JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

ARTICLE

pubs.acs.org/JACS

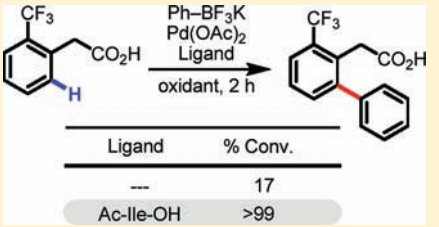
# Ligand-Accelerated Cross-Coupling of C(sp$^2$)−H Bonds with Arylboron Reagents

Keary M. Engle, Peter S. Thuy-Boun, Michael Dang, and Jin-Quan Yu*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information

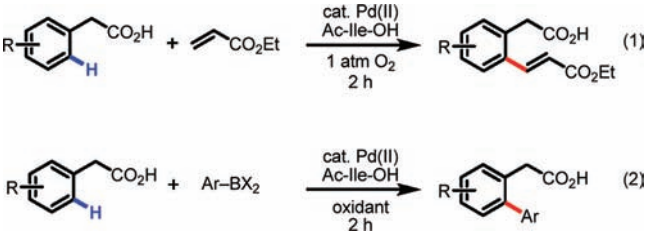
**ABSTRACT:** A ligand-accelerated Pd(II)-catalyzed C(sp$^2$)−H/arylboron cross-coupling reaction of phenylacetic acid substrates is reported. Using Ac-Ile-OH as the ligand and $Ag_2CO_3$ as the oxidant, a fast, high-yielding, operationally simple, and functional group-tolerant protocol has been developed for the cross-coupling of phenylacetic acid substrates with aryltrifluoroborates. This ligand scaffold has also been shown to improve catalysis using 1 atm $O_2$ as the sole reoxidant, which sheds light on the path forward in developing optimized ligands for aerobic C−H/arylboron cross-coupling.




## 1. INTRODUCTION

Since the 1970s, the discovery and development of Pd(0)-catalyzed reactions of aryl and alkyl halides have revolutionized how organic chemists envision forming new carbon−carbon (C−C) and carbon−heteroatom (C−Y) bonds.[1,2] The versatility and practicality of these transformations stem from specially tailored phosphine and *N*-heterocyclic carbene (NHC) ligands, which can accelerate both oxidative addition and reductive elimination, thereby enhancing the overall catalytic efficiency and broadening substrate scope.[2] In contrast, fewer ligands are compatible with analogous Pd(II)-catalyzed carbon−hydrogen (C−H) bond functionalization reactions,[3−10] which has hampered progress in this area. Recently, our group made strides on this front with the discovery that mono-*N*-protected amino acid ligands[4] could accelerate Pd(II)-catalyzed C−H olefination reactions along a Pd(II)/Pd(0) catalytic cycle (eq 1).[5] On the basis of preliminary mechanistic data,[5c] we believe that the observed acceleration derives from an increase in the rate of C−H cleavage. This calls into question whether mono-*N*-protected amino acids would be compatible with Pd(II)-catalyzed cross-coupling reactions of C−H bonds with organometallic reagents (eq 2),[7,11,12] which have completely different elementary steps following C−H cleavage (transmetalation and reductive elimination). Identification of appropriate ligand scaffolds capable of accelerating C−H/R−M cross-coupling reactions is fundamentally important for improving the scope and practicality of this new class of reactions that are still in their infancy.

In early 2006, our group reported the first Pd(II)-catalyzed cross-coupling reaction of C(sp$^2$)−H bonds and organometallic reagents.[12] Since that initial report, our group[13,14] and others[15,16] have gone on to expand this mode of reactivity to an increasingly versatile collection of substrates and coupling partners.[17−21] Generally speaking, however, the catalytic efficiency across these examples remains unsatisfactory,[16] pointing to a need for ligands to enhance reactivity and turnover. Because catalytic C−H/R−M cross-coupling possesses several fundamentally distinct elementary steps (C−H cleavage, transmetalation, reductive elimination, and reoxidation), it remains a significant challenge to identify ligands that are compatible with all of these steps. Nevertheless, encouraged by our work in ligand-accelerated C−H olefination, we sought to establish a ligand-accelerated Pd(II)-catalyzed cross-coupling reaction of organoboron reagents with phenylacetic acids, a major class of synthetically versatile substrates. This particular reaction intrigued us because original methodology from our lab[13] suffered from several limitations, including long reaction times (48 h), incompatibility with oxidants that are operationally convenient to use such as Ag(I) salts, the need for high-pressure $O_2$ (20 atm), and limited substrate scope.[22]




Herein, we disclose the results of our studies, which represent to the best of our knowledge the first example of ligand-accelerated Pd(II)-catalyzed C(sp$^2$)−H/arylboron cross-coupling. By using amino acid ligands in conjunction with $Ag_2CO_3$ as a stoichiometric reoxidant, we have developed a new protocol for the functionalization of phenylacetic acid substrates that offers shorter reaction times, improved substrate scope, and higher yields compared to our previous method.[13] By using ligand acceleration under aerobic conditions, we also demonstrate that good yields can be obtained under relatively low pressures of $O_2$. Importantly, this work establishes that mono-*N*-protected amino acids are promising ligand scaffolds for further optimization owing to their compatibility with the transmetalation, reductive elimination, and reoxidation steps in C−H/R−M cross-coupling.

**Received:** April 29, 2011
**Published:** September 12, 2011





dx.doi.org/10.1021/ja203978r | *J. Am. Chem. Soc.* 2011, 133, 18183–18193

## 2. RESULTS AND DISCUSSION

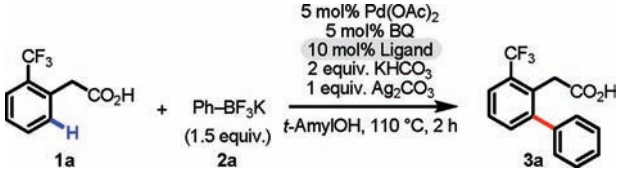
We began by revisiting our previously reported conditions.[13] One of the drawbacks that hampered the practical utility of that protocol was the need for high-pressure $O_2$ (20 atm), which signaled to us that reoxidation of Pd(0) to catalytically active Pd(II) was problematic (see below for a depiction of the speculative catalytic cycle). Thus, for the purposes of achieving efficient turnover under mild conditions, we first turned our attention to other reoxidants, with the long-term goal of developing conditions in which 1 atm air could be used as the sole reoxidant. After extensive screening, it was found that $Ag_2CO_3$ functioned smoothly for these purposes, giving high conversions in this ligand-accelerated C−H/arylboron cross-coupling reaction.[23] It should be noted that, although using $Ag_2CO_3$ is unsuitable for large-scale industrial production, we opted to use it here in the interest of developing a highly convenient protocol for use in academic and medicinal chemistry laboratories.

For our optimization studies, we selected 2-trifluoromethylphenylacetic acid (**1a**) as our screening substrate because it was known to be relatively unreactive in the absence of ligands (entry 1, Table 1).[22] Using $Ag_2CO_3$ as the oxidant, we examined the effect of amino acid ligands. We first probed a range of commercially available mono-*N*-Boc-protected amino acids (entries 2−8), and among those examined, we found those with hydrophobic residues on the backbone (e.g., Ala, Val, Leu, Ile, and Phe) to be highly effective. We then optimized the *N*-protecting group (entries 8−14), which led to identification of Ac-Ile-OH as an optimal ligand. Substitution of the nitrogen atom with an electron-withdrawing group was necessary for reactivity, as use of both Me-Ile-OH and H-Ile-OH shut down the reaction (entries 9 and 10). This observation suggests that an electron-deficient Pd(II) center is necessary for substrate coordination and subsequent C−H cleavage. We observed that, with 5 mol % $Pd(OAc)_2$, Ac-Ile-OH loadings of 2.5, 5, 10, and 15 mol % gave nearly identical initial rates (as approximated by measuring the conversion at 20 min) and overall conversion after 2 h. Given that Ac-Ile-OH is relatively inexpensive, 10 mol % ligand was used throughout this work for convenience in weighing.

In our previous studies using $O_2$ as the oxidant,[13,14b] the presence of 1,4-benzoquinone (BQ) was found to be crucial for both the C−C reductive elimination[12a,24,25] and reoxidation steps. In contrast, in this protocol using $Ag_2CO_3$, BQ was not required. 5 mol% BQ was used merely to improve reproducibility. Here, the diminished importance of BQ is likely related to the ability of $Ag_2CO_3$ to promote both C−C reductive elimination through one-electron oxidation[26] and reoxidation of Pd(0) by an inner-sphere mechanism, whereby electron transfer proceeds through a putative Pd−Ag interaction.[25]

Acceptable conversions were obtained with representative substrates during our initial screen with 1 equiv of $Ag_2CO_3$

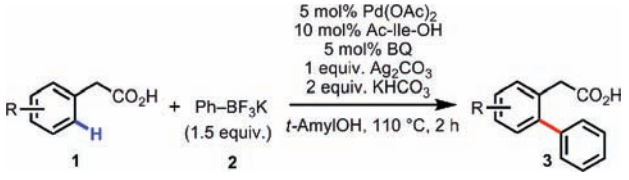
**Table 1. Ligand Optimization**[a]

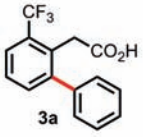
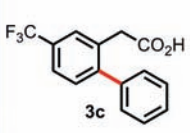
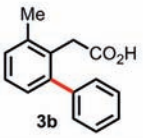
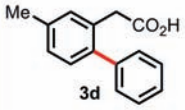



| entry | ligand[b] | % conv. | entry | ligand[b] | % conv. |
|---|---|---|---|---|---|
| 1 | – | 13 | 9 | H-IIe-OH | 0 |
| 2 | Boc-Gly-OH | 61 | 10 | Me-IIe-OH | 0 |
| 3 | Boc-Ala-OH | 77 | 11 | formyl-IIe-OH | 62 |
| 4 | Boc-Phe-OH | 83 | 12 | Ac-IIe-OH | 89 |
| 5 | Boc-Val-OH | 82 | 13 | Fmoc-IIe-OH | 79 |
| 6 | Boc-Leu-OH | 81 | 14 | Cbz-IIe-OH | 76 |
| 7 | Boc-*t*-Leu-OH | 79 | 15 | Ac-Val-OH | 79 |
| 8 | Boc-IIe-OH | 81 | 16 | Ac-Leu-OH | 87 |

[a] The conversion was determined by $^1$H NMR analysis of the crude reaction mixture. [b] Boc = *tert*-butyloxycarbonyl, Cbz = carbobenzyloxy, Fmoc = fluorenylmethyloxycarbonyl, Ac = acetyl.

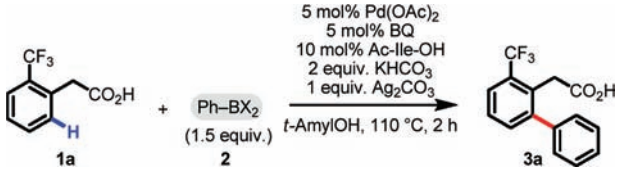
**Table 2. Initial Results with Representative Phenylacetic Acids**[a]

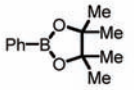
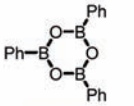
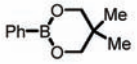
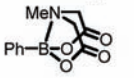



| Product | Ligand | % Conv. | Product | Ligand | % Conv. |
|---|---|---|---|---|---|
|  3a | --- | 13 |  3c | --- | 12 |
| | Ac-Ile-OH | 89 | | Ac-Ile-OH | 77 |
|  3b | --- | 16 |  3d | --- | 33 |
| | Ac-Ile-OH | 69 | | Ac-Ile-OH | 62 |

[a] The conversion was determined by $^1$H NMR of the crude reaction mixture

**Table 3. Examination of Arylboron Coupling Partners**[a]




| Entry | Ph–$BX_2$ | % Conv. | Entry | Ph–$BX_2$ | % Conv. |
|---|---|---|---|---|---|
| 1 | Ph–$BF_3K$ | 89 [>99][b] | 4 | Ph–$B(OH)_2$ | 6 |
| 2 |  | 85 [>99][b] | 5 |  | 9 |
| 3 |  | 58 | 6 |  | 1 |

[a] The conversion was determined by $^1$H NMR of the crude reaction mixture. [b] The bracketed value denotes the conversion with $PhBX_2$ (3.0 equiv) and $Ag_2CO_3$ (2.0 equiv) under otherwise identical reaction conditions.

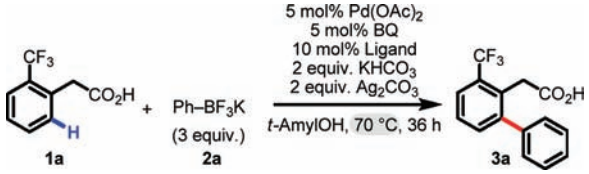
and 1.5 equiv of $PhBF_3K$ (Table 2).[27] However, we found that phenylacetic acid starting materials were difficult to separate from the arylated products on millimolar scale. Thus, in order to simplify purification and improve operational simplicity, we sought to refine the conditions to drive the reaction to completion. We further examined alternative arylboron coupling partners (Table 3) and found that both aryltrifluoroborates and the pinacol esters of arylboronic acids (ArBPin) provided nearly equivalent product yields. We hypothesized that under our conditions undesired homocoupling was consuming both oxidant and the arylboron reagent. We thus increased the amount of $Ag_2CO_3$ to 2 equiv and arylboron reagent to 3 equiv and observed that quantitative conversion of **3a** could be achieved (entries 1 and 2).[28] Under these conditions, we found that the reaction worked equally well under $N_2$, $O_2$, or air.

We also found that the reaction could also be performed at a lower temperature, albeit with extended reaction time (Table 4). For example at 70 °C, the reaction to form **3a** was found to proceed to >99% conversion using Ac-Ile-OH as the ligand and 16% in the absence of ligand after 36 h.

We next examined the effect of the ligand on the rate profile with substrate **1a**. Two independent reactions were set up in the presence and absence of Ac-Ile-OH and allowed to run for 2 h. During this time period, small aliquots were removed at regular intervals and analyzed by $^1$H NMR to determine the conversion. This process was repeated three times, and the data were averaged. The results, plotted in Figure 1, show a roughly 8-fold increase in the initial rate using Ac-Ile-OH.[29] We observed a slight deviation from strict linearity in the early part of the reaction profile, presumably due to slow release of the aryltrifluoroborate to the active boronic acid or boronate species via hydrolysis during the course of the reaction.[27d] This effect became more pronounced at lower temperature. Nevertheless, a clear rate increase in the presence of Ac-Ile-OH is evident from the data.

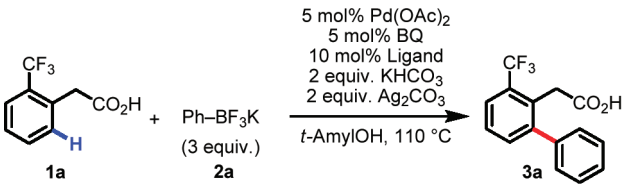
Next, we probed phenylacetic acid substrate scope (Table 5). To our delight, we found that our new protocol was highly tolerant

**Table 4. Conversion of 1a to 3a at 70 °C**[a]




| entry | ligand | % conv. |
|---|---|---|
| 1 | – | 16 |
| 2 | Ac-Ile-OH | >99 |

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




| Entry | Ligand | Initial Rate (M/min) |
|---|---|---|
| 1 | --- | $4.5 \times 10^{-4}$ |
| 2 | Ac-Ile-OH | $3.7 \times 10^{-3}$ |

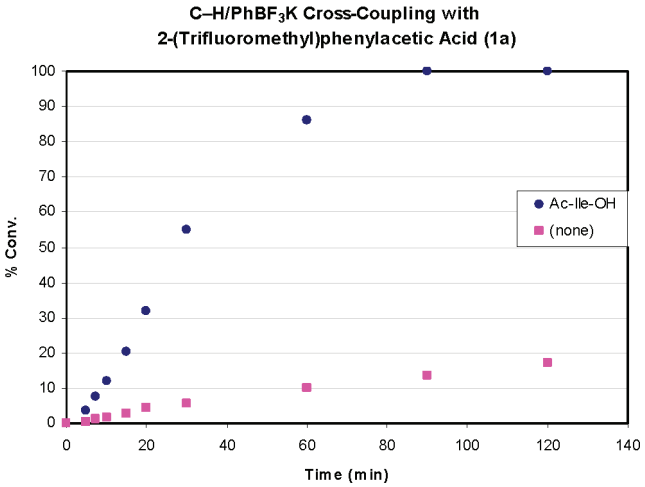
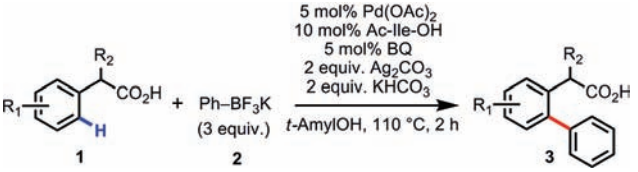


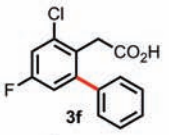
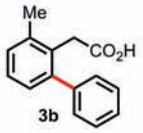
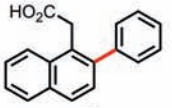
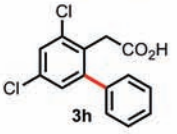
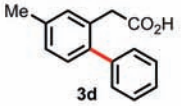
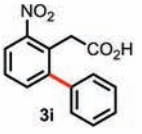
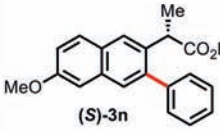
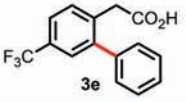
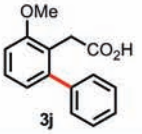
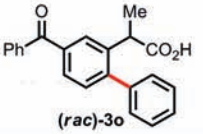

**Figure 1.** Rate profile for the reaction of **1a** with **2a** in the presence and absence of Ac-Ile-OH. Each data point represents the average of three independent trials. The initial rates are calculated for the data points in the 5−20-min time interval using linear regression. Beyond 2 h, no additional product conversion was observed in the trials without ligand. See Supporting Information (SI) for detailed experimental procedures.

of a variety of different substituents including alkyl groups (**3b** and **3d**), alkoxy groups (**3j**, **3k**, and (*S*)-**3n**), and halides (**3f**−**3h**). Notably strongly electron-withdrawing groups, such trifluoromethyl (**3a**, **3c**, and **3e**), nitro (**3i**), and ketone ((*rac*)-**3o**) groups also gave high yields, which qualitatively suggests that simple electrophilic palladation is not the operative mechanism for C−H cleavage. Our protocol was found to tolerate monosubstitution at the $\alpha$-position ((*rac*)-**3m**), (*S*)-**3n**, and (*rac*)-**3o**), providing a


dx.doi.org/10.1021/ja203978r |J. Am. Chem. Soc. 2011, 133, 18183–18193

**Table 5. Phenylacetic Acid Substrate Scope**[a]




| Product | Ligand | % Conv. | Product | Ligand | % Conv. | Product | Ligand | % Conv. |
|---|---|---|---|---|---|---|---|---|
|  **3a** | --- | 17 |  **3f** | --- | 5 |  **3k** | --- | 72 |
| | Ac-Ile-OH | >99 (98) | | Ac-Ile-OH | >99 (98) | | Ac-Ile-OH | 96 (85) |
|  **3b** | --- | 44 |  **3g** | --- | 20 |  **3l** | --- | 22 |
| | Ac-Ile-OH | >99 (97) | | Ac-Ile-OH | 97 (96) | | Ac-Ile-OH | >99 (80) |
|  **3c** | --- | 6 |  **3h** | --- | 10 |  **(*rac*)-3m** | --- | 24[d] |
| | Ac-Ile-OH | >99 (97) | | Ac-Ile-OH | >99 (98) | | Ac-Ile-OH | 78 (73)[d] |
|  **3d** | --- | 63 |  **3i** | --- | 2 |  **(*S*)-3n** | --- | 41[e] |
| | Ac-Ile-OH | >99 (95) | | Ac-Ile-OH | 87 (69) | | Ac-Ile-OH | >99 (97)[e,f] |
|  **3e** | --- | 6 |  **3j** | --- | 38 |  **(*rac*)-3o** | --- | 16[d] |
| | Ac-Ile-OH | 57 (52)[b,c] | | Ac-Ile-OH | >99 (94) | | Ac-Ile-OH | 89 (83)[d] |

[a] The conversion was determined by $^1$H NMR of the crude reaction mixture. Isolated yield is given in parentheses. [b] 1.1 equiv of $PhBF_3K$ was used. [c] 28% of the diarylated product (**3e′**) was also isolated. [d] Racemic starting material was used. [e] Enantiopure starting material was used. [f] The product was isolated in >99:1 er, as determined by chiral HPLC (see SI).

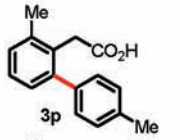
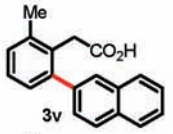
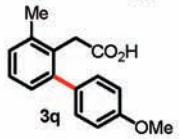
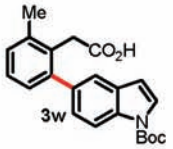
means for the diversification of nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen ((*S*)-**1n**) and ketoprofen ((*rac*)-**1o**), which gave products (*S*)-**3n** and (*rac*)-**3o**, respectively. Importantly, we found that the chiral center in (*S*)-**3n** did not epimerize under the reaction conditions when an enantiopure starting material was used. With chiral $\alpha$-substituted starting material (*rac*)-**3m**, racemic and enantiopure ligands were found to give comparable yields (see SI). $\alpha,\alpha$,-Disubstituted substrates were found to give substantially lower yields under these conditions.[30] In the absence of a sterically bulky group at the *ortho*-, *meta*-, or $\alpha$-positions, the reaction gave primarily the diarylated product, but acceptable yields of the monoarylated product could be obtained by using 1.1 equiv of the coupling partner (e.g., **3e**). For each substrate, we ran a control experiment in the absence of Ac-Ile-OH. Generally, the presence of Ac-Ile-OH drastically improved the yield. In the absence of ligand, only two electron-rich substrates, **3d** and **3k**, gave over 60% conversion. Substrates bearing electron-withdrawing substituents (e.g., **3a**, **3c**, **3e**, **3f**−**3i**) were highly unreactive in the absence of Ac-Ile-OH.

Subsequently, we investigated the compatibility of our protocol with various substituted arylboron coupling partners (Table 6). We were pleased to find that several differently substituted aryltrifluoroborates were well tolerated, giving excellent conversions (**3p**−**3v**). Importantly, we were also able to couple a heterocyclic compound under our new conditions (**3w**). Arylboron reagents bearing substituents at the *ortho*-position were found to be unreactive, presumably due to steric encumbrance.

We then shifted our focus to establishing a ligand-accelerated protocol in which $O_2$ was used as the terminal reoxidant (Table 7).[31] We again examined amino acid ligands, first turning our attention to commercially available mono-*N*-Boc-protected amino acids (entries 2−10). Of those tested, Boc-Val-OH (entry 10) was found to be optimal. We then sought to tune the *N*-protecting group by modulating the steric and electronic properties of the chelating nitrogen atom (entries 11−19). However, other amide (entries 13−15) and carbamate (entries 16−19) protecting groups, were found to offer no further improvements. The optimal ligand from above, Ac-Ile-OH, gave reproducibly lower conversion than Boc-Val-OH (entry 20) For the remainder of the aerobic studies described herein, Boc-Val-OH was used as the ligand.

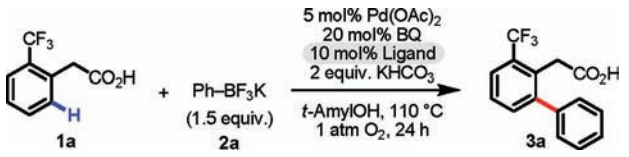
To probe the efficacy of this reaction under different pressures, reactions were conducted at 1 atm, 5 atm, and 20 atm $O_2$ and

**Table 6. Aryltrifluoroborate Scope**[a,b]

| Product | Ligand | % Conv. | Product | Ligand | % Conv. | Product | Ligand | % Conv. |
|---|---|---|---|---|---|---|---|---|
|  3p | --- | 19 |  3s | --- | 46 |  3v | --- | 18 |
| | Ac-Ile-OH | >99 (99) | | Ac-Ile-OH | >99 (87) | | Ac-Ile-OH | >99 (87) |
|  3q | --- | 23 |  3t | --- | 28 |  3w | --- | 6[c] |
| | Ac-Ile-OH | >99 (92) | | Ac-Ile-OH | >99 (94) | | Ac-Ile-OH | 44 (37)[c] |
|  3r | --- | 12 |  3u | --- | 19 | | | |
| | Ac-Ile-OH | >99 (95) | | Ac-Ile-OH | >99 (98) | | | |

[a] The conversion was determined by $^1$H NMR of the crude reaction mixture. Isolated yield is given in parentheses. [b] The reaction conditions were identical to those used in Table 5. [c] The corresponding ArBPin (3 equiv) coupling partner was used.

**Table 7. Ligand Optimization under 1 atm $O_2$**[a]

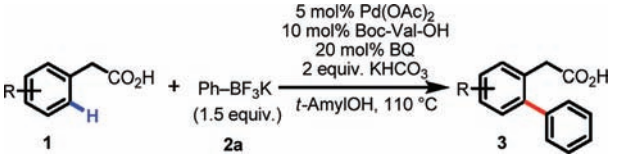


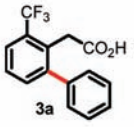
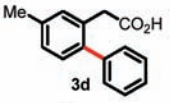

| entry | ligand[b] | % conv. | entry | ligand[b] | % conv. |
|---|---|---|---|---|---|
| 1 | – | 9 | 11 | H-Val-OH | 6 |
| 2 | Boc-Ala-OH | 39 | 12 | formyl-Val-OH | 52 |
| 3 | Boc-Phe-OH | 48 | 13 | Ac-Val-OH | 52 |
| 4 | Boc-Ser-OH | 26 | 14 | Piv-Val-OH | 9 |
| 5 | Boc-Thr(*t*-Bu)-OH | 40 | 15 | Ada-Val-OH | 24 |
| 6 | Boc-Aib-OH | 44 | 16 | Me($O_2$C)-Val-OH | 50 |
| 7 | Boc-Leu-OH | 57 | 17 | Et($O_2$C)-Val-OH | 46 |
| 8 | Boc-*t*-Leu-OH | 57 | 18 | Cbz-Val-OH | 52 |
| 9 | Boc-IIe-OH | 49 | 19 | *i*-Bu($O_2$C)-Val-OH | 49 |
| 10 | Boc-Vla-OH | 65 | 20 | Ac-IIe-OH | 56 |

[a] The conversion was determined by $^1$H NMR analysis of the crude reaction mixture. [b] Aib = $\alpha$-aminoisobutyric acid, Ada =1-adamantyl-(CO), Piv = pivaloyl.

20 atm air, and three representative substrates were examined (Table 8).[32] We found that raising the $O_2$ pressure from 1 to 5 atm improved the conversions. However, further increasing the $O_2$ pressure from 5 to 20 atm had a comparatively modest effect. BQ was required for catalytic turnover. Using 5 mol % BQ gave the fastest initial rates; however, 20 mol % BQ was optimal for overall yield (see SI). Given that our old protocol required 20 atm $O_2$/48 h to achieve moderate turnover,[13,22] these data serve as compelling evidence that further ligand-optimization could lead to practical C–H/R–M cross-coupling reactions under ambient air. Moreover, the fact that both 5 and 20 atm $O_2$ gave similar conversions after 8 h shows that, above 5 atm $O_2$, pressure may no longer be a critical variable for enabling turnover in the presence of Boc-Val-OH. For each data point in

**Table 8. Results under Different Conditions Using $O_2$ as the Terminal Oxidant**[a]




| | | % Conv. | | | |
|---|---|---|---|---|---|
| Product | Ligand | 1 atm $O_2$ (24 h) | 5 atm $O_2$ (8 h) | 20 atm $O_2$ (8 h) | 20 atm air (8 h) |
|  3a | --- | 12 | 32 | 26 | 30 |
| | Boc-Val-OH | 65 | 96 (91) | 97 (93) | 77 |
|  3d | --- | 21 | 31 | 49 | 35 |
| | Boc-Val-OH | 53 | 75 | 72 (68) | 73 |
|  3h | --- | 4 | 8 | 13 | 8 |
| | Boc-Val-OH | 17 | 62 | 83 (74) | 49 |

[a] The conversion was determined by $^1$H NMR of the crude reaction mixture. Isolated yield is given in parentheses. After the times shown, no additional product formation was observed.

Table 8, a control experiment was performed in the absence of ligand, and substantially lower conversions were observed in each case.

A thorough understanding of the mechanism of this reaction will require detailed computational, kinetic, and structural analysis, efforts that are currently underway in our laboratory and in collaboration with other groups. In the meantime, we would like to highlight several observations that we have made thus far

to help frame future mechanistic studies. The reaction begins with formation of the catalytically active Pd(II) species, which we speculate to be a monomeric Pd(II)-catalyst with a single bound amino acid, consistent with our earlier work in this area.[4a,4b,33] Attempts to isolate and characterize the active Ac-Ile-OH-bound Pd(II) catalyst and test its reactivity, however, have not been fruitful thus far.[34,35]

Two different pathways would then theoretically lead to a common $[Pd(II)Ar_1Ar_2]$ intermediate (Scheme 1). In Path A, transmetalation to generate a $[Pd(II)Ar_1]$ species would precede C−H cleavage. In Path B, on the other hand, C−H cleavage would take place first, followed by transmetalation. Although we cannot definitively rule out Path A, we currently favor Path B on the basis of the fact that the reactivity trends in Table 5 (both with and without Ac-Ile-OH) closely parallel those seen in Pd(II)-catalyzed C−H olefination of phenylacetic acids,[5c] where C−H cleavage is thought to be the first step of the catalytic cycle.

To understand the mechanism of carboxylate-directed C−H cleavage in this reaction,[5c,7a,36−38] we first took note of the tolerance for both electron-donating and electron-withdrawing substituents on the aromatic ring in the presence of Ac-Ile-OH (Table 5). To further probe the relative reactivities of electron-rich and electron-poor phenylacetic acids, we performed competition experiments between substrates **1a** and **1b** under abridged reaction times to measure the relative initial rates (Table 9).[39] We found that in the absence of ligand, electron-rich substrate **1b** gave a higher initial rate. In the presence of Ac-Ile-OH, we found that electron-poor substrate **1a** gave a higher initial rate. The results were consistent with the single-component initial rate data (Table 10). Overall, the trends from these competition experiments are very similar to what we observed in ligand-accelerated C−H olefination.[5c] Based on these findings, we propose that the C−H cleavage event proceeds via a concerted metalation/deprotonation pathway in the presence of Ac-Ile-OH, and an electrophilic palladation mechanism in the absence of Ac-Ile-OH (Figure 2).[5c,40,41]

Subsequent to C−H cleavage, transmetalation takes place with the organoboron reagent to generate a diaryl Pd(II) species. Because competitive Pd(II)-mediated homocoupling of the organometallic reagents is known to be fast,[12] we speculate that the use of $ArBF_3K$ reagents[27] as the coupling partners helps to suppress this undesired pathway.[42] Importantly, it has previously been found that Ag(I) salts facilitate transmetalation in cross-coupling reactions.[12b,14a,18f,43] Reductive elimination from the $[Pd(II)Ar_1Ar_2]$ species, which could be induced by BQ or Ag(I),[12a,24−26] then forges the new key C−C bond to give the arylated phenylacetic acid product.

Reoxidation of Pd(0) by Ag(I) or $O_2$ then takes place to regenerate catalytically active Pd(II) and closes the catalytic cycle. The mechanism of reoxidation with $O_2$ warrants some additional discussion. Previously, in our ligand-accelerated C−H olefination work,[5c] efficient catalysis (TON > 450, TON = turnover number) was achieved under only 1 atm $O_2$ (Scheme 2). In the present case of ligand-accelerated C−H/R−$BX_2$ cross-coupling, the maximum TONs using 1 atm $O_2$ are roughly 30−40-fold

**Scheme 1. Possible Reaction Pathways**

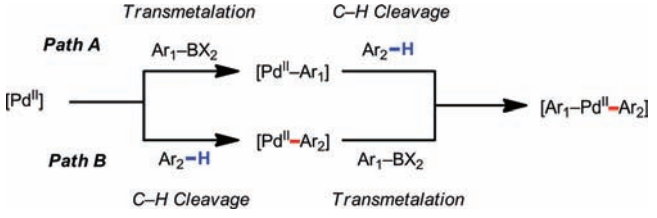
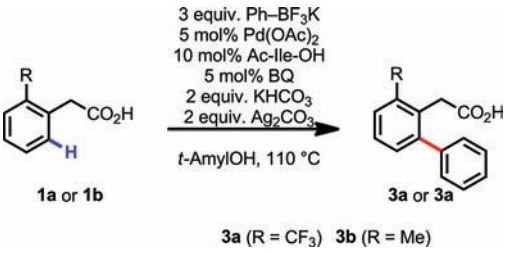


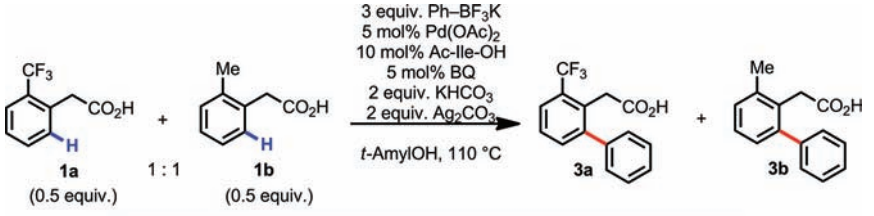

**Table 10. Comparison of the Initial Rates for Single-Component Reactions of 1a and 1b in the Presence and Absence of Ac-Ile-OH**[a,b]




| entry | ligand | $k_{3a}$ ([M]/min) | $k_{3b}$ ([M]/min) | $k_{3a}/k_{3b}$ |
|---|---|---|---|---|
| 1 | – | $4.5 \times 10^{-4}$ | $7.1 \times 10^{-4}$ | 0.66 |
| 2 | Ac-IIe-OH | $3.7 \times 10^{-3}$ | $1.5 \times 10^{-3}$ | 2.47 |

[a] See SI for experimental details. [b] As was discussed with Figure 1, slight deviations from linearity were observed in the early parts of the rate profiles. Linear regression was used here with the understanding that it introduces some degree of error.

**Table 9. One-Pot Intermolecular Competition Experiment Data**[a]




| Entry | Ligand | Time (min) | % Conv. **3a** | % Conv. **3b** | $k_{3a}$ / $k_{3b}$ |
|---|---|---|---|---|---|
| 1 | --- | 60 | 9 | 18 | 0.48 |
| 2 | Ac-Ile-OH | 20 | 36 | 16 | 2.17 |

[a] The conversions were determined by $^1$H NMR of the crude reaction mixture. See SI for experimental details.

lower. For instance, 65% conversion of product **3a** with 5 mol % $Pd(OAc)_2$ was observed after 24 h at 1 atm $O_2$, representing a TON of 13 (Scheme 2 and Table 8). It is also noteworthy that BQ is not required for catalysis in the case of aerobic C−H olefination but is required in aerobic C−H/R−$BX_2$ cross-coupling; in the absence of BQ, only 5% conversion of **3a** was observed after 24 h under 1 atm $O_2$ (see SI).[44] Given the similarity of the reaction conditions in these two transformations, it is possible that this discrepancy in catalytic efficiency stems from a difference in the mechanism of reoxidation. In C−H olefination, the substrate disengages from the catalyst following a $\beta$-hydride elimination event, generating a [Pd(II)(H)(X)] species (Scheme 3). This intermediate can then react with $O_2$ along two possible pathways, direct hydrogen atom abstraction (HAA), or a reductive elimination/oxygenation/protonation sequence (HXRE).[31,45] In contrast, in the case of C−H/R−$BX_2$ cross-coupling, C−C reductive elimination, possibly promoted by BQ,[12a,24,25] generates the product along with concomitant formation of a [Pd(0)] species (Scheme 4). [Pd(0)] is then reoxidized to [Pd(II)] either by BQ or by $O_2$.[46]

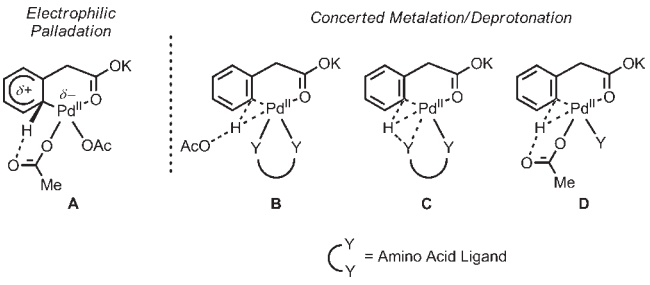
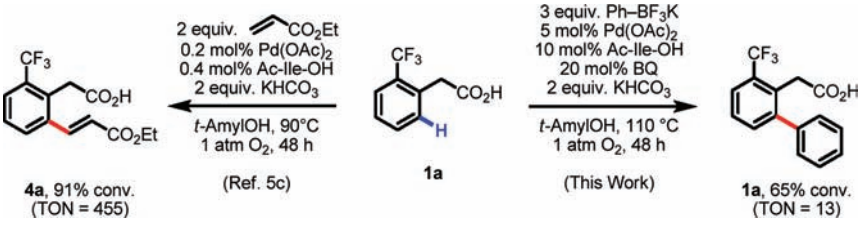



**Figure 2.** Proposed mechanisms for Pd(II)-mediated C−H cleavage. In the absence of ligand, we propose an electrophilic palladation mechanism (**A**). In the presence of ligand, we propose a concerted metalation/deprotonation mechanism with external (**B**) or internal (**C** and **D**) base.

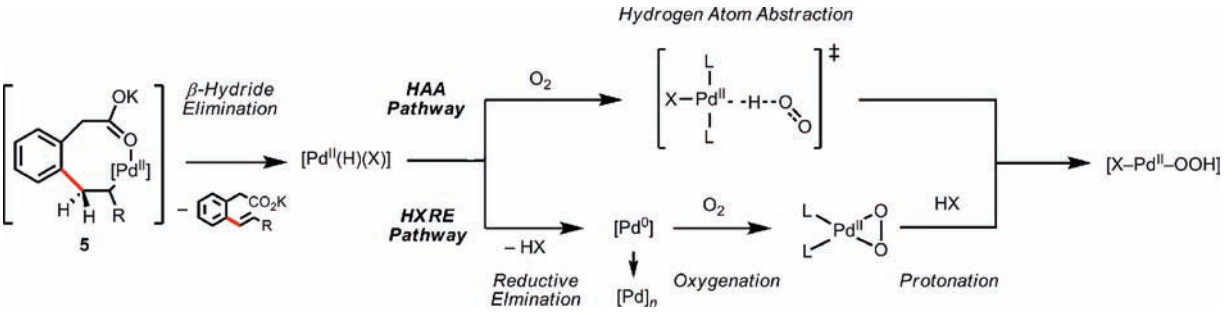
Detailed mechanistic and computational studies have found that either HAA or HXRE pathways can be favored, depending on the ligand environment of the [Pd(II)(H)(X)] complex and the reaction conditions.[45] In the presence of mono-*N*-protected amino acid ligands, however, the reactivity patterns of [Pd(H)(X)] intermediates have not yet been established. In our two catalytic systems (Schemes 2−4), catalyst deactivation is expected to take place primarily *via* aggregation of [Pd(0)] intermediates to $[Pd]_n$ (Pd black). Thus, one possible explanation for the markedly higher catalytic efficiency in C−H olefination would be to invoke a HAA mechanism for reoxidation in that reaction (Scheme 3), whereby [Pd(0)] species are avoided all together. However, other explanations could also potentially account for the observed differences in catalytic efficiency between the two reactions. For example, the coordination of a C=C moiety of the olefin coupling partner and/or olefinated product, could serve to stabilize reduced [Pd(0)] following HXRE in the C−H olefination reaction, decreasing the likelihood of precipitation to Pd black.[33] Another explanation could be that the higher temperature in C−H/R−$BX_2$ cross-coupling (110 °C compared to 90 °C for C−H olefination), which we have found to be necessary for good conversion, possibly because of the higher energetic barrier for C−C reductive elimination compared with that for $\beta$-hydrogen elimination, could be detrimental for catalyst lifetime. Further mechanistic and computational studies are necessary to elucidate the viability of these different scenarios for reoxidation with $O_2$.

The proposed Pd(II)/Pd(0) catalytic cycle is depicted in Scheme 5. The process begins with substrate coordination and subsequent C−H cleavage, which is presumably facilitated by the bound amino acid ligand. Transmetalation takes place, followed by reductive elimination to forge the key C−C bond with concomitant generation of Pd(0). Reoxidation with Ag(I) or $O_2$/BQ regenerates the active catalyst.

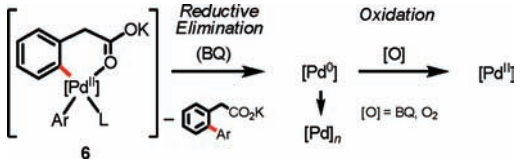
**Scheme 2. Comparison between Ligand-Accelerated Pd(II)-Catalyzed C−H Olefination and C−H/R−$BX_2$ Cross-Coupling under 1 atm $O_2$**[5c]



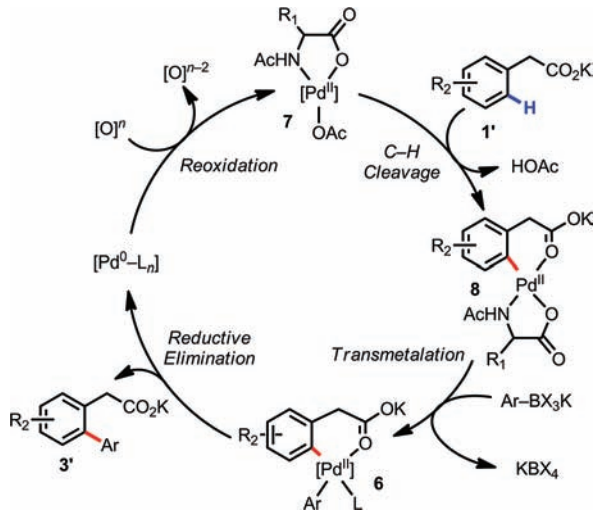

**Scheme 3. Possible Reoxidation Pathways in Ligand-Accelerated C−H Olefination**[5c]



**Scheme 4. Reoxidation Pathway in Ligand-Accelerated C−H/R−$BX_2$ Cross-Coupling**




**Scheme 5. Proposed Catalytic Cycle**




## 3. CONCLUSION

In summary, we report an efficient ligand-accelerated Pd(II)-catalyzed C($sp^2$)−H/arylboron cross-coupling reaction. Using mono-*N*-protected amino acid ligands, we were able to develop conditions to broaden phenylacetic acid substrate scope, shorten reaction times, improve product yields, and reduce catalyst loadings. We anticipate that our new operationally simple protocol using $Ag_2CO_3$ will find widespread applications in academic and medicinal chemistry laboratories. Of equal importance, we have achieved progress toward the development of a complementary, practical aerobic protocol for this Pd(II)-catalyzed cross-coupling reaction using 1 atm $O_2$ as the sole reoxidant. Upon further development, the aerobic reaction will provide an expedient and high-yielding method for large-scale production of biaryl molecules, which are especially prevalent in pharmaceuticals.

## 4. EXPERIMENTAL SECTION

**4.1. General Information.** Unless otherwise noted, all materials were used as received from commercial sources without further purification. Phenylacetic acid substrates were purchased from Acros, Sigma-Aldrich, TCI, Alfa-Aesar, and MP Biomedical and were used as received. 2-(Trifluoromethyl)phenylacetic acid (**1a**) was purchased from TCI; samples of **1a** from other commercial sources were found to give inconsistent results. Organoboron coupling partners were procured from Frontier Scientific, Sigma Aldrich, and Combi-Blocks and used as received. 1,4-Benzoquininone (BQ) was sublimed prior to use. *t*-AmylOH was purchased from Sigma-Aldrich. Newly opened and/or freshly distilled samples of *t*-AmylOH gave the most consistent results. Commercially available amino acid ligands were purchased from Bachem, EMD, or Novabiochem. To examine whether racemic Ac-Ile-OH would give better yields with chiral (racemic) substrates, Ac-D-Ile-OH was prepared.[47] All other ligands were prepared following literature precedent.[5c] 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 min. Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on Varian Inova (400 and 100 MHz, respectively) and Bruker DRX equipped with a 5 mm DCH cryoprobe (600 and 150 MHz, respectively) instruments internally referenced to tetramethylsilane 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. The enantiomeric ratio of **Me-(*S*)-3n** was determined by integration of the HPLC trace, acquired using an Agilent Technologies 1200 series HPLC system with an integrate diode array detector. High-resolution mass spectra were recorded at the Center for Mass Spectrometry, The Scripps Research Institute.

**4.2. Rate Profile Measurements with 2-(Trifluoromethyl)-phenylacetic Acid (1a) and *o*-Tolylacetic Acid (1b).** For each substrate, two different reaction conditions were examined: (1) without Ac-Ile-OH and (2) with Ac-Ile-OH. A 100-mL Schlenk tube containing a magnetic stir bar was charged with **1a** (or **1b**) (1.00 mmol), phenyltrifluoroborate (**2a**) (552.0 mg, 3.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol), BQ (5.4 mg, 0.050 mmol), Ac-Ile-OH (8.7 mg, 0.05 mmol) (when used), $KHCO_3$ (200.2 mg, 2.0 mmol), $Ag_2CO_3$ (551.5 mg, 2.0 mmol), and *t*-AmylOH (5.0 mL). The reaction tube was capped with a rubber septum, then stirred at 110 °C. At the indicated time points, a small aliquot (<0.1 mL) was removed from the vial. The aliquots were added to independent 10-mL scintillation vials containing a biphasic mixture of 2.0 N HCl solution (1.0 mL) and diethyl ether (2.0 mL). An 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 **1a**, 3.79 ppm for **3a**, 3.67 ppm for **1b**, and 3.63 ppm for **3b**). The procedure was repeated three times. The resulting data were plotted, and linear regression of the time points in the 5−20 min period established the initial rate. The results are shown in Tables S4−S7 and Figures S1−S4 (SI).

**4.3. General Procedure for Pd(II)-Catalyzed C−H/Organoboron Cross-Coupling with Phenylacetic Acids (1) and Potassium Trifluoroborates (2) Using $Ag_2CO_3$ as the Oxidant.** A 25-mL sealed tube equipped with a magnetic stir bar was charged with the phenylacetic acid substrate (**1**) (0.50 mmol), the aryltrifluoroborate (**2**) (1.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ (2.7 mg, 0.025 mmol), Ac-Ile-OH (8.7 mg, 0.05 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), $Ag_2CO_3$ (275.8 mg, 1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction tube was capped and immediately transferred to an oil bath at 110 °C. After being allowed to stir vigorously for 2 h, the reaction vessel was removed from the oil bath and 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 proton signals; **3** generally appears upfield from **1**. To isolate the pure product **3**, the biphasic mixture was basified with concentrated aqueous NaOH until the pH > 12 (as monitored by pH paper), the resulting solution was extracted with DCM (2 × 10 mL) to remove BQ and the biaryl homocoupling byproduct, and the organic layers were back-extracted once with 2.0 N NaOH (10 mL). The combined aqueous layers were acidified *via* dropwise addition of concentrated HCl until the pH < 2, and the solution was extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over

anhydrous $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel flash column chromatography using 2:1 hexanes/EtOAc (with 3% HOAc) as the eluent. Products **3i**, (*rac*)-**3o**, **3s**, and **3w** were prepared on a 0.2 mmol scale, using the same relative amounts of reagents. For each substrate, a control experiment in the absence of Ac-Ile-OH was run, and the conversion was determined in a similar manner; however, the product (which was generally observed in scant quantities) was not isolated. The results in the presence and absence of ligand are shown in Tables 5 and 6.

**4.4. General Procedure for Pd(II)-Catalyzed C−H/Organoboron Cross-Coupling with Phenylacetic Acids (1) and Potassium Trifluoroborates (2) Using $O_2$ (or Air) as the Oxidant.** For experiments using >1 atm of pressure, a 45-mL high-pressure vessel was used. For experiments using 1 atm of pressure, a 50 mL Schlenk-type sealed tube (with a Teflon high-pressure valve and side arm) was used. The reaction flask was equipped with a magnetic stir bar and was charged with the phenylacetic acid substrate (**1**) (0.50 mmol), the aryltrifluoroborate (**2**) (0.75 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ (10.8 mg, 0.1 mmol), Boc-Val-OH (10.9 mg, 0.05 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction vessel was capped and adjusted to the appropriate pressure of $O_2$ (or air). *A note of caution: when working with high-pressure $O_2$, proper safety measures (including the use of a blast shield) should be taken.* After being allowed to stir vigorously for the appropriate time, the reaction vessel was removed from the oil bath and cooled to 0 °C in an ice bath. The pressure was released, and 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 $^1H$ NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets; **3** generally appears upfield from **1**. To isolate the pure product (**3**), the biphasic mixture was basified with concentrated aqueous NaOH until the pH > 12 (as monitored by pH paper), the resulting solution was extracted with DCM (2 × 10 mL) to remove BQ and biphenyl (the undesired homocoupling byproduct), and the organic layers were back-extracted once with 2.0 M NaOH (10 mL). The combined aqueous layers were acidified *via* dropwise addition of concentrated HCl until the pH < 2, and the solution was extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel flash column chromatography using 2:1 hexanes/EtOAc (with 3% HOAc) as the eluent. For each substrate under each of the conditions reported, a control experiment in the absence of Ac-Ile-OH was run, and the conversion was determined in a similar manner; however, the product (which was generally observed in scant quantities) was not isolated. The results are shown in Table 8.

## ■ ASSOCIATED CONTENT

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

## ■ AUTHOR INFORMATION

**Corresponding Author**
yu200@scripps.edu

## ■ ACKNOWLEDGMENT

We gratefully acknowledge TSRI, the NIH (NIGMS, 1 R01 GM084019-02), Amgen, and Eli Lilly for financial support. This work was funded by the A. P. Sloan Foundation (fellowship to J.-Q.Y.); TSRI, the NSF GRFP, the NDSEG Fellowship program, and the Skaggs Oxford Scholarship program (predoctoral fellowships to K.M.E.); and the ACS SEED program (high school internship funding for M.D.). We thank David W. Shia (Torrey Pines High School) for assistance in collecting the rate profile data. We are grateful to Frontier Scientific for the generous donation of organoboron reagents. TSRI Manuscript no. 21064.

## ■ REFERENCES

(1) Reviews of Pd(0)-catalyzed C−C bond-forming reactions in total synthesis: (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.

(2) For perspectives on the importance of ligand design in Pd(0) chemistry, see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211. (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544. (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

(3) Selected reviews of Pd-catalyzed C−H functionalization: (a) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35–41. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (d) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (f) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (h) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292.

(4) Amino acid ligands were first identified as effective ligand scaffolds for Pd(II)-catalyzed C−H functionalization reactions during our studies of enantioselective C−H functionalization: (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882–4886. (b) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460–461. For an early report describing stoichiometric asymmetric cyclopalladation of (dimethylamino)methylferrocene in the presence of Ac-Val-OH, see: (c) Sokolov, V.-I.; Troitskaya, L. L.; Khrushchova, N. S. *J. Organomet. Chem.* **1983**, *250*, 439–446.

(5) (a) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315–319. (b) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 6169–6173. (c) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137–14151.

(6) More recently, success has also been found using amino acid ligands to promote Pd(II)-catalyzed C−H functionalization with directing groups other than carboxylates: (a) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916–5921. (b) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222–7228. (c) Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; Yu, J.-Q. *Chem. Sci.* **2011**, *2*, 967–971. (d) Huang, C.; Chattopadhyay, B.; Gevorgyan, V. *J. Am. Chem. Soc.* **2011**, *133*, 12406–12409.

(7) Reviews of Pd(II)-catalyzed C−H/R−M cross-coupling from our group: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (b) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, *50*, 605–616.

(8) Pyridine ligands have been shown to enhance catalytic turnover in Pd(II)-catalyzed C−H functionalization reactions: (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578–9579. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175. (c) Zhang, J.; Khaskin, E.; Anderson, N. P.; Zavalij, P. Y.; Vedernikov, A. N. *Chem. Commun.* **2008**, 3625–3627. (d) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074. (e) Izawa, Y.; Stahl, S. S. *Adv. Synth. Catal.* **2010**, *352*, 3223–3229. (f) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209–213. Arnold and Sanford have reported a bidentate NHC-alkoxide ligand that stabilizes cyclopalladated Pd(IV) intermediates but leads to lower activity in Pd(II)/Pd(IV) catalysis: (g) Arnold, P. L.; Sanford, M. S.; Pearson, S. M. *J. Am. Chem. Soc.* **2009**, *131*, 13912–13913. Liu and co-workers have recently reported an example in which an NHC ligand was found to promote a phenol-directed C−H activation/C−O cyclization reaction along a Pd(II)/Pd(0) catalytic cycle: (h) Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250–9253.

(9) For a review of ligand-accelerated catalysis, see: Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1995**, *34*, 1059–1070.

(10) For the initial reports of Pd(II)-mediated C(aryl)−H olefination, see: (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119–1122. (b) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett.* **1968**, *9*, 3863–3865.

(11) Examples of Pd-catalyzed C−H arylation using other modes of catalysis: (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021. (b) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046–4048. (c) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331.

(12) For the first reports of Pd(II)-catalyzed C−H/R−M cross-coupling, see: (a) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78–79. (b) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634–12635.

(13) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676–17677.

(14) (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511. (b) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191.

(15) Examples of Pd(II)-catalyzed C−H/R−M cross-coupling from other groups: (a) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066–6067. (b) Kawai, H.; Kobayashi, Y.; Oi, S.; Inoue, Y. *Chem. Commun.* **2008**, 1464–1466. (c) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708–3709. (d) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473–1476. (e) Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2008**, *73*, 7428–7431. (f) Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4235–4238. (g) Zhou, H.; Xu, Y.-H.; Chung, W.-J.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5355–5357. (h) Wei, Y.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 3346–3349. (i) Liang, Z.; Yao, B.; Zhang, Y. *Org. Lett.* **2010**, *12*, 3185–3187. (j) Tredwell, M. J.; Gulias, M.; Bremeyer, N. G.; Johansson, C. C. C.; Collins, B. S. L.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1076–1079. (k) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387–2391. (l) Schnapperelle, I.; Breitenlechner, S.; Bach, T. *Org. Lett.* **2011**, *13*, 3640–3643. (m) Mochida, K.; Kawasumi, K.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 10716–10719.

(16) One elegant approach to improve reactivity with electron-rich substrates has been the use of more electrophilic Pd(II) catalysts: Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 4978–4979.

(17) Aryl carboxylic acid derivatives have been found to be effective organometallic reagent surrogates (*via* decarboxlation) in Pd(II)-catalyzed R−H/R−$CO_2$H cross-coupling. For leading references, see: (a) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312–6314. (b) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194–4195. (c) Li, M; Ge, H. *Org. Lett.* **2010**, *12*, 3464–3467.

(18) Examples of stoichiometric palladacycle/R−M coupling: (a) Murahashi, S.-I.; Tanba, Y.; Yamamura, M.; Moritani, I. *Tetrahedron Lett.* **1974**, *15*, 3749–3752. (b) Yamamura, M.; Moritani, I.; Murahashi, S.-I. *Chem. Lett.* **1974**, *3*, 1423–1424. (c) Kasahara, A.; Izumi, T.; Maemura, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1878–1880. (d) Murahashi, S.-I.; Tamba, Y.; Yamamura, M.; Yoshimura, N. *J. Org. Chem.* **1978**, *43*, 4099–4106. (e) Louie, J.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **1996**, *35*, 2359–2361. (f) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856–11857. In one case, Pd(0) was found to catalyze the intermolecular cross-coupling of 2,4,6-tri-*tert*-butylbromobenzene with arylboronic acids *via* an unusual intervening C($sp^3$)−H cleavage step following oxidative addition: (g) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

(19) Examples of Rh(I)-catalyzed C−H/R−M cross-coupling: (a) Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439–2440. (b) Vogler, T.; Studer, A. *Org. Lett.* **2007**, *10*, 129–131.

(20) Examples of Ru(0)-catalyzed C−H/R−M cross-coupling: (a) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698–1699. (b) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221. For Ru(II)-catalyzed C−H/R−M cross-coupling, see:(c) Li, H.; Wei, W.; Xu, Y.; Zhang, C.; Wan, X. *Chem. Commun.* **2011**, *47*, 1497–1499.

(21) In an intriguing recent report, it was found that nucleophilic aryl-centered radicals, generated from arylboronic acids in the presence of catalytic Ag(I), could add to electron-poor heterocycles: Seiple, I. B.; Shun, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196.

(22) In ref 13 the substrate scope was largely limited to $\alpha$-substituted and $\alpha,\alpha$,-disubstiuted phenylacetic acids, in which palladation is more favorable owing to the Thorpe−Ingold effect. The reaction conditions reported in that reference were as follows: $ArBF_3K$ (1.2 equiv), Pd-$(OAc)_2$ (10 mol %), BQ (0.5 equiv), $K_2HPO_4$ (1.5 equiv), *t*-BuOH (solvent), 110 °C, $O_2$ (20 atm), 48 h. Under those conditions, many substrates gave unsatisfactory product conversions. Representative examples include **3a** (44%), **3d** (56%), and **3h** (17%). (See SI for further details.) It is important to note that, thoughout this work, we used 5 mol % $Pd(OAc)_2$.

(23) In ref 13 it was stated that Ag(I) salts completely inhibited the transformation under the reported reaction conditions (given above). That claim does not seem to be true across all reaction conditions.

(24) For an example of olefin-promoted reductive elimination from Pd(II), see: (a) Kurosawa, H.; Emoto, M.; Ohnishi, H.; Miki, K.; Kasai, N.; Tatsumi, K.; Nakamura, A. *J. Am. Chem. Soc.* **1987**, *109*, 6333–6340. BQ has previously been found to promote reductive elimination in a Stille coupling reaction involving allyl halides: (b) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B. *Chem.—Eur. J.* **2001**, *7*, 2481–2489. For the effects of BQ as a ligand in Pd-catalyzed C−H cleavage/C−C bond−forming reactions, see: (c) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587. (d) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905.

(25) For an elegant study of reductive elimination of $C_2H_6$ from a [Pd(II)$Me_2$] complex using different methods, including treatment with BQ or Ag(I) salts, see: Lanci, M. P.; Remy, M. S.; Kaminsky, W.; Mayer, J. M.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 15618–15620.

(26) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478–1491.

(27) For perspectives on the use of $RBF_3K$ reagents, see: (a) Darses, S.; Genet, J.-P. *Chem. Rev.* **2007**, *108*, 288–325. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286. (c) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027. (d) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5156–5160. For the use of MIDA-boronates, see: (e) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717.

(28) For detailed data concerning the effects of $PhBF_3K/Ag_2CO_3$ loading, see SI.

(29) Due to averaging effects, in Figure 1 it appears as if the reaction in the presence of Ac-Ile-OH decelerates after 20 min. However, in individual trials the rate appears to be nearly constant for time points from 20 min until the reactions proceed to completion.

(30) High conversion with $\alpha,\alpha$,-disubstituted phenylacetic acids can be obtained using the conditions reported in ref 13. With these substrates, the use of mono-*N*-protected amino acid ligands does not seem to improve the reactivity.

(31) Reviews of aerobic Pd(II)-catalyzed oxidation chemistry: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (b) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362–367. (c) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854–3867.

(32) Although at the present time high pressure $O_2$ poses a safety risk when used at elevated termperatures, the advent of flow technology may soon render this approach more tenable. For leading references, see: (a) Ye, X.; Johnson, M. D.; Diao, T.; Yates, M. H.; Stahl, S. S. *Green Chem.* **2010**, *12*, 1180–1186. (b) Murphy, E. R.; Martinelli, J. R.;

Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1734–1737. (c) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596–1598. (d) Saaby, S.; Knudsen, K. R.; Ladlow, M.; Ley, S. V. *Chem. Commun.* **2005**, 2909–2911.

(33) Sale, D. A.; Engle, K. M.; Yu, J.-Q.; Blackmond, D. G. *Submitted*.

(34) We have found Ac-Ile-OH-bound Pd(II) complexes to be difficult to characterize due to their poor solubility in nonpolar solvents. The use of more polar coordinating solvents introduces the possibility that a solvent molecule could displace a ligand on Pd(II) and/or cause disaggregation of any oligomeric Pd(II) species. Furthermore, interpretation of the spectral data for multinuclear Ac-Ile-OH-bound Pd(II) complexes tends to be challenging owing to the possibility of *cis*/*trans*-isomerism. For a report in which cyclopalladated complexes containing acetyl-protected amino acid ligands were synthesized and characterized, see: Navarro, R.; García, J.; Urriolabeitia, E. P.; Cativiela, C.; Diaz-de-Villegas, M. D. *J. Organomet. Chem.* **1995**, *490*, 35–43.

(35) We tested the activity of one amorphous "[Pd(Ac-Ile-OH)(OAc)]" complex and found that using 5 mol % catalyst with no additional ligand under otherwise identical reaction conditions to those depicted in Table 5 gave 85% conversion after 2 h. This "[Pd(Ac-Ile-OH)(OAc)]" complex was synthesized using the following procedure: To a flame-dried 20-mL round-bottom flask containing a magnetic stir bar were added $Pd(OAc)_2$ (0.056 g, 0.25mmol), Ac-Ile-OH (0.043 g, 0.25mmol), and $\alpha,\alpha,\alpha$-trifluorotoluene (4 mL). The resulting mixture was capped and allowed to stir at ambient temperature for 4 h. Solvent was removed *in vacuo*, giving amorphous "[Pd(Ac-Ile-OH)(OAc)]" as a dark-orange powder in quantitative yield. Broad peaks were observed in its NMR spectra (in $CDCl_3$), and it was not further characterized.

(36) Examples of countercation-promoted, carboxylated-directed Pd(II)-catalyzed C−H functionalization from our group: (a) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215–5219. (b) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082–14083. (c) Mei, T.-S.; Wang, D.-H.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 3140–3143. (d) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097–6100. (e) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654–14655.

(37) Examples of carboxylate-directed Pd(II)-catalyzed C−H functionalization reactions from other groups: (a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211–5215. (b) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879–9884. (c) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006–14008. For a review, see: (d) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395–3409. Carboxylate-directed *ortho*-thallation is a known means of generating organothallium compounds which can be used in Pd(II)-catalyzed functionalization reactions: (e) Larock, R. C.; Fellows, C. A. *J. Am. Chem. Soc.* **1982**, *104*, 1900–1907.

(38) For a review of the complex-induced proximity effect (CIPE), see: Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306–312.

(39) It is important to clarify that if the C−H cleavage step is not rate-limiting under either of the two reaction conditions (i.e., in the presence of absence of Ac-Ile-OH), then the relative reaction rates would actually be reflective of the energy barriers for other elementary steps in the catalytic cycle. Regardless of what the rate-determining step is, the qualitative observation of high reactivity with electron-poor substrates is difficult to explain were one to invoke a traditional electrophilic palladation mechanism.

(40) In ref 5c, we used the term "proton abstraction". The term "concerted metallation/deprotonation" is more commonly used in the literature, so we use it here to convey the same meaning.

(41) For studies concerning the mechanistic aspects C−H cleavage in Pd(II)-catalyzed reactions, see: (a) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629–2638. (b) Canty, A. J.; van Koten, G. *Acc. Chem. Res.* **1995**, *28*, 406–413. (c) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440–6444. For experimental and computational evidence of concerted metalation/deprotonation, see: (d) Gómez, M.; Granell, J.; Martinez, M. *Organometallics* **1997**, *16*, 2539–2546. (e) Gómez, M.; Granell, J.; Martinez, M. *J. Chem. Soc., Dalton Trans.* **1998**, 37–44. (f) Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **2000**, *19*, 3895–3908. (g) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755. (h) Roiban, G.-D.; Serrano, E.; Soler, T.; Aullón, G.; Grosu , I.; Cativiela, C.; Martínez, M.; Urriolabeitia, E. P. *Inorg. Chem.* **2011**, *50*, 8132–8143. For reviews of carboxylate-assisted C−H cleavage in transition metal catalysis, see: (i) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (j) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118–1126.

(42) Even still, $^1$H NMR analysis of the crude reaction mixtures revealed substantial homocoupling of the $ArBF_3K$ reagents (and the ArBPin reagents) under our optimized conditions.

(43) For an early report of Ag(I)'s efficacy in promoting transmetallation in Pd(0)-catalyzed Suzuki−Miyaura coupling reactions, see: Uenishi, J.; Beau, J. M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756–4758.

(44) To clarify, we noted previously that when Ag(I) is used as the reoxidant for C−H/R−$BX_2$ cross-coupling, BQ *is not* required and was used only to improve reproducibility. In the case of reoxidation with $O_2$, BQ *is* required for catalysis.

(45) (a) Keith, J. M.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2005**, *127*, 13172–13179. (b) Konnick, M. M.; Gandhi, B. A.; Guzei, I. A.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2904–2907. (c) Keith, J. M.; Muller, R. P.; Kemp, R. A.; Goldberg, K. I.; Goddard, W. A., III; Oxgaard, J. *Inorg. Chem.* **2006**, *45*, 9631–9633. (d) Popp, B. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 4410–4422. (e) Keith, J. M.; Goddard, W. A., III; Oxgaard, J. *J. Am. Chem. Soc.* **2007**, *129*, 10361–10369. (f) Konnick, M. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 5753–5762. (g) Popp, B. V.; Stahl, S. S. *Chem.—Eur. J.* **2009**, *15*, 2915–2922. (h) Keith, J. M.; Goddard, W. A., III *J. Am. Chem. Soc.* **2009**, *131*, 1416–1425. (I) Konnick, M. M.; Decharin, N.; Popp, B. V.; Stahl, S. S. *Chem. Sci.* **2011**, *2*, 326–330. (j) Decharin, N.; Popp, B. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 13268–13271.

(46) Decharin, N.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 5732–5735.

(47) Sims, J. W.; Schmidt, E. W. *J. Am. Chem. Soc.* **2008**, *130*, 11149–11155.