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

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Abstract

Directed C–H activation has emerged as a major approach for developing synthetically useful reactions, owing to the proximity-induced reactivity and selectivity enabled by coordinating functional groups[1–6]. In contrast, development of palladium-catalyzed non-directed C–H activation has faced significant challenges associated with the lack of sufficiently active palladium catalysts[7–8]. Current palladium catalysts are only reactive with electron-rich arenes unless an excess of arene is used[9–18], which limits synthetic applications. Herein, we disclose a 2-pyridone ligand that significantly enhances the reactivity of a palladium catalyst, allowing for Pd(II)-catalyzed non-directed C–H activation of a broad range of aromatic substrates using the various arenes as the limiting reagent. The significance of this finding is demonstrated by the direct functionalization of advanced synthetic intermediates, drug molecules, and natural products that cannot be utilized in excessive quantities. The potential of this methodology to be expanded to a variety of transformations is indicated by the development of both C–H olefination and C–H carboxylation protocols. Furthermore, the site selectivity in this transformation 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.

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

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 the screening of sulfonamide derived coupling partners. J.-Q.Y. conceived this concept and prepared this manuscript with feedback from P.W., P.V. and G.X.

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The development of palladium-catalyzed synthetically useful C–H activation reactions faces two well-known challenges: the poor reactivity of palladium catalysts towards C–H bonds and the difficulty in discerning multiple C–H bonds within a given substrate. Typically, directing groups are employed to address these two problems simultaneously by exploiting a complex-induced proximity effect[1–6]. Extensive research on various directing group designs[1–6] and strategies[19–21], as well as the development of ligands which accelerate C–H functionalization[22], has significantly improved the practicality and utility of this approach. Ligand-acceleration has enabled palladium catalysts to functionalize remote C–H bonds of aromatic substrates by recognition of distance and geometry[23–24]. (Figure 1a). Despite the tremendous potential of directed C–H activation where proximal or distal site-selectivity can be controlled, the importance of non-directed C–H activation reactions using one equivalent of arenes cannot be overemphasized. Non-directed C–H functionalization may reach sites that are currently not accessible by a directed approach as demonstrated by Ir(III)-catalyzed C–H borylation chemistry[25–26]. Furthermore, substrates that do not contain appropriate directing groups can only be functionalized using a non-directed approach.

The first hurdle along the path towards developing Pd(II)-catalyzed non-directed C–H activation reactions is the inherently low reactivity of C–H bonds with palladium catalysts. The significance of this challenge is best illustrated by the lack of progress in the Fujiwara-Moritani olefination reaction of arenes, initially observed in 1967[9]. Sixty years after this initial observation, a large excess of arene substrate is still required to achieve sufficient reactivity with palladium catalysts in a general manner by creating a high molarity of the substrate[9–14] (Figure 1a). Furthermore, such electrophilic palladation reactions, analogous to S_EAr, are also limited to electron-rich arenes[27–28] which prevents the use of a wide range of synthetically useful electron-deficient arenes[9]. Herein, we report the discovery of an electron-deficient 2-pyridone ligand that promotes palladium-catalyzed non-directed C–H olefination and carboxylation using both electron-deficient and -rich arene as the limiting reagent (Figure 1b). The structures of a pre-catalyst [$Pd_3(\mu^2\text{-OH})$(**L69**)$_5$] as well as of a 1,10-phenanthroline stablilized Pd(Phen)(**L69**)$_2$ complex are characterized by X-ray crystallography (Figure 1c), which provide insight into the coordination mode of these ligands with palladium catalyst. Comprehensive kinetic and DFT studies indicate that the pyridone ligand is likely to serve as an X-type ligand to palladium and can also act as internal base to cleave the C–H bond via concerted metalation deprotonation (CMD) mechanism (Figure 1b). Both simple and heterocyclic arenes are compatible with this protocol. These reactions are also applied to late-stage modification of amino acids, dyes, and pharmaceuticals. While site selectivity is predominantly dictated by the intrinsic electronic and steric bias, ligand influence is also shown to enhance the selectivity with a few classes of arenes that are not possible previously (Figure 1d).

Guided by our recent success in developing ligand-accelerated, directed C–H activation, we embarked on a quest to discover and develop highly active ligands to achieve non-directed C–H activation with Pd(II) catalysts using arene substrates as the limiting reagent. To best evaluate the ligand effects on both 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

1,2-dichlorobenzene was found to proceed in the presence of a catalytic amount of $Pd(OAc)_2$ and 3.0 equivalents of silver acetate in HFIP to provide the olefinated products in a mere 8% yield with poor site selectivity (β/α = 1.0/1.0). With these established initial conditions, a wide range of ligands commonly used in catalysis were evaluated. Phosphine ligands, *N*-heterocyclic carbene ligands (NHC), oxazoline ligands, pyridine ligands, phenanthroline and 1,10-phenanthrolin-2-ol did not display an improvement in reactivity for this reaction (see supplementary information). The first noticeable ligand enhancement was observed with mono-protected amino acid (MPAA) ligands, which could improve the yield twofold (16% combined yield). The improved selectivity (α/β = 1.6/1.0) is important evidence for ligand involvement in the C–H activation step. Although further screening of other MPAA ligands did not improve the yield, we found that 3-acetylamino-2-hydroxypyridine ligand (**L19**), previously disclosed for *meta*-C–H functionalization[29], provided a nearly threefold improvement of the reactivity (21% vs. 8% yield). Following this lead, we extensively evaluated a variety of mono-protected 3-amino-2-hydroxypyridine ligands (**L20–L50**), and found that TFA-protected 3-amino-5-(trifluoromethyl)pyridin-2-ol (**L31**) afforded a significant improvement in both yield (62%) and selectivity (β/α = 2.3/1.0). Interestingly, ligand **L51** (5-trifluoromethyl-2-pyridone) which is devoid of the TFA-protected amino moiety, also imparts reactivity to the palladium catalyst, albeit less significantly than **L31** (24% yield). This finding is in line with our previous report on the use of 3-acetylamino-2-hydroxypyridine ligands wherein we showed that the 3-acetylamino group has a positive influence on the reaction, but the pyridone moiety is crucial to the reactivity[29]. This prompted us to perform further ligand screening with a focus on evaluating a diverse range of substituted 2-pyridones. To our delight, we found that the highly electron-deficient 3,5-bis(trifluoromethyl)-pyridin-2(1*H*)-one (**L69**) significantly 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 employing 30 mol % ligand **L69** and 2.0 equivalents of ethyl acrylate.

To elucidate the role of the ligand **L69** and the origin of this unprecedented reactivity using arene as the limiting reagent, we carried out comprehensive structural characterization, kinetic studies and DFT studies. We first obtained and characterized [Pd(Phen)(**L69**)$_2$] and the trimeric [$Pd_3(\mu^2$-OH)(**L69**)$_5$] complexes through X-ray crystallography (Figure 1c). The coordination mode of **L69** in these complexes is shown to be analogous to that found with carboxylates[30], which is also consistent with the most favorable transition state proposed by our DFT studies (Figure 1b). The KIE experiments (k_H/k_D = 2.9) using benzene as a model substrate with ethyl acrylate indicates that the C–H bond cleavage is the rate-limiting step. Further kinetic investigation shows that the ligand **L69** increases the initial rate by a factor of 1.4 (see supplementary information). In addition, the reaction profile using 1,2-dichlorobenzene as substrate indicates that the ligand plays a dual role in this reaction. The ligand not only accelerates the initial rate of this reaction by 3-fold but also prevents catalyst decomposition by forming a more stable complex with palladium. Such stabilizing effect is crucial for maintaining the catalyst efficiency in this non-directed C–H activation reaction with arene as the limiting reagent. Notably, 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 support this hypothesis, we performed DFT studies to calculate transition state energies for the C–H cleavage step using palladium complexes containing two acetates, one acetate and one pyridone, and two pyridone ligands respectively. We observed that with each successive replacement of an acetate with the pyridone ligand, the relative Gibbs free energy as well as the Gibbs free energy of activation for the C–H activation transition state decreases. The most favorable transition state (as shown in Figure 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 center and serves as an internal base to cleave the C–H bond via concerted metalation deprotonation (CMD) mechanism (see supplementary information). This transition state has a Gibbs free energy of activation which is 4.8 kcal/mol lower than the one without pyridone 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 1,2-dichlorobenzene is more dramatic. Detailed studies are underway to understand the effect of HFIP and silver acetate on the reaction rate to get a more quantitative prediction that can be used for further catalyst design and development. Finally, the compelling site-selectivity favoring the β-position observed with the naphthalene contrasts the α-selectivity with the conventional Friedel-Crafts type palladation pathway (see supplementary information).

With the optimal conditions in hand, we next examined the substrate generality using ethyl acrylate as the coupling partner. As summarized in Figure 2, both electron-rich and electron-deficient arenes are suitable substrates, delivering the mono-olefinated products in moderate to high yield (**3a–3ak**). Notably, di-olefinated products were also formed as minor products when employing highly reactive substrates (see supporting information for details). Gratifyingly, the use of chloroform as 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 $HCCl_3$ (45% mono and 36% di in HFIP). Mono-alkylated arenes were olefinated at the less sterically hindered *meta*- and *para*-positions in good yields (**3b–**3**e**). Anisole provided the *ortho*- and *para*-isomers as the major products due to electronic effects (**3f**), while the bulkier silyl protected phenol gave the *para*-olefinated product as the major isomer (**3g** and **3h**). Notably, less reactive electron-deficient arenes are also olefinated using this new catalytic system, highlighting the significance of the ligand acceleration. Subjecting substrates bearing 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 products (**3r**) in 68% yield with a 13.5/1.0 selectivity ratio (β/α). The significant improvement of the regioselectivity by the ligand is particularly noteworthy (Figure 1d.) and it appears that the ligand enhances the contribution of sterics to determining the selectivity. Di-substituted, and tri-substituted aromatics were also examined (**3s–3ag** and **3ah–3ak**). The selectivity of symmetrical 1,2-disubstituted arenes, as well as 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**) in excellent selectivity, respectively. Substrates with less sterically hindered substituents such as chloro- and fluoro-

reacted to provide a mixture of α- and β-olefinated products (**3u** and **3v**), though the β-olefinated products predominate as the major isomer. Methyl 3-(trifluoromethyl)benzoate was transformed to the *meta*-product (**3ab**) as a single isomer due to a combination of electronic and steric influence. Symmetrical 1,4-disubstituted aromatics are also suitable substrates for this reaction and generally undergo mono-functionalization in high yields (**3ac** and **3ad**). Notably, 4-substituted anisoles are olefinated at the *ortho*-position exclusively, due 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**). Interestingly, 2,6-disubstituted aryl boronate ester is also compatible under the conditions (**3ak**). Overall, a variety of heterocyclic aromatics were then investigated. Olefination of thiophene, furan, benzothiophene, and benzofuran occured 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**), likely due to the high reactivity of the pyrrole. 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 also olefinated to provide the corresponding diene products (**3bb–3bd**).

The scope of the olefin coupling partners was evaluated using *o*-xylene as the model substrate (Figure 3a). α, β-Unsaturated olefins served as particularly effective coupling partners for this Pd-catalyzed 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 all compatible with these reaction conditions conditions providing the desired olefinated products in moderate to excellent yields (**4e–4o**). It is worth noting that acrylic acid, acrylamide and acrolein are often incompatible with Pd-catalyzed 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. While 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**). The gram-scale C–H olefination of *o*-xylene with acrolein using 5 mol% $Pd(OAc)_2$ and 15 mol% **L69** was also performed, and provided the desired product in 83% yield (see Supplementary Information). It is noteworthy that the ligand **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 proceeded to develop a challenging non-directed C–H carboxylation reaction (Figure 3b). Gratifyingly, we found that ligand **L69** can promote the C–H carboxylation of arenes using the 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 were 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 using one equivalent of arene presents an opportunity for late-stage functionalization of C–H bonds not accessible by directing group strategies due to distance, geometry, or compatibility (Figure 4). C–H olefination of amino acid derivatives proceeded smoothly to give the desired products in 68% and 52% yield, respectively (**7a** and **7b**). [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–h**). A variety of pharmaceuticals including fenofibrate, gemfibrozil, diflunisal, viloxazine, and betaxolol were also olefinated to give the products in 47–91% yields (**7i–m**).

In summary, the discovery of 2-pyridone ligand scaffold has afforded a significantly more reactive Pd(II) catalyst for non-directed C–H functionalizations. DFT studies have proposed that the ligand serves as an X-type ligand as well as an internal base to accelerate the C–H cleavage step via concerted metalation deprotonation (CMD) mechanism. The structural characterization and kinetic behavior of the precatalyst also sheds light on the structure of the active catalyst which, in turn, is supported by DFT calculations. Owing to the development of the ligand **L69**, non-directed C–H olefination and carboxylation has been achieved for the first time using the arene as the limiting reagent in the absence of a directing group. A substantial influence of the ligand on site selectivity has also been observed in a few classes of arene substrates. Due to the compatibility of both electron-rich and electron-deficient arenes, this reaction opens an avenue for the diversification of advanced synthetic intermediates, natural products, dyes, and drug molecules.

Methods Summary

General procedure for the Pd/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 TLC to afford the desired arylated product. Full experimental details and characterization of new compounds can be found in the Supplementary Information.

Data Availability

The data supporting the findings of this study are available within the article and its Supplementary Information files. Metrical parameters for the structure of Pd(Phen)(**L69**)$_2$, Pd$_3$(μ^2-OH)(**L69**)$_5$ complex and **7d** (see Supplementary Information) 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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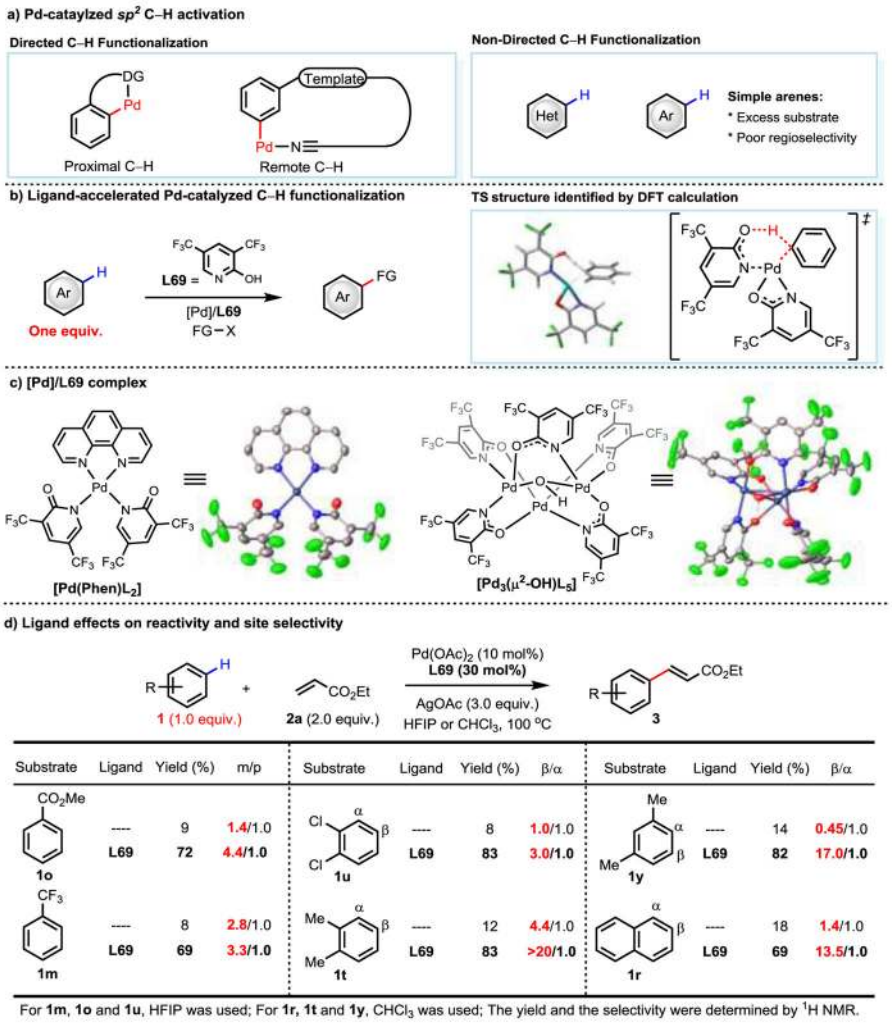

Figure 1. C–H functionalization of arenes

a, Pd-catalyzed Csp^2–H functionalization. DG, directing group. **b**, Ligand-accelerated Pd-catalyzed C–H functionalization. L; Ligand. 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. **c**, Crystal structure of Pd/**L69. d**, Ligand effects on reactivity and site selectivity for selected substrates. HFIP, hexafluoroisopropanol. $CHCl_3$, chloroform.

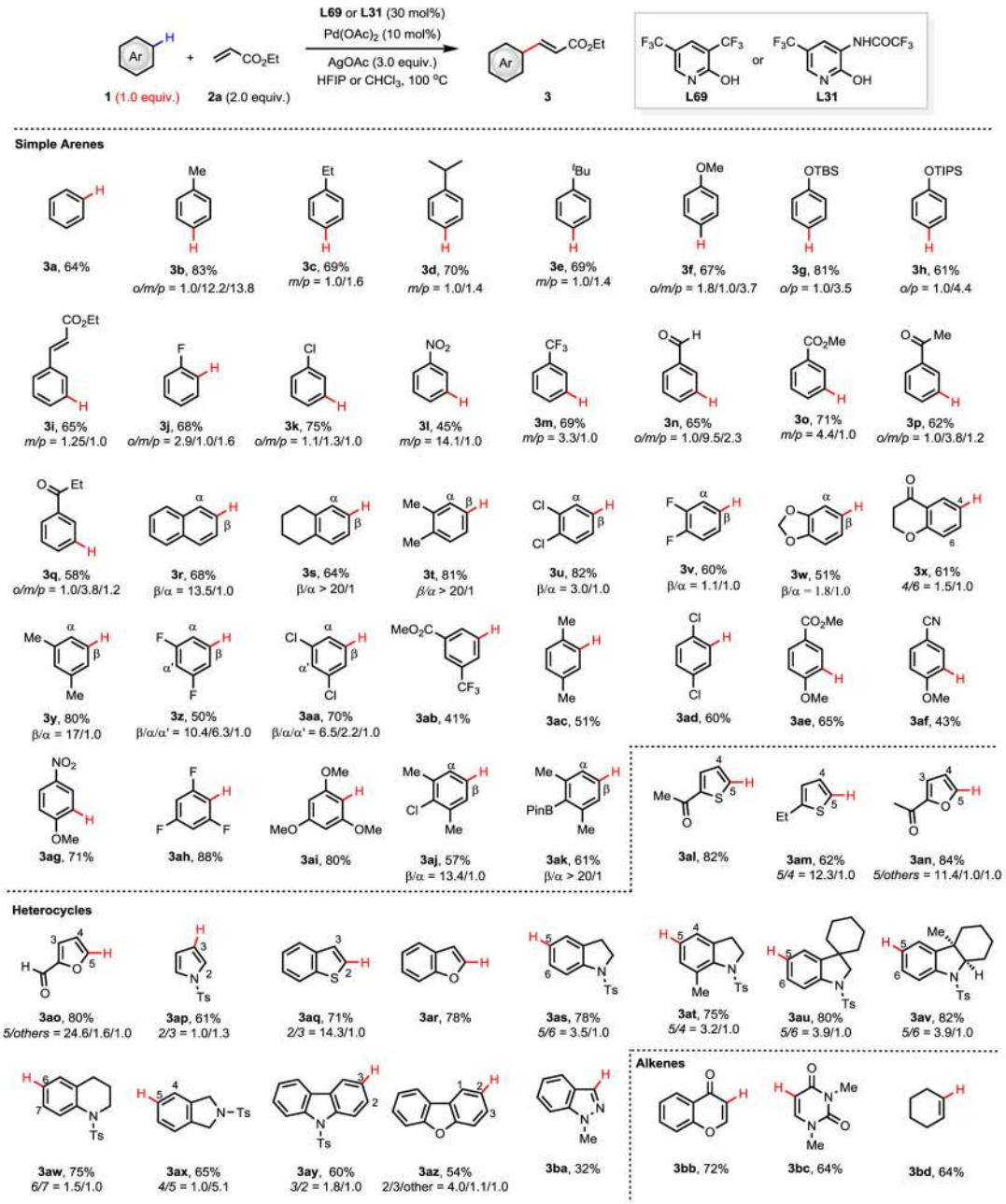

Figure 2. The C–H olefination of arenes and heterocycles

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**, **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**, substrates (0.2 mmol), ethyl acrylate (0.1 mmol) were used in $CHCl_3$.

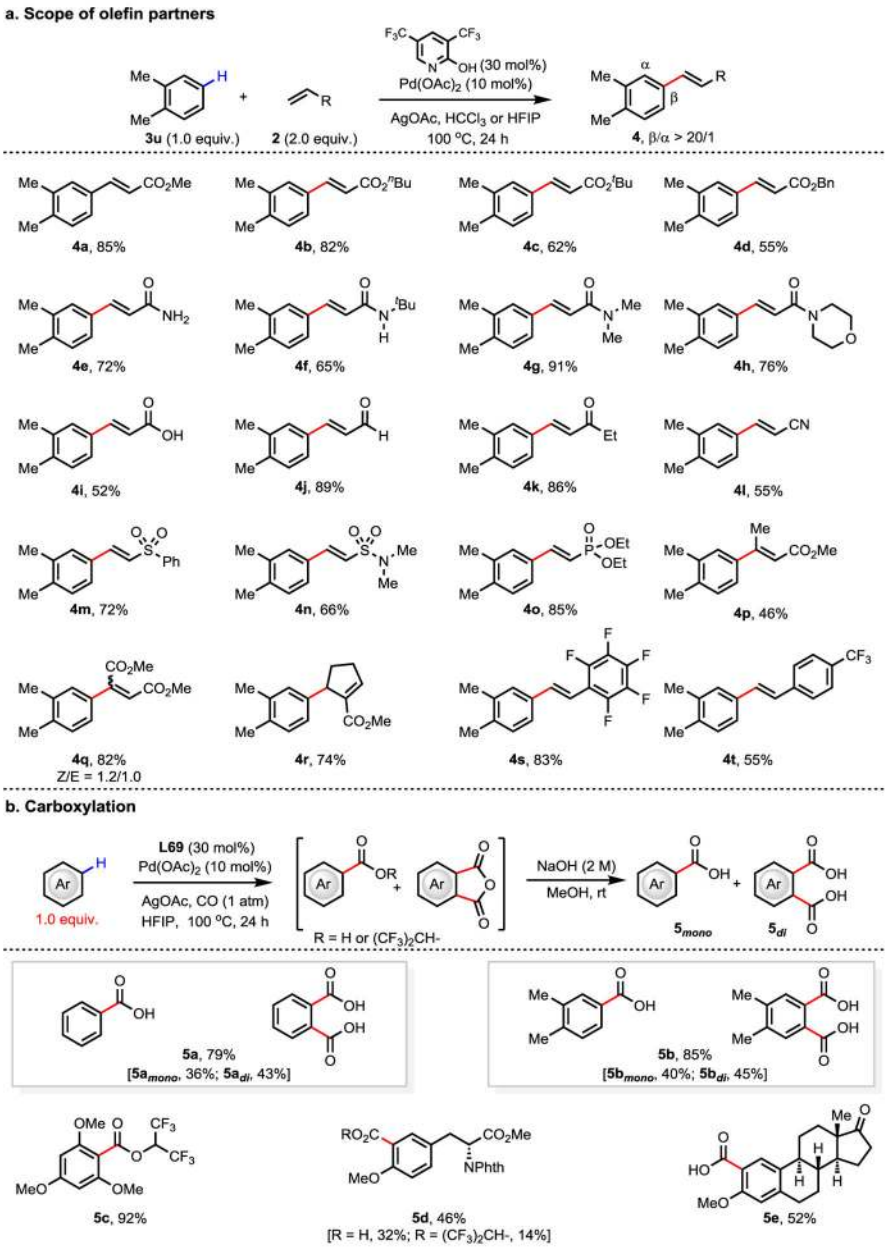

Figure 3. The scope of olefin partners and carboxylation

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, 4p**, the reaction was conducted in $HCCl_3$; 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 %), L (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.

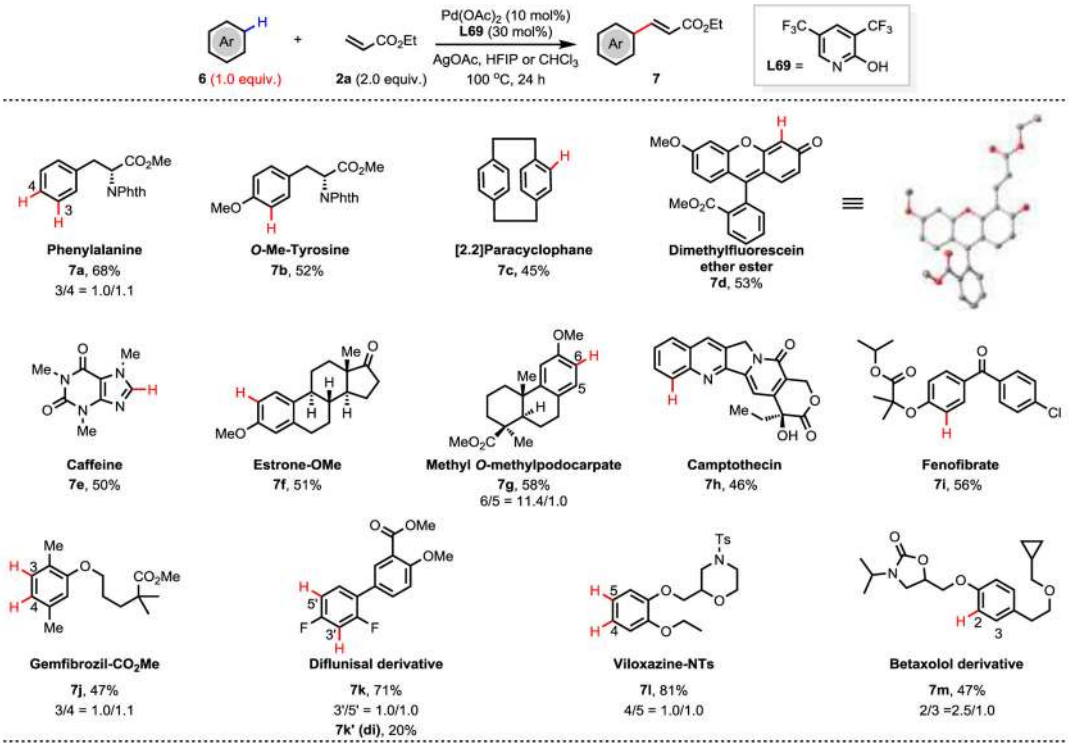

Figure 4. Late-stage functionalization of natural products and drug molecules

Phth, Phthaloyl; TBS, *tert*-butyldimethylsilyl; Ts, 4-toluenesulfonyl; HFIP, hexafluoroisopropanol. 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 was conducted for 16 h. For **7g**, chloroform was used instead of HFIP.