ORGANIC CHEMISTRY

External oxidant-compatible phosphorus(III)-directed site-selective C–H carbonylation

Ben Dong[1]*, Jiasheng Qian[1,2]*, Mingjie Li[1]*, Zheng-Jun Wang[1], Minyan Wang[1], Dingyi Wang[1], Chengkai Yuan[1], Ying Han[1], Yue Zhao[1], Zhuangzhi Shi[1†]

The first development of an external oxidant-compatible system involving a phosphorus(III)-directed C–H functionalization has been uncovered. An efficient C–H esterification of indoles with CO and alcohols has been reported in which the high reactivity and the exclusive C7-selectivity derives from the selection of a P(III)–directing group and the utilization of benzoquinone as an external oxidant with palladium catalysis. This strategy shows many advantages, involving an easily accessible and removable directing group, the use of cheap carbonylation sources, a broad substrate scope, and excellent positional selectivity. Two cyclopalladated intermediates were confirmed by x-ray analysis, uncovering key mechanistic features of this P(III)-directed C–H metalation event.

INTRODUCTION

C–H bond functionalization is a topic of intense interest because it represents an ideal synthetic pathway (*1*–*6*). Because complex organic molecules usually contain multiple C–H bonds with small differences in activation barriers, controlling the regioselectivity represents a key challenge in this field. An efficient strategy to solve this is the use of substrates bearing directing groups, which deliver the metal to access proximal C–H bonds through a cyclometallated process. To regenerate the transition metal catalysts, many C–H functionalization reactions require external oxidants (*7*–*9*). Coordination of transition metals with O, N, or S atoms in functional groups has been developed, all of which are compatible with oxidants (Fig. 1A, left) (*10*–*14*). Recently, phosphorus(III)–chelation assisted C–H functionalization has been disclosed with transition metal catalysis, but external oxidants cannot be used in these reactions (*15*–*22*). P(III) functional groups are usually unstable in the presence of oxidants due to the ease of forming P(V) species, (*23*) thus limiting the applicability of this chemistry (Fig. 1A, right). Undoubtedly, the development of an oxidant-compatible system offers a key to conduct diverse P(III)-directed C–H functionalization.

Using CO as a low-cost and abundant C1 source, extensive research efforts have been made toward the C–H carbonylation of heterocycles with transition metal catalysis (*24*–*26*). Typically, C–H carbonylation of N-protected indoles can selectively generate C3-carbonyl indoles (Fig. 1B, top) (*27*–*31*). Recently, several groups have also achieved the site-selective C–H carbonylation of indoles at the C2-position, (*32*–*36*), especially by the CO insertion, with the aid of directing groups at the N atom (Fig. 1B, bottom). Because of the inherent reactivity of these two positions in indoles, the C7-selectivity faces substantial challenges (*37*–*42*).

Indoles bearing C7 carbonyl groups are extremely important for drug finding, exhibiting a number of pharmacological activities such as inhibitor of severe acute respiratory syndrome coronavirus (SARS-CoV) (*43*), prostaglandin E2 receptor subtype 4 (EP4) antagonist (*44*), 5-HT2A antagonist (*45*), and inhibitor of HIV-1 (Fig. 1C) (*46*). In this context, an indirect method to access these compounds involved the reduction of indoles to the indolines and then ortho-selective esterification, followed by oxidation (Fig. 1D, top) (*47*–*50*). Here, we develop a P(III)-directed C7-selective C–H esterification of indoles by palladium catalysis in which the CO and alcohols are used as the carbonylative sources (Fig. 1D, bottom). The key factor of the transformation is to find a suitable oxidative system, which cannot only regenerate the catalyst but also suppress the oxidation of the P(III) species.

RESULTS

Reaction condition optimization

Our study began with the three-component reaction of *N*–P^{t}Bu$_2$ indole **1a**, EtOH (**2a**), and CO gas to form C7-esterification product **3aa** (Table 1). The optimized conditions were achieved with 10 mol% of Pd(OAc)$_2$ and 3.0 equivalent of benzoquinone (BQ) as the external oxidant in *N*,*N*′-dimethylformamide (DMF) under 1 atm of CO within 36 hours at 110°C. Under these conditions, the desired product **3aa** (with x-ray structure) was generated and isolated with an 85% yield (entry 1). The oxidized byproducts **1a**′ and **3aa**′ and the isomers **4aa** and **5aa** were not observed, showing that the *N*-P^{t}Bu$_2$ group worked very well under such conditions. Oxidant selection was found to have a marked impact on the conversion. When the reaction was conducted with other oxidants like AgOAc, Cu(OAc)$_2$ or O$_2$, the desired product **3aa** was not formed. Instead, a large amount of the indole **1a**′ was produced (entries 2 to 4). Other transition metals including [Rh(OAc)$_2$]$_2$ and RhCl$_3$ showed lower reactivity for this reaction (entries 5 to 6), and the iridium catalyst completely failed (entry 7). The indole **1a**′ with the P(V) directing group can undergo Pd-catalyzed C7-selective C–H arylation (*51*) and alkynylation (*52*) using Ag and Cu salts as the oxidants, which did not provide the corresponding product **3aa**′ in the presence of BQ as the oxidant (entry 8). In addition, other P(III) directing groups including N–PCy$_2$ and N–P^{i}Pr$_2$ were failed under the standard reaction conditions, because the oxidized by-products generated. These results confirm the importance of using bulky N-P^{t}Bu$_2$ group for this transformation as well. The reaction maintained a good reactivity when lowering the reaction temperature to 100°C (entry 9). Last, a control experiment showed that the carbonylation process completely failed without the catalyst (entry 10).

[1]State Key Laboratory of Coordination Chemistry, Chemistry and Biomedicine Innovation Center (ChemBIC), School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093 (China). [2]College of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002 (China).
*These authors contributed equally to this work.
†Corresponding author. Email: shiz@nju.edu.cn

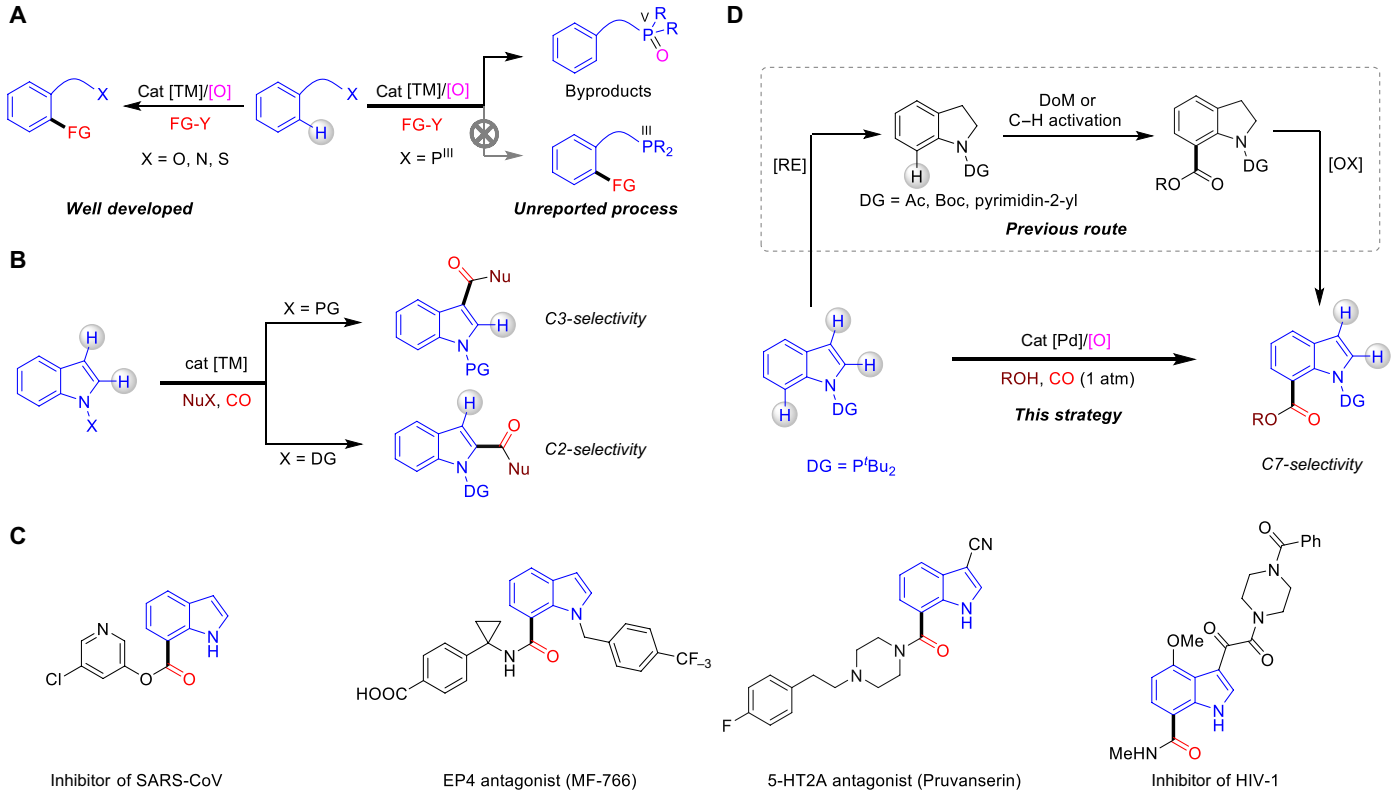
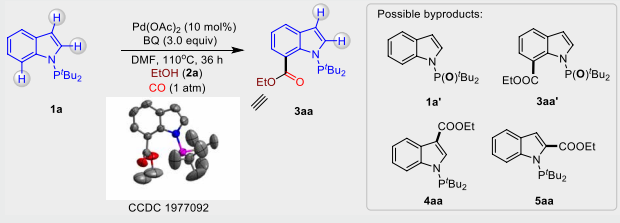


Fig. 1. P(III)-directed C–H functionalization under oxidative conditions. (**A**) Directed C–H functionalizations under oxidative reaction conditions. TM, transition metal; FG, functional group; FG-Y, functional group. (**B**) Previous works on indole C–H carbonylation. DG, directing group; PG, protecting group. (**C**) Selected drug active molecules bearing C7-carbonyl indoles. (**D**) Previous routes to indole C7-carbonylation and this strategy. DoM, directed ortho metalation.

Table 1. Reaction development. Reaction conditions: 10 mol% catalyst, **1a** (0.20 mmol), **2a** (5.0 mmol), oxidant (0.60 mmol), solvent (2.0 ml), 36 hours, under 1 atm of CO pressure.



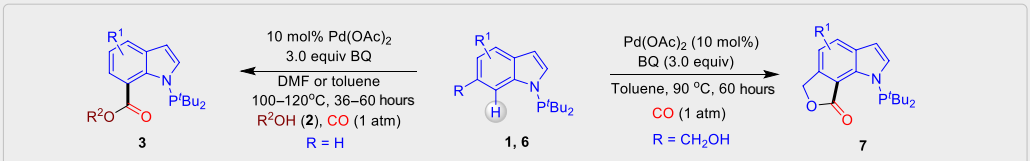
Entry	Variation from the standard conditions	Yield of 3aa (%)*
1	None	85
2	Using AgOAc instead of BQ	0
3	Using $Cu(OAc)_2$ instead of BQ	0
4	Using O_2 instead of BQ	0
5	Using $[Rh(OAc)_2]_2$ instead of $Pd(OAc)_2$	36
6	Using $RhCl_3$ instead of $Pd(OAc)_2$	42
7	Using $[Ir(cod)_2Cl]_2$ instead of $Pd(OAc)_2$	0
8	Using **1a'** instead of **1a**	0
9	At 100°C	77
10	Without $Pd(OAc)_2$	0

*Isolated yield.

Scope of the methodology

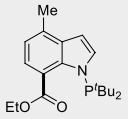
With the optimal reaction conditions in hand, the reaction of ethanol (**2a**) with a broad range of indoles was first investigated (Table 2A). *N*-P^{t}Bu$_2$ Indoles containing methyl (**1b**-**d**), phenyl (**1e**-**g**), methoxy (**1h**-**i**) and phenylthio (**1j**) substituents at the C3 to C6 positions performed facile esterification, delivering carboxylic esters **3ba** and **3ia** in 56 to 86% yields. The electron-deficient substituents on indole skeleton such as F (**3 ka**), Cl (**3la**), CF_3 (**3ma**), ester (**3na**), cyano (**3oa**), and acetyl (**3pa**) groups were converted in good efficiency. In addition, this system was also tolerant of alkenyl (**3qa**) and alkynyl (**3ra**) groups. 3,3′-diindolylmethane **1s** with two *N*-P^{t}Bu$_2$ groups could be subjected to dual C–H esterification affording indole **3sa** in a moderate yield. Next, we investigated *N*-P^{t}Bu$_2$ indole **1a** with different alcohols (Table 2C). The functional group tolerance of this transformation was well demonstrated by the case that primary, secondary, and tertiary alcohols could all be equally accommodated (**3ab**-**3ae**). Moreover, alcohols bearing NMe_2 (**3af**), Cl (**3ag**) and alkenyl (**3ah**-**3ai**) groups could also be installed on the esters. In addition, late-stage esterification of complex indoles **1t**-**u** with ethanol (**2a**) proceeded readily, producing products **3ta**-**3ua** without any racemization (Table 2C). Treatment of indole **1a** with alcohol **2j** derived from lithocholic acid afforded the desired adduct **3aj** in a useful efficiency as well. Notably, although a large excess of alcohols should be used at the current reaction conditions, the unreacted complex alcohols could be recovered after the reaction. Furthermore, this strategy could be used in intramolecular cyclocarbonylation to build lactone frameworks on the benzene core of indoles (Table 2D). Using indole **6a** as a substrate, the intramolecular esterification

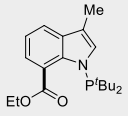
Table 2. C7-selective C–H esterification of indoles. Standard conditions: $Pd(OAc)_2$ (10 mol%), **1** (0.20 mmol), **2** (5.0 mmol), BQ (0.60 mmol), and DMF (**A**)/toluene (**B** and **C**), at 110°C, 36 hours, under 1 atm of CO pressure; isolated yields.

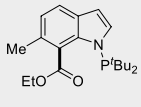


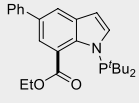
Indoles

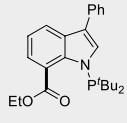
A

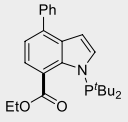

3ba, 75%

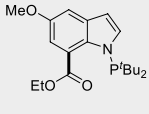

3ca, 56%

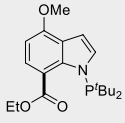

3da, 81%*

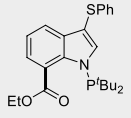

3ea, 80%*

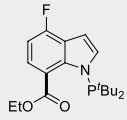

3fa, 76%

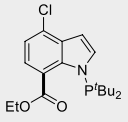

3ga, 74%


3ha, 68%

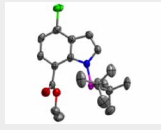

3ia, 47%*

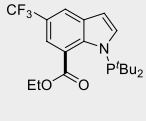

3ja, 86%†

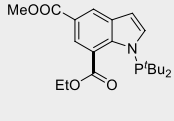

3ka, 72%

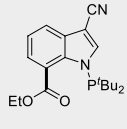

3la, 50%

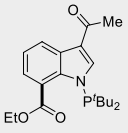
≡

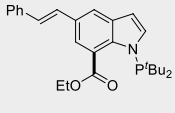

CCDC 1977096

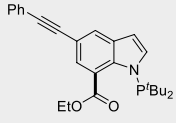

3ma, 71%†

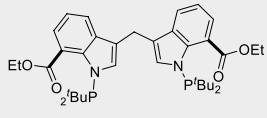

3na, 92%‡


3oa, 57%‡


3pa, 45%§

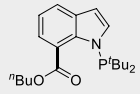

3qa, 47%†

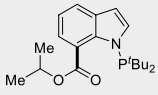

3ra, 49%†

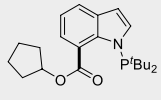

3sa, 46%‖

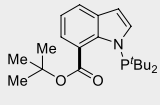
Alcohols

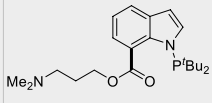
B

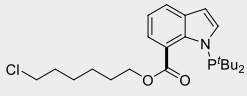

3ab, 94%

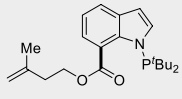

3ac, 73%

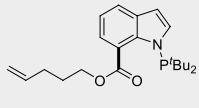

3ad, 58%


3ae, 55%


3af, 68%

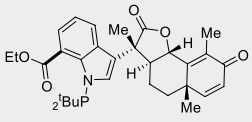

3ag, 55%

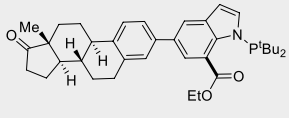

3ah, 74%

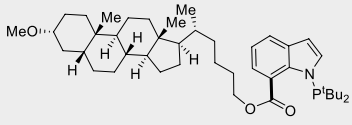

3ai, 80%

Late-stage modifications

C

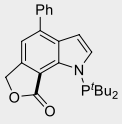

3ta, 51%

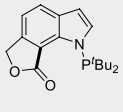

3ua, 45%


3aj, 41%¶

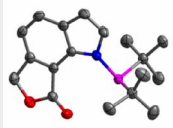
Intramolecular cyclocarbonylation#

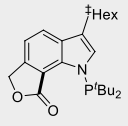
D

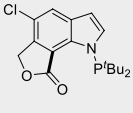

7a, 78%


7b, 69%

≡


CCDC 1977093


7c, 54%


7d, 49%

*EtOH (6.0 mmol), 120°C, 60 hours. †EtOH (6.0 mmol), 60 hours, toluene. ‡Toluene, 100°C, 60 hours. §Toluene/DMF(1:1, v/v), 48 hours. ‖EtOH (12.0 mmol), 60 hours, BQ (1.2 mmol). ¶**2j** (3.0 mmol). #$Pd(OAc)_2$ (10 mol%), **6** (0.20 mmol), BQ (0.60 mmol), and toluene (2.0 ml), at 90°C, 60 hours, under 1 atm of CO pressure.

reaction could give product **7a** in 78% yield. Other indoles such as **6b-6d** carried out C–H lactonization successfully.

Synthetic applications

A benefit of this strategy is that the deprotection of *N*–P^{t}Bu$_2$ group in product **3aa** can form N–H free indole **8** in nearly full conversion by treatment with tetrabutylammonium fluoride (TBAF) under mild reaction conditions (Fig. 2). This compound is highly suitable to undergo various subsequent transformations, showing great potential of this method. For instance, compound **8** can undergo hydrolysis to carboxylic acid **9**, selective reduction to aldehyde **10** and alcohol **11**, and amidation to product **12** (amines cannot be used as the nucleophiles directly in this C–H carbonylation.) in high efficiency. Benzylation of **8** provided product **13** in a 63% yield, which was a key intermediate of drug candidate MF-766 for treating inflammatory pain. (*45*) In addition, biologically and pharmacologically active molecules including the inhibitor of SARS-CoV (*43*) and the 5-HT2A receptor antagonist pruvanserin (*44*) could also be prepared from indole **8**.

DISCUSSION

Intrigued by this *N*-P^{t}Bu$_2$ chelation-assisted C–H esterification, we decided to investigate the C–H activation process (Fig. 3). When 1.0 equivalent of indole **1a** was allowed to react with stoichiometric Pd(OAc)$_2$, a cyclometalated Pd^{II} dimer **14** was obtained and confirmed by x-ray analysis (Fig. 3A) (*53*–*54*). The ranges of the bond lengths and angles surrounding Pd atoms are 1.984(4) to 2.2592(10) Å and 82.80 to 176.15(12)°, respectively. The τ4 values of 0.123 and

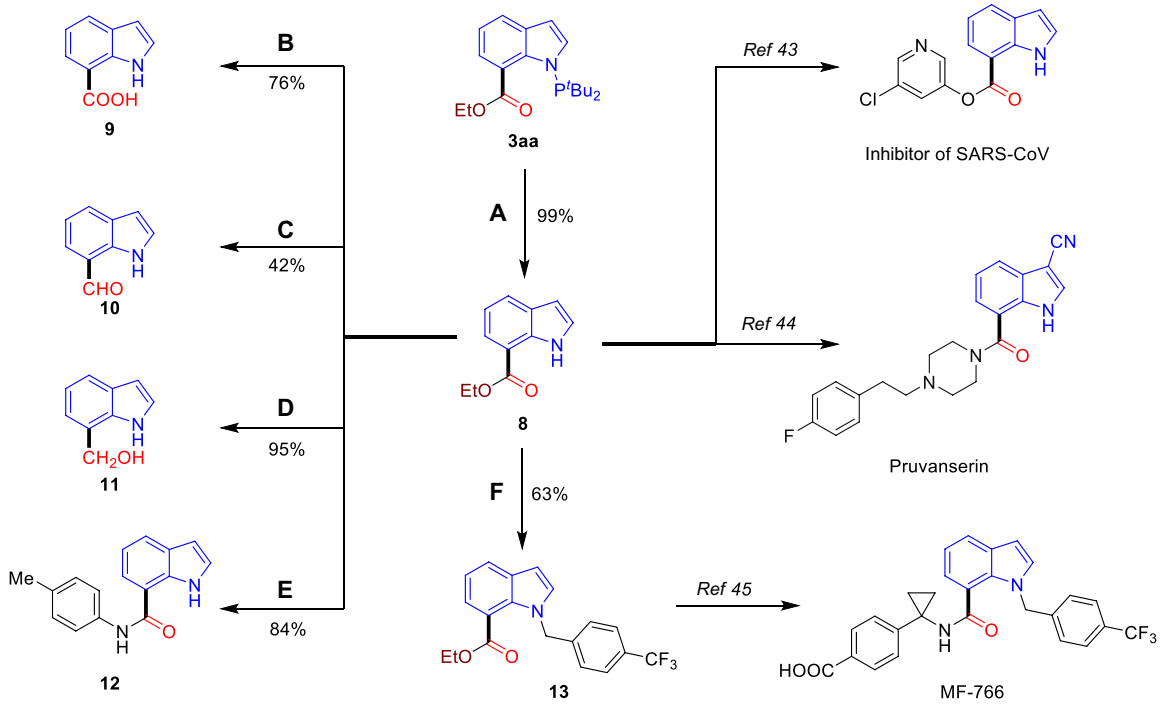


Fig. 2. Synthetic applications. Reagents and conditions: (**A**) TBAF, tetrahydrofuran (THF), room temperature (rt)., 7 hours; (**B**) NaOH, EtOH, 80°C, 3 hours; (**C**) Ir(coe)$_2$Cl$_2$, Et$_2$SiH$_2$, dichloromethane, 50°C; (**D**) LiAlH$_4$, THF, 80°C, 2 hours, (**E**) 4-MePhNH$_2$, Lithium Hexamethyldisilazide (LiHMDS), toluene, rt., 15 hours; (**F**) 4-CF$_3$-BzBr, NaH, DMF, 0°C, 1 hour.

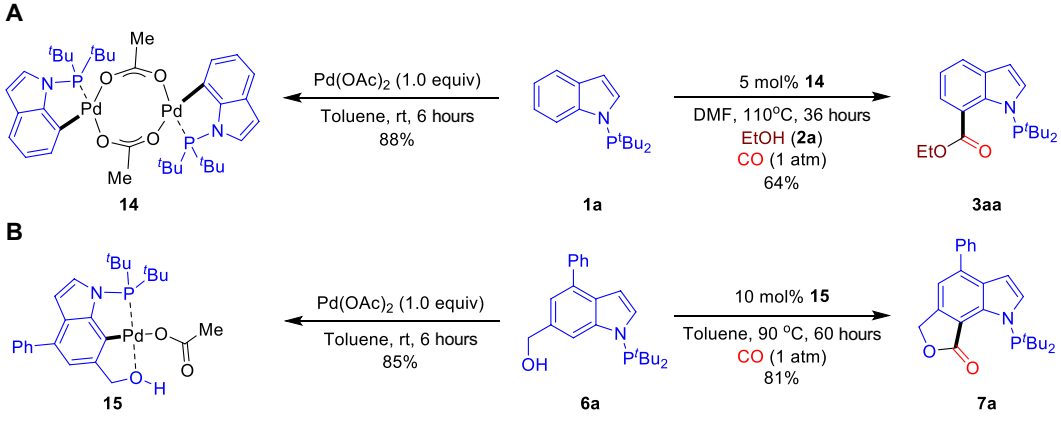


Fig. 3. Mechanistic experiments. (**A**) Cyclopalladation of indole **1a** to a bimetallic Pd(II) complex **14**. (**B**) Cyclopalladation of indole **6a** to a monometallic Pd(II) complex **15**.

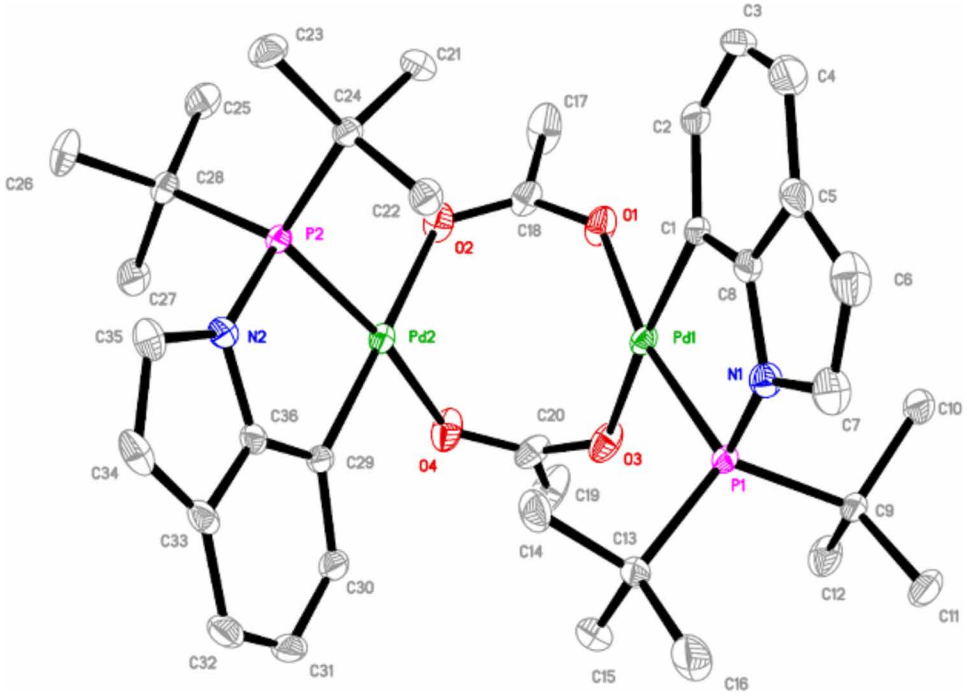


Fig. 4. Single Crystal X-ray Diffraction (SXRD) structure of 14 (CCDC 1977094). Ellipsoids are set to 30% probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths and angles: C(1)-Pd(1) 1.989(4) Å, C(29)-Pd(2) 1.984(4) Å, O(1)-Pd(1) 2.098(2) Å, O(2)-Pd(2) 2.114(3) Å, O(3)-Pd(1) 2.126(3) Å, O(4)-Pd(2) 2.076(3) Å, P(1)-Pd(1) 2.2592(10) Å, P(2)-Pd(2) 2.2453(11) Å, C(1)-Pd(1)-O(1) 90.81(15)°, C(1)-Pd(1)-O(3) 173.29(13)°, O(1)-Pd(1)-O(3) 86.96(13)°, C(1)-Pd(1)-P(1) 82.80(11)°, O(1)-Pd(1)-P(1) 169.33(8)°, O(3)-Pd(1)-P(1) 98.41(8)°, C(29)-Pd(2)-O(4) 92.52(15)°, C(29)-Pd(2)-O(2) 176.15(12)°, O(4)-Pd(2)-O(2) 85.30(13)°, C(29)-Pd(2)-P(2) 84.00(11)°, O(4)-Pd(2)-P(2) 170.15(8)°, and O(2)-Pd(2)-P(2) 97.63(8)°.

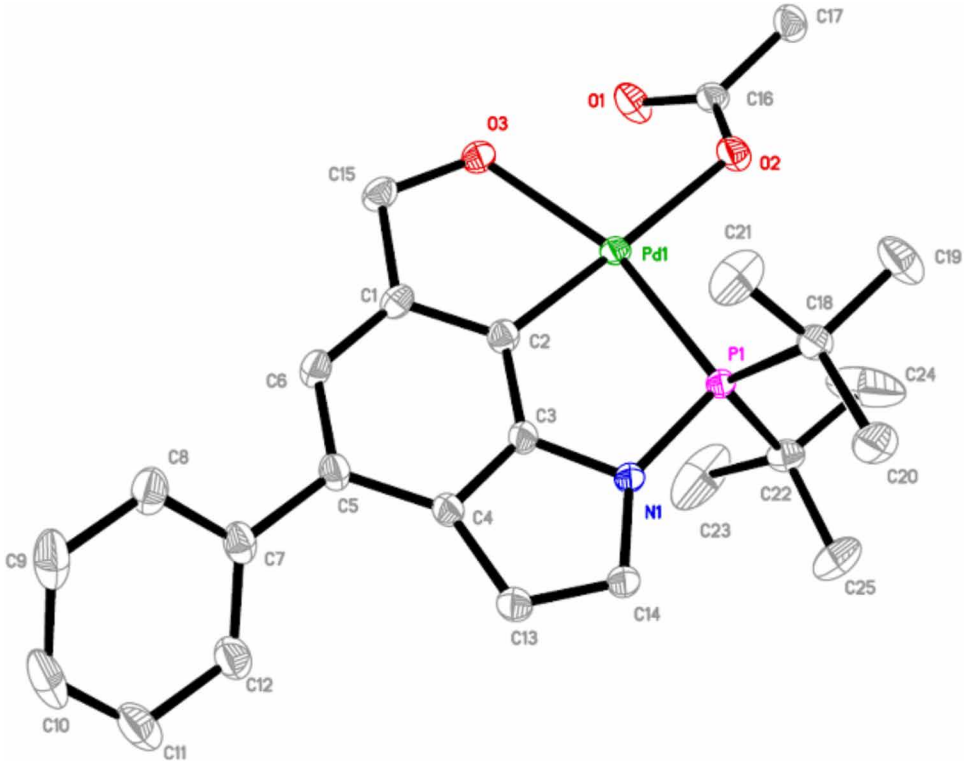


Fig. 5. SXRD structure of 15 (CCDC 1977095). Ellipsoids are set to 30% probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths and angles: C(2)-Pd(1) 1.923(4) Å, O(2)-Pd(1) 2.129(3) Å, O(3)-Pd(1) 2.165(2) Å, P(1)-Pd(1) 2.2411(9) Å, P(2)-Pd(2) 2.2359(9) Å, C(2)-Pd(1)-O(2) 176.49(13)°, C(2)-Pd(1)-O(3) 77.83(12)°, O(2)-Pd(1)-O(3) 101.27(10)°, C(2)-Pd(1)-P(1) 82.67(11)°, O(2)-Pd(1)-P(1) 98.06(7)°, O(3)-Pd(1)-P(1) 160.39(7)°, C(36)-Pd(2)-O(5) 171.37(12)°, C(36)-Pd(2)-O(4) 77.82(12)°, O(5)-Pd(2)-O(4) 93.56(9)°, C(36)-Pd(2)-P(2) 82.79(10)°, O(5)-Pd(2)-P(2) 105.81(7)°, and O(4)-Pd(2)-P(2) 160.12(7)°.

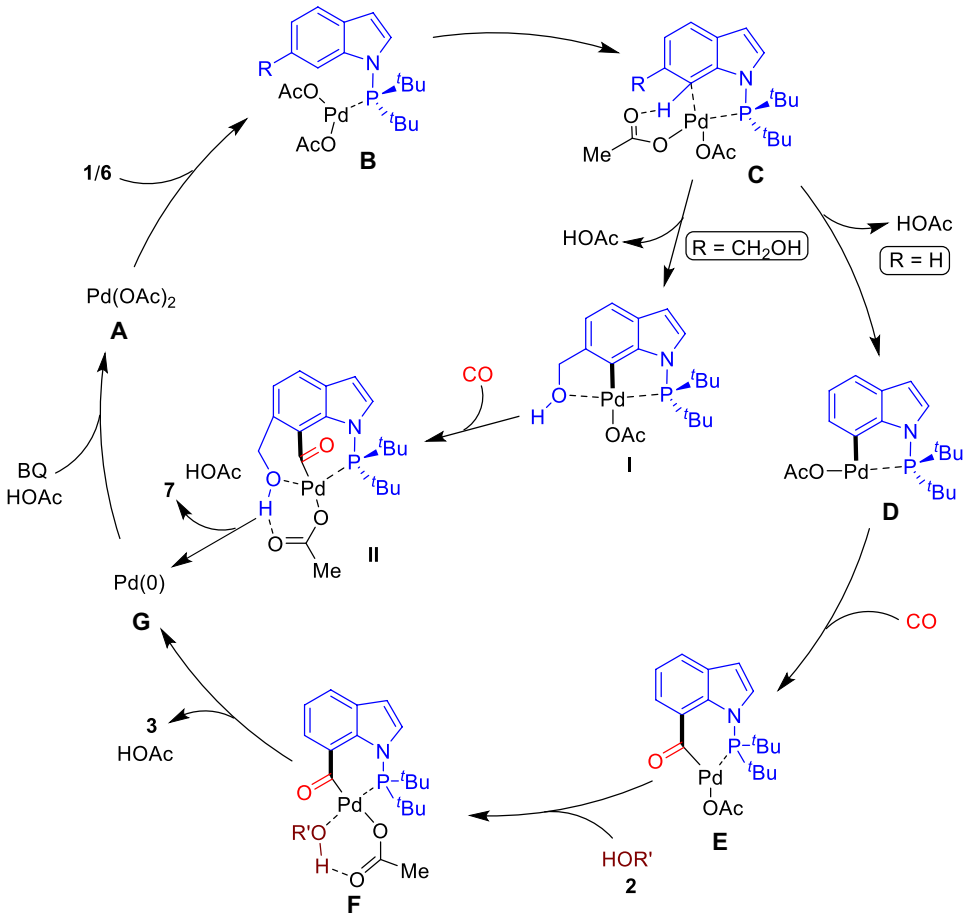


Fig. 6. Plausible reaction pathways. Dimmer structures are omitted for clarity.

0.097 indicate the four-coordinate geometry around Pd atoms is quite close to square planar (Fig. 4). On the other hand, $Pd(OAc)_2$ used in C–H metalation of indole **6a** gave a monometallic cyclopalladated complex **15** (Fig. 3B). Characterized by x-ray analysis, the palladium nuclei in compound **15** are chelated by OH and *N*-P^{t}Bu$_2$ ligands (Fig. 5). The Pd-centered bond lengths and angles are in the range of 1.917(4) to 2.2411(9) Å and 77.82(12) to 176.49(13)°, respectively. Complex **15** has τ4 values of 0.164 and 0.202, which fits with the description of square-planar geometry. Furthermore, products **3aa** and **7a** could be respectively generated using complexes **14** and **15** as the catalysts, which were indicated to be viable intermediates in the reactions.

According to the above experiments, we proposed the possible reaction pathways in Fig. 6. The palladium species **A** first chelates to indole **1/6**, generating complex **B**. Then, the carboxylate-assisted C–H activation (*55*, *56*) via **C** delivers palladacycle **D**. Subsequent CO insertion into the C–Pd bond yields complex **E**. Ligand exchange between the acetate group and alcohol **2** followed by a further reductive elimination (**F**) can produce product **3** and Pd(0) species **G**. Last, oxidation of **G** by BQ and in situ formed AcOH can reform catalytic species **A**. In the case of indole **4**, C–H metalation of complex **B** can generate a monometallic complex **I**. This intermediate undergoes CO insertion to form intermediate **II**, which can lead to the cyclization product **7** by reductive elimination and generates Pd species **G**.

CONCLUSION

In conclusion, we have uncovered the oxidant-compatible system for Pd-catalyzed *N*-P^{t}Bu$_2$-directed site-selective C–H esterification of indoles at C7-position. This strategy can efficiently override the traditional selectivity on pyrrole core the indole. The selection of BQ as the external oxidant can prevent the oxidation of the directing group. This chemistry represents an important advancement in the implementation of P(III)-directed C–H functionalization.

MATERIALS AND METHODS

General information

All new compounds were fully characterized. Compounds were visualized by exposure to ultraviolet light. All reactions and manipulations involving air- or moisture-sensitive compounds were performed using standard Schlenk techniques or in a glovebox. Toluene was purified using a Pure Solv MD-5 solvent purification system, from Innovative Technology Inc., by passing the solvent through two activated alumina columns after purging with argon. ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra were recorded on a Bruker AVANCE III 400 MHz or 500 MHz spectrometer. Chemical shifts (δ values) were reported in parts per million (ppm) with $CDCl_3$ (7.26 and 77.16 ppm for ^{1}H and ^{13}C, respectively). Mass spectra were conducted at an Agilent 6540 Ultra-High-Definition accurate-mass quadrupole time-of-flight liquid chromatography/mass spectrometry system and the Thermo

Fisher Scientific TRACE 1300 ISQ LT gas chromatography/mass spectrometry system. Infrared (IR) spectra were recorded on a Bruker Fourier transform IR spectrometer. All reactions were carried out in flame-dried 25-ml Schlenk tubes with Teflon screw caps under argon. $Pd(OAc)_2$ were purchased from Strem. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

General procedure for directed C7 carbonylation of different indoles with EtOH (2a)

Indole substrates **1a** (0.20 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), BQ (65.1 mg, 0.6 mmol), alcohol (5.0 or 6.0 mmol and 25.0 or 30.0 equiv), and anhydrous DMF or toluene (2 ml) was added to an oven-dried 25 ml Schlenk tube under Ar atmosphere. Then, the tube was purged and charged by three freeze-pump-thaw cycles with CO (1 atm) in balloon and sealed. The reaction mixture was stirred at 110°C for 36 to 48 hours and then cooled to room temperature and purified by flash column chromatography on silica gel using petroleum ether/EtOAc mixture as an eluent to afford the desired compound.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/51/eabd1378/DC1

REFERENCES AND NOTES

1. P. B. Arockiam, C. Bruneau, P. H. Dixneuf, Ruthenium(II)-catalyzed C–H bond activation and functionalization. *Chem. Rev.* **112**, 5879–5918 (2012).
2. L. Ping, D. S. Chung, J. Bouffard, S.-g. Lee, Transition metal-catalyzed site- and regio-divergent C–H bond functionalization. *Chem. Soc. Rev.* **46**, 4299–4328 (2017).
3. Z. Dong, Z. Ren, S. J. Thompson, Y. Xu, G. Dong, Transition-metal-catalyzed C–H alkylation using alkenes. *Chem. Rev.* **117**, 9333–9403 (2017).
4. D.-S. Kim, W.-J. Park, C.-H. Jun, Metal–organic cooperative catalysis in C–H and C–C bond activation. *Chem. Rev.* **117**, 8977–9015 (2017).
5. C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, A comprehensive overview of directing groups applied in metal-catalysed C–H functionalisation chemistry. *Chem. Soc. Rev.* **47**, 6603–6743 (2018).
6. Q. Zhao, G. Meng, S. P. Nolan, M. Szostak, N-heterocyclic carbene complexes in C–H activation reactions. *Chem. Rev.* **120**, 1981–2048 (2020).
7. Z. Shi, C. Zhang, C. Tang, N. Jiao, Recent advances in transition-metal catalyzed reactions using molecular oxygen as the oxidant. *Chem. Soc. Rev.* **41**, 3381–3430 (2012).
8. C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, Oxidative coupling between two hydrocarbons: An update of recent C–H functionalizations. *Chem. Rev.* **115**, 12138–12204 (2015).
9. Y. Yang, J. Lan, J. You, Oxidative C–H/C–H coupling reactions between two (hetero) arenes. *Chem. Rev.* **117**, 8787–8863 (2017).
10. T. W. Lyons, M. S. Sanford, Palladium-catalyzed ligand-directed C–H functionalization reactions. *Chem. Rev.* **110**, 1147–1169 (2010).
11. K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, Weak coordination as a powerful means for developing broadly useful C–H functionalization reactions. *Acc. Chem. Res.* **45**, 788–802 (2012).
12. D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, Rhodium catalyzed chelation-assisted C–H bond functionalization reactions. *Acc. Chem. Res.* **45**, 814–825 (2012).
13. F. Zhang, D. R. Spring, Arene C–H functionalisation using a removable/modifiable or a traceless directing group strategy. *Chem. Soc. Rev.* **43**, 6906–6919 (2014).
14. J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, Palladium-catalyzed transformations of alkyl C–H bonds. *Chem. Rev.* **117**, 8754–8786 (2017).
15. Z. Zhang, P. H. Dixneuf, J.-F. Soulé, Late stage modifications of P-containing ligands using transition-metal-catalysed C–H bond functionalisation. *Chem. Commun. (Camb)* **54**, 7265–7280 (2018).
16. X. Qiu, M. Wang, Y. Zhao, Z. Shi, Rhodium(I)-catalyzed tertiary phosphine directed C–H arylation: rapid construction of ligand libraries. *Angew. Chem. Int. Ed. Engl.* **56**, 7233–7237 (2017).
17. J. Wen, D. Wang, J. Qian, D. Wang, C. Zhu, Y. Zhao, Z. Shi, Rhodium-catalyzed P^{III}-directed *ortho*-C–H borylation of arylphosphines. *Angew. Chem. Int. Ed. Engl.* **58**, 2078–2082 (2019).
18. S. E. Wright, S. Richardson-Solorzano, T. N. Stewart, C. D. Miller, K. C. Morris, C. J. A. Daley, T. B. Clark, Accessing ambiphilic phosphine boronates through C–H borylation by an unforeseen cationic iridium complex. *Angew. Chem. Int. Ed. Engl.* **58**, 2834–2838 (2019).
19. D. Wang, B. Dong, Y. Wang, J. Qian, J. Zhu, Y. Zhao, Z. Shi, Rhodium-catalysed direct hydroarylation of alkenes and alkynes with phosphines through phosphorous-assisted C–H activation. *Nat. Commun.* **10**, 3539 (2019).
20. D. Wang, Y. Zhao, C. Yuan, J. Wen, Y. Zhao, Z. Shi, Rhodium(II)-catalyzed dehydrogenative silylation of biaryl-type monophosphines with hydrosilanes. *Angew. Chem. Int. Ed. Engl.* **58**, 12529–12533 (2019).
21. Z. Zhang, T. Roisnel, P. H. Dixneuf, J.-F. Soulé, Rh^{I}-catalyzed P^{III}-directed C–H bond alkylation: Design of multifunctional phosphines for carboxylation of aryl bromides with carbon dioxide. *Angew. Chem. Int. Ed. Engl.* **58**, 14110–14114 (2019).
22. J. Wen, B. Dong, J. Zhu, Y. Zhao, Z. Shi, Revealing silylation of $C(sp^2)$/$C(sp^3)$–H bonds in arylphosphines by ruthenium catalysis. *Angew. Chem. Int. Ed. Engl.* **59**, 10909–10912 (2020).
23. Y.-N. Ma, S.-X. Li, S.-D. Yang, New approaches for biaryl-based phosphine ligand synthesis via P=O directed C–H functionalizations. *Acc. Chem. Res.* **50**, 1480–1492 (2017).
24. J.-B. Peng, F.-P. Wu, X.-F. Wu, First-row transition-metal-catalyzed carbonylative transformations of carbon electrophiles. *Chem. Rev.* **119**, 2090–2127 (2019).
25. C. Zhu, J. Liu, M.-B. Li, J.-E. Bäckvall, Palladium-catalyzed oxidative dehydrogenative carbonylation reactions using carbon monoxide and mechanistic overviews. *Chem. Soc. Rev.* **49**, 341–353 (2020).
26. R. Lang, J. Wu, L. Shi, C. Xia, F. Li, Regioselective Rh-catalyzed direct carbonylation of indoles to synthesize indole-3-carboxylates. *Chem. Commun. (Camb)* **47**, 12553–12555 (2011).
27. R. Lang, L. Shi, D. Li, C. Xia, F. Li, A general method for palladium-catalyzed direct carbonylation of indole with alcohol and phenol. *Org. Lett.* **14**, 4130–4133 (2012).
28. J. Tjutrins, B. A. Arndtsen, An electrophilic approach to the palladium-catalyzed carbonylative C–H functionalization of heterocycles. *J. Am. Chem. Soc.* **137**, 12050–12054 (2015).
29. M.-N. Zhao, L. Ran, M. Chen, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, Palladium-catalyzed carbonylation of indoles for synthesis of indol-3-yl aryl ketones. *ACS Catal.* **5**, 1210–1213 (2015).
30. J. Liu, H. Li, R. Dühren, J. Liu, A. Spannenberg, R. Franke, R. Jackstell, M. Beller, Markovnikov-selective palladium catalyst for carbonylation of alkynes with heteroarenes. *Angew. Chem. Int. Ed. Engl.* **56**, 11976–11980 (2017).
31. S.-W. Yuan, H. Han, Y.-L. Li, X. Wu, X. Bao, Z.-Y. Gu, J.-B. Xia, Intermolecular C–H amidation of (Hetero)arenes to produce amides through rhodium-catalyzed carbonylation of nitrene intermediates. *Angew. Chem. Int. Ed. Engl.* **58**, 8887–8892 (2019).
32. W. Liu, J. Bang, Y. Zhang, L. Ackermann, Manganese(I)-catalyzed C–H aminocarbonylation of heteroarenes. *Angew. Chem. Int. Ed. Engl.* **54**, 14137–14140 (2015).
33. F. Zhou, D.-S. Wang, X. Guan, T. G. Driver, Nitroarenes as the nitrogen source in intermolecular palladium-catalyzed aryl C–H bond aminocarbonylation reactions. *Angew. Chem. Int. Ed. Engl.* **56**, 4530–4534 (2017).
34. U. K. Sharma, H. P. L. Gemoets, F. Schröder, T. Noël, E. V. Van der Eycken, Merger of visible-light photoredox catalysis and C–H activation for the room-temperature C-2 acylation of indoles in batch and flow. *ACS Catal.* **7**, 3818–3823 (2017).
35. C. Zhu, T. Pinkert, S. Greßies, F. Glorius, One-pot C–H formylation enabled by relay catalysis of Manganese(I) and Iron(III). *ACS Catal.* **8**, 10036–10042 (2018).
36. K. Zhao, R. Du, B. Wang, J. Liu, C. Xia, L. Yang, $RhCl_3{\cdot}3H_2O$-catalyzed regioselective $C(sp^2)$–H alkoxycarbonylation: Efficient synthesis of indole- and pyrrole-2-carboxylic acid esters. *ACS Catal.* **9**, 5545–5551 (2019).
37. L. Xu, C. Zhang, Y. He, L. Tan, D. Ma, Rhodium-catalyzed regioselective C7-functionalization of *N*-pivaloylindoles. *Angew. Chem. Int. Ed. Engl.* **55**, 321–325 (2016).
38. C. N. Kona, Y. Nishii, M. Miura, Iridium-catalyzed direct C4- and C7-selective alkynylation of indoles using sulfur-directing groups. *Angew. Chem. Int. Ed. Engl.* **58**, 9856–9860 (2019).
39. X. Qiu, H. Deng, Y. Zhao, Z. Shi, Rhodium-catalyzed, P-directed selective C7 arylation of indoles. *Sci. Adv.* **4**, eaau6468 (2018).
40. J. Lv, X. Chen, X.-S. Xue, B. Zhao, Y. Liang, M. Wang, L. Jin, Y. Yuan, Y. Han, Y. Zhao, Y. Lu, J. Zhao, W.-Y. Sun, K. N. Houk, Z. Shi, Metal-free directed sp^2-C–H borylation. *Nature* **575**, 336–340 (2019).
41. J. Lv, B. Zhao, Y. Yuan, Y. Han, Z. Shi, Boron-mediated directed aromatic C–H hydroxylation. *Nat. Commun.* **11**, 1316 (2020).
42. I. Choi, A. M. Messinis, L. Ackermann, C7-indole amidations and alkenylations by ruthenium(II) catalysis. *Angew. Chem. Int. Ed. Engl.* **59**, 12534–12540 (2020).
43. A. K. Ghosh, G. Gong, V. Grum-Tokars, D. C. Mulhearn, S. C. Baker, M. Coughlin, B. S. Prabhakar, K. Sleeman, M. E. Johnson, A. D. Mesecar, Design, synthesis and antiviral efficacy of a series of potent chloropyridyl ester-derived SARS-CoV 3CLpro inhibitors. *Bioorg. Med. Chem. Lett.* **18**, 5684–5688 (2008).

44. H. Crassier, H. Boettcher, U. Eckert, A. Bathe, S. Emmert, Procedure for the production of (3-cyano-1H-indol-7-yl)-[4-(4-fluorophenylethyl)piperazin-1-yl]methanone and its salts. *Ger. Offen.* **2002**, 10102944 (2002).
45. J. Colucci, M. Boyd, C. Berthelette, J.-F. Chiasson, Z. Wang, Y. Ducharme, R. Friesen, M. Wrona, J.-F. Levesque, D. Denis, M.-C. Mathieu, R. Stocco, A. G. Therien, P. Clarke, S. Rowland, D. Xu, Y. Han, Discovery of 4-{1-[({1-[4-(trifluoromethyl)benzyl]-1*H*-indol-7-yl}carbonyl)amino]cyclopropyl}benzoic acid (MF-766), a highly potent and selective EP_4 antagonist for treating inflammatory pain. *Bioorg. Med. Chem. Lett.* **20**, 3760–3763 (2010).
46. K.-S. Yeung, Z. Qiu, Q. Xue, H. Fang, Z. Yang, L. Zadjura, C. J. D'Arienzo, B. J. Eggers, K. Riccardi, P.-Y. Shi, Y.-F. Gong, M. R. Browning, Q. Gao, S. Hansel, K. Santone, P.-F. Lin, N. A. Meanwell, J. F. Kadow, Inhibitors of HIV-1 attachment. Part 7: Indole-7-carboxamides as potent and orally bioavailable antiviral agents. *Bioorg. Med. Chem. Lett.* **23**, 198–202 (2013).
47. D. D. Miller, P. Bamborough, J. A. Christopher, I. R. Baldwin, A. C. Champigny, G. J. Cutler, J. K. Kerns, T. Longstaff, G. W. Mellor, J. V. Morey, M. A. Morse, H. Nie, W. L. Rumsey, J. J. Taggart, 3,5-disubstituted-indole-7-carboxamides: The discovery of a novel series of potent, selective inhibitors of IKK-β. *Bioorg. Med. Chem. Lett.* **21**, 2255–2258 (2011).
48. W.-Y. Yu, W. N. Sit, K.-M. Lai, Z. Zhou, A. S. C. Chan, Palladium-catalyzed oxidative ethoxycarbonylation of aromatic C–H bond with diethyl azodicarboxylate. *J. Am. Chem. Soc.* **130**, 3304–3306 (2008).
49. Y. Shin, S. Sharma, N. K. Mishra, S. Han, J. Park, H. Oh, J. Ha, H. Yoo, Y. H. Jung, I. S. Kim, Direct and site-selective palladium-catalyzed C-7 acylation of indolines with aldehydes. *Adv. Syn. Cat.* **357**, 594–600 (2015).
50. R. Du, K. Zhao, J. Liu, F. Han, C. Xia, L. Yang, $RhCl_3{\cdot}3H_2O$-catalyzed C7-selective C–H carbonylation of indolines with co and alcohols. *Org. Lett.* **21**, 6418–6422 (2019).
51. Y. Yang, X. Qiu, Y. Zhao, Y. Mu, Z. Shi, Palladium-catalyzed C–H arylation of indoles at the C7-position. *J. Am. Chem. Soc.* **138**, 495–498 (2016).
52. S. Fang, G. Jiang, M. Li, Z. Liu, H. Jiang, W. Wu, Palladium-catalyzed regioselective C–H alkynylation of indoles with haloalkynes: Access to functionalized 7-alkynylindoles. *Chem. Comm. (Camb)* **55**, 13769–13772 (2019).
53. N. R. Deprez, M. S. Sanford, Synthetic and mechanistic studies of Pd-catalyzed C–H arylation with diaryliodonium salts: Evidence for a bimetallic high oxidation state Pd intermediate. *J. Am. Chem. Soc.* **131**, 11234–11241 (2009).
54. D. C. Powers, T. Ritter, Bimetallic Pd(III) complexes in palladium-catalysed carbon–heteroatom bond formation. *Nat. Chem.* **1**, 302–309 (2009).
55. L. Ackermann, Carboxylate-assisted transition-metal-catalyzed C–H bond functionalizations: Mechanism and scope. *Chem. Rev.* **111**, 1315–1345 (2011).
56. L. Ackermann, Carboxylate-assisted ruthenium-catalyzed alkyne annulations by C–H/Het–H bond functionalizations. *Acc. Chem. Res.* **47**, 281–295 (2014).

Acknowledgments

Funding: We thank the National Natural Science Foundation of China (grants 21672097 and 21972064), the National Natural Science Foundation of Jiangsu Province (grant BK20170632), the Excellent Youth Foundation of Jiangsu Scientific Committee (grant BK20180007), and the "Innovation & Entrepreneurship Talents Plan" of Jiangsu Province for financial supports. **Author contributions:** Z.S. conceived the concept, directed the project, and wrote the paper. B.D., J.Q., M.L., Z.-J.W., D.W., and C.Y. performed the experiments. Y.Z. performed the crystallographic studies. M.W. and Y.H. discussed the results. **Competing interests:** The authors declare that they have no competing interests. **Data and materials availability:** All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. Additional data related to this paper may be requested from the authors.

Submitted 9 June 2020
Accepted 2 November 2020
Published 16 December 2020
10.1126/sciadv.abd1378

Citation: B. Dong, J. Qian, M. Li, Z.-J. Wang, M. Wang, D. Wang, C. Yuan, Y. Han, Y. Zhao, Z. Shi, External oxidant-compatible phosphorus(III)-directed site-selective C–H carbonylation. *Sci. Adv.* **6**, eabd1378 (2020).