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Ligand-accelerated non-directed C–H functionalization of arenes

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The directed activation of carbon–hydrogen bonds (C–H) is important in the development of synthetically useful reactions, owing to the proximity-induced reactivity and selectivity that is enabled by coordinating functional groups[1–6]. Palladium-catalysed non-directed C–H activation could potentially enable further useful reactions, because it can reach more distant sites and be applied to substrates that do not contain appropriate directing groups; however, its development has faced substantial challenges associated with the lack of sufficiently active palladium catalysts[7,8]. Currently used palladium catalysts are reactive only with electron-rich arenes, unless an excess of arene is used[9–18], which limits synthetic applications. Here we report a 2-pyridone ligand that binds to palladium and accelerates non-directed C–H functionalization with arene as the limiting reagent. This protocol is compatible with a broad range of aromatic substrates and we demonstrate direct functionalization of advanced synthetic intermediates, drug molecules and natural products that cannot be used in excessive quantities. We also developed C–H olefination and carboxylation protocols, demonstrating the applicability of our methodology to other transformations. The site selectivity in these transformations is governed by a combination of steric and electronic effects, with the pyridone ligand enhancing the influence of sterics on the selectivity, thus providing complementary selectivity to directed C–H functionalization.

Extensive research on various directing-group designs[1–6] and strategies[19–21] for C–H functionalization, as well as the development of ligands that accelerate it[22], has greatly improved the practicality and utility of this approach. Ligand-induced acceleration has enabled palladium catalysts to functionalize remote C–H bonds of aromatic substrates by 'recognizing' distance and geometry[23,24] (Fig. 1a). Despite the potential of directed C–H activation reactions where proximal or distal site selectivity can be controlled, non-directed C–H functionalization can reach sites that are not currently accessible by a directed approach, as demonstrated by Ir(III)-catalysed C–H borylation chemistry[25,26]. Furthermore, substrates that do not contain appropriate directing groups can be functionalized only when using a non-directed approach. The challenges involved in achieving Pd(II)-catalysed non-directed C–H activation reactions are best illustrated by the lack of progress over the past 60 years in the Fujiwara–Moritani olefination reaction of arenes, for which a large excess of arene is still required to achieve sufficient reactivity with palladium catalysts. Furthermore, such electrophilic palladation reactions, which are analogous to electrophilic aromatic substitution reactions, are limited to electron-rich arenes[27,28].

We discovered an electron-deficient 2-pyridone ligand that enables palladium-catalysed non-directed C–H olefination and carboxylation of both electron-deficient and electron-rich arenes, allowing arene to be used as the limiting reagent (Fig. 1b). We characterize the structures of a pre-catalyst $Pd_3(\mu^2\text{-OH})(\mathbf{L69})_5$ and of a 1,10-phenanthroline-stabilized $Pd(Phen)(\mathbf{L69})_2$ complex (where **L69** is the highly electron-deficient ligand 3,5-bis(trifluoromethyl)-pyridin-2(1*H*)-one) using X-ray crystallography (Fig. 1c), which provide insight into the coordination mode of these ligands with a palladium catalyst. Kinetic and density functional theory (DFT) studies indicate that the pyridone ligand is likely to serve as an X-type ligand to palladium and can also act as an internal base to cleave the C–H bond via the concerted metalation deprotonation mechanism (Fig. 1b). Simple and heterocyclic arenes are both compatible with this protocol. We also apply these reactions to the late-stage modification of amino acids, dyes and pharmaceuticals. Although site selectivity is predominantly dictated by the intrinsic electronic and steric bias of the arene substrates, the presence of the ligand leads to unprecedented enhancement in selectivity with a few classes of arenes (Fig. 1d).

Guided by recent success in developing ligand-accelerated directed C–H activation[22], we set out to develop highly active ligands for Pd(II) to achieve non-directed C–H activation with arene as the limiting reagent (for details see Methods section 'Ligand optimization for non-directed C–H activation of simple arenes' and Supplementary Information, Schemes S1–S5). In short, we evaluated the ligands with 1,2-dichlorobenzene (**1u**) as a model substrate because it displayed poor reactivity and low β/α selectivity under previously reported conditions[13]. After evaluating various mono-protected 3-amino-2-hydroxypyridine ligands and 2-pyridone ligands, we found that **L69** promoted the reaction, allowing formation of the olefinated product (**3u**) in 70% yield with improved site selectivity ($\beta/\alpha = 3.0/1.0$). The yield was further improved to 85% (82% isolated yield) by using 30 mol% **L69** and 2.0 equiv. ethyl acrylate.

To elucidate the role of **L69** and the origin of this unprecedented reactivity when using arene as the limiting reagent, we carried out structural characterization, kinetic studies and DFT studies. We first obtained and characterized $Pd(Phen)(\mathbf{L69})_2$ and the trimeric $Pd_3(\mu^2\text{-OH})(\mathbf{L69})_5$ complexes using X-ray crystallography (Fig. 1c). The coordination mode of **L69** in these complexes is shown to be analogous to that found with carboxylates[29] and consistent with the most favourable transition state proposed by our DFT studies (Fig. 1b). The kinetic-isotope-effect experiments ($k_H/k_D = 2.9$) using benzene as a model substrate with ethyl acrylate indicate that the C–H bond cleavage is the rate-limiting step. Further kinetic investigation shows that **L69** increases the initial rate by a factor of 1.4 (see Supplementary Fig. S5). In addition, the reaction profile using **1u** as the substrate indicates that the ligand has a dual role in this reaction: it not only accelerates the initial rate of the reaction by a factor of three, but also prevents catalyst decomposition by forming a more stable complex with palladium. Such a stabilizing effect is crucial for maintaining the catalyst efficiency in this non-directed C–H activation reaction with arene as the limiting reagent.

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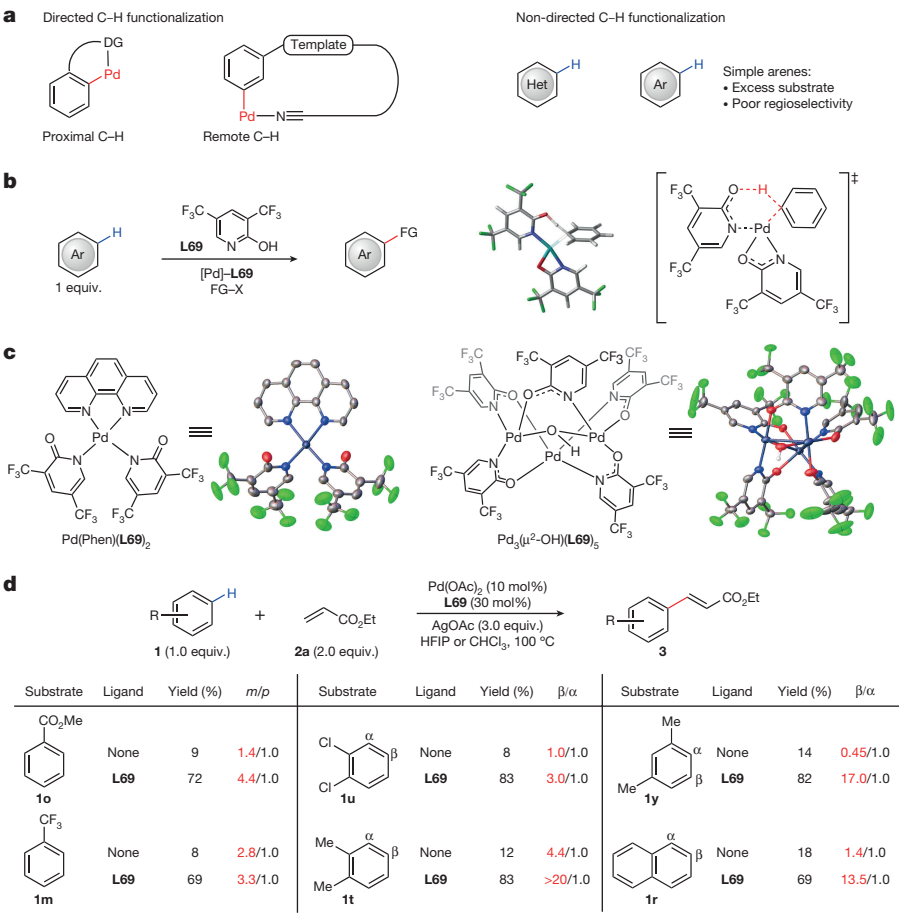

Figure 1 | C–H functionalization of arenes. a, Directed (left) and non-directed (right) palladium-catalysed C(sp^2)–H functionalization. DG, directing group. The current limitations in non-directed C–H activation are that excess substrate is required and regioselectivity is poor. **b**, Ligand-accelerated Pd-catalysed C–H functionalization (left). L, Ligand; FG, functional group. The DFT-optimized C–H activation transition state at the M06/SDD,6-311+G(d,p)(SMD)//B3LYP/LANL2DZ,6-31G(d) level of theory is shown on the right; the double dagger represents transition state. **c**, Crystal structures of the palladium–**L69** complexes. **d**, Ligand effects on reactivity and site selectivity for selected substrates. HFIP, hexafluoroisopropanol; $CHCl_3$, chloroform. For **1m**, **1o** and **1u**, HFIP was used; for **1r**, **1t** and **1y**, $CHCl_3$ was used. The yield and selectivity were determined by ^{1}H NMR; the red colouring highlights the enhancement in the regioselectivity. *m*/*p* is the ratio of olefination products at the *meta*- and *para*- positions; β/α is the ratio of olefination products at the β- and α- positions.

Interestingly, electron-deficient arenes are nearly unreactive in the absence of **L69**. With C–H cleavage being the rate-limiting step in this reaction, it is plausible that the observed rate enhancement is due to the involvement of pyridone ligands in the C–H cleavage step. To obtain support for this hypothesis, we performed DFT studies to calculate the transition-state energies for the C–H cleavage step using palladium complexes containing two acetates, one acetate and one pyridone, or two pyridone ligands. We observed that with each successive replacement of an acetate with a pyridone ligand, the relative Gibbs free energy and the Gibbs free energy of activation for the C–H activation transition state decrease. The most favourable transition state (as shown in Fig. 1b) consists of palladium coordinated to two pyridone ligands, one of which serves as an X-type ligand and binds in a κ-2 fashion. The second pyridone ligand coordinates to palladium through the nitrogen centre and serves as an internal base to cleave the C–H bond via the concerted metalation deprotonation mechanism (see Supplementary Information section 3.17). The Gibbs free energy of activation for this transition state is 4.8 kcal mol^{-1} lower than that for the corresponding transition state with two acetates as the ligand. Although our preliminary DFT studies overestimate the rate enhancement of relatively reactive benzene by the new ligand, the rate enhancement observed with electron-deficient **1u** is more marked. Detailed studies are underway to help to understand the effect of hexafluoroisopropanol (HFIP) and silver acetate on the reaction rate to obtain a more quantitative prediction, which could then be used for further catalyst design and development. Finally, the compelling site selectivity that we observed with the naphthalene contrasts the α-selectivity of the conventional Friedel–Crafts-type palladation pathway by favouring the β-position instead (see Supplementary Information, Scheme S6).

Using these optimal conditions, we next examined the generality of the substrate by using ethyl acrylate as the coupling partner. As summarized in Fig. 2, electron-rich and electron-deficient arenes are both suitable substrates, delivering the mono-olefinated products in moderate to high yields (**3a**–**3ak**). Di-olefinated products were also formed as minor products when using highly reactive substrates (see Supplementary Information section 3.4). The use of chloroform as the solvent reduces the amount of di-olefination products; for example, benzene afforded the mono-olefinated product **3a** in 64% yield and a mixture of di-olefinated products in 18% yield in $CHCl_3$ (compared with 45% mono-olefinated product and 36% di-olefinated products in HFIP). Mono-alkylated arenes were olefinated at the less sterically hindered *meta*- and *para*-positions in good yields (**3b**–**3e**). Anisole provided the *ortho*- and *para*-isomers as the main products, owing to electronic effects (**3f**), whereas the bulkier silyl-protected phenol gave the *para*-olefinated product as the main isomer (**3g** and **3h**).

Less-reactive electron-deficient arenes are also olefinated using this catalytic system, highlighting the importance of the ligand acceleration. Subjecting substrates with strongly electron-withdrawing groups, such as nitro, trifluoromethyl, aldehyde, ester, ketone and nitrile, to these olefination conditions afforded the corresponding products in moderate to good yields with synthetically useful *meta*-selectivity (**3l**–**3q** and **3af**). Naphthalene also provided the mono-olefinated product (**3r**) in 68% yield, with a 13.5/1.0 selectivity ratio (β/α). The improvement in the regioselectivity by the ligand is particularly noteworthy (Fig. 1d); it seems that the ligand enhances the contribution of sterics in determining the selectivity. We also examined di-substituted and tri-substituted aromatics (**3s**–**3ag** and **3ah**–**3ak**, respectively). The selectivity of symmetric 1,2-disubstituted arenes and of 1,3-disubstituted arenes is primarily governed by sterics; for example, 1,2,3,4-tetrahydronaphthalene, *o*-xylene and *m*-xylene afforded the β-olefinated products (**3s**, **3t** and **3y**, respectively) in excellent selectivity. Substrates with less sterically hindered substituents such as 1,2-dichlorobenzene and 1,2-difluorobenzene reacted to provide a mixture of α- and β-olefinated products (**3u** and **3v**), although the β-olefinated products

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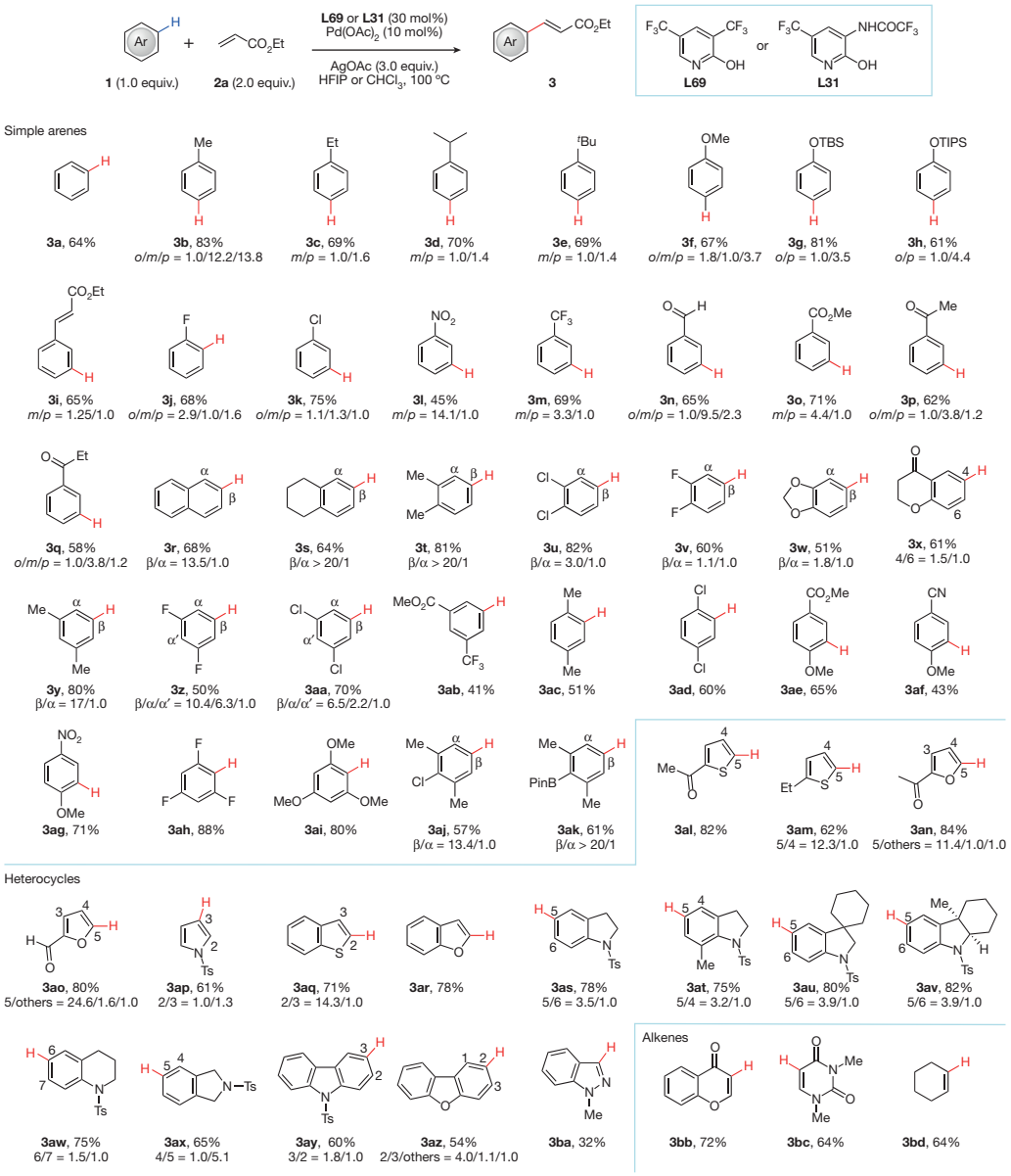

Figure 2 | C–H olefination of arenes and heterocycles. TBS, *tert*-butyldimethylsilyl; TIPS, triisopropylsilyl; Pin, pinacolate; Ts, 4-toluenesulfonyl. The values under each structure indicate isolated yields. Reaction conditions: $Pd(OAc)_2$ (10 mol%), **L69** (30 mol%), AgOAc (3.0 equiv.), HFIP (0.5 ml), 100 °C, 24 h; for **3a**, **3r**, **3t**, **3w**, **3y**, **3ai**, **3aj**, **3ak**, **3an**, **3ao**, **3ay**, **3az** and **3bb**, $CHCl_3$ (0.5 ml) was used instead of HFIP; for **3j** and **3k**, 2,2,2-trifluoro-*N*-(2-hydroxy-5-(trifluoromethyl)pyridin-3-yl) acetamide (**L31**; 20 mol%) was used instead of **L69**; for **3l** and **3ab**, $Pd(OAc)_2$ (20 mol%), **L69** (60 mol%) and ethyl acrylate (1.2 equiv.) were used; for **3as**–**3ax**, the reaction was conducted at 90 °C; for **3al**, **3am**, **3aq** and **3ar**, Ag_2CO_3 (1.5 equiv.) was used instead of AgOAc; for **3am**, the reaction time was shortened to 12 h; for **3ap**, the reaction was conducted at 60 °C; for **3ar**, the reaction time was shortened to 8 h; for **3bd**, substrate (0.2 mmol), ethyl acrylate (0.1 mmol) were used in $CHCl_3$. The red bonds signify the site for C–H activation corresponding to the major product.

predominate as the major isomer. Methyl 3-(trifluoromethyl)benzoate was transformed to the *meta*-product (**3ab**) as a single isomer, owing to a combination of electronic and steric influence. Symmetric 1,4-disubstituted aromatics are also suitable substrates for this reaction and generally undergo mono-functionalization in high yields (**3ac** and **3ad**). 4-substituted anisoles are olefinated exclusively at the *ortho*-position, owing to electronic effects (**3ae**–**3ag**). 1,3,5- and 1,2,3-trisubstituted arenes also react smoothly, providing the desired products in high yields (**3ah**–**3ak**). 2,6-Disubstituted aryl boronate ester is also compatible under the conditions (**3ak**).

We then investigated various heterocyclic aromatics. Olefination of thiophene, furan, benzothiophene and benzofuran occurred at the electron-rich positions to give the desired products selectively (**3al**–**3ar**). Use of pyrrole led to a mixture of 2- and 3-olefinated products (**3ap**), probably owing its high reactivity. Indolines, 1,2,3,4-tetrahydroquinoline, isoindoline, carbazole, dibenzofuran and indazole are also compatible with this non-directed C–H activation, generating the desired products in moderate to good yields (**3as**–**3ba**). Furthermore, vinylic C–H bonds in cyclic alkenes were olefinated to provide the corresponding diene products (**3bb**–**3bd**).

We evaluated the scope of the olefin coupling partners by using *o*-xylene as the model substrate (Fig. 3a). α,β-Unsaturated olefins served as particularly effective coupling partners for this palladium-catalysed olefination reaction (**4a**–**4r**); for example, the reactions with acrylate derivatives proceeded in 55%–85% yields (**4a**–**4d**). Other electron-withdrawing groups attached to the olefins, including carboxylic acid, amide, aldehyde, ketone, nitrile, sulfone, sulfonamide and phosphonate, are also compatible with these reaction conditions, providing the desired olefinated products in moderate to excellent yields (**4e**–**4o**). We note that acrylic acid, acrylamide and acrolein are often incompatible with palladium-catalysed C–H olefination reactions. 1,2-Disubstituted α,β-unsaturated olefins including crotonate (**4p**), maleate (**4q**) and cyclic tri-substituted olefin (**4r**) were also found to be suitable coupling partners. Although both the aryl C–H bonds and vinylic C–H bonds of styrenes are reactive under these conditions, electron-deficient styrene derivatives can be used as coupling partners (**4s** and **4t**). We also performed a gram-scale C–H olefination of *o*-xylene with acrolein using 5 mol% $Pd(OAc)_2$ and 15 mol% **L69**, which provided the desired product in 83% yield; **L69** was recovered in 87% yield.

To demonstrate the potential generality of ligand-accelerated non-directed C–H activation to provide a wide range of transformations, we have also developed a non-directed C–H carboxylation reaction (Fig. 3b). We found that **L69** can promote the C–H carboxylation of arenes with

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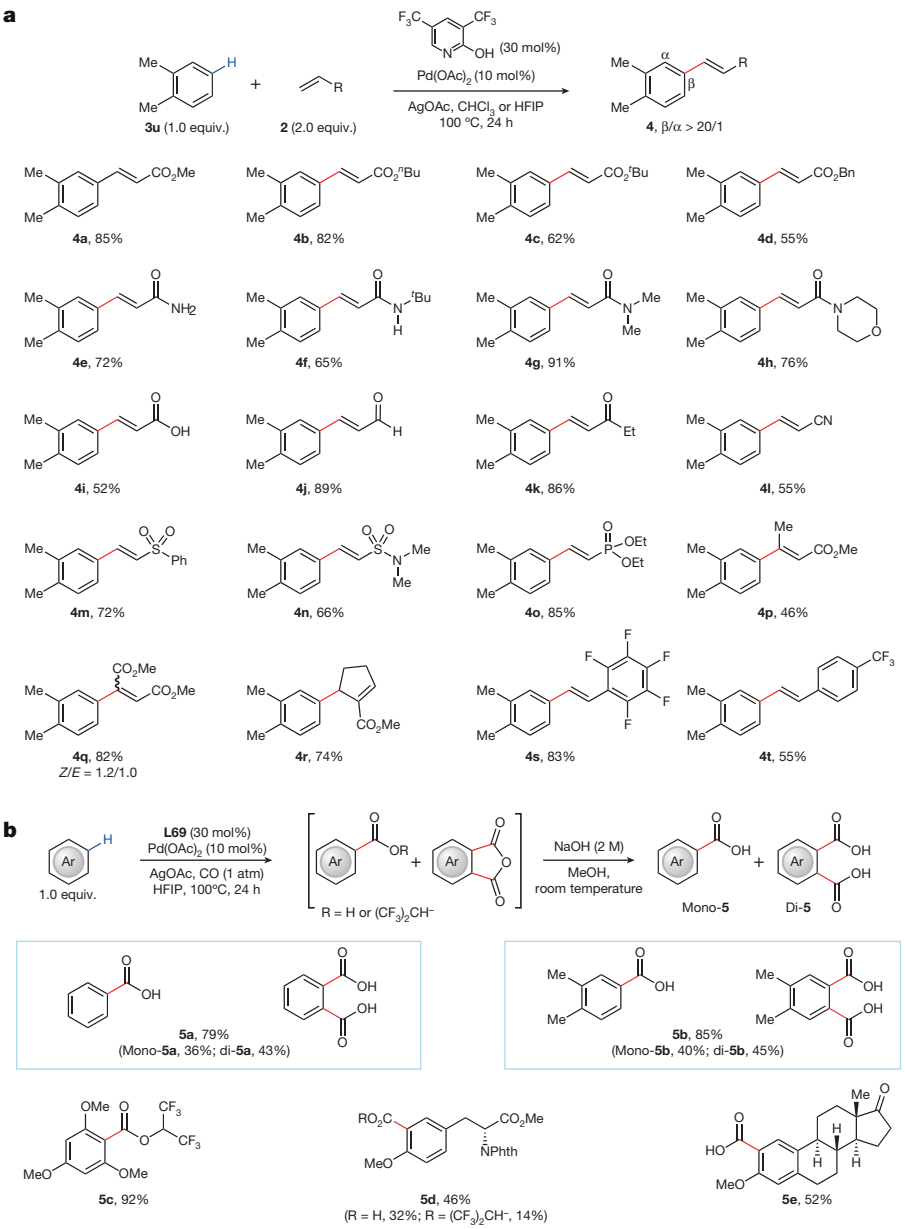

Figure 3 | Scope of olefin partners and carboxylation. a, Scope of olefin coupling partners. HFIP, hexafluoroisopropanol. Reaction conditions: *o*-xylene (0.1 mmol), olefin (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), **L69** (30 mol%), AgOAc (3.0 equiv.), HFIP (0.5 ml), 100 °C, 24 h; for **4a**–**4d**, **4i**, **4l** and **4p**, the reaction was conducted in $CHCl_3$; for **4c**, the reaction time was shortened to 16 h. **b**, Carboxylation of simple arenes. Phth, phthaloyl. Reaction conditions: substrate (0.2 mmol), CO (1 atm), $Pd(OAc)_2$ (10 mol%), **L69** (30 mol%), AgOAc (3.0 equiv.), HFIP (2.0 ml), 100 °C, 24 h; then NaOH (1.5 ml, 2 M), MeOH (2.0 ml), 12 h; for **5d** and **5e**, substrate (0.1 mmol) was used; for **5c** and **5d**, the products were isolated before hydrolysis.

arene as the limiting reagent under an atmosphere of carbon monoxide. The reaction produces a mixture of the mono-HFIP ester and phthalic anhydride derivatives. The phthalic anhydride derivatives arise from an *ortho*-C–H carboxylation reaction directed by the product of the first carboxylation. A mixture of mono-acid and phthalic acid derivatives can be obtained after treatment with an aqueous NaOH solution in methanol. Benzene and *o*-xylene were tested under the standard conditions and transformed to the mono- and di-acids in 79% and 85% combined yield, respectively (**5a** and **5b**). Direct carboxylation of 1,3,5-trimethoxybenzene gave the corresponding HFIP-ester in 92% yield (**5c**). Bioactive molecules *O*-methyl-tyrosine derivative (**5d**) and estrone 3-methyl ether (**5e**) were also subjected to the carboxylation procedure, affording the desired products in moderate yields.

The development of ligand-accelerated, non-directed C–H functionalization with one equivalent of arene presents an opportunity for late-stage functionalization of C–H bonds that are not accessible by directing group strategies, owing to distance, geometry or compatibility (Fig. 4). C–H olefination of amino-acid derivatives proceeded smoothly to give the desired products in 68% and 52% yield (**7a** and **7b**, respectively). [2.2]Paracyclophane, a commonly used ligand scaffold, was olefinated in 45% yield (**7c**). Fluorescein derivative (**6d**), a well-known dye and fluorescence probe, was olefinated in 53% yield (**7d**). Interestingly, the most active site for **6d** is the α-position of the carbonyl group adjacent to the oxo-bridge. In addition, natural products including caffeine, estrone, podocarpic-acid derivatives and camptothecin were tested under the standard conditions, delivering the targets in moderate yields (**7e**–**7h**). Various pharmaceuticals including fenofibrate, gemfibrozil, diflunisal, viloxazine and betaxolol were also olefinated to give the products in 47%–91% yield (**7i**–**7m**).

In summary, the 2-pyridone ligand scaffold affords a much more reactive and stable Pd(II) catalyst for non-directed C–H functionalization. Through the development of the ligand **L69**, we achieved non-directed C–H olefination and carboxylation with arene as the limiting reagent. We also observed that the ligand has a substantial influence on site selectivity in a few classes of arene substrates. Owing to the compatibility of both electron-rich and electron-deficient arenes, this reaction provides a way to diversify advanced synthetic intermediates, natural products, dyes and drug molecules.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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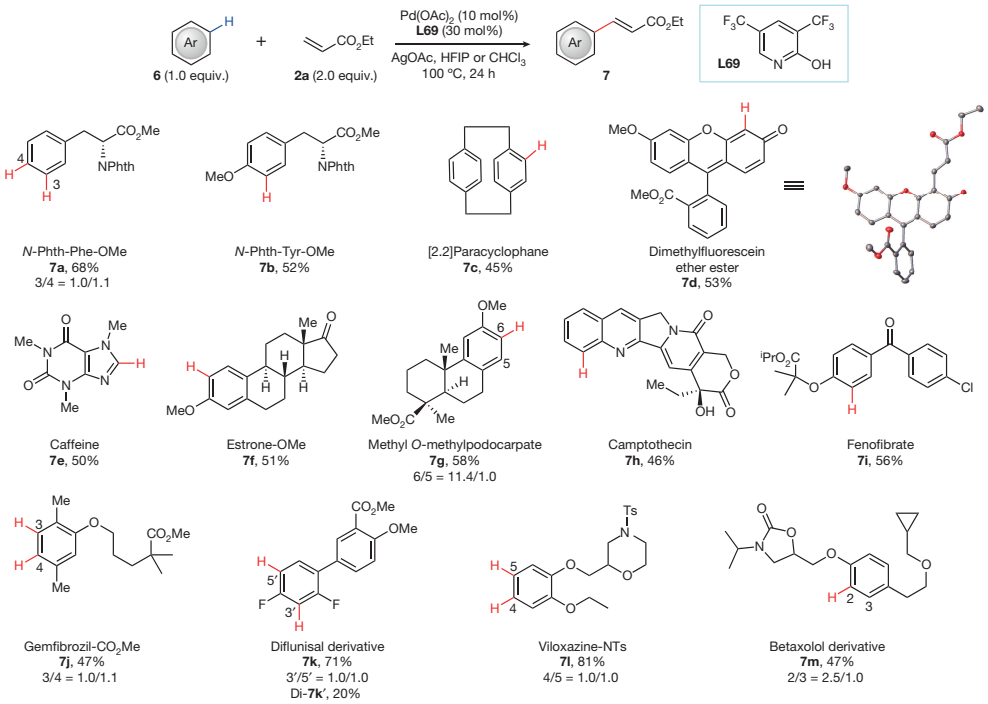

Figure 4 | Late-stage functionalization of natural products and drug molecules. Phth, phthaloyl; Ts, 4-toluenesulfonyl; HFIP, hexafluoroisopropanol; Phe, phenylalanine; Tyr, tyrosine. The values under each structure indicate isolated yields. Reaction conditions: substrate (0.1 mmol), ethyl acrylate (0.2 mmol), $Pd(OAc)_2$ (10 mol%), **L69** (30 mol%), AgOAc (3.0 equiv.), HFIP (0.5 ml), 100 °C, 24 h; for **7d**, **7f** and **7i**, the reaction time was shortened to 16 h; for **7g**, chloroform was used instead of HFIP.

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Supplementary Information is available in the online version of the paper.

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Author Contributions P.W. developed the ligands and the reactions. P.V. performed the DFT calculations. G.X. performed the kinetic study. J.S., S.T. and P.T.W.C. separated the isomers using preparative HPLC. J.X.Q. and M.A.P. participated in the screening of acrylamide-derived coupling partners and investigation of the C–H olefination reaction for amino acid substrates. M.E.F. performed preliminary studies on 2-hydroxypyridine ligands. K.-S.Y. helped with the screening of sulphonamide-derived coupling partners. J.-Q.Y. conceived the concept and prepared the manuscript with feedback from P.W., P.V. and G.X.

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METHODS

Ligand optimization for non-directed C–H activation of simple arenes. To best evaluate the ligand effects on reactivity and site selectivity, we selected 1,2-dichlorobenzene (**1u**) as a model substrate because it displayed poor reactivity and low β/α selectivity under previously reported conditions[13]. In the absence of ligand, olefination of **1u** was found to proceed in the presence of a catalytic amount of $Pd(OAc)_2$ and 3.0 equiv. silver acetate in HFIP to provide the olefinated products in 8% yield with poor site selectivity (β/α = 1.0/1.0). A wide range of ligands that are commonly used in catalysis were then evaluated. Phosphine ligands, *N*-heterocyclic carbene ligands, oxazoline ligands, pyridine ligands, phenanthroline and 1,10-phenanthrolin-2-ol did not display an improvement in reactivity for this reaction (see Supplementary Information, Scheme S1). The first noticeable ligand enhancement was observed with mono-protected amino acid ligands, which improved the combined yield to 16%. The improved selectivity (α/β = 1.6/1.0) is evidence of ligand involvement in the C–H activation step. Although further screening of other mono-protected amino acid ligands did not improve the yield, we found that the ligand 3-acetylamino-2-hydroxypyridine (**L19**), previously disclosed for *meta*-C–H functionalization[30], provided an improvement of the reactivity by a factor of nearly three (21% versus 8% yield). Following this lead, we evaluated various mono-protected 3-amino-2-hydroxypyridine ligands (**L20**–**L50**) and found that trifluoroacetyl-protected 3-amino-5-(trifluoromethyl)pyridin-2-ol (**L31**) afforded a substantial improvement in yield (62%) and selectivity (β/α = 2.3/1.0). Interestingly, **L51** (5-trifluoromethyl-2-pyridone), which is devoid of the trifluoroacetyl-protected amino moiety, also imparts reactivity to the palladium catalyst, albeit less substantially than does **L31** (24% yield). This finding is in line with a previous report on the use of 3-acetylamino-2-hydroxypyridine ligands, wherein it was shown that the 3-acetylamino group has a positive influence on the reaction, but the pyridone moiety is crucial to the reactivity[30]. This prompted us to perform further ligand screening with a focus on evaluating a diverse range of substituted 2-pyridones. We found that the highly electron-deficient 3,5-bis(trifluoromethyl)-pyridin-2(1*H*)-one (**L69**) greatly promoted the reaction, allowing formation of **3u** in 70% yield with improved site selectivity (β/α = 3.0/1.0). The yield was further improved to 85% (82% isolated yield) by using 30 mol% **L69** and 2.0 equiv. ethyl acrylate.

General procedure for the palladium/pyridone-promoted non-directed C–H activation of simple arenes. Substrate (0.1 mmol), ethyl acrylate (0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol%), **L69** (3.0 mg, 20 mol%), AgOAc (50.1 mg, 0.3 mmol) and HFIP or $CHCl_3$ (0.5 ml) were added to a 2-dram vial. The vial was capped and closed tightly, then the reaction mixture was stirred at 100 °C for 24 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and washed with dichloromethane as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative thin-layer chromatography to afford the desired arylated product. Full experimental details and characterization of new compounds are provided in Supplementary Information.

Data availability. The data that support the findings of this study are available within the paper and its Supplementary Information. Metrical parameters for the structures of Pd(Phen)(**L69**)$_2$, the $Pd_3(\mu^2\text{-OH})$(**L69**)$_5$ complex and **7d** are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference numbers CCDC 1552055, CCDC 1538821 and CCDC 1538820, respectively.

30. Wang, P. *et al.* Ligand-promoted *meta*-C–H arylation of anilines, phenols, and heterocycles. *J. Am. Chem. Soc.* **138,** 9269–9276 (2016).

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