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Direct C-H Bond Imidation with Benzoyl Peroxide as Both Mild Oxidant and Reagent

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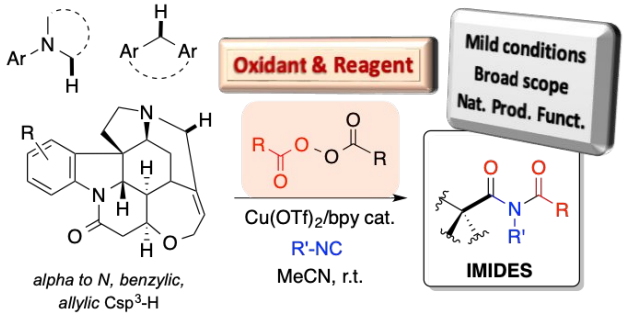


Abstract

A simple and mild Cu-catalyzed oxidative three-component oxidative Ugi-type method for the synthesis of a variety of substituted imides has been developed. In this direct imidation approach, benzoyl peroxide serves as both the oxidant and carboxylate source, allowing not only the functionalization of C(sp^3)-H bonds in alpha position to an amine, but also benzylic substrates. This procedure presents a wide substrate-type and functional group tolerance. Moreover, the mildness of the method permitted to extend its applicability to the late stage functionalization of complex natural products such as the alkaloids Brucine and Strychnine, leading to interesting highly functionalized imide derivatives. Based on experimental and computational studies, a plausible mechanism has been proposed.

Introduction

Imides are an important class of compounds present in natural products and with a wide application spectrum in the polymer, agrochemical and pharmaceutical industry.[1] Although they are structurally related to anhydrides, imides are more resistant toward hydrolysis, which makes them highly interesting for the development of new drug targets less susceptible to fast biodegradation (Figure 1). Thus, besides the more acknowledged cyclic imides, such as Lenalidomide (**I**)[2] or Amonafine (**II**)[3] with anti-cancer properties, acyclic imide-containing compounds have recently awakened high interest due their rich potential in medical applications.[1,4] In particular, they present interesting activities as antibiotic (e.g. natural product Fumaramidmycin) (**III**)),[5] anti-cancer (e.g. PI3K inhibitor **IV**)[6] or pulmonary hypertension treatment (e.g. endothelin antagonist **V**)[7] agents.

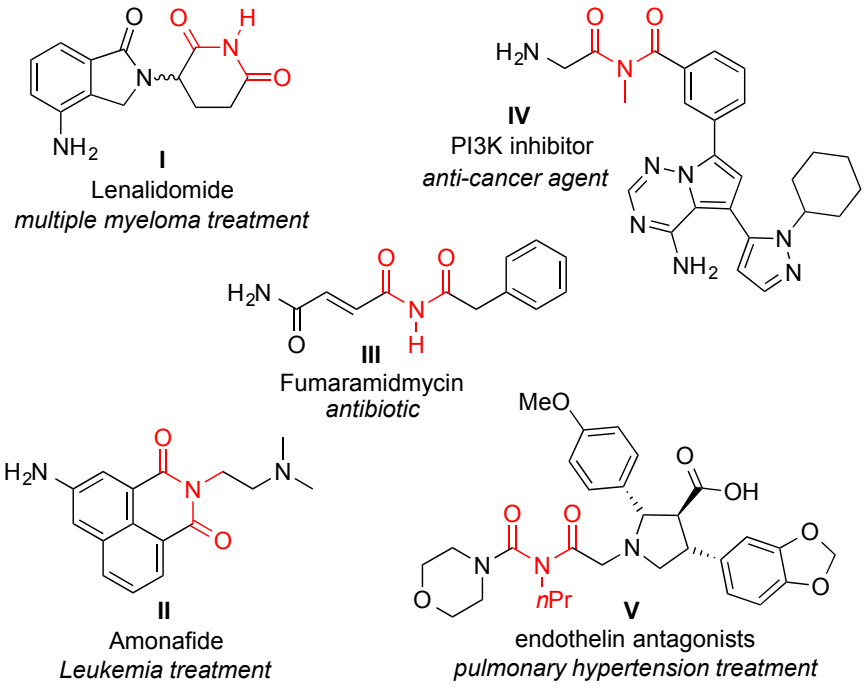
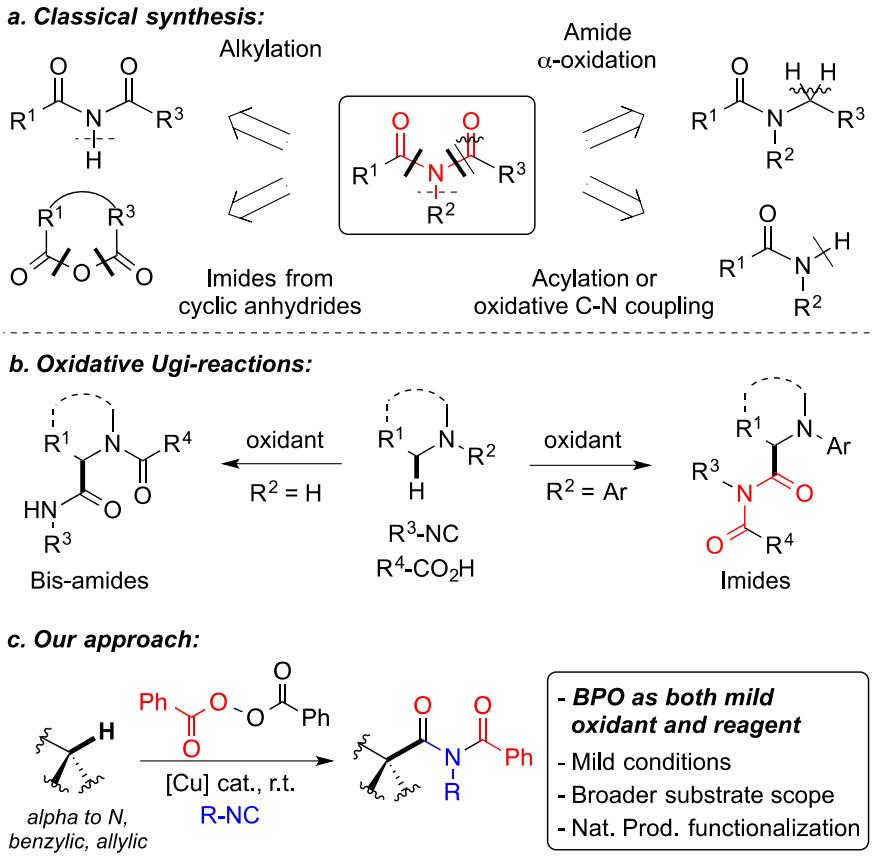


Figure 1. Selected representative bioactive imides.

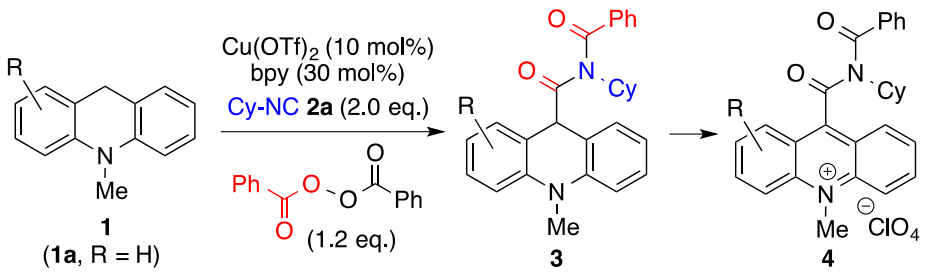
Considering the high applicability of imides, several approaches for their synthesis, such as by N-alkylation, reaction of amines with the corresponding cyclic imides, amide α-oxidation, and *N*-acylation or C-N oxidative coupling of amides, have been developed (Scheme 1, a).[8] Another important approach relies on the variant of the Ugi multicomponent reaction with secondary amines.[9] However, new straightforward methods based on C-H bond functionalization of readily available

substrates are still highly desirable.[10] In this regard, the oxidative Ugi-type reaction between amines, isocyanides and carboxylic acids has been recently introduced as a powerful alternative (Scheme 1, b).[11] Nevertheless, the methods are restricted to amine substrates with activated α-C-H bonds, leading to bis-amides[11] or imides[111] depending on the substitution at the nitrogen atom.



Scheme 1. Synthesis of imides and the oxidative Ugi-type approach.

Continuing our research program on mild, selective oxidative C-H functionalization,[12] and aiming at overcoming some of the current restrains, we have recently developed a method, in which benzylic substrates such as acridanes **1** could now be imidated (Scheme 2).[13] Thus, we have established an original approach for the preparation of an innovative family of acridinium photocatalysts **3** based on a Cu-catalyzed oxidative Ugi-type strategy using benzoyl peroxide (BPO) as key step.



Scheme 2. Oxidative Ugi-type conditions for the synthesis of acridinium photocatalysts.

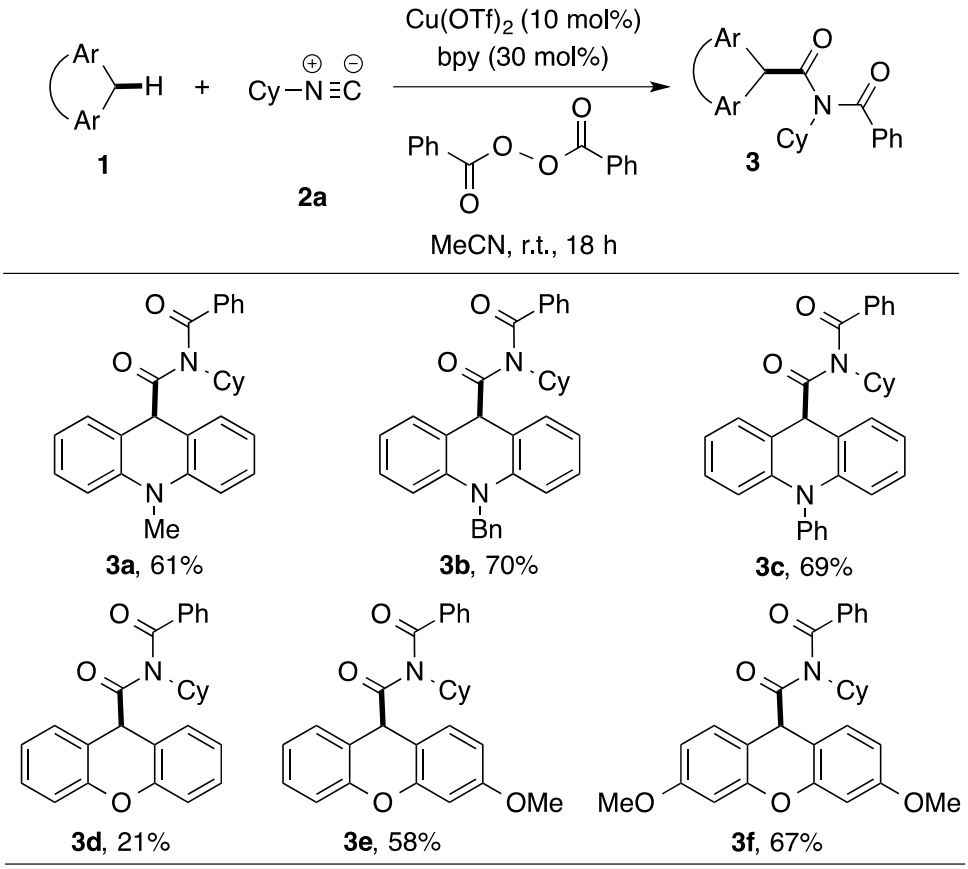
Herein, we present the applicability, scope and mechanism of our novel approach using benzoyl peroxide as both mild oxidant and carboxylate reagent in oxidative Ugi-type reactions (Scheme 1, c). This mild and robust procedure allows not only the functionalization of classical substrates with C-H bonds in alpha position to a N-atom, but also benzylic derivatives, as well as complex alkaloid natural products.

Results and Discussion

To test the feasibility of the method for a broad substrate scope, we decided to start our study with the barely explored dibenzylic substrates in oxidative Ugi-reactions (Table 1). Following the initial optimized conditions for N-methyl acridane (**1a**),[13] several acridanes and xanthenes were subjected to the oxidative Ugi-reaction with cyclohexyl isocynanide (**2a**). Thus, the reactions were carried out using 10 mol% of $Cu(OTf)_2$ as catalyst and 30 mol% of the 2,2'-bipyridine (bpy) ligand, in combination with 1.2 equivalents of BPO and 2.0 equivalents of the isocyanide reagent at room temperature. The reaction tolerated well various N-alkylic (**1a**, Me and **1b**, Bn) and arylic (**1c**, Ph) substituted acridanes, providing to the corresponding imides **3a-c** in good yields (66-70%). It is worthy to note that in the case of the N-alkyl substituted derivatives **1a** and **1b**, a selective addition to the benzylic position occurred, without any substitution at the α-alkyl group of the amine. Similarly, the reaction of xanthene (**1d**) with **2a** delivered the desired imide **3d**, however the yield was significantly lower compared to its parent nitrogen-derivative **1a** (21% vs. 66%). This could be explained due to the fact that acridanes are electron richer heterocycles than xanthenes. Therefore,

methoxy substituted derivatives were next reacted under the standard conditions, leading to the corresponding imides **3e** and **3f** in good yields (58 and 67%, respectively).

Table 1. Reaction with dibenzylic substrates[a),b)]

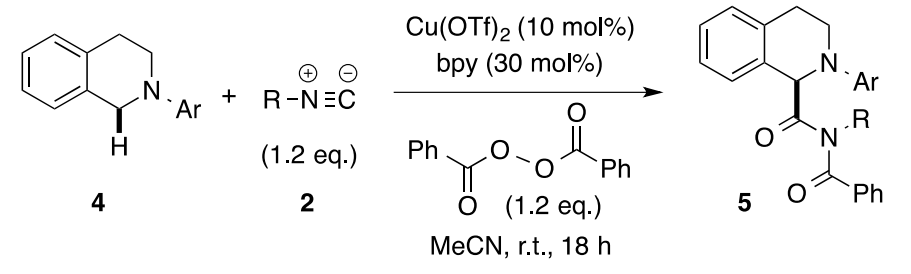


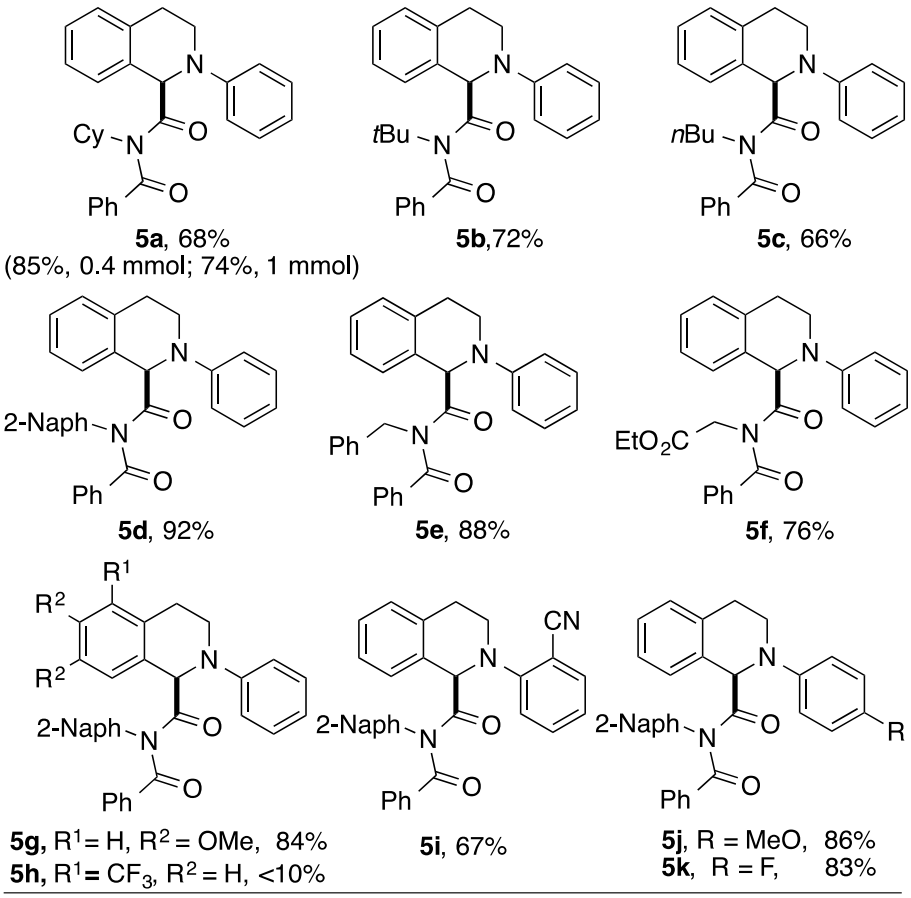
[a)] Substrate **1** (0.2 mmol, 1.0 eq.), isocyanide **2a** (2.0 eq.), benzoyl peroxide (1.2 equiv.), $Cu(OTf)_2$ (10 mol%) and 2,2'-bipyridyl (30 mol%) in MeCN (0.1 M) at r.t. for 18 h in a pressure schlenk tube under N_2 atmosphere. [b)] Isolated yields.

Encouraged by these results, we continued our investigations with N-aryl tetrahydroisoquinolines (THIQs) as typical substrates in oxidative Csp^3-H functionalization (Table 2).[10] We found out that the reaction of this type of cyclic heterocycles was highly effective, allowing reducing the amount of the isocyanide reagent from 2.0 to 1.2. equivalents and the easy scaling up of the reaction of the prototypical N-phenyl THIQ **4a** with **2a** from 0.2 and 0.4 to 1 mmol (**5a**, 68, 85 and 74%, respectively). Moreover, in this case other isocyanide with alkylic (**2b**, *t*Bu and **2c**, *n*Bu), arylic (**2d**,

2-naphtyl), benzylic (**2e**) or ethylacetate rests (**2f**) provided the corresponding imides **5b-f** in good to excellent yields (66-92%). Finally, the effect on the reactivity of various substituents at the THIQ core or N-aryl group were explored (**5g-k**). Electron rich THIQs provided the products in excellent yields (**5g**), while electron deficient derivatives were not efficiently enrolled in the reaction (e.g. **4h**). Conversely, both electron donating (OMe) and withdrawing (CN, F) groups at the N-aryl moiety were well tolerated, giving consistent high yields.

Table 2. Oxidative Ugi-reaction with THIQs **4**[a),b)]

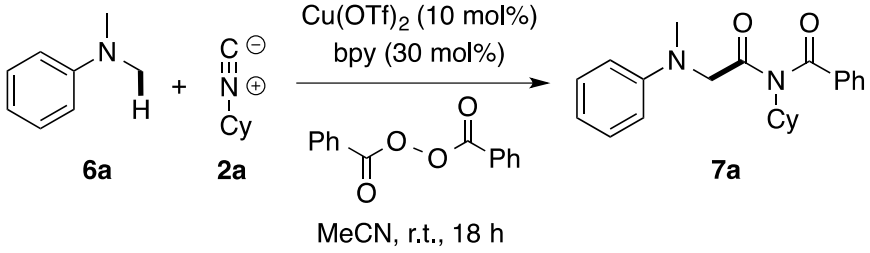




[a)] THIQ **4** (0.2 – 1.0 mmol, 1.0 eq.), **2** (1.2 eq.), benzoyl peroxide (1.2 eq.), $Cu(OTf)_2$ (10 mol%) and 2,2'-bipyridyl (30 mol%) in MeCN (0.1 M) at r.t. for 18 h in a pressure schlenk tube under N_2 atmosphere. [b)] Isolated yield.

The methodology was next extended to N,N-dimethyl anilines. It turned out that this type of compounds reacts sluggish under the conditions given above for THIQs. Therefore, a short re-optimization of the reaction of N,N-dimethyl aniline (**6a**) with isocyanide **2a** was first carried out (Table 3). While an excess of the isocyanide was crucial (entries 1-5), an increase of the amount of peroxide (entry 6) or the use of higher concentrations (from 0.1 to 0.2 and 0.4 M, entries 7 and 8) did not improve the yield. As a result, the best yield (entry 4, 50%) was obtained when employing 2 equivalents of **2a**, as in the initial conditions for the benzylic derivatives (see Table 1).

Table 3. Re-optimization of the reaction for N,N-dimethyl aniline[a)]



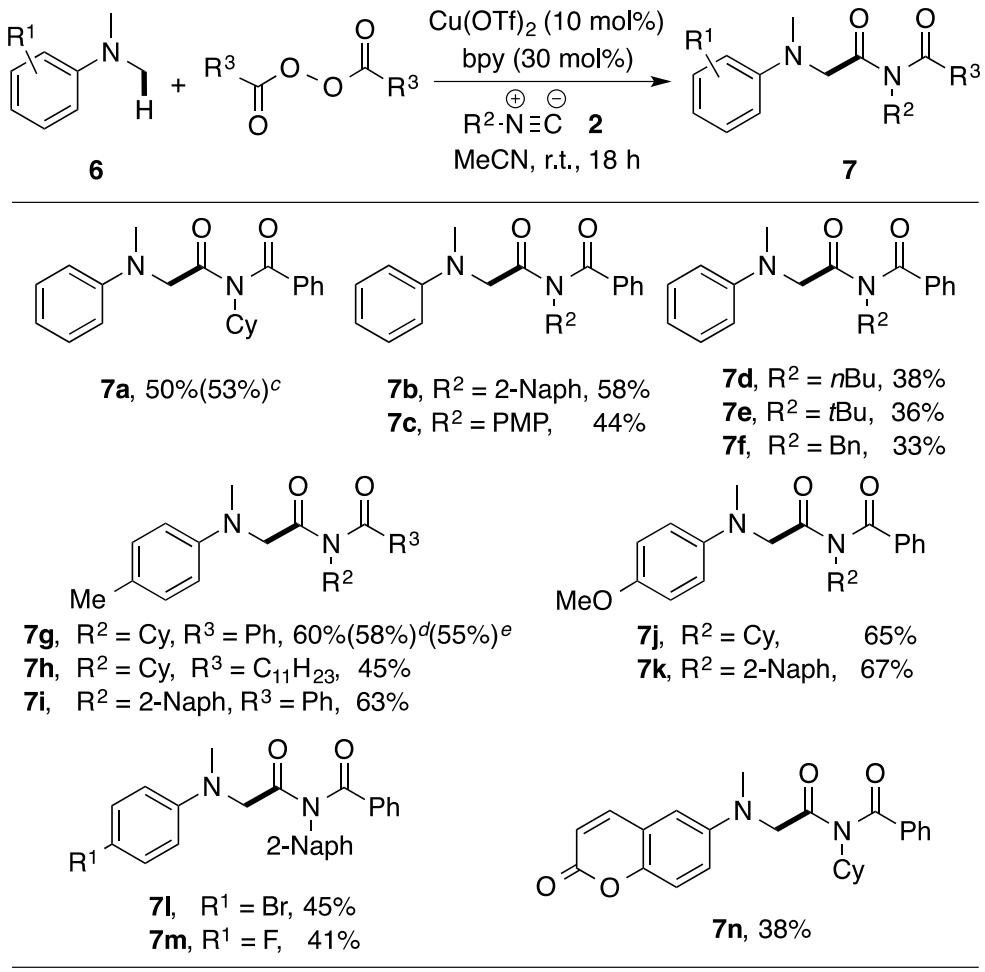
Entry	**2a** (eq.)	BPO (eq.)	[M]	Yield (%)[b)]
1	1.2	1.2	0.1	36
2	1.6	1.2	0.1	42
3	1.8	1.2	0.1	45
4	**2.0**	**1.2**	**0.1**	**50**
5	2.4	1.2	0.1	47
6	2.0	1.4	0.1	46
7	2.0	1.2	0.2	35
8	2.0	1.2	0.4	32

[a)] N,N-Dimethyl aniline (**6a**) (0.2 mmol, 1.0 eq.), isocyanide **2a**, benzoyl peroxide, $Cu(OTf)_2$ (10 mol%) and 2,2'-bipyridyl (30 mol%) in MeCN (0.1 M) at r.t. for 18 h in a pressure schlenk tube under N_2 atmosphere. [b)] Isolated yield.

The scope of the reaction with anilines **6** was then investigated (Table 4). Although in systematically inferior conversions than the THIQs **4**, N,N-dimethyl anilines **6** also did react with a variety of aryl and alkyl-substituted isocyanides **2** to form the imides **7b-f**. However, the best results were obtained with the cyclohexyl and 2-naphthyl isocyanides (50 and 59% yield; **7a** and **7b**, respectively). Consequently, they were next employed in the reaction with differently para-substituted anilines. The

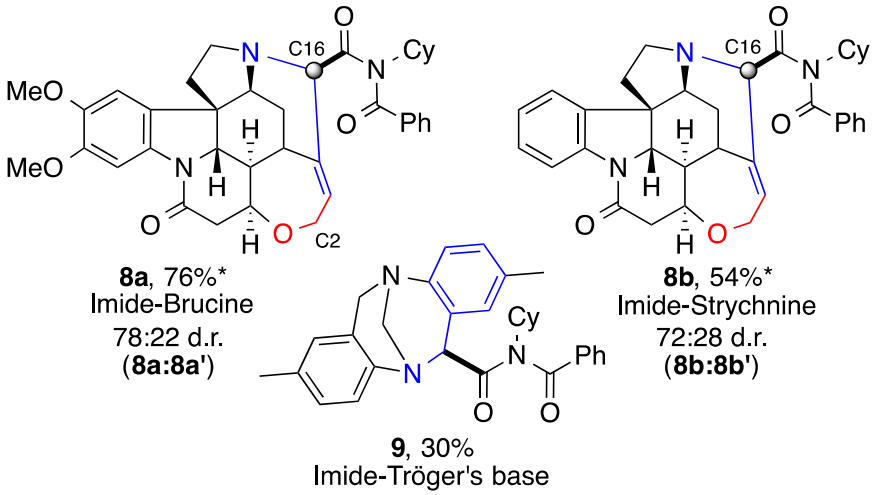
4-methyl and methoxy derivatives **7g-k** were obtained in good yields (60-67%), while the anilines bearing halogen atoms (such as bromo or fluoro) gave the products **7l-m** in moderate yields. It is also important to note that not only benzoyl peroxide but also other substituted derivatives such as lauroyl peroxide could be used as both oxidant and carboxylic reagent, providing the imide **7h** with a C11-alkylic chain product in 45% yield. Moreover, more demanding bio-derivatives such as the N,N-dimethyl coumarin **6n** could also be enrolled, forming the imide **7n** in a 38% yield. Furthermore, the reaction with **6a** and **6b** as representative substrates could be efficiently carried out up to a gram-scale (**6b**, 7 mmol), leading to **7a** and **7g** in similar good yields.

Table 4. Scope of the reaction with N,N-dimethyl anilines **6**[a),b)]



[a)] N,N-Dimethyl aniline **6** (0.2 mmol, 1.0 eq.), isocyanide **2** (2.0 eq.), peroxide (1.2 equiv.), $Cu(OTf)_2$ (10 mol%) and 2,2'-bipyridyl (30 mol%) in MeCN (0.1 M) at r.t. for 18 h in a pressure schlenk tube under N_2 atmosphere. [b)] Isolated yield. [c)] 0.5 mmol scale. [d)] 3 mmol scale. [e)] 7 mmol scale.

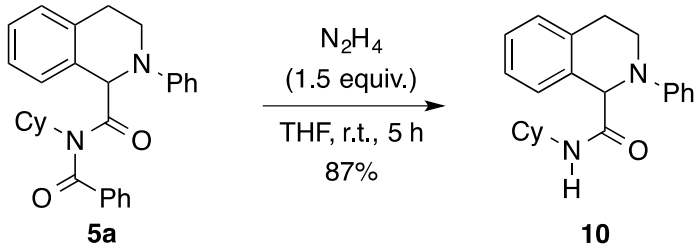
Finally, we challenged our method with more complex molecules such as the natural products brucine and strychnine, possessing two reactive allylic C-H bonds in alpha position to nitrogen (blue) or oxygen (red) (Figure 2). We were delighted to observe the imidation of these alkaloids in good to high yields (54-76%) and in a high regioselectivity towards the allylic position in alpha to the N-atom (**8** and **8'**) vs. to the O-atom[14] (**8**$^{\#}$) (e.g. **8a:8a':8a**$^{\#}$ in a 3.5:1.0:1.2 ratio, and with a 78:22 d.r. for **8a/8a'**, see Exp. Sect. and S.I.). Furthermore, the Tröger's base selectively reacted as well, delivering the corresponding mono-imide **9** in a moderate 30% yield.



*As a mixture of C16/C2 diastereo- and regioisomers (see Exp. Sect. and S.I.)

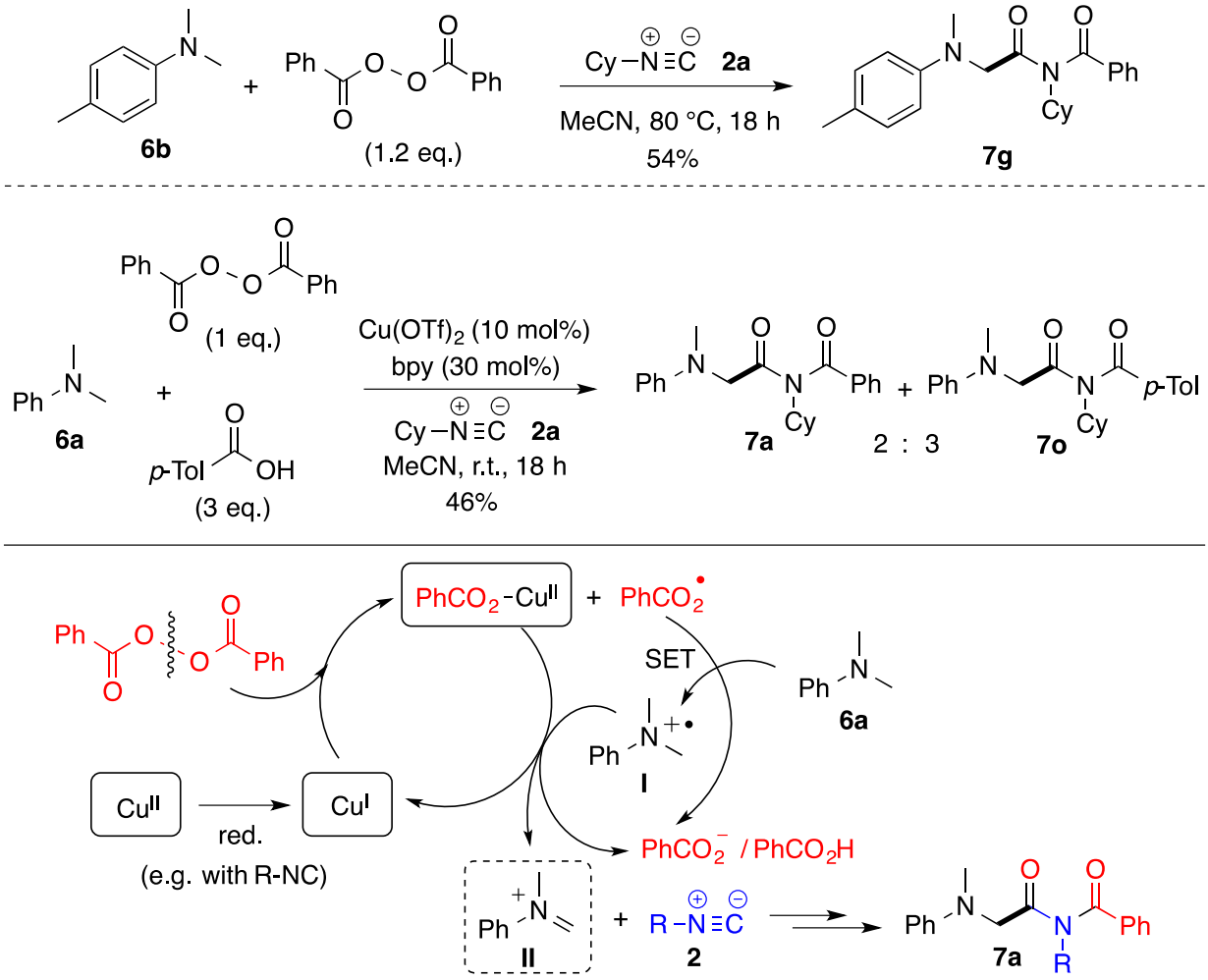
Figure 2. C-H bond imidation of natural products.

Moreover, we probed that the imide unit could be transformed into the corresponding amide by acyl-group elimination upon treatment with hydrazine. This was illustrated with the model THIQ-imide product **5a**, which undergoes a mild benzoyl deprotection leading to the amide **10** in a good 87% yield (Scheme 3).



Scheme 3. Representative N-benzoyl deprotection of the imide group to the corresponding amide.

In order to shed some light into the mechanism of this oxidative Ugi-type reaction with benzoyl peroxide, the role of the Cu-catalyst was studied. Thus, the reaction of **6b** in the absence of the $CuOTf_2$/bpy catalytic system under heating conditions (80 °C) for promoting the thermal homolytic cleavage of the BPO oxidant required for the first step led to a 54% yield of the Ugi-product **7g**.[15] This shows that the Cu-catalyst only plays a key role in the activation of the oxidant. Moreover, a competition experiment with **6a** and 1 equivalent of BPO in the presence of 3 equivalents of *p*-toluic acid was performed (Scheme 4). Then, the products **7a** and **7o** were obtained in a statistical 2:3 ratio in a 46% yield, which indicates the in situ formation of 2 equivalents of benzoate from BPO during the course of the reaction. Based on these experimental observations and previous reports,[10,12b,16] the initial oxidation of the substrate should proceed through a Cu^{I}-catalyzed homolytic cleavage of BPO to benzoyl radical, which upon a single electron transfer (SET) forms the radical cation **I** (or corresponding benzylic radical for substrates **1**) and one equivalent of benzoate. Subsequently, **I** suffers a second oxidation with the generated Cu^{II}-carboxylate to provide the iminium intermediate **II** that further reacts with the isocyanide and free carboxylate.



Scheme 4. Mechanistic studies and proposed first-step Cu-catalyzed C-H oxidation mechanism.

Assuming the in situ formation of the cationic iminium intermediates and carboxylate as described above, a density functional theory (DFT) mechanistic study was next carried out. The reaction profile with N,N-dimethyl aniline (**6a**) as model substrate was analyzed computationally starting with the iminium intermediate **II** as initial point (Figure 3). The calculations were performed at DFT level of theory using the M06-2X functional[17] with the 6-31++G(d,p)[18] basis set within the Gaussian 09 software.[19] The relative Gibbs free energies were calculated including entropic effects at 298.15K and a 1 M concentration with corrections for low vibration modes (<100 wavenumbers)[20] using the python code[21] on the top of the gas phase optimized geometries. The solvation effects of acetonitrile were also calculated at the BP86/TZVP[22] level of theory with the COSMOtherm program,[23] and the solvation energies were added to the Gibbs free energies. The connections between minima (all

positive frequencies) and transition states (one negative eigenvalue of the Hessian) on the Gibbs free energy surfaces were assured by intrinsic reaction coordinate calculations. The computational study unveiled a mechanism that proceeds via two consecutive steps according to the equation:

$$A + B + C \longrightarrow (ABC) \longrightarrow intermediate \overset{rearrangement}{\Longleftrightarrow} product\ \mathbf{7}$$

Therefore, the Gibbs free energy profiles were constructed for the reaction between three molecules: the iminium intermediate **II** (**A**) formed from **6a** upon a first oxidation with BPO, methylisocyanide (**B**) and benzoate (**C**). We considered both a i) concerted or a ii) stepwise reaction mechanisms involving the calculated intermediate **III** formed from the three components (**A**+**B**+**C**), which undergoes a further Mumm-rearrangement[24] leading to the product **7a**. Figure T1 shows the computed free energy profile for the most probable concerted mechanism, which presents a barrier of 5.4 kcal mol^{-1} (**TS1**), leading to a notably more stable intermediate **III** (-42.2 kcal mol^{-1}) (see S.I. for all found pathways). The next step involves a small barrier for the rotation along the N-C-C-N and C-C-O-C dihedral angles in **TS2** (approx. 9 kcal mol^{-1}). Finally, the product **7a** is formed in a concerted step via a Mumm-type rearrangement through a barrier (**TS3**) at -15.6 kcal mol^{-1} lower than the reference point (see S.I. for details).

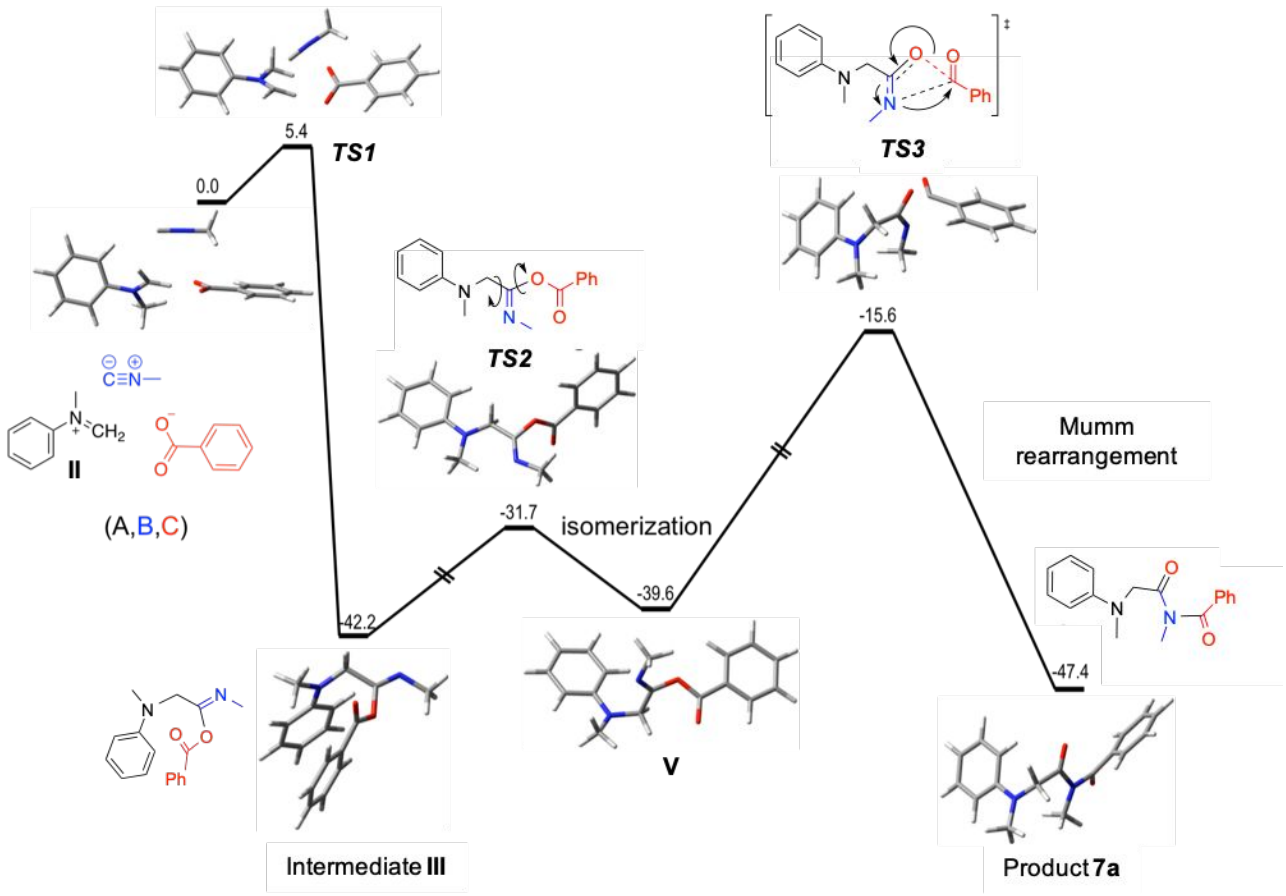


Figure 3. The free reaction pathway calculated at DFT-M06-2X/6-31G(d,p) level of theory for the reaction **6a**. The relative Gibbs free energies with corrections for low frequencies and solvation effects of acetonitrile are in kcal mol^{-1}.

Conclusion

In summary, we have developed a general Cu-catalyzed oxidative Ugi-type three-component reaction for the synthesis of valuable imides using benzoyl peroxide as mild oxidant and carboxylate source. Besides the more classical substrates employed in oxidative C(sp^3)-H functionalization such as tertiary amines like tetrahydroisoquinolines or N,N-dimethylanilines, this benign method also allows to enrol dibenzylic substrates to generate valuable imide-substituted compounds. It was also shown that the procedure could be extended to other acyl peroxides such as lauroyl peroxide, although the benzoyl substitution provided the best results. Moreover, the mildness of the process permitted to extend its applicability to the late stage functionalization of complex natural products such as the alkaloids Brucine and Strychnine, leading to demanding highly functionalized imide derivatives.

Based on experimental and computational studies, a plausible mechanism has been proposed, in which three weakly interacting substrate molecules form in a concerted manner a covalently bonded intermediate that undergoes a further Mumm-type rearrangement leading to the final imide product.

Experimental Section

General Experimental Methods

^{1}H and ^{13}C spectra were recorded in $CDCl_3$ (reference signals:[25] ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm, $CDCl_3$) on a Bruker ARX-300, a Bruker ARX-400 or a Jeol JNM-ECS 400 MHz. Chemical shifts (δ) are given in ppm and spin-spin coupling constants (*J*) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F254 and I_2 served as staining agent. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). Exact masses (HRMS) were recorded on an Agilent Q-TOF 6540 UHD spectrometer using electrospray ionization (ESI) techniques or on an Finnigan MAT SSQ 710 A spectrometer using electron impact (EI) techniques. The starting materials acridanes[12b] and xanthenes **1**,[12b,26] N-aryl THIQs **4**[27] and N,N-dimethyl anilines **6**[28] were prepared following known literature procedures. CH_3CN was distilled over CaH_2. Commercially available benzoyl peroxide contains the 30% w/w of water. In order to remove the water, the oxidant was dissolved in ethyl acetate and the obtained solution was washed 3 times with brine. The obtained organic phase was dried under $MgSO_4$, filtered, the solvent evaporated and the obtained white solid dried under vacuum. Other solvents and commercially available reagents were used without further purification.

General procedure for the oxidative Ugi-reaction: In an oven-dried screw cap schlenk under nitrogen atmosphere, anhydrous $Cu(OTf)_2$ (7.2 mg, 0.02 mmol, 10 mmol%) (note: avoid moisture, copper(II) triflate is slightly hydroscopic. The catalyst was pre-dried at 50 °C for several hours under high vacuum), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%) and the substrate (0.20 mmol, 1.0 equiv.) were added following this order. The mixture was dissolved in acetonitrile (0.1 M), and the isocyanide **2** (2.0 equiv.; or 1.2 equiv. for THIQs) and benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2

equiv.) were then added. The obtained mixture was stirred at room temperature for 18 h. After evaporating the solvent, the crude product was purified by flash column chromatography using a hexane/ethyl acetate mixture as eluent.

***N*-benzoyl-N-cyclohexyl-10-methyl-acridane-9-carboxamide (3a):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a white solid (51.8 mg, 0.122 mmol, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.73 (m, 2H), 7.70 – 7.64 (m, 1H), 7.59 – 7.52 (m, 2H), 7.26 – 7.20 (m, 2H), 6.96 – 6.91 (m, 2H), 6.88 – 6.83 (m, 2H), 6.76 – 6.71 (m, 2H), 4.94 (s, 1H), 4.02 (tt, *J* = 12.0, 3.6 Hz, 1H), 3.40 (s, 3H), 1.80 – 1.67 (m, 2H), 1.65 – 1.56 (m, 2H), 1.52 – 1.42 (m, 1H), 1.32 – 1.25 (m, 2H), 1.16 – 0.96 (m, 3H). The spectroscopic data are in accordance with the literature.[13]

***N*-benzoyl-N-cyclohexyl-10-benzyl-xanthene-9-carboxamide (3b):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a white solid (70.1 mg, 0.140 mmol, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.75 (m, 2H), 7.75 – 7.67 (m, 1H), 7.64 – 7.55 (m, 2H), 7.33 – 7.21 (m, 3H), 7.20 – 7.15 (m, 2H), 7.14 – 7.05 (m, 2H), 6.89 – 6.82 (m, 2H), 6.79 – 6.73 (m, 4H), 5.19 (s, 2H), 5.01 (s, 1H), 4.06 (tt, *J* = 12.1, 3.5 Hz, 1H),1.82 – 1.69 (m, 2H), 1.67 – 1.60 (m, 2H), 1.56 – 1.47 (m, 1H), 1.34 – 1.26 (m, 2H), 1.17 – 0.99 (m, 3H). The spectroscopic data are in accordance with the literature.[13]

***N*-benzoyl-N-cyclohexyl-10-phenyl-acridane-9-carboxamide (3c):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as slightly yellow solid (68.1 mg, 0.138 mmol, 69 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.77 (m, 2H), 7.75 – 7.65 (m, 1H), 7.63 – 7.54 (m, 4H), 7.53 – 7.45 (m, 1H), 7.42 – 7.35 (m, 2H), 7.03 – 6.95 (m, 2H), 6.85 – 6.76 (m, 4H), 6.34 (d, *J* = 8.2 Hz, 2H), 5.09 (s, 1H), 4.10 (tt, *J* = 11.9, 3.5 Hz, 1H), 1.84 – 1.73 (m, 2H), 1.66 – 1.59 (m, 2H), 1.55 – 1.46 (m, 1H), 1.35 – 1.27 (m, 2H), 1.18 – 0.99 (m, 3H). The spectroscopic data are in accordance with the literature.[13]

***N*-Benzoyl-*N*-cyclohexyl-xanthene-9-carboxamide (3d):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a white solid

(17 mg, 0.04 mmol, 21 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.81 (m, 2H), 7.72 – 7.65 (m, 1H), 7.61 – 7.54 (m, 2H), 7.27 – 7.22 (m, 2H), 7.14 – 7.11 (m, 2H), 7.04 – 6.98 (m, 2H), 6.95 – 6.91 (m, 2H), 4.98 (s, 1H), 4.05 (tt, *J* = 12.0, 3.6 Hz, 1H), 1.86 – 1.71 (m, 3H), 1.66 – 1.59 (m, 2H), 1.45 – 1.37 (m, 2H), 1.13 – 0.96 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.0, 175.3, 152.3, 133.5, 129.6, 129.5, 129.2 128.4, 123.3, 119.6, 117.3, 116.8, 59.8, 49.1, 29.8, 26.3, 25.2. HRMS (ESI-TOF): m/z [M+H]$^+$ Calcd for $C_{27}H_{26}NO_3$ 412.1907; found 412.1912.

***N*-Benzoyl-*N*-cyclohexyl-3methoxy-xanthene-9-carboxamide (3e):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a white solid (53 mg, 0.12 mmol, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 2H), 7.73 – 7.66 (m, 1H), 7.62 – 7.55 (m, 2H), 7.28 – 7.22 (m, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 7.03 – 6.98 (m, 1H), 6.95 – 6.91 (m, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.92 (s, 1H), 4.07 (tt, *J* = 12.1, 3.1 Hz, 1H), 3.80 (s, 3H), 1.88 – 1.74 (m, 2H), 1.70 – 1.61 (m, 2H), 1.54 – 1.41 (m, 3H), 1.18 – 0.99 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ176.3, 175.2, 160.3, 153.1, 152.1, 137.2, 133.5, 129.5, 129.4, 129.0, 128.9, 128.4, 123.2, 119.8, 119.7, 117.1, 111.7, 111.6, 110.2, 102.0, 59.6, 55.5, 48.4, 29.8, 26.2, 25.2. HRMS (ESI-TOF): m/z [M+H]$^+$ Calcd for $C_{28}H_{28}NO_4$ 442.2013; found 442.2022.

***N*-Benzoyl-*N*-cyclohexyl-3,6-dimethoxy-xanthene-9-carboxamide (3f):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 4:1) as a white solid (63 mg, 0.13 mmol, 67 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.76 (m, 2H), 7.72 – 7.65 (m, 1H), 7.63 – 7.50 (m, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 2.6 Hz, 2H), 6.60 (d, *J* = 2.5 Hz, 1H), 6.58 (d, *J* = 2.6 Hz, 1H), 4.84 (s, 1H), 4.07 (tt, *J* = 12.0, 3.6 Hz, 1H), 1.88 – 1.74 (m, 2H), 1.69 – 1.62 (m, 2H), 1.53 – 1.42 (m, 3H), 1.19 – 1.01 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.7, 175.3, 160.3, 153.0, 137.3, 133.5, 129.5, 129.5, 129.0, 111.91, 110.1, 102.0, 59.7, 55.6, 47.8, 29.9, 26.3, 25.2. HRMS (ESI-TOF): m/z [M+H]$^+$ Calcd for $C_{29}H_{30}NO_5$ 472.2118; found 472.2126.

***N*-Benzoyl-*N*-cyclohexyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (5a):** According to the general procedure, the title product was provided after flash column chromatography

(hexane/EtOAc, 8:2) as an orange solid (60 mg, 0.136 mmol, 68 %). The scale-up reactions using 0.4 mmol (84 mg) and 1 mmol (209 mg) of **4a**, led to the product in 85% (149 mg, 0.34 mmol) and 74% (325 mg, 0.74 mmol), respectively. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.30 – 7.22 (m, 2H), 7.18 – 7.05 (m, 4H), 6.95 – 6.85 (m, 3H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.32 (d, *J* = 8.0 Hz, 2H), 4.93 (s, 1H), 4.10 (tt, *J* = 11.7, 3.2 Hz, 1H), 3.63 – 3.46 (m, 1H), 3.22 (ddd, *J* = 13.9, 11.1, 4.6 Hz, 1H), 2.62 (ddd, *J* = 16.6, 11.1, 5.6 Hz, 1H), 2.48 (d, *J* = 15.1 Hz, 1H), 2.01 (qd, *J* = 12.1, 3.2 Hz, 1H), 1.84 – 1.57 (m, 5H), 1.49 (d, *J* = 11.5 Hz, 1H), 1.27 – 0.94 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.6, 171.5, 146.4, 135.0, 134.4, 132.4, 131.6, 130.1, 128.8, 128.7, 128.1, 127.5, 125.8, 120.7, 116.6, 61.1, 58.6, 44.6, 31.6, 29.2, 26.3, 25.4, 25.2. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{29}H_{31}N_2O_2$ 439.2380; found 439.2407.

***N*-Benzoyl-*N*-(*tert*-butyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (5b):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a yellow solid (120 mg, 0.29 mmol, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.48 (m, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.26 – 7.12 (m, 4H), 7.08 (td, *J* = 7.4, 1.2 Hz, 1H), 6.92 – 6.79 (m, 3H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.09 (d, *J* = 8.0 Hz, 2H), 4.97 (s, 1H), 3.30 – 3.20 (m, 1H), 3.17 – 3.03 (m, 1H), 2.53 (dd, *J* = 11.7, 5.6 Hz, 1H), 2.46 – 2.39 (m, 1H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.6, 170.5, 145.0, 136.3, 134.3, 132.5, 131.8, 130.5, 128.9, 128.8, 128.6, 128.0, 127.5, 125.8, 120.8, 116.7, 61.2, 59.2, 44.8, 28.7, 25.2. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{27}H_{29}N_2O_2$ 413.2224; found 413.2229.

***N*-Benzoyl-*N*-butyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (5c):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as an orange oil (107 mg, 0.26 mmol, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 3H), 7.39 – 7.36 (m, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.18 (m, 2H), 7.12 – 7.07 (m, 3H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.9 Hz, 2H), 5.67 (s, 1H), 3.74 – 3.59 (m, 3H), 3.56 – 3.42 (m, 1H), 2.85 – 2.72 (m, 2H), 1.63 – 1.42 (m, 2H), 1.24 (h, *J* = 7.4 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.4, 173.6, 147.7, 135.0, 134.3, 132.5, 132.2, 129.1, 128.8,

128.4, 127.7, 126.1, 120.1, 116.4, 61.2, 47.5, 44.7, 30.9, 26.2, 20.2, 13.7. HRMS (ESI-TOF): m/z [M + H]$^+$ Calcd for $C_{27}H_{29}N_2O_2$ 413.2224; found 413.2231.

***N*-Benzoyl-*N*-(naphthalene-2-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline-8-carboxamide (5d):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a colorless solid (179 mg, 0.37 mmol, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.9, 4.3 Hz, 2H), 7.56 – 7.52 (m, 1H), 7.44 – 7.39 (m, 3H), 7.36 – 7.29 (m, 2H), 7.29 – 7.22 (m, 2H), 7.22 – 7.16 (m, 2H), 7.12 (tt, *J* = 7.2, 4.3 Hz, 5H), 7.00 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.71 – 6.66 (m, 2H), 6.07 (s, 1H), 3.72 – 3.61 (m, 1H), 3.50 (dt, *J* = 12.3, 5.3 Hz, 1H), 2.82 (t, *J* = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.4, 171.7, 148.1, 136.6, 135.6, 133.8, 133.4, 132.4, 132.3, 132.2, 129.9, 129.3, 129.2, 128.9, 128.7, 128.3, 128.0, 127.8, 126.6, 126.4, 126.0, 125.4, 120.1, 116.4, 61.6, 44.9, 27.0. HRMS (ESI-TOF): m/z [M + H]$^+$ Calcd for $C_{33}H_{27}N_2O_2$ 483.2067; found 483.2074.

***N*-Benzoyl-*N*-benzyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (5e):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as an orange solid (156 mg, 0.35 mmol, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 5H), 7.16 – 7.08 (m, 7H), 7.06 – 7.01 (m, 2H), 6.99 (d, *J* = 7.4 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 8.5 Hz, 2H), 5.58 (s, 1H), 4.86 (d, *J* = 14.9 Hz, 1H), 4.74 (d, *J* = 14.9 Hz, 1H), 3.53 (dt, *J* = 13.0, 5.2 Hz, 1H), 3.34 (ddd, *J* = 13.0, 8.8, 5.5 Hz, 1H), 2.77 – 2.52 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.7, 173.6, 147.7, 137.1, 135.3, 134.5, 132.4, 132.1, 129.1, 129.0, 128.8, 128.7, 128.5, 128.4, 128.3, 127.8, 127.6, 126.2, 120.0, 116.1, 61.5, 50.7, 44.7, 26.1. HRMS (ESI-TOF): m/z [M + H]$^+$ Calcd for $C_{30}H_{27}N_2O_2$ 447.2067; found 447.2070.

Ethyl *N*-benzoyl-*N*-(2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonyl)glycinate (5f): According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a yellow solid (169 mg, 0.38 mmol, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H), 7.47 – 7.41 (m, 1H), 7.34 – 7.30 (m, 1H), 7.29 – 7.24 (m, 2H), 7.22 – 7.18 (m, 2H), 7.10 – 7.04 (m, 3H), 6.82 – 6.75 (m, 1H), 6.61 (d, *J* = 7.9 Hz, 2H), 5.65 (s, 1H), 4.43 (d, *J* =

17.2 Hz, 1H), 4.26 (d, *J* = 17.2 Hz, 1H), 4.14 (qd, *J* = 7.1, 2.5 Hz, 2H), 3.74 – 3.65 (m, 1H), 3.61 (ddd, *J* = 13.1, 8.6, 6.0 Hz, 1H), 2.80 – 2.73 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 175.7, 172.8, 168.6, 147.8, 135.2, 133.9, 132.7, 131.7, 129.2, 129.1, 128.9, 128.8, 128.5, 127.8, 126.1, 120.3, 116.5, 61.6, 61.3, 48.3, 45.0, 25.9, 14.2. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{27}H_{27}N_2O_4$ 443.1971; found 443.2003.

***N*-Benzoyl-6,7-dimethoxy-*N*-(naphthalen-2-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (5g):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a brown solid (185 mg, 0.34 mmol, 84 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.43 – 7.40 (m, 2H), 7.38 (s, 1H), 7.23 – 7.15 (m, 5H), 7.12 (s, 1H), 6.97 (s, 1H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 2H), 6.67 (s, 1H), 6.03 (s, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.72 – 3.66 (m, 1H), 3.59 – 3.52 (m, 1H), 2.80 (t, *J* = 5.7 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 176.4, 171.5, 148.7, 147.9, 147.6, 136.5, 133.6, 133.4, 132.3, 132.1, 130.0, 129.3, 129.2, 128.3, 127.9, 127.7, 126.6, 126.5, 125.8, 125.2, 123.8, 119.9, 116.3, 111.6, 111.3, 61.1, 55.9, 55.9, 45.2, 26.3. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{35}H_{31}N_2O_4$ 543.2284 ; found 543.2293.

***N*-benzoyl-2-(2-cyanophenyl)-*N*-cyclohexyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (5i):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a yellow solid (137 mg, 0.27 mmol, 67 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.9, 4.0 Hz, 2H), 7.64 (dt, *J* = 8.6, 1.8 Hz, 3H), 7.51 – 7.45 (m, 2H), 7.45 – 7.38 (m, 3H), 7.38 – 7.31 (m, 1H), 7.30 – 7.26 (m, 3H), 7.26 – 7.21 (m, 3H), 7.16 (dd, *J* = 5.3, 3.7 Hz, 1H), 6.96 (td, *J* = 7.6, 1.0 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.06 (s, 1H), 4.03 (dd, *J* = 7.8, 4.2 Hz, 2H), 2.86 – 2.72 (m, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 175.2, 173.1, 153.2, 136.4, 135.3, 134.6, 134.0, 133.7, 133.3, 132.4, 132.3, 131.1, 130.2, 129.6, 129.5, 129.2, 128.5, 128.4, 128.1, 127.9, 127.8, 127.6, 127.2, 126.8, 126.6, 126.5, 125.9, 122.5, 121.0, 118.4, 105.9, 62.6, 46.9, 26.3. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{34}H_{26}N_3O_2$ 508.2025; found 508.2037.

***N*-Benzoyl-2-(4-methoxyphenyl)-*N*-(naphthalene-2-yl)-1,2,3,4-tetrahydroisoquinoline-8-carboxamide (5j):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a brown solid (174 mg, 0.34 mmol, 86 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.63 (m, 1H), 7.60 (dd, *J* = 9.0, 3.0 Hz, 2H), 7.51 – 7.47 (m, 1H), 7.44 (d, *J* = 5.6 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.30 – 7.27 (m, 2H), 7.26 – 7.20 (m, 2H), 7.13 – 7.10 (m, 2H), 7.09 – 7.06 (m, 2H), 7.01 – 6.97 (m, 1H), 6.58 – 6.53 (m, 2H), 6.46 – 6.40 (m, 2H), 5.70 (s, 1H), 3.57 (s, 3H), 3.52 (ddd, *J* = 10.3, 7.4, 5.1 Hz, 1H), 3.36 – 3.26 (m, 1H), 2.75 – 2.53 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.8, 170.9, 154.4, 141.7, 136.3, 135.1, 133.7, 133.4, 132.6, 132.1, 131.9, 131.8, 130.1, 129.3, 129.2, 128.9, 128.8, 128.2, 127.9, 127.7, 127.2, 126.6, 126.5, 125.2, 119.4, 114.5, 61.8, 55.6, 46.0, 26.2. HRMS (ESI-TOF): m/z [M + H]$^+$ Calcd for $C_{34}H_{29}N_2O_3$ 513.2173; found 513.2189.

***N*-Benzoyl-2-(4-fluorophenyl)-*N*-(naphthalene-2-yl)-1,2,3,4-tetrahydroisoquinoline-8-carboxamide (5k):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a brown solid (165 mg, 0.33 mmol, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.9 Hz, 2H), 7.58 – 7.52 (m, 1H), 7.51 – 7.44 (m, 2H), 7.39 (dd, *J* = 6.8, 2.1 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.31 – 7.25 (m, 2H), 7.24 – 7.12 (m, 4H), 7.10 (dd, *J* = 7.1, 1.9 Hz, 1H), 7.05 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.77 (dd, *J* = 9.1, 8.3 Hz, 2H), 6.53 (dd, *J* = 9.1, 4.4 Hz, 2H), 5.88 (s, 1H), 4.00 – 3.55 (m, 1H), 3.52 – 3.21 (m, 1H), 2.76 (dd, *J* = 7.2, 4.9 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.0, 171.4, 158.7, 156.3, 144.3, 136.4, 135.2, 133.7, 133.4, 132.7, 132.2, 131.7, 130.0, 129.4, 129.2, 128.9, 128.4, 128.0, 127.9, 127.8, 126.7, 126.6, 126.4, 125.7, 125.2, 118.4, 118.3, 115.8, 115.6, 61.8, 45.9, 26.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -123.88. HRMS (ESI-TOF): m/z [M + H]$^+$ Calcd for $C_{33}H_{26}FN_2O_2$ 501.1973; found 501.1979.

***N*-Cyclohexyl-*N*-(*N*-methyl-*N*-phenylglycyl)benzamide (7a):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a yellow oil (35 mg, 0.10 mmol, 50 %). The scale-up reaction using 0.5 mmol (61 mg) of **6a** led to the product in 53% (93 mg, 0.27 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 3H), 7.30 (t, *J* = 7.8 Hz,

2H), 7.14 (td, *J* = 7.4, 1.9 Hz, 2H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.43 (d, *J* = 7.9 Hz, 2H), 3.99 (tt, *J* = 11.9, 3.4 Hz, 1H), 3.86 (s, 2H), 2.60 (s, 3H), 1.91 (qd, *J* = 12.5, 12.1, 3.6 Hz, 2H), 1.72 (m, 4H), 1.22 – 1.16 (m, 4H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 174.2, 173.2, 133.0, 130.2, 129.2, 129.1, 128.6, 122.1, 118.8, 113.5, 58.8, 58.4, 40.1, 30.1, 26.4, 25.3. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{22}H_{27}N_2O_2$ 351.2073; found 351.2076.

***N*-(*N*-Methyl-*N*-phenylglycyl)-*N*-(naphthalen-2-yl)benzamide (7b):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as an orange oil (47 mg, 0.12 mmol, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 10.8, 7.7 Hz, 2H), 7.69 – 7.62 (m, 1H), 7.45 – 7.40 (m, 5H), 7.32 – 7.23 (m, 4H), 7.11 (t, *J* = 7.7 Hz, 2H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 2H), 4.46 (s, 2H), 2.89 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 176.1, 172.1, 148.7, 136.0, 133.5, 133.1, 132.6, 132.3, 130.0, 129.6, 129.4, 128.3, 128.0, 127.8, 126.7, 126.7, 125.9, 125.3, 118.3, 112.8, 58.6, 40.7. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{26}H_{23}N_2O_2$ 395.1754; found 395.1776.

***N*-(4-Methoxyphenyl)-*N*-(*N*-methyl-*N*-phenylglycyl)benzamide (7c):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a red oil (34 mg, 0.09 mmol, 44 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 3H), 7.27 – 7.21 (m, 2H), 7.20 – 7.14 (m, 2H), 6.98 – 6.92 (m, 2H), 6.83 – 6.75 (m, 3H), 6.69 – 6.64 (m, 2H), 4.42 (s, 2H), 3.71 (s, 3H), 2.90 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 176.1, 172.2, 158.9, 148.8, 133.59, 132.4, 131.1, 129.9, 129.3, 128.8, 128.2, 118.0, 114.8, 112.7, 58.6, 55.5, 40.6. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{23}H_{23}N_2O_3$ 375.1709; found 375.1710.

***N*-Butyl-*N*-(*N*-methyl-*N*-phenylglycyl)benzamide (7d):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a yellow oil (26 mg, 0.08 mmol, 38 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 3H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.18 (dd, *J* = 8.6, 7.4 Hz, 2H), 6.76 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 2H), 4.18 (s, 2H), 3.65 – 3.58 (m, 2H), 2.82 (s, 3H), 1.51 (ddt, *J* = 12.5, 7.7, 3.9 Hz, 2H), 1.21 (tq, *J* = 14.8, 7.7 Hz, 2H), 0.81 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 175.0, 174.1, 148.8, 134.3, 132.7,

130.3, 129.2, 128.8, 118.1, 112.9, 58.6, 46.9, 40.3, 31.1, 20.1, 13.7. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{20}H_{25}N_2O_2$ 325.1916; found 325.1924.

***N*-(*tert*-Butyl)-*N*-(*N*-methyl-*N*-phenylglycyl)benzamide (7e):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a yellow oil (23 mg, 0.07 mmol, 36 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 8.2, 1.0 Hz, 2H), 7.50 – 7.39 (m, 1H), 7.23 (t, J = 7.9 Hz, 2H), 7.09 (td, J = 7.3, 2.0 Hz, 2H), 6.75 (t, J = 7.3 Hz, 1H), 6.32 (d, J = 8.1 Hz, 2H), 3.83 (s, 2H), 2.52 (s, 3H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.8, 172.5, 148.2, 135.5, 133.3, 129.3, 129.0, 128.4, 118.6, 113.1, 59.6, 58.9, 39.6, 28.5. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{20}H_{25}N_2O_2$ 325.1916; found 325.1940.

***N*-Benzyl-*N*-(*N*-methyl-*N*-phenylglycyl)benzamide (7f):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a yellow oil (25 mg, 0.07 mmol, 33 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 1H), 7.43 (dd, J = 8.2, 1.2 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.26 – 7.20 (m, 3H), 7.20 – 7.13 (m, 4H), 6.76 (t, J = 7.3 Hz, 1H), 6.55 – 6.50 (m, 2H), 4.87 (s, 2H), 4.19 (s, 2H), 2.80 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.3, 174.1, 149.1, 137.3, 134.8, 133.0, 129.6, 129.1, 129.1, 129.0, 128.5, 128.0, 118.5, 113.3, 58.9, 50.3, 40.5. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{23}H_{23}N_2O_2$ 359.1760; found 359.1774.

***N*-Cyclohexyl-*N*-(*N*-methyl-*N*-(*p*-tolyl)glycyl)benzamide (7g):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a yellow oil (44 mg, 0.12 mmol, 60 %). The scale-up reactions using 3 mmol (406 mg) and 7 mmol (1.0 g) of **6g**, led to the product in 58% (637 mg,1.75 mmol) and 55% (1.40 g, 3.89 mmol), respectively. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 8.2, 1.3 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.31 (d, J = 7.7 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.36 (d, J = 8.6 Hz, 2H), 4.02 (tt, J = 12.0, 3.6 Hz, 1H), 3.79 (s, 2H), 2.53 (s, 3H), 2.24 (s, 3H), 1.88 (qd, J = 12.5, 3.7 Hz, 2H), 1.78 – 1.67 (m, 4H), 1.24 – 1.03 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.9, 172.9, 145.9, 135.1, 132.90 129.6, 129.4, 129.1, 128.6, 114.2, 59.0, 58.3, 40.5, 30.2, 26.4, 25.3, 20.5. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{23}H_{29}N_2O_3$ 365.2224; found 365.2241.

***N*-Cyclohexyl-*N*-(*N*-methyl-*N*-(*p*-tolyl)glycyl)dodecanamide (7h):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 10:1) as a yellow oil (40 mg, 0.09 mmol, 45 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.2 Hz, 2H), 6.56 (d, *J* = 8.7 Hz, 2H), 4.31 (s, 2H), 3.73 – 3.62 (tt, *J* = 12.2, 3.4 Hz, 1H), 2.98 (s, 3H), 2.49 (t, *J* = 7.5 Hz, 2H), 2.23 (s, 3H), 2.17 (m, 2H), 1.83 – 1.78 (m, 2H), 1.64 – 1.60 (m, 4H), 1.30 (m, 4H), 1.26 (m 18H), 0.88 (t, *J* = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 177.7, 171.2, 130.7, 130.3, 127.2, 122.7, 55.0, 45.6, 37.3, 33.9, 32.0, 31.1, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.8, 25.7, 24.9, 22.8, 14.3. HRMS (ESI-TOF): m/z [M + H]$^+$ Calcd for $C_{28}H_{47}N_2O_2$ 443.3638; found 443.3657.

***N*-(*N*-Methyl-*N*-(*p*-tolyl)glycyl)-*N*-(naphthalen-2-yl)benzamide (7i):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a yellow oil (47 mg, 0.13 mmol, 63 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 11.3, 9.1 Hz, 2H), 7.69 – 7.64 (m, 1H), 7.43 (td, *J* = 8.1, 2.4 Hz, 5H), 7.32 – 7.23 (m, 2H), 7.12 (t, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.61 (d, *J* = 8.6 Hz, 2H), 4.40 (s, 2H), 2.85 (s, 3H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.6, 172.2, 146.9, 136.3, 133.8, 133.5, 132.9, 132.6, 130.4, 130.2, 129.8, 128.6, 128.3, 128.1, 127.9, 127.0, 126.1, 125.6, 113.5, 59.1, 41.1, 20.8. HRMS (ESI-TOF): m/z [M + H]$^+$ Calcd for $C_{27}H_{25}N_2O_2$ 409.1916; found 409.1921.

***N*-Cyclohexyl-*N*-(*N*-(4-methoxyphenyl)-*N*-methylglycyl)benzamide (7j):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a yellow oil (50 mg, 0.13 mmol, 65 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 6.75 – 6.69 (m, 2H), 6.43 – 6.38 (m, 2H), 4.06 (tt, *J* = 11.8, 3.4 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 2H), 2.47 (s, 3H), 1.84 (dd, *J* = 12.3, 9.3 Hz, 2H), 1.71 (t, *J* = 15.6 Hz, 4H), 1.24 – 1.03 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.0, 172.5, 153.4, 142.5, 135.3, 132.8, 129.1, 128.5, 115.7, 114.5, 59.19, 58.1, 55.8, 40.9, 30.2, 26.4, 25.4. HRMS (ESI-TOF): m/z [M + H]$^+$ Calcd for $C_{23}H_{29}N_2O_3$ 381.2178; found 381.2192.

***N*-(*N*-(4-Methoxyphenyl)-*N*-methylglycyl)-*N*-(naphthalen-2-yl) benzamide (7k):** According to the general procedure, the title product was provided after flash column chromatography

(hexane/EtOAc, 9:1) as an orange oil (55 mg, 0.13 mmol, 67 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 10.6, 7.7 Hz, 2H), 7.68 – 7.65 (m, 1H), 7.44 (ddd, *J* = 9.6, 7.6, 2.3 Hz, 5H), 7.30 (t, J = 7.4 Hz, 1H), 7.22 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 2H), 6.91 – 6.82 (m, 2H), 6.67 – 6.64 (m, 2H), 4.36 (s, 2H), 3.80 (s, 3H), 2.82 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.0, 172.5, 153.4, 142.5, 135.3, 132.8, 130.6, 129.1, 128.5, 115.7, 114.5, 59.2, 58.1, 55.8, 40.9, 30.2, 26.4, 25.4. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{27}H_{25}N_2O_3$ 425.1865; found 425.1849.

***N*-(*N*-(4-Bromophenyl)-*N*-methylglycyl)-*N*-(naphthalen-2-yl)benzamide (7l):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as a yellow-brown solid (43 mg, 0.09 mmol, 4 5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 13.0, 7.7 Hz, 2H), 7.71 – 7.65 (m, 1H), 7.48 – 7.42 (m, 5H), 7.36 – 7.33 (m, 2H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.22 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 2H), 6.61 – 6.55 (m, 2H), 4.47 (s, 2H), 2.90 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.4, 172.1, 147.9, 135.8, 133.4, 133.1, 132.8, 132.4, 132.1, 123.0, 129.7, 129.0, 128.4, 128.0, 127.8, 127.2, 126.9, 126.8, 126.1, 125.3, 114.4, 110.3, 58.6, 40.7. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{26}H_{22}BrN_2O_2$ 473.0865; found 473.0887.

***N*-(*N*-(4-Fluorophenyl)-*N*-methylglycyl)-*N*-(naphthalen-2-yl)benzamide (7m):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 9:1) as an orange oil (33 mg, 0.08 mmol, 41 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.70 (m, 2H), 7.73 – 7.61 (m, 1H), 7.52 – 7.40 (m, 5H), 7.33-7.11 (m, 4H), 7.09 – 6.92 (m, 2H), 6.61 (m, 2H), 4.44 (m, 2H), 3.08 – 2.70 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.8, 172.0, δ 156.4 (d, *J* = 236.7 Hz), 145.3, 135.9, 133.5, 133.1, 132.7, 132.3, 130.0, 129.6, 129.0, 128.3, 128.0, 127.8, 126.8 (d, *J* = 4.0 Hz), 125.9, 125.2, 115.8 (d, *J* = 22.2 Hz), 114.0 (d, *J* = 7.4 Hz), 58.9, 41.1. ^{19}F NMR (375 MHz, $CDCl_3$) δ -127.23. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{26}H_{22}FN_2O_2$ 413.1665; found 413.1694.

***N*-Cyclohexyl-*N*-(*N*-methyl-*N*-(2-oxo-2H-chromen-6-yl)glycyl)benzamide (7n):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 8:2) as a yellow oil (34 mg, 0.08 mmol, 38 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 4H),

7.38 – 7.31 (m, 2H), 7.14 (d, *J* = 9.1 Hz, 1H), 6.64 (dd, *J* = 9.1, 3.0 Hz, 1H), 6.44 (d, *J* = 3.0 Hz, 1H), 6.40 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.99 (tt, *J* = 11.9, 3.6 Hz, 1H), 3.91 (s, 2H), 2.66 (s, 3H), 1.97 – 1.83 (m, 2H), 1.82 – 1.63 (m,4H), 1.27 – 1.08 (m, 4H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.4, 161.3, 159.1, 147.4, 145.4, 143.6, 134.8, 133.7, 129.2, 128.8, 119.2, 117.9, 117.4, 117.2, 110.5, 58.9, 58.8, 40.5, 30.2, 26.3, 25.3. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{25}H_{27}N_2O_4$ 419.1971; found 419.1970.

(4a*R*,4a1*R*,5a*S*,8a*R*,8a1*S*,15a*S*)-*N*-Benzoyl-N-cyclohexyl-10,11-dimethoxy-14-oxo-2,4a,4a1,5,5a, 7,8,8a1,15,15a decahydro-14H-4,6-methanoindolo[3,2,1-ij]oxepino[2,3,4-de]pyrrolo[2,3-h]quinoline-16-carboxamide (8a): According to the general procedure, the title product was provided after flash column chromatography (DCM + 1% NEt_3) as a white solid (87 mg, 0.14 mmol, 76 %) as a 3.5:1.0:1.2 mixture of isomers **8a:8a':8a#** and in a diastereomeric ratio of 78:22 (**8a:8a'**). The scale-up reaction using 0.5 mmol (197 mg) of brucine led to the product in 78% (243 mg, 0.39 mmol) and the same isomeric distribution. HRMS (ESI-TOF): m/z $[M + H]^+$ Calcd for $C_{37}H_{42}N_3O_6$ 624.3074; found 624.3076.

The diasteroisomers (C16-epimers) **8a** and **8a'** were isolated using a preparative Knauer-HPLC (Nucleodur 100-10 C18sec, CH_3CN:H_2O 99:1, flow rate 2.5 mL/min):

8a (major isomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.48 – 7.39 (m, 5H), 6.67 (s, 1H), 5.68 (t, *J* = 7.5 Hz, 1H), 4.58 (tt, *J* = 11.7, 3.8 Hz, 1H), 4.26 (dt, *J* = 8.5, 3.3 Hz, 1H), 4.06 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.97 – 3.92 (m, 1H), 3.92 – 3.90 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.81 (d, *J* = 10.8 Hz, 1H), 3.13 – 3.10 (m, 1H), 3.09 – 3.05 (m, 1H), 2.62 – 2.59 (m, 1H), 2.59 – 2.55 (m, 1H), 2.32 – 2.26 (m, 1H), 2.10 (d, *J* = 13.7 Hz, 1H), 2.05 – 2.01 (m, 1H), 1.96 – 1.91 (m, 2H), 1.88 – 1.84 (m, 2H), 1.73 – 1.69 (m, 2H), 1.63 – 1.59 (m, 2H), 1.55 (dt, *J* = 10.8, 3.4 Hz, 1H), 1.50 (d, *J* = 14.8 Hz, 1H), 1.39 – 1.34 (m, 2H), 1.18 – 1.14 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 173.4, 167.7, 158.4, 149.3, 145.3, 139.3, 139.0, 138.1, 135.8, 131.4, 128.3, 121.2, 109.7, 100.3, 78.0, 68.7, 64.8, 60.9, 57.1, 56.8, 56.2, 56.0, 51.3, 47.5, 46.3, 42.3, 42.0, 33.9, 33.2, 33.1, 31.4, 30.9, 26.6, 26.4, 25.6, 25.3, 24.9.

8a' (minor diastereoisomer): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.65 (d, *J* = 7.4 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 3H), 6.84 (s, 1H), 6.08 – 6.06 (m, 1H), 4.67 – 4.61 (m, 1H), 4.33 (dd, *J* = 14.3, 7.2 Hz, 1H), 4.26 (d, *J* = 8.9 Hz, 1H), 4.20 (d, *J* = 6.2 Hz, 1H), 4.14 (d, *J* = 7.3 Hz, 1H), 4.00 (d, *J* = 9.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.67 (d, *J* = 10.4 Hz, 1H), 3.58 (d, *J* = 6.1 Hz, 1H), 3.25 – 3.23 (m, 1H), 3.21 (d, *J* = 3.6 Hz, 1H), 3.11 – 3.06 (m, 2H), 2.93 (dd, *J* = 15.1, 6.5 Hz, 1H), 2.87 – 2.82 (m, 2H), 2.60 (dd, *J* = 17.6, 3.0 Hz, 2H), 2.16 – 2.12 (m, 2H), 1.81 – 1.77 (m, 4H), 1.57 – 1.55 (m, 2H), 1.13 (d, *J* = 11.7 Hz, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 179.7, 177.5, 174.0, 167.1, 147.4, 146.1, 144.2, 134.8, 129.3, 128.6, 127.9, 123.9, 104.2, 100.0, 99.8, 98.9, 82.9, 67.1, 63.2, 55.6, 55.5, 55.4, 52.0, 51.7, 48.4, 47.9, 41.5, 41.2, 40.7, 38.7, 30.1, 29.7, 28.8, 25.3, 25.3, 24.8, 24.0.

The isomeric compound **8a#** (benzylic and alpha to O-atom) could not be isolated and characterized due to decomposition during the purification process.

(4a*R*,4a1*R*,5a*S*,8a*R*,8a1*S*,15a*S*)-*N*-Benzoyl-*N*-cyclohexyl-14-oxo-2,4a,4a1,5,5a,7,8,8a1,15,15a-decahydro-14H-4,6-methanoindolo[3,2,1-ij]oxepino[2,3,4-de]pyrrolo[2,3-h]quinoline-16-carboxamide (8b): According to the general procedure, the title product was provided after flash column chromatography (DCM + 1% NEt_3) as a white solid (62 mg, 0.11 mmol, 54 %) as a 2.5:1.4:1.0 mixture of isomers **8b:8b':8b#** and in a diastereomeric ratio of 72:28 (**8b:8b'**). The scale-up reaction using 0.5 mmol (167 mg) of strychnine, led to the product in 53% (149 mg, 0.27 mmol) and the same isomeric distribution. HRMS (ESI-TOF): m/z [M + H]$^+$ Calcd for $C_{35}H_{38}N_3O_4$ 564.2862; found 564.2865.

The diasteroisomers (C16-epimers) **8b** and **8b'** were isolated using a preparative Knauer-HPLC (Nucleodur 100-10 C18sec, CH_3CN:H_2O 99:1, flow rate 2.5 mL/min):

8b (major isomer): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 6.9 Hz, 1H), 7.62 – 7.59 (m, 1H), 7.52 – 7.46 (m, 3H), 7.44 – 7.40 (m, 1H), 7.25 – 7.21 (m, 1H), 7.18 (dt, *J* = 7.4, 1.2 Hz, 1H), 7.10 (td, *J* = 7.5, 1.1 Hz, 1H), 5.62 (s, 1H), 4.28 (tt, *J* = 12.1, 3.7 Hz, 1H), 3.94 (dt, *J* = 8.4, 4.2 Hz, 1H), 3.85 (dd, *J* = 12.9, 11.0 Hz, 1H), 3.81 (s, 1H), 3.66 (d, *J* = 10.1 Hz, 1H), 3.57 (dd, *J* = 12.8, 6.6 Hz, 1H), 3.42 – 3.35 (m, 1H), 3.20 – 3.16 (m, 1H), 3.15 – 3.11 (m, 1H), 2.98 (dd, *J* = 16.6, 8.5 Hz, 1H), 2.92 – 2.89

(m, 1H), 2.47 (dd, *J* = 16.6, 4.4 Hz, 1H), 2.23 (dt, *J* = 13.7, 8.5 Hz, 1H), 2.18 (dt, *J* = 13.5, 3.6 Hz, 1H), 2.05 (dd, *J* = 12.9, 4.4 Hz, 1H), 1.98 – 1.95 (m, 1H), 1.86 (ddd, *J* = 14.0, 10.2, 3.9 Hz, 1H), 1.83 – 1.79 (m, 2H), 1.65 – 1.61 (m, 1H), 1.55 – 1.51 (m, 1H), 1.42 (d, *J* = 7.9 Hz, 3H), 1.26 (d, *J* = 8.8 Hz, 2H), 1.20 – 1.14 (m, 1H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 174.0, 170.3, 166.8, 141.6, 137.3, 133.8, 133.4, 131.4, 130.4, 129.5, 129.2, 128.7, 128.6, 126.9, 124.7, 122.0, 116.2, 78.2, 69.1, 64.4, 59.1, 58.5, 55.3, 53.7, 46.9, 41.3, 33.4, 32.2, 31.9, 28.8, 27.1, 26.5, 26.3, 25.7, 25.4, 24.9, 22.9.

8b' (minor diastereoisomer): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 – 7.84 (m, 2H), 7.62 – 7.56 (m, 2H), 7.55 – 7.51 (m, 2H), 7.48 – 7.45 (m, 1H), 7.25 – 7.22 (m, 1H), 7.08 (td, *J* = 7.5, 1.1 Hz, 1H), 7.01 (dd, *J* = 7.7, 1.3 Hz, 1H), 5.92 – 5.78 (m, 1H), 4.44 (d, *J* = 14.2 Hz, 1H), 4.20 (dt, *J* = 8.4, 3.3 Hz, 1H), 4.16 – 4.06 (m, 2H), 3.97 – 3.92 (m, 1H), 3.82 (d, *J* = 10.5 Hz, 1H), 3.70 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.37 (d, *J* = 3.3 Hz, 1H), 3.07 (dd, *J* = 17.3, 8.4 Hz, 1H), 2.95 (dd, *J* = 5.2, 2.2 Hz, 1H), 2.82 (s, 1H), 2.81 – 2.74 (m, 1H), 2.64 – 2.60 (m, 1H), 2.59 – 2.54 (m, 1H), 2.29 – 2.21 (m, 1H), 2.15 (dt, *J* = 15.2, 4.4 Hz, 1H), 2.08 (t, *J* = 9.0 Hz, 1H), 1.95 (h, *J* = 3.6 Hz, 2H), 1.68 – 1.64 (m, 1H), 1.61 (d, *J* = 12.9 Hz, 1H), 1.50 (d, *J* = 15.2 Hz, 1H), 1.45 – 1.42 (m, 1H), 1.29 (td, *J* = 11.3, 9.7, 4.9 Hz, 2H), 1.13 (dt, *J* = 13.1, 3.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 171.9, 169.4, 166.5, 149.3, 142.0, 137.2, 136.0, 133.6, 132.4, 130.3, 129.2, 129.0, 128.6, 128.2, 124.6, 122.5, 116.4, 77.5, 65.9, 64.5, 62.7, 59.9, 57.5, 55.7, 52.9, 49.0, 47.8, 42.4, 41.6, 31.2, 29.5, 27.5, 26.4, 26.3, 25.5.

The isomeric compound **8b#** (benzylic and alpha to O-atom) could not be isolated and characterized due to decomposition during the purification process.

***N*-Benzoyl-*N*-cyclohexyl-2,8-dimethyl-6H,12H-5,11-methanodibenzo[*b,f*][1,5]diazocine-6-carboxamide (9):** According to the general procedure, the title product was provided after flash column chromatography (hexane/EtOAc, 4:1) as a white solid (29 mg, 0.06 mmol, 29 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.50 – 7.41 (m, 3H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.00 – 6.96 (m, 1H), 6.93 – 6.88 (m, 2H), 6.65 (s, 1H), 6.51 (s, 1H), 4.86 (d, *J* = 17.3 Hz, 1H), 4.30 – 4.16 (m, 2H), 3.94 (d, *J* = 17.3 Hz, 1H), 3.80 (d, *J* = 16.6 Hz, 1H), 3.62 (d, *J* = 16.5 Hz, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 1.75 – 1.64 (m, 3H), 1.56 – 1.49 (m, 2H), 1.38 – 1.31 (m, 1H), 1.23 – 1.11 (m, 3H), 1.09 –

1.00 (m, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 171.2, 170.4, 146.7, 140.7, 137.2, 134.8, 134.0, 132.3, 128.9, 128.8, 128.5, 128.3, 127.8, 127.4, 126.9, 126.8, 125.5, 125.0, 74.5, 58.2, 58.0, 53.7, 31.1, 28.8, 26.4, 25.4, 21.1. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{31}H_{34}N_3O_2$ 480.2646; found 480.2651.

Deprotection of the benzoyl group:

***N*-Cyclohexyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (10):** In an oven-dried screw cap schlenk under nitrogen atmosphere, the imide **5a** (0.1 mmol, 1.0 equiv.) was solved in 1 mL dry THF. Then hydrazine (1 M in THF) (0.15 mmol, 1.5 equiv.) was added and the solution was stirred at room temperature for 5 h. The solvent was removed under vacuum and the crude was purified by flash column chromatography (hexane/EtOAc, 8:2), obtaining the product (29.1 mg, 0.087 mmol, 87 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 6.9, 2.1 Hz, 1H), 7.27 – 7.23 (m, 2H), 7.20 – 7.15 (m, 2H), 7.10 – 7.07 (m, 1H), 6.87 – 6.84 (m, 2H), 6.71 (d, J = 8.6 Hz, 1H), 4.89 (s, 1H), 3.81 – 3.76 (m, 1H), 3.65 (dddd, J = 10.8, 8.8, 6.8, 4.4 Hz, 1H), 3.26 (td, J = 10.7, 4.1 Hz, 1H), 3.04 – 2.85 (m, 2H), 1.82 – 1.67 (m, 2H), 1.61 – 1.44 (m, 4H), 1.11 – 0.86 (m, 4H). The spectroscopic data are in accordance with the literature.[29]

Associated Content

The following file is available free of charge: **Supporting Information**. Competitive mechanistic experiments, quantum chemistry calculations and proposed mechanism, copies of NMRs of the products (PDF).

Author Information

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