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Room Temperature, Metal-catalyzed Oxidative Acylation of Electron-deficient Heteroarenes with Alkynes, its Mechanism and Application Studies

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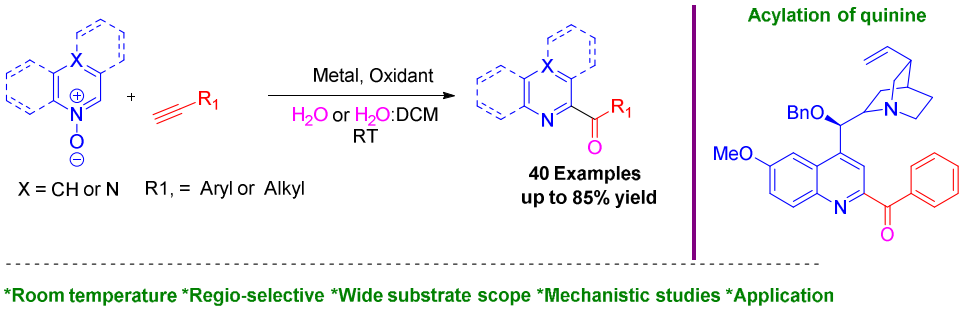


Abstract:

Herein, we report an original one-step, simple, room-temperature, regio-selective Minisci reaction for the acylation of electron-deficient heteroarenes with alkynes. The method has broad functional group compatibility and gives exclusively mono-acylated products in good to excellent yields. The mechanistic pathway has been analyzed based on a series of experiments confirming the involvement of a radical pathway. The ^{18}O-labeling experiment suggested that water is a source of oxygen in the acylated product and head space GC-MS experiment shows the C-C cleavage occurs *via* release as CO_2.

Introduction:

Minisci's reaction presents an attractive approach for the C-H functionalization of electron-deficient heteroarenes. Over the last decade, this approach has been studied in depth with respect to its diversity, mechanism and application.[1,2] Minisci's reaction has been successfully employed for the acylation, alkylation, arylation, carbamoylation, amidoalkylation, etc. of electron-deficient heteroarenes.[3,4] Among these, acylation and alkylation reactions are considered the most important because of the wide occurrence of the produced structures in natural products[5,6] and bio-active compounds.[7, 2a,8] The synthesis of acylated and alkylated heteroarenes has been achieved using several donor compounds. Acylation has been performed with oxo-acid, aldehyde, methylarene,and selenoester groups,[1a,9,10,11,12] while alkylation has been achieved with acids, alcohols, alkyl boronic acids and their salts, xanthates, acetals, and alkyl halides (Figure 1).[3,13] Under oxidative conditions, these donors are converted into nucleophilic carbon-centered radicals and subsequently react with electrophilic heteroarenes to furnish the corresponding coupled products. In spite of the wide diversity of products that can be produced, use of these methods includes several drawbacks, such as high reaction temperatures, requirement of a stoichiometric amount of catalysts and poor regio-selectivity. Consequently, the development of an effective alternative method with a wide substrate scope and an ambient reaction temperature is highly desired. It has also been documented that heteroatom (*O*, *N*, *P,* and *S*)-based radicals can behave electrophilically, and many examples have been reported wherein radicals of this type were coupled with electron-rich nucleophiles, such as alkenes, alkynes, and heteroarenes.[14] Two notable examples are the difunctionalization of olefinic and acetylenic compounds and related reactions[14a] and the coupling of the α-C(sp^3)-H of amides with azoles.[14b] Considering our interest in radical-based reactions,[5b,14b,15] we proposed that if readily prepared heteroarene *N*-oxides can be converted *in situ* into corresponding electrophilic *N*-oxide radicals under

oxidative reaction conditions, this electrophilic radical can then react with electron-rich species such as acetylenic derivatives and provide a complementary approach for the regio-selective generation of 2-substituted heteroarenes (Figure 1).

For this synthetic approach, a new chemical reaction method has been successfully developed for the simple acylation of electron-deficient heteroarenes. The present approach uses the Minisci reaction with reverse (umpolung) reactivity of coupling partners, deviating from the classical mechanism. This new synthetic pathway allows for the preparation of heteroarenes with high regio-selectivity and good to excellent yields

Figure 1. Previous and present approaches for the synthesis of 2-substituted heteroarenes

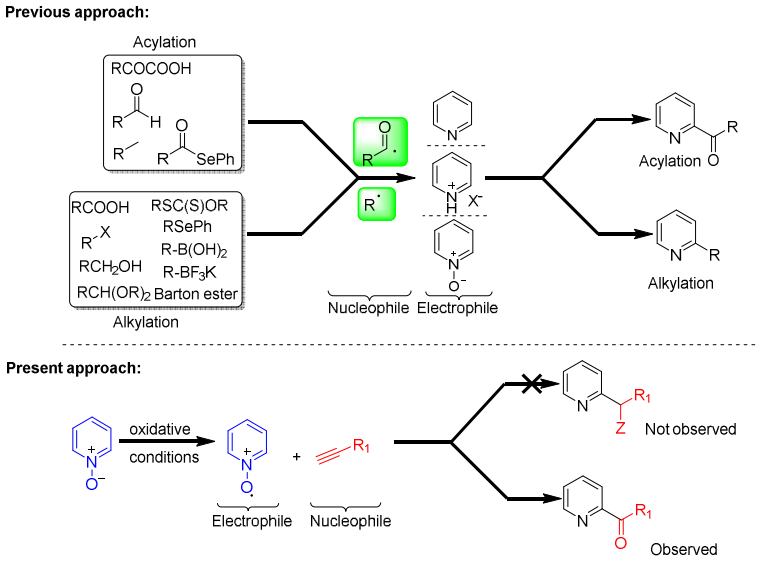
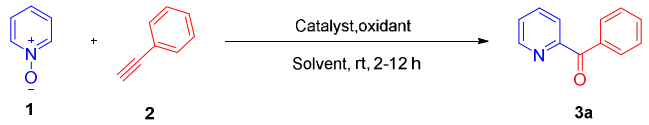


Table 1. Optimization of the Reaction Conditions[a]



1 2 3a

Entry	Catalyst (eq)	Oxidant (equiv.)	Solvent	Product (% yield)
1	$AgNO_3$ (0.2)	TBHP (3)	DCM:H_2O (1:3)	NR
2	$AgNO_3$ (0.2)	$K_2S_2O_8$ (3)	DCM:H_2O (1:3)	84
3	$AgNO_3$ (0.2)	$K_2S_2O_8$ (3)	Toluene:H_2O (1:3)	60
4	$AgNO_3$ (0.2)	$K_2S_2O_8$ (3)	DCE:H_2O (1:3)	77
5	$AgNO_3$ (0.2)	$K_2S_2O_8$ (3)	H_2O (3 ml)	85
6	$AgNO_3$ (0.2)	$K_2S_2O_8$ (3)	DCM (3 ml)	NR
7	$AgNO_3$ (0.2)	$K_2S_2O_8$ (3)	ACN (3 ml)	NR
8	Ag_2O (0.2)	$K_2S_2O_8$ (3)	H_2O (3 ml)	80
9	AgF(II) (0.2)	$K_2S_2O_8$ (3)	H_2O (3 ml)	70
10	AgF(I) (0.2)	$K_2S_2O_8$ (3)	H_2O (3 ml)	75
11	Ag_2CO_3 (0.2)	$K_2S_2O_8$ (3)	H_2O (3 ml)	82
12	$Ag_2C_2H_3O_2$ (0.2)	$K_2S_2O_8$ (3)	H_2O (3 ml)	NR
13	$AgNO_3$ (0.2)	$K_2S_2O_8$ (1)	H_2O (3 ml)	75
14	$AgNO_3$ (0.2)	$K_2S_2O_8$ (2)	H_2O (3 ml)	80
15	$AgNO_3$ (0.2)	-	H_2O (3 ml)	NR
16	-	$K_2S_2O_8$ (3)	DCM:H_2O (1:3)	18
17	-	$K_2S_2O_8$ (3)	H_2O (3 ml)	18
18	-	$K_2S_2O_8$ (5)	H_2O (3 ml)	21

[a]Reaction conditions (unless otherwise noted): **1** (0.5 mmol), **2.** (0.6 mmol), $AgNO_3$ (0.1 mmol) and $K_2S_2O_8$ (1.5 mmol), solvent (4 ml).

Results and discussion:

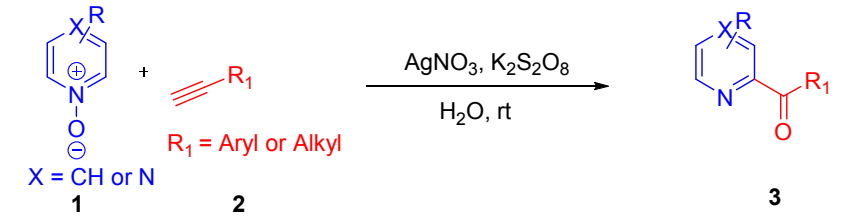
We selected pyridine-*N*-oxide and phenylacetylene as the coupling partners to test the proposed method (Table 1). The study beganwith treatment of the selected substrates with silver nitrate (0.2 eq.) as a catalyst and TBHP (3 eq.) as an oxidant in a dichloromethane:water (DCM:H_2O) solvent system at room temperature. Unfortunately, no coupling was observed under these reaction conditions. In the next experiment, the oxidant was replacedby potassium persulfate ($K_2S_2O_8$, 3eq.) and coupling was observed with the isolated product identified as 2-acylated pyridine **3a** (entry 2). The coupled product **3a** was isolated in 84% yield. Under other solvent systems, such as toluene:water and 1,2-dichloroethane:water (DCE:H_2O), the reaction proceeded but with comparatively lower yields (entries 3-4). When the reaction was attempted in water alone, coupling also proceeded efficiently (entry 5), similarly to that observed in the DCM:water system. However, when the

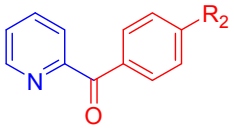
reaction was performed in DCM and acetonitrile (ACN), no coupling was observed (entries 6-7). In an attempt to further refine the process, $AgNO_3$ was changed to Ag_2O, AgF(II), AgF(I), Ag_2CO_3 and $Ag_2C_2H_3O_2$, but no advantage was observed with the use of these alternative catalysts (entries 8-12). When the amount of $K_2S_2O_8$ added was changed, the formation of the coupled product was however affected (entries 13-14). No coupling was observed when $K_2S_2O_8$ was removed from the reaction mixture entirely (entry 15). When the reaction was conducted in the presence of the oxidant alone, coupling was observed, but with a lower yield of 18% (entry 16), which suggested that $K_2S_2O_8$ is crucial. Additional experiments were performed using varied amounts of $K_2S_2O_8$ and different solvent systems, but all of these experimental reaction conditions afforded the final product in low yields (entries 17-18). From the screening studies, the best coupling conditions were identified as 0.2 eq. of $AgNO_3$ and 3 eq. of $K_2S_2O_8$ in a water or DCM:water system at room temperature (entries 2 and 5).

Equipped with a set of standard conditions, we then explored its diversity by conducting reaction using various pyridine-*N*-oxides and acetylenes. Interestingly, the scope of this approach was found to be very broad. Various aliphatic and aromatic acetylenes, including those with both electron-donating and electron-withdrawing substituents, can be successfully used (Scheme 1). According to Scheme 1, pyridine-*N*-oxides underwent a smooth coupling reaction with electron-donating phenylacetylenes such as 4-ethynyltoluene, 4-ethynylanisole and 4-ethynyl biphenyl to afford the corresponding coupled products **3b**, **3c** and **3d** in yields of 74, 76 and 46%, respectively. Similarly, electron-withdrawing phenyl acetylenes such as 1-ethynyl-4-fluorobenzene, 1-chloro-4-ethynylbenzene, 1-ethynyl-4-(trifluoromethyl)benzene and 1-ethynyl-4-(nitro)benzene also underwent reaction with pyridine-*N*-oxide **1** and furnished the corresponding acylated products **3e**, **3f**, **3g** and **3h** in good to moderate yields (45-77%). When pyridine-*N*-oxide **1** was treated with 1-ethynyl-4-phenoxybenzene, the

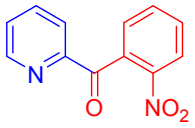
corresponding 2-acylated product **3i** was obtained in a 59% yield. Pyridine-*N*-oxide **1** also reacted well with *ortho*-substituted and bisubstituted phenylacetylenes such as 1-ethynyl-2-nitrobenzene and 1-ethynyl-4-fluoro-3-methylbenzene, and the respective products **3j** and **3k** were obtained in yields of 50 and 56%, respectively. The observed smooth reaction of acetylenes containing electron-withdrawing substituents are considered to be one of the major advantages of the proposed method.

Scheme 1. Substrate scope

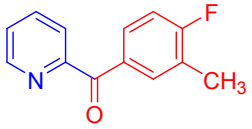




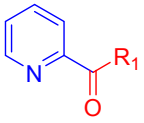
3a: R_2 = 4-H; 85%
3b: R_2 = 4-OMe; 74%
3c: R_2 = 4-Me; 76%
3d: R_2 = 4-Phenyl; 46%
3e: R_2 = 4-F; 77%
3f : R_2 = 4-Cl; 62%
3g: R_2 = 4-CF_3; 48%
3h: R_2 = 4-NO_2; 45%
3i: R_2 = 4-Phenoxy; 59%



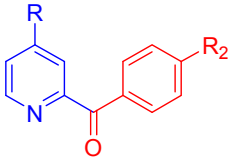
3j, 50%



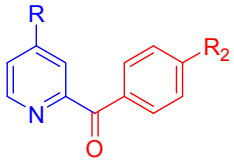
3k, 56%



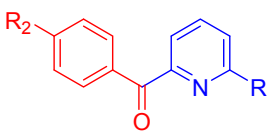
 # 3l: R_1 = butyl; 38%
 # 3m: R_1 = hexyl; 37%



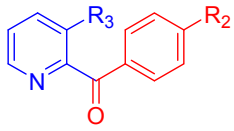
3n: R = 4-Me, R_2 = 4-H; 78%
3o: R = 4-Me, R_2 = 4-F; 73%



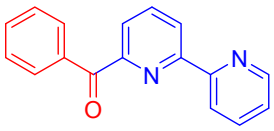
3p: R = 4-NO_2, R_2 = 4-H; 55%
3q: R = 4- NO_2, R_2 = 4-F; 44%
#3r: R = 4-CF_3, R_2 = 4-H; 42%
#3s: R = 4-CF_3, R_2 = 4-F; 42%
#3t: R = 4-CN, R_2 = 4-H; 25%



3u: R = 2-Me, R_2 = 4-H; 74%
3v: R = 2-Me, R_2 = 4-F; 72%
3w: R = 2-OMe, R_2 = 4-H; 71%

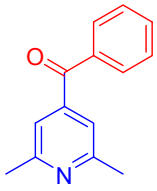


3x, R_2 = 4-H; 28%, 3x' = <10%
(3x = C2, 3x' = C6), R_3 = CH_3
3y, R_2 = 4-F; 31%, 3y' = <10%
(3y = C2, 3y' = C6),R_3 = CH_3
3z, R_2 = 4-H; 37%, 3z' = <10%
(3z = C2, 3z' = C6), R_3 = Br



3aa, 35%

3ab, 30%



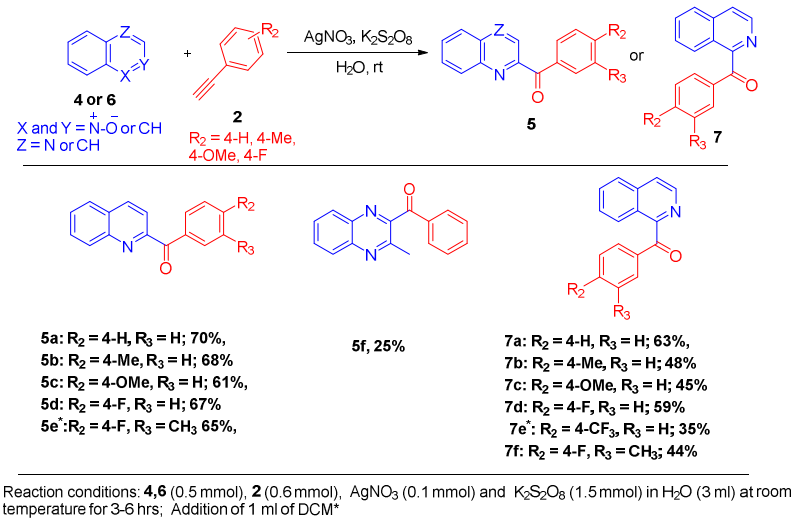
3ac, 0%

Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), $AgNO_3$ (0.1mmol) and $K_2S_2O_8$ (1.5 mmol) in H_2O (3 ml) at room temperature for 3-4 hrs. 5eq of acetylene,# 1ml of DCM,#Time of reaction 12 hrs.#

Similarly, the reaction of pyridine-*N*-oxide **1** with aliphatic acetylenes such as 1-Hexyne and 1-octyne was tested under the optimized conditions, resulting in production of the corresponding coupled products **3l** and **3m** but at comparatively lower yields (~38%). Substituted pyridine-*N*-oxides were also used to examine the further potential diversification of the method applications. Reaction of 4-methyl, 2-methyl and 2-methoxy pyridine-*N*-oxides

with substituted and unsubstituted phenylacetylenes afforded the corresponding products (**3n**, **3o**, **3u**, **3v** and **3w**) in good to excellent yields (71-78%). Pyridine-*N*-oxides with electron-withdrawing substituents, such as 4-nitro, 4-(trifluoromethyl) and 4-cyno groups, were also analyzed and afforded the corresponding 2-acylated products **3p-3t** in low to moderate yields (23-55%). When 3-methyl pyridine-*N*-oxide was treated with phenylacetylene and 1-ethynyl-4-fluorobenzene, however, it afforded a separable mixture of the 2-substituted products **3x, 3y** and **3z** in a moderate yield of 38, 41 and 47% respectively along with traces of the 6-substituted products **3x**, **3y'**and **3z'**. Reaction of 2,2'-bipyridyl-*N*-oxide was also found to furnish the coupled product **3aa** in 35% yield. Treatments of pyrazine, diazine, with phenylacetylene produced are the action that generated the acylated product **3ab** in a yield of 30%. In the case of lutidine-*N*-oxide, where both the 2nd and 6th positions were blocked, coupling was not detected, suggesting that a free C-H bond on the heteroatom adjacent to the nitrogen is necessary for the successful coupling reaction.

Scheme 2. Substrate scope

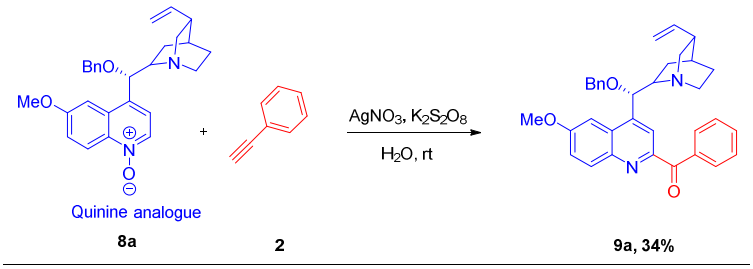


Reaction conditions: **4,6** (0.5 mmol), **2** (0.6 mmol), $AgNO_3$ (0.1 mmol) and $K_2S_2O_8$ (1.5 mmol) in H_2O (3 ml) at room temperature for 3-6 hrs; Addition of 1 ml of DCM*

After investigating the scope of pyridine-*N*-oxides and acetylenes suitable for application in the oxidative acylation, we focused our attention on the determination of the scope of fused

heteroarenes (Scheme 2) that could be successfully used. Pleasingly, a variety of fused heteroarenes were found to react smoothly with the acetylenes. Reaction of quinoline *N*-oxide with substituted and unsubstituted phenylacetylenes provided 2-acylated products **5a**-**5e** in good yields (61-70%). Under the same optimized reaction conditions, quinoxaline *N*-oxide was also found to react with acetylene to produce the acylated product **5f** in a 25% yield. Isoquinoline *N*-oxide also reacted smoothly with substituted and unsubstituted acetylenes under the optimized conditions (Scheme 2). These reactions occurred in the presence of both electron-withdrawing and electron-donating containing substituents on the phenylacetylenes to gave the C-1 arylated coupled products **7a-7f** but at comparatively lower yields (35-63%) than those obtained with quinoline *N*-oxide.

Scheme 3. Substrate scope



Reaction conditions: **8a** (0.5 mmol), **2** (0.6 mmol), $AgNO_3$ (0.1 mmol) and $K_2S_2O_8$ (1.5 mmol) in H_2O (3 ml) at room temperature for 4 hrs.

A notable potential application for the present method is the acylation of the well-known natural product quinine, an anti-malarial drug. Under the optimized reaction conditions, when quinine analogue **8a** was reacted with phenylacetylene (Scheme 3), the reaction proceeded and the corresponding coupled product **9a** was obtained in a moderate yield of 34%. The successful acylation of quinine-based functional molecules further widen its utility towards functionalization and diversification of this type of heterocycle, opening new avenues for the functionalization of compounds like quinine to decrease side effects.[16]

Scheme 4. Control experiments:

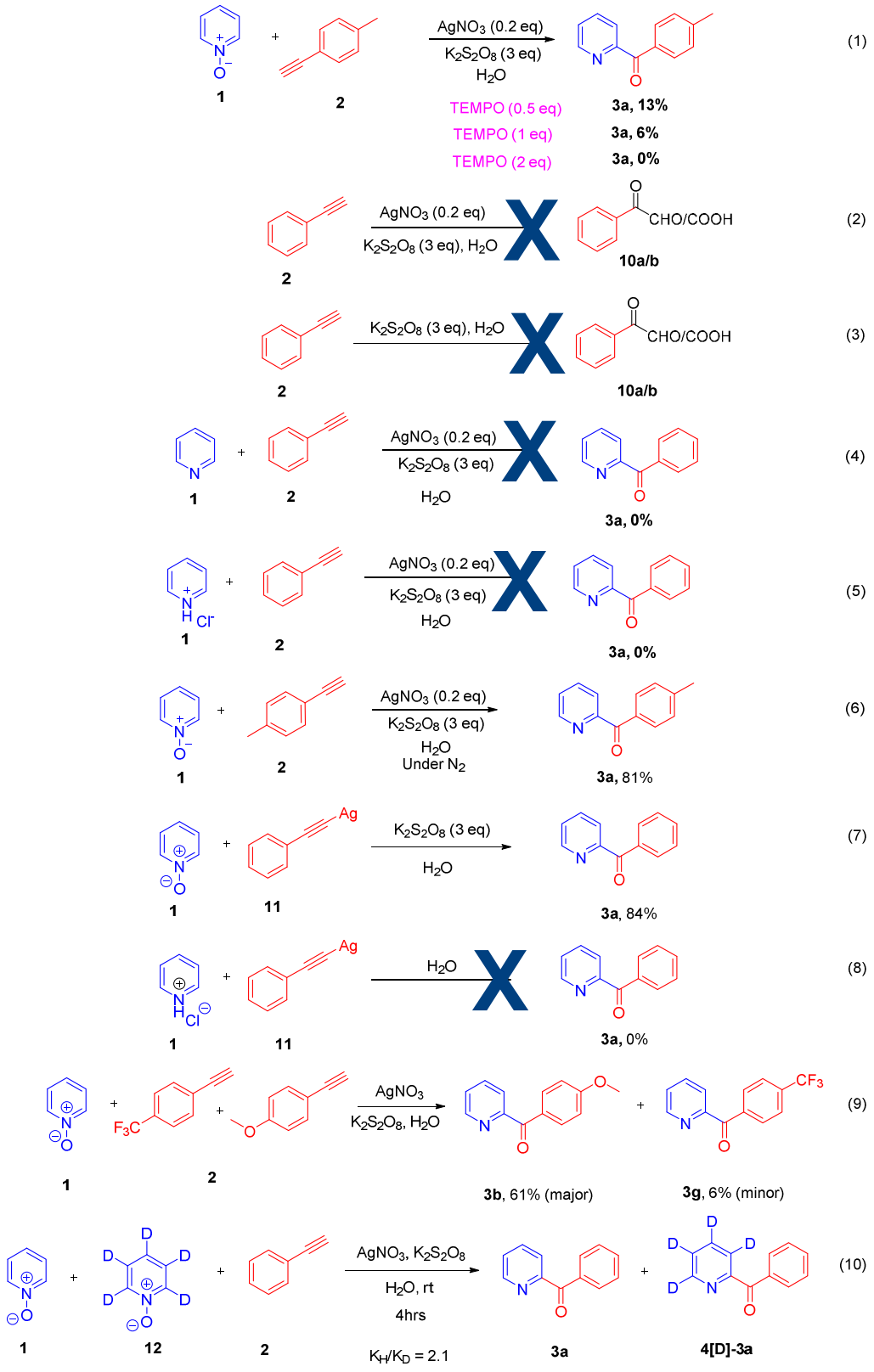
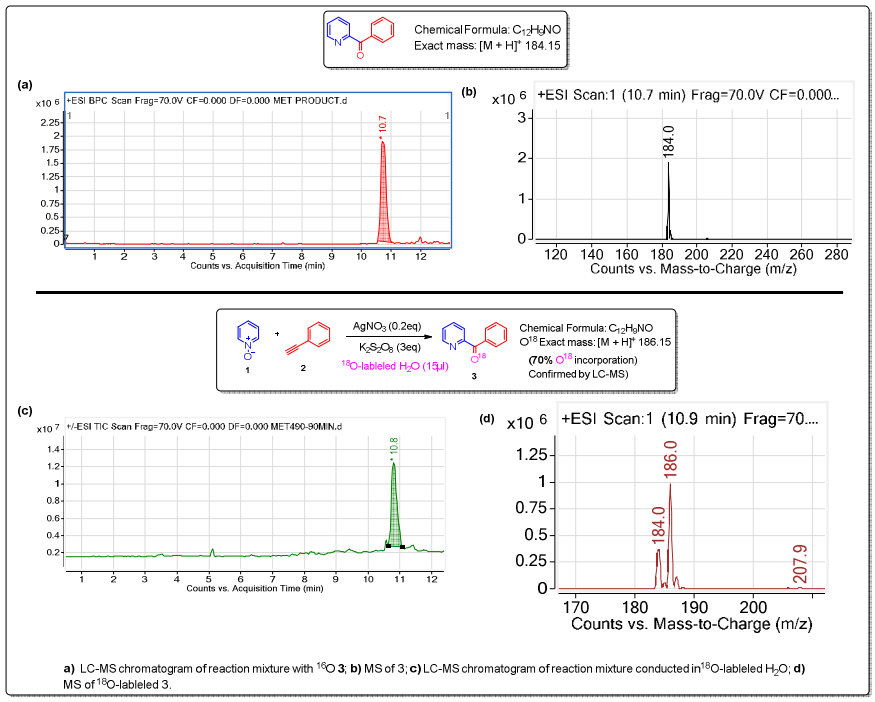


Figure 2. Isotope experiment



a) LC-MS chromatogram of reaction mixture with ^{16}O **3**; **b)** MS of 3; **c)** LC-MS chromatogram of reaction mixture conducted in ^{18}O-labeled H_2O; **d)** MS of ^{18}O-labeled 3.

To gain insight into the reaction mechanism, a series of control experiments were performed (eq. 1-10, Scheme 4) When the reactions were performed in the presence of free radical scavengers such as TEMPO, the formation of the product **3a**, was significantly suppressed (eq. 1), confirming the involvement of a radical pathway. The pathway for the conversion of phenylacetylenes into glycoxal/glyoxylic acid **10a/b** and subsequent coupling with heteroarenes *via* decarboxylation was ruled out by performing the reaction with phenylacetylene underoxidative conditions and looking for the formation of glycoxal/glyoxylic acid **10a/b** (eq. 2-3). Under these conditions, no glycoxal/glycoxylic acid **10a/b** formation was observed, suggesting that the present reaction proceeded through an alternative pathway. When the reaction was performed with pyridine and its salt, no coupled product was observed, again ruling out the possibility of the formation of glycoxal/glycoxylic acid **10a/b** and its involvement (eq. 4-5). The reaction under a nitrogen atmosphere preceded smoothly, suggested that atmosphere oxygen does not play any role in the reaction (eq. 6).

Next, we conducted the reaction in the presence of ^{18}O-labelled water, wherein LC–MS analysis showed a 70% presence of ^{18}O in the product[17] (Figure 2) suggested that water is the source of oxygen atom in acylated product. The phenyl acetylene is known to form silver acetylide on reaction with silver salt and its existence in the present conditions was also confirmed. When the heteroarene *N*-oxide **1** was treated with preformed silver acetylide **10** (prepared by known procedure),[18] the corresponding coupled product was obtained (eq. 7) suggested its role in the present reaction. The reaction of pyridine salt when tried with silver acetylide, no product formation was seen, again suggested that *N*-oxide is important for the reaction (eq. 8). In another attempt, the intermolecular competition experiment was also carried out (eq. 9), indicating that electron density on the phenyl rings plays an important role in reaction rate, also explaining the reason for lower yield in case of electron-withdrawing group containing substrates. A kinetic isotope effect (KIE) experiment was conducted with pyridine *N*-oxide **1** and its deuterated analogue (eq. 10 and Figure S1 of Supporting Information(SI)) and K_H/K_D ratio was found to be 2.1 suggested that the C–H bond cleavage may also be involved in the rate-limiting step although it is not conclusive at the present stage (need further investigation).The reaction involves the C-C bond cleavage and release of CO_2 was understood by carrying out the reaction in a specialized head space sealed bottle and analyzed the volatiles in GC-MS instrument. Samples were collected after regular interval of times has shown two peaks in the chromatogram at the retention time of 2.3 and 6.8 with *m/z* of 44 and 102 Da which correspond to CO_2 and phenyl acetylene **2** (Figure 3 and S2 of SI). Figure 3 shows the percentage of CO_2 and phenyl acetylene at different interval of time, where CO_2 concentration constantly increased with time, suggested the C-C cleavage involved the release of CO_2 under present oxidative conditions. On the basis of literature precedents[14b,19-21] and our experiments, the following cascade is proposed for the present method (Figure 4). First, a persulfate radical anion ($SO4^{-}$) generated through the reaction of

silver nitrate and persulfate abstracts an electron from the *N*-oxide **1** to generate the radical intermediate $\mathbf{I_1}$,[21c] which acts as an electrophile and react with *in situ*generated silver acetylide (Figure S3b of SI) to furnish the intermediate $\mathbf{I_2}$ (*path a*),which is confirmed by LC-MS (Fig S4a-b of SI). The possibility of *path b*, similar to Cu-catalyzed Miura method[20] couldn't be ruled out but reaction between two electron rich species is energetically less favourable, however, the formation of radical $\mathbf{I_1}$ will converts **1** into electrophilic species which easily facilitate the reaction. No reaction in the absence of persulfate (entry 15, Table 1) as well as in the presence of TEMPO also suggested the involvement of radical pathway. The intermediate $\mathbf{I_2}$ may proceed further by either ketene based intermediate $\mathbf{I_3}$ or metalloketene based intermediate $\mathbf{I_4}$.[19] During intermediate capturing experiment, ketene based intermediate $\mathbf{I_3}$ was observed (Figure S5b of SI) suggested the involvement of ketene based intermediate $\mathbf{I_3}$ in the present method. The intermediate $\mathbf{I_3}$ will further undergo reaction with water and generate intermediate $\mathbf{I_4}$, similar to Wolf-rearrangement,[21] which will isomerize into more stable acid-based intermediate $\mathbf{I_6}$. The intermediate $\mathbf{I_6}$ will form silver carboxylate $\mathbf{I_7}$ (captured in LC-MS study (Figure S5a of SI), which undergoes decarboxylation in the presence of Ag^{2+}. Then $\mathbf{I_7}$ undergoes decarboxylation (release of CO_2 is confirmed by GC-MS, Figure S2 of SI) followed by electron-loss and water attack (confirmed by $H_2{}^{18}O$ experiment) to give final 2-acylated product **3.**

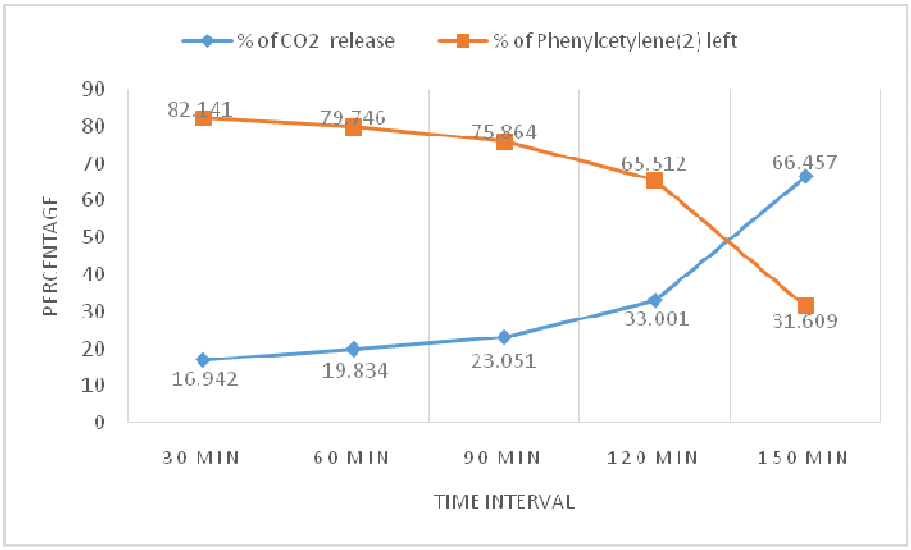


Figure 3: Headspace GC-MS analysis for the release of CO_2

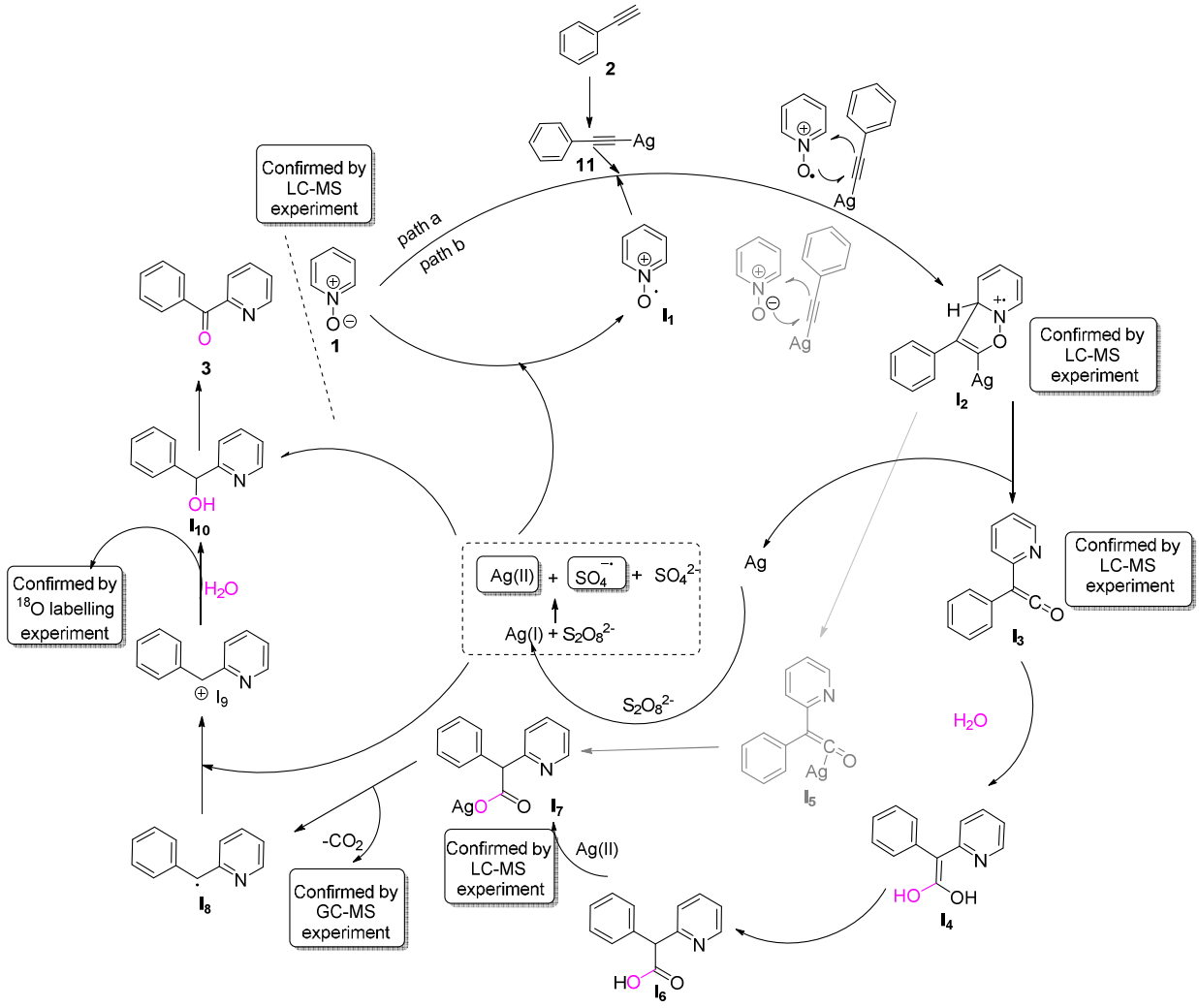


Figure 4. Plausible reaction mechanism

In summary, we have developed an original regio-selective acylation method for electron-deficient heteroarenes using various types of alkynes. The optimized method presents a unique and powerful approach for the functionalization of the C-H bond of heteroarenes. The room temperature, open-atmosphere operation and regio-selectivity of the present method are its main advantages over previously reported methods. The optimized method has worked with wide range of substrates. Additionally, direct acylation of functional molecules such as 2,2'-bipyridine and quinine was also achieved using the proposed method.

Experimental section:

General Information

All the reactions were performed at room temperature in air and monitored by using pre-coated silica gel TLC (60 F254, 20 × 20 cm). TLC plates were visualized by exposing UV spectrometry at 254 nm or by iodine vapors or by charring in Dragendorff reagent. Buchi rotavapor was used for concentration of organic solvents. Compounds were purified by flash column chromatography on flash silica gel 230−400 mesh size. All the ^{1}H NMR spectra were recorded with 400 and 500 MHz NMR instruments. Chemical data for protons are given in parts per million (ppm, scale) relative to TMS and referenced to the residual proton in the NMR solvent ($CDCl_3$: δ 7.26, or other solvents as mentioned). MestReNova software was used to process NMR spectra. The coupling constant (*J*) are in Hz. Mass spectra were obtained by using Q-TOF-LC/MS spectrometer, using electron spray ionization. All the heteroarene *N*-oxides were synthesized in the lab by following reported procedures.[22-25]

General Procedure for oxidative acylated reaction:

In a 10 ml Round bottom flask, to a solution of **1**or **4** or **6** or **8a** (0.5mmol, 1eq) in H_2O (3 ml) were added **2** (0.6 mmol), $AgNO_3$ (0.1 mmol), $K_2S_2O_8$ (1.5 mmol). The resulting solution was stirred at room for several hours (Schemes 2-5). After completion, the reaction mixture was transferred to separation funnel, 20 ml of bicarbonate solution were added, and reaction mixture was extracted with dichloromethane (3x20ml). The combined organic layers were dried over $NaSO_4$, filtered and concentrated. The crude material was purified by column chromatography using ethylacetate/ hexane as eluent to afford **3 or 5 or 7 or 9.**

Phenyl(pyridin-2-yl)methanone[26] (3a, Scheme 1)

TLC R_f= 0.5 **(**10% EtOAc/Hexane**)**; Yield 85% (77.8 mg); Light yellow solid, m.p. 42-44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.7 Hz, 1H), 8.12 – 8.02 (m, 3H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.59 (dd, *J* = 10.6, 4.2 Hz, 1H), 7.49 (dd, *J* = 10.5, 4.4 Hz, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 193.5, 155.1, 148.5, 137.0, 136.3, 132.9, 130.9, 128.1, 126.1, 124.61; HRMS (ESI+) calcd. for: $C_{12}H_{10}NO$ 184.0757 (M+ H), found 184.0751.

(4-Methoxyphenyl)(pyridin-2-yl)methanone[26] (3b, Scheme 1)

TLC R_f = 0.5 **(**10 % EtOAc/Hexane**)**; Yield 74% (78.8 mg); White solid, mp. 95-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.7 Hz, 1H), 8.12 (d, *J* = 8.9 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.86 (td, *J* = 7.7, 1.6 Hz, 1H), 7.46 – 7.43 (m, 1H), 6.96 (t, *J* = 5.8 Hz, 2H), 3.87 (s, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 163.6, 155.8, 148.3, 136.9, 133.5, 129.0, 125.7, 124.5, 113.5, 55.4; MS (ESI+) found for: $C_{13}H_{12}NO_2$ 214.10 (M+H).

Pyridin-2-yl(*p*-tolyl)methanone[26] (3c, Scheme 1) TLC R_f = 0.5 **(**10 % EtOAc/Hexane**)**; Yield 76% (74.8 mg); Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.7 Hz, 1H), 7.99 (dd, *J* = 13.2, 8.0 Hz, 3H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 155.5, 148.5, 143.7, 136.9, 133.7, 131.1, 128.8, 125.9, 124.4, 21.6; HRMS (ESI+) calcd. for: $C_{13}H_{12}NO$ 198.0913 (M+ H), found 198.0909.

[1,1'-Biphenyl]-4-yl(pyridin-2-yl)methanone (3d, Scheme 1)

TLC R_f = 0.5 **(**10% EtOAc/Hexane**)**; Yield 46% (59.5 mg); yellow crystalline solid; m.p. 87.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.7 Hz, 1H), 8.20 – 8.13 (m, 2H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.92 (td, *J* = 7.7, 1.7 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.65 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.53 – 7.44 (m, 3H), 7.44 – 7.36 (m, *J* = 8.4, 6.3 Hz, 1H);^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3, 155.3, 148.5, 145.6, 140.2, 137.0, 135.0, 131.6, 128.9, 128.1, 127.3, 126.9, 126.1, 124.6; HRMS (ESI+) calcd. for: $C_{18}H_{14}NO$ 260.1070. (M+H), found 260.1067.

(4-Fluorophenyl)(pyridin-2-yl)methanone[26](3e, Scheme 1)

TLC R_f = 0.4 **(**10% EtOAc/Hexane**)**; Yield 77% (77 mg); White solid; m.p. 80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.7 Hz, 1H), 8.23 – 8.13 (m, 2H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.19 – 7.09 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.0 165.7 (d, *J* = 255.53 Hz), 155.0, 146.4, 137.1,133.8 (d, *J* = 10.1 Hz), 132.5 (d, *J* = 3.03 Hz), 126.2, 124.6, 115.2 (d, *J* = 22.22 Hz); HRMS (ESI+) calcd. for: $C_{12}H_9FNO$ 202.0663.(M+H), found 202.0674.

(4-Chlorophenyl)(pyridin-2-yl)methanone[26] (3f, Scheme 1)

TLC R_f = 0.4 **(**10% EtOAc/Hexane**)**; Yield 62% (67.2 mg); Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.6 Hz, 1H), 8.11 – 8.03 (m, 3H), 7.90 (td, *J* = 7.7, 1.6 Hz, 1H), 7.54 – 7.40 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 154.7, 148.5, 139.4, 137.1, 134.6, 132.5, 128.4, 126.4, 124.6; HRMS (ESI+) cald. for $C_{12}H_9ClNO$ 218.0373 found 218.0367 (M+H).

Pyridin-2-yl(4-(trifluoromethyl)phenyl)methanone[26] (3g, Scheme 1)

TLC R_f = 0.4 **(**10% EtOAc/Hexane**)**; Yield 48% (60.2 mg); yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.7 Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 2H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.93 (td, *J* = 7.7, 1.7 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.52 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H); ^{13}C NMR (101MHz, $CDCl_3$) δ 192.6, 154.2, 148.6, 139.4, 137.2, 133.9 (d, *J* = 33.33Hz) 131.2, 126.7, 125.0 (q, *J* = 4.04Hz), 124.7, 122.4; HRMS (ESI+) calcd. for: $C_{13}H_9F_3NO$ 252.0631. (M+ H), found 252.0634.

(4-Nitrophenyl)(pyridin-2-yl)methanone[27] (3h, Scheme 1)

TLC R_f= 0.3 **(**10% EtOAc/Hexane**)**; Yield 45% (51.3 mg); pale yellow solid; m.p. 98 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.7 Hz, 1H), 8.26 (d, *J* = 8.9 Hz, 2H), 8.22 – 8.16 (m, 2H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.52 – 7.45 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 153.7, 149.9, 148.8, 141.6, 137.4, 132.4, 126.9, 125.2; HRMS (ESI+) calcd. for: $C_{12}H_9N_2O_3$ 229.0608. (M+ H), found 229.0611.

(4-Phenoxyphenyl)(pyridin-2-yl)methanone (3i, Scheme 1)

TLC R_f = 0.6 **(**10% EtOAc/Hexane**)**; Yield 59% (81.1 mg); pale brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 – 8.69 (m, 1H), 8.14 – 8.09 (m, 2H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.09 (dt, *J* = 9.0, 1.8 Hz, 2H), 7.05 – 7.01 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 162.0, 155.5, 155.4, 154.1, 148.4, 137.1, 133.5, 130.6, 130.0, 126.0, 124.6, 124.6, 120.3, 117.0; HRMS (ESI+) calcd. For: $C_{18}H_{14}NO_2$ 276.1019. (M+ H), found 276.1029.

(2-Nitrophenyl)(pyridin-2-yl)methanone[28] (3j, Scheme 1)

TLC R_f = 0.3 **(**10% EtOAc/Hexane**)**; Yield 50% (57 mg); light red solid; m.p. 115 $^{\circ}$C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.7 Hz, 1H), 8.29 (d, *J* = 7.9 Hz, 1H), 8.20 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.92 (td, *J* = 7.7, 1.7 Hz, 1H), 7.80 (td, *J* = 7.5, 1.1 Hz, 1H), 7.69 (td, *J* = 8.1, 1.4 Hz, 1H), 7.61 (dd, *J*= 7.5, 1.4 Hz, 1H), 7.44 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4, 152.6, 149.2, 137.1, 135.6, 134.1, 130.7, 129.4, 127.1, 123.5, 122.6; HRMS (ESI+) calcd. for: $C_{12}H_9N_2O_3$ 229.0608. (M+ H), found 229.0598

(4-Fluoro-3-methylphenyl)(pyridin-2-yl)methanone (3k, Scheme 1)

TLC R_f = 0.3 **(**10% EtOAc/Hexane**)**; Yield 56% (60.2 mg); cream solid; m.p. 56.7 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 – 8.66 (m, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 8.00 – 7.92 (m, 2H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 7.09 (t, *J* = 8.9 Hz, 1H), 2.33 (d, *J* = 1.8 Hz, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 164.4 (d, *J* = 254.52Hz), 155.2, 148.4, 137.0, 134.7 (d, *J* = 7.07Hz), 132.3 (d, *J* = 3.03Hz), 132.2 (d, *J* = 10.1 Hz), 126.1, 124.5, 124.9 (d, *J* = 18.18 Hz), 114.8 (d, *J* = 23.23 Hz), 14.5 (d, *J* = 4.04 Hz); HRMS (ESI+) calcd. for: $C_{13}H_{11}FNO$ 216.0819. (M+ H), found 216.0795.

1-(Pyridin-2-yl)pentan-1-one[29] (3l, Scheme 1)

TLC R_f = 0.5 **(**10% EtOAc/Hexane**)**; Yield 21% (17.1 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.4 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.82 (td, *J* = 7.7, 1.6 Hz, 1H), 7.54 – 7.37 (m, 1H), 3.22 (dd, *J* = 14.8, 7.4 Hz, 2H), 1.72 (dt, *J* = 15.1, 7.5 Hz, 2H), 1.42 (dd, *J* = 15.0, 7.4 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.2, 153.4, 148.9, 136.8, 126.9, 121.8, 37.4, 26.1, 22.4, 13.9; HRMS (ESI+) calcd. for: $C_{10}H_{14}NO$ 164.1070. (M+ H), found 164.1052.

1-(pyridin-2-yl)heptan-1-one (3m, Scheme 1)

TLC R_f = 0.2 **(**10% EtOAc/Hexane**)**; Yield 20% (20.5 mg); Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.63 (m, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 3.21 (t, *J* = 7.5 Hz, 2H), 1.75 – 1.69 (m, 2H), 1.45 – 1.29 (m, 6H), 0.89 – 0.86 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 153.6, 148.9, 136.8, 126.9, 121.7, 37.7, 31.7, 29.0, 23.9, 22.5, 14.0; HRMS (ESI+) calcd. for: $C_{12}H_{18}NO$ 192.1383 (M+ H), found 192.1384.

(4-Methylpyridin-2-yl)(phenyl)methanone[30] (3n, Scheme 1)

TLC R_f = 0.5**(**10% EtOAc/Hexane**)**; Yield 78% (77.1 mg); Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 5.0 Hz, 1H), 8.03 (d, *J* = 7.2 Hz, 2H), 7.84 (s, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.31 – 7.25 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.2, 155.0, 148.3, 136.5, 132.8, 130.9, 128.1, 126.9, 125.3, 21.1; HRMS (ESI+) calcd. for: $C_{13}H_{12}NO$ 198.0913. (M+ H), found 198.0936.

(4-Fluorophenyl)(4-methylpyridin-2-yl)methanone[31] (3o, Scheme 1)

TLC R_f = 0.4 **(**10% EtOAc/Hexane**)**; Yield 73% (78.4 mg); White solid; m.p. 95.1 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.9 Hz, 1H), 8.19 – 8.12 (m, 2H), 7.87 (d, *J* = 0.6 Hz, 1H), 7.31 (d, *J* = 4.9 Hz, 1H), 7.19 – 7.10 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 165.7 (d, *J* = 255.53 Hz), 154.8, 148.5, 148.3,133.7 (d, *J* = 9.09Hz), 132.7 (d,*J* = 4.04 Hz), 127.1, 125.4, 115.2 (d, *J* = 22.22 Hz), 21.1; MS (ESI+) found for: $C_{13}H_{11}FNO$ 216.15.

(4-Nitropyridin-2-yl)(phenyl)methanone (3p, Scheme 1)

TLC R_f = 0.3 **(**10% EtOAc/Hexane**)**; Yield 55% (62.7 mg); light orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 5.3 Hz, 1H), 8.79 (d, *J* = 2.1 Hz, 1H), 8.29 – 8.20 (m, 3H), 7.26 – 7.18 (m, 2H); ^{13}C NMR (101MHz, $CDCl_3$) δ 191.2, 157.9, 154.9, 150.8, 135.2, 133.6, 131.0, 128.4, 118.2; HRMS (ESI+) calcd. for: $C_{12}H_9N_2O_3$ 229.0608 (M+ H), found 229.0608.

(4-Fluorophenyl)(4-nitropyridin-2-yl)methanone (3q, Scheme 1)

TLC R_f = 0.2 (10% EtOAc/Hexane); Yield 44% (54.1 mg); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 5.3 Hz, 1H), 8.79 (d, *J* = 2.1 Hz, 1H), 8.29 – 8.20 (m, 3H), 7.26 – 7.18 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.3, 166.1 (d, *J* = 257.55 Hz), 157.7, 155.0, 150.7, 133.9 (d,*J* = 9.09 Hz), 131.5 (d, *J* = 3.03 Hz), 118.3, 117.5, 115.6 (d, *J* = 22.22 Hz); HRMS (ESI+) calcd. for: $C_{12}H_8FN_2O_3$ 247.0513. (M+ H), found 247.0506.

Phenyl(4-(trifluoromethyl)pyridin-2-yl)methanone[32] (3r, Scheme 1)

TLC R_f = 0.4 (10% EtOAc/Hexane); Yield 30% (37.6 mg); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 5.0 Hz, 1H), 8.29 (s, 1H), 8.14 – 8.05 (m, 2H), 7.72 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.63 (ddd, *J* = 8.7, 2.5, 1.2 Hz, 1H), 7.51 (dd, *J* = 10.7, 4.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 156.3, 149.5, 139.7 (d, *J* = 35.35 Hz), 135.5, 133.4, 131.0, 128.3, 123.8, 121.6 (q, *J* = 3.03 Hz), 120.5 (q, *J* = 3.03 Hz); MS (ESI+) found for: $C_{13}H_9F_3NO$ 252.0631 (M+H).

(4-Fluorophenyl)(4-(trifluoromethyl)pyridin-2-yl)methanone(3s, Scheme 1)

TLC R_f = 0.4 (10% EtOAc/Hexane); Yield 24% (32.2 mg); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 5.0 Hz, 1H), 8.30 (s, 1H), 8.26 – 8.13 (m, 1H), 7.73 (d, *J* = 4.9 Hz, 1H), 7.24 – 7.12 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 166.0 (d, *J* = 256.54 Hz), 156.18, 149.4, 133.9 (d, *J* = 9.09 Hz), 131.8 (d, *J* = 3.03 Hz), 123.7, 121.6 (d, *J* = 3.03 Hz), 120.5 (d, *J* = 4.04 Hz) 115.5 (d, *J* = 22.22 Hz); HRMS (ESI+) calcd. for: $C_{13}H_8F_4NO$ 270.0537. (M+ H), found 270.0526.

2-Benzoylisonicotinonitrile[33] (3t, Scheme 1)

TLC R_f = 0.5 (10% EtOAc/Hexane); Yield 23% (23.9mg); brown solid; m.p. 93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 4.9 Hz, 1H), 8.28 (s, 1H), 8.11 – 8.05 (m, 2H), 7.71 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6, 156.1, 149.4, 135.1, 133.6, 131.0, 128.4, 127.3, 126.4, 121.9, 115.9; HRMS (ESI+) calcd. for: $C_{13}H_9N_2O$ 209.0709, (M+ H), found 209.0699.

(6-Methylpyridin-2-yl)(phenyl)methanone[26] (3u, Scheme 1)

TLC R_f = 0.5 (10% EtOAc/Hexane); Yield 74% (72.8 mg); Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.05 (m, 1H), 7.80 – 7.70 (m, 1H), 7.62 – 7.54 (m, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.33 (dd, *J* = 6.8, 1.8 Hz, 1H), 2.63 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 157.7, 154.7, 137.0, 136.3, 132.8, 131.2, 128.0, 125.7, 121.6, 24.5; HRMS (ESI+) calcd. for: $C_{13}H_{12}NO$ 198.0913, (M+ H), found 198.0935.

(4-Fluorophenyl)(6-methylpyridin-2-yl)methanone (3v, Scheme 1)

TLC R_f = 0.5 (10% EtOAc/Hexane); Yield 72% (77.4 mg); White crystals; m.p. 55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.15 (m, 2H), 7.80 (dt, *J* = 15.1, 7.4 Hz, 2H), 7.36 (d, *J* =

7.4 Hz, 1H), 7.21 – 7.11 (m, 2H), 2.64 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 165.7 (d, *J* = 255.53 Hz), 157.6, 154.6, 137.1, 133.9 (d, *J* = 9.09 Hz), 132.6 (d, *J* = 3.03 Hz), 125.8, 121.6, 115.1 (d, *J* = 22.22 Hz), 24.4; HRMS (ESI+) calcd. for: $C_{13}H_{11}FNO$ 216.0819. (M+H), found 216.0818.

(6-Methoxypyridin-2-yl)(phenyl)methanone (3w, Scheme 1)

TLC R_f = 0.5 **(**10% EtOAc/Hexane**)**; Yield 71% (75.6 mg); light brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.7 Hz, 1H), 8.12 (d, *J* = 8.9 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.86 (td, *J* = 7.7, 1.6 Hz, 1H), 7.51 – 7.39 (m, 1H), 6.96 (t, *J* = 5.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 163.6, 155.8, 148.3, 136.9, 133.5, 129.0, 125.7, 124.5, 113.5, 55.4; HRMS (ESI+) calcd. for: $C_{13}H_{12}NO_2$ 214.0863. (M+H), found 214.0861.

(3-Methylpyridin-2-yl)(phenyl)methanone (3x, Scheme 1)

TLC R_f = 0.3**(**10% EtOAc/Hexane**)**; Yield 28% (27 mg); brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.6 Hz, 1H), 7.96 – 7.75 (m, 2H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.33 (dd, *J* = 7.8, 4.7 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 155.1, 145.9, 138.9, 136.5, 133.3, 132.8, 130.4, 128.4, 124.5, 18.35; HRMS (ESI+) calcd. for: $C_{13}H_{12}NO$ 198.0913. (M+H), found 198.0925.

(4-Fluorophenyl)(3-methylpyridin-2-yl)methanone (3y, Scheme 1)

TLC R_f = 0.3**(**10% EtOAc/Hexane**)**; Yield 41% (44 mg); brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 3.9 Hz, 1H), 7.95 – 7.84 (m, 2H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.32 (dd, *J* = 7.8, 4.7 Hz, 1H), 7.16 – 7.06 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 165.9 (d, *J* = 296.94 Hz), 154.7, 145.9, 139.1, 133.2 (d, *J* = 10.1 Hz), 133.0, 132.9 (d, *J* = 3.03 Hz) 124.7, 115.5 (d, *J* = 22.22 Hz), 18.4; HRMS (ESI+) calcd. for: $C_{13}H_{11}FNO$ 216.0819. (M+H), found 216.0847.

(3-Bromopyridin-2-yl)(phenyl)methanone[34] (3z, Scheme 1)

TLC R_f = 0.2 **(**10% EtOAc/Hexane**)**; Yield 37% (48.5 mg); yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.02 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.87 – 7.81 (m, 2H), 7.61 (dd, *J* = 10.5, 4.3 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.32 (dd, *J* = 8.2, 4.7 Hz, 1H);
MS (ESI+) calcd. for: $C_{17}H_{13}N_2O$ 262.10 (M+H).

[2,2'-Bipyridin]-6-yl(phenyl)methanone[35] (3aa, Scheme 1)

TLC R_f = 0.3 **(**20% EtOAc/Hexane**)**; Yield 35% (45.5 mg); light yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.67 (m, 1H), 8.65 (dd, *J* = 7.7, 1.2 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.22 – 8.16 (m, 2H), 8.08 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.03 (t, *J* = 7.7 Hz, 1H), 7.78 (td, *J* = 7.8, 1.8 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.51 (dd, *J* = 10.5, 4.7 Hz, 2H), 7.35 – 7.30 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 155.4, 154.9, 154.2, 149.2, 137.9, 137.0, 136.4, 132.8,

131.2, 128.0, 124.4, 124.1, 123.3, 121.3; HRMS (ESI+) calcd. for: $C_{17}H_{13}N_2O$ 261.1022. (M+H), found 261.1025.

Phenyl(pyrazin-2-yl)methanone[36] (3ab, Scheme 1)

TLC R_f = 0.2 (10% EtOAc/Hexane); Yield 30% (13.6 mg); brown gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, *J* = 1.4 Hz, 1H), 8.78 (d, *J* = 2.5 Hz, 1H), 8.69 (dd, *J* = 2.4, 1.5 Hz, 1H), 8.10 – 8.06 (m, 2H), 7.67 – 7.61 (m, 1H), 7.51 (dd, *J* = 10.7, 4.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 150.0, 146.8, 146.1, 142.9, 135.5, 133.5, 130.1, 128.4; MS (ESI+) found for: $C_{11}H_9N_2O$ 185.30 (M+H).

Phenyl(quinolin-2-yl)methanone[37] (5a, Scheme 2)

TLC R_f = 0.4 (10% EtOAc/Hexane); Yield 70% (81.5 mg); red solid; m.p. 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.5 Hz, 1H), 8.26 – 8.16 (m, 3H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.77 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.49 (dd, *J* = 10.6, 4.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 154.8, 146.8, 137.0, 136.2, 133.0, 131.4, 130.6, 130.0, 128.9, 128.4, 128.1, 127.6, 120.7; HRMS (ESI+) calcd. for: $C_{16}H_{12}NO$ 234.0913. (M+ H), found 234.0916.

Quinolin-2-yl(*p*-tolyl)methanone[38] (5b, Scheme 2)

TLC R_f = 0.5 (10% EtOAc/Hexane); Yield 68% (83.9 mg); brown solid; m.p. 62-64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.78 (t, *J* = 4.2 Hz, 1H), 7.71 – 7.58 (m, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 2.46 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4, 193.2, 155.1, 146.7, 143.9, 136.9, 133.6, 131.5, 130.5, 129.9, 128.8, 128.8, 128.2, 127.6, 120.7, 21.7; HRMS (ESI+) calcd. for: $C_{17}H_{14}NO$ 248.1070. (M+ H), found 248.1060.

(4-Methoxyphenyl)(quinolin-2-yl)methanone[38] (5c, Scheme 2)

TLC R_f = 0.4 (10% EtOAc/Hexane); Yield 61% (80.2 mg); White solid; m.p. 65-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 – 8.24 (m, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.85 – 7.72 (m, 1H), 7.66 (dd, *J* = 11.0, 4.0 Hz, 1H), 7.07 – 6.91 (m, 1H), 3.91 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.1, 163.7, 155.4, 146.7, 136.9, 133.9, 130.4, 130.0, 129.0, 128.8, 128.1, 127.6, 120.9, 113.5, 55.5; HRMS (ESI+) calcd. for: $C_{17}H_{14}NO_2$ 264.1019 (M+ H), found 264.1013.

(4-Fluorophenyl)(quinolin-2-yl)methanone[39] (5d, Scheme 2)

TLC R_f = 0.5 (10% EtOAc/Hexane); Yield 67% (84 mg); white solid; m.p. 131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dq, *J* = 5.0, 2.7 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.80 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.23 – 7.15 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 165.8 (d, *J* = 255.5), 154.5, 146.6,

137.2, 134.2 (d, *J* = 10.1Hz), 132.5 (d, *J* = 3.03 Hz) 130.5, 130.1, 128.9, 128.53, 127.6, 120.7, 115.2 (d, *J* = 22.22 Hz); HRMS (ESI+) calcd. for: $C_{16}H_{11}FNO$ 252.0819. (M+ H), found 252.0812.

(4-Fluoro-3-methylphenyl)(quinolin-2-yl)methanone (5e, Scheme 2)

TLC R_f = 0.5 **(**10% EtOAc/Hexane); Yield 65% (85.8mg); creamish solid; m.p. 103.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.18 – 8.06 (m, 3H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 8.8 Hz, 1H), 2.36 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 164.5 (d, *J* = 254 Hz), 154.7, 146.7, 137.1, 135.1 (d, *J* = 6.6 Hz), 132.2 (d, *J* = 4.04 Hz), 131.7 (d, *J* = 9.3 Hz), 130.5, 130.1, 128.9, 128.4, 127.6, 125.0 (d, *J* = 17.7 Hz), 120.8, 114.8 (d, *J* = 23.23 Hz), 14.6(d, *J* = 3.5 Hz); HRMS (ESI+) calcd. for: $C_{17}H_{13}FNO$ 266.0976. (M+ H), found 266.0980.

(3-Methylquinoxalin-2-yl)(phenyl)methanone (5f, Scheme 2)

TLC R_f = 0.2 **(**10% EtOAc/Hexane); Yield 25% (31mg); light brown solid; m.p. 75.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.5 Hz, 2H), 7.96 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.87 – 7.80 (m, 1H), 7.79 – 7.73 (m, 1H), 7.65 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 2.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 152.3, 150.8, 142.1, 139.4, 135.6, 134.1, 131.2, 130.7, 129.7, 129.5, 128.7, 128.6, 22.7; HRMS (ESI+) calcd. for: $C_{16}H_{13}N_2O$ 249.1022. (M+ H), found 249.1026.

Isoquinolin-1-yl(phenyl)methanone[39](7a, Scheme 2)

TLC R_f = 0.3 **(**10% EtOAc/Hexane**)**; Yield 63% (73.3 mg); Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.6 Hz, 1H), 8.27 – 8.19 (m, 1H), 7.96 (dt, *J* = 10.4, 5.1 Hz, 3H), 7.82 (d, *J* = 5.6 Hz, 1H), 7.80 – 7.72 (m, 1H), 7.63 (ddd, *J* = 12.0, 7.1, 1.2 Hz, 2H), 7.48 (dd, *J* = 10.6, 4.8 Hz, 2H); HRMS (ESI+) calcd. for: $C_{16}H_{12}NO$ 234.0913 (M+ H), found 234.0911.

Isoquinolin-1-yl(*p*-tolyl)methanone[39](7b, Scheme 2)

TLC R_f = 0.3 **(**10% EtOAc/Hexane**)**; Yield 48% (58.8 mg); Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 5.6 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 5.6 Hz, 1H), 7.72 (t, *J* = 7.3 Hz, 1H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4, 156.9, 144.6, 141.2, 136.7, 134.2, 130.8, 130.6, 129.2, 128.1, 127.0, 126.4, 126.2, 122.3, 21.7; HRMS (ESI+) calcd. for: $C_{17}H_{14}NO$ 248.1070 (M+ H), found 248.1066.

Isoquinolin-1-yl(4-methoxyphenyl)methanone[39](7c, Scheme 2)

TLC R_f = 0.3 **(**10% EtOAc/Hexane**)**; Yield 45% (59.1 mg); Brown solid; m.p. 73-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 5.7 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.97 – 7.88 (m,

3H), 7.79 (d, *J* = 5.6 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.63 – 7.58 (m, 1H), 6.99 – 6.91 (m, 2H), 3.88 (s, 3H); HRMS (ESI+) calcd. for: $C_{17}H_{14}NO_2$ 264.1019 (M+ H), found 264.0987.

(4-Fluorophenyl)(isoquinolin-1-yl)methanone[39](7d, Scheme 2)

TLC R_f = 0.3 **(**10% EtOAc/Hexane**)**; Yield 59% (74 mg); Brown solid; m.p. 94-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J*= 5.6 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.06 – 7.97 (m, 2H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 5.6 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.19 – 7.10 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0, 166.1 (d, *J* = 257.5 Hz), 156.0, 141.1, 136.8, 133.5 (d, *J* = 9.09 Hz), 133.1 (d, *J*= 2.02 Hz), 130.8, 128.4, 127.15, 126.4, 126.1, 122.7, 115.6 (d, *J* = 22.22 Hz); HRMS (ESI+) calcd. for: $C_{16}H_{11}FNO$ 252.0819. (M+ H), found 252.0817.

Isoquinolin-1-yl(4-(trifluoromethyl)phenyl)methanone[38](7e, Scheme 2)

TLC R_f = 0.4 **(**10% EtOAc/Hexane**)**; Yield 35% (52.7mg); White solid; m.p. 96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.6 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 5.6 Hz, 1H), 7.82 – 7.72 (m, 3H), 7.71 – 7.65 (m, 1H); HRMS (ESI+) calcd. for: $C_{17}H_{11}F_3NO$ 302.0787. (M+ H), found 302.0788.

(4-Fluoro-3-methylphenyl)(isoquinolin-1-yl)methanone (7f, Scheme 2)

TLC R_f = 0.4 **(**10% EtOAc/Hexane**)**; Yield 44% (58.3 mg); White solid; m.p. 81.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 5.6 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.88 – 7.71 (m, 4H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 8.9 Hz, 1H), 2.30 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.4, 164.8 (d, *J* = 255.53 Hz), 156.3, 141.1, 136.7, 134.4 (d, *J* = 7.07Hz), 132.8 (d, *J* = 4.04 Hz), 130.9 (d, *J* = 5.05 Hz), 130.7, 128.3, 127.1, 126.4, 126.1, 125.4 (d, *J* = 18.18 Hz), 122.6, 115.2 (d, *J* = 24.24 Hz) 14.5 (d, *J* = 3.03 Hz); HRMS (ESI+) calcd. for: $C_{17}H_{13}FNO$ 266.0976. (M+ H), found 266.0982.

(4-((1S)-(Benzyloxy)((1S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-6-methoxyquinolin-2-yl)(phenyl)methanone (9a, Scheme3)

TLC R_f = 0.3 **(**5% MeOH/DCM**)**; Yield 34% (108.5 mg); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.29 – 8.22 (m, 2H), 8.14 (d, *J* = 9.2 Hz, 1H), 7.82 (s, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.41 – 7.33 (m, 5H), 5.61 (ddd, *J* = 17.2, 10.3, 6.7 Hz, 1H), 5.09 – 5.03 (m, 2H), 4.63 (dd, *J* = 38.3, 10.7 Hz, 2H), 4.19 (s, 3H), 3.49 – 3.36 (m, 2H), 3.20 – 3.08 (m, 2H), 2.69 (s, 2H), 2.09 (s, 1H), 1.66 – 1.48 (m, 3H), 0.87 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3, 161.0, 151.5, 143.3, 136.6, 136.3, 133.0, 132.9, 131.4, 129.7, 128.7, 128.3, 128.2, 128.1, 124.1, 118.3, 117.3, 101.0, 77.3, 77.2, 77.0, 76.7, 72.0, 59.6, 54.6, 43.7, 37.1, 31.9, 27.0, 24.5, 18.9; HRMS (ESI+) calcd. for: $C_{34}H_{35}N_2O_3$ 519.2642. (M+ H), found 519.2649.

ASSOCIATED CONTENT:

Supporting Information Copies of NMR, HRMS, LCMS and GCMS spectra are provided. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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