ORGANIC CHEMISTRY

Pharmaceutical diversification via palladium oxidative addition complexes

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Palladium-catalyzed cross-coupling reactions have transformed the exploration of chemical space in the search for materials, medicines, chemical probes, and other functional molecules. However, cross-coupling of densely functionalized substrates remains a major challenge. We devised an alternative approach using stoichiometric quantities of palladium oxidative addition complexes (OACs) derived from drugs or drug-like aryl halides as substrates. In most cases, cross-coupling reactions using OACs proceed under milder conditions and with higher success than the analogous catalytic reactions. OACs exhibit remarkable stability, maintaining their reactivity after months of benchtop storage under ambient conditions. We demonstrated the utility of OACs in a variety of experiments including automated nanomole-scale couplings between an OAC derived from rivaroxaban and hundreds of diverse nucleophiles, as well as the late-stage derivatization of the natural product k252a.

Palladium-catalyzed carbon-carbon (*1*) and carbon-heteroatom (*2*, *3*) bond-forming reactions have had a major impact on the practice of organic synthesis and have become mainstays of modern drug discovery (*4*, *5*). To date, most catalytic coupling methods have been developed using relatively simple model substrates (*6*). In contrast, the structurally complex substrates typically encountered in applied settings often contain functional groups or substructures that can inhibit catalyst turnover or participate in unproductive side reactions. For example, many pharmaceutically relevant heterocycles are competent ligands for transition metal catalysts (*7*) and thus often function as competitive catalyst inhibitors or displace activating ligands, leading to inactive complexes (*8*). In practice, these mechanistic vulnerabilities manifest as failed reactions; indeed, surveys of electronic notebooks (*9*) and systematic evaluation of reactivity patterns of collections of drug-like substrates (*10*, *11*) indicate that Pd-catalyzed cross-coupling reactions of complex substrates fail frequently, with failure rates above 50% for some chemistries. With the trend toward increasing structural complexity in synthetic drugs (*12*), new cross-coupling approaches that exhibit greater reaction scope and reliability will greatly facilitate the invention of new medicines.

The generally accepted mechanism of Pd-catalyzed cross-coupling reactions (Fig. 1A) involves catalyst activation, oxidative addition, nucleophile association or transmetallation, deprotonation, reductive elimination, and catalyst regeneration steps. Because a successful reaction outcome requires the efficient operation of each of these steps, interference from a highly functionalized molecule with any one step could, in principle, disrupt the entire desired catalytic reaction. We reasoned that a Pd-mediated cross-coupling reaction, where an equivalent of an isolated oxidative addition complex (OAC; Fig. 1B) (*13*) is used as the substrate, might improve the likelihood that the reaction would succeed. By design, such reactions initiate as close to the product-forming step as possible (Fig. 1A, highlighted region). Performing reactions with the use of an OAC as the substrate obviates the requirement for multiple rounds of catalyst turnover to form substantial amounts of product. Although an OAC-mediated cross-coupling reaction requires the use of one equivalent of palladium and ligand, the cost of these reagents on a typical drug discovery scale (~$1 for a 25 mg–scale reaction) is much less than that of a densely functionalized drug-like substrate.

Palladium-mediated reactions are often used instead of catalytic methods in settings where first-pass reaction performance is considerably more important than reagent cost, such as bioconjugation (*14*–*16*), peptide modification (*17*), total synthesis (*18*–*20*), radiolabeling (*21*, *22*), PET imaging (*23*), and mechanistic inquiry (*24*, *25*). In previous studies from our group, relatively simple organopalladium complexes were used with high-complexity nucleophiles such as peptides, proteins, and antibodies. With this precedent, we wondered whether similar organometallic complexes could be formed from complex, drug-like aryl halides, and whether such OACs would be stable, isolable, and practical for use in a drug discovery context.

Indeed, organopalladium complexes derived from drugs can be readily formed and isolated. Initial efforts focused on coupling the anticancer drug gefitinib to morpholine via the isolated complex **1** (Fig. 1C), which was prepared by reacting gefitinib with the easily accessible Pd(0) precursor [(^{t}BuXPhos)Pd]$_2$(COD) (*26*) at room temperature. An extensive survey of ligands, solvents, and bases revealed ^{t}BuXPhos with the phosphazene base P$_2$-Et (*9*–*11*) as the optimal ligand-base combination for this coupling (*27*). The desired product **2** was formed in 83% yield in just 2 hours at room temperature by using ^{t}BuXPhos with P$_2$-Et in tetrahydrofuran (THF) as solvent, whereas the analogous catalytic reaction using 5 mole % (mol %) ^{t}BuXPhos Pd G3 failed completely. Using **1**, reaction performance was generally insensitive to the choice of solvent [dimethyl sulfoxide (DMSO), dimethylformamide, 2-methyl-THF, toluene], and the coupling proceeded effectively at concentrations as low as 0.01 M, potentially facilitating automated (*9*, *28*, *29*) or microfluidic synthesis (*30*, *31*).

The stability of **1** was tested by storing it in a vial on the benchtop under an atmosphere of air. After 6 months, there was no observable loss of purity or reactivity. Complex **1** also exhibited good solution stability, providing comparable yields whether a solution of the complex was freshly prepared or aged for 18 hours prior to reaction setup. In contrast to most catalytic C–N cross-coupling reactions, reactions of **1** could also be performed under an atmosphere of air with only slightly lower efficiency (*27*). Similarly, the OAC of the anticoagulant drug rivaroxaban (**3**) could be isolated and coupled with morpholine in 82% yield (Fig. 1D) to provide **4**, whereas the corresponding catalytic reaction gave a meager 2% yield. Analysis of **3** by single-crystal x-ray diffraction confirmed the structure of this organopalladium complex derived from rivaroxaban, a marketed drug (Fig. 1D).

Following these encouraging initial results, we tested the generality of the OAC protocol on a diverse set of drugs and drug-like aryl halides (Fig. 2) whose complexity is represented by a computed score (C_{QSAR}) according to a recently reported model (*12*). Several of these substrates had been tested previously as part of a chemistry informer library (*10*) and provided consistently low performance in C–N cross-coupling reactions using state-of-the-art catalytic conditions based on Pd, Cu, or Ni metallophotoredox (*32*). The OACs derived from these halides, either used as isolated solids or generated in situ, readily coupled at room temperature with multiple classes of amine nucleophiles to provide products **5** to **15** (Fig. 2). In all cases, the corresponding catalytic reactions were less efficient and sometimes failed completely (compare **9** and **10**, Fig. 2). Although the use of isolated OACs improved the likelihood that the first reaction attempt would succeed, some substrates were still problematic, such as **15** (Fig. 2) (*27*). In addition, whereas the OAC method demonstrated a distinct advantage over the catalytic method for most substrates of moderate to high complexity (C_{QSAR} = 2.5 to 3.5), for a simple substrate such as **16** (C_{QSAR} = 1.1) there was no significant difference between the two protocols. On occasion, we observed a minor

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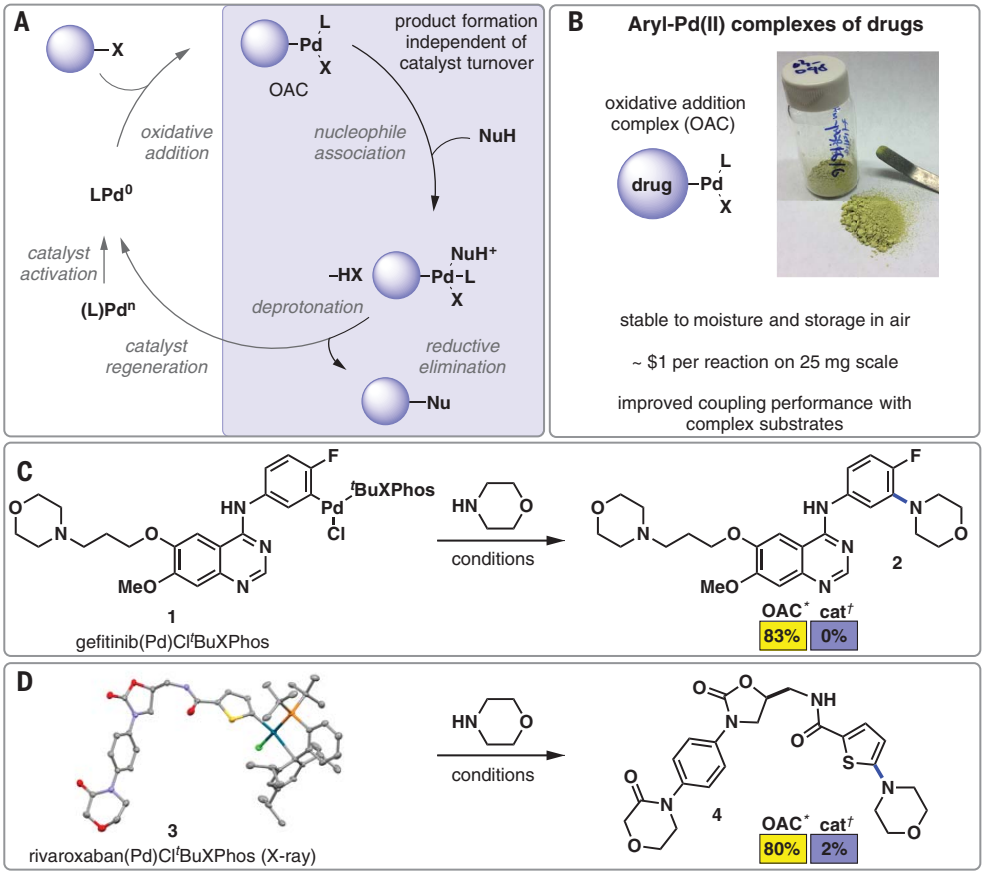

Fig. 1. Robust cross-coupling of drug-like molecules using Pd-based oxidative addition complexes (OACs). (**A**) Use of isolated OACs circumvents many challenges associated with achieving successful cross-coupling of complex substrates. (**B**) OACs are stable, readily handled, and economical at discovery scale. (**C** and **D**) The complexes (^{t}BuXPhos)Pd•gefitinib (**1**) (C) and (^{t}BuXPhos)Pd•rivaroxaban (**3**) (D) smoothly couple with morpholine to give **2** and **4**, respectively, whereas the analogous catalytic reactions failed. *Starting from (L)Pd•drug: P_2-Et, THF, room temperature (rt), 2 hours. †Starting from aryl halide: 5 mol % ^{t}BuXPhos Pd G3, P_2-Et, THF, rt, 18 hours.

complication that substrates or products underwent apparent decomposition reactions that were attributed to the L•Pd(0) species generated from the OAC during the product release step. In such cases (**5**–**7**, **11**, **12**, Fig. 2), this decomposition could be mitigated by adding a sacrificial aryl halide such as 4-bromoanisole to quench the L•Pd(0) species (*27*). Overall, the results in Fig. 2 indicate that this cross-coupling protocol can be used with a high rate of success on a variety of complex aryl halides and diverse amine coupling partners to obtain sufficient product to test biological and physical properties.

We also investigated the use of a stoichiometric quantity of ^{t}BuXPhos Pd G3 for these transformations. We hypothesized that this approach would form, in situ, the same OACs generated from [(^{t}BuXPhos)Pd]$_2$(COD). We observed the rapid formation of OAC ***3*** after mixing rivaroxaban, P_2-Et, and 100 mol % of ^{t}BuXPhos Pd G3 as judged by ^{31}P nuclear magnetic resonance. In the presence of morpholine and excess P_2-Et, however, formation of ***3*** could not be detected because cross-coupling to produce **4** was complete before we were able to analyze the first reaction time point (<2 min). After mixing aryl halides and amines with 100 mol % ^{t}BuXPhos Pd G3 and P_2-Et, anilines **2**, **4**, **7**, **12**, and **14** were produced in 55%, 88%, 68%, 68%, and 43% yield, respectively. This is comparable to the yields observed using isolated OACs (Figs. 1 and 2). In situ formation of OACs using ^{t}BuXPhos Pd G3 and related Pd(II) complexes enhances the applicability of the OAC strategy, because many air- and moisture-stable Pd complexes are commercially available. However, this approach requires the use of an excess of base to form Pd(0). Additionally, one equivalent of a carbazole byproduct is formed during the activation of the Pd complex. Both of these attributes can complicate purification of the coupling product. In addition, the in situ formation of OACs is challenging with aryl halides that have low solubility in organic solvents, potentially limiting the application of this approach in automated or flow synthesis. In contrast, every OAC we generated from [(^{t}BuXPhos)Pd]$_2$(COD) was soluble under the reaction conditions described. As an example, rivaroxaban (precursor to ***3***) was insoluble in DMSO, whereas the corresponding isolated OAC ***3*** rapidly and completely dissolved in the same solvent.

The high solubility of OACs in organic solvents makes them attractive substrates for use in automated parallel synthesis or microfluidic synthesis. This was demonstrated by synthesizing more than 200 analogs of ***3*** in parallel via nanoscale synthesis (Fig. 3). Cross-coupling reactions of ***3*** with 384 diverse C-, N-, O-, and S-nucleophiles were performed using a nanoscale robotic platform (*9*), and the desired products were observed in 206 of the 384 distinct reactions (>10% conversion observed in 139 instances). For comparison, in the analogous catalytic cross-coupling of the corresponding aryl halide rivaroxaban (**17**) performed with the same 384 nucleophiles, products were observed in 39 instances (>10% conversion observed in one reaction; Fig. 3).

During a medicinal chemistry campaign, it is desirable to have modular control over target structures. It was therefore interesting that from a single set of reaction conditions, OAC ***3*** had relatively consistent coupling performance across a diverse set of nucleophiles: 49% of the amines (n = 172), 37% of the alcohols (n = 30), 36% of the thiols (n = 14), and 42% of the boronic acids or boronic esters (n = 12) showed >10% conversion to product. Although more than half of the nucleophiles in every class did not deliver appreciable amounts of product, the corresponding catalytic method showed >10% conversion to product for just one nucleophile, likely owing in part to the fragile nature of the oxazolidinone ring of **17**. Selected C–N cross-coupling examples from the nanoscale synthesis experiment were repeated at 20 mg scale, and products **18** to **24** were formed in 41 to 86% yield. Except for the reaction to form product **25** from a sterically hindered amine, the Pd-based couplings using OAC ***3*** delivered more product than the analogous catalytic reactions (Fig. 3).

To further demonstrate the breadth of cross-coupling reactions that can be executed from preformed OACs, we subjected ***3*** to a variety of carbon-carbon and carbon-heteroatom bond-forming reaction conditions to generate a rich array of products from this complex drug core

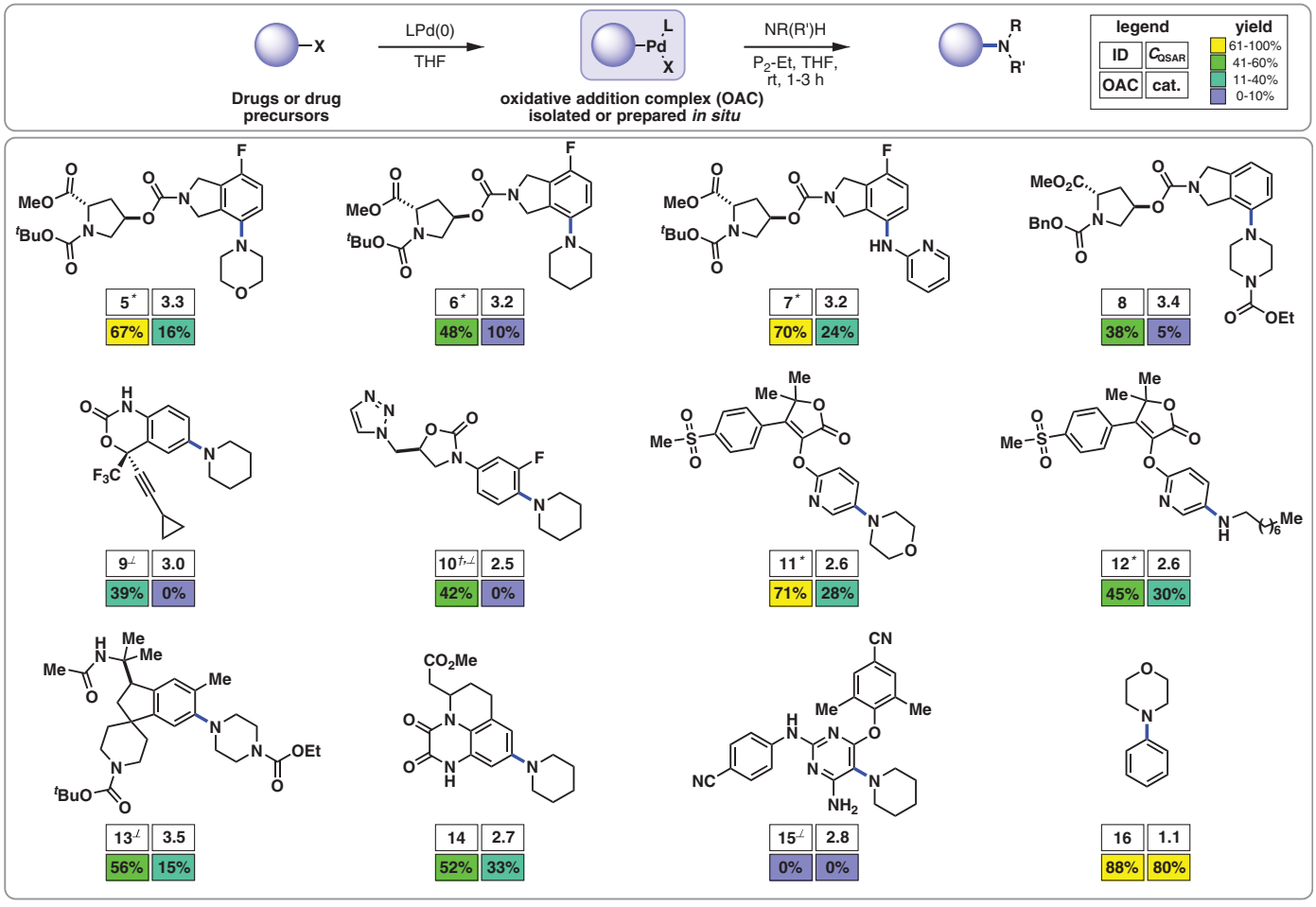

Fig. 2. Complex aryl halide couplings. *1.0 equiv 4-bromoanisole added. †1.0 equiv amine and 1.0 equiv P_2-Et. ⊥Oxidative addition performed in situ. Yields from OACs are the average of two runs and were in good agreement, except for compound **12** where some variability was observed. See (*27*) for details.

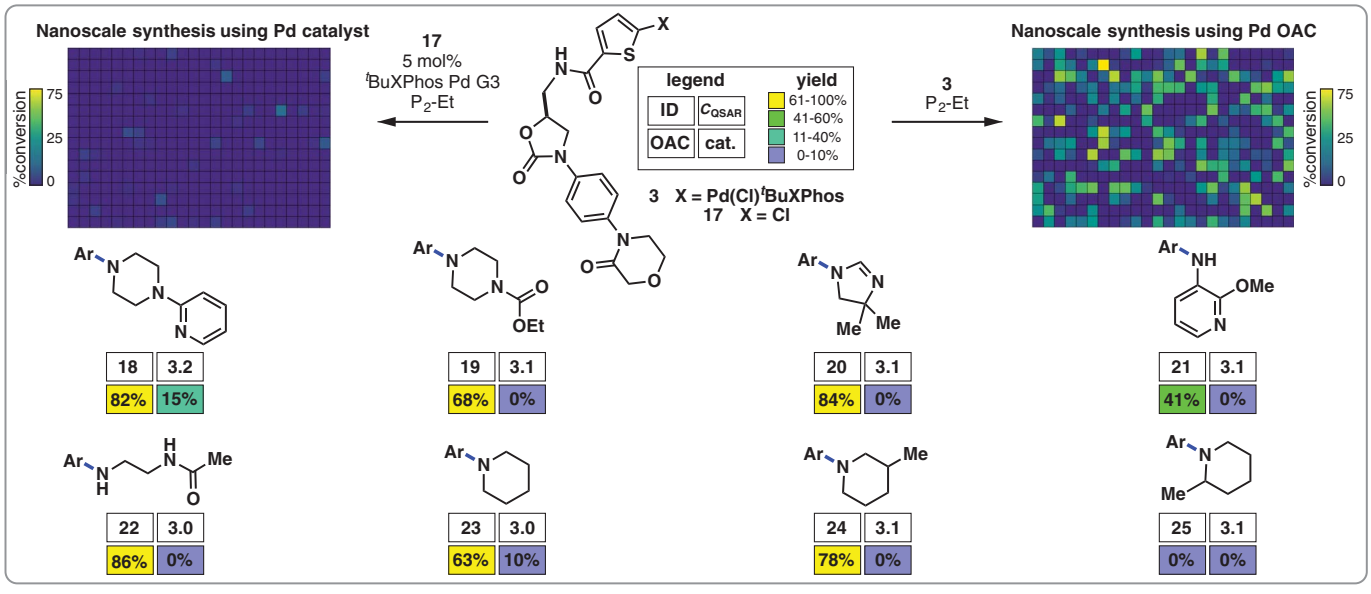

Fig. 3. Nanoscale coupling of rivaroxaban with 384 diverse nucleophiles. Reactions were performed at 0.05 mg scale on a robotic platform to compare the performance of **17** (conditions: 5 mol % ^{t}BuXPhos Pd G3, P_2-Et, DMSO, rt, 18 hours) to the performance of **3** (P_2-Et, DMSO, rt, 2 hours) in coupling reactions with 384 diverse nucleophiles. Select examples from nanoscale synthesis (**18**–**24**) were repeated at 20 mg scale. See (*27*) for details.

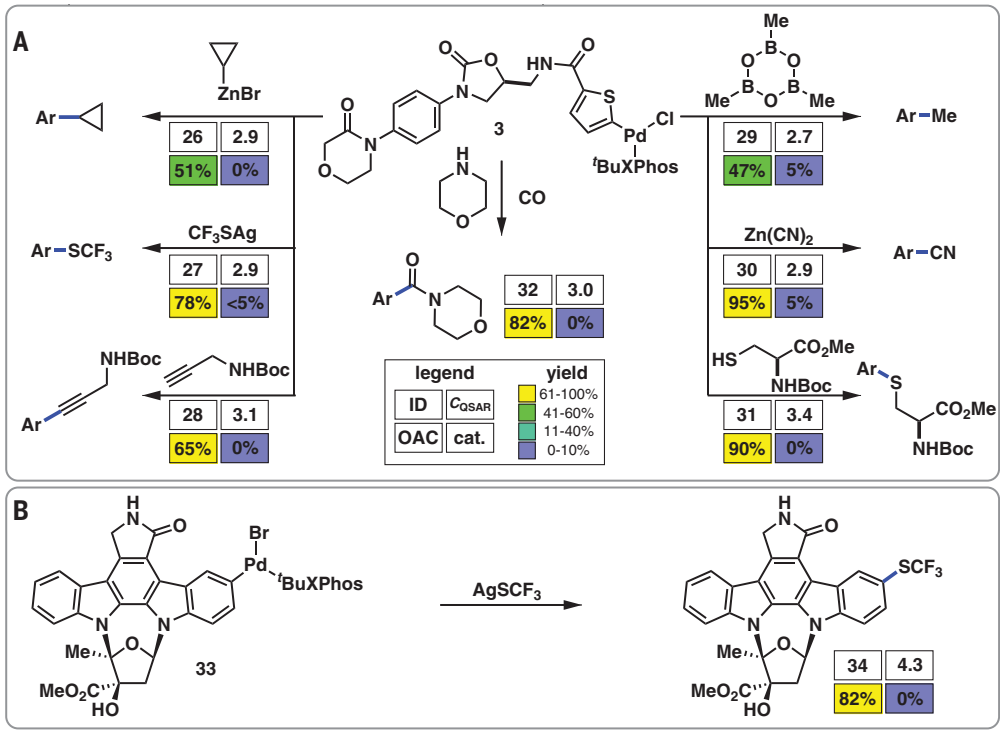

Fig. 4. Late-stage derivatization of the drug rivaroxaban and the natural product k252a. (**A**) Complex **3** readily participates in diverse coupling transformations. (**B**) Complex **33** derived from natural product k252a is readily trifluoromethylthiolated. In all cases, analogous catalytic reactions gave <5% yield. See (*27*) for details.

(Fig. 4A). Reactions of ***3*** with carbon-based nucleophiles such as cyclopropyl zinc bromide (**26**), *N*-Boc-propargyl amine (**28**), methyl boroxine (**29**), and zinc cyanide (**30**) gave the corresponding cross-coupling products in good to excellent yields. Compound ***3*** also reacted efficiently with S-based nucleophiles such as silver trifluoromethyl sulfide (**27**) and *N*-Boc-cysteine (**31**). The potential for OACs to participate in carbonylative amination was demonstrated by the formation of amide ***32*** in 82% yield from the reaction of ***3*** with morpholine under an atmosphere of carbon monoxide. Finally, complex ***33*** (Fig. 4B), prepared via selective bromination of the natural product k252a followed by reaction with $(^t\text{BuXPhosPd})_2$(COD), underwent cross-coupling smoothly with silver trifluoromethyl sulfide to provide ***34*** (C_{QSAR} = 4.3) in 82% yield. As with all other substrates examined in this study, the reaction based on use of OACs succeeded while the corresponding catalytic reactions were much lower-yielding or failed altogether.

Our data suggest that the use of OACs will increase the success rate of cross-coupling reactions and will accelerate access to molecules of high complexity. For most of the transformations described, successful catalytic conditions could likely be identified given sufficient time and resources spent on optimization. However, it is precisely time and resources that are in short supply during drug discovery. In practical terms, synthetic methods that increase the speed and efficiency with which new molecules can be accessed for primary testing will have a positive impact on pharmaceutical development overall. Beyond this, methods such as these that allow access to high-complexity chemical space offer the potential to change the types of molecules that medicinal chemists target for biological testing. In this context, we believe that the use of preformed organometallic complexes, such as the Pd-based OACs described here, holds tremendous promise for translating catalytic methods of limited scope into high-value chemical transformations that operate on complex molecules, opening new synthetic possibilities for molecule inventors.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/363/6425/405/suppl/DC1
Materials and Methods
Figs. S1 to S17
Tables S1 to S4
NMR Spectra
References (*33*–*37*)

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Embedding palladium ahead of time

Palladium-catalyzed cross-coupling is one of the most widely applied reaction classes in pharmaceutical research. The metal is adept at connecting aromatic rings to one another or to nitrogen centers. However, functional complexity can obstruct the reaction, necessitating laborious ligand optimization. Uehling *et al.* mitigated this problem by isolating the stable product of palladium's reaction with a complex aryl halide ahead of time. Subjecting these compounds to downstream coupling reactions substantially improved yields.

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