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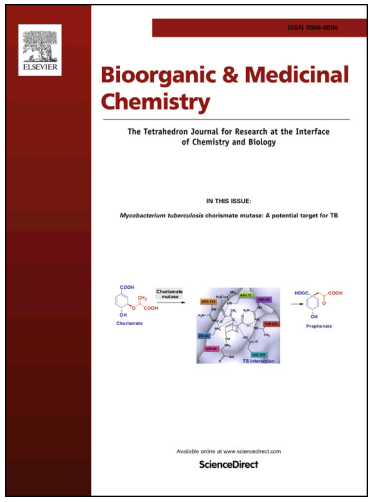

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Graphical Abstract

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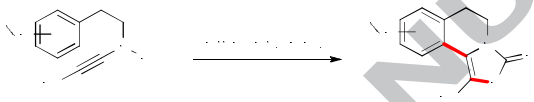

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ABSTRACT

The transition metal-free intramolecular regioselective domino cyclization of N-Boc protected ynamides has been developed to provide the corresponding tetrahydroisoquinoline-oxazo-2(3*H*)-ones in moderate to good yields.

1. Introduction

Oxazol-2(3*H*)-ones are among the valuable building blocks in organic synthesis;[1] they have been found to exhibit potent biological activities, such as antibacterial, antitumor, cyclooxygenase-2 inhibitory, neuroleptic, and herbicidal activities as shown in Figure 1.[2] Various classical methods have been developed toward the synthesis of substituted oxazol-2(3*H*)-ones and most of them have relied on carbonyl condensation to establish cyclic carbamate moiety.[3] The new developments for the synthesis of 3,5-disubstituted oxazol-2(3*H*)-ones recently utilized Au(I)-,[4] Pd(II)-,[5] or Cu(I)-catalyzed[6] cycloisomerizations of ynamides[7] bearing alkoxy carbamate as the nitrogen protecting groups. These cycloisomerizations provide an efficient and rapid access to 3,5-disubstituted oxazol-2(3*H*)-ones. Interestingly, Zhu and co-worker described an elegant synthesis of various 3,4,5-trisubstituted oxazol-2(3*H*)-one derivatives using the palladium-catalyzed coupling of ynamides with aryl halides (Scheme 1a).[8] Moreover, the palladium-catalyzed cycloisomerization-halogenation reaction sequence of ynamides, developed by Zhu and co-workers, resulted in a variety of 4-halo-oxazol-2(3*H*)-one derivatives which further underwent Suzuki–Miyaura cross-coupling reactions leading to a wide range of 3,4,5-trisubstituted oxazol-2(3*H*)-one derivatives (Scheme 1b).[9a] In addition, the transition metal-free iodocyclization of ynamides also provided the corresponding 4-iodo-oxazol-2(3*H*)-ones by using NIS-K_2CO_3 condition.[9b] Alternatively, the intermolecular iodoamination of terminal ynamides followed by palladium-catalyzed Suzuki–Miyura cross-coupling/cyclization reaction was an efficient synthetic strategy for the synthesis of 3,4,5-trisubstituted oxazol-2(3*H*)-one derivatives (Scheme 1c).[10] Although the new developments for the synthesis of

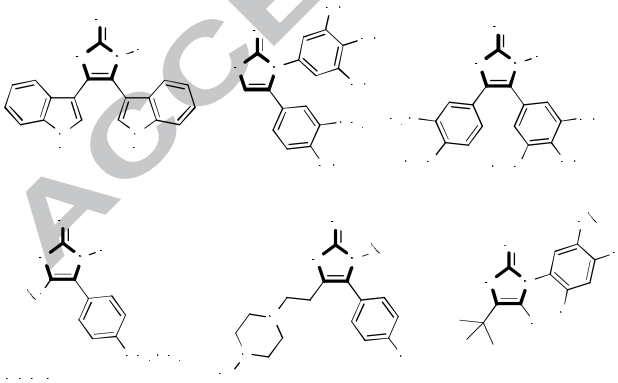

Figure 1. Biologically important molecules that contained the oxazo-2(3*H*)-one skeleton.

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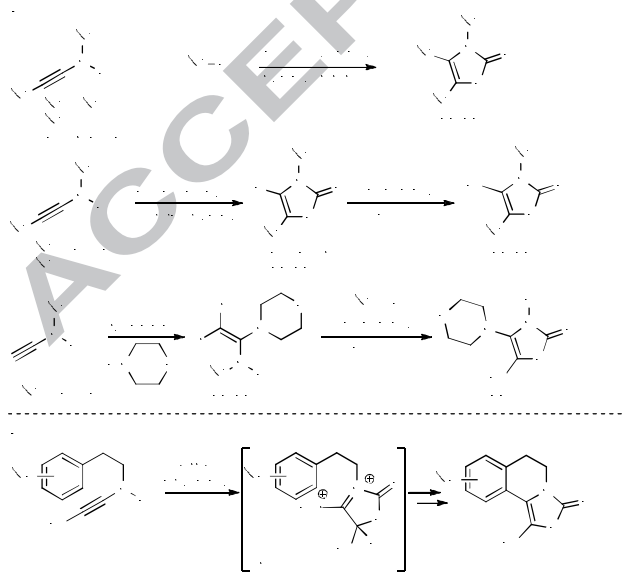
polysubstituted oxazol-2(3*H*)-one from ynamides have been widely studied, but those reactions are only restricted to the ynamides bearing an N-aryl or N-benzyl moiety. Thus, the modifications and transformations for the new types of N-substituted ynamides to prepare the valuable N-containing heterocycles still remain a challenge awaiting new breakthroughs.

Recently, hypervalent iodine reagents have been vastly applied in a number of significant transformations due to their useful oxidizing properties, benign environmental character, ease of handling, low toxicity, and commercial availability.[11] [Bis(trifluoroacetoxy)iodo]benzene (BTI or PIFA) is one of the most important hypervalent iodine reagents which has been employed as a mild oxidant for many transformations, for example, intramolecular oxidative biaryl coupling,[12] intramolecular electrophilic aromatic amidation,[13] intramolecular alkene amidation,[14] and intramolecular alkyne amidation.[15] The modes of activations of PIFA usually involve the activation of electron-rich aromatic compounds, substituted alkenes or alkynes. The activation properties of PIFA as an excellent activator of alkynes moiety has prompted us to hypothesize that the ynamide bearing 3,4-dimethoxyphenylethane and *tert*-butyloxy carbamate moieties on the nitrogen atom could react with PIFA in the presence of Lewis acid via cycloisomerization to form a new C–O bond (Scheme 1d). The resulting oxazol-2(3*H*)-one intermediate could then isomerize to the reactive N-acyl iminium ion which further reacts with the electron-rich aromatic ring via the Pictet–Spengler type reaction to establish a new C–C bond regioselectively.[16] This would be the first example for the synthesis of such 3,4,5-trisubstituted oxazol-2(3*H*)-one from the corresponding ynamide in a domino metal-free fashion. Moreover, the desired product, which possesses a tetrahydroisoquinoline core structure, could be biologically active or provide opportunities for further transformations to other important core structures, such as the phthalide tetrahydroisoquinoline derivatives.[16a,17] The similar tetrahydroisoquinoline-oxazol-2(3*H*)-one core structures have also been obtained as the products from the oxidation of ethyl 1-benzylidene tetrahydroisoqunoline carboxylate derivatives by using stoichiometric amount of toxic $Pb(OAc)_4$ with a very limited substrate scope.[18] Hence, we now report the new development on PIFA mediated domino regioselective double



Scheme 1. Cyclization of the N-alkynyl alkyloxycarbamate to 3,4,5-trisubstituted oxazol-2(3*H*)-ones.

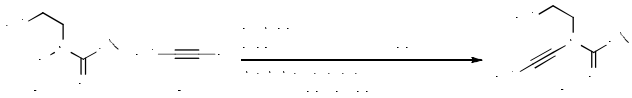
cyclization of ynamides to afford the corresponding tetrahydroisoquinoline-oxazol-2(3*H*)-ones in moderate to good yields.

2. Results and discussion

The initial study was the synthesis of ynamide **3a** via copper-catalyzed direct cross-coupling of *tert*-butyl 3,4-dimethoxyphenethylcarbamate and phenylethynyl bromide under basic conditions.[19] We found that the use of $CuSO_4 \cdot 5H_2O$ as a catalyst[4b,19c] gave the desired ynamide **3a** in a low yield of 10% and homocoupling of phenylethynyl bromide was observed. Increasing the amount of $CuSO_4 \cdot 5H_2O$ along with prolonging the reaction time did not improve yield of ynamide **3a**. The alternative method using CuI as a catalyst[19b] in the presence of KHMDS gave the ynamide **3a** in only 10%. Interestingly, we found that the addition rate of KHMDS solution was crucial for this cross-coupling reaction, as adding the KHMDS solution gradually over 3 hours via syringe pump furnished the desired ynamide **3a** in yields up to 75%.[20] Since CuI method provided the best yield of the ynamide **3a**, this method was employed for the preparation of various ynamides **3a**-**r** in yields ranging from 15 to 98% (Table 1, entries 1-16).[21]

With these ynamides in hand, we next investigated their PIFA-mediated domino regioselective cyclization and the results are shown in Table 2. We initially studied the reaction of the ynamide **3a** in the presence of PIFA (1.1 equiv) in CH_2Cl_2 at –78 °C to room temperature for 18 h; however, only the starting material **3a** was recovered (Table 2, entry 1). Surprisingly, adding 1.2 equivalent of $BF_3 \cdot OEt_2$ to the reaction mixture of

Table 1.
Synthesis of ynamides 3 using CuI-catalyzed cross-coupling reactions.



Entry	Ar^1	Ar^2	R	**3** (%)[a]
1	3,4-$(MeO)_2$-C_6H_3	Ph	*t*-Bu	**3a**, 75
2		3,4-$(MeO)_2$-C_6H_3	*t*-Bu	**3b**, 49
3		3,4-OCH_2O-C_6H_3	*t*-Bu	**3c**, 98
4		*o*-MeO-C_6H_4	*t*-Bu	**3d**, 72
5		*m*-MeO-C_6H_4	*t*-Bu	**3e**, 24
6		*p*-MeO-C_6H_4	*t*-Bu	**3f**, 56
7		*p*-F-C_6H_4	*t*-Bu	**3g**, 76
8	3,4-OCH_2O-C_6H_3	Ph	*t*-Bu	**3h**, 65
9		3,4-$(MeO)_2$-C_6H_3	*t*-Bu	**3i**, 72
10		3,4-OCH_2O-C_6H_3	*t*-Bu	**3j**, 70
11		*o*-MeO-C_6H_4	*t*-Bu	**3k**, 76
12		*m*-MeO-C_6H_4	*t*-Bu	**3l**, 29
13		*p*-MeO-C_6H_4	*t*-Bu	**3m**, 56
14		*p*-F-C_6H_4	*t*-Bu	**3n**, 44
15	3,4,5-$(MeO)_3$-C_6H_2	Ph	*t*-Bu	**3o**, 53
16		3,4-$(MeO)_2$-C_6H_3	*t*-Bu	**3p**, 69
17	Ph	Ph	*t*-Bu	**3q**, 15
18	3,4-$(MeO)_2$-C_6H_3	Ph	Et	**3r**, 68

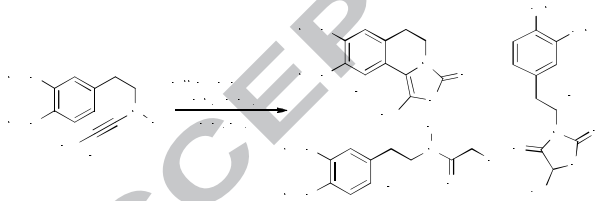
[a] Isolated yield after column chromatography on silica.

ynamide **3a** and PIFA in CH_2Cl_2 at –78 °C at which the reaction was kept for 4 h gave full conversion and oxazol-2(3*H*)-one **4a** was isolated in 40% yield along with oxazolidine-2,4-dione **5a** and the corresponding imide **6a** in the ratio of 3:1:3, respectively (Table 2, entry 2). Increasing the equivalents of $BF_3{\cdot}OEt_2$ to 1.5 and 2.0 at –78 °C could lower the amount of oxazolidine-2,4-dione **5a**, but the desired oxazol-2(3*H*)-one **4a** product was isolated in 33 and 43% yield, respectively (Table 2, entries 3-4). These results indicated that oxazolidine-2,4-dione **5a** could be derived from the key intermediate of this domino reaction and oxazol-2(3*H*)-one **4a** might easily decompose under strongly acidic conditions. In addition, the formation of imide **6a** has been investigated previously to occur by an acid-catalyzed hydration of the ynamide derivatives.[22] Thus, 4 Å molecular sieve was added in order to minimize the amount of moisture in the reaction mixture; consequently, the ratio of oxazol-2(3*H*)-one **4a** to imide **6a** improved to 8:3 (Table 2, entry 5). Finally, the effect of the temperature was examined. We found that the yield of the corresponding oxazol-2(3*H*)-one **4a** increased up to 59%, while the reaction was performed at –96 °C for 3 h, most likely to be due to the slower rate of decomposition of oxazol-2(3*H*)-one **4a** at this temperature than at higher ones (Table 2, entry 6). Additionally, other solvents, such as chloroform, 1,2-dichloroethane, acetonitrile, toluene, Et_2O and acetone, were also examined but all gave unsatisfied results.[23]

The optimal condition (Table 2, entry 6) was then employed for converting various ynamides **3b**-**p** to the corresponding products to establish the scope and generality of this novel method as shown in Table 3. From the yields, it could be clearly seen that, for the similar aryl group (Ar^2) on ring C, the ynamides with 3,4-dimethoxyphenyl as the aryl ring A provided the corresponding oxazol-2(3*H*)-ones in slightly higher yields than those containing a 3,4-methylenedioxyphenyl as the ring A (Table 3, entries 1-14). The presence of an additional electron-donating methoxy group as the 3,4,5-trimethoxyphenyl group on ring A of the ynamides **3o** and **3p**, when compared with **3a** and **3b**, lowered the yields of the products **4o** and **4p** dramatically to be in the range of 20-22% (Table 3, entries 13-14). Nevertheless, the principal effect for the production of oxazol-2(3*H*)-ones apparently depended on the substitution pattern of the aryl ring C. The 3,4-dimethoxyphenyl substituent on the ring C produced the low yield of oxazol-2(3*H*)-ones **4b** and **4p** perhaps due to the relatively facile decomposition under strongly acidic conditions (Table 3, entries 2 and 16). On the other hand, ynamides with 3,4-methylenedioxyphenyl, *ortho*-methoxyphenyl, or *meta*-methoxyphenyl as the aryl ring C all gave the corresponding products **4c**-**e** and **4j**-**l** in yields ranging from 41 to 72% (Table 3, entries 3-5 and 10-12). However, the ynamides with *para*-methoxyphenyl as the aryl ring C provided the corresponding oxazol-2(3*H*)-ones **4f** and **4m** in 31-39% yield plausibly due to their more labile nature under strongly acidic conditions (Table 3, entries 6 and 13). The electron withdrawing group effect on aryl ring C was also investigated and we found that ynamides **3g** and **3n** with *para*-fluorophenyl as the aryl ring C gave the corresponding products **4g** and **4n** in 36-38% yield (Table 3, entries 7 and 14).

Further studies were carried out in order to investigate and propose a reaction mechanism which can account for the observed experimental results. We anticipated that the C–O bond formation might rapidly occur first and the subsequent intramolecular electrophilic addition from the electron-rich aromatic ring could then take place. During the optimization reaction condition, we found that ynamide **3a** was completely consumed within 10 minutes after addition of $BF_3{\cdot}OEt_2$ (1.2 equiv) to provide **4a** and **5a** in the ratio of 1:1. On the other hand, when the ynamide **3r** bearing an ethyloxy carbamate moiety was then evaluated under the similar optimized condition, the reaction did not provide any product (Scheme 2a). Moreover, ynamide **3q**, bearing phenyl groups both at the terminal alkyl and alkyne moieties, under our optimized condition provided only the

Table 2.
Optimization of reaction conditions.



Entry	$BF_3{\cdot}OEt_2$ (equiv)	Temp (°C)	Time (h)	Ratio **4a**:**5a**:**6a**[a]	**4a** (%)[b]
1	-	–78 to rt	18	-	nr[c]
2	1.2	–78	4	3:1:3	40
3	1.5	–78	3	16:1:28	33
4	2.0	–78	3	21:1:20	43
5[d]	2.0	–78	3	8:1:3	38
6[d]	2.0	–96	3	8:1:2	59

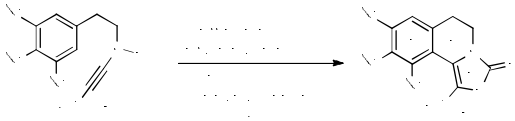
[a] Ratio was detemined by integration of the ^{1}H NMR of the crude product.

[b] Isolated yield after preparative thin-layer chromatography.

[c] nr = no reaction.

[d] 4 Å molecular sieve was added.

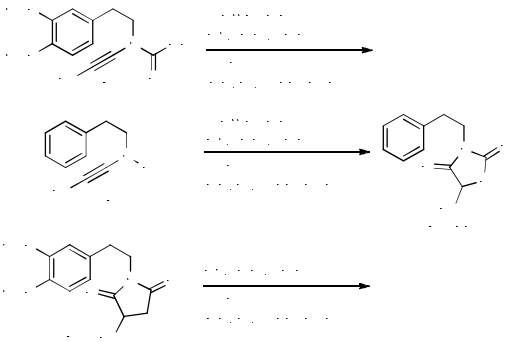
Table 3.
PIFA–$BF_3{\cdot}OEt_2$ mediated intramolecular regioselective domino cyclization of ynamides 3.



Entry	Ynamide	R	Ar^2	**4** (%)[a]
1	**3a**	$R^1 = R^2 = MeO$, $R^3 = H$	Ph	**4a**, 59
2[b]	**3b**		3,4-$(MeO)_2$-C_6H_3	**4b**, 19
3[b]	**3c**		3,4-OCH_2O-C_6H_3	**4c**, 41
4	**3d**		*o*-MeO-C_6H_4	**4d**, 69
5	**3e**		*m*-MeO-C_6H_4	**4e**, 72
6	**3f**		*p*-MeO-C_6H_4	**4f**, 31
7	**3g**		*p*-F-C_6H_4	**4g**, 36
8	**3h**	R^1–$R^2 = OCH_2O$, $R^3 = H$	Ph	**4h**, 44
9	**3i**		3,4-$(MeO)_2$-C_6H_3	**4i**, 56
10	**3j**		3,4-OCH_2O-C_6H_3	**4j**, 50
11	**3k**		*o*-MeO-C_6H_4	**4k**, 62
12	**3l**		*m*-MeO-C_6H_4	**4l**, 51
13	**3m**		*p*-MeO-C_6H_4	**4m**, 39
14	**3n**		*p*-F-C_6H_4	**4n**, 38
15[b]	**3o**	$R^1 = R^2 = R^3 = MeO$	Ph	**4o**, 20
16	**3p**		3,4-$(MeO)_2$-C_6H_3	**4p**, 22

[a] Isolated yield after preparative thin-layer chromatography.

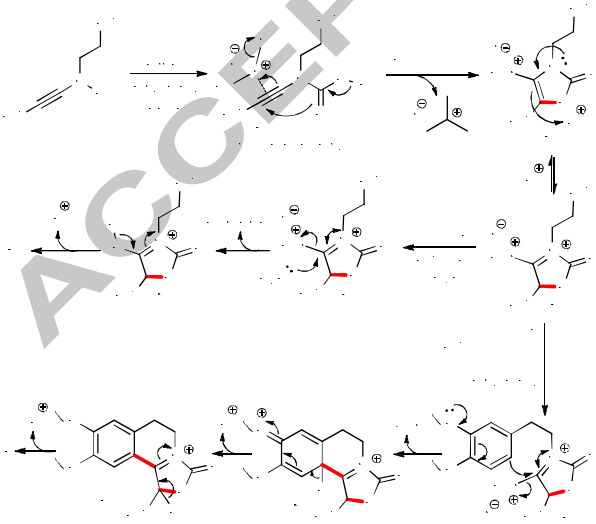
[b] The reaction was carried out for 30 min.



Scheme 2. Experiments for mechanistic study.

oxazolidine-2,4-dione **5b** in 61% yield as the product (Scheme 2b). These results suggested that the first cyclization took place rapidly under our standard condition and *tert*-butyl carbamate functional group plays an important role for the *5-endo-dig* ring closure. The C–O bond cleavage property of the *tert*-butyl group under Lewis acid condition in comparison with that of the ethyl carbamate might account for the different results. Thus, once the N-acyl iminium ion was formed, an appropriate nucleophile, such as the electron-rich aromatic rings, would attack at the reactive center. On the other hand, ynamide **3q** without electron-rich aromatic rings provided the corresponding oxazolidine-2,4-dione **5b** as the major product. In addition, oxazolidine-2,4-dione **5a** should be considered as a precursor of N-acyl iminium ion intermediate for Pictet-Spengler cyclization under Lewis acid condition. However, treatment of **5a** in the presence of 2 equivalents of $BF_3{\cdot}OEt_2$ under optimized reaction condition resulted in no reaction (Scheme 2c).

Based on both experimental evidences and the reported literatures, we propose a plausible mechanism for the formation of oxazol-2(3*H*)-one **4** and oxazolidine-2,4-dione **5** as shown in Scheme 3. The activation of the triple bond of ynamide by PIFA leads to the formation of the iodonium intermediate **A**.[15c,f] Subsequently, an intramolecular regioselective *5-endo-dig* ring closure of intermediate **A** occurs upon its reaction with the first equivalent of $BF_3{\cdot}OEt_2$ thereby generating the *tert*-butyl cation and trifluoroacetate anion, leading to the enamine **B**. The enamine-iminium tautomerism of intermediate **B** results in the



Scheme 3. Proposed mechanism for the formation of oxazol-2(3*H*)-one **4** and oxazolidine-2,4-dione **5**.

formation of the key intermediate N-acyl iminium ion **C** which can be readily attacked by nucleophiles. In path A, the Pictet-Spengler type reaction occurs when Ar^1 is an electron-rich aromatic, activated by the second equivalent of $BF_3{\cdot}OEt_2$, thereby creating a new C–C bond of cation **D**. The subsequent rearomatization of cation **D** followed by elimination of a proton of N-acyl iminium ion **E** leads to the formation of the desired oxazol-2(3*H*)-ones **4**. In path B, in case when the N-acyl iminium ion **C** did not react with the aromatic Ar^1, water could act as a nucleophile instead and attack at the reactive center of N-acyl iminium ion **C** after aqueous work up, thus leading to the cation **F**. Tautomerism of cation **F** leads to the corresponding oxazolidine-2,4-dione **5**. It is noteworthy that because oxazolidine-2,4-dione **5** was always observed as a byproduct in different ratios with the oxazol-2(3*H*)-one **4**, the second cyclization of **C** to **D** (path A) could be relatively slower than the generation of **C**.

3. Conclusion

In summary, we have developed a novel method for the synthesis of tetrahydroisoquinoline-oxazol-2(3*H*)-ones based on the intramolecular regioselective domino cyclization of ynamides. This transition metal-free process allows for the rapid production of tetrahydroisoquinoline-oxazol-2(3*H*)-one building blocks useful for the synthesis of new bioactive products. Further studies on the application of hypervalent iodine mediated reactions of ynamides and the derived products are being conducted and will be reported in due course.

4. Experimental

4.1. General information

Unless otherwise noted, reactions were run in oven-dried round-bottomed flasks. Toluene was purified by the solvent purification system. Dichloromethane was dried over CaH_2, distilled under argon atmosphere, and kept over 4 Å molecular sieve prior to use. PIFA, as received from the suppliers, was dried under vacuum at room temperature for 48 h and kept in argon-filled glove box. All other compounds were used as received from the suppliers. The crude reaction mixtures were concentrated by a rotary evaporator that removed organic solvents under reduced pressure. Column chromatography was performed using silica gel 60 [particle size 60-200 μm (70-230 mesh ASTM) or 40-63 μm (230-400 mesh ASTM)]. Preparative thin-layer chromatography was performed using silica gel 60 PF_{254}. Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F_{254} aluminum sheets. Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker AVIII-300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) or a Bruker AVIII-HD-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) using deuterochloroform as solvents with tetramethylsilane as an internal standard. Chemical shifts for ^{1}H NMR spectra were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), doublet of doublet (dd) and doublet of doublet of doublet (ddd). Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrophotometer using the universal attenuated total reflectance (ATR) technique and were reported in wavenumbers (cm^{-1}). Low resolution mass spectra were determined using a Thermo Scientific DSQ II single quadrupole GC/MS with FOCUS GC. High resolution mass spectra (HRMS) were obtained using time-of-flight (TOF) via atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) on Bruker MicroTOF spectrometer. Melting points were determined

on Electrothermal 9100 melting point apparatus and reported without correction.

4.2. General procedure for the synthesis of ynamide 3.

A 50 mL 2-neck round bottom flask equipped with a condenser and a septum was charged with *tert*-butyl 3,4-dimethoxyphenethylcarbamate, (bromoethynyl)benzene (1.5 equiv), CuI (0.2 equiv), 1,10-phenanthroline (0.22 equiv) under argon atmosphere. Subsequently, toluene was added and the reaction mixture was stirred at 90 °C for 5 minute. A solution of KHMDS (1.2 equiv) was slowly added to the reaction mixture using syringe pump over 3 h. The resulting dark-brown solution was stirred at 90 °C for 18 h and cooled to room temperature. The reaction mixture was quenched with the mixture of conc. ammonium hydroxide/brine (1:1), stirred at room temperature for 30 min, and extracted with EtOAc. The combined organic layers were dried over anh. Na_2SO_4 and concentrated in vacuo.

4.2.1. *tert*-Butyl 3,4-dimethoxyphenethyl(phenylethynyl)carbamate (3a)

tert-Butyl 3,4-dimethoxyphenethylcarbamate (1.27 g, 4.50 mmol), (bromoethynyl)benzene (1.22 g, 6.75 mmol), CuI (171 mg, 0.90 mmol), 1,10-phenanthroline (178 mg, 0.99 mmol) and KHMDS (0.45 *M* in toluene, 12.0 mL, 5.40 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 20:1 to 5:1 + 1% Et_3N as eluent) to obtain **3a** (1.28 g, 75%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43-7.34 (m, 2H), 7.34-7.21 (m, 3H), 6.85-6.73 (m, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.72 (t, *J* = 7.5 Hz, 2H), 2.96 (t, *J* = 7.5 Hz, 2H), 1.46 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.8, 148.9, 147.7, 130.7, 128.2, 127.1, 123.7, 120.9, 112.2, 111.4, 83.8, 82.3, 70.7, 55.9, 55.8, 50.4, 33.8, 27.9 ppm; IR (neat): ν_{max} = 2973, 2934, 2242, 1716, 1592, 1515, 1454, 1393, 1368, 1305, 1261, 1238, 1143, 1029, 853, 806, 754 cm^{-1}; EI-MS: *m/z* (relative intensity) = 381 (0.1, M^+), 325 (17), 266 (13), 165 (51), 152 (22), 151 (26), 150 (13), 130 (16), 57 (100); TOF-HRMS calcd. for $C_{23}H_{28}NO_4$ $(M + H)^+$ 382.2013, found 382.2018.

4.2.2. *tert*-Butyl 3,4-dimethoxyphenethyl((3,4-dimethoxyphenyl)ethynyl)carbamate (3b)

tert-Butyl 3,4-dimethoxyphenethylcarbamate (111 mg, 0.50 mmol), 4-(bromoethynyl)-1,2-dimethoxybenzene (157 mg, 0.65 mmol), CuI (19.0 mg, 0.10 mmol), 1,10-phenanthroline (22.5 mg, 0.13 mmol) in toluene (3 mL) and KHMDS (0.50 *M* in toluene, 1.30 mL, 0.65 mmol) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 4:1 + 1% Et_3N as eluent) to obtain **3b** (107 mg, 49%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.00 (br.d, *J* = 8.6 Hz, 1H), 6.90 (br.s, 1H), 6.84-6.77 (m, 4H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.71 (t, *J* = 7.4 Hz, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 1.47 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.8, 148.79, 148.76, 148.5, 147.6, 130.7, 124.2, 120.9, 115.7, 114.1, 112.1, 111.3, 111.0, 82.2, 82.1, 70.2, 55.81, 55.77, 55.76, 55.71, 50.5, 33.8, 27.9 ppm; IR (neat): ν_{max} = 2935, 2837, 2245, 1715, 1596, 1577, 1509, 1463, 1416, 1387, 1305, 1253, 1238, 1136, 1024, 851, 806, 762 cm^{-1}; EI-MS: *m/z* (relative intensity) = 441 (0.3, M^+), 385 (19), 279 (12), 221 (37), 178 (25), 164 (59), 150 (14), 149 (80), 97 (49), 85 (33), 83 (38), 71 (73), 69 (100); TOF-HRMS calcd. for $C_{25}H_{31}NO_6Na$ $(M + Na)^+$ 464.2044, found 464.2048.

4.2.3. *tert*-Butyl (benzo[*d*][1,3]dioxol-5-ylethynyl)(3,4-dimethoxyphenethyl)carbamate (3c)

tert-Butyl 3,4-dimethoxyphenethylcarbamate (563 mg, 2.00 mmol), 5-(bromoethynyl)benzo[*d*][1,3]dioxole (900 mg, 4.00 mmol), CuI (76.0 mg, 0.40 mmol), 1,10-phenanthroline (79.3 mg, 0.44 mmol) in toluene (5 mL) and KHMDS (0.50 *M* in toluene, 8.00 mL, 4.00 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 20:1 to 5:1 + 1% Et_3N as eluent) to obtain **3c** (832 mg, 98%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.90 (br.d, *J* = 7.6 Hz, 1H), 6.86-6.70 (m, 5H), 5.96 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.70 (t, *J* = 7.3 Hz, 2H), 2.94 (t, *J* = 7.3 Hz, 2H), 1.46 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.9, 148.9, 147.7, 147.3, 147.1, 130.7, 125.2, 120.9, 116.8, 112.2, 111.3, 111.2, 108.3, 101.1, 82.3, 82.0, 70.3, 55.9, 55.8, 50.5, 33.8, 27.9 ppm; IR (neat): ν_{max} = 2935, 2247, 1717, 1592, 1515, 1493, 1447, 1388, 1368, 1305, 1261, 1236, 1154, 1032, 935, 853, 809, 763 cm^{-1}; EI-MS: *m/z* (relative intensity) = 425 (2, M^+), 369 (99), 341 (15), 310 (16), 293 (9), 279 (8), 205 (30), 174 (17), 167 (19), 165 (55), 164 (69), 151 (57), 149 (100), 121 (11), 107 (13), 71 (26); TOF-HRMS calcd for $C_{24}H_{27}NO_6Na$ $(M + Na)^+$ 448.1731, found 448.1730.

4.2.4. *tert*-Butyl 3,4-dimethoxyphenethyl((2-methoxyphenyl)ethynyl)carbamate (3d)

tert-Butyl 3,4-dimethoxyphenethylcarbamate (422 mg, 1.50 mmol), 1-(bromoethynyl)-2-methoxybenzene (633 mg, 3.00 mmol), CuI (57.0 mg, 0.30 mmol), 1,10-phenanthroline (59.5 mg, 0.33 mmol) in toluene (5 mL) and KHMDS (0.48 *M* in toluene, 4.10 mL, 1.95 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 40:1 to 4:1 + 1% Et_3N as eluent) to obtain **3d** (442 mg, 72%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (br.d, *J* = 7.1 Hz, 1H), 7.27-7.19 (m, 1H), 6.93-6.77 (m, 5H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.74 (t, *J* = 7.5 Hz, 2H), 3.00 (t, *J* = 7.5 Hz, 2H), 1.47 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.2, 153.7, 148.8, 147.6, 132.3, 130.9, 128.4, 120.9, 120.3, 113.0, 112.2, 111.3, 110.6, 87.5, 82.1, 67.2, 55.8, 55.7, 55.6, 50.3, 33.6, 27.9 ppm; IR (neat): ν_{max} = 2967, 2936, 2245, 1712, 1592, 1514, 1463, 1391, 1366, 1236, 1156, 1027, 852, 807, 754 cm^{-1}; EI-MS: *m/z* (relative intensity) = 411 (0.3, M^+), 355 (31), 354 (33), 296 (19), 280 (11), 164 (100), 160 (13), 151 (43), 121 (5); TOF-HRMS calcd for $C_{24}H_{29}NO_5Na$ $(M + Na)^+$ 434.1938, found 434.1936.

4.2.5. *tert*-Butyl 3,4-dimethoxyphenethyl((3-methoxyphenyl)ethynyl)carbamate (3e)

tert-Butyl 3,4-dimethoxyphenethylcarbamate (422 mg, 1.50 mmol), 1-(bromoethynyl)-3-methoxybenzene (633 mg, 3.00 mmol), CuI (57.0 mg, 0.30 mmol), 1,10-phenanthroline (59.5 mg, 0.33 mmol) in toluene (5 mL) and KHMDS (0.48 *M* in toluene, 4.10 mL, 1.95 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 20:1 to 5:1 + 1% Et_3N as eluent) to obtain **3e** (147 mg, 24%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ:7.20 (dd, *J* = 8.0, 7.9 Hz, 1H), 6.97 (br.d, *J* = 7.4 Hz, 1H), 6.91 (br.s, 1H), 6.84-6.75 (m, 4H), 3.87 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.72 (t, *J* = 7.4 Hz, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 1.46 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.2, 153.6, 148.8, 147.6, 130.6, 129.1, 124.6, 123.1, 120.8, 115.7, 113.3, 112.1, 111.3, 83.6, 82.2, 70.6, 55.75, 55.65, 55.0, 50.3, 33.7, 27.8 ppm; IR (neat): ν_{max} = 2977, 2937, 2245, 1718, 1598, 1516, 1453, 1390, 1368, 1236, 1155, 1029, 850, 763, 687 cm^{-1}; EI-MS: *m/z* (relative intensity) = 411 (0.2, M^+), 354 (47), 296 (24), 165 (100), 164 (16), 152 (30), 150 (18); TOF-HRMS calcd for $C_{24}H_{29}NO_5Na$ $(M + Na)^+$ 434.1938, found 434.1947.

4.2.6. *tert*-Butyl 3,4-dimethoxyphenethyl((4-methoxyphenyl)ethynyl)carbamate (3f)

tert-butyl 3,4-dimethoxyphenethylcarbamate (281 mg, 1.00 mmol), 1-(bromoethynyl)-4-methoxybenzene (422 mg, 2.00 mmol), CuI (38.1 mg, 0.20 mmol), 1,10-phenanthroline (39.6 mg, 0.22 mmol) in toluene (4 mL) and KHMDS (0.45 *M* in toluene, 2.70 mL, 1.20 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 30:1 to 5:1 + 1% Et_3N as eluent) to obtain **3f** (232 mg, 56%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (br. d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.82-6.77 (m, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.70 (t, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 1.46 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.8, 153.7, 148.7, 147.5, 132.3, 130.6, 120.8, 115.5, 113.7, 112.1, 111.2, 82.0, 81.9, 70.0, 55.7, 55.6, 55.0, 50.3, 33.6, 27.7 ppm; IR (neat): ν_{max} = 2936, 2835, 2244, 1717, 1607, 1515, 1457, 1393, 1368, 1285, 1245, 1157, 1030, 833 cm^{-1}; EI-MS: *m/z* (relative intensity) = 411(0.3, M^+), 355 (43), 327 (14), 296 (13), 165 (100), 160 (32), 151 (39); TOF-HRMS calcd for $C_{24}H_{29}NO_5Na$ $(M + Na)^+$ 434.1938, found 434.1936.

4.2.7. *tert*-Butyl 3,4-dimethoxyphenethyl((4-fluorophenyl)ethynyl)carbamate (3g)

tert-Butyl 3,4-dimethoxyphenethylcarbamate (281 mg, 1.00 mmol), 1-(bromoethynyl)-4-fluorobenzene (299 mg, 1.50 mmol), CuI (38.0 mg, 0.20 mmol), 1,10-phenanthroline (40.0 mg, 0.22 mmol) in toluene (4 mL) and KHMDS (0.45 *M* in toluene, 3.30 mL, 1.50 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 10:1 to 7:1 + 1% Et_3N as eluent) to obtain **3g** (305 mg, 76%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34 (br.s, 2H), 6.99 (dd, *J* = 8.8, 8.7 Hz, 2H), 6.80 (s, 1H), 6.79 (d, *J* = 9.4 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.71 (t, *J* = 7.4 Hz, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 1.48 (br.s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 161.9 (d, *J* = 248.0 Hz), 153.74, 148.8, 147.7, 132.5, 130.6, 120.9, 119.7, 115.4 (d, *J* = 22.0 Hz), 112.1, 111.3, 83.3, 82.4, 69.6, 55.9, 55.8, 50.3, 33.8, 27.9 ppm; IR (neat): ν_{max} = 2977, 2936, 2245, 1718, 1600, 1511, 1455, 1393, 1368, 1307, 1289, 1261, 1236, 1151, 1029, 941, 835, 812, 761 cm^{-1}; EI-MS: *m/z* (relative intensity) = 399 (0.1, M^+), 343 (24), 342 (10), 284 (15), 165 (54), 152 (23), 151 (14), 148 (17), 57 (100); TOF-HRMS calcd. for $C_{23}H_{26}FNO_4Na$ $(M + Na)^+$ 422.1738, found 422.1744.

4.2.8. *tert*-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)(phenylethynyl)carbamate (3h)

tert-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (531 mg, 2.00 mmol), (bromoethynyl)benzene (724 mg, 4.00 mmol), CuI (76.2 mg, 0.40 mmol), 1,10-phenanthroline (79.3 mg, 0.44 mmol) in toluene (5 mL) and KHMDS (0.48 *M* in toluene, 5.00 mL, 2.40 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 100:1 to 20:1 + 1% Et_3N as eluent) to obtain **3h** (475 mg, 65%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43-7.33 (m, 2H), 7.33-7.23 (m, 3H), 6.79-6.68 (m, 3H), 5.91 (s, 2H), 3.69 (t, *J* = 7.4 Hz, 2H), 2.93 (t, *J* = 7.4 Hz, 2H), 1.48 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.8, 147.6, 146.2, 131.9, 130.7, 128.2, 127.1, 123.6, 121.9, 109.4, 108.3, 100.8, 83.8, 82.4, 70.8, 50.6, 34.0, 28.0 ppm; IR (neat): ν_{max} = 2978, 2933, 2887, 2242, 1717, 1503, 1490, 1443, 1393, 1368, 1306, 1245, 1147, 1039, 930, 856, 809, 754 cm^{-1}; EI-MS: *m/z* (relative intensity) = 365 (1, M^+), 309 (82), 281 (10), 265 (12), 239 (10), 235 (14), 206 (5), 149 (100), 136 (57), 135 (62), 130 (42), 119 (26), 91 (42), 77 (23); TOF-HRMS calcd. for $C_{22}H_{23}NO_4Na$ $(M + Na)^+$ 388.1519, found 388.1519.

4.2.9. *tert*-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)((3,4-dimethoxyphenyl)ethynyl)carbamate (3i)

tert-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (531 mg, 2.00 mmol), 4-(bromoethynyl)-1,2-dimethoxybenzene (964 mg, 4.00 mmol), CuI (76.2 mg, 0.40 mmol), 1,10-phenanthroline (79.3 mg, 0.44 mmol) in toluene (5 mL) and KHMDS (0.50 *M* in toluene, 6.00 mL, 3.00 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 15:1 to 10:1 + 1% Et_3N as eluent) to obtain **3i** (616 mg, 72%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.00 (br.d, *J* = 9.1 Hz, 1H), 6.90 (s, 1H), 6.82-6.67 (m, 4H), 5.89 (s, 2H), 3.87 (s, 6H), 3.68 (t, *J* = 7.1 Hz, 2H), 2.92 (t, *J* = 7.1 Hz, 2H), 1.47 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.8, 148.7, 148.5, 147.5, 146.1, 131.9, 124.2, 121.8, 115.7, 114.1, 110.9, 109.3, 108.2, 100.7, 82.2, 82.0, 70.1, 55.9, 55.8, 50.6, 33.9, 27.9 ppm; IR (neat): ν_{max} = 2925, 2247, 1716, 1596, 1515, 1490, 1443, 1390, 1365, 1245, 1140, 1027, 937, 854, 809, 763 cm^{-1}; EI-MS: *m/z* (relative intensity) = 425 (6, M^+), 370 (22), 369 (100), 368 (23), 343 (17), 341 (27), 325 (14), 322 (30), 221 (31), 207 (11), 190 (35), 178 (26), 165 (14), 151 (41), 149 (71), 148 (46), 135 (83), 119 (19), 91 (32); TOF-HRMS calcd. for $C_{24}H_{27}NO_6Na$ $(M + Na)^+$ 448.1731, found 448.1726.

4.2.10. *tert*-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)(benzo[*d*][1,3]dioxol-5-ylethynyl)carbamate (3j)

tert-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (265 mg, 1.00 mmol), 5-(bromoethynyl)benzo[*d*][1,3]dioxole (450 mg, 2.00 mmol), CuI (38.1 mg, 0.20 mmol), 1,10-phenanthroline (39.6 mg, 0.22 mmol) in toluene (4 mL) and KHMDS (0.40 *M* in toluene, 3.00 mL, 1.20 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:CH_2Cl_2; 4:1 to 1:1 + 1% Et_3N as eluent) to obtain **3j** (286 mg, 70%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.90 (d, *J* = 7.3 Hz, 1H), 6.83 (s, 1H), 6.78-6.66 (m, 4H), 5.96 (s, 2H), 5.91 (s, 2H), 3.66 (t, *J* = 7.3 Hz, 2H), 2.91 (t, *J* = 7.3 Hz, 2H), 1.47 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.7, 147.5, 147.2, 147.0, 146.0, 131.8, 125.2, 121.7, 116.7, 111.1, 109.2, 108.2, 108.1, 101.0, 100.6, 82.1, 81.9, 70.2, 50.6, 33.8, 27.8 ppm; IR (neat): ν_{max} = 2978, 2894, 2249, 1717, 1504, 1491, 1456, 1388, 1369, 1305, 1246, 1154, 1039, 936, 855, 809 cm^{-1}; EI-MS: *m/z* (relative intensity) = 409 (1, M^+), 353 (25), 325 (5), 295 (5), 279 (8), 221 (10), 174 (14), 167 (28), 149 (100), 135 (21), 113 (15), 111 (16), 99 (12), 97 (26), 85 (22), 83 (23), 71 (47), 69 (39); TOF-HRMS calcd. for $C_{23}H_{23}NO_6Na$ $(M + Na)^+$ 432.1418, found 432.1425.

4.2.11. *tert*-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)((2-methoxyphenyl)ethynyl)carbamate (3k)

tert-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (398 mg, 1.50 mmol), 1-(bromoethynyl)-2-methoxybenzene (633 mg, 3.00 mmol), CuI (57.1 mg, 0.30 mmol), 1,10-phenanthroline (59.5 mg, 0.33 mmol) in toluene (5 mL) and KHMDS (0.48 *M* in toluene, 4.10 mL, 1.95 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:CH_2Cl_2; 2:1 to 1:1 + 1% Et_3N as eluent) to obtain **3k** (450 mg, 76%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 (br.d, *J* = 6.7 Hz, 1H), 7.21 (dd, *J* = 8.7, 7.3 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 6.73 (s, 2H), 5.87 (s, 2H), 3.86 (s, 3H), 3.71 (t, *J* = 7.4 Hz, 2H), 2.97 (t, *J* = 7.4 Hz, 2H), 1.47 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.2, 153.6, 147.5, 146.0, 132.2, 132.0, 128.3, 121.8, 120.3, 112.9, 110.5, 109.3, 108.1, 100.6, 87.4, 82.1, 67.2, 55.6, 50.5, 33.7, 27.8 ppm; IR (neat): ν_{max} =

2978, 2937, 2244, 1717, 1491, 1444, 1392, 1369, 1308, 1246, 1151, 1010, 932, 752 cm^{-1}; EI-MS: *m/z* (relative intensity) = 395 (0.44, M^+), 339 (64), 338 (26), 264 (6), 160 (38), 149 (100), 135 (18), 123 (11), 119 (32), 91 (28), 57 (63); TOF-HRMS calcd. for $C_{23}H_{25}NO_5Na$ $(M + Na)^+$ 418.1625, found 418.1634.

4.2.12. *tert*-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)((3-methoxyphenyl)ethynyl)carbamate (3l)

tert-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (398 mg, 1.50 mmol), 1-(bromoethynyl)-3-methoxybenzene (633 mg, 3.00 mmol), CuI (57.1 mg, 0.30 mmol), 1,10-phenanthroline (59.5 mg, 0.33 mmol) in toluene (5 mL) and KHMDS (0.48 *M* in toluene, 4.10 mL, 1.95 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 40:1 to 20:1 + 1% Et_3N as eluent) to obtain **3l** (173 mg, 29%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.20 (dd, *J* = 8.0, 7.9 Hz, 1H), 6.97 (br.d, *J* = 7.5 Hz, 1H), 6.90 (br.s, 1H), 6.81 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.77-6.67 (m, 3H), 5.90 (s, 2H), 3.80 (s, 3H), 3.69 (t, *J* = 7.4 Hz, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 1.48 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.2, 153.6, 147.5, 146.1, 131.8, 129.1, 124.6, 123.2, 121.8, 115.7, 113.4, 109.3, 108.2, 100.7, 83.6, 82.3, 70.6, 55.1, 50.5, 33.9, 27.8 ppm; IR (neat): ν_{max} = 2978, 2937, 2245, 1717, 1598, 1574, 1490, 1445, 1389, 1368, 1293, 1246, 1153, 1039, 935, 851, 808, 780 cm^{-1}; EI-MS: *m/z* (relative intensity) = 395 (1, M^+), 339 (67), 311 (10), 295 (12), 269 (8), 265 (9), 160 (44), 149 (100), 136 (31), 119 (13), 91 (13); TOF-HRMS calcd. for $C_{23}H_{26}NO_5$ $(M + H)^+$ 396.1806, found 396.1809.

4.2.13. *tert*-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)((4-methoxyphenyl)ethynyl)carbamate (3m)

tert-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (398 mg, 1.50 mmol), 1-(bromoethynyl)-4-methoxybenzene (633 mg, 3.00 mmol), CuI (57.1 mg, 0.30 mmol), 1,10-phenanthroline (59.5 mg, 0.33 mmol) in toluene (5 mL) and KHMDS (0.48 *M* in toluene, 3.80 mL, 1.80 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 20:1 to 15:1 + 1% Et_3N as eluent) to obtain **3m** (333 mg, 56%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.33 (dd, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.77-6.67 (m, 3H), 5.90 (s, 2H), 3.80 (s, 3H), 6.67 (t, *J* = 7.4 Hz, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.47 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.0, 153.9, 147.6, 146.1, 132.5, 132.0, 121.9, 115.7, 113.8, 109.4, 108.3, 100.8, 82.2, 70.2, 55.2, 50.6, 34.0, 28.0 ppm; IR (neat): ν_{max} = 2977, 2932, 2244, 1717, 1607, 1514, 1490, 1444, 1393, 1368, 1308, 1286, 1245, 1154, 1037, 935, 831, 810 cm^{-1}; EI-MS: *m/z* (relative intensity) = 395 (1, M^+), 339 (59), 311 (18), 295 (12), 265 (5), 191 (4), 160 (41), 149 (100), 135 (36), 119 (26), 91 (25); TOF-HRMS calcd. for $C_{23}H_{25}NO_5Na$ $(M + Na)^+$ 418.1625, found 418.1625.

4.2.14. *tert*-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)((4-fluorophenyl)ethynyl)carbamate (3n)

tert-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (106 mg, 0.40 mmol), 1-(bromoethynyl)-4-fluorobenzene (119 mg, 0.60 mmol), CuI (15.0 mg, 0.08 mmol), 1,10-phenanthroline (16.0 mg, 0.09 mmol) in toluene (2 mL) and KHMDS (0.45 *M* in toluene, 1.30 mL, 0.60 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 30:1 + 1% Et_3N as eluent) to obtain **3n** (67.0 mg, 44%) as a pale yellow oil. ^1H-NMR (400 MHz, $CDCl_3$) δ: 7.34 (br.s, 2H), 6.99 (dd, *J* = 8.8, 8.7 Hz, 2H), 6.75 (d, *J* = 7.7 Hz, 1H), 6.74 (s, 1H), 6.70 (d, *J* = 7.8 Hz, 2H), 5.90 (s, 2H), 3.68 (t, *J* = 7.3 Hz, 2H), 2.91 (t, *J* = 7.3 Hz, 2H), 1.47 (br.s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 161.8 (d, *J* = 248.1 Hz), 153.7, 147.6, 146.1, 132.5, 131.8, 121.9, 119.6, 115.4 (d, *J* = 22.0 Hz), 109.3, 108.3, 100.8, 83.2, 82.4, 69.6, 50.5, 34.0, 27.9 ppm; IR (neat): ν_{max} = 2980, 2933, 2246, 1717, 1601, 1510, 1490, 1444, 1393, 1368, 1307, 1293, 1246, 1227, 1149, 1039, 930, 834, 811, 760 cm^{-1}; EI-MS: *m/z* (relative intensity) = 383 (0.4, M^+), 327 (38), 326 (12), 283 (6), 257 (5), 253 (6), 178 (8), 149 (50), 148 (32), 136 (25), 135 (14), 119 (10), 91 (13), 57 (100); TOF-HRMS calcd. for $C_{22}H_{22}FNO_4Na$ $(M + Na)^+$ 406.1425, found 406.1424.

4.2.15. *tert*-Butyl (phenylethynyl)(3,4,5-trimethoxyphenethyl)carbamate (3o)

tert-Butyl 3,4,5-trimethoxyphenethylcarbamate (623 mg, 2.00 mmol), (bromoethynyl)benzene (724 mg, 4.00 mmol), CuI (76.2 mg, 0.40 mmol), 1,10-phenanthroline (79.3 mg, 0.44 mmol) in toluene (5 mL) and KHMDS (0.48 *M* in toluene, 5.00 mL, 2.40 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 20:1 to 5:1 + 1% Et_3N as eluent) to obtain **3o** (432 mg, 53%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.41-7.34 (m, 2H), 7.34-7.24 (m, 3H), 6.48 (s, 2H), 3.85 (s, 6H), 3.81 (s, 3H), 3.74 (t, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 7.3 Hz, 2H), 1.48 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.4, 152.9, 136.3, 133.5, 130.4, 127.9, 126.9, 123.3, 105.6, 83.4, 82.0, 70.6, 60.3, 55.7, 49.7, 34.2, 27.6 ppm; IR (neat): ν_{max} = 2937, 2242, 1717, 1590, 1508, 1457, 1393, 1368, 1239, 1126, 1011, 825, 755 cm^{-1}; EI-MS: *m/z* (relative intensity) = 411 (0.1, M^+), 355 (20), 296 (6), 195 (97), 181 (40), 165 (11), 148 (10), 130 (26), 121 (12), 103 (14), 91 (16), 77 (12), 57 (100); TOF-HRMS calcd. for $C_{24}H_{30}NO_5$ $(M + H)^+$ 412.2119, found 412.2109.

4.2.16. *tert*-Butyl ((3,4-dimethoxyphenyl)ethynyl)(3,4,5-trimethoxyphenethyl)carbamate (3p)

tert-Butyl 3,4,5-trimethoxyphenethylcarbamate (623 mg, 2.00 mmol), 4-(bromoethynyl)-1,2-dimethoxybenzene (964 mg, 4.00 mmol), CuI (76.2 mg, 0.40 mmol), 1,10-phenanthroline (79.3 mg, 0.44 mmol) in toluene (5 mL) and KHMDS (0.48 *M* in toluene, 5.00 mL, 2.40 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 10:1 to 3:1 + 1% Et_3N as eluent) to obtain **3p** (651 mg, 69%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.00 (br.d, *J* = 8.0 Hz, 1H), 6.91 (s, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.48 (s, 2H), 3.88 (s, 6H), 3.85 (s, 6H), 3.81 (s, 3H), 3.73 (t, *J* = 7.1 Hz, 2H), 2.95 (t, *J* = 7.1 Hz, 2H), 1.47 (br.s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.4, 152.7, 148.5, 148.2, 136.2, 133.5, 123.9, 115.3, 113.8, 110.7, 105.5, 81.8, 81.7, 70.0, 60.2, 55.5, 55.4, 49.8, 34.1, 27.5 ppm; IR (neat): ν_{max} = 2937, 2838, 2247, 1716, 1590, 1513, 1457, 1417, 1386, 1368, 1305, 1239, 1153, 1127, 1024, 852, 810, 762 cm^{-1}; EI-MS: *m/z* (relative intensity) = 471 (0.03, M^+), 415 (73), 221 (56), 206 (9), 194 (100), 181 (40), 179 (41), 165 (16), 151 (10), 137 (9), 107 (6), 91 (8), 77 (8); TOF-HRMS calcd. for $C_{26}H_{33}NO_7Na$ $(M + Na)^+$ 494.2149, found 494.2137.

4.2.17. *tert*-Butyl phenethyl(phenylethynyl)carbamate (3q)

tert-Butyl phenethylcarbamate (443 mg, 2.00 mmol), (bromoethynyl)benzene (543 mg, 3.00 mmol), CuI (76.2 mg, 0.40 mmol), 1,10-phenanthroline (79.3 mg, 0.44 mmol) in toluene (5 mL) and KHMDS (0.48 *M* in toluene, 3.80 mL, 1.80 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 100:0 to 30:1 + 1% Et_3N as eluent) to obtain **3q** (94.4 mg, 15%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.33-7.10 (m, 10H), 3.66 (t, *J* = 7.5 Hz, 2H), 2.94 (t, *J* = 7.5 Hz, 2H), 1.39 (s,

9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.7, 152.1, 138.2, 130.8, 129.0, 128.5, 128.2, 127.1, 126.5, 83.8, 82.3, 80.9, 50.4, 34.3, 27.93, 27.85 ppm; IR (neat): ν_{max} = 2979, 2933, 2244, 1720, 1455, 1393, 1368, 1307, 1248, 1150, 753, 691 cm^{-1}; EI-MS: *m/z* (relative intensity) = 321 (8, M^+), 265 (19), 264 (15), 221 (44), 220 (10), 130 (50), 105 (100), 91 (8), 79 (9), 77 (7), 57 (73); TOF-HRMS calcd. for $C_{21}H_{23}NO_2Na$ $(M + Na)^+$ 344.1621, found 344.1628.

4.2.18. Ethyl 3,4-dimethoxyphenethyl(phenylethynyl)carbamate (3r)

Ethyl 3,4-dimethoxyphenethylcarbamate (253 mg, 1.00 mmol), (bromoethynyl)benzene (362 mg, 2.00 mmol), CuI (38.1 mg, 0.20 mmol), 1,10-phenanthroline (39.6 mg, 0.22 mmol) in toluene (5 mL) and KHMDS (0.48 *M* in toluene, 3.20 mL, 1.50 mmol) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 10:1 to 5:1 + 1% Et_3N as eluent) to obtain **3r** (241 mg, 68%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43-7.36 (m, 2H), 7.35-7.25 (m, 3H), 6.84-6.76 (m, 3H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.78 (t, *J* = 7.5 Hz, 2H), 2.98 (t, *J* = 7.5 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.1, 148.9, 147.7, 131.1, 130.5, 128.2, 127.5, 123.3, 120.9, 112.1, 111.3, 83.0, 70.8, 63.1, 55.9, 55.8, 51.2, 33.7, 14.3 ppm; IR (neat): ν_{max} = 2982, 2936, 2835, 2243, 1719, 1592, 1515, 1464, 1443, 1403, 1373, 1261, 1236, 1141, 1105, 1027, 805, 755, 692 cm^{-1}; EI-MS: *m/z* (relative intensity) = 353 (36, M^+), 352 (100), 325 (28), 324 (38), 297 (22), 280 (7), 165 (29), 164 (72), 151 (60), 150 (13), 149 (13), 130 (22), 117 (29), 105 (13), 103 (14), 91 (8); TOF-HRMS calcd. for $C_{21}H_{24}NO_4$ $(M + H)^+$ 354.1699, found 354.1706.

4.3. General procedure for PIFA-BF_3·OEt_2 mediated domino cyclization.

A 25 mL round bottom flask was charged with ynamide **3**, PIFA (1.1 equiv) and 4 Å molecular sieve in dry CH_2Cl_2 at room temperature under argon atmosphere. Then the reaction mixture was cooled to −96 °C using a MeOH/liquid N_2 bath, followed by addition of BF_3·OEt_2 (2.0 equiv). The reaction mixture was stirred at −96 °C for 3 h, quenched with sat. $NaHCO_3$ (5 mL) at −96 °C, and allowed to warm up to room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anh. Na_2SO_4 and concentrated in vacuo.

4.3.1. 8,9-Dimethoxy-1-phenyl-5,6-dihydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4a)

Ynamide **3a** (202 mg, 0.53 mmol), PIFA (251 mg, 0.58 mmol), 4 Å molecular sieve (500 mg) and BF_3·OEt_2 (131 μL, 1.06 mmol) in dry CH_2Cl_2 (5 mL) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 4:1 to 1:1 + 1% Et_3N as eluent) to obtain **4a** (101 mg, 59%) as a white solid (m.p. 148-149 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 6.9 Hz, 2H), 7.45-7.30 (m, 3H), 7.16 (s, 1H), 6.76 (s, 1H), 3.91 (s, 3H), 3.82 (t, *J* = 6.2 Hz, 2H), 3.64 (s, 3H), 3.01 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.4, 149.4, 147.8, 133.0, 128.6, 128.5, 126.52, 126.49, 119.2, 116.7, 111.3, 107.0, 55.9, 55.7, 38.3, 28.9 ppm; IR (neat): ν_{max} = 2938, 1757, 1515, 1381, 1265, 1214, 1100, 1048, 750, 700 cm^{-1}; EI-MS: *m/z* (relative intensity) = 323 (100, M^+), 294 (12), 267 (26), 266 (35), 264 (15), 236 (5), 178 (11), 161 (7), 149 (19), 111 (8), 105 (30), 97 (13), 77 (36), 69 (29), 57 (31); TOF-HRMS calcd. for $C_{19}H_{18}NO_4$ $(M + H)^+$ 324.1230, found 324.1238.

3-(3,4-Dimethoxyphenethyl)-5-phenyloxazolidine-2,4-dione (5a): (20 mg, 11%) as a yellow viscos oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42-7.33 (m, 3H), 7.21-7.13 (m, 2H), 6.75-6.66 (m, 3H), 5.62 (s, 1H), 3.85 (s, 3H), 3.98-3.76 (m, 2H), 3.80 (s, 3H), 2.99 (t, *J* = 7.3 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.8, 154.8, 148.6, 147.6, 131.3, 129.4, 128.8, 128.6, 125.9, 120.6, 111.6, 110.9, 79.8, 55.4, 40.6, 32.1 ppm; IR (neat): ν_{max} = 2939, 1815, 1736, 1592, 1515, 1443, 1411, 1366, 1263, 1237, 1149, 1105, 1026, 808, 761, 734, 699 cm^{-1}; EI-MS: *m/z* (relative intensity) = 341 (28, M^+), 165 (12), 164 (100), 151 (64), 149 (33), 135 (4), 121 (5), 105 (10), 91 (10), 84 (14), 77 (10); TOF-HRMS calcd. for $C_{19}H_{19}NO_5Na$ $(M + Na)^+$ 364.1155, found 364.1168.

***tert*-Butyl 3,4-dimethoxyphenethyl(2-phenylacetyl)carbamate (6a)**: (11 mg, 5%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.18 (m, 5H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.74-6.66 (m, 2H), 4.22 (s, 2H), 3.88 (t, *J* = 7.7 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 2.76 (t, *J* = 7.7 Hz, 2H), 1.48 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 174.0, 153.0, 148.9, 147.6, 135.1, 131.4, 129.5, 128.3, 126.7, 120.8, 112.2, 111.3, 83.0, 55.9, 55.8, 46.5, 44.5, 34.5, 27.9 ppm; IR (neat): ν_{max} = 2975, 2934, 1731, 1688, 1515, 1455, 1359, 1262, 1236, 1143, 1030, 852, 772 cm^{-1}; EI-MS: *m/z* (relative intensity) = 399 (4, M^+), 299 (2), 180 (3), 165 (13), 164 (100), 151 (22), 149 (7), 91 (19), 77 (3); TOF-HRMS calcd. for $C_{23}H_{29}NO_5Na$ $(M + Na)^+$ 422.1938, found 422.1937.

4.3.2. 1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4b)

Ynamide **3b** (44.2 mg, 0.10 mmol), PIFA (47.3 mg, 0.11 mmol), 4 Å molecular sieve (200 mg) and BF_3·OEt_2 (25 μL, 0.20 mmol) in dry CH_2Cl_2 (3 mL) were employed. The reaction was carried out at −96 °C for 30 min. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 1:1 + 1% Et_3N as eluent) to obtain **4b** (7.3 mg, 19%) as a pale yellow solid (m.p. 89-93 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.18 (s, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.75 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 3.83 (t, *J* = 6.2 Hz, 2H), 3.66 (s, 3H), 3.01 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 153.5, 149.5, 149.5, 149.1, 148.0, 133.2, 126.4, 121.2, 119.7, 118.4, 117.1, 111.5, 111.0, 110.0, 107.2, 56.03, 55.99, 38.5, 29.0 ppm; IR (neat): ν_{max} = 2935, 2839, 1753, 1594, 1511, 1464, 1379, 1321, 1263, 1133, 1097, 1023, 858 cm^{-1}; EI-MS: *m/z* (relative intensity) = 383 (31, M^+), 355 (21), 327 (36), 326 (42), 324 (100), 312 (87), 296 (24), 249 (22), 204 (16), 178 (93), 165 (99), 161 (38), 149 (64), 137 (24), 123 (95), 111 (32), 105 (38), 97 (44), 83 (48), 71 (44), 69 (47); TOF-HRMS calcd. for $C_{21}H_{21}NO_6Na$ $(M + Na)^+$ 406.1261, found 406.1252.

4.3.3. 1-(Benzo[*d*][1,3]dioxol-5-yl)-8,9-dimethoxy-5,6-dihydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4c)

Ynamide **3c** (42.6 mg, 0.10 mmol), PIFA (47.3 mg, 0.11 mmol), 4 Å molecular sieve (200 mg) and BF_3·OEt_2 (25 μL, 0.20 mmol) in dry CH_2Cl_2 (3 mL) were employed. The reaction was carried out at −96 °C for 30 min. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 1:1 + 1% Et_3N as eluent) to obtain **4c** (15.1 mg, 41%) as a pale yellow solid (m.p. 171-174 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22-7.10 (m, 2H), 7.16 (s, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.74 (s, 1H), 6.01 (s, 2H), 3.91 (s, 3H), 3.82 (t, *J* = 6.2 Hz, 2H), 3.68 (s, 3H), 3.00 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 153.4, 149.4, 148.02, 147.98, 133.0, 126.4, 122.4, 121.0, 118.5, 116.9, 111.4, 108.5, 107.3,

107.2, 101.4, 56.0, 55.9, 38.5, 29.0 ppm; IR (neat): ν_{max} = 2932, 2905, 1753, 1610, 1514, 1489, 1381, 1271, 1237, 1213, 1095, 1034, 925 cm^{-1}; EI-MS: *m/z* (relative intensity) = 367 (100, M$^+$), 360 (8), 352 (8), 311 (25), 310 (34), 249 (14), 204 (9), 178 (9), 149 (37), 135 (12), 112 (21), 97 (11), 83 (15); TOF-HRMS calcd. for $C_{20}H_{17}NO_6Na$ (M + Na)$^+$ 390.0948, found 390.0944.

4.3.4. 8,9-Dimethoxy-1-(2-methoxyphenyl)-5,6-dihydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4d)

Ynamide **3d** (80.8 mg, 0.20 mmol), PIFA (92.9 mg, 0.22 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (50 μL, 0.40 mmol) in dry CH_2Cl_2 (3 mL) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 1:1 + 1% Et_3N as eluent) to obtain **4d** (47.6 mg, 69%) as a white solid (m.p. 163-165 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.41 (ddd, *J* = 7.6, 7.6, 1.7 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.72 (s, 1H), 6.63 (s, 1H), 3.89 (s, 3H), 3.87 (t, *J* = 6.4 Hz, 2H), 3.75 (s, 3H), 3.51 (s, 3H), 3.03 (t, *J* = 6.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.4, 154.0, 149.0, 147.6, 131.3, 131.0, 129.6, 125.4, 120.5, 120.4, 117.4, 117.2, 111.2, 110.9, 107.7, 55.9, 55.5, 55.4, 38.3, 28.5 ppm; IR (neat): ν_{max} = 2938, 2840, 1748, 1598, 1515, 1490, 1463, 1433, 1262, 1248, 1212, 1168, 1094, 1051, 1021, 863, 789, 751 cm^{-1}; EI-MS: *m/z* (relative intensity) = 353 (100, M$^+$), 338 (6), 310 (8), 296 (10), 294 (39), 135 (23); TOF-HRMS calcd. for $C_{20}H_{20}NO_5$ (M + H)$^+$ 354.1336, found 354.1341.

4.3.5. 8,9-Dimethoxy-1-(3-methoxyphenyl)-5,6-dihydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4e)

Ynamide **3e** (91.1 mg, 0.22 mmol), PIFA (105 mg, 0.24 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (56 μL, 0.44 mmol) in dry CH_2Cl_2 (3 mL) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 1:1 + 1% Et_3N as eluent) to obtain **4e** (56.8 mg, 72%) as a white solid (m.p. 156-158 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35-7.26 (m, 2H), 7.25-7.19 (m, 2H), 6.89 (ddd, *J* = 6.9, 2.4, 2.4 Hz, 1H), 6.76 (s, 1H), 3.92 (s, 3H), 3.83 (t, *J* = 6.2 Hz, 2H), 3.82 (s, 3H), 3.67 (s, 3H), 3.01 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.8, 153.4, 149.6, 147.9, 133.0, 129.7, 129.5, 126.6, 119.4, 118.8, 116.8, 114.8, 111.7, 111.4, 107.4, 56.0, 55.8, 55.3, 38.4, 29.0 ppm; IR (neat): ν_{max} = 2939, 2839, 1751, 1604, 1575, 1513, 1464, 1427, 1378, 1267, 1239, 1210, 1101, 1035, 862, 783, 749 cm^{-1}; EI-MS: *m/z* (relative intensity) = 353 (100, M$^+$), 338 (7), 324 (6), 296 (20), 282 (17), 135 (10), 107 (5); TOF-HRMS calcd. for $C_{20}H_{20}NO_5$ (M + H)$^+$ 354.1336, found 354.1344.

4.3.6. 8,9-Dimethoxy-1-(4-methoxyphenyl)-5,6-dihydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4f)

Ynamide **3f** (41.2 mg, 0.10 mmol), PIFA (47.3 mg, 0.11 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (25 μL, 0.20 mmol) in dry CH_2Cl_2 (3 mL) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 2:1 + 1% Et_3N as eluent) to obtain **4f** (11.0 mg, 31%) as a white solid (m.p. 164-167 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 8.8 Hz, 2H), 7.13 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.74 (s, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.83 (t, *J* = 6.2 Hz, 2H), 3.65 (s, 3H), 3.00 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.0, 153.6, 149.3, 148.0, 133.2, 128.4, 126.2, 121.0, 118.2, 117.2, 114.1, 111.4, 107.0, 56.0, 55.9, 55.4, 38.5, 29.0 ppm; IR (neat): ν_{max} = 2936, 2840, 1749, 1608, 1506, 1464, 1381, 1296, 1250, 1231, 1212, 1170, 1093, 1025, 834, 791, 749, 733 cm^{-1}; EI-MS: *m/z* (relative intensity) = 353 (100, M$^+$), 338 (12), 324 (6), 297 (16), 296 (20), 294 (21), 282 (12), 266 (6), 176 (4), 135 (55), 107 (4); TOF-HRMS calcd. for $C_{20}H_{19}NO_5Na$ (M + Na)$^+$ 376.1155, found 376.1161.

4.3.7. 1-(4-fluorophenyl)-8,9-dimethoxy-5,6-dihydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4g)

Ynamide **3g** (60.0 mg, 0.15 mmol), PIFA (71.0 mg, 0.17 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (38 μL, 0.30 mmol) in dry CH_2Cl_2 (2 mL) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 3:2 + 1% Et_3N as eluent) to obtain **4g** (18.2 mg, 36%) as a pale yellow solid (m.p. 59-61 °C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.12 (dd, *J* = 8.7, 8.6 Hz, 2H), 7.07 (s, 1H), 6.76 (s, 1H), 3.92 (s, 3H), 3.83 (t, *J* = 6.2 Hz, 2H), 3.66 (s, 3H), 3.02 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 162.7 (d, *J* = 249.8 Hz), 153.4, 149.6, 148.0, 132.2, 128.7 (d, *J* = 8.2 Hz), 126.6, 124.8 (d, *J* = 3.6 Hz), 119.2, 116.6, 115.8 (d, *J* = 21.9 Hz), 111.5, 106.9, 56.0, 55.9, 38.4, 29.0 ppm; IR (neat): ν_{max} = 2929, 2848, 1751, 1610, 1516, 1505, 1465, 1380, 1262, 1228, 1213, 1169, 1159, 1090, 1042, 1013, 839, 805, 785, 749 cm^{-1}; EI-MS: *m/z* (relative intensity) = 341 (100, M$^+$), 312 (10), 285 (23), 284 (28), 282 (24), 221 (9), 178 (20), 167 (6), 161 (9), 149 (16), 127 (17), 123 (27), 111 (9), 97 (13), 83 (14), 81 (15), 71 (19), 69 (22); TOF-HRMS calcd. for $C_{19}H_{16}FNO_4Na$ (M + Na)$^+$ 364.0956, found 364.0948.

4.3.8. 1-Phenyl-5,6-dihydro-3*H*-[1,3]dioxolo[4,5-*g*]oxazolo[4,3-*a*]isoquinolin-3-one (4h)

Ynamide **3h** (200 mg, 0.55 mmol), PIFA (259 mg, 0.60 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (135 μL, 1.10 mmol) in dry CH_2Cl_2 (5 mL) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 5:1 to 2:1 + 1% Et_3N as eluent) to obtain **4h** (74.4 mg, 44%) as a pale yellow solid (m.p. 187-189 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66-7.59 (m, 2H), 7.46-7.32 (m, 3H), 7.08 (s, 1H), 6.74 (s, 1H), 5.96 (s, 2H), 3.80 (t, *J* = 6.2 Hz, 2H), 2.98 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.4, 148.2, 146.8, 133.6, 128.8, 128.7, 128.3, 128.1, 126.7, 119.2, 118.0, 109.0, 104.4, 101.4, 38.4, 29.6 ppm; IR (neat): ν_{max} = 2922, 1749, 1502, 1480, 1447, 1383, 1254, 1161, 1037, 933, 866, 735, 694 cm^{-1}; EI-MS: *m/z* (relative intensity) = 307 (100, M$^+$), 278 (23), 250 (61), 221 (7), 149 (17), 139 (8), 116 (9), 105 (38), 102 (8), 89 (9), 77 (45); TOF-HRMS calcd. for $C_{18}H_{13}NO_4Na$ (M + Na)$^+$ 330.0737, found 330.0743.

4.3.9. 1-(3,4-Dimethoxyphenyl)-5,6-dihydro-3*H*-[1,3]dioxolo[4,5-*g*]oxazolo[4,3-*a*]isoquinolin-3-one (4i)

Ynamide **3i** (50.5 mg, 0.12 mmol), PIFA (56.2 mg, 0.13 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (30 μL, 0.24 mmol) in dry CH_2Cl_2 (3 mL) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 2:1 + 1% Et_3N as eluent) to obtain **4i** (24.6 mg, 56%) as a pale yellow solid (m.p. 134-136 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.21 (s, 1H), 7.20 (d, *J* = 2.0 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.74 (s, 1H), 5.96 (s, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.80 (t, *J* = 6.2 Hz, 2H), 2.98 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.3, 149.5, 149.1, 148.0, 146.8, 133.7, 127.9, 120.9, 119.7, 118.3, 118.2, 111.3, 109.9, 109.0, 104.3, 101.4, 56.0, 55.9, 38.4, 29.6 ppm; IR (neat): ν_{max} = 2926, 1752, 1516, 1483, 1415, 1385, 1262, 1228, 1175, 1144, 1034, 929, 857, 749 cm^{-1}; EI-MS: *m/z* (relative intensity) = 367 (0.5, M$^+$), 287 (9), 285 (26), 232 (13), 230 (20), 208 (100), 195 (41), 180 (17), 167 (18), 139 (10), 118 (9), 97 (9), 77 (13); TOF-HRMS calcd. for $C_{20}H_{17}NO_6Na$ (M + Na)$^+$ 390.0948, found 390.0949.

4.3.10. 1-(Benzo[*d*][1,3]dioxol-5-yl)-5,6-dihydro-3*H*-[1,3]dioxolo[4,5-*g*]oxazolo[4,3-*a*]isoquinolin-3-one (4j)

Ynamide **3j** (26.6 mg, 0.07 mmol), PIFA (30.7 mg, 0.07 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (16 μL, 0.13 mmol) in dry CH_2Cl_2 (2 mL) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 2:1 + 1% Et_3N as eluent) to obtain **4j** (11.4 mg, 50%) as a pale yellow solid (m.p. 203-206 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.12 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.05 (s, 2H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.73 (s, 1H), 6.02 (s, 2H), 5.96 (s, 2H), 3.79 (t, *J* = 6.2 Hz, 2H), 2.96 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.3, 148.2, 148.1, 148.0, 146.8, 133.4, 127.9, 122.1, 121.4, 118.5, 118.1, 109.0, 108.8, 107.5, 104.4, 101.43, 101.38, 38.4, 29.6 ppm; IR (neat): ν_{max} = 2923, 1748, 1502, 1480, 1443, 1384, 1258, 1229, 1095, 1069, 1031, 926, 858, 813, 748 cm^{-1}; EI-MS: *m/z* (relative intensity) = 351 (100, M^+), 322 (17), 295 (54), 294 (62), 265 (18), 176 (16), 161 (22), 149 (67), 147 (12), 133 (10), 121 (29), 89 (13); TOF-HRMS calcd. for $C_{19}H_{13}NO_6Na$ $(M + Na)^+$ 374.0635, found 374.0645.

4.3.11. 1-(2-Methoxyphenyl)-5,6-dihydro-3*H*-[1,3]dioxolo[4,5-*g*]oxazolo[4,3-*a*]isoquinolin-3-one (4k)

Ynamide **3k** (99.0 mg, 0.25 mmol), PIFA (118 mg, 0.28 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (63 μL, 0.50 mmol) in dry CH_2Cl_2 (3 mL) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 1:1 + 1% Et_3N as eluent) to obtain **4k** (52.5 mg, 62%) as a white solid (m.p. 186-188 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.41 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.05 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.70 (s, 1H), 6.56 (s, 1H), 5.91 (s, 2H), 3.84 (t, *J* = 6.3 Hz, 2H), 3.76 (s, 3H), 3.00 (t, *J* = 6.3 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.2, 153.8, 147.6, 146.5, 131.1, 131.0, 130.0, 127.0, 120.8, 120.4, 118.5, 117.3, 111.4, 108.4, 104.9, 101.1, 55.3, 38.2, 29.1 ppm; IR (neat): ν_{max} = 2967, 2916, 1738, 1494, 1465, 1435, 1384, 1285, 1252, 1030, 1020, 934, 882, 763, 750, 741 cm^{-1}; EI-MS: *m/z* (relative intensity) = 337 (100, M^+), 308 (5), 280 (14), 278 (47), 178 (13), 149 (7), 135 (35), 123 (8); TOF-HRMS calcd. for $C_{19}H_{16}NO_5$ $(M + H)^+$ 338.1023, found 338.1027.

4.3.12. 1-(3-Methoxyphenyl)-5,6-dihydro-3*H*-[1,3]dioxolo[4,5-*g*]oxazolo[4,3-*a*]isoquinolin-3-one (4l)

Ynamide **3l** (93.0 mg, 0.24 mmol), PIFA (111 mg, 0.25 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (59 μL, 0.47 mmol) in dry CH_2Cl_2 (3 mL) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 2:1 + 1% Et_3N as eluent) to obtain **4l** (40.8 mg, 51%) as a white solid (m.p. 171-176 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 (dd, *J* = 8.0, 7.7 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 7.14 (s, 1H), 6.90 (dd, *J* = 8.1, 2.5 Hz, 1H), 6.73 (s, 1H), 5.96 (s, 2H), 3.81 (s, 3H), 3.79 (t, *J* = 6.2 Hz, 2H), 2.97 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.7, 153.2, 148.2, 146.8, 133.4, 129.8, 129.4, 128.2, 119.4, 118.9, 117.9, 115.0, 111.6, 108.9, 104.5, 101.4, 55.3, 38.3, 29.5 ppm; IR (neat): ν_{max} = 2904, 1751, 1598, 1575, 1477, 1429, 1384, 1288, 1260, 1228, 1168, 1034, 926, 864, 792, 749 cm^{-1}; EI-MS: *m/z* (relative intensity) = 337 (100, M^+), 308 (12), 281 (14), 280 (34), 278 (16), 266 (22), 149 (10), 135 (19), 123 (8), 107 (12); TOF-HRMS calcd. for $C_{19}H_{16}NO_5$ $(M + H)^+$ 338.1023, found 338.1015.

4.3.13. 1-(4-Methoxyphenyl)-5,6-dihydro-3*H*-[1,3]dioxolo[4,5-*g*]oxazolo[4,3-*a*]isoquinolin-3-one (4m)

Ynamide **3m** (110 mg, 0.28 mmol), PIFA (131 mg, 0.30 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (70 μL, 0.55 mmol) in dry CH_2Cl_2 (4 mL) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 2:1 + 1% Et_3N as eluent) to obtain **4m** (36.3 mg, 39%) as a white solid (m.p. 164-167 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54 (d, *J* = 8.9 Hz, 2H), 7.03 (s, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.72 (s, 1H), 5.95 (s, 2H), 3.85 (s, 3H), 3.79 (t, *J* = 6.2 Hz, 2H), 2.97 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.0, 153.4, 148.0, 146.8, 133.7, 128.5, 127.7, 120.7, 118.3, 118.2, 114.3, 108.9, 104.2, 101.3, 55.3, 38.4, 29.5 ppm; IR (neat): ν_{max} = 2902, 2841, 1750, 1665, 1598, 1503, 1481, 1385, 1295, 1249, 1174, 1033, 933, 834 cm^{-1}; EI-MS: *m/z* (relative intensity) = 337 (100, M^+), 322 (7), 308 (12), 281 (17), 280 (27), 266 (8), 135 (48), 107 (5); TOF-HRMS calcd. for $C_{19}H_{16}NO_5$ $(M + H)^+$ 338.1023, found 338.1015.

4.3.14. 1-(4-fluorophenyl)-5,6-dihydro-3*H*-[1,3]dioxolo[4,5-*g*]oxazolo[4,3-*a*]isoquinolin-3-one (4n)

Ynamide **3n** (63.0 mg, 0.16 mmol), PIFA (78.0 mg, 0.18 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (41 μL, 1.06 mmol) in dry CH_2Cl_2 (2 mL) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 3:1 + 1% Et_3N as eluent) to obtain **4n** (20.4 mg, 38%) as a white solid (m.p. 163-166 °C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.60 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.12 (dd, *J* = 8.6, 8.6 Hz, 2H), 7.00 (s, 1H), 6.75 (s, 1H), 5.97 (s, 2H), 3.80 (t, *J* = 6.2 Hz, 2H), 2.98 (t, *J* = 6.2 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 162.7 (d, *J* = 249.7 Hz), 153.2, 148.3, 146.9, 132.6, 128.8 (d, *J* = 8.3 Hz), 128.1, 124.5 (d, *J* = 3.5 Hz), 119.1, 117.8, 116.0 (d, *J* = 22.0 Hz), 109.1, 104.1, 101.4, 38.4, 29.5 ppm; IR (neat): ν_{max} = 2919, 2856, 1752, 1602, 1509, 1481, 1386, 1254, 1230, 1159, 1069, 1037, 934, 839, 820, 749 cm^{-1}; EI-MS: *m/z* (relative intensity) = 325 (100, M^+), 296 (26), 295 (20), 269 (35), 268 (55), 239 (13), 221 (39), 207 (11), 178 (51), 167 (13), 161 (24), 149 (49), 127 (18), 123 (46), 111 (19), 97 (26), 83 (28), 73 (28), 71 (42), 69 (27); TOF-HRMS calcd. for $C_{18}H_{12}FNO_4Na$ $(M + Na)^+$ 348.0643, found 348.0635.

4.3.15. 8,9,10-Trimethoxy-1-phenyl-5,6-dihydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4o)

Ynamide **3o** (41.2 mg, 0.10 mmol), PIFA (47.3 mg, 0.11 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (25 μL, 0.20 mmol) in dry CH_2Cl_2 (3 mL) were employed. The reaction was carried out at –96 °C for 30 min. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 2:1 + 1% Et_3N as eluent) to obtain **4o** (7.0 mg, 20%) as a white solid (m.p. 81-83 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42-7.36 (m, 2H), 7.36-7.28 (m, 3H), 6.62 (s, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 3.79 (t, *J* = 6.0 Hz, 2H), 3.34 (s, 3H), 2.98 (t, *J* = 6.0 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.0, 153.8, 150.7, 141.1, 135.9, 131.0, 129.8, 128.0, 127.3, 127.1, 115.8, 112.1, 107.2, 61.2, 60.0, 56.2, 38.7, 30.7 ppm; IR (neat): ν_{max} = 2937, 2842, 1752, 1597, 1516, 1464, 1419, 1377, 1240, 1198, 1128, 1024 cm^{-1}; EI-MS: *m/z* (relative intensity) = 353 (100, M^+), 296 (12), 294 (16), 282 (17), 219 (30), 194 (11), 178 (25), 164 (72), 151 (26), 149 (13), 105 (36); TOF-HRMS calcd. for $C_{20}H_{19}NO_5Na$ $(M + Na)^+$ 376.1155, found 376.1163.

4.3.16. 1-(3,4-Dimethoxyphenyl)-8,9,10-trimethoxy-5,6-dihydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4p)

Ynamide **3p** (47.2 mg, 0.10 mmol), PIFA (47.3 mg, 0.11 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (25 μL, 0.20 mmol) in dry CH_2Cl_2 (3 mL) were employed. After usual workup, the crude product was purified by preparative thin-layer chromatography (SiO_2, hexane:EtOAc; 1:1 + 1% Et_3N as eluent) to obtain **4p** (13.9 mg, 22%) as a pale yellow solid (m.p. 56-57 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.98 (dd, J = 8.3, 2.0 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.62 (s, 1H), 3.92 (s, 6H), 3.83 (s, 3H), 3.82 (s, 3H), 3.79 (t, J = 6.0 Hz, 2H), 3.38 (s, 3H), 2.98 (t, J = 6.0 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.8, 150.6, 149.0, 147.9, 141.2, 136.0, 131.0, 122.6, 120.2, 114.9, 112.3, 110.6, 110.1, 107.3, 61.2, 60.2, 56.1, 55.9, 38.7, 30.8 ppm; IR (neat): ν_{max} = 2936, 2840, 1750, 1599, 1514, 1464, 1416, 1376, 1320, 1256, 1240, 1173, 1125, 1107, 1063, 1025, 981, 810, 764, 749 cm^{-1}; EI-MS: *m/z* (relative intensity) = 413 (98, M^+), 398 (12), 368 (7), 356 (12), 354 (14), 342 (19), 311 (11), 219 (23), 207 (28), 194 (28), 178 (24), 167 (27), 165 (100), 149 (50), 137 (31), 127 (25), 111 (27), 97 (44), 85 (31), 83 (40), 71 (58), 69 (70), 57 (79); TOF-HRMS calcd. for $C_{22}H_{24}NO_7$ $(M + H)^+$ 414.1547, found 414.1541.

4.3.17. 3-Phenethyl-5-phenyloxazolidine-2,4-dione (5b)

Ynamide **3q** (64.3 mg, 0.20 mmol), PIFA (94.6 mg, 0.22 mmol), 4 Å molecular sieve (200 mg) and $BF_3{\cdot}OEt_2$ (30 μL, 0.24 mmol) in dry CH_2Cl_2 (3 mL) were employed. After usual workup, the crude product was purified by column chromatography (SiO_2, hexane:EtOAc; 50:1 to 10:1 + 1% Et_3N as eluent) to obtain **5b** (34.2 mg, 61%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42-7.34 (m, 3H), 7.30-7.15 (m, 7H), 5.62 (s, 1H), 3.96-3.77 (m, 2H), 3.02 (t, J = 7.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.0, 155.0, 136.7, 131.4, 129.7, 129.0, 128.9, 128.7, 127.0, 126.1, 80.1, 41.2, 33.1 ppm; IR (neat): ν_{max} = 3031, 2947, 1816, 1738, 1442, 1412, 1338, 1146, 1106, 1010, 760, 698 cm^{-1}; EI-MS: *m/z* (relative intensity) = 281(0.4, M^+), 279 (7), 227 (5), 183 (4), 167 (17), 150 (11), 149 (100), 129 (6), 113 (6), 104 (8), 97 (9), 85 (11), 83 (14), 73 (13), 71 (24), 69 (21), 60 (10), 57 (37); TOF-HRMS calcd. for $C_{17}H_{15}NO_3Na$ $(M + Na)^+$ 304.0944, found 304.0946.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://

References and notes

1. (a) Knight, D. W. in *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chatopadhyay, S. K., Eds.; Wiley–VCH: Weinheim; **2011**, p 403; (b) Fearnley, S. P. *Curr. Org. Chem.* **2004**, *8*, 1289.
2. (a) Kudo, N.; Taniguchi, M.; Furuta, S.; Sato, K.; Endo, T.; Honma, T. *J. Agric. Food Chem.* **1998**, *46*, 5305; (b) Pereira, E. R.; Sancelme, M.; Voldoire, A.; Prudhomme, M. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2503; (c) Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010; (d) Daneshtalab, M. *Top. Heterocycl. Chem.* **2006**, *2*, 153; (e) Nam, N.-H.; Kim, Y.; You, Y.-J.; Hong, D.-H.; Kim, H.-M.; Ahn, B.-Z. *Biorg. Med. Chem. Lett.* **2001**, *11*, 3073; (f) Cascio, G.; Manghisi, E.; Fregnan, G. *J. Med. Chem.* **1989**, *32*, 2241; (g) Puig, C.; Crespo, M. I.; Godessart, N.; Feixas, J.; Ibarzo, J.; Jiménez, J.-M.; Soca, L.; Cardelús, I.; Heredia, A.; Miralpeix, M.; Puig, J.; Beleta, J.; Huerta, J. M.; López, M.; Segarra, V.; Ryder, H.; Palacios, J. M. *J. Med. Chem.* **2000**, *43*, 214.
3. (a) Aichaoui, H.; Jacques, H.; Poupaert, J. H.; Lesieur, D.; Hénichart, J.-P. *Tetrahedron* **1991**, *47*, 6649; (b) Hamad, M. O.; Kiptoo, P. K.; Stinchcomb, A. L.; Crooks, P. A. *Bioorg. Med. Chem.* **2006**, *14*, 7051; (c) Savarimuthu, S. A.; Thomas, S. A.; Prakash, D. G.; Gandh, T. *ChemistrySelect* **2016**, *1*, 2035.
4. (a) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Synlett* **2007**, 1763; (b) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925.
5. Lu, Z.; Xu, X.; Yang, Z.; Kong, L.; Zhu, G. *Tetrahedron Lett.* **2012**, *53*, 3433.
6. Lu, Z.; Yang, Z.; Cui, W.; Zhu, G. *Chem. Lett.* **2012**, *41*, 636.
7. For recent reviews see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064; (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840; (c) Evano, G.; Jouvin, K.; Coste, A. *Synthesis* **2013**, *45*, 17; (d) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560.
8. Lu, Z.; Cui, W.; Xia, S.; Bai, Y.; Luo, F.; Zhu, G. *J. Org. Chem.* **2012**, *77*, 9871.
9. (a) Huang, H.; He, G.; Zhu, G.; Zhu, X.; Qiu, S.; Zhu, H. *J. Org. Chem.* **2015**, *80*, 3480; (b) Huang, H.; Zhu, X.; He, G.; Liu, Q.; Fan, J.; Zhu, H. *Org. Lett.* **2015**, *17*, 2510.
10. Huang, H.; Tang, L.; Han, X.; He, G.; Xi, Y.; Zhu, H. *Chem. Commun.* **2016**, *52*, 4321.
11. For recent reviews, see: (a) Zhdankin, V. V. *ARKIVOC* **2009**, 1; (b) Tellitu, I.; Domínguez, E. *Synlett* **2012**, *23*, 2165; (c) Kita, Y.; Dohi, T. *Chem. Rec.* **2015**, *15*, 886; (d) Narayan, R.; Manna, S.; Antonchick, A. P. *Synlett* **2015**, *26*, 1785; (e) Arnold, A. M.; Ulmer, A.; Gulder, T. *Chem. Eur. J.* **2016**, *22*, 8728; (f) Wang, L.; Liu, J. *Eur. J. Org. Chem.* **2016**, *2016*, 1813; (g) Li, Y.; Hari, D. P.; Vita, M. V.; Waser, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 4436; (h) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328; (i) Dohi, T.; Kita, Y. *Curr. Org. Chem.* **2016**, *20*, 580.
12. (a) Kita, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 1119; (b) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5857; (c) Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. *Chem. Commun.* **1996**, 1481; (d) Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698; (e) Arisawa, M.; Utsumi, S.; Nakajima, M.; Ramesh, N. G.; Tohma, H.; Kita, Y. *Chem. Commun.* **1999**, 469; (f) Moreno, I.; Tellitu, I.; SanMartín, R.; Badía, D.; Carrillo, L.; Domínguez, E. *Tetrahedon Lett.* **1999**, *40*, 5067; (g) Olivera, R.; SanMartín, R.; Pascual, S.; Herrero, M.; Domínguez, E. *Tetrahedron Lett.* **1999**, *40*, 3479; (h) Tohma, H.; Morioka, H.; Takizawa, S.; Arisawa, M.; Kita, Y. *Tetrahedron* **2001**, *57*, 345; (i) Moreno, I.; Tellitu, I.; SanMartín, R.; Domínguez, E. *Synlett,* **2001**, 1161; (j) Moreno, I.; Tellitu, I.; Etayo, J.; SanMartín, R.; Domínguez, E. *Tetrahedron* **2001**, *57*, 5403; (k) Tohma, T.; Iwata, M.; Maegawa, T.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 9241; (l) Hamamoto, H.; Anilkumar, G.; Tohma, H.; Kita, Y. *Chem. Eur. J.* **2002**, *8* , 5377; (m) Hamamoto, H.; Anilkumar, G.; Tohma, H.; Kita, Y. *Chem. Commun.* **2002**, 450; (n) Moreno, I.; Tellitu, I.; Domínguez, E.; SanMartín, R. *Eur. J. Org. Chem.* **2002**, *2002*, 2126; (o) Olivera, R.; SanMartín, R.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2002**, *58*, 3021; (p) Tohma, H.; Iwata, M.; Maegawa, T.; Kiyono, Y.; Maruyama, A.; Kita, Y. *Org. Biomol. Chem.* **2003**, *1*, 1647; (q) Hamamoto, H.; Shiozaki, Y.; Nambu, H.; Hata, K.; Tohma, H.; Kita, Y. *Chem. Eur. J.* **2004**, *10*, 4977; (r) Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007; (s) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797; (t) Wada, Y.; Harayama, Y.; Kamimura, D.; Yoshida, M.; Shibata, T.; Fujiwara, K.; Morimoto, K.; Fujioka, H.; Kita, Y. *Org. Biomol. Chem.* **2011**, *9*, 4959; (u) Morimoto, K.; Nakae, T.; Yamaoka, N.; Dohi, T.; Kita, Y. *Eur. J. Org. Chem.* **2011**, *2011*, 6326; (v) Hackelöer, K.; Schnakenburg, G.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2011**, *2011*, 6314.
13. (a) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435; (b) Herrero, M. T.; Tellitu, I.; Domínguez, E.; Hernández, S.; Moreno, I.; SanMartín, R. *Tetrahedron* **2002**, *58*, 8581; (c) Herrero, M. T.; Tellitu, T.; Domínguez, D.; Moreno, I.; SanMartín, R. *Tetrahedron Lett.* **2002**, *43*, 8273; (d) Herrero, M. T.; Tellitu, I.; Hernández, S.; Domínguez, E.; Moreno, I.; SanMartín, R. *ARKIVOC* **2002**, 31; (e) Correa, A.; Herrero, M. T.; Tellitu, I.; Domínguez, E.; Moreno,

I.; SanMartin, R. *Tetrahedron* **2003**, *59*, 7103; (f) Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. *J. Org. Chem.* **2003**, *68*, 6739; (g) Correa, A.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartín, R. *J. Org. Chem.* **2005**, *70*, 2256; (h) Amano, Y.; Nishiyama, S. *Tetrahedron Lett.* **2006**, *47*, 6505; (i) Du, Y.; Liu, R.; Linn, G.; Zhao, K. *Org. Lett.* **2006**, *8*, 5919; (j) Ban, X.; Pan, Y.; Lin, Y.; Wang, S.; Du, Y.; Zhao, K. *Org. Biomol. Chem.* **2012**, *10*, 3606.

14. (a) Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartín, R. *Tetrahedron Lett.* **2003**, *44*, 3483; (b) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartín, R. *J. Org. Chem.* **2006**, *71*, 8316; (c) Tsukamoto, M.; Murata, K.; Sakamoto, T.; Saito, S.; Kikugawa, Y. *Heterocycles* **2008**, *75*, 1133; (d) Wardrop, D. J.; Bowen, E. G.; Forslund, R. E.; Sussman, A. D.; Weerasekera, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 1188; (e) Wardrop, D. J.; Yermolina, M. V.; Bowen, E. G. *Synthesis* **2012**, *44*, 1199.
15. (a) Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartín, R. *Org. Lett.* **2005**, *7*, 3073; (b) Pardo, L. M.; Tellitu, I.; Domínguez, E. *Synthesis* **2010**, 971; (c) Tellitu, I.; Serna, S.; Domínguez. E. *ARKIVOC* **2010**, 7; (d) Pardo, L. M.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2012**, *68*, 3692; (e) Pardo, L. M.; Tellitu, I.; Domínguez, E. *Synlett,* **2012**, *23*, 881; (f) Couto, I.; Pardo, L. M.; Tellitu, I.; Domínguez, E. *J. Org. Chem.* **2012**, *77*, 11192.
16. (a) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem.* **1983**, *48*, 3835; (b) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047; (c) Martínez-Estibalez; U.; Gómez-SanJuan, A.; García-Calvo, O.; Aranzamendi, E.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2011**, *2011*, 3610.
17. (a) Rein, K. S.; Gawley, R. E. *J. Org. Chem.* **1991**, *56*, 1564; (b) Orito, K.; Miyazawa, M.; Suginome, H. *Tetrahedron* **1995**, *51*, 2489; (c) Gawley, R. E.; Zhang, P. *J. Org. Chem.* **1996**, *61*, 8103; (d) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. *J. Org. Chem.* **1999**, *64*, 6583.
18. Lenz, G. R.; Costanza, C. *J. Org. Chem.* **1988**, *53*, 1176.
19. (a) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011; (b) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681; (c) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170; (d) Chen, Z.; Zeng, W.; Jiang, H.; Liu, L. *Org. Lett.* **2012**, *14*, 5385; (e) Jin, X.; Yamaguchi, K.; Mizuno, N. *Chem. Commun.* **2012**, *48*, 4974.
20. For screening of copper salts and bases, see: supplementary information.
21. It is noteworthy that ynamides **3a**-**3r** were unstable on silica gel, thus the mixture of 1% Et_3N in eluent must be used for chromatography.
22. (a) Gourdet, B.; Smith, D. L.; Lam, H. W. *Tetrahedron* **2010**, *66*, 6026; (b) Wang, K.-B.; Ran, R.-Q.; Xiu, S.-D.; Li, C.-Y. *Org. Lett.* **2013**, *15*, 2374; (c) Jadhav, A. M.; Pagar, V. V.; Huple, D. B.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2015**, *54*, 3812; (d) Li, L.; Zhou, B.; Wang, Y.-H.; Shu, C.; Pan, Y.-F.; Lu, X.; Ye, L.-W. *Angew. Chem., Int. Ed.* **2015**, *54*, 8245.
23. For screening of solvents, see: supplementary information.