OL | Organic Letters

pubs.acs.org/OrgLett Letter

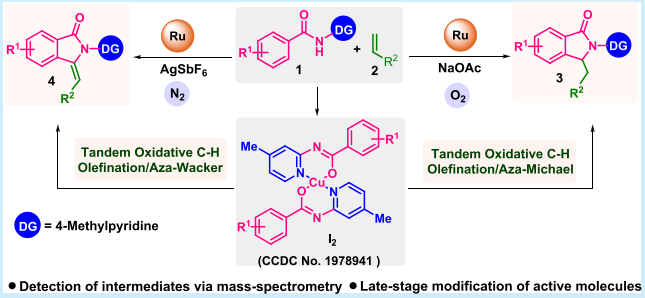
Ru(II)-Catalyzed Oxidative Olefination of Benzamides: Switchable Aza-Michael and Aza-Wacker Reaction for Synthesis of Isoindolinones

Manoj Kumar,[†] Shalini Verma,[†] and Akhilesh K. Verma*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01237 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Selective tandem oxidative C−H olefination−aza-Michael/aza-Wacker reaction of *N*-arylbenzamides is achieved by fine-tuning between base and additive to access valuable 3-oxoisoindolinyls and 3-oxoisoindolinylidenes, respectively. Careful optimization and control experiments provides a guiding principle in the design of a proposed catalytic cycle. The copper−iminium complex acting as a precursor for the binding of Ru catalyst was isolated and confirmed by X-ray diffraction. The versatility of this catalytic system has been demonstrated by the synthesis of biologically relevant molecules.



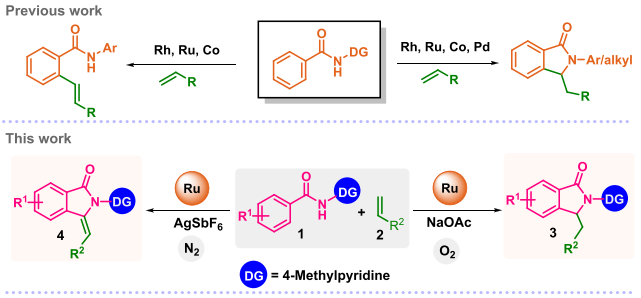
Isoindoline represents an important structural motif owing to its fascinating biological and physiological properties. The isoindoline core has been found to serve as a key precursor for the synthesis of valuable drug molecules and complex natural products.[1] Considering the enormous potential of isoindolines, immense effort toward the development of new synthetic strategies for their synthesis is not surprising.[2] In the ensuing years, auxiliary-assisted transition-metal-catalyzed C−H olefination followed by oxidative annulation has been executed successfully in this area. Although extensive studies have been done on *ortho*-C−H olefination of unactivated arenes to access alkenylated[3] and alkylated[4] arenes, only a modest success has been achieved for the tandem oxidative annulation of alkenylated arenes to synthesize isoindolines. In this regard, most of the established methods rely on use of expensive metal-based catalytic system.[5] In particular, the precious Rh catalyst gains considerable attention due to its high catalytic activity in C−H functionalization.[6] Despite having impressive advances, the use of expensive rhodium metal necessitates the development of an efficient strategy utilizing relatively inexpensive, yet sustainable, catalyst. Recently, the use of ruthenium catalyst in C−H activation has spurred considerable interest in a plethora of organic transformations.[7] In particular, the use of Ru(II) species for C−H olefination of unactivated arenes is currently under development.[8] In 2015, Jeganmohan et al. reported the only Ru catalyzed synthesis of isoindolines by cyclization of *N*-alkylbenzamides with allylic alcohols.[9a] Subsequently, Ackermann et al. introduced bidentate 8-aminoquinoline and tosyl auxiliaries for Co- and Ru-catalyzed oxidative C−H alkenylation.[9b,c] More recently, Zhang et al. developed a multicomponent synthesis of isoindolinones by Rh(III) relay catalysis.[6e] The reaction does not require the prepreparation of amide substrate and demonstrates the use of *N*-pyridin-2-yl benzamide as an effective directing group.

To date, we are unaware of any precedent on Ru-catalyzed tandem oxidative C−H olefination/aza-Michael and aza-Wacker reaction of *N*-arylbenzamides with *α,β*-unsaturated esters to access isoindolinones (Scheme 1). Owing to the easy accessibility and preparation of *α,β*-unsaturated esters, they have been widely used as coupling partners for oxidative C−H alkenylation[3a−c] and alkylation;[4a,b] however, only a limited number of studies have appeared in literature on their use for isoindoline synthesis.[6a,b,8] Employing *α,β*-unsaturated esters as coupling partners provides the synthesized motifs, leading to their easy modification to access synthetically useful molecules.[10] Further, the choice of directing group is also crucial to induce reactivity and selectivity in reaction. The small difference in directing group can lead to change in reaction pathway. In most of the reported Ru-catalyzed reactions, use of directing groups is limited to *N*-alkylamides,[8,9a] while *N*-aromatic amides are shown to be less favorable due to steric interactions.[8c] In contrast, the present work makes effective use of *N*-pyridylamides as directing group to synthesize *N*-pyridylisoindolines which are documented to show potent antitumor activity and DNA binding features.[11] Inspired by the

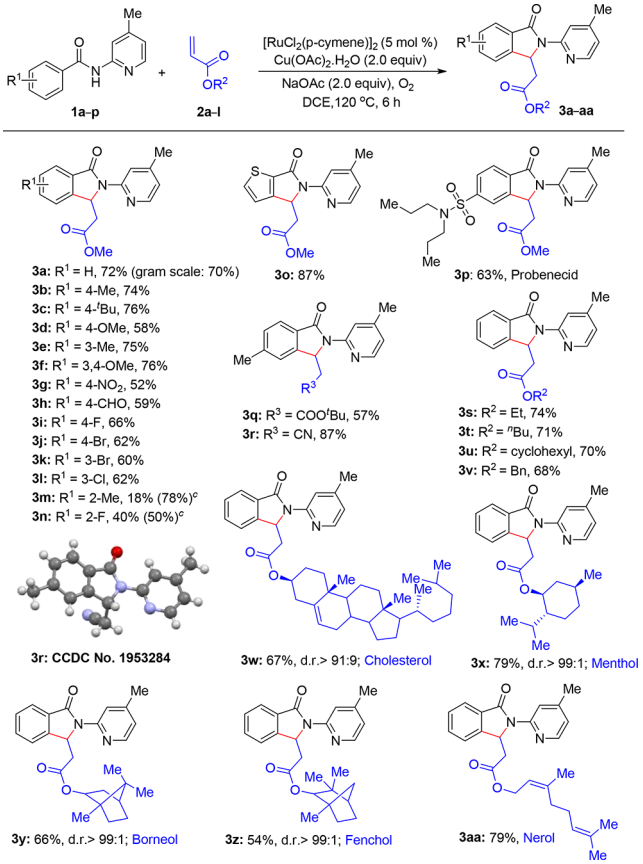
Received: April 7, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01237
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of 3-Oxoisoindolinones



Scheme 2. Synthesis of Substituted 3-Oxoisoindolinyls[a]

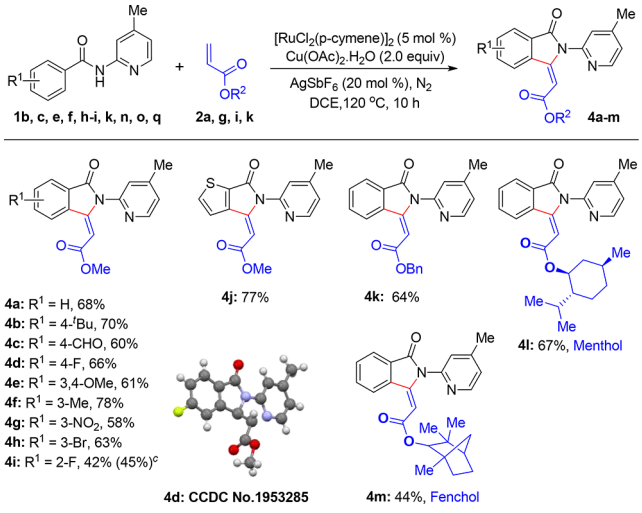


[a]Reactions were performed using 0.5 mmol of **1**, 3.0 equiv of **2**, [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), NaOAc (2.0 equiv), and $Cu(OAc)_2.H_2O$ (2.0 equiv) in 2 mL of DCE under O_2 at 120 °C for 6 h. [b]Isolated yield. [c]Recovered starting material.

elegant contribution of momentous isoindolines in pharmaceuticals and our continuous efforts[12] in developing efficient methodologies for the synthesis of diversified heterocycles, we herein report the selective synthesis of valuable 3-oxoisoindolinyls and 3-oxoisoindolinylidenes by tandem oxidative C−H olefination/aza-Michael and aza-Wacker reaction of amides (Scheme 1). A plausible reaction cycle is provided, strongly supported by performed series of control experiments and characterization of reaction intermediates by mass spectrometry and X-ray diffraction.

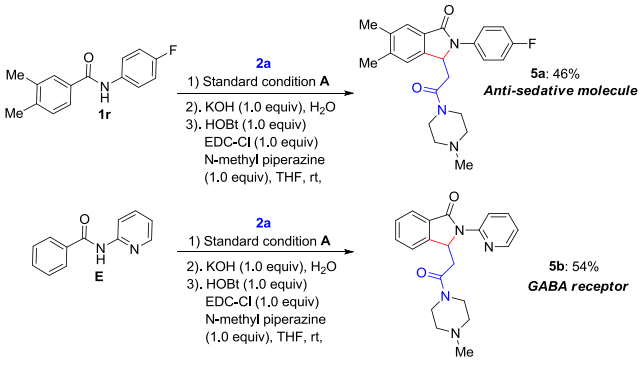
During our investigation (for detailed information, see the Supporting Information) using *N*-(4-methylpyridin-2-yl)-benzamide **1a** with methyl acrylate **2a** as model substrate, we initially observed formation of two products, **3a** and **4a**. On

Scheme 3. Synthesis of Substituted 3-Oxoisoindolinylidenes[a]



[a]Reactions were performed using 0.5 mmol of **1**, 3.0 equiv of **2**, [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $AgSbF_6$ (20 mol %), and $Cu(OAc)_2.H_2O$ (2.0 equiv) in 2 mL of DCE under N_2 at 120 °C for 10 h. [b]Isolated yield. [c]Recovered starting material.

Scheme 4. Synthesis of Biologically Active Molecules

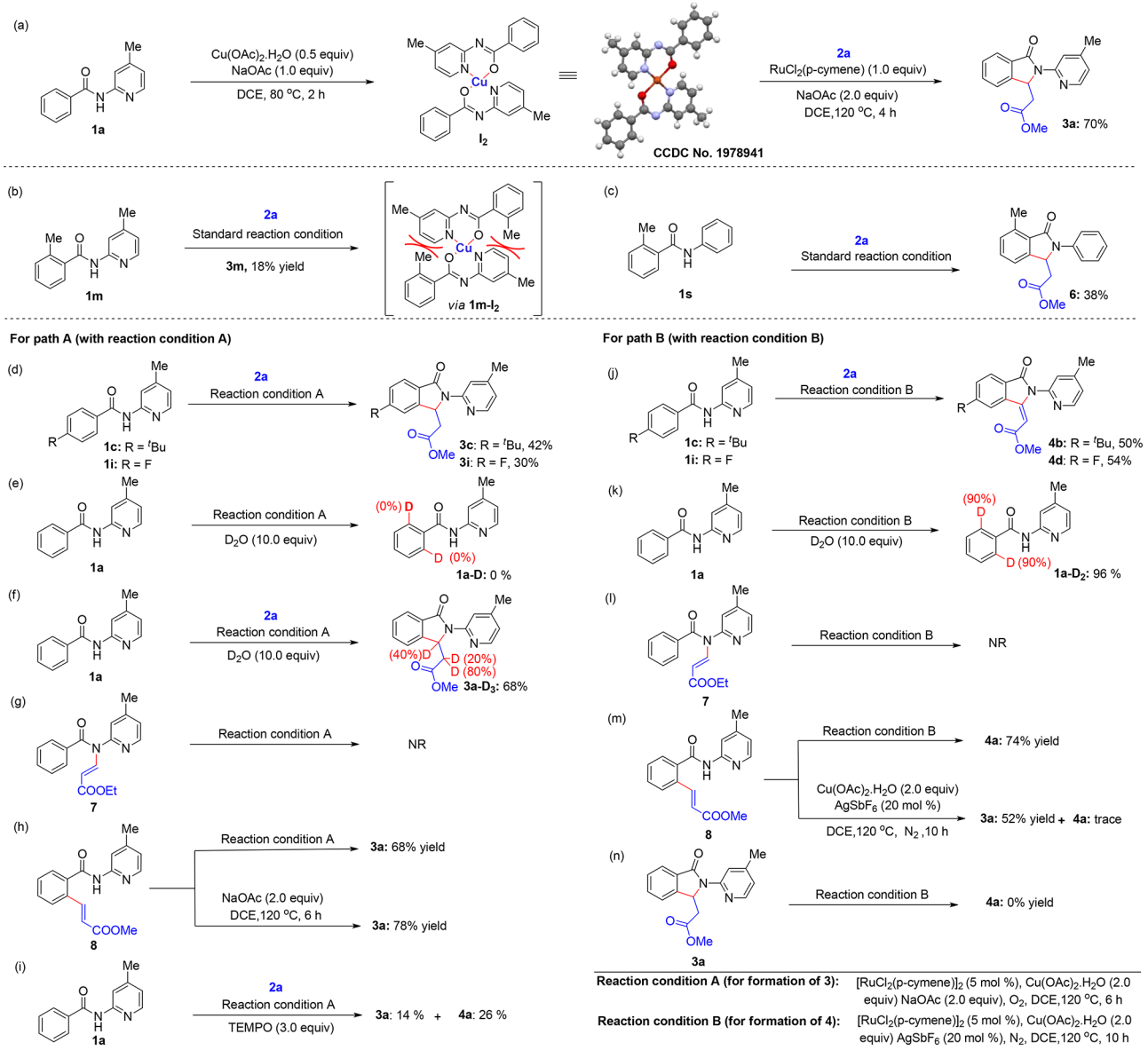


further screening, we found that reaction **1a** with **2a** in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $AgSbF_6$ (20 mol %), and $Cu(OAc)_2.H_2O$ (2.0 equiv) in DCE under N_2 atmosphere at 120 °C for 10 h gave the product **4a** exclusively in 68% yield. As the product **3a** was supposed to be formed by tandem aza-Michael, we hypothesized that the addition of base could enhance the formation of **3a**. Pleasingly, addition of NaOAc (2.0 equiv) instead of $AgSbF_6$ under O_2 atmosphere delivers the product **3a** in 72% yield. With promising conditions, the scope of the reaction was evaluated for the synthesis of 3-oxoisoindolinyls (Scheme 2). Various substituted benzamides were subjected to react with methyl acrylate **2a** under optimal reaction conditions (Table S5, entry 3). The reaction of substrates **1b−d** bearing electron-releasing substituents such as −Me, −^{t}Bu, and −OMe at the 4-position afforded the desired products **3b−d** in 58−76% yields.

It is worthwhile to note that substrate **1e** bearing −Me at the 3-position provided exclusively mono-olefinated products **3e** in 75% yield. Likewise, 3,4-OMe-containing substrate **1f** delivered the product **3f** in comparable yield. Further, substrates **1g−j** bearing strong electron-withdrawing −NO_2, −CHO, and halogens, such as −F and −Br at the 4-position, were reacted smoothly to afford the corresponding products **3g−j** in 52−

https://dx.doi.org/10.1021/acs.orglett.0c01237
Org. Lett. XXXX, XXX, XXX−XXX

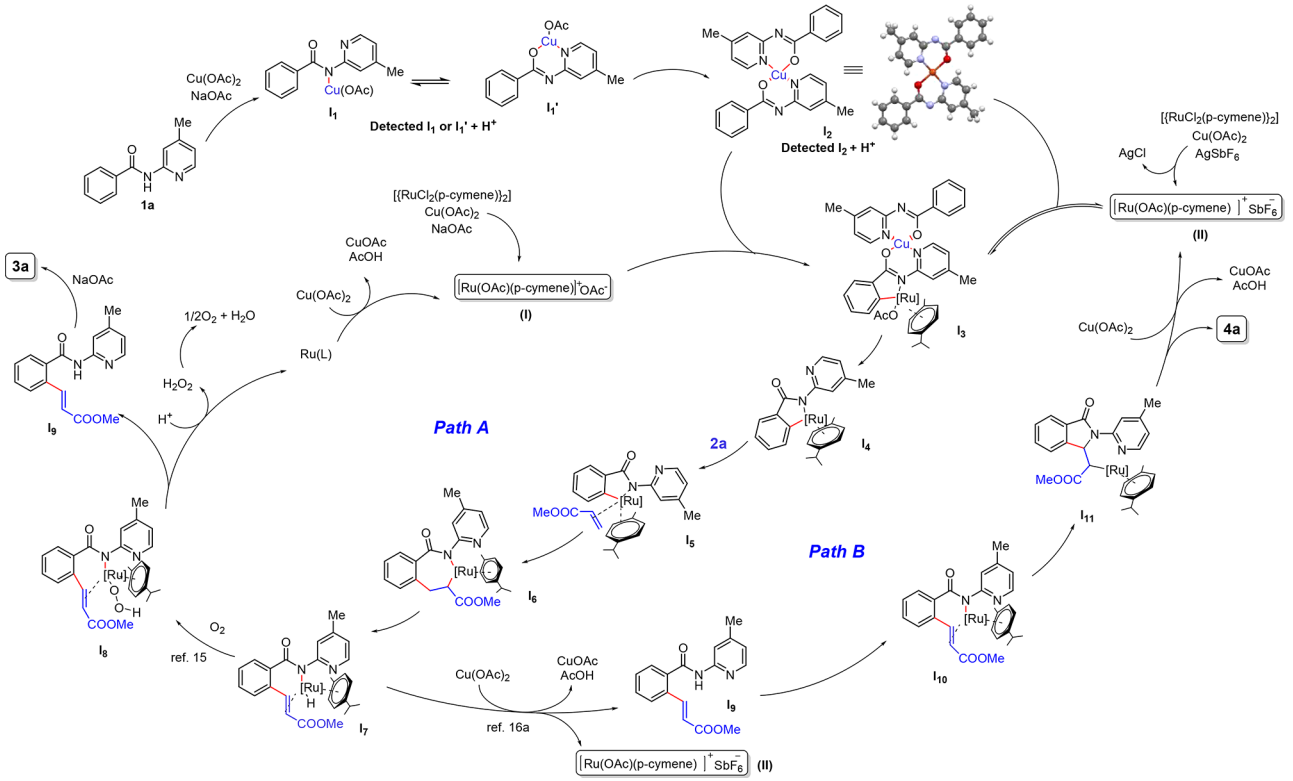
Scheme 5. Control Experiments



66% yields. The reaction is marginally affected by the presence of halogens such as −Br and −Cl at the 3-position of substrate **1k** and **1l**, providing the products **3k** and **3l** in 60% and 62% yields, respectively. Substrate **1m** having −Me at the 2-position also participated in the reaction and provided the desired product **3m** in 18% yield only. The reason might be the steric hindrance created by the methyl group, as the less sterically hindered substrate **1n** having −F at the 2-position affords the product **3n** in 40% yield. Notably, the tolerance of nitro, aldehyde, and halogen substituents facilitates the additional modification of the products. Additionally, heteroaromatic substrate **1o** participates well in the reaction to give the desired product **3o** in 87% yield. Probenecid, medicinally relevant molecule derived benzamide **1p**, successfully provided the desired product **3p**, albeit in moderate yield. Next, the scope of acrylates as a coupling partner was examined. The reaction of substrate **1b** with ^{t}butyl acrylate **2b** and acrylonitrile **2c** delivers the products **3q** and **3r** in 57% and 87% yields, respectively. Likewise, ethyl, ^{n}butyl, cyclohexyl, and benzyl acrylates **2d**−**g** with substrate **1a** gave the compounds **3s**−**v** in 68−74% yields. This method is not limited to the use of simple acrylates; natural product containing acrylates **2h**−**l** were also found to be viable, as demonstrated by the successful synthesis of corresponding compounds **3w**−**aa** in good yields. This also shows that steric bulk at the ester group can be tolerated in these reactions. According to the optimal reaction conditions (Table S4, entry 2), switching the catalytic conditions to the Ru/$AgSbF_6$ system led to the formation of 3-oxoisoindoliny-lidenes via aza-Wacker cyclization. Intrigued by the result, we proceeded to examine the scope of the reaction using differently substituted benzamides (Scheme 3). Electron-rich substrate **1c** containing −^{t}Bu at the 4-position gave the products **4b** in 70% yield. Electron-deficient substrates bearing a free −CHO group (**1h**) and −F (**1i**) at the 4-position were also compatible providing the desired product **4c** and **4d** in 60% and 66% yields, respectively. 3,4-OMe substituted substrate **1f** furnished the product **4e** selectively in 61% yield. Importantly, substrates **1e**, **1q**, and **1k** containing −Me, $-NO_2$, and −Br at the 3-position were compatible, providing the corresponding products **4f**−**h** in 58−78% yields. The

https://dx.doi.org/10.1021/acs.orglett.0c01237
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 6. Plausible Mechanistic Pathway



substrate **1n** substituted with −F at the 2-position also reacted well to give the desired product **4i**, albeit in slightly lower yield. Moreover, substrate **1o** bearing a thiophene core also underwent the reaction to give the product **4j** in 77% yield. Next, to test the viability of acrylate as coupling partner, substrate **1a** was reacted with benzyl acrylate **2g** and the reaction proceeded smoothly to give the desired product **4k** in synthetically useful yield. Interestingly, menthol and fenchol derived acrylate **2i** and **2k** were also found to be compatible, providing the desired product **4l** and **4m** in 67% and 44% yields, respectively.

To probe the applicability of the protocol, the reaction of **1a** was conducted on a gram scale, providing 70% yield (900 mg) of the desired product **3a** (Scheme 2). Further, the antisedative molecule **5a**[11b] and GABA receptor **5b**[11a] were synthesized efficiently under the standard protocol, which compares favorably with the previously reported protocols (Scheme 4).

In order to realize a plausible mechanistic pathway, some aspects of the reaction mechanism were investigated. Initially, the intermediate $\mathbf{I_2}$ was isolated and further treated with 1.0 equiv of $RuCl_2$(*p*-cymene) to yield **3a** (Scheme 5a). The reaction of **1m** gives only 18% yield of **3m** (Scheme 5b) while that of **1s** gave the product **6** in 38% yield (Scheme 5c), thereby providing the evidence for the formation of **1m-I**$_2$. This is further supported by the 40% yield of **3n** in the case of less sterically hindered fluoro-containing substrate **1n** (Scheme 2).

After this, reactions were conducted under reaction conditions A to provide the catalytic cycle for the formation of product **3a**. The competition experiment between **1c** and **1i** furnished the corresponding products **3c** and **3i** in 42% and 30% yields, respectively (Scheme 5d). Further, reaction of **1a** was conducted in the presence of 10.0 equiv of D_2O, and no incorporation of D in **1a** suggests the irreversibility of C−H bond activation (Scheme 5e).[13] Addition of 10.0 equiv of D_2O to the reaction of **1a** with **2a** yields the product **3a-D**$_3$ (Scheme 5f). Incorporation of D at the α- and β-positions of the carbonyl group of **3a-D**$_3$ strongly supports the formation of **3a** via alkenylation followed by aza-Michael reaction.[14] The reaction of **7** with **2a** did not afford the desired product (Scheme 5g); however, reaction of **8** successfully affords the desired product (Scheme 5h), which clearly indicates that the reaction proceeds via *ortho*-C−H alkenylation instead of N−H alkenylation. Moreover, reaction of **8** with NaOAc successfully yields **3a** in comparable yield in the presence as well as in the absence of O_2 (Scheme 5h). The comparable yield of **3a** in all conditions (Scheme 5h) concludes that Ru and O_2 are required only up to the formation of alkenylated species **8** and further proceed by aza-Michael reaction. In order to conclude the role of O_2, 3.0 equiv of TEMPO was added to reaction mixture (Scheme 5i). Under these conditions, **3a** was obtained in 14% yield along with 26% yield of **4a**, which indicates the involvement of O_2 in the reaction via a free-radical pathway for formation of **3a**. The decrease in yield of **3a** and studies on aerobic oxidation of Ru transfer hydrogenation catalysts provides the evidence of Ru−hydroperoxo intermediacy.[15] Subsequently, reactions were performed using reaction condition **B** to analyze the catalytic cycle for the formation of product **4a**. The intermolecular competition between **1c** and **1i** delivered 50% yield of **4b** and 54% yield of **4d** (Scheme 5j). The reaction of **1a** in the presence of 10.0 equiv of D_2O led to 90% incorporation of D in **1a** to give 96% of **1a-D**$_2$ (Scheme 5k), which confirms the reversibility of the C−H bond activation step.[13] The reaction of **7** did not lead to the formation of product **4a** (Scheme 5l), though the reaction of **8** successfully provides the product **4a** in 74% yield (Scheme 5m) suggesting the intermediacy of **8** instead of **7**. Furthermore, reaction of **8** with $AgSbF_6$ does not favor the

https://dx.doi.org/10.1021/acs.orglett.0c01237
Org. Lett. XXXX, XXX, XXX−XXX

formation of **4a** (Scheme 5m). After *ortho*-C−H alkenylation, Ru thus appears to involve in the catalytic cycle. Also, treatment of **3a** under the optimized reaction conditions failed to produce **4a** (Scheme 5n), therefore ruling out the possibility of intermediacy of **3a** and suggesting an aza-Wacker pathway.

On the basis of the results of control experiments and the literature precedents,[16] a plausible catalytic cycle is proposed in Scheme 6. At first, the coordination of **1a** with $Cu(OAc)_2$ resulted in the formation of square planar iminium complex $\mathbf{I_2}$ via intermediate $\mathbf{I_{1'}}$. Meanwhile, the 18e$^-$ complex of Ru was dissociated to species **(I)** (under reaction conditions A) or species **(II)** (under reaction conditions B)[16a,c] which gets ligated to the lone pair of iminium nitrogen of $\mathbf{I_2}$ to give key intermediate $\mathbf{I_3}$. Intermediate $\mathbf{I_3}$ gets dissociated to $\mathbf{I_4}$ in which nitrogen atom of amide gets strongly coordinated to Ru with the release of AcOH. The alkene **2a** then coordinates to Ru in $\mathbf{I_4}$ to afford $\mathbf{I_5}$, followed by its insertion between Ru−C bond to give intermediate $\mathbf{I_6}$. β-Hydride elimination of intermediate $\mathbf{I_6}$ affords Ru ligated alkenylated benzamide $\mathbf{I_7}$. It is very interesting to note that intermediate $\mathbf{I_7}$ reacts differently under oxygen and nitrogen atmosphere to yield two different products, **3a** and **4a**. In the case of oxygen atmosphere, O_2 gets inserted into Ru−H bond in $\mathbf{I_7}$ via single-electron transfer to provid Ru-hydroperoxo [Ru-OOH] intermediate $\mathbf{I_8}$.[15] Following protonolysis, $\mathbf{I_8}$ gives the *ortho*-alkenylated product $\mathbf{I_9}$, H_2O_2h and Ru species. The corresponding Ru species was further oxidized to Ru(II) active species **I** in the presence of $Cu(OAc)_2$ to again take part in the catalytic cycle and the alkenylated product $\mathbf{I_9}$ undergoes aza-Michael in the presence of NaOAc to give the desired product **3a**. In contrast, under N_2 atmosphere, intermediate $\mathbf{I_7}$ affords the alkenylated product $\mathbf{I_9}$ in the presence of $Cu(OAc)_2$ and regenerates the Ru species **(II)**.[16c] Subsequently, the amide group of $\mathbf{I_9}$ then coordinates Ru species **(II)** to give intermediate $\mathbf{I_{10}}$.[16a] Intramolecular coordinative insertion in $\mathbf{I_{10}}$ resulted into the formation of intermediate $\mathbf{I_{11}}$. The intermediate $\mathbf{I_{11}}$ further undergoes β-Hydride elimination in the presence of $Cu(OAc)_2$ to provide the expected product **4a** and regenerate the Ru active species **(II)**.[16a]

In conclusion, we have reported a Ru-catalyzed synthesis of isoindolinones with ample scope. Interestingly, fine-tuning of the reaction condition led to the formation of two different products by switching the reaction pathway. The findings of control experiments provide valuable support for the proposed mechanistic pathway. The isolation of an intermediate $\mathbf{I_2}$ and experimental data led us to propose that the Ru species binds to the substrate in its imine form rather than in its amide form. A useful antisedative molecule and a GABA-inhibitor were synthesized successfully using the protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01237.

Data and spectral copies of ^{1}H, ^{13}C NMR and HRMS for target compounds (PDF)

Accession Codes

CCDC 1953284−1953285 and 1978941 contain 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

Akhilesh K. Verma − *Department of Chemistry, University of Delhi, Delhi 110007, India;* orcid.org/0000-0001-7626-5003; Email: averma@acbr.du.ac.in

Authors

Manoj Kumar − *Department of Chemistry, University of Delhi, Delhi 110007, India*

Shalini Verma − *Department of Chemistry, University of Delhi, Delhi 110007, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01237

Author Contributions

†M.K. and S.V. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research work was supported by SERB (EEQ/2018/000317) (M.K.) and (S.V.) are thankful to CSIR for fellowships.

■ REFERENCES

(1) (a) Boger, D. L.; Lee, J. K.; Goldberg, J.; Jin, Q. Two comparisons of the performance of positional scanning and deletion synthesis for the identification of active constituents in mixture combinatorial libraries. *J. Org. Chem.* **2000**, *65*, 1467. (b) Chia, Y.-C.; Chang, F.-R.; Teng, C.-M.; Wu, Y.-C. Aristolactams and Dioxoaporphines from Fissistigma balansae and Fissistigma oldhamii. *J. Nat. Prod.* **2000**, *63*, 1160. (c) Honma, T. K.; Hayashi, T.; Hashimoto, A. N.; Machida, T. K.; Iwama, F. T.; Ikeura, C. M.; Suzuki-Takahashi, I. I. Y.; Hayama, I.T. S.; Morishima, N. H. Structure-Based Generation of a New Class of Potent Cdk4 Inhibitors: New de Novo Design Strategy and Library Design. *J. Med. Chem.* **2001**, *44*, 4615. (d) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. Isoindolinone enantiomers having affinity for the dopamine D4 receptor. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499.

(2) (a) Barrio, P.; Ibanez, I.; Herrera, L.; Roman, R.; Catalan, S.; Fustero, S. Asymmetric Synthesis of Fluorinated Isoindolinones through Palladium-Catalyzed Carbonylative Amination of Enantioenriched Benzylic Carbamates. *Chem. - Eur. J.* **2015**, *21*, 11579. (b) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. Asymmetric Brønsted acid catalyzed isoindoline synthesis: enhancement of enantiomeric ratio by stereoablative kinetic resolution. *Angew. Chem., Int. Ed.* **2008**, *47*, 5661. (c) Devineau, A.; Pousse, G.; Taillier, C.; Blanchet, J. One-Pot Hydroxy Group Activation/Carbon-Carbon Bond Forming Sequence Using a Brønsted Base/Brønsted Acid System. *Adv. Synth. Catal.* **2010**, *352*, 2881. (d) Mancuso, R.; Ziccarelli, I.; Armentano, D.; Marino, N.; Giofrè, S. V.; Gabriele, B.; Rouden, J.; Dalla, V. Divergent palladium iodide catalyzed multicomponent carbonylative approaches to functionalized isoindolinone and isobenzofuranimine derivatives. *J. Org. Chem.* **2014**, *79*, 3506. (e) Laha, J. K.; Hunjan, M. K.; 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. (f) Zhou, X.; Xu, H.; Yang, Q.; Chen, H.; Wang, S.; Zhao, H. Co(II)/Cu(II)-cocatalyzed

oxidative C−H/N−H functionalization of benzamides with ketones: a facile route to isoindolin-1-ones. *Chem. Commun.* **2019**, *55*, 8603.

(3) (a) Ma, W.; Mei, R.; Tenti, G.; Ackermann, L. Ruthenium (II)-Catalyzed Oxidative C-H Alkenylations of Sulfonic Acids, Sulfonyl Chlorides and Sulfonamides. *Chem. - Eur. J.* **2014**, *20*, 15248. (b) Gong, T.-J.; Xiao, B.; Liu, Z.-J.; Wan, J.; Xu, J.; Luo, D.-F.; Fu, Y.; Liu, L. Rhodium-catalyzed selective C−H activation/olefination of phenol carbamates. *Org. Lett.* **2011**, *13*, 3235. (c) Park, S. H.; Kim, J. Y.; Chang, S. Rhodium-catalyzed selective olefination of arene esters via C− H bond activation. *Org. Lett.* **2011**, *13*, 2372. (d) Patureau, F. W.; Glorius, F. Rh catalyzed olefination and vinylation of unactivated acetanilides. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (e) Singh, K. S.; Dixneuf, P. H. Ruthenium (II)-catalyzed alkenylation of ferrocenyl ketones via C−H bond activation. *Organometallics* **2012**, *31*, 7320. (f) Li, B.; Devaraj, K.; Darcel, C.; Dixneuf, P. H. Ruthenium (II) catalysed synthesis of unsaturated oxazolines via arene C−H bond alkenylation. *Green Chem.* **2012**, *14*, 2706. (g) Reddy, M. C.; Jeganmohan, M. Ruthenium-catalyzed ortho alkenylation of aromatic nitriles with activated alkenes *via* C−H bond activation. *Chem. Commun.* **2015**, *51*, 10738.

(4) (a) Shibata, K.; Chatani, N. Rhodium-Catalyzed Alkylation of C−H Bonds in Aromatic Amides with α,β-Unsaturated Esters. *Org. Lett.* **2014**, *16*, 5148. (b) Sivasakthikumaran, R.; Jambu, S.; Jeganmohan, M. Asymmetric Alkylation of N-Sulfonylbenzamides with Vinyl Ethers via C−H Bond Activation Catalyzed by Hydroxoiridium/Chiral Diene Complexes. *J. Org. Chem.* **2019**, *84*, 3977. (c) 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. (d) 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. (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. (f) Martinez, R.; Genet, J.-P.; Darses, S. Anti-Markovnikov hydroarylation of styrenes catalyzed by an in situ generated ruthenium complex. *Chem. Commun.* **2008**, 3855.

(5) (a) 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. (b) Wang, F.; Song, G.; Li, X. Rh (III)-Catalyzed Tandem Oxidative Olefination− Michael Reactions between Aryl Carboxamides and Alkenes. *Org. Lett.* **2010**, *12*, 5430. (c) Ramesh, B.; Tamizmani, M.; Jeganmohan, M. Rhodium(III)-Catalyzed Redox-Neutral 1,1-Cyclization of N-Methoxy Benzamides with Maleimides via C−H/N−H/N−O Activation: Detailed Mechanistic Investigation. *J. Org. Chem.* **2019**, *84*, 4058. (d) Xia, C.; White, A. J. P.; Hii, K. K. M. Synthesis of Isoindolinones by Pd-Catalyzed Coupling between N-Methoxybenzamide and Styrene Derivatives. *J. Org. Chem.* **2016**, *81*, 7931. (e) 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. (f) Son, S.-M.; Seo, Y. J.; Lee, H.-K. Stereoselective synthesis of 1, 3-disubstituted isoindolines via Rh (III)-catalyzed tandem oxidative olefination−cyclization of 4-aryl cyclic sulfamidates. *Chem. Commun.* **2016**, *52*, 4286. (g) Liao, K.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L. Site-selective and stereoselective functionalization of unactivated C−H bonds. *Nature* **2016**, *533*, 230. (h) Davies, H. M. L.; Morton, D. Recent advances in C−H functionalization. *J. Org. Chem.* **2016**, *81*, 343. (i) Manna, M. K.; Hossian, A.; Jana, R. Merging C−H Activation and Alkene Difunctionalization at Room Temperature: A Palladium-Catalyzed Divergent Synthesis of Indoles and Indolines. *Org. Lett.* **2015**, *17*, 672. (j) Li, L.; Zhang, X. G.; Zhang, X. H. Palladium-Catalyzed C(sp^2)−H Olefination/Annulation Cascades of Aryl Carboxamides Assisted by N,S-Bidentate Auxiliary. *Synthesis* **2019**, *51*, 3077. (k) Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. New Heteroannulation Reactions of N-Alkoxybenzamides by Pd(II) Catalyzed C-H Activation. *Org. Lett.* **2011**, *13*, 5326.

(6) (a) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Rhodium catalyzed chelation-assisted C−H bond functionalization reactions. *Acc. Chem. Res.* **2012**, *45*, 814. (b) Satoh, T.; Miura, M. Oxidative Coupling of Aromatic Substrates with Alkynes and Alkenes under Rhodium Catalysis. *Chem. - Eur. J.* **2010**, *16*, 11212. (c) Song, G.; Wang, F.; Li, X. C−C, C−O and C−N bond formation via rhodium (III)-catalyzed oxidative C−H activation. *Chem. Soc. Rev.* **2012**, *41*, 3651. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-catalyzed C− C bond formation via heteroatom-directed C− H bond activation. *Chem. Rev.* **2010**, *110*, 624. (e) Zhang, Y.; Zhu, H.; Huang, Y.; Hu, Q.; He, Y.; Wen, Y.; Zhu, G. Multicomponent Synthesis of Isoindolinones by Rh(III) Relay Catalysis: Synthesis of Pagoclone and Pazinaclone from Benzaldehyde. *Org. Lett.* **2019**, *21*, 1273. (f) Wang, D.; Yu, X.; Xu, X.; Ge, B.; Wang, X.; Zhang, Y. Non-Coordinating-Anion-Directed Reversal of Activation Site: Selective C-H Bond Activation of *N*-Aryl Rings. *Chem. - Eur. J.* **2016**, *22*, 8663.

(7) (a) Bruneau, C.; Dixneuf, P. H. Ruthenium(II)-Catalysed Functionalisation of C−H Bonds with Alkenes: Alkenylation versus Alkylation. *Top. Organomet. Chem.* **2015**, *55*, 137. (b) Nareddy, P.; Jordan, F.; Szostak, M. Recent Developments in Ruthenium-Catalyzed C−H Arylation: Array of Mechanistic Manifold. *ACS Catal.* **2017**, *7*, 5721. (c) Mandal, A.; Dana, S.; Chowdhury, D.; Baidya, M. Recent Advancements in Transition-Metal-Catalyzed One-Pot Twofold Unsymmetrical Difunctionalization of Arenes. *Chem. - Asian J.* **2019**, *14*, 4074. (d) 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.

(8) (a) 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. (b) Nakanowatari, S.; Ackermann, L. Ruthenium (II)-Catalyzed C-H Functionalizations with Allenes: Versatile Allenylations and Allylations. *Chem. - Eur. J.* **2015**, *21*, 16246. (c) Bechtoldt, A.; Tirler, C.; Raghuvanshi, K.; Warratz, S.; Kornhaaß, C.; Ackermann, L. Ruthenium Oxidase Catalysis for Site-Selective C−H Alkenylations with Ambient O2 as the Sole Oxidant. *Angew. Chem., Int. Ed.* **2016**, *55*, 264.

(9) (a) Manoharan, R.; Jeganmohan, M. Synthesis of isoindolinones via a ruthenium-catalyzed cyclization of N-substituted benzamides with allylic alcohols. *Chem. Commun.* **2015**, *51*, 2929. (b) Ma, W.; Ackermann, L. Cobalt(II)-Catalyzed Oxidative C−H Alkenylations: Regio- and Site-Selective Access to Isoindolin-1-one. *ACS Catal.* **2015**, *5*, 2822. (c) Bechtoldt, A.; Tirler, C.; Raghuvanshi, K.; Warratz, S.; Kornhaaß, C.; Ackermann, L. Ruthenium Oxidase Catalysis for Site-Selective C−H Alkenylations with Ambient O_2 as the Sole Oxidant. *Angew. Chem., Int. Ed.* **2016**, *55*, 264.

(10) See Scheme 4.

(11) (a) Sović, I.; Pavelić, S. K.; Markova, C. E.; Ilić, N.; Nhili, R.; Depauw, S.; David-Cordonnier, M.-H.; Karminski-Zamola, G. Novel phenyl and pyridyl substituted derivatives of isoindolines: Synthesis, antitumor activity and DNA binding features. *Eur. J. Med. Chem.* **2014**, *87*, 372. (b) Kanamitsu, N.; Osaki, T.; Itsuji, Y.; Yoshimura, M.; Tsujimoto, H.; Soga, M. Novel water-soluble sedative-hypnotic agents: isoindolin-1-one derivatives. *Chem. Pharm. Bull.* **2007**, *55*, 1682.

(12) (a) Kumar, M.; Verma, S.; Mishra, P. K.; Verma, A. K. Cu (II)−Mediated ortho−C− H Amination of Arenes with Free Amines. *J. Org. Chem.* **2019**, *84*, 8067. (b) Kumar, M.; Verma, S.; Kumar, A.; Mishra, P. K.; Ramabhadran, R. O.; Banerjee, S.; Verma, A. K. Mechanistic insights of Cu (II)-mediated ortho-C−H amination of arenes by capturing fleeting intermediates and theoretical calculations. *Chem. Commun.* **2019**, *55*, 9359. (c) Kumar, P.; Garg, V.; Kumar, M.; Verma, A. K. Rh(III)-catalyzed alkynylation: synthesis of functionalized quinolines from aminohydrazones. *Chem. Commun.* **2019**, *55*, 12168. (d) Brahmchari, D.; Verma, A. K.; Mehta, S. Regio- and

https://dx.doi.org/10.1021/acs.orglett.0c01237
Org. Lett. XXXX, XXX, XXX−XXX

Stereoselective Synthesis of Isoindolin-1-ones through BuLi-Mediated Iodoaminocyclization of 2-(1-Alkynyl)benzamides. *J. Org. Chem.* **2018**, *83*, 3339.
(13) Ferrer Flegeau, E.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. Autocatalysis for C−H bond activation by ruthenium (II) complexes in catalytic arylation of functional arenes. *J. Am. Chem. Soc.* **2011**, *133*, 10161.
(14) Bechtoldt, A.; Ackermann, L. Ruthenium (II) biscarboxylate-Catalyzed Hydrogen-Isotope Exchange by Alkene C− H Activation. *ChemCatChem* **2019**, *11*, 435.
(15) (a) Heiden, Z. M.; Rauchfuss, T. B. Homogeneous catalytic reduction of dioxygen using transfer hydrogenation catalysts. *J. Am. Chem. Soc.* **2007**, *129*, 14303. (b) Huynh, M. H. V.; Meyer, T. J. Proton-Coupled Electron Transfer. *Chem. Rev.* **2007**, *107*, 5004. (c) Perry, R. H.; Brownell, K. R.; Chingin, K.; Cahill, T. J.; Waymouth, R. M.; Zare, R. N. Transient Ru-methyl formate intermediates generated with bifunctional transfer hydrogenation catalysts. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 2246.
(16) (a) 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. (b) Naruto, M.; Saito, S. Cationic mononuclear ruthenium carboxylates as catalyst prototypes for self-induced hydrogenation of carboxylic acids. *Nat. Commun.* **2015**, *6*, 8140. (c) Leitch, J. A.; Wilson, P. B.; McMullin, C. L.; Mahon, M. F.; Bhonoah, Y.; Williams, I. H.; Frost, C. G. Ruthenium(II)-Catalyzed C−H Functionalization Using the Oxazolidinone Heterocycle as a Weakly Coordinating Directing Group: Experimental and Computational Insights. *ACS Catal.* **2016**, *6*, 5520. (d) Ghosh, K.; Shankar, M.; Rit, R. K.; Dubey, G.; Bharatam, P. V.; Sahoo, A. K. Sulfoximine-Assisted One-Pot Unsymmetrical Multiple Annulation of Arenes: A Combined Experimental and Computational Study. *J. Org. Chem.* **2018**, *83*, 9667. (e) Shan, C.; Zhu, L.; Qu, L.-B.; Bai, R.; Lan, Y. Mechanistic view of Ru-catalyzed C−H bond activation and functionalization: computational advances. *Chem. Soc. Rev.* **2018**, *47*, 7552.

https://dx.doi.org/10.1021/acs.orglett.0c01237
Org. Lett. XXXX, XXX, XXX−XXX