JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

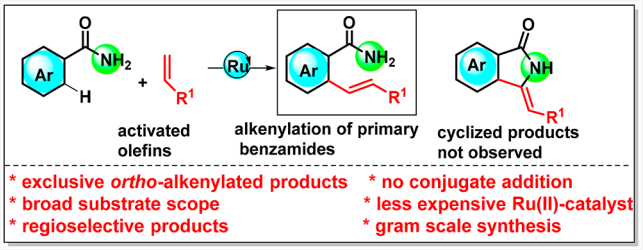
Ru(II)-Catalyzed Controlled Cross-Dehydrogenative Coupling of Benzamides with Activated Olefins via Weakly Coordinating Primary Amides

Akanksha Singh Baghel, Anjali Aghi, and Amit Kumar*

Cite This: J. Org. Chem. 2021, 86, 9744−9754 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Ru(II)-catalyzed regioselective *ortho*-alkenylation of primary benzamides with activated olefins has been realized over the competitive cyclized products. This reaction overall proceeds via a cross-dehydrogenative coupling (CDC) reaction using a simple and weakly coordinating primary amide group in the presence of an inexpensive Ru(II) salt and allows the controlled introduction of olefin motifs at the *ortho*-position of benzamides. The key to the success of this strategy depends on fine-tuning the reaction conditions. The developed protocol has demonstrated excellent regio/diastereoselectivity and a good functional group tolerance with wide substrate scope and obviates the requirement of external auxiliaries as well as the costly metal catalyst. Detailed mechanistic studies indicate the involvement of the base-assisted internal electrophilic-type substitution (BIES) step in the reaction mechanism.



INTRODUCTION

Carbon−carbon bond formation, viz., transition-metal-catalyzed 2-fold C−H activation (also known as the Fujiwara−Moritani reaction), using directing groups are one of the most powerful and alternate synthetic tools to the conventional organic synthesis and cross-coupling methodologies.[1] Therefore, the directing group-assisted site-selective C−H bond functionalization reactions have gained a lot of emphasis from chemists including the industrial chemists, owing to their sustainable aspects (atom and step-economical nature).[2] However, these strategies, in general, require two extra steps: preinstallation followed by the removal of the directing group after the desired operation and eventually generate extra chemical waste and unsuitable for large-scale syntheses.[3] Hence, such approaches are not well accepted in contemporary science. To render these approaches for the broad audience, in the recent past, organic chemists have started utilizing a common functional motif as a desired directing group for regioselective C−H bond transformation, as they circumvent the requirements of preinstallation/removal of bulky and costly auxiliaries and, to some extent, satisfy the parameters of sustainable chemistry.[4]

Amides are one of the fundamental functional groups that frequently present as a key structural unit in many active drugs such as gilteritinib (anticancer activity), ribavirin (hepatitis C), and safinamide (Parkinson's disease), and natural products.[5] On the other hand, the presence of the N and O atoms, respectively, in an amide group, imparts the ability to act as a soft ligand and further coordinate with the transition-metal salts to generate the stable cyclometalated species.

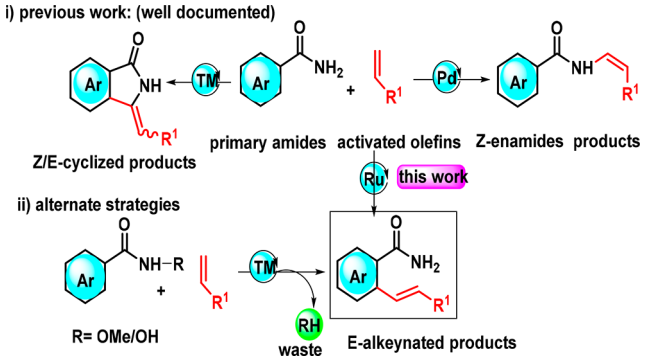
Therefore, N-substituted amides (secondary/tertiary) have been frequently employed as optimal directing groups for site-selective C−H bond transformation reactions.[6] While the secondary and tertiary amides have found enormous success in C−H activation reactions, their unsubstituted counterparts such as primary amides have found limited success by virtue of their weak-coordination ability toward the metal catalyst.[7] Ideally, the usage of a primary amide moiety as a directing group is more valuable and sustainable from the step-economy point.

In this context, a major breakthrough was reported by Glorius et al. in 2011,[8] where the primary amide group was employed as a directing group for *ortho*-alkenylation of benzamides with unactivated olefins using a costly Rh(III) catalyst. Interestingly, when activated olefins were employed as coupling partners, the corresponding *E*-exocyclized butyrolactams were obtained exclusively (Scheme 1, eq i). Indeed, Laha and Jeganmohan et al. also reported the formation of cyclic *E*/*Z*-butyrolactams derivatives under Pd(II) or Ru(II) catalytic conditions from primary benzamides with activated olefins

Received: May 9, 2021
Published: July 1, 2021

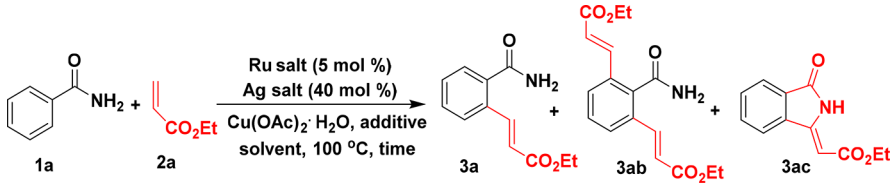
https://doi.org/10.1021/acs.joc.1c01090
J. Org. Chem. 2021, 86, 9744−9754

Scheme 1. Transition-Metal-Catalyzed Amide-Directed Coupling Reactions of Benzamides with Activated Olefins



(Scheme 1, eq i, left side).[9] The outcome of these results can be attributed to the existence of a free $-NH_2$ group, which subsequently undergoes a cyclization process via the aza-Michael addition reaction in the presence of a metal catalyst. On the other hand, Chang and Panda et al. disclosed the generation of *Z*-enamides from primary benzamides with activated olefins under Pd(II) catalytic conditions (Scheme 1, eq i, right side).[10] Therefore, the controlled introduction of olefins at *ortho*-positions of electron-deficient benzamides, exclusively, is by no mean a routine transformation as several other competitive side product formations are possible in these conditions. Very recently, with a single example, Wang and a co-worker revealed the controlled formation of *ortho*-alkenylated benzamide using primary amide as a directing group using an expensive Ir(III) catalyst in an optimal yield.[11] Indeed, *ortho*-alkenylated benzamides can be synthesized from *N*-methoxy-benzamides using a Ru(II) salt as a catalyst (Scheme 1, eq ii).[12] However, the major disadvantage of this method lies with the usage of prefunctionalized directing groups and the generation of 1.0 equiv of byproducts. Later on, Ackerman and co-worker disclosed an alternate protocol for making this class of compounds using hydroximic acid as a directing group, which eventually circumvent the aforementioned drawback.[12] Whereas, under the reported method, only selected examples of activated olefins and benzamides were tested. Therefore, the development of a new synthetic strategy, which can follow the sustainability concept for the controlled introduction of an olefin moiety on primary benzamides

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	oxidant	additive	silver salt	yield (%)[b] (3a/3ab/3ac)
1	DCE	$Cu(OAc)_2·H_2O$	AcOH	$AgBF_4$	60:19:5
2	DCE	$Cu(OAc)_2·H_2O$	AcOH	$AgBF_4$	72[c]:7:trace
3	ACN	$Cu(OAc)_2·H_2O$	AcOH	$AgBF_4$	nr
4	benzene	$Cu(OAc)_2·H_2O$	AcOH	$AgBF_4$	68[c]:4:trace
5	toluene	$Cu(OAc)_2·H_2O$	AcOH	$AgBF_4$	22[c]:trace:trace
6	cholorobenzene	$Cu(OAc)_2·H_2O$	AcOH	$AgBF_4$	58[c]: 10:trace
7	DCE	$Cu(OAc)_2·H_2O$	AcOH	$AgBF_4$	75[d]:7: trace
8	DCE	$Cu(OAc)_2·H_2O$	TFA	$AgBF_4$	nr
9	DCE	$Cu(OAc)_2·H_2O$	PivOH	$AgBF_4$	27[c]:trace:trace
10	DCE	$Cu(OAc)_2·H_2O$	MsOH	$AgBF_4$	nr
11	DCE	$CuCl_2$	AcOH	$AgBF_4$	nr
12	DCE	$Cu(TFA)_2·H_2O$	AcOH	$AgBF_4$	10[c]:trace:trace
13	DCE	$Cu(OAc)_2$	AcOH	$AgBF_4$	49[c]:4:trace
14	DCE	$Cu(OAc)_2·H_2O$	CsOAc	$AgBF_4$	trace:4:31[e]
15	DCE	$Cu(OAc)_2·H_2O$	K_2CO_3	$AgBF_4$	trace:trace:55[e]
16	DCE	$Cu(OAc)_2·H_2O$	$NaOAc·3H_2O$	$AgBF_4$	26[e]:12:trace
17	DCE	$Cu(OAc)_2·H_2O$	NaOAc	$AgBF_4$	55[e]: 10:5
18	DCE	$Cu(OAc)_2·H_2O$		$AgBF_4$	46[c]: trace:trace
19	DCE	$Cu(OAc)_2·H_2O$	AcOH	$AgSbF_6$	26[c]:trace:trace
20	DCE	$Cu(OAc)_2·H_2O$	AcOH	$AgCO_2CH_3$	20[c]:trace:trace
21	DCE	$Cu(OAc)_2·H_2O$	AcOH	Ag_2CO_3	35[c]:trace:trace
22	DCE	$Cu(OAc)_2·H_2O$	AcOH	Ag_2O	23[c]:trace:trace
23	DCE	$Cu(OAc)_2·H_2O$	AcOH	$AgNO_3$	nr
24	DCE	$Cu(OAc)_2·H_2O$	AcOH	$AgCO_2CF_3$	14[c]:trace:trace
25	DCE	$Cu(OAc)_2·H_2O$	AcOH		nr
26	DCE		AcOH	$AgBF_4$	nr

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), oxidant (1.5 equiv), acid additive (10.0 equiv), silver salt (40.0 mol %), and solvent (2.0 mL) at 100 °C for 16 h. [b]Isolated yield of product. [c]The reaction was carried out for 8 h. [d]2.0 equiv of **2a** was used. [e]Base additive (1.0 equiv); ACN = acetonitrile, DCE = 1,2-dichloroethane; nr = no reaction.

https://doi.org/10.1021/acs.joc.1c01090
J. Org. Chem. 2021, 86, 9744−9754

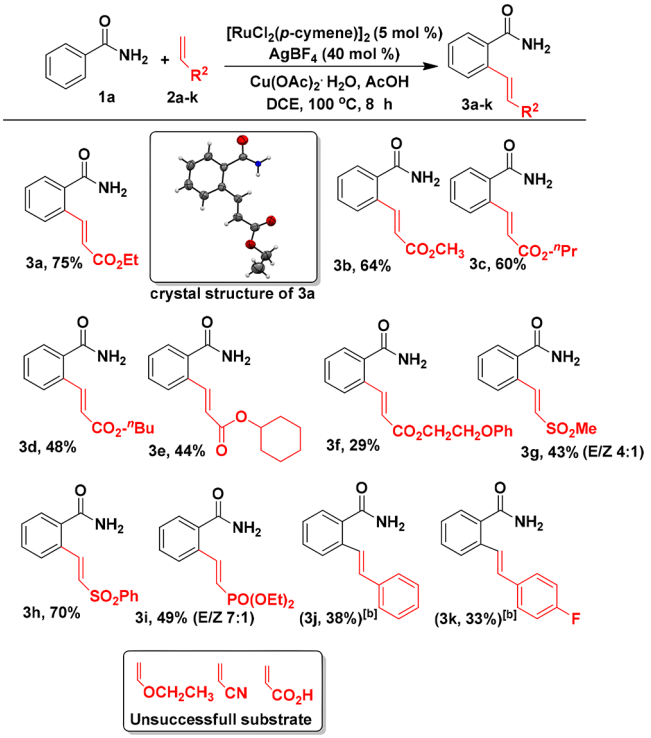
without affording the cyclized products, would be a valuable addition to the literature. In continuation of our research interest in weakly coordinating primary amide-directed C−H bond functionalization of aromatic compounds,[13] herein, we report the first general *ortho*-alkenylation of primary benzamides with activated olefins using a Ru(II) salt as a catalyst (Scheme 1). Major features of this developed method include the following: (i) the use of versatile and less expensive a Ru(II)-salt as a catalyst, (ii) the first general and controlled *ortho*-alkenylation of benzamides with activated olefins via a weakly coordinating primary amide group, (iii) no requirements of external and bulky auxiliaries, and (iv) the $-NH_2$ group of amide does not participate in the cyclization process and remained intact postoperation.

RESULTS AND DISCUSSION

With this understanding, we initiated our work by selecting primary benzamide (**1a**) and highly activated ethyl acrylate (**2a**) as benchmark substrates and Ru(II) salt as the optimal catalyst.[14] The detailed results are summarized in Table 1. The first reaction was carried out using the external oxidant $Cu(OAc)_2{\cdot}H_2O$ and $AgBF_4$ as halogen exchangers to make more reactive cationic Ru(II) species in DCE solvent at 100 °C for 16 h. The outcome of the reaction was quite impressive by affording the desired *ortho*-alkenylated benzamide (**3a**) in 60% yield along with the formation of dialkenylated benzamide (**3ab**) and cyclized product (**3ac**) in 19% and 5% yields, respectively (entry 1). Taking the inspiration from this initial result, we started optimizing the various reaction parameters such as the nature of the solvents, reaction time, temperature, additives, and oxidants. For instance, when the reaction was carried out under similar conditions for 8 h, gratifyingly, the corresponding *ortho*-alkenylated primary benzamide (**3a**) was isolated in 72% yield (entry 2). In the reaction, dialkenylated **3ab** and cyclized (**3ac**) products were observed only in a very trace amount. Spectroscopic evidence confirms excellent *E*-stereoselectivity in the product (**3a**). After that, we screened the reaction solvents such as benzene, toluene, chlorobenzene, and ACN (entries 2−6), and it was observed that DCE is the best choice among all other solvents. Moreover, the loading of ethyl acrylate played a minor role in increasing the yield of the desired product (**3a**). For instance, the yield of (**3a**) increased slightly (75%, entry 7) when the reaction was performed with 2.0 equiv of acrylate. Similarly, we also tested other acidic additives such as AcOH, TFA, PivOH, and MsOH (entries 8−10) for the reaction optimization. Among them, under the AcOH conditions, the desired product (**3a**) was obtained in the best yield (75%, entry 7). After that, reactions were also tested with other oxidants such as $CuCl_2$, $Cu(TFA)_2{\cdot}H_2O$, $Cu(OAc)_2$, and $Cu(OAc)_2{\cdot}H_2O$ (entries 11−13), and the yield of the desired product did not improve under these conditions. Strikingly, when the reactions were carried out in the presence of base additives (K_2CO_3 and CsOAc, entries 14 and 15), only a trace amount of desired product (**3a**) was formed. However, the cyclized product (**3ac**) was procured in an optimal yield (31%, entry 14). It is important to note that, under NaOAc conditions, alkenylated benzamide **3a** was isolated as a major product, albeit in a lower yield (entries 16 and 17). On the other side, when the reaction was carried out in the absence of acetic acid (entry 18), the yield of desired product (**3a**) was decreased dramatically (46%) and eventually endorses the importance of acetic acid in this reaction condition. Further, screening of other silver salts ($AgSbF_6$, Ag_2CO_3, Ag_2O, AgOAc, $AgNO_3$, and $AgCO_2CF_3$, entries 19−24) afforded the corresponding product (**3a**) in a somewhat lower yield. Importantly, when the reaction was performed in the absence of copper and silver salts, product (**3a**) was not formed and eventually dictates their importance in this transformation (entries 25 and 26). After careful optimization, the reaction conditions described in entry 7 (Table 1) were selected as a standard condition for further exploration.

Having assimilated the optimal reaction conditions, we sought to explore the substrate generality of this controlled cross-dehydrogenative coupling reaction. A series of activated olefins were examined as coupling partners with benzamide (**1a**), and the results are summarized in Scheme 2. For

Scheme 2. Scope of Activated Olefins[a]



[a]For reaction conditions, see Table 1, entry 7. [b]1.0 equiv of NaOAc instead of AcOH. Isolated yields of products are reported after column purification

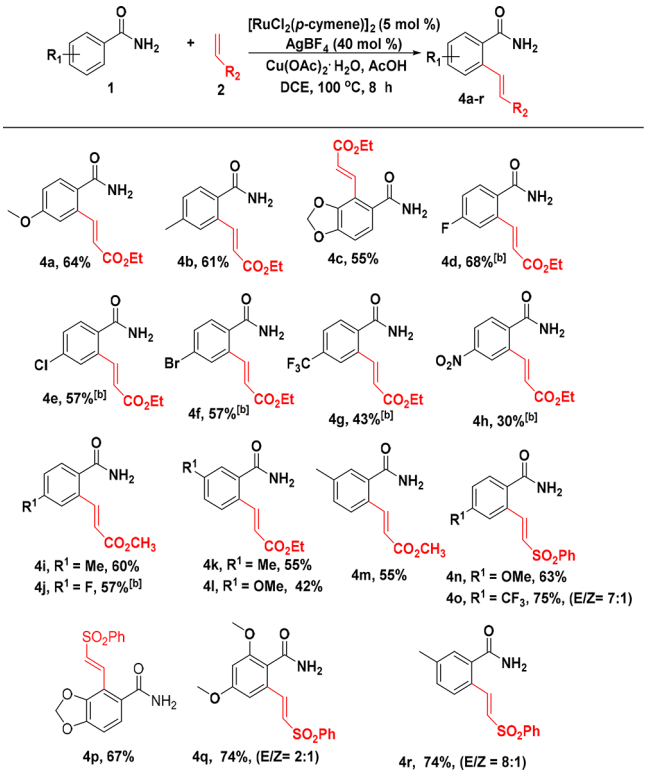
example, when methyl-, ethyl-, propyl-, *n*-butyl-, and cyclohexyl-substituted acrylates were treated under the optimized reaction conditions, the corresponding monoselective *ortho*-alkenylated benzamides (**3a−3e**) were obtained in moderate to good yields (44−75%) with excellent diastereoselectivity (*E*) without affording the cyclized product, which was the major concern. Indeed, all isolated compound structures were characterized through detailed NMR studies and further supported by a single X-ray diffraction analysis of the compound (**3a** or details, see Supporting Information). Similarly, other activated olefins such as phenoxyethyl acrylate (**2f**), methyl vinyl sulfone (**2g**), phenyl vinyl sulfone (**2h**), and diethyl vinyl phosphate (**2i**) furnished the corresponding *mono-E*-alkenylated products (**3f−3i**) in the range of 29−70% yields. Moreover, the developed strategy also extended with unactivated olefins such as styrene and 4-fluoro-styrene, and the desired products (**3j** and **3k**) were isolated under the slightly modified reaction conditions, albeit in low yields, 38%

https://doi.org/10.1021/acs.joc.1c01090
J. Org. Chem. 2021, 86, 9744−9754

and 33%, respectively. However, when the reaction was carried out with ethyl vinyl ether, acrylonitrile, and acrylic acid under the established reaction conditions, no desired products were formed.

Next, we explore the scope of this transformation concerning various substituted benzamides with activated olefins (Scheme 3). Electron-donating groups such as methoxy, methyl, and

Scheme 3. Substrate Scope with Regard to the Arylamides and Olefins[a]



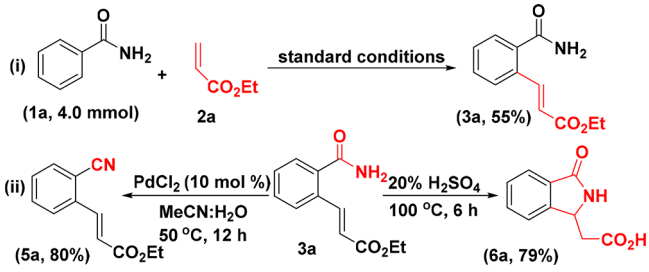
[a]For reaction conditions, see Table 1, entry 7. [b]1.0 equiv of NaOAc was used instead of AcOH

3,4-dioxy at *para* positions of the aryl ring underwent a smooth cross-dehydrogenative coupling reaction to give the corresponding *mono-E*-alkenylated products (**4a**–**4c**) in good yields (55–64%). Importantly, in the case of 3,4-dioxy-benzamide (**1c**), the olefin motif was introduced at the sterically crowded *ortho*-position of the aryl ring over the least hindered site.

On the other side, when the reaction was performed with electron-withdrawing substituted benzamides with activated olefins, the overall reaction was found to be sluggish and afforded a mixture of *ortho*-alkenylated and alkylated benzamides. Interestingly, changing the AcOH additive to NaOAc afforded the *ortho*-alkenylated products in good yields with high diastereoselective. Similarly, when the *meta*-substituted benzamides (**1k**–**1m**) were reacted with olefins, *ortho-E*-alkenylation took place at the sterically least hindered position of the aryl ring, except in the case of 3,4-dioxy benzamide, whereas differently substituted benzamides were coupled with phenyl vinyl sulfone (**2h**) to afford the desired alkenylated derivatives via a controlled cross-dehydrogenative process in good yields. For instance, when *p*-methoxy benzamide and 3,4-dioxy benzamide were employed to react with phenyl vinyl sulfone, products (**4n**, **4p**) were obtained in good yields with a high *E*-diastereoselectivity (63–67%). In contrast, methyl-, trifluoromethyl-, and 3,4 dimethoxy-substituted benzamides reacted efficiently with phenyl vinyl sulfone (**2h**) and gave the desired products (**4o**, **4q**, **4r**) in excellent yields with moderate to good diastereoselectivity (*E*/*Z* = 2:1 to 8:1).

Furthermore, to demonstrate the synthetic practicality of this established method, a gram-scale synthesis was performed under standard conditions (Scheme 4, eq i). Fortunately, the

Scheme 4. Scale-up Synthesis and Synthetic Derivatization



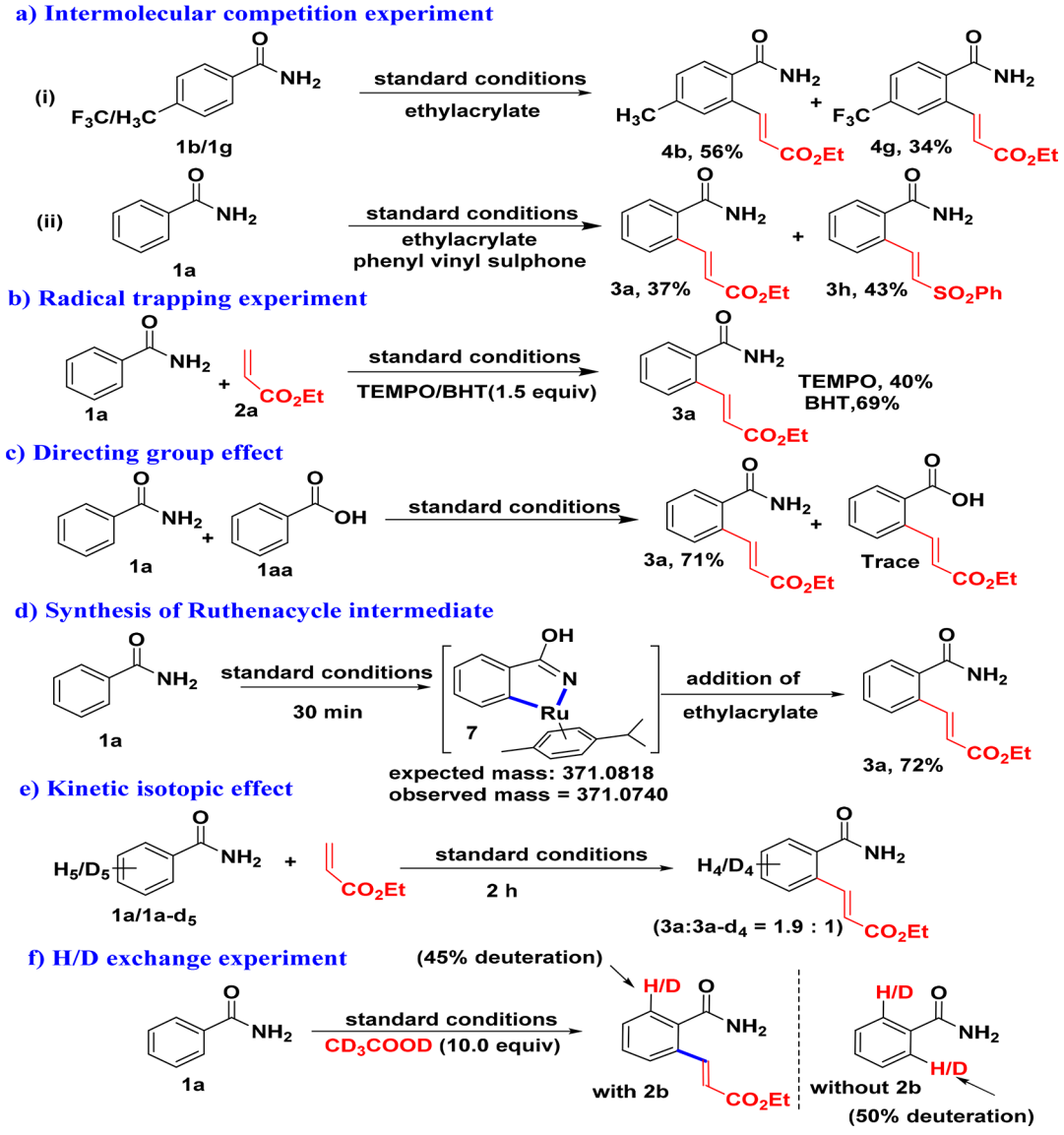
ortho-E-alkenylated product (**3a**) was obtained in 55% yield with a slight decrease in the overall yield. In addition, the synthetic utility of the corresponding product was portrayed through the postsynthetic modification process (Scheme 4, eq ii). For example, treatment of *ortho*-alkenylated benzamide (**3a**) with a catalytic amount of $PdCl_2$ in the mixture of CH_3CN-H_2O solvent afforded the *ortho*-alkenylated benzonitrile (**5a**) in an 80% yield. Also, when *ortho-E*-alkenylated benzamide (**3a**) was treated with 20% H_2SO_4 at 100 °C for 6 h, interestingly, the annulated product (**6a**) was obtained in good yield.

To shed some light on the reaction mechanism pathway, we performed additional control experiments (Scheme 5). Intermolecular competition experiments with an equimolar amount of electron-rich (**1b**) and electron-deficient (**1g**) benzamides with ethyl acrylate under the standard reaction conditions, the desired products were obtained in a ratio of 1.6:1 (**4b**/**4g**, Scheme 5a, eq i) and suggest that this transformation overall proceeds via base-assisted internal electrophilic-type substitution (BIES) over the concerted metalation–deprotonation (CMD) pathway Similarly, the competition reaction between two different activated olefins (**2a** and **2h**) with **1a** gave an approximately equal ratio of corresponding products (**3a**/**3h**, 1:1.1) and demonstrate a similar reactivity toward the benzamides (Scheme 5a, eq ii). Further, the presence of a stoichiometric amount of radical scavengers such as TEMPO and BHT had a negligible effect on the reaction outcome under given conditions, which eventually ruled out the intermediacy of radical species in this process (Scheme 5b). On the other hand, when a competition reaction with a primary benzamide and benzoic acid with a limiting reagent of acrylate was carried out, interestingly, only *ortho-E*-alkenylated benzamide (**3a**) was obtained in a 71% yield, and the result demonstrates the better coordinating ability of amide over acid in this reaction conditions (Scheme 5c).

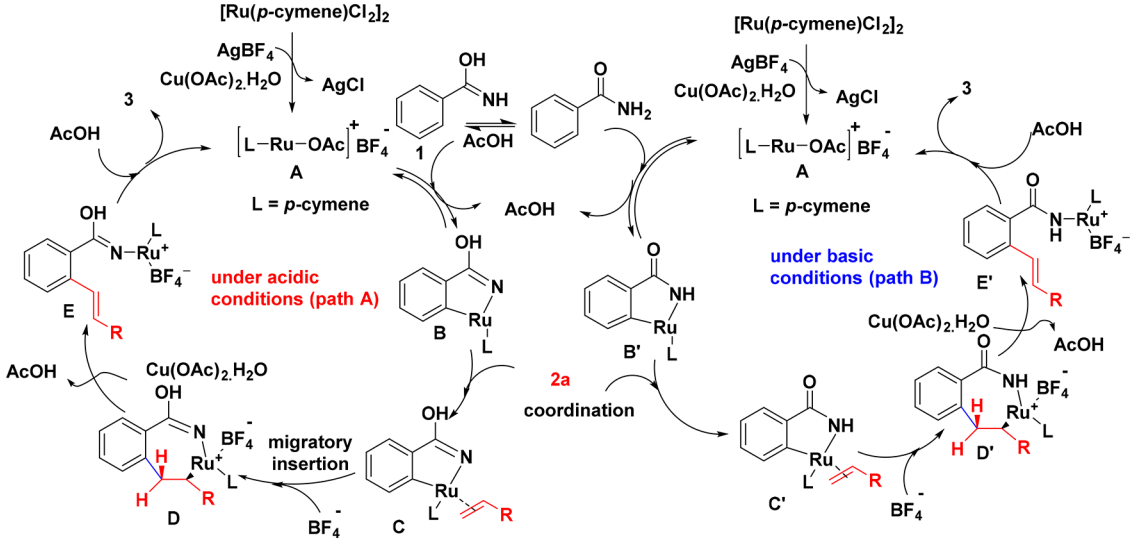
Notably, when a mass spectrometer was recorded for the crude reaction mixture (without the addition of acrylate), a *m*/*z* peak was observed at 371.0740 $[M + H]^+$, which ultimately corresponds to the ruthenacycle intermediate **7** (Scheme 5d). Indeed, the kinetic isotope effect value (KIE ≈ 1.9) was obtained through the competition experiment and illustrates

https://doi.org/10.1021/acs.joc.1c01090
J. Org. Chem. 2021, 86, 9744–9754

Scheme 5. Mechanistic Experiments



Scheme 6. Proposed Reaction Mechanism



https://doi.org/10.1021/acs.joc.1c01090
J. Org. Chem. 2021, 86, 9744−9754

that the cleavage of the C−H bond is the rate-determining step (RDS) in this catalytic cycle (Scheme 5e). Further, the H/D exchange reaction was carried out with CD_3COOD, in both cases (absence and presence of acrylate **2a**), and significant deuterium (up to 50%) incorporation was observed at *ortho*-positions of the product (**3a**) and benzamide (**1a**) as confirmed by ^{1}H NMR analysis (Scheme 5f). This result eventually endorses the reversible nature of C−H metalation in the time scale of the reaction.

Based on these supporting pieces of evidence and literature precedence,[15] a probable reaction mechanism for a control cross-dehydrogenative coupling reaction via a weakly coordinating primary amide group has been depicted in Scheme 6.

First, active cationic Ru(II) species **A** is formed via the anion exchange process in the presence of $AgBF_4$ and $Cu(OAc)_2\cdot H_2O$ salt and, subsequently, the coordination of an imidic nitrogen atom (OH—C═NH) (in situ generated from amide **1** under acidic conditions, path A)[13b] to the active Ru(II)-species **A**, followed by *ortho*-metalation via a base-assisted internal electrophilic-type substitution (BIES) pathway to generate a five-membered ruthenacycle **B**. After that, seven-membered ruthenacycle species **D** formed via the coordination/migratory insertion step in the presence of activated olefin (**2a**). Concomitantly, *β*-hydride elimination of intermediate **D** in the presence of $Cu(OAc)_2\cdot H_2O$ affords *ortho-E*-alkenylated species **E**. Finally, in the presence of acetic acid, the desired product (**3**) formed with the regeneration of active Ru(II) species **A**, which further participate in the catalytic cycle. However, under basic conditions (path B), we believe that reaction would have initiated with coordination of amide nitrogen (−NH) of benzamide (**1**) with species **A**, followed by *ortho*-metalation to generate a five-membered ruthenacycle **B′**. After that, seven-membered ruthenacycle species **D′** formed via the coordination/migratory insertion step. Finally, reductive elimination affords the corresponding *ortho-E*-alkenylated benzamide (**3**)

In summary, we have developed an efficient and controlled strategy for *ortho*-alkenylation of electron-deficient benzamides with activated olefins using a weakly coordinating primary amide group in the presence of an inexpensive Ru(II) salt. Under the reported conditions, exclusive *ortho*-alkenylated benzamide derivatives were obtained with high mono and diastereoselectivity without affording the annulated products, which was the major concern. Free-form amides were further manipulated under the appropriate reaction conditions to make the value-added derivatives. The developed strategy overall circumvents the prerequirement of external auxiliaries and the need for expensive catalysts and provides the direct route to make the alkenylated benzamides in one step. Detailed mechanistic experiments suggest the involvement of the reversible C−H bond metalation step and base-assisted internal electrophilic-type substitution (BIES) pathway and that the fine-tuning of reaction conditions is a key to the success of the controlled introduction of olefins.

EXPERIMENTAL SECTION

General Consideration. Unless otherwise noted, all reagents were purchased from a commercial supplier and used without further purification. All of the benzamides were prepared by following the reported procedure in literature,[16] and acrylates were purchased from Sigma-Aldrich and Alfa Aesar. All reactions were run in sealed tubes, and the indicated temperature was that of an oil bath. 1,2-Dichloroethane was dried prior to use. ^{1}H NMR spectra were recorded at 400 MHz, $^{13}C\{^1H\}$ NMR spectra were recorded at 100 MHz, and $CDCl_3$ and DMSO-d_6 were used as a solvent. Chemical shifts are reported in δ ppm referenced to $CDCl_3$ (δ 7.26), DMSO-d_6 (δ 2.50) for ^{1}H NMR, and $CDCl_3$ (δ 77.0) and DMSO-d_6 (δ 39.5) for ^{13}C NMR. The following abbreviations were used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiple; br, broad singlet and coupling constant (hertz). Infrared spectra were recorded by an FT-IR apparatus. High-resolution mass spectra (HRMS) spectra were obtained on an ESI-TOF (electron spray ionization-time-of-flight) spectrometer, and acetonitrile was used to dissolve the sample. Melting points were recorded with an automated melting point apparatus without correction. Column chromatography was performed on silica gel (100−200) mesh using ethyl acetate and hexanes as eluents in different ratios.

General Procedure for the Synthesis of *ortho*-Alkenylated Benzamide Derivatives (GP-A). To a clean oven-dried 15 mL sealed tube equipped with a magnetic stir bar were sequentially added benzamide (0.25 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene}]_2$ (5 mol %, 7.6 mg), acrylate derivatives (0.5 mmol, 2.0 equiv), and $Cu(OAc)_2\cdot H_2O$ (0.375 mmol, 1.5 equiv). Then DCE (2.0 mL) was added, followed by acetic acid (150 μL), into the reaction mixture. Subsequently, $AgBF_4$ (0.1 mmol, 0.4 equiv) was added under a nitrogen atmosphere, and the reaction tube flushed with nitrogen. The tube was tightly closed and placed in a preheated oil bath with stirring for 8 h. The reaction was monitored by TLC, and after completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and neutralized with $NaHCO_3$. After extraction with ethyl acetate (20 mL × 3), the organic layer was dried over sodium sulfate. The combined organic layer was concentrated under a vacuum, and the crude mixture was purified by column chromatography silica gel using ethyl acetate/hexanes as an eluent.

*(E)-Ethyl 3-(2-Carbamoylphenyl)acrylate (**3a**).* Following GP-A, the title compound was isolated as a white solid (40.5 mg, 75% yield). Mp: 161−163 °C. R_f (6:4 hexane/ethyl acetate) = 0.4. IR (ATR): 3373, 3177, 2921, 1715,1636, 1315, 1181 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ 8.00−7.95 (m, 2H), 7.91−7.82 (m, 1H), 7.61 (s, 1H), 7.47 (m, 3H), 6.58 (d, J = 16.0 Hz, 1H), 4.18 (t, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO) δ 170.1, 166.2, 142.1, 138.1, 131.5, 129.9, 129.8, 127.6, 126.8, 119.3, 60.1, 14.2. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{14}NO_3$ [M+ H]$^+$, 220.0968; found, 220.0975.

*(E)-Methyl 3-(2-Carbamoylphenyl)acrylate (**3b**).* Following GP-A, the title compound was isolated as a white solid (33 mg, 64% yield). Mp: 141−143 °C. R_f (6:4 hexane/ethyl acetate) = 0.4. IR (ATR): 3365, 3182, 1695, 1634, 1271, 1195, 1167, 979 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ 7.98 (d, J = 16.0 Hz, 2H), 7.91−7.82 (m, 1H), 7.59 (s, 1H), 7.48 (dd, J = 4.3, 3.2 Hz, 3H), 6.59 (d, J = 16.0 Hz, 1H), 3.72 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 170.1, 166.6, 142.3, 138.1, 131.5, 129.9, 129.8, 127.6, 126.8, 119.0, 51.6. HRMS (ESI-TOF): m/z calcd for $C_{11}H_{12}NO_3$ [M + H]$^+$, 206.0812; found, 206.0816.

*(E)-Propyl 3-(2-Carbamoylphenyl)acrylate (**3c**).* Following GP-A, the title compound was isolated as a white solid (35.3 mg, 60% yield). Mp: 143−145 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3406, 3297, 2978, 1703, 1639, 1320, 1186, 769, 622 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ 7.99 (d, J = 16.0 Hz, 2H), 7.89 (dd, J = 6.8, 2.6 Hz, 1H), 7.62 (s, 1H), 7.47 (dd, J = 5.0, 3.4 Hz, 3H), 6.59 (d, J = 16.0 Hz, 1H), 4.10 (t, J = 6.7 Hz, 2H), 1.65 (dd, J = 14.2, 7.0 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 170.1, 166.2, 142.2, 138.0, 131.5, 129.9, 129.8, 127.6, 126.8, 119.3, 65.5, 21.6, 10.3. HRMS (ESI-TOF): m/z calcd for $C_{13}H_{16}NO_3$ [M + H]$^+$, 234.1125; found, 234.1116.

*(E)-Butyl 3-(2-Carbamoylphenyl)acrylate (**3d**).* Following GP-A, the title compound was isolated as a white solid (30 mg, 48% yield). Mp: 140−141 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3364, 3182, 1712, 1643, 1275, 1169, 977, 761 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 16.0 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 7.43 (dd, J = 15.4, 7.3 Hz, 2H), 6.39 (d, J = 15.9 Hz, 1H), 6.28 (s, 1H), 5.99 (s, 1H), 4.18 (t, J = 6.7 Hz, 2H), 1.74−1.57 (m, 2H), 1.41 (dd, J = 15.0, 7.5 Hz, 2H), 0.95 (t, J = 7.4

https://doi.org/10.1021/acs.joc.1c01090
J. Org. Chem. 2021, 86, 9744−9754

Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.7, 166.6, 141.9, 135.8, 133.1, 130.7, 129.7, 127.7, 127.3, 121.0, 64.6, 30.7, 19.1, 13.7. HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{18}NO_3$ $[M + H]^+$, 248.1281; found, 248.1285.

*(E)-Cyclohexyl 3-(2-Carbamoylphenyl)acrylate (**3e**).* Following GP-A, the title compound was isolated as a white solid (30 mg, 44% yield). Mp: 132−134 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3402, 3201, 2930, 2860, 1702, 1640, 1167, 1016 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 15.9 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.42 (dd, *J* = 15.0, 7.5 Hz, 2H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.31 (s, 1H), 6.03 (s, 1H), 4.90−4.80 (m, 1H), 1.88 (d, *J* = 8.9 Hz, 2H), 1.75 (dd, *J* = 8.8, 3.7 Hz, 2H), 1.53−1.22 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.7, 165.9, 141.6, 135.8, 133.1, 130.7, 129.6, 127.8, 127.3, 121.6, 72.9, 31.6, 25.4, 23.7. HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{20}NO_3$ $[M + H]^+$, 274.1438; found, 274.1433.

*(E)-2-Phenoxyethyl 3-(2-Carbamoylphenyl)acrylate (**3f**).* Following GP-A, the title compound was isolated as a white solid (23 mg, 29% yield). Mp: 156−158 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3368, 3176, 1709, 1643, 1503, 1238, 1208, 979, 750 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 8.09−7.85 (m, 3H), 7.61 (s, 1H), 7.52−7.42 (m, 3H), 7.36−7.23 (m, 2H), 6.96 (dd, *J* = 13.9, 7.6 Hz, 3H), 6.65 (d, *J* = 16.0 Hz, 1H), 4.53−4.46 (m, 2H), 4.28−4.20 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 170.1, 166.2, 158.2, 142.7, 138.1, 131.5, 129.9, 129.8, 129.6, 127.6, 126.9, 120.9, 118.9, 114.5, 65.7, 62.8. HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{18}NO_4$ $[M + H]^+$, 312.1230; found, 312.1225.

*2-(2-(Methylsulfonyl)vinyl)benzamide (E/Z = 4:1) (**3g**).* Following GP-A, the title compound was isolated as a white solid (24 mg, 43% yield). Mp: 170−172 °C. R_f (5:5 hexane/ethyl acetate) = 0.4. IR (ATR): 3374, 3179, 1648, 1620, 1398, 1285, 1122, 970, 746 cm^{-1}. *E*-Isomer ^1H NMR (400 MHz, DMSO): δ 8.02 (s, 1H), 7.88 (d, *J* = 15.6 Hz, 2H), 7.64 (s, 1H), 7.57−7.45 (m, 4H), 3.09 (s, 3H). *Z*-Isomer ^1H NMR (400 MHz, DMSO): δ 7.40 (dt, *J* = 10.3, 7.0 Hz, 1H), 7.31 (t, *J* = 7.1 Hz, 0.35H), 3.00 (s, 0.78H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 170.8, 169.7, 139.0, 138.0, 136.8, 135.9, 130.5, 130.2, 130.0, 129.9, 129.7, 129.2, 127.9, 127.4, 127.2, 126.6, 54.9, 42.6. HRMS (ESI-TOF): *m/z* calcd for $C_{10}H_{12}NO_3S$ $[M + H]^+$, 226.0532; found, 226.0528.

*(E)-2-(2-(Phenylsulfonyl)vinyl)benzamide (**3h**).* Following GP-A, the title compound was isolated as a white solid (62 mg, 70% yield). Mp: 203−204 °C. R_f (5:5 hexane/ethyl acetate) = 0.4. IR (ATR): 1694, 1424, 1378. ^1H NMR (400 MHz, DMSO): δ 8.10−7.98 (m, 1H), 7.89 (m, 4H), 7.81−7.63 (m, 5H), 7.62−7.56 (d, *J* = 15.6 Hz, 1H), 7.55−7.48 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 169.7, 140.6, 139.9, 138.1, 133.7, 130.6, 130.0, 129.9, 129.7, 129.5, 128.9, 127.9, 127.7, 127.5, 127.1. HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{14}NO_3S$ $[M + H]^+$, 288.0689; found, 288.0686.

*Diethyl 2-Carbamoylstyrylphosphonate (E/Z = 7:1) (**3i**).* Following GP-A, the title compound was isolated as a white solid (32.6 mg, 49% yield). Mp: 126−128 °C. R_f (ethyl acetate) = 0.4. IR (ATR): 3368, 3190, 2984, 2924, 1665, 1380, 1225, 1021, 958, 856 cm^{-1}. *E*-Isomer ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.89−7.85 (m, 1H), 7.74 (d, *J* = 17.6 Hz, 1H), 7.71−7.58 (m, 1H), 7.52−7.41 (m, 3H), 6.54 (dd, *J* = 18.3, 17.7 Hz, 1H), 4.06−3.97 (m, 4H), 1.28−1.23 (m, 6H). *Z*-Isomer ^1H NMR (400 MHz, DMSO): δ 7.38−7.22 (m, 0.88H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.1, 170.1, 145.1, 137.7, 132.4, 132.1, 129.7, 127.5, 126.5, 117.1, 115.3, 61.4, 61.3, 61.0, 16.2, 16.2. HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{19}NO_4P$ $[M + H]^+$, 284.1046; found, 284.1045.

*(E)-2-Styrylbenzamide (**3j**).* Following GP-A, the title compound was isolated as a white solid (21 mg, 38% yield). Mp: 189−191 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3398, 3173, 1642, 1620, 1493, 1395, 962, 757,630 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 7.90−7.81 (m, 2H), 7.55−7.26 (m, 10H), 7.22 (d, *J* = 16.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 170.8, 137.1, 136.5, 134.5, 129.7, 129.5, 128.8, 127.8, 127.5, 127.2, 126.5, 126.1, 125.4. HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{14}NO$ $[M + H]^+$, 224.1070; found, 224.1068.

*(E)-2-(4-Fluorostyryl)benzamide (**3k**).* Following GP-A, the title compound was isolated as a white solid (20 mg, 33% yield). Mp: 176−178 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3375, 3180, 1637, 1622, 1508, 1400, 1231, 959, 816, 748, 633 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 7.88 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.56 (dd, *J* = 8.1, 5.8 Hz, 2H), 7.45 (dd, *J* = 16.0, 5.5 Hz, 4H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.27−7.18 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 170.7, 162.9, 160.5, 136.5, 134.5, 133.7, 129.6, 128.6, 128.4, 128.3, 127.6, 127.3, 126.1, 125.4, 115.8, 115.6. HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{13}NOF$ $[M + H]^+$, 242.0976; found, 242.0973.

*(E)-Ethyl 3-(2-Carbamoyl-5-methoxyphenyl)acrylate (**4a**).* Following GP-A, the title compound was isolated as a white solid (38.5 mg, 64% yield). Mp: 167−169 °C. R_f (6:4 hexane/ethyl acetate) = 0.3. IR (ATR): 3355, 3181, 1713, 1640, 1614, 1563, 1398, 1296, 1232, 1032, 810, 678, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 15.9 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 5.88 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.1, 166.4, 161.3, 142.4, 135.5, 129.8, 127.9, 121.3, 115.2, 112.4,, 60.7, 55.5, 14.3. HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{16}NO_4$ $[M + H]^+$, 250.1074; found, 250.1080.

*(E)-Ethyl 3-(2-Carbamoyl-5-methylphenyl)acrylate (**4b**).* Following GP-A, the title compound was isolated as a white solid (35 mg, 61% yield). Mp: 172−174 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3363, 3181, 1709, 1636, 1312, 1275, 1176, 977, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 16.0 Hz, 1H), 7.54−7.39 (m, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 6.38 (d, *J* = 16.0 Hz, 1H), 5.92 (s, 1H), 5.83 (s, 1H),4.25 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.5, 166.5, 142.2, 141.1, 133.3, 132.9, 130.55, 128.0, 127.9, 120.9, 60.6, 21.4, 14.3. HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{16}NO_3$ $[M + H]^+$, 234.1125; found, 234.1117.

*(E)-Ethyl 3-(5-Carbamoylbenzo[d][1,3]dioxol-4-yl)acrylate (**4c**).* Following GP-A, the title compound was isolated as a white solid (36 mg, 55% yield). Mp: 207−209 °C. R_f (6:4 hexane/ethyl acetate) = 0.3. IR (ATR): 3374, 3194, 1705, 1640, 1607, 1455,1385, 1248, 1189,1071, 1054, 914, 675 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 7.90 (d, *J* = 16.3 Hz, 2H), 7.49 (s, 1H), 7.03−701 (m, 2H), 6.67 (d, *J* = 16.2 Hz, 1H), 6.20 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 169.4, 166.3, 148.4, 146.9, 137.6, 131.5, 121.9, 121.9, 114.7, 108.8, 102.2, 60.2, 14.1. HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{14}NO_5$ $[M + H]^+$, 264.0866; found, 264.0874.

*(E)-Ethyl 3-(2-Carbamoyl-5-fluorophenyl)acrylate (**4d**).* Following GP-A, the title compound was isolated as a white solid (41 mg, 68% yield). Mp: 164−166 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3321,, 3144, 1669, 1622, 1587,1414, 1396, 1226, 1158, 852 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 7.95−7.91 (m, 2H), 7.79 (dd, *J* = 10.5, 2.4 Hz, 1H), 7.63 (s, 1H), 7.54 (dd, *J* = 8.5, 5.9 Hz, 1H), 7.31 (td, *J* = 8.5, 2.5 Hz, 1H), 6.69 (d, *J* = 16.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 169.3, 165.9, 162.5 (d, $^1J_{C-F}$ = 247.2 Hz) 140.9 (d, $^4J_{C-F}$ = 2.0 Hz), 134.5 (d, $^3J_{C-F}$ = 8.2 Hz), 130.2 (d, $^3J_{C-F}$ = 8.7 Hz), 120.8, 116.7 (d, $^2J_{C-F}$ = 22.3 Hz) 113.4 (d, $^2J_{C-F}$ = 22.7 Hz), 60.2, 14.2. HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{13}FNO_3$ $[M + H]^+$, 238.0874; reported, 238.0876.[12a]

*(E)-Ethyl 3-(2-Carbamoyl-5-chlorophenyl)acrylate (**4e**).* Following GP-A, the title compound was isolated as a white solid (37 mg, 57% yield). Mp: 196−198 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3378, 3202, 1691, 1656, 1371, 1281, 1245, 1038, 645, cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 8.05−7.97 (m, 2H), 7.89 (d, *J* = 16.0 Hz, 1H), 7.68 (s, 1H), 7.54−7.47 (m, 2H), 6.71 (d, *J* = 16.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 169.2, 165.9, 140.5, 136.5, 134.6, 133.8, 129.5, 126.6, 120.9, 60.2, 14.2. HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{13}ClNO_3$ $[M + H]^+$, 254.0578; found, 254.0570.

*(E)-Ethyl 3-(5-Bromo-2-carbamoylphenyl)acrylate (**4f**).* Following GP-A, the title compound was isolated as a white solid (40 mg, 57%

https://doi.org/10.1021/acs.joc.1c01090
J. Org. Chem. 2021, 86, 9744−9754

yield). Mp: 198−200 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3373, 3203, 16942, 1652, 1384, 1370,1290, 1243, 1198, 1039, 979, 872 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 8.11 (d, J = 1.7 Hz, 1H), 8.02 (s, 1H), 7.88 (d, J = 16.0 Hz, 1H), 7.66 (dd, J = 8.3, 1.8 Hz, 2H), 7.42 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 16.0 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 169.2, 165.9, 140.4, 136.9, 133.9, 132.4, 129.6, 129.4, 123.2, 120.9, 60.2, 14.2. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{12}BrNNaO_3$ $[M + Na]^+$, 319.9893; found, 319.9889.

*(E)-Ethyl 3-(2-Carbamoyl-5-(trifluoromethyl)phenyl)acrylate (**4g**).* Following GP-A, the title compound was isolated as a white solid (31 mg, 43% yield). Mp: 188−190 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3374, 3203, 1694, 1657, 1321, 1276, 1177, 1133, 1040 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 8.19−8.17 (m, 2H), 7.85−7.81 (m, 3H), 7.67 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 16.0 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 169.1, 165.0, 141.6, 140.1, 139.6, 131.0 (q, $^1J_{C-F}$ = 271 Hz), 130.2 (q, $^2J_{C-F}$ = 32 Hz), 128.5, 126.3 (q, $^3J_{C-F}$ = 3.8 Hz), 125.0, 124.8, 123.8 (q, $^3J_{C-F}$ = 3.8 Hz), 121.6, 60.3, 14.1. HRMS (ESI-TOF): m/z calcd for $C_{13}H_{13}F_3NO_3$ $[M + H]^+$, 288.0848; found, 288.0851.

*(E)-Ethyl 3-(2-Carbamoyl-5-nitrophenyl)acrylate (**4h**).* Following GP-A, the title compound was isolated as a white solid (20 mg, 30% yield). Mp: 189−191 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3351, 3210, 1679, 1518, 1353, 1285, 1212, 1178, 1040 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 8.64 (d, J = 2.0 Hz, 1H), 8.30−8.20 (m, 2H), 7.93−7.84 (m, 2H), 7.72 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 16.0 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO): δ 168.6, 166.2, 165.7, 149.1, 148.2, 143.3, 140.0, 139.63, 133.1, 129.1, 128.9, 124.2, 123.5, 122.4, 121.8, 60.4, 14.2. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{13}N_2O_5$ $[M + H]^+$, 265.0819; found, 265.0827.

*(E)-Methyl 3-(2-Carbamoyl-5-methylphenyl)acrylate (**4i**).* Following GP-A, the title compound was isolated as a white solid (33 mg, 60% yield). Mp: 206−208 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3373, 3194, 1695, 1655, 1389, 1301, 1226, 1034, 871 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 16.0 Hz, 1H), 7.51−7.43 (m, 2H), 7.23 (d, J = 7.8 Hz, 1H), 6.39 (d, J = 16.0 Hz, 1H), 5.82 (s, 2H), 3.80 (s, 3H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 170.0, 166.6, 142.5, 139.5, 135.0, 131.7, 130.4, 127.7, 127.2, 118.6, 51.5, 20.7. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{14}NO_3$ $[M + H]^+$, 220.0968; found, 220.0976.

*(E)-Methyl 3-(2-Carbamoyl-5-fluorophenyl)acrylate (**4j**).* Following GP-A, the title compound was isolated as a white solid (31 mg, 57% yield). Mp: 189−191 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3389, 3204, 1697, 1652, 1392, 1304, 1217, 1034, 976 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 8.03−7.90 (m, 2H), 7.79 (dd, J = 10.4, 2.5 Hz, 1H), 7.65−7.50 (m, 2H), 7.31 (td, J = 8.5, 2.5 Hz, 1H), 6.70 (d, J = 16.0 Hz, 1H), 3.73 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 169.2, 166.4, 162.5(d, $^1J_{C-F}$ = 245.0 Hz), 141.0(d, $^4J_{C-F}$ = 2.0 Hz), 134.43, 130.2(d, $^3J_{C-F}$ = 9 Hz), 120.5, 116.7(d, $^2J_{C-F}$ = 21.7 Hz), 113.4(d, $^2J_{C-F}$ = 22.7 Hz), 51.65. HRMS (ESI-TOF): m/z calcd for $C_{11}H_{11}FNO_3$ $[M + H]^+$, 224.0717; found, 224.0712.

*(E)-Ethyl 3-(2-Carbamoyl-4-methylphenyl)acrylate (**4k**).* Following GP-A, the title compound was isolated as a white solid (32 mg, 55% yield). Mp: 177−179 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3380, 3209, 1688, 1652, 1385, 1301, 1278, 1043, 978, 832 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 7.93 (d, J = 16.0 Hz, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.56 (s, 1H), 7.28 (d, J = 7.6 Hz, 2H), 6.53 (d, J = 16.0 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.35 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 170.2, 166.3, 142.0, 139.9, 138.1, 130.4, 128.7, 128.1, 126.8, 118.3, 60.0, 20.8, 14.2. HRMS (ESI-TOF): m/z calcd for $C_{13}H_{16}NO_3$ $[M + H]^+$, 234.1125; found, 234.1129.

*(E)-Ethyl 3-(2-Carbamoyl-4-methoxyphenyl)acrylate (**4l**).* Following GP-A, the title compound was isolated as a white solid (26 mg, 42% yield). Mp: 178−180 °C. R_f (6:4 hexane/ethyl acetate) = 0.3. IR (ATR): 3380, 3209, 1688, 1652, 1385, 1301, 1278, 1043, 978, 832 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 15.9 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.11−6.92 (m, 2H), 6.31 (d, J = 15.9 Hz, 1H), 6.04 (s, 1H), 5.87 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.8, 160.7, 141.2, 137.5, 128.8, 125.1, 118.9, 116.7, 112.8, 60.5, 55.6, 14.3. HRMS (ESI-TOF): m/z calcd for $C_{13}H_{16}NO_4$ $[M + H]^+$, 250.1074; found, 250.1082.

*(E)-Methyl 3-(2-Carbamoyl-4-methylphenyl)acrylate (**4m**).* Following GP-A, the title compound was isolated as a white solid (30 mg, 55% yield). Mp: 195−197 °C. R_f (6:4 hexane/ethyl acetate) = 0.5. IR (ATR): 3399, 3192, 1702, 1643, 1393, 1273, 1242, 11175, 1018, 832 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 7.94 (d, J = 16.1 Hz, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.56 (s, 1H), 7.29 (d, J = 7.5 Hz, 2H), 6.54 (d, J = 16.0 Hz, 1H), 3.71 (s, 3H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 170.2, 166.7, 143.0, 142.2, 139.9, 138.1, 130.4, 128.7, 128.1, 126.7, 117.9, 51.5, 20.8. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{14}NO_4$ $[M + H]^+$, 220.0968; found, 220.0960.

*(E)-4-Methoxy-2-(2-(phenylsulfonyl)vinyl)benzamide (**4n**).* Following GP-A, the title compound was isolated as a white solid (48 mg, 63% yield). Mp: 175−177 °C. R_f (5:5 hexane/ethyl acetate) = 0.3. IR (ATR): 3450, 3159, 1668, 1597, 1392, 1296, 1246, 1139, 1083, 1027, 833 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 8.12 (d, J = 15.4 Hz, 1H), 7.93 (d, J = 7.5 Hz, 3H), 7.78−7.59 (m, 5H), 7.55−7.51 (m, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.07−7.03 (m, 1H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 169.4, 160.3, 140.6, 140.3, 133.7, 132.3, 130.2, 129.8, 129.6, 129.0, 127.7, 127.2, 116.6, 111.9, 55.7. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{16}NO_4S$ $[M + H]^+$, 318.0795; found, 318.0793.

*2-(2-(Phenylsulfonyl)vinyl)-4-(trifluoromethyl)benzamide (E/Z = 7:1) (**4o**).* Following GP-A, the title compound was isolated as a white solid (69 mg, 75% yield). Mp: 215−217 °C. R_f (5:5 hexane/ethyl acetate) = 0.4. IR (ATR): 3367, 3168, 1661, 1609, 1330, 1308, 1280, 1124, 1080, 850 cm-^{1}. *E* isomer- ^1H NMR (400 MHz, DMSO): δ 8.25 (d, J = 18.1 Hz, 2H), 7.97−7.84 (m, 7H), 7.73 (m, 6H). *Z* isomer- ^1H NMR (400 MHz, DMSO) 8.15 (d, J = 14.5 Hz, 0.27 H), 7.63−7.52 (m, 0.48). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 168.7, 141.8, 140.1, 137.6, 132.5 (q, $^1J_{C-F}$ = 271 Hz), 130.8, 130.3 (q, $^2J_{C-F}$ = 32 Hz), 129.6 (q, $^2J_{C-F}$ = 26 Hz), 128.9, 127.7, 127.1 (q, $^3J_{C-F}$ = 2.8 Hz), 124.9, 124.4 (q, $^3J_{C-F}$ = 3.4 Hz). HRMS (ESI-TOF): m/z calcd for $C_{16}H_{12}F_3NNaO_3S$ $[M + Na]^+$, 378.0382; found, 378.0391.

*(E)-4-(2-(Phenylsulfonyl)vinyl)benzo[d][1,3]dioxole-5-carboxamide (**4p**).* Following GP-A, the title compound was isolated as a white solid (55 mg, 67% yield). Mp: 201−203 °C. R_f (5:5 hexane/ethyl acetate) = 0.4. IR (ATR): 3401, 3204, 2887, 1656, 1454, 1445, 1296, 1254, 1142, 1067, 923, 830 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 8.01 (d, J = 15.6 Hz, 1H), 7.97−7.88 (m, 2H), 7.73 (d, J = 7.3 Hz, 1H), 7.66 (t, J = 7.5 Hz, 2H), 7.52 (s, 2H), 7.25 (d, J = 15.6 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.17 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO): δ 169.1, 148.7, 147.2, 140.4, 135.3, 133.8, 130.9, 130.7, 129.8, 127.2, 122.3, 112.8, 109.4, 102.5. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{13}NNaO_5S$ $[M + Na]^+$, 354.0407; found, 354.0411.

*3,5-Dimethoxy-2-(2-(phenylsulfonyl)vinyl)benzamide (E/Z = 2:1) (**4q**).* Following GP-A, the title compound was isolated as a white solid (56 mg, 74% yield). Mp: 215−217 °C. R_f (5:5 hexane/ethyl acetate) = 0.4. IR (ATR): 3395, 3206, 1652, 1600, 1388, 1300, 1282, 1140, 1081, 973,861 cm^{-1}. *E*-Isomer ^1H NMR (400 MHz, DMSO): δ 8.02 (s, 1H), 7.95−7.62 (m, 13H),7.27 (d, J = 15.4 Hz, 1H), 6.70 (br.s, 1H), 6.64 (br.s, 1H), 3.90 (s, 3H), 3.86 (s, 3H). *Z*-Isomer ^1H NMR (400 MHz, DMSO): δ 7.43 (s, 0.51H), 6.55 (s, 0.65H), 6.50 (s, 0.57H), 3.75 (s, 1.91H), 3.66 (s, 1.87H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 170.4, 169., 162.1, 161.0, 158.9, 158.2, 142.9, 141.3, 138.9, 138.7, 136.0, 133.8, 133.3, 129.6, 129.4, 127.7, 127.2, 126.9, 115.0, 110.1, 105.1, 103.7, 99.3, 99.1, 56.2, 55.8, 55.8, 55.3, 54.6, 20.5. HRMS (ESI-TOF): m/z calcd for $C_{17}H_{18}NO_5S$ $[M + H]^+$, 348.0900; found, 348.0901.

*5-Methyl-2-(2-(phenylsulfonyl)vinyl)benzamide (E/Z = 8:1) (**4r**).* Following GP-A, the title compound was isolated as a white solid (56 mg, 74% yield). Mp: 215−217 °C. R_f (5:5 hexane/ethyl acetate) = 0.4. IR (ATR): 3395, 3206, 1652, 1600, 1388, 1300, 1282,, 1140, 1081, 973,861 cm^{-1}. *E*-Isomer ^1H NMR (400 MHz, DMSO): δ 8.02−7.93 (m, 2H), 7.90 (d, J = 7.4 Hz, 2H), 7.69 (m, 5H), 7.51 (d, J

https://doi.org/10.1021/acs.joc.1c01090
J. Org. Chem. 2021, 86, 9744−9754

= 15.4 Hz, 1H), 7.35 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 2.72 (s, 3H). *Z*-Isomer ^{1}H NMR (400 MHz, DMSO) 7.18 (s, 0.13H), 7.11 (t, J = 6.0 Hz, 0.23H) 2.26 (s, 0.36H). ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 169.8, 140.8, 140.7, 139.7, 138.2, 133.6, 130.5, 129.6, 128.3, 127.9, 127.4, 127.2, 127.1, 20.8. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{16}NO_3S$ [M + H]$^+$, 302.0845; found, 302.0852.

Procedure for Scale-up Synthesis. To a clean oven-dried 100 mL sealed tube equipped with a magnetic stir bar were sequentially added benzamide **1a** (4.0 mmol, 1 equiv), [$RuCl_2$(*p*-cymene]$_2$ (5 mol %, 122.4 mg), ethyl acrylate (8.0 mmol, 2.0 equiv), and $Cu(OAc)_2\cdot H_2O$ (6 mmol, 1.5 equiv). Then DCE (25.0 mL) was added, followed by acetic acid (2.2 mL), into the reaction mixture. Subsequently, $AgBF_4$ (1.6 mmol, 0.4 equiv) was added under a nitrogen atmosphere, and the reaction tube was flushed with nitrogen three times. The tube was tightly closed and placed in a preheated oil bath with stirring for 8 h. The reaction was monitored by TLC, and after completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and neutralized with $NaHCO_3$. After extraction with ethyl acetate (20 mL × 3), the organic layer was dried over sodium sulfate. The combined organic layer was concentrated under a vacuum, and the crude mixture was purified by column chromatography silica gel using ethyl acetate/hexanes as an eluent. The desired product was isolated in 55% yield (482 mg).

*Procedure for the Synthesis of (E)-Ethyl 3-(2-Cyanophenyl)-acrylate (**5a**).* By following a reported procedure,[17] **3a** (0.2 mmol, 43 mg) in CH_3CN/H_2O (1:1) was treated with $PdCl_2$ (10 mol %, 3.5 mg) at 50 °C for 12 h. After completion, the reaction mixture was quenched with water and extracted with ethyl acetate (10 mL × 3). The solvent was removed in a vacuum, and the crude product was purified by column chromatography as a white solid (32 mg, 80% yield). R_f (9:1 hexane/ethyl acetate) = 0.5. Mp: 69−71 °C. IR (ATR): 2999, 2907, 2298, 1715, 1639, 1473, 1358, 1311, 1272, 1178, 976 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ 8.12 (d, J = 8.0 Hz, 1H), 7.93 (dd, J = 7.7, 1.0 Hz, 1H), 7.84−7.73 (m, 2H), 7.63 (dd, J = 7.7, 0.9 Hz, 1H), 6.90 (d, J = 15.9 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 165.5, 138.9, 136.4, 133.7, 133.5, 130.8, 127.5, 122.9, 117.2, 111.7, 60.6, 14.1. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{11}NNaO_2$ [M + Na]$^+$, 224.0682; found, 224.0686.

*Procedure for the Synthesis of 2-(3-Oxoisoindolin-1-yl)acetic Acid (**6a**).* By following a reported procedure,[18] a mixture of **3a** (0.2 mmol, 46 mg) was prepared in 20% (v/v) H_2SO_4 (2.5 mL) and heated at 100 °C for 6 h. After completion of the reaction, the mixture was cooled to room temperature, diluted with water and then extracted with ethyl acetate (15 mL × 3). The organic layer was dried in a vacuum. Recrystallization with dichloromethane and hexane produced a white solid (30 mg, 79% yield). Mp: 146−148 °C. IR (ATR): 3106, 1746, 1704, 1288, 1215,1077, 1063, 1007, 923, 740 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ 7.85−7.70 (m, 3H), 7.60 (dd, J = 9.2, 5.6 Hz, 1H), 5.88 (dd, J = 8.1, 4.2 Hz, 1H), 3.16 (dd, J = 16.8, 4.3 Hz, 1H), 2.73 (dd, J = 16.8, 8.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 171.0, 169.9, 149.5, 134.5, 129.5, 125.7, 125.1, 122.9, 77.7. HRMS (ESI-TOF): m/z calcd for $C_{10}H_{10}NO_3$ [M+ H]$^+$, 192.0655, found, 192.0654.

Procedure for Intermolecular Competition Experiment between 1b and 1g. A suspension of [$RuCl_2$(*p*-cymene]$_2$ (7.6 mg, 5.0 mol %), **1b** (0.25 mmol, 1.0 equiv), **1g** (0.25 mmol, 1.0 equiv), **2b** (0.5 mmol, 2.0 equiv), $AgBF_4$ (20 mg, 40 mol %), $Cu(OAc)_2\cdot H_2O$ (75 mg, 1.5 equiv), and AcOH (150 μL, 10.0 equiv) was stirred in DCE (2.0 mL) for 8 h at 100 °C. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and neutralized with $NaHCO_3$. After extraction with ethyl acetate (20 mL × 3), the organic layer was dried over sodium sulfate. The combined organic layer was concentrated under a vacuum, and the crude mixture was purified by column chromatography silica gel using ethyl acetate/hexanes as an eluent. Compounds (**4b** and **4g**) were obtained in 56% and 34% yields, respectively, in a ratio of 1.6:1.

Procedure for Intermolecular competition experiment between 2a and 2h. A suspension of [$RuCl_2$(*p*-cymene]$_2$ (7.6 mg, 5.0 mol %), **1a** (0.25 mmol, 1.0 equiv), **2a** (0.5 mmol, 2.0 equiv), **2h** (0.5 mmol, 2.0 equiv), $AgBF_4$ (20 mg, 40 mol %), $Cu(OAc)_2\cdot H_2O$ (75 mg, 1.5 equiv), and AcOH (150 μL, 10.0 equiv) was stirred in DCE (2.0 mL) for 8 h at 100 °C. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and neutralized with $NaHCO_3$. After extraction with ethyl acetate (20 mL × 3), the organic layer was dried over sodium sulfate. The combined organic layer was concentrated under a vacuum, and the crude mixture was purified by column chromatography silica gel using ethyl acetate/hexanes as an eluent. Compounds **3a** and **3h** were obtained in 37% and 43% yields, respectively, in a ratio of 1:1.6 (**3a**/**3h**).

Kinetic Isotope Effect Experiment: Procedure for Intermolecular Competition Experiment between 1a and 1a-D_5. To a oven-dried sealed tube, following the general procedure, benzamide (**1a**) (30 mg, 0.25 mmol), deuterated benzamide (**1a-D_5**) (32 mg, 0.25 mmol), [$RuCl_2$(*p*-cymene]$_2$ (5 mol %, 7.6 mg), (**2b**, 0.75 mmol, 2.0 equiv), $AgBF_4$ (0.4 equiv, 20 mg), $Cu(OAc)_2\cdot H_2O$ (1.5 equiv, 75 mg), and DCE (2.0 mL) were added. The mixture was stirred at 100 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and neutralized with $NaHCO_3$. After extraction with ethyl acetate (20 mL × 3), the organic layer was dried over sodium sulfate. The combined organic layer was concentrated under a vacuum, and the crude mixture was purified by column chromatography silica gel and ethyl acetate/hexanes as an eluent to give 37% of the product in a combined yield. The ratio of (**3b**) and (**3b-D_4**) was determined by ^{1}H NMR analysis and found to be $k_H/k_D \approx 1.98{:}1$

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01090.

Detailed information on experimental procedures, characterization data, spectra, and crystallographic data (PDF)

Accession Codes

CCDC 2069798 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Amit Kumar − *Department of Chemistry, Indian Institute of Technology Patna, Bihta, Bihar 801106, India;* orcid.org/0000-0002-1683-7740; Email: amitkt@iitp.ac.in, amitktiitk@gmail.com

Authors

Akanksha Singh Baghel − *Department of Chemistry, Indian Institute of Technology Patna, Bihta, Bihar 801106, India*

Anjali Aghi − *Department of Chemistry, Indian Institute of Technology Patna, Bihta, Bihar 801106, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c01090

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Authors gratefully acknowledge the Indian Institute of Technology (IIT) Patna for financial support. The authors also acknowledge SAIF-IIT Patna for providing XRD facilities.

This work is dedicated to Prof. Y. D. Vankar (Department of Chemistry, IISER Trivandrum) on the occasion of his 70th birthday.

REFERENCES

(1) For selected reviews, see: (a) Dalton, T.; Faber, T.; Glorius, F. C−H Activation: Toward Sustainability and Applications. *ACS Cent. Sci.* **2021**, *7*, 245−261. (b) 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. (c) Huang, C.-Y.; Kang, H.; Li, J.; Li, C.-J. En Route to Intermolecular Cross-Dehydrogenative Coupling Reactions. *J. Org. Chem.* **2019**, *84*, 12705−12721. (d) Gensch, T.; James, M. J.; Dalton, T.; Glorius, F. Increasing Catalyst Efficiency in C−H Activation Catalysis. *Angew. Chem., Int. Ed.* **2018**, *57*, 2296−2306. (e) Gensch, T.; Hopkinson, M.; Glorius, F.; Wencel-Delord, J. Mild metal-catalyzed C−H activation: examples and concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900−2936. (f) Hartwig, J. F.; Larsen, M. A. Undirected, Homogeneous C−H Bond Functionalization: Challenges and Opportunities. *ACS Cent. Sci.* **2016**, *2*, 281−292. (g) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon−Carbon Bonds by Oxidizing Two Carbon−Hydrogen Bonds. *Chem. Rev.* **2011**, *111*, 1215−1292. (h) Jun, C.-H. Transition metal-catalyzed carbon−carbon bond activation. *Chem. Soc. Rev.* **2004**, *33*, 610−618. (i) Moritanl, I.; Fujiwara, Y. Aromatic substitution of styrene-palladium chloride complex. *Tetrahedron Lett.* **1967**, *8*, 1119−1122.

(2) See a few important citations: (a) Xia, Y.; Dong, G. Temporary or removable directing groups enable activation of unstrained C−C bonds. *Nat. Rev. Chem.* **2020**, *4*, 600−614. (b) Dey, A.; Sinha, S. K.; Achar, T. K.; Maiti, D. Accessing Remote meta- and para-C(sp^2)−H Bonds with Covalently Attached Directing Groups. *Angew. Chem., Int. Ed.* **2019**, *58*, 10820−10843. (c) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. Transition metal-catalyzed C−H bond functionalizations by the use of diverse directing groups. *Org. Chem. Front.* **2015**, *2*, 1107−1295. (d) Zhang, F.; Spring, D. R. Arene C−H functionalisation using a removable/modifiable or a traceless directing group strategy. *Chem. Soc. Rev.* **2014**, *43*, 6906−6919. (e) Rouquet, G.; Chatani, N. Catalytic Functionalization of C(sp^2)−H and C(sp^3)−H Bonds by Using Bidentate Directing Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−1174. (f) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. Beyond Directing Groups: Transition-Metal-Catalyzed C−H Activation of Simple Arenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236−10254.

(3) (a) Rej, S.; Chatani, N. Rhodium-Catalyzed C(sp2)- or C(sp^3)−H Bond Functionalization Assisted by Removable Directing Groups. *Angew. Chem., Int. Ed.* **2019**, *58*, 8304−8329. (b) Gandeepan, P.; Ackermann, L. Transient Directing Groups for Transformative C−H Activation by Synergistic Metal Catalysis. *Chem.* **2018**, *4*, 199−222. (c) St John-Campbell, S.; Bull, J. A. Transient imines as 'next generation' directing groups for the catalytic functionalization of C−H bonds in a single operation. *Org. Biomol. Chem.* **2018**, *16*, 4582−4595. (d) Frost, C. G.; Paterson, A. J. Directing Remote Meta-C−H Functionalization with Cleavable Auxiliaries. *ACS Cent. Sci.* **2015**, *1*, 418−419. (e) Li, J.; Warratz, S.; Zell, D.; De Sarkar, S.; Ishikawa, E. E.; Ackermann, L. N-Acyl Amino Acid Ligands for Ruthenium(II)-Catalyzed meta-C−H tert-Alkylation with Removable Auxiliaries. *J. Am. Chem. Soc.* **2015**, *137*, 13894−13901. (f) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. Use of a Readily Removable Auxiliary Group for the Synthesis of Pyrrolidones by the Palladium-Catalyzed Intramolecular Amination of Unactivated γ C(sp^3)−H Bonds. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124−11128.

(4) For selected examples, see: (a) Huang, Z.; Lumb, J.-P. Phenol-Directed C−H Functionalization. *ACS Catal.* **2019**, *9*, 521−555. (b) Sambiagio, C.; Schonbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnurch, M. A comprehensive overview of directing groups applied in metal-catalysed C−H functionalisation chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603−6743. (c) Font, M.; Quibell, J. M.; Perry, G. J. P.; Larrosa, I. The use of carboxylic acids as traceless directing groups for regioselective C−H bond functionalization. *Chem. Commun.* **2017**, *53*, 5584−5597. (d) Das, R.; Kumar, G. S.; Kapur, M. Amides as Weak Coordinating Groups in Proximal C−H Bond Activation. *Eur. J. Org. Chem.* **2017**, *2017*, 5439−5459. (e) Ma, W.; Gandeepan, P.; Li, J.; Ackermann, L. Recent advances in positional-selective alkenylations: removable guidance for twofold C−H activation. *Org. Chem. Front.* **2017**, *4*, 1435−1467. (f) 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. (g) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. Transition metal-catalyzed ketone-directed or mediated C−H functionalization. *Chem. Soc. Rev.* **2015**, *44*, 7764−7786. (h) Qi, Z.; Wang, M.; Li, X. Rh(III)-Catalyzed synthesis of sultones through C−H activation directed by a sulfonic acid group. *Chem. Commun.* **2014**, *50*, 9776−9778.

(5) (a) Mori, M.; Kaneko, N.; Ueno, Y.; Yamada, M.; Tanaka, R.; Saito, R.; Shimada, I.; Mori, K.; Kuromitsu, S. Gilteritinib, a FLT3/AXL inhibitor, shows antileukemic activity in mouse models of FLT3 mutated acute myeloid leukemia. *Invest. New Drugs* **2017**, *35*, 556−565. (b) Li, H.; Kim, F. S.; Ren, G.; Hollenbeck, E. C.; Subramaniyan, S.; Jenekhe, S. A. Tetraazabenzodifluoranthene Diimides: Building Blocks for Solution-Processable n-Type Organic Semiconductors. *Angew. Chem., Int. Ed.* **2013**, *52*, 5513−5517. (c) Valeur, E.; Bradley, M. Amide bond formation: beyond the myth of coupling reagents. *Chem. Soc. Rev.* **2009**, *38*, 606−631. (d) Caccia, C.; Maj, R.; Calabresi, M.; Maestroni, S.; Faravelli, L.; Curatolo, L.; Salvati, P.; Fariello, R. G. Safinamide. *Neurology* **2006**, *67*, S18. (e) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. Analysis of the reactions used for the preparation of drug candidate molecules. *Org. Biomol. Chem.* **2006**, *4*, 2337−2347. (f) Crespo, L.; Sanclimens, G.; Pons, M.; Giralt, E.; Royo, M.; Albericio, F. Peptide and Amide Bond-Containing Dendrimers. *Chem. Rev.* **2005**, *105*, 1663−1682. (g) Hadziyannis, S. J.; Sette, H., Jr; Morgan, T. R.; Balan, V.; Diago, M.; Marcellin, P.; Ramadori, G.; Bodenheimer, H., Jr; Bernstein, D.; Rizzetto, M. Peginterferon-α2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann. Intern. Med.* **2004**, *140*, 346−355. (h) Bergbreiter, D. E.; Osburn, P. L.; Li, C. Soluble Polymer-Supported Catalysts Containing Azo Dyes. *Org. Lett.* **2002**, *4*, 737−740.

(6) (a) Zhang, Y.; Struwe, J.; Ackermann, L. Rhodium-Catalyzed Electrooxidative C−H Olefination of Benzamides. *Angew. Chem., Int. Ed.* **2020**, *59*, 15076−15080. (b) Bu, Q.; Rogge, T.; Kotek, V.; Ackermann, L. Distal Weak Coordination of Acetamides in Ruthenium (II)-Catalyzed C− H Activation Processes. *Angew. Chem., Int. Ed.* **2018**, *57*, 765−768. (c) Manikandan, R.; Jeganmohan, M. Temperature-controlled redox-neutral ruthenium-(II)-catalyzed regioselective allylation of benzamides with allylic acetates. *Org. Biomol. Chem.* **2016**, *14*, 7691−7701. (d) Park, J.; Han, S.; Jeon, M.; Mishra, N. K.; Lee, S.-Y.; Lee, J. S.; Kwak, J. H.; Um, S. H.; Kim, I. S. Redox-Neutral Rh(III)-Catalyzed Olefination of Carboxamides with Trifluoromethyl Allylic Carbonate. *J. Org. Chem.* **2016**, *81*, 11353−11359. (e) Lu, Y.; Wang, H.-W.; Spangler, J. E.; Chen, K.; Cui, P.-P.; Zhao, Y.; Sun, W.-Y.; Yu, J.-Q. Rh(III)-catalyzed C−H olefination of N-pentafluoroaryl benzamides using air as the sole oxidant. *Chem. Sci.* **2015**, *6*, 1923−1927. (f) Wang, Y.; Li, C.; Li, Y.; Yin, F.; Wang, X.-S. Rhodium-Catalyzed C−H Olefination of Aryl Weinreb Amides. *Adv. Synth. Catal.* **2013**, *355*, 1724−1728.

(7) (a) Jambu, S.; Shambhavi, C. N.; Jeganmohan, M. Aerobic Oxidative C−H Olefination of Arylamides with Unactivated Olefins via a Rh(III)-Catalyzed C−H Activation. *Org. Lett.* **2021**, *23*, 2964−2970. (b) Logeswaran, R.; Jeganmohan, M. Rhodium(III)-Catalyzed Aerobic Oxidative C−H Olefination of Unsaturated Acrylamides with Unactivated Olefins. *Org. Lett.* **2021**, *23*, 767−771. (c) Hei, Y.-Y.; Song, J.-L.; Zhan, X.-C.; Zhang, X.-G.; Deng, C.-L. The rhodium-catalyzed selective oxidative Heck reaction of amides with allylic esters. *Tetrahedron Lett.* **2019**, *60*, 1557−1561. (d) Li, J.; Liu, J.; Yin, J.; Zhang, Y.; Han, W.; Lan, J.; Wu, D.; Bin, Z.; You, J. Double ortho-C−H Activation/Annulation of Benzamides with Aryl Alkynes: A

https://doi.org/10.1021/acs.joc.1c01090
J. Org. Chem. 2021, 86, 9744−9754

Route to Double-Helical Polycyclic Heteroaromatics. *J. Org. Chem.* **2019**, *84*, 15697−15705. (e) Li, Z.-L.; Wu, P.-Y.; Cai, C. Nickel-catalyzed regioselective C−H halogenation of electron-deficient arenes. *New J. Chem.* **2019**, *43*, 3462−3468. (f) Shrestha, R.; Khanal, H. D.; Lee, Y. R. One-pot construction of diverse and functionalized isochromenoquinolinediones by Rh(III)-catalyzed annulation of unprotected arylamides with 3-diazoquinolinediones and their application for fluorescence sensor. *RSC Adv.* **2019**, *9*, 17347−17357. (g) Zhao, R.; Lu, W. Palladium-Catalyzed β-Arylation of Amide via Primary sp3C−H Activation. *Organometallics* **2018**, *37*, 2188−2192. (h) Wu, Y.; Sun, P.; Zhang, K.; Yang, T.; Yao, H.; Lin, A. Rh(III)-Catalyzed Redox-Neutral Annulation of Primary Benzamides with Diazo Compounds: Approach to Isoquinolinones. *J. Org. Chem.* **2016**, *81*, 2166−2173. (i) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. Rhodium-catalyzed Oxidative Coupling/Cyclization of Benzamides with Alkynes via C−H Bond Cleavage. *Chem. Lett.* **2010**, *39*, 744−746.

(8) Patureau, F. W.; Besset, T.; Glorius, F. Rhodium-Catalyzed Oxidative Olefination of C−H Bonds in Acetophenones and Benzamides. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064−1067.

(9) (a) Laha, J. K.; Kaur Hunjan, M.; Bhimpuria, R. A.; Kathuria, D.; Bharatam, P. V. Geometry Driven Intramolecular Oxidative Cyclization of Enamides: An Umpolung Annulation of Primary Benzamides with Acrylates for the Synthesis of 3-Methyleneisoindolin-1-ones. *J. Org. Chem.* **2017**, *82*, 7346−7352. (b) Reddy, M. C.; Jeganmohan, M. Ruthenium-Catalyzed Cyclization of Aromatic Nitriles with Alkenes: Stereoselective Synthesis of (Z)-3-Methyleneisoindolin-1-ones. *Org. Lett.* **2014**, *16*, 4866−4869.

(10) (a) Panda, N.; Jena, A. K.; Raghavender, M. Stereoselective Synthesis of Enamides by Palladium Catalyzed Coupling of Amides with Electron Deficient Olefins. *ACS Catal.* **2012**, *2*, 539−543. (b) Lee, J. M.; Ahn, D.-S.; Jung, D. Y.; Lee, J.; Do, Y.; Kim, S. K.; Chang, S. Hydrogen-Bond-Directed Highly Stereoselective Synthesis of Z-Enamides *via* Pd-Catalyzed Oxidative Amidation of Conjugated Olefins. *J. Am. Chem. Soc.* **2006**, *128*, 12954−12962.

(11) Bao, R.-P.; Chen, X.; Li, C.; Wang, D.-H. Ir(III)-Catalyzed Mono-Olefination of Aryl C−H Bonds Using − SCF_3 as a Weak Directing Group. *Org. Lett.* **2019**, *21*, 8116−8121.

(12) (a) Yang, F.; Ackermann, L. Dehydrative C−H/N−OH Functionalizations in H_2O by Ruthenium(II) Catalysis: Subtle Effect of Carboxylate Ligands and Mechanistic Insight. *J. Org. Chem.* **2014**, *79*, 12070−12082. (b) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. Rh(III)-Catalyzed Directed C−H Olefination Using an Oxidizing Directing Group: Mild, Efficient, and Versatile. *J. Am. Chem. Soc.* **2011**, *133*, 2350−2353. (c) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. Ruthenium-Catalyzed Oxidative C−H Bond Olefination of N-Methoxybenzamides Using an Oxidizing Directing Group. *Org. Lett.* **2012**, *14*, 736−739.

(13) (a) Jaiswal, Y.; Mandal, S.; Das, P.; Kumar, A. One-Pot Synthesis of Orange-Red Fluorescent Dimeric 2H-Pyrrolo[2,3-c]isoquinoline-2,5(3H)-diones from Benzamides and Maleimides via Ru(II)-Catalyzed Sequential C−C/C−N/C−C Bond Formation. *Org. Lett.* **2020**, *22*, 1605−1610. (b) Jaiswal, Y.; Kumar, A. Acid-promoted palladium(II)-catalyzed ortho-halogenation of primary benzamides: En route to halo-arenes. *Catal. Commun.* **2019**, *131*, 105784. (c) Jaiswal, Y.; Kumar, Y.; Kumar, A. The palladium(II)-catalyzed regioselective ortho-C−H bromination/iodination of arylacetamides with in situ generated imidic acid as the directing group: mechanistic exploration. *Org. Biomol. Chem.* **2019**, *17*, 6809−6820. (d) Jaiswal, Y.; Kumar, Y.; Kumar, A. Palladium-Catalyzed Regioselective C−H Alkenylation of Arylacetamides via Distal Weakly Coordinating Primary Amides as Directing Groups. *J. Org. Chem.* **2018**, *83*, 1223−1231. (d) Jaiswal, Y.; Kumar, Y.; Thakur, R.; Pal, J.; Subramanian, R.; Kumar, A. Primary Amide Directed Regioselective ortho-C−H-Arylation of (Aryl)Acetamides. *J. Org. Chem.* **2016**, *81*, 12499−12505.

(14) (a) Duarah, G.; Kaishap, P. P.; Begum, T.; Gogoi, S. Recent Advances in Ruthenium(II)-Catalyzed C−H Bond Activation and Alkyne Annulation Reactions. *Adv. Synth. Catal.* **2019**, *361*, 654−672. (b) Kommagalla, Y.; Mullapudi, V. B.; Francis, F.; Ramana, C. V. Ruthenium(ii)-catalyzed switchable C3-alkylation versus alkenylation with acrylates of 2-pyridylbenzofurans via C−H bond activation. *Catal. Sci. Technol.* **2015**, *5*, 114−117. (c) Padala, K.; Jeganmohan, M. Ruthenium-Catalyzed Ortho-Alkenylation of Aromatic Ketones with Alkenes by C−H Bond Activation. *Org. Lett.* **2011**, *13*, 6144−6147. (d) Martinez, R.; Simon, M.-O.; Chevalier, R.; Pautigny, C.; Genet, J.-P.; Darses, S. C−C Bond Formation via C−H Bond Activation Using an in Situ-Generated Ruthenium Catalyst. *J. Am. Chem. Soc.* **2009**, *131*, 7887−7895. (e) Martinez, R.; Chevalier, R.; Darses, S.; Genet, J.-P. A Versatile Ruthenium Catalyst for C−C Bond Formation by C−H Bond Activation. *Angew. Chem., Int. Ed.* **2006**, *45*, 8232−8235.

(15) (a) Singh, K. S. Recent Advances in C−H Bond Functionalization with Ruthenium-Based Catalysts. *Catalysts* **2019**, *9*, 173. (b) Manikandan, R.; Jeganmohan, M. Recent advances in the ruthenium(II)-catalyzed chelation-assisted C−H olefination of substituted aromatics, alkenes and heteroaromatics with alkenes via the deprotonation pathway. *Chem. Commun.* **2017**, *53*, 8931−8947. (c) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. Weakly Coordinating Directing Groups for ruthenium(II)-Catalyzed C−H Activation. *Adv. Synth. Catal.* **2014**, *356*, 1461−1479.

(16) (a) Moorthy, J. N.; Singhal, N. Facile and highly selective conversion of nitriles to amides via Indirect acid-catalyzed hydration using TFA or AcOH−H_2SO_4. *J. Org. Chem.* **2005**, *70*, 1926. (b) Veisi, H.; Maleki, B.; Hamelian, M.; Ashrafi, S. S. Chemoselective hydration of nitriles to amides using hydrated ionic liquid (IL) Tetrabutylammonium hydroxide (TBAH) as a green catalyst. *RSC Adv.* **2015**, *5*, 6365.

(17) Maffioli, S. I.; Marzorati, E.; Marazzi, A. Mild and Reversible Dehydration of Primary Amides with $PdCl_2$ in Aqueous Acetonitrile. *Org. Lett.* **2005**, *7*, 5237−5239.

(18) Stadler, A.; Pichler, S.; Horeis, G.; Kappe, C. O. Microwave-enhanced reactions under open and closed vessel conditions. A case study. *Tetrahedron* **2002**, *58*, 3177−3183.

https://doi.org/10.1021/acs.joc.1c01090
J. Org. Chem. 2021, 86, 9744−9754