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Article

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Oxidative Cyclization of *β*-Aminoacrylamides Mediated by PhIO: Chemoselective Synthesis of Isoxazoles and 2*H*-Azirines

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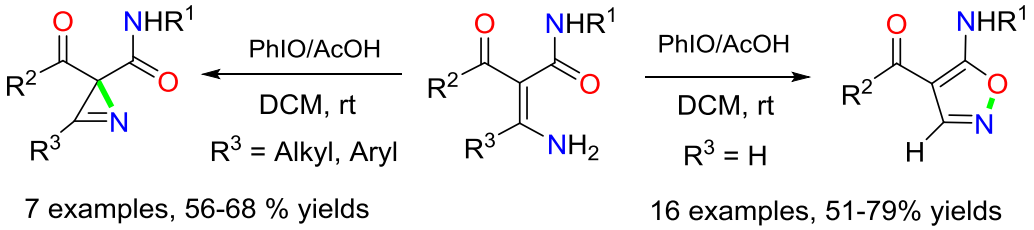
Abstract



Cyclization of a variety of *β*-amino acrylamides in the presence of iodosobenzene (PhIO) is described. This process features mild reaction conditions, simple execution and high chemoselectivity, and thereby provides an efficient protocol for the divergent synthesis of substituted isoxazoles and 2*H*-azirines via switchable N-O and N-C bond formation controlled by simply varying the *β*-substituent R^3 of the readily available substrates.

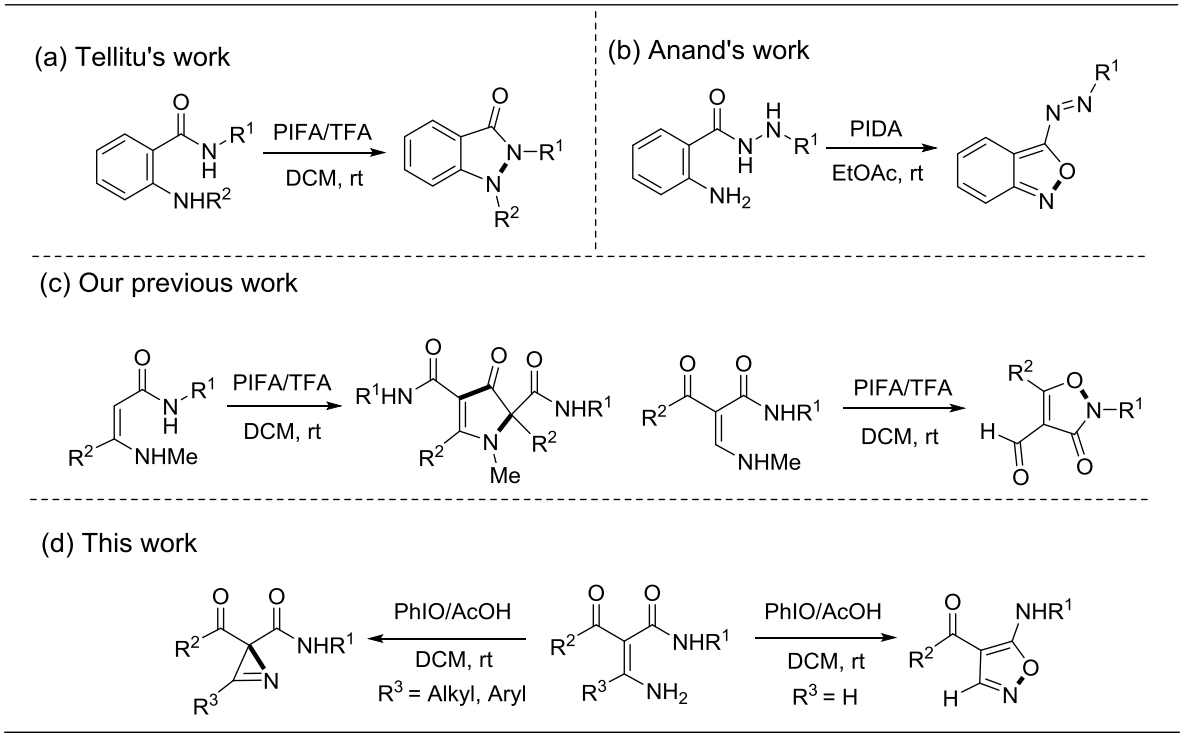
Introduction

Five-membered aza-heterocycles, such as isoxazoles and pyrazoles, have attracted significant research for their presence in numerous natural products and designed molecules along with diverse bioactivities,[1,2] and found widespread applications in organic synthesis,[3] medicinal chemistry,[4] and agrochemistry.[5] Thus, the development of convenient, efficient, and in particular environmentally benign synthetic approaches to construct N-C and N-X (X = N, O, S) bonds has emerged as a continuing focus in synthetic chemistry.[6,7] In this context, the functionalization of various amides mediated by hypervalent iodine reagents represents one of the most straightforward and fascinating protocols to access various nitrogen-containing compounds.[8,9]

In the early 1990s, Kikugawa et al discovered that *N*-acyl nitrenium ions could be generated by the oxidation of amides with phenyliodine(III)-bis(trifluoroacetate) (PIFA), and demonstrated their potential in electrophilic aromatic substitution to create N-C linkage.[10] In 2006, Tellitu et al successfully achieved the synthesis of indazolones via PIFA-mediated intramolecular N-N bond formation of anthranilamides (Scheme 1a)[11]. Most recently, Anand et al reported the synthesis of benzisoxazoles, instead of indazolones, via phenyliodine (III) diacetate (PIDA)-mediated intramolecular N-O bond formation of 2-amino- benzohydrazides (Scheme 1b).[12]

During the course of our studies on the reactions of various functionalized *β*-oxo amides mediated by hypervalent iodine reagents, we developed efficient synthesis of isothiazol-3(2*H*)-ones, [13] spiro-fused pyrazolin-5-one *N*-oxides,[14] 2,5-dihydrofurans[15] and spiro-fused dihydrofuran-3(2*H*)-ones,[16] respectively, in which N-S, N-N or C-O bond is formed. In contrast to Tellitu's work,[11] we noted that treatment of different *β*-aminoacrylamides with PIFA delivered pyrrolin-4-ones[17] and isoxazol-3(2*H*)-ones[18] via N-C and N-O bond formation, respectively, and the product with N-N bond formation was not even detected within these reactions (Scheme 1c). Clearly, it is only small variation on the chemical structures of substrates that caused the significant influence on their oxidative reaction orientation and selectivity.

Scheme 1. Hypervalent Iodine Reagent-Mediated Cyclizations.



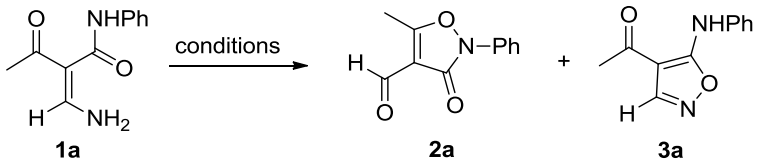
In connection with our previous work and following with our research on the synthesis of highly valuable heterocycles from *β*-oxo amide derivatives, we investigated the reaction behaviors of *α*-acyl-*β*-aminoacrylamides towards different hypervalent iodine (III) reagents. As a result, we developed an efficient divergent synthesis of substituted isoxazoles and 2*H*-azirines from *α*-acyl-*β*-amino acrylamides mediated by PhIO via switchable N-O bond and N-C bond formation depending on the nature of *β*-substituent R^3 of the readily available substrates (Scheme 1d). Herein, we wish to report our experimental results and present a proposed mechanism involved in the oxidative cyclization reactions.

Results and Discussion

According to our reported procedure,[19] a series of *β*-aminoacrylamides **1** were prepared from commercially available *β*-oxo amides. From these substrates, *α*-acetyl-*β*-amino-*N*-phenyl acrylamide **1a** was selected as the model compound for the subsequent investigation in the presence of different

hypervalent iodine reagents. The reaction of **1a** and PIFA (1.5 equiv) was first attempted in the presence of trifluoroacetic acid (TFA, 1.0 equiv) in dichloromethane (DCM) at room temperature. As indicated by TLC, the reaction took place, but it finally formed an inseparable mixture (Table 1, entry 1). From the ^{1}H NMR spectra of the mixture, some characteristic signals of isoxazol-3(2*H*)-one **2a** could be observed (see Supporting Information), which is consistent with our previous reported results.[18] To our delight, treatment of **1a** with PIDA, a less potent oxidant than PIFA, in the presence of TFA (1.0 equiv) in DCM at room temperature furnished a main product, which was characterized as 1-[5-(phenylamino) isoxazol-4-yl]ethan-1-one **3a** on the basis of its spectral and analytical data (Table 1, entry 2). Similarly, the reaction of **1a** with PIDA and acetic acid (AcOH) also generated **3a** (Table 1, entry 3). The structure of **3a** was further elucidated by X-ray diffraction analysis (see supporting information). Indeed, the similar phenomenon wherein PIFA and PIDA exhibited different reaction behaviors was found by Li and coworkers in the oxidative reactions of enamines,[20] and this might originate from their different oxidativities.

Table 1. Reaction of 1a under Different Conditions.[a]



1a **2a** **3a**

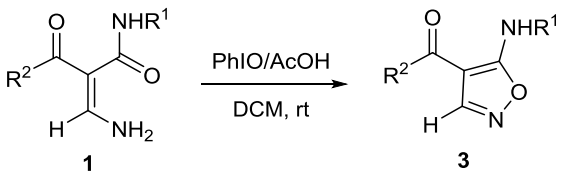
Entry	Oxidant (equiv)	Additive (equiv)	Solvent	Time (h)	Yield[b] (%)
1	PIFA (1.5)	TFA (1.0)	CH_2Cl_2	12.0	mixture
2	PIDA (1.5)	TFA (1.0)	CH_2Cl_2	12.0	45(26)
3	PIDA (1.5)	AcOH (1.0)	CH_2Cl_2	12.0	51(18)
4	PhIO (1.5)	AcOH (1.0)	CH_2Cl_2	12.0	57(15)
5	PhIO (2.0)	AcOH (1.0)	CH_2Cl_2	1.3	68
6	**PhIO (2.0)**	**AcOH (2.0)**	**CH_2Cl_2**	**1.0**	**76**

7	PhIO (2.0)	TFA (2.0)	CH_2Cl_2	1.6	64
8	PhIO (2.0)	CF_3CH_2OH (2.0)	CH_2Cl_2	3.0	59
9	PhIO (2.0)	$BF_3{\cdot}OEt_2$ (2.0)	CH_2Cl_2	1.0	mixture
10	PIDA (2.0)	—	CH_2Cl_2	1.0	73
11	PhIO (2.0)	AcOH (2.0)	CH_3CN	12.0	18(66)
12	PhIO (2.0)	AcOH (2.0)	THF	12.0	26(52)
13	PhIO (2.0)	AcOH (2.0)	toluene	12.0	42(38)

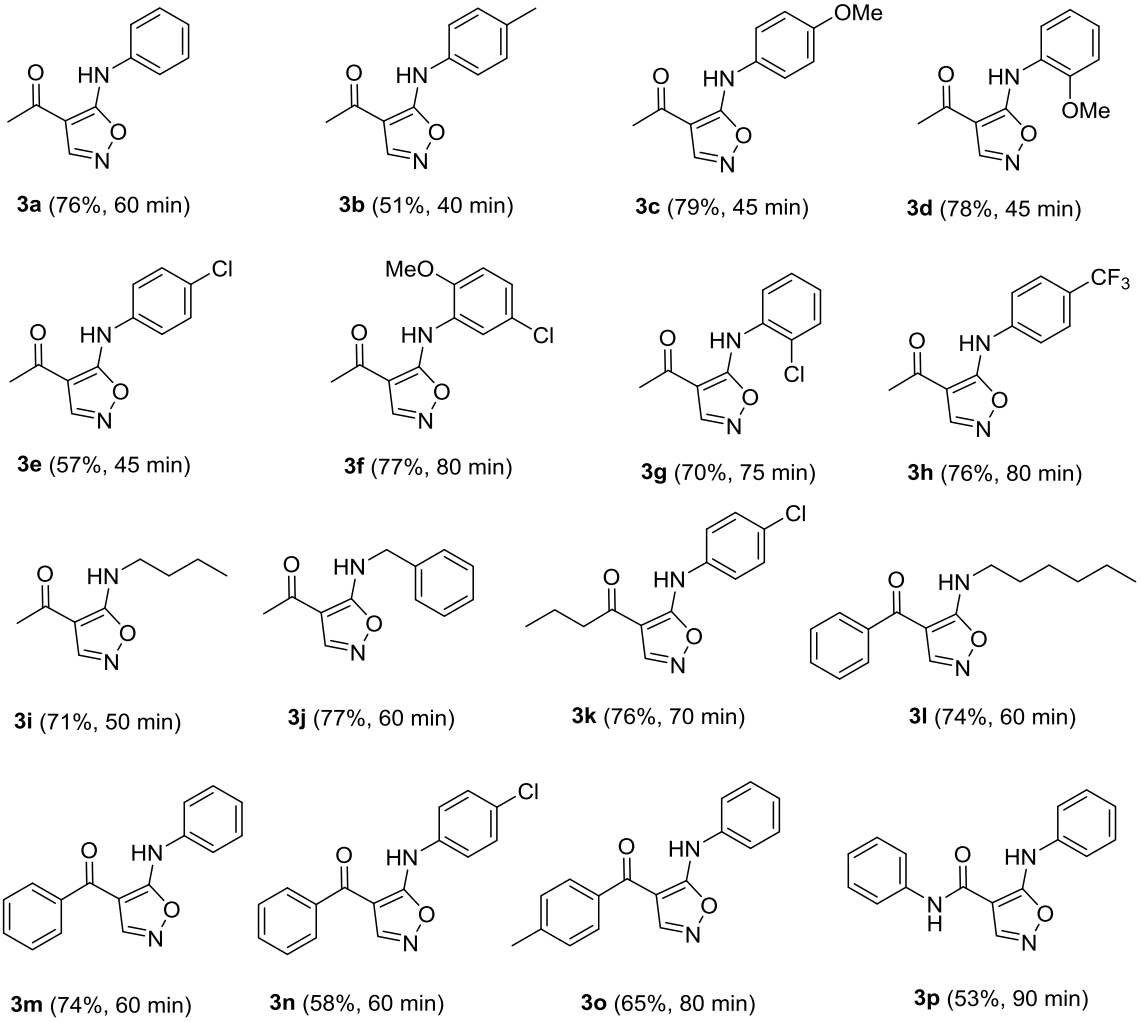
[a] Reagents and conditions: **1a** (1.0 mmol), solvent (10.0 mL), rt. [b] The data in parentheses for the recovery of **1a**.

An extensive optimization of various reaction parameters, including hypervalent iodines, additives, and solvents, was then investigated, and some results are summarized in Table 1. It was observed that the yield of **3a** was slightly improved when PhIO was employed (entry 4), and the conversion of **1a** was accelerated by increase of PhIO to 2.0 equivalents (entries 5 and 6). These results reveal that the oxidativity of hypervalent iodine reagents and their loading dosages have significant influences on the reaction of acrylamide **1a**.[18] Further experiments demonstrate that acetic acid is more effective than other tested additives (entries 5-9). Considering that PIDA could be generated from PhIO in the presence of AcOH in DCM at room temperature,[20] we conducted a reaction of **1a** with PIDA (2.0 equiv), which afforded **3a** in 73% yield (entry 10). The solvent screening revealed that the reaction of **1a** and PhIO could take place in acetonitrile, THF or toluene, but the conversion of **1a** was slow and the yield of **3a** was quite lower (entries 11-13).

Table 2. Synthesis of Isoxazoles 3 from *β*-Aminoacrylamides 1.[a]



1 3

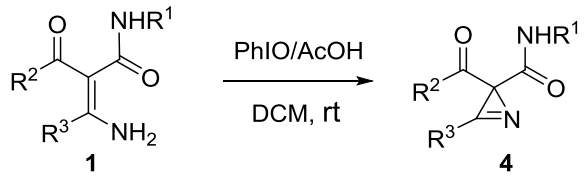


[a] Reagents and conditions: **1** (1.0 mmol), PhIO (2.0 mmol), AcOH (2.0 mmol), DCM (10.0 mL), rt; The data in parentheses: yield and reaction time.

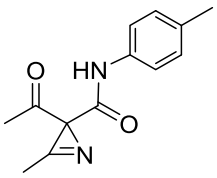
With the optimal reaction conditions in hand, the scope and limitations of the PhIO-mediated oxidative transformation were then explored. Thus, a series of *β*-aminoacrylamides **1** were treated with PhIO (2.0 equiv) and AcOH (2.0 equiv) in DCM at room temperature, and some of the results are summarized in Table 2. It was found that the reactions of **1b-j** bearing varied electron-donating/ electron-withdrawing *N*-aryl, *N*-alkyl and *N*-benzylamide group R^1 proceeded smoothly and furnished the corresponding isoxazoles **3b-j** in moderate to good yields. The versatility of this isoxazole synthesis was further evaluated by performing *β*-amino acryl amides **1k-p** bearing varied alkyl, aryl or amino groups R^2 under the identical conditions to afford the corresponding isoxazoles **3k-p** in good

yields. Therefore, we developed a protocol for the operationally simple and efficient construction of **N-O** bond in a chemoselective manner, which also provided a straightforward synthesis of substituted isoxazoles of type **3** from functionalized acrylamides **1**.

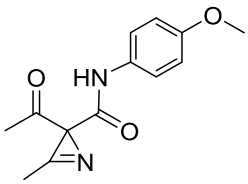
Table 3. Synthesis of 2*H*-azirines 4 from *β*-Aminoacrylamides 1.[a]



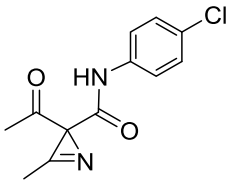
1 **4**



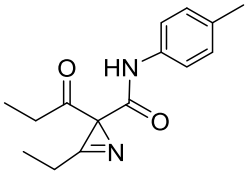
4q (63%, 5.0 h)



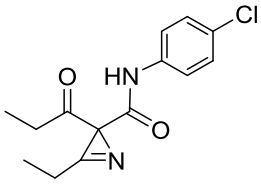
4r (62%, 5.0 h)



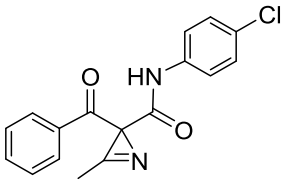
4s (68%, 5.5 h)



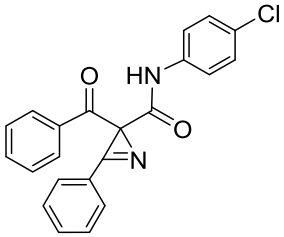
4t (64%, 4.0 h)



4u (67%, 4.5 h)



4v (58%, 5.0 h)



4w (56%, 5.5 h)

[a] Reagents and conditions: **1** (1.0 mmol), PhIO (2.0 mmol), AcOH (2.0 mmol), DCM (10.0 mL), rt.
[b] The data in parentheses: yield for **4** and reaction time.

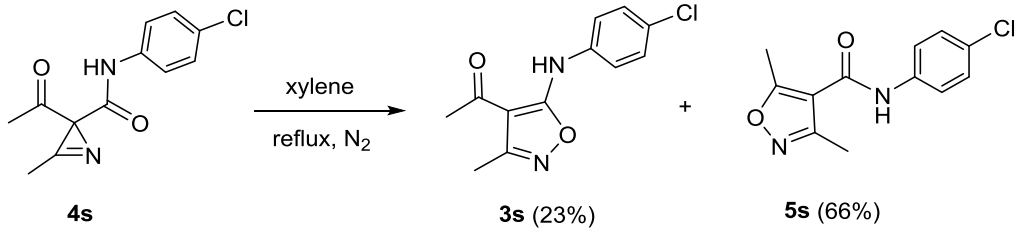
Notably, when acrylamide **1q** bearing a *β*-methyl substituent R^3 was subjected to the identical conditions as described for **3a** in entry 6, Table 1, the reaction proceeded smoothly to give a major product, which was characterized as 2-acetyl-*N*-(4-methoxyphenyl)-3-methyl-2*H*-azirine-2-carboxamide **4q**, instead of the corresponding isoxazole **3q**, on the basis of its spectral and analytical data (Table 3). Comparison of the ^{13}C NMR spectra between **4q** and **3b** let us establish the structure of **4q** without difficulty (see supporting information). In the ^{13}C NMR spectra of **3b**, a characteristic peak appears at 98 ppm assigned to the signal of $C_{(sp2)}$-2 of isoxazole ring. In the ^{13}C NMR spectra of **4q**,

however, the peak at this region disappears, and a new peak appears at 45 ppm which is easily assigned to the signal of $C_{(sp3)}$-2 of 2*H*-azirine ring.[21,22]

In the same fashion, acrylamides **1r-w** decorated by varied alkyl and aryl groups R^3 at *β*-position were exclusively converted into the corresponding fully substituted 2*H*-azirines **4r-w** in moderate to fairly good yields (Table 3). These results indicated that the nature of *β*-substituent R^3 is of crucial importance for the transformation of acrylamides **1** mediated by PhIO. Namely, the chemoselective synthesis of isoxazoles **3** or 2*H*-azirines **4** can be switched by simply varying the *β*-substituent of *α*-acyl-*β*-aminoacrylamides **1**. Actually, 2*H*-azirines are highly strained and reactive three-membered aza-heterocycles, and extensively studied for their presence in some natural products and their utility as versatile intermediates for the synthesis of other aza-heterocycles.[23,24]

Consequently, we selected **4s** as a model compound and subjected it to thermolysis conditions, *i.e.* in xylene under reflux in the N_2 atmosphere. The reaction proceeded smoothly as indicated by TLC results and furnished two products, which were characterized as isomeric isoxazoles **3s** and **5s** on the basis of their spectral and analytical data (Scheme 2).[21] Obviously, **3s** and **5s** were formed through chemoselective rearrangement of 2*H*-azirine **4s**,[25,26] and the selectivity might be attributed to the different reactivity of *O*-atom in a ketone or an amide group.[27] This finding provided an alternative protocol for the synthesis of fully substituted isoxazoles of type **3** and **5**.

Scheme 2. Thermolysis of 2*H*-azirine 4s

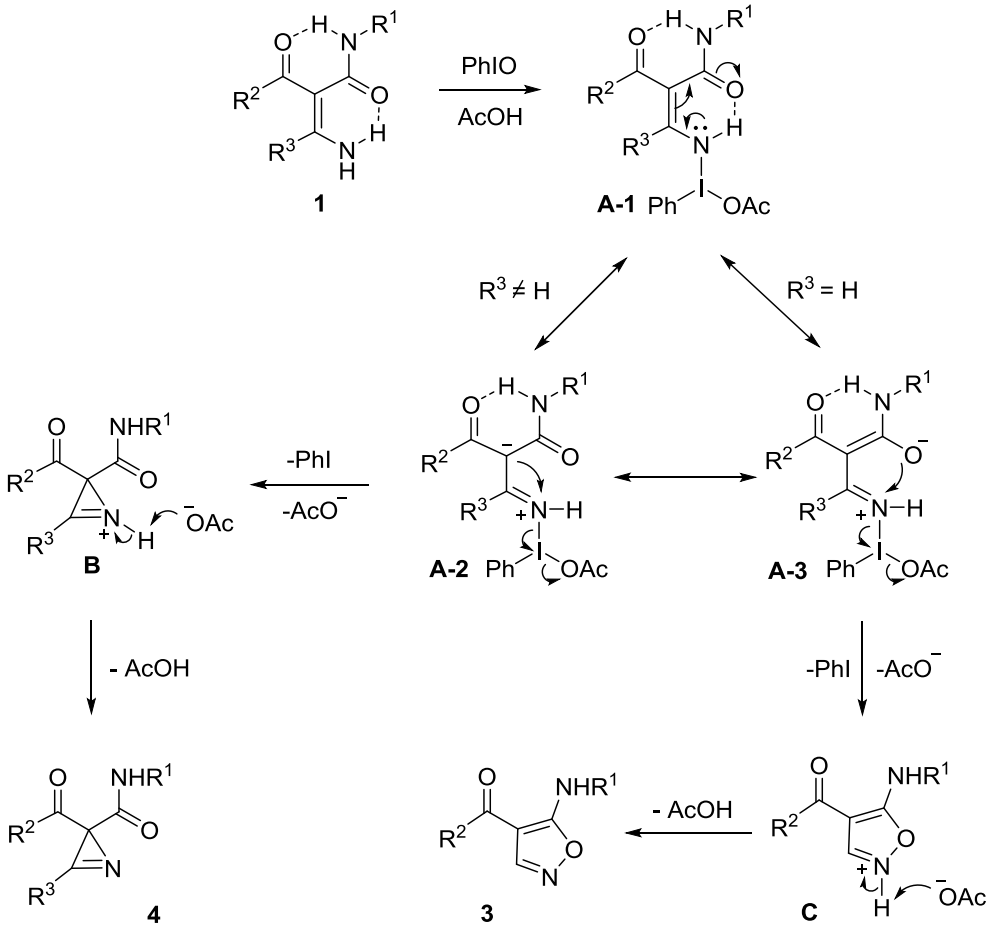


4s **3s** (23%) **5s** (66%)

On the basis of all the obtained results, a mechanism for the metal-free oxidative reaction of *α*-acyl-*β*-aminoacrylamides **1** is proposed as illustrated in Scheme 3. The transformation is initiated from the nucleophilic addition of acetic acid to idosobenzene to form a tricoordinated iodine species,

i.e. PIDA.[20] Acrylamide **1** reacts with the *in-situ* generated PIDA to give an intermediate **A-1**,[21] which can also be represented by its resonance structures, carbanion **A-2** and enolate ion **A-3**.[27,28] For both electronic and steric effects, carbanion **A-2** is a favorable form when R^3 is alkyl or aryl group, wherein carbanion is particularly stabilized by the adjacent electron-withdrawing carbonyl groups and iminium moiety, and undergoes a cyclization to afford intermediate **B** along with the release of phenyl iodide and acetate anion.[21] The deprotonation of **B** by acetate anion produces the title 2*H*-azirine **4**. While R^3 is H, the formation of planar conjugated enolate ion **A-3** is viable not only for the small size of R^3 but also for the ease of charge delocalization. The subsequent cyclization of **A-3** takes place to form intermediate **C**, which is deprotonated to give the product isoxazole **3**.

Scheme 3. Plausible Mechanism for the Reaction of *β*-Amino acrylamides 1.



Conclusions

In summary, we developed a facile and efficient divergent synthesis of isoxazoles and 2*H*-azirines by oxidative cyclization of a variety of *β*-amino acrylamides in the presence of iodosobenzene (PhIO), wherein N-O or N-C bond formation is controlled by simply varying the *β*-substituent of the readily available substrates. The mild reaction conditions, simplicity of execution, high chemoselectivity, and synthetic potential of the products make this novel protocol very attractive. Further work on the reaction mechanism, the scope expansion and the utility of this metal catalyst-free protocol are currently underway in our laboratory.

Experimental Section

General Experimental

All reagents were purchased from commercial sources and used without treatment unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 ^{o}C at 300 MHz (or 400 MHz) and 100 MHz (or 75 MHz), respectively, with TMS as internal standard. IR spectra (KBr) were recorded on FTIR-spectrophotometer in the range of 400-4000 cm^{-1}. High resolution mass spectra were recorded on a LTQ-Orbitrap mass spectrometer using ESI mode. Melting points were determined on a micro-melting point apparatus, and uncorrected.

Preparation and analytical data of *β*-aminoacrylamides 1

General procedure A for the preparation of 1a-o: [19] To a well-stirred solution of *α*-acyl-*β*-dimethyaminoacrylamide (5.0 mmol) in ethanol (15.0 mL) was added NH_4OAc (0.96 g, 12.5 mmol) at room temperature. Then the reaction mixture was heated and stirred under reflux until the completion of the reaction as indicated by TLC. The resulting mixture was poured into saturated aqueous NaCl (100.0 mL). The precipitated solid was collected by filtration, washed with water (3 × 20.0 mL), and dried *in vacuo* to give compound **1**.

β-Aminoacrylamides **1a-f** are known compounds. They were prepared and their analytical data

(for ^{1}H NMR spectra, see supporting Information) are in good agreement with those reported in the literature.[19]

2-(Aminomethylene)-3-oxo-N-phenylbutanamide ***(1a)****.* Prepared from 2-[(dimethylamino) methylene]-3-oxo-*N*-phenylbutanamide (1.16 g, 5.0 mmol) via general procedure A. Compound **1a** was obtained as a white solid (0.92 g, 90%).

2-(Aminomethylene)-3-oxo-N-(p-tolyl)butanamide ***(1b)****.* Prepared from 2-[(dimethylamino) methylene]-3-oxo-*N*-(p-tolyl)butanamide (1.23 g, 5.0 mmol) via general procedure A. Compound **1a** was obtained as a white solid (0.95 g, 87%).

2-(Aminomethylene)-N-(4-methoxyphenyl)-3-oxobutanamide ***(1c)****.* Prepared from 2-[(dimethyl-amino)methylene]-*N*-(4-methoxyphenyl)-3-oxobutanamide (1.31 g, 5.0 mmol) via general procedure A. Compound **1a** was obtained as a white solid (1.06 g, 91%).

2-(Aminomethylene)-N-(2-methoxyphenyl)-3-oxobutanamide ***(1d)****.* Prepared from 2-[(dimethyl-amino)methylene]-*N*-(2-methoxyphenyl)-3-oxobutanamide (1.31 g, 5.0 mmol) via general procedure A. Compound **1a** was obtained as a white solid (1.04 g, 89%).

2-(Aminomethylene)-N-(4-chlorophenyl)-3-oxobutanamide ***(1e)****.* Prepared from *N*-(4-chloro-phenyl)-2-[(dimethylamino)methylene]-3-oxobutanamide (1.33 g, 5.0 mmol) via general procedure A. Compound **1a** was obtained as a white solid (1.05 g, 88%).

2-(Aminomethylene)-N-(2-chloro-6-methoxyphenyl)-3-oxobutanamide ***(1f)****.* Prepared from *N*-(2-chloro-6-methoxyphenyl)-2-[(dimethylamino)methylene]-3-oxobutanamide (1.48 g, 5.0 mmol) via general procedure A. Compound **1a** was obtained as a white solid (1.15 g, 86%).

2-(Aminomethylene)-N-(2-chlorophenyl)-3-oxobutanamide ***(1g)****.* Prepared from *N*-(2-chloro phenyl)-2-[(dimethylamino)methylene]-3-oxobutanamide (1.33 g, 5.0 mmol) via general procedure A. Compound **1g** was obtained as a white solid (1.11 g, 93%). mp 183-184 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.08 (s, 1H), 10.20 (bs, 1H), 8.39 (d, J = 8.1 Hz, 1H), 7.98-8.05 (m, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 6.98-7.03 (m, 1H), 5.94 (bs, 1H), 2.34 (s, 3H); ^{13}C {^{1}H} NMR (100

MHz, DMSO-d_6): δ 195.4, 166.6, 161.0, 135.5, 128.6, 126.9, 123.1, 121.6, 121.1, 100.7, 25.6; IR (KBr): v = 3204, 2958, 1642, 1618, 1454, 1401, 755 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{12}ClN_2O_2$ 239.0582; Found 239.0578.

*2-(Aminomethylene)-3-oxo-N-[4-(trifluoromethyl)phenyl]butanamide (**1h**).* Prepared from 2-[(dimethylamino)methylene]-3-oxo-*N*-[4-(trifluoromethyl)phenyl]butanamide (1.50 g, 5.0 mmol) via general procedure A. Compound **1h** was obtained as a white solid (1.20 g, 88%). mp 189-190 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 11.94 (s, 1H), 10.25 (bs, 1H), 7.99-8.07 (m, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H), 5.89 (bs, 1H), 2.34 (s, 3H); ^{13}C {^1H} NMR (100 MHz, DMSO-d_6): δ 195.7, 166.8, 161.2, 141.9, 125.5, 124.0 (q, $^1J_{CF}$ = 270), 122.3 (q, $^2J_{CF}$ = 30), 118.8, 100.5, 25.6; IR (KBr): v = 3332, 3239, 2943, 1638, 1619, 1455, 1403, 776 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{12}F_3N_2O_2$ 273.0845; Found 273.0839.

*2-(Aminomethylene)-N-butyl-3-oxobutanamide (**1i**).* Prepared from *N*-butyl-2-[(dimethylamino) methylene]-3-oxobutanamide (1.06 g, 5.0 mmol) via general procedure A. Compound **1i** was obtained as a yellowish solid (0.78 g, 85%). mp 37-38 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 10.28 (s, 1H), 9.52 (s, 1H), 7.85-7.93 (m, 1H), 5.81 (s, 1H), 3.26-3.32 (m, 2H), 2.24 (s, 3H), 1.48-1.58 (m, 2H), 1.32-1.44 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 196.0, 169.1, 158.7, 103.5, 38.1, 31.5, 26.0, 20.2, 13.7; IR (KBr): v = 3334, 2960, 2932, 1639, 1613, 1454, 1399, 740 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_9H_{17}N_2O_2$ 185.1279; Found 185.1272.

*2-(Aminomethylene)-N-benzyl-3-oxobutanamide (**1j**).* Prepared from *N*-benzyl-2-[(dimethylamino) methylene]-3-oxobutanamide (1.23 g, 5.0 mmol) via general procedure A. Compound **1j** was obtained as a white solid (0.98 g, 90%). mp 94-95 ^oC; ^1H NMR (300 MHz, DMSO-d_6): δ 9.90-9.94 (m, 2H), 8.45 (bs, 1H), 7.99-8.07 (m, 1H), 7.20-7.34 (m, 5H), 4.39(d, J = 6.0 Hz, 2H), 2.18 (s, 3H); ^{13}C {^1H} NMR (100 MHz, DMSO-d_6): δ 194.8, 168.2, 160.1, 139.4, 127.8, 126.7, 126.2, 100.8, 40.8, 25.5; IR (KBr): v = 3313, 3239, 2955, 1639, 1541, 1497, 1453, 1396 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd

for $C_{12}H_{15}N_2O_2$ 219.1128; Found 219.1125.

*2-(Aminomethylene)-N-(4-chlorophenyl)-3-oxohexanamide (**1k**).* Prepared from *N*-(4-chloro phenyl)-2-[(dimethylamino)methylene]-3-oxohexanamide (1.47 g, 5.0 mmol) via general procedure A. Compound **1k** was obtained as a white solid (1.21 g, 91%). mp 150-151 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.87 (s, 1H), 10.26 (bs, 1H), 8.01-8.08 (m, 1H), 7.55-7.60 (m, 2H), 7.27-7.30 (m, 2H), 5.87 (bs, 1H), 2.58 (t, J = 7.2 Hz, 2H), 1.65-1.77 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.0, 167.7, 158.6, 137.1, 128.8, 128.4, 121.8, 103.1, 39.6, 19.2, 14.0; IR (KBr): ν = 3327, 3191, 2962, 1643, 1614, 1536, 1454, 1400, 829 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{16}ClN_2O_2$ 267.0895; Found 267.0885.

*3-Amino-2-benzoyl-N-hexylacrylamide (**1l**).* Prepared from 2-benzoyl-3-(dimethylamino)-*N*-hexylacrylamide (1.51g, 5.0 mmol) via general procedure A. Compound **1l** was obtained as a yellowish solid (1.18 g, 86%). mp 48-49 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.27 (s, 1H), 9.51 (s, 1H), 7.54-7.61 (m, 1H), 7.40-7.45 (m, 5H), 5.72 (s, 1H), 3.32-3.38 (m, 2H), 1.55-1.64 (m, 2H), 1.31-1.42 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 196.2, 169.1, 162.2, 140.5, 130.1, 128.2, 128.1, 102.9, 38.5, 31.5, 29.5, 26.8, 22.5, 14.0; IR (KBr): ν = 3304, 2952, 1639, 1613, 1454, 1399, 740 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{23}N_2O_2$ 275.1754; Found 275.1743.

*3-Amino-2-benzoyl-N-phenylacrylamide (**1m**).* Prepared from 2-benzoyl-3-(dimethylamino)-*N*-phenylacrylamide (1.47 g, 5.0 mmol) via general procedure A. Compound **1m** was obtained as a white solid (1.18 g, 89%). mp 150-152 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.65 (s, 1H), 10.24 (bs, 1H), 7.63-7.72 (m, 3H), 7.40-7.51 (m, 5H), 7.34 (t, J = 7.8 Hz, 2H), 7.09 (t, J = 7.2 Hz, 1H), 5.89 (bs, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 196.4, 167.5, 162.8, 140.2, 138.2, 130.4, 128.8, 128.3, 128.1, 123.8, 120.8, 102.9; IR (KBr): ν = 3368, 3223, 2973, 1648, 1536, 1444, 1371, 1319 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}N_2O_2$ 267.1128; Found 267.1125.

*3-Amino-2-benzoyl-N-(4-chlorophenyl)acrylamide (**1n**).* Prepared from 2-benzoyl-*N*-(4-chloro phenyl)-3-(dimethylamino)acrylamide (1.64 g, 5.0 mmol) via general procedure A. Compound **1n** was

obtained as a white solid (1.41 g, 94%). mp 146-148 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.71 (s, 1H), 10.20 (bs, 1H), 7.67-7.73 (m, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.41-7.50 (m, 5H), 7.29 (d, J = 8.8 Hz, 2H), 5.87 (bs, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 196.4, 167.4, 162.8, 140.0, 136.9, 130.5, 128.8, 128.5, 128.4, 128.1, 121.8, 102.9; IR (KBr): v = 3337, 3412, 2964, 1647, 1596, 1533, 1492, 1401, 833 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{14}ClN_2O_2$ 301.0738; Found 301.0729.

*3-Amino-2-(4-methylbenzoyl)-N-phenylacrylamide (**1o**).* Prepared from 3-(dimethylamino)-2-(4-methylbenzoyl)-*N*-phenylacrylamide (1.54 g, 5.0 mmol) via general procedure A. Compound **1o** was obtained as a white solid (1.23 g, 88%). mp 137-138 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.67 (s, 1H), 10.17 (bs, 1H), 7.63-7.74 (m, 3H), 7.30-7.41 (m, 4H), 7.23 (d, J = 7.8 Hz, 2H), 7.08 (t, J = 7.5 Hz, 1H), 5.86 (bs, 1H), 2.41 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 196.4, 167.6, 162.6, 140.9, 138.2, 137.4, 128.9, 128.8, 128.4, 123.7, 120.8, 102.9, 21.4; IR (KBr): v = 3340, 3231, 2955, 1648, 1579, 1535, 1443, 753 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{17}N_2O_2$ 281.1285; Found 281.1277.

General procedure B for the preparation of 2-(Aminomethylene)-N^1,N^3-diphenylmalonamide 1p: To a well-stirred solution of 2-[(dimethylamino)methylene]-N^1,N^3-diphenylmalonamide (1.55 g, 5.0 mmol) in ethanol (15.0 mL) was added aqueous ammonia (aq. 25%, 1.0 mL, 12.5 mmol) at room temperature. The reaction mixture was kept at room temperature under stirring until the completion of the reaction as indicated by TLC. The resulting mixture was poured into saturated aqueous NaCl (100.0 mL). The precipitated solid was collected by filtration, washed with water (3 × 20.0 mL), and dried *in vacuo* to give **1p** as a white solid (0.84 g, 60%). mp 162-163 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.42 (s, 1H), 9.66 (s, 1H), 9.27-9.33 (m, 1H), 8.21 (bs, 1H), 7.87-7.95 (m, 1H), 7.56 (t, J = 7.2 Hz, 4H), 7.26-7.32 (m, 4H), 6.98-7.05(m, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d6): δ 168.4, 166.7, 154.6, 139.0, 138.5, 128.3, 127.9, 122.3, 122.0, 120.1, 118.7, 92.8; IR (KBr): v = 3335, 1655, 1639, 1611, 1453, 1404, 787 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{16}N_3O_2$ 282.1237; Found 282.1234.

General procedure C for the preparation of 1q-w:[29] To a well-stirred solution of enaminone (10.0 mmol) and aryl isocyanate (10.0 mmol) in CH_2Cl_2 (20.0 mL) was added $Ni(acac)_2$ (0.15 g, 0.6 mmol) at room temperature. Then the reaction mixture was heated and stirred under reflux until the completion of the reaction as indicated by TLC. The resulting mixture was poured into saturated aqueous NaCl (100.0 mL) and extracted with CH_2Cl_2 (3 × 30.0 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel using EtOAc-petroleum as the eluent to give compound **1**.

*2-Acetyl-3-amino-N-(p-tolyl)but-2-enamide (**1q**)*. Prepared from 4-aminopent-3-en-2-one (0.99 g, 10.0 mmol) and 4-methylphenyl isocyanate (1.34 g, 10.0 mmol) via general procedure C. The crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 5:1) to give **1q** as a yellowish solid (1.16 g, 50%). mp 155-157 ^oC; ^1H NMR (300 MHz, DMSO-d_6): δ 10.19 (d, J = 4.8 Hz, 1H), 9.98 (s, 1H), 7.90 (d, J = 4.5 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 2.24 (s, 3H), 2.00 (s, 3H)， 1.95 (s, 3H); ^{13}C {^1H} NMR (100 MHz, DMSO-d_6): δ 191.5, 167.6, 161.6, 136.7, 131.4, 128.4, 118.6, 108.0, 27.1, 19.9, 19.4; IR (KBr): v = 3314, 2963, 1667, 1635, 1602, 1448, 1401, 813 cm^{-1}. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{13}H_{16}N_2O_2Na$ 255.1104; Found 255.1100.

*2-Acetyl-3-amino-N-(4-methoxyphenyl)but-2-enamide (**1r**)*. Prepared from 4-aminopent-3-en-2-one (0.99 g, 10.0 mmol) and 4-methoxyphenyl isocyanate (1.51 g, 10.0 mmol) via general procedure C. The crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 5:1) to give **1r** as a yellowish solid (1.27 g, 51%). mp 174-176 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 10.18 (d, J = 4.4 Hz, 1H), 9.91 (s, 1H), 7.86 (d, J = 3.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 3.71 (s, 3H), 2.00 (s, 3H), 1.95 (s, 3H); ^{13}C {^1H} NMR (100 MHz, DMSO-d_6): δ 191.5, 167.3, 161.5, 154.7, 132.4, 120.1, 113.2, 108.0, 54.6, 27.1, 19.4; IR (KBr): v = 3186, 3135, 2954, 1659,

1639, 1614, 1509, 1412, 777 cm^{-1}. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{13}H_{16}N_2O_3Na$ 271.1053; Found 271.1046.

*2-Acetyl-3-amino-N-(4-chlorophenyl)but-2-enamide (**1s**).* Prepared from 4-aminopent-3-en-2-one (0.99 g, 10.0 mmol) and 4-chlorophenyl isocyanate (1.55 g, 10.0 mmol) via general procedure C. The crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 5:1) to give **1s** as a yellowish solid (1.24 g, 49%). mp 179-180 ^oC; ^1H NMR (300 MHz, DMSO-d_6): δ 10.22 (s, 2H), 7.98 (d, J = 4.5 Hz, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 2.00 (s, 3H), 1.95 (s, 3H); ^{13}C {^1H} NMR (75 MHz, DMSO-d_6): δ 191.5, 168.0, 162.0, 138.2, 128.0, 126.1, 120.1, 107.7, 27.3, 19.5; IR (KBr): ν = 3234, 3131, 2960, 1659, 1639, 1611, 1454, 1401, 776 cm^{-1}. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{13}ClN_2O_2Na$ 275.0558; Found 275.0553.

*3-Amino-2-propionyl-N-(p-tolyl)pent-2-enamide (**1t**).* Prepared from 5-aminohept-4-en-3-one (1.27 g, 10.0 mmol) and 4-methylphenyl isocyanate (1.34 g, 10.0 mmol) via general procedure C. The crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 4:1) to give **1t** as a white solid (1.38 g, 53%). mp 182-183 ^oC; ^1H NMR (300 MHz, DMSO-d_6): δ 10.18 (d, J = 4.5 Hz, 1H), 10.05 (s, 1H), 7.75 (d, J = 4.5 Hz, 1H), 7.54(d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 2.33 (q, J = 7.2 Hz, 2H), 2.24 (s, 3H), 2.19 (t, J = 7.5 Hz, 2H), 1.12 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C {^1H} NMR (75 MHz, DMSO-d_6): δ 195.0, 167.6, 165.9, 136.8, 131.5, 128.5, 118.6, 107.2, 31.5, 26.3, 20.0, 12.5, 8.8; IR (KBr): ν = 3334, 3101, 2970, 2932, 1632, 1615, 1464, 1398, 747 cm^{-1}. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{15}H_{20}N_2O_2Na$ 283.1417; Found 283.1408.

*3-Amino-N-(4-chlorophenyl)-2-propionylpent-2-enamide (**1u**).* Prepared from 5-aminohept-4-en-3-one (1.27 g, 10.0 mmol) and 4-chlorophenyl isocyanate (1.55 g, 10.0 mmol) via general procedure C. The crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 5:1) to give **1u** as a white solid (1.40 g, 50%). mp 187-189 ^oC; ^1H NMR (300 MHz, DMSO-d_6): δ 10.30 (s, 1H), 10.21 (d, J = 4.5 Hz, 1H), 7.81 (d, J = 4.8 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.35 (d, J =

8.7 Hz, 2H), 2.32 (q, *J* = 7.5 Hz, 2H), 2.20 (q, *J* = 7.5 Hz, 2H), 1.11 (t, *J* = 7.5 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6): δ 194.9, 168.0, 166.2, 138.2, 128.1, 126.2, 120.0, 106.9, 31.6, 26.3, 12.5, 8.8; IR (KBr): ν = 3238, 2953, 2932, 1656, 1603, 1494, 1389, 693 cm^{-1}. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{17}ClN_2O_2Na$ 303.0871; Found 303.0865.

*3-Amino-2-benzoyl-N-(4-chlorophenyl)but-2-enamide (**1v**).* Prepared from 3-amino-1-phenylbut-2-en-1-one (1.61 g, 10.0 mmol) and 4-chlorophenyl isocyanate (1.55 g, 10.0 mmol) via general procedure C. The crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 4:1) to give **1v** as a yellowish solid (1.51 g, 48%). mp 167-168 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.54 (s, 1H), 9.96 (s, 1H), 8.37 (s, 1H), 7.47-7.50 (m, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.20-7.28 (m, 5H), 2.09 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 198.1, 168.7, 167.4, 143.2, 137.3, 131.9, 128.8, 128.7, 128.5, 128.3, 121.8, 102.2, 25.6; IR (KBr): ν = 3337, 2852, 1659, 1639, 1614, 1455, 1407, 786 cm^{-1}. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{15}ClN_2O_2Na$ 337.0714; Found 337.0704.

*3-Amino-2-benzoyl-N-(4-chlorophenyl)-3-phenylacrylamide (**1w**).* Prepared from 3-Amino-1,3-diphenylprop-2-en-1-one (2.23 g, 10.0 mmol) and 4-chlorophenyl isocyanate (1.55 g, 10.0 mmol) via general procedure C. The crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 5:1) to give **1w** as a yellowish solid (1.77 g, 47%). mp 154-156 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.87 (s, 1H), 10.44 (s, 1H), 8.09 (d, *J* = 7.2 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.51-7.58 (m, 4H), 7.37-7.48 (m, 5H), 7.30-7.34 (m, 2H), 6.45 (s, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 199.0, 170.6, 167.1, 142.8, 138.3, 137.2, 130.7, 130.7, 128.9, 128.9, 128.8, 128.4, 128.3, 127.5, 121.6, 102.4; IR (KBr): ν = 3331, 3335, 1639, 1615, 1526, 1454, 696 cm^{-1}. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{17}ClN_2O_2Na$ 399.0871; Found 399.0860.

Preparation and analytical data of products 3 and 4

General procedure D: To a well-stirred solution of PhIO (0.44 g, 2.0 mmol) and AcOH (0.12 g, 2.0 mmol) in CH_2Cl_2 (10.0 mL) was added *β*-aminoacrylamide **1** (1.0 mmol) at room temperature. The reaction mixture was kept at room temperature under stirring until the completion of the reaction as indicated by TLC. The resulting mixture was poured into saturated aqueous NaCl (100.0 mL) and extracted with CH_2Cl_2 (3 × 20.0 mL). The combined organic phase was washed with water (3 × 20.0 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel using EtOAc-petroleum as the eluent to give product **3** or **4**.

*1-[5-(Phenylamino)isoxazol-4-yl]ethanone (**3a**)*. Prepared from **1a** (0.20 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3a** as a white solid (0.15 g, 76%). mp 99-100 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.36 (s, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 2.40 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.3, 166.6, 149.2, 136.4, 129.5, 124.6, 119.0, 97.9, 27.2; IR (KBr): v = 3237, 3071, 2921, 1647, 1611, 1579, 1541, 1460, 1242, cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{11}N_2O_2$ 203.0815; Found 203.0809.

X-ray Crystal Data for **3a:** white crystal, M = 202.21, orthorhombic, $P2_12_12_1$, a = 6.5102(6) Å, *b* = 10.6554(10) Å, c = 14.2094(13) Å, α = 90.00°, β = 90.00°, γ = 90.00 °, V = 985.69(16) Å^3, Z = 4, T = 273.15 K, F000 = 424.0, F000' = 424.19, R = 0.0447(1708), *wR2* = 0.1099(1993). CCDC deposition number: 1834343. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0)1223 762911; or deposit@ccdc.cam.ac.uk).

*1-[5-(p-Tolylamino)isoxazol-4-yl]ethanone (**3b**).* Prepared from **1b** (0.22 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 6:1) to give **3b** as a yellowish solid (0.11 g, 51%). mp 132-134 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.91 (s, 1H), 8.34 (s, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 2.39 (s, 3H), 2.35 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.2, 166.6, 149.2, 134.4, 133.9, 130.0,

119.1, 97.7, 27.1, 20.8; IR (KBr): ν = 3229, 3102, 2926, 1654, 1601, 1565, 1558, 1467, 1246, 812 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{13}N_2O_2$ 217.0972; Found 217.0964.

*1-[5-[(4-Methoxyphenyl)amino]isoxazol-4-yl)ethanone (**3c**).* Prepared from **1c** (0.23 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3c** as a yellowish solid (0.18 g, 79%). mp 167-168 ℃; ^1H NMR (300 MHz, $CDCl_3$): δ 9.83 (s, 1H), 8.33 (s, 1H), 7.37 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 3.81 (s, 3H), 2.39 (s, 3H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ191.1, 166.6, 156.8, 149.3, 129.5, 121.0, 114.6, 97.5, 55.5, 27.1; IR (KBr): ν = 3237, 3134, 2924, 1659, 1614, 1591, 1562, 1462, 1393, 1263, 822 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{13}N_2O_3$ 233.0921; Found 233.0916.

*1-{5-[(2-Methoxyphenyl)amino]isoxazol-4-yl}ethanone (**3d**).* Prepared from **1d** (0.23 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3d** as a yellowish solid (0.18 g, 78%). mp 105-106 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 10.47 (s, 1H), 8.36 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 3.97 (s, 3H), 2.41 (s, 3H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 191.0, 166.4, 149.3, 148.1, 126.4, 124.5, 121.1, 118.1, 110.5, 98.4, 56.0, 27.2; IR (KBr): ν = 3267, 3025, 2942, 1651, 1613, 1585, 1550, 1498, 1463, 1254, 750 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{13}N_2O_3$ 233.0921; Found 233.0912.

*1-{5-[(4-Chlorophenyl)amino]isoxazol-4-yl}ethanone (**3e**).* Prepared from **1e** (0.24 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 6:1) to give **3e** as a yellowish solid (0.14 g, 57%). mp 171-172 ℃; ^1H NMR (300 MHz, $CDCl_3$): δ 9.99 (s, 1H), 8.37 (s, 1H), 7.34-7.42 (m, 4H), 2.41 (s, 3H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 191.5, 166.4, 149.2, 135.1, 129.9, 129.6, 120.3, 98.1, 27.3; IR (KBr): ν = 3238, 3193, 1656, 1605, 1568, 1538, 1433, 1392, 1244, 825 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{10}ClN_2O_2$ 237.0425; Found 237.0420.

*1-{5-[(5-Chloro-2-methoxyphenyl)amino]isoxazol-4-yl}ethanone (**3f**).* Prepared from **1f** (0.27 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3f** as a yellowish solid (0.21 g, 77%). mp 128-129 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.47 (s, 1H), 8.38 (s, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.06 (dd, J_1 = 2.4 Hz, J_2 = 8.7 Hz,1H), 6.86 (d, J = 8.7 Hz, 1H), 3.97 (s, 3H), 2.42 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 191.2, 166.0, 149.2, 146.5, 127.3, 126.2, 123.8, 117.9, 111.3, 98.6, 56.3, 27.2; IR (KBr): v = 3261, 3062, 2954, 1652, 1618, 1582, 1551, 1497, 1255, 853, 727 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{12}ClN_2O_3$ 267.0531; Found 267.0525.

*1-{5-[(2-Chlorophenyl)amino]isoxazol-4-yl}ethanone (**3g**).* Prepared from **1g** (0.24 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3g** as a yellowish solid (0.17 g, 70%). mp 116-117 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.65 (s, 1H), 8.41 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 2.44 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.5, 166.3, 149.2, 133.9, 129.8, 128.0, 124.9, 122.9, 119.2, 98.8, 27.3; IR (KBr): v = 3103, 3059, 2922, 1649, 1611, 1571, 1545, 1455, 1379, 1247, 736 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{10}ClN_2O_2$ 237.0425; Found 237.0419.

*1-{5-{[4-(Trifluoromethyl)phenyl]amino}isoxazol-4-yl}ethanone (**3h**).* Prepared from **1h** (0.27 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3h** as a yellowish solid (0.21 g, 76%). mp 154-155 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.16 (s, 1H), 8.40 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 2.43 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.8, 166.3, 149.2, 139.5, 126.9, 126.4 (q, $^1J_{CF}$ = 33), 124.0 (q, $^2J_{CF}$ = 270), 118.6, 98.5, 27.4; IR (KBr): v = 3238, 3170, 1658, 1618, 1594, 1542, 1333, 1248, 1115, 836 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{10}F_3N_2O_2$ 271.0689; Found 271.0685.

*1-[5-(Butylamino)isoxazol-4-yl]ethanone (**3i**).* Prepared from **1i** (0.18 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) to give **3i** as a yellowish solid (0.13 g, 71%). mp 53-54 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.74 (s, 1H), 3.46 (q, J = 6.9 Hz, 2H), 2.30 (s, 3H), 1.57-1.69 (m, 2H), 1.34-1.46 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 190.7, 169.6, 149.9, 96.4, 42.3, 31.7, 27.0, 19.8, 13.6; IR (KBr): v = 3202, 2906, 2854, 1656, 1589, 1433, 1247, 815 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_9H_{15}N_2O_2$ 183.1128; Found 183.1135.

*1-[5-(Benzylamino)isoxazol-4-yl]ethanone (**3j**).* Prepared from **1j** (0.22 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3j** as a white solid (0.17 g, 77%). mp 84-85 ℃; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.25 (s, 1H), 8.05 (s, 1H), 7.30-7.39 (m, 5H), 4.64 (d, J = 6.3 Hz, 2H), 2.31 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 190.7, 169.4, 149.9, 136.5, 128.8, 128.0, 127.5, 96.6, 46.4, 26.9; IR (KBr): v = 3313, 3031, 2959, 1647, 1594, 1548, 1435, 1169, 952, 738 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{13}N_2O_2$ 217.0972; Found 217.0970.

*1-{5-[(4-Chlorophenyl)amino]isoxazol-4-yl}butan-1-one (**3k**).* Prepared from **1k** (0.27 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3k** as a yellowish solid (0.20 g, 76%). mp 132-133 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.08 (s, 1H), 8.38 (s, 1H), 7.33-7.42 (m, 4H), 2.67 (t, J = 7.2 Hz, 2H), 1.69-1.81 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 194.6, 166.5, 148.8, 135.2, 129.7, 129.6, 120.1, 97.7, 41.8, 18.0, 13.8; IR (KBr): v = 3244, 2972, 1644, 1613, 1575, 1546, 1434, 1213, 1163, 821 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{14}ClN_2O_2$ 265.0738; Found 265.0733.

*[5-(Hexylamino)isoxazol-4-yl](phenyl)methanone (**3l**).* Prepared from **1l** (0.27 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 11:1) to give **3l** as a white solid (0.20 g, 74%). mp 73-74 ℃; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.18 (s, 1H), 7.71-7.74 (m, 2H), 7.46-7.58 (m, 3H), 3.53 (q, J = 6.9 Hz, 2H), 1.66-1.76 (m, 2H), 1.22-1.44 (m, 6H), 0.90 (t, J = 6.6 Hz, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 187.3, 171.1, 150.5, 139.0, 131.7, 128.6, 127.7, 95.1, 42.6, 31.3, 29.6, 26.3, 22.5, 14.0; IR (KBr): v = 3280, 2918, 1648, 1592, 1547, 1446, 899, 744 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_2$ 273.1598; Found 273.1622.

*Phenyl[5-(phenylamino)isoxazol-4-yl]methanone (**3m**).* Prepared from **1m** (0.27 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3m** as a yellowish solid (0.20 g, 74%). mp 191-193 ℃; ^1H NMR (300 MHz, $CDCl_3$): δ 10.45 (s, 1H), 8.46 (s, 1H), 7.78-7.81 (m, 2H), 7.51-7.63 (m, 5H), 7.43 (t, J = 8.4 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 187.9, 168.2, 150.0, 138.7, 136.5, 132.2, 129.6, 128.8, 127.9, 124.9, 119.3, 96.8; IR (KBr): v = 3234, 3064, 1629, 1600, 1570, 1541, 1445, 1263, 1133, 899, 738 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}N_2O_2$ 265.0972; Found 265.0987.

*{5-[(4-Chlorophenyl)amino]isoxazol-4-yl}(phenyl)methanone (**3n**).* Prepared from **1n** (0.30 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3n** as a yellowish solid (0.17 g, 58%). mp 156-158 ℃; ^1H NMR (300 MHz, $CDCl_3$): δ 10.46 (s, 1H), 8.47 (s, 1H), 7.79 (d, J = 7.2 Hz, 2H), 7.46-7.61 (m, 5H), 7.38 (d, J = 9.0 Hz, 2H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 188.0, 168.0, 150.0, 138.5, 135.1, 132.4, 130.1, 129.7, 128.9, 127.9, 120.5, 96.9; IR (KBr): v = 3278, 3153, 1651, 1622, 1584, 1556, 1461, 1248, 835, 738 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{12}ClN_2O_2$ 299.0582; Found 299.0578.

*[5-(Phenylamino)isoxazol-4-yl](p-tolyl)methanone (**3o**).* Prepared from **1o** (0.28 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3o** as a yellowish solid (0.18 g, 65%). mp 142-143 ℃; ^1H NMR (300 MHz, $CDCl_3$): δ 10.46 (s, 1H), 8.47 (s, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 7.8 Hz,

2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 2.45 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 187.6, 168.1, 149.9, 142.9, 136.5, 135.9, 129.5, 129.4, 128.0, 124.7, 119.2, 96.6, 21.5; IR (KBr): v = 3237, 3050, 1638, 1601, 1581, 1541, 1500, 1458, 1264, 1133, 905 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{15}N_2O_2$ 279.1128; Found 279.1126.

*N-Phenyl-5-(phenylamino)isoxazole-4-carboxamide (**3p**).* Prepared from **1p** (0.28 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3p** as an orange solid (0.15 g, 53%). mp 130-131 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (s, 1H), 8.32 (s, 1H), 7.46-7.55 (m, 3H), 7.43 (s, 1H), 7.32-7.41 (m, 5H), 7.11-7.21 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.3, 161.5, 146.9, 137.1, 136.9, 129.5, 129.1, 124.9, 124.0, 121.0, 118.5, 89.5; IR (KBr): v = 3351, 3294, 1659, 1632, 1597, 1531, 1445, 1314, 1247, 750 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{14}N_3O_2$ 280.1081; Found 280.1070.

*2-Acetyl-3-methyl-N-(p-tolyl)-2H-azirine-2-carboxamide (**4q**).* Prepared from **1q** (0.23 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 4:1) to give **4q** as a yellowish solid (0.15 g, 63%). mp 102-104 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.59 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 2.65 (s, 3H), 2.31 (s, 3H), 1.95 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 207.2, 164.5, 155.0, 135.1, 134.1, 129.4, 120.1, 45.4, 27.9, 20.8, 11.7; IR (KBr): v = 3238, 3193, 2920, 1656, 1605, 1592, 1568, 1471, 1392, 1241, 825 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{15}N_2O_2$ 231.1128; Found 231.1123.

*2-Acetyl-N-(4-methoxyphenyl)-3-methyl-2H-azirine-2-carboxamide (**4r**).* Prepared from **1r** (0.25 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 4:1) to give **4r** as a yellowish solid (0.15 g, 62%). mp 78-79 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.56 (s, 1H), 7.50 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 2.65 (s, 3H), 1.95 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 207.2, 164.4, 156.4, 155.0, 130.8, 121.6, 114.0, 55.4, 45.3, 27.8, 11.6; IR (KBr): v = 3272, 3224, 2973, 1692,

1660, 1554, 1511, 1366, 1258, 1175, 837 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{15}N_2O_3$ 247.1077; Found 247.1069.

*2-Acetyl-N-(4-chlorophenyl)-3-methyl-2H-azirine-2-carboxamide (**4s**).* Prepared from **1s** (0.25 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 4:1) to give **4s** as a yellowish solid (0.17 g, 68%). mp 127-128 ℃; ^1H NMR (300 MHz, $CDCl_3$): δ 10.76 (s, 1H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 2.66 (s, 3H), 1.95 (s, 3H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 207.2, 164.8, 154.7, 136.2, 129.4, 128.9, 121.3, 45.3, 27.8, 11.6; IR (KBr): *v* = 3248, 3215, 1691, 1594, 1547, 1494, 1401, 1281, 1173, 826 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{12}ClN_2O_2$ 251.0582; Found 251.0572.

*3-Ethyl-2-propionyl-N-(p-tolyl)-2H-azirine-2-carboxamide (**4t**).* Prepared from **1t** (0.26 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 9:1) to give **4t** as a yellowish solid (0.17 g, 64%). mp 89-91 ℃; ^1H NMR (300 MHz, $CDCl_3$): δ 10.74 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 2.86-3.02 (m, 2H), 2.33-2.44 (m, 2H), 2.31 (s, 3H), 1.81-1.94 (m, 1H), 1.43 (t, *J* = 7.5 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 209.7, 164.8, 157.8, 135.1, 133.9, 129.4, 120.0, 45.6, 32.9, 20.8, 19.9, 8.9, 7.2; IR (KBr): *v* = 3263, 2940, 2925, 1692, 1604, 1553, 1405, 1318, 820 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O_2$ 259.1441; Found 259.1458.

*N-(4-Chlorophenyl)-3-ethyl-2-propionyl-2H-azirine-2-carboxamide (**4u**).* Prepared from **1u** (0.28 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) to give **4u** as a white solid (0.19 g, 67%). mp 117-119 ℃; ^1H NMR (300 MHz, $CDCl_3$): δ 10.90 (s, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 2.87-3.02 (m, 2H), 2.29-2.43 (m, 1H), 1.80-1.94 (m, 1H), 1.44 (t, *J* = 7.5 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 209.8, 165.1, 157.6, 136.3, 129.2, 128.9, 121.2, 45.5, 32.9, 19.9, 9.0, 7.1; IR (KBr): *v* = 3280, 2938, 2897, 1689, 1622, 1561, 1435, 1324, 832 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{16}ClN_2O_2$ 279.0895; Found 279.0909.

*2-Benzoyl-N-(4-chlorophenyl)-3-methyl-2H-azirine-2-carboxamide (**4v**).* Prepared from **1v** (0.31 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **4v** as a yellowish solid (0.18 g, 58%). mp 120-122 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.32 (s, 1H), 7.67 (d, J = 7.2 Hz, 2H), 7.51-7.59 (m, 3H), 7.40-7.45 (m, 2H), 7.30 (d, J = 8.7 Hz, 2H), 2.56 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 200.6, 165.3, 157.0, 136.3, 136.2, 132.7, 129.5, 129.1, 128.5, 128.4, 121.3, 44.9, 12.3; IR (KBr): v = 3241, 2790, 1647, 1573, 1552, 1498, 1394, 1235, 819, 741 cm^{-1}. HRMS (ESI) *m/z*: [M + H]$^+$ Calcd for $C_{17}H_{14}ClN_2O_2$ 313.0738; Found 313.0743.

*2-Benzoyl-N-(4-chlorophenyl)-3-phenyl-2H-azirine-2-carboxamide (**4w**).* Prepared from **1w** (0.38 g, 1.0 mmol) via general procedure D. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) to give **4w** as a yellowish solid (0.21 g, 56%). mp 134-136 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1H), 7.90-7.93 (m, 2H), 7.76-7.79 (m, 2H), 7.65-7.70 (m, 1H), 7.55-7.61 (m, 4H), 7.50 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.8 Hz 2H), 7.28-7.32 (m, 2H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 199.9, 165.1, 156.5, 136.2, 135.7, 134.8, 132.9, 131.0, 129.6, 129.5, 129.0, 128.7, 128.4, 121.2, 120.6, 45.5; IR (KBr): v = 3226, 2927, 1663, 1597, 1536, 1493, 1401, 1246, 824, 725, 693 cm^{-1}. HRMS (ESI) *m/z*: [M + H]$^+$ Calcd for $C_{22}H_{16}ClN_2O_2$ 375.0895; Found 375.0887.

Preparation and analytical data of products 3s and 5s

General procedure E: The solution of **4s** (0.25 g, 1.0 mmol) in xylene (5.0 mL) was heated to reflux under stirring in N_2 atmosphere until the completion of the reaction as indicated by TLC. The resulting mixture was poured into saturated aqueous NaCl (30.0 mL) and extracted with CH_2Cl_2 (3 × 15.0 mL). The combined organic phase was washed with water (3 × 20.0 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) to give products **3s** and **5s**.

*1-{5-[(4-Chlorophenyl)amino]-3-methylisoxazol-4-yl}ethanone (**3s**).* Prepared from **4s** (0.25 g, 1.0 mmol) via general procedure E. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 7:1) to give **3s** as a yellowish solid (0.06 g, 23%). mp 109-111 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.49 (s, 1H), 7.28-7.35 (m, 4H), 2.47 (d, J = 5.7 Hz, 6H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 193.0, 155.1, 149.7, 136.1, 129.5, 128.6, 119.4, 115.6, 25.7, 13.8; IR (KBr): v = 3247, 3028, 2922, 1694, 1595, 1551, 1489, 1436, 1245, 748 cm^{-1}. HRMS (ESI) *m/z*: [M + H]$^{+}$ Calcd for $C_{12}H_{12}ClN_2O_2$ 251.0582; Found 251.0569.

*N-(4-Chlorophenyl)-3,5-dimethylisoxazole-4-carboxamide (**5s**).* Prepared from **4s** (0.25 g, 1.0 mmol) via general procedure E. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) to give **5s** as a yellowish solid (0.17 g, 66%). mp 128-129 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 1H), 7.62 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 2.64 (s, 3H), 2.44 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6): δ 159.6, 158.0, 152.9, 137.1, 128.3, 127.9, 126.7, 121.3, 12.8, 10.9; IR (KBr): v = 3224, 2928, 1646, 1615, 1571, 1438, 1231, 784 cm^{-1}. HRMS (ESI) *m/z*: [M + H]$^{+}$ Calcd for $C_{12}H_{12}ClN_2O_2$ 251.0582; Found 251.0565.

Associated Content

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Note

The authors declare no competing financial interest.

Supporting Information

The supporting Information is available free of charge on the ACS Publication website at DOI:10.1021/acs.joc.XXXXXXXX.

X-ray crystallographic data (CIF file) of **3a**. ^{1}H and ^{13}C NMR spectra copies of compounds **1**-**5** (PDF).

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References

1 For selected monographs, see: (a) Lang, S. A.; Lin, Y.-I. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, UK, 1984; Vol. 6, pp 1-130. (b) Elguero, J. In *Comprenhensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 3, pp 1-75. (c) Sutharchanadevi, M.; Muragan, R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 3, pp 221-260. (d) Giomi, D.; Cordero, F. M.; Machetti, F. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Joule, J., Eds.; Elsevier: Oxford, UK, 2008; Vol. 4, pp 365-485.

2 For selected examples, see: (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. Transition Metal-Mediated Synthesis of Monocyclic Aromatic Heterocycles. *Chem. Rev.* **2013**, *113*, 3084-3213. (b) Li, C.; Kelly, W. L. Recent Advances in Thiopeptide Antibiotic Biosynthesis. *Nat. Prod. Rep.* **2010**, *27*, 153-164. (c) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. Impact of Natural Products on Developing New Anti-Cancer Agents. *Chem Rev*. **2009**, *109*, 3012-3043. (d)

Sperry, J.; Wright, D. Furans, Thiophenes and Related Heterocycles in Drug Discovery. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723-740. (e) Cicchi, S.; Cordero, F. M.; Giomi, D. Chapter 5.7 Five-Membered Ring Systems: With O&N Atoms. *Prog. Heterocycl. Chem.* **2003**, *15*, 261-283. (f) Balkenhohl, F.; Von Dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. Combinatorial Synthesis of Small Organic Molecules. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2288-2337. (g) Kochetkov, N. K.; Sokolov, S. D. Recent Developments in Isoxazole Chemistry. *Adv. Heterocycl. Chem.* **1963**, *2*, 365-422.

3 (a) Baraldi, P.; Barco, A.; Benetti, S.; Pollini, G.; Simoni, D. Synthesis of Natural Products *via* Isoxazoles. *Synthesis* **1987**, *10*, 857-869. (b) Manning, J.; Davies, H. One-Pot Synthesis of Highly Functionalized Pyridines *via* a Rhodium Carbenoid Induced Ring Expansion of Isoxazoles. *J. Am. Chem. Soc.* **2008**, *130*, 8602-8603.

4 (a) Frolund, B.; Jorgensen, A. T.; Tagmose, L.; Stensbol, T. B.; Vestergaard, H. T.; Engblom, C.; Kristiansen, U.; Sanchez, C.; Krogsgaard-Larsen, P.; Liljefors, T. Novel Class of Potent 4-Arylalkyl Substituted 3-Isoxazolol $GABA_A$ Antagonists: Synthesis, Pharmacology, and Molecular Modeling. *J. Med. Chem.* **2002**, *45*, 2454-2468. (b) Lee, Y.; Park, S.; Kim, B. Synthesis of 5-Isoxazol-5-yl-2'-Deoxyuridines Exhibiting Antiviral Activity Against HSV and Several RNA Viruses. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1126-1128. (c) Jensen, A. A.; Plath, N.; Pedersen, M. H. F.; Isberg, V.; Krall, J.; Wellendorph, P.; Stensbol, T. B.; Gloriam, D. E.; Krogsgaard-Larsen, P.; Frølund, B. Design, Synthesis, and Pharmacological Characterization of *N*- and *O*-Substituted 5,6,7,8-Tetrahydro-4*H*-Isoxazolo[4,5-d]Azepin-3-ol Analogues: Novel 5-HT_{2A}/5-HT_{2C} Receptor Agonists with Pro-Cognitive Properties. *J. Med. Chem.* **2013**, *56*, 1211-1227. (d) Tully, D. C.; Rucker, P. V.; Chianelli, D.; Williams, J.; Vidal, A.; Alper, P. B.; Mutnick, D.; Bursulaya, B.; Schmeits, J.; Wu, X.; Bao, D.; Zoll, J.; Kim, Y.; Groessl, T.; McNamara, P.; Seidel, H. M.; Molteni, V.; Liu, B.; Phimister, A.; Joseph, S. B.; Laffitte, B. Discovery of Tropifexor (LJN452), a

Highly Potent Non-Bile Acid FXR Agonist for the Treatment of Cholestatic Liver Diseases and Nonalcoholic Steatohepatitis (NASH). *J. Med. Chem.* **2017**, *60*, 9960-9973.

5 (a) Kobinata, K.; Sekido, S. Uramoto, M. Ubukato, M. Osada, H. Yamaguchi, I.; Isono, K. Isoxazole-4-Carboxylic Acid as a Metabolite of *Streptomyces* sp. and Its Herbicidal Activity. *Agric. Biol. Chem.* **1991**, *55*, 1415-1416. (b) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. Pyrazoles as Drugs: Facts and Fantasies. *Targets Heterocycl. Syst.* **2002**, *6*, 52-98.

6 (a) Hirayama, T.; Ueda, S.; Okada, T.; Tsurue, N.; Okuda, K.; Nagasawa, H. Facile One‐Pot Synthesis of [1, 2, 3]Triazolo[1, 5-*α*]Pyridines from 2-Acylpyridines by Copper(II)-Catalyzed Oxidative N−N Bond Formation. *Chem. Eur. J.* **2014**, *20*, 4156-4162. (b) Patil, N. T.; Shinde, V. S.; Sridhar, B. Relay Catalytic Branching Cascade: A Technique to Access Diverse Molecular Scaffolds. *Angew. Chem., Int. Ed.* **2013**, *125*, 2307-2311. (c) Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. Intramolecular Fe(II)-Catalyzed N−O or N−N Bond Formation from Aryl Azides. *Org. Lett.* **2010**, *12*, 2884-2887.

7 (a) Maiti, S.; Achar, T. K.; Mal, P. An Organic Intermolecular Dehydrogenative Annulation Reaction. *Org. Lett.* **2017**, *19*, 2006-2009. (b) Huang, J.; He, Y.; Wang, Y.; Zhu, Q. Synthesis of Benzimidazoles by PIDA-Promoted Direct C(sp^2) −H Imidation of *N*-Arylamidines. *Chem. Eur. J.* **2012**, *18*, 13964-13967. (c) Xiang, D.; Xin, X.; Liu, X.; Zhang, R.; Yng, J.; Dong, D. Regioselective Synthesis of 3-Arylamino- and 5-Arylaminoisoxazoles from Enaminones. *Org. Lett.* **2012**, *14*, 644-647. (d) Cho, S. H.; Yoon, J.; Chang, S. Intramolecular Oxidative C−N Bond Formation for the Synthesis of Carbazoles: Comparison of Reactivity between the Copper-Catalyzed and Metal-Free Conditions. *J. Am. Chem. Soc.* **2011**, *133*, 5996-6005. (e) Wang, K.; Xiang, D.; Liu, J.; Pan, W.; Dong, D. Efficient and Divergent Synthesis of Fully Substituted 1*H*-Pyrazoles and Isoxazoles from Cyclopropyl Oximes. *Org. Lett.* **2008**, *10*, 1691-1694.

8 For reviews, see: (a) Zhdankin, V. V.; Stang, P. J. Chemistry of Polyvalent Iodine. *Chem. Rev.* **2008**, *108*, 5299-5358. (b) Duschek, A.; Kirsch, S. F. 2-Iodoxybenzoic Acid−A Simple Oxidant

with a Dazzling Array of Potential Applications. *Angew. Chem., Int. Ed.* **2011**, *50*, 1524-1552. (c) Louillat, M. L.; Patureau, F. W. Oxidative C–H Amination Reactions. *Chem. Soc. Rev.* **2014**, *43*, 901-910. (d) Yoshimura, A.; Zhdankin, V. V. Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chem. Rev.* **2016**, *116*, 3328-3435.

9 For oxidation of amides mediated by hypervalent iodine reagents, see: (a) Shang, S.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. Intramolecular Metal−Free Oxidative Aryl–Aryl Coupling: An Unusual Hypervalent-Iodine Mediated Rearrangement of 2-Substituted N-Phenylbenzamides. *Angew. Chem., Int. Ed.* **2014**, *53*, 6216-6219. (b) Manna, S.; Antonchick, A. P. Organocatalytic Oxidative Annulation of Benzamide Derivatives with Alkynes. *Angew. Chem., Int. Ed.* **2014**, *53*, 7324-7327. (c) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. Novel Alternative for the N−S Bond Formation and Its Application to the Synthesis of Benzisothiazol-3-ones. *Org. Lett.* **2006**, *8*, 4811-4813. (d) Serna, S.; Tellitu, I.; Dominguez, E.; SanMartin, R. Expeditious Approach to 5-Aroyl-pyrrolidinones by a Novel PIFA-Mediated Alkyne Amidation Reaction. *Org. Lett.* **2005**, *7*, 3073-3076. (e) Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. Intramolecular Cyclization with Nitrenium Ions Generated by Treatment of *N*-Acylaminophthalimides with Hypervalent Iodine Compounds: Formation of Lactams and Spiro-Fused Lactams. *J. Org. Chem.* **2003**, *68*, 6739-6744. (f) Itoh, N.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. Introduction of a Hydroxy Group at the Para Position and *N*-Iodophenylation of *N*-Arylamides Using Phenyliodine(III) Bis(Trifluoroacetate). *J. Org. Chem.* **2002**, *67*, 7424-7428. (g) Kita,Y.; Tohma, H.; Kikichi, K.; Inagaki, M.; Yakura, T. Hypervalent Iodine Oxidation of *N*-Acyltyramines: Synthesis of Quinol Ethers, Spirohexadienones, and Hexahydroindol-6-ones. *J. Org. Chem.* **1991**, *56*, 435-438.

10 Kikugawa, Y.; Kawase, M. An Electrophilic Aromatic Substitution by *N*-Methoxyamides *via* Hypervalent Iodine Intermediates. *Chem. Lett.* **1990**, *19*, 581-582.

11 Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. Novel Alternative for the N−N Bond Formation through a PIFA-Mediated Oxidative Cyclization and Its Application to the Synthesis of Indazol-3-ones. *J. Org. Chem.* **2006**, *71*, 3501-3505.

12 Anand, D.; Patel, O. P. S.; Maurya, R. K.; Kant, R.; Yadav, P. P. Substrate Controlled Synthesis of Benzisoxazole and Benzisothiazole Derivatives *via* $PhI(OAc)_2$-Mediated Oxidation Followed by Intramolecular Oxidative O–N/S–N Bond Formation. *J. Org. Chem.* **2015**, *80*, 12410-12419.

13 Huang, J.; Lu, Y.; Qiu, B.; Liang, Y.; Li, N.; Dong, D. One-Pot Synthesis of Substituted Isothiazol-3(2*H*)-ones: Intramolecular Annulation of *α*-Carbamoyl Ketene-*S*,*S*-acetals *via* PIFA-Mediated N-S Bond Formation. *Synthesis* **2007**, *18*, 2791-2796.

14 Wang, K.; Fu, X.; Liu, J.; Liang, Y.; Dong, D. PIFA-Mediated Oxidative Cyclization of 1-Carbamoyl-1-Oximylcycloalkanes: Synthesis of Spiro-Fused Pyrazolin-5-one *N*-Oxides. *Org. Lett.* **2009**, *11*, 1015-1018.

15 Liu, X.; Xin, X.; Xiang, D.; Liang, Y.; Xin, X.; Li, W.; Dong, D. One-Pot Synthesis of Substituted 2,5-Dihydrofurans from *β*-oxo Amides and Cinnamaldehydes. *RSC Adv.* **2013**, *3*, 1346-1349.

16 Yuan, J.; Zhang, Q.; Yu, M.; Huang, P.; Zhang, R.; Dong, D. Phenyliodine (III) Diacetate Mediated Oxidative Cyclization of 1-Alkenoyl-1-carbamoyl Cycloalkanes: Access to Spiro-Fused Dihydrofuran-3(2*H*)-ones. *Org. Lett.* **2015**, *17*, 5012-5015.

17 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.

18 Yuan, J.; Rao, C. B.; Zhang, Q.; Zhang, R.; Liang, Y.; Zhang, N.; Dong, D. PIFA-Mediated Oxidative Cyclization Reactions of α-Acyl Acrylamides: A Synthetic Route to Substituted Isoxazol-3(2*H*)-ones. *Synthesis* **2018**, *50*, 1875-1882.

19 (a) Zhang, R.; Liang, Y. J.; Zhou, G. Y.; Wang, K. W.; Dong, D. W. Vilsmeier Reaction of Enaminones: Efficient Synthesis of Halogenated Pyridin-2(1*H*)-ones. *J. Org. Chem.* **2008**, *73*,

9504-9507. (b) Zhang, R.; Zhang, D.; Liang, Y.; Zhou, G.; Dong, D. Vilsmeier Reaction of 3-Aminopropenamides: One-Pot Synthesis of Pyrimidin-4(3*H*)-ones. *J. Org. Chem.* **2011**, *76*, 2880-2883.

20 Rao, C. B.; Yuan, J.; Zhang, Q.; Zhang, R.; Zhang, N.; Fang, J.; Dong, D. Iodosobenzene-Mediated *α*-Acyloxylation of 1,3-Dicarbonyl Compounds with Carboxylic Acids and Insight into the Reaction Mechanism. *J. Org. Chem.* **2018**, *83*, 2904-2911.

21 Li, X.; Du, Y.; Liang, Z.; Li, X.; Pan, Y.; Zhao, K. Simple Conversion of Enamines to 2*H*-Azirines and Their Rearrangements under Thermal Conditions. *Org. Lett.* **2009**, *11*, 2643-2646.

22 Sun, X.; Lyu, Y.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. Formation of Functionalized 2*H*-Azirines through PhIO-Mediated Trifluoroethoxylation and Azirination of Enamines. *Org. Lett.* **2013**, *15*, 6222-6225.

23 For reviews and monographs, see: (a) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; Manuel de los Santos. Preparation, Properties and Synthetic Applications of 2*H*-Azirines a Review. *J. Org. Prep. Proc. Int.* **2002**, *34*, 219-269. (b) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; Manuel de los Santos, J. 2*H*-Azirines as Synthetic Tools in Organic Chemistry. *Eur. J. Org. Chem.* **2001**, *13*, 2401-2414. (c) Pinho e Melo, T. M. V. D.; Rocha Gonsalves, A. M. d'A. Exploiting 2-Halo-2*H*-Azirine Chemistry. *Curr. Org. Chem.* **2004**, *1*, 275-292. (d) Khlebnikov, A. F.; Novikov, M. S. Recent Advances in 2*H*-Azirine Chemistry. *Tetrahedron* **2013**, *69*, 3363-3401. (e) Padwa, A. in *Comprehensive Heterocyclic Chemistry III*; Elsevier, Ltd.: Amsterdam, 2008; Vol. 1, pp 1-104.

24 For selected examples, see: (a) Miller, T. W.; Tristram, E. W.; Wolf, F. J. Azirinomycin. II. *J. Antibiot.* **1971**, *24*, 48-50. (b) Salomon, C. E.; Williams, D. H.; Faulkner, D. J. New Azacyclopropene Derivatives from Dysidea Fragilis Collected in Pohnpei. *J. Nat. Prod.* **1995**, *58*, 1463-1466. (c) Skepper, C. K.; Molinski, T. F. Long-Chain 2*H*-Azirines with Heterogeneous Terminal Halogenation from the Marine Sponge Dysidea fragilis. *J. Org. Chem.* **2008**, *73*,

2592-2597. (d) Jiang, Y.; Park, C.-M.; Loh, T.-P. Transition-Metal-Free Synthesis of Substituted Pyridines *via* Ring Expansion of 2-Allyl-2*H*-azirines. *Org. Lett.* **2014**, *16*, 3432-3435. (e) Li, T.; Xin, X.; Wang, C.; Wang, D.; Wu, F.; Li, X.; Wan, B. Cu-Catalyzed Ring Opening Reaction of 2*H*-Azirines with Terminal Alkynes: An Easy Access to 3-Alkynylated Pyrroles. *Org. Lett.* **2014**, *16*, 4806-4809. (f) Zhao, M.-N.; Ren, Z.-H.; Yang, D.-S.; Guan, Z.-H. Iron-Catalyzed Radical Cycloaddition of 2*H*-Azirines and Enamides for the Synthesis of Pyrroles. *Org. Lett.* **2018**, *20*, 1287-1290.

25 For Lewis acid-mediated ring-expansion of 2*H*-azirines, see: Jana, S.; Clements, M. D.; Sharp, B. K.; Zheng, N. Fe(II)-Catalyzed Amination of Aromatic C−H Bonds *via* Ring Opening of 2*H*-Azirines: Synthesis of 2,3-Disubstituted Indoles. *Org. Lett.* **2010**, *12*, 3736-3739.

26 For base-mediated ring-expansion of 2*H*-azirines, see: (a) Duan, X.; Yang, K.; Lu, J.; Kong, X.; Liu, N.; Ma, J. Base-Mediated Cascade Substitution–Cyclization of 2*H*-Azirines: Access to Highly Substituted Oxazoles. *Org. Lett.* **2017**, *19*, 3370-3373. (b) Ning, Y.; Otani, Y.; Ohwada, T. Base-Induced Transformation of 2-Acyl-3-alkyl-2*H*-azirines to Oxazoles: Involvement of Deprotonation- Initiated Pathways. *J. Org. Chem.* **2017**, *82*, 6313-6326.

27 Ning, Y.; Otani, Y.; Ohwada, T. Contrasting C- and O-Atom Reactivities of Neutral Ketone and Enolate Forms of 3-Sulfonyloxyimino-2-Methyl-1-Phenyl-1-Butanones. *J. Org. Chem.* **2018**, *83*, 203-219.

28 Gilli, P.; Bertolasi, V.; Ferretti, V.; Gilli, G. Evidence for Intramolecular N−H ⋯ O Resonance-Assisted Hydrogen Bonding in *β*-Enaminones and Related Heterodienes. A Combined Crystal-Structural, IR and NMR Spectroscopic, and Quantum-Mechanical Investigation. *J. Am. Chem. Soc.* **2000**, *122*, 10405-10417.

29 Sheibani, H.; Seifi, M. Nickel Acetylacetonate [$Ni(acac)_2$] and Montmorillonite K-10 Promoted Regioselective C-Acylation of *β*-Enamino Compounds. *ARKIVOC* **2009**, *xii*, 98-105.