Overcoming the limitations of directed C–H functionalizations of heterocycles

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In directed C–H activation reactions, any nitrogen or sulphur atoms present in heterocyclic substrates will 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 discovery1–3, in which regard they have attracted much interest from pharmaceutical companies4–6. Here we report a robust and synthetically useful method 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 that promotes 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 localized near the target C–H bond, avoiding interference from any nitrogen or sulphur atoms present in the heterocyclic substrates. This reaction overrides the conventional positional selectivity patterns observed with substrates containing strongly coordinating heteroatoms, including nitrogen, sulphur and phosphorus. Thus, this operationally simple aerobic reaction demonstrates that it is possible to bypass 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 molecule7–9. The potential application of C–H activation technologies in the rapid synthesis and diversification of novel heterocycles has attracted widespread attention from the pharmaceutical industry10–13. 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 reactions, and activation of both proximate14–15 and remote16–17 C–H bonds has proven feasible. The use of a weakly coordinating functional group to achieve high effective molarity of the catalyst around the C–H bond of interest has greatly expanded the substrate scope of these processes12. Unfortunately, these C–H functionalization processes are generally incompatible with the majority of medicinally important heterocyclic substrates because the heteroatoms can interfere with the catalyst15–18. For example, two strategies have recently been developed to protect pyridines with Lewis acid or N-oxide formation in order to prevent the classic cyclopalladation and perform the desired allylic C–H acetoxylation18. In directed C–H activation, strongly coordinating nitrogen, sulphur and phosphorous heteroatoms often outcompete the directing groups for catalyst binding, thus preventing activation of the C–H bonds proximate to the directing groups (Fig. 1a). When coordinated to a heterocycle, the catalyst is either unreactive due to the lack of a proximate C–H bond or only capable of activating the C–H bonds adjacent to the coordinating heteroatom. This inherent drawback of directed C–H activation, especially with Pd(0) catalysts, is currently a major obstacle to widespread application of C–H functionalization in heterocycle-based medicinal chemistry. Similarly, C–H functionalization of heterocycles using non-directed approaches has found limited success in terms of substrate scope and efficiency19–20.

Here we report an aerobic C–H functionalization reaction that effectively overcomes catalyst poisoning by heterocycles and overrides the commonly observed positional selectivity dictated by heterocycles. The catalytic cycle begins with the on-site generation of a reactive Pd(II) species (Fig. 1b). To this end, a Pd(0) precursor coordinates with a simple, carboxylic-acid-derived N-methoxy amide directing group (CONOMe)27, which promotes subsequent oxidation of Pd(0) to Pd(II) by air present in the reaction mixture28. The directing group is the only anionic X-type ligand in the reaction mixture that can be incorporated into the resulting PdX2 species. Thus, any Pd(0) species in solution that are transiently coordinated to a neutral σ-donor heterocycle (L-type ligand) must migrate to the CONOMe directing group in order to form the reactive PdX2 species which then cleave adjacent C–H bonds, thereby bypassing the adverse effects of heterocycles. Remarkably, the commonly observed positional selectivity dictated by heterocycles.

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observed positional selectivity patterns dictated by the well-known cyclopalladation in heterocycles are overridden (Fig. 1c), even when C–H bonds are present ortho to strongly coordinating heteroatoms. Since C–H palladation is often the selectivity-determining step, we anticipate this switch of positional selectivity could be extended to other C–H activation transformations on further development.

We began our investigations using CONHOMe (ref. 27). A lack of heterocyclic substrates among extensive reports on the use of this otherwise powerful directing group indicates widespread heterocycle poisoning in directed C–H activation. To verify this assessment, we performed an extensive survey by applying the previously reported reactions using the N-methoxy amide directing group to representative heterocyclic substrates shown in Fig. 1c. We found that no protocol was compatible with these heterocyclic substrates (for details, see Supplementary Information). We surmised that a novel approach would be needed to overcome the strong coordination of Pd(II) species with heterocycles. Pd(II)X₃ catalysts are 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 than the Pd(II) catalysts. 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 Pd(II)X₂ 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 before 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 (Fig. 2a) and employed CONHOMe to develop a highly efficient C–H functionalization reaction in the presence of a catalytic amount of Pd₂(dba)₃ (dba, dibenzylideneacetone). We anticipated that Pd(0) would be converted to Pd(II) (ArCONOMe)₂ in the presence of an oxidant. Pd(0) was identified as an ideal oxidant in that it would avoid the introduction of other anions²⁸. 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 chemistry²⁸, indicating the involvement of a new isocyanide insertion pathway. To rationalize the formation of 3a, we reacted 2,6-difluoro-N-methoxybenzamide (A) with 25 mol% Pd₂(dba)₃ under the reaction conditions given in Supplementary Information, attempting to identify potential Pd(II) intermediates before the C–H activation event (Fig. 2b). We were able to characterize a new C-aminidyl 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-aminidyl Pd(II) precursor D. The chloride in E is probably incorporated from the CHCl₃ contained in commercial Pd₂(dba)₃ via anionic exchange with D. In hindsight, it is crucial that the unexpected C-aminidyl Pd(II) species 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 a 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; see Supplementary Information for details).

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 found that the reaction of furans, benzofurans and benzothiophenes proceeds 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 anaminated pyridine (5o), provide further evidence that this catalytic

| Entry | Catalyst (mol%) | Atmosphere | Yield (%) |
|-------|-----------------|------------|-----------|
| 1     | Pd₂(dba)₃ (2.5) | Air        | 94(93)    |
| 2     | Pd₂(dba)₃ (2.5) | Ar         | trace     |
| 3     | Pd₂(dba)₃ (2.5) | O₂         | 37        |

Figure 2 | Discovery of an efficient aerobic C–H activation reaction. a, A catalytic C–H activation reaction using air as the sole oxidant. See Supplementary Information for experimental details; yields were determined by 1H NMR analysis with dibromomethane as an internal standard; the yield in parentheses in column 4 is the isolated yield. b, Characterization of a reactive C-aminidyl Pd(II) intermediate. The reaction scheme shows on-site generation of Pd(II) precursor B by air oxidation; migratory insertion into isocyanide to form C; acyl migration leading to D; and anion exchange to give E. c, Gram-scale reaction and diverse transformations. Red text highlights low catalyst loading and the use of air as the inexpensive oxidant.
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 to be due to the known facile reduction of Pd(OAc)₂ to Pd(0) by isocy anide. 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, namely Cl⁻, TFA⁻ and OTF⁻. We found that these anions consistently prevent the desired reaction (see Supplementary Information).

**Figure 3 | Scope of the reaction.** Top row, reagents and products. a. Directed C–H functionalization of arenes; for each compound, the isolated yield is shown in percent, together with the duration of the reaction. b. Directed C–H functionalization of heterocycles; yield and duration are shown as in a.
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 use of directed C–H functionalization reactions in substrates containing heterocycles. Not surprisingly, reaction of para-(2-pyridyl)benzamide (6a; Fig. 4a) with Pd(OAc)\(_2\) or Pd(TFA)\(_2\) in the absence of t-BuNC gave exclusively the cyclopalladation product directed by the pyridine, suggesting that pyridine is a stronger coordinating group than CONHOMe (for X-ray characterization of the cyclopalladation intermediate formed from 6a, see Supplementary Information). However, the unprecedented compatibility of our catalytic system with heterocyclic substrates prompted us to examine whether our system could 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. With our 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, no traces of this intermediate can be detected throughout our standard reaction when Pd\(_2\)(dba)\(_3\) is used as the catalyst. These experiments suggest that the use of Pd\(_2\)(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, 85–98% yield) for these substrates. In light of the well-known directing power of oxazoline in ortho-palladation\(^{12}\), para- and meta-oxazolinyl substituted substrates 6g and 6h were also subjected to 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 owing to the electron-deficiency of the pyridine ring, which deactivates the C–H bonds ortho to the CONHOMe group. We found 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 H\(_2\) followed by treatment with trifluoroacetic acid. Our new catalytic system provides an operationally simple and versatile route to access medicinally important lactams (8a–d)\(^{12}\). We anticipate that the switch of the positional selectivity in the cyclopalladation step, often as the selectivity-determining step, could be exploited in other catalytic C–H activation transformations.

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