

E-mail: luosz@tsinghua.edu.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the Natural Science Foundation of China (21572232, 21672217 and 21861132003), the China Postdoctoral Science Foundation (2019M650621) and Tsinghua University for financial support. S. L. is supported by the National Program of Top-notch Young Professionals. The Tsinghua Xuetang Talents Program is acknowledged for providing computational resources.

REFERENCES

(1) For recent reviews on enamine catalysis, see: (a) Zhang, L.; Fu, N.; Luo, S. Pushing the Limits of Aminocatalysis: Enantioselective Transformations of α-Branched β-Ketocarbonyls and Vinyl Ketones by Chiral Primary Amines. *Acc. Chem. Res.* **2015**, *48*, 986-997. (b) Bertelsen, S.; Jørgensen, K. A. Organocatalysis—After the Gold Rush. *Chem. Soc. Rev*. **2009**, *38*, 2178-2189. (c) Melchiorre, P.;

Marigo, M.; Carlone, A.; Bartoli, G. Asymmetric Aminocatalysis—Gold Rush in Organic Chemistry. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138-6171. (d) Dondoni, A.; Massi, A. Asymmetric Organocatalysis: From Infancy to Adolescence. *Angew. Chem., Int. Ed*. **2008**, *47*, 4638-4660. (e) Barbas, C. F. Organocatalysis Lost: Modern Chemistry, Ancient Chemistry, and an Unseen Biosynthetic Apparatus. *Angew. Chem., Int. Ed*. **2008**, *47*, 42-47. (f) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. *Chem. Rev*. **2007**, *107*, 5471-5569. (g) Erkkilä, A.; Majander, I.; Pihko, P. M. Iminium Catalysis. *Chem. Rev*. **2007**, *107*, 5416-5470. (h) Marigo, M.; Jørgensen, K. A. Organocatalytic Direct Asymmetric α-heteroatom Functionalization of Aldehydes and Ketones. *Chem. Commun*. **2006**, 2001-2011. (i) Lelais, G.; MacMillan, D. W. C. Modern Strategies in Organic Catalysis: The Advent and Development of Iminium Activation. *Aldrichimica Acta*, **2006**, *39*, 79-87.

(2) For recent representative examples on chemistry oxidation, see: (a) Zhu, L.; Zhang, L.; Luo, S. Catalytic Desymmetrizing Dehydrogenation of 4-Substituted Cyclohexanones through Enamine Oxidation. *Angew. Chem., Int. Ed*. **2018**, *57*, 2253-2258. (b) Zhu, L.; Zhang, L.; Luo, S. Catalytic Asymmetric β-C–H Functionalizations of Ketones via Enamine Oxidation. *Org. Lett.* **2018**, *20*, 1672-1675. (c) Wang, D.; Zhang, L.; Luo, S. Enantioselective Decarboxylative α-Alkynylation of β-Ketocarbonyls via a Catalytic α-Imino Radical Intermediate. *Org. Lett*. **2017**, *19*, 4924-4927. (d) Capacci, A. G.; Malinowski, J. T.; McAlpine, N. J.; Kuhne, J.; MacMillan, D. W. C. Direct, Enantioselective α-Alkylation of Aldehydes Using Simple Olefins. *Nat. Chem.* **2017**, *9*, 1073−1077. (e) Næsborg, L.; Leth, L. A.; Reyes-Rodríguez, G. J.; Palazzo, T. A.; Corti, V.; Jørgensen, K. A. Direct Enantio- and Diastereoselective Oxidative Homocoupling of Aldehydes. *Chem. - Eur. J.* **2018**, *24*, 14844-14848. (f) Leth, L. A.; Næsborg, L.; Reyes-Rodríguez, G. J.; Tobiesen, H. N.; Iversen, M. V.; Jørgensen, K. A. Enantioselective Oxidative Coupling of Carboxylic Acids to α‑Branched Aldehydes. *J. Am. Chem. Soc.* **2018**, *140*, 12687−12690. For electrochemistry oxidation, see: (g) Ho, X. H.; Mho, S. I.; Kang, H.; Jang, H. Y. Electro-Organocatalysis: Enantioselective α-Alkylation of Aldehydes. *Eur. J. Org. Chem*. **2010**, *2010*, 4436-4441. (h) Bui, N. N.; Ho, X. H.; Mho, S. I.; Jang, H. Y. Organocatalyzed α-Oxyamination of Aldehydes Using Anodic Oxidation. *Eur. J. Org. Chem*.

2009, *2009*, 5309-5312. For a review, see: (i) Zhu, L.; Wang, D.; Jia, Z.; Lin, Q.; Huang, M.; Luo, S. Catalytic Asymmetric Oxidative Enamine Transformations. *ACS Catal.* **2018**, *86*, 5466-5484 and references cited therein.

(3) (a) MacMillan, D. W. C. The Advent and Development of Organocatalysis. *Nature* **2008**, *455*, 304-308. (b) Mečiarová, M.; Tisovský, P.; Šebesta, R. Enantioselective Organocatalysis using SOMO Activation. *New J. Chem.* **2016**, *40*, 4855-4864 and references cited therein.

(4) List, B. The Ying and Yang of Asymmetric Aminocatalysis. *Chem. Commun.* **2006**, 819-824.

(5) (a) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. Structure-Nucleophilicity Relationships for Enamines. *Chem. - Eur. J.* **2003**, *9*, 2209-2218. (b) Kanzian, T.; Lakhdar, S. Mayr, H. Kinetic Evidence for the Formation of Oxazolidinones in the Stereogenic Step of Proline-Catalyzed Reactions. *Angew. Chem., Int. Ed.* **2010**, *49*, 9526-9529. (c) Lakhdar, S.; Maji, B.; Mayr, H. Imidazolidinone-Derived Enamines: Nucleophiles with Low Reactivity. *Angew. Chem., Int. Ed.* **2012**, *51*, 5739-5742. (d) Erdmann, H.; An, F.; Mayer, P.; Ofial, A. R.; Lakhdar, S.; Mayr, H. Structures and Reactivities of 2-Trityl- and 2-(Triphenylsilyl)pyrrolidine-Derived Enamines: Evidence for Negative Hyperconjugation with the Trityl Group. *J. Am. Chem. Soc.* **2014**, *136*, 14263-14269. (e) Timofeeva, D. S.; Mayer, R. J.; Mayer, P.; Ofial, A. R.; Mayr, H. Which Factors Control the Nucleophilic Reactivities of Enamines? *Chem. Eur. J.* **2018**, *24*, 5901-5910.

(6) (a) Fritsch, J. M.; Weingarten, H. Electrolytic oxidations of organics. I. Oxidative coupling of vinylidenebisdimethylamine to 1,1,4,4-tetrakis(dimethylamino)butadiene. *J. Am. Chem. Soc.* **1968**, *90*, 793-795. (b) Fritsch, J. M.; Weingarten, H.; Wilson, J. D. Electrolytic oxidations of organic compounds. II. N,N-dimethylaminoalkenes. *J. Am. Chem. Soc.* **1970**, *92*, 4038-4046. (c) Masui, M.; Ueda, C.; Moriguchi, T.; Michida, T.; Kataoka, M.; Ohmori, H. Anodic Dimerization of Enamines, 2-Cyano-2-phenylvinylamines. *Chem. Pharm. Bull.* **1984**, *32*, 1392-1400. (d) Schoeller, W. W.; Niemann, J.; Rademacher, P. On the Electrochemical Oxidation of Enamines. *J. Chem. Soc., Perkin Trans. 2* **1988**, 369-373. (e) Renaud, P.; Schubert, S. Reductive Alkylation of Enamines with Chloromethyl p-Tolyl Sulfone via a Radical Chain Process. *Angew. Chem., Int. Ed.* **1990**, *29*, 433-434. (f) Audebert, P.; Bekolo, H.; Cossy, J.; Bouzide, A. Electrochemical Evidence for

Intramolecular Reactions of the Electrogenerated Cation - Radicals of Some Amidoenamines. *J. Electroanal. Chem*. **1995**, *389*, 215-218. (g) Tabaković, I. Anodic Oxidation of Enaminones. *Electrochim. Acta* **1995**, *40*, 2809 -2813.

(7) Feng, C. L.; Chu, N. N.; Zhang, S. G.; Cai, J.; Chen, J. Q.; Hu, H. Y.; Ji, M. Solvent-Free Synthesis of β-Enamino Ketones and Esters Catalyzed by Recyclable Iron(III) Triflate. *Chem. Pap.* **2014**, *68*, 1097-1103.

(8) For recent representative examples: (a) Cheng, J.; Liu, X.; VandeVondele, J.; Sulpizi, M.; Sprik, M. Redox Potentials and Acidity Constants from Density Functional Theory Based Molecular Dynamics. *Acc. Chem. Res.* **2014**, *47*, 3522-3529. (b) Jono, R.; Tateyama, Y.; Yamashita, K. A Method to Calculate Redox Potentials Relative to the Normal Hydrogen Electrode in Nonaqueous Solution by Using Density Functional Theory-Based Molecular Dynamics. *Phys. Chem. Chem. Phys.* **2015**, *17*, 27103-27108. (c) Ho, J. Are Thermodynamic Cycles Necessary for Continuum Solvent Calculation of pK_as and Reduction Potentials? *Phys. Chem. Chem. Phys.* **2015**, *17*, 2859-2868. (d) Isegawa, M.; Neese, F.; Pantazis, D. A. Ionization Energies and Aqueous Redox Potentials of Organic Molecules: Comparison of DFT, Correlated ab Initio Theory and Pair Natural Orbital Approaches. *J. Chem. Theory Comput.* **2016**, *12*, 2272-2284. (e) Shen, L.; Zeng, X.; Hu, H.; Hu, X.; Yang, W. T. Accurate Quantum Mechanical/Molecular Mechanical Calculations of Reduction Potentials in Azurin Variants. *J. Chem. Theory Comput.* **2018,** *14*, 4948-4957. For a perspective, see: (f) Marenich, A. V.; Ho, J.; Coote, M. L.; Cramer, C. J.; Truhlar, D. G. Computational Electrochemistry: Prediction of Liquid-Phase Reduction Potentials. *Phys. Chem. Chem. Phys.* **2014**, *16*, 15068-15106 and references cited therein.

(9) Gaussian 09, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari,

K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.

(10) See Supporting Information for details.

(11) (a) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Acc. Chem. Res.* **2008***, 41*, 157-167. (b) Zhao, Y.; Truhlar, D. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. *Theor*. *Chem*. *Acc*. **2008**, *120*, 215-241.

(12) (a) Cancès, E.; Mennucci, B.; Tomasi, J. A New Integral Equation Formalism for the Polarizable Continuum Model: Theoretical Background and Applications to Isotropic and Anisotropic Dielectrics. *J. Chem. Phys.* **1997**, *107*, 3032-3041. (b) Tomasi, J.; Mennucci, B.; Cancès, E. The IEF Version of the PCM Solvation Method: An Overview of a New Method Addressed to Study Molecular Solutes at the QM ab Initio Level. *J. Mol. Struct. (Theochem)* **1999**, *464*, 211-226. (c) Tomasi, J.; Mennucci, B.; Cammi, R. Quantum Mechanical Continuum Solvation Models. *Chem. Rev.* **2005**, *105*, 2999-3093.

(13) For absolute potential of the standard hydrogen electrode and the problem of interconversion of potentials in different solvents, see: Isse, A. A.; Gennaro, A. Absolute Potential of the Standard Hydrogen Electrode and the Problem of Interconversion of Potentials in Different Solvents. *J. Phys. Chem. B* **2010**, *114,* 7894-7899.

(14) (a) Grimme, S. Supramolecular Binding Thermodynamics by Dispersion-Corrected Density Functional Theory. *Chem. - Eur. J.* **2012**, *18*, 9955-9964. (b) Alecu, I. M.; Zheng, J.; Zhao, Y.; Truhlar, D. G. Computational Thermochemistry: Scale Factor Databases and Scale Factors for Vibrational Frequencies Obtained from Electronic Model Chemistries. *J. Chem. Theory Comput.* **2010**, *6*, 2872-2887. (c) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Use of Solution-Phase Vibrational Frequencies in Continuum Models for the Free Energy of Solvation. *J.*

Phys. Chem. B **2011**, *115*, 14556-14562.

(15) Funes-Ardoiz, I.; Paton, R. S. GoodVibes, v2.0.1; 2017, DOI: 10.5281/zenodo.884527.

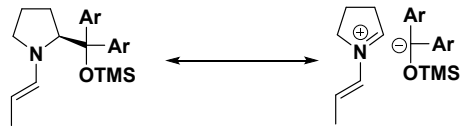
(16) NBO Version 3.1, Glendening, E. D.; Reed, A. E.; Carpenter, J.; Weinhold. E. F.

(17) Conversion to voltages *vs.* SCE involved the subtraction of 0.03 V for Ag/AgCl electrode. (a) Roth, H. G.; Romero, N. A.; Nicewicz, D. A. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry. *Synlett* **2016**, *27*, 714-723. (b) Pavlishchuk, V. V.; Addison, A. W. *Inorg. Chim. Acta* **2000**, *298*, 97-102.

(18) For conformations of tertiary enamines, see: (a) Seebach, D.; Grošelj, U.; Badine, D. M.; Schweizer, W. B.; Beck, A. K. Isolation and X-Ray Structures of Reactive Intermediates of Organocatalysis with Diphenylprolinol Ethers and with Imidazolidinones. *Helv. Chim. Acta* **2008**, *91*, 1999-2034. (b) Grošelj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K.; Krossing, I.; Klose, P.; Hayashi, Y.; Uchimaru, T. Structures of the Reactive Intermediates in Organocatalysis with Diarylprolinol Ethers. *Helv. Chim. Acta* **2009**, *92*, 1225-1259. (c) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. The Elusive Enamine Intermediate in Proline-Catalyzed Aldol Reactions: NMR Detection, Formation Pathway, and Stabilization Trends. *Angew. Chem., Int. Ed.* **2010**, *49*, 4997-5003. (d) Bock, D. A.; Lehmann, C. W.; List, B. Crystal Structures of Proline-Derived Enamines. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20636-20641. (e) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. Distinct Conformational Preferences of Prolinol and Prolinol Ether Enamines in Solution Revealed By NMR. *Chem. Sci.* **2011**, *2*, 1793-1803. For conformations of secondary enamines, see: (f) Huang, H.; Jacobsen, E. N. Highly Enantioselective Direct Conjugate Addition of Ketones to Nitroalkenes Promoted by A Chiral Primary Amine-Thiourea Catalyst. *J. Am. Chem. Soc.* **2006**, *128*, 7170-7171. (g) Lalonde, M. P.; Chen, Y. G.; Jacobsen, E. N. A Chiral Primary Amine Thiourea Catalyst for the Highly Enantioselective Direct Conjugate Addition of α,α-Disubstituted Aldehydes to Nitroalkenes. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366-6370. (h) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. A Simple Primary-Tertiary Diamine-Brønsted Acid Catalyst for Asymmetric Direct Aldol Reactions of Linear Aliphatic Ketones. *J. Am. Chem. Soc.* **2007**, *129*, 3074-3075. (i) Zhang, L.; Luo, S. Bio-inspired Chiral Primary Amine Catalysis. *Synlett* **2012**, *23*, 1575-1589.

(19) (a) Kirby, A. J. *Stereoelectronic Effects*; Oxford University Press: Oxford, U.K., 1996. (b) Alabugin, I. V., Gilmore, K. M.; Peterson, P. W. Hyperconjugation. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2011**, *1*, 109-141.

(20) According to the second order perturbation theory analysis of the Fock matrix, the stabilization energies associated with the negative hyperconjugation (delocalization of electrons from the lone pairs at nitrogen atom LPN to σ*C—C) are 8.46 and 9.26 kcal/mol for enamine **13E** and **14E**, respectively. The electron-deficient prolinol silyl ether **14** enhances the negative hyperconjugation effect and reduces the electronic density at nitrogen atom thus making the enamine more difficult to be oxidized.



Ar = Ph or 3,5-diCF_3Ph

(21) (a) Evans, D. H. One-Electron and Two-Electron Transfers in Electrochemistry and Homogeneous Solution Reactions. *Chem. Rev.* **2008**, *108*, 2113-2144. (b) Kalinowski, M. K.; Krygowski, T. M. Application of the LFER in Organic Electrochemistry: Interpretation of the Hammett Reaction Constant (σ) for Processes of Reversible Electroreduction in Aprotic Solvents. *Croat. Chem. Acta* **1985**, *58*, 107-126. (c) Miller, L. L.; Nordblom, G. D.; Mayeda, E. A. A Simple, Comprehensive Correlation of Organic Oxidation and Ionization Potentials. *J. Org. Chem.* **1972**, *37*, 916-918. (d) Parker, V, D. Energetics of Electrode Reactions. II. The Relationship between Redox Potentials, Ionization Potentials, Electron Affinities, and Solvation Energies of Aromatic Hydrocarbons. *J. Am. Chem. Soc.* **1976**, *98*, 98-103. (e) Fry, A. J.; Fox, P. C. An Improved Correlation between Polarographic Reduction Potential and Huckel Lumo Energy. Application to Non-Benzenoid Hydrocarbons. *Tetrahedron* **1986**, *42*, 5255-5266.

(22) Mayr, H.; Patz, M. Scales of Nucleophilicity and Electrophilicity: A System for Ordering Polar Organic and Organometallic Reactions. *Angew. Chem., Int. Ed.* **1994**, *33*, 938- 957.

(23) (a) Domingo, L. R.; Pérez, P. The Nucleophilicity *N* Index in Organic Chemistry. *Org. Biomol. Chem.* **2011**, *9*, 7168-7175. (b) Niyazymbetovt, M. E.; Evans, D. H. Oxidation Potential as a Measure of the Effect of Environment on the Reactivity of Anionic Nucleophiles. *J. Chem. Soc., Perkin Trans.*

2 **1993**, 1333-1338.

(24) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. Reference Scales for the Characterization of Cationic Electrophiles and Neutral Nucleophiles. *J. Am. Chem. Soc.* **2001**, *123*, 9500-9512.

(25) Mulliken spin population analysis was conducted as implanted in Gaussian 09 program. Becke spin population analysis was conducted using Multiwfn. Lu, T. Chen, F. *J. Comput. Chem.* **2012**, *33*, 580-592.

(26) Um, J. M.; Gutierrez, O.; Schoenebeck, F.; Houk, K. N.; MacMillan, D. W. C. Nature of Intermediates in Organo-SOMO Catalysis of α-Arylation of Aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 6001-6005.

(27) (a) Bordwell, F. G.; Cheng. J.-P. Radical-Cation Acidities in Solution and in the Gas Phase. *J. Am. Chem. Soc.* **1989**, *111*, 1792. (b) Yu, A.; Liu, Y.; Li, Z.; Cheng, J.-P. Computation of pK_a Values of Substituted Aniline Radical Cations in Dimethylsulfoxide Solution. *J. Phys. Chem. A* **2007**, *111*, 9978-9987.

(28) (a) Goulet-Hanssens, A.; Rietze, C.; Titov, E.; Abdullahu, L.; Grubert, L.; Saalfrank, P.; Hecht, S. Hole Catalysis as a General Mechanism for Efficient and Wavelength-Independent Z/E Azobenzene Isomerization. *Chem* **2018**, *4*, 1740-1755. (b) Hwang, J. Y.; Baek, J. H.; Shin, T. I.; Shin, J. H.; Oh, J. W.; Kim, K. P.; You, Y.; Kang, E. J. Single-Electron-Transfer Strategy for Reductive Radical Cyclization: $Fe(CO)_5$ and Phenanthroline System. *Org. Lett.* **2016**, *18*, 4900-4903.

(29) Terrett, J. A.; Clift, M. D.; MacMillan, D. W. C. Direct β-Alkylation of Aldehydes via Photoredox Organocatalysis. *J. Am. Chem. Soc.* **2014**, *136*, 6858-6861.

(30) (a) Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. Photochemistry and Photophysics of Coordination Compounds: Iridium. *Top. Curr. Chem.* **2007**, *281*, 143-203. (b) Kalyanasundaram, K. Photophysics, Photochemistry and Solar Energy Conversion with Tris(bipyridyl)ruthenium(II) and Its Analogues. *Coord. Chem. Rev.* **1982**, *46*, 159-244. (c) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium(III)

Complex. *Chem. Mater.* **2005**, *17*, 5712-5719.

(31) Xu, C.; Zhang, L.; Zhou, P.; Luo, S.; Cheng, J.-P. A Practical Protocol for Asymmetric Synthesis of Wieland-Miescher and Hajos-Parrish Ketones Catalyzed by a Simple Chiral Primary Amine. *Synthesis* **2013**, *45*, 1939-1945.

(32) (a) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. Expedient Construction of the [7–5–5] All-Carbon Tricyclic Core of the Daphniphyllum Alkaloids Daphnilongeranin B and Daphniyunnine D. *Org. Lett.* **2012**, *14*, 1684-1687. (b) Cossy J.; Thellend, A. A 4-Dimethylaminopyridine-Catalyzed Aminolysis of β-Ketoesters. Formation of ß-Ketoamides. *Synthesis* **1989**, 753-755. (c) Kalaitzakis, D.; Rozzell, J. D.; Smonou, I.; Kambourakis, S. Synthesis of Valuable Chiral Intermediates by Isolated Ketoreductases: Application in the Synthesis of α-Alkyl-β-hydroxy Ketones and 1,3-Diols. *Adv. Synth. Catal*. **2006**, *348*, 1958-1969.

(33) (a) Xu, C.; Zhang, L.; Luo, S. Asymmetric Enamine Catalysis with β-Ketoesters by Chiral Primary Amine: Divergent Stereocontrol Modes. *J. Org. Chem.* **2014**, *79*, 11517-11526. (b) Xu, C.; Zhang, L.; Luo, S. Merging Aerobic Oxidation and Enamine Catalysis in the Asymmetric α-Amination of β-Ketocarbonyls Using N-Hydroxycarbamates as Nitrogen Sources. *Angew. Chem., Int. Ed.* **2014**, *53*, 4149-4153.

(34) (a) Wang, D.; Zhang, L.; Luo, S. Visible Light Promoted β-C-H Alkylation of β-Ketocarbonyls via a β-Enaminyl Radical Intermediate. *Chin. J. Chem.* **2018**, *36*, 311-320. (b) Dürbeck, H. W.; Duttka, L. L. Conjugated Enamine-III: Spectroscopic Studies on the Structure-cis-fixed, Cyclic β-enamino Esters, with Special Emphasis on Internal Hydrogen Bonds. *Tetrahedron* **1973**, *29*, 4285-4290. (c) Stevens, C. V.; Kesteleyn, B.; Rosas Alonso, E.; De Kimpe, N. Synthesis of 3-chloroanthranilates from α,γ,γ-trichloro-β-iminoesters. *Tetrahedron* **2001**, *57*, 7685-7692. (d) Zhao, Y.; Deng, D.-S.; Ma, L.-F.; Ji, B.-M.; Wang, L.-Y. A New Copper-Based Metal-Organic Framework as a Promising Heterogeneous Catalyst for Chemo- and Regio-Selective Enamination of β-Ketoesters. *Chem. Commun.* **2013**, *49*, 10299-10301. (e) Cromwell, N. H.; Babson, R. D.; Harris, C. E. α,β-Unsaturated Aminoketones. VIII.[1] Reaction of Primary Amines with 1,3-Diketones and Bromine Derivatives of Benzalacetophenone. Ethylene Imines. *J. Am. Chem. Soc. 1943*, **65**, 312–315. (f)

Winck, C. R.; Darbem, M. P.; Gomes, R. S.; Rinaldi, A. W.; Domingues, N. L. C. Zn[aminoacid]$_2$ Hybrid Materials Applied as Heterogeneous Catalysts in the Synthesis of β-enaminones. *Tetrahedron Lett.* **2014**, *55*, 4123-4125. (g) Deng, D.; Xiao, L.; Chung, I.; Kim, I. S.; Gopiraman, M. Industrial-Quality Graphene Oxide Switched Highly Efficient Metal- and Solvent-Free Synthesis of β-Ketoenamines under Feasible Conditions. *ACS Sustainable Chem. Eng.* **2017**, *5*, 1253-1259. (h) Boehme, H.; Braun, R. β-substituted Enamines, II. Reactions of Primary Amines with 2-chloro-1,3-dicarbonyl Compounds. *Justus Liebigs Ann. Chem.* **1971**, *744*, 20-26. (i) Bhattacherjee, D.; Thakur, V.; Shil, A. K.; Das, P. Hypervalent Iodine-Promoted Aromatization of Exocyclic β-Enaminones for the Synthesis of meta-N,N-Diarylaminophenols. *Adv. Synth. Catal.* **2017**, *359*, 2202-2208.

(35) (a) Docken, J. S.; Houkom, E. C.; Jorgenson, R. A.; Ostercamp, D. L.; Tweed, G. A.; Werth, R. G. Vinylogous Systems. 4. Mass Spectra of Vinylogous Ureas and Ureides. *J. Org. Chem.* **1978**, *43*, 505-509. (b) Bartoli, G.; Cimarelli, C.; Dalpozzo, R.; Palmieri, G. A Versatile Route to β-enamino Esters by Acylation of lithium Enamines with Diethyl Carbonate or Benzyl Chloroformate. *Tetrahedron* **1995**, *51*, 8613-8622. (c) Chevalley, A.; Férézou, J.-P. One-Pot Formation of Aza-Enolates from Secondary Amines and Condensation to Esters and Alkyl Bromides. *Tetrahedron* **2012**, *68*, 5882-5889. (d) Bartoli, G. Cimarelli, C.; Palmieri, G.; Bosco, M.; Dalpozzo, R. Reactivity of Imine Anions with Esters: A General Method for the Synthesis of Enamino Ketones. *Synthesis* **1990**, *10*, 895-897. (e) Braibante, H. T. S.; Braibante, M. E. F.; Rosso, G. B.; Oriques. D. A. Preparation of β-enamino Carbonylic Compounds Using Microwave Radiation/K-10. *J. Braz. Chem. Soc.* **2003**, *14*, 994-997. (f) Epifano, F.; Genovese, S.; Curini, M. Ytterbium Triflate Catalyzed Synthesis of β-enaminones. *Tetrahedron Lett.* **2007**, *48*, 2717-2720.

(36) (a) Krogsgaard-Larsen, P.; Christensen, S.; Hjeds, H. Organic Hydroxylamine Derivatives. VII. Isoxazolin-5-ones. An Investigation of a Reaction Sequence Previously Stated to Give 3-Hydroxyisoxazoles. *Acta chem. Scand.* **1973**, *27*, 2802-2812. (b) Xin, D.; Burgess, K. A Chemoselective Route to β-Enamino Esters and Thioesters. *Org. Lett.* **2014**, *16*, 2108-2110. (c) Xu,

F.; Lv, H.-X.; Wang, J.-P.; Tian, Y.-P.; Wang, J.-J. A Mild Method for the Synthesis of β-Enaminones and β-Enamino Esters Using KH_2PO_4 as Catalyst. *J. Chem. Res.* **2008**, *2008*, 707. (d) Martins, M. A. P.; Guarda, E. A.; Frizzo, C. P.; Marzari, M. R. B.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. An Ionic Liquid as Reaction Medium for the Synthesis of Halo-Containing β-Enaminones at Room Temperature. *Monatsh. Chem.* **2008**, *139*, 1321-1327. (e) Huang, J.; Liang, Y.; Pan, W.; Yang, Y.; Dong, D. Efficient Synthesis of Highly Substituted Pyrrolin-4-ones via PIFA-Mediated Cyclization Reactions of Enaminones. *Org. Lett.* **2007**, *9*, 5345- 5348. (f) Denissen, W.; Winne, J. M.; Du Prez, F. E.; Rivero, G.; Nicola, R.; Leibler, L. Vinylogous Urethane Vitrimers. *Adv. Funct. Mater.* **2015**, *25*, 2451-2457. (g) Sarkar, R.; Mukhopadhyay, C. Cu Catalyzed Cross-Dehydrogenative Coupling Reaction for the Synthesis of 3-Hydroxy-2-Pyrrolidinones. *Tetrahedron Lett.* **2018**, *59*, 3069-3076.

(37) (a) Harrad, M. A.; Outtouch, R.; Ait Ali, M.; Firdoussi, L. E.; Karim, A.; Roucoux, A. $Ca(CF_3COO)_2$: An Efficient Lewis Acid Catalyst for Chemo- and Regio-selective Enamination of β-Dicarbonyl Compounds. *Catalysis Communications* **2010**, *11*, 442- 446. (b) Bhargava, S. S.; Saharia, G. S. Studies in Cycloheptane Series. 21. Condensation of Ethyl Cycloheptan-1-One-2-Carboxylate with Aromatic Primary Amines and Synthesis of 2,3-Pentamethylene-Aryl-Substituted-4-Quinolones. *Indian J. Chem.* **1972**, *10*, 955-956. (c) Neupane, P.; Li, X.; Jung, J. H.; Lee, Y. R.; Kim, S. H. Efficient One-Pot Synthesis of Cyclic β-Enaminoamides by Thermal Wolff Rearrangement of Cyclic 2-Diazo-1,3-Dicarbonyls and Conversion to Uracil Derivatives. *Tetrahedron* **2012**, *68*, 2496-2508. (d) Cheng, G.; Zeng, X.; Shen, J.; Wang, X.; Cui, X. A Metal-Free Multicomponent Cascade Reaction for the Regiospecific Synthesis of 1,5-Disubstituted 1,2,3-Triazoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 13265-13268.

(38) (a) Fretz, H.; Gaugler, M.; Schneider, J. 3-(Arylamino)quinolin-2(1H)- and -4(1H)-ones: Reinvestigation of the Reaction between Ethyl 2-Chloro-3-(phenylamino)but-2-enoate and Arylamines. *Helv. Chim. Acta* **2000**, *83*, 1145-1150. (b) Bhattacherjee, D.; Thakur, V.; Sharma, S.; Kumar, S.; Bharti, R.; Reddy, C. B.; Das, P. Iodine(III)-Promoted Ring Contractive Cyanation of Exocyclic β-Enaminones for the Synthesis of Cyanocyclopentanones. *Adv. Synth. Catal.* **2017**, *359*, 2209-2214. (c) Šimůnek, P.; Lusková, L.; Svobodová, M.; Bertolasi, V.; Lyčka, A.; Macháček, V.

Synthesis and Structure of Some Azo Coupled Cyclic β-enaminones. *Magn. Reson. Chem*. **2007**, *45*, 330-339.