



Published in final edited form as:

Nature. 2014 November 20; 515(7527): 389–393. doi:10.1038/nature13885.

Bypassing the Limitations of Directed C–H Functionalizations of Heterocycles

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Abstract

In directed C–H activation reactions, nitrogen and sulfur atoms present in heterocyclic substrates coordinate strongly with metal catalysts. This coordination, which can lead to catalyst poisoning or C–H functionalization at an undesired position, limits the application of C–H activation reactions in heterocycle-based drug discovery.^{1–5} Herein, we report a robust and synthetically useful reaction that overcomes the complications associated with performing C–H functionalization reactions on heterocycles. Our approach employs a simple *N*-methoxy amide group, which serves as both a directing group and an anionic ligand to promote the *in situ* generation of the reactive PdX₂ (X = ArCONOMe) species from a Pd(0) source using air as the sole oxidant. In this way, the PdX₂ species is inherently anchored in close proximity with the target C–H bond adjacent to CONHOMe group, thus avoiding the interference from various heterocycles. Remarkably, this reaction overrides the conventional positional selectivity patterns observed with substrates containing strongly coordinating heteroatoms, including nitrogen, sulfur, and phosphorus. Thus, this operationally simple aerobic reaction demonstrates the feasibility of bypassing a fundamental limitation that has long plagued applications of directed C–H activation in medicinal chemistry.

Heterocycles are commonly found in drug candidates owing to their ability to improve solubility and reduce the lipophilicity of a drug molecule.^{1–2} The potential application of C–H activation technologies in the rapid synthesis and diversification of novel heterocycles has attracted widespread attention from the pharmaceutical industry.^{3–5} One of the most significant challenges in the application of C–H functionalization reactions is achieving robust control of positional selectivity. Directed C–H metalation has recently emerged as a reliable approach for achieving a diverse collection of selective C–H functionalization

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

Author Contributions Y.-J.L. and H.X. performed the reaction discovery experiments and contributed equally. W.-J.K., H.X. and M.S. performed the reactions with the heterocyclic substrates. H.-X.D. and J.-Q.Y. conceived the concept and directed the project and prepared this manuscript.

The authors declare no competing financial interests: details accompany the full-text HTML version of the paper at www.nature.com/nature.

known to strongly coordinate with neutral σ -donors such as pyridines. On the other hand, Pd(0) species possess a comparatively weaker affinity for this type of ligand because they are more nucleophilic rather than electrophilic. We, therefore, focused on the design of a catalytic system that would begin with Pd(0) species, which could coordinate comparatively weakly with both pyridine and the directing group in a reversible manner. We hypothesized that a specifically designed anionic directing group, if coordinated to Pd(0) species, could accelerate the generation of the reactive PdX₂(II) species if this directing group were the sole X-type ligand in the reaction mixture (Fig. 1b).²⁸ Once generated on-site, the resulting PdX₂ species could potentially cleave a C–H bond adjacent to the directing group prior to being scavenged by the pyridyl group. In essence, the pyridyl group would serve as a Pd(0) reservoir, rather than poisoning Pd(II). To establish the feasibility of this approach, we used a simple arene substrate **1a** and employed CONHOMe to develop a highly efficient C–H functionalization reactions in the presence of catalytic amount of Pd₂(dba)₃. We anticipated that Pd(0) would be converted to Pd(II)(ArCONOMe)₂ in the presence of an oxidant. Air was identified as an ideal oxidant in that it would avoid the introduction of other anions.²⁸ Through extensive screening (see supplementary information), we found that arene **1a** reacts with 1.5 equiv of isocyanide **2** in the presence of 2.5 mol% Pd₂(dba)₃ in 1,4-dioxane under 1 atm air at 80 °C for 30 min to give *ortho*-functionalized 3-(imino)isoindolinone **3a** in 93% isolated yield (Fig. 2a).

The structure of **3a** was unexpected based on earlier precedents in isocyanide insertion chemistry,²⁹ indicating the involvement of a new isocyanide insertion pathway. To rationalize the formation of **3a**, we reacted 2,6-difluoro-*N*-methoxybenzamide (**1u**) with 25 mol% Pd₂(dba)₃ under the reaction conditions, attempting to identify potential Pd(II) intermediates prior to the C–H activation event (Fig. 2b). We were able to characterize a new C-amidinyl Pd(II) species **E** by X-ray crystallography, which allows us to propose an intriguing reaction pathway. We speculate that the initially formed Pd(II) species **B** undergoes migratory insertion with *t*-BuNC to give **C**, which then rearranges to form C-amidinyl Pd(II) precursor **D**. The chloride in **E** is likely incorporated from the CHCl₃ contained in commercial Pd₂(dba)₃ via anionic exchange with **D**. In hindsight, it is crucial that the unexpected C-amidinyl Pd(II) species **D** or **E** is able to cleave the C–H bonds in a highly efficient manner.

The use of air as an oxidant is essential for this transformation (Fig. 2a, entries 1, 2). Interestingly, a significantly lower yield is obtained when the reaction is conducted under O₂ (1 atm). Presumably, in high concentration, O₂ can intercept one of the intermediates in the catalytic cycle. The efficiency of this catalytic system was further demonstrated by running the reaction on gram-scale using 0.5 mol% Pd₂(dba)₃ to afford product in 89% isolated yield, albeit with a prolonged reaction time (24 h) (Fig. 2c). To demonstrate the synthetic utility of this C–H functionalization process, **3a** was readily converted to a number of synthetically versatile building blocks including an ester, an amine and a lactam via one or two-step procedures (Fig. 2c, for details see supplementary information).

The scope of arene substrates was surveyed using 2.5 mol% Pd₂(dba)₃ (Fig. 3a). A variety of substituents on the aryl ring were well tolerated (**3a–t**). These results demonstrate that the on-site generation of Pd(II) precursor **B** using air as the oxidant and subsequent C–H

functionalizations are feasible. The fast rate of this reaction encouraged us to examine whether heteroatom poisoning could be overcome using this new reaction pathway. We were pleased to find that the reaction of furans, benzofurans and benzothiophenes proceed smoothly to afford the desired products **5a–e** in 86–98% yields (Fig. 3b). Indole, pyrrole, thiazole, pyrazole, and imidazole substrates are also converted to the corresponding functionalized products **5f–k** in good yields (74–99%). The strongly coordinating nitrogen atoms in pyridines and quinolines are well-known to poison directed C–H activation under Pd(II) catalysis. Thus, the excellent yields obtained with various pyridine substrates (**5l–q**), including an aminated pyridine (**5o**), provide further evidence that this catalytic system can overcome severe heteroatom poisoning. Acetyl-protected tetrahydroquinoline- and indoline-containing substrates can also be functionalized, giving **5r** and **5s**. A free amino group is tolerated, albeit resulting lower yield (**5r'**, **51%**). A phosphoryl group is also compatible (**5t**).

The importance of using a Pd(0) source to enter the catalytic cycle is further supported by the lack of reactivity using commonly employed Pd(II) sources, including PdCl₂, Pd(TFA)₂ and Pd(OTf)₂, in place of Pd₂(dba)₃. In particular, exposing **4m**, a representative pyridine-containing substrate, to the reaction conditions using these catalysts led to full recovery of starting material in the presence or absence of dba ligand (Fig 3b). The desired product, **5m**, was formed in 40% yield, however, when 5 mol% Pd(OAc)₂ was used as the catalyst. This is most likely due to the known facile reduction of Pd(OAc)₂ to Pd(0) by isocyanide.³⁰ To seek experimental evidence in support of this reasoning, we stirred Pd(OAc)₂, PdCl₂, Pd(TFA)₂ and Pd(OTf)₂ separately with *t*-BuNC in dioxane at 80 °C. We found that Pd(OAc)₂ was completely reduced to Pd(0) within 30 min while other Pd(II) catalysts remained intact (For details see supplementary information). To further demonstrate the importance of the on-site generation of PdX₂ (X = ArCONOMe) from Pd(0) in the absence of external anions, we also carried out the standard reaction in the presence of different anions, Cl⁻, TFA⁻, OTf⁻. We found these anions consistently prevent the desired reaction (see supplementary information).

It is well established that substrates containing C–H bonds *ortho* to strongly coordinating heterocycles will undergo facile heterocycle-directed *ortho*-cyclopalladation. This reactivity can inhibit the activation of a target C–H bond that is proximate to a weaker directing group (here, the CONHOMe functional group),^{10–12} which may prevent the employment of directed C–H functionalization reactions in substrates containing heterocycles. Not surprisingly, reaction of *para*-(2-pyridyl)benzamide (**6a**) with Pd(OAc)₂ or Pd(TFA)₂ in the absence of *t*-BuNC gave exclusively cyclopalladation product directed by the pyridine, suggesting pyridine is a stronger coordinating group than CONHOMe group (for X-ray characterization of the cyclopalladation intermediate formed from **6a** see supplementary information). The unprecedented compatibility of our catalytic system with heterocycles substrates, however, prompted us to examine whether our new catalytic system can override the conventional heterocycle-directed cyclopalladation.

We chose as a test substrate *para*-(2-pyridyl)benzamide (**6a**) (Fig. 4a), which has a 2-pyridyl group *para* to the *N*-methoxy amide directing group. Remarkably, with our new catalytic system, C–H functionalization proceeds exclusively at the position *ortho* to the CONHOMe

group to provide the desired product **7a** in 97% isolated yield. To investigate the origin of the observed switch of positional selectivity, we reacted **6a** with various Pd(II) catalysts under the classic cyclopalladation conditions. As expected, palladation at the position *ortho* to the pyridyl group occurs to give the cyclopalladate intermediate in quantitative yield (see supplementary information). In contrast, not traces of this intermediate can be detected throughout our standard reaction when Pd₂dba₃ is used as the catalyst. These experiments suggest that the use of Pd₂(dba)₃ catalyst under our aerobic conditions effectively avoids the conventional pyridyl-directed *ortho*-palladation pathway. We subsequently replaced the pyridine with other medicinally important heterocycles including a quinoline, pyrazine, pyrimidine, pyrazole and thiazole. Uniformly excellent yields of the desired C–H functionalization products are obtained (**7b–f**, 76–98% yield) for these substrates. In light of the well-known directing power of oxazoline in *ortho*-palladation,¹² *para*- and *meta*-oxazolinylyl substituted substrates **6g** and **6h** were also subjected our standard reaction conditions. In both cases, only the desired C–H functionalization products are formed (**7g** and **7h**, 91 and 76% yield, respectively).

We further explored the utility of this catalytic system for 2-phenylpyridine substrates containing the CONHOMe group on the pyridine ring (**6i–p**) (Fig. 4b). We anticipated that achieving reactivity and positional selectivity with these substrates could be particularly challenging due to the electron-deficiency of the pyridine ring, which deactivates the C–H bonds *ortho* to the CONHOMe group. We were pleased to find that C–H functionalization of these 2-phenylpyridine substrates occurs exclusively *ortho* to the *N*-methoxy amide group, affording the desired products in good to excellent yields (**7i–p**, 74–90% yield).

Finally, representative C–H functionalization products from this reaction were converted to synthetically useful lactams by hydrogenolysis with Pd/C under H₂ followed by treatment with trifluoroacetic acid. This new catalytic system provides an operationally simple and versatile route to access medicinally important lactams (**8a–d**).^{1–2}

In summary, we have developed a catalytic system that overcomes the poisoning effect of heterocycles and overrides the inherent positional selectivity dictated by strongly coordinating heteroatoms. The switch of the positional selectivity in the cyclopalladation step, often as the selectivity-determining step, will be exploited in other catalytic C–H activation transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We gratefully acknowledge the Shanghai Institute of Organic Chemistry, the Chinese Academy of Sciences, the CAS/SAFEA International Partnership Program for Creative Research Teams, NSFC-21121062, and The Recruitment Program of Global Experts for financial support. We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 1R01 GM102265) for their financial support.

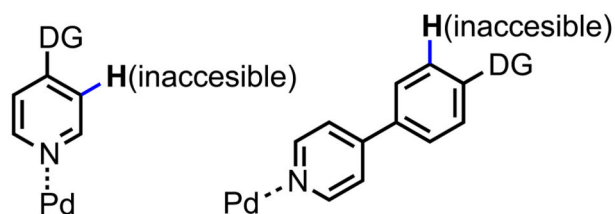
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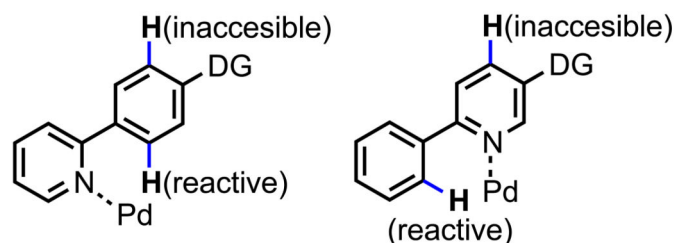
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a Fundamental limitations of directed C–H functionalization of heterocycles

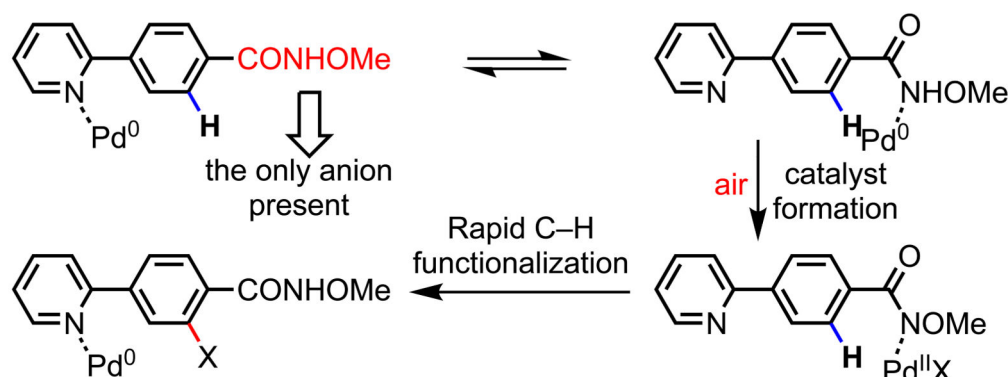
Poisoning reactivity



Restricting positional selectivity



b Approach: on-site generation of a Pd(II) catalyst assisted by the anionic directing group



c Overriding site-selectivity dictated by the strongly coordinating heterocycles

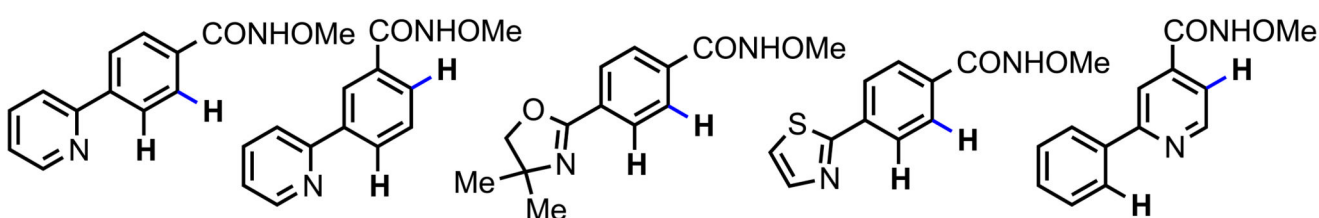


Figure 1. Development of a catalytic system to overcome fundamental limitations of heterocyclic C–H bond functionalizations

a, Adverse effects of strong coordination between Pd(II) catalysts and heterocycles. **b,** Avoiding heterocycle poisoning via on-site generation of Pd(II) catalysts. **c,** Overriding the conventional positional selectivity directed by heterocycles.

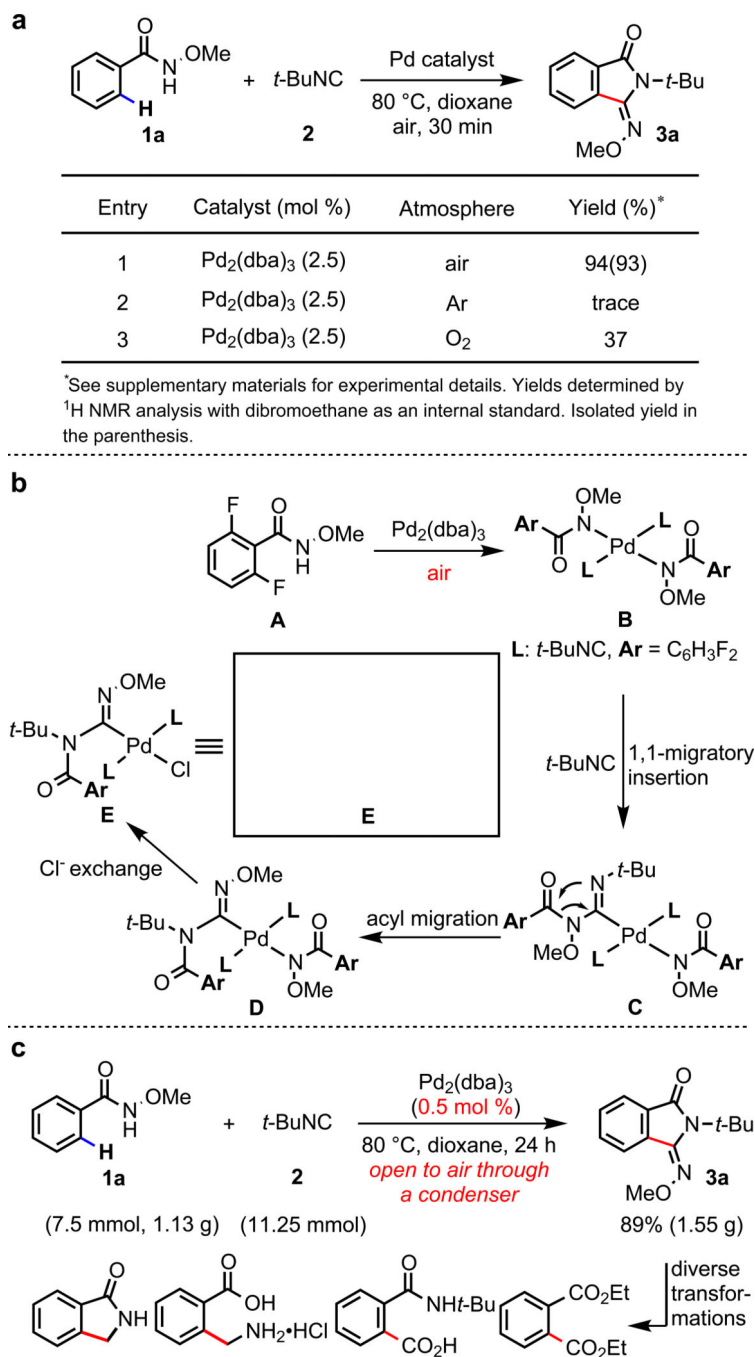
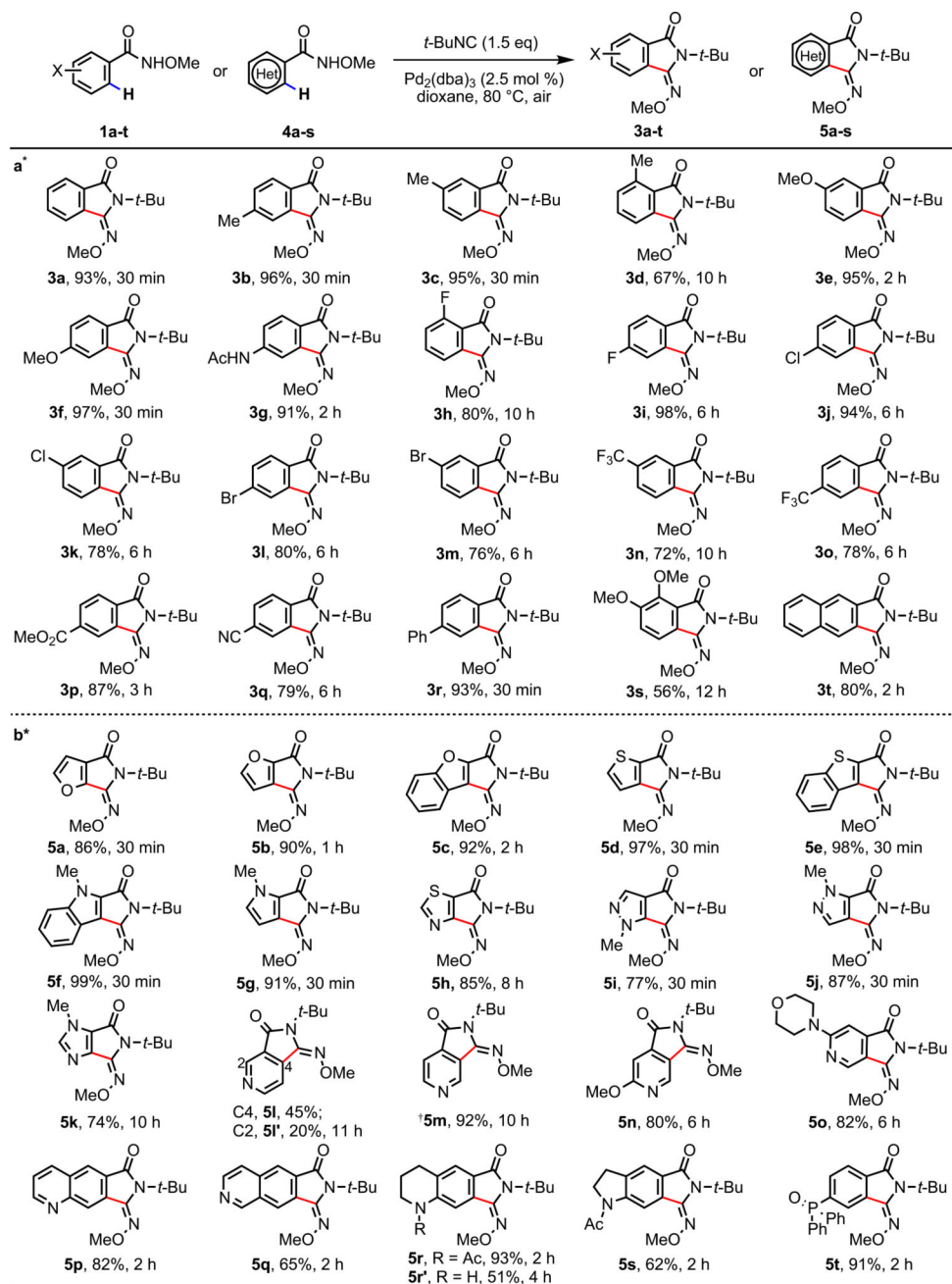
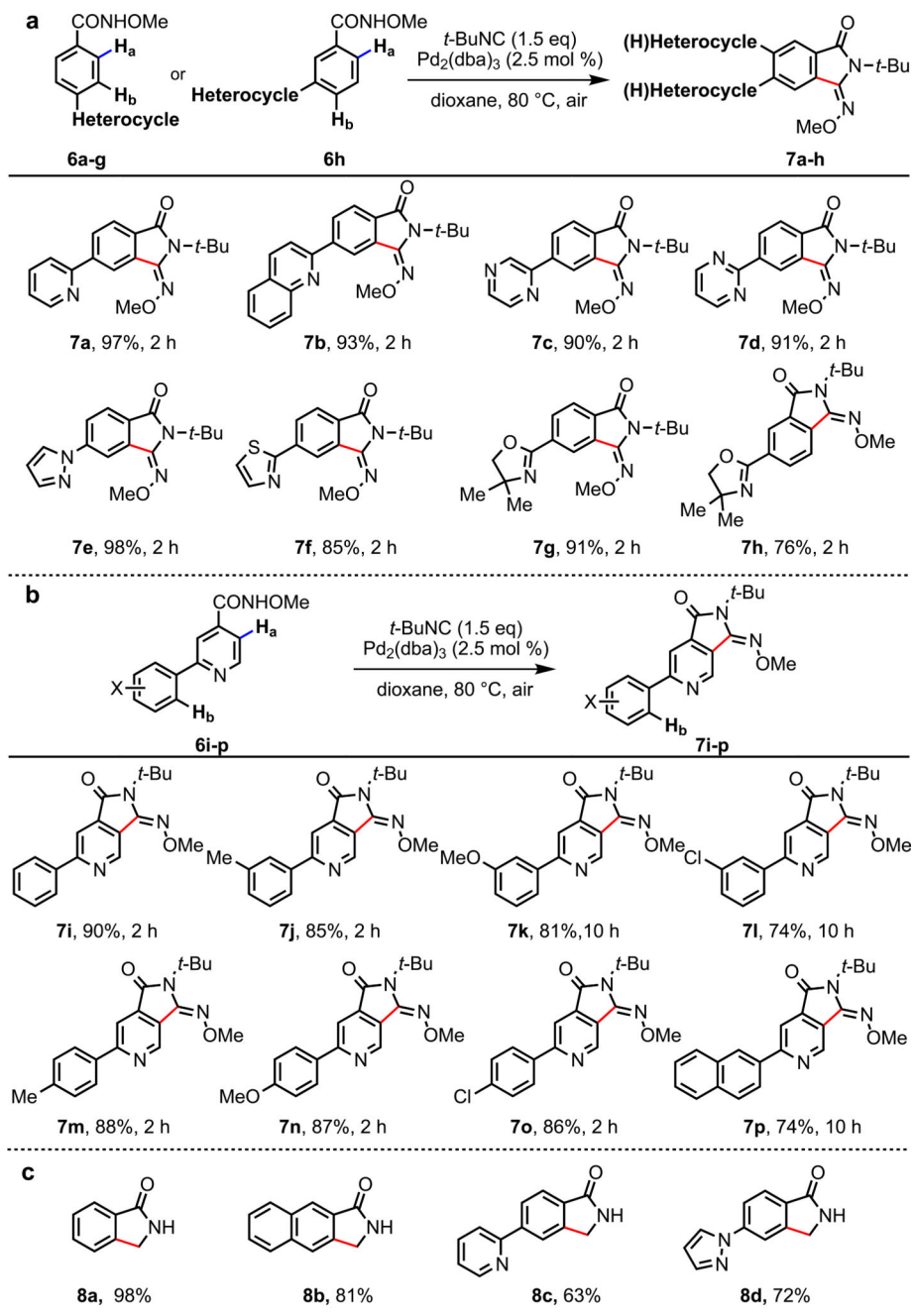


Figure 2. Discovery of an efficient aerobic C–H activation reaction

a, A catalytic C–H activation reaction using air as the sole oxidant. **b**, Characterization of a reactive C-amidynyl Pd(II) intermediate. **c**, Gram-scale reaction and diverse transformations.

**Figure 3. Scope of the Reaction**

a, Directed C–H functionalization of arenes. **b**, Directed C–H functionalization of heterocycles.



For each entry number, data are reported as isolated yield. See supplementary materials for experimental details.

Figure 4. Overriding the conventional positional selectivity dictated by heterocycles
a, b, Reactions of substrates prone to heterocycle-directed cyclometalation. **c**, Lactam products formed *via* hydrogenation and removal of the *t*-butyl groups (yields over two steps are shown).