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Rhodium(III)-Catalyzed C6-Selective Arylation of 2-Pyridones and Related Heterocycles Using Quinone Diazides: Syntheses of Hetero-Arylated Phenols

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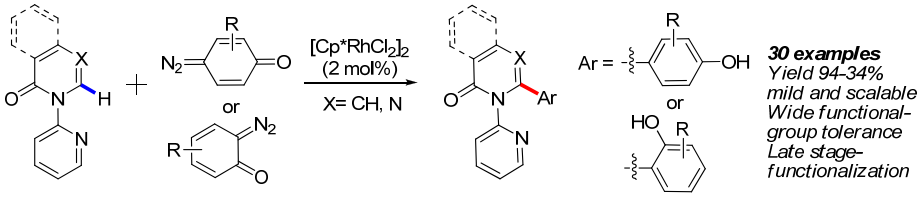
Supporting Information Placeholder



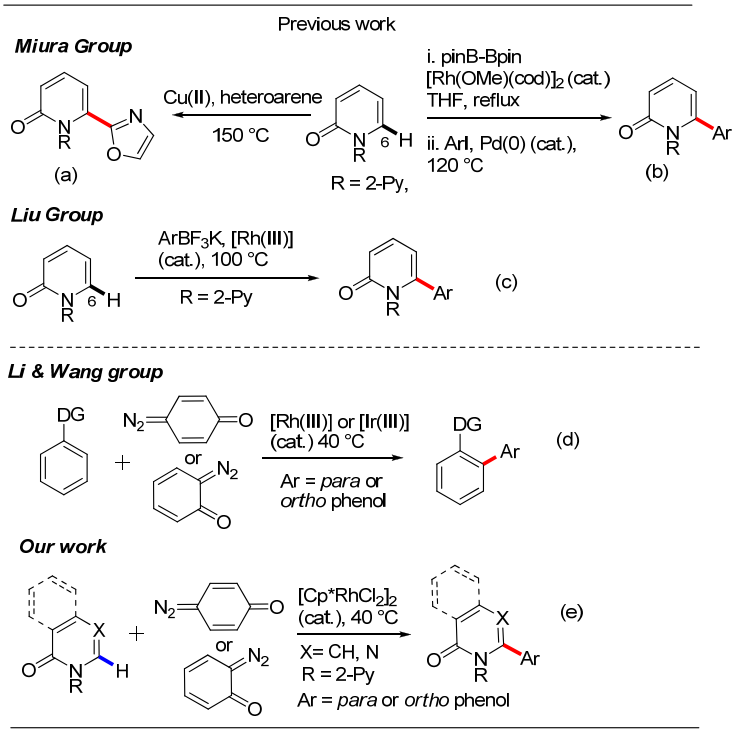
ABSTRACT: An efficient, direct C6-arylation of 2-pyridones has been successfully accomplished with quinone diazides under Rh(III) catalyzed redox neutral condition. The optimized method is simple, mild and highly regioselective with broad range of substrate scope. The strict regioselectivity is guided by the pyridyl substituent attached to the nitrogen of pyridone ring. As the directing 2-pyridyl group can easily be removed at any suitable stage after functionalization, the method provides a facile access to complex heteroarylated phenol moieties by wide-ranging heterocyclic scaffolds.

INTRODUCTION:

Straightforward regioselective functionalizations of 2-pyridone moiety, a common scaffold in many ligands, pharmaceuticals and natural products have received a significant attention to the synthetic organic community in recent years.[1,2] Due to the significant advancement of transition metal catalyzed direct C-H bond functionalization,[3,4] a number of studies were carried out to introduce functional groups on different strategic locations of pyridone derivatives with an admirable degree of selectivity.[5,6] A variety of transition metal catalysed carbon-carbon bond formation reactions were studied at the relatively electron rich C3 and C5 positions of 2-pyridone ring. On the contrary, the selective functionalization at the more electron deficient C6 position is still underexplored.[6] A redox neutral, direct regio and stereoselective alkenylation and alkylation of 2-pyridone motif were described by the Nakao and Hiyama group using Ni(0)/aluminium cooperative catalysis.[6a,b] Recently, 1,6 annulated 2-

pyridones were synthesized by Cramer and co-workers using intramolecular nickel/aluminium catalysis.[6c] Very recently, our group[6d] and Liu group[6e] demonstrated C6-alkylation of 2-pyridone ring using diazocarbonyl compound or organoboron reagents under Rh(III) catalysis. Another rhodium catalyzed C6 alkynylation followed by annulation was developed by Li and co-workers.[6f] In an elegant approach, regioselective C6 alkynylation of 2-pyridones was developed using Rh(III) catalyst.[6g] Despite the advancement in the direct carbon-carbon bond formations at the C6 position of 2-pyridone ring, the regioselective arylation at the C6 position of 2-pyridone is still under developed. To shed light on this unexplored synthetic challenge, the Miura and Hirano group revealed a copper-mediated C6-selective oxidative heteroarylation of 2-pyridones with 1,3-azoles (Scheme 1a).[7] Recently, this group found that direct catalytic C6-arylation of 2-pyridone was troublesome.[8]

Scheme 1: **C6 selective arylation of 2-pyridones**



To address this challenge, they executed a thought provoking strategy using the Rh(I) catalyzed C6-borylation of 2-pyridones followed by Suzuki-Miyaura cross coupling (Scheme 1b). Very recently in an elegant approach, Liu and co-workers also showed a rhodium catalysed C6-arylation method using trifluoroborate reagents at higher temperature (Scheme 1c).[6e]

Although originally planned for cyclopropanation transformations in classical synthesis, carbenoid species have proven to be suitable synthons in a myriad of significant reactions.[9] Directed C-H metalation, metal-carbene formation followed by migratory insertion with diazo compounds has recently achieved a considerable attention compared to the traditional reactions of carbenoid.[10] Among the diverse diazo compounds, quinone diazides can be considered as a class of underexplored diazo

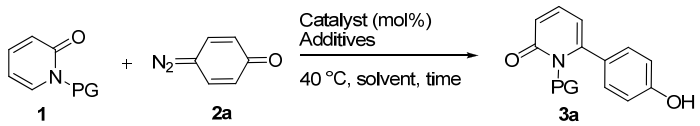
compounds, although easily prepared, having two electron acceptor groups.[11,12] After the Baran group's systematic study on olefin functionalization using the quinone diazides[13], Li and Wang group very recently revisited this class of diazo compounds for the quick and facile synthesis of arylated phenols (Scheme 1d) under Rh(III) or Ir(III) catalyzed mild conditions.[14] Additionally, using the developed protocol they were able to introduce the phenolic moieties at the C2 position of *N*-protected indole scaffold. In this perspective, it is essential to mention that the development of mild and catalytic methods to prepare unprotected phenol derivatives without using additional oxidant or harsh reaction conditions is still a challenging task. [15]

In continuation with our curiosity in the directed functionalization of unactivated C-H bonds using versatile diazo compounds,[6d,16] we hypothesized that quinone diazides can be explored for the challenging C6-arylation of 2-pyridones under mild conditions.[3h] Herein, we report the Rh(III) catalysed C6 selective direct arylation of 2-pyridone using quinone diazides under mild condition (Scheme 1e). The developed protocol is extended by its extensive scope with strict regioselectivity profile, thus providing a direct method to synthesize diverse heteroarylated phenols.

RESULT AND DISCUSSION:

We initiated our study by focusing the reaction of 2-pyridone (1) with quinone diazide (2a) in the presence of $(Cp^*RhCl_2)_2$ (2 mol%, Cp*=pentamethylcyclopentadiene) and $AgSbF_6$ (8 mol%) in 1, 2 dichloroethane (DCE) at 40 °C.

Table 1: Optimization for C6 selective arylation of 2-Pyridones[a]



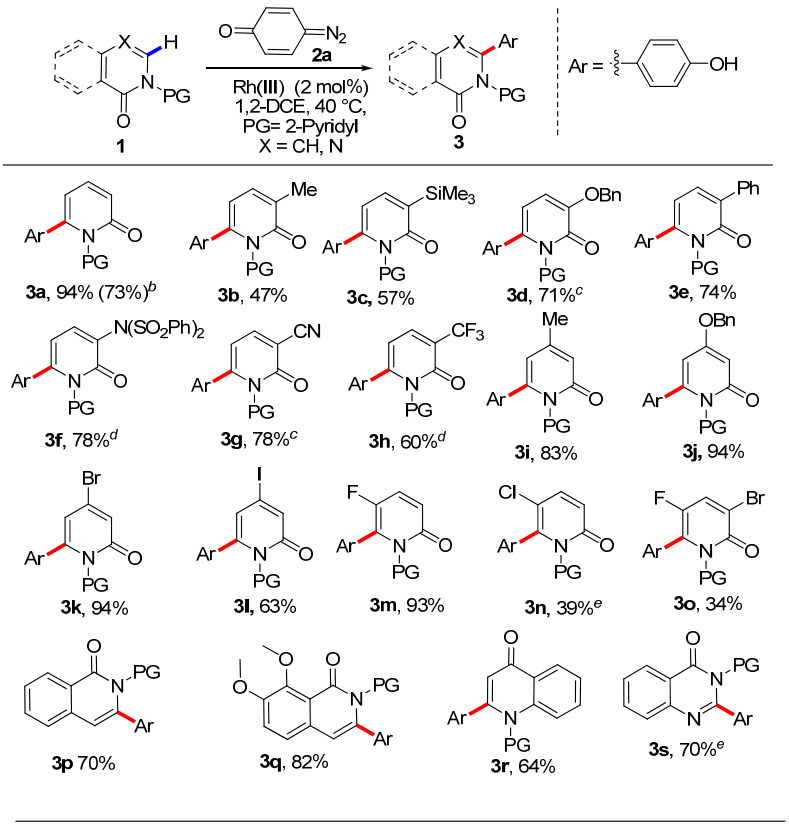
Entry.	PG	Additive (mol%)	Solvent	Time (h)	Yeild (%)[b]
1.	H	PivOH (50)	DCE	24	n.d.
2	Ac	PivOH (50)	DCE	24	n.d.
3	Py	-	DCE	12	34
4	Py	AcOH (50)	DCE	12	92
5	**Py**	**PivOH (50)**	**DCE**	**12**	**94**
6	Py	PivOH (20)	DCE	12	51
7[c]	Py	PivOH (50)	DCE	24	n.d.
8[d]	Py	PivOH (50)	DCE	24	n.d.
9	Py	PivOH (100)	DCE	12	74
10[e]	Py	PivOH (50)	DCE	24	49
11	Py	Ad-COOH (50)	DCE	12	72
12	Py	BzOH (50)	DCE	12	trace
13	Py	*p*-TSA (50)	DCE	12	trace
14	Py	PivOH (50)	1,4-dioxane	12	76
15	Py	PivOH (50)	Acetonitrile	12	trace
16	Py	PivOH (50)	Ethanol	12	38
17	Py	PivOH (50)	DMF	12	25
18	Py	PivOH (50)	Toluene	12	trace
19[f]	Py	PivOH (50)	DCE	24	15
20[g]	Py	PivOH (50)	DCE	24	trace

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $(Cp^*RhCl_2)_2$ (2 mol%), $AgSbF_6$ (8 mol%), 40 °C, 0.1 M. [b]Isolated Yields. [c] Without additive $AgSbF_6$. [d]Without $(Cp^*RhCl_2)_2$. [e]$(Cp^*RhCl_2)_2$ (1 mol%), $AgSbF_6$ (4 mol%). [f]Reaction conditions: $(Cp^*IrCl_2)_2$ (2 mol%), $AgSbF_6$ (8 mol%), 40 °C, 0.1 M. [g]Reaction conditions: $[Ru(p\text{-cymene})Cl_2]_2$ (2 mol%), $AgSbF_6$ (8 mol%), 40 °C, 0.1 M. DCE = 1,2-dichloroethane. n.d. = not detected. Ad-CO_2H = 1-adamantanecarboxylic acid.

In initial attempts with the unprotected 2-pyridone or acetyl protected 2-pyridone as starting materials, we were unsuccessful to obtain any desired arylated product (Table 1, entries 1-2). Gratifyingly, 1-(2-pyridyl)-2-pyridone (**1a**) afforded 34% isolated yield of desired C6-arylated product **3a** (Table 1, entry 3). Next, to improve the yield, several reaction conditions were screened. Satisfyingly, when acetic acid was tested as the additive, desired product was obtained in impressive 92% yield (Table 1, entry 4). Moreover, the use of bulky pivalic acid as the additive, isolated yield of the desired product could only be improved marginally to 94% (Table 1, entry 5). Though, the decrease in amount of pivalic acid led to provide reduced yield of the desired product (Table 1, entry 6). There was no formation of product while anyone of the Rh(III) catalyst or $AgSbF_6$ was absent in the reaction mixture (Table 1, entries 7-8). Additional increase of pivalic acid reduced the formation of desired product (Table 1, entry 9). Furtheremore, the decrease in catalyst loading or switching over to sterically more crowded carboxylic acid like 1-adamantanecarboxylic acid did not improve the best yield (Table 1, entries 10-11). Additives like benzoic acid or *p*-toluenesulfonic acid were also tested for this transformation, but there were only trace amount of desired product formation (Table 1, entries 12-13). In general, much poorer yields were obtained during the screening of other solvents (Table 1, entries 14-18). Incidentally, other cheaper transition metal catalysts like $(Cp^*IrCl_2)_2$ or $[Ru(p\text{-cymene})Cl_2]_2$ did not turned to be a effective catalyst under the optimized conditions (Table 1, entries 19-20).

With the optimized reaction conditions available, we examined the scope and limitations of this reaction. Consequently, the substrate scope of the pyridones and related heterocycles were explored thoroughly (Scheme 2). Substitutions at C3 position of 2-pyridones with variant electronic and steric properties furnished satisfying yields of corresponding desired products (Scheme 2, **3b**-**3h**). 2-Pyridones with electron donating groups at C3 position provided the desired product (Scheme 2, **3b**-**3f**) in moderate to good yields. Electron withdrawing groups at this position also exhibited nicely to provide the desired products (Scheme 2, **3g**-**3h**). To our delight, substitutions at the C4 position of 2-pyridones with electron donating groups or halides gave the wanted product in good to excellent yields (Scheme 2, **3i**-**3l**). The tolerance of halide groups under the optimized conditions showed the future synthetic utility of the developed method (Scheme 2, **3k**-**3l**). To address the steric effect near the reaction centre, we explored the C5 substituted 2-pyridones (Scheme 2, **3m**-**3n**). At per our expectations, increase of the steric bulk at the C5 position of 2-pyridones reduces the desired product formation even under more drastic conditions. Interestingly, 3,5-dihalosubstituted-2-pyridone also worked though with poor yield (Scheme 2, **3o**).

Scheme 2: C6-Arylation of 2-pyridones and related heterocyclic scaffolds with 2a[a]



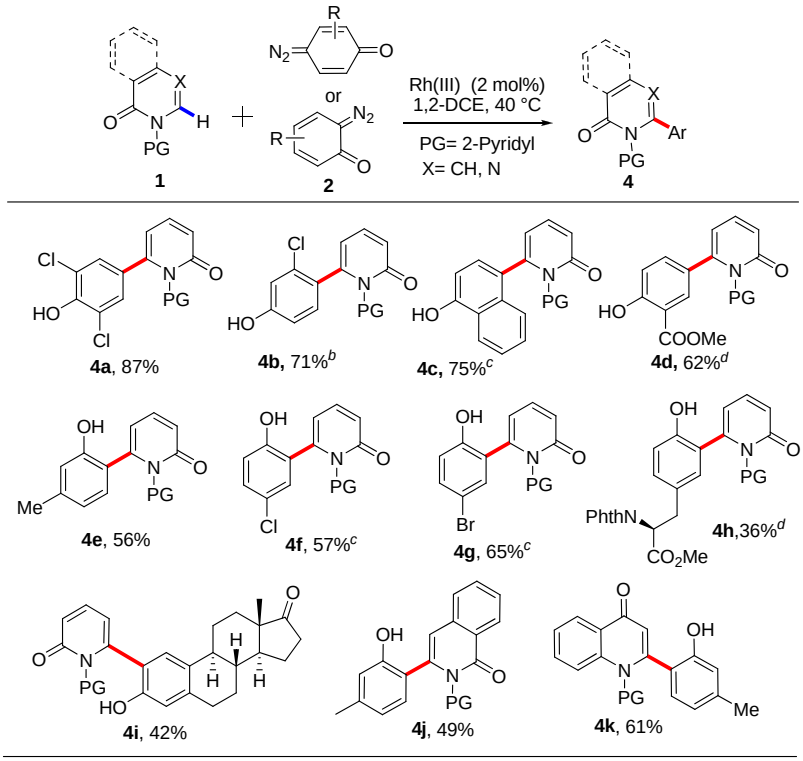
[a]Reaction conditions: 1 (0.1 mmol), 2a (0.2 mmol), [(Cp*RhCl$_2$)$_2$] (2 mol%), AgSbF$_6$ (8 mol%), PivOH (50 mol%), 0.1 M, 40 °C, 6-12 h. [b]Reaction conditions: 1 (3 mmol scale), 36 h. [c]Reaction continued for 24 h. [d]Reaction conditions: (Cp*RhCl$_2$)$_2$ was used in 3 mol% for 24 h. [e]at 80 °C for 12 h.

Gratifyingly, isoquinolone derivatives afforded the respective C6-arylated product in good yields (Scheme 2, **3p**-**3q**). Notably, 4-quinolone scaffold was also directly arylated at its C2 position to offer its corresponding product (Scheme 2, **3r**) with good yield. Interestingly, in the case of 4-quinolone there was no C8 arylation observed. Nitrogen containing another important heterocyclic scaffold quinazolone derivative was also regioselectively arylated (Scheme 2, **3s**). The chemoselectivity profile of our method is efficiently described by the fact that an extensive variety of 2-pyridones and related heterocycles were arylated. As a demonstration of scalability, **1a** could be transformed into its corresponding arylated product with 30-fold increased scale in 73% isolated yield (Scheme 2, **3a**).

After successful exploration of several 2-pyridones, the scope of different quinone diazides was investigated. Substituted phenols coupled at their para position with 2-pyridone moiety were synthesized successfully (Scheme 3, **4a**-**4d**) in good to excellent yields. Notably, substituted phenols coupled at their *ortho* position with pyridones, isoquinolone and 4-quinolone

were also synthesized in moderate to good yield (Scheme 3, **4e**-**4g**, **4j**-**4k**). The current procedure might be applicable for the late-stage functionalization of natural products or pharmaceutical compounds because of its operational simplicity and mild reaction conditions.[17] To illustrate the potential application of the developed method, amino acid like tyrosine derivative and steroid like estrone derivative were subjected to couple with 2-pyridone. To our great pleasure, these direct regioselective couplings occurred smoothly, albeit in lower yields (Scheme 3, **4h**-**4i**).

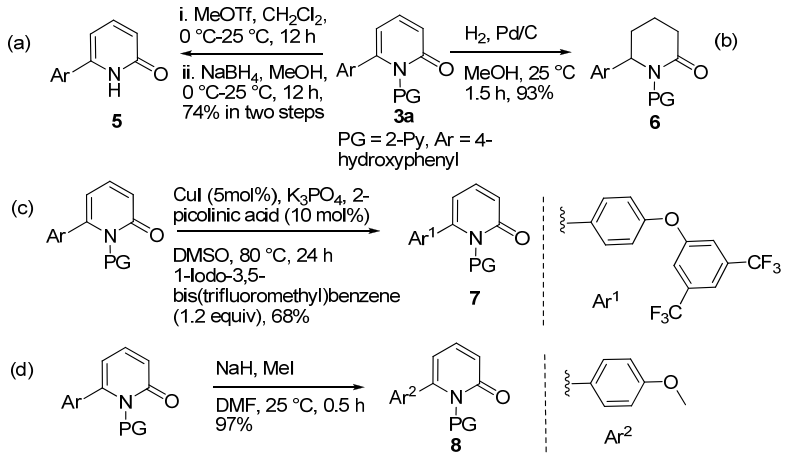
Scheme 3: **Regioselective arylation with various quinone diazides**[a]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), $(Cp^*RhCl_2)_2$ (2 mol%), $AgSbF_6$ (8 mol%), PivOH (50 mol%), 0.1 M, 40 °C, 12 h. [b]at 80 °C for 24 h. [c]Reation continued for 24 h. [d]$(Cp^*RhCl_2)_2$ was used in 4 mol%.

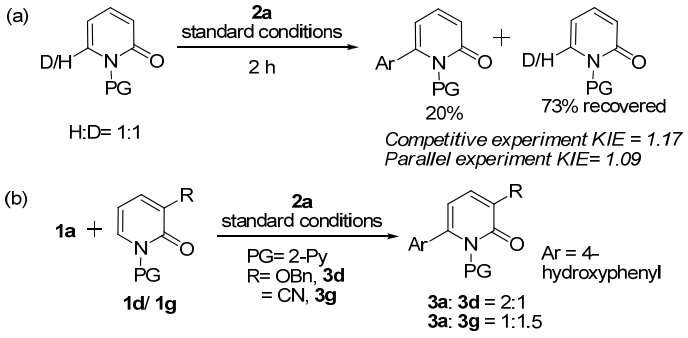
To shed light on the broad synthetic utility of the present reaction, further functionalization of C6-arylated 2-pyridone was carried out. The footprint of the directing group was removed from **3a** *via* quaternization–hydride reduction[18] at room temperature to provide free pyridone derivative **5** in good yield (Scheme 4a). Furthermore, hydrogenation of **3a** offered C6-arylated piperidin-2-one derivative **6** in 93% yield (Scheme 4b).[21] A C-O coupling offered product **7** (Scheme 4c) in 68% yield.[22]

Scheme 4: Transformation of product molecule



Finally, the phenolic OH group was protected with methyl group to provide the literature known compound **8** (Scheme 4d).[6e] To acquire some indirect evidences on the mechanism of the developed reaction, a series of control experiments were carried out. A kinetic isotope effect value 1.17 was measured *via* the ^{1}H NMR analysis of the mixture of recovered starting materials. In competitive parallel experiments the average kinetic isotope effect value of 1.09 was found *via* the isolation of final products. These results suggested that the C-H bond activation at the C6 position of 2-pyridone ring was not the rate determining step (Scheme 5a). To know the electronic effect of the pyridone substrates on the rate of the reaction, when **1a** and **1d** were chosen to react with **2a** under optimized conditions, the initial kinetics of the reaction was monitored. The reaction favored the formation of **3a** over **3d** in a 2:1 ratio. To verify the above trend, **1a** and **1g** were taken for intermolecular competition experiment with **2a**. The product ratio found **3a**:**3g** in 1:1.5 ratio, suggested that the electron deficient 2-pyridone was kinetically more favored (Scheme 5b).

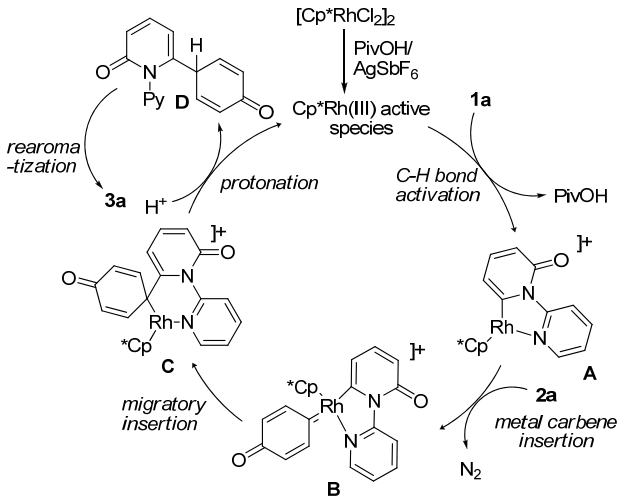
Scheme 5: Control experiments



Based on the preliminary investigations and literature pre-cendents,[10,14,19] a plausible mechanism is proposed (Scheme 6). Initially, a cationic Rh(III) species was generated with the help of Ag salt and PivOH *via* ligand exchange. Next, it coordinated to pyridine nitrogen atom and underwent C-H bond cleavage through pivalate-assisted concerted metalation–deprotonation (CMD) to furnish rhodacycle intermediate **A**. Subsequently, quinonediazide(**2a**) reacted with **A** to generate metal-carbenoid

intermediate **B** with the extrusion of N_2. Then migratory insertion gave a six-membered intermediate **C**. Finally, the protonation followed by rearomatization provided the desired C6-arylated product (**3a**) and the active Rh(III) catalyst was regenerated. The detailed mechanism of this trans-formation remains unclear at this stage.

Scheme 6: **Proposed mechanism**



CONCLUSION:

In summary, we have developed a simple and efficient procedure for the redox-neutral, Rh(III) catalyzed direct site selective C-H arylation of 2-pyridones and related heterocycles with quinone diazides under mild conditions using 2-pyridyl ring as a directing group. The developed method offers rapid synthesis of wide-ranging hetero arylated phenols. The reaction proceeded with broad scope and wide functional group tolerance. The protocol will be useful for late stage functionalization of biologically important scaffolds. Currently, attempts are being directed to the total syntheses of bioactive natural products having such nitrogen containing heterocyclic scaffolds using the procedure developed herein.

EXPERIMENTAL SECTION:

General information: Unless otherwise noted, all commercially available compounds were used as provided without further purification. Solvents for chromatography were technical grade. Analytical thin layer chromatography (TLC) was performed on Merck pre-coated silica gel 60 F_{254}. Visualization on TLC was achieved by the use of UV light (254 nm). Solvents mixtures were understood as volume/ volume. Column chromatography was undertaken on silica gel (230-400 mesh). Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, td = triplet of doublet, ddd = doublet of doublet of doublet, m = multiplet. Coupling constants, *J*, were reported in hertz unit (Hz). The spectra were fully decoupled by broad band proton decoupling.

Chemical shifts were reported in ppm referenced to the centre of a triplet at 77.16 ppm of chloroform-d ($CDCl_3$) and centre of a heptet at 39.52 for DMSO-D6. In case of Infrared (IR) spectra frequencies are given in reciprocal centimetres (cm^{-1}), only selected absorbance peaks are reported and KBr is used as the matrix. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. Substrates which are not commercially available were synthesised according to the reported procedures.

General procedure for synthesis of substituted 1-(2-Pyridyl)-2-pyiridones:[20a] Substituted 2-hydroxypyridine (1 mmol), copper(I) iodide (10 mol%), and potassium carbonate (1 mmol) were taken in DMSO (2 mL) and 2-bromopyridine (2 mmol) was added to the resulting mixture. The mixture was stirred at 150 ^{o}C for 12 h under nitrogen atmosphere. The resulting mixture was allowed to cool to room temperature and then quenched with water. Extraction with ethyl acetate, concentrated under reduced pressure, and silica gel column purification with 1:1 ethyl acetate in hexane afforded 2*H*-[1,2'-Bipyridin]-2-one derivatives in 50-90% yield.

Procedure for synthesis of substituted 1-(2-Pyridyl)-2-pyiridone 1c:[20]

The compound was prepared in overall 61% yield by the known literature procedure[20b] followed by the general procedure to synthesize substituted 1-(2-Pyridyl)-2-pyiridones[20a].

Anlytical data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.6 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.89 – 7.77 (m, 2H), 7.51 (dd, *J* = 6.3, 2.1 Hz, 1H), 7.33 – 7.27 (m, 1H), 6.29 (t, *J* = 6.7 Hz, 1H), 0.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 152.3, 148.9, 146.5, 137.5, 136.9, 133.7, 122.9, 121.6, 106.5, -1.7. FT-IR: $\widetilde{\nu}$ = 3304, 3108, 3057, 2953, 2900, 2852, 1844, 1640, 1598, 1535, 1469, 1440, 1343, 1308, 1274, 1258, 1239 cm^{-1}. GCMS value (EI) m/z for $C_{13}H_{16}N_2OSi$ $(M)^+$ is 244.31.

Procedure for synthesis of substituted 1-(2-Pyridyl)-2-pyiridone 1f:[20c] 2*H*-[1,2'-bipyridin]-2-one (**1a**) (2 mmol) was dissolved in 1,2-DCE in a round bottom flask. Then CuCl (10 mol%), 1,10-phenanthroline (10 mol%) and NFSI (1.2 equiv.) were added. The reaction mixture was allowed to stir at 90 °C for 6 h. After completion of the reaction, compound **1f** was purified by silica gel column purification with 1:1 ethyl acetate in hexane (v/v) mixture in 85% yield. The compound structure was unequivocally determined by spectroscopic and single crystal X-ray data (see Supporting information Table 1, Figure S3).

Analytical data: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.5 Hz, 1H), 8.06 (d, *J* = 7.2 Hz, 5H), 7.83 – 7.76 (m, 2H), 7.63 (t, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 8.1 Hz, 4H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.32 (m, 1H), 6.29 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.6, 151.2, 149.0, 144.8, 139.3, 139.0, 138.0, 134.1, 129.2, 128.9, 125.6, 123.7, 121.4, 105.0. FT-IR: $\widetilde{\nu}$ = 3102, 3071, 2929, 1668, 1616, 1584, 1543, 1467, 1450, 1360, 1345, 1314, 1274, 1259, 1224 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}N_3O_5S_2$ 468.0682; Found 468.0663.

General procedure for the preparation of 4-quinone diazide and its derivatives (2a-2d):[13, 14] 4-Amino phenols (10 mmol) were dissolved in 50 mL ethanol, then conc. HCl (12 N) was added to it drop wise (5 mL, 100 mmol) at 0 ^{o}C. The mixture was allowed to stir at the same temperature for another 10 min. Then an ice cold solution of $NaNO_2$ (30 mmol) was added to the mixture dropwise. The resulting mixture was allowed to stir at 0 ^{o}C for 2 h. Then it was diluted with 50 mL cold dichloromethane, followed by the addition of ice. Then the mixture was stirred vigorously with cold solution of K_2CO_3 (70 mmol). The organic layer was separated with dichloromethane and the aqueous layer was extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated on vaccum at low temperature. Then it was directly used in the next reaction without further purification.

General procedure for the preparation of 2-quinone diazide and its derivatives (2e-2i):[13, 14] 2-Quinone diazide and its derivatives were synthesized following the same general procedure of synthesizing 4-quinone diazdes and its derivatives.

Procedure for the preparation of 2h:[23]

(*L*)-Tyrosin methyl ester (6 mmol) was taken in dry THF (20 mL), in a 50 mL round bottom flask. Then triethyl amine (1.4 equiv.) and ethyl 1,3-dioxoisoindoline-2-carboxylate (1.1 equiv.) were added to it. The reaction mixture was allowed to reflux for 24 h with vigorous stirring under argon atmosphere. After completion of the reaction, reaction mixture was cooled to room temperature and filtered. Filtrate was concentrated *in vaccuo* and the residue was dissolved in dichloromethane. Then mixture was washed with 10% $NaHCO_3$ solution and acidified to pH 2 by adding HCl (2 N). After that, it was extracted with dichloromethane, washed with water and brine. The organic part was evaporated *in vaccuo* and dried over anhydrous sodium sulphate. The crude product was purified by flash column chromatography. Phthalimide protected (*L*)-Tyrosin methyl ester was obtained as white solid in 90% yield. The analytical data of the product is identical with the known literature data.[23a]

Phthalimide protected (*L*)-Tyrosin methyl ester compound (5 mmol) was dissolved in anhydrous dichloromethane (25 mL) in a 50 mL round bottom flask and *tert*-butyl nitrite (3 equiv.) was added drop wise to the reaction mixture and allowed to stir for 3 h at the room temperature. Then the *ortho*-nitro tyrosine derivative [(*S*)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(4-hydroxy-3-nitrophenyl)propanoate] was purified by flash column chromatography in 85% yield.[23b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.90 (s, 1H), 7.80 (dt, *J* = 7.2, 3.5 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.41 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 5.09 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.78 (s, 3H), 3.63 – 3.45 (m, 2H). Immediately, *ortho* nitro tyrosine derivative (3 mmol) was dissolved in methanol (10 mL) in a 25 mL round bottom flask. Then it was filled with argon and Pd/C (10 mol%) was added to it. After that, round bottom flask was evacuated and refilled with H_2 filled balloon. Next it was allowed to stir at room temperature for overnight. Further, the reaction mixture was filtered through a celite pad and

washed with ethyl acetate. The filtrate was concentrated *in vaccuo* to give the amine [(*S*)-methyl 3-(3-amino-4-hydroxyphenyl)-2-(1,3-dioxoisoindolin-2-yl)propanoate] in 99% yield. The analytical data of the product is identical with the known literature data.[23c] Finally the compound **2h** was obtained through the general procedure for the preparation of 2-quinone diazide[13, 14] and directly used in next step without further purification.

Procedure for the preparation of 2i:[24]

The literature known amino estrone compound[24] was converted to its quinone diazide derivative using the general procedure[13, 14] and directly used in next step without further purification.

General procedure for Rhodium (III) catalyzed C6 selective arylation of 2-pyridones with quinone diazides: 1-(2-Pyridyl)-2-pyiridone or its other derivatives (0.1 mmol) were dissolved in a 10 mL screw cap vial with 1 mL of dry 1,2 DCE. Then $(Cp^*RhCl_2)_2$ (2 mol %), $AgSbF_6$ (8 mol%), PivOH (0.5 equiv) and 4-quinonediazide (0.2 mmol) were added to the reaction mixture at the room temperature. Then the reaction mixture was allowed to warm up to 40 °C-80 °C and stirred for 12 h. After the completion of the reaction, the reaction mixture was directly purified by the silica gel column chromatography using 1:1 to 9:1 ethyl acetate in hexane (v/v) mixture.

Procedure for the synthesis of compound 5, Removal of directing group:[18] Compound **3a** (0.4 mmol) was taken in a 25 mL round bottom flask charged with a magnetic stirrer and dissolved in dry DCM (5 mL). The mixture was cooled to 0 °C, MeOTf (1.5 equiv.) was added to it drop wise. Then the reaction mixture was allowed warm to room temperature and allowed to stir for 12 h. The volatile materials are removed in vaccuo and the mixture was again dissolved in dry methanol (5 mL). Then the mixture was cooled to 0 °C and sodium borohydride (4 equiv.) was added to it potion wise. The reaction mixture was allowed to warm at room temperature and additionally stirred for another 12 h. Finally the reaction mixture was quenched with water and extracted with ethyl acetate. Organic layer was dried over anhydrous sodium sulphate, concentrated in vaccuo. The product was purified by flash chromatography using NH-bind silica using 1:1 to 9:1 ethyl acetate in hexane (v/v) mixture to give product **5** in 74%

Procedure for the synthesis of compound 6, hydrogenation of 3a:[21] Compound **3a** (0.2 mmol) was taken in a 25 mL round bottom flask charged with a magnetic stirring bar and dissolved in 5 mL of methanol. Then it was filled with nitrogen and Pd/C (10 mol %) was added to it. Then round bottom flask was evacuated and again filled with H_2. The reaction mixture was allowed to stir at room temperature for 1.5 h and it was monitored by TLC. After the completion of the reaction, mixture was passed through celite pad and washed with ethyle acetate. Then the organic solution was concentrated *in vaccuo* to give hydrogenated product **6** in 93% yield.

Synthesis of compound 7:[22] Compound **3a** (0.1 mmol) was taken in a 10 mL screw cap vial charged with a magnetic stirring bar and dissolved in 1 mL DMSO. Then CuI (5 mol%), K_3PO_4 (2 equiv.) and 2-picolinic acid (10 mol%) were added to it. Finally 1-iodo-3,5-bis(trifluoromethyl)benzene (1.2 equiv.) was added to it drop wise and the reaction mixture was allowed to heat at 80 °C for 24 h. After completion of the reaction, product **7** was purified by flash column chromatography in 68% yield with 1:1 ethyl acetate in hexane (v/v) mixture.

Methylation of the phenolic –OH of 3a, synthesis of compound 8:[6e] Compound **3a** (0.1 mmol) was taken in a 10 mL round bottom flask charged with a magnetic stirring bar and dissolved in 2 mL dry DMF. The reaction mixture was cooled to 0 °C in an ice bath. Then NaH (1.5 equiv.) was added to it followed by drop wise addition of MeI (2 equiv.). The reaction mixture was allowed to warm to room temperature. Consumption of starting material was checked by TLC. After 0.5 h reaction was quenched by water and extracted by ethyl acetate. Organic layer was dried over anhydrous sodium sulphate, concentrated in vaccuo. The product was purified by flash chromatography to give product **8** in 97% yields with 1:1 ethyl acetate in hexane (v/v) mixture. The spectral data's are well matched with the literature data.

Competitive Experiments:

KIE Experiment 1: 0.1 mmol of **1a** and 0.1 mmol of [D_1]-**1a** were taken in a 10 mL screw cap vial and dissolved in 2 mL of 1,2-dichloroethane. Then $(Cp^*RhCl_2)_2$ (2 mol %), $AgSbF_6$ (8 mol%), PivOH (0.5 equiv) and **2a** (0.2 mmol) were added to the reaction mixture at the room temperature. Then reaction was allowed to run for 2 h at 40 °C and monitored by TLC. After 2 h, the reaction mixture was directly purified by silica gel column chromatography using 1:1 ethyl acetate in hexane (v/v) mixture. The remaining starting materials were recovered in 73% and analyzed by ^{1}H NMR to find the ratio of **1a** and [D_1]-**1a.** The calculated KIE was 1.17 (see the Supporting Information, Figure S1).

KIE Experiment 2: An intermolecular kinetic isotope experiment was performed through the competitive reaction between **1a** and [D_1]-**1a** with compound **2a** using our developed optimized conditions in parallel way. Both the reactions were stopped after 2 h and product **3a** was isolated separately by flash silica gel column chromatography. The reactions were repeated three times. Based on the isolated yields, KIE values were calculated as 1.10, 1.06, and 1.11. So the average k_H/k_D was 1.09.

Control experiments:

Experiment 1:

Pyridyl pyridone **1a** (0.1 mmol) and **1d** (0.1 mmol) were taken in a 10 mL screw cap vial and dissolved in 2 mL of 1,2-dichloroethane. Then $(Cp^*RhCl_2)_2$ (2 mol %), $AgSbF_6$ (8 mol%), PivOH (0.5 equiv) and **2a** (0.2 mmol) were added to the reaction mixture at the room temperature. The reaction was allowed to stir for 12 h and the progress of the reaction was

monitored by TLC. After 12 h, reaction mixture was directly filtered through a flash column chromatography. The crude mixture of products **3a** and **3d** was analyzed by ^{1}H NMR and the ratio found to be **3a**:**3d** was 2:1 (see Supporting Information, Figure S2).

Experiment 2:

Pyridyl pyridone **1a** (0.1 mmol) and **1g** (0.1 mmol) were taken in a 10 mL screw cap vial and dissolved in 2 mL of 1,2-dichloroethane. Then $(Cp^*RhCl_2)_2$ (2 mol %), $AgSbF_6$ (8 mol%), PivOH (0.5 equiv) and **2a** (0.2 mmol) were added to the reaction mixture at room temperature. The reaction was allowed to stir for 12 h and the progress of the reaction was monitored by TLC. After 12 h reaction mixture was filtered through a flash column chromatography. The ratio of products **3a** and **3g** was calculated based on the isolated yields and it was found to be 1:1.5.

Large scale synthesis: 1-(2-Pyridyl)-2-pyiridone (**1a**, 3.0 mmol) were dissolved in a 25 mL round bottom flask with 10 mL of dry 1, 2 DCE. Then $[(Cp^*RhCl_2)_2]$ (2 mol %), $AgSbF_6$ (8 mol%), PivOH (0.5 equiv.) and 4-quinone diazide (**2a**, 2 equiv.) were added to the reaction mixture at the room temperature. Then the reaction mixture was allowed to warm up to 40 °C and stirred for 36 h. After the completion of the reaction, reaction mixture was directly loaded to the column and product **3a** was purified with 1:1 ethyl acetate in hexane (v/v) mixture to give 73% yield.

6-(4-Hydroxyphenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**3a**): Yield 94% (24.8 mg), brown amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.37 (d, *J* = 3.7 Hz, 1H), 7.81 (td, *J* = 7.7, 1.8 Hz, 1H), 7.55 (dd, *J* = 9.2, 6.9 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.31 – 7.25 (m, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.53 (d, *J* = 8.6 Hz, 2H), 6.47 (d, *J* = 9.0 Hz, 1H), 6.24 (d, *J* = 6.4 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.4, 157.4, 152.1, 149.3, 148.8, 140.6, 137.9, 130.2, 125.7, 125, 123.5, 118.4, 114.7, 106.8. FT-IR: $\widetilde{\nu}$ = 3191, 3099, 3007, 2945, 2810, 2682, 2615, 2492, 2365, 1645, 1610, 1594, 1542, 1466, 1393, 1291, 1250 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{13}N_2O_2$ 265.0972; Found 265.0986.

6-(4-Hydroxyphenyl)-3-methyl-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**3b**): Yield 47% (13.1 mg), brown amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.37 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.80 (td, *J* = 7.7, 2.0 Hz, 1H), 7.45 (dd, *J* = 6.9, 1.3 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.31 – 7.25 (m, 1H), 6.91 (dd, *J* = 8.7, 2.3 Hz, 2H), 6.57 – 6.49 (m, 2H), 6.17 (d, *J* = 6.9 Hz, 1H), 2.05 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.7, 157.2, 152.4, 148.7, 146.6, 137.9, 137.4, 130.1, 126.8, 125.9, 125.0, 123.4, 114.6, 106.3, 16.8. FT-IR: $\widetilde{\nu}$ = 3430, 3152, 2955, 2923, 2853, 2569, 2439, 1642, 1607, 1584, 1552, 1508, 1464, 1437, 1396, 1375, 1358, 1271 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}N_2O_2$ 279.1128; Found 279.1145.

6-(4-Hydroxyphenyl)-1-(pyridin-2-yl)-3-(trimethylsilyl)pyridin-2(1*H*)-one (**3c**): Yield 57% (19.2 mg), white amorphous solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (s, 1H), 8.37 (d, *J* = 4.4 Hz, 1H), 7.79 (m, 1H), 7.61 (d, *J* = 6.6 Hz,

1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.21 (m, 1H), 6.93 (d, *J* = 7.2 Hz, 2H), 6.54 (d, *J* = 7.2 Hz, 2H), 6.26 (d, *J* = 5.8 Hz, 1H), 0.22 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 157.5, 152.3, 150.4, 148.7, 146.7, 137.9, 130.1, 128.4, 125.7, 125.1, 123.4, 114.7, 107, -1.61. FT-IR: $\widetilde{\nu}$ = 3427, 3233, 2951, 2898, 2797, 1633, 1610, 1575, 1560, 1542, 1509, 1468, 1436, 1383, 1335, 1273, 1246, 1222 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{19}H_{21}N_2O_2Si$ 337.1367; Found 337.1391.

3-(Benzyloxy)-6-(4-hydroxyphenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**3d**): Yield 71% (26.3 mg), yellow amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.38 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.81 (td, *J* = 7.7, 1.9 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.36 (dd, *J* = 7.9, 5.2 Hz, 2H), 7.29 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.51 (d, *J* = 8.4 Hz, 2H), 6.14 (d, *J* = 7.6 Hz, 1H), 5.11 (s, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 157.8, 157.0, 152.0, 148.7, 147.0, 140.4, 138.0, 136.6, 130.3, 128.5, 128.0 (d, *J* = 21.7 Hz), 125.8, 125.0, 123.5, 115.9, 114.6, 105.4, 69.9. FT-IR: $\widetilde{\nu}$ = 3431, 3117, 2926, 1651, 1600, 1513, 1469, 1444, 1432, 1382, 1395, 1280, 1243 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{19}N_2O_3$ 371.1390; Found 371.1399.

6-(4-Hydroxyphenyl)-3-phenyl-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**3e**): Yield 74% (25.1 mg), yellow amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.66 (s, 1H), 8.41 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.83 (td, *J* = 7.9, 2.0 Hz, 1H), 7.78 (d, *J* = 7.4 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.37 – 7.26 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.57 (d, *J* = 8.3 Hz, 2H), 6.38 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.3, 157.5, 152.4, 148.7, 148.6, 138.3, 138, 136.6, 130.1, 128.3, 128.2, 127.9, 127.4, 125.6, 125.1, 123.5, 114.7, 107. FT-IR: $\widetilde{\nu}$ = 3451, 3057, 2928, 2801, 2665, 2596, 1648, 1609, 1552, 1511, 1471, 1428, 1391, 1351, 1273, 1233 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{22}H_{17}N_2O_2$ 341.1285; Found 341.1275.

***N*-(6-(4-Hydroxyphenyl)-2-*oxo*-1-(pyridin-2-yl)-1,2-dihydropyridin-3-yl)-*N*-(phenylsulfonyl)benzenesulfonamide** (**3f**): Yield 78% (43.6 mg), pale yellow amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.38 (d, *J* = 5.0 Hz, 1H), 8.05 – 7.87 (m, 5H), 7.85 (t, *J* = 7.6 Hz, 2H), 7.77 (t, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 4H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.57 (d, *J* = 8.3 Hz, 2H), 6.37 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.8, 158, 152.4, 151.3, 148.9, 144.6, 138.3, 134.5, 130.2, 129.2, 128.4, 124.7, 124.6, 124, 121.4, 114.9, 106.2. FT-IR: $\widetilde{\nu}$ = 3422, 3153, 3064, 2953, 2851, 1675, 1603, 1560, 1536, 1513, 1474, 1448, 1438, 1370, 1351, 1312, 1274, 1227 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{28}H_{22}N_3O_6S_2$ 560.0945; Found 560.0936.

6-(4-Hydroxyphenyl)-2-*oxo*-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carbonitrile (**3g**): Yield 78% (22.5 mg), brown amorphous solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.41 (d, *J* = 3.8 Hz, 1H), 8.29 (d, *J* = 7.6 Hz, 1H), 7.92 – 7.84 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.33 (m, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.58 (d, *J* = 8.6 Hz, 2H), 6.49 (d, *J* = 7.6 Hz,

1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.2, 158.4, 155.2, 150.8, 148.9, 148.4, 138.4, 130.2, 124.7, 124.3, 124.2, 116.3, 114.9, 107.3, 101.4. FT-IR: $\tilde{\nu}$ = 3420, 3307, 3198, 2928, 2224, 2145, 1654, 1637, 1608, 1589, 1552, 1509, 1467, 1437, 1348, 1272, 1221 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{12}N_3O_2$ 290.0924; Found 290.0938.

6-(4-Hydroxyphenyl)-1-(pyridin-2-yl)-3-(trifluoromethyl)pyridin-2(1*H*)-one (**3h**): Yield 60% (19.9 mg), pale brown amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.41 (d, *J* = 4.9 Hz, 1H), 8.08 (d, *J* = 7.4 Hz, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.39 – 7.30 (m, 2H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 2H), 6.41 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 158.4, 158.1, 154.1, 151.1, 148.9, 140.3 (q, *J* = 4.4 Hz), 138.3, 130.2, 125, 124.6, 124.1, 119.4 (q, *J* = 541.2 Hz), 116.3, 114.8, 105.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ, -63.95. FT-IR: $\tilde{\nu}$ = 3430, 3099, 2932, 2863, 1675, 1664, 1600, 1560, 1513, 1439, 1405, 1322, 1281, 1235 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{12}F_3N_2O_2$ 333.0845; Found 333.0841.

6-(4-Hydroxyphenyl)-4-methyl-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**3i**): Yield 83% (23.1 mg), brown amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.36 (d, *J*= 5.9 Hz, 1H), 7.79 (t, *J*= 8.6 Hz, 1H), 7.33 (d, *J*= 7.9 Hz, 1H), 7.27 (dd, *J*= 6.8, 5.0 Hz, 1H), 6.93 (d, *J*= 8.6 Hz, 2H), 6.53 (d, *J*= 8.6 Hz, 2H), 6.28 (s, 1H), 6.12 (s, 1H), 2.21 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.3, 157.4, 152.1, 151.6, 148.7, 148, 137.9, 130.1, 125.7, 125.1, 123.4, 116.6, 114.6, 109.3. FT-IR: $\tilde{\nu}$ = 3443, 3154, 2959, 2925, 2851, 1651, 1613, 1592, 1561, 1545, 1508, 1467, 1432, 1383, 1277, 1268, 1233 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}N_2O_2$ 279.1128; Found 279.1146.

4-(Benzyloxy)-6-(4-hydroxyphenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**3j**): Yield 94% (34.8 mg), yellow amorphous solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (s, 1H), 8.34 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.78 (td, *J* = 7.6, 1.8 Hz, 1H), 7.55 – 7.30 (m, 6H), 7.26 (dd, *J* = 7.6, 5.0 Hz, 1H), 6.98 – 6.89 (m, 2H), 6.57 – 6.48 (m, 2H), 6.06 – 5.92 (m, 2H), 5.18 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.7, 163.9, 157.6, 152, 149.4, 148.7, 137.9, 135.9, 130.1, 128.6, 128.3, 128, 125.5, 125.4, 123.4, 114.7, 101.3, 96.2, 69.8. FT-IR: $\tilde{\nu}$ = 3402, 3196, 1645, 1592, 1546, 1513, 1459, 1429, 1364, 1270, 1258, 1229 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}N_2O_3$ 371.1390; Found 371.1390.

4-Bromo-6-(4-hydroxyphenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**3k**): Yield 94% (32.1 mg), yellow amorphous solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.38 (d, *J* = 4.3 Hz, 1H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.35 – 7.26 (m, 1H), 6.97 (d, *J* = 7.6 Hz, 2H), 6.83 (s, 1H), 6.54 (d, *J* = 7.6 Hz, 2H), 6.48 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 157.9, 151.3, 149.8, 148.8, 138.1, 136, 130.3, 124.9, 124.2, 123.8, 119.9, 114.8, 110.3. FT-IR: $\tilde{\nu}$ = 3420, 3080, 2793, 2665, 2599, 1673, 1636, 1523, 1399, 1306, 1230 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{12}{}^{79}BrN_2O_2$ 343.0077; Found 343.0084.

6-(4-Hydroxyphenyl)-4-iodo-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**3l**): Yield 63% (24.5 mg), Pale brown amorphous solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.38 (d, *J* = 4.1 Hz, 1H), 7.83 (t, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.83 (s, 1H), 6.54 (d, *J* = 8.4 Hz, 2H), 6.48 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.1, 157.9, 151.3, 149.8, 148.8, 138.1, 135.9, 130.2, 124.9, 124.2, 123.8, 119.9, 114.7, 110.3. FT-IR: $\tilde{\nu}$ = 3433, 3273, 2256. 2129, 1654, 1639, 1384 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{12}IN_2O_2$ 390.9938; Found 390.9955.

5-Fluoro-6-(4-hydroxyphenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**3m**): Yield 93% (26.2 mg), pale yellow amorphous solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.36 (d, *J* = 4.8 Hz, 1H), 7.87 – 7.66 (m, 2H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.31 – 7.22 (m, 1H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.63 – 6.49 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5, 157.8, 151.3, 148.8, 145.1, 142.8, 138.1, 134.7 (d, *J*= 28 Hz), 132.8 (d, *J*= 28 Hz) , 131.3, 125, 123.7, 119.9 (d, *J*= 7.3 Hz), 118.9, 114.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -146.9; FT-IR: $\tilde{\nu}$ = 3420, 3238, 3064, 1662, 1610, 1575, 1546, 1508, 1465, 1434, 1419, 1365, 1288, 1227, 1203 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{12}FN_2O_2$ 283.0877; Found 283.0890.

5-Chloro-6-(4-hydroxyphenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**3n**): Yield 39% (11.6 mg), brown amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.67 (s, 1H), 8.34 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.76 (td, *J* = 7.7, 1.9 Hz, 1H), 7.72 (d, *J* = 9.9 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.24 (m, 1H), 7.01 – 6.88 (m, 2H), 6.64 – 6.49 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.0, 157.5, 151.8, 148.8, 145.9, 141.9, 138.1, 124.8, 123.6, 122.6, 120.5, 114.6, 111. FT-IR: $\tilde{\nu}$ = 3427, 3135, 2955, 2924, 2854, 2561, 1647, 1610, 1592, 1573, 1557, 1501, 1466, 1432, 1343, 1286, 1215, 1203 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{12}{}^{35}ClN_2O_2$ 299.0582; Found 299.0608.

3-Bromo-5-fluoro-6-(4-hydroxyphenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**3o**): Yield 34% (12.2 mg), yellow amorphous solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.43 (d, *J* = 7.9 Hz, 1H), 8.37 (d, *J* = 4.3 Hz, 1H), 7.82 (td, *J* = 7.9, 1.8 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.30 (dd, *J* = 7.4, 4.9 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158, 157.2, 151.1, 148.9, 144.2, 141.9, 138.4, 134.7 (d, *J*= 28.7 Hz), 134.6 (d, *J*= 28.7 Hz), 131.3, 124.4 (d, *J*= 75.5 Hz), 118.1 (d, *J*= 1.2 Hz), 114.9, 114.2 (d, *J* = 9.6 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -145.67. FT-IR: $\tilde{\nu}$ = 3422, 3269, 3075, 1667, 1531, 1432, 1288, 1208 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{11}{}^{79}BrFN_2O_2$ 360.9982; Found 360.9982.

3-(4-Hydroxyphenyl)-2-(pyridin-2-yl)isoquinolin-1(2*H*)-one (**3p**): Yield 70% (22.0 mg), reddish brown amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.60 (s, 1H), 8.39 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 7.86 – 7.70 (m, 3H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.67 (s, 1H), 6.56 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.2, 157.1, 152.4, 148.7, 143.2, 137.9, 136.9, 133.2, 130.3, 127.2, 126.8,

126.5, 126.3, 125.4, 124.4, 123.4, 114.6, 106.5. FT-IR: $\widetilde{\nu}$ = 3421, 2954,2924, 1618, 1458, 1371, 1340, 1273 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{15}N_2O_2$ 315.1128; Found 315.1137.

3-(4-Hydroxyphenyl)-7,8-dimethoxy-2-(pyridin-2-yl)isoquinolin-1(2*H*)-one (**3q**): Yield 82% (30.7 mg), reddish amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.53 (s, 1H), 8.38 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.80 (td, *J* = 7.6, 1.9 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.27 (m, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.64 – 6.42 (m, 3H), 3.89 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.3, 156.9, 152.8, 151.3, 148.7, 148.6, 140.9, 137.7, 132 , 130.1, 126.3, 125.6, 123.1, 122.5, 119.5, 118.9, 114.6, 106, 60.8, 56.4. FT-IR: $\widetilde{\nu}$ = 3472, 3201, 3056, 3003, 2934, 2838, 1664, 1650, 1611, 1588, 1512, 1489, 1469, 1433, 1380, 1284, 1238, 1179 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_4$ 375.1339; Found 375.1351.

2-(4-Hydroxyphenyl)-1-(pyridin-2-yl)quinolin-4(1*H*)-one (**3r**): Yield 64% (20.1 mg), brown amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.62 (dd, *J* = 4.9, 2 Hz, 1H), 8.25 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.90 (td, *J* = 7.7, 2.0 Hz, 1H), 7.58 (m, 1H), 7.50 – 7.36 (m, 3H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.6 (d, *J* = 8.3 Hz 2H), 6.15 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.3, 157.8, 153.6, 152.1, 149.6, 141.7, 139.5, 132.2, 130.6, 125.7, 125.4, 125.3, 125.2, 124.6, 123.8, 117.8, 114.8, 111.2. FT-IR: $\widetilde{\nu}$ = 3433, 3072, 2963, 2914, 2791, 2672, 2593, 2278, 1599, 1559, 1504, 1485, 1436, 1406, 1321, 1278, 1262 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{15}N_2O_2$ 315.1128; Found: 315.1135.

2-(4-Hydroxyphenyl)-3-(pyridin-2-yl)quinazolin-4(3*H*)-one (**3s**): Yield 70% (22.0 mg), blackish amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.82 (s, 1H), 8.44 (d, *J* = 4.8 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 7.90 (t, *J* = 7.6 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.65 – 7.55 (m, 2H), 7.37 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.58 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.6, 158.3, 154.5, 151.3, 149, 147.4, 138.4, 135.1, 130.6, 127.5, 127.1, 126.4, 125.9, 125.2, 124, 120.3, 114.5. FT-IR: $\widetilde{\nu}$ = 3430, 2923, 2804, 2668, 2356, 2321, 1686, 1592, 1467, 1345, 1331, 1274, 1239 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{14}N_3O_2$ 316.1081; Found 316.1080.

6-(3,5-Dichloro-4-hydroxyphenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**4a**): Yield 87% (28.9 mg), yellow amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.54 (s, 1H), 8.40 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.88 (td, *J* = 7.8, 1.9 Hz, 1H), 7.58 (dd, *J* = 9.3, 6.9 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.34 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.14 (s, 2H), 6.54 (d, *J* = 6.7 Hz, 1H), 6.36 (d, *J* = 6.7 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.1, 151.6, 149.2, 148.9, 146.1, 140.6, 138.2, 129.0, 127.5, 125.3, 123.9, 121.6, 119.7, 107.6. FT-IR: $\widetilde{\nu}$ = 3416, 3137, 3071, 2615, 1656, 1594, 1577, 1546, 1489, 1466, 1413, 1395, 1378, 1296, 1272, 1235 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{11}{}^{35}Cl_2N_2O_2$ 333.0192; Found 333.0204.

6-(2-Chloro-4-hydroxyphenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**4b**): Yield 71% (21.1 mg), brown amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.33 (d, *J* = 5.5 Hz, 1H), 7.80 (td, *J* = 7.8, 1.9 Hz, 1H), 7.58 (dd, *J* = 9.4, 6.7 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.25 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.54 (d, *J* = 9.2 Hz, 2H), 6.23 (d, *J* = 6.7 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.1, 158.4, 151.4, 148.7, 145.9, 140.4, 137.8, 132.8, 123.9, 123.6, 119.8, 115.2, 113.6, 107.9. FT-IR: $\widetilde{\nu}$ = 3420, 3083, 2967, 2929, 2856, 2762, 2656, 2591, 1646, 1608, 1592, 1572, 1540, 1490, 1468, 1431, 1382, 1348, 1288, 1266, 1223 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{12}{}^{35}ClN_2O_2$ 299.0582; Found 299.0595.

6-(4-hydroxynaphthalen-1-yl)-1-(pyridin-2-yl)pyridine-2(1H)-one (**4c**): Yield 75% (23.5 mg), brown amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.68 – 7.62 (m, 3H), 7.50 – 7.37 (m, 3H), 7.15-7.04 (m, 3H), 6.66 (d, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 9.5 Hz, 1H), 6.29 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.5, 153.8, 151.9, 148.4, 147.7, 140.5, 137.5, 132.1, 129.3, 126.8, 124.8, 123.8, 123.3, 122.5, 122.0, 119.3, 108.5, 106.7. FT-IR: $\widetilde{\nu}$ = 3420, 3056, 2921, 2638, 2538, 1654, 1576, 1543, 1464, 1432, 1374, 1350, 1293, 1266 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{20}H_{15}N_2O_2$ 315.1128; Found 315.1140.

Methyl 2-hydroxy-5-(6-oxo-1-(pyridin-2-yl)-1,6-dihydropyridin-2-yl)benzoate (**4d**): Yield 62% (19.9 mg), brown oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.38 (d, *J* = 4.2 Hz, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.58 (m, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.23 (d, *J* = 6.6 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 6.52 (d, *J* = 8.6Hz, 1H), 6.32 (d, *J* = 6.6 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.1, 162.2, 159.4, 151.7, 148.9, 147.7, 140.6, 138.2, 135.4, 130.7, 126.1, 125, 123.7, 119.3, 117.1, 113, 107.1, 52.5. FT-IR: $\widetilde{\nu}$ = 3421, 3265, 1663, 1592, 1546, 1490, 1470, 1438, 1340, 1298, 1280, 1248, 1216 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{18}H_{15}N_2O_4$ 323.1026; Found 323.1037.

6-(2-Hydroxy-4-methylphenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**4e**): Yield 56% (15.6 mg), brown amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.08 (d, *J* = 3.5 Hz, 1H), 7.80 (t, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.07(t, *J* = 6.6, 5.1 Hz, 1H), 7.03 – 6.94 (m, 2H), 6.31 – 6.17 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 168.6, 162.9, 162.8, 151, 147.4, 140.9, 140.3, 140.2, 130.2, 125.7, 123, 119, 111.4, 20.7. FT-IR: $\widetilde{\nu}$ = 3412, 3053, 2923, 2855, 2712, 2565, 1648, 1617, 1590, 1573, 1543, 1516, 1465, 1432, 1414, 1382, 1237 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{15}N_2O_2$ 279.1128; Found 279.1120.

6-(5-Chloro-2-hydroxyphenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**4f**): Yield 57% (17.0 mg), pale brown amorphous solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.29 (d, *J* = 4.5 Hz, 1H), 7.80 (t, *J* = 7.8 Hz, 1H), 7.56 (t, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.24 (t, d, *J* = 6.1 Hz, 1H), 7.14 – 6.99 (m, 2H), 6.60 (d, *J* = 8.7 Hz, 1H), 6.51 (d, *J* = 8.7 Hz, 1H), 6.24 (d, *J* =

6.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 153, 151.5, 148.1, 145.1, 140.4, 137.3, 130, 129.8, 124.4, 123.6, 123.5, 121.5, 119.4, 116.7, 107.5. FT-IR: $\tilde{\nu}$ = 3412, 3069, 2959, 2859, 2762, 2704, 2569, 2365, 1654, 1603, 1576, 1543, 1497, 1467, 1435, 1420, 1277, 1209 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{12}{}^{35}ClN_2O_2$ 299.0582; Found 299.0588.

6-(5-Bromo-2-hydroxyphenyl)-1-(pyridin-2-yl)pyridine-2(1*H*)-one (**4g**): Yield 65% (22.2 mg), brown amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.29 (d, *J* = 4.7 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.57 (dd, *J* = 9.3, 6.8 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.27 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.24 – 7.11 (m, 2H), 6.54 (dd, *J* = 21.3, 8.9 Hz, 2H), 6.25 (d, *J* = 6.7 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.2, 153.6, 151.5, 148.2, 145.0, 140.6, 137.4, 132.9, 132.7, 124.5, 124.2, 123.6, 119.4, 117.3, 109, 107.7. FT-IR: $\tilde{\nu}$ = 3436, 3044, 3021, 2959, 2925, 2854, 2673, 2545, 1672, 1602, 1560, 1546, 1491, 1468, 1438, 1420, 1370, 1290 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{12}{}^{79}BrN_2O_2$ 343.0077; Found 343.0067.

(*S*)-Methyl-2-(1,3-dioxoisoindolin-2-yl)-3-(4-hydroxy-3-(6-oxo-1-(pyridin-2-yl)-1,6-dihydropyridin-2-yl)phenyl)propanoate (**4h**): Yield 36% (17.8 mg), brown gummy oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 7.91 (m, 5H), 7.64 (t, *J* = 7.9 Hz, 1H), 7.46 – 7.30 (m, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.11 – 6.97 (m, 1H), 6.88 – 6.80 (m, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.43 (d, *J* = 9.1 Hz, 1H), 6.37 (d, *J* = 8.3 Hz, 1H), 5.10 (d, *J* = 4.9 Hz, 1H), 3.67 (s, 3H), 3.27 (m, 2H), 3.11 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169, 166.9, 162.1, 152.4, 151.5, 147.8, 146.8, 140.3, 136.9, 135.1, 131, 130.7, 130.6, 126.2, 124.2, 123.6, 123.1, 121.9, 118.8, 115.1, 107, 52.7, 52.6, 32.7. FT-IR: $\tilde{\nu}$ = 3422, 2952, 2855, 2926, 1774, 1744, 1716, 1654, 1617, 1543, 1508, 1467, 1432, 1388, 1244 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{28}H_{22}N_3O_6$ 496.1503; Found 496.1530.

6-((8*R*,9*S*,13*S*,14*S*)-3-Hydroxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*cyclopenta[*a*]phenanthren-2-yl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**4i**): Yield 42% (18.5 mg), pale brown gummy oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.31 (d, *J* = 9.2 Hz, 1H), 7.77 (t, *J* = 7.7 Hz, 1H), 7.53 (dd, *J* = 9.2, 6.8 Hz, 1H), 7.42- 7.32 (m, 1H), 7.25- 7.23 (m, 1H), 6.81 (s, 1H), 6.45 (d, *J* = 9.2 Hz, 1H), 6.33 (s, 1H), 6.17 (d, *J* = 6.8 Hz, 1H), 2.63 (dd, *J* = 7.5, 3.2 Hz, 2H), 2.41 (dd, *J* = 19.2, 8.7 Hz, 1H), 2.15 (m, 1H), 2.10 – 1.95 (m, 2H), 1.95 – 1.87 (m, 1H), 1.87 – 1.78 (m, 1H), 1.72 (d, *J* = 12.6 Hz, 1H), 1.51 (m, 1H), 1.41 (m, 1H), 1.37 – 1.27 (m, 2H), 1.22 (d, *J* = 15.8 Hz, 2H), 0.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 219.5, 162.4, 152, 151.7, 148.2, 145.4, 140.4, 138.1, 137.3, 129.5, 127.6, 123.3, 119.5, 118.4, 114.9, 107.6, 49.4, 47.2, 42.9, 37.7, 35.3, 31.2, 28.5, 25.8, 25.4, 21.1, 13.4. FT-IR: $\tilde{\nu}$ = 3433, 3238, 2926, 2859, 1735, 1654, 1544, 1436 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{28}H_{29}N_2O_3$ 441.2173; Found 441.2182.

3-(2-Hydroxy-4-methylphenyl)-2-(pyridin-2-yl)isoquinolin-1(2*H*)-one (**4j**): Yield 49% (16.1 mg), brown gummy oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.30 (dd, *J* = 5.0, 1.8 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 7.80 – 7.76 (m, 2H), 7.72

(d, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J*= 7.8 Hz, 1H), 7.25 (dd, *J* = 7.6, 4.9 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.59 (s, 1H), 6.46 (d, *J* = 7.8 Hz, 1H), 6.42 (s, 1H), 2.10 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.1, 154.1, 152.1, 148.2, 139.4, 137.3, 137, 133, 130.9, 127.1, 126.7, 126.3, 124.7, 124.5, 123.3, 119.8, 119, 115.6, 107.1, 20.9. FT-IR: $\widetilde{\nu}$ = 3439, 3276, 3075, 2921, 2859, 1654, 1624, 1590, 1497, 1482, 1467, 1432, 1374, 1340, 1288, 1242 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O_2$: 329.1285; found 329.1298.

2-(2-Hydroxy-4-methylphenyl)-1-(pyridin-2-yl)quinolin-4(1*H*)-one (**4k**): Yield 61% (20.0 mg), brown gummy oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 8.52 (d, *J* = 4.7 Hz, 1H), 8.26 (d, *J* = 7.7 Hz, 1H), 7.90 (t, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.42 (m, 2H), 6.90 (s, 1H), 6.68 (d, *J* = 8.6 Hz, 1H), 6.54 – 6.43 (m, 2H), 6.06 (s, 1H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.2, 153.8, 151.5, 151.1, 149.5, 141.6, 140.1, 139, 132.1, 130.3, 125.2, 125.1, 124.6, 123.7, 119.4, 119.1, 117.6, 115.9, 111.8, 20.8. FT-IR: $\widetilde{\nu}$ = 3422, 3057, 2923, 2854, 2700, 2567, 1624, 1594, 1543, 1490, 1466, 1414, 1437, 1320, 1286, 1258, 1226 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O_2$ 329.1285; Found 329.1298.

6-(4-Hydroxyphenyl)pyridin-2(1*H*)-one (**5**): Yield 74% (55.4 mg, 0.4 mmol), pale yellow amorphous solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 9.89 (s, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.46 (t, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 2H), 6.49 (d, *J* = 8.4 Hz, 1H), 6.25 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3, 158.9, 140.9, 130.1, 128.2, 115.5, 114.9. FT-IR: $\widetilde{\nu}$ = 3430, 2955, 2926, 2854, 1654, 1608, 1509, 1459, 1377 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{10}NO_2$ 188.0706; Found 188.0721.

6-(4-Hydroxyphenyl)-1-(pyridin-2-yl)piperidin-2-one (**6**): Yield 93% (49.9 mg, 0.2 mmol), colorless gummy liquid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.31 (d, *J* = 4.1 Hz, 1H), 7.66 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.07 (m, 1H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.60 (d, *J* = 8.2 Hz, 2H), 5.66 (t, *J* = 5.2 Hz, 1H), 2.60 (m, 1H), 2.45 (m, 1H), 2.17 (m, 1H), 1.90 (m, 1H), 1.69 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.1, 156.1, 153.7, 147.8, 136.7, 132, 127.7, 123.3, 121, 114.9, 59.7, 32.6, 31.5, 17. FT-IR: $\widetilde{\nu}$ = 3434, 2951, 1630, 1590, 1521, 1469, 1428, 1406, 1376, 1331, 1293, 1278, 1235 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{17}N_2O_2$ 269.1285; Found 269.1281.

6-(4-(3,5-*bis*(Trifluoromethyl)phenoxy)phenyl)-1-(pyridin-2-yl)pyridin-2(1*H*)-one (**7**): Yield 68% (32.4 mg), white amorphous solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.76 (td, *J* = 7.9, 1.9 Hz, 1H), 7.61 (s, 1H), 7.52 (dd, *J* = 9.3, 6.8 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.24 (m, 5H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.35 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 158.4, 155, 152, 149.3, 148, 140, 138, 133.4 (q, *J* = 31 Hz), 132.4, 131.2, 124.7, 123.6, 122.9 (q, *J* = 273.5 Hz), 120.8, 119.6, 118 (q, *J* = 3.5 Hz), 116.7 (q, *J*= 4 Hz), 107.9. ^{19}F NMR (376 MHz,

$CDCl_3$) δ -63. FT-IR: $\tilde{\nu}$ = 3398, 3067, 2952, 1670, 1600, 1551, 1502, 1463, 1436, 1415, 1378, 1282, 1243 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{15}F_6N_2O_2$ 477.1032; Found 477.1019.

6-(4-methoxyphenyl)-2*H*-[1,2'-bipyridin]-2-one (**8**)[6e], yield 97% (27.0 mg), pale yellow amorphous solid, ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 2.6 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.21 (dd, *J* = 7.8, 4.6 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 6.56 (d, *J* = 9.4 Hz, 1H), 6.34 (d, *J* = 7.0 Hz, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 159.9, 152.1, 149.3, 149.2, 141.3, 138.8, 130.4, 127.1, 124.6, 124.0, 119.5, 113.7, 109.1, 55.4. FT-IR: $\tilde{\nu}$ = 3412, 3052, 2998, 2959, 2926, 2836, 1655, 1608, 1591, 1545, 1508, 1465, 1433, 1380, 1294 cm^{-1}. GCMS value (EI) m/z for $C_{24}H_{15}F_6N_2O_2$ $(M)^+$ is 278.32.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of new compounds (^1H, ^{13}C NMR spectra). 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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REFERENCES

(1) (a) Crozet, M. D.; George, P.; Crozet, M. P.; Vanelle, P. *Molecules* **2005**, *10*, 1318. (b) Magedov, I. V.; Manpadi, M.; Ogasawara, M. A.; Dhawan, A. S.; Rogelj, S.; Slambrouck, S. V.; Steelant, W. F. A.; Evdokimov, N. M.; Uglinskii, P. Y.; Elias, E. M.; Knee, E. J.; Tongwa, P.; Antipin, M. Y.; Kornienko, A. *J. Med. Chem.* **2008**, *51*, 2561. (c) Heeb, S.; Fletcher, M. P.; Chhabra,

S. R.; Diggle, S. P.; Williams, P.; Camara, M. *FEMS Microbiol Rev.* **2011**, *35*, 247. (d) Schröder, P.; Förster, T.; Kleine, S., Becker, C.; Richters, A.; Ziegler, S., Rauh, D., Kumar, K. Waldmann, H.; *Angew. Chem. Int. Ed*. **2015**, *54*, 12398. (e) Jessen, H. J.; Gademann, K. *Nat. Prod. Rep*. **2010**, *27*, 1168.

(2) (a) Wu, Y.; Chen, Y.-Q.; Liu, T.; Eastgate, M. D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 14554. (b) Wang, P.; Li, G.-C.; Jain, P.; Farmer, M. E.; He, J.; Shen, P.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 14092. (c) Wang, P.; Farmer, M. E.; Huo, X.; Jain, P.; Shen, P.-X.; Ishoey, M.; Bradner, J. E.; Wisniewski, S. R.; Eastgate, M. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 9269.

(3) Recent reviews on transition metal catalyzed C-H functionalizations: (a) Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Chem. Sci*. **2014**, *5*, 2146; (b) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front*. **2014**, *1*, 843; (c) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front*. **2015,** *2*, 1107. (d) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986. (e) Yadav, M. R.; Rit, R. K.; Majji, S.; Sahoo, A. K. *Asian J. Org. Chem*. **2015**, 4, 846. (f) Yang, L.; Huang, H. M. *Chem. Rev*. **2015**, *115*, 3468. (g) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622. (h) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900.

(4) For reviews on Rh(III)-catalyzed C–H functionalizations, see: (a) Satoh, T.; Miura, M. *Chem. - Eur. J*. **2010**, *16*, 11212. (b) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev*. **2012**, *41*, 3651. (d) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellmann, J. A. *Acc. Chem. Res*. **2012**, *45* , 814. (e) Colby, D. A.; Bergman, R. G.; Ellmann, J. A. *Chem. Rev*. **2010**, *110* , 624.

(5) (a) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. *Chem. -Eur. J.* **2013**, *19*, 7691. (b) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2014**, *79*, 1377. (c) Modak, A.; Rana, S.; Maiti, D. *J. Org. Chem.* **2015**, *80*, 296. (d) Anagnostaki, E. E.; Fotiadou, A. D.; Demertzidou, V.; Zografos, A. L. *Chem. Commun.* **2014**, *50*, 6879. (e) Min, M.; Kim, Y.; Hong, S.; *Chem. Commun.* **2013**, *49*, 196. (f) Cheng, D.; Gallagher, T. *Org. Lett.* **2009**, *11*, 2639. (g) Itahara, T.; Ouseto, F. *Synthesis*, **1984**, 488; (h) Chen, Y.; Wang, F.; Jia, A.; Li, X. *Chem. Sci.* **2012**, *3*, 3231.

(6) (a) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 15996. (b) Tamura, R.; Yamada, Y.; Nakao, Y.; Hiyama, T. *Angew. Chem. Int. Ed.* **2012**, *124*, 5777. (c) Donets, P. A.; Cramer, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 633. (d) Das, D.; Biswas, A.; Karmakar, U.; Chand, S.; Samanta, R. *J. Org. Chem*. **2016**, *81*, 842. (e) Peng, P.; Wang, J.; Jiang, H.; Liu, H. *Org. Lett.* **2016**, *18*, 5376. (f) Li, T.; Wang, Z.; Xu, K.; Liu, W.; Zhang, X.; Mao, W.; Guo, Y.; Ge, X.; Pan, F. *Org. Lett.* **2016**, *18*, 1064. (g) Li, Y.; Xie, F.; Li, X. *J. Org. Chem*. **2016**, *81*, 715. (h) Peng, P. F.; Wang, J.; Li, C. P.; Zhu, W.; Jiang, H. L.; Liu, H. *RSC Adv*. **2016**, *6*, 57441. (i) Yu, S.; Li, Y.; Zhou, X.; Wang, H.; Kong, L.; Li, X. *Org. Lett*. **2016**, *18*, 2812.

(7) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 10784.

(8) Miura, W.; Hirano, K.; Miura, M. *Org. Lett*. **2016**, *18*, 3742.

(9) Recent reviews on metal carbene insertion in C-H bonds: (a) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, A. *Chem. Rev*. **2015**, *115*, 9981. (b) Caballero, A.; Pérez, P. J. *Chem. Soc. Rev*. **2013**, *42*, 8809. (c) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev*. **2011**, *40*, 1857. (d) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev*. **2010**, *110*, 704. (e) Wang, B.; Qiu, D.; Zhang, Y.; Wang, J. *Beilstein J. Org. Chem*. **2016**, *12*, 796.

(10) Few recent selected references: (a) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986 and references cited therein (b) Wang, J.; Wang, M.; Chen, K.; Zha, S.; Song, C.; Zhu, J. *Org. Lett*. **2016**, *18*, 1178. (c) Wang, J.; Zha, S.; Chen, K.; Zhang, F. Zhu, J. *Org. Biomol. Chem*. **2016**, *14*, 4848. (d) Wu, Y.; Sun, P.; Zhang, K.; Yang, T.; Yao, H.; Lin A. *J. Org. Chem.* **2016**, *81*, 2166. (e) Zhou,T.; Li, B.; Wang, B. *Chem. Commun*. **2016**, *52*, 14117. (f) Chen, X.; Hu, X.; Bai, S.; Deng, Y.; Jiang, H.; Zeng, W. *Org. Lett*. **2016**, *18*, 192. (g) Srinivasarao, A.; Ravi, M.; Kumara Swamy, K. C. *Eur. J. Org. Chem*. **2016**, *2016*, 5697. (h) Lv, H.; Xu, W. L.; Lin, K.; Shi, J.; Yi, W. *Eur. J. Org. Chem*. **2016**, *2016*, 5637.

(11) For selected application of quinone diazides, see: (a) Mori, H.; Tando, I.; Tanaka, H. *Macromolecules,* **2010**, *43*, 7011. (b) Wallraff, G. M.; Hinsberg, W. D. *Chem. Rev*. **1999**, *99*, 1801. (c) Olszewski, J. D.; Marshalla, M.; Sabat, M.; Sundberg, R. J. *J. Org. Chem*. **1994**, *59*, 4285. (d) Bouchet, M. J.; Rendon, A.; Wermuth, C. G.; Goeldner, M.; Hirth, C. *J. Med. Chem.* **1987**, *30*, 2222. (e) Ohno, T.; Martín, N.; Knight, B.; Wudl, F.; Suzuki, T.; Yu, H. *J. Org. Chem*. **1996**, 61, 1306. (f) Knight, B.; Martín, N.; Ohno, T.; Ortí, E.; Rovira, C.; Veciana, J.; Vidal-Gancedo, J.; Viruela, P.; Viruela, R.; Wudl, F. *J. Am. Chem. Soc*. **1997**, *119*, 9871.

(12) (a) Ershov, V. V.; Nikiforvo, G. A.; De Jonge, C. R. H. I. *Studies in Organic Chemistry*: Quinonediazides, Elsevier, Amsterdam, 1981. (b) Griesbeck, A. G.; Zimmermann, E. in *Science of Synthesis*, ed. Griesbeck, A. G. Thieme, Stuttgart, **2000**, *28*, 807.

(13) Dao, H.-T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2014**, *53*, 14382.

(14) Zhang, S.; Jiang, C.; Wu, J.; Liu, X.; Li, Q.; Huang, Z.; Li, D.; Wang, H. *Chem. Commun*. **2015**, *51*, 10240.

(15) Recent Selected References: (a) Zhang, X.; Wang, F.; Qi, Z.; Yu, S.; Li, X. *Org. Lett*. **2014**, *16*, 1586. (b) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J. *J. Am. Chem. Soc*. **2014**, *136*, 6904. (c) Xiang, J. –C.; Cheng, Y.; Wang, M.; Wu, Y.-D.; Wu, A. –X. *Org. Lett*. **2016**, *18*, 4360. (d) Shen, Y.; Qi, J.; Mao, Z.; Cui, S. *Org. Lett*. **2016**, *18*, 2722. (e) Speck, K.; Karaghiosoff, K.; Magauer, T. *Org. Lett*. **2015**, *17*, 1982. (f) Yu, D.-G.; de Azambuja, F.; Glorius, F. *Angew. Chem. Int. Ed*. **2014**, *53*, 7710.

(16) Biswas, A.; Karmakar, U.; Pal, A.; Samanta, R. *Chem. Eur. J*. **2016**, *22*, 13826.

(17) (a) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev*. **2009**, *38*, 3010. (b) Antos, J. M.; McFarland, J. M.; Iavarone, A. T.; Francis, M. B. *J. Am. Chem. Soc*. **2009**, *131*, 6301. (c) Mcmurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.*

2011, *40*, 1885. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960. (e) Chen, D. Y.-K.; Youn, S. W. *Chem. Eur. J.* **2012**, *18*, 9452.

(18) Smout, V.; Peschiulli, A.; Verbeeck, S.; Mitchell, E. A.; Herrebout, W.; Bultinck, P.; Velde, C. M. L. V.; Berthelot, D.; Meerpoel, L.; Maes, B. U. W. *J. Org. Chem.* **2013**, *78*, 9803.

(19) (a) Zhou, T.; Guo, W.; Xia, Y. *Chem. -Eur. J.* **2015**, *21*, 9209. (b) Chan, W.-W.; Lo, S. –F.; Zhou, Z.; Yu, W. –Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565. (c) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. (d) Brasse, M.; Campora, J.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2013**, *135*, 6427. (e) Walsh, A. P.; Jones, W. D. *Organometallics* **2015**, *34*, 3400.

(20) (a) Sughara, M.; Ukita, T. *Chem. Pharm. Bull.* **1997**, *45*, 719. (b) Walters, M. A.; Shay, J. J. *Synth. Commun*. **1997**, *27*, 3573. (c) Kawakami, K.; Murakami, K.; Itami, K. *J. Am. Chem. Soc*. **2015**, *137*, 2460.

(21) Meissner, R. S.; Perkins, J. J.; Duong, L. T.; Hartman, G. D.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.-T.; Nagy, R. M.; Naylor-Olsen, A.; Rodan, G. A.; Rodan, S. B.; Whitman, D. B.; Wesolowski, G. A.; Duggan, M. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 25.

(22) Patra, T.; Bag, S.; Kancherla, R.; Mondal, A.; Dey, A.; Pimparkar, S.; Agasti, S.; Modak, A.; Maiti, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 7751.

(23) (a) Zhang, X.-S.; Li, Z.-W.; Shi, Z.-J. *Org. Chem. Front.* **2014**, *1*, 44. (b) Koley, D.; Colón, O. C.; Savinov, S. N. *Org. Lett.* **2009**, *11*, 4172. (c) Guzowa, K.; Szmigiel, D.; Wroblewski, D.; Milewska, M.; Karolczak, J.; Wiczk, W. *J. Photochem. Photobiol. A: Chem.* **2007**, *187*, 87.

(24) (a) Poirier, J.-M.; Vottero, C. *Tetrahedron,* **1989,** *45,* 1415. (b) Woo, L.W. L.; Leblond, B.; Purohit, A.; Potter, B. V. L. *Bioorg. Med. Chem.* **2012**, *20*, 2506.