EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701323

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701323

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10.1002/ejoc.201701323

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Novel DEAD-Promoted Oxidative Ugi-Type Reaction Including an Unprecedented Ugi-Amidation Assisted by Dicarboxylic Acids

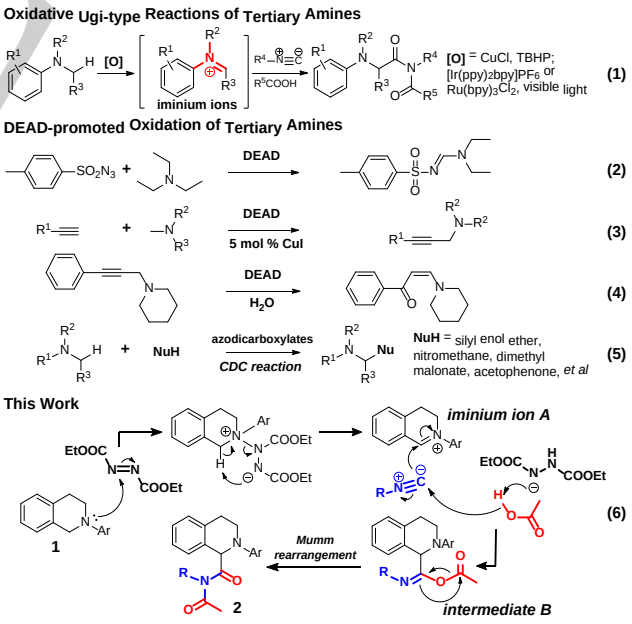
Jiankun Wang,[a] Yilin Sun,[a] Guangji Wang,*[a] and Le Zhen*[a]

Abstract: A mild and metal-free DEAD-promoted oxidative Ugi-type reaction of tertiary amines has been demonstrated, giving facile access to α-amino amides and imides with diverse functional groups in good isolated yields. This Ugi-type approach achieves an unprecedented synthesis of α-amino amide analogues with the assistance of dicarboxylic acids, but not water, for the introduction of carbonyl oxygen of the amide moiety. Mechanistic studies indicated that the dicarboxylic acids may readily undergo an intramolecular annulation, instead of the Mumm rearrangement, affording the desired amide with one molecule of anhydride released.

Introduction

The Ugi reaction is now a cornerstone multicomponent reaction (MCR) to construct privileged structures for chemical libraries and drug research. Extensive studies have been devoted to the advancement of this isocyanide-based transformation.[1,2] In traditional Ugi processes, primary amines are always required due to the involvement of the irreversible acyl migration (Mumm rearrangement); secondary or tertiary amines, by contrast, are rarely employed, because of the failure of the key transacylation at the amino nitrogen. Over the recent decade, an assortment of attractive Ugi-type variants utilizing secondary amines as starting materials has been developed.[3] Notably, isocyanide-based MCRs of secondary amines under oxidative conditions were pioneeringly developed by Zhu's group, employing IBX as a mild and efficient oxidant.[3b] This significant work first introduced the concept of oxidative Ugi-type reaction, extending the scope and versatility of MCRs. Furthermore, we are also fascinated by the oxidative Ugi-type reactions of tertiary amines, in which the substrates are directly converted into iminium ions under varying oxidants, followed by the nucleophilic attack of isocyanides (Scheme 1, eq 1).[4] For example, three-component assemblies using copper and peroxides as oxidants were reported by Xie in 2010.[4a] Alternatively, photoredox-catalyzed oxidative Ugi-type reactions were first accomplished by Rueping's group in 2013.[4c] However, it is noteworthy that the catalysts used are limited to metal Lewis acid or Ru-/Ir-based photoredox ones, potentially limiting the practicality in gram-scale synthesis and reducing the operational simplicity of oxidative Ugi-type reactions. We recently reported a Brønsted acid-catalyzed two starting materials-three components reaction (2SM-3CR) involving the oxidation of tertiary amines triggered by 1,5-hydride shift.[5] Nevertheless, it is still of great significance to develop more efficient and practical oxidative Ugi-type reactions without the assistance of metal catalysts.

Diethyl azodicarboxylate (DEAD) is mostly known for the essential role in the Mitsunobu reaction,[6] as well as its strong electrophilic character and particular transformation for Huisgen zwitterion.[7] Recently, DEAD-promoted oxidation of tertiary amines has been revealed in numerous chemical reactions.[8,9] In 2008, the pioneering work was performed by Li's group. Tertiary amines treated with DEAD were oxidized to the corresponding enamine, reacting with sulfonyl azide through 1,3-dipolar addition (Scheme 1, eq 2).[9b] Later, the same group widened their concept in DEAD-promoted alkynylation and hydration of tertiary amines (Scheme 1, eq 3 and 4).[9c,d] Quite recently, a wide range of nucleophiles were successfully applied for the oxidative cross dehydrogenative coupling (CDC) of the α-positions to nitrogen mediated by DEAD or other azodicarboxylates (Scheme 1, eq 5).[9e-i] Mechanistic study established by Akiyama and colleagues revealed DEAD as a bifunctional reagent (both oxidant and base) in DEAD-promoted oxidative coupling of THIQ derivatives.[9j] As the above studies revealed, the DEAD-assisted oxidations are general and efficient which encourage us to eagerly incorporate this promising dehydrogenation approach into novel versions of oxidative Ugi-type reaction.



Scheme 1. Oxidative Ugi-type Reactions and DEAD-promoted Oxidation of Tertiary Amines

We preliminarily supposed that *N*-aryl 1,2,3,4-tetrahydro-isoquinolines could experience novel oxidative Ugi-type

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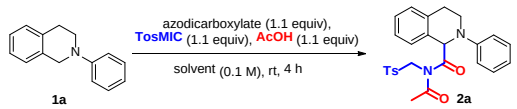
reactions mediated by DEAD. The plausible reaction pathway was illustrated in Scheme 1, eq 6. The iminium ion **A** could be formed via a nucleophilic addition-initiated dehydrogenation of **1**, pairing with its basic counter anion (1H-DEAD anion).[9b-d] Next, iminium ion **A** would readily undergo the nucleophilic attack of the isocyanide, and meanwhile the 1H-DEAD anion could deprotonate the acetic acid, giving rise to the imino anhydride intermediate **B**. The subsequent Mumm rearrangement could occur at the isocyanide nitrogen, facilitating the complete of the oxidative Ugi-type reaction and furnishing bisamide **2**. DEAD, doubly functioned as both oxidant and base, transformed into 2H-DEAD.

Results and Discussion

Table 1. Optimization of Reaction Conditions. [a]

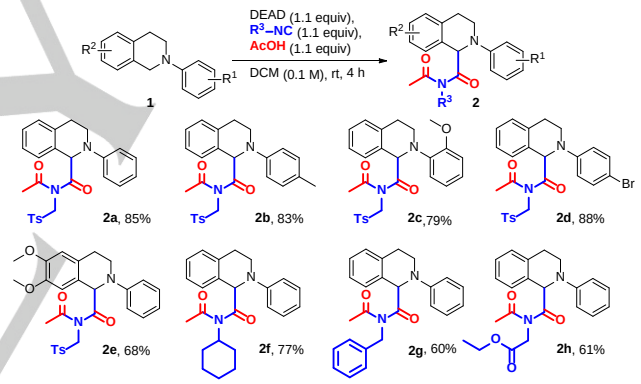


Entry	Azodicarboxylate	Solvent	Yield[b]
1	DEAD	CH_3CN	75
2	DIAD	CH_3CN	64
3	DBAD	CH_3CN	10
4	DEAD	DCM	85
5	DEAD	toluene	86
6	DEAD	DCE	78
7	DEAD	THF	21
8	DEAD	DMF	36
9[c]	DEAD	DCM	86
10[d]	DEAD	DCM	82
11[e]	DEAD	DCM	70
12[f]	DEAD	DCM	83

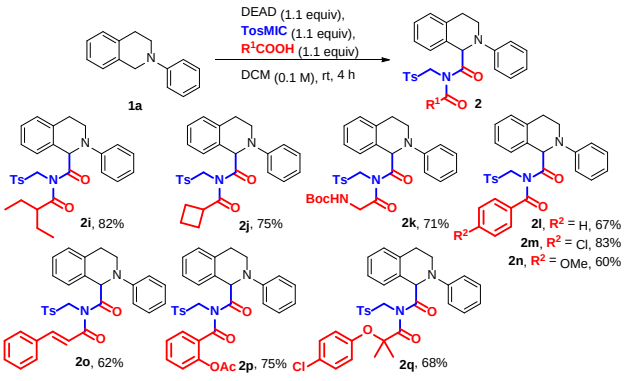
[a] **1a** (0.3 mmol), azodicarboxylate (0.33 mmol), TosMIC (0.33 mmol), AcOH (0.33 mmol), solvent (3.0 mL). DEAD and TosMIC were added at the same time. [b] Isolated yield. [c] DEAD (0.66 mmol). [d] TosMIC (0.66 mmol). [e] AcOH (0.66 mmol). [f] **1a** was treated with DEAD for 2 h, and subsequently TosMIC and AcOH were added. TosMIC = *p*-toluenesulfonyl isocyanide. DIAD = diisopropyl azodicarboxylate. DBAD = di-*tert*-butyl azodicarboxylate.

We commenced our study using 2-phenyl-1,2,3,4-tetrahydroisoquinoline **1a** and *p*-toluenesulfonyl isocyanide (TosMIC) as model substrates, choosing AcOH as a third component. The reaction was carried out in the presence of 1.1 equiv of azodicarboxylate at room temperature for 4 hours. With DEAD and diisopropyl azodicarboxylate (DIAD) in CH_3CN, the reaction proceeded smoothly to afford the desired product **2a** in moderate yield (Table 1, entries 1−2). When di-*tert*-butyl azodicarboxylate (DBAD) was used, **2a** was isolated only in 10% yield (Table 1, entry 3). To our delight, excellent yields were obtained when DCM or toluene was selected as solvent (Table 1, entries 4−5). However, other solvents led to a decreased reactivity (Table 1, entries 6−8). Twice the amount of DEAD, TosMIC or AcOH were tested, providing no yield improvement (Table 1, entries 9−11). The pretreatment of **1a** with DEAD did not affect the yield (Table 1, entry 12). According to the above results, the oxidative Ugi-type reaction of **1a**, TosMIC (1.1 equiv) and AcOH (1.1 equiv), with DEAD (1.1 equiv) as the oxidant, was optimally carried out in DCM (0.1 M) at room temperature.

The scope of substrates **1** and isocyanides were next explored under the optimized reaction conditions (Scheme 2). Electron-donating groups (e.g., 4-methyl and 2-methoxy) and electron-withdrawing group (e.g., 4-bromo) on the nitrogen-linked benzene ring were well-tolerated, giving the corresponding products **2b−d** in 79−88% yields. In addition, a substrate carrying 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline moiety provided **2e** in 68% yields. To probe the generality of this protocol further, various isocyanides were subjected to the oxidative Ugi-type reaction, furnishing the corresponding products **2f−h** in 60−77% yields.



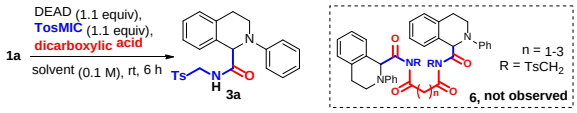
Scheme 2. Scope of Substrates **1** and Isocyanides



Scheme 3. Scope of Acids

After having identified the desired compatibility of derivatives of **1** and isocyanides, we turned our attention into the reactivity of acid (Scheme 3). An array of acids was well-tolerated in this reaction: branched and cyclic acids (e.g., 2-ethylbutyric acid and cyclobutane carboxylic acid) were suitable reactants, providing **2i** and **2j** in good yields. *N*-(*tert*-Butoxycarbonyl)glycine performed smoothly to afford **2k** in 71% yields. The reactivity remained when benzoic acids (e.g., benzoic acid, 4-chlorobenzoic acid, 4-methoxybenzoic acid) were used, giving access to **2l−n** in 60−83% yields. Cinnamic acid was also tested, and the desired product **2o** was isolated in 62% yields. Interestingly, the derivatization of pharmacologically active compounds was also achieved with our method. The aspirin derivative **2p** was prepared in 75% yields, and the amidation of the active metabolite of clofibrate provided **2q** in 68% yields.

Table 2. Optimization of the Ugi-amidation Conditions. [a]

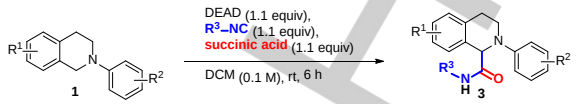


Entry	Additives	Solvent	Yield[b]
1[c]	succinic acid	DCM	33
2[d]	glutaric acid	DCM	37
3	succinic acid	DCM	82
4	glutaric acid	DCM	73
5	malonic acid	DCM	50
6	succinic acid	CH_3CN	71
7	succinic acid	DCE	69
8	succinic acid	toluene	78
9	H_2O (5 equiv)	DCM	trace
10[e]	succinic acid + H_2O (5 equiv)	DCM	10

[a] **1a** (0.3 mmol), DEAD (0.33 mmol), TosMIC (0.33 mmol), dicarboxylic acid (0.33 mmol), solvent (3.0 mL). [b] Isolated yield. [c] succinic acid (0.18 mmol). [d] glutaric acid (0.18 mmol). [e] succinic acid (0.06 mmol).

Since diverse acids were applicable, we attempted to employ dicarboxylic acids to afford dimeric products **6** (Table 2).[10] To our surprise, **6** were not observed during the reaction using 0.6 equiv of succinic acid or glutaric acid, but, even more interestingly, amide **3a** was obtained instead (Table 2, entries 1−2). Next, we doubled the amount of dicarboxylic acids, making a dramatic improvement in the isolated yield of **3a** (Table 2, entries 3−4). Malonic acid was also tolerated in the reaction (Table 2, entry 5).[11] DCM was a better choice than other solvents examined, including CH_3CN, DCE and toluene (Table 2, entries 6−8). Notably, unlike in the typical truncated Ugi reaction, water was poor nucleophilic reagent for attacking the nitrilium ion (Table 2, entry 9). We reduced the equivalent of succinic acid by the addition of exogenous water, providing **3a** only in 10% yields (Table 2, entry 10), which demonstrated the dicarboxylic acid indeed participated the reaction, but did not just act like a mediator for water addition to the nitrilium ion.

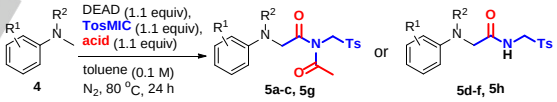
Table 3. Scope of Substrates **1** and Isocyanides.



Entry	1	R^1	R^2	R^3	3	Yield[a]
1	**1a**	H	H	CH_2Ts	**3a**	82
2	**1b**	H	4-Me	CH_2Ts	**3b**	79
3	**1c**	H	2-OMe	CH_2Ts	**3c**	78
4	**1d**	H	4-Br	CH_2Ts	**3d**	85
5	**1e**	6,7-OMe	H	CH_2Ts	**3e**	65
6	**1f**	5-OMe	H	CH_2Ts	**3f**	72
7	**1g**	7-NO_2	H	CH_2Ts	**3g**	55
8	**1a**	H	H	Cy	**3h**	70
9	**1a**	H	H	*t*-Bu	**3i**	43
10	**1a**	H	H	Bn	**3j**	62
11	**1a**	H	H	CH_2CO_2Et	**3k**	72

[a] Isolated yield.

Table 4. Scope of Noncyclic Anilines.



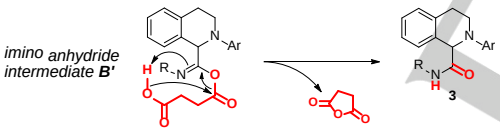
Entry	4	R^1	R^2	Acid	5	Yield[a]
1	**4a**	H	Me	AcOH	**5a**	47
2	**4b**	4-Me	Me	AcOH	**5b**	59
3	**4c**	4-Br	Me	AcOH	**5c**	52
4	**4a**	H	Me	succinic acid	**5d**	61
5	**4b**	4-Me	Me	succinic acid	**5e**	49
6	**4c**	4-Br	Me	succinic acid	**5f**	55
7	**4d**	H	Et	AcOH	**5g**	15
8	**4d**	H	Et	succinic acid	**5h**	11

[a] Isolated yield.

With optimal conditions in hand, we investigated the influence of the electronic nature of the aromatic rings (R^1 and R^2, Table 3). The substrates with electron-donating (e.g., 4-methy, 2-methoxy) or electron-withdrawing (e.g., 4-bromo) group were applicable, furnishing **3b−d** in 78−85% yields. Moreover,

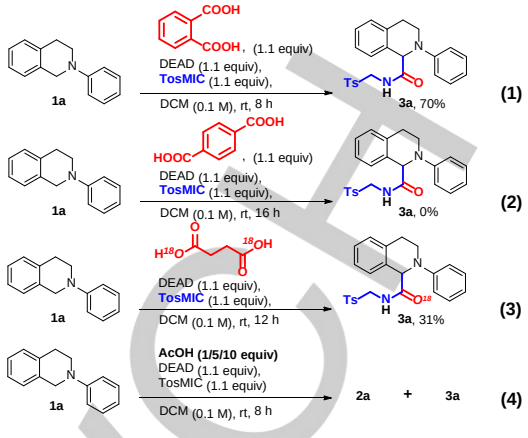
electron-rich (e.g., 6,7-dimethoxy, 5-methoxy) and electron-poor (e.g., 7-nitro) substituents on the 1,2,3,4-tetrahydroisoquinoline moiety were both tolerable and gave **3e−g** in good yields. The protocol scope was further explored by varying the R^3 group of the isocyanides (Table 3, entries 8−11). Similar results were observed when isocyanide derivatives were examined, giving **3h**, **3j** and **3k** in 62−72% yields. When *tert*-butyl isocyanide was employed, however, the desired product **3l** was obtained only in 43% yield.

To highlight the utility of this method, we further employed non-cyclic anilines **4** as substrates (Table 4). Based on the conditions determined, toluene was selected as the solvent. The non-cyclic substrates **4a**-**c** gave the desired product **5a-f** in moderate yield (47−61%), with lengthened reaction time and increased temperature. In addition, electron-donating and electron-withdrawing substituents on the phenyl ring were found to be well-tolerated in this process. The *N*-ethyl-*N*-methylaniline **4d** provided the *N*-methyl-derivatives **5g** and **5h** in 15% and 11% yields, respectively. The steric effect of *N*-ethyl may be responsible for the dramatic decrease of yields.[12] *N*,*N*-dimethylcyclohexylamine and *N*-benzoyl 1,2,3,4-tetrahydro isoquinoline were also employed, however, no desired product was observed.[13] Furthermore, gram-scale preparation was carried out with increased concentrations of reactants, providing **2a**, **3a**, **5a** and **5d** in desired yields (for more details, see SI). Since IBX was a representative organic oxidant for oxidative Ugi-type reaction, the comparison between IBX and DEAD as oxidants was also carried out, indicating our protocol more suitable and effective for the oxidative Ugi-type reactions of tertiary amines (for more details, see SI).



Scheme 4. Proposed Dicarboxylic Acid-based Mechanism

In the light of the above experiment results, a dicarboxylic acid-based mechanism was proposed (Scheme 4). When the imino anhydride intermediate **B'** was formed (see Scheme 1, eq 6), out of the ordinary, an intramolecular annulation occured at the carbonyl, instead of the Mumm rearrangement, affording the amide **3** with one molecule of succinic anhydride released.



Scheme 5. Control Experiments.

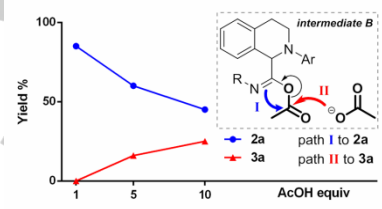
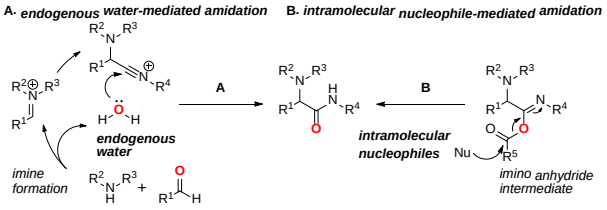


Figure 1. The yield of **2a** and **3a** with different equiv of AcOH.

To confirm the reaction pathway further, several control experiments were performed (Scheme 5). Phthalic acid was well tolerated, providing **3a** in 70% yields (eq 1). Terephthalic acid, by contrast, did not lead to the production of **3a** (eq 2). Therefore the dicarboxylic acids capable of transforming into the corresponding cyclic anhydride are essential for the introduction of carbonyl oxygen. Subsequently, we used ^{18}O-labeled succinic acid to probe the origin of the oxygen in **3a**. As we expected, ^{18}O-labeled **3a** was obtained in 31% yields (eq 3).[14] Furthermore, based on the proposed behavior of intermediate **B'** we speculated that even intermolecular nucleophilic attack could compete with the Mumm rearrangement at carbonyl. Therefore, competitive experiments were designed with the addition of excessive AcOH (5 equiv and 10 equiv, eq 4). Finally, we isolated **3a** in 16% and 25% yields, respectively (Figure 1).[15] Together, the control experiments verified that dicarboxylic acids could deliver one oxygen atom to **3a** via self-annulation during the amidation.



Scheme 6. Insertion of the Amide Carbonyl Oxygen in Ugi-amidation.

Based on the above mechanism, our method could be considered as a representative Ugi-MCR concisely providing α-amino amides without water as a nucleophile.[16,17] Unlike the typical Ugi-amidation utilizing endogenous water generated during the imine or iminium ion formation [3g-h, 5, 16], the amide carbonyl oxygen in this protocol was introduced through an intramolecular nucleophilic attack on the imino anhydride intermediate (Scheme 6) [17]. Notably, dicarboxylic acid was served as a readily accessible and highly reactive alternative to water for the insertion of the amide carbonyl oxygen, especially when the water added could not facilitate amide formation (Table 2, entry 9). Studies are in progress to boarden the application of the dicarboxylic acid-assisted Ugi-MCRs in our group.

Conclusions

In conclusion, we herein report a DEAD-promoted oxidative Ugi-type reaction of tertiary amines, furnishing α-amino amides and imides with diverse substitutes. Notably, an unprecedented amidation assisted by dicarboxylic acids has been disclosed, which provide a solution for poor reactivity of water in some Ugi reaction. Dicarboxylic acids are supposed to be cost effective and operationally simple alternatives to water. Moreover, the reaction proceeded with broad substrate scope under mild and practical conditions, affording the target compounds in good yields. Further exploration of DEAD-promoted oxidation is now ongoing in our laboratory.

Experimental Section

General procedure for synthesis of compound 2:

A 10 mL flask was charged with **1a-e** (0.3 mmol), isocyanide**s** (0.33 mmol) and acid (0.33 mmol) in DCM (3.0 mL). To the flask was added DEAD (52 μL, 58 mg, 0.33 mmol, 1.1 equiv) and the resulting mixture stirred at room temperature. The reaction was monitored by TLC until complete consumption. The solvent was directly removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 50:1-5:1) to give the desired products **2a-q**, which was further purified by trituration in ether or ether/hexane.

***N*-acetyl-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2a)**, white solid, 118 mg, 85% yield. m.p. 148–150°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 2H), 7.38 – 7.29 (m, 1H), 7.28 – 7.13 (m, 6H), 7.11 – 7.01 (m, 1H), 6.97 – 6.79 (m, 3H), 6.34 (s, 1H), 5.41 (AB, *J* = 15.0 Hz, 1H), 4.75 (AB, *J* = 15.0 Hz, 1H), 3.79 – 3.56 (m, 1H), 3.47 – 3.26 (m, 1H), 2.90 – 2.71 (m, 1H), 2.71 – 2.51 (m, 1H), 2.34 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.54, 172.45, 147.93, 145.53, 135.42, 133.97, 131.10, 129.88, 129.57, 128.85, 128.80, 128.46, 127.91, 126.27, 120.48, 116.52, 62.91, 61.26, 44.98, 25.82, 25.53, 21.69. HRMS (ESI) calcd. for $C_{26}H_{27}N_2O_4S$ $[M+H]^+$ 463.1686, found 463.1698.

***N*-acetyl-2-(*p*-tolyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2b)**, white solid, 119 mg, 83% yield. m.p. 150–152°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.9 Hz, 2H), 7.47 – 7.39 (m, 1H), 7.36 – 7.26 (m, 4H), 7.19 – 7.14 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 6.31 (s, 1H), 5.55 (AB, *J* = 15.0 Hz, 1H), 4.86 (AB, *J* = 15.1 Hz, 1H), 3.75 (d, *J* = 11.4 Hz, 1H), 3.47 – 3.35 (m, 1H), 2.97 – 2.83 (m, 1H), 2.73 – 2.61 (m, 1H), 2.46 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.58, 172.31, 145.67, 145.53, 135.30, 134.11, 131.03, 130.43, 130.15, 129.89, 128.97, 128.87, 128.63, 127.81, 126.20, 117.38, 62.81, 61.44, 45.38, 25.89, 25.10, 21.71, 20.45. HRMS (ESI) calcd. for $C_{27}H_{29}N_2O_4S$ $[M+H]^+$ 477.1843, found 477.1858.

***N*-acetyl-2-(2-methoxyphenyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2c)**, white solid, 117 mg, 79% yield. m.p. 204–206°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.34 (m, 1H), 7.34 – 7.26 (m, 4H), 7.21 – 7.15 (m, 1H), 7.14 – 7.08 (m, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.90 – 6.80 (m, 2H), 6.10 (s, 1H), 5.49 (AB, *J* = 15.0 Hz, 1H), 4.74 (AB, *J* = 15.1 Hz, 1H), 3.87 (s, 3H), 3.57 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.42 – 3.29 (m, 1H), 2.95 – 2.83 (m, 1H), 2.73 – 2.62 (m, 1H), 2.44 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.90, 172.31, 152.80, 145.41, 137.76, 135.20, 134.09, 131.66, 129.84, 129.08, 128.88, 128.25, 127.51, 126.00, 124.70, 121.82, 121.17, 111.77, 62.67, 62.22, 55.41, 44.42, 26.17, 25.60, 21.71. HRMS (ESI) calcd. for $C_{27}H_{29}N_2O_5S$ $[M+H]^+$ 493.1792, found 493.1803.

***N*-acetyl-2-(4-bromophenyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2d)**, white solid, 143 mg, 88% yield. m.p. 144–146°C ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 2H), 7.44 – 7.36 (m, 3H), 7.35 – 7.30 (m, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.22 – 7.15 (m, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.48 (s, 1H), 5.44 (AB, *J* = 15.1 Hz, 1H), 4.87 (AB, *J* = 15.1 Hz, 1H), 3.71 – 3.62 (m, 1H), 3.56 – 3.46 (m, 1H), 2.93 – 2.84 (m, 1H), 2.80 (dt, *J* = 16.1, 5.5 Hz, 1H), 2.44 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.34, 172.79, 147.10, 145.66, 135.57, 134.01, 132.33, 131.09, 129.97, 128.79, 128.25, 126.55, 117.29, 112.06, 63.26, 61.35, 44.96, 25.92, 25.76, 21.71. HRMS (ESI) calcd. for $C_{26}H_{26}N_2O_4SBr$ $[M+H]^+$ 541.0791, found 541.0808.

***N*-acetyl-6,7-dimethoxy-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2e)**, light yellow solid, 107 mg, 68% yield. m.p. 176–178°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.9 Hz, 2H), 7.36 – 7.25 (m, 4H), 7.03 – 6.93 (m, 4H), 6.64 (s, 1H), 6.29 (s, 1H), 5.52 (AB, *J* = 15.0 Hz, 1H), 4.85 (AB, *J* = 15.2 Hz, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.77 (d, *J* = 13.6 Hz, 1H), 3.49 – 3.37 (m, 1H), 2.92 – 2.75 (m, 1H), 2.62 (dt, *J* = 16.3, 4.0 Hz, 1H), 2.44 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.63, 172.42, 148.88, 148.08, 147.71, 145.60, 134.18, 129.91, 129.60, 128.79, 127.63, 122.78, 120.76, 116.99, 111.53, 111.19, 62.92, 61.09, 56.13, 55.85, 45.19, 25.87, 24.99, 21.71. HRMS (ESI) calcd. for $C_{28}H_{31}N_2O_6S$ $[M+H]^+$ 523.1897, found 523.1909.

***N*-acetyl-*N*-cyclohexyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2f)**, colorless glass, 87 mg, 77% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 1H), 7.25 – 7.14 (m, 4H), 7.14 – 7.05 (m, 1H), 6.92 (d, *J* = 8.2 Hz, 2H), 6.77 (t, *J* = 7.2 Hz, 1H), 6.10 (s, 1H), 3.68 – 3.57 (m, 1H), 3.56 – 3.42 (m, 2H), 3.03 – 2.75 (m, 2H), 2.12 (s, 3H), 2.00 – 1.81 (m, 1H), 1.81 – 1.59 (m, 3H), 1.53 – 1.34 (m, 2H), 1.15 – 0.91 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.13, 174.51, 148.65, 135.46, 132.53, 129.23, 128.39, 127.70, 126.34, 119.11, 115.42, 63.33, 59.17, 44.78, 30.67, 29.49, 27.44, 26.44, 25.56, 25.07. HRMS (ESI) calcd. for $C_{24}H_{29}N_2O_2$ $[M+H]^+$ 377.2224, found 377.2239.

***N*-acetyl-*N*-benzyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2g)**, colorless glass, 69 mg, 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 4H), 7.19 – 7.08 (m, 5H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.84 – 6.70 (m, 3H), 6.59 (s, 1H), 4.99 (d, *J* = 16.8 Hz, 1H), 4.57 (d, *J* = 16.8 Hz, 1H), 3.80 – 3.67 (m, 1H), 3.62 – 3.49 (m, 1H), 3.04 – 2.90 (m, 1H), 2.90 – 2.77 (m, 1H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.53, 174.49, 148.89, 136.76, 136.20, 132.62, 129.32, 128.74, 128.56, 127.86, 127.32, 127.24, 126.42, 126.06, 118.94, 115.14, 62.16, 48.07,

44.29, 27.31, 25.69. HRMS (ESI) calcd. for $C_{25}H_{25}N_2O_2$ $[M+H]^+$ 385.1911, found 385.1924.

Ethyl *N*-acetyl-*N*-(2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonyl) glycinate (2h), colorless glass, 70 mg, 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 1H), 7.24 – 7.13 (m, 4H), 7.13 – 7.04 (m, 1H), 6.93 – 6.75 (m, 3H), 5.99 (s, 1H), 4.38 (AB, *J* = 17.9 Hz, 1H), 4.26 (AB, *J* = 17.9 Hz, 1H), 4.14 – 3.90 (m, 2H), 3.59 (t, *J* = 6.1 Hz, 2H), 2.99 – 2.73 (m, 2H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.98, 173.57, 168.34, 148.45, 135.46, 131.54, 129.36, 128.85, 127.86, 127.82, 126.31, 120.24, 116.49, 62.88, 61.46, 46.04, 45.53, 26.63, 26.01, 13.96. HRMS (ESI) calcd. for $C_{22}H_{25}N_2O_4$ $[M+H]^+$ 381.1809, found 381.1825.

***N*-(2-ethylbutanoyl)-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2i)**, white solid, 128 mg, 82% yield. m.p. 118–120°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.9 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.36 – 7.26 (m, 6H), 7.20 – 7.13 (m, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.44 (s, 1H), 5.62 (AB, *J* = 15.2 Hz, 1H), 4.90 (AB, *J* = 15.2 Hz, 1H), 3.85 (d, *J* = 13.3 Hz, 1H), 3.54 – 3.43 (m, 1H), 3.07 – 2.98 (m, 1H), 2.97 – 2.87 (m, 1H), 2.69 (d, *J* = 16.2 Hz, 1H), 2.45 (s, 3H), 1.69 – 1.59 (m, 2H), 1.55 – 1.45 (m, 1H), 1.45 – 1.36 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.51, 175.39, 147.89, 145.45, 135.36, 134.21, 131.09, 129.85, 129.68, 129.02, 128.99, 128.93, 127.92, 126.28, 120.57, 116.60, 62.73, 61.54, 47.84, 45.40, 24.67, 21.68, 11.67, 11.09. HRMS (ESI) calcd. for $C_{30}H_{35}N_2O_4S$ $[M+H]^+$ 519.2312, found 519.2327.

***N*-(cyclobutanecarbonyl)-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2j)**, white solid, 113 mg, 75% yield. m.p. 104–106°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.38 (m, 1H), 7.33 – 7.29 (m, 4H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.19 – 7.13 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 2H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.48 (s, 1H), 5.44 (AB, *J* = 15.1 Hz, 1H), 4.84 (AB, *J* = 15.1 Hz, 1H), 3.81 – 3.68 (m, 2H), 3.49 (ddd, *J* = 13.5, 9.4, 4.9 Hz, 1H), 2.89 (ddd, *J* = 15.6, 9.5, 5.6 Hz, 1H), 2.74 (dt, *J* = 16.2, 4.6 Hz, 1H), 2.43 (s, 3H), 2.33 – 2.09 (m, 4H), 2.02 – 1.89 (m, 1H), 1.88 – 1.77 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.34, 174.35, 148.02, 145.45, 135.61, 134.14, 131.42, 129.87, 129.55, 128.92, 128.82, 128.49, 127.93, 126.25, 120.16, 116.22, 62.76, 61.04, 44.83, 40.60, 25.64, 24.99, 21.67, 17.55. HRMS (ESI) calcd. for $C_{29}H_{31}N_2O_4S$ $[M+H]^+$ 503.1999, found 503.2010.

tert-Butyl (2-oxo-2-(2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamido)ethyl)carbamate (2k), white solid, 123 mg, 71% yield. m.p. 138–140°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.40 (m, 1H), 7.37 – 7.28 (m, 6H), 7.21 – 7.12 (m, 1H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.35 (s, 1H), 5.57 (AB, *J* = 15.2 Hz, 1H), 5.00 (s, 1H), 4.95 (AB, *J* = 15.2 Hz, 1H), 4.37 (d, *J* = 18.9 Hz, 1H), 4.27 (dd, *J* = 18.7, 5.0 Hz, 1H), 3.91 – 3.82 (m, 1H), 3.52 – 3.37 (m, 1H), 2.95 – 2.84 (m, 1H), 2.66 (d, *J* = 16.7 Hz, 1H), 2.46 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.38, 172.65, 155.62, 147.75, 145.74, 135.34, 134.03, 130.50, 130.05, 129.73, 129.07, 128.79, 128.77, 128.04, 126.35, 121.13, 117.24, 79.93, 62.45, 61.22, 46.86, 45.50, 28.33, 24.79, 21.72. HRMS (ESI) calcd. for $C_{31}H_{36}N_3O_6S$ $[M+H]^+$ 578.2319, found 578.2334.

***N*-benzoyl-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2l)**, white solid, 105 mg, 67% yield. m.p. 144–146°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.9 Hz, 2H), 7.55 (t, *J* = 7.1 Hz, 3H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 2H), 7.26 – 7.17 (m, 3H), 7.15 – 7.04 (m, 3H), 6.85 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 2H), 5.67 (s, 1H), 5.26 (AB, *J* = 14.2 Hz, 1H), 5.08 (AB, *J* = 14.2 Hz, 1H), 3.66 – 3.55 (m, 1H), 3.46 – 3.34 (m, 1H), 2.83 – 2.65 (m, 2H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.84, 171.25, 147.41, 145.32, 135.03, 134.52, 133.03, 132.72, 131.04, 129.87, 129.28, 129.04, 128.94, 128.75, 128.51, 127.80, 126.05, 120.54, 116.61, 65.75, 60.60, 44.96, 25.74, 21.66. HRMS (ESI) calcd. for $C_{31}H_{29}N_2O_4S$ $[M+H]^+$ 525.1843, found 525.1853.

***N*-(4-chlorobenzoyl)-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2m)**, off-white solid, 139 mg, 83% yield. m.p. 132–134°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.9 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.37 – 7.27 (m, 4H), 7.27 – 7.17 (m, 3H), 7.12 (t, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 7.0 Hz, 1H), 6.88 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 2H), 5.53 (s, 1H), 5.25 (AB, *J* = 14.2 Hz, 1H), 5.08 (AB, *J* = 14.1 Hz, 1H), 3.69 – 3.58 (m, 1H), 3.38 – 3.24 (m, 1H), 2.83 – 2.71 (m, 1H), 2.66 (d, *J* = 16.4 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.63, 169.98, 147.05, 145.44, 139.43, 134.77, 134.51, 131.24, 130.63, 130.46, 129.92, 129.09, 128.94, 128.84, 128.70, 127.87, 126.06, 120.94, 116.68, 65.73, 60.61, 44.92, 25.51, 21.66. HRMS (ESI) calcd. for $C_{31}H_{28}N_2O_4SCl$ $[M+H]^+$ 559.1453, found 559.1467.

***N*-(4-methoxybenzoyl)-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2n)**, white solid, 100 mg, 60% yield. m.p. 164–166°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 6.0 Hz, 3H), 7.23 – 6.97 (m, 5H), 6.81 (t, *J* = 8.0 Hz, 3H), 6.52 (d, *J* = 8.1 Hz, 2H), 5.53 (s, 1H), 5.23 (AB, *J* = 14.1 Hz, 1H), 5.03 (AB, *J* = 14.1 Hz, 1H), 3.85 (s, 3H), 3.63 – 3.48 (m, 1H), 3.40 – 3.23 (m, 1H), 2.80 – 2.55 (m, 2H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.78, 170.42, 163.59, 147.49, 145.16, 134.99 134.62, 131.63, 131.12, 129.77, 129.00, 128.91, 128.67, 127.66, 125.93, 124.95, 120.37, 116.59, 113.78, 65.93, 60.56, 55.50, 44.95, 25.71, 21.60 HRMS (ESI) calcd. for $C_{32}H_{31}N_2O_5S$ $[M+H]^+$ 555.1948, found 555.1961.

***N*-cinnamoyl-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2o)**, yellow solid, 102 mg, 62% yield. m.p. 128–130°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 15.4 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.52 – 7.37 (m, 6H), 7.35 – 7.22 (m, 6H), 7.21 – 7.12 (m, 1H), 7.03 – 6.79 (m, 4H), 6.39 (s, 1H), 5.51 (AB, *J* = 14.9 Hz, 1H), 4.99 (AB, *J* = 14.9 Hz, 1H), 3.80 – 3.64 (m, 1H), 3.62 – 3.45 (m, 1H), 2.98 – 2.67 (m, 2H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.30, 171.04, 150.60, 149.39, 147.99, 138.35, 137.04, 136.72, 134.08, 133.49, 132.53, 132.04, 131.49, 131.36, 131.16, 131.04, 130.56, 128.95, 122.64, 121.77, 118.71, 66.38, 63.97, 47.55, 28.62, 24.27. HRMS (ESI) calcd. for $C_{33}H_{31}N_2O_4S$ $[M+H]^+$ 551.1999, found 551.2018.

2-((2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonyl)(tosylmethyl)carbamoyl)phenyl acetate (2p), white solid, 131 mg, 75% yield. m.p. 118–120°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 6H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.87 (t, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 2H), 6.34 (s, 1H), 5.17 – 5.06 (m, 2H), 3.73 – 3.65 (m, 1H) 3.65 – 3.58 (m, 1H), 2.98 – 2.89 (m, 1H), 2.89 – 2.80 (m, 1H), 2.40 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.20, 169.49, 168.69, 148.18, 148.04, 145.23, 136.05, 134.91, 133.12, 131.73, 130.54, 129.87, 129.25, 128.75, 128.54, 128.38, 128.08, 126.44, 126.29, 125.99, 123.54, 119.35, 115.34, 65.33, 60.85, 44.71, 26.44, 21.64, 20.77. HRMS (ESI) calcd. for $C_{33}H_{31}N_2O_6S$ $[M+H]^+$ 583.1897, found 583.1917.

***N*-(2-(4-chlorophenoxy)-2-methylpropanoyl)-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2q)**, light-yellow solid, 126 mg, 68% yield. m.p. 136–138°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.22 (t, *J* = 7.7 Hz, 3H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 2H), 6.10 (s, 1H), 5.58 – 5.44 (m, 2H), 3.75 (d, *J* = 13.2 Hz, 1H), 3.57 – 3.46 (m, 1H), 2.92 – 2.81 (m, 1H), 2.62 – 2.54 (m, 1H), 2.48 (s, 3H), 1.68 (s, 3H), 1.48 (s, 3H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 179.50, 174.06, 151.76, 147.78, 145.27, 135.30, 134.79, 131.18, 129.77, 129.66, 129.42, 129.25, 129.20, 128.99, 128.89, 127.77, 125.85, 124.45, 120.31, 116.51, 84.71, 64.91, 60.93, 44.46, 27.06, 26.59, 24.73, 21.69. HRMS (ESI) calcd. for $C_{34}H_{34}N_2O_5SCl$ $[M+H]^+$ 617.1871, found 617.1886. **General procedure for synthesis of compound 3:**

A 10 mL flask was charged with **1a-g** (0.3 mmol), isocyanide**s** (0.33 mmol) and succinic acid (39 mg, 0.33 mmol) in DCM (3.0 mL). To the flask was added DEAD (52 μL, 58 mg, 0.33 mmol, 1.1 equiv) and the resulting mixture stirred at room temperature. The reaction was monitored by TLC until complete consumption. The solvent was directly removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 30:1-2:1) to give the desired products **3a-k**, which was further purified by trituration in ether or ether/hexane.

2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3a), white solid, 103 mg, 82% yield. m.p. 110–112°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (t, *J* = 7.0 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.41 – 7.13 (m, 5H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 2H), 5.11 – 4.77 (m, 2H), 4.32 (ABX, *J* = 14.2, 5.7 Hz, 1H), 4.09 – 3.88 (m, 1H), 3.39 – 3.11 (m, 2H), 3.11 – 2.94 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.63, 150.49, 146.25, 136.23, 135.15, 133.25, 131.09, 130.89, 130.26, 129.70, 129.08, 129.04, 128.15, 121.43, 116.01, 66.89, 61.38, 46.23, 30.41, 23.04. HRMS (ESI) calcd. for $C_{24}H_{25}N_2O_3S$ $[M+Na]^+$ 421.1580, found 421.1593.

2-(p-tolyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3b), white solid, 103 mg, 79% yield. m.p. 118–120°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (t, *J* = 7.0 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.27 – 7.19 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.80 (d, *J* = 8.1 Hz, 2H), 4.95 – 4.84 (m, 2H), 4.35 (ABX, *J* = 14.3, 5.7 Hz, 1H), 3.97 – 3.84 (m, 1H), 3.33 – 3.11 (m, 2H), 3.03 (dt, *J* = 15.5, 3.4 Hz, 1H), 2.38 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.37, 146.95, 144.82, 134.81, 133.71, 131.84, 130.01, 129.67, 128.80, 128.31, 127.70, 127.58, 126.68, 115.10, 65.58, 59.96, 45.33, 29.07, 21.64, 20.35. HRMS (ESI) calcd. for $C_{25}H_{27}N_2O_3S$ $[M+H]^+$ 435.1737, found 435.1751.

2-(2-methoxyphenyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3c), white solid, 105 mg, 78% yield. m.p. 104–106°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (t, *J* = 6.9 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.30 – 7.21 (m, 2H), 7.22 – 7.13 (m, 3H), 7.11 – 7.04 (m, 3H), 7.00 (t, *J* = 7.6 Hz, 1H), 4.97 (s, 1H), 4.60 (ABX, *J* = 14.2, 7.2 Hz, 1H), 4.52 (ABX, *J* = 14.2, 6.6 Hz, 1H), 4.04 (s, 3H), 3.46 – 3.35 (m, 1H), 3.24 – 3.16 (m, 1H), 3.16 – 3.06 (m, 1H), 2.86 (dt, *J* = 15.8, 4.1 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.38, 154.37, 144.66, 138.98, 134.80, 133.77, 131.89, 129.63, 128.54, 128.44, 128.40, 127.11, 126.12, 126.03, 123.61, 121.10, 111.82, 64.27, 60.53, 55.69, 48.32, 29.20, 21.67. HRMS (ESI) calcd. for $C_{25}H_{27}N_2O_4S$ $[M+H]^+$ 451.1686, found 451.1696.

2-(4-bromophenyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3d), white solid, 130 mg, 85% yield. m.p. 144–146°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (t, *J* = 7.0 Hz, 1H), 7.52 – 7.16 (m, 8H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 4.95 – 4.74 (m, 2H), 4.40 (ABX, *J* = 14.2, 5.9 Hz, 1H), 4.04 – 3.79 (m, 1H), 3.39 – 3.12 (m, 2H), 3.12 – 2.91 (m, 1H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.26, 149.46, 146.40, 135.98, 135.06, 133.60, 132.92, 131.13, 130.14, 129.65, 129.28, 129.11, 128.28, 117.49, 113.63, 66.73, 61.36, 46.25, 30.29, 23.06. HRMS (ESI) calcd. for $C_{24}H_{24}N_2O_3SBr$ $[M+H]^+$ 499.0686, found 499.0703.

6,7-dimethoxy-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3e), white solid, 94 mg, 65% yield. m.p. 152–154°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.5, 5.5 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.85 (s, 1H), 6.74 (s, 1H), 4.93 (ABX, *J* = 14.2, 8.5 Hz, 1H), 4.81 (s, 1H), 4.29 (ABX, *J* = 14.3, 5.5 Hz, 1H), 3.98 (s, 3H), 3.96 – 3.90 (m, 1H), 3.82 (s, 3H), 3.26 (td, *J* = 10.9, 3.2 Hz, 1H), 3.21 – 3.11 (m, 1H), 2.96 (dt, *J* = 15.6, 3.5 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.57, 149.19, 148.65, 147.84, 144.92, 133.84, 129.56, 129.46, 128.33, 126.89, 123.45, 120.16, 114.86, 111.24, 110.39, 65.04, 59.80, 56.00, 55.85, 45.00, 28.64, 21.50. HRMS (ESI) calcd. for $C_{26}H_{29}N_2O_5S$ $[M+H]^+$ 481.1792, found 481.1803.

5-methoxy-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3f), white solid, 97 mg, 72% yield. m.p. 144–146°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (t, *J* = 7.0 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.40 – 7.28 (m, 2H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.96 (t, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 4.92 (ABX, *J* = 14.2, 8.4 Hz, 1H), 4.84 (s, 1H), 4.34 (ABX, *J* = 14.2, 5.6 Hz, 1H), 4.05 – 3.76 (m, 4H), 3.35 – 3.09 (m, 2H), 3.00 (d, *J* = 16.3 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.92, 160.55, 150.54, 146.25, 137.51, 131.32, 131.05, 130.87, 129.75, 125.35, 121.40, 115.99, 114.12, 114.01, 66.37, 61.29, 56.71, 46.11, 30.66, 22.98. HRMS (ESI) calcd. for $C_{25}H_{27}N_2O_4S$ $[M+H]^+$ 451.1686, found 451.1699.

7-nitro-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3g), white solid, 77 mg, 55% yield. m.p. 215–218°C. ^{1}H NMR (300 MHz, DMSO) δ 9.40 (t, *J* = 6.5 Hz, 1H), 8.34 (d, *J* = 2.4 Hz, 1H), 8.23 – 8.09 (m, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.34 – 7.10 (m, 4H), 6.93 – 6.68 (m, 3H), 5.40 (s, 1H), 4.81 – 4.60 (m, 2H), 3.87 – 3.66 (m, 1H), 3.50 – 3.34 (m, 1H), 3.20 – 2.94 (m, 2H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 173.13, 150.09, 147.66, 146.18, 145.95, 136.60, 136.54, 131.26, 131.10, 130.94, 129.97, 124.86, 124.23, 119.77, 115.17, 63.22, 62.06, 44.50, 29.40, 22.87. HRMS (ESI) calcd. for $C_{24}H_{23}N_3O_5SNa$ $[M+Na]^+$ 488.1251, found 488.1263.

***N*-cyclohexyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3h)**, white solid, 70 mg, 70% yield. m.p. 128–130°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 2H), 7.21 – 7.12 (m, 2H), 7.08 (d, *J* = 6.2 Hz, 1H), 6.92 – 6.78 (m, 3H), 6.69 (d, *J* = 8.7 Hz, 1H), 4.89 (s, 1H), 3.84 – 3.72 (m, 1H), 3.72 – 3.54 (m, 1H), 3.33 – 3.20 (m, 1H), 3.07 – 2.82 (m, 2H), 1.83 – 1.72 (m, 1H), 1.72 – 1.61 (m, 1H), 1.60 – 1.41 (m, 3H), 1.35 – 1.13 (m, 2H), 1.13 – 0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.04, 149.50, 134.44, 132.86, 129.29, 128.95, 127.42, 127.31, 126.63, 119.50, 114.64, 114.56, 65.73, 48.12, 44.97, 32.94, 32.72, 28.88 25.43, 24.75, 24.64. HRMS (ESI) calcd. for $C_{22}H_{27}N_2O$ $[M+H]^+$ 335.2118, found 335.2134.

***N*-(tert-butyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3i)**, white solid, 40 mg, 43% yield. m.p. 94–96°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.53 (m, 1H), 7.47 – 7.10 (m, 5H), 7.09 – 6.88 (m, 3H), 6.78 (s, 1H), 4.90 (s, 1H), 3.94 – 3.73 (m, 1H), 3.46 – 3.29 (m, 1H), 3.17 – 2.92 (m, 2H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.68, 150.97 135.76, 134.38, 130.72, 130.37, 128.95, 128.67, 128.00, 121.10, 116.46, 67.58, 52.35, 46.64, 30.16, 30.02. HRMS (ESI) calcd. for $C_{20}H_{25}N_2O$ $[M+H]^+$ 309.1961, found 309.1972.

***N*-benzyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3j)**, white solid, 64 mg, 62% yield. m.p. 144–146°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.53 (m, 1H), 7.29 – 7.18 (m, 4H), 7.19 – 7.07 (m, 4H), 7.03 – 6.92 (m, 2H), 6.93 – 6.81 (m, 3H), 5.02 (s, 1H), 4.42 – 4.24 (m, 2H), 3.86 – 3.69 (m, 1H), 3.34 – 3.18 (m, 1H), 3.11 – 2.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.31, 149.36, 138.14, 134.49, 132.61, 129.37, 128.86, 128.53, 127.63, 127.47, 127.37, 127.27, 126.74, 119.74, 114.90,

65.54, 45.20, 43.41, 28.97. HRMS (ESI) calcd. for $C_{23}H_{23}N_2O$ $[M+H]^+$ 343.1805, found 343.1818.

ethyl (2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonyl)glycinate (3k), white solid, 73 mg, 72% yield. m.p. 92–94°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 1H), 7.35 (t, *J* = 5.7 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.21 – 7.15 (m, 2H), 7.14 – 7.05 (m, 1H), 6.94 – 6.78 (m, 3H), 4.99 (s, 1H), 4.15 – 3.96 (m, 3H), 3.89 – 3.76 (m, 2H), 3.37 – 3.24 (m, 1H), 3.18 – 3.02 (m, 1H), 3.00 – 2.86 (m, 1H), 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.50, 169.58, 149.30, 134.90, 132.45, 129.35, 129.04, 127.57, 127.53, 126.64, 119.48, 114.56, 114.48, 65.37, 61.38, 44.79, 41.32, 28.53, 14.05. HRMS (ESI) calcd. for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ 339.1703, found 339.1718.

General procedure for synthesis of compound 5:

A 10 mL two-neck flask was charged with **4** (0.3 mmol), TosMIC (65 mg, 0.33 mmol) and acid (0.33 mmol) in toluene (3.0 mL). After the two-neck flask was evacuated and back filled with nitrogen, DEAD (52 μL, 58 mg, 0.33 mmol, 1.1 equiv) was added and the resulting mixture was heated at 80 °C for 24 h. The reaction was monitored by TLC until complete consumption. The solvent was directly removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 15:1-2:1) to give the desired products **5a-h**, which was further purified by trituration in ether.

***N*-acetyl-2-(methyl(phenyl)amino)-*N*-(tosylmethyl)acetamide (5a)**, white solid, 53 mg, 47% yield. m.p. 104–106°C ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 2H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 2H), 5.22 (s, 2H), 4.61 (s, 2H), 2.92 (s, 3H), 2.54 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.34, 172.31, 148.71, 145.78, 134.31, 130.02, 129.17, 128.88, 117.48, 112.36, 63.39, 58.52, 39.06, 25.52, 21.70. HRMS (ESI) calcd. for $C_{19}H_{23}N_2O_4S$ $[M+H]^+$ 375.1373, found 375.1388.

***N*-acetyl-2-(methyl(p-tolyl)amino)-*N*-(tosylmethyl)acetamide (5b)**, white solid, 69 mg, 59% yield. m.p. 130–132°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H), 6.48 (d, *J* = 8.3 Hz, 2H), 5.12 (s, 2H), 4.46 (s, 2H), 2.79 (s, 3H), 2.42 (s, 3H), 2.36 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.44, 172.23, 146.59, 145.72, 134.23, 129.97, 129.70, 128.88, 126.74, 112.65, 63.26, 58.73, 39.27, 25.52, 21.68, 20.21. HRMS (ESI) calcd. for $C_{20}H_{25}N_2O_4S$ $[M+H]^+$ 389.1530, found 389.1539.

***N*-acetyl-2-((4-bromophenyl)(methyl)amino)-*N*-(tosylmethyl) acetamide (5c)**, white solid, 71 mg, 52% yield. m.p. 126–128°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.6 Hz, 2H), 5.20 (s, 2H), 4.59 (s, 2H), 2.88 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.75, 173.29, 149.23, 147.30, 135.75, 133.22, 131.47, 130.24, 115.38, 110.83, 64.88, 59.95, 40.53, 26.91, 23.13. HRMS (ESI) calcd. for $C_{19}H_{22}N_2O_4SBr$ $[M+H]^+$ 453.0478, found 453.0490.

2-(methyl(phenyl)amino)-*N*-(tosylmethyl)acetamide (5d), white solid, 61 mg, 61% yield. m.p. 114–116°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.9 Hz, 2H), 7.44 – 7.17 (m, 5H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 2H), 4.71 (d, *J* = 6.9 Hz, 2H), 3.78 (s, 2H), 3.02 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.66, 150.45, 146.88, 135.38, 131.33, 130.86, 130.22, 121.00, 120.67, 114.91, 61.34, 59.92, 41.45, 23.14. HRMS (ESI) calcd. for $C_{17}H_{21}N_2O_3S$ $[M+H]^+$ 333.1267, found 333.1279.

2-(methyl(p-tolyl)amino)-*N*-(tosylmethyl)acetamide (5e), white solid, 51 mg, 49% yield. m.p. 132–134°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.8 Hz, 2H), 7.42 (s, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 4.72 (d, *J* = 6.7 Hz, 2H), 3.73 (s, 2H), 2.98 (s, 3H), 2.49 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.84, 148.43, 146.85, 135.40, 131.35, 131.31, 130.24, 130.15, 115.27, 61.34, 60.27, 41.76, 23.14, 21.69. HRMS (ESI) calcd. for $C_{18}H_{23}N_2O_3S$ $[M+H]^+$ 347.1424, found 347.1437.

2-((4-bromophenyl)(methyl)amino)-*N*-(tosylmethyl)acetamide (5f), white solid, 68 mg, 55% yield. m.p. 148–150°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.31 (m, 4H), 7.29 – 7.20 (m, 1H), 6.55 (d, *J* = 8.8 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 2H), 3.77 (s, 2H), 3.00 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.18, 149.40, 147.00 135.28, 133.56, 131.36, 130.13, 116.42, 112.79, 61.32, 59.65, 41.57, 23.16. HRMS (ESI) calcd. for $C_{17}H_{20}N_2O_3SBr$ $[M+H]^+$ 411.0373, found 411.0385.

***N*-acetyl-2-(ethyl(phenyl)amino)-*N*-(tosylmethyl)acetamide (5g)**, white solid, 17 mg, 15% yield. m.p. 98–100°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 7.7 Hz, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 2H), 5.24 (s, 2H), 4.54 (s, 2H), 3.30 (q, *J* = 7.1 Hz, 2H), 2.50 (s, 3H), 2.45 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.15, 169.55, 144.89, 143.06, 131.57, 127.29, 126.51, 126.18, 114.62, 109.79, 60.68, 53.58, 43.35, 22.79, 19.02, 9.70. HRMS (ESI) calcd. for $C_{20}H_{25}N_2O_4S$ $[M+H]^+$ 389.1530 found 389.1544.

2-(ethyl(phenyl)amino)-*N*-(tosylmethyl)acetamide (5h), white solid, 11 mg, 11% yield. m.p. 106–108°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.28 (m, 5H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 2H), 4.69 (d, *J* = 6.9 Hz, 2H), 3.78 (s, 2H), 3.45 (q, *J* = 7.0 Hz, 2H), 2.49 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.42, 147.38, 145.39, 133.90, 129.88, 129.52, 128.75, 118.92, 113.71, 59.87, 55.36, 46.45, 21.72, 11.49.HRMS (ESI) calcd. for $C_{18}H_{23}N_2O_3S$ $[M+H]^+$ 347.1424, found 347.1436.

Acknowledgements

This project is supported by the National Natural Science Foundation of China (grants 81602966, 81530098) and the Province Natural Science Foundation of Jiangsu (BK20160759), the National Major Scientific and Technological Special Project for "Significant New Drugs Development" (2015ZX09501001) and the Fundamental Research Funds for the Central Universities (2016ZPY013).

Keywords: MCRs • Oxidative Ugi reaction• DEAD • Metal-free • Oxidation

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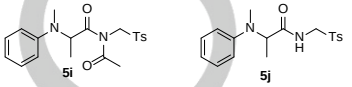
[11] The reaction solution changed into dark brown; while the one employed succinic acid or glutaric acid was light yellow and slightly cloudy.

[12] The regioisomer of **5g** and **5h** were not observed.



[13] When we employed the *N*,*N*-dimethylcyclohexylamine as the substrate, a highly nonideal mixture was observed by the thin-layer chromate graphy. After DEAD was dropwise added, the yellow color of DEAD faded away, which indicated the nucleophilic addition between amine and DEAD might be almost complete. While the corresponding nitrilium ion derived from the trialkyl amine could not be trapped by TosMIC in the Ugi reaction. When *N*-benzoyl 1,2,3,4-tetrahydroisoquinoline was used, however, the reaction did not proceed and no desired product was observed. We supposed that the amide nitrogen was not capable of carrying a nucleophilic attack on DEAD.

[14] The ^{18}O-labled succinic acid was pre-prepared by the hydrolysis of succinyl chloride with $H_2{}^{18}O$. For more details, see the SI.

[15] Compound **3a** was tested to be steady in the DCM solution of AcOH. For more details, see the SI.

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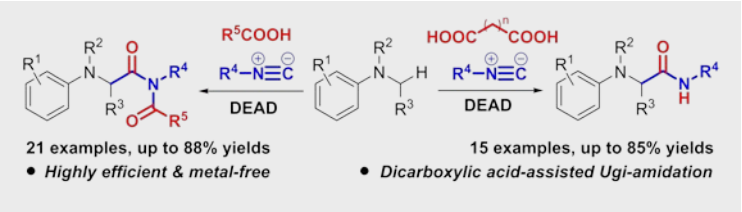

Utilize mono- or dicarboxylic acids? α-Amino imides or amides could be respectively obtained through this novel DEAD-promoted oxidative Ugi-type reaction. This metal-free transformation features high efficiency and good tolerance with diverse functional groups. Mechanistic studies indicated the dicarboxylic acids may readily undergo an intramolecular annulation, instead of the Mumm rearrangement, affording the amides with one molecule of anhydride released.

Ugi-type reaction *

Jiankun Wang, Yilin Sun, Guangji Wang, and Le Zhen**

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Novel DEAD-Promoted Oxidative Ugi-Type Reaction Including an Unprecedented Ugi-Amidation Assisted by Dicarboxylic Acids