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Article

Harnessing Vinyl Acetate as an Acetylene Equivalent in Redox-Neutral Cp*Co(III)-Catalyzed C−H Activation/Annulation for the Synthesis of Isoquinolones and Pyridones

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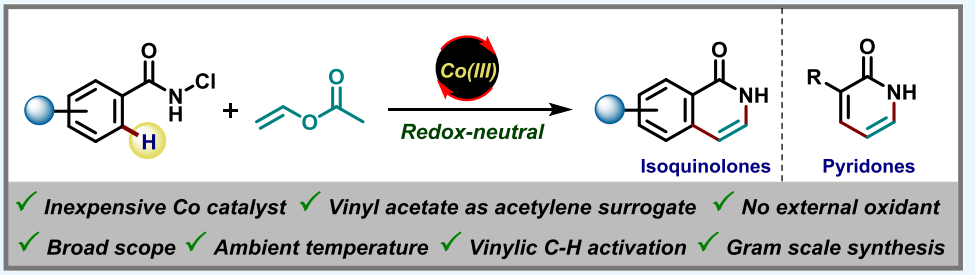

ABSTRACT: We have developed Cp*Co(III)-catalyzed redox-neutral synthesis of 3,4-unsubstituted isoquinoline 1(2*H*)-ones at ambient temperature using *N*-chloroamides as a starting material. The reaction utilizes vinyl acetate as an inexpensive and benign acetylene surrogate. The N−Cl bond of the *N*-chlorobenzamides plays the role of an internal oxidant and hence precludes the need for an external oxidant. The reaction works with a wide range of substrates having various functional groups and a substrate containing a heterocyclic ring. Notably, the reaction is extended to the *N*-chloroacrylamides in which vinylic C−H activation occurs to furnish the 2-pyridone derivatives. Preliminary mechanistic studies were also conducted to shed light on the mechanism of this reaction.

INTRODUCTION

Isoquinolin-1(2*H*)-one is a privileged scaffold that often encounters many naturally occurring alkaloids, and it also constitutes a core framework in many medicinally important pharmaceutical drugs possessing anticancer, antiviral, and antidiabetic activities (Figure 1).[1] Although, there are various methods available for the synthesis of isoquinolone derivatives,[2] the utilization of transition-metal-catalyzed C−H annulation has gained a lot of prominence due to the step and atom-economic nature of these reactions.[3] Early reports on C−H activation for the synthesis of isoquinolones rely on the oxidative-cyclization strategies, which often suffer from the drawback of using a stoichiometric amount of metal oxidants such as $Cu(OAc)_2$ and Ag_2CO_3.[4] These metal oxidants subsequently lead to the generation of metal wastes at the end of the reaction. In order to circumvent the issue of using an external oxidant, redox-neutral C−H annulation reactions involving oxidizing directing groups came into limelight.[5]

The seminal work in the area of C−H functionalization using oxidizing groups was reported by groups of Glorius, Fagnou, Hartwig, Cui & Wu, and Yu.[6] In these transformations, where an oxidizing directing group has been employed, the reactions can be conducted without any external oxidant because the directing group plays a dual role, i.e., direct the C−H metalation and oxidize the metal back to its active oxidation state. In 2014, Marsden et al. reported Cp*Rh(III)-catalyzed [4 + 2] annulation of *N*-pivaloyl benzamides with vinyl acetate as an acetylene equivalent for the synthesis of isoquinolones (Scheme 1a).[7] In 2021, Baidya et al., during their studies on the synthesis of aminal motifs via Ru(II)-catalyzed C−H activation/annulation of *N*-methoxybenzamides with enamides, also reported 3 examples for isoquinolone synthesis using vinyl acetate as a coupling partner at 60 °C (Scheme 1a).[8] However, the requirement of precious transition metals like Rh and Ru makes these protocols cost-intensive. Moreover, these methods are only limited to aromatic C−H functionalizations. Hence, it is highly desirable to develop a cost-efficient method for the synthesis of isoquinolone derivative as well as pyridone moiety via vinylic C−H activation.

Recent developments in the area of C−H functionalization have shifted the focus toward the utility of inexpensive and earth-abundant first-row transition metals (e.g., Co, Cu, Fe, Ni,

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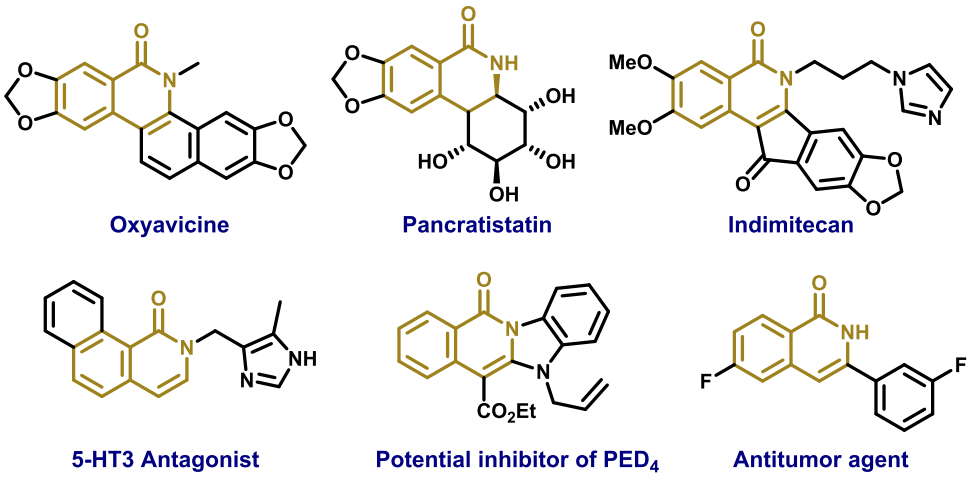
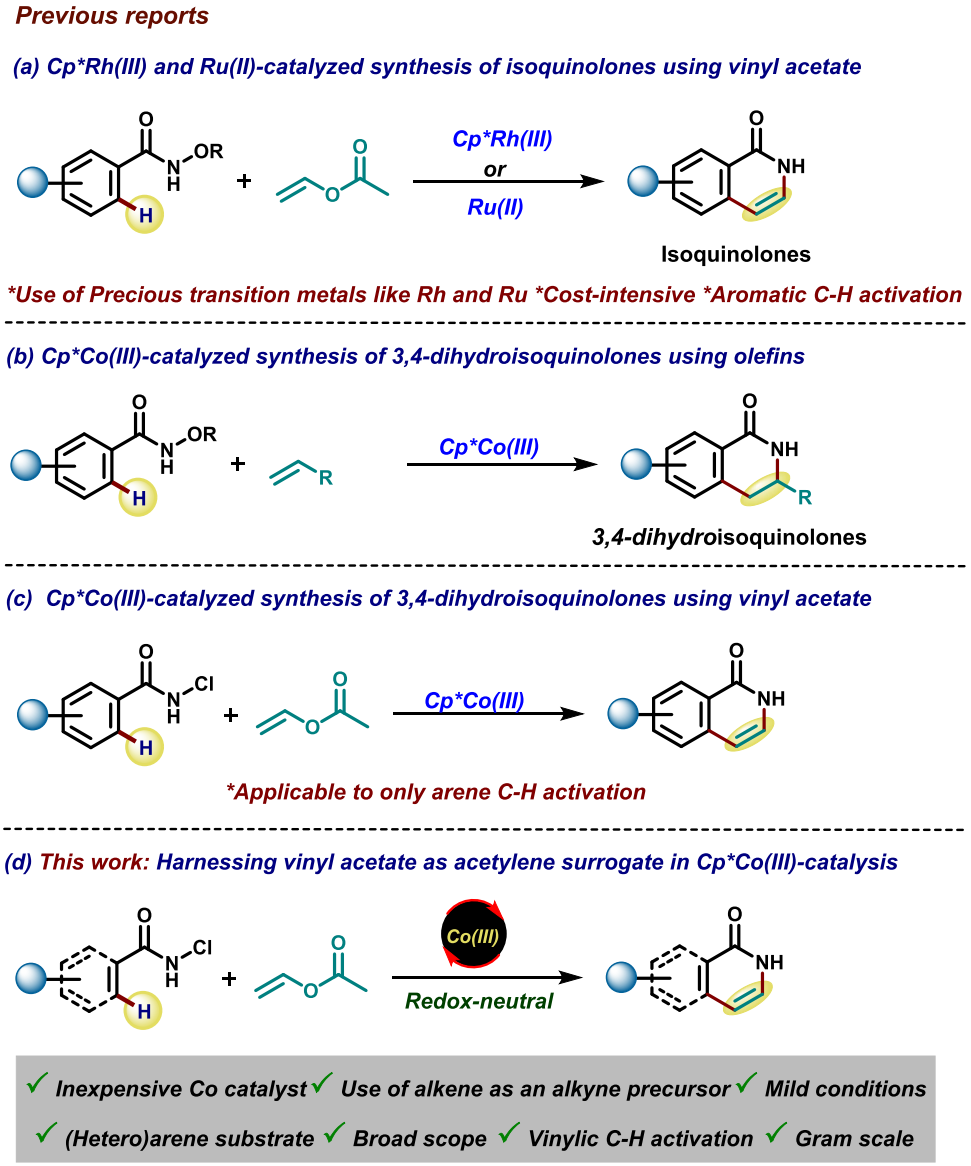


Figure 1. Representative examples of naturally occurring and medicinally important isoquinolone derivatives.

Scheme 1. Transition-Metal-Catalyzed Synthesis of Isoquinolone Derivatives via [4 + 2] Annulation Reactions



and Mn) in these transformations.[9] In this regard, Cp*Co(III)-catalysis has seen significant development in the area of C−H functionalization.[10] This is accounted for the low cost, easy preparation, and air stability of Cp*Co(III) catalysts. Various

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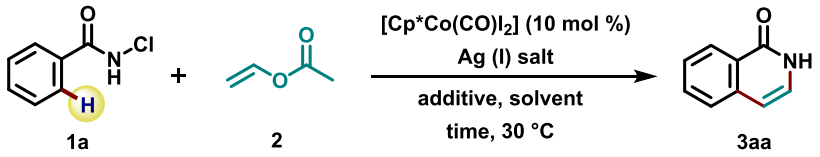
Table 1. Optimization Study[a]



entry	Ag(I) salt	additive (equiv)	solvent	time (h)	yield (%)[b]
1		NaOAc (1.2)	TFE	12	56
2		NaOAc (1.5)	TFE	12	68
3	$AgSbF_6$	NaOAc (1.5)	TFE	12	19
4	AgOTf	NaOAc (1.5)	TFE	12	21
5	AgOAc	NaOAc (1.5)	TFE	12	89
6	AgOAc	CsOAc (1.5)	TFE	12	61
7	AgOAc	KOAc (1.5)	TFE	12	66
8	AgOAc	LiOAc (1.5)	TFE	12	22
9	AgOAc	$Ca(OH)_2$ (1.5)	TFE	12	n.d.
10	AgOAc	PivOH (1.5)	TFE	12	trace
11	AgOAc	NaOAc (1.5)	1,2-DCE	12	44
12	AgOAc	NaOAc (1.5)	MeOH	12	22
13	AgOAc	NaOAc (1.5)	1,4-dioxane	12	trace
14	AgOAc	NaOAc (1.5)	TFE	12	83[c]
15	AgOAc	NaOAc (1.5)	TFE	12	72[d]
16	AgOAc	NaOAc (1.5)	TFE	8	66
17	AgOAc	NaOAc (1.5)	TFE	4	54
18	AgOAc	NaOAc (1.5)	TFE	12	76[e]
19	AgOAc	NaOAc (1.5)	TFE	12	n.d.[f]
20	AgOAc		TFE	12	<5%

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.50 mmol, 5.0 equiv), [Cp*Co(CO)I_2] (10.0 mol %), Ag(I) salt (20.0 mol %), and additives in solvent (0.6 mL) for given time at 30 °C. [b]Yields are based on crude ^{1}H NMR (internal standard: 1,1,2,2 tetrachloroethane). [c]3.0 equiv of **2** was used. [d]2.0 equiv of **2** was used. [e][Cp*Co(CO)I_2] (5.0 mol %) and AgOAc (10 mol %) were used. [f]Without [Cp*Co(CO)I_2]. n.d. = not detected. TFE = 2,2,2-trifluoroethanol.

elegant approaches for the synthesis of isoquinolones were also reported under Cp*Co(III)-catalysis utilizing *N*-methoxyamide as a substrate, wherein the N−O bond works as an internal oxidant.[11] In 2017, Zhu et al. introduced *N*-chlorobenzamide as a novel oxidizing group, in which the role of internal oxidant is played by the N−Cl bond. They have reported [4 + 2] annulation reactions of *N*-chlorobenzamides with alkyne and alkenes using Cp*Co(III)-catalysis.[12,13] When alkyne has been used as a coupling partner, it resulted in the formation of isoquinolone derivatives, whereas the use of alkene leads to the generation of 3,4-dihydroisoquinolones (Scheme 1b). Following these reports, *N*-chlorobenzamide has been effectively used as an efficient oxidizing directing group for various transformations.[14] In continuation of our interest in high-valent Co(III)-catalysis[15] and mild C−H functionalizations,[16] herein, we report the synthesis of isoquinolones via Cp*Co(III)-catalyzed annulation between *N*-chlorobenzamides and vinyl acetate at ambient temperature (Scheme 1d). During the preparation of the manuscript, Jeganmohan's group reported a similar synthetic protocol for the synthesis isoquinolones via Cp*Co(III)-catalyzed [4 + 2] C−H activation/annulation of *N*-chlorobenzamides with vinyl acetate and vinyl ketones (Scheme 1c).[17] However, their scope is limited to only arene C−H functionalization, whereas our protocol can also be applied successfully for vinylic C−H bond activation along with arene C−H functionalization. In this reaction vinyl acetate acts as a synthetic equivalent for acetylene. The reaction demonstrated a good functional group and broad scope. The reaction was also applicable to the *N*-chloroacrylamide derivative where the reaction proceeds via vinylic C−H activation, which was otherwise elusive by previously reported methods.[7,8]

RESULTS AND DISCUSSION

In order to optimize the reaction parameters, we conducted a series of reactions between *N*-chlorobenzamide (**1a**) and vinyl acetate (**2**) using [Cp*Co(CO)I_2] (10 mol %) as a catalyst keeping the temperature constant at 30 °C (Table 1). We were glad to see the formation of isoquinolone **3aa** in 56% yield in our very first attempt when the reaction was performed between **1a** (0.1 mmol) and **2** (5 equiv) in the presence of 10 mol % of [Cp*Co(CO)I_2] and NaOAc (1.2 equiv) using 2,2,2-trifluoroethanol (TFE) as a solvent for 12 h (Table 1, entry 1). An increase in the amount of NaOAc to (1.5 equiv) led to a slight increase in the product formation (Table 1, entry 2). Surprisingly, the introduction of Ag(I) salts, such as $AgSbF_6$ and AgOTf, led to diminished yields (Table 1, entries 3−4). However, we were pleased with the formation of isoquinolone **3aa** in an excellent yield (89%), when AgOAc (20 mol %) was used (Table 1, entry 5). Various other additives such as CsOAc, KOAc, LiOAc, $Ca(OH)_2$, and PivOH were ineffective compared with NaOAc (Table 1, entries 6−10). The reaction was found to be sluggish in other solvents like 1,2-DCE, MeOH, and 1,4-dioxane (Table 1, entries 11−13).

Reducing the equivalents of vinyl acetate resulted in a decrease in the yield of the product (Table 1, entries 14−15). A similar decline in the yield was observed when the reaction was run for a shorter duration (Table 1, entries 16−17). When the catalyst loading was reduced to 5 mol %, it furnished the annulated product in 76% yield (Table 1, entries 18). We did

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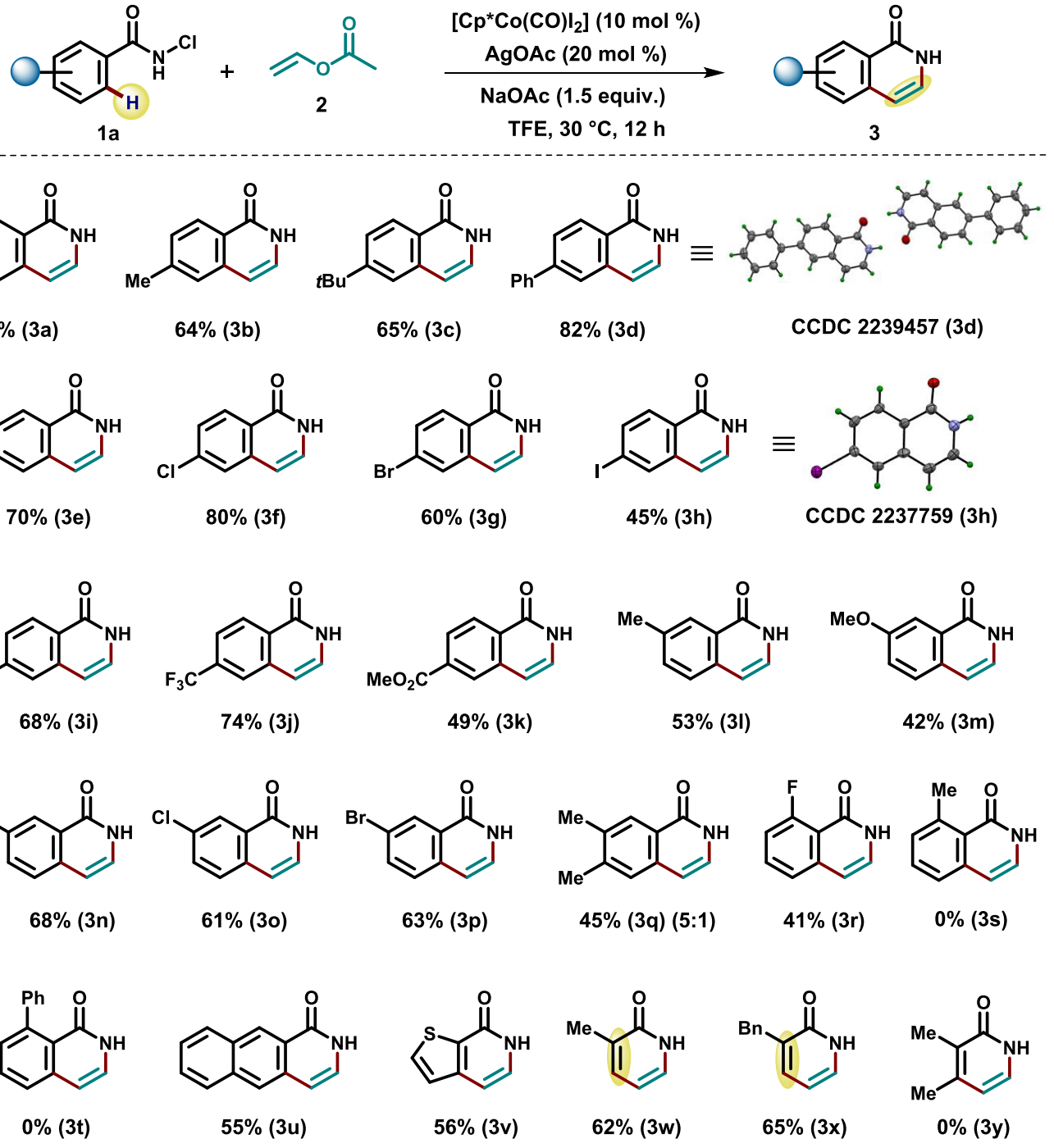
Scheme 2. Scope of *N*-Chlorobenzamides[a]



[a]Reaction conditions: **1** (0.6 mmol), **2** (5.0 equiv), [Cp*Co(CO)I_2] (10 mol %), AgOAc (20 mol %), and NaOAc (1.5 equiv) in TFE (2.5 mL) at 30 °C for 12 h. Isolated yields are given. TFE = 2,2,2-trifluoroethanol.

not observe any product formation in the absence of a cobalt catalyst and only a trace amount without NaOAc (Table 1, entries 19−20).

After optimizing the reaction parameters, we have applied this method for the synthesis of various isoquinolone derivatives using differently functionalized *N*-chlorobenzamides (Scheme 2). The reaction worked with *N*-chlorobenzamides having electron-donating substituents such as *t*-Bu, Me, and Ph at the *para*-position (**3b**−**3d**). Moreover, X-ray crystallographic analysis further confirmed the structure of the isoquinolone **3d**. Gratifyingly, the reaction tolerated all four halogens at the *para*-position (**3e**−**3h**).[18] This gives the scope for further synthetic manipulations of the isoquinolone derivatives by performing different cross-coupling reactions. Furthermore, the structure of the 4-iodo isoquinolone derivative (**3h**) was confirmed by X-ray analysis. The reaction also worked well with electron-withdrawing functional groups such as NO_2, CF_3, and CO_2Me (**3i**−**3k**). The reaction was highly regioselective in the case of *meta*-substituted *N*-chlorobenzamides and was applicable to both electron-

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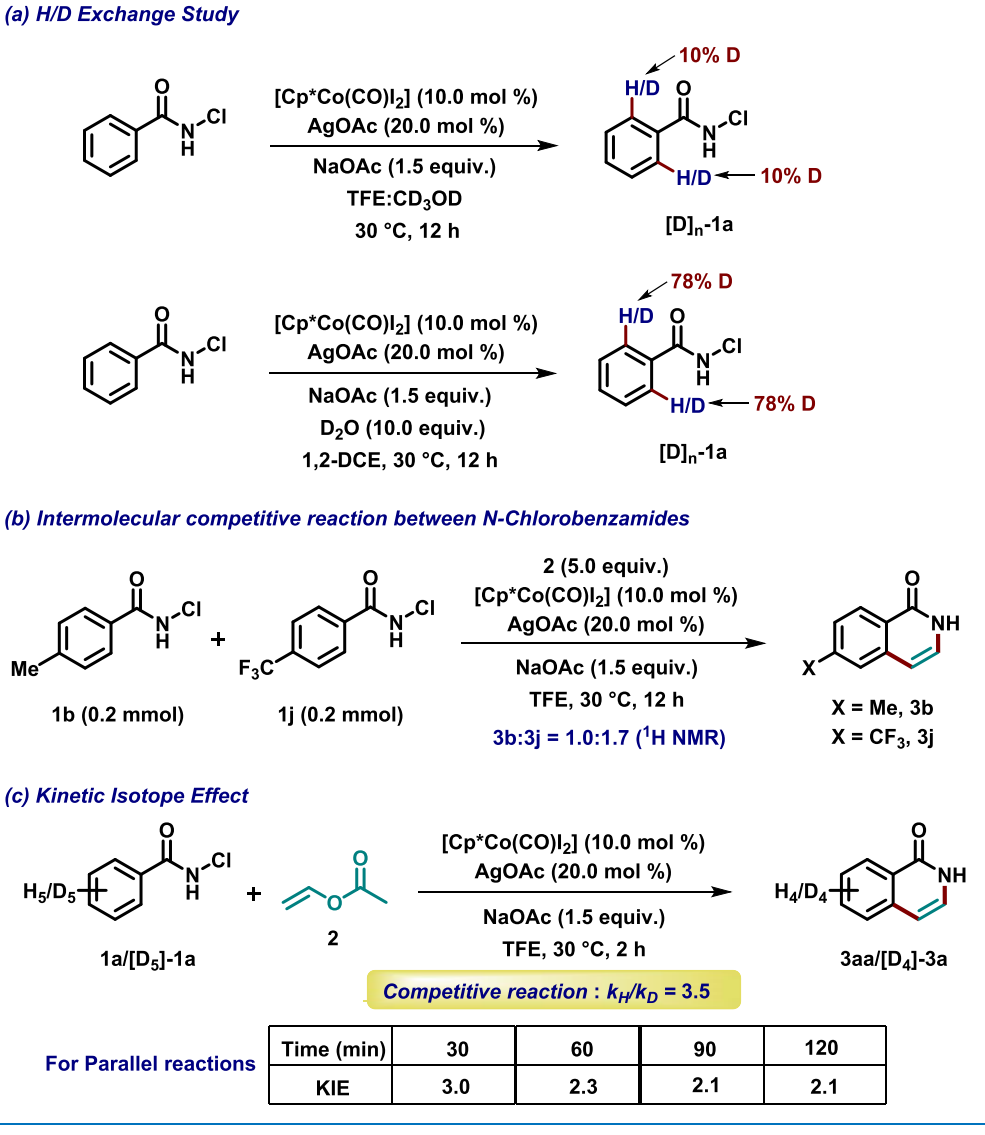
Scheme 3. Mechanistic Findings



For Parallel reactions

Time (min)	30	60	90	120
KIE	3.0	2.3	2.1	2.1

donating and electron-withdrawing substituents furnishing the required annulated products in moderate to good yields (**3l**–**3p**).

However, when the reaction was performed with *N*-chloro-3,4-dimethylbenzamide (**1q**), it resulted in the formation of a inseparable mixture of regioisomeric products in a 5:1 ratio. The major product (**3q**) is formed by the C−H functionalization at a less hindered position. Next, we tested various *ortho*-substituted *N*-chlorobenzamides. The reaction proceeded well with a 41% yield in the case of F substituent (**3r**). However, the reaction failed to produce any desired product in the case of *ortho*-methyl and *ortho*-phenyl substituents (**3s**–**3t**). The reaction was successfully applied to *N*-chloro-2-naphthamide also furnishing the isoquinolone derivative (**3u**) in moderate yield. We were pleased to observe that the current protocol is compatible with a substrate bearing a thiophene ring (**3v**). Further, this protocol was extended to the vinylic C−H activation, wherein *N*-chloromethacrylamide derivatives were converted into the corresponding pyridone derivatives (**3w**–**3x**) in good yields. However, the reaction failed to produce any product with (*E*)-*N*-chloro-2-methylbut-2-enamide (**1y**) as a substrate. The gram-scale synthesis of isoquinolone **3a** was also carried out using 5 mol % of [Cp*Co(CO)I_2] and 10 mol % of AgOAc with 74% yield (see the Supporting Information).

Finally, we have performed a few mechanistic experiments in order to understand the mechanism of the current reaction (Scheme 3). When the H/D exchange experiment was performed using CD_3OD in TFE as a solvent, we did not observe any significant amount of deuterium incorporation at the *ortho*-position in the starting material (Scheme 3a). This might be due to the rapid deuterium exchange with the solvent TFE. Therefore, we have performed a similar reaction in 1,2-DCE using D_2O as the D-source. This resulted in the incorporation of 78% of D incorporation at each *ortho*-position of [**D**]$_n$-**1a**. This result led us to conclude that, in the current reaction, the C−H activation step is reversible. When the intermolecular competitive reaction was performed with *N*-chlorbenzamides having an electron-donating Me and an electron-withdrawing CF_3 group at *para*-positions, it was found that the substrate having an electron-withdrawing CF_3 group reacts preferably compared to the substrate having an electron-donating Me group (Scheme 3b). This observation can be concluded in terms of carboxylate-assisted C−H activation.[19] In order to determine the nature of the C−H activation step,

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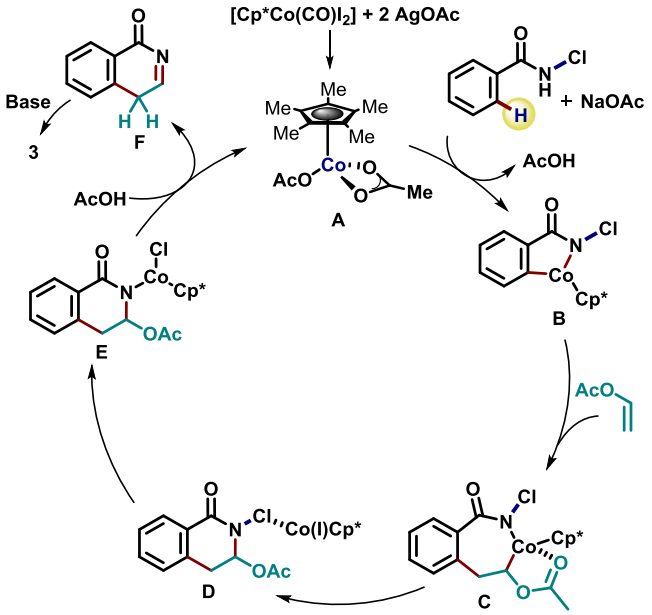
we have performed the KIE experiments. The KIE value obtained from the competitive experiment was found to be 3.5 (Scheme 3c).

Then, we performed parallel reactions at 30, 60, 90, and 120 min, which resulted in the KIE values of 3.0, 2.3, 2.1, and 2.1, respectively (Scheme 3c). These KIE values indicate that the C−H activation might be the rate-determining step.

Based on the mechanistic experiments and relevant reports,[7,8] a plausible mechanism for the current [4 + 2] annulation reaction is depicted in Scheme 4. The catalytic

Scheme 4. Plausible Mechanism



cycle begins with the formation of catalytically active Co(III) species **A** by the reaction between [Cp*Co(CO)I_2] and AgOAc. At the same time, NaOAc deprotonates the *N*-chlorobenzamide, which in turn undergoes *ortho*-metalation with **A** to form a five-membered cobaltacycle **B**. Subsequently, regioselective insertion of vinyl acetate into the cobaltacycle **A** led to the formation of a seven-membered cobaltacycle species **C**. The regioselectivity of the vinyl acetate insertion is governed by the weak chelation between the carbonyl oxygen of the vinyl acetate and the cobalt center.

The intermediate **C** upon migratory insertion results in the formation of a N−Cl isoquinolone **D** along with the generation of Cp*Co(I) species. The Cp*Co(I) get oxidizes back to Cp*Co(III) via oxidative addition into the N−Cl bond to form species **E**. This step is responsible for the redox-neutral nature of this reaction. The intermediate **E** upon acetate elimination and subsequent protodemetalation furnishes an intermediate **F** along with concomitant generation of catalytically active Co(III) species **A**. Finally, isoquinolone **F** upon base-mediated tautomerization leads to the formation of the desired isoquinolone **3**.

CONCLUSIONS

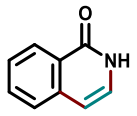
In conclusion, an efficient redox-neutral protocol has been developed for the synthesis of isoquinolones starting from *N*-chlorobenzamides and vinyl acetate using an inexpensive Co(III) catalyst. The reaction utilizes vinyl acetate as a cheap and safe acetylene surrogate. The reaction can be performed at ambient temperature without the requirement of any inert conditions. Also, the reaction demonstrated an excellent functional group tolerance along with a broad scope and gram-scale applicability. The reaction can be extended for the synthesis of a pyridine derivative via vinylic C−H functionalization. The preliminary mechanistic studies revealed that the C−H activation proceeds via the base assistance, and it might be the rate-determining step.

EXPERIMENTAL SECTION

General Remarks. All commercial reagents and solvents were used without additional purification, unless otherwise stated. Column chromatography was performed on silica gel (100−200 mesh) using a suitable solvent system. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 500 MHz. High-resolution mass spectrometry (HRMS) spectra were recorded using electrospray ionization time-of-flight (ESI-TOF) techniques. The starting *N*-chlorobenzamides were prepared from commercially available carboxylic acids in 2 steps following the literature protocol.[12] Vinyl acetate is commercially available and used as such without any further purification.

General Procedure for the Cp*Co(III)-Catalyzed C−H Functionalization of *N*-Chlorobenzamides with Vinyl Acetate. To a screw-capped seal tube vial with a Teflon stir bar was added *N*-chlorobenzamide **1** (0.6 mmol, 1.0 equiv), vinyl acetate **2** (3.0 mmol, 258.0 mg, 5.0 equiv), [Cp*Co(CO)I_2] (10.0 mol %, 28.5 mg), AgOAc (20.0 mg, 20 mol %), NaOAc (73.8 mg, 1.5 equiv), and TFE (2,2,2-trifluoroethanol) (3.6 mL) under an air atmosphere. The reaction mixture was stirred at 30 °C for 12 h. Then, it was filtered through a short pad of celite, and the celite pad was washed with DCM (15 mL × 2). The solvent was removed using a rotary evaporator, and the residue was purified by silica gel column chromatography using *n*-hexane/EtOAc as an eluent to give the desired isoquinolone derivatives. The yields were calculated with respect to *N*-chlorobenzamides, which are the limiting agents.

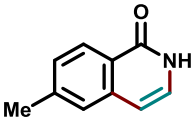
Spectral Data of All Compounds. *Isoquinolin-1(2H)-one (**3a**).*[7]



3a

White solid (73.2 mg, 84%); eluent (50−60% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.27 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.72−7.65 (m, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.50−7.43 (m, 1H), 7.17 (d, J = 7.0 Hz, 1H), 6.54 (d, J = 7.1 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.9, 137.9, 132.3, 128.9, 126.7, 126.3, 126.2, 126.1, 104.6.

*6-Methylisoquinolin-1(2H)-one (**3b**).*[20]



3b

Yellow solid (61.0 mg, 64%); eluent (70−80% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.14 (brs, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.29 (dd, J = 8.2, 1.3 Hz, 1H), 7.13 (d, J = 6.7, 1H), 6.45 (d, J = 7.1 Hz, 1H), 2.41 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.6, 142.1, 137.6, 128.8, 127.5, 126.5, 125.5, 123.8, 104.2, 21.0.

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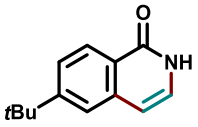
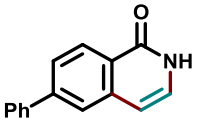
*6-(tert-Butyl)isoquinolin-1(2H)-one (**3c**).*[20]



3c

Yellow solid (78.5 mg, 65%); eluent (50−60% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.15 (brs, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 1.5 Hz, 1H), 7.54 (dd, J = 8.7, 1.8 Hz, 1H), 7.13 (m, 1H), 6.53 (d, J = 7.1 Hz, 1H), 1.32 (s, 9H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.6, 155.0, 137.8, 128.7, 126.4, 124.1, 123.9, 122.0, 104.9, 34.7, 30.8.

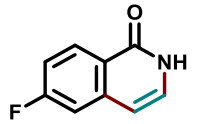
*6-Phenylisoquinolin-1(2H)-one (**3d**).*[20]



3d

White solid (109.0 mg, 82%); eluent (60−65% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.27 (brs, 1H), 8.24 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.84−7.73 (m, 3H), 7.52 (t, J = 7.6 Hz, 2H), 7.44 (t, J = 7.4 Hz, 1H), 7.25−7.15 (m, 1H), 6.62 (d, J = 7.1 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.6, 143.7, 139.2, 138.4, 129.3, 129.0, 128.2, 127.4, 127.0, 125.0, 124.9, 123.9, 104.8.

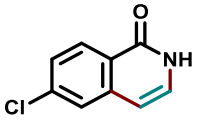
*6-Fluoroisoquinolin-1(2H)-one (**3e**).*[7]



3e

White solid (68.3 mg, 70%); eluent (50−60% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.32 (brs, 1H), 8.22 (dd, J = 8.9, 5.9 Hz, 1H), 7.48 (dd, J = 10.1, 2.6 Hz, 1H), 7.31 (td, J = 8.9, 2.7 Hz, 1H), 7.26−7.19 (m, 1H), 6.53 (d, J = 7.1 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 164.4 (d, J_{C-F} = 248.9 Hz), 161.2, 140.4 (d, J_{C-F} = 10.6 Hz), 130.5, 130.2 (d, J_{C-F} = 10.2 Hz), 123.0, 114.8 (d, J_{C-F} = 23.6 Hz), 110.9 (d, J_{C-F} = 21.8 Hz), 104.2; **^{19}F NMR (470 MHz, DMSO-d_6)** δ −107.4.

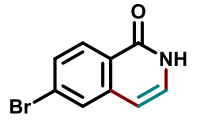
*6-Chloroisoquinolin-1(2H)-one (**3f**).*[20]



3f

White solid (86.2 mg, 80%); eluent (80−85% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.38 (brs, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.78 (d, J = 1.7 Hz, 1H), 7.48 (dd, J = 8.5, 1.9 Hz, 1H), 7.23 (d, J = 7.1 Hz, 1H), 6.53 d, J = 7.2 Hz, 1H; **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.2, 139.4, 137.2, 130.5, 128.9, 126.3, 125.2, 124.6, 103.6.

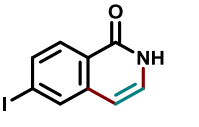
*6-Bromoisoquinolin-1(2H)-one (**3g**).*[7]



3g

Yellow solid (80.7 mg, 60%); eluent (100% ethyl acetate); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.27 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 1.8 Hz, 1H), 7.61 (dd, J = 8.4, 2.0 Hz, 1H), 7.26−7.15 (m, 1H), 6.52 (d, J = 7.1 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.2, 139.5, 130.4, 129.0, 128.9, 128.2, 126.2, 124.8, 103.4.

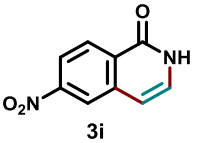
*6-Iodoisoquinolin-1(2H)-one (**3h**).*[7]



3h

Yellow solid (73.3 mg, 45%); eluent (80−90% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.36 (brs, 1H), 8.13 (m, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 8.3, 1.2 Hz, 1H), 7.27−7.13 (m, 1H), 6.49 (d, J = 7.1 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.5, 139.5, 134.7, 134.5, 130.1, 128.5, 125.1, 103.3, 100.5.

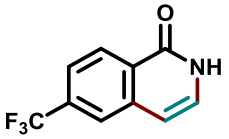
*6-Nitroisoquinolin-1(2H)-one (**3i**).*[17]



3i

Yellow solid (77.6 mg, 68%); eluent (80−90% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.65 (s, 1H), 8.62 (d, J = 2.4 Hz, 1H), 8.38 (d, J = 8.8 Hz, 1H), 8.18 (dd, J = 8.7, 2.3 Hz, 1H), 7.40−7.29 (m, 1H), 6.81 (d, J = 7.1 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 160.8, 149.7, 138.6, 131.3, 129.6, 129.0, 121.8, 119.7, 104.6.

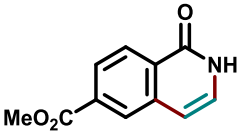
*6-(Trifluoromethyl)isoquinolin-1(2H)-one (**3j**).*[7]



3j

White solid (94.6 mg, 74%); eluent (80−85% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.50 (brs, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H), 7.72 (dd, J = 8.3, 0.8 Hz, 1H), 7.30 (d, J = 7.1 Hz, 1H), 6.70 (d, J = 7.1 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.0 (s), 138.1 (s), 132.1 (q, J = 31.7 Hz), 130.6 (s), 128.4 (s), 128.1 (s), 123.8 (q, J = 272.9 Hz), 123.5 (d, J = 3.4 Hz), 121.8 (d, J = 2.0 Hz), 104 (s); **^{19}F NMR (470 MHz, DMSO-d_6)** δ −61.5.

*Methyl 1-Oxo-1,2-dihydroisoquinoline-6-carboxylate (**3k**).*[17]



3k

Yellow solid (59.7 mg, 49%); eluent (100% ethyl acetate); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.41 (brs, 1H), 8.28 (m, 2H), 7.96 (dd, J = 8.4, 1.5 Hz, 1H), 7.24 (m, 1H), 6.70 (d, J = 7.1 Hz, 1H), 3.91 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 165.7, 161.2, 137.8, 132.7, 129.9, 128.8, 127.7, 127.3, 125.6, 104.6, 52.4.

https://doi.org/10.1021/acsomega.3c02352
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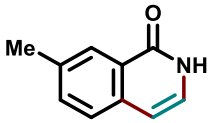
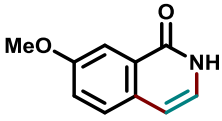
*7-Methylisoquinolin-1(2H)-one (**3l**).*[20]



3l

Yellow solid (50.6 mg, 53%); eluent (70−80% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.10 (brs, 1H), 7.99 (s, 1H), 7.51 (dt, J = 8.0, 4.8 Hz, 2H), 7.08 (d, J = 7.1 Hz, 1H), 6.49 (d, J = 7.1 Hz, 1H), 2.42 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.7, 135.7, 135.5, 133.5, 127.9, 126.1, 126.0, 104.4, 20.9 (one carbon is missing in the aromatic region due to the overlap).

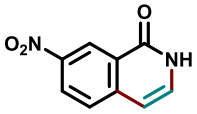
*7-Methoxyisoquinolin-1(2H)-one (**3m**).*[8]



3m

Yellow solid (44.1 mg, 42%); eluent (100% ethyl acetate); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.20 (brs, 1H), 7.66−7.51 (m, 2H), 7.31 (dd, J = 8.5, 2.8 Hz, 1H), 7.04 (d, J = 6.8 Hz, 1H), 6.51 (d, J = 7.1 Hz, 1H), 3.85 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.5, 157.9, 131.8, 128.0, 127.3, 126.4, 122.1, 107.1, 1045, 55.3.

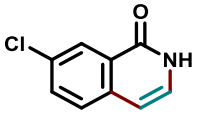
*7-Nitroisoquinolin-1(2H)-one (**3n**).*



3n

Yellow solid (77.6 mg, 68%); eluent (70−75% ethyl acetate in hexane); m.p. 220−222 °C; **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.77 (brs, 1H), 8.87 (s, 1H), 8.43 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.49−7.39 (m, 1H), 6.72 (d, J = 6.7 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.2, 145.1, 142.9, 133.5, 128.1, 126.2, 125.7, 122.7, 104.1; **HRMS (ESI)** m/z calcd. for $C_9H_7N_2O_3$ $[M + H]^+$: 191.0457, found: 191.0485.

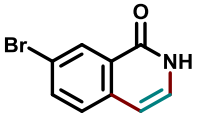
*7-Chloroisoquinolin-1(2H)-one (**3o**).*[17]



3o

White solid (65.7 mg, 61%); eluent (100% ethyl acetate); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.31 (brs, 1H), 8.12 (d, J = 1.7 Hz, 1H), 7.70 (d, J = 2.1 Hz, 2H), 7.19 (d, J = 7.1 Hz, 1H), 6.56 (d, J = 7.1 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 160.7, 136.5, 132.4, 130.8, 129.5, 128.5, 127.2, 125.6, 104.0.

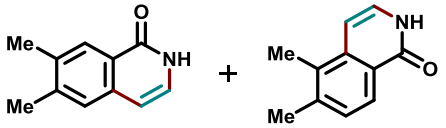
*7-Bromoisoquinolin-1(2H)-one (**3p**).*[17]



3p

Yellow solid (84.7 mg, 63%); eluent (100% ethyl acetate); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.32 (brs, 1H), 8.27 (d, J = 2.1 Hz, 1H), 7.83 (dd, J = 8.6, 2.3 Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.21 (d, J = 7.0 Hz, 1H), 6.55 (d, J = 7.2 Hz, 1H); **^{13}C NMR (125 MHz, DMSO-d_6)** δ 160.5, 136.7, 134.9, 129.5, 128.7, 128.5, 127.5, 118.8, 103.9.

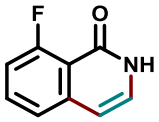
*6,7-Dimethylisoquinolin-1(2H)-one (**3q**) and 5,6-Dimethylisoquinolin-1(2H)-one (**3q'**).*[17]



3q **3q'**

White solid (46.8 mg, 45%); eluent (80−90% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.03 (s, 1H), 7.93 (s, 1H), 7.40 (s, 1H), 7.11−7.00 (m, 1H), 6.42 (d, J = 7.1 Hz, 1H), 2.34 (s, 6H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.6, 141.7, 136.0, 135.2, 127.9, 126.6, 126.2, 124.2, 104.1, 19.6, 19.4.

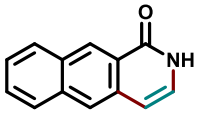
*8-Fluoroisoquinolin-1(2H)-one (**3r**).*[17]



3r

White solid (40.9 mg, 41%); eluent (80−85% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.24 (brs, 1H), 7.65 (td, J = 7.9, 4.9 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.17 (m, 2H), 6.52 (dd, J = 7.2, 2.2 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 161.6 (d, J_{C-F} = 261.1 Hz), 159.3 (d, J_{C-F} = 2.7 Hz), 140.9, 133.4 (d, J_{C-F} = 9.9 Hz), 130.2, 122.3, 114.9 (d, J_{C-F} = 5.4 Hz), 112.8 (d, J_{C-F} = 21.2 Hz), 104.0; **^{19}F NMR (470 MHz, DMSO-d_6)** δ −111.2.

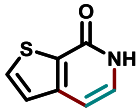
*Benzo[g]isoquinolin-1(2H)-one (**3u**).*[20]



3u

Yellow solid (64.4 mg, 55%); eluent (80−90% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.02 (brs, 1H), 8.87 (s, 1H), 8.20−8.13 (m, 2H), 8.02 (d, J = 8.4 Hz, 1H), 7.66−7.61 (m, 1H), 7.58−7.52 (m, 1H), 7.11 (dd, J = 7.2, 5.7 Hz, 1H), 6.64 (d, J = 7.2 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 162.2, 134.8, 133.8, 130.9, 129.2, 128.0, 127.8, 127.4, 125.7, 124.9, 123.9, 104.5 (one carbon is missing in the aromatic region due to the overlap).

*Thieno[2,3-c]pyridin-7(6H)-one (**3v**).*[7]



3v

Yellow solid (50.8 mg, 56%); eluent (80−90% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.47 (brs, 1H), 8.02 (d, J = 4.9 Hz, 1H), 7.37 (d, J = 4.9 Hz, 1H), 7.26 (d, J = 6.8 Hz, 1H), 6.71 (d, J = 6.9 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 158.4, 146.1, 133.6, 130.1, 129.1, 124.9, 102.0.

https://doi.org/10.1021/acsomega.3c02352
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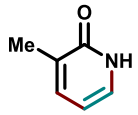
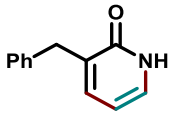
*3-Methylpyridin-2(1H)-one (**3w**).*



3w

Yellow solid (40.6 mg, 62%); eluent (80−90% ethyl acetate in hexane); m.p. 144−146 °C; **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.42 (brs, 1H), 7.29−7.25 (m, 1H), 7.19 (dd, J = 6.7, 1.6 Hz, 1H), 6.06 (t, J = 6.6 Hz, 1H), 1.96 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 162.7, 137.6, 132.3, 128.5, 104.6, 16.3; **HRMS (ESI)** m/z calcd. for C_6H_8NO $[M + H]^+$: 110.0606, found: 110.0649.

*3-Benzylpyridin-2(1H)-one (**3x**).*[21]



3x

Brown solid (72.1 mg, 65%); eluent (80−90% ethyl acetate in hexane); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.40 (brs, 1H), 7.25−7.17 (m, 5H), 7.16−7.11 (m, 2H), 6.06 (t, J = 6.6 Hz, 1H), 3.67 (s, 2H); **^{13}C NMR (125 MHz, DMSO-d_6)** δ 162.2, 140.2, 138.0, 133.1, 132.1, 128.8, 128.3, 125.9, 104.8, 35.5.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c02352.

Experimental procedure for optimization studies, mechanistic studies, characterization of isoquinolone derivatives (^{1}H, ^{13}C NMR spectra), and X-ray structures of **3d** and **3h** (PDF)

PAB_YO_515A_RT_Cu (CIF)

PAB_YO_VINYL_ACETATE_Rt_Cu (CIF)

Accession Codes

CCDC 2239457 and 2237759 contain the supporting crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/datarequest/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Author Contributions

[§]T.R., A.G., and Y.N.A. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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