OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

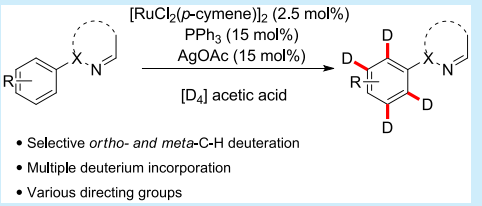
Ruthenium-Catalyzed *ortho*- and *meta*-H/D Exchange of Arenes

Liang-Liang Zhao, Wei Liu, Zengyu Zhang, Hongyan Zhao, Qi Wang, and Xiaoyu Yan*

Department of Chemistry, Renmin University of China, Beijing 100872, China

Supporting Information

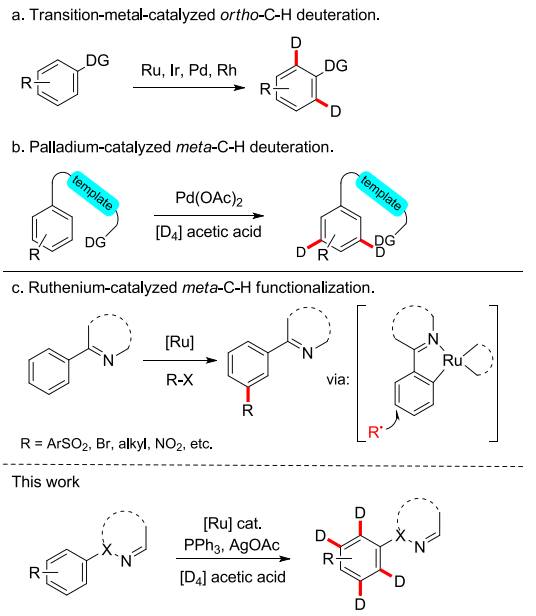
ABSTRACT: Ruthenium-catalyzed aromatic H/D exchange in [D_4]acetic acid has been developed. By using *N*-heteroarenes as directing groups, both *ortho* and *meta* positions are selectively deuterated with high levels of D incorporation. Moreover, this strategy provides an alternative way to achieve *meta*-C−H activation.



Incorporation of deuterium atoms into a specific molecule has been an advanced research focus in recent years, for the broad application of deuterated compounds in studying biological and chemical processes[1] and mass spectrometry.[2] In particular, the special ability to change the ADME properties of the known drug candidates has paved the way for numerous breakthroughs in pharmacokinetics as well as in pharmaceutical industry. In 2017, the first deuterated drug, deutetrabenazine, was approved by the Food and Drug Administration, which pointed out a clearer pathway for the development of deuterated compounds in clinical medicine.[3] Generally, most of simple deuterium-labeled compounds can be accessed through multistep synthetic routes from deuterated precursors. However, when it comes to complex molecule structures or specific deuterium labeling positions, a direct hydrogen isotope exchange (HIE) method would be the optimal choice. Although transition metal-catalyzed H/D exchange protocols have been well established,[4] challenges in regioselective hydrogen isotope exchange remain. Deuteration of *ortho*-C−H of arenes assisted by various directing groups with Ir,[5] Pd,[6] Rh,[7] or Ru[8] as the catalyst has been extensively explored (Scheme 1a); nevertheless, remote C−H bond deuteration of arenes remains elusive. In 2016, Chirik and co-workers disclosed a Fe-catalyzed strategy that allowed for deuteration and tritiation at selective and complementary positions to existing previously reported transition metal catalysis strategies.[9] Very recently, the groups of Maiti[10] and Dai[11] independently reported a novel palladium-catalyzed selective *meta*-C−H bond H/D exchange of arenes. In these strategies, to restrain *ortho*-C−H activation and to realize *meta*-C−H bond deuteration efficiently, a meticulously designed long-reaching directing template is introduced into the substrates (Scheme 1b).

Ruthenium-catalyzed functionalization of the *meta*-C−H bond has been an advanced topic due to the relatively simple catalytic system and starting materials, because of pioneering work reported by Frost[12] and Ackermann[13] in 2011. After years of research, ruthenium-catalyzed *meta*-C−H functionalization had been well studied,[14] such as sulfonation,[12,15] bromination,[16] alkylation,[17] nitration,[18] difluoroalkylation,[19] and benzylation.[20] Radical trapping and isotope labeling experiments were carried out to explore the reaction mechanism. These results revealed that the *ortho*-C−H bonds were easily deuterated in D_2O,[16,17b,18a,b] because of *ortho*-C−H bond activation enabled by cyclometalation. Nevertheless, addition to the *meta* position of the cyclometalated intermediate proceeded through a radical pathway (Scheme 1c), rather than S_EAr proposed in the very beginning.[12] Thus, it was difficult to achieve ruthenium-catalyzed deuteration of the *meta*-C−H bond due to the challenging radical H/D exchange. We envisioned that the S_EAr pathway would be preferred while increasing the electron density of the metal center as well as using a polar deuterated

Scheme 1. Metal-Catalyzed Selective C−H Deuteration Assisted by Directing Groups



Received: November 6, 2019

DOI: 10.1021/acs.orglett.9b03955
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Screening of Reaction Conditions for Deuteration of 1[a]

entry	catalyst	ligand	solvent	additive	*o*/*m*[b]	yield[c] (%)
1	$[RuCl_2(p\text{-cymene})]_2$	–	CH_3COOD	AgOAc	69/10	77
2	$[RuCl_2(p\text{-cymene})]_2$	MesCOOH	CH_3COOD	AgOAc	75/12	77
3	$[RuCl_2(p\text{-cymene})]_2$	PPh_3	CH_3COOD	AgOAc	67/75	76
4	$Ru(PPh_3)_3Cl_2$	–	CH_3COOD	AgOAc	72/65	65
5	$Ru(PPh_3)_2ClCp$	–	CH_3COOD	AgOAc	75/12	88
6	Ru_3CO_{12}	PPh_3	CH_3COOD	–	81/9	81
7	$[RuCl_2(p\text{-cymene})]_2$	PPh_3	CD_3COOD	AgOAc	93/84	80

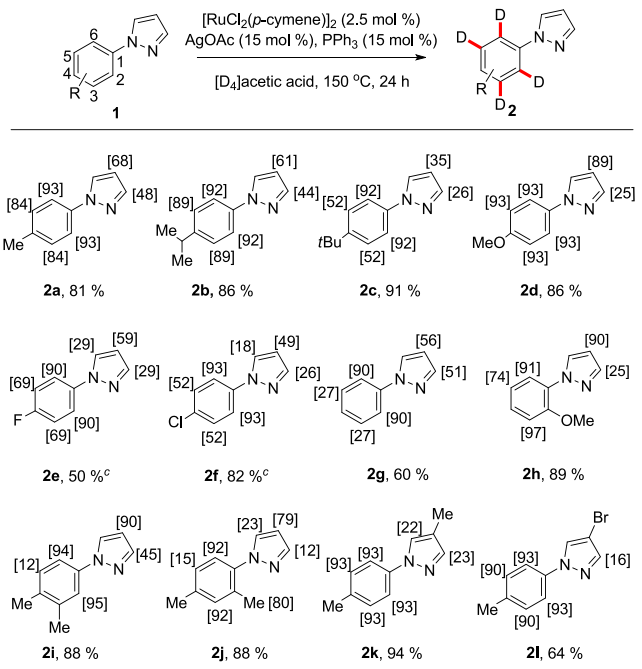
[a]Reaction conditions: **1a** (0.2 mmol), [Ru] (5 mol %), ligand (15 mol %), additive (15 mol %), and solvent (0.8 mL) in a sealed tube, 150 °C, 24 h. [b]Deuterium incorporation determined by ^{1}H NMR spectroscopic analysis. [c]Isolated yields.

solvent to achieve *meta*-C−H H/D exchange (see the Supporting Information for details). Herein, we report ruthenium-catalyzed *ortho*- and *meta*-H/D exchange reaction with PPh_3 as the ligand in $[D_4]$acetic acid. The reaction is accomplished with high levels of D incorporation with various *N*-heteroarenes as directing groups.

We began our study of the H/D exchange reaction of **1a** in $[D_1]$acetic acid with $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and AgOAc as the chloride scavenger. The *ortho*-C−H bond was deuterated by 69%, while 10% *meta* deuteration was detected (Table 1, entry 1). This inspiring result initiated us to explore an efficient way to achieve a high level of deuterium incorporation at *ortho* and *meta* positions simultaneously. We assumed that the addition of an electron-rich ligand would increase the electron density of the cyclometalated intermediate, which may be beneficial for H/D exchange at *meta* positions via the S_EAr pathway. MesCOOH, widely used in other reports as a ligand, was tested to serve as a ligand but proved to be ineffective for *meta*-C−H deuteration (entry 2). Impressively, 75% deuterium incorporation at *meta* positions as well as 67% at *ortho* positions of the benzene ring was observed when PPh_3 was used as the ligand under the same conditions (entry 3). Other [Ru] catalysts for *meta*-C−H activation were subsequently applied to the reaction (entries 4−6). $Ru(PPh_3)_3Cl_2$ showed a slightly lower catalytic activity with 65% and 72% deuterium incorporation at the *meta* and *ortho* positions, respectively. However, $Ru(PPh_3)_2ClCp$ and Ru_3CO_{12} were not suitable for this reaction system, while trace deuterium atoms were introduced at the *meta* positions. The level of deuterium incorporation was 93% when $[D_4]$acetic acid was used (entry 7). The yields at *meta* and *ortho* positions were increased to 84%, and we should note that moderate H/D exchange of the directing group was also observed in the meantime.

With the optimized reaction conditions in hand, we investigated the substrate scope with pyrazole as the directing group under the best conditions (Scheme 2). Substituents at the benzene ring had little influence on the results for the deuteration rate at *ortho* positions; all examples gave more than 90% D incorporation (**2a**−**2j**). Steric hindrance and electronic properties of the substituents at the *para* position had a strong influence on *meta* H/D exchange (**2a**−**2f**). Only 52% deuteration at the *meta* position was observed when a bulky *tert*-butyl was substituted at the *para* position (**2c**). Electron-donating groups, like methyl and methoxy, delivered better

Scheme 2. Deuteration of the *ortho*- and *meta*-C−H Bond of 1-Phenylpyrazole Derivatives[a,b]



[a]Standard reaction conditions, isolated yield. [b]Deuterium incorporation determined by ^{1}H NMR spectroscopic analysis shown in brackets. [c]CH_2Br_2 used as an internal standard for deuteration analysis.

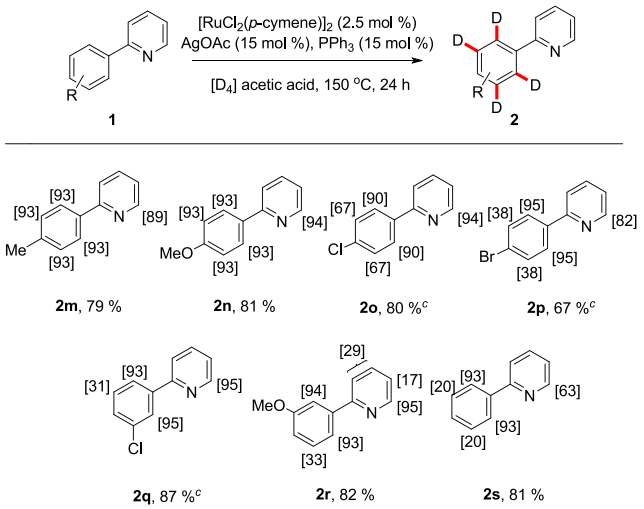
deuterium incorporation at *meta* positions then those of electron-withdrawing halide groups, which further supported the S_EAr process in achieving *meta*-C−H bond activation. Only 27% *meta*-C−H was deuterated for **2g**, probably due to the decreased electron density of the benzene ring. A strong electron-donating methoxy group at the *ortho* position gave 97%, 74%, and 91% deuteration at positions C3, C5, and C6, respectively (**2h**). The lower level of deuteration at position C5 compared with that at position C3 is probably due to the steric effect during S_EAr deuteration of a ruthenacycle intermediate. 3,4- and 2,4-dimethyl-substituted **2i** and **2j** delivered only 12% and 15% deuteration, respectively, at the position C5 for the same reason. Substituents at the pyrazole moiety were also investigated (**2k** and **2l**), and both electron-donating and -withdrawing substituents gave excellent

DOI: 10.1021/acs.orglett.9b03955
Org. Lett. XXXX, XXX, XXX−XXX

deuteration at the *ortho* and *meta* positions, although a relatively lower yield of **2l**.

We next devoted our efforts to investigate the application of this protocol to 2-phenylpyridine derivatives (Scheme 3). The

Scheme 3. Deuteration of the *ortho*- and *meta*-C−H Bond of 2-Phenylpyridine Derivatives[a,b]



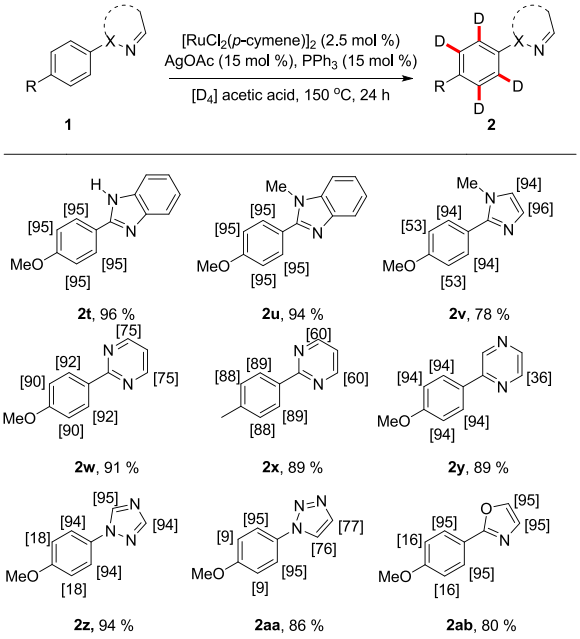
[a]Standard reaction conditions, isolated yield. [b]Deuterium incorporation determined by ^{1}H NMR spectroscopic analysis shown in brackets. [c]CH_2Br_2 used as an internal standard for deuteration analysis.

substrate applicability was similar to those of 2-phenylpyrazole directives. All examples gave excellent deuteration at *ortho* positions of the benzene ring; moreover, inevitable deuteration of the directing group occurred. Electron-donating groups at the *para* position afforded >90% deuterium incorporation at the *meta* position (**2m** and **2n**), while electron-withdrawing halide groups gave lower deuteration rates (**2o** and **2p**). However, *meta*-substituted derivatives (**2q** and **2r**) afforded poor deuterium incorporation at the other *meta* position, even though a strong electron-donating methoxyl group that was introduced did not significantly improve the result. Only 20% *meta*-C−H bonds were exchanged with deuterium in the case of **2s**.

Nitrogen heterocyclic compounds found broad applications in biological and pharmaceutical science. To demonstrate whether other nitrogen heterocyclic arenes are competent with respect to this method as directing groups to achieve multiple-site deuteration, several nitrogen heterocyclic arene derivatives were synthesized as shown in Scheme 4. Benzimidazole derivatives **2t** and **2u** were well suited to this method, giving >90% deuteration at the *ortho* and *meta* positions with high yields, while imidazole derivative **2v** gave degressive deuteration at the *meta* positions. To our delight, pyrimidine and pyrazine derivatives (**2w**−**2y**) also proved to be good directing groups as high levels of deuterium incorporation were detected. However, substrates with 1,2,4-triazole, 1,2,3-triazole, and oxazole as directing groups delivered poor deuteration at *meta* positions but excellent deuteration at *ortho* positions as well as the *N*-heterocyclic arene section (**2z**, **2aa**, and **2ab**).

In summary, we have disclosed a new method for selective *ortho*-C−H and *meta*-C−H H/D exchange of arenes catalyzed by Ru with PPh_3 and AgOAc as the additive and [D_4]acetic acid as the deuterium source and solvent. In this novel strategy,

Scheme 4. Deuteration of the *ortho*- and *meta*-C−H Bond Directed by Other *N*-Heterocycles[a,b]



[a]Standard reaction conditions, isolated yield. [b]Deuterium incorporation determined by ^{1}H NMR spectroscopic analysis shown in brackets.

a variety of substituents were tolerated and the reaction gave good to excellent D incorporation at the *ortho* and *meta* positions. Various *N*-heteroarenes were also competent as the directing group. More importantly, this strategy represents a new way for Ru-catalyzed *meta*-C−H bond activation of arenes, instead of the radical process. Further investigations are still in progress in this area.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03955.

Experimental procedures, characterization of new compounds, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yanxy@ruc.edu.cn.

ORCID

Xiaoyu Yan: 0000-0003-3973-3669

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (21602249).

■ REFERENCES

(1) For recent reviews, see: (a) Pirali, T.; Serafini, M.; Cargnin, S.; Genazzani, A. A. Applications of Deuterium in Medicinal Chemistry. *J. Med. Chem.* **2019**, *62*, 5276−5297. (b) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. Deuterium- and Tritium-Labelled Compounds:

DOI: 10.1021/acs.orglett.9b03955
Org. Lett. XXXX, XXX, XXX−XXX

Applications in the Life Sciences. *Angew. Chem., Int. Ed.* **2018**, *57*, 1758−1784. (c) Gant, T. G. Using deuterium in drug discovery: leaving the label in the drug. *J. Med. Chem.* **2014**, *57*, 3595−611. (d) Yang, J. *Deuterium: Discovery and Applications in Organic Chemistry*; Elsevier: Amsterdam, 2016. (e) Liuni, P.; Olkhov-Mitsel, E.; Orellana, A.; Wilson, D. J. Measuring Kinetic Isotope Effects in Enzyme Reactions Using Time-Resolved Electrospray Mass Spectrometry. *Anal. Chem.* **2013**, *85*, 3758−3764. (f) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C-H Bond Functionalization by Transition-Metal Complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066−3072. (g) Mutlib, A. E. Application of Stable Isotope-Labeled Compounds in *Meta*bolism and in *Meta*bolism-Mediated Toxicity Studies. *Chem. Res. Toxicol.* **2008**, *21*, 1672−1689.

(2) (a) Stokvis, E.; Rosing, H.; Beijnen, J. H. Stable isotopically labeled internal standards in quantitative bioanalysis using liquid chromatography/mass spectrometry: necessity or not? *Rapid Commun. Mass Spectrom.* **2005**, *19*, 401−407. (b) Hewavitharana, A. K. Matrix matching in liquid chromatography−mass spectrometry with stable isotope labelled internal standards -Is it necessary? *J. Chromatogr. A* **2011**, *1218*, 359−361. (c) Jemal, M.; Xia, Y.-Q. LC-MS Development Strategies for Quantitative Bioanalysis. *Curr. Drug Metab.* **2006**, *7*, 491−502. (d) Voronin, K.; Allentoff, A. J.; Bonacorsi, S. J.; Mapelli, C., Jr.; Gong, S. X.; Lee, V.; Riexinger, D.; Sanghvi, N.; Jiang, H.; Zeng, J. Synthesis of a stable isotopically labeled universal surrogate peptide for use as an internal standard in LC-MS/MS bioanalysis of human IgG and Fc-fusion protein drug candidates. *J. Labelled Compd. Radiopharm.* **2014**, *57*, 579−583. (e) Atzrodt, J.; Derdau, V. Pd- and Pt-catalyzed H/D exchange methods and their application for internal MS standard preparation from a Sanofi-Aventis perspective. *J. Labelled Compd. Radiopharm.* **2010**, *53*, 674−685.

(3) Schmidt, C. First deuterated drug approved. *Nat. Biotechnol.* **2017**, *35*, 493−494.

(4) (a) Yang, H.; Zarate, C.; Palmer, W. N.; Rivera, N.; Hesk, D.; Chirik, P. J. Site-Selective Nickel-Catalyzed Hydrogen Isotope Exchange in N-Heterocycles and Its Application to the Tritiation of Pharmaceuticals. *ACS Catal.* **2018**, *8*, 10210−10218. (b) Lockley, W. J. S.; Heys, J. R. Metal-catalyzed hydrogen isotope exchange labelling: a brief overview. *J. Labelled Compd. Radiopharm.* **2010**, *53*, 635−644. (c) Heys, J. R. Nickel-catalyzed hydrogen isotope exchange. *J. Labelled Compd. Radiopharm.* **2010**, *53*, 716−721. (d) Chappelle, M. R.; Hawes, C. R. The use of metal-catalyzed hydrogen isotope exchange in the contract supply of tritiated compounds. *J. Labelled Compd. Radiopharm.* **2010**, *53*, 745−751. (e) Junk, T.; Catallo, W. J. Hydrogen isotope exchange reactions involving C-H (D, T) bonds. *Chem. Soc. Rev.* **1997**, *26*, 401−406. (f) Sawama, Y.; Monguchi, Y.; Sajiki, H. Efficient H-D Exchange Reactions Using Heterogeneous Platinum-Group Metal on Carbon-H_2-D_2O System. *Synlett* **2012**, *23*, 959−972. (g) Hatano, M.; Nishimura, T.; Yorimitsu, H. Selective H/D Exchange at Vinyl and Methylidene Groups with D_2O Catalyzed by an Iridium Complex. *Org. Lett.* **2016**, *18*, 3674−3677. (h) Bai, W.; Lee, K. H.; Tse, S. K. S.; Chan, K. W.; Lin, Z.; Jia, G. Ruthenium-Catalyzed Deuteration of Alcohols with Deuterium Oxide. *Organometallics* **2015**, *34*, 3686−3698. (i) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. The Renaissance of H/D Exchange. *Angew. Chem., Int. Ed.* **2007**, *46*, 7744−7765.

(5) (a) Kerr, W. J.; Lindsay, D. M.; Owens, P. K.; Reid, M.; Tuttle, T.; Campos, S. Site-Selective Deuteration of N-Heterocycles via Iridium-Catalyzed Hydrogen Isotope Exchange. *ACS Catal.* **2017**, *7*, 7182−7186. (b) Kerr, W. J.; Reid, M.; Tuttle, T. Iridium-Catalyzed C-H Activation and Deuteration of Primary Sulfonamides: An Experimental and Computational Study. *ACS Catal.* **2015**, *5*, 402−410. (c) Nilsson, G. N.; Kerr, W. J. The Development and Use of Novel Iridium Complexes as Catalysts for *Ortho*-Directed Hydrogen Isotope Exchange Reactions. *J. Labelled Compd. Radiopharm.* **2010**, *53*, 662−667. (d) Lockley, W. J. S. Hydrogen Isotope Labelling Using Iridium(I) Dionates. *J. Labelled Compd. Radiopharm.* **2010**, *53*, 668−673. (e) Lockley, W. J. S. 30 Years with *Ortho*-Directed Hydrogen Isotope Exchange Labeling. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 779−788.

(6) (a) Ma, S.; Villa, G.; Thuy-Boun, P. S.; Homs, A.; Yu, J.-Q. Palladium-Catalyzed *Ortho*-Selective C-H Deuteration of Arenes: Evidence for Superior Reactivity of Weakly Coordinated Palladacycles. *Angew. Chem., Int. Ed.* **2014**, *53*, 734−737. (b) Zhao, D.; Luo, H.; Chen, B.; Chen, W.; Zhang, G.; Yu, Y. Palladium-Catalyzed H/D Exchange Reaction with 8-Aminoquinoline as the Directing Group: Access to *ortho*-Selective Deuterated Aromatic Acids and β-Selective Deuterated Aliphatic Acids. *J. Org. Chem.* **2018**, *83*, 7860−7866. (c) Liu, W.; Xu, X.; Zhao, H.; Yan, X. Palladium-Catalyzed Site-Selective Hydrogen Isotope Exchange (HIE) Reaction of Arylsulfonamides using Amino Acid Auxiliary. *Tetrahedron* **2018**, *74*, 4111−4118. (d) Agasti, S.; Maity, S.; Szabo, K. J.; Maiti, D. Palladium-Catalyzed Synthesis of 2,3-Disubstituted Benzofurans: An Approach Towards the Synthesis of Deuterium Labeled Compounds. *Adv. Synth. Catal.* **2015**, *357*, 2331. (e) Sharma, U.; Kancherla, R.; Naveen, T.; Agasti, S.; Maiti, D. Palladium-Catalyzed Annulation of Diarylamines with Olefins through C-H Activation: Direct Access to N-Arylindoles. *Angew. Chem., Int. Ed.* **2014**, *53*, 11895. (f) Guin, S.; Dolui, P.; Zhang, X.; Paul, S.; Singh, V. K.; Pradhan, S.; Chandrashekar, H. B.; Anjana, S. S.; Paton, R. S.; Maiti, D. Iterative Arylation of Amino Acids and Aliphatic Amines via δ-C(sp^3)-H Activation: Experimental and Computational Exploration. *Angew. Chem., Int. Ed.* **2019**, *58*, 5633. (g) Deb, A.; Singh, S.; Seth, K.; Pimparkar, S.; Bhaskararao, B.; Guin, S.; Sunoj, R. B.; Maiti, D. View Author Information Experimental and Computational Studies on Remote γ-C(sp^3)-H Silylation and Germanylation of Aliphatic Carboxamides. *ACS Catal.* **2017**, *7*, 8171. (h) Deb, A.; Bag, S.; Kancherla, R.; Maiti, D. Palladium-Catalyzed Aryl C−H Olefination with Unactivated, Aliphatic Alkenes. *J. Am. Chem. Soc.* **2014**, *136*, 13602. (i) Deb, A.; Hazra, A.; Peng, Q.; Paton, R. S.; Maiti, D. Detailed Mechanistic Studies on Palladium-Catalyzed Selective C-H Olefination with Aliphatic Alkenes: A Significant Influence of Proton Shuttling. *J. Am. Chem. Soc.* **2017**, *139* (2), 763.

(7) (a) Chen, S.; Song, G.; Li, X. Chelation-Assisted Rhodium Hydride-Catalyzed Regioselective H/D Exchange in Arenes. *Tetrahedron Lett.* **2008**, *49*, 6929−6932. (b) Hesk, D.; Jones, J. R.; Lockley, W. J. S. Regiospecific Tritium Labeling of Aromatic Acids, Amides, Amines and Heterocyclics Using Homogeneous Rhodium Trichloride and Ruthenium Acetylacetonate Catalysts. *J. Labelled Compd. Radiopharm.* **1990**, *28*, 1427−1436. (c) Lockley, W. J. S. Regioselective Labelling of Anilides with Deuterium. *J. Labelled Compd. Radiopharm.* **1985**, *22*, 623−630.

(8) (a) Piola, L.; Fernandez-Salas, J. A.; Manzini, S.; Nolan, S. P. Regioselective Ruthenium Catalyzed H-D Exchange Using D_2O as the Deuterium Source. *Org. Biomol. Chem.* **2014**, *12*, 8683−8688. (b) Gröll, B.; Schnürch, M.; Mihovilovic, M. D. Selective Ru (0)-Catalyzed Deuteration of Electron-Rich and Electron-Poor Nitrogen Containing Heterocycles. *J. Org. Chem.* **2012**, *77*, 4432−4437. (c) Prades, A.; Poyatos, M.; Peris, E. (η6-Arene) ruthenium (N-heterocyclic carbene) Complexes for the Chelation-Assisted Arylation and Deuteration of Arylpyridines: Catalytic Studies and Mechanistic Insights. *Adv. Synth. Catal.* **2010**, *352*, 1155−1162.

(9) Pony Yu, R.; Hesk, D.; Rivera, N.; Pelczer, I.; Chirik, P. J. Iron-catalysed tritiation of pharmaceuticals. *Nature* **2016**, *529*, 195−199.

(10) Bag, S.; Petzold, M.; Sur, A.; Bhowmick, S.; Werz, D. B.; Maiti, D. Palladium-Catalyzed Selective *meta*-C-H Deuteration of Arenes: Reaction Design and Applications. *Chem. - Eur. J.* **2019**, *25*, 9433−9437.

(11) Xu, H.; Liu, M.; Li, L.-J.; Cao, Y.-F.; Yu, J.-Q.; Dai, H.-X. Palladium-Catalyzed Remote *meta*-C-H Bond Deuteration of Arenes Using a Pyridine Template. *Org. Lett.* **2019**, *21*, 4887−4891.

(12) Saidi, O.; Marafie, J.; Ledger, A. E.; Liu, P. M.; Mahon, M. F.; Kociok-Kohn, G.; Whittlesey, M. K.; Frost, C. G. Ruthenium-catalyzed *meta* sulfonation of 2-phenylpyridines. *J. Am. Chem. Soc.* **2011**, *133*, 19298−19301.

DOI: 10.1021/acs.orglett.9b03955
Org. Lett. XXXX, XXX, XXX−XXX

(13) Ackermann, L.; Hofmann, N.; Vicente, R. Carboxylate-Assisted Ruthenium-Catalyzed Direct Alkylations of Ketimines. *Org. Lett.* **2011**, *13*, 1875.
(14) (a) Leitch, J. A.; Frost, C. G. Ruthenium-catalyzed sigma-activation for remote *meta*-selective C-H functionalization. *Chem. Soc. Rev.* **2017**, *46*, 7145−7153. (b) Khan, F. F.; Sinha, S. K.; Lahiri, G. K.; Maiti, D. Ruthenium-Mediated Distal C-H Activation. *Chem. - Asian J.* **2018**, *13*, 2243. (c) Ping, L.; Chung, D. S.; Bouffard, J.; Lee, S. Transition metal-catalyzed site- and regio-divergent C−H bond functionalization. *Chem. Soc. Rev.* **2017**, *46*, 4299.
(15) Li, G.; Zhu, B.; Ma, X.; Jia, C.; Lv, X.; Wang, J.; Zhao, F.; Lv, Y.; Yang, S. Ruthenium-Catalyzed *ortho*/*meta*-Selective Dual C−H Bonds Functionalization of Arenes. *Org. Lett.* **2017**, *19*, 5166−5169.
(16) (a) Teskey, C. J.; Lui, A. Y. W.; Greaney, M. F. Ruthenium-Catalyzed *meta*-Selective C-H Bromination. *Angew. Chem., Int. Ed.* **2015**, *54*, 11677. (b) Yu, Q.; Hu, L.; Wang, Y.; Zheng, S.; Huang, J. Directed *meta*-Selective Bromination of Arenes with Ruthenium Catalysts. *Angew. Chem., Int. Ed.* **2015**, *54*, 15284.
(17) (a) Wang, X.-G.; Li, Y.; Liu, H.-C.; Zhang, B.-S.; Gou, X.-Y.; Wang, Q.; Ma, J.-W.; Liang, Y.-M. Three-Component Ruthenium-Catalyzed Direct *Meta*-Selective C−H Activation of Arenes: A New Approach to the Alkylarylation of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 13914−13922. (b) Gandeepan, P.; Koeller, J.; Korvorapun, K.; Mohr, J.; Ackermann, L. Visible-Light-Enabled Ruthenium-Catalyzed *meta*-C-H Alkylation at Room Temperature. *Angew. Chem., Int. Ed.* **2019**, *58*, 9820−9825. (c) Sagadevan, A.; Greaney, M. F. *meta*-Selective C-H Activation of Arenes at Room Temperature Using Visible Light: Dual-Function Ruthenium Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 9826−9830. (d) Li, J.; Korvorapun, K.; De Sarkar, S.; Rogge, T.; Burns, D. J.; Warratz, S.; Ackermann, L. Ruthenium(II)-catalyzed remote C-H alkylations as a versatile platform to *meta*-decorated arenes. *Nat. Commun.* **2017**, *8*, 15430. (e) Paterson, A. J.; St John-Campbell, S.; Mahon, M. F.; Press, N. J.; Frost, C. G. Catalytic *meta*-selective C−H functionalization to construct quaternary carbon centers. *Chem. Commun.* **2015**, *51*, 12807. (f) 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. (g) Hofmann, N.; Ackermann, L. meta-Selective C−H Bond Alkylation with Secondary Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 5877.
(18) (a) Fan, Z.; Li, J.; Lu, H.; Wang, D.-Y.; Wang, C.; Uchiyama, M.; Zhang, A. Monomeric Octahedral Ruthenium(II) Complex Enabled *meta*-C−H Nitration of Arenes with Removable Auxiliaries. *Org. Lett.* **2017**, *19*, 3199. (b) Fan, Z.; Ni, J.; Zhang, A. *Meta*-Selective C_{Ar}-H Nitration of Arenes through a $Ru_3(CO)_{12}$-Catalyzed *Ortho*-Metalation Strategy. *J. Am. Chem. Soc.* **2016**, *138*, 8470.
(19) (a) Ruan, Z.; Zhang, S.-K.; Zhu, C.; Ruth, P. N.; Stalke, D.; Ackermann, L. Ruthenium(II)-Catalyzed *meta* C-H Mono- and Difluoromethylations by Phosphine/Carboxylate Cooperation. *Angew. Chem., Int. Ed.* **2017**, *56*, 2045. (b) Li, Z.-Y.; Li, L.; Li, Q.-L.; Jing, K.; Xu, H.; Wang, G.-W. Ruthenium-Catalyzed *meta*-Selective C-H Mono- and Difluoromethylation of Arenes through *ortho*-Metalation Strategy. *Chem. - Eur. J.* **2017**, *23*, 3285. (c) Yuan, C. C.; Chen, X. L.; Zhang, J. Y.; Zhao, Y. S. *meta*-Selective C-H difluoromethylation of various arenes with a versatile ruthenium catalyst. *Org. Chem. Front.* **2017**, *4*, 1867.
(20) (a) Li, G.; Li, D.; Zhang, J.; Shi, D.-Q.; Zhao, Y. Ligand-Enabled Regioselectivity in the Oxidative Cross-coupling of Arenes with Toluenes and Cycloalkanes Using Ruthenium Catalysts: Tuning the Site-Selectivity from the *ortho* to *meta* Positions. *ACS Catal.* **2017**, *7*, 4138. (b) Li, B.; Fang, S. L.; Huang, D. Y.; Shi, B. F. Ru-Catalyzed *Meta*-C-H Benzylation of Arenes with Toluene Derivatives. *Org. Lett.* **2017**, *19*, 3950−3953.

DOI: 10.1021/acs.orglett.9b03955
Org. Lett. XXXX, XXX, XXX−XXX