Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201701476

Link to VoR: http://dx.doi.org/10.1002/adsc.201701476

10.1002/adsc.201701476

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

The catalyst-controlled divergent cascade reactions of homopropargylic amines and nitrones: Synthesis of pyrroloisoxazolidines and γ-lactams

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Received: ((will be filled in by the editorial staff))

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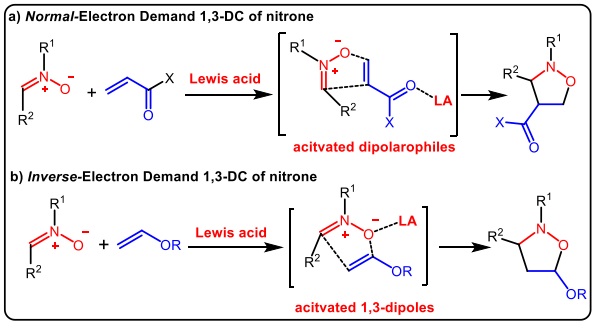
Abstract. Two controllable one-pot cascade cyclization reactions of homopropargylic amines and nitrones were developed by using different metal Cu and Ag salts. The pyrroloisoxazolidines and γ-lactams were obtained in good to high yields, respectively. Herein, nitrones played dual roles, both as 1,3-dipoles and oxidants, and four stereocenters were simultaneously formed in the hydroamination cyclization-1,3-dipolar cycloaddition cascade reaction of homopropargylic amines and nitrones in the presence of AgOAc.

Keywords: Homopropargylic amines; Nitrones; Hydroamination cyclization cascade reaction; Oxidation; 1,3-Dipolar cycloaddition

Introduction

The 1,3-dipolar cycloaddition reaction is a very important reaction in the field of organic synthetic chemistry. Among them, [3+2]-cycloaddition reactions of nitrones with olefins are well-developed for the construction of complex molecules, particularly alkaloids.[1] The cycloadducts, isoxazolidines, have high synthetic potential based on their transformations to γ-amino alcohols through reductive cleavage of the nitrogen-oxygen bond or lactam antibiotics through cleavage rearrangement.[2] Traditionally, 1,3-dipolar cycloadditions are carried out thermally. But since Kanemasa et al.[3a] reported that Lewis acids could accelerate 1,3-dipolar cycloaddition reaction to achieve both high *regio*- and *endo*/*exo*-selectivity, many metal-based catalysts, such as zinc, titanium, and magnesium salts, have been proposed for 1,3-dipolar cycloaddition reaction of nitrones.[3] Activation modes of the Lewis acid catalysts are different in the *normal*- or *inverse*-electron demand cycloaddition reactions (Scheme 1).[4] In the former, the dipolarophiles are activated by the Lewis acid catalysts to become more electron-deficient, thus being easily attacked by the oxygen anion of the nitrones, but the Lewis acid catalysts activate the 1,3-dipoles to make the iminium ions more electron-deficient, and the electron-rich olefins dipolarophiles attack the activated nitrones in the latter. Notably, the coordination of nitrones with the Lewis acid catalysts may lead to a fatal decrease of catalytic activity or deoxygenation of nitrones. For example, Sandhu reported that the nitrones could be easily transformed to imines by reduction or using various Lewis acid catalysts, such as $InCl_3$, $Zn(OTf)_2$ and $Cu(OTf)_2$.[5] Nevertheless, the studies on the nitrones as oxidants for providing oxygen sources are hardly explored besides some studies of pyridine *N*-oxides.[6]



Scheme 1. The activated modes of 1,3-dipolar cycloaddition reactions of nitrones.

On the other hand, the hydroamination cyclization of homopropargylic amines are generally performed in the presence of the metal salts (Cu, Ag, Au, Pt, etc.) or strong bases, and afford dihydropyrrole intermediates, which may act as dipolarophiles. Our group had developed a series of hydroamination cyclization [2+4]- or [4+2]-cycloaddition cascade reactions of homopropargylic amines for the

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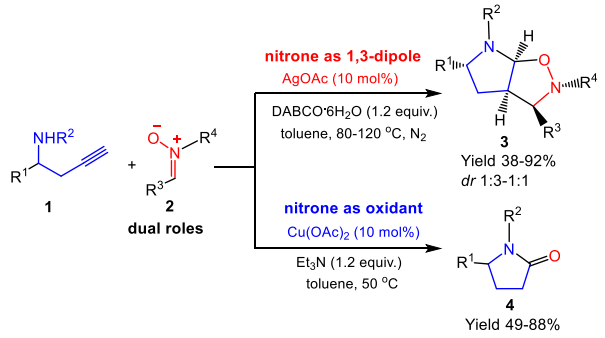
synthesis of diverse 5-6-6 or 5-6-5 fused *N*-containing heterocycles.[7] As a continuation of our ongoing work, we planned to employ nitrones as 1,3-dipoles to perform the hydroamination cyclization-[2+3]-cycloaddition via an *inverse*-electron demand mode with homopropargylic amines for the construction of fused pyrroloisoxazolidines, which are ubiquitous in biologically and pharmaceutically interesting molecules.[8] Unexpectedly, two different products, the pyrroloisoxazolidines **3** and γ-lactams **4**, were controllably obtained through using different metal catalysts $Cu(OAc)_2$ and AgOAc, respectively (Scheme 2). Obviously, herein the nitrones played dual roles, both as 1,3-dipoles and oxidants for providing oxygen source.



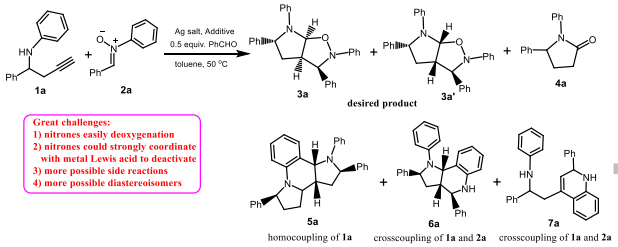
Scheme 2. The catalysts-controlled divergent cascade reactions of homopropargylic amines **1** and nitrones **2**.

Results and Discussion

In our initial study, we selected the homopropargylic amine **1a** and nitrone **2a** as model substrates. However, it was frustrating that the diverse possible products (**3a-7a**) were generated at the same time in the presence of $Cu(OTf)_2$ no matter how we changed the experimental parameters, which included the temperature, solvents, additives and the reaction system concentration as well as the amount of the $Cu(OTf)_2$ and additives (Table S1). For example, as the desired product **3a** was delivered in low or moderate yield through the hydroamination cyclization-1,3-dipolar cycloaddition cascade reaction, the homopropargylic amine **1a** might perform the formal dimerization to give the **5a**. Additionally, due to the fact that nitrone **2a** easily deoxygenated in the presence of $Cu(OTf)_2$,[5] the generated imine might also react with homopropargylic amine **1a** to render **6a** and **7a.** Simultaneously, the lactam **4a** might also be obtained due to the oxidability of nitrone.

Considering that, we selected another relatively weak Lewis acidic Ag salt to catalyze the reaction between homopropargylic amine **1a** and nitrone **2a** (Table 1). As a result, these three salts, such as $AgSbF_6$, Ag_2O and AgI displayed no catalytic activity (entries 1-3) with the starting materials remaining untouched (entries 1-3). The AgOTf gave a trace of the target molecule **3a** and a great amount of **1a** and **2a** was recovered (entry 4). Employing AgOAc as a catalyst, although only low yield of **3a** (36%) was obtained with most of **1a** being decomposed, no other side products (**4a-7a**) were observed (entry 5). This result led us to further fine-tune the other various Lewis bases in the presence of AgOAc. Consequently, the DABCO·$6H_2O$ provided the best yield of 75% using 3.0 equiv. nitrone **2a** at 80 °C (entries 6-16). Additionally, we attempted to carry out this reaction in the absence of PhCHO, it was unexpectedly observed that nearly the same yield of **3a** could be generated (Entry 17). Therefore, the optimal reaction conditions were confined as follows: 10 mol% AgOAc, 1.2 equiv. DABCO·$6H_2O$, 3.0 equiv. nitrone, at 80 °C under N_2 atmosphere. To the best of our knowledge, this reaction was the first report about the catalytic without a stoichiometric amount of Ag salts applied in the hydroamination cyclization of alkynes. It should be noted that part of the starting material **1a** suffered decomposition in all cases of other Lewis bases except for the production of **3a** in low yields (entries 6-14). Moreover, the diastereoselectivities ratios of the products in all cases were nearly 1:1 based on the ^1H NMR of crude products. The absolute configuration of *endo*-**3a** was unambiguously confirmed by an X-ray single-crystal diffraction (Figure 1).[9]

Table 1. The screening on the reaction conditions of homopropargylic amine **1a** and nitrone **2a** for the synthesis of pyrroloisoxazolidines[a)]



Entry	Catalyst	Lewis Base	**3a** Yield (%)[b)]
1	$AgSbF_6$	Et_3N	N.R.
2	Ag_2O	Et_3N	N.R.
3	AgI	Et_3N	N.R.
4	AgOTf	Et_3N	8
5	AgOAc	Et_3N	36
6	AgOAc	2,6-Lutidine	38
7	AgOAc	$^iPr_2NEt$	31
8	AgOAc	DMAP	22
9	AgOAc	NMM	22
10	AgOAc	DBU	21
11	AgOAc	TMEDA	21
12	AgOAc	$^iPr_2NH$	64
13	AgOAc	DABCO	45
14	AgOAc	DABCO.$6H_2O$	67
15[c)]	AgOAc	DABCO.$6H_2O$	75
16[d)]	**AgOAc**	**DABCO.$6H_2O$**	**76,75**[e)]
17[f)]	AgOAc	DABCO.$6H_2O$	76[e)]

[a)] Reaction conditions: under an N_2 atmosphere, homopropargylic amine **1a** (33.1 mg, 0.15 mmol), nitrone **2a** (44.4 mg, 0.225 mmol, 1.5 equiv.), Lewis base (1.2 equiv.), PhCHO (8 mg, 0.075 mmol, 0.5 equiv.), catalyst (10 mol%) and PhMe (2 mL) were sequentially added into

a Schlenk tube.The reaction was carried out under the given reaction conditions and the products were subsequently detected by TLC. [b] The yield was determined by ^{1}H NMR using 1,4-dioxane as an internal standard. [c] 3.0 equiv. nitrone **2a**. [d] 3.0 equiv. nitrone **2a**, 80 °C. [e] Isolated yield. [f] no PhCHO.

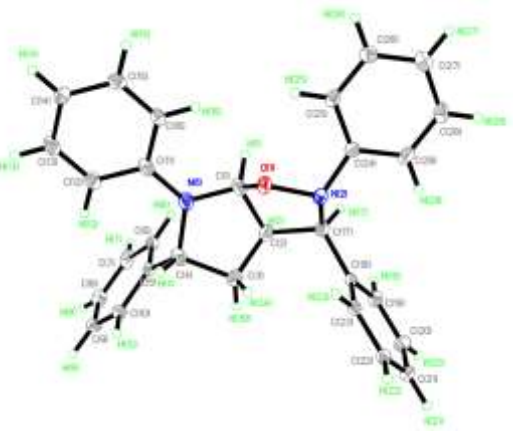
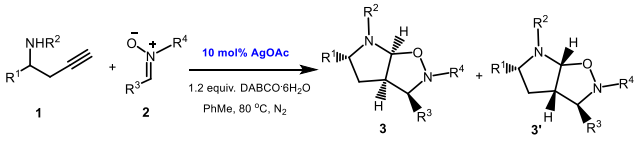
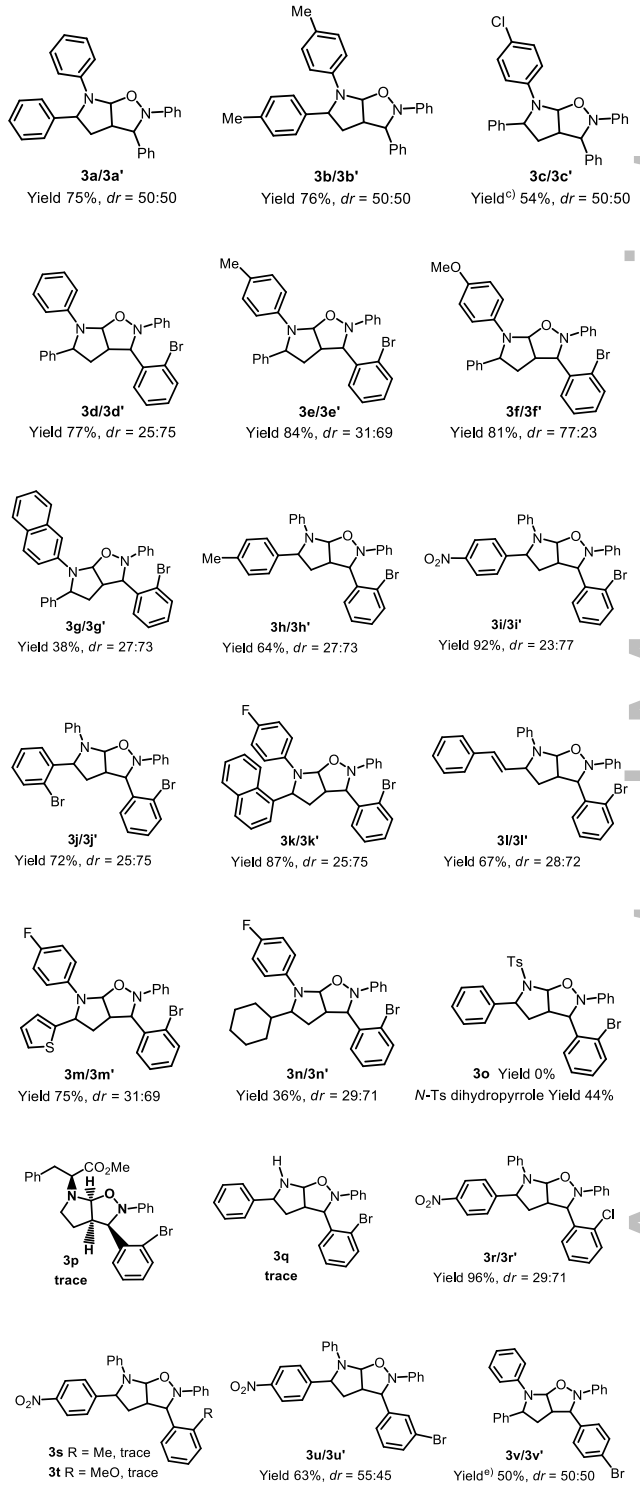


Figure 1. The ORTEP drawing of ***endo*-3a**.

The scope of homopropargylic amines and nitrones were then investigated. As shown in Table 2, all aryl substituted homopropargylic amines **1** and nitrones **2** (*N*-terminal or *C*-terminal) were competent in our methodology. And these reactions could afford the hydroamination cyclization-[2+3]-cycloadducts in good to high yields for the homopropargylic amines bearing with cycloalkyl or steric hindrance naphthyl or heteroaryl whether on the *C*-terminal (**3k**-**3n**) or *N*-terminal (**3g**). Notably, the **3l'** contained a small amount of another diastereoisomer. Unfortunately, when employing other *N*-alkyl substituted or unsubstituted homopropargylic amines or nitrones, these reactions were sluggish. For example, *N*-Ts homopropargylic amine only rendered the hydroamination cyclization product dihydropyrrole in 44% yield without further [2+3]-dipolar cycloadduct **3o** generated. As for the **3p**, **3s** and **3t**, only traces of target compounds were obtained with a large amount of the starting materials left remaining. In the cases of *N*-H homopropargylic amine and *N*-alkyl (Me and Bn) nitrones, the reactions were complicated with slight spots observed in the thin layer chromatography (TLC) plate (**3q**, **3w** and **3x**). The homopropargylic amine bearing 2-OH-aryl group on the *C*-terminal was decomposed under the standard reaction conditions without the target compound **3y** generated. Summarily, it could be found that the nitrones have some limitations. Only *N*-phenylnitrones with phenyl and electron-withdrawing substituted phenyl (*o*-Br, *o*-Cl (**3r**), *m*-Br (**3u**) and *p*-Br (**3V**)) on the *C*-terminal were applicable for our methodology. And the *exo*-configuration **3'** products were major in all cases of the nitrones with *o*-bromo or *o*-chlorophenyl substitutents on the *C*-terminal, whereas for the unsubstituted phenyl or other site-substituted phenylnitrones, the products were obtained in nearly 1:1 ratio of *endo*-**3**/*exo*-**3'** configuration.

Table 2. The scope of homopropargylic amines and nitrones[a,b]





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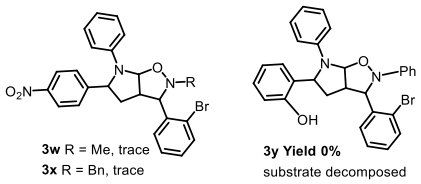
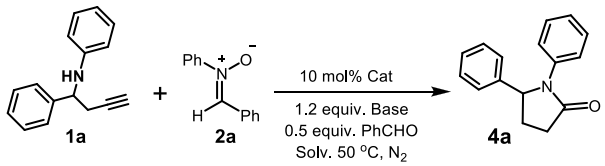


[a] Reaction conditions: under an N_2 atmosphere, homopropargylic amines **1** (0.15 mmol), nitrones **2** (0.45 mmol, 3.0 equiv.), DABCO·6H_2O (1.2 equiv.), AgOAc (2.5 mg, 0.015 mmol, 0.1 equiv.) and PhMe (2 mL) were sequentially added into a Schlenk tube. The reaction was carried out at 80 °C and detected by TLC. [b] Isolated yield. [c] Using 20 mol% AgOAc, 120 °C. [d] The product was the dimerization compound **5r** of homopropargylic amine. [e] The temperature was 120 °C.

In Table S1, the γ-lactam **4a** was always generated as a major side product. We, therefore, anticipated that a single lactam could be obtained through controlling reaction conditions. The Lewis bases were first examined in the presence of $Cu(OTf)_2$. It was found that the Et_3N gave the best results (Table 3, entries 1-5). Subsequently, the Cu(I) and other Cu(II) salts were carefully screened and high yield of lactam **4a** (88%) could be achieved with the $Cu(OAc)_2$ catalyst (entries 6-12). The solvents were also further investigated and the PhMe was found to be the optimal media (entries 13-17). Adjusting other experimental parameters, such as the **1a**/**2a** ratio, the loading of $Cu(OAc)_2$, with or without aldehyde and N_2 or air (entries 18-21), we observed that using 5 mol% $Cu(OAc)_2$ and 1.2 equiv. Et_3N, the reaction of **1a** and **2a** in ratio 1/1.5 also gave a good yield of lactam at 50 °C under N_2 atmosphere in the absence of an aldehyde (entry 20).

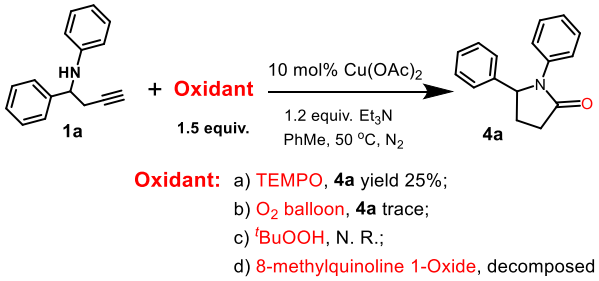
Table 3. Optimization of reaction conditions of homopropargylic amine **1a** and nitrone **2a** for the synthesis of lactam[a]



Entry	Catalyst	Base	the solvent	Yield (%)[b]
1	$Cu(OTf)_2$	Et_3N	PhMe	63
2	$Cu(OTf)_2$	DBU	PhMe	55
3	$Cu(OTf)_2$		PhMe	10
4	$Cu(OTf)_2$	*t*-BuOK	PhMe	29
5[c]	$Cu(OTf)_2$	K_2CO_3	PhMe	trace
6	$CuCl_2$	Et_3N	PhMe	51
7	$CuBr_2$	Et_3N	PhMe	65
8	CuCl	Et_3N	PhMe	46
9	CuBr	Et_3N	PhMe	73
10	CuI	Et_3N	PhMe	70
11	$Fe(OTf)_3$	Et_3N	PhMe	N.R.
12	**$Cu(OAc)_2$**	**Et_3N**	**PhMe**	**88**
13	$Cu(OAc)_2$	Et_3N	DCE	40
14	$Cu(OAc)_2$	Et_3N	CH_2Cl_2	46
15	$Cu(OAc)_2$	Et_3N	THF	80
16	$Cu(OAc)_2$	Et_3N	DMF	72
17	$Cu(OAc)_2$	Et_3N	CH_3OH	59
18[d]	$Cu(OAc)_2$	Et_3N	PhMe	80
19[e]	$Cu(OAc)_2$	Et_3N	PhMe	84
20[f]	**$Cu(OAc)_2$**	**Et_3N**	**PhMe**	**80**
21[f,g]	$Cu(OAc)_2$	Et_3N	PhMe	72

[a] Reaction conditions: to a dried Schlenk tube were added homopropargylic amine **1a** (66.4 mg, 0.3 mmol, 1.5 equiv.), nitrone **2a** (0.2 mmol, 1.0 equiv), catalyst (10 mol%), and the reaction vessel was evacuated and backfilled with nitrogen three times. Then the solvent (2 mL), base (1.2 equiv.), and benzaldehyde (10.6 mg, 0.5 equiv.) were added under a nitrogen atmosphere. The reaction mixture was stirred at 50 °C for about 5 h until complete disappearance of **2a** (monitored by TLC). [b] Isolated yield. [c] K_2CO_3 cannot dissolve in the PhMe. But it can dissolve in the THF and can obtain 25% yield. [d] No aldehyde. [e] No aldehyde, $Cu(OAc)_2$ (1.8 mg, 5 mol%). [f] No aldehyde, $Cu(OAc)_2$ (1.8 mg, 5 mol%), **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.3 mmol, 1.5 equiv). [g] air.

Since the nitrone **2a** only acted as an oxygen source in this reaction, with the removal of imine which could not further react with the excess homopropargylic amine **1a** (Scheme S1), we attempted to apply other oxidants[10], such as TEMPO, O_2 balloon, ^{t}BuOOH and 8-methylquinoline 1-oxide under the standard reaction conditions. Unfortunately, the results were unsatisfactory (Scheme 3). Nevertheless, using other similar nitrones **2**, the expected lactams could be obtained in moderate to good yields (Table S2). The reason remained unclear at present. Maybe the nitrones possess certain special oxidability for providing the oxygen.



Scheme 3. The screening of other oxidants for the homopropargylic amine **1a**.

This hydroamination cyclization-oxidation cascade reaction was further studied by modifying the homopropargylic amines substrates under the optimized reaction conditions (Table 3, entry 20). As shown in Table 4, various aryl substituted homopropargylic amines whether on the *C*-terminal or *N*-terminal, could all render good yields of target compounds (**4a-4h**, **4k-4r**). The homopropargylic

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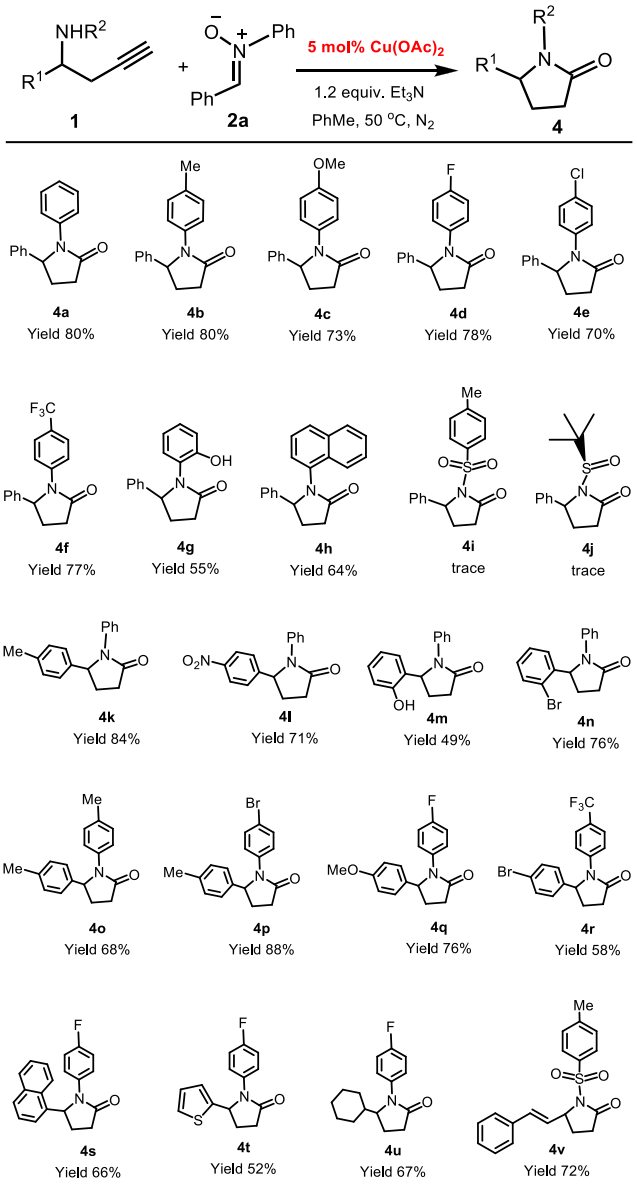
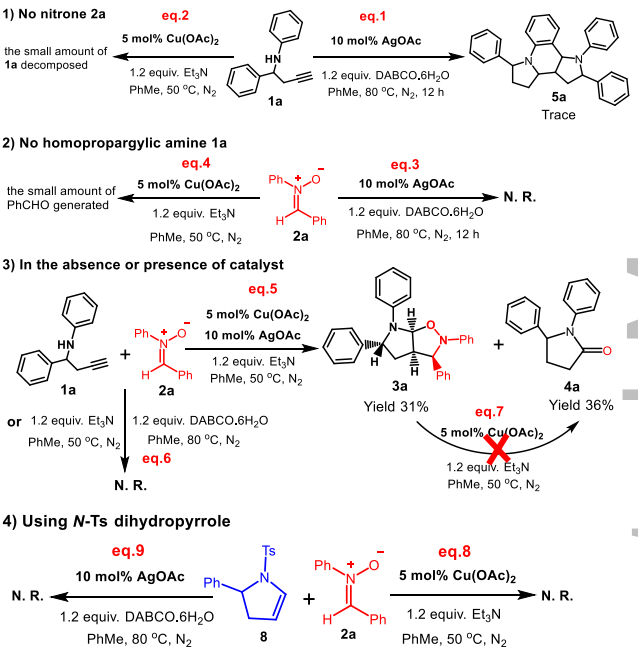
amines bearing steric hindrance naphthyl, heteroaryl, cyclohexyl and cinnamyl substituents on the *C*-terminal were also good candidates (**4s**-**4v**). However, only traces of lactams were observed in the cases of the *N*-Ts and *N*-^{t}BuSO homopropargylic amines (**4i** and **4j**).

Table 4. The scope of homopropargylic amines **1** and nitrone **2a**[a,b]



[a] Reaction conditions: $Cu(OAc)_2$ (5mol%), Et_3N (1.2 equiv.), **1** (0.2 mmol), and **2a** (0.3 mmol, 1.5 equiv.) at 50 °C in PhMe (2 mL) under N_2 atmosphere. [b] Isolated yield.

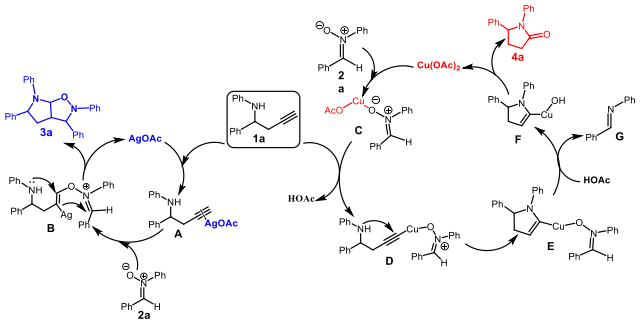
In a bid to gain insight into the above two cascade reaction mechanisms, we performed some additional control experiments (**Scheme 4**). In eq.1 and eq.2, the great amount of homopropargylic amine **1a** remained in the absence of nitrone **2a**, with the trace of a formal dimerization product **5a** generated in AgOAc and a small amount of **1a** decomposed in $Cu(OAc)_2$. The results of these two experiments indicated the requisite of the nitrone **2a**. Moreover, it could be found that the nitrone **2a** was more easily subjected to deoxygenation with $Cu(OAc)_2$ than AgOAc according to the eq.3 and eq.4. Additionally, when adding two catalysts $Cu(OAc)_2$ and AgOAc together into the reaction system of **1a** and **2a**, only the product **4a** was formed within 2 h, but **3a** was also slowly generated with the prolonged reaction time for 7 h (eq.5). No reaction occurred in the presence of Lewis base without any metal catalyst (eq.6). Moreover, the isolated product **3a** could not be further transformed to **4a** under the standard reaction conditions for the synthesis of γ-lactam (eq.7). From all of these experiments, we could reveal that the activity of $Cu(OAc)_2$ was higher than that of AgOAc in our reactions. On the other hand, because of the instability and inseparability of *N*-Ph dihydropyrrole, we had no choice but to choose the *N*-Ts dipyrroline **8** as an alternative to react with nitrone **2a** in these two optimal catalytic systems (Scheme 4, eq.8 and eq.9). Consequently, the starting materials remained nearly untouched in two cases.



Scheme 4. The controlled experiments

Based on all of the above results and precedents in the literature,[11] two possible cascade reaction mechanisms were proposed for the synthesis of pyrroloisoxazolidines and lactams, respectively (**Scheme 5**). In the presence of AgOAc, the homopropargylic amine **1a** was first activated by the AgOAc to give intermediate **A**, attacked by the oxygen anion of the nitrone **2a**, to form **B**, which subsequently underwent intramolecular hydro-amination cyclization and attacked the imine ion to give the expected cycloadduct **3a** with the removal of AgOAc. While in the case of the $Cu(OAc)_2$, the nitrone **2a** was coordinated with $Cu(OAc)_2$ to form

high active species **C**, which was attacked by the homopropargylic amine **1a** to give the alkynyl copper compound **D**. This intermediate underwent intramolecular hydroamination cyclization to afford the species **E**, which suffered the cleavage of N-O bond to render the intermediate **F** in the presence of HOAc with the removal of imine **G** traced by the ^{1}H NMR of crude product. The intermediate **F** was finally transformed to target compound **4a** with the removal of Cu salt.



Scheme 5. The possible mechanisms for these two hydroamination cyclization cascade reactions of homopropargylic amines and nitrones.

Conclusion

In summary, two novel catalysts-controlled cascade reactions between homopropargylic amines and nitrones were developed, namely, in the presence of AgOAc, the formal hydroamination cyclization-[2+3] cycloaddition cascade reaction occurred and gave an access to the fused pyrroloisoxazolidines **3** with most of *exo*-configurations, whereas with $Cu(OAc)_2$, the γ-lactams **4** were generated in good yields through the hydroamination cyclization-oxidation cascade reaction. The AgOAc and $Cu(OAc)_2$ displayed different catalytic properties. And the nitrones played dual roles in these two reactions, one as 1,3-dipoles, the other acted as oxidants for providing the oxygen. Studies of the additional applications of pyrroloisoxazolidines and asymmetric transformations of homopropargylic amines are in progress in our group.

Experimental Section

The Synthesis of homopropargylic amines[7] and nitrones 2 was performed according to the literature [12]

Synthesis and Characterization of the pyrrolo-isoxazolidines 3

To a dried Schlenk tube were sequentially added homopropargylic amines **1** (0.15 mmol, 1.0 equiv.), nitrones **2** (0.45 mmol, 3.0 equiv), AgOAc (2.5 mg, 10 mol%), $DABCO.6H_2O$ (39.6 mg, 1.2 equiv), the corresponding aldehyde (0.5 equiv) and PhMe solvent (2 mL) under a nitrogen atmosphere. After the reaction was finished as indicated by TLC (reaction time for about 10 h), the resulting mixture was allowed to cool to room temperature and was concentrated in vacuo. The crude product obtained was determined by ^{1}H NMR to give the *dr* value and purified by column chromatography on silica gel (PE/EtOAc = 150:1) to afford **3**.

Synthesis and Characterization of the γ-lactams 4

To a dried Schlenk tube were added $Cu(OAc)_2$ (1.8 mg, 5 mol%), nitrone (0.3 mmol, 1.5 equiv), the homopropargylic amine (0.2 mmol, 1 equiv.) , and the reaction vessel was evacuated and backfilled with nitrogen three times. Then the PhMe solvent (2mL) and NEt_3 (1.2eq) were added under a nitrogen atmosphere. The reaction mixture was stirred at 50 °C for about 2 h until complete disappearance of **1a** (monitored by TLC). The crude product was purified by column chromatography on silica gel (PE/EtOAc=5:1) to afford **4a** as yellow solid, 38mg, 80%.

2-((1-phenylbut-3-yn-1-yl)amino)phenol (1g): yield: 3.286 g (69%); yellow liquid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 – 7.22 (m, 2H), 7.22 – 7.15 (m, 2H), 7.14 – 7.07 (m, 1H), 6.56 (ddd, *J* = 6.8, 3.9, 2.3 Hz, 2H), 6.48 (td, *J* = 7.5, 1.6 Hz, 1H), 6.34 (dd, *J* = 8.1, 1.6 Hz, 1H), 4.87 (s, 2H), 4.36 (t, *J* = 6.3 Hz, 1H), 2.66 – 2.49 (m, 2H), 1.93 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 142.1, 135.4, 128.7, 127.7, 126.6, 121.5, 119.0, 114.9, 114.5, 80.7, 71.5, 57.4, 28.1. HRMS (ESI+) calculated for $C_{16}H_{16}NO$ ($M+H^+$) 238.1232; found 238.1230.

(*Z*)-*N*-benzylideneaniline oxide (2a): yield: 1.716 g (44%); white solid; mp 111.9-113.5 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.92 (s, 1H), 7.77 (dd, *J* = 7.6, 2.2 Hz, 2H), 7.48 (dt, *J* = 3.8, 1.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2, 134.7, 131.1, 130.8, 130.1, 129.3, 129.2, 128.8, 121.9.

(*Z*)-*N*-(2-bromobenzylidene)aniline oxide (2d): yield: 1.928 g (35%); yellow solid; mp 55.8-61.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.42 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.33 (s, 1H), 7.73 – 7.68 (m, 2H), 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44 – 7.34 (m, 4H), 7.20 (td, *J* = 7.6, 1.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 133.2, 133.0, 131.9 130.3, 129.8, 129.6, 129.3, 127.9, 124.2, 121.9.

(*Z*)-*N*-(2-chlorobenzylidene)aniline oxide (2r): yield: 2.09 g (45%); yellow solid; mp 80.0-83.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.53 (dd, *J* = 7.7, 2.0 Hz, 1H), 8.43 (s, 1H), 7.83 – 7.75 (m, 2H), 7.48 (ddd, *J* = 11.4, 6.4, 2.1 Hz, 4H), 7.39 (ddd, *J* = 9.6, 7.5, 1.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 133.7, 131.6, 130.6, 130.3, 129.6, 129.4, 129.3, 128.4, 127.3, 121.9.

(*Z*)-*N*-(2-methylbenzylidene)aniline oxide (2s): yield: 2.156 g (51%); yellow solid; mp 84.5-87.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.27 (dd, *J* = 5.7, 3.8 Hz, 1H), 7.95 (s, 1H), 7.67 – 7.60 (m, 2H), 7.41 – 7.31 (m, 3H), 7.26 – 7.20 (m, 2H), 7.13 (dd, *J* = 5.5, 3.5 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 137.0, 131.9, 130.7, 130.3, 129.9, 129.2, 129.0, 127.9, 126.4, 121.9, 20.0.

(*Z*)-*N*-(2-methoxybenzylidene)aniline oxide (2t): yield: 2.672g (59%); yellow liquid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.40 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.30 (s, 1H), 7.73 – 7.65 (m, 2H), 7.44 – 7.27 (m, 5H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 3.77 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 149.6, 132.2, 129.7, 129.4, 129.1, 128.7, 121.8, 120.8, 119.8, 109.9, 55.6.

(*Z*)-*N*-(3-bromobenzylidene)aniline oxide (2u): yield: 2.24 g (40%); yellow solid; mp 96.8-99.2 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.61 (t, *J* = 1.8 Hz, 1H), 8.19 – 8.06 (m, 1H), 7.81 (s, 1H), 7.70 – 7.63 (m, 2H), 7.49 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.41 – 7.34 (m, 3H), 7.25 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9,

133.8, 133.2, 132.5, 131.4, 130.3, 130.2, 129.3, 127.6, 122.8, 121.7.

(*Z*)-*N*-(4-bromobenzylidene)aniline oxide (2v): yield: 3.194 g (58%); white solid; mp 166.5-167.5 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 – 8.22 (m, 2H), 7.90 (s, 1H), 7.78 – 7.73 (m, 2H), 7.63 – 7.56 (m, 2H), 7.51 – 7.43 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1, 133.5, 132.0, 130.4, 130.2, 129.7, 129.3, 124.9, 121.8.

(*Z*)-*N*-(2-bromobenzylidene)methanamine oxide (2w): yield: 2.0 g (93%); white solid; mp 76.0-79.3 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.21 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.77 (s, 1H), 7.54 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.32 (td, *J* = 7.8, 1.3 Hz, 1H), 7.22 – 7.11 (m, 1H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8, 132.9, 131.5, 129.6, 129.4, 127.8, 123.2, 55.4. HRMS (ESI+) calculated for $C_8H_8BrNNaO$ ($M+Na^+$) 235.9687; found 235.9685.

(*Z*)-*N*-(2-bromobenzylidene)-1-phenylmethanamine oxide (2x): yield: 1.884 g (65%); white solid; mp 66.3 - 68.4 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.28 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.90 (s, 1H), 7.58 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.46 – 7.39 (m, 3H), 7.38 – 7.33 (m, 1H), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H), 5.09 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1, 132.9, 132.8, 131.5, 129.51, 129.48, 129.4, 129.2, 129.1, 127.7, 123.5, 72.1.

2,3,5,6-tetraphenylhexahydro-*2H*-pyrrolo[3,2-*d*] isoxazole (3a) [*dr* = 50:50]: yield: 47 mg (75%); yellow solid; mp 157.3-158.3 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 3H), 7.38 – 7.31 (m, 3H), 7.31 – 7.26 (m, 3H), 7.23 (d, *J* = 6.5 Hz, 2H), 7.21 – 7.10 (m, 6H), 7.10 – 6.90 (m, 8H), 6.89 – 6.73 (m, 5H), 6.29 (d, *J* = 5.9 Hz, 0.5H), 6.24 (d, *J* = 5.2 Hz, 1H), 5.06 (d, *J* = 8.0 Hz, 1H), 4.93 (t, *J* = 6.8 Hz, 1.5H), 4.79 (s, 0.5H), 3.62 (dtd, *J* = 15.3, 7.4, 5.2 Hz, 1H), 3.42 (q, *J* = 8.0 Hz, 0.5H), 2.60 (dq, *J* = 12.7, 9.8, 9.2 Hz, 1.5H), 2.16 (ddd, *J* = 12.0, 8.5, 2.3 Hz, 0.5H), 1.45 (ddd, *J* = 12.5, 7.7, 1.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 151.1, 144.2, 144.1, 142.7, 142.6, 141.2, 138.0, 129.12, 129.08, 128.92, 128.88, 128.86, 128.8, 128.73, 127.65, 127.0, 126.71, 125.67, 125.6, 122.3, 121.2, 118.5, 116.1, 115.0, 114.7, 114.6, 94.6, 93.0, 74.5, 71.0, 64.5, 64.1, 54.2, 50.6, 39.8, 35.9. HRMS (ESI+) calculated for $C_{29}H_{27}N_2O$ ($M+H^+$) 419.2123; found 419.2116.

2,3-diphenyl-5,6-di-*p*-tolylhexahydro-*2H*-pyrrolo [3,2-*d*]isoxazole (3b) [*dr* = 50:50]: yield: 51 mg (76%); white solid; mp 74.1-77.3 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 – 7.51 (m, 2H), 7.45 – 7.27 (m, 10H), 7.24 (d, *J* = 2.1 Hz, 1H), 7.18 – 7.12 (m, 3H), 7.09 – 6.99 (m, 11H), 6.98 – 6.93 (m, 5H), 6.92 – 6.84 (m, 3H), 6.77 – 6.69 (m, 4H), 6.27 (dd, *J* = 6.1, 2.6 Hz, 1H), 6.22 (dd, *J* = 5.4, 2.2 Hz, 1H), 5.02 (d, *J* = 8.1 Hz, 1H), 4.95 (d, *J* = 5.9 Hz, 1H), 4.88 (d, *J* = 8.0 Hz, 1H), 4.81 (s, 1H), 3.61 (ddt, *J* = 10.9, 8.1, 5.8 Hz, 1H), 3.42 (q, *J* = 8.1 Hz, 1H), 2.57 (dddd, *J* = 21.8, 14.0, 9.9, 2.0 Hz, 2H), 2.29 (dd, *J* = 6.4, 2.2 Hz, 6H), 2.25 (t, *J* = 3.1 Hz, 6H), 2.18 – 2.09 (m, 1H), 1.46 – 1.37 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 151.2, 142.0, 141.8, 141.3, 139.9, 139.8, 138.2, 136.60, 136.58, 129.7, 129.63, 129.57, 129.5, 128.9, 128.8, 128.7, 127.6, 127.5, 127.1, 126.7, 125.64, 125.57, 122.17, 121.16, 116.0, 115.00, 114.98, 114.6, 94.9, 93.3, 74.6, 71.0, 64.3, 63.9, 54.2, 50.6, 39.9, 36.1, 21.2, 20.6. HRMS (ESI+) calculated for $C_{31}H_{31}N_2O$ ($M+H^+$) 447.2436; found 447.2437.

6-(4-chlorophenyl)-2,3,5-triphenylhexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3c) [*dr* = 50:50]: yield: 37 mg (54%); white solid; mp 113.0-116.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 7.7 Hz, 2H), 7.35 (tt, *J* = 16.8, 7.4 Hz, 9H), 7.25 – 7.18 (m, 5H), 7.13 (d, *J* = 8.8 Hz, 6H), 7.01 (q, *J* = 7.4 Hz, 7H), 6.95 – 6.84 (m, 3H), 6.72 (t, *J* = 9.1 Hz, 4H), 6.26 (d, *J* = 5.9 Hz, 1H), 6.20 (d, *J* = 5.4 Hz, 0.9H), 5.02 (d, *J* = 7.9 Hz, 0.9H), 4.88 (dd, *J* = 12.2, 7.8 Hz, 1.9H), 4.81 (s, 1H), 3.67 – 3.57 (m, 0.9H), 3.45 (q, *J* = 8.1 Hz, 1H), 2.58 (td, *J* = 10.7, 10.3, 5.1 Hz, 1.9H), 2.17 (ddd, *J* = 11.6, 8.5, 2.5 Hz, 1H), 1.48 (dd, *J* = 11.5, 9.0 Hz, 0.9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9, 150.6, 142.9, 142.7, 142.2, 141.0, 137.6, 129.03, 128.98, 128.94, 128.91, 128.86, 128.84, 128.78, 127.73, 127.29, 127.2, 127.1, 126.7, 125.63, 125.57, 123.6, 123.5, 122.7, 121.4, 116.8, 116.2, 116.0, 114.6, 94.6, 92.9, 74.5, 70.8, 64.6, 64.2, 54.3, 50.9, 39.8, 36.0. HRMS (ESI+) calculated for $C_{29}H_{26}ClN_2O$ ($M+H^+$) 453.1734; found 453.1723.

3-(2-bromophenyl)-2,5,6-triphenylhexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3d) [*dr* = 25:75]: yield: 58 mg (77%); yellow solid, mp 149.5-151.7 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.79 (dd, *J* = 7.8, 1.7 Hz, 0.6H), 7.57 (ddd, *J* = 8.0, 3.8, 1.2 Hz, 1.6H), 7.38 – 7.32 (m, 2H), 7.32 – 7.24 (m, 3H), 7.23 – 7.11 (m, 11H), 7.06 – 7.02 (m, 1H), 7.01 – 6.94 (m, 4H), 6.94 – 6.90 (m, 2H), 6.86 (dd, *J* = 7.9, 6.7 Hz, 1H), 6.83 – 6.75 (m, 5H), 6.27 (d, *J* = 5.2 Hz, 0.6H), 6.23 (d, *J* = 6.0 Hz, 1H), 5.24 (d, *J* = 7.5 Hz, 0.6H), 5.19 (s, 1H), 5.01 (dd, *J* = 8.3, 2.0 Hz, 0.6H), 4.83 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.92 (dtd, *J* = 10.1, 7.8, 5.2 Hz, 0.6H), 3.39 (td, *J* = 8.8, 5.8 Hz, 1H), 2.60 (dt, *J* = 12.8, 8.6 Hz, 1H), 2.42 (ddd, *J* = 12.5, 10.2, 8.2 Hz, 0.6H), 2.25 (ddd, *J* = 12.8, 8.9, 2.5 Hz, 1H), 1.47 (ddd, *J* = 12.5, 8.0, 2.1 Hz, 0.6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.11, 151.09, 144.1, 144.0, 142.8, 142.5, 140.2, 137.8, 132.8, 130.0, 129.3, 129.2, 129.12, 129.09, 129.0, 128.9, 128.8, 128.1, 127.8, 127.11, 127.06, 125.64, 125.57, 122.6 122.2, 122.1, 121.2, 118.7, 118.6, 115.2, 115.1, 114.7, 114.1, 95.0, 93.6, 74.2, 71.0, 64.9, 64.1, 53.7, 48.2, 40.0, 35.5. HRMS (ESI+) calculated for $C_{29}H_{26}BrN_2O$ ($M+H^+$) 497.1229; found 497.1226.

3-(2-bromophenyl)-2,5-diphenyl-6-(*p*-tolyl)hexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3e) [*dr* = 31:69]: yield: 65 mg (84%); yellow solid; mp 170.8-173.5 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.78 (dd, *J* = 7.8, 1.7 Hz, 0.4H), 7.56 (ddd, *J* = 8.0, 3.9, 1.3 Hz, 1.4H), 7.39 – 7.23 (m, 4H), 7.22 – 7.11 (m, 8H), 7.05 – 6.89 (m, 10H), 6.89 – 6.83 (m, 1H), 6.74 – 6.66 (m, 3H), 6.25 (d, *J* = 5.2 Hz, 0.4H), 6.21 (d, *J* = 6.0 Hz, 1H), 5.23 (d, *J* = 7.6 Hz, 0.4H), 5.18 (s, 1H), 4.97 (dd, *J* = 8.2, 2.2 Hz, 0.4H), 4.79 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.90 (dtd, *J* = 9.9, 7.8, 5.1 Hz, 0.4H), 3.46 – 3.29 (m, 1H), 2.58 (dt, *J* = 12.8, 8.6 Hz, 1H), 2.42 – 2.35 (m, 0.4H), 2.23 (d, *J* = 5.0 Hz, 5.2H), 1.46 (ddd, *J* = 12.5, 8.1, 2.3 Hz, 0.4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 151.2, 143.0, 142.7, 141.71, 141.68, 140.3, 137.9, 132.8, 129.9, 129.70, 129.66, 129.3, 129.1, 128.9, 128.9, 128.9, 128.8, 128.0, 127.8, 127.6, 127.04, 126.98, 125.7, 125.6, 122.5, 122.2, 122.0, 121.1, 115.1, 115.1, 114.7, 114.1, 95.2, 93.9, 74.3, 71.1, 64.8, 64.1, 53.7, 48.1, 40.0, 35.6, 20.6. HRMS (ESI+) calculated for $C_{30}H_{28}BrN_2O$ ($M+H^+$) 511.1385; found 511.1382.

3-(2-bromophenyl)-6-(4-methoxyphenyl)-2,5-diphenyl-hexahydro-*2H*-pyrrolo[3,2-*d*] isoxazole (3f): yield: 22 mg (28%); yellow solid; mp 166.5-170.8 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34 (td, *J* = 7.6, 1.3 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.25 – 7.22 (m, 2H), 7.18 (td, *J* = 7.5, 1.7 Hz, 2H), 7.05 (dd, *J* = 7.0, 1.8 Hz, 2H), 7.01 – 6.93 (m, 3H), 6.83 – 6.71 (m, 4H), 6.24 (d, *J* = 5.2 Hz, 1H), 5.22 (d, *J* = 7.6 Hz, 1H), 4.94 (dd, *J* = 8.1, 2.9 Hz, 1H), 3.97 – 3.86 (m, 1H), 3.73 (s, 3H), 2.34 (dt, *J* = 12.5, 8.6 Hz, 1H), 1.49 (ddd, *J* = 12.4, 8.2, 2.9 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 151.0, 142.8, 138.2, 137.9, 132.8, 130.0, 129.3, 129.1, 128.9, 127.8, 127.1, 125.8, 122.2, 122.1, 116.1, 115.3, 114.7, 94.3, 71.1, 64.9, 55.7, 48.2, 35.8. HRMS (ESI+) calculated for $C_{30}H_{28}BrN_2O_2$ ($M+H^+$) 527.1334; found 527.1333.

3-(2-bromophenyl)-6-(4-methoxyphenyl)-2,5-diphenyl-hexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3f'): yield: 42 mg (53%); yellow solid; mp 160.3-164.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.35 (td, *J* = 7.6, 1.3 Hz, 1H), 7.25 – 7.12 (m, 6H), 7.00 – 6.94 (m, 2H), 6.92 – 6.83 (m, 3H), 6.81 – 6.66 (m, 4H), 6.21 (d, *J* = 5.9 Hz, 1H), 5.19 (s, 1H), 4.72 (dd, *J* = 8.1, 3.2 Hz, 1H), 3.73 (s, 3H), 3.38 (td, *J*

= 8.2, 5.6 Hz, 1H), 2.59 (dt, *J* = 12.9, 8.2 Hz, 1H), 2.22 (ddd, *J* = 12.6, 9.0, 3.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 151.0, 143.1, 140.4, 138.1, 132.8, 129.1, 128.91, 128.90, 128.8, 128.0, 127.0, 125.7, 122.6, 121.1, 116.3, 114.6, 114.1, 95.6, 74.3, 64.1, 55.7, 53.8, 40.4. HRMS (ESI+) calculated for $C_{30}H_{28}BrN_2O_2$ ($M+H^+$) 527.1334; found 527.1330.

3-(2-bromophenyl)-6-(naphthalen-2-yl)-2,5-diphenylhexahydro-*2H*-pyrrolo[3,2-d]isoxazole (3g) [*dr* = 27:73]: yield: 31 mg (38%); yellow solid; mp 197.9-201.6 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.79 (dd, *J* = 7.8, 1.7 Hz, 0.5H), 7.74 – 7.67 (m, 3H), 7.64 – 7.54 (m, 3H), 7.43 – 7.27 (m, 6H), 7.26 – 7.07 (m, 13H), 7.07 – 6.97 (m, 5H), 6.97 – 6.92 (m, 2H), 6.89 – 6.84 (m, 1H), 6.41 (d, *J* = 5.4 Hz, 0.5H), 6.37 (d, *J* = 6.0 Hz, 1H), 5.26 (d, *J* = 4.6 Hz, 1.5H), 5.15 (dd, *J* = 8.0, 2.6 Hz, 0.5H), 4.97 (dd, *J* = 8.3, 2.6 Hz, 1H), 4.06 – 3.92 (m, 0.5H), 3.46 (td, *J* = 8.7, 5.8 Hz, 1H), 2.65 (dt, *J* = 12.9, 8.5 Hz, 1H), 2.45 (ddd, *J* = 12.6, 9.5, 8.1 Hz, 0.5H), 2.31 (ddd, *J* = 12.8, 8.9, 2.7 Hz, 1H), 1.58 – 1.53 (m, 0.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 150.7, 142.7, 142.4, 141.9, 141.9, 140.2, 137.7, 134.7, 134.6, 132.9, 132.8, 130.0, 129.37, 129.36, 129.2, 129.1, 128.99, 128.96, 128.95, 128.94, 128.91, 128.86, 128.8, 128.1, 127.8, 127.8, 127.8, 127.6, 127.2, 127.1, 126.72, 126.67, 126.27, 126.26, 125.7, 125.6, 122.9, 122.6, 122.4, 122.3, 121.2, 117.5, 117.3, 115.7, 114.1, 110.0, 109.8, 95.3, 93.7, 74.4, 70.9, 64.9, 64.2, 53.9, 48.3, 40.0, 35.7. HRMS (ESI+) calculated for $C_{33}H_{28}BrN_2O$ ($M+H^+$) 547.1385; found 547.1383.

3-(2-bromophenyl)-2,6-diphenyl-5-(*p*-tolyl)hexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3h) [dr = 27:73]: yield: 49 mg (64%); yellow solid; mp 73.3-78.5 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.78 (dd, *J* = 7.8, 1.7 Hz, 0.25H), 7.56 (ddd, *J* = 8.1, 4.8, 1.2 Hz, 1.25H), 7.35 (td, *J* = 7.7, 1.3 Hz, 1H), 7.28 (dd, *J* = 8.7, 7.2 Hz, 1H), 7.17 (dtd, *J* = 18.2, 8.7, 7.9, 4.7 Hz, 7H), 7.07 – 6.96 (m, 4H), 6.92 (t, *J* = 6.2 Hz, 3H), 6.85 (d, *J* = 7.7 Hz, 3H), 6.80 (d, *J* = 7.9 Hz, 4H), 6.25 (d, *J* = 5.2 Hz, 0.25H), 6.21 (d, *J* = 6.0 Hz, 1H), 5.27 – 5.23 (m, 0.25H), 5.18 (s, 1H), 5.04 – 4.94 (m, 0.25H), 4.81 (dd, *J* = 8.2, 2.3 Hz, 1H), 3.91 (dtd, *J* = 10.2, 7.7, 5.1 Hz, 0.25H), 3.38 (td, *J* = 8.9, 5.9 Hz, 1H), 2.58 (dt, *J* = 12.8, 8.6 Hz, 1H), 2.40 (dt, *J* = 10.4, 2.2 Hz, 0.25H), 2.27 (d, *J* = 8.3 Hz, 3.75H), 2.24 – 2.19 (m, 1H), 1.45 (ddd, *J* = 10.4, 7.0, 1.7 Hz, 0.25H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 151.1, 144.1, 140.3, 139.8, 139.4, 137.9, 136.7, 136.6, 132.8, 129.9, 129.6, 129.6, 129.3, 129.2, 129.1, 129.1, 128.9, 128.8, 128.1, 127.8, 125.6, 125.5, 122.5, 122.2, 122.1, 121.2, 118.6, 118.5, 115.1, 115.0, 114.6, 114.1, 95.0, 93.7, 74.2, 71.0, 64.7, 63.9, 53.7, 48.2, 40.0, 35.5, 29.9, 21.2. HRMS (ESI+) calculated for $C_{30}H_{28}BrN_2O$ ($M+H^+$) 511.1385; found 511.1380.

3-(2-bromophenyl)-5-(4-nitrophenyl)-2,6-diphenylhexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3i) [*dr* = 23:77]: yield: 75 mg (92%); yellow solid; mp 114.5-118.4 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (dd, *J* = 10.4, 8.6 Hz, 2.72H), 7.84 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.75 (dd, *J* = 7.8, 1.7 Hz, 0.36H), 7.61 – 7.55 (m, 1.36H), 7.35 (tt, *J* = 7.3, 1.7 Hz, 2H), 7.31 – 7.25 (m, 1H), 7.23 – 7.10 (m, 9H), 7.02 – 6.93 (m, 1.36H), 6.91 – 6.79 (m, 5H), 6.77 – 6.70 (m, 3H), 6.29 (dd, *J* = 9.7, 5.6 Hz, 1.36H), 5.20 (d, *J* = 4.2 Hz, 1.36H), 5.06 (dd, *J* = 8.2, 3.1 Hz, 0.36H), 4.84 (dd, *J* = 8.4, 3.3 Hz, 1H), 3.91 (qd, *J* = 8.2, 5.2 Hz, 0.36H), 3.39 (td, *J* = 8.6, 6.2 Hz, 1H), 2.70 (dt, *J* = 13.2, 8.3 Hz, 1H), 2.41 (dt, *J* = 12.9, 8.7 Hz, 0.36H), 2.22 (ddd, *J* = 12.7, 9.0, 3.4 Hz, 1H), 1.49 (ddd, *J* = 12.8, 8.1, 3.0 Hz, 0.36H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 150.6, 150.5, 150.4, 147.2, 147.2, 143.4, 143.3, 139.8, 137.4, 133.0, 132.9, 129.8, 129.5, 129.3, 129.3, 129.1, 129.0, 128.7, 128.1, 127.9, 126.6, 126.5, 124.4, 124.4, 122.5, 122.2, 121.3, 119.4, 119.3, 115.6, 115.4, 115.1, 114.1, 114.0, 94.8, 93.3, 74.1, 70.8, 64.0, 63.3, 53.7, 48.2, 39.9, 35.5. HRMS (ESI+) calculated for $C_{29}H_{25}BrN_3O_3$ ($M+H^+$) 542.1079; found 542.1075.

3,5-bis(2-bromophenyl)-2,6-diphenylhexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3j) [*dr* = 25:75]: yield: 62 mg (72%); white solid; mp 62.8-66.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 0.22H), 7.60 – 7.53 (m, 2.44H), 7.36 (t, *J* = 7.4 Hz, 1.22H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.13 (m, 6H), 7.09 – 7.02 (m, 2.44H), 7.00 – 6.85 (m, 4H), 6.82 (t, *J* = 7.2 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 4H), 6.33 (d, *J* = 5.2 Hz, 0.22H), 6.26 (d, *J* = 5.9 Hz, 1H), 5.33 – 5.29 (m, 0.22H), 5.21 (s, 1.22H), 5.15 (d, *J* = 8.2 Hz, 1H), 3.88 (p, *J* = 8.0 Hz, 0.22H), 3.33 (td, *J* = 9.0, 5.9 Hz, 1H), 2.65 (dt, *J* = 13.1, 8.8 Hz, 1H), 2.45 (dt, *J* = 13.0, 8.7 Hz, 0.22H), 2.29 (ddd, *J* = 12.0, 9.1, 2.1 Hz, 1H), 1.49 (dd, *J* = 13.3, 9.3 Hz, 0.22H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9, 150.8, 143.6, 140.7, 140.5, 140.1, 137.5, 133.6, 133.5, 132.8, 130.1, 129.4, 129.2, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.1, 128.0, 127.9, 127.8, 127.0, 126.8, 122.6, 122.3, 122.3, 122.2, 121.3, 118.9, 118.8, 115.5, 115.0, 114.9, 114.1, 95.0, 93.6, 74.1, 70.8, 64.3, 63.8, 53.6, 48.2, 38.0, 33.5. HRMS (ESI+) calculated for $C_{29}H_{25}Br_2N_2O$ ($M+H^+$) 575.0334; found 575.0332.

3-(2-bromophenyl)-6-(4-fluorophenyl)-5-(naphthalen-1-yl)-2-phenylhexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3k) [*dr* = 25:75]: yield: 74 mg (87%); white solid; mp 90.6-93.7 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 – 7.80 (m, 4H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.52 (ddd, *J* = 12.2, 7.2, 2.3 Hz, 5H), 7.40 – 7.26 (m, 3H), 7.18 (dtd, *J* = 21.1, 7.5, 1.4 Hz, 4H), 6.98 (ddt, *J* = 7.1, 2.2, 1.0 Hz, 3H), 6.95 – 6.82 (m, 5H), 6.72 – 6.65 (m, 3H), 6.33 (d, *J* = 5.2 Hz, 0.26H), 6.27 (d, *J* = 5.9 Hz, 1H), 5.71 (d, *J* = 7.7 Hz, 0.26H), 5.56 (d, *J* = 8.2 Hz, 1H), 5.23 (d, *J* = 5.0 Hz, 1.26H), 4.02 – 3.85 (m, 0.26H), 3.38 (td, *J* = 8.9, 5.8 Hz, 1H), 2.75 (dt, *J* = 12.6, 8.8 Hz, 1H), 2.63 – 2.56 (m, 0.26H), 2.38 (ddd, *J* = 12.7, 8.9, 2.2 Hz, 1H), 1.58 – 1.54 (m, 0.26H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 155.3, 151.2, 150.8, 140.3, 140.0, 137.6, 136.2, 136.1, 134.4 (d, *J* = 2.7 Hz), 132.9, 132.8, 130.4, 130.3, 129.9, 129.4, 129.3, 129.2, 129.13, 129.07, 128.8, 128.0, 127.8, 127.8, 126.34, 126.27, 126.1, 125.9, 125.8, 125.7, 125.6, 125.5, 122.9 122.8, 122.6, 122.4, 122.3, 121.3, 115.8, 115.8, 115.7, 115.6, 115.5, 114.1, 95.4, 93.9, 74.1, 70.8, 61.8, 61.2, 54.2, 48.9, 38.6, 34.2. HRMS (ESI+) calculated for $C_{33}H_{27}BrFN_2O$ ($M+H^+$) 565.1291; found 565.1288.

3-(2-bromophenyl)-2,6-diphenyl-5-((*E*)-styryl)-hexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3l) [3l/3l'= 28:72]: yield: 15 mg (19%); yellow solid; mp 177.5-180.5 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.27 – 7.15 (m, 10H), 7.15 – 7.08 (m, 2H), 6.96 – 6.85 (m, 5H), 6.79 – 6.71 (m, 1H), 6.27 (dd, *J* = 16.0, 1.1 Hz, 1H), 6.08 – 5.90 (m, 2H), 5.16 (d, *J* = 7.6 Hz, 1H), 4.54 (tt, *J* = 6.1, 1.7 Hz, 1H), 3.90 (dtd, *J* = 10.0, 7.8, 5.2 Hz, 1H), 2.13 (ddd, *J* = 12.5, 10.0, 8.0 Hz, 1H), 1.42 (ddd, *J* = 12.6, 7.9, 2.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1, 144.4, 137.9, 136.6, 132.8, 130.4, 130.2, 129.9, 129.3, 129.2, 129.1, 128.7, 127.8, 127.7, 126.5, 122.2, 122.1, 118.7, 115.1, 114.6, 93.2, 71.1, 62.5, 48.6, 32.8. HRMS (ESI+) calculated for $C_{31}H_{28}BrN_2O$ ($M+H^+$) 523.1385; found 523.1384.

3-(2-bromophenyl)-2,6-diphenyl-5-((*E*)-styryl)-hexahydro-*2H*-pyrrolo[3,2-d]isoxazole (3l') [*dr* = 83:17]: yield: 38 mg (48%); yellow solid; mp 64.6-67.9 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (dd, *J* = 8.0, 4.3 Hz, 2H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 3H), 7.23 – 7.14 (m, 14H), 7.08 (ddd, *J* = 20.9, 7.5, 4.4 Hz, 12H), 7.00 (d, *J* = 8.1 Hz, 5H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.80 (dq, *J* = 12.7, 7.6 Hz, 7H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.20 (d, *J* = 16.0 Hz, 1H), 5.99 – 5.88 (m, 2H), 5.71 (dd, *J* = 16.1, 7.7 Hz, 1H), 5.64 (d, *J* = 6.4 Hz, 1H), 5.21 (s, 1H), 5.12 (s, 1H), 4.35 (q, *J* = 7.6 Hz, 2H), 3.35 (q, *J* = 8.3 Hz, 1H), 3.22 (q, *J* = 7.9 Hz, 1H), 2.61 (dt, *J* = 13.5, 8.6 Hz, 1H), 2.36 (dt, *J* = 12.9, 8.2 Hz, 1H), 2.19 (ddd, *J* = 12.4, 8.7, 2.9 Hz, 1H), 2.06 (dt, *J* = 13.6, 7.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3, 151.0, 145.8, 144.5, 140.5, 140.3, 136.7, 136.5, 132.8, 132.6, 131.0, 130.5, 130.4, 129.2, 129.1, 128.9, 128.8, 128.6, 128.5, 128.1, 128.1, 127.7, 127.6, 126.48, 126.46, 122.6, 122.5, 121.2, 121.1, 119.3,

118.6, 115.1, 115.0, 114.4, 114.1, 98.7, 94.4, 74.5, 74.1, 63.0, 61.6, 54.7, 54.1, 37.6, 37.3. HRMS (ESI+) calculated for $C_{31}H_{28}BrN_2O$ ($M+H^+$) 523.1385; found 523.1382.

3-(2-bromophenyl)-6-(4-fluorophenyl)-2-phenyl-5-(thiophen-2-yl)hexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3m) [*dr* = 31:69]: yield: 59 mg (75%); white solid; mp 141.6-145.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 0.6H), 7.59 (d, *J* = 7.9 Hz, 1.6H), 7.31 (dt, *J* = 21.3, 7.6 Hz, 3H), 7.22 – 7.05 (m, 6H), 7.02 – 6.79 (m, 14H), 6.75 (d, *J* = 3.4 Hz, 0.6H), 6.69 (d, *J* = 3.4 Hz, 1H), 6.12 (d, *J* = 5.4 Hz, 0.6H), 6.08 (d, *J* = 6.0 Hz, 1H), 5.20 (d, *J* = 7.3 Hz, 2.2H), 5.05 (dd, *J* = 7.8, 2.6 Hz, 1H), 4.09 (dq, *J* = 15.1, 7.9, 7.2 Hz, 0.6H), 3.51 (q, *J* = 8.1 Hz, 1H), 2.59 (dt, *J* = 13.2, 8.0 Hz, 1H), 2.36 (ddt, *J* = 17.1, 12.8, 7.3 Hz, 1.6H), 1.63 (td, *J* = 8.6, 7.8, 4.1 Hz, 0.6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 158.0, 155.7, 155.6, 150.7, 150.5, 147.5, 147.4, 140.3, 140.3 (d, *J* = 1.9 Hz), 140.0, 137.5, 132.9, 132.9, 129.9, 129.4, 129.2, 129.1, 129.0, 128.8, 128.0, 127.8, 127.04, 127.00, 125.7, 124.2, 124.1, 123.8, 123.7, 122.64, 122.60, 122.5, 122.3, 121.2, 116.3, 116.2, 116.1, 116.0, 115.9, 115.80, 115.78, 115.57, 115.56, 114.1, 94.9, 93.4, 73.9, 70.8, 60.8, 60.0, 54.1, 48.6, 40.5, 36.1. HRMS (ESI+) calculated for $C_{27}H_{23}BrFN_2OS$ ($M+H^+$) 521.0698; found 521.0695.

3-(2-bromophenyl)-5-cyclohexyl-6-(4-fluorophenyl)-2-phenylhexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3n) [*dr* = 29:71]: yield: 28 mg (36%); yellow liquid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.8 Hz, 0.2H), 7.54 (ddd, *J* = 7.9, 6.5, 1.3 Hz, 1.2H), 7.28 – 7.22 (m, 1.2H), 7.21 – 7.13 (m, 1H), 7.10 (td, *J* = 7.7, 1.8 Hz, 1.2H), 7.02 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.98 – 6.91 (m, 2.4H), 6.90 – 6.85 (m, 0.4H), 6.83 – 6.70 (m, 6H), 5.91 (d, *J* = 5.3 Hz, 0.2H), 5.83 (d, *J* = 6.1 Hz, 1H), 5.09 (s, 1.2H), 3.87 – 3.78 (m, 0.4H), 3.69 (dt, *J* = 8.8, 2.2 Hz, 1H), 3.26 (td, *J* = 9.2, 6.1 Hz, 1H), 2.20 (ddd, *J* = 13.3, 9.4, 1.9 Hz, 1H), 1.88 (dt, *J* = 13.3, 8.8 Hz, 1H), 1.76 – 1.60 (m, 3H), 1.57 – 1.50 (m, 3H), 1.42 – 1.31 (m, 2H), 1.22 – 1.03 (m, 3H), 1.01 – 0.64 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 157.3, 155.3, 155.0, 151.2, 151.0, 140.6, 140.2, 138.0, 132.8, 132.8, 130.1, 129.3, 129.1, 128.8, 128.0, 127.7, 122.7, 122.2 (d, *J* = 4.6 Hz), 121.0, 116.2, 116.1, 116.00, 115.96, 115.8, 115.7, 115.3, 113.9, 94.4, 93.2, 75.2, 71.6, 65.2, 64.4, 55.6, 49.6, 38.4, 37.7, 31.0, 30.1, 29.8, 26.9, 26.6, 26.5, 26.4, 26.3, 26.1. HRMS (ESI+) calculated for $C_{29}H_{31}BrFN_2O$ ($M+H^+$) 521.1604; found 521.1602.

3-(2-chlorophenyl)-5-(4-nitrophenyl)-2,6-diphenylhexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3r) [*dr* = 29:71]: yield: 76 mg (96%); yellow solid; mp 86.0-90.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (dd, *J* = 11.2, 8.7 Hz, 2.64H), 7.75 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.69 – 7.66 (m, 0.32H), 7.33 – 7.29 (m, 1.32H), 7.20 (dtd, *J* = 15.4, 7.6, 1.6 Hz, 3H), 7.15 – 7.02 (m, 7H), 6.93 – 6.85 (m, 1H), 6.83 – 6.71 (m, 4H), 6.68 – 6.61 (m, 2.64H), 6.21 (dd, *J* = 7.8, 5.6 Hz, 1.32H), 5.15 (d, *J* = 8.3 Hz, 1.32H), 4.98 (dd, *J* = 8.3, 2.9 Hz, 0.32H), 4.75 (dd, *J* = 8.4, 3.3 Hz, 1H), 3.79 (qd, *J* = 8.1, 5.2 Hz, 0.32H), 3.30 (td, *J* = 8.5, 6.1 Hz, 1H), 2.59 (dt, *J* = 13.1, 8.2 Hz, 1H), 2.33 (dt, *J* = 12.8, 8.7 Hz, 0.32H), 2.11 (ddd, *J* = 12.8, 9.0, 3.4 Hz, 1H), 1.44 – 1.38 (m, 0.32H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 150.6, 150.4, 147.2, 147.2, 143.4, 143.3, 138.3, 135.8, 132.3, 132.0, 129.7, 129.6, 129.4, 129.3, 129.3, 129.2, 129.1, 129.0, 128.4, 127.5, 127.3, 126.6, 126.5, 124.4, 124.3, 122.5, 121.3, 121.3, 119.4, 119.3, 115.6, 115.4, 115.0, 114.1, 114.0, 94.8, 93.2, 71.9, 68.7, 64.0, 63.3, 53.5, 48.2, 39.8, 35.5. HRMS (ESI+) calculated for $C_{29}H_{24}ClN_3NaO_3$ ($M+Na^+$) 520.1404; found 520.1402.

3-(3-bromophenyl)-5-(4-nitrophenyl)-2,6-diphenylhexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3u): yield: 22 mg (27%); yellow solid; mp 66.5-70.4 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 8.7 Hz, 2H), 7.52 (t, *J* = 1.8 Hz, 1H), 7.38 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 3H), 7.18 – 7.10 (m, 4H), 6.93 (dd, *J* = 15.1, 7.5 Hz, 3H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 2H), 6.21 (d, *J* = 5.2 Hz, 1H), 5.06 (dd, *J* = 8.2, 2.7 Hz, 1H), 4.83 (d, *J* = 7.2 Hz, 1H), 3.51 (p, *J* = 7.6 Hz, 1H), 2.51 (dt, *J* = 12.9, 8.8 Hz, 1H), 1.42 (ddd, *J* = 12.8, 8.0, 2.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5, 150.4, 147.3, 143.5, 140.2, 131.1, 130.5, 130.0, 129.4, 129.1, 126.7, 125.7, 124.4, 123.2, 123.0, 119.5, 116.4, 115.1, 92.9, 70.4, 63.9, 50.5, 35.9. HRMS (ESI+) calculated for $C_{29}H_{24}BrN_3NaO_3$ ($M+Na^+$) 564.0899; found 564.0895.

3-(3-bromophenyl)-5-(4-nitrophenyl)-2,6-diphenylhexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3u'): yield: 29 mg (36%); yellow solid; mp 76.3-80.8 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 8.7 Hz, 2H), 7.68 (t, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.25 (s, 1H), 7.21 (dd, *J* = 8.2, 6.1 Hz, 4H), 7.15 (t, *J* = 7.8 Hz, 2H), 6.94 – 6.81 (m, 4H), 6.74 (d, *J* = 8.2 Hz, 2H), 6.34 (d, *J* = 5.8 Hz, 1H), 4.93 (dd, *J* = 8.2, 3.1 Hz, 1H), 4.81 (s, 1H), 3.40 (q, *J* = 7.9 Hz, 1H), 2.63 (dt, *J* = 12.9, 8.3 Hz, 1H), 2.14 (ddd, *J* = 12.4, 8.8, 3.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5, 150.4, 147.3, 143.3, 143.1, 131.0, 130.6, 129.8, 129.3, 129.0, 126.6, 125.3, 124.4, 123.2, 121.7, 119.5, 115.4, 114.5, 94.5, 73.9, 63.3, 54.1, 39.6. HRMS (ESI+) calculated for $C_{29}H_{24}BrN_3NaO_3$ ($M+Na^+$) 564.0899; found 564.0897.

3-(4-bromophenyl)-2,5,6-triphenylhexahydro-*2H*-pyrrolo[3,2-*d*]isoxazole (3v) [*dr* = 50:50]: yield: 37 mg (50%); yellow solid; mp 126.9-129.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 (dd, *J* = 8.1, 5.2 Hz, 3H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.25 (m, 3H), 7.24 – 7.09 (m, 9H), 7.07 – 7.02 (m, 1H), 7.02 – 6.96 (m, 3H), 6.94 – 6.83 (m, 3H), 6.83 – 6.74 (m, 4H), 6.24 (dd, *J* = 11.6, 5.4 Hz, 1.44H), 5.05 (d, *J* = 8.0 Hz, 0.44H), 4.94 – 4.86 (m, 1.44H), 4.76 (s, 1H), 3.58 (q, *J* = 7.6, 6.7 Hz, 0.44H), 3.37 (q, *J* = 8.4 Hz, 1H), 2.56 (dtd, *J* = 13.6, 8.3, 4.3 Hz, 1.44H), 2.15 (ddd, *J* = 12.4, 8.6, 2.2 Hz, 1H), 1.49 – 1.43 (m, 0.44H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0, 150.8, 144.1, 144.0, 142.6, 142.5, 140.2, 137.2, 132.0, 131.9, 129.2, 129.1, 129.0, 128.92, 128.89, 128.79, 128.5, 127.2, 125.7, 125.6, 122.5, 121.6, 121.53, 121.47, 118.7, 116.0, 115.1, 114.7, 114.6, 94.6, 93.2, 73.8, 70.5, 64.6, 64.1, 54.1, 50.4, 39.7, 35.9. HRMS (ESI+) calculated for $C_{29}H_{26}BrN_2O$ ($M+H^+$) 497.1229; found 97.1225

1,5-diphenylpyrrolidin-2-one (4a): yield: 38 mg (80%); yellow solid; mp 98.7-101.3 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.34 – 7.13 (m, 7H), 7.04 (t, *J* = 7.4 Hz, 1H), 5.24 (dd, *J* = 7.4, 4.5 Hz, 1H), 2.81 – 2.69 (m, 1H), 2.68 – 2.54 (m, 2H), 1.99 (ddd, *J* = 11.8, 8.8, 5.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 141.4, 138.3, 129.1, 128.8, 127.8, 126.0, 125.0, 122.3, 64.0, 31.3, 29.3. HRMS (ESI+) calculated for $C_{16}H_{16}NO$ ($M+H^+$) 238.1232; found 238.1229.

5-phenyl-1-(p-tolyl)pyrrolidin-2-one (4b): yield: 40 mg (80%); white solid; mp 101.1-103.1 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 7.8 Hz, 4H), 7.17 – 7.10 (m, 3H), 6.95 (d, *J* = 8.1 Hz, 2H), 5.13 (dd, *J* = 7.3, 4.6 Hz, 1H), 2.73 – 2.61 (m, 1H), 2.60 – 2.44 (m, 2H), 2.15 (s, 3H), 1.98 – 1.83 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 141.6, 135.8, 134.7, 129.3, 129.0, 127.8, 126.1, 122.4, 64.1, 31.2, 29.3, 20.9. HRMS (ESI+) calculated for $C_{17}H_{18}NO$ ($M+H^+$) 252.1388; found 252.1381.

1-(4-methoxyphenyl)-5-phenylpyrrolidin-2-one (4c): yield: 39 mg (73%); yellow solid, mp 82.7-84.3 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 – 7.06 (m, 7H), 6.68 (d, *J* = 8.5 Hz, 2H), 5.08 (dd, *J* = 7.4, 4.7 Hz, 1H), 3.62 (s, 3H), 2.73 – 2.60 (m, 1H), 2.59 – 2.46 (m, 2H), 1.92 (td, *J* = 11.0, 8.7, 5.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 156.9, 141.5, 131.3, 129.0, 127.8, 126.2, 124.2, 114.0, 64.4, 55.4, 31.1, 29.2. HRMS (ESI+) calculated for $C_{17}H_{18}NO_2$ ($M+H^+$) 268.1338; found 268.1332.

1-(4-fluorophenyl)-5-phenylpyrrolidin-2-one (4d): yield: 40 mg (78%); white solid; mp 92.9-95.4 °C; ^{1}H

NMR (400 MHz, Chloroform-*d*) δ 7.25 (ddd, *J* = 20.0, 8.4, 5.4 Hz, 4H), 7.17 (d, *J* = 7.0 Hz, 1H), 7.15 – 7.09 (m, 2H), 6.84 (t, *J* = 8.7 Hz, 2H), 5.11 (dd, *J* = 7.3, 4.9 Hz, 1H), 2.74 – 2.63 (m, 1H), 2.62 – 2.47 (m, 2H), 2.03 – 1.80 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 159.8 (d, *J* = 244.7 Hz), 141.1, 134.3, 129.1, 128.0, 126.1, 124.2 (d, *J* = 8.0 Hz), 115.5 (d, *J* = 22.4 Hz). 64.2, 31.2, 29.2. HRMS (ESI+) calculated for $C_{16}H_{15}FNO$ ($M+H^+$) 256.1138; found 256.1129.

1-(4-chlorophenyl)-5-phenylpyrrolidin-2-one (4e) yield: 38 mg (70%); yellow solid; mp 83.3-85.3 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 8.5 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.17 (d, *J* = 6.6 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 4H), 5.13 (dd, *J* = 7.2, 4.7 Hz, 1H), 2.73 – 2.62 (m, 1H), 2.61 – 2.46 (m, 2H), 1.97 – 1.79 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 141.0 136.9, 130.1, 129.2, 128.8, 128.0, 125.9, 123.3, 63.9, 31.2, 29.2. HRMS (ESI+) calculated for $C_{16}H_{15}ClNO$ ($M+H^+$) 272.0842; found 272.0840.

5-phenyl-1-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one (4f): yield: 47 mg (77%); yellow oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 5.21 (dd, *J* = 7.3, 4.3 Hz, 1H), 2.76 – 2.64 (m, 1H), 2.56 (tt, *J* = 13.8, 8.5 Hz, 2H), 1.95 (dq, *J* = 11.8, 4.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 141.1 (d, J = 68.8 Hz), 129.4, 128.2, 126.4 (d, *J* = 32.8 Hz), 125.9 (q, *J* = 3.7 Hz), 125.8, 125.5, 122.8, 121.3, 63.6, 31.3, 29.3. HRMS (ESI+) calculated for $C_{17}H_{15}F_3NO$ ($M+H^+$) 306.1106; found 306.1102.

1-(2-hydroxyphenyl)-5-phenylpyrrolidin-2-one (4g): yield: 28 mg (55%); Yellow solid; mp 161.9-163.2 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (s, 1H), 7.25 – 7.16 (m, 2H), 7.16 – 7.06 (m, 3H), 7.02 – 6.90 (m, 2H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.71 – 6.59 (m, 1H), 5.43 – 5.32 (m, 1H), 2.82 – 2.57 (m, 3H), 2.13 – 1.95 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 151.0, 140.4, 129.1, 128.1, 127.9, 126.9, 125.9, 122.7, 120.9, 120.7, 65.5, 31.3, 30.7. HRMS (ESI+) calculated for $C_{16}H_{16}NO_2$ ($M+H^+$) 254.1181; found 254.1175.

1-(naphthalen-2-yl)-5-phenylpyrrolidin-2-one (4h): yield: 37 mg (64%); white solid; mp 138.4-140.5 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 2.1 Hz, 1H), 7.65 – 7.52 (m, 4H), 7.28 (p, *J* = 6.5 Hz, 2H), 7.17 (p, *J* = 6.8, 5.8 Hz, 4H), 7.13 – 7.08 (m, 1H), 5.27 (dd, *J* = 7.7, 4.5 Hz, 1H), 2.77 – 2.64 (m, 1H), 2.62 – 2.48 (m, 2H), 1.94 (dq, *J* = 9.4, 5.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 141.3, 135.9, 133.4, 130.9, 129.1, 128.5, 127.9, 127.5, 126.3, 126.0, 125.5, 121.5, 120.0, 64.1, 31.4, 29.3, 29.3. HRMS (ESI+) calculated for $C_{20}H_{18}NO$ ($M+H^+$) 288.1388; found . 288.1388

1-phenyl-5-(p-tolyl)pyrrolidin-2-one (4k): yield: 42 mg (84%); white solid; mp 116.8-119.7 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.30 (m, 2H), 7.16 (td, *J* = 7.4, 1.6 Hz, 2H), 7.03 (s, 4H), 7.00 – 6.93 (m, 1H), 5.14 (dd, *J* = 7.6, 4.5 Hz, 1H), 2.73 – 2.61 (m, 1H), 2.59 – 2.45 (m, 2H), 2.21 (s, 3H), 1.97 – 1.83 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 138.4, 138.3, 137.5, 129.7, 128.7, 125.9, 124.9, 122.3, 63.8, 31.4, 29.5, 21.2. HRMS (ESI+) calculated for $C_{17}H_{18}NO$ ($M+H^+$) 252.1388; found 252.1387.

5-(4-nitrophenyl)-1-phenylpyrrolidin-2-one (4l): yield: 40 mg (71%); yellow solid; mp 139.0-141.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 – 8.04 (m, 2H), 7.40 – 7.26 (m, 4H), 7.24 – 7.12 (m, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 5.32 (dd, *J* = 7.4, 5.1 Hz, 1H), 2.64 (dddd, *J* = 20.3, 17.9, 10.8, 4.8 Hz, 3H), 2.04 – 1.76 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 147.6, 137.7, 129.0, 127.0, 125.5, 124.4, 122.2, 63.1, 31.1, 28.9. HRMS (ESI+) calculated for $C_{16}H_{15}N_2O_3$ ($M+H^+$) 283.1083; found 283.1079.

5-(2-hydroxyphenyl)-1-phenylpyrrolidin-2-one (4m): yield: 25 mg (49%); yellow solid; mp 194.8-197.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.35 – 7.18 (m, 3H), 7.06 (dt, *J* = 16.7, 8.2 Hz, 3H), 6.88 – 6.67 (m, 2H), 6.03 (s, 1H), 5.59 (t, *J* = 5.4 Hz, 1H), 2.76 (q, *J* = 11.3, 10.0 Hz, 1H), 2.61 (d, *J* = 12.7 Hz, 2H), 2.09 (d, *J* = 11.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 153.3, 138.3, 128.8, 127.1, 127.1, 125.1, 122.2, 120.8, 115.9, 59.5, 31.7, 27.1. HRMS (ESI+) calculated for $C_{16}H_{16}NO_2$ ($M+H^+$) 254.1181; found 254.1174

5-(2-bromophenyl)-1-phenylpyrrolidin-2-one (4n): yield: 48 mg (76%); yellow liquid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.35 – 7.26 (m, 3H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.12 (dt, *J* = 21.2, 7.1 Hz, 3H), 5.68 (d, *J* = 6.8 Hz, 1H), 2.70 (tq, *J* = 19.7, 6.7 Hz, 3H), 2.01 (d, *J* = 10.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 139.7, 138.2, 133.5, 129.3, 128.9, 128.1, 126.8, 124.8, 122.4, 121.2, 62.8, 31.1, 27.2. HRMS (ESI+) calculated for $C_{16}H_{15}BrNO$ ($M+H^+$) 316.0337; found 316.0328.

1,5-di-*p*-tolylpyrrolidin-2-one (4o): yield: 36 mg (68%); yellow solid; mp 129.3-131.5 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 9.0 Hz, 3H), 7.03 (s, 4H), 6.97 (d, *J* = 8.1 Hz, 2H), 5.11 (t, *J* = 6.0 Hz, 1H), 2.68 (p, *J* = 11.4 Hz, 1H), 2.59 – 2.45 (m, 2H), 2.22 (s, 3H), 2.17 (s, 3H), 1.91 (d, *J* = 12.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 138.5, 137.4, 135.7, 134.6, 129.7, 129.3, 126.0, 122.4, 63.9, 31.3, 29.4, 21.2, 20.9. HRMS (ESI+) calculated for $C_{18}H_{20}NO$ ($M+H^+$) 266.1545; found . 266.1544.

1-(4-bromophenyl)-5-(*p*-tolyl)pyrrolidin-2-one (4p): yield: 56 mg (88%); yellow solid; mp 98.3-100.8 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 1.6 Hz, 4H), 7.15 – 7.04 (m, 4H), 5.18 (dd, *J* = 7.3, 4.6 Hz, 1H), 2.74 (t, *J* = 10.1 Hz, 1H), 2.67 – 2.52 (m, 2H), 2.31 (s, 3H), 1.99 (d, *J* = 12.0 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 137.9, 137.8, 137.5, 131.8, 129.9, 125.9, 123.6, 117.9, 63.6, 31.3, 29.4, 21.2. HRMS (ESI+) calculated for $C_{17}H_{17}BrNO$ ($M+H^+$) 330.0494; found 330.0489.

1-(4-fluorophenyl)-5-(4-methoxyphenyl)pyrrolidin-2-one (4q): yield: 43 mg (76%); yellow liquid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 (ddd, *J* = 7.1, 4.8, 2.5 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.84 (t, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.2 Hz, 2H), 5.13 – 4.97 (m, 1H), 3.67 (s, 3H), 2.65 (q, *J* = 10.4 Hz, 1H), 2.59 – 2.44 (m, 2H), 2.00 – 1.83 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 159.8 (d, *J* = 244.4 Hz), 159.3, 134.3 (d, *J* = 3.2 Hz).133.0, 127.4, 124.4 (d, *J* = 7.8 Hz), 115.5 (d, *J* = 22.6 Hz), 114.5, 63.8, 55.3, 31.2, 29.4. HRMS (ESI+) calculated for $C_{17}H_{17}FNO_2$ ($M+H^+$) 286.1243; found 286.1242.

5-(4-bromophenyl)-1-(4-(trifluoromethyl)phenyl) pyrrolidin-2-one (4r): yield: 45 mg (58%); yellow solid; mp 97.0-99.6 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.41 – 7.34 (m, 2H), 7.07 – 6.93 (m, 2H), 5.18 (dd, *J* = 7.1, 4.6 Hz, 1H), 2.73 – 2.49 (m, 3H), 2.00 – 1.77 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 140.4 (d, *J* = 129.5 Hz), 132.5, 127.5, 126.6 (d, *J* = 33.0 Hz), 126.0 (q, *J* = 3.8 Hz).125.4, 122.7, 122.0, 121.4, 63.0, 31.2, 29.1. HRMS (ESI+) calculated for $C_{17}H_{14}BrF_3NO$ ($M+H^+$) 384.0211; found 384.0204.

1-(4-fluorophenyl)-5-(naphthalen-1-yl)pyrrolidin-2-one (4s): yield: 40 mg (66%); Yellow solid; mp 104.7-106.3 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.83 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.58 – 7.36 (m, 4H), 7.31 – 7.23 (m, 1H), 7.21 – 7.10 (m, 1H), 6.87 – 6.72 (m, 2H), 5.90 (d, *J* = 7.7 Hz, 1H), 2.85 – 2.38 (m, 3H), 2.02 (q, *J* = 10.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 160.6, 158.2, 135.4, 134.8, 134.4, 130.1, 129.5, 128.5, 126.8, 126.1, 125.5, 122.6, 122.3, 115.5 (d, *J* = 22.1 Hz), 60.5, 31.2, 27.7.

HRMS (ESI+) calculated for $C_{20}H_{17}FNO$ ($M+H^+$) 306.1294; found 306.1289.

1-(4-fluorophenyl)-5-(thiophen-2-yl)pyrrolidin-2-one (4t): yield: 27 mg (52%); white solid, mp 110.5-112.8 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 (dd, *J* = 8.5, 4.7 Hz, 2H), 7.12 (d, *J* = 4.7 Hz, 1H), 6.89 (t, *J* = 8.4 Hz, 2H), 6.80 (s, 2H), 5.37 (t, *J* = 6.0 Hz, 1H), 2.74 (dd, *J* = 16.9, 8.0 Hz, 1H), 2.58 (h, *J* = 7.3 Hz, 2H), 2.11 (q, *J* = 7.0, 6.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 161.5, 159.1, 144.8, 133.8, 126.9, 125.5, 125.4, 125.3, 125.2, 115.8, 115.6, 60.4, 31.0, 29.5. HRMS (ESI+) calculated for $C_{14}H_{13}FNOS$ ($M+H^+$) 262.0702; found 262.0696.

5-cyclohexyl-1-(4-fluorophenyl)pyrrolidin-2-one (4u): yield: 35 mg (67%); white solid; mp 123.2-125.9 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (dd, *J* = 8.6, 4.8 Hz, 2H), 7.09 (t, *J* = 8.4 Hz, 2H), 4.13 (dt, *J* = 8.3, 3.9 Hz, 1H), 2.67 – 2.41 (m, 2H), 2.24 – 2.07 (m, 1H), 1.97 (ddt, *J* = 14.3, 10.1, 5.1 Hz, 1H), 1.82 – 1.44 (m, 6H), 1.27 – 0.90 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 161.7, 159.2, 133.79, 133.76, 126.3, 126.3, 116.1, 115.8, 64.5, 39.2, 31.6, 29.2, 26.5, 26.3, 25.8, 25.2, 19.3. HRMS (ESI+) calculated for $C_{16}H_{21}FNO$ ($M+H^+$) 262.1607; found 262.1598.

(*E*)-5-styryl-1-tosylpyrrolidin-2-one (4v): yield: 49 mg (72%); yellow solid; mp 115.1-116.8 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.17 (m, 6H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.57 (d, *J* = 15.7 Hz, 1H), 5.93 (dd, *J* = 15.7, 8.2 Hz, 1H), 5.00 (t, *J* = 7.7 Hz, 1H), 2.57 – 2.44 (m, 1H), 2.42 – 2.28 (m, 5H), 1.91 – 1.78 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 145.0, 136.0, 135.7, 133.2, 129.5, 128.8, 128.7, 128.4, 126.7, 126.4, 62.0, 30.8, 26.1, 21.7. HRMS (ESI+) calculated for $C_{19}H_{20}NO_3S$ ($M+H^+$) 342.1164; found 342.1161.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (grants 21372120) and Tianjin Natural Science Foundation of China (17JCZDJC37300) as well as the National Key Research and Development Program of China (2017YFD0201404) for this work. And we also thank the support from the Collaborative Innovation Center of Chemical Science and Engineering (Tianjin).

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[9] Crystal data for the compound *endo*-**3a**: $C_{29}H_{26}N_2O$, MW) 418.52, Monoclinic, $P2_1/c$, Final R indices [I>2ó(I)], R1) 0.0824, wR2) 0.1985, R indices (all data) R1) 0.0862, wR2) 0.2009, a = 11.6449 (14) Å, b = 10.0539 (11) Å, c = 19.051 (2) Å, V) 2193.7 (4) Å^3, T) 113 K, Z) 4. Reflections collected/unique: 23372/6704 (Rint) 0.028), number of observations [>2ó(I)] 3581, parameters) 289, Goodness-of-fit on F^2) 1.037. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 1574260.

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10.1002/adsc.201701476

FULL PAPER

The catalysts-controlled divergent cascade reactions of homopropargylic amines and nitrones: Synthesis of pyrroloisoxazolidines and γ-lactams

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Yuanfang Kong, Yingze Liu, Boyi Wang, Shengli Li, Lingyan Liu*, Weixing Chang, Jing Li*