OL | Organic Letters

Letter

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

pubs.acs.org/OrgLett

# Palladium-Catalyzed Hydrocarbonylative Cyclization Enabled by Formal Insertion of Aromatic C═N Bonds into Pd−Acyl Bonds

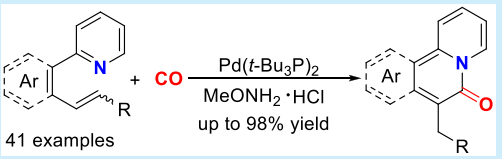
Xibing Zhou,[†] Anrong Chen,[†] Wei Du,[‡] Yawen Wang,[‡] Yu Peng,[‡] and Hanmin Huang*[,†,‡]

[†]Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, Center for Excellence in Molecular Synthesis, University of Science and Technology of China, Chinese Academy of Sciences, Hefei, 230026, People's Republic of China

[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, 730000, People's Republic of China

Supporting Information

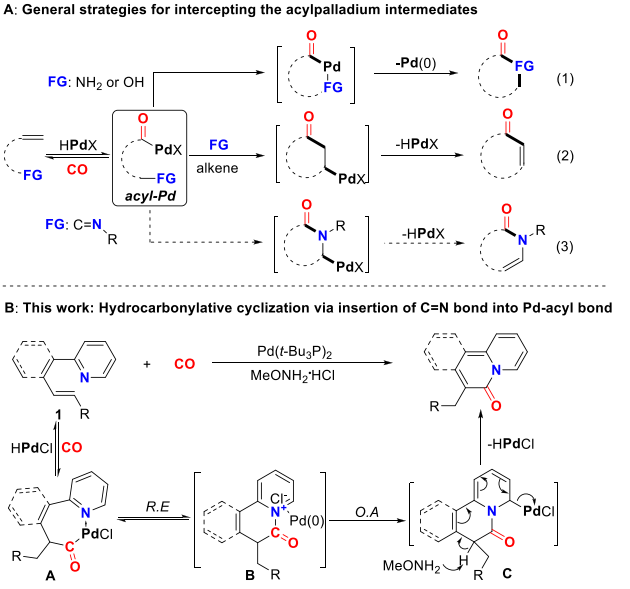
**ABSTRACT:** An efficient new formal insertion strategy via combination of reductive elimination and oxidative addition sequence was reported, in which the transient *N*-acyliminium ions formed via hydrocarbonylation function as key intermediates. This strategy has enabled a novel palladium-catalyzed hydrocarbonylative cyclization of azaarene-tethered alkenes or dienes via sequential insertion of a C═C bond, CO, and a C═N bond into palladium−hydride bonds. This method provides a new and highly efficient synthetic approach to quinolizinones and its derivatives with extended $\pi$-conjugated systems, possessing tunable emission wavelengths and good photoluminescence capabilities.






Transition-metal-catalyzed carbonylation reactions are widely utilized, not only for the industrial production of fine and bulk chemicals, but also for the preparation of natural products and bioactive compounds.[1] Among them, the palladium-catalyzed hydrocarbonylation of alkenes or alkynes constitutes one of the most atom-economical and efficient processes, considering the easy availability of alkenes and alkynes, as well as the synthetic versatility of carbonyl-containing products.[2] The synthetic significance of this transformation is further enhanced when it is applicable to the construction of *N*-heterocycles, which are important and privileged structures in bioactive compounds.[3] Mechanistically, acylpalladium complexes are recognized as key intermediates in these reactions. Therefore, understanding the reactivity of acylpalladium complexes and development of new strategies for intercepting them are crucial for new reaction discovery.[4] One of the general strategies to intercept the acylpalladium species is by using nucleophiles, whereby the corresponding carboxylic acids and their derivatives can be produced (Scheme 1A-1).[1,2] As an alternative strategy, the insertion of unsaturated 2$\pi$-units into the Pd-acyl bond has also long been pursued and strenuously developed.[5] However, the scope of the unsaturated 2$\pi$-units that can undergo such a insertion sequence have been primarily restricted to nonpolar carbon−carbon multiple bonds (Scheme 1A-2). There are very few examples of those that bring about the insertion of carbon−nitrogen double bonds (C═N) into the M−acyl bond, although it would be potentially utilized for construction of amide bonds (Scheme 1A-3).[6] Moreover, to the best of our knowledge, catalytic hydrocarbonylation reactions proceeded via sequential insertion of C═C, CO, and aromatic C═N bonds into palladium−hydride bonds remain largely elusive.[6c] The underlying reason might be attributed to the tendency for electrophilic metals to form $\sigma$-complexes with the N atom of C═N bonds, instead of $\pi$-complexes, because of the Lewis basicity of the nitrogen, which makes the C═N insertion unfavorable.[7]

**Scheme 1. Hydrocarbonylative Cyclization via Sequential C═C, CO, and C═N Bond Insertion**




Stimulated by the pharmaceutical importance of carbonyl-containing *N*-heterocycles and the pivotal role of amide-bond

**Received:** October 4, 2019

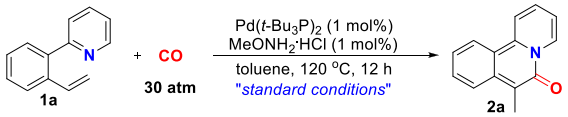



DOI: 10.1021/acs.orglett.9b03503
Org. Lett. XXXX, XXX, XXX−XXX

formation in synthetic organic chemistry, we have been fascinated by the transition-metal-catalyzed hydrocarbonylation reaction with C═N bonds of azaarenes as 2$\pi$-units to intercept the active acylpalladium species. However, since the aromatic C═N bonds were confined in the azaarene rings, the insertion of the C═N bond into the M−acyl bond is more challenging, exacerbated by the inherent aromaticity. Previous work in this area has recourse to the developing efficient strategies for dearomatization of azaarenes to convert the dative M−N bonds into the corresponding covalent M−N bonds prior to the reductive elimination step. However, these systems suffer from the significant disadvantage that they require special substrates that could undergo proton shift for dearomatization,[8] which limits the substrate scope and could not be applied in the hydrocarbonylative reactions. To address these challenges, the identification of an efficient strategy for insertion or formal insertion of the aromatic C═N bond into the M−acyl bond is in high demand. Being aware that pyridine-derived *N*-acyliminium ions could be facilely formed through the reductive elimination of C═N bond-coordinated $\sigma$-complexes and are capable of undergoing oxidative addition with low-valent metal to form the corresponding metal−carbon complexes,[9] we reasoned that the formal insertion of the C═N bond into the M−acyl bonds could be furnished via the sequential reductive elimination and oxidative addition of the C═N bond-coordinated $\sigma$-complexes. Herein, we report that a highly efficient palladium-catalyzed hydrocarbonylative cyclization of azaarene-tethered alkenes or dienes through sequential insertion of C═C, CO, and aromatic C═N bond into the palladium−hydride bond, which leads to the development of a new and efficient reaction for construction of quinolizinones that comprise the core of numerous bioactive agents and fluorophores (Scheme 1B).[10] Kinetic isotope effect experiments and control experiments suggested that the palladium-complex **C** is indeed involved in the present reaction, which underwent a unique long-distance reductive elimination to recycle the catalyst and deliver the desired products. To the best of our knowledge, this is the first direct observation of the formal insertion of aromatic C═N bonds into palladium−acyl bonds. The interest in this chemistry lies in not only the establishing new carbonylative cyclization reactions, but also the potentially new route to C−N bond formation.

To test this hypothesis, initial studies were focused on the reaction of 2-(2-vinylphenyl)pyridine **1a** with CO in the presence of Pd catalyst (see Table 1). After extensive examination of different reaction parameters, the mixture containing Pd($t$-$Bu_3P$)$_2$ (1 mol %) as the catalyst and MeONH$_2$·HCl (1 mol %) as an additive in toluene at 120 °C under 30 atm of CO facilitated the desired reaction, and the product **2a** was obtained in 97% isolated yield (Table 1, entry 1). As expected, controlling experiments clearly demonstrated the crucial roles of the catalyst and acid for maintaining the reaction efficiency (Table 1, entries 2 and 3). Various palladium catalyst systems that consisted of different phosphine ligands employing PdBr$_2$(cod) as a palladium precursor were screened, but all resulted in lower efficiency except $t$-$Bu_3P$ (Table 1, entries 4−7). We also attempted to investigate the impact of acid on the reactivity of the process, while no satisfactory result was obtained by using other Brønsted acids (Table 1, entries 8−10). Regarding the solvent effect, toluene was the most effective for this transformation (Table 1, entries 11−13). The efficiency of the reaction

**Table 1. Optimization of Reaction Conditions**[a]




| entry | variations from "standard conditions" | yield[b] (%) |
|---|---|---|
| 1 | **none** | **97** |
| 2 | without MeONH$_2$·HCl | 0 |
| 3 | without Pd($t$-$Bu_3P$)$_2$ | 0 |
| 4 | PdBr2(cod) (5 mol %)/Davephos (11 mol %) | 61 |
| 5 | PdBr$_2$(cod) (5 mol %)/$PCy_3$ (11 mol %) | 25 |
| 6 | PdBr$_2$(cod) (5 mol %)/$t$-$Bu_3P$ (11 mol %) | 83 |
| 7 | PdBr$_2$(cod) (5 mol %)/Xantphos (6 mol %) | 33 |
| 8 | replace MeONH$_2$·HCl with $NH_4Cl$ | trace |
| 9 | replace MeONH$_2$·HCl with NMP·HCl | 85 |
| 10 | replace MeONH$_2$·HCl with $PhSO_3H$ | trace |
| 11 | replace toluene with MeCN | 76 |
| 12 | replace toluene with DMSO | 83 |
| 13 | replace toluene with DME | 91 |
| 14 | CO (20 atm) | 65 |
| 15 | PdClH($t$-$Bu_3P$)$_2$, without MeONH$_2$·HCl | 92 |
| 16[c] | Pd($t$-$Bu_3P$)$_2$ (0.1 mol %) | 77 (1.61 g) |

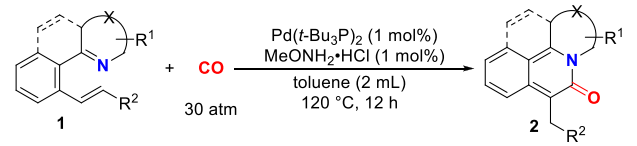
[a]Standard conditions: **1a** (0.3 mmol), CO (30 atm), Pd($t$-$Bu_3P$)$_2$ (1 mol %), MeONH$_2$·HCl (1 mol %), toluene (2.0 mL), 120 °C, 12 h. [b]Isolated yield. [c]24 h.

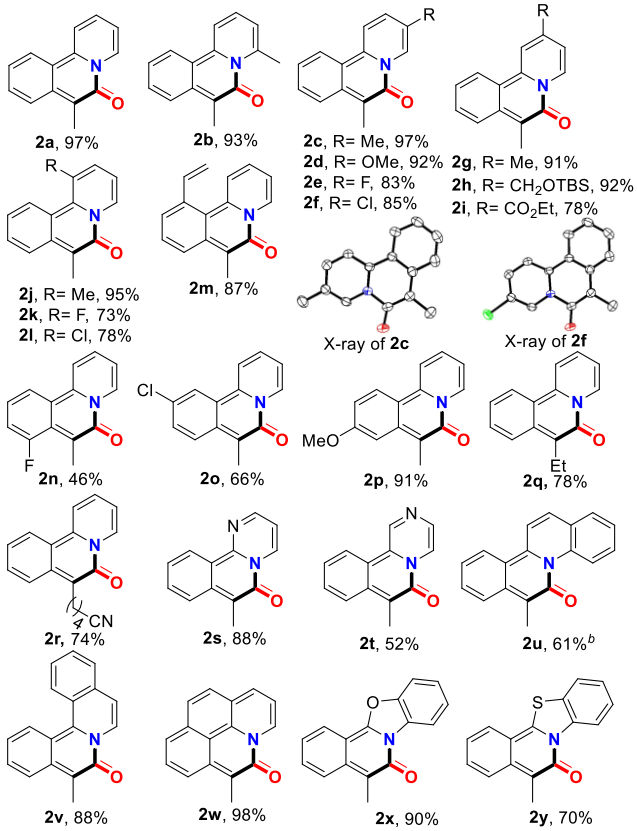
decreased under 20 atm of CO atmosphere (Table 1, entry 14). Almost the same efficiency was observed when PdClH($t$-$Bu_3P$)$_2$ was utilized as a catalyst in the absence of acid, which confirmed that the reaction was initiated by the Pd−H species (Table 1, entry 15). In addition, the method is synthetically useful, with a good efficiency maintained when running the reaction on a large scale in the presence of 0.1 mol % of Pd($t$-$Bu_3P$)$_2$ (Table 1, entry 16).

With the optimal reaction conditions identified, the investigation into the substrate scope for the present carbonylative cyclization reaction was pursued. As shown in Table 2, for 2-(2-vinylphenyl)pyridines, a series of functional groups contained in the pyridine core were compatible with the present catalytic system, and the desired products were isolated in good to excellent yields (73%−97% yields, **2a**−**2l**). The reaction seems to be less efficient for the substrates bearing electron-withdrawing groups on the pyridine ring, which might be due to the decreased nucleophilicity incurred by the electron-withdrawing substituents. On the other hand, the electron-donating and electron-withdrawing groups contained in the phenyl ring were tolerated well (**2m**−**2p**). Notably, product **2m** with an intact alkene on the phenyl-ring indicated the good tolerance of these reaction conditions and provided the opportunity for further elaborations. Interestingly, nonterminal alkenes with pendent functional groups, such as nitrile, were also feasible substrates, affording the desired products **2q** and **2r** in good yields. When pyridine core was replaced with pyrimidine (**1s**), pyrazine (**1t**), quinoline (**1u**), isoquinoline (**1v**), and 7,8-benzoquinoline (**1w**), the carbonylation reaction still proceeded well to give the corresponding products **2s**−**2w** in moderate to excellent yields (52%−98% yields). To our delight, benzoxazole (**1x**) and benzothiazole (**1y**) tethered alkenes were also found to be suitable for the present reaction to give the (**2x** and **2y**) in good to excellent yields. The structure of **2c** and **2f** were confirmed by X-ray diffraction (XRD) analysis.


DOI: 10.1021/acs.orglett.9b03503
Org. Lett. XXXX, XXX, XXX−XXX

**Table 2. Substrate Scope of Azaarene-Tethered Alkene**[a]



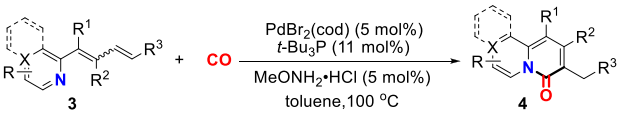



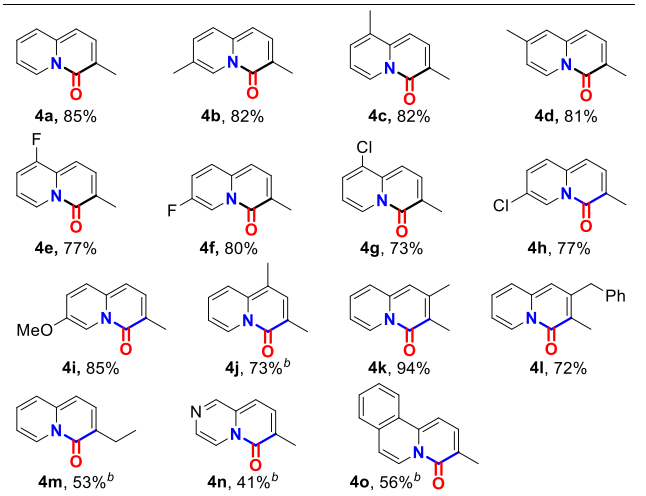

[a]Reaction conditions: **1** (0.3 mmol), Pd($t$-$Bu_3P$)$_2$(1 mol %), $MeONH_2$·HCl (1 mol %), CO (30 atm), toluene (2 mL), 120 °C, 12 h, isolated yield. [b]Pd($t$-$Bu_3P$)$_2$ (2 mol %), $MeONH_2$·HCl (2 mol %).

Inspired by the above results, we extended the present reaction to azaarene-tethered dienes. With $PdBr_2$(cod)/$t$-$Bu_3P$ as a catalyst precursor, a series of pyridine dienes bearing electron-withdrawing or electron-donating substituents on the pyridine ring were compatible, giving the expected products **4a**–**4i** in good to excellent yields (see Table 3). Furthermore, the presence of an alkyl group on the double bond of the diene provides the corresponding adducts in 53%–94% yields (**4j**–**4m**), while 2-(3-methylbuta-1,3-dien-1-yl)pyridine could not be converted to the desired product. Under the slightly modified reaction conditions, 2-(buta-1,3-dien-1-yl)pyrazine **3n** and 1-(buta-1,3-dien-1-yl)isoquinoline **3o** could also be converted to the corresponding adducts in moderate yields. It is noteworthy both the *E*-isomer and the *Z*-isomer could be efficiently converted to the desired cycloadducts.

Compounds listed in Tables 2 and 3 exhibit interesting photophysical properties. The different emission bands from 480 nm to 624 nm were observed by tuning the substituent group and extension of the $\pi$-conjugated systems. (See the Supporting Information.) Accordingly, the fluorescence colors including blue, green, yellow, orange, and red covers almost the full color wavelengths of the visible spectrum. These

**Table 3. Substrate Scope of Azaarene-Diene**[a]



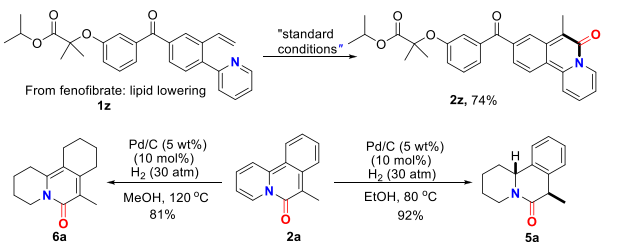

[a]Reaction conditions: **3** (0.3 mmol), CO (20 atm), $PdBr_2$(cod) (5 mol %), $t$-$Bu_3P$ (11 mol %), $MeONH_2$·HCl (5 mol %), toluene (2 mL), 120 °C, 12 h, isolated yield. [b]$MeONH_2$·HCl (0.03 mmol), CO (40 atm), 120 °C, 24 h.

fluorophores have good photoluminescence capabilities with $\Phi_F$ values ranging from 0.002 to 0.79. The relatively large Stokes shifts were also obtained (see the Supporting Information). This salient feature of these compounds indicated that they should find broad applications in material chemistry.[11]

This transformation is amenable to late-stage carbonylative functionalization of intermediates in the synthesis of complex molecules for biological evaluation. One example is Fenofibrate, which is a drug for lipid-lowering therapy.[12] Introducing a pyridine and alkene moieties into the backbone of Fenofibrate delivers **1z**. Treatment of **1z** with CO under the standard reaction conditions gives the product **2y** in 74% isolated yield. Moreover, the obtained cycloadducts are useful synthetic intermediates. For example, the Pd/C-catalyzed reduction of **2a** with $H_2$ in EtOH formed piperidine **5a** in 92% yield as a 20:1 mixture of *trans* and *cis* isomers. In addition, compound **6a** was obtained in 81% yield at 120 °C in MeOH, under otherwise identical conditions (see Scheme 2).

To gain insight into the mechanism, we conducted competition experiments between 2-(2-vinylphenyl)pyridine and deuterated analogue 2-(2-vinylphenyl)pyridine (see Scheme 3) with various substrates containing substituents in

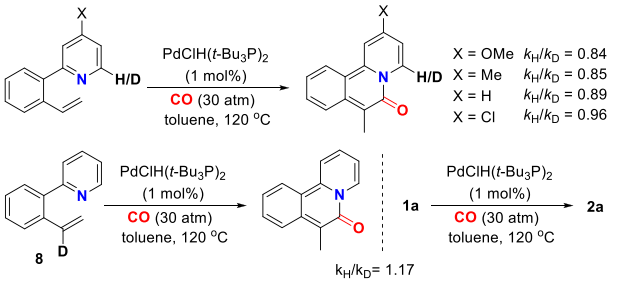
**Scheme 2. Synthetic Applications**






DOI: 10.1021/acs.orglett.9b03503
Org. Lett. XXXX, XXX, XXX–XXX

**Scheme 3. Kinetic Isotope Effect Experiments**




the *para*-position of pyridine. On the insertion of pyridyl C═N bond into the Pd-acyl bond, the $\alpha$-carbon adjacent to N atom undergoes a formal rehybridization from $sp^2$ to $sp^3$, which, in principle, should lead to the observation of an inverse secondary isotope effect ($k_H/k_D < 1$) if this formal insertion is turnover-limiting.[13] Furthermore, the magnitude of $k_H/k_D$ should vary in concert with the position of the transition state: later transition states, in which $\alpha$-carbon adjacent to N atom has more $sp^3$ character, should exhibit smaller values of $k_H/k_D$. In this context, the substrates with electron-donating substituents on the pyridine ring possessing lower oxidation ability should hold later transition states, since the corresponding oxidative addition of *N*-acyliminium ions **B** to Pd(0) is more difficult.[14] The observed secondary isotope effects ($k_H/k_D < 1$) are indicative of significant $Csp^2$ to $Csp^3$ rehybridization in the transition state for the cyclization process. These results also support in a compelling and quantitative manner that the palladium-complex **C** is most likely formed in the catalytic system. Furthermore, the experimental data reveal a direct correlation between $k_H/k_D$ and $\sigma_p$ (see Figure 1), indicating that the electronic character

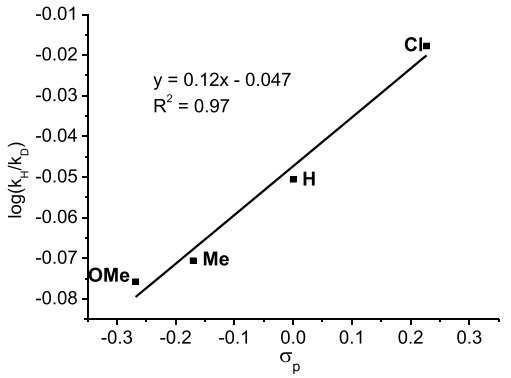
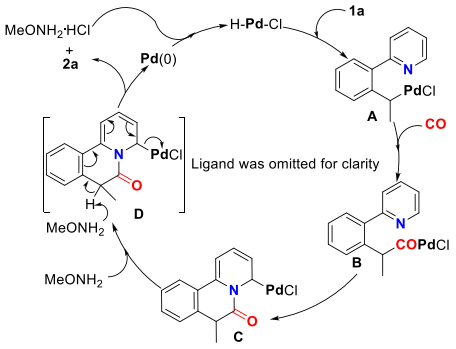



**Figure 1.** Correlation of the kinetic isotope effect in the hydrocarbonylative cyclization of 2-(2-vinylphenyl)pyridine versus 2-(2-vinylphenyl)pyridine-6-*d*, as a function of the $\sigma_p$ values of substituent X in substrates.

of the pyridine moiety does indeed alter the rate of oxidative addition of *N*-acyliminium ions to Pd(0). On the other hand, the independent measurement of the reaction rate of **2a** and deuterated analogue **8** (reaction rate was estimated by determining the reaction yields over time via $^1$H NMR) revealed only a small difference in rate ($k_H/k_D$ = 1.17). This value suggests that C−H cleavage is not turnover-limiting.

On the basis of the above experimental data, a plausible reaction mechanism was proposed (see Scheme 4). The reaction was initiated by the formation of the Pd−H species and followed by sequential C═C bond, CO, and formal C═N

**Scheme 4. Proposed Catalytic Cycle**




bond insertion to give the key intermediate **C**, which underwent long-distance reductive elimination promoted by the base to give the desired product and Pd(0). The Pd(0) reacted with $MeONH_2$·HCl to form the active Pd−H species for the next catalytic cycle.

In conclusion, we have developed a first catalytic protocol for formal insertion of aromatic C═N bonds into Pd-acyl bonds, which enabled an highly efficient palladium-catalyzed hydrocarbonylative cyclization of azaarene-tethered alkenes or dienes. The reaction is compatible with a diverse range of alkenes and azaarenes and allows the efficient synthesis of quinolizinone and its derivatives with lower catalyst loading. Preliminary mechanistic studies suggested that the catalytic reaction proceeds via sequential insertion of the C═C bond, CO, and the C═N bond into the palladium−hydride bond. Furthermore, this transformation leads to the formation of a family of fluorophores. More mechanistic investigation and further applications of this chemistry are underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03503.

Experimental details and full spectroscopic data for all new compounds (PDF)

### Accession Codes

CCDC 1905727 and 1905732 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

*E-mail: hanmin@ustc.edu.cn.

### ORCID

Yu Peng: 0000-0002-3862-632X

Hanmin Huang: 0000-0002-0108-6542

### Notes

The authors declare no competing financial interest.



DOI: 10.1021/acs.orglett.9b03503
Org. Lett. XXXX, XXX, XXX−XXX

## ■ ACKNOWLEDGMENTS

This research was supported by the National Natural Science Foundation of China (Nos. 21790333, 21702197, and 21672199).

## ■ REFERENCES

(1) (a) Beller, M. *Catalytic Carbonylation Reactions*; Springer: Berlin, Germany, 2006. (b) Kollár, L. *Modern Carbonylation Methods*; Wiley−VCH: Weinheim, Germany, 2008. (c) Wu, X.-F.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylative Coupling Reactions BetweenAr-X and Carbon Nucleophiles. *Chem. Soc. Rev.* **2011**, *40*, 4986−5009. (d) Wu, X.-F.; Neumann, H.; Beller, M. Synthesis of Heterocycles via Palladium-Catalyzed Carbonylations. *Chem. Rev.* **2013**, *113*, 1−35.

(2) (a) Kiss, G. Palladium-Catalyzed Reppe Carbonylation. *Chem. Rev.* **2001**, *101*, 3435−3456. (b) Wu, X.-F.; Fang, X.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. Transition-Metal-Catalyzed Carbonylation Reactions of Olefins and Alkynes: A Personal Account. *Acc. Chem. Res.* **2014**, *47*, 1041−1053.

(3) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845−5859.

(4) Trzeciak, A. M.; Ziolkowski, J. J. Structural and Mechanistic Studies of Pd-Catalyzed C-C Bond Formation: The Case of Carbonylation and Heck Reaction. *Coord. Chem. Rev.* **2005**, *249*, 2308−2322.

(5) (a) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. Palladium-Catalyzed Cross-Carbonylation of Aryl Iodides and 1-Aryl-2-Alkyn-1-Ones. *J. Org. Chem.* **1992**, *57*, 4754−4756. (b) Satoh, T.; Itaya, T.; Okuro, K.; Miura, M.; Nomura, M. Palladium-Catalyzed Cross-Carbonylation of Aryl Iodides with Five-Membered Cyclic Olefins. *J. Org. Chem.* **1995**, *60*, 7267−7271. (c) Okuro, K.; Alper, H. Palladium-Catalyzed Carbonylation of *o*-Iodophenols with Allenes. *J. Org. Chem.* **1997**, *62*, 1566−1567. (d) Gagnier, S. V.; Larock, R. C. Palladium-Catalyzed Carbonylative Cyclization of Unsaturated Aryl Iodides and Dienyl Triflates, Iodides, and Bromides to Indanones and 2-Cyclopentenones. *J. Am. Chem. Soc.* **2003**, *125*, 4804−4807. (e) Ye, F.; Alper, H. Ionic-Liquid-Promoted Palladium-Catalyzed Multicomponent Cyclocarbonylation of o-Iodoanilines and Allenes To Form Methylene-2,3-Dihydro-1H-Quinolin-4-Ones. *J. Org. Chem.* **2007**, *72*, 3218−3222. (f) Wu, X.-F.; Neumann, H.; Spannenberg, A.; Schulz, T.; Jiao, H.; Beller, M. Development of a General Palladium-Catalyzed Carbonylative Heck Reaction of Aryl Halides. *J. Am. Chem. Soc.* **2010**, *132*, 14596−14602. (g) Wu, X.-F.; Neumann, H.; Beller, M. Palladium-Catalyzed Coupling Reactions: Carbonylative Heck Reactions To Give Chalcones. *Angew. Chem., Int. Ed.* **2010**, *49*, 5284−5288. (h) Bloome, K. S.; Alexanian, E. J. Palladium-Catalyzed Carbonylative Heck-Type Reactions of Alkyl Iodides. *J. Am. Chem. Soc.* **2010**, *132*, 12823−12825.

(6) (a) Kacker, S.; Kim, J. S.; Sen, A. Insertion of Imines into Palladium-Acyl Bonds: Towards Metal-Catalyzed Alternating Copolymerization of Imines with Carbon Monoxide To Form Polypeptides. *Angew. Chem., Int. Ed.* **1998**, *37*, 1251−1253. (b) Dghaym, R. D.; Yaccato, K. J.; Arndtsen, B. A. The Novel Insertion of Imines into a Late-Metal-Carbon $\sigma$-Bond: Developing a Palladium-Mediated Route to Polypeptides. *Organometallics* **1998**, *17*, 4−6. (c) Davis, J. L.; Arndtsen, B. A. Comparison of Imine to Olefin Insertion Reactions: Generation of Five- and Six-Membered Lactams via a Nickel-Mediated CO, Olefin, CO, Imine Insertion Cascade. *Organometallics* **2011**, *30*, 1896−1901. (d) Beller, M.; Eckert, M. Amidocarbonylation-An Efficient Route to Amino Acid Derivatives. *Angew. Chem., Int. Ed.* **2000**, *39*, 1010−1027. (e) Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. The Use of Carbon Monoxide and Imines as Peptide Derivative Synthons: A Facile Palladium-Catalyzed Synthesis of a-Amino Acid Derived Imidazolines. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228−3230. (f) Bontemps, S.; Quesnel, J. S.; Worrall, K.; Arndtsen, B. Palladium-Catalyzed Aryl Iodide Carbonylation as a Route to Imidazoline Synthesis: Design of a Five-Component Coupling Reaction. *Angew. Chem., Int. Ed.* **2011**, *50*, 8948−8951.

(7) Fryzuk, M. D.; Piers, W. E. Reactions of Binuclear Rhodium Hydrides with Imines: Factors Influencing the Insertion of Carbon-Nitrogen Double Bonds into Rhodium-Hydride Bonds. *Organometallics* **1990**, *9*, 986−998.

(8) (a) Yu, H.; Zhang, G.; Huang, H. Palladium-Catalyzed Dearomative Cyclocarbonylation via C-N Bond Activation. *Angew. Chem., Int. Ed.* **2015**, *54*, 10912−10916. (b) Xie, Z.; Luo, S.; Zhu, Q. Pd-Catalyzed C($sp^2$)-H Carbonylation of 2-Benzylpyridines for the Synthesis of Pyridoisoquinolinones. *Chem. Commun.* **2016**, *52*, 12873−12876.

(9) (a) Graham, T. J. A.; Shields, J. D.; Doyle, A. G. Transition Metal-Catalyzed Cross Coupling with *N*-acyliminium Ions Derived from Quinolines and Isoquinolines. *Chem. Sci.* **2011**, *2*, 980−984. (b) Sylvester, K. T.; Wu, K.; Doyle, A. G. Mechanistic Investigation of the Nickel-Catalyzed Suzuki Reaction of N, O-Acetals: Evidence for Boronic Acid Assisted Oxidative Addition and an Iminium Activation Pathway. *J. Am. Chem. Soc.* **2012**, *134*, 16967−16970. (c) Chau, S. T.; Lutz, J. P.; Wu, K.; Doyle, A. G. Nickel-Catalyzed Enantioselective Arylation of Pyridinium Ions: Harnessing an Iminium Ion Activation Mode. *Angew. Chem., Int. Ed.* **2013**, *52*, 9153−9156. (d) Lutz, J. P.; Chau, S. T.; Doyle, A. G. Nickel-Catalyzed Enantioselective Arylation of Pyridine. *Chem. Sci.* **2016**, *7*, 4105−4109.

(10) (a) Martin, J. R.; Moreau, J.-L.; Jenck, F. Evaluation of the Dependence Liability of Quinolizinones Acting as Partial Agonists at the Benzodi Azepine Receptor. *Drug Dev. Res.* **1995**, *36*, 141−149. (b) Chen, M.-H.; Fitzgerald, P.; Singh, S. B.; O'Neill, E. A.; Schwartz, C. D.; Thompson, C. M.; O'Keefe, S. J.; Zaller, D. M.; Doherty, J. B. Synthesis and Biological Activity of Quinolinone and Dihydroquinolinone p38 MAP Kinase Inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2222−2226. (c) Kim, J. H.; Gensch, T.; Zhao, D.; Stegemann, L.; Strassert, C. A.; Glorius, F. $Rh^{III}$-Catalyzed C-H Activation with Pyridotriazoles: Direct Access to Fluorophores for Metal-Ion Detection. *Angew. Chem., Int. Ed.* **2015**, *54*, 10975−10979. (d) Zhao, D.; Kim, J. H.; Stegemann, L.; Strassert, C. A.; Glorius, F. Cobalt(III)-Catalyzed Directed C-H Coupling with Diazo Compounds: Straightforward Access towards Extended $\pi$-Systems. *Angew. Chem., Int. Ed.* **2015**, *54*, 4508−4511.

(11) Müllen, K.; Scherf, U. *Organic Light Emitting Devices, Synthesis Properties and Applications*; Wiley−VCH:Weinheim, Germany, 2005.

(12) Balfour, J. A.; McTavish, D.; Heel, R. C. Fenofibrate. *Drugs* **1990**, *40*, 260−290.

(13) (a) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Guler, M. L.; Ishida, T.; Jacobsen, E. N. The Mechanistic Basis for Electronic Effects on Enantioselectivity in the (salen)Mn(III)-Catalyzed Epoxidation Reaction. *J. Am. Chem. Soc.* **1998**, *120*, 948−954. (b) Jones, W. D. Isotope Effects in C-H Bond Activation Reactions by Transition Metals. *Acc. Chem. Res.* **2003**, *36*, 140−146. (c) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006; Chapter 8. (d) Gomez-Gallego, M.; Sierra, M. A. Kinetic Isotope Effects in the Study of Organometallic Reaction Mechanisms. *Chem. Rev.* **2011**, *111*, 4857−4963. (e) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C-H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066−3072.

(14) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010; pp 349.



DOI: 10.1021/acs.orglett.9b03503
*Org. Lett.* XXXX, XXX, XXX−XXX