JOC The Journal of Organic Chemistry

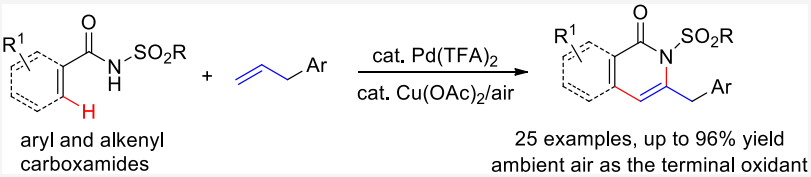
pubs.acs.org/joc Article

Palladium-Catalyzed Regioselective C−H Functionalization/Annulation Reaction of Amides and Allylbenzenes for the Synthesis of Isoquinolinones and Pyridinones

Rong Zhong, Yong Xu, Manman Sun,* and Yurong Wang*

Cite This: J. Org. Chem. 2021, 86, 5255−5264 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A regioselective C−H functionalization/annulation reaction of *N*-sulfonyl amides and allylbenzenes through a palladium-catalyzed C(sp^2)−H allylation/aminopalladation/β−H elimination/isomerization sequence has been reported. Various aryl and alkenyl carboxamides are found to be efficient substrates to construct isoquinolinones and pyridinones in up to 96% yield. Using ambient air as the terminal oxidant is another advantage regarding environmental friendliness and operational simplicity.

INTRODUCTION

The transition-metal-catalyzed C−H functionalization/annulation reaction represents one of the powerful approaches in organic synthesis,[1] as it provides a remarkable atom and step economic tool to access a variety of valuable cyclic products from easily accessible starting materials. Among the numerous unsaturated substrates for the annulation reactions, alkenes have attracted increasing interest among chemists. Impressive [n + 1] and [n + 2] annulation reactions have been made with conjugated alkenes, such as acrylates[2] and styrenes,[3] and even aliphatic alkenes.[4] However, the transition-metal-catalyzed C−H functionalization reaction with alkenes, especially with aliphatic alkenes, still suffers from poor regioselectivities,[5] such as functionalization of C_a or C_b, elimination of the β−H or C−X bond (X = C, N, O), and cleavage of the carbon−carbon double bond or the allylic C(sp^3)−H bond. Generally, the developed methods for controlling the regioselectivity of alkenes include the judicious choice of the transition-metal catalyst,[6] the ligand,[7] and the directing group.[8] Hence, the highly regioselective control of the C−H functionalization reaction with alkenes to undergo an innovative annulation process is of importance and highly desired.

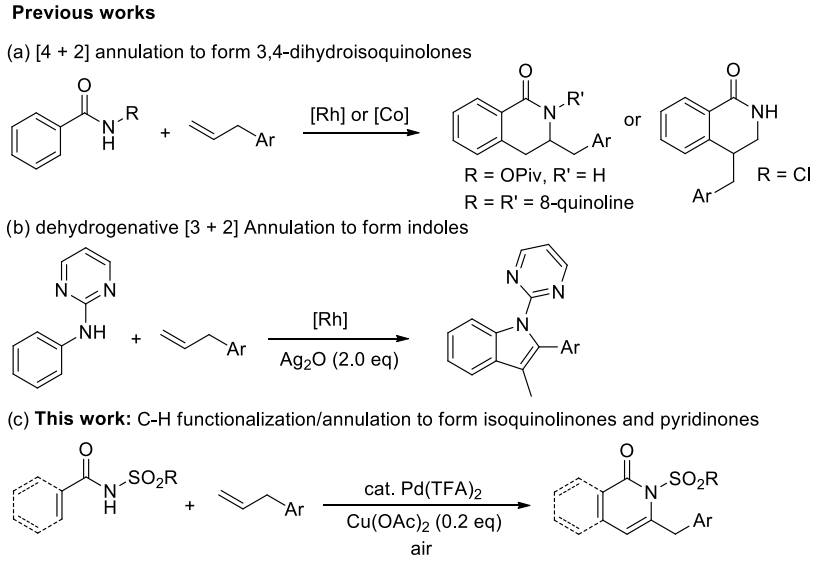
Allylbenzenes are useful starting materials employed in the directed C−H functionalization of arenes. However, most of the directed C−H functionalization of arenes with allylbenzenes generated the alkenylic[6c,9] or allylic adducts.[6d−f,8a,10] To realize the annulation process, the judicious choice of the directing group proves to be crucial. Several [4 + 2] annulations of benzamides and allylbenzenes catalyzed by rhodium or cobalt complexes have been reported for the formation of 3,4-dihydroisoquinolones,[4b,11] in which the directing group imparted sufficient stabilization to the metalacyclic intermediate formed from alkene insertion or reacted as an internal oxidant (Scheme 1a). A rhodium-catalyzed oxidative annulation of anilines and allylbenzenes has also been reported via allylic C−H activation to deliver a variety of indoles,[12] in which the directing group was thought as an efficient ligand to form the catalytically active complex in promoting C(sp^3)−H activation of allylbenzenes (Scheme 1b). Herein, we describe an innovative palladium-catalyzed C−H functionalization/annulation reaction of amides and allylbenzenes for the synthesis of isoquinolinones and pyridinones through a C(sp^2)−H allylation/aminopalladation/β−H elimination/isomerization sequence, in which the sulfonyl group in the amides plays an important role[2a,3a,13] (Scheme 1c). It should be mentioned that the reported palladium-catalyzed annulation reactions of *N*-sulfonyl amides and aliphatic alkenes favored the C(sp^2)−H alkenylation/aza-Wacker-type cyclization process to form a five-membered fused aza-heterocycle,[2a] due to the formation of a thermodynamically favored alkenylic intermediate. Hence, the highly regioselective C(sp^2)−H allylation/annulation reaction of amides and allylbenzenes to form the six-membered fused aza-heterocycle is challenging and rewarding.

Besides the distinctive C−H functionalization/annulation reaction feature, this approach provides rapid access to

Received: January 19, 2021
Published: March 22, 2021

https://doi.org/10.1021/acs.joc.1c00150
J. Org. Chem. 2021, 86, 5255−5264

Scheme 1. C−H Functionalization/Annulation Reactions with Allylbenzenes



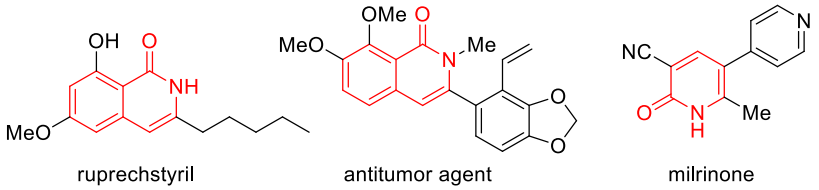


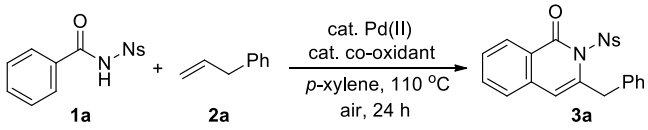
Figure 1. Examples of bioactive compounds containing the isoquinolone and the pyridinone core.

isoquinolones and pyridinones, which present as core structural scaffolds in many natural products and pharmaceuticals of biological interest (Figure 1).[14] Albeit with several well-investigated methods for the synthesis of isoquinolinones, such as the intramolecular aminocarbonylation annulation reaction,[15] the 6π-electrocyclization reaction,[16] Larock-type heteroannulation reaction,[17] and the C−H functionalization/annulation reaction of benzamides with alkynes[18] or allenes,[19] using the easily accessible alkenes as privileged synthons in the C−H functionalization/annulation reaction is still a valuable protocol. Additionally, using air as the terminal oxidant is another advantage regarding environmental friendliness and operational simplicity.

RESULTS AND DISCUSSION

Inspired by the efficient reaction conditions obtained from our previous efforts in the C−H functionalization/annulation reactions of benzamides,[13b,20] we initially selected *N*-((4-nitrophenyl)sulfonyl)benzamide **1a** and allylbenzene **2a** as the model substrates to react with 10 mol % $Pd(TFA)_2$ and 20 mol % $Cu(OAc)_2$ in *p*-xylene at 110 °C under air (Table 1). To our delight, the desired product **3a** was obtained in 88% yield after 24 h (entry 1). Switching the catalyst to $PdCl_2$ and $Pd(OAc)_2$, both the yields decreased (entries 2 and 3). Adding the DMSO, Ac-Gly-OH, or 1,10-phenanthroline ligand to the reaction also did not improve the yield (entries 4−6). Further, 1,10-phenanthroline proved to not be a suitable ligand for this C−H functionalization/annulation reaction, which favored another tandem process of C−H olefination/aza-Wackertype cyclization to form a five-membered fused aza-heterocycle.[2a] No desired product **3a** was detected in the absence of a catalyst (entry 7). Then, other co-oxidants such as Ag_2CO_3, BQ, $K_2S_2O_8$, and $PhI(OAc)_2$ were examined. Diminished yields or the trace product indicated that $Cu(OAc)_2$ was most effective (entries 8−11). Decreasing the amount of $Cu(OAc)_2$ to 10 mol % decreased the yield to 64% (entry 12). Omitting $Cu(OAc)_2$ and reacting with an O_2 balloon led to a sharp decrease of the yield to 34% (entry 13). Reducing the

Table 1. Screening of Reaction Conditions[a]



1a 2a 3a

entry	catalyst	co-oxidant	yield (%)[b]
1	$Pd(TFA)_2$	$Cu(OAc)_2$	88%
2	$PdCl_2$	$Cu(OAc)_2$	55%
3	$Pd(OAc)_2$	$Cu(OAc)_2$	50%
4	$Pd(TFA)_2$/DMSO	$Cu(OAc)_2$	76%
5	$Pd(TFA)_2$/Ac-Gly-OH	$Cu(OAc)_2$	87%
6	$Pd(TFA)_2$/1,10-phenanthroline	$Cu(OAc)_2$	15%
7		$Cu(OAc)_2$	
8	$Pd(TFA)_2$	Ag_2CO_3	52%
9	$Pd(TFA)_2$	BQ	26%
10	$Pd(TFA)_2$	$K_2S_2O_8$	trace
11	$Pd(TFA)_2$	$PhI(OAc)_2$	trace
12[c]	$Pd(TFA)_2$	$Cu(OAc)_2$	64%
13[d]	$Pd(TFA)_2$	O_2	34%
14[e]	$Pd(TFA)_2$	$Cu(OAc)_2$	73%

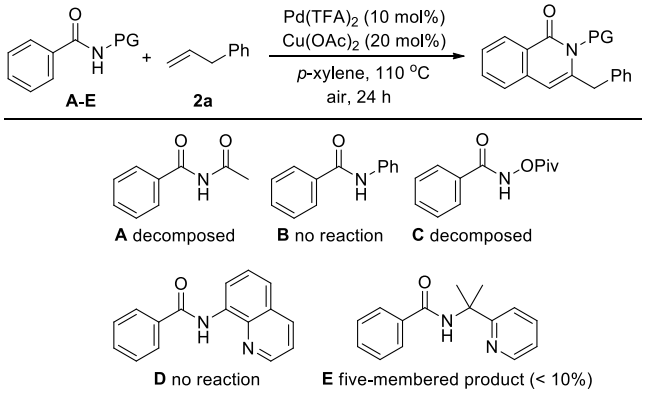
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.02 mmol), co-oxidant (0.04 mmol), and *p*-xylene (2 mL) at 110 °C under air for 24 h. [b]Isolated yield. [c]$Cu(OAc)_2$ (0.02 mmol) was used. [d]With an O_2 balloon. [e]At 100 °C.

https://doi.org/10.1021/acs.joc.1c00150
J. Org. Chem. 2021, 86, 5255−5264

temperature to 100 °C decreased the yield to 73% (entry 14). Eventually, the optimal conditions of C−H functionalization annulation with allylbenzenes were established as using $Pd(TFA)_2$ (10 mol %) as the catalyst and $Cu(OAc)_2$ (20 mol %) as the co-oxidant in *p*-xylene at 110 °C under air for 24 h.

To evaluate the influence of the directing groups, benzamides protected by the Ac, Ph, or OPiv group (**A**−**C**) were conducted in the C−H functionalization/annulation reaction under the optimal reaction conditions (Scheme 2).

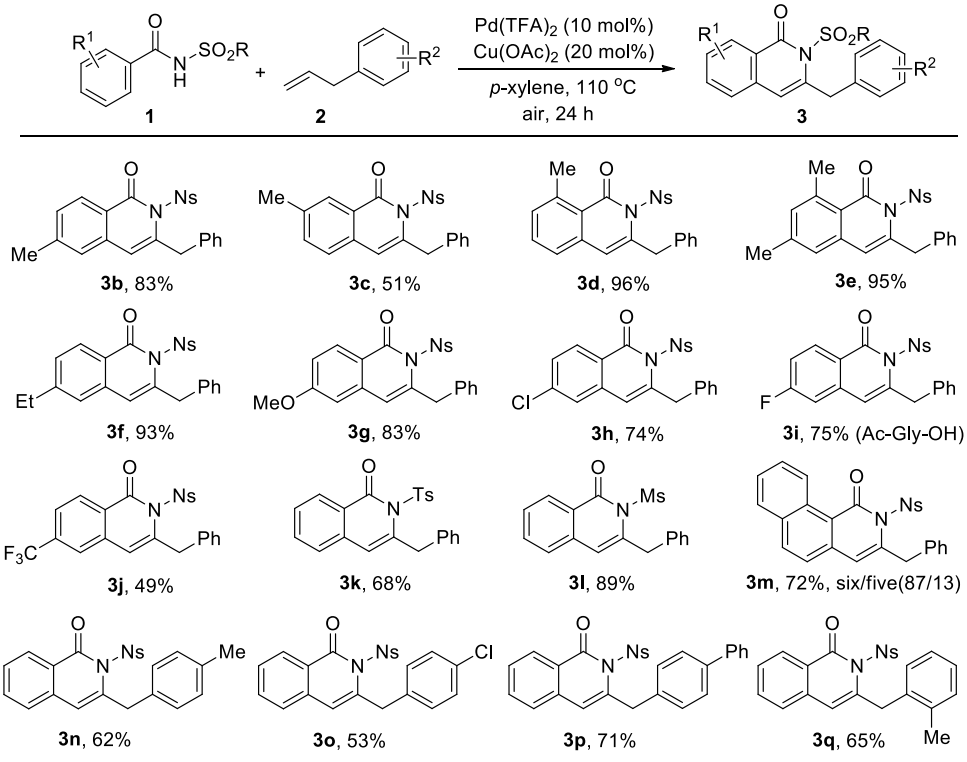
Scheme 2. Evaluation of Directing Groups



Unfortunately, these benzamides failed to generate the desired products, and they decomposed (**A** and **C**) or remained intact (**B**). Benzamides bearing 8-aminoquinoline[21] (**D**) and 2-pyridinylisopropyl[22] (**E**) directing groups have also been examined, delivering unreacted starting materials and a small amount of a five-membered byproduct through the tandem process of C−H olefination/aza-Wackertype cyclization.[2a] These results suggested that the sulfonyl group in the amides plays an important role.

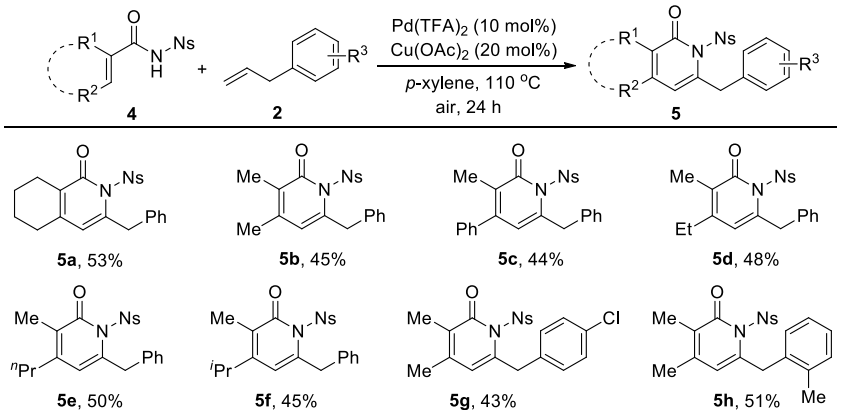
With the optimized reaction conditions in hand, the scope of the C−H functionalization/annulation reaction was investigated, as depicted in Scheme 3. Both electron-donating and electron-withdrawing substituents on the phenyl ring of benzamides were well tolerated, achieving the desired products **3b**−**3j** in moderate to excellent yields. Among them, electron-rich benzamides performed better than electron-deficient benzamides (cf. **3b**, **3f**, **3g** vs **3h**−**3j**). The product **3i** was obtained in 75% yield with the help of the 20 mol % Ac-Gly-OH ligand. The meta-substituted benzamide exhibited moderate reactivity to take place at the less sterically hindered position, giving product **3c** in 51% yield. Gratifyingly, the ortho-substituted benzamides functioned excellently, and products **3d** and **3e** were formed, respectively, in 96 and 95% yields. Switching the N-protecting group to Ts or Ms did not retard the annulation reaction, delivering the product **3k** and **3l** in yields of 68 and 89%, respectively. Then, other *N*-sulfonyl aryl carboxamides were examined. *N*-((4-Nitrophenyl)sulfonyl)-1-naphthamide worked well under the standard reaction conditions to synthesize the desired product **3m** in 72% yield, while a small amount of a five-membered byproduct was formed.[2a] *N*-Sulfonyl heteroaryl carboxamides such as benzofuran-2-carboxamide and furan-2-carboxamide were not compatible with this annulation reaction (see the Supporting Information). Subsequently, the variations of allylbenzenes were explored. Both electron-donating and electron-withdrawing substituted allylbenzenes reacted smoothly to afford the desired products **3n**−**3q** in moderate yields. The internal allylbenzene such as but-2-en-1-ylbenzene failed to generate any product with *N*-((4-nitrophenyl)-sulfonyl)benzamide **1a**. When an aliphatic alkene such as 1-decene was applied as the substrate, the annulation reaction

Scheme 3. Scope of *N*-Sulfonyl Benzamides and Allylbenzenes

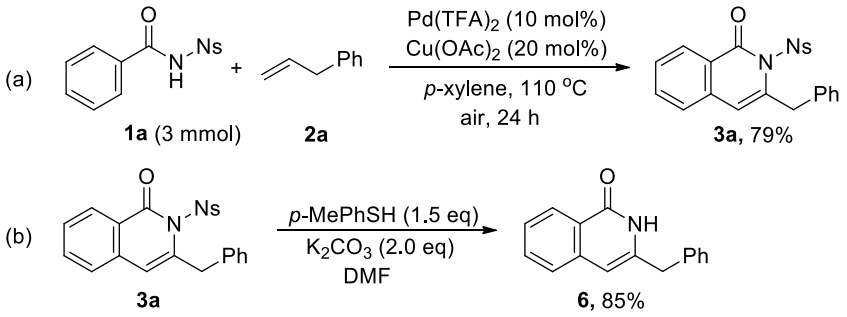


https://doi.org/10.1021/acs.joc.1c00150
J. Org. Chem. 2021, 86, 5255−5264

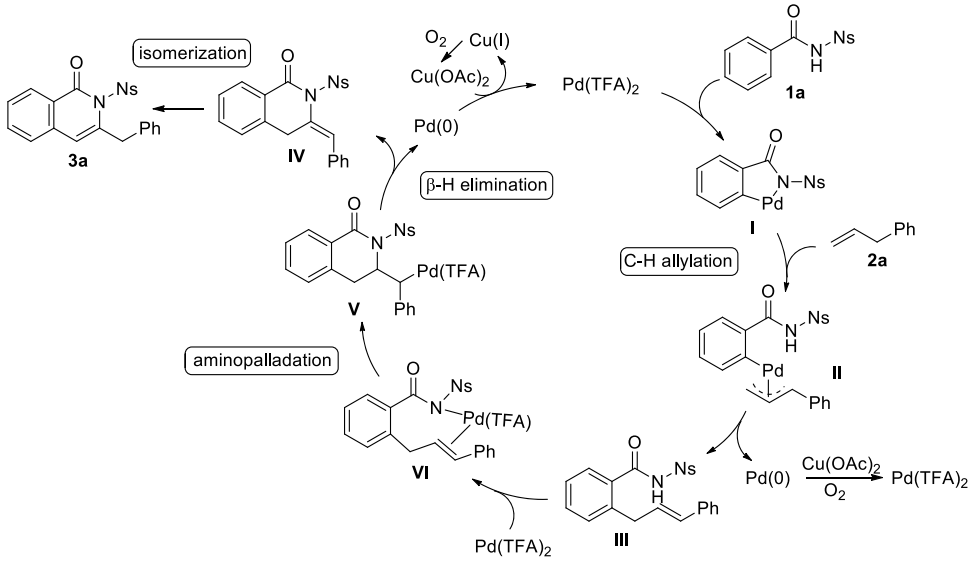
Scheme 4. Scope of Alkenyl Carboxamides



Scheme 5. Gram-Scale Synthesis and Synthetic Transformation



Scheme 6. Proposed Plausible Mechanism



became messy, which did not yield the desired product (see the Supporting Information).

We eventually turned our attention to different alkenyl carboxamides[4c,20b,23] to synthesize pyridinones (Scheme 4). Cyclohex-1-enecarboxamide and α,β-disubstituted acrylamides engaged well in this annulation reaction under the standard reaction conditions to furnish the desired products **5a**−**5f** in 44−53% yields. β-Substituted acrylamides, such as cinnamamide, α-substituted acrylamides, such as α-phenylacrylamide and α-benzylacrylamide, and dihydropyrancarboxamides were unsuitable substrates for this annulation reaction with intact starting materials or undesired products (see the Supporting Information). These results suggest that the conformation maintained by α-substitution and β-substitution in starting materials is essential for this C−H functionalization/annulation reaction. Substituted allylbenzenes were further investigated with 2-methylbut-2-enamide, achieving the corresponding products **5g** and **5h** in moderate yields.

To further showcase the synthetic feasibility of this methodology, a gram-scale annulation reaction of substrates **1a** and **2a** was conducted under optimized reaction conditions. Gratifyingly, the desired product **3a** was isolated in 79% yield

https://doi.org/10.1021/acs.joc.1c00150
J. Org. Chem. 2021, 86, 5255−5264

(Scheme 5a). Furthermore, the N-protecting group could be smoothly removed by treatment with *p*-MePhSH and K_2CO_3 in DMF, giving the product **6** in 85% yield (Scheme 5b).[24]

Based on all of the abovementioned results and by analogy with previously reported processes,[2a,13b,25] we proposed a plausible mechanism as depicted in Scheme 6 using **1a** and **2a** as the model substrates. Initially, C(sp^2)−H activation was initiated via the deprotonation of the acid N−H bond to form a N−Pd bond, which was followed by a palladation process to furnish a five-membered palladacycle **I**. Then, after coordination of allylbenzene **2a** to palladacycle **I**, the tandem removal of an allylic hydrogen (**II**) and reductive elimination of a C−C bond process delivered the C(sp^2)−H allylation intermediate **III** and Pd(0) species.[10a,b,13b] Subsequently, another N−Pd bond (**VI**) was formed by the deprotonation of the acid N−H bond in intermediate **III**. Aminopalladation of the carbon−carbon double bond (**V**) followed by *β*−H elimination (**IV**)[2b,3a,26] and isomerization resulted in formation of the desired product **3a**.[27] Finally, the regenerated Pd(0) species was oxidized to a Pd(II) catalyst by $Cu(OAc)_2$ and O_2 in the air to participate in the next cycle.

CONCLUSIONS

In summary, we have developed a highly regioselective C−H functionalization/annulation reaction of *N*-sulfonyl amides with allylbenzenes through a palladium-catalyzed C(sp^2)−H allylation/aminopalladation/*β*−H elimination/isomerization sequence. The innovative annulation reaction delivers a valuable protocol for biologically important isoquinolinones and pyridinones from the easily accessible alkenes. Using ambient air as the terminal oxidant is another advantage regarding environmental friendliness and operational simplicity.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer, and tetramethylsilane (TMS) or $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR) was used as a reference. Data for ^{1}H were reported as follows: chemical shift (ppm) and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad singlet). Data for ^{13}C NMR were reported as ppm. A high-resolution mass spectra analysis was performed on a Waters SYNAPT G2-Si mass spectrometer. Melting points were determined using a X-4 digital micromelting point apparatus. Thin-layer chromatography (TLC) was performed, and visualization of the compounds was accomplished with UV light (254 nm). Flash column chromatography was performed on silica gel (200−300 mesh). Amides **1** and **4a**−**4c** were prepared according to the known literature.[13b] Allylbenzene **2a** was purchased from commercial sources. Substituted allylbenzenes were prepared according to the known literature.[10a] Purchased reagents and solvents were used without further purification.

General Procedure for the Synthesis of Alkenyl Carboxamides 4. To a suspension solution of the corresponding acid (6 mmol, 1.0 equiv) in CH_2Cl_2 (80 mL) was added DMF (11 mg, 0.15 mmol, 2.5 mol %) at 0 °C. Oxalyl chloride (1.08 mL, 12 mmol, 2.0 equiv) was subsequently added dropwise using a syringe. The reaction was allowed to warm to room temperature gradually and stirred for another 3 h. Then, the reaction mixture was evaporated to afford the acid chloride, which was used without any further purification. To a round-bottom flask under N_2 was added 4-nitrobenzenesulfonamide (1.01 g, 5 mmol, 1.0 equiv), DMAP (61 mg, 0.5 mmol, 10 mol %), Et_3N (1.7 mL, 12.5 mmol, 2.5 equiv), and EtOAc (10 mL). The abovementioned acid chloride was then added at 0 °C for over 15 min. The mixture was stirred for 1 h in an oil bath at 55 °C under N_2, cooled to room temperature, and quenched with HCl (1 N, 20 mL). The resulting mixture was then extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to obtain the pure product **4**.

(E)-2-Methyl-N-((4-nitrophenyl)sulfonyl)pent-2-enamide ***(4d)***. White solid; 1.1 g; 74% yield; R_f = 0.58 (hexane/EtOAc = 1/1 as the eluent); mp = 88−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.96 (br, 1H), 8.38 (d, *J* = 8.9 Hz, 2H), 8.30 (d, *J* = 9.0 Hz, 2H), 6.50 (t, *J* = 6.8 Hz, 1H), 2.22−2.14 (m, 2H), 1.77 (s, 3H), 1.02 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ* 167.0, 150.7, 144.2, 144.1, 130.1, 128.6, 124.1, 22.3, 12.8, 12.0; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na]^+$ ($C_{12}H_{14}N_2O_5SNa$) 321.0521, found 321.0520.

(E)-2-Methyl-N-((4-nitrophenyl)sulfonyl)hex-2-enamide ***(4e)***. White solid; 1.2 g; 79% yield; R_f = 0.49 (hexane/EtOAc = 1/1 as the eluent); mp = 77−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.69 (br, 1H), 8.40 (d, *J* = 9.0 Hz, 2H), 8.32 (d, *J* = 8.9 Hz, 2H), 6.51 (t, *J* = 6.8 Hz, 1H), 2.16 (q, *J* = 7.3 Hz, 2H), 1.79 (s, 3H), 1.50−1.41 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ* 165.7, 150.8, 144.1, 142.8, 130.1, 129.2, 124.1, 30.9, 21.7, 13.9, 12.2; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na]^+$ ($C_{13}H_{16}N_2O_5SNa$) 335.0678, found 335.0671.

(E)-2,4-Dimethyl-N-((4-nitrophenyl)sulfonyl)pent-2-enamide ***(4f)***. White solid; 1.1 g; 71% yield; R_f = 0.55 (hexane/EtOAc = 1/1 as the eluent); mp = 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.01 (br, 1H), 8.38 (d, *J* = 8.9 Hz, 2H), 8.31 (d, *J* = 8.9 Hz, 2H), 6.33 (d, *J* = 9.5 Hz, 1H), 2.65−2.56 (m, 1H), 1.78 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ* 166.3, 150.8, 149.3, 144.1, 130.1, 126.9, 124.2, 28.3, 21.7, 12.0; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na]^+$ ($C_{13}H_{16}N_2O_5SNa$) 335.0678, found 335.0674.

General Procedure for the Synthesis of Compounds 3 and 5. An oven-dried Schlenk tube equipped with a Teflon valve was charged with a magnetic stir bar, substrate **1** or **4** (0.2 mmol, 1.0 equiv), $Pd(TFA)_2$ (6.6 mg, 0.02 mmol, 10 mol %), $Cu(OAc)_2$ (7.3 mg, 0.04 mmol, 20 mol %), and *p*-xylene (2 mL). Allylbenzene **2** (0.4 mmol, 2.0 equiv) was added. The reaction mixture was stirred in an oil bath at 110 °C for 24 h under air. Then, the resulting suspension was cooled to room temperature, filtered through a pad of filter paper, and washed with ethyl acetate (50 mL). After evaporating the solvent under reduced pressure, the residue was purified by column chromatography on silica gel to give the pure product **3** or **5**.

3-Benzyl-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one ***(3a)***. Light yellow solid; 73.9 mg; 88% yield; R_f = 0.44 (hexane/EtOAc = 5/1 as the eluent); mp = 193−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.42−8.36 (m, 4H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.45−7.40 (m, 2H), 7.37−7.31 (m, 4H), 7.16 (d, *J* = 7.7 Hz, 1H), 6.82 (s, 1H), 4.00 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ* 163.1, 150.6, 145.3, 137.9, 134.3, 134.1, 130.4, 130.3, 130.0, 129.0, 128.7, 128.1, 128.0, 127.7, 127.2, 126.8, 124.1, 32.1; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na]^+$ ($C_{22}H_{16}N_2O_5SNa$) 443.0678, found 443.0676.

3-Benzyl-6-methyl-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one ***(3b)***. Light yellow solid; 71.8 mg; 83% yield; R_f = 0.44 (hexane/EtOAc = 5/1 as the eluent); mp = 208−209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.41−8.35 (m, 4H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.38−7.31 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 6.80 (s, 1H), 3.96 (s, 2H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ* 163.2, 150.5, 145.6, 145.4, 137.9, 134.1, 130.7, 130.3, 129.4, 129.0, 128.7, 128.6, 128.0, 127.8, 127.7, 124.2, 124.1, 32.0, 21.7; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na]^+$ ($C_{23}H_{18}N_2O_5SNa$) 457.0834, found 457.0837.

3-Benzyl-7-methyl-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one ***(3c)***. Light yellow solid; 44.3 mg; 51% yield; R_f = 0.46 (hexane/EtOAc = 5/1 as the eluent); mp = 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.41−8.35 (m, 4H), 7.76 (s, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.37−7.32 (m, 3H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.81 (s, 1H), 3.96 (s, 2H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ* 163.3, 150.5, 145.3, 137.7, 135.2, 135.0, 134.1, 130.6, 130.3, 129.5, 129.0, 128.7, 128.0, 127.8, 127.1, 126.5, 124.1, 31.7,

https://doi.org/10.1021/acs.joc.1c00150
J. Org. Chem. 2021, 86, 5255−5264

21.0; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{23}H_{18}N_2O_5SNa$) 457.0834, found 457.0839.

*3-Benzyl-8-methyl-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one (**3d**).* Light yellow solid; 83.3 mg; 96% yield; R_f = 0.48 (hexane/EtOAc = 5/1 as the eluent); mp = 189−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40−8.33 (m, 4H), 7.41 (t, J = 7.3 Hz, 2H), 7.35−7.29 (m, 4H), 7.12 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 7.4 Hz, 1H), 6.83 (s, 1H), 3.92 (s, 2H), 2.58 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.5, 150.5, 145.6, 143.0, 138.7, 134.3, 133.1, 131.4, 130.22, 130.20, 129.0, 128.7, 128.0, 127.9, 125.4, 124.9, 124.1, 33.2, 22.1; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{23}H_{18}N_2O_5SNa$) 457.0834, found 457.0832.

*3-Benzyl-6,8-dimethyl-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one (**3e**).* Light yellow solid; 85.1 mg; 95% yield; R_f = 0.49 (hexane/EtOAc = 5/1 as the eluent); mp = 175−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39−8.32 (m, 4H), 7.41 (t, J = 7.4 Hz, 2H), 7.36−7.31 (m, 3H), 6.93 (s, 1H), 6.81 (s, 1H), 6.79 (s, 1H), 3.89 (s, 2H), 2.53 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.5, 150.4, 145.7, 144.1, 143.0, 138.8, 134.4, 132.2, 130.4, 130.1, 129.0, 128.7, 127.9, 127.7, 125.6, 124.0, 122.6, 33.1, 22.0, 21.4; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{24}H_{20}N_2O_5SNa$) 471.0991, found 471.0985.

*3-Benzyl-6-ethyl-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one (**3f**).* Light yellow solid; 83.3 mg; 93% yield; R_f = 0.45 (hexane/EtOAc = 5/1 as the eluent); mp = 176−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41−8.35 (m, 4H), 7.87 (d, J = 8.1 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 7.37−7.32 (m, 3H), 7.15 (d, J = 8.1 Hz, 1H), 6.97 (s, 1H), 6.80 (s, 1H), 3.98 (s, 2H), 2.63 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.1, 151.7, 150.5, 145.4, 138.0, 134.2, 130.6, 130.3, 129.5, 129.1, 128.7, 128.0, 127.8, 127.5, 126.6, 124.3, 124.1, 32.1, 29.0, 15.0; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{24}H_{20}N_2O_5SNa$) 471.0991, found 471.0986.

*3-Benzyl-6-methoxy-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one (**3g**).* Light yellow solid; 74.7 mg; 83% yield; R_f = 0.47 (hexane/EtOAc = 3/1 as the eluent); mp = 190−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40−8.35 (m, 4H), 7.90 (d, J = 8.8 Hz, 1H), 7.42 (t, J = 7.4 Hz, 2H), 7.36−7.32 (m, 3H), 6.88−6.74 (m, 2H), 6.61 (s, 1H), 3.97 (s, 2H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.3, 162.8, 150.5, 145.6, 140.3, 134.2, 131.7, 130.6, 130.2, 129.0, 128.7, 128.0, 127.7, 124.1, 119.3, 113.8, 111.8, 55.6, 32.4; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{23}H_{18}N_2O_6SNa$) 473.0783, found 473.0774.

*3-Benzyl-6-chloro-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one (**3h**).* Light yellow solid; 67.2 mg; 74% yield; R_f = 0.45 (hexane/EtOAc = 5/1 as the eluent); mp = 216−217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43−8.35 (m, 4H), 7.90 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 7.37 (d, J = 7.1 Hz, 1H), 7.34−7.28 (m, 3H), 7.17 (s, 1H), 6.83 (s, 1H), 3.97 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.3, 150.6, 145.1, 140.8, 139.6, 133.8, 130.9, 130.4, 129.7, 129.0, 128.8, 128.5, 128.3, 128.2, 127.3, 125.3, 124.1, 31.9; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{22}H_{15}ClN_2O_5SNa$) 477.0288, found 477.0281.

*3-Benzyl-6-fluoro-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one (**3i**).* Light yellow solid; 65.7 mg; 75% yield; R_f = 0.42 (hexane/EtOAc = 5/1 as the eluent); mp = 193−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44−8.33 (m, 4H), 7.99 (dd, J = 8.8, 5.6 Hz, 1H), 7.43 (t, J = 7.3 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 7.4 Hz, 2H), 7.02 (td, J = 8.5, 2.5 Hz, 1H), 6.86 (dd, J = 8.5, 2.4 Hz, 1H), 6.83 (s, 1H), 3.99 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.05−102.11 (m, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 166.0 (C−F, $^1J_{C-F}$ = 258.0 Hz), 162.2, 150.6, 145.2, 141.0 (C−F, $^3J_{C-F}$ = 9.2 Hz), 133.8, 132.4 (C−F, $^3J_{C-F}$ = 10.2 Hz), 130.3, 129.8, 129.0, 128.9, 128.4, 128.3, 124.1, 123.2 (C−F, $^4J_{C-F}$ = 2.8 Hz), 115.4 (C−F, $^2J_{C-F}$ = 22.3 Hz), 114.2 (C−F, $^2J_{C-F}$ = 22.6 Hz), 32.1; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{22}H_{15}FN_2O_5SNa$) 461.0583, found 461.0582.

*3-Benzyl-2-((4-nitrophenyl)sulfonyl)-6-(trifluoromethyl)-isoquinolin-1(2H)-one (**3j**).* Light yellow solid; 47.8 mg; 49% yield; R_f = 0.48 (hexane/EtOAc = 5/1 as the eluent); mp = 174−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45−8.36 (m, 4H), 8.10 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.47−7.43 (m, 3H), 7.37 (t, J = 7.2 Hz, 1H), 7.33 (d, J = 7.3 Hz, 2H), 6.87 (s, 1H), 4.07 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.34 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.9, 150.7, 144.9, 138.7, 135.5 (C−F, $^2J_{C-F}$ = 33.0 Hz), 133.7, 130.4, 130.1, 129.9, 129.3, 129.0, 128.9, 128.9, 128.4, 124.6 (C−F, $^3J_{C-F}$ = 3.6 Hz), 124.3 (C−F, $^3J_{C-F}$ = 3.7 Hz), 124.2, 123.1 (C−F, $^1J_{C-F}$ = 271.7 Hz), 31.9; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{23}H_{15}F_3N_2O_5SNa$) 511.0551, found 511.0548.

*3-Benzyl-2-tosylisoquinolin-1(2H)-one (**3k**).* Light yellow solid; 53.0 mg; 68% yield; R_f = 0.56 (hexane/EtOAc = 5/1 as the eluent); mp = 179−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 7.0 Hz, 1H), 7.46−7.38 (m, 3H), 7.36−7.29 (m, 6H), 7.12 (d, J = 7.6 Hz, 1H), 6.84 (s, 1H), 3.96 (s, 2H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.9, 143.8, 136.9, 135.7, 133.5, 132.7, 123.0, 128.5, 128.2, 128.0, 127.9, 127.5, 126.7, 126.4, 126.3, 125.9, 31.0, 20.6; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{23}H_{19}NO_3SNa$) 412.0983, found 412.0981.

*3-Benzyl-2-(methylsulfonyl)isoquinolin-1(2H)-one (**3l**).* White solid; 55.9 mg; 89% yield; R_f = 0.48 (hexane/EtOAc = 3/1 as the eluent); mp = 159−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 8.7 Hz, 1H), 7.43−7.37 (m, 3H), 7.34−7.27 (m, 3H), 7.17 (d, J = 7.6 Hz, 1H), 6.67 (s, 1H), 3.98 (s, 2H), 3.63 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.3, 138.2, 134.3, 134.1, 130.5, 129.4, 129.0, 128.6, 127.8, 127.6, 127.2, 126.8, 44.1, 32.1; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{17}H_{15}NO_3SNa$) 336.0670, found 336.0674.

*3-Benzyl-2-((4-nitrophenyl)sulfonyl)benzo[h]isoquinolin-1(2H)-one (**3m**).* Light yellow solid; 67.7 mg; 72% yield; R_f = 0.40 (hexane/EtOAc = 5/1 as the eluent); mp = 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, J = 8.9 Hz, 1H), 8.40−8.36 (m, 4H), 7.93 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.63−7.58 (m, 1H), 7.49 (t, J = 7.1 Hz, 1H), 7.45−7.40 (m, 2H), 7.38−7.33 (m, 3H), 7.21 (d, J = 8.4 Hz, 1H), 6.92 (s, 1H), 4.11 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.5, 150.5, 145.6, 139.5, 135.3, 134.2, 133.1, 131.5, 130.3, 129.4, 129.1, 129.0, 128.8, 128.6, 128.5, 128.1, 126.6, 125.9, 124.4, 124.1, 121.8, 33.6; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{26}H_{18}N_2O_5SNa$) 493.0834, found 493.0841.

*3-(4-Methylbenzyl)-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one (**3n**).* Light yellow solid; 53.8 mg; 62% yield; R_f = 0.44 (hexane/EtOAc = 5/1 as the eluent); mp = 201−202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43−8.34 (m, 4H), 7.96 (dd, J = 7.9, 1.4 Hz, 1H), 7.48 (td, J = 7.5, 1.5 Hz, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.25−7.20 (m, 4H), 7.15 (d, J = 7.5 Hz, 1H), 6.78 (s, 1H), 4.01 (s, 2H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.2, 150.5, 145.4, 138.1, 134.3, 131.1, 130.3, 129.8, 129.4, 129.4, 129.0, 128.1, 127.7, 127.2, 126.9, 124.1, 32.1, 21.3; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{23}H_{18}N_2O_5SNa$) 457.0834, found 457.0829.

*3-(4-Chlorobenzyl)-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one (**3o**).* Light yellow solid; 48.1 mg; 53% yield; R_f = 0.45 (hexane/EtOAc = 5/1 as the eluent); mp = 205−206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44−8.34 (m, 4H), 7.96 (d, J = 7.8 Hz, 1H), 7.50 (t, J = 7.1 Hz, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 6.9 Hz, 2H), 7.16 (d, J = 7.7 Hz, 1H), 6.77 (s, 1H), 3.97 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.0, 150.6, 145.1, 137.6, 134.5, 134.1, 132.5, 130.9, 130.4, 130.3, 129.4, 129.0, 127.9, 127.2, 126.74, 126.71, 124.1, 32.0; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{22}H_{15}ClN_2O_5SNa$) 477.0288, found 477.0288.

*3-([1,1′-Biphenyl]-4-ylmethyl)-2-((4-nitrophenyl)sulfonyl)-isoquinolin-1(2H)-one (**3p**).* Light yellow solid; 70.4 mg; 71% yield; R_f = 0.45 (hexane/EtOAc = 5/1 as the eluent); mp = 155−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42−8.37 (m, 4H), 7.98 (d, J = 7.2 Hz, 1H), 7.68−7.61 (m, 4H), 7.51−7.46 (m, 3H), 7.43−7.39 (m, 3H), 7.34 (t, J = 7.8 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 6.85 (s, 1H), 4.06 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.1, 150.6, 145.3, 140.9, 140.3, 137.9, 134.3, 133.0, 130.40, 130.35, 129.5, 129.0, 128.9, 127.8, 127.69, 127.65, 127.4, 127.2, 127.0, 126.8, 124.1, 32.2; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{28}H_{20}N_2O_5SNa$) 519.0991, found 519.0997.

*3-(2-Methylbenzyl)-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one (**3q**).* Light yellow solid; 56.4 mg; 65% yield; R_f = 0.48 (hexane/

https://doi.org/10.1021/acs.joc.1c00150
J. Org. Chem. 2021, 86, 5255−5264

EtOAc = 5/1 as the eluent); mp = 168−169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41−8.36 (m, 4H), 7.98 (d, J = 7.1 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.28−7.22 (m, 3H), 7.18 (d, J = 7.1 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 6.81 (s, 1H), 3.81 (s, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.3, 150.8, 145.3, 138.1, 137.3, 134.33, 133.27, 130.7, 130.32, 130.31, 129.5, 129.0, 128.4, 127.7, 127.1, 127.0, 125.9, 124.1, 32.3, 20.1; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{23}H_{18}N_2O_5SNa$) 457.0834, found 457.0838.

3-Benzyl-2-((4-nitrophenyl)sulfonyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**5a**). Light yellow solid; 44.9 mg; 53% yield; R_f = 0.43 (hexane/EtOAc = 5/1 as the eluent); mp = 177−178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.3 Hz, 2H), 8.32 (d, J = 8.6 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.34−7.28 (m, 3H), 6.66 (s, 1H), 3.34 (s, 2H), 2.23−2.07 (m, 4H), 1.65−1.58 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.8, 151.2, 150.4, 145.8, 134.1, 130.1, 129.8, 129.1, 128.6, 127.9, 126.4, 126.0, 124.1, 34.0, 30.4, 22.7, 21.6, 21.5; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{22}H_{20}N_2O_5SNa$) 447.0991, found 447.0999.

6-Benzyl-3,4-dimethyl-1-((4-nitrophenyl)sulfonyl)pyridin-2(1H)-one (**5b**). Light yellow solid; 35.8 mg; 45% yield; R_f = 0.46 (hexane/EtOAc = 5/1 as the eluent); mp = 190−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 9.0 Hz, 2H), 8.31 (d, J = 8.9 Hz, 2H), 7.41 (t, J = 7.3 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.29 (d, J = 7.0 Hz, 2H), 6.68 (s, 1H), 3.41 (s, 2H), 1.86 (s, 3H), 1.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.0, 150.4, 149.1, 145.7, 134.0, 130.1, 129.5, 129.1, 128.6, 127.9, 126.4, 124.4, 124.0, 35.2, 20.3, 11.8; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{20}H_{18}N_2O_5SNa$) 421.0834, found 421.0838.

6-Benzyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-4-phenylpyridin-2(1H)-one (**5c**). Yellow solid; 40.5 mg; 44% yield; R_f = 0.46 (hexane/EtOAc = 5/1 as the eluent); mp = 166−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44−8.37 (m, 4H), 7.41−7.29 (m, 8H), 7.11−7.06 (m, 2H), 6.76 (s, 1H), 3.72 (s, 2H), 1.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.6, 150.5, 150.3, 145.6, 138.0, 133.9, 130.2, 129.6, 129.0, 128.9, 128.7, 128.7, 129.0, 127.4, 126.8, 125.7, 124.1, 35.3, 13.6; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{25}H_{20}N_2O_5SNa$) 483.0991, found 483.0991.

6-Benzyl-4-ethyl-3-methyl-1-((4-nitrophenyl)sulfonyl)pyridin-2(1H)-one (**5d**). Light yellow solid; 39.6 mg; 48% yield; R_f = 0.45 (hexane/EtOAc = 5/1 as the eluent); mp = 141−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 9.0 Hz, 2H), 8.32 (d, J = 8.9 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.29 (d, J = 7.4 Hz, 2H), 6.68 (s, 1H), 3.39 (s, 2H), 2.20 (q, J = 7.6 Hz, 2H), 1.76 (s, 3H), 0.97 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.4, 154.2, 150.4, 145.7, 134.1, 130.1, 130.0, 129.0, 128.7, 127.9, 126.3, 124.1, 123.7, 32.8, 27.1, 11.44, 11.38; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{21}H_{20}N_2O_5SNa$) 435.0991, found 435.0995.

6-Benzyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-4-propylpyridin-2(1H)-one (**5e**). Light yellow solid; 42.6 mg; 50% yield; R_f = 0.54 (hexane/EtOAc = 5/1 as the eluent); mp = 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 9.0 Hz, 2H), 8.32 (d, J = 8.9 Hz, 2H), 7.43−7.38 (m, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 7.1 Hz, 2H), 6.68 (s, 1H), 3.37 (s, 2H), 2.16 (t, J = 7.8 Hz, 2H), 1.76 (s, 3H), 1.42−1.33 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.4, 152.8, 150.4, 145.7, 134.1, 130.1, 129.9, 129.0, 128.7, 127.9, 126.3, 124.4, 124.1, 35.8, 33.3, 20.5, 13.9, 11.7; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{22}H_{22}N_2O_5SNa$) 449.1147, found 449.1153.

6-Benzyl-4-isopropyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-pyridin-2(1H)-one (**5f**). Light yellow solid; 38.3 mg; 45% yield; R_f = 0.57 (hexane/EtOAc = 5/1 as the eluent); mp = 173−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.9 Hz, 2H), 8.32 (d, J = 9.0 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 7.1 Hz, 2H), 6.68 (s, 1H), 3.28 (s, 2H), 2.93−2.86 (m, 1H), 1.78 (s, 3H), 0.92 (d, J = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.7, 157.4, 150.4, 145.8, 134.2, 130.4, 130.1, 128.8, 128.7, 127.8, 126.2, 124.1, 122.9, 30.7, 27.9, 19.5, 11.3; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{22}H_{22}N_2O_5SNa$) 449.1147, found 449.1149.

6-(4-Chlorobenzyl)-3,4-dimethyl-1-((4-nitrophenyl)sulfonyl)-pyridin-2(1H)-one (**5g**). Light yellow solid; 37.2 mg; 43% yield; R_f = 0.43 (hexane/EtOAc = 5/1 as the eluent); mp = 167−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.8 Hz, 2H), 8.30 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.63 (s, 1H), 3.36 (s, 2H), 1.87 (s, 3H), 1.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.9, 150.5, 148.7, 145.5, 133.8, 132.5, 130.3, 130.2, 130.0, 128.9, 125.1, 124.5, 124.1, 35.1, 20.3, 11.8; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{20}H_{17}ClN_2O_5SNa$) 455.0444, found 455.0443.

3,4-Dimethyl-6-(2-methylbenzyl)-1-((4-nitrophenyl)sulfonyl)-pyridin-2(1H)-one (**5h**). Light yellow solid; 42.0 mg; 51% yield; R_f = 0.48 (hexane/EtOAc = 5/1 as the eluent); mp = 147−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.9 Hz, 2H), 8.32 (d, J = 8.9 Hz, 2H), 7.26−7.20 (m, 3H), 7.17 (d, J = 7.1 Hz, 1H), 6.67 (s, 1H), 3.22 (s, 2H), 2.31 (s, 3H), 1.86 (s, 3H), 1.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.2, 150.4, 149.3, 145.7, 137.2, 133.2, 130.3, 130.1, 129.8, 129.0, 128.2, 125.8, 125.5, 124.5, 124.1, 35.3, 20.3, 20.1, 11.9; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{21}H_{20}N_2O_5SNa$) 435.0991, found 435.0996.

Procedure for the Scale-Up Synthesis of Compound 3a. An oven-dried Schlenk tube equipped with a Teflon valve was charged with a magnetic stir bar, substrate **1a** (918 mg, 3.0 mmol, 1.0 equiv), $Pd(TFA)_2$ (99.6 mg, 0.3 mmol, 10 mol %), $Cu(OAc)_2$ (109.2 mg, 0.6 mmol, 20 mol %), *p*-xylene (30 mL), and **2a** (708 mg, 6.0 mmol, 2.0 equiv). The reaction mixture was stirred in an oil bath at 110 °C for 24 h under air. Then, the resulting suspension was cooled to room temperature, filtered through a pad of filter paper, and washed with ethyl acetate (200 mL). After evaporating the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (PE/EA = 5:1) to give the pure product **3a** (995 mg, 79% yield).

Procedure for the Deprotection Reaction. A round-bottom flask was charged with a stir bar, compound **3a** (84 mg, 0.2 mmol, 1.0 equiv), K_2CO_3 (55.2 mg, 0.4 mmol, 2.0 equiv), *p*-MePhSH (37.2 mg, 0.3 mmol, 1.5 equiv), and DMF (4 mL). After being stirred at ambient temperature overnight, the mixture was diluted with water, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed sequentially with water (1 × 30 mL) and saturated NaCl solution (1 × 30 mL), dried over Na_2SO_4, and concentrated under reduced pressure to obtain the crude product, which was further purified by silica gel chromatography to provide the desired product **6**.

3-Benzylisoquinolin-1(2H)-one (**6**). Yellow solid; 40 mg; 85% yield; R_f = 0.45 (hexane/EtOAc = 2/1 as the eluent); mp = 189−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (br, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.63 (td, J = 7.6, 7.0, 1.4 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.42 (t, J = 7.1 Hz, 1H), 7.37−7.26 (m, 5H), 6.32 (s, 1H), 3.94 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.0, 140.0, 138.3, 136.3, 132.7, 129.2, 128.9, 127.4, 127.3, 126.2, 125.9, 124.6, 105.0, 39.6; HRMS (ESI-TOF) m/z calcd for $[M + Na]^+$ ($C_{16}H_{13}NONa$) 258.0895, found 258.0887. The analysis data were identical with the reported data.[28]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00150.

NMR (^{1}H, ^{13}C, ^{19}F) spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Manman Sun − *Advanced Research Institute and Department of Chemistry, Taizhou University, Taizhou 318000, P. R. China;* orcid.org/0000-0003-1126-8777; Email: sunmm@tzc.edu.cn

https://doi.org/10.1021/acs.joc.1c00150
J. Org. Chem. 2021, 86, 5255−5264

Yurong Wang − *School of Pharmaceutical Science, Zhejiang Chinese Medical University, Hangzhou 310053, P. R. China*; Email: yrwang1024@hotmail.com

Authors

Rong Zhong − *School of Pharmaceutical Science, Zhejiang Chinese Medical University, Hangzhou 310053, P. R. China*

Yong Xu − *School of Pharmaceutical Science, Zhejiang Chinese Medical University, Hangzhou 310053, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00150

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Science Foundation of Zhejiang Province (No. LQ20B020007).

■ REFERENCES

(1) For selected reviews, see: (a) Yang, Y.; Li, K.; Cheng, Y.; Wan, D.; Li, M.; You, J. Rhodium-Catalyzed Annulation of Arenes with Alkynes through Weakly Chelation-Assisted C−H Activation. *Chem. Commun.* **2016**, *52*, 2872−2884. (b) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. A Simple and Versatile Amide Directing Group for C−H Functionalizations. *Angew. Chem., Int. Ed.* **2016**, *55*, 10578−10599. (c) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C−H Activation. *Chem. Rev.* **2019**, *119*, 2192−2452. (d) Baccalini, A.; Faita, G.; Zanoni, G.; Maiti, D. Transition Metal Promoted Cascade Heterocycle Synthesis through C−H Functionalization. *Chem. - Eur. J.* **2020**, *26*, 9749−9783. (e) Liao, G.; Wu, Y.-J.; Shi, B.-F. Noncovalent Interaction in Transition Metal-Catalyzed Selective C−H Activation. *Acta Chim. Sin.* **2020**, *78*, 289−298. (f) Song, L.; Van der Eycken, E. V. Transition Metal-Catalyzed Intermolecular Cascade C−H Activation/Annulation Processes for the Synthesis of Polycycles. *Chem. - Eur. J.* **2021**, *27*, 121−144.

(2) (a) Zhu, C.; Falck, J. R. *N*-Acylsulfonamide Assisted Tandem C−H Olefination/Annulation: Synthesis of Isoindolinones. *Org. Lett.* **2011**, *13*, 1214−1217. (b) Li, D.-D.; Yuan, T.-T.; Wang, G.-W. Synthesis of Isoindolinones via Palladium-Catalyzed C−H Activation of *N*-Methoxybenzamides. *Chem. Commun.* **2011**, *47*, 12789−12791. (c) Kumar, M.; Verma, S.; Verma, A. K. Ru(II)-Catalyzed Oxidative Olefination of Benzamides: Switchable Aza-Michael and Aza-Wacker Reaction for Synthesis of Isoindolinones. *Org. Lett.* **2020**, *22*, 4620−4626. (d) Zhao, H.; Wang, T.; Qing, Z.; Zhai, H. Cobalt-Catalyzed 2-(1-Methylhydrazinyl)pyridineassisted Cyclization of Thiophene-2-carbohydrazides with Maleimides: Efficient Synthesis of Thiophene-Fused Pyridones. *Chem. Commun.* **2020**, *56*, 5524−5527.

(3) (a) Youn, S. W.; Ko, T. Y.; Kim, Y. H.; Kim, Y. A. Pd(II)/Cu(II)-Catalyzed Regio- and Stereoselective Synthesis of (*E*)-3-Arylmethyleneisoindolin-1-ones Using Air as the Terminal Oxidant. *Org. Lett.* **2018**, *20*, 7869−7874. (b) Zhang, L.-B.; Zhu, M.-H.; Du, W.-B.; Ni, S.-F.; Wen, L.-R.; Li, M. Silver-Promoted Regioselective [4 + 2] Annulation Reaction of Indoles with Alkenes to Construct Dihydropyrimidoindolone Scaffolds. *Chem. Commun.* **2019**, *55*, 14383−14386. (c) Cui, W.-J.; Wu, Z.-J.; Gu, Q.; You, S.-L. Divergent Synthesis of Tunable Cyclopentadienyl Ligands and Their Application in Rh-Catalyzed Enantioselective Synthesis of Isoindolinone. *J. Am. Chem. Soc.* **2020**, *142*, 7379−7385.

(4) (a) Tang, S.; Wang, D.; Liu, Y.; Zeng, L.; Lei, A. Cobalt-Catalyzed Electrooxidative C−H/N−H [4 + 2] Annulation with Ethylene or Ethyne. *Nat. Commun.* **2018**, *9*, No. 798. (b) Kalsi, D.; Barsu, N.; Chakrabarti, S.; Dahiya, P.; Rueping, M.; Sundararaju, B. C−H and N−H Bond Annulation of Aryl Amides with Unactivated Olefins by Merging Cobalt(III) and Photoredox Catalysis. *Chem. Commun.* **2019**, *55*, 11626−11629. (c) Lee, S.; Semakul, N.; Rovis, T. Direct Regio- and Diastereoselective Synthesis of δ-Lactams from Acrylamides and Unactivated Alkenes Initiated by Rh^{III}-Catalyzed C−H Activation. *Angew. Chem., Int. Ed.* **2020**, *59*, 4965−4969.

(5) (a) Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. Catalytic Selective Synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 10954−10990. (b) Deb, A.; Maiti, D. Emergence of Unactivated Olefins for the Synthesis of Olefinated Arenes. *Eur. J. Org. Chem.* **2017**, *2017*, 1239−1252. (c) Jambu, S.; Jeganmohan, M. Rhodium(III)-Catalyzed C−H Olefination of Aromatic/Vinyl Acids with Unactivated Olefins at Room Temperature. *Org. Lett.* **2020**, *22*, 5057−5062.

(6) (a) Tsai, A.; Brasse, M.; Bergman, R.; Ellman, J. A. Rh(III)-Catalyzed Oxidative Coupling of Unactivated Alkenes via C−H Activation. *Org. Lett.* **2011**, *13*, 540−542. (b) Takahama, Y.; Shibata, Y.; Tanaka, K. Oxidative Olefination of Anilides with Unactivated Alkenes Catalyzed by an (Electron-Deficient η^5-Cyclopentadienyl)-Rhodium(III) Complex Under Ambient Conditions. *Chem. - Eur. J.* **2015**, *21*, 9053−9056. (c) Xue, X.; Xu, J.; Zhang, L.; Xu, C.; Pan, Y.; Xu, L.; Li, H.; Zhang, W. Rhodium(III)-Catalyzed Direct C−H Olefination of Arenes with Aliphatic Olefins. *Adv. Synth. Catal.* **2016**, *358*, 573−583. (d) Maity, S.; Kancherla, R.; Dhawa, U.; Hoque, E.; Pimparkar, S.; Maiti, D. Switch to Allylic Selectivity in Cobalt-Catalyzed Dehydrogenative Heck Reactions with Unbiased Aliphatic Olefins. *ACS Catal.* **2016**, *6*, 5493−5499. (e) Maity, S.; Dolui, P.; Kancherla, R.; Maiti, D. Introducing Unactivated Acyclic Internal Aliphatic Olefins into a Cobalt Catalyzed Allylic Selective Dehydrogenative Heck Reaction. *Chem. Sci.* **2017**, *8*, 5181−5185. (f) Baccalini, A.; Vergura, S.; Dolui, P.; Maiti, S.; Dutta, S.; Maity, S.; Khan, F. F.; Lahiri, G. K.; Zanoni, G.; Maiti, D. Cobalt-Catalyzed C(sp^2)−H Allylation of Biphenyl Amines with Unbiased Terminal Olefins. *Org. Lett.* **2019**, *21*, 8842−8846.

(7) (a) Chen, M. S.; White, M. C. A Sulfoxide-Promoted, Catalytic Method for the Regioselective Synthesis of Allylic Acetates from Monosubstituted Olefins via C−H Oxidation. *J. Am. Chem. Soc.* **2004**, *126*, 1346−1347. (b) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Ligand-Accelerated C−H Activation Reactions: Evidence for a Switch of Mechanism. *J. Am. Chem. Soc.* **2010**, *132*, 14137−14151. (c) Lu, M.-Z.; Chen, X.-R.; Xu, H.; Dai, H.-X.; Yu, J.-Q. Ligand-Enabled *ortho*-C−H Olefination of Phenylacetic Amides with Unactivated Alkenes. *Chem. Sci.* **2018**, *9*, 1311−1316. (d) Shen, J.; Xu, B.; Zhang, M.; Su, W. Branched-Selective Decarboxylative Heck Reaction with Electronically Unbiased Olefins. *Eur. J. Org. Chem.* **2018**, *2018*, 2768−2773. (e) Lin, H.-C.; Xie, P.-P.; Dai, Z.-Y.; Zhang, S.-Q.; Wang, P.-S.; Chen, Y.-G.; Wang, T.-C.; Hong, X.; Gong, L.-Z. Nucleophile-Dependent *Z*/*E*- and Regioselectivity in the Palladium-Catalyzed Asymmetric Allylic C−H Alkylation of 1,4-Dienes. *J. Am. Chem. Soc.* **2019**, *141*, 5824−5834.

(8) (a) Takahama, Y.; Shibata, Y.; Tanaka, K. Heteroarene-Directed Oxidative sp^2 C−H Bond Allylation with Aliphatic Alkenes Catalyzed by an (Electron-Deficient η^5-Cyclopentadienyl)rhodium(III) Complex. *Org. Lett.* **2016**, *18*, 2934−2937. (b) Sun, Q.-Y.; Li, Z.; Xu, Z.; Zheng, Z.-J.; Cao, J.; Yang, K.-F.; Cui, Y.-M.; Xu, L.-W. $PdCl_2(CH_3CN)_2$-Catalyzed Regioselective C−H Olefinations of 2-Amino Biaryls with Vinylsilanes as Unactivated Alkenes. *Chem. Commun.* **2019**, *55*, 6229−6232. (c) Jayakumar, J.; Vedarethinam, G.; Hsiao, H.-C.; Sun, S.-Y.; Chuang, S.-C. Cascade One-Pot Synthesis of Orange-Red-Fluorescent Polycyclic Cinnolino[2,3-f]phenanthridin-9-ium Salts by Palladium(II)-Catalyzed C−H Bond Activation of 2-Azobiaryl Compounds and Alkenes. *Angew. Chem., Int. Ed.* **2020**, *59*, 689−694. (d) Zhan, B.-B.; Jia, Z.-S.; Luo, J.; Jin, L.; Lin, X.-F.; Shi, B.-F. Palladium-Catalyzed Directed Atroposelective C-H Allylation via β−H Elimination: 1,1-Disubstituted Alkenes as Allyl Surrogates. *Org. Lett.* **2020**, *22*, 9693−9698. (e) Wu, M.-J.; Chu, J.-H. Directing Group Assists in Transition Metal-Catalyzed Siteselective C−H Bond Activation/Transformations. *J. Chin. Chem. Soc.* **2020**, *67*, 399−421.

(9) (a) Deb, A.; Bag, S.; Kancherla, R.; Maiti, D. Palladium-Catalyzed Aryl C−H Olefination with Unactivated, Aliphatic Alkenes. *J. Am. Chem. Soc.* **2014**, *136*, 13602−13605. (b) Seth, K.; Bera, M.; Brochetta, M.; Agasti, S.; Das, A.; Gandini, A.; Porta, A.; Zanoni, G.; Maiti, D. Incorporating Unbiased, Unactivated Aliphatic Alkenes in

Pd(II)-Catalyzed Olefination of Benzyl Phosphonamide. *ACS Catal.* **2017**, *7*, 7732−7736.
(10) (a) Jiang, H.; Yang, W.; Chen, H.; Li, J.; Wu, W. Palladium-Catalyzed Aerobic Oxidative Allylic C−H Arylation of Alkenes with Polyfluorobenzenes. *Chem. Commun.* **2014**, *50*, 7202−7204. (b) Wang, G.-W.; Zhou, A.-X.; Li, S.-X.; Yang, S.-D. Regio- and Stereoselective Allylic C-H Arylation with ElectronDeficient Arenes by 1,1′-Bi-2-naphthol-Palladium Cooperation. *Org. Lett.* **2014**, *16*, 3118−3121. (c) Manoharan, R.; Sivakumar, G.; Jeganmohan, M. Cobalt-Catalyzed C−H Olefination of Aromatics with Unactivated Alkenes. *Chem. Commun.* **2016**, *52*, 10533−10536. (d) Lerchen, A.; Knecht, T.; Koy, M.; Ernst, J. B.; Bergander, K.; Daniliuc, C. G.; Glorius, F. Non-Directed Cross-Dehydrogenative (Hetero)arylation of Allylic C(sp^3)−H bonds enabled by C−H Activation. *Angew. Chem., Int. Ed.* **2018**, *57*, 15248−15252.
(11) (a) Guimond, N.; Gorelsky, S. I.; Fagnou, K. Rhodium(III)-Catalyzed Heterocycle Synthesis Using an Internal Oxidant: Improved Reactivity and Mechanistic Studies. *J. Am. Chem. Soc.* **2011**, *133*, 6449−6457. (b) Hyster, T. K.; Dalton, D. M.; Rovis, T. Ligand Design for Rh(III)-Catalyzed C−H Activation: An Unsymmetrical Cyclopentadienyl Group Enables a Regioselective Synthesis of Dihydroisoquinolones. *Chem. Sci.* **2015**, *6*, 254−258. (c) Yu, X.; Chen, K.; Wang, Q.; Zhang, W.; Zhu, J. Co(III)-Catalyzed *N*-Chloroamide-Directed C−H Activation for 3,4-Dihydroisoquinolone Synthesis. *Org. Chem. Front.* **2018**, *5*, 994−997.
(12) Liu, Y.; Yang, Y.; Wang, C.; Wang, Z.; You, J. Rhodium(III)-Catalyzed Regioselective Oxidative Annulation of Anilines and Allylbenzenes via C(sp^3)−H/C(sp^2)−H Bond Cleavage. *Chem. Commun.* **2019**, *55*, 1068−1071.
(13) (a) Xia, X.-F.; Wang, Y.-Q.; Zhang, L.-L.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. Palladium-Catalyzed C−H Activation and Intermolecular Annulation with Allenes. *Chem. - Eur. J.* **2014**, *20*, 5087−5091. (b) Sun, M.; Chen, W.; Xia, X.; Shen, G.; Ma, Y.; Yang, J.; Ding, H.; Wang, Z. Palladium-Catalyzed Tandem Dehydrogenative [4 + 2] Annulation of Terminal Olefins with *N*-Sulfonyl Amides via C−H Activations. *Org. Lett.* **2020**, *22*, 3229−3233. (c) Large, B.; Terrasson, V.; Prim, D. *N*-Tosylcarboxamide in C−H Functionalization: More than a Simple Directing Group. *Processes* **2020**, *8*, 981−994.
(14) (a) Pettit, G. R.; Meng, Y.; Herald, D. L.; Graham, K. A. N.; Pettit, R. K.; Doubek, D. L. Isolation and Structure of Ruprechstyril from *Ruprechtia tangarana*. *J. Nat. Prod.* **2003**, *66*, 1065−1069. (b) Torres, M.; Gil, S.; Parra, M. New Synthetic Methods to 2-Pyridone Rings. *Curr. Org. Chem.* **2005**, *9*, 1757−1779. (c) Khadka, D. B.; Yang, S. H.; Cho, S. H.; Zhao, C.; Cho, W.-J. Synthesis of 12-Oxobenzo[*c*]phenanthridinones and 4-Substituted 3-Arylisoquinolones via Vilsmeiere−Haack Reaction. *Tetrahedron* **2012**, *68*, 250−261. (d) Woon, E. C. Y.; Sunderland, P. T.; Paine, H. A.; Lloyd, M. D.; Thompson, A. S.; Threadgill, M. D. One-Pot Tandem Hurtley−Retro-Claisen−Cyclisation Reactions in the Synthesis of 3-Substituted Analogues of 5-Aminoisoquinolin-1-one (5-AIQ), a Water-Soluble Inhibitor of PARPs. *Bioorg. Med. Chem.* **2013**, *21*, 5218−5227. (e) Huang, X.; Rao, A.; Zhou, W.; Aslanian, R.; Nargund, R.; Buevich, A.; Zhang, L.-K.; Qiu, H.; Yang, X.; Garlisi, C.; Correll, C.; Palani, A. The Synthesis of 2,3,6-Trisubstituted 1-Oxo-1,2-dihydroisoquinolines as Potent $CRTh_2$ Antagonists. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 5344−5348.
(15) (a) Dieudonné-Vatran, A.; Azoulay, M.; Florent, J.-C. A New Access to 3-Substituted-1(2*H*)-isoquinolone by Tandem Palladium-Catalyzed Intramolecular Aminocarbonylation Annulation. *Org. Biomol. Chem.* **2012**, *10*, 2683−2691. (b) He, Y.; Yuan, C.; Jiang, Z.; Shuai, L.; Xiao, Q. Expeditious Synthesis of Isoquinolone Derivatives by Rhodium(I)- Catalyzed Annulation Reaction through C−C Bond Cleavage. *Org. Lett.* **2019**, *21*, 185−189.
(16) Lee, J.; Kim, H. Y.; Oh, K. Tandem Reaction Approaches to Isoquinolones from 2-Vinylbenzaldehydes and Anilines via Imine Formation-6π-Electrocyclization-Aerobic Oxidation Sequence. *Org. Lett.* **2020**, *22*, 474−478.
(17) Weng, W.-Z.; Xie, J.; Zhang, B. Mild and Efficient Synthesis of Indoles and Isoquinolones via a Nickel-Catalyzed Larock-Type Heteroannulation Reaction. *Org. Biomol. Chem.* **2018**, *16*, 3983−3988.
(18) For selected examples, see (a) Ackermann, L. Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C−H/Het−H Bond Functionalizations. *Acc. Chem. Res.* **2014**, *47*, 281−295. (b) Zhao, Y.; Shi, C.; Su, X.; Xia, W. Synthesis of Isoquinolones by Visible-Light-Induced Deaminative [4+2] Annulation Reactions. *Chem. Commun.* **2020**, *56*, 5259−5262.
(19) (a) Boobalan, R.; Kuppusamy, R.; Santhoshkumar, R.; Gandeepan, P.; Cheng, C.-H. Access to Isoquinolin-1(2*H*)-ones and Pyridones by Cobalt-Catalyzed Oxidative Annulation of Amides with Allenes. *ChemCatChem* **2017**, *9*, 273−277. (b) Meyer, T. H.; Oliveira, J. C. A.; Sau, S. C.; Ang, N. W. J.; Ackermann, L. Electrooxidative Allene Annulations by Mild Cobalt-Catalyzed C−H Activation. *ACS Catal.* **2018**, *8*, 9140−9147. (c) Mei, R.; Fang, X.; He, L.; Sun, J.; Zou, L.; Ma, W.; Ackermann, L. Cobaltaelectro-Catalyzed Oxidative Allene Annulation by Electro-Removable Hydrazides. *Chem. Commun.* **2020**, *56*, 1393−1396.
(20) (a) Sun, M.; Wu, H.; Xia, X.; Chen, W.; Wang, Z.; Yang, J. Asymmetric Palladium-Catalyzed C−H Functionalization Cascade for Synthesis of Chiral 3,4-Dihydroisoquinolones. *J. Org. Chem.* **2019**, *84*, 12835−12847. (b) Sun, M.; Li, J.; Chen, W.; Wu, H.; Yang, J.; Wang, Z. Palladium-Catalyzed [4 + 2] Annulation of Aryl and Alkenyl Carboxamides with 1,3-Dienes via C−H Functionalization: Synthesis of 3,4-Dihydroisoquinolones and 5,6-Dihydropyridinones. *Synthesis* **2020**, *52*, 1253−1265. (c) Sun, M.; Chen, W.; Wu, H.; Xia, X.; Yang, J.; Wang, L.; Shen, G.; Wang, Z. Vinylogous Elimination/C−H Functionalization/Allylation Cascade Reaction of Allenoate Adducts: Synthesis of Ring-Fused Dihydropyridinones. *Org. Lett.* **2020**, *22*, 8313−8319.
(21) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. Highly Regioselective Arylation of sp^3 C−H Bonds Catalyzed by Palladium Acetate. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. (b) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon−Hydrogen Bonds. *Acc. Chem. Res.* **2015**, *48*, 1053−1064. (c) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C−H Bond Functionalization Chemistry for the Expedient Construction of C−C Bonds. *Chem. Rev.* **2020**, *120*, 1788−1887.
(22) (a) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. Stereoselective Synthesis of Chiral α-Amino-β-Lactams through Palladium(II)-Catalyzed Sequential Monoarylation/Amidation of C(sp^3)−H Bonds. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588−13592. (b) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. Pd(II)-Catalyzed Alkoxylation of Unactivated C(sp^3)−H and C(sp^2)−H Bonds Using A Removable Directing Group: Efficient Synthesis of Alkyl Ethers. *Chem. Sci.* **2013**, *4*, 4187−4192. (c) Zhou, T.; Jiang, M.-X.; Yang, X.; Yue, Q.; Han, Y.-Q.; Ding, Y.; Shi, B.-F. Synthesis of Chiral β-Lactams by Pd-Catalyzed Enantioselective Amidation of Methylene C(sp^3)−H Bonds. *Chin. J. Chem.* **2020**, *38*, 242−246.
(23) (a) Wu, J.; Wang, D.; Wan, Y.; Ma, C. Rhodium-Catalyzed Tunable Oxidative Cyclization Toward the Selective Synthesis of α-Pyrones and Furans. *Chem. Commun.* **2016**, *52*, 1661−1664. (b) Song, S.; Lu, P.; Liu, H.; Cai, S.-H.; Feng, C.; Loh, T.-P. Switchable C−H Functionalization of *N*-Tosyl Acrylamides with Acryloylsilanes. *Org. Lett.* **2017**, *19*, 2869−2872.
(24) Nayak, S.; Ghosh, N.; Prabagar, B.; Sahoo, A. K. *p*-TsOH Promoted Au(I)-Catalyzed Consecutive Endo Cyclization of Yne-Tethered Ynamide: Access to Benzofused Dihydroisoquinolones. *Org. Lett.* **2015**, *17*, 5662−5665.
(25) (a) Yang, G.; Zhang, W. Regioselective Pd-Catalyzed Aerobic Aza-Wacker Cyclization for Preparation of Isoindolinones and Isoquinolin-1(2*H*)-ones. *Org. Lett.* **2012**, *14*, 268−271. (b) Yang, G.; Shen, C.; Zhang, W. An Asymmetric Aerobic Aza-Wacker-Type Cyclization: Synthesis of Isoindolinones Bearing Tetrasubstituted Carbon Stereocenters. *Angew. Chem., Int. Ed.* **2012**, *51*, 9141−9145.
(26) Ding, Y.; Han, Y.-Q.; Wu, L.-S.; Zhou, T.; Yao, Q.-J.; Feng, Y.-L.; Li, Y.; Kong, K.-X.; Shi, B.-F. Pd(II)-Catalyzed Tandem

https://doi.org/10.1021/acs.joc.1c00150
J. Org. Chem. 2021, 86, 5255−5264

Enantioselective Methylene C(sp^3)−H Alkenylation−Aza-Wacker Cyclization to Access β-Stereogenic γ-Lactams. *Angew. Chem., Int. Ed.* **2020**, *59*, 14060−14064.
(27) (a) Cajaraville, A.; López, S.; Varela, J. A.; Saá, C. Rh(III)-Catalyzed Tandem C−H Allylation and Oxidative Cyclization of Anilides: A New Entry to Indoles. *Org. Lett.* **2013**, *15*, 4576−4579. (b) Xia, Y.-Q.; Dong, L. Ruthenium(II)-Catalyzed Indolo[2,1-a]isoquinolines Synthesis by Tandem C−H Allylation and Oxidative Cyclization of 2-Phenylindoles with Allyl Carbonates. *Org. Lett.* **2017**, *19*, 2258−2261. (c) Manna, M. K.; Bairy, G.; Jana, R. Sterically Controlled Ru(II)-Catalyzed Divergent Synthesis of 2-Methylindoles and Indolines through a C−H Allylation/Cyclization Cascade. *J. Org. Chem.* **2018**, *83*, 8390−8400.
(28) Rouquet, G.; Moore, D.; Spain, M.; Allwood, D. M.; Battilocchio, C.; Blakemore, D. C.; Fish, P. V.; Jenkinson, S.; Jessiman, A. S.; Ley, S. V.; McMurray, G.; Storer, R. I. Design, Synthesis, and Evaluation of Tetrasubstituted Pyridines as Potent 5-HT_{2C} Receptor Agonists. *ACS Med. Chem. Lett.* **2015**, *6*, 329−333.

https://doi.org/10.1021/acs.joc.1c00150
J. Org. Chem. 2021, 86, 5255−5264