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Ligand-Accelerated C–H Activation Reactions: Evidence for a Switch of Mechanism

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Abstract

Initial rate studies have revealed dramatic acceleration in aerobic Pd(II)-catalyzed C–H olefination reactions of phenylacetic acids when mono-*N*-protected amino acids are used as ligands. In light of these findings, systematic ligand tuning was undertaken, which has resulted in drastic improvements in substrate scope, reaction rate, and catalyst turnover. We present evidence from intermolecular competition studies and kinetic isotope effect experiments that implies that the observed rate increases are a result of acceleration in the C–H cleavage step. Furthermore, these studies suggest that the origin of this phenomenon is a change in the mechanism of C–H cleavage from electrophilic palladation to proton abstraction.

1. Introduction

Pd(0)-catalyzed reactions of aryl and alkyl halides (R–X) have revolutionized the field of synthetic organic chemistry since the early 1970s, when the first reports describing the catalytic coupling of aryl halides and olefins were independently disclosed by Mizoroki and Heck.[1] Subsequent to that work, an array of carbon–carbon[2–8] and carbon–heteroatom[8–12] bond–forming reactions have been developed based on Pd(0)/Pd(II) redox catalysis, with increasing levels of efficiency, practicality, and reliability. The power of this class of catalytic reactions stems from the diverse reactivity of the [Pd(II)–R] intermediates, which are commonly generated from oxidative addition of the R–X group to Pd(0) (Scheme 1).

Fascinated and inspired by this diverse reactivity, our research group has focused on mimicking this catalysis using Pd(II)-mediated C–H activation as an entry point to form the [Pd(II)–R] species.[13–14] At the outset we recognized that the precise molecular structure of [Pd(II)–R] intermediates generated in this manner, which could exist as monomeric, dimeric, or trimeric species, would likely be more complex than that of those made from oxidative addition of an aryl halide to Pd(0), which are predominantly monomeric. Nevertheless, our group[15–19] and others[20–29] have demonstrated several catalytic reactions in which [Pd(II)–R] intermediates generated by C–H activation react with strong oxidants to induce reductive elimination from high-energy Pd(III)[30,31] or Pd(IV)[32] species. Despite our early success in this direction, the bulk of our efforts have centered on developing novel carbon–carbon and carbon–heteroatom bond–forming reactions along a Pd(II)/Pd(0) catalytic cycle. This strategy has proven to be a remarkably fruitful research area, as many of the reactions depicted in Scheme 1 have already been demonstrated.[33–40]

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Supporting Information Avialable. Detailed experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

In comparison to the state of the art in traditional Pd(0) coupling chemistry, C–H activation reactions using Pd(II)/Pd(0) catalysis remain underdeveloped. The principal driving force that has propelled Pd(0)-catalyzed coupling chemistry during the past several decades has been the development of bulky phosphine and *N*-heterocyclic carbene (NHC) ligands that promote both the oxidative addition and reductive elimination steps, thereby improving the reaction rate, lowering the requisite catalyst loading, and expanding the substrate scope.[41] The advancements in ligand design have resulted in truly practical and operationally simple reactions that have found a myriad of applications, including numerous examples in natural product total synthesis.[42]

In sharp contrast, though several notable achievements have been made in the area of Pd(II)-catalyzed C–H activation,[14] a pervasive limitation that has hampered efforts in this field is the dearth of suitable ligand scaffolds that can accelerate C–H cleavage. (Throughout the text, we use the term “C–H cleavage” to refer to the general process of carbon–hydrogen bond breaking along any of a variety of mechanistic pathways.) In this respect, several challenges must be overcome to design suitable ligands. One problem is that many of the common phosphine and NHC ligands are too strong of σ-donors and outcompete the substrate molecule for binding to Pd(II) or render the metal-center overly electron-rich for C–H activation. A second related problem is devising reaction conditions that facilitate controlled assembly of a pre-transition state Pd(II) complex with one molecule of substrate and one molecule of ligand because the two different molecules must have well matched coordinative affinity for Pd(II) (Scheme 2).

To engineer a reaction system in which the ligand plays a dominant role in influencing the reactivity and/or selectivity, utilizing a functional group capable of directing C–H cleavage via *weak coordination* is highly advantageous. Our group has pursued this strategy by developing reactions that are compatible with substrates containing commonly occurring Lewis basic moieties that form low-energy interactions with Pd(II)[14i] (*e.g.*, carboxylic acids, triflimides, and alcohols). In these cases, C–H cleavage does not occur as easily as with many of the other commonly utilized directing groups (*e.g.*, pyridines, oxazolines and oximes), which has given us a unique opportunity to probe how external ligands change the activation energy of the C–H cleavage step. Recently, our group has reported successful examples of using chiral mono-*N*-protected amino acid ligands to control the enantio-[43,44] and positional[45] selectivity of C–H cleavage, which serves as evidence that the ligands are coordinated to Pd(II) during the C–H cleavage event and are influencing the corresponding transition state energies. Moreover, as part of our group's interest in Pd(II)-catalyzed C–H olefination,[35,44–56] a research field that was initiated by the seminal contributions of Fujiwara and Moritani in the late 1960s,[33–34] we have found success in using mono-*N*-protected amino acid ligands to promote C–H activation of generally unreactive substrates that are strongly electron-deficient or those that contain remote, weakly coordinating directing groups.[45,49g,49i] Given the need for new ligands to accelerate C–H activation and enable the diverse reactivity depicted in Scheme 1, at this stage it is critical to elucidate more fully whether the improved reactivity observed using amino acid ligands is a result of ligand-induced acceleration (*i.e.*, a decrease in the activation energy) and if so, whether the amino acid core structure can be further tuned to offer improved reactivity, reduced reaction times, and lower catalyst loading.[57]

Herein we report the results of our efforts to investigate these questions. Initial rate studies have revealed a dramatic rate increase in the presence of amino acid ligands, which, taken in the context of other data, is suggestive of acceleration in the C–H cleavage step. The results from these initial rate studies prompted us to undertake further ligand optimization, which has led to drastically improved reaction conditions. Finally, we present evidence from intermolecular competition experiments and kinetic isotope (KIE) experiments that suggest

that coordination of amino acid ligands to Pd(II) leads to a change in the reaction mechanism.

Results and Discussion

2.1. Preliminary Initial Rate Studies

We have previously reported a Pd(II)-catalyzed mono-selective C–H olefination reaction of phenylacetic acid substrates.[45] In that report, we demonstrated preliminary results utilizing mono-*N*-protected amino acid ligands to promote C–H olefination with unreactive substrates, including hydrocinnamic acids (which are challenging because of the remoteness of the carboxylate directing group) and phenylacetic acid substrates bearing electron-withdrawing groups (*e.g.*, CF_3 and NO_2).

We began our investigation by revisiting the data from our initial report. In particular we were interested in determining whether the improved yield after 48 h stemmed from improved catalyst lifetime or increased initial reaction rate (Scheme 3). Using the C–H olefination of **1** to **1a** as a model study, we ran parallel reactions, quenching them at regular intervals and determining the conversion by ^{1}H NMR of the crude reaction mixtures. We then plotted the conversion versus time under four different reaction conditions: (1) without Boc-Val-OH, without 1,4-benzoquinone (BQ), (2) without Boc-Val-OH, with BQ, (3) with Boc-Val-OH, without BQ, (4) with Boc-Val-OH, with BQ. The results from these studies are shown in Figure 1.

In the absence of BQ, we observed a 36-fold rate increase for reactions with Boc-Val-OH compared to those without this ligand (from 1.3×10^{-4} M/min to 4.7×10^{-3} M/min). To our surprise, we observed that BQ substantially decreased the reaction rate both with and without Boc-Val-OH. Previously, during our investigation to develop a highly mono-selective C–H olefination reaction with phenylacetic acid substrates, BQ was found to be beneficial for improving the overall yield after 48 h and controlling the mono/di selectivity with more reactive substrates. The observation that BQ leads to a decrease in the initial reaction rate, is consistent with it being found to improve the mono/di selectivity with more reactive substrates. Additionally, though BQ lowers the initial reaction rate, it also seems to be capable of improving the overall turnover number given a sufficiently long reaction time (particularly in the case of reactions run in the absence of amino acid ligands).

In light of these results, we wondered whether this trend was unique to electron-deficient substrates. Thus, we performed an analogous set of experiments with a more electron-rich substrate, **2**, and found a 15-fold rate increase for reactions using with Boc-Val-OH compared to those without it (from 3.5×10^{-4} M/min to 5.2×10^{-3} M/min) (Figure 2).

With this information in hand, we next sought to determine optimal conditions for Pd(II)-catalyzed C–H olefination of **1** in an effort to improve the reaction rate, catalytic turnover, and substrate scope, which we viewed as central to advancing the versatility and practicality of the transformation.[14i]

2.2. Ligand Optimization

Our efforts to develop an improved reaction protocol for our aerobic Pd(II)-catalyzed C–H olefination reaction centered on the identification of an optimal ligand in terms of reaction rate and overall yield. To begin, we sought to identify the most active ligand backbones by examining a set of commercially *N*-Boc-protected amino acids (Table 1). For our screening studies, we selected a highly abridged reaction time of 20 minutes in order to see the comparative kinetic behavior of the different ligands. Notably, in the absence of ligand, the reaction was found to give less than 5% conversion (Entry 1). Prior to our investigation, we

hypothesized that the bite angle between the two coordination sites on the amino acid ligand could have a dramatic impact on the catalytic activity of Pd(II), as it would presumably effect the geometry of the coordination assembly in the pre-transition state. We probed Boc-Gly-OH (Entry 9) (with no substitution at the alpha position, and hence a large bite angle) and a quaternary substituted amino acids with a smaller bite angles (Entry 14), and found that both of these ligand structures resulted in slower reactions than mono-α-substituted ligands. Among this group, Boc-Val-OH was the best, providing **1a** in 46% conversion after 20 minutes (Entry 3). As a control experiment, we also examined other commonly used organic acids, representative examples of which are shown in Table 1 (Entries 17 and 18; see Supporting Information for additional results). These other acids uniformly gave low conversions, suggesting that coordination of both the carboxylate group and the protected amino group with Pd(II) is crucial for rate acceleration.

Following identification of valine as a highly reactive amino acid backbone, we sought to optimize the *N*-protecting group (Table 2). In an initial control experiment, we found that *N*-protection was required, as the reaction did not proceed with unprotected H-Val-OH (Entry 1). With this information in hand, we examined several commercially available *N*-protected valine amino acid ligands (Entries 1–3, 6, 7, and 12) and subsequently prepared several new ligands (Entries 4, 5, and 8–11). Because Boc protecting groups were found to be highly reactive, we examined other carbamate protecting groups with different steric properties (Entries 7–11 and 13), but did not observe any improvement. We moved on to amide protecting groups (Entries 3–5 and 12). Among the amide protecting groups examined, ligands bearing less sterically demanding groups (Entries 3 and 6) were found to give better conversions than those with sterically bulky protecting groups (Entries 4, 5, and 12), with Ac-Val-OH giving the best conversion (57%) (Entry 3).

Having found that the acetyl protecting group was highly reactive when used with valine, we wondered whether additional fine-tuning of the ligand backbone of *N*-acetyl-protected amino acids might result in further improvement in the catalyst activity (Table 3). To our delight, when we examined the *N*-acetyl-protected versions of a selected set of ligands from Table 1, we found improved yields for nearly every ligand that we probed relative to its Boc-protected counterpart. Ac-Ile-OH and Ac-Ala-OH were found to be the most reactive, giving **1a** in 72% and 71% conversion, respectively. Quantitative conversion of **1** to **1a** could be achieved by extending the reaction time to 2 hours (Entry 5).

We also probed the effect of amino acid ligand loading and found that when the reaction was run with anywhere between 5–15 mol% Ac-Ile-OH, the conversions were similar after 20 min. 2.5 mol% Ac-Ile-OH led to lower conversion (see Supporting Information). Similarly, we found that between 1 and 2 equivalents of olefin led to similar reaction rates and overall yields; with 3 equivalents of olefin, the reaction rate decreased. Because the reagents used in these experiments were readily available, we elected to use 2 equiv. Ac-Ile-OH (relative to $Pd(OAc)_2$) and 2 equiv. olefin (relative to substrate) as the conditions for the investigations below (Sections 2.3–2.5). The reaction could be run effectively at temperatures between 50–110 °C (see Supporting Information), with lower temperatures giving decreased reaction rates. For example, at 50 °C, the reaction took 48 hours to reach >90% conversion. Running the reaction at 110 °C, >90% conversion could be achieved after 20 minutes (Entry 6, Table 3). The use of higher temperatures, such as 130 °C, reduced the reaction rate, presumably due to catalyst decomposition.

2.3 Low Catalyst Loadings/Air (1 atm) as the Reoxidant

Having identified Ac-Ile-OH as a superior ligand for reaction rate (*i.e.*, turnover frequency, TOF) in the Pd(II)-catalyzed *ortho*-C–H olefination of **1**, we became interested in examining the efficiency of the catalytic turnover under these conditions. We began by reducing the

catalyst loading to 1 mol% $Pd(OAc)_2$ and running parallel reactions under 1 atm O_2 (Table 4). Gratifyingly, we found that efficient catalysis could still be achieved under these conditions, such that **1a** could be prepared in 96% conversion (94% yield) after 4 h.

This result encouraged us to further lower the catalyst loading to 0.2 mol% $Pd(OAc)_2$ (Table 5). Again, we found that highly efficient catalysis could be maintained under these conditions, and we were able to synthesize **1a** with 91% conversion (83% yield) after an extended reaction time of 48 h. Notably, this result represents a TON of 455, which is among the highest reported for an aerobic C–H activation reaction.[46,47] We further demonstrated the scalability of this chemistry by using the conditions described in Table 5 to prepare over 1 gram of **1a** from **1** using only 2.2 mg of $Pd(OAc)_2$. Following an aqueous quench and extraction with organic solvent, **1a** could be obtained from the crude reaction mixture in 76% yield after recrystallization (Scheme 4).

Though 1 atm O_2 is a highly convenient oxidant, in terms of operational simplicity, being able to use 1 atm air (which is 21% O_2) is highly desirable because it obviates the need to store compressed O_2 in the laboratory. To examine whether O_2 could be replaced with air, we used 1 mol% $Pd(OAc)_2$ and ran parallel reactions in sealed tubes under air (Table 6). (Having a sealed vessel is necessary due to the volatility of ethyl acrylate.) Under these conditions, **1a** could be synthesized in 87% conversion (78% yield) after an extended reaction time of 48 h.

Given the low catalyst loading, relatively mild reaction conditions, and the fact that the only byproduct in the catalytic cycle is water, this chemistry is highly atom-economical[58] and falls in line with goals of green chemistry.[59]

2.4. Substrate Scope for Accelerated C–H Olefination

Under the optimized conditions, a wide variety of phenylacetic acid substrates were highly reactive, generally giving the desired C–H olefinated products in quantitative yields (Table 7). The substrate scope was found to be remarkably broad, as the reaction tolerated electron-donating methoxy (**5a** and **10a**) and alkyl groups (**2a** and **4a**), as well as fluorides (**6a**) and chlorides (**7a**), the latter offering a unique opportunity for subsequent Pd(0)-mediated coupling chemistry. Bromides and iodides were found to be unreactive in C–H olefination. Arenes bearing electron-withdrawing substituents, including trifluoromethyl (**1a** and **3a**), nitro (**8a**), and ketone (**9a**) groups, gave good to excellent yields. In an effort to demonstrate the potential applicability of this chemistry in drug diversification, we targeted ketoprofen (**9**) and naproxen (**10**), two commercially available non-steroidal anti-inflammatory drugs (NSAIDs), and observed that they could be directly *ortho*-olefinated to give **9a** and **10a** in nearly quantitative isolated yields.

For each substrate, we ran two control experiments in the absence of Ac-Ile-OH: with BQ (our original mono-selective procedure) and without. In all cases, the presence of Ac-Ile-OH led to higher conversions, but the improvement was most pronounced with electron-poor substrates. Interestingly, for electron-rich arenes (**2a**, **4a**, **5a**, and **10a**), relatively high conversions could be obtained after 2 h without Ac-Ile-OH if BQ was removed. As discussed above, in the absence of amino acid ligands, BQ allows for control of mono/di-selectivity and leads to higher TONs in many instances; however, in the case of these particular substrates (*i.e.*, electron-rich arenes containing an *ortho* or *meta*-blocking group) BQ does not offer a clear benefit and only serves to reduce the reaction rate. In general, electron-deficient substrates were found to exhibit low reactivity in the absence of ligand (**1a** and **3a**). The presence of a nitro group rendered the arene totally unreactive (**8a**) without ligand.

In accordance with our earlier observations,[45] **8a** was found to decarboxylate under the reaction conditions, leading to exclusive formation of the corresponding decarboxylated product **8a'** after 48 h. This reaction is triggered by the installation of the electron-withdrawing olefin, which further stabilizes anionic charge at the benzylic position through resonance effects. It is important to note here, that prior to our identification of Ac-Ile-OH as a ligand for accelerated C–H olefination, **8a** could not be obtained in appreciable yields because using other ligands, it was found to decarboxylate to **8a'** faster than it could be generated from C–H olefination of **8**. In contrast, under these new conditions, **8a** could be isolated in 70% yield after 2 h. This reaction was monitored over time using ^{1}H NMR, and the results are depicted in Table 8.

The phenylacetic acid substrates shown in Table 7 all contain a sterically bulky blocking substituent at the *ortho*- or *meta*- positions. For those that are not of this type, the ligand-accelerated C–H olefination conditions that we report here will lead to significant formation of the di-*ortho*-olefinated byproduct over time. Indeed, concurrent to this work, we developed a robust method for direct 2,6-diolefination of phenylacetic and hydrocinnamic acids (Scheme 5).[49i] For 2,6-diolefination, Ac-Ile-OH, which we use throughout this paper, gave irreproducible results, and Ac-Val-OH was found to be superior. Current investigations are underway in our laboratory to design a ligand that will offer enhanced reactivity but will stop after a single olefination event, thereby obviating the need for a proximate blocking group.

We next sought to examine the scope of olefin coupling partners that could be used under our accelerated reaction conditions (Table 9). A variety of acrylates (**1a**–**1c**), styrenes (**1d** and **1e**), and vinyl ketones (**1g** and **1h**) were found to be highly reactive, generally offering quantitative yields after 2 h (10 h in the case of **1e** and **1h**).

Consistent with our earlier observation,[45,49i] linear alkenes were also compatible, fashioning the non-conjugated product **1f**. We hypothesize that this product is formed as a consequence of the mechanistic scenario depicted in Scheme 6, wherein coordination of the carboxylate directing group restricts bond rotation, which makes β-hydride elimination away from the aromatic ring more kinetically favorable. Notably, this result represents a formal C–H allylation, and as such, provides access to a novel class of non-conjugated products. Efforts to carry out C–H olefination with vinyl sulfones, sulfonates, phosphonates, and nitriles were unsuccessful. Moreover, internal alkenes, such as *trans*-methyl crotonate and *trans*-methyl cinnamate, were found to be unreactive with **1** under these conditions.

It is worth noting here that the phenylacetic acid substrate scope and olefin scope studies were run using 5 mol% $Pd(OAc)_2$ under 1 atm O_2, but using lower catalyst loadings (0.2–1 mol%) and/or air as the oxidant would likely give similar yields after extended reaction times (4–48 h), as demonstrated above.

2.5. Mechanistic Considerations

To elucidate fully the origin of the observed ligand-promoted acceleration, insights from a number of different techniques are needed, including isolation and characterization of the putative intermediates, kinetic determination of the rate law, and computational modeling of possible reaction pathways. In collaboration with other research groups, our laboratory is currently pursuing these investigations. In the meantime, we have performed two key sets of experiments, measuring the intermolecular KIE and observing the relationship between initial rate and the electronic properties of the substrate through competition experiments. The resulting data provide evidence that the overall rate increase stems from acceleration in the C–H cleavage step and that the mechanism of C–H cleavage changes from electrophilic palladation to proton abstraction when amino acid ligands are coordinated to Pd(II).

Historically speaking, the mechanism of C(sp^2)–H cleavage by Pd(II) has attracted a great deal of attention.[60] During the past few decades, three leading transition state proposals have emerged, with the operative mechanism thought to depend on the individual system in question (Scheme 7). One mechanism is electrophilic palladation *via* an arenium (Wheland) intermediate, originally proposed by Ryabov and coworkers in 1985 (**A**).[60a] In this case, Pd(II) coordinates to the π-system of the arene, and the resulting Wheland species transfers a proton to a bound acetate to generate the cyclopalladated intermediate. In electrophilic palladation, the efficacy of C–H activation is highly dependent on the electronic properties of the arene, with electron-rich substrates giving better reactivity. A second mechanism, oxidative addition, was proposed by Canty and van Koten in 1995, in which the C–H bond oxidatively adds to Pd(II) to generate a short-lived Pd(IV) species that can reductively eliminate HX to generate the Pd(II)-cyclopalladated intermediate (**B**).[60b] Lastly a third mechanism is proton abstraction, first put forward by Martinez in 1997 (**C**).[60c,d] Subsequent computational work by Davies and Macgregor in 2005 supported a similar mechanism (**D**).[60f] In proton abstraction, C–H cleavage proceeds *via* the concerted transfer of the hydrogen atom to an intramolecular base, without substantial build up of positive charge on the arene. Martinez suggested that this process proceeds *via* a four-membered transition state,[60c] but later evidence from Davies and Macgregor pointed to a six-membered transition state.[60f] Proton abstraction is thought to operate *via* an agostic interaction, rather than through a Wheland intermediate;[60f] as such, the rate dependence of the electronic properties of substituents is less pronounced.

It is worth mentioning that proton abstraction with Pd(II) is conceptually related to the mechanism for C–H activation in Pd(0)/ArX chemistry (**E–G**, Scheme 8).[61] However, the latter belongs to a different reactivity paradigm, in which the Pd(II) species is attached to a phosphine ligand and an aryl fragment and is thus rendered nucleophilic. Though the mechanism for Pd(II)-mediated C–H cleavage has been studied for a longer period of time, arguably the mechanism at play in Pd(0)/ArX chemistry is better understood due to pioneering studies by Eschavarren and Fagnou.[61b–f]

Regarding our studies of Pd(II)-mediated C–H cleavage with phenylacetic acids, qualitatively speaking, the data that we obtained using our original Pd(II)-catalyzed mono-selective C–H olefination reaction[45] are consistent with an electrophilic palladation mechanism. The reaction was found to be high yielding when substrates with electron-donating groups (*e.g.*, methoxy and methyl) were used, and to be low yielding or unreactive for substrates with electron-withdawing groups (*e.g.*, CF_3 and NO_2). In particular, without amino acid ligands, we found substrate **8**, which contains an *ortho*-nitro group, to be totally unreactive after 48 h, with only starting material recovered (and <5% decarboxylation) (Scheme 9). In sharp contrast, in the presence of Ac-Ile-OH gave 70% yield of **8a** after only 2 h. Viewed in conjunction with data in Figures 1 and 2, this data suggests two points: (1) the amino acid ligands are not merely enhancing the TON, but are generating a more reactive catalyst, (2) electrophilic palladation no longer seems to be the operative mechanism.

To investigate whether a departure from the electrophilic palladation pathway or a drastic increase in the electrophilic property of the Pd(II) catalyst is responsible for the reactivity of **8**, we carried out intermolecular competition experiments between electron-rich and electron-poor substrates (Table 10). We selected **1** and **2** for analysis because they are roughly isosteric to one another and do not contain strongly chelating functional groups on the aromatic ring. We began by submitting a one-to-one mixture of **1** and **2** to the reaction conditions in the absence of amino acid ligand and found that **2** reacted preferentially, consistent with our hypothesis for electrophilic palladation. We then repeated these experiments in the presence of two ligands: Boc-Val-OH, which we found to be an active

ligand in our early studies,[45] and Ac-Ile-OH, which proved to be optimal throughout this investigation. When Boc-Val-OH was used, the relative reaction rate of **1** to **2** increased to the point where the two substrates were reacting almost at the same speed (*i.e.*, k_1/k_2 changed from 0.22 to 0.58). Strikingly, when we examined Ac-Ile-OH, we found a reversal in relative reactivity, such that electron-poor substrate **1** now reacted almost twice as fast as electron-rich substrate **2** (k_1/k_2 = 1.87). This same trend held for individually measured rates for the single-component reactions of **1** and **2** (Table 11).

Next, we sought to determine whether the differences in these relative rate profiles could be attributed to mechanistic changes in C–H cleavage and also to test the hypothesis that the ligand-induced rate increases were a result of acceleration in the C–H cleavage step. We prepared deuterium-labeled compound **12**, a representative electron-rich substrate, and used it to perform intermolecular KIE experiments (Table 12). In the absence of ligand, we observed a large KIE of 6.1, suggesting that cleavage of the C–H bond is the rate-limiting step. In the presence of Boc-Val-OH, though the absolute reaction rates of both **2** and **12** were found to be substantially greater, the measured KIE was roughly the same (5.5), suggesting that C–H cleavage was still the rate-limiting step. Interestingly, with Ac-Ile-OH, the ligand that gives the fastest overall rate, the KIE had markedly decreased to 1.7, suggesting that the rate of C–H cleavage had increased to the point where it was no longer the slow step in the catalytic cycle. In this case, the moderate KIE (between 1 and 2) is consistent with C–H cleavage taking place before the rate-limiting step.

Taken together, the data from the competition experiments and the KIE experiments paint an interesting picture for the operative mechanisms in these systems. Our tentative hypothesis is that in the absence of amino acid ligands, among the three possible pathways (**H–J**, Scheme 10), the reaction proceeds through an electrophilic palladation mechanism (**H**). At first glance, the large KIE of 6.1 (Entry 1, Table 12) would seem to contradict this proposal since electrophilic aromatic substitution reactions (including electrophilic palladation processes) often have small KIE values.[62] In these cases, deprotonation is assumed to be fast relative to formation of the arenium species. However, in cases where the rate of deprotonation is slow, larger KIE values have been observed.[49c,63] Thus if we follow this logic and invoke an electrophilic palladation mechanism, then with electron-rich substrates, such as **2**, palladation to generate the putative Wheland intermediate is fast, and intramolecular deprotonation by internally bound acetate is the rate-limiting step, which is consistent with the large KIE of 6.1 for electron-rich substrates (**2** and **12**). In contrast, with electron-poor substrates, such as **1**, palladation to form the Wheland intermediate is less favorable, and thus becomes rate-limiting, in accordance with the results of the competition experiments.

With the amino acid ligands, several possibilities exist (**K–P**, Scheme 11), again falling within the three general classifications described above. It is important to recognize that when Ac-Ile-OH is used, the KIE data suggests that C–H cleavage is not rate-limiting; thus the results of the competition experiments (Table 10, Entry 3 and Table 11, Entry 3) need to be interpreted cautiously because the relative rate changes reflect an elementary step other than C–H cleavage. Nevertheless, the high levels of reactivity with both electron-poor and electron-rich substrates would seem to argue against an electrophilic palladation mechanism (**K** and **L**). Furthermore, in the case of Boc-Val-OH the KIE data indicates that C–H cleavage is still rate-limiting, yet in competition experiments (Table 10, Entry 2 and Table 11, Entry 2) electron-poor and electron-rich substrates were found to react with similar rates, suggesting that electrophilic palladation (which we hypothesize is operative in the ligand-free conditions) is not operative. Though we cannot rule out the possibility that Boc-Val-OH and Ac-Ile-OH promote different mechanisms, we suspect that they coordinate to Pd(II) in an identical bidentate fashion and thus affect C–H cleavage similarly. Because previous

computational studies have not found oxidative addition mechanisms to be energetically favorable (**M**),[60f] our current understanding would support one of the proton abstraction mechanisms (**N–P**). Here, the weak and reversible bidentate coordination of the amino acid ligand likely plays a crucial role in facilitating the initial agostic interaction between Pd(II) and the C–H bond and then in shuttling the hydrogen atom to an internal (**O** and **P**) or external (**N**) base. Across the various ligands that enhanced reactivity in these studies (Tables 1–3), it is possible that multiple C–H cleavage mechanisms are at play simultaneously (or that the operative mechanism is substrate-dependent).

As mentioned above, our selection of Boc-Val-OH and Ac-Ile-OH for these mechanistic studies was motivated by the finding that these ligands were highly reactive in our early work[45] and present work, respectively. Valine and isoleucine–derived ligands were found to show similar levels of activity when Boc-protected (Table 1, comparing Entries 3 and 4) and Ac-protected (Table 3, comparing Entries 1 and 5), consistent with the fact that their side chains differ only by a remotely located methyl group. Thus, the origin of the observed differences in catalysis between Boc-Val-OH and Ac-Ile-OH likely originate primarily from the different steric and electron properties of the *N*-protecting groups.

A detailed analysis of how the amino acid ligands affect the transition state energies of various C–H cleavage processes remains a point to be clarified by computational studies. Given the dramatic effect that small perturbations in the structure of the amino acid side chain and the *N*-protecting group have on the observed reactivity and on the competition and KIE studies, the precise role of the ligands is likely quite complex. Here, we put forward general mechanistic models to guide future analysis (Scheme 11). An important question that remains to be addressed is what coordination mode the amino acid ligand adopts with Pd(II) in the transition state. In our previous work using mono-*N*-protected amino acid ligands for enantioselective C–H activation,[43–44] our working stereomodel suggests that the ligand is coordinated in a bidentate fashion throughout the C–H cleavage process. However, if we invoke a bidentate coordination mode for the ligand (**L–O**), Pd(II) will be coordinatively saturated when bound to the carboxylate directing group and the C–H bond (through an agostic interaction) in the pre-transition state. This implies that traditional intramolecular deprotonation by bound acetate (**A**, **C**, and **D**, Scheme 7) is no longer viable since the bound acetate must be displaced in order for the C–H agostic interaction to occur. Thus, in this case, deprotonation is likely occurring either by an external base (**N**) or by one of the basic groups from the ligand (**L**, **O**, and **P**). On the other hand, the amino acid ligand could adopt a monodentate coordination mode in the transition state (**K** and **P**), in which case, the models discussed in Scheme 7 could still be applicable.

An overall proposal for the catalytic cycle is depicted in Scheme 12. Following coordination of the substrate to Pd(II), carboxylate-directed C–H cleavage takes place to generate the reactive cyclopalladated intermediate. Coordination of an olefin followed by 1,2-migratory cleavage effects formation of the new C–C bond. β-Hydride elimination and reductive elimination give the desired product with concomitant formation of a Pd(0) species, which can be reoxidized by molecular oxygen[46,47,64] to regenerate Pd(II) and close the catalytic cycle.

3. Conclusion

We have developed an improved protocol for aerobic Pd(II)-catalyzed C–H olefination of phenylacetic acid substrates through the discovery of a novel ligand, Ac-Ile-OH, which is capable of accelerating the reaction. This ligand offers dramatically improved substrate scope, reaction rate, and catalyst lifetime. Catalyst loadings as low as 0.2 mol% and reaction times as fast as 20 minutes were demonstrated. Moreover, the reaction could be run using air

as the terminal oxidant. We disclosed evidence based on initial rate studies, reactivity trends, competition experiments, and KIEs that suggests that the increased reaction rates stem from acceleration in the C–H cleavage step. Furthermore, this data points to a change in mechanism of C–H cleavage from electrophilic palladation to proton abstraction or oxidative addition when amino acid ligands are added to the reaction. Efforts are currently underway in our laboratory to examine whether amino acid ligands are competent in accelerating Pd(II)-mediated C–H cleavage with other directing groups. Our preliminary results concerning ligand-enabled C–H olefination of phenethyl alcohol substrates are promising in this respect.[49g] Additionally, if the observed rate enhancement truly stems from acceleration in the C–H cleavage step, as we now presume, other Pd(II)-catalyzed C–H functionalization reactions should, in principle, benefit from amino acid ligands. This hypothesis is also being actively investigated by our group at the present time.

4. Experimental Section

4.1. General Information

Unless otherwise noted, all materials were used as received from commercial sources without further purification. The phenylacetic acid substrates and olefin coupling partners were purchased from Acros, Sigma-Aldrich, TCI and Alfa-Aesar and were used as received. 2-(Trifluoromethyl)phenylacetic acid (**1**) was purchased from TCI; samples of **1** from other commercial sources were found to give irreproducible results. 1,4-Benzoquinone (BQ) was sublimed prior to used. Freshly distilled methyl vinyl ketone was used in the synthesis of **1g**. Commercially available organic acid ligands were purchased from Acros, Sigma Aldrich, and Alfa Aesar. In the optimization studies **5a** was used as a ligand; its synthesis is described herein. Commercially available amino acid ligands were purchased from Bachem, EMD, or Novabiochem. **L4** was prepared according to a method developed by Burgess.[65] **L6** was prepared according to a literature procedure.[66] All others were prepared following literature precedent.[43,67] Palladium acetate and potassium hydrogen carbonate were purchased from Sigma-Aldrich and Fisher, respectively, and were used without further purification. All reactions were run on hot plates with oil baths calibrated to an external thermometer. Prior to beginning an experiment, the hot plate was turned on, and the oil bath was allowed to equilibrate to the desired temperature for 30 minutes. Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury (300 MHz and 75 MHz, respectively), Varian Inova (400 MHz and 100 MHz, respectively) and Bruker DRX (500 MHz and 125 MHz, respectively) instruments internally referenced to $SiMe_4$ or chloroform signals. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and a = apparent. High resolution mass spectra were recorded at the Center for Mass Spectrometry, The Scripps Research Institute.

4.2 General procedure for determining the initial reaction rate for C–H olefination of 1 (or 2) under different conditions

Four different reaction conditions were examined: (1) without Boc-Val-OH, without BQ, (2) without Boc-Val-OH, with BQ, (3) with Boc-Val-OH, without BQ, (4) with Boc-Val-OH, with BQ. To establish the initial rate under each of the conditions, four parallel reactions were set up simultaneously. Four 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) were obtained, each equipped with a magnetic stir bar. Each tube was charged with **1** (or **2**) (0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), BQ (2.7 mg, 0.025 mmol) (when used), Boc-Val-OH (10.9 mg, 0.05 mmol) (when used), ethyl acrylate (106 μL, 1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction tubes were capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm, balloon) (×3). The reaction mixtures were stirred at room temperature for 5 min, then at 90

°C for the appropriate time. At regular intervals (every 5 minutes, or every 30 minutes), one of the reactions would be removed from the hot plate and cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were then added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1**, 4.01 ppm for **1a**, 3.67 ppm for **2**, and 3.84 ppm for **2a**). For each condition, this process was repeated three times. The resulting data was plotted, and linear regression established the initial rate. Representative data for the determination of one initial rate are shown in Figure S1.

4.3 General procedure for mono-*N*-protected L-valine ligands[43,67]

A 500 mL round bottom flask equipped with a magnetic stir bar was charged with distilled H_2O (100 mL) and NaOH (100 mmol, 4.0 g). The resulting solution was cooled to 0 °C in an ice bath. L-valine (35 mmol, 4.1 g) was added, and the solution was stirred until it was homogeneous. The flask was equipped with an addition funnel. The corresponding carbonyl chloride (45.5 mmol) in 1,4-dioxane (40 mL) was added dropwise. The reaction mixture was then allowed to stir at room temperature overnight. The following morning, the solution was extracted with Et_2O (3 × 50 mL), and the organic layers were discarded. The aqueous layer was again cooled to 0 °C in an ice bath, and concentrated HCl was added dropwise until the pH had reached 2 (as observed by pH paper). The aqueous solution was extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product. The pure product was obtained following recrystallization from Et_2O/hexanes or column chromatography using 15:1 DCM:MeOH as the solvent system. For a general depiction of this procedure, see Scheme S1.

4.4 Ligand optimization for Pd(II)-catalyzed olefination with 2-(Trifluoromethyl)phenylacetic acid (1)

A 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar was charged with **1** (102.1 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), ligand (0.05 mmol), ethyl acrylate (106 μL, 1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction tube was capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm, balloon) (×3). The reaction mixture was stirred at room temperature for 5 min, then at 90 °C for the appropriate time. The reaction vessel was removed from the oil bath and immediately cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1** and 4.01 ppm for **1a**). When indicated, the reactions were performed in triplicates, and the values shown represent the average result from the three experiments. In our initial efforts, we measured the conversion after 2 h (Table S1), but we observed quantitative conversion for many ligands. We then adjusted our assay and examined the conversion after 20 min (Tables S2 and S3).

4.5 Additional optimization for Pd(II)-catalyzed olefination with 2-(Trifluoromethyl)phenylacetic acid (1)

The effects of ligand loading (Table S4), olefin loading (Table S5), and reaction temperature (Tables S6–S10) were explored using Ac-Ile-OH as the ligand. A 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar was charged with **1** (102.1 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), Ac-Ile-OH, ethyl acrylate, and *t*-AmylOH (2.5 mL). The reaction tube was capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm,

balloon) (×3). The reaction mixture was stirred at room temperature for 5 min, then at the appropriate temperature for the indicated time. The reaction vessel was then cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1** and 4.01 ppm for **1a**). When indicated, the reactions were performed in triplicates, and the values shown represent the average result from the three experiments.

4.5 General procedure for Pd(II)-catalyzed *ortho*-C–H olefination of phenylacetic acids 1–10

A 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar was charged with the phenylacetic acid starting material (**1–10**) (0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), ligand (0.05 mmol), the olefin coupling partner (1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction tube was capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm, balloon) (×3). The reaction mixture was stirred at room temperature for 5 min, then at 90 °C for 2 h (longer, when noted). The reaction vessel was then cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrate *in vacuo.* The resulting residue was purified by silica gel flash column chromatography using 3:1 hexanes:EtOAc (with 3% HOAc) as the eluent. For a general depiction of this procedure, see Scheme S2.

4.6 Procedure for intermolecular competition experiments between compounds 1 and 2

A 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar was charged with **1** (51.1 mg, 0.25 mmol), **2** (37.6 mg, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), ligand (0.05 mmol), ethyl acrylate (106 μL, 1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction tube was capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm, balloon) (×3). The reaction mixture was stirred at room temperature for 5 min, then at 90 °C for the appropriate time. The reaction vessel was then cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1**, 4.01 ppm for **1a**, 3.67 ppm for **2**, and 3.84 ppm for **2a**). The results are shown in Table S11.

4.7 Procedure for initial rate studies for single-component reactions of 1 and 2

The procedure for reactions run with and without Boc-Val-OH is described on page S-2. An identical protocol was followed to determine the initial rate in the presence of Ac-Ile-OH (8.7 mg, 0.05 mmol), with reactions stopped at 5 min, 7.5 min, 10 min, and 15 min. The reactions were repeated three times, and determination of the initial rate was performed using linear regression. The overall results are shown in Table S12.

4.8 Procedure for intermolecular kinetic isotope experiments between compounds 2 and 12

To a 20 mL scintillation vial were added, **2** (15.0 mg, 0.1 mmol), **12** (15.7 mg, 0.1 mmol), and $CDCl_3$ (0.5 mL). The solution was stirred until homogenous, and a small aliquot was taken for ^{1}H NMR analysis to ensure that the weighed quantities corresponded to a mixture with 50% ± 2% of each component. The solvent was removed *in vacuo*, and the mixture of **2** and **12** was transferred in *t*-AmylOH (1 mL) to a 50 mL Schlenk-type sealed tube (with a

Teflon high pressure valve and side arm) equipped with a magnetic stir bar. $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), $KHCO_3$ (40.0 mg, 0.4 mmol), ligand (0.02 mmol), and ethyl acrylate (43 μL, 0.4 mmol) were then added. The reaction tube was capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm, balloon) (×3). The reaction mixture was stirred at room temperature for 5 min, then at 90 °C for the appropriate time. The reaction vessel was then cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion of **2a**, $X_{2a,}$ was determined by integration of the methyl proton signals, which appear as singlets (approximately 2.32 ppm for **2** and 2.36 ppm for **2a**). The total conversion X_{total} was determined by integration of the benzylic methylene group signals, which also appear as singlets (3.67 ppm for **2**/**12** and 3.84 ppm for **2a**/**12a**). The conversion of **12a**, X_{12a}, could then be determined from the following formula:

$$X_{12a}=2 \cdot X_{total} - X_{2a}$$

The experiments were repeated three times without ligand, three times with Boc-Val-OH, and five times with Ac-Ile-OH. The results are shown in Table S13.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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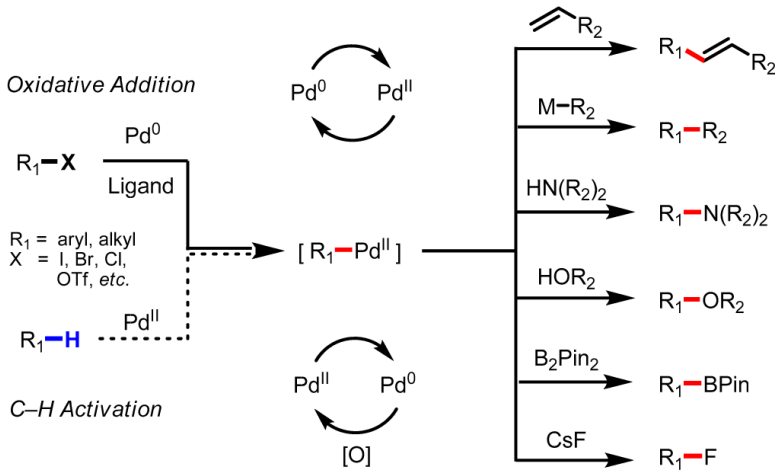
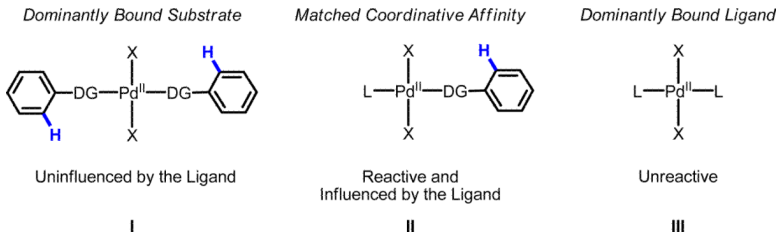
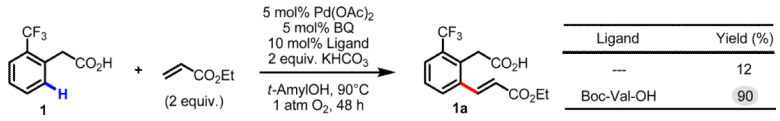


Scheme 1.
The versatile reactivity of [Pd(II)–R] intermediates.

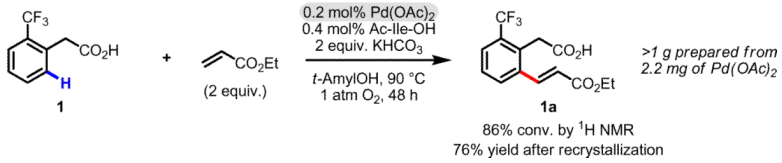


Scheme 2.

Depiction of three scenarios for the pre-transition state coordination structures prior to Pd(II)-mediated C–H cleavage: (**I**) The substrate contains a strong directing group (DG) and is dominantly bound to Pd(II), precluding ligand (L) coordination. The reaction may take place, but the transition state energy for C–H cleavage will be unaffected by the ligand. (**II**) The substrate and ligand possess matched coordinative affinities for Pd(II), allowing one molecule of each to bind. The reaction may take place, and the transition state energy for C–H cleavage will be affected by ligand binding. (**III**) The ligand is a strong σ-donor and outcompetes substrate molecules for coordination to Pd(II). The reaction will not take place.

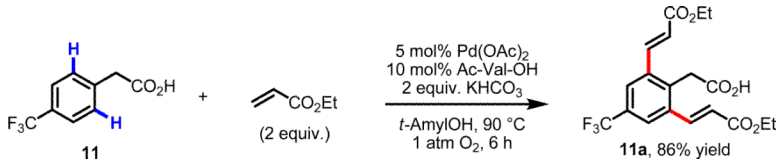


Scheme 3.
Preliminary results for ligand-promoted C–H olefination of **1**.[45]



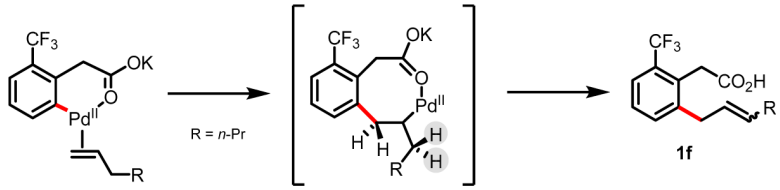
Scheme 4.

Gram-scale synthesis of **1a** using 0.2 mol% $Pd(OAc)_2$ and 1 atm O_2.



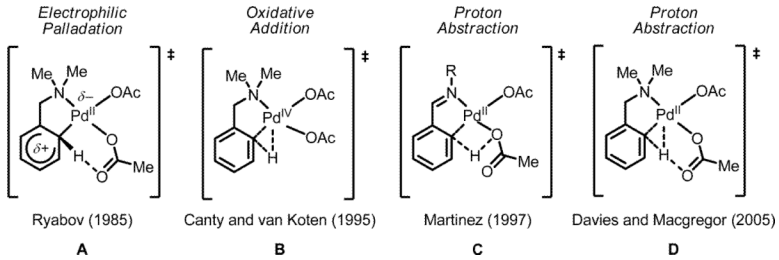
Scheme 5.

A representative example of our previously reported 2,6-diolefination reaction of phenylacetic acids using Ac-Val-OH.[49i]

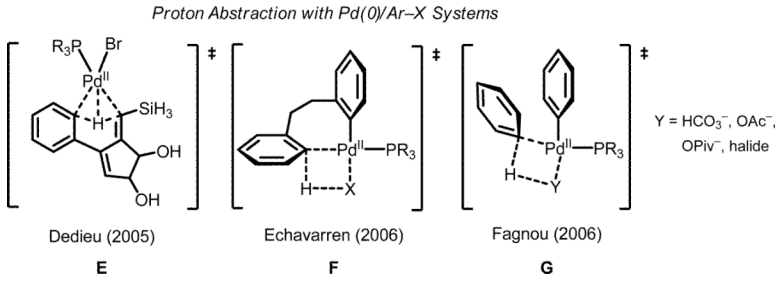


Scheme 6.

Mechanistic hypothesis to explain the preferential formation of **1f**, rather than the thermodynamically favored conjugated product.

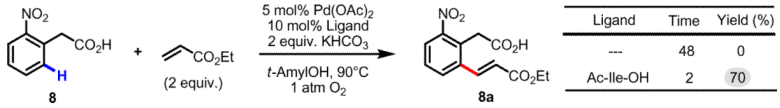


Scheme 7.
Mechanistic models for the C–H cleavage transition state with Pd(II).



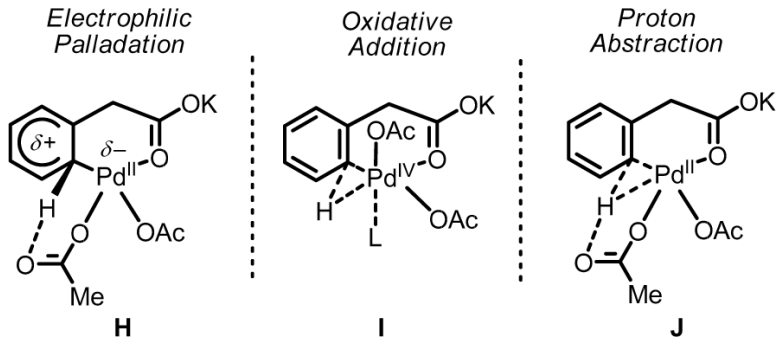
Scheme 8.

Conceptually relevant proton abstraction mechanistic proposals for Pd(0)/ArX catalytic systems.



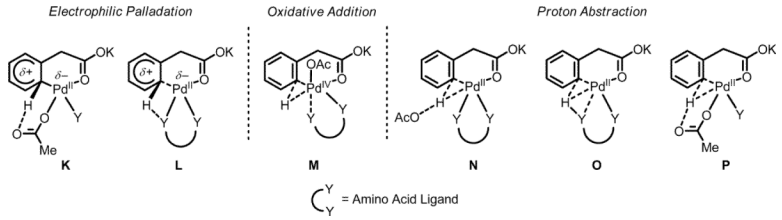
Scheme 9.

Qualitative evidence for a change in the mechanism of C–H cleavage: C–H activation of highly electron-deficient arenes in the presence of Ac-Ile-OH.



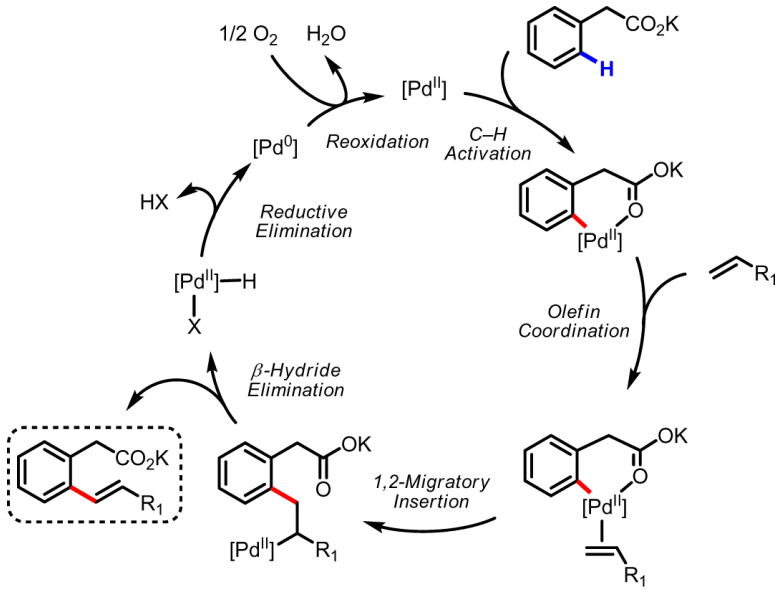
Scheme 10.

Possible mechanisms for C–H cleavage without ligands: electrophilic palladation (**H**), oxidative addition (**I**), and proton abstraction (**J**).

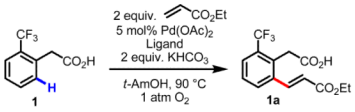


Scheme 11.

Possible mechanisms for C–H cleavage: (**K** and **L**) electrophilic palladation, (**M**) oxidative addition, (**N–P**) and proton abstraction.



Scheme 12.
Proposed catalytic cycle.



Entry	Ligand 1	Ligand 2	Rate (M/min)
1	---	---	1.3×10^{-4}
2	---	BQ	4.8×10^{-5}
3	Boc-Val-OH	---	4.7×10^{-3}
4	Boc-Val-OH	BQ	3.4×10^{-4}

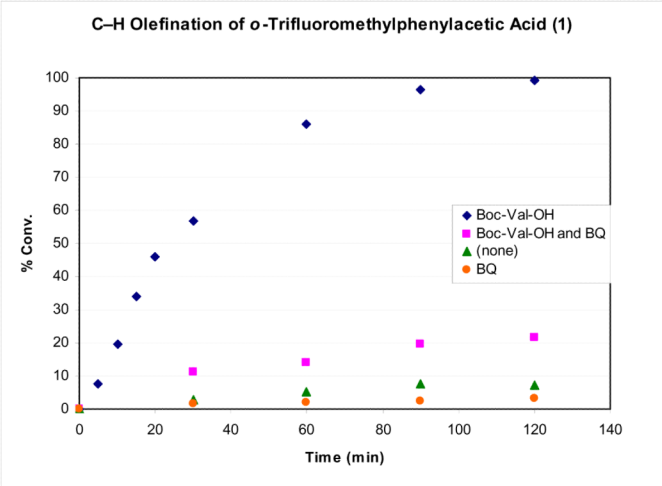
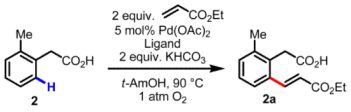


Figure 1.

Initial rate studies of C–H olefination of *o*-trifluoromethylphenylacetic acid (**1**). BQ (5 mol %) and Boc-Val-OH (10 mol%). Each data point represents the average of three trials, with the exception of the Boc-Val-OH trials from 60 min to 120 min, which represent single trials. See Supporting Information for experimental details.



Entry	Ligand 1	Ligand 2	Rate (M/min)
1	---	---	3.5×10^{-4}
2	---	BQ	1.0×10^{-4}
3	Boc-Val-OH	---	5.2×10^{-3}
4	Boc-Val-OH	BQ	4.2×10^{-4}

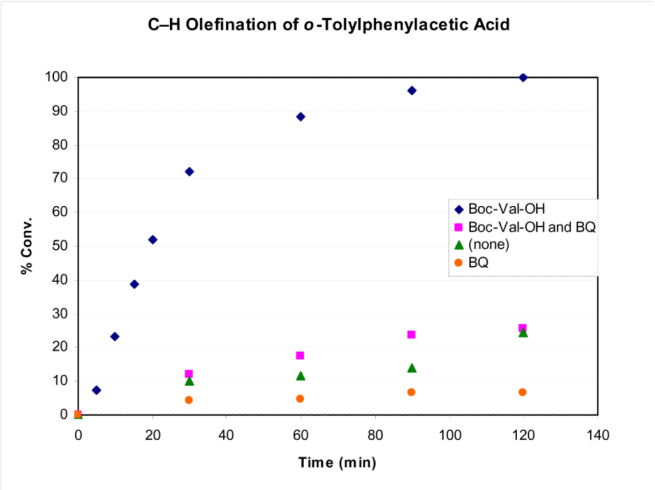
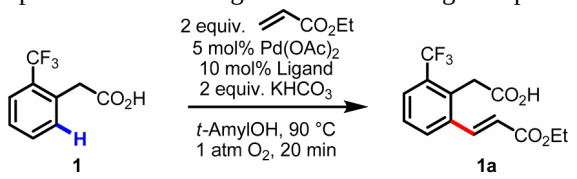


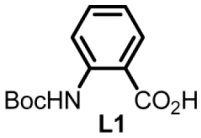
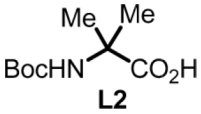
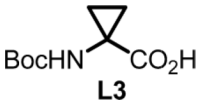
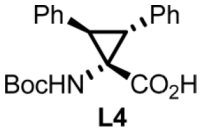
Figure 2.

Kinetic studies of C–H olefination of *o*-tolylacetic acid (**2**). BQ (5 mol%) and Boc-Val-OH (10 mol%). Each data point represents the average of three trials, with the exception of the Boc-Val-OH trials from 60 min to 120 min, which represent single trials. See Supporting Information for experimental details.

Table 1

Optimization of the ligand backbone using Boc-protected amino acids.



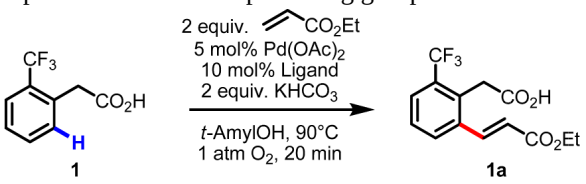
Entry	Ligand	% Conv.
1	---	<5
2	BQ	<5
3	Boc-Val-OH	46[b]
4	Boc-Ile-OH	37
5	Boc-Leu-OH	37
6	Boc-*t*-Leu-OH	38
7	Boc-Nva-OH	30
8	Boc-Ala-OH	28
9	Boc-Gly-OH	17
10	Boc-Phe-OH	33
11	Boc-Ser-OH	8
12	Boc-β-Ala-OH	8
13	 **L1**	6
14	 **L2**	21
15	 **L3**	5
16	 **L4**	16
17	PivOH	<5
18	*p*-TsOH·H_2O	0

[a]The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture.

[b]Average of three trials.

Table 2

Optimization of the *N*-protecting group on valine.



Entry	Ligand	% Conv.
1	H-Val-OH	0
2	Boc-Val-OH	46[b]
3	Ac-Val-OH	57
4	Ada-Val-OH[c]	4
5	Piv-Val-OH	2
6	Formyl-Val-OH	31
7	Fmoc-Val-OH	19
8	MeO_2C-Val-OH	21
9	EtO_2C-Val-OH	26
10	*i*-BuO_2-C-Val-OH	27
11	Cbz-Val-OH	18
12	Bz-Val-OH	3
13	Men-Val-OH[d]	39

[a]The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture.

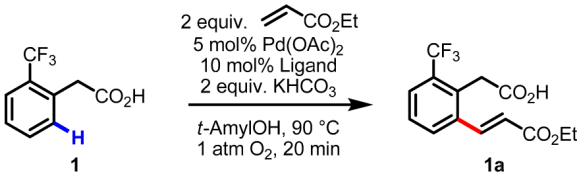
[b]Average of three trials.

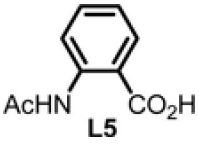
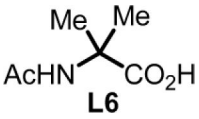
[c]Ada = Adamantyl(OC).

[d]Men = (−)-Menthyl(O_2C).

Table 3

Reexamination of alternative ligand backbones using Ac as the protecting group.[a]



Entry	Ligand	% Conv.
1	Ac-Val-OH	57
2	Ac-Leu-OH	55
3	Ac-Ala-OH	71
4	Ac-Gly-OH	51
5	Ac-Ile-OH	72[b][>99][c]
6	Ac-Ile-OH	93[d]
7	Ac-Phe-OH	60
8	 L5	5
9	 L6	31

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture.

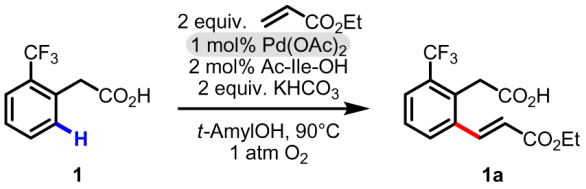
[b] Average of three trials.

[c] The bracketed value represents the conversion after 2 h.

[d] 110 °C.

Table 4

C–H olefination of **1** using 1 mol% $Pd(OAc)_2$ and 1 atm O_2.[a]



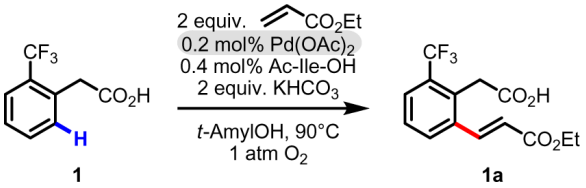
1 **1a**

Entry	Time (h)	% Conv.
1	0	0
2	1	34
3	2	67
4	3	93
5	4	98 (94)

[a]The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yield is given in parentheses.

Table 5

C–H olefination of **1** using 0.2 mol% $Pd(OAc)_2$ and 1 atm O_2.[a]



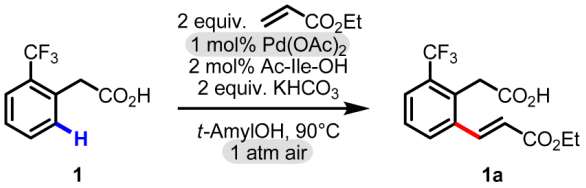
1 **1a**

Entry	Time (h)	% Conv.
1	0	0
2	4	15
3	20	52
4	48	91 (83)

[a]The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture.

Table 6

C–H olefination of **1** using 1 mol% $Pd(OAc)_2$ and 1 atm air.[a]



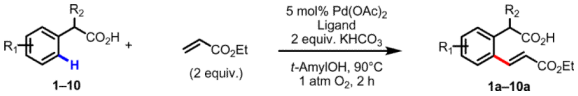
1 **1a**

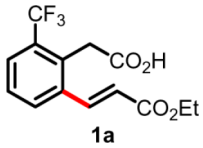
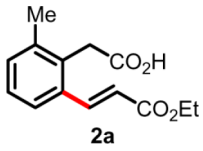
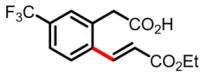
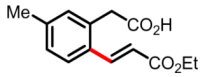
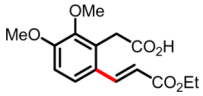
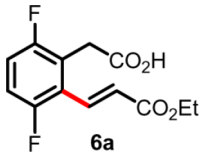
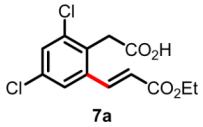
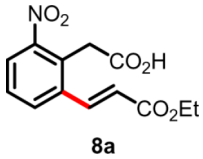
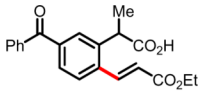
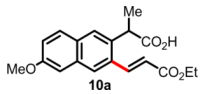
Entry	Time (h)	% Conv.
1	0	0
2	1	2
3	2	6
4	12	29
5	24	68
6	48	87 (78)

[a]The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yield is given in parentheses.

Table 7

Accelerated Pd(II)-catalyzed C–H olefination of phenylacetic acid substrates **1–10**.[a,b]



Product	Ligand	% Conv.
 **1a**	---	7[c]
	BQ	3[c]
	Ac-Ile-OH	>99 (96)
 **2a**	---	25[c]
	BQ	7[c]
	Ac-Ile-OH	98 (97)
 **3a**	---	2
	BQ	1
	Ac-Ile-OH	>99 (98)
 **4a**	---	64
	BQ	9
	Ac-Ile-OH	88 (83)[d]
 **5a**	---	93 (92)
	BQ	12
	Ac-Ile-OH	>99 (95)
 **6a**	---	6
	BQ	2
	Ac-Ile-OH	>99 (99)
 **7a**	---	8[e]
	BQ	3[e]
	Ac-Ile-OH	>99 (99)[e]
 **8a**	---	0
	BQ	0
	Ac-Ile-OH	72 (70)[f]
 **9a**	---	10
	BQ	5
	Ac-Ile-OH	>99 (98)
 **10a**	---	44[g]
	BQ	23
	Ac-Ile-OH	>99 (94)

[a] 5 mol% BQ (when used), 10 mol% Ac-Ile-OH (when used).

[b] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yield is given in parentheses.

[c] Average of three trials.

[d] An additional 11% of the di-ortho-olefinated product was observed by ^{1}H NMR.

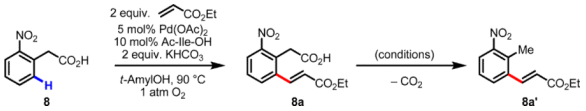
[e] 6 h.

[f] An additional 6% of the decarboxylated product was formed.

[g] An additional 4% of a positional isomer was formed.

Table 8

Accelerated Pd(II)-catalyzed C–H olefination of **8**.[a]

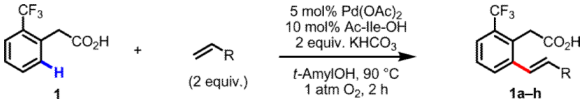


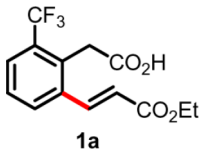
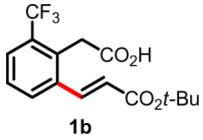
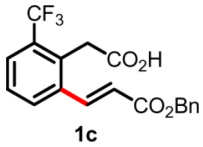
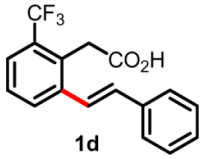
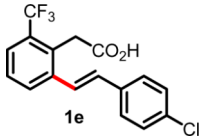
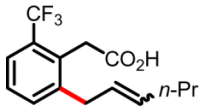
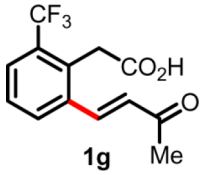
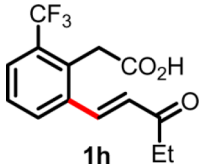
Entry	Time (h)	%8	%8a	% 8a'
1	0	100	0	0
2	2	19	72 (70)	6 (6)
3	6	15	43	29
4	12	6	39	36
5	24	5	15	59
6	48	4	0	75 (71)

[a]The % composition was determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. Isolated yield is given in parentheses. Less than 5% of 2-nitrotoluene (from direct decarboxylation of **8**) was observed by ^{1}H NMR in entries 2–6.

Table 9

Accelerated Pd(II)-catalyzed C–H olefination of **1** with various olefin coupling partners.[a,b]



Product	Additive/Ligand	% Conv.
 **1a**	---	7[c]
	BQ	3[c]
	Ac-Ile-OH	>99 (96)
 **1b**	---	6
	BQ	2
	Ac-Ile-OH	>99 (99)
 **1c**	---	8
	BQ	3
	Ac-Ile-OH	>99 (90)
 **1d**	---	7
	BQ	2
	Ac-Ile-OH	>99 (99)
 **1e**	---	13[d]
	BQ	4[d]
	Ac-Ile-OH	70 (65)[d]
 **1f** *E:Z* = 4:1	---	0[d]
	BQ	0[d]
	Ac-Ile-OH	82 (62)[d]
 **1g**	---	0
	BQ	0
	Ac-Ile-OH	>99 (94)
 **1h**	---	0[d]
	BQ	0[d]
	Ac-Ile-OH	>99 (97>[d]

[a] 5 mol% BQ (when used), 10 mol% Ac-Ile-OH (when used).

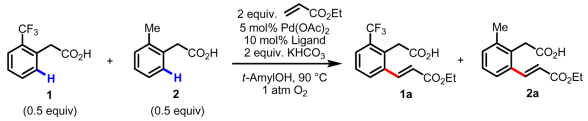
[b] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yield is given in parentheses.

[c] Average of three trials.

[d] 10 h.

Table 10

One-pot intermolecular competition experiment data.[a]

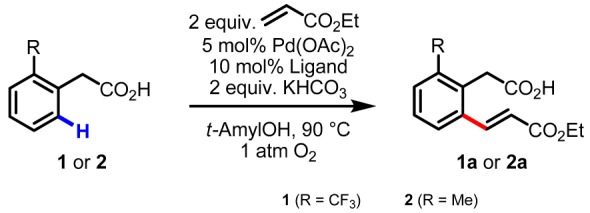


Entry	Ligand	Time (min)	% Conv. 1a	% Conv. 2a	k_1/k_2
1	---	120	3	14	0.22
2	Boc-Val-OH	10	18	30	0.58
3	Ac-Ile-OH	10	40	21	1.87

[a]The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. See Supporting Information for experimental details.

Table 11

Comparison of initial rates for single-component reactions of **1** and **2** under the different conditions shown.[a]

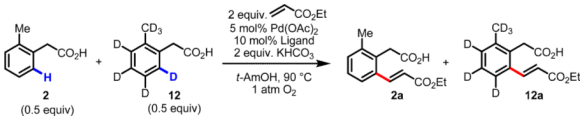


Entry[a]	Ligand	k_1 ([M]/min)	k_2 ([M]/min)	k_1 / k_2
1	---	1.3×10^{-4}	3.5×10^{-4}	0.37
2	Boc-Val-OH	4.7×10^{-3}	5.2×10^{-3}	0.90
3	Ac-Ile-OH	7.6×10^{-3}	5.5×10^{-3}	1.38

[a] See Supporting Information for experimental details.

Table 12

Intermolecular KIE experiments.[a]



Entry	Ligand	k_H / k_D
1	---	6.1
2	Boc-Val-OH	5.5
3	Ac-Ile-OH	1.7

[a] See Supporting Information for experimental details.