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Transition Metal Free One-Pot Tandem Synthesis of 3-Ketoisoquinolines from Aldehydes and Phenacyl azides

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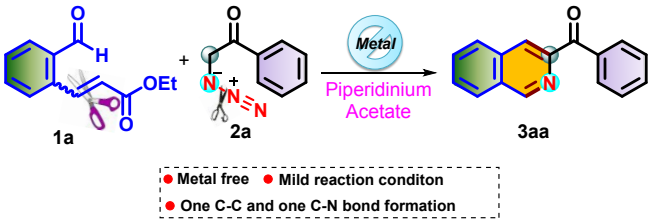
ABSTRACT: An efficient and transition metal-free strategy for the synthesis of 3-keto-isoquinolines in one-pot has been developed from the easily accessible 2-(formylphenyl)acrylates and phenacyl azides. Various substituted aldehydes and phenacyl azides were successfully employed in this transformation to furnish a variety 3-keto-isoquinolines in very good yields. A number of controlled experiments were conducted to postulate the reaction mechanism. Secondary functionalizations of 2-keto-isoquinolins were also performed to showcase the synthetic utility.



INTRODUCTION

Isoquinoline is considered to be one of the most privileged nitrogen-containing heterocycle frequently encountered in numerous natural products and FDA-approved drugs (Fig.-1, **A-C**).[1-2] In particular, the compounds containing 3-substituted isoquinoline framework have exhibited many significant biological activities, including cardiovascular agent, antihypertensive, anticancer, and phosphodiesterase inhibitor activities (Fig.-1, **D-G**).[3] Additionally, 3-substituted isoquinolines also serve as an immediate precursor to many biologically important natural products.[4] In addition, this key heterocyclic core has also found broad applications in both, drug designing and material sciences because of their pharmacophoric and chelating properties.[5]

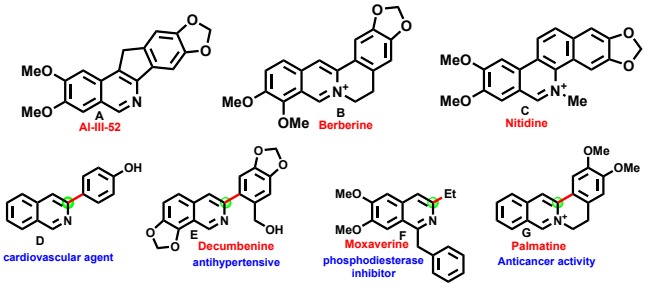
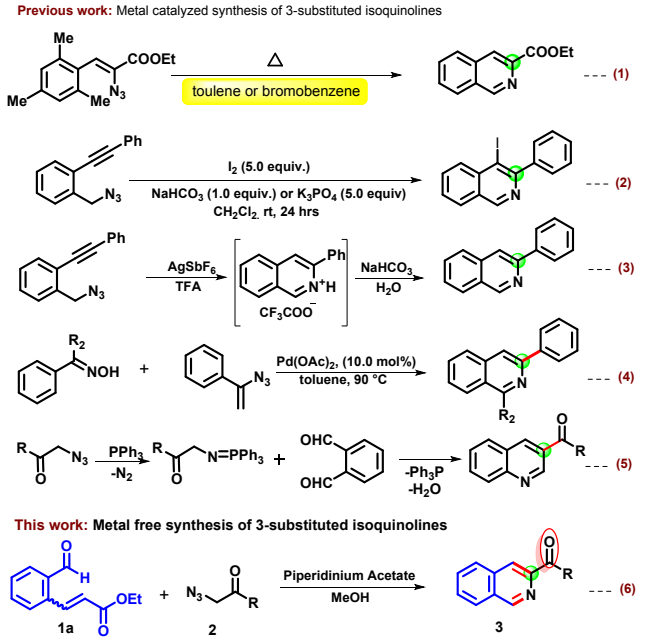


Figure 1. Biologically active molecules containing substituted quinolines.

Considering the wide utility of 3-substituted isoquinolines, several approaches have been reported for their synthesis.[6] Traditional methods such as the Pictet-Spengler, the Bischler-Napieralski, and the Pomeranz-Fritsch reactions have been well explored for the synthesis of isoquinolines.[7] New protocols involving metal-catalyzed photoredox reaction, C−H activation, and cycloadditions have also been appeared in the literature for the synthesis of substituted isoquinolines.[8] In this context, Charles W. Rees and coworkers have contributed significantly in developing new methodologies for the synthesis of substituted isoquinolines.[9a-b] For example, they accomplished the isoquinoline synthesis *via* nitrene insertion generated *in situ* from thermal decomposition of vinyl azides under neutral conditions (Scheme 1, eq.-1).[9b] Recently, Y.



Scheme 1. Strategies for the synthesis of 3-substituted isoquinolines

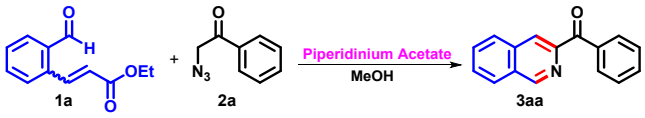
Yamamato and coworkers developed iodine mediated electrophilic intramolecular cyclization of 2-alkynyl benzyl

azides to get access to substituted isoquinolines (Scheme 1, eq.-2).[9c] Y. M. Liang and coworkers reported silver catalyzed intramolecular cyclization of 2-alkynyl benzylazides to corresponding 3-substituted isoquinolines (Scheme 1, eq.-3).[9d] Very recently, Jiang's group reported an efficient and novel methodology for the synthesis of 3-substituted isoquinolines *via* Pd (II)-catalyzed cyclization reaction of oximes with vinyl azides (Scheme 1, eq.-4).[9e] R. Guilard and coworkers have described a transition metal free approach for the synthesis of 3-ketoisoquinolines via one pot cyclocondensation between o-phthalaldehyde and iminophosphoranes generated in situ from corresponding azides. Though, all these methods allow a convenient access to 3-substituted isoquinolines but the use of expensive transition metals and stoichiometric amount of reagents, limited availability of starting materials and limited substrate scopes are the disadvantages associated with them. Therefore, the development of an efficient, mild and metal-free approach for the synthesis of 3-substituted isoquinolines from easily available starting materials is highly desirable. As a part of our continuing research interest in pharmaceutically important heterocyclic frameworks,[10a-c] we have recently developed various new methods for the synthesis substituted quinolines.[10d-f] In continuation of same research programme, herein we report a transition metal free approach for the synthesis of 3-ketoisoquinolines from 2-(formylphenyl) acrylates and phenacyl azides *via* sequential Knoevenagel condensation, amination followed by elimination reactions reaction cascade in one pot.

RESULT AND DISCUSSION

To commence our study, ethyl 3-(2-formylphenyl)acrylate (**1a**) and phenacyl azide (**2a**) were chosen as model substrates for this one-pot tandem reaction and the details are summarized in Table-1. Our first attempt by reacting ethyl 3-(2-formylphenyl)acrylate (**1a**, 0.5 mmol) and phenacyl azide (**2a**, 0.5 mmol) in MeOH (2.0 mL) in the presence of DBU (0.6 mmol) at room temperature was failed and could not produce the desired product even in trace amount (Table-1, entry-1). Using stronger base such as NaOH also did not give the aimed product (entry-2). Next, we attempted this one pot tandem reaction in the presence of acids such *p*-TSA and AcOH but none of them afforded the desired product (entry 3 & 4). To our surprise, the desired product (**3aa**) was formed albeit in very low yield (7%), when piperidine was used as an additive (entry-5). Further, use of piperidinium acetate as a base at ambient temperature improved the yield of product **3aa** to 23% (entry-6). Prolonging the reaction time furnished the desired product in similar yield (45%) (entry-7). However, performing the reaction at 60 °C for 6 h gave better yield (58%) of desired **3aa** (entry-8). Interestingly the yield of the product **3aa** improved drastically when the reaction mixture was initially stirred at room temperature for 3h and then heated at 60 °C for another 3h (70%) (entry-9). A similar yield (72%) of desired **3aa** was obtained when reaction mixture heated 80 °C (entry-10). Yield of **3aa** was slightly improved when the reaction was performed at 80 °C (72%, entry-10). Change of solvents such as EtOH, CH_3CN, DMF, and THF did not improve the reaction outcome and furnished the desired product in inferior yields (entries 11-14). We next performed the reaction in the presence of catalytic amount of piperidinium acetate (0.05 mmol) however, only trace amount of desired product **3aa** was observed (entry-15). After having the optimized reaction conditions (Table-1, entry 10), the scope of the reaction with respect to various 2-(formylphenyl)acrylate (**1a-1l**) and

Table-1 Optimization of reaction conditions[a]



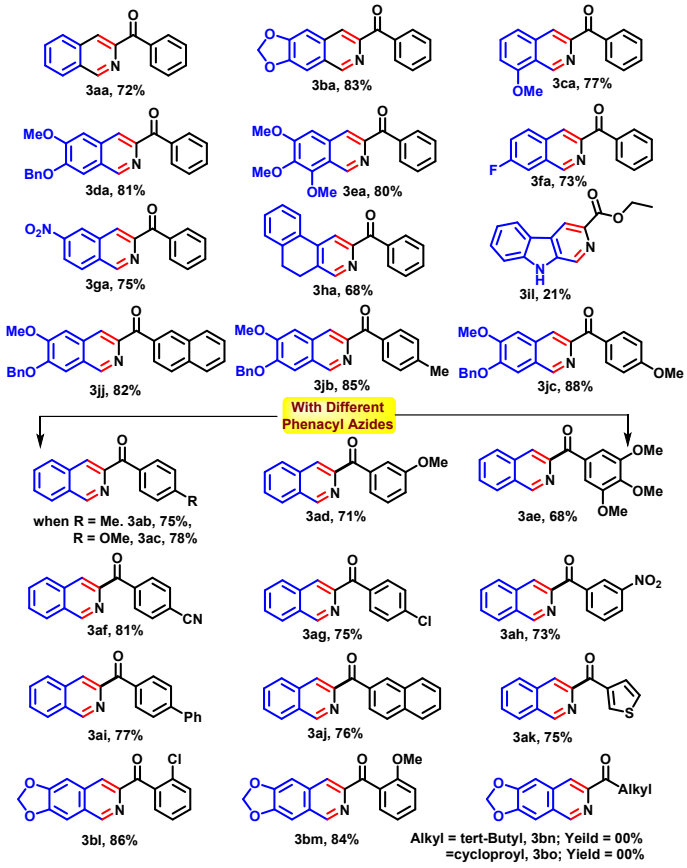
En.	Base/acid /additive	Solvent	Temp[c]	Time (h)	Yields[b]
1	DBU	MeOH	rt	6	n.o.
2	NaOH	MeOH	rt	6	n.o.
3	*p*-TSA	MeOH	rt	6	n.o.
4	AcOH	MeOH	rt	6	n.o.
5	Piperidine	MeOH	rt	6	7%
6	PA	MeOH	rt	6	23%
7	PA	MeOH	rt	12	45%
8	PA	MeOH	60 °C	6	58%
9	PA	MeOH	60 °C	3	70%[d]
10	**PA**	**MeOH**	**80 °C**	**3**	**72%[d]**
11	PA	EtOH	80 °C	3	69%[d]
12	PA	CH_3CN	80 °C	3	43%[d]
13	PA	DMF	80 °C	3	trace[d]
14	PA	THF	80 °C	3	52%[d]
15	PA	MeOH	80 °C	3	trace[e]

[a]Reaction was performed using **1a** (0.5 mmol), **2** (0.5 mmol), base/acid/additive (1 mmol) and solvent (2.0 mL) under nitrogen atmosphere; [b] isolated yield; [c] rt = room temperature; [d] when reaction mixture was stirred at rt for 3 h then heated at 60 - 80 °C; [e] when PA was used in catalytic amount (10 mole%); n.o = not observed; PA = piperidinium acetate.

phenacyl azides (**2a-2l**) was evaluated. As shown in Table 2, a wide range substituted 2-(formylphenyl)acrylates (**1b-1l**) were reacted effectively with phenacyl azides (**2a-2c, 2j** & **2l**) and furnished the desired products in excellent yields. 3-(2-formylphenyl)acrylates containing both electron donating group (**1b-1e**) and electron withdrawing groups (**1f-1g**) at aromatic ring readily furnished the corresponding 3-ketoisoquinolines in very good yields. Various functional groups such as methylenedioxy (**1b**), methoxy (**1c**), phenoxy (**1d**), fluoro (**1f**), and nitro (**1g**) groups were well tolerated in this one-pot tandem reaction. Furthermore, 1-formylnaphthalen-2-yl)acrylate (**1h**) smoothly reacted with phenacyl azide (**2a**) leading to the formation of desired 3-keto-isoquinoline (**3ha**) in excellent yield. Moreover, 3-formyl-1*H*-indol-2-yl)acrylate (**1i**) was treated with ethyl 2-azidoacetate (**2l**) under optimized reaction conditions to produce the desired product (**3il**) in very low (21%) yield. The substrate scope of the present methodology was further extended to various substituted phenacyl azides (**2a-2k**). The phenacyl azides bearing both electron donating (**2b-2e**) and electron

withdrawing (**2f-2j**) groups at aromatic ring reacted well to furnish the desired products (**3af-3aj**) in high yields. To our delight, heterocyclic azide (**2k**) also easily participated in this reaction to form the desired **3ak** in 75% yield. Next, the ortho substituted phenacyl azide (2l & 2m) also readily participated under the standard

Table 2 Scope with different 2-(formylphenyl)acrylate and phenacyl azides

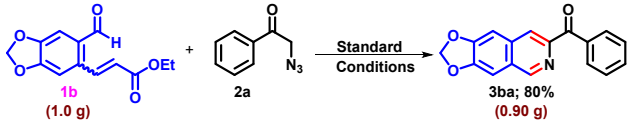


[a]Reaction was performed using **1a** (0.5 mmol), **2** (0.5 mmol), piperidinium acetate (1 mmol) and solvent (2.0 mL) at room temperature 3h, then 80 °C; 3h; Yield = isolated yield.

conditions to form the desired product **3bl** and **3bm** in 86% and 84% yields respectively. On the other hand, azidomethyl alkyl ketones such as *tert*-butyl (**2n**) and cyclopropyl (**2o**) groups were found to be unsuccessful to give the desired products.

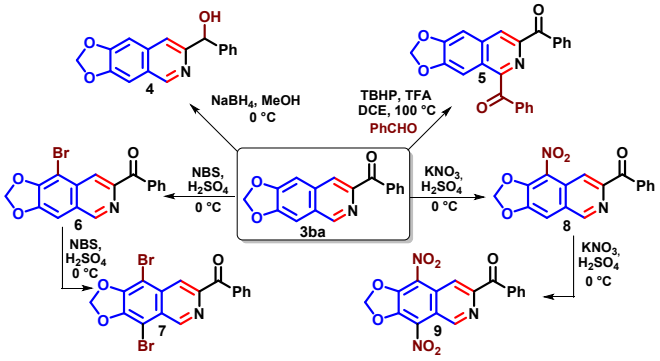
The practicality of present strategy was extended by demonstrating a gram scale synthesis wherein, **3ba** was prepared in 80% yield from 2-formyl α,β-unsaturated ester **1b** and phenacyl azide **2a** in a one pot reaction under standard condition (Scheme 2).

Scheme-2 gram scale synthesis **3ba**



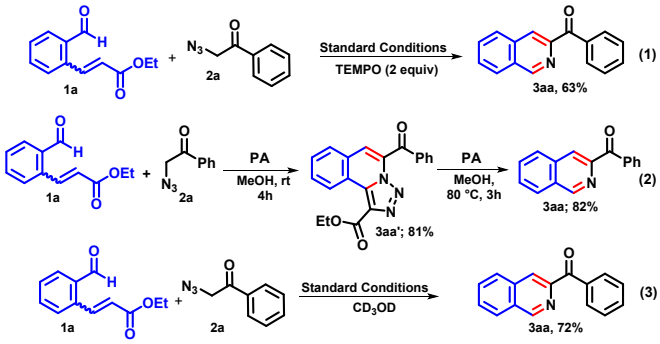
Compound **3ba** was further utilized for the secondary modifications as depicted in Scheme 3. Initially, the carbonyl group of **3ba** was reduced by $NaBH_4$ in MeOH to form the corresponding product **4**. In another set of transformation, compound **3ba** was treated with benzaldehyde in presence of TBHP/TFA in DCE solvent to obtain 1-benzoylated product **5**.[11a] 3-ketoisoquinoline (**3ba**) was further subjected to mono and di bromination as well as nitrantion in H_2SO_4 at 0 °C to form corresponding mono (**6**) and dibromo (**7**) and mono nitro (**8**) and di nitro (**9**) substituted products respectively in very good yields.[11b]

Scheme 3. Synthetic utility



In order to gain insight into the reaction, various controlled experiments were carried out. When the reaction was performed in the presence of TEMPO under the optimized condition, leading the formation of desired **3aa** in 63% yield confirmed that no radical mechanism is involved (Scheme 4, eq.-1). Furthermore, we isolated the bicyclic triazole intermediate **3aa'** in 81% yield by quenching the reaction mixture after 4 h of stirring at room temperature. Then the intermediate **3aa'** was heated at 80 °C for 3 hrs in the presence of piperidinium acetate furnished the desired product **3aa** in 82% yields. This experiment suggests that the reaction is proceeding through intermediate **3aa'** (Scheme 4, eq. -2). Next in order to check the origin of proton a deuterium labeling experiment was conducted by reacting 2-(formylphenyl)acrylate (**1a**) with phenacyl azide (**2a**) in the presence of CD_3OD solvent under standard condition (Scheme 4, eq.-3). However, only non-deuterated product **3aa** was formed in 72% yield. This result clearly indicates that solvent is not primary H donor in this reaction.

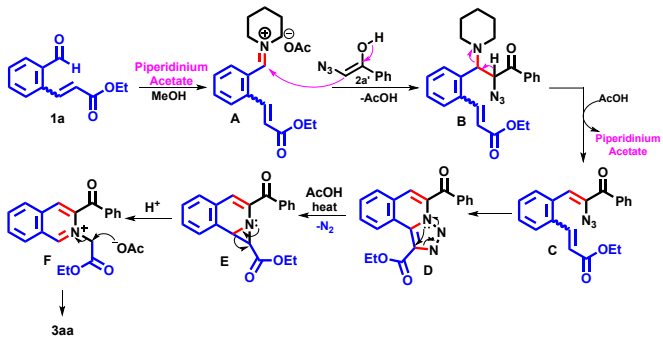
Scheme 4. Mechanistic Insights



Based on the preliminary mechanistic experiments and previous literature reports[12] a mechanistic rationale is proposed in Scheme 5. Initially, aldehyde reacts with piperidinium acetate to form iminium cation salt (**A**), which on nucleophilic addition by enol (**2a'**) gives rise to intermediate

B, which gets converted into vinyl azide intermediate **C** with elimination of piperidinium acetate.[12a] The intermediate **B** then undergoes to intermolecular 1,3-dipolar cycloaddition between azide and unsaturated ester to form the bicyclic triazole (**D**) intermediate **D**. The triazole intermediate **D** on heating rearranges to aziridine intermediate **E** via denitrogenation of azide.[12b] The intermediate **E** then undergoes to aromatization followed by aziridine ring opening to give the intermediate **F**. The C-N bond of intermediate might be getting cleaved by nucleophlic addition of acetate ion to furnish the desired **3aa.**[12c]

Scheme 5. Possible reaction mechanism



CONCLUSION

In summary, we have developed an efficient and transition metal-free approach for the synthesis of 3-keto isoquinolines from 2-(formylphenyl) acrylates and phenacyl azides involving Knoevenagel condensation, amination and elimination reactions cascades in one-pot. This reaction works well with the substituted 2-(formylphenyl) acrylates and phenacyl azides furnishing a series of 3-keto isoquinolines. In addition, efficient conversion of these heterocyles into various other pharmacologically important molecules have also been illustrated.

EXPERIMENTAL SECTION

General Information

All the reagents and chemicals were purchased from commercial sources and used without further purification. Common laboratory solvents (LR grade) were purchased from domestic suppliers. Analytical thin layer chromatography was performed with E. Merck silica gel 60 F aluminium plates and visualized under UV 254 nm radiation. NMR spectra were measured with 300, 400, and 500 MHz instruments. Chemical shifts are reported in δ units, parts per million (ppm) downfield from TMS. Coupling constants (*J*) are in hertz (Hz) and are unadjusted; therefore, due to limits in resolution, in some cases there are small differences (<1 Hz) in the measured *J* value of the same coupling constant determined from different signals. Splitting patterns are designed as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; tt, triplet of triplets; m, multiplet; br, broad. ESI-MS and ESI-HRMS spectra were obtained on a ion trap mass spectrometer. Melting points were determined on a Kofler block and are uncorrected. All the new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, and Mass-Spectroscopy and HRMS analysis.

General experimental procedure for the synthesis of 2-(formylphenyl)acrylates (1a–1i): To a solution o-bromobenzaldehyde (185 mg, 1 mmol) in DMF (3.0 mL) was added K_2CO_3 (207.3 mg, 1.5 mmol), Bu_4NOAc (856.56 mg, 3 mmol), KCl (111.8 mg, 1.5 mmol), $Pd(OAc)_2$ (22.45 mg, 0.1 mmol), ethyl acrylate (120.1 mg, 1.2 mmol) and was stirred for 5 min at room temperature. The reaction mixture was then allowed to attain the temperature 90 ºC in oil bath and stirred for 12h. The reaction mixture was then diluted with ether and the resulting mixture was filtered through a small band of Celite. The filtrate was then diluted with water and extracted with ether. The organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum. The crude product which was purified by column chromatography using a mixture of ethyl acetate/petroleum ether (30%) on silica gel to provide the desired **1a** in an 80% isolated yield.

*ethyl 3-(2-formylphenyl)acrylate (**1a**)*:[13a-b] Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **1a** as yellow oil in (163 mg, 80%); mp 61 − 63 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) 10.31 (s, 1H), 8.52 (d, *J* = 15.9 Hz, 1H), 7.88 (dd, *J* = 5.5, 2.8 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.59 – 7.54 (m, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). Spectral data were consistent with data reported in the literature.[12a-b]

*Ethyl (E)-3-(6-formylbenzo[d][1,3]dioxol-5-yl)acrylate (**1b**)*:[13c] Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **1b** as yellow solid (204 mg, 82%); mp 108 − 110 °C; R_f = 0.5 (40% ethyl acetate in hexane); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.27 (s, 1H), 8.42 (d, J = 15.7 Hz, 1H), 7.35 (s, 1H), 7.06 (s, 1H), 6.31 (d, *J* = 15.7 Hz, 1H), 6.11 (s, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). Spectral data were consistent with data reported in the literature.[13c]

*Ethyl (E)-3-(2-formyl-6-methoxyphenyl)acrylate (**1c**)*: Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **1c** as brown solid (183 mg, 78%); mp 67 - 69 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.36 (s, 1H), 8.44 (d, *J* = 15.8 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.38 (d, *J* = 2.8 Hz, 1H), 7.15 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 190.9, 166.5, 161.0, 139.6, 135.1, 129.4, 129.4, 121.3, 120.8, 114.4, 60.7, 55.7, 14.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{15}O_4$ 235.0964; Found 235.0964.

*Ethyl (E)-3-(5-(benzyloxy)-2-formyl-4-methoxyphenyl)acrylate (**1d**)*: Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 50/50) to afford **1d** as yellow solid (272 mg, 80%); mp 128 - 130 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.31 (s, 1H), 8.42 (d, *J* = 15.8 Hz, 1H), 7.49 – 7.38 (m, 5H), 7.37 – 7.32 (m, 1H), 7.10 (s, 1H), 6.23 (d, *J* = 15.7 Hz, 1H), 5.25 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 189.2, 166.3, 152.8, 151.0, 139.3, 135.6, 131.4, 128.8, 128.4, 127.9, 127.4, 121.8, 111.4, 111.0, 71.0, 60.8, 56.2, 14.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{21}O_5$ 341.1383; Found 341.1392.

*Ethyl (E)-3-(6-formyl-2,3,4-trimethoxyphenyl)acrylate (**1e**):* Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **1e** as white solid (238 mg, 81%); mp 91 - 93 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.17 (s, 1H), 8.08 (d, *J* = 16.1 Hz, 1H), 7.30 (s, 1H), 6.24 (d, *J* = 16.1 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.88 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 189.9, 166.2, 154.2, 152.4, 147.1, 135.7, 130.4, 126.5, 126.2, 107.3, 61.1, 61.0, 60.8, 56.2, 14.3; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{19}O_6$ 295.1176; Found 295.1176.

*Ethyl (E)-3-(5-fluoro-2-formylphenyl)acrylate (**1f**):*[13b] Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **1f** as white solid (167 mg, 75%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.25 (s, 1H), 8.49 (d, *J* = 15.9 Hz, 1H), 7.92 (dd, *J* = 8.6, 5.8 Hz, 1H), 7.31 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.27 – 7.21 (m, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). Spectral data were consistent with data reported in the literature [13b].

*Ethyl 3-(2-formyl-4-nitrophenyl)acrylate (**1g**):*[13c] Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **1g** as pale yellow solid (192 mg, 77%); mp 61 - 63 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.35 (s, 1H), 8.72 (d, *J* = 2.4 Hz, 1H), 8.49 – 8.42 (m, 2H), 7.81 (d, *J* = 8.5 Hz, 1H), 6.48 (d, *J* = 15.9 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). Spectral data were consistent with data reported in the literature.[13c]

*Ethyl (E)-3-(1-formyl-3,4-dihydronaphthalen-2-yl)acrylate (**1h**):*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **1h** as brown oil (195 mg, 76%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.11 (s, 1H), 7.84 (d, *J* = 15.9 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.34 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.26 – 7.23 (m, 1H), 6.20 (d, *J* = 15.9 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.85 – 2.76 (m, 2H), 2.67 – 2.57 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 191.1, 165.3, 147.9, 138.4, 138.1, 136.8, 132.6, 130.7, 129.1, 128.2, 126.93, 126.8, 61.1, 27.3, 20.5, 14.2; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{16}H_{17}O_3$ 257.1172; Found 257.1172.

*Ethyl 3-(3-formyl-1H-indol-2-yl)acrylate **(1i):***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 40/60) to afford **1h** as white solid (153 mg, 63%); mp 252 - 254 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) 11.50 (s, 1H), 10.41 (d, *J* = 2.5 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 8.13 (dd, *J* = 16.0, 2.5 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.29 – 7.24 (m, 1H), 6.79 (dd, *J* = 16.0, 2.4 Hz, 1H), 4.32 (qd, *J* = 7.1, 2.6 Hz, 2H), 1.37 (td, *J* = 7.1, 2.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 184.6, 166.2, 140.2, 137.1, 130.4, 126.2, 125.6, 123.1, 122.0, 121.7, 117.7, 111.6, 61.0, 14.3; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{14}NO_3$ 244.0968; Found 244.0968.

General experimental procedure for the synthesis of α-azido ketones (2a-2k): All the α-azido ketones were synthesized from corresponding α-bromo ketones (1 mmol) and sodium azide (3.3 mmol) by using reported procedure described in reference [12a].

*2-Azido-1-phenylethan-1-one **(2a):**[14a]*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 80/20) to afford **2a** as yellow oil (153 mg, 95%); ^{1}H NMR (400 MHz, Chloroform-*d*) 7.91 (ddd, *J* = 7.0, 3.2, 1.6 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (dd, *J* = 10.9, 4.5 Hz, 2H), 4.56 (s, 2H). Spectral data were consistent with data reported in the literature.[14a]

*2-Azido-1-(p-tolyl)ethan-1-one **(2b):**[14a]*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 80/20) to afford **2b** as white solid (170 mg, 97%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.53 (s, 2H), 2.43 (s, 3H). Spectral data were consistent with data reported in the literature.[14a]

*2-Azido-1-(4-methoxyphenyl)ethan-1-one **(2c):**[14a]*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **2c** as white solid (187 mg, 98%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 4.51 (s, 2H), 3.89 (s, 3H). Spectral data were consistent with data reported in the literature. [14a]

*2-Azido-1-(3-methoxyphenyl)ethan-1-one **(2d):**[14b]*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **2d** as colorless oil (180 mg, 94%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (s, 1H), 7.44 (t, *J* = 1.4 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.17 (ddd, *J* = 8.0, 2.6, 1.4 Hz, 1H), 4.55 (s, 2H), 3.87 (s, 3H). Spectral data were consistent with data reported in the literature. [14b]

*2-Azido-1-(3,4,5-trimethoxyphenyl)ethan-1-one **(2e):**[14b]*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **2e** as white solid (241 mg, 96%)**;** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.14 (s, 1H), 4.53 (s, 2H), 3.91 (s, 3H), 3.90 (s, 6H). Spectral data were consistent with data reported in the literature.[14b]

*4-(2-Azidoacetyl)benzonitrile **(2f):**[14a]*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **2f** as white solid (177 mg, 95%)**;** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 4.58 (s, 2H). Spectral data were consistent with data reported in the literature. [14a]

*2-Azido-1-(4-chlorophenyl)ethassn-1-one **(2g):**[14a]*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **2g** as white solid (190 mg, 97%)**;** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 4.53 (s, 2H). Spectral data were consistent with data reported in the literature. [14a]

2-Azido-1-(3-nitrophenyl)ethan-1-one **(2h):**[14c]

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **2h** as yellow solid (192 mg, 93%)**;** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.73 (t, *J* =

1.9 Hz, 1H), 8.49 (ddd, *J* = 8.2, 2.2, 1.1 Hz, 1H), 8.32 – 8.21 (m, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 4.63 (s, 2H). Spectral data were consistent with data reported in the literature. [14c]

1-([1,1'-Biphenyl]-4-yl)-2-azidoethan-1-one ***(2i):*** [14d]

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **2i** as white solid (225 mg, 95%)**;** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.66 – 7.61 (m, 2H), 7.52 – 7.46 (m, 2H), 7.44 (dd, *J* = 5.0, 3.6 Hz, 1H), 4.60 (s, 2H). Spectral data were consistent with data reported in the literature.[14d]

2-Azido-1-(naphthalen-2-yl)ethan-1-one ***(2j):*** [14a]

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **2j** as white solid (203 mg, 96%)**;** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.36 (s, 1H), 7.93 (dd, *J* = 7.3, 6.1 Hz, 2H), 7.87 (dd, *J* = 14.5, 8.4 Hz, 2H), 7.63 – 7.58 (m, 1H), 7.57 – 7.51 (m, 1H), 4.66 (s, 2H). Spectral data were consistent with data reported in the literature. [14a]

2-Azido-1-(thiophen-3-yl)ethan-1-one ***(2k):*** [14a]

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **2k** as light brown solid (162 mg, 97%)**;** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.55 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.39 (dd, *J* = 5.1, 2.9 Hz, 1H), 4.44 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, Chloroform-*d*) δ 187.6, 139.0, 132.7, 127.1, 126.5, 55.4.

2-azido-1-(2-chlorophenyl)ethan-1-one ***(2l):*** [14a]

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **2l** as colorless (187 mg, 96%)**;** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.2 Hz, 1H), 7.47 – 7.44 (m, 2H), 7.38 (ddd, *J* = 7.7, 5.8, 2.8 Hz, 1H), 4.52 (s, 2H). Spectral data were consistent with data reported in the literature.[14a]

2-azido-1-(2-methoxyphenyl)ethan-1-one ***(2m):*** [14b]

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **2n** as colorless oil (181 mg, 95%)**;** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.53 (ddd, *J* = 8.4, 7.3, 1.8 Hz, 1H), 7.08 – 7.01 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 4.51 (s, 2H), 3.93 (s, 3H). Spectral data were consistent with data reported in the literature.[14b]

1-azido-3,3-dimethylbutan-2-one ***(2n):*** [14f]

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 90/10) to afford **2n** as colorless oil (128 mg, 91%)**;** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07 (s, 2H), 1.17 (s, 9H). Spectral data were consistent with data reported in the literature.[14f]

2-azido-1-cyclopropylethan-1-one ***(2o):***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 90/10) to afford **2o** as brown oil (112 mg, 90%)**;** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (s, 2H), 1.95 (tt, *J* = 7.8, 4.5 Hz, 1H), 1.16 (dd, *J* = 7.8, 3.4 Hz, 2H), 1.01 (dq, *J* = 11.3, 3.8 Hz, 2H); **^{13}C{^{1}H} NMR** (125 MHz, Chloroform-*d*) δ = 204.3, 57.9, 18.3, 11.7

General experimental procedure for the synthesis of 3-ketoisoquinolines (3aa-3ak): 2-(formylphenyl) acrylate (**1a**) (102.1 mg, 0.5 mmol) and α-azido ketone (**2a**) (80.6 mg, 0.5 mmol) and MeOH (3.0 mL) were taken in a 10 mL round bottom flask then freshly prepared piperidinium acetate (145.2 mg, 1.0 mmol) was added. The reaction mixture was initially stirred at room temperature for 3 h after that the reaction temperature was increased to 80 °C in oil bath and stirred at this temperature for another 3 hrs. After complete consumption of starting materials, (reaction monitored by TLC) MeOH was removed under reduced pressure and get crude product which was purified by column chromatography using a mixture of ethyl acetate/petroleum ether (40%) on silica gel to provide the desired **3aa** in an 72% isolated yield.

Isoquinolin-3-yl(phenyl)methanone ***(3aa)****.*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3aa** as a white solid (84 mg, 72%); mp. 80 - 82 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.34 (s, 1H), 8.48 (s, 1H), 8.08 (dd, *J* = 8.2, 1.1 Hz, 3H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.85 – 7.72 (m, 2H), 7.67 – 7.58 (m, 1H), 7.51 (dd, *J* = 10.4, 4.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 194.4, 151.6, 148.9, 137.0, 135.6, 132.7, 131.1, 130.9, 129.6, 129.4, 128.2, 128.1, 127.6, 123.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}NO$ 234.0913; Found 234.0930.

[1,3]Dioxolo[4,5-g]isoquinolin-7-yl(phenyl)methanone ***(3ba)****.*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 65/35) to afford **3ba** as light yellow solid (115 mg, 83%); mp 141 - 143 °C; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.05 (s, 1H), 8.31 (s, 1H), 8.10 – 8.04 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (dd, *J* = 16.2, 8.7 Hz, 2H), 7.29 (s, 1H), 7.23 (s, 1H), 6.17 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, Chloroform-*d*) δ 194.4, 151.5, 150.2, 149.2, 148.1, 137.2, 134.1, 132.5, 130.8, 128.0, 127.5, 122.8, 103.9, 103.3, 102.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{12}NO_3$ 278.0812; Found 278.0838.

(8-Methoxyisoquinolin-3-yl)(phenyl)methanone ***(3ca).***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 65/35) to afford **3ca** as white solid (101 mg, 77%); mp 150 - 152 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.18 (s, 1H), 8.35 (s, 1H), 8.11 – 8.04 (m, 2H), 7.96 (d, *J* = 9.0 Hz, 1H), 7.59 (qt, *J* = 5.5, 1.6 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.36 (dt, *J* = 6.7, 3.4 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 3.98 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) 194.6, 161.4, 150.7, 149.4, 137.7, 137.1, 132.6, 130.9, 129.2, 128.1, 125.4, 122.5, 122.5, 105.5, 55.6; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}NO_2$ 264.1019; Found 264.1033.

(7-(Benzyloxy)-6-methoxyisoquinolin-3-yl)(phenyl)methano-ne ***(3da)****.*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3da** as white solid (149 mg, 81%); mp 143 – 145 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.05 (s, 1H), 8.34 (s, 1H), 8.06 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.61 – 7.56 (m, 1H), 7.50 (td, *J* = 7.0, 3.3 Hz, 4H), 7.45 – 7.40 (m, 2H), 7.39 – 7.35 (m, 1H), 7.33 (s, 1H),

7.24 (s, 1H), 5.33 (s, 2H), 4.06 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ 194.5, 153.8, 151.2, 148.9, 147.9, 137.3, 135.8, 132.4, 132.4, 130.8, 128.8, 128.3, 128.0, 127.4, 125.9, 122.2, 107.1, 106.2, 70.9, 56.2; MS (ESI): HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{20}NO_3$ 370.1438; Found 370.1462.

Phenyl(6,7,8-trimethoxyisoquinolin-3-yl)methanone ***(3ea).***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3ea** as white solid (129 mg, 80%); mp 153 – 155 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.45 (s, 1H), 8.30 (s, 1H), 8.07 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.04 (s, 1H), 4.14 (s, 3H), 4.04 (s, 3H), 4.02 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ 194.5, 157.4, 149.0, 148.7, 145.9, 142.9, 137.1, 133.6, 132.5, 130.9, 128.1, 122.0, 120.9, 102.1, 61.9, 61.3, 56.2; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}NO_4$ 324.1230; Found 324.1250.

(7-Fluoroisoquinolin-3-yl)(phenyl)methanone ***(3fa)****.*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 65/35) to afford **3fa** as white solid (92 mg, 73%); mp 128 – 130 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.30 (s, 1H), 8.50 (s, 1H), 8.07 (dd, *J* = 8.0, 7.0 Hz, 2H), 8.06 – 7.98 (m, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.66 – 7.55 (m, 2H), 7.51 (dd, *J* = 11.5, 4.2 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, Chloroform-*d*) δ 194.0, 162.3 (d, *J* = 253.2 Hz), 150.7, 150.7, 148.6, 136.9, 132.7, 131.1 (d, *J* = 8.8 Hz), 130.9, 130.5 (d, *J* = 8.9 Hz), 128.1, 123.2, 121.8 (d, *J* = 25.5 Hz), 111.0 (d, *J* = 21.0 Hz); ^{19}F NMR (375 MHz, Chloroform-*d*) δ 107.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{11}FNO$ 252.0819; Found 252.0823.

(6-Nitroisoquinolin-3-yl)(phenyl)methanone ***(3ga).***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 65/35) to afford **3ga** as white solid (104 mg, 75%); mp 153 – 155 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.34 (s, 1H), 9.03 (s, 1H), 8.64 (s, 1H), 8.54 – 8.41 (m, 2H), 8.12 (d, *J* = 7.0 Hz, 1H), 8.07 (d, *J* = 7.2 Hz, 1H), 7.90 – 7.78 (m, 2H), 7.72 (t, *J* = 8.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz Chloroform-*d*) δ 191.6, 151.7, 147.9, 138.4, 136.5, 135.7, 131.4, 130.1, 129.2, 128.4, 127.8, 126.8, 126.2, 124.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{11}N_2O_3$ 279.0764; Found 279.0778.

(5,6-Dihydrobenzo[f]isoquinolin-2-yl)(phenyl)methanone ***(3ha).***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 65/35) to afford **3ha** as thick oil (97 mg, 68%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.05 (s, 1H), 8.13 – 8.08 (m, 2H), 7.95 (s, 1H), 7.87 (d, *J* = 7.2 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.52 – 7.47 (m, 2H), 7.36 (tdd, *J* = 8.8, 7.3, 1.6 Hz, 2H), 7.30 (dd, *J* = 7.2, 1.4 Hz, 1H), 3.02 – 2.92 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ 193.8, 153.3, 146.6, 143.7, 137.8, 136.6, 132.9, 132.8, 130.9, 130.0, 129.3, 128.6, 128.1, 127.5, 124.0, 124.0, 28.2, 27.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{16}NO$ 286.1226; Found 286.1243.

Ethyl 9H-pyrido[3,4-b]indole-3-carboxylate ***(3il).***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 55/45) to afford **3il** as white solid (25 mg, 21%); mp 235 - 237 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.91 (bs, 1H), 9.19 (d, *J* = 0.5 Hz, 1H), 8.91 (s, 1H), 8.20 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.60 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1H), 7.37 – 7.31 (m, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ 166.3, 141.2, 137.7, 137.4, 133.6, 129.0, 121.8, 121.6, 120.8, 120.7, 117.9, 112.5, 61.6, 14.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}N_2O_2$ 241.0977; Found 241.0975.

(7-(Benzyloxy)-6-methoxyisoquinolin-3-yl)(naphthalen-2-yl)methanone ***(3jj).***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 50/50) to afford **3jj** as white solid (172 mg, 82%); mp 152 - 154 °C; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.01 (s, 1H), 8.55 (s, 1H), 8.31 (s, 1H), 8.05 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.86 (dd, *J* = 8.2, 4.3 Hz, 2H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.45 (dd, *J* = 10.8, 4.0 Hz, 3H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.31 – 7.25 (m, 2H), 7.18 (s, 1H), 5.26 (s, 2H), 3.98 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ 194.4, 153.9, 151.2, 149.0, 148.1, 135.8, 135.3, 134.6, 132.9, 132.4, 129.8, 129.7, 128.8, 128.5, 128.3, 128.2, 127.8, 127.7, 127.4, 126.4, 126.0, 122.3, 107.1, 106.2, 70.9, 56.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{22}NO_3$ 420.1594; Found: 420.1600.

(7-(Benzyloxy)-6-methoxyisoquinolin-3-yl)(p-tolyl)methanone ***(3jb)****.*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3jb** as white solid (163 mg, 85%); mp 155 - 157 °C; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.05 (s, 1H), 8.31 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.54 – 7.48 (m, 2H), 7.45 – 7.39 (m, 2H), 7.39 – 7.34 (m, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 7.28 (s, 1H), 7.24 (s, 1H), 5.33 (s, 2H), 4.05 (s, 3H), 2.44 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, Chloroform-*d*) δ 194.2, 153.8, 151.1, 148.9, 148.2, 143.2, 135.8, 134.6, 132.4, 131.0, 130.8, 128.8, 128.3, 127.4, 125.9, 122.10, 107.1, 106.1, 70.9, 56.2, 21.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}NO_3$ 384.1594; Found 384.1599.

(*7-(Benzyloxy)-6-methoxyisoquinolin-3-yl)(4-methoxyphenyl) methanone* ***(3jc)****.*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3jc** as white solid (176 mg, 88%); mp 161 - 163 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.04 (s, 1H), 8.30 (s, 1H), 8.13 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 7.1 Hz, 2H), 7.46 – 7.35 (m, 3H), 7.33 (s, 1H), 7.23 (s, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.33 (s, 2H), 4.05 (s, 3H), 3.89 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, Chloroform-*d*) δ 192.8, 163.2, 153.8, 151.1, 148.6, 148.4, 135.8, 133.4, 132.5, 129.95, 128.8, 128.3, 127.4, 125.8, 121.9, 113.4, 107.1, 106.1, 70.9, 56.2, 55.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}NO_4$ 400.1543; Found: 400.1555.

Isoquinolin-3-yl(p-tolyl)methanone ***(3ab)****.*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3ab** as white solid (93 mg, 75%); mp 116 - 118 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.39 (s, 1H), 8.45 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.00 (dd, *J* = 13.9, 8.1 Hz, 3H), 7.88 – 7.73 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ 193.5, 151.4, 148.4, 143.7, 135.8, 134.2,

131.5, 131.0, 129.6, 129.4, 128.9, 128.2, 127.9, 123.6, 21.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}NO$ 248.1070; Found: 248.1098.

*Isoquinolin-3-yl(4-methoxyphenyl)methanone (**3ac**).*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3ac** as white solid (103 mg, 78%); mp 124 - 126 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.34 (s, 1H), 8.44 (s, 1H), 8.19 – 8.11 (m, 2H), 8.08 (d, *J* = 7.7 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.78 (pd, *J* = 7.0, 1.4 Hz, 2H), 7.04 – 6.96 (m, 2H), 3.90 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 192.7, 163.4, 151.4, 149.5, 135.7, 133.4, 131.0, 129.6, 129.4, 129.2, 128.1, 127.6, 123.1, 113.5, 55.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}NO_2$ 264.1019; Found 264.1035.

*Isoquinolin-3-yl(3-methoxyphenyl)methanone **(3ad)**.*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3ad** as white solid (93 mg, 71%); mp 132 - 134 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.35 (s, 1H), 8.45 (s, 1H), 8.08 (dd, *J* = 7.9, 0.9 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.85 – 7.73 (m, 2H), 7.65 – 7.60 (m, 2H), 7.45 – 7.38 (m, 1H), 7.19 – 7.13 (m, 1H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 194.2, 159.4, 151.7, 148.9, 139.3, 138.3, 135.6, 131.1, 129.5, 129.1, 128.2, 127.7, 123.8, 119.3, 115.0, 114.0, 29.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}NO_2$ 264.1019; Found 264.1021.

*Isoquinolin-3-yl(3,4,5-trimethoxyphenyl)methanone (**3ae**).*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 55/45) to afford **3ae** as white solid (110 mg, 68%); mp 158 - 160 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.34 (s, 1H), 8.47 (s, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.80 (dt, *J* = 15.9, 7.0 Hz, 2H), 7.41 (s, 2H), 3.95 (s, 3H), 3.90 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 193.1, 152.7, 151.5, 149.2, 142.4, 135.7, 131.9, 131.1, 129.5, 129.4, 128.2, 127.6, 123.5, 108.7, 60.9, 56.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}NO_4$ 324.1230; Found 324.1256.

*4-(Isoquinoline-3-carbonyl)benzonitrile (**3af**).*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3af** as white solid (104 mg, 81%); mp 126 - 128 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.31 (s, 1H), 8.59 (s, 1H), 8.24 – 8.19 (m, 2H), 8.10 (dd, *J* = 7.7, 1.1 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.88 – 7.78 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 192.7, 151.6, 147.7, 140.7, 135.6, 131.8, 131.4, 131.3, 130.0, 129.8, 128.4, 127.7, 123.9, 118.3, 115.6; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{11}N_2O$ 259.0866; Found: 259.0875.

*(4-Chlorophenyl)(isoquinolin-3-yl)methanone **(3ag).***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3ag** as white solid (101 mg, 75%); mp 141 - 143 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.32 (s, 1H), 8.51 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 3H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.86 – 7.74 (m, 2H), 7.48 (d, *J* = 8.5 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 192.9, 151.5, 148.5, 139.1, 135.6, 135.3, 132.4, 131.2, 129.6, 128.4, 128.3, 128.1, 127.6, 123.5; HRMS (ESI) m/z: $[M + H]^+$ and $[M + 2]^+$ calcd for $C_{16}H_{11}ClNO$ 268.0524 and 270.0494; Found: 268.0538 and 270.0507.

*Isoquinolin-3-yl(3-nitrophenyl)methanone **(3ah).***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3ah** as white solid (102 mg, 73%); mp 136 – 138 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.34 (s, 1H), 9.05 – 9.02 (m, 1H), 8.63 (s, 1H), 8.52 – 8.48 (m, 1H), 8.45 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 8.12 (dd, *J* = 7.9, 0.8 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.88 – 7.79 (m, 2H), 7.71 (dd, *J* = 10.0, 5.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 191.6, 151.7, 147.9, 147.6, 138.4, 136.5, 135.7, 131.4, 130.1, 129.9, 129.2, 128.4, 127.8, 126.8, 126.2, 124.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{11}N_2O_3$ 279.0764; Found 279.0784.

*[1,1'-Biphenyl]-4-yl(isoquinolin-3-yl)methanone **(3ai).***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **3ai** as white solid (119 mg, 77%); mp 121 - 123 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.41 (s, 1H), 8.52 (s, 1H), 8.19 – 8.16 (m, 2H), 8.12 (d, *J* = 8.1 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.82 – 7.77 (m, 1H), 7.76 – 7.72 (m, 2H), 7.69 – 7.65 (m, 2H), 7.49 (dd, *J* = 10.3, 4.8 Hz, 2H), 7.43 – 7.38 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 193.5, 151.5, 148.4, 145.5, 140.2, 135.8, 135.6, 131.5, 131.4, 129.6, 129.5, 128.9, 128.3, 128.1, 127.8, 127.3, 126.9, 123.6; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{16}NO$ 310.1226; Found 310.1251

*Isoquinolin-3-yl(naphthalen-2-yl)methanone (**3aj**).*

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **3aj** as light yellow solid (108 mg, 76%); mp 154 - 156 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.42 (s, 1H), 8.64 (s, 1H), 8.53 (s, 1H), 8.14 (dt, *J* = 9.1, 4.5 Hz, 2H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.86 – 7.77 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 193.8, 151.6, 148.5, 135.8, 135.5, 134.2, 133.1, 132.4, 131.4, 129.7, 129.6, 129.5, 128.4, 128.3, 128.0, 127.9, 127.8, 126.6, 126.2, 123.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}NO$ 284.1070; Found: 284.1085.

*Isoquinolin-3-yl(thiophen-3-yl)methanone **(3ak).***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 70/30) to afford **3ak** as white solid (90 mg, 75%); mp 107 – 109 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.35 (s, 1H), 8.91 (dd, *J* = 2.9, 1.1 Hz, 1H), 8.58 (s, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.92 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.85 – 7.69 (m, 2H), 7.36 (dd, *J* = 5.1, 3.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 186.2, 151.4, 149.1, 140.4, 136.7, 135.7, 131.0, 129.7, 129.5, 129.4, 128.3, 127.6, 125.0, 123.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{10}NOS$ 240.0478; Found: 240.0506.

*[1,3]dioxolo[4,5-g]isoquinolin-7-yl(2-chlorophenyl)methanone **(3bl):***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 65/35) to afford **3bl** as white solid (134 mg, 86%); mp 184 - 186 °C; ^{1}H NMR (400 MHz, Chloroform-d) δ 9.00 (s, 1H), 8.37 (s, 1H), 7.52 (dd, J = 6.7, 1.3 Hz, 1H),

7.47 – 7.42 (m, 2H), 7.42 – 7.36 (m, 1H), 7.26 (s, 1H), 7.24 (s, 1H), 6.16 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-d) δ 195.5, 151.6, 150.7, 150.0, 147.0, 139.0, 134.0, 131.8, 131.3, 130.0, 129.8, 128.1, 126.7, 122.5, 104.3, 103.5, 102.3; HRMS (ESI) m/z: $[M + H]^+$ and $[M + 2]^+$ calcd for $C_{17}H_{11}ClNO_3$ 312.0422, 314.0392; Found: 312.0432, 314.0409.

[1,3]dioxolo[4,5-g]isoquinolin-7-yl(2-methoxyphenyl)methanone ***(3bm):***

Purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/40) to afford **3bm** as white solid (129 mg, 84%); mp 205–207 °C; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.99 (s, 1H), 8.27 (s, 1H), 7.54 – 7.46 (m, 2H), 7.25 (s, 1H), 7.22 (s, 1H), 7.07 (td, *J* = 7.5, 0.9 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.15 (s, 2H), 3.68 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ 196.36, 158.17, 151.45, 150.29, 149.71, 148.59, 134.04, 132.42, 130.22, 129.12, 127.78, 121.81, 120.65, 111.78, 104.19, 103.48, 102.15, 55.84; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{14}NO_4$ 308.0917; Found: 308.0927.

[1,3]Dioxolo[4,5-g]isoquinolin-7-yl(phenyl)methanol (**4**).

To a solution of **3ba** (0.14 g, 0.5 mmol) in MeOH (3.0 mL) was added $NaBH_4$ (0.04 g, 1.0 mmol) at 0 °C in two portions and the reaction mixture was stirred vigorously for another 30 mins. After complete consumption of starting material, (reaction monitored by TLC), MeOH was removed under reduced pressure and water (10.0 mL) was added to the residue. The aqueous lawyer was then extracted with ethyl acetate (10 mL × 3) and the combined organic lawyers were dried over anhydrous $MgSO_4$. Solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography (mesh silica gel 100-200) using ethyl acetate/hexane (60:40) as eluent to afford the desired hydroxyl product **4** as thick oil (0.13 g) in 92% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.92 (s, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.39 – 7.30 (m, 3H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.16 (s, 1H), 6.97 (s, 1H), 6.07 (s, 2H), 5.88 (s, 1H), 4.00 – 3.62 (bs, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ 153.9, 151.4, 148.8, 148.5, 143.5, 135.1, 128.5, 127.7, 127.0, 125.2, 117.1, 103.0, 102.6, 101.7, 75.2; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}NO_3$ 280.0968; Found 280.0981.

*[1,3]Dioxolo[4,5-g]isoquinoline-5,7-diylbis(phenylmethanone) (**5**).*

To a solution of compound **3ba** (0.14 g, 0.5 mmol) in DCE (2.0 mL) in 10 mL sealed tube was added benzaldehyde (0.1 g, 1.0 mmol), TFA (0.057 g, 0.5 mmol) and TBHP (5–6 M solution in decane, 1.5 mmol). The reaction mixture was then stirred at 100 °C in oil bath for 10 h. The reaction mixture was then cooled to 0 °C and treated with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (3 x 10 mL), and the combined organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography using ethyl acetate/hexane (35%) as the eluent to afford **5** (0.16 g) as sticky solid in 83% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 8.17 – 8.09 (m, 2H), 7.99 – 7.91 (m, 2H), 7.62 (dd, *J* = 9.5, 5.3 Hz, 2H), 7.48 (dt, *J* = 11.4, 7.5 Hz, 3H), 7.38 – 7.30 (m, 3H), 6.17 (s, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, Chloroform-*d*) δ 194.5, 192.9, 152.7, 151.6, 151.3, 146.4, 136.7, 136.6, 135.7, 133.5, 132.6, 131.2, 130.8, 128.3, 127.8, 125.4, 124.4, 104.3, 102.5, 102.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{16}NO_4$ 382.1074; Found: 382.1081.

*(9-Bromo-[1,3]dioxolo[4,5-g]isoquinolin-7-yl)(phenyl) methanone(**6**).*

A 10 mL round-bottomed flask is charged with concentrated sulfuric acid (96%, 3.0 mL) and cooled to 0 °C. **3ba** (0.14 g, 0.5 mmol) was slowly added to the well stirred acid maintaining internal temperature 30 °C. The solution was then cooled to -10 °C a dry ice-acetone bath. The N-bromosuccinimide (0.098 g, 0.55 mmol) was added slowly over a period of half an hour maintaining reaction temp -10 °C. After complete consumption of starting material (monitored by TLC), the resulting reaction mixture was poured onto ice. The resulting mixture is stirred while the pH is adjusted to 9.0 using 25% aq NH_3 with the internal temperature maintained below 25 °C. The resulting alkaline suspension is added to 10 mL of diethyl ether and the biphasic system is vigorously mixed. The two clear phases are separated and the aqueous phase was extracted by diethyl ether. The combined organic layer was dried over Na_2SO_4 and solvent was then removed under reduced pressure. The residue was purified by column chromatography using ethyl acetate/hexane (50%) as the eluent to afford **6** as white solid (0.16 g) in 87% yield. mp 186 −188 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.41 (s, 1H), 8.30 (s, 1H), 8.19 – 8.05 (m, 2H), 7.67 – 7.57 (m, 1H), 7.56 – 7.46 (m, 2H), 7.20 (s, 1H), 6.25 (s, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, Chloroform-*d*) δ 194.0, 150.8, 149.0, 148.7, 148.2, 136.9, 135.3, 132.7, 130.9, 128.1, 125.2, 122.3, 103.4, 102.4, 97.1; HRMS (ESI) m/z: $[M + H]^+$ and $[M + 2]^+$ calcd for $C_{17}H_{11}BrNO_3$ 355.9917, 357.9896; Found: 355.9916, 357.9897.

*(4,9-Dibromo-[1,3]dioxolo[4,5-g]isoquinolin-7-yl)(phenyl) methanone (**7**).*

A 10 mL round bottom flask was charged with concentrated sulfuric acid (96%, 3 mL) and cooled to 0 °C. **3ba** (0.14 g, 0.5 mmol) was slowly added to the well stirred acid maintaining internal temperature 30 °C. The solution was then cooled to -10 °C a dry ice-acetone bath. The N-bromosuccinimide (0.195 g, 1.10 mmol) was added slowly over a period of half an hour maintaining reaction temp -10 °C. After complete consumption of starting material (monitored by TLC), the resulting reaction mixture was poured onto ice. The resulting mixture is stirred while the pH is adjusted to 9.0 using 25% aq NH_3 with the internal temperature maintained below 25 °C. The resulting alkaline suspension is added to 10 mL of diethyl ether and the biphasic system is vigorously mixed. The two clear phases are separated and the aqueous phase was extracted by diethyl ether. The combined organic layer was dried over Na_2SO_4 and solvent was then removed under reduced pressure. The residue was purified by column chromatography using ethyl acetate/hexane (45%) as the eluent to furnish dibromo compound **7** (0.16 g) as white solid in 74% yield; mp 206 - 208 °C^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.42 (s, 1H), 8.63 (s, 1H), 8.12 – 8.07 (m, 2H), 7.65 – 7.58 (m, 1H), 7.55 – 7.47 (m, 2H), 6.33 (s, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, Chloroform-*d*) δ 193.6, 150.0, 149.3, 148.5, 148.0, 136.7, 134.3, 132.8, 130.9, 128.1, 125.6, 120.5, 102.7, 97.2, 96.5; HRMS (ESI) m/z: $[M + H]^+$ and [M +

2]$^+$ calcd for $C_{17}H_{10}Br_2NO_3$ 433.9022, 435.9001; Found: 433.9018, 435.9001.

*(9-Nitro-[1,3]dioxolo[4,5-g]isoquinolin-7- yl)(phenyl) methanone (**8**).*

A 10 mL round bottom flask was charged with concentrated sulfuric acid (96%, 3 mL) and cooled to 0 °C. **3ba** (0.14 g, 0.5 mmol) was slowly added to the well stirred acid maintaining internal temperature 30 °C. The solution was then cooled to -10 °C a dry ice-acetone bath. The Potassium nitrate (0.050 g, 0.5 mmol) was added slowly maintaining reaction temp -10 °C. The reaction was then allowed to stir at 0 °C for 30 mins. After complete consumption of starting material (monitored by TLC), the resulting reaction mixture was poured onto ice. The resulting mixture is stirred while the pH is adjusted to 9.0 using 25% aq NH_3 with the internal temperature maintained below 25 °C. The resulting alkaline suspension was added to diethyl ether (10.0 mL) and the biphasic system is vigorously mixed. The two clear phases are separated and the aqueous phase was extracted by diethyl ether. The combined organic layer was dried over Na_2SO_4 and solvent was then removed under reduced pressure to give the crude product **8** which was then purified by column chromatography using ethyl acetate/hexane (50%) as the eluent to afford pure **8** (0.14 g) as light yellow solid in 85% yield; mp 152 - 154 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.79 (s, 1H), 8.36 (s, 1H), 8.12 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.50 (dd, *J* = 19.4, 11.9 Hz, 2H), 7.42 (s, 1H), 6.40 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, Chloroform-*d*) δ 193.3, 151.6, 149.8, 146.8, 145.3, 136.4, 134.0, 133.0, 131.0, 128.2, 122.1, 119.1, 117.1, 108.2, 104.5; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{11}N_2O_5$ 323.0663; Found: 323.0662.

*(4,9-Dinitro-[1,3]dioxolo[4,5-g]isoquinolin-7-yl)(phenyl) methanone (**9**).*

A 10 mL round bottom flask was charged with concentrated sulfuric acid (96%, 3.0 mL) and cooled to 0 °C. **3ba** (0.14 g, 0.5 mmol) was slowly added to the well stirred acid maintaining internal temperature 30 °C. The solution was then cooled to -10 °C a dry ice-acetone bath. The Potassium nitrate (0.111 g, 1.1 mmol) was added slowly maintaining reaction temp -10 °C. The reaction was then allowed to stir at 0 °C for 30 mins. After complete consumption of starting material (monitored by TLC), the resulting reaction mixture was poured onto ice. The resulting mixture is stirred while the pH is adjusted to 9.0 using 25% aq NH_3 with the internal temperature maintained below 25 °C. The resulting alkaline suspension was added to diethyl ether (10.0 mL) and the biphasic system is vigorously mixed. The two clear phases are separated and the aqueous phase was extracted by diethyl ether. The combined organic layer was dried over Na_2SO_4 and solvent was then removed under reduced pressure to give the crude product **9** which was then purified by column chromatography using ethyl acetate/hexane (50%) as the eluent to afford pure **9** (0.14 g) in 76% yield as yellow solid; mp 155−157 °C; R_f = 0.5 (50% ethyl acetate in hexane; ^{1}H NMR (300 MHz, Chloroform-*d* + DMSO *d6*) δ 9.77 (s, 1H), 9.01 (s, 1H), 8.55 (d, *J* = 8.7 Hz, 2H), 8.47 (dd, *J* = 22.7, 15.7 Hz, 2H), 7.78 (t, *J* = 7.9 Hz, 1H), 6.51 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d* + DMSO *d6*) δ 195.4, 157.2, 153.1, 152.7, 149.8, 142.7, 141.8, 139.1, 134.7, 131.8, 130.4, 127.8, 124.2, 113.4, 110.4; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{10}N_3O_7$ 368.0513; Found: 368.0516.

*Ethyl-5-benzoyl-[1,2,3]triazolo[5,1-a]isoquinoline-1-carboxylate **(3aa').***

White solid, Yield: 81% (0.14 g), mp 126−128 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.84 (d, *J* = 8.1 Hz, 1H), 7.99 – 7.77 (m, 5H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.60 (s, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 4.59 (q, *J* = 7.1 Hz, 2H), 1.53 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, Chloroform-*d*) δ 187.5, 162.3, 135.8, 134.4, 134.0, 132.2, 132.1, 131.0, 130.5, 130.0, 129.9, 128.9, 128.5, 128.5, 123.4, 119.9, 61.8, 14.4; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{20}H_{15}N_3NaO_3$ 368.1006; Found 368.1025.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
^{1}H and ^{13}C NMR spectra all products (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Scott, J. D.; Williams, R. M. Chemistry and Biology of the Tetrahydroisoquinoline Antitumor Antibiotics. *Chem. Rev*. **2002**, *102*, 1669 – 1730. (b) Bentley, K. W. The Isoquinoline Alkaloids; Hardwood Academic: Amsterdam, The Netherlands, **1998**; Vol. 1 (c) Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y.-J.; Angoh, G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Kellner, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P. G. Total Synthesis of Crystalline (.+-.)-Fredericamycin A. Use of Radical Spirocyclization, *J. Am. Chem. Soc*. **1994**, *116*, 11275 - 11286. (d) Gatland, A. E.; Pilgrim, B. S.; Procopiou, P. A.; Donohoe, T. J. Short and Efficient Syntheses of Protoberberine Alkaloids using Palladium-Catalyzed Enolate Arylation. *Angew. Chem. Int. Ed*. **2014**, *53*, 14555 - 14558. (e) Bao, X.; Cao, Y.-X.; Chu, W.-D.; Qu, H.; Du, J.-Y.; Zhao, X.- H.; Ma, X.-Y.; Wang, C.-T.; Fan, C. A. Bioinspired Total Synthesis of Montanine-TypeAmaryllidaceaeAlkaloids. *Angew. Chem. Int. Ed.* **2013**, *52*, 14167 - 14172. (f) Chrzanowska, M.; Grajewska, A.; Rozwadowska, M. D. Asymmetric Synthesis of Isoquinoline Alkaloids: 2004 – 2015. *Chem. Rev.* **2016**, *116*, 12369 - 12465. (g) Wada, Y.; Nishida, N.; Kurono, N.; Ohkuma, T.; Orito, K. Synthesis of a 3-Arylisoquinoline Alkaloid, Decumbenine B. *Eur. J. Org. Chem.* **2007**, *2007*, 4320 - 4327.

(2) (a) Song, Y.; Shao, Z.; Dexheimer, T. S.; Scher, E. S.; Pommier Y.; Cushman, M. Structure-Based Design, Synthesis, and Biological Studies of New Anticancer Norindenoisoquinoline Topoisomerase I Inhibitors. *J. Med. Chem.* **2010**, *53*, 1979 – 1789. (b) Wu, W.; Zhou, H. R.; Bursian, S. J. Link, J. E.; Pestka, J. J. Emetic responses to T-2 toxin, HT-2 toxin and emetine

correspond to plasma elevations of peptide YY3-36 and 5-hydroxytryptamine. *Arch. Toxicol*., **2016**, *90*, 997 - 1007. (c) Panzer, A.; Joubert, A. M.; Bianchi, P. C.; Hamel, E.; Seegers, J. C. The effects of chelidonine on tubulin polymerisation, cell cycle progression and selected signal transmission pathways. *Eur. J. Cell Biol.,* **2001**, *80*, 111- 118. (d) Wang, Q.; Li, X. Rhodium/copper-cocatalyzed annulation of benzylamines with diazo compounds: access to fused isoquinolines. *Org. Chem. Front*., **2016**, *3*, 1159 - 1162.

(3) (a) Xu, X. Y.; Qin, G. W.; Xu, R. S.; Zhu, X. Z. Total synthesis of decumbenine B, *Tetrahedron* **1998**, *54*, 14179 - 14188. (b) Timari, G.; Soos, T.; Hajos, G.; Messmer, A.; Nacsa, J.; Molnar, J. Synthesis of novel ellipticine analogues and their inhibition of Moloney leukaemia reverse transcriptase. *Bioorg. Med. Chem. Lett.* **1996**, *23*, 2831 - 2836. (c) Cho, W.-J.; Min, S. Y.; Le, T. N.; Kim, T. S. Synthesis of new 3-Arylisoquinolinamines: effect on topoisomerase I inhibition and cytotoxicity. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 4451 - 4454. (d) Cho, W.-J.; Park, M.-J.; Chung B.-H.; Lee, C.-O. Synthesis and biological evaluation of 3-arylisoquinolines as antitumor agents. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 41 - 46. (e) McCall, D. L. C.; Alexander, J.; Barber, J.; Jaouhari, R. G.; Satoskar, A.; Waigh, R. D.; The first protoberberine alkaloid analogue with in vivo antimalarial activity. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1663 – 1666.

(4) (a) Nonaka G.; Nishioka, I. Alkaloids of Corydalis incisa PERS. III. The Structures of Corydamine Hydrochloride and N-Formyl Corydamine. *Chem. Pharm. Bull*. **1973**, *21*, 1410 - 1414. (b) Zhang, G. -L.; Rucker, G.; Breitmaier, E.; Mayer, R. Alkaloids from Hypecoum leptocarpum. *Phytochemistry*. **1995**, *40*, 1813 – 1816. (c) Sun, Y.; Xun, K.; Wang, Y.; Chen, X. A systematic review of the anticancer properties of berberine, a natural product from Chinese herbs, *Anti-Cancer Drugs*. **2009**, *20*, 757 – 769. (d) Mach, U. R.; Hackling, A. E.; Perachon, S.; Ferry, S.; Wermuth, C. G.; Schwartz, J.-C.; Sokoloff, P.; Stark, H. Development of Novel 1,2,3,4-Tetrahydroisoquinoline Derivatives and Closely Related Compounds as Potent and Selective Dopamine D_3 Receptor Ligands. *Chem. Bio. Chem.* **2004**, *5*, 508 – 518.

(5) (a) Dubost, E.; Dumas, N.; Fossey, C.; Magnelli, R.; Butt-Gueulle, S.; Ballandonne, C.; Caignard, D. H.; Dulin, F.; Santos, J. S. d.-O.; Millet, P.; Charnay, Y.; Rault, S.; Cailly, T.; Fabis. Synthesis and Structure–Affinity Relationships of Selective High-Affinity 5-HT4 Receptor Antagonists: Application to the Design of New Potential Single Photon Emission Computed Tomography Tracers, F. *J. Med. Chem*. **2012**, *55*, 9693 - 9707. (b) Fisher, N. I.; Hamer, F. M. Cyanine dyes containing an isoquinoline nucleus. *J. Chem. Soc.* **1934**, *0*, 1905 - 1910. (c) Su, Y.-J.; Huang, H.-L.; Li, C.-L.; Chien, C.-H.; Tao, Y.-T.; Chou, P.-T.; Datta, S.; Liu, R.-S. Highly Efficient Red Electrophosphorescent Devices Based on Iridium Isoquinoline Complexes: Remarkable External Quantum Efficiency Over a Wide Range of Current. *Adv. Mater*. **2003**, *15*, 884 - 888.

(6) (a) Yang, Y.-Y.; Shou, W.-G.; Chen, Z.-B.; Hong, D.; Wang, Y.-G. A Tandem Approach to Isoquinolines from 2-Azido-3-arylacrylates and α-Diazocarbonyl Compounds. *J. Org. Chem.* **2008**, *73*, 3928 – 3930. (b) Konno, T.; Chae, J.; Miyabe, T.; Ishihara, T. Regioselective One-Step Synthesis of 4-Fluoroalkylated Isoquinolines via Carbopalladation Reaction of Fluorine-Containing Alkynes. *J. Org. Chem.* **2005**, *70*, 10172 – 10174. (c) Dai, G. X.; Larock, R. C. Synthesis of 3,4-Disubstituted Isoquinolines via Palladium-Catalyzed Cross-Coupling of 2-(1-Alkynyl)benzaldimines and Organic Halides. *J. Org. Chem.* **2003**, *68*, 920 – 928. (d) Ichikawa, J.; Wada, Y.; Miyazaki, H.; Mori, T.; Kuroki, H. Ring-Fluorinated Isoquinoline and Quinoline Synthesis: Intramolecular Cyclization of o-Cyano- and o-Isocyano-β,β-difluorostyrenes. *Org. Lett.* **2003**, *5*, 1455 – 1458. (e) Saini, G.; Kumar, P.; Kumar, G. S.; Mangadan, A. R. K.; Kapur, M. Palladium-Catalyzed α-Arylation of Silylenol Ethers in the Synthesis of Isoquinolines and Phenanthridines. *Org. Lett*. **2018**, *20*, 441 - 444. (f) Wu, X.; Ding, G.; Yang, L.; Lu, W.; Li, W.; Zhang, Z.; Xie, X.; Alkoxide-Catalyzed Hydrosilylation of Cyclic Imides to Isoquinolines via Tandem Reduction and Rearrangement. *Org. Lett.* **2018**, *20*, 5610 - 5613. (g) Wang, L.; Studer, A. 1-Trifluoromethylisoquinolines from α-Benzylated Tosylmethyl Isocyanide Derivatives in a Modular Approach. *Org. Lett.* **2017**, *19,* 5701 - 5704. (h) Kuai, C.; Wang, L.; Li, B.; Yang, Z.; Cui, X. Cobalt-Catalyzed Selective Synthesis of Isoquinolines Using Picolinamide as a Traceless Directing Group. *Org. Lett.* **2017**, *19*, 2102 – 2105. (i) Gutierrez, S.; Coppola, A.; Sucunza, D.; Burgos, C.; Vaquero, J. J. Synthesis of 1-Substituted Isoquinolines by Heterocyclization of TosMIC Derivatives: Total Synthesis of Cassiarin A. *Org. Lett*. **2016**, *18*, 3378 – 3381. (j) Zeng, Z.; Jin, H.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Gold (III)-Catalyzed SiteSelective and Divergent Synthesis of 2-Aminopyrroles and Quinoline Based Polyazaheterocycles. *Angew. Chem., Int. Ed*. **2018**, *57*, 16549− 16553.

(7) (a) Bischler, A.; Napieralski, B. Zur Kenntniss einer neuen Isochinolinsynthese. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903 - 1908. (b) Pictet, A.; Spengler, T. Über die Bildung von Isochinolin-derivaten durch Einwirkung von Methylal auf Phenyl-äthylamin, Phenyl-alanin und Tyrosin. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030 - 2036. (c) Pomeranz, C. *Monatsh. Chem*. **1893**, *14*, 116 - 119. (d) Fritsch, P. Synthesen in der Isocumarin und Isochinolinreihe, *Ber. Dtsch. Chem. Ges*. **1893**, *26*, 419 - 422.

(8) (a) Liu, W.; Liu, S.; Jin, R.; Guo, H.; Zhao, J. Novel strategies for catalytic asymmetric synthesis of C1-chiral 1,2,3,4-tetrahydroisoquinolines and 3,4-dihydrotetrahydroisoquinolines. *Org. Chem. Front*. **2015**, *2*, 288 - 299. (b) Gulías, M.; Mascareñas, J. L. Metal-Catalyzed Annulations through Activation and Cleavage of C-H Bonds. *Angew. Chem. Int. Ed.* **2016**, *55*, 11000 - 11019. (c) De, S.; Mishra, S.; Kakde, B. N.; Dey, D.; Bisai, A. Expeditious Approach to Pyrrolophenanthridones, Phenanthridines, and Benzo[c]phenanthridines via Organocatalytic Direct Biaryl-Coupling Promoted by Potassium tert-Butoxide. *J. Org. Chem*. **2013**, *78*, 7823 - 7844. (d) Han, W.; Zhou, X.; Yang, S.; Xiang, G.; Cui, B.; Chen, Y. Palladium-Catalyzed Nucleophilic Substitution/C–H Activation/Aromatization Cascade Reaction: One Approach To Construct 6-Unsubstituted Phenanthridines. *J. Org. Chem.* **2015**, *80*, 11580 - 11587. (e) Guimond, N.; Fagnou, K. Isoquinoline Synthesis via Rhodium-Catalyzed Oxidative Cross-Coupling/Cyclization of Aryl Aldimines and Alkynes. *J. Am. Chem. Soc*. **2009**, *131*, 12050 - 12051. (f) Tiwari, V. K.; Kamal, N.; Kapur, M. One Substrate, Two Modes of C–H Functionalization: A Metal-Controlled Site-Selectivity Switch in C–H Arylation Reactions. *Org. Lett*. **2017**, *19*, 262 - 265.

(9) (a) Hickey, D. M. B.; Moody, C. J.; Rees, C. W. Synthesis of lsoquinolines from Azidocinnamates; the Effect of Iodine. *J. Chem. Soc. Chem. Commun*. **1982**, *1982*, 3 - 4*;* (b) Gilchrist, T. L.; Rees, C.W.; Rodrigues J. A. R. Synthesis of Fused Pyridines under Neutral Conditions. *J. Chem. Soc. Perkin Trans. 1,* **1979**, *1979*, 627 – 628. (c) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Huo, Z.; Yamamoto, Y. Iodine-Mediated Electrophilic Cyclization of 2-Alkynyl-1-methylene Azide Aromatics Leading to Highly Substituted Isoquinolines and Its Application to the Synthesis of Norchelerythrine. *J. Am. Chem. Soc*. **2008**, *130*, 15720 - 15725. (d) Niu, Y.- N.; Yan, Z.-Y.; Gao, G.-L.; Wang, H.-L.; Shu, X.-Z.; Ji, K.-G.; Liang, Y.- M. Synthesis of Isoquinoline Derivatives via Ag-Catalyzed Cyclization of 2-Alkynyl Benzyl Azides. *J. Org. Chem.* **2009**, *74*, 2893 - 2896. (e) Zhu, Z.; Tang, X.; Li, X.; Wu, W.; Deng, G.; Jiang, H. Palladium-Catalyzed C–H Functionalization of Aromatic Oximes: A Strategy for the Synthesis of Isoquinolines. *J. Org. Chem.* **2016**, *81*, 1401 - 1409. (f) Aubert. T.; Farnier, M.; Hanquet, B.; Guilard, R. A New Versatile Synthesis of Isoquinolines by Condensation of Iminophosphoranes with o-Phthalaldehyde. *Synth. Commun*. **1987**, *17*, 1831 – 1837. (g) Aubert, T.; Farnier, M.; R. Et.; Guilard, R. Nouvelle voie de synthese d'isoindolones et d'isoquinoleines par condensation d'iminophosphoranes avec l'ortho-phtalaldehyde: reactions, mecanismes et etude structural. *Can. J. Chem*. **1990**, *68*, 842 – 851.

(10) (a) Tiwari, D. K.; Pogula, J.; Sridhar, B.; Tiwari, D. K.; Likhar, P. R. Nano-copper catalysed highly regioselective synthesis of 2,4-disubstituted pyrroles from terminal alkynes and isocyanides. *Chem. Commun*. **2015**, *51*, 13646 - 13649; (b) Tiwari, D. K.; Phanindrudu, M.; Aravilli, V. K.; Sridhar, B.; Likhar, P. R.; Tiwari, D. K. Magnetically recoverable Cu^0/Fe_3O_4 catalyzed highly regioselective synthesis of 2,3,4-trisubstituted pyrroles from unactivated terminal alkynes and isocyanides. *Chem. Commun*. **2015**, *52*, 4675 – 4679. (c) Phanindrudu, M.; Tiwari, D. K.; Sridhar, B.; Likhar P. R.; Tiwari, D. K. Magnetically separable nano-copper catalysed unprecedented stereoselective synthesis of *E*-vinyl sulfones from tosylmethyl isocyanide and alkynes: TosMIC as a source of the sulfonyl group. *Org. Chem. Front.* **2016**, *3*, 795 - 798; (d) Tiwari, D. K.; Phanindrudu, M.; Wakade, S. B.; Nanubolu, J. B.; Tiwari, D. K. α,β-Functionalization of saturated ketones with anthranils via Cu-catalyzed sequential dehydrogenation/aza-Michael addition/annulation cascade reactions in one-pot. *Chem. Commun*. **2017**, *53*, 5302 - 5304. (e) Wakade, S. B.; Tiwari, D. K..; Ganesh, P. S. K. P.; Phanindrudu, M.; Likhar, P. R.; Tiwari, D. K. Transition-Metal-Free Quinoline Synthesis from Acetophenones and Anthranils via Sequential One-Carbon Homologation/Conjugate Addition/Annulation Cascade. *Org. Lett*. **2017**, *19*, 4948 - 4951. (f) Phanindrudu, M.; Wakade, S. B.; Tiwari, D. K.; Likhar, P. R.; Tiwari, D. K. Transition-Metal-Free Approach for the Synthesis of 4-Aryl-quinolines from Alkynes and Anilines. *J. Org. Chem*. **2018**, *16*, 9137 - 9143.

(11) (a) Chen, J.; Wan, M.; Hua, J.; Sun, Y.; Lv Z.; Li, W.; Liu, L. TBHP/TFA mediated oxidative cross-dehydrogenative coupling of N-heterocycles with aldehydes. *Org. Biomol. Chem*. **2015**, *13*, 11561–11566. (b) Brown W. D.; Gouliaev, A. H. *Organic Syntheses*, **2005**, *81*, 98 - 104.

(12) (a) Maurya, R. A.; Adiyala, P. R.; Chandrasekhar, D.; Reddy, C. N.; Kapure, J. S.; Kamal, A. Rapid Access to Novel 1,2,3-Triazolo-Heterocyclic Scaffolds via Tandem Knoevenagel Condensation/Azide–Alkyne 1,3-Dipolar Cycloaddition Reaction in One Pot. *ACS Comb. Sci*. **2014**, *16*, 466 - 477. (b) Vebrel, J.; Carrie, R. Étude de la diastéréoselectivité de la cycloaddition dipolaire-1,3: Reaction des azides sur les methoxycarbonyl-3 dihydro-1,2 naphtalenes substitues et quelques composes apparentes. *Tetrahedron,* **1983**, *39*, 4163 – 4174. (c) Kanomata, N.; Sakaguchi, R.; Sekine, K.; Yamashita, S.; Tanaka, H. Enantioselective Cyclopropanation Reactions with Planar-Chiral Pyridinium Ylides: A Substituent Effect and a Remote Steric Effect. *Adv. Synth. Catal.* **2010**, *352*, 2966 – 2978.

(13) (a) Youn, S. W.; Song, H. S.; Park, J. H. NHC-catalyzed oxidative cyclization reaction for the synthesis of 3-substituted phthalides. *Org. Biomol. Chem.* **2014**, *12*, 2388 – 2393. (b) Zhang, T.; Wu, L.; Li, X. Rh(III)-Catalyzed Olefination of *N*-Sulfonyl Imines: Synthesis of *Ortho*-Olefinated Benzaldehydes. *Org. Lett.* **2013**, *15*, 6294 - 6297. (c) Fustero, S.; Moscardo, J.; Sa´nchez-Rosello, M.; Rodrı´guez, E.; Barrio, P. Tandem Nucleophilic Addition−Intramolecular Aza-Michael Reaction: Facile Synthesis of Chiral Fluorinated Isoindolines. *Org. Lett.* **2010**, *12*, 5494 – 5497.

(14) (a) Wei, W.; Cui, H.; Yue, H.; Yang, D., Visible-light-enabled oxyazidation of alkenes leading to α-azidoketones in air. *Green Chem*. **2018**, *20*, 3197 – 3202. (b) Hossain, A.; Vidyasagar, A.; Eichinger, C.; Lankes, C.; Phan, J.; Rehbein, J.; Reiser, O., Visible-Light-Accelerated Copper(II)-Catalyzed Regio- and Chemoselective Oxo-Azidation of Vinyl Arenes. *Angew. Chem. Int. Ed*. **2018**, *57,* 8288 - 8292. (c) Hussain, M. I.; Feng, Y.; Hu, L.; Deng, Q.; Zhang, X.; Xiong, Y. Copper-Catalyzed Oxidative Difunctionalization of Terminal Unactivated Alkenes. *J. Org. Chem.* **2018**, *83*, 7852. (d) Moumne, R.; Larue, V.; Seijo, B.; Lecourt, T.; Micouin, L.; Tisn, C. Tether influence on the binding properties of $tRNA^{Lys}_3$ ligands designed by a fragment-based approach. *Org. Biomol. Chem*. **2010**, *8*, 1154 - 1159. (e) Chang, D.; Zhu, D.; Shi, L. [3 + 2] Cycloadditions of Azides with Arynes via Photolysis of Phthaloyl Peroxide Derivatives. *J. Org. Chem.* **2015**, *80*, 5928 – 5933.