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Pd(II)-Catalyzed C−H Functionalizations Directed by Distal Weakly Coordinating Functional Groups

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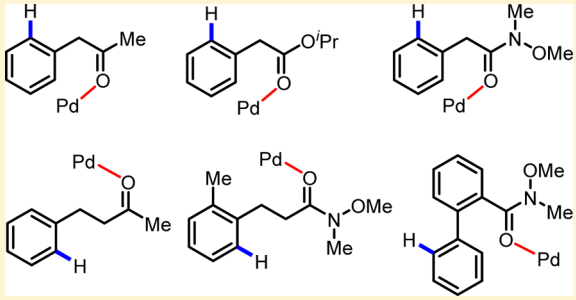
Supporting Information

ABSTRACT: *Ortho*-C(sp^2)−H olefination and acetoxylation of broadly useful synthetic building blocks phenylacetyl Weinreb amides, esters, and ketones are developed without installing an additional directing group. The interplay between the distal weak coordination and the ligand-acceleration is crucial for these reactions to proceed under mild conditions. The tolerance of longer distance between the target C−H bonds and the directing functional groups also allows for the functionalizations of more distal C−H bonds in hydrocinnamoyl ketones, Weinreb amides, and biphenyl Weinreb amides. Mechanistically, the coordination of these carbonyl groups and the bisdentate amino acid ligand with Pd(II) centers provides further evidence for our early hypothesis that the carbonyl groups of the potassium carboxylate are responsible for the directed C−H activation of carboxylic acids.



1. INTRODUCTION: ADVANTAGES OF WEAK COORDINATION

σ-Chelation-assisted C−H palladation processes (cyclopalladation) have been extensively exploited to develop Pd-catalyzed C−H activation/carbon−carbon and carbon−heteroatom bond forming reactions.[1] In turn, the development of these reactions has contributed to an improved mechanistic understanding of several key redox manifolds in Pd catalysis, namely, Pd(0)/Pd(II), Pd(II)/Pd(0), and Pd(II)/Pd(IV) processes.[1] However, the need for a preinstalled strongly coordinating directing group has impeded the widespread application of these transformations as disconnections in synthesis,[2] particularly when the installation or removal of the directing group is not operationally simple.[1]

From the viewpoint of reactivity and catalysis, the broadly held notion that a strongly coordinating directing group is required to achieve robust cyclopalladation originates largely from empirical observation and has generally deterred the development and application of simple directing groups (DG).[3,4] While strongly coordinating directing groups do facilitate the formation and characterization of thermodynamically stable palladacycles, it is debatable whether the strong coordination is necessarily advantageous in catalytic C−H functionalization reactions.[1r] First, the coordination of two strongly coordinating substrates to a Pd center can be problematic, and the addition of a strong acid is often necessary to prevent the formation of this unreactive complex.[5] Second, strongly coordinated palladacycles are often thermodynamically stable and, as such, are unreactive toward functionalization reagents under mild conditions (Figure 1a). On the other hand, cyclopalladation intermediates with weaker coordinating directing groups are less favored in the thermodynamic equilibrium but should be more reactive toward a functionalization reagent. Although present in low concentrations, the transient and less stable palladacycle intermediates can react with electrophiles or nucleophiles to give the desired product via kinetic control analogous to the mechanistic notion in asymmetric hydrogenation established by Halpern (Figure 1a).[6] Indeed, a weakly coordinating substrate (phenyl acetic acid) undergoes much faster Pd-catalyzed H−D exchange in the presence of DOAc than the strongly coordinating 2-phenylpyridine.[7] Furthermore, a weakly bound palladacycle may also undergo reversible dissociation from the directing group to provide a coordination site that may be needed for subsequent functionalization step (Figure 1b), for example, transmetalation with organometallic reagents or migratory insertion with olefins. The heightened reactivity of weakly bound palladacycles may enable the use of milder conditions and broader range of reagents for the discovery of new C−H functionalization processes. Indeed, a number of unprecedented Pd-catalyzed catalytic C−H functionalization transformations were discovered recently using weakly coordinating directing groups including hydroxylation, trifluoromethylation, and borylation of sp^2 C−H bonds, as well as olefination and alkynylation of sp^3 C−H bonds.[8−10] Most notably, the remote *meta*-C−H activation demonstrates the power of weakly coordinating directing groups which dissociate from the Pd center to allow for the coupling of sterically hindered disubstituted olefins.[8t] With this analysis in mind, we have focused our efforts on improving our understanding of the underlying principles for the use of weak σ-chelation to direct C−H activation and

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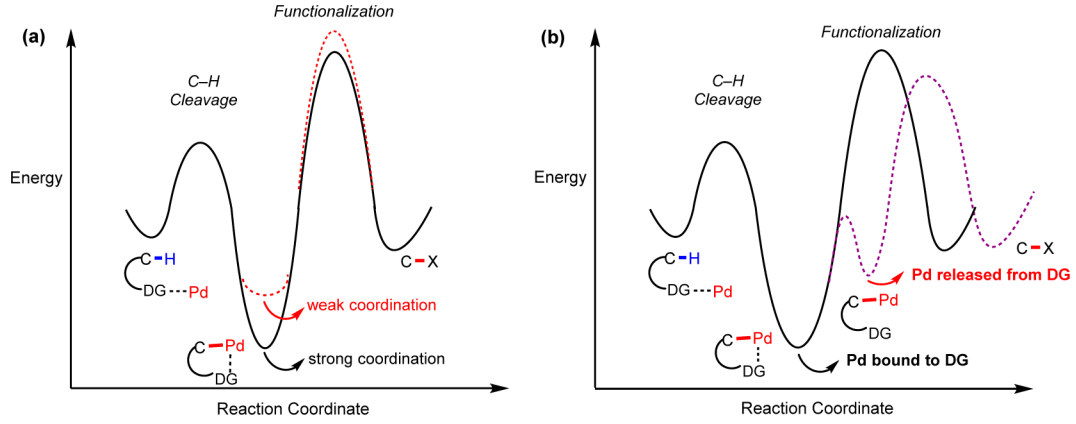

Figure 1. Energy diagram of weak coordination promoted C−H activation.

developing reaction conditions for these types of C−H activation reactions.

Toward this goal, we began to study the effect of both coordination strength and conformation on the C−H activation step. By investigating the stereochemistry of the C−H cleavage step through the use of a chiral oxazoline directing group, we found that the dihedral angle between the C−H and Pd−OAc bonds is critical (Figure 2).[11a] A decrease in this dihedral angle significantly favors C−H activation. In contrast, reduction of coordination strength by increasing the steric hindrance of the directing group does not adversely affect reactivity.[1r] This hypothesis was recently supported by an extensive computational study and conformational analysis.[11b]

Following this primitive rationale, we systematically developed a number of C−H activation/carbon−carbon and carbon−heteroatom bond forming reactions using a weakly coordinating *N*-Boc carbamate or an alkali carboxylate as the directing group (Figure 2).[8a−c] In each of these cases the carbonyl group (C═O) is proposed to coordinate to the Pd(II) center in a geometrically similar fashion to our original oxazoline (C═N) directing group, although the possibility of Pd(II) coordinating with carboxylate as an anion has always been raised.[8b] Such coordination induces a minimum dihedral angle between the C−H and Pd−OAc bonds with a relatively low entropic cost and is expected to have superior reactivity based on the Martinez' pioneering work on the Pd(II)-mediated C−H deprotonation by Pd−OAc,[12a,b] later adopted as CMD mechanism in Pd(0)/ArI chemistry.[12c] These studies led to our subsequent development of several weakly coordinating directing groups derived from carboxylic acids (CONHOMe,[8d] $CONHC_6F_4CF_3$[8o]) or amines (NHTf[8e]) (Figure 2). These directing groups can effectively promote cyclopalladation of $C(sp^2)$−H or $C(sp^3)$−H bonds via five-membered palladacycles. The superior directing power of CONHOMe group has been demonstrated in a wide range of Pd(II),[10k−p] Rh(III), and Ru(II) catalyzed-C−H activation reactions.[13]

The superior directing power of the carbonyl groups in carboxylate and acidic amides promoted us to develop analogous reactions using ester, ketone, and Weinreb amide substrates. ^{1}H NMR studies of the coordination between ester, ketone, and Weinreb amides and Pd(II) show that these substrates are much less coordinative than 2-phenylpyridine (see Supporting Information). Encouragingly, a number of *ortho*-C−H functionalizations of esters, ketones, and Weinreb amides using Pd,[10a−j] Rh,[14a−i] and Ru[14j−r] catalysts have been successfully developed recently. However, similar to Murai's Ru(0)-catalyzed C−H activation reactions of acetophenone,[15] the utility of these very weakly coordinating directing groups has been largely limited to the more reactive benzoyl substrates. First, the conjugation of the carbonyl with the arene minimizes the dihedral angle between the metal and C−H bonds. Second, the formation of the thermodynamically favored five-membered palladacycle also provides a driving force (Figure 2b). In contrast, the activation of distal C−H of esters, ketones, and Weinreb amides remains a significant challenge,[10b,c,q] for example, phenylacetone, Weinreb amides of phenylpropionic acids and biphenyl carboxyl acids (Figure 2d). Compared to the benzoic acid or acetophenone, the freely rotating sp^3 carbon center between the directing carbonyl group and the aryl C−H bonds in phenyl acetic acid and phenylpropionic acid backbones significantly increases the entropic barrier for assembling the desired transition state. The six- and seven-membered cyclopalldation is also less favored in general. Herein we report Pd(II)-catalyzed *ortho*-C−H functionalization of phenylacetyl or phenylpropionate backbone directed by Weinreb amide, ester, and ketones, further demonstrating the feasibility of using simple and ubiquitous functional groups to direct distal C−H activation reactions. The carbon skeletons of phenylacetyl carboxylates and ketones are common in pharmaceuticals and natural products (Figure 3). These new reactions also allow for diversification of abundant starting materials based on phenyl acetyl backbones. Mechanistically, the coordination of these carbonyl groups and the bisdentate amino acid ligand with Pd(II) centers provides further evidence for our early hypothesis that the weakly coordinating carbonyl groups of the potassium carboxylate are responsible for the directed C−H activation of carboxylic acids (Figure 2).

2. RESULTS AND DISCUSSION

2.1. Olefination. Encouraged by our recently disclosed Pd(II)-catalyzed *ortho*-C−H olefination of arenes directed by weakly coordinating alkyl ethers promoted by a monoprotected amino acid ligands,[8v] we were prompted to explore the olefination of commonly used Weinreb amide, ester, or ketone without installing additional directing groups. Compared to the benzoyl-derived ketone, ester, and amide substrates, the presence of an extra methylene group between the aryl ring and the directing group is expected to incur additional entropic cost during the assembly of the desired pretransition state. We initiated our efforts with Weinreb amide substrates as we suspected that these substrates would be slightly more

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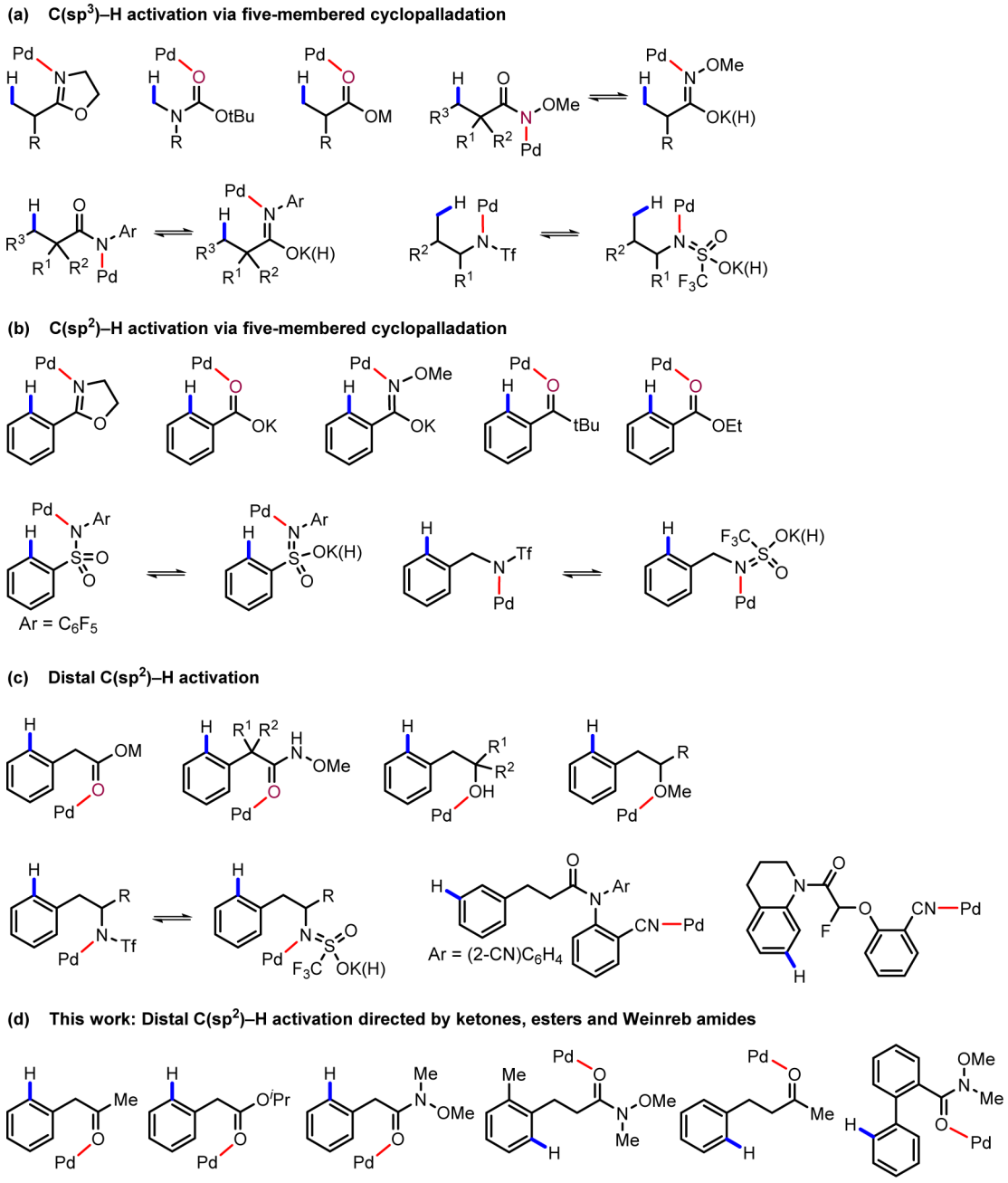

Figure 2. Systematic design and development of weakly coordinating directing groups.

coordinative and reactive than the corresponding ester or ketone analogue. After a survey of reaction conditions (see the Supporting Information), we established that treatment of amide **1a** with ethyl acrylate, silver carbonate, 10 mol % palladium acetate, and 20 mol % of the Ac-Gly-OH ligand in hexafluoroisopropanol (HFIP) at 80 °C for 24 h provides the desired olefinated product in 87% yield (mono/di =1/2) (Table 1). Without addition of the Ac-Gly-OH ligand, only a trace amount of olefinated product was detected, thus demonstrating the importance of the interplay between the weak coordination and the ligand acceleration.[8n,16] The olefination of **1a** was also scaled up to 0.6 g (3.35 mmol) to give 62% of $\mathbf{3a}_{mono}$ and 33% of $\mathbf{3a}_{di}$ products. This reaction is compatible with phenylacetyl amides with electron-donating (**1b**–**e**) or electron-withdrawing groups (**1f**–**j**) and can be extended to the hydrocinnamic Weinreb amide **1k** to provide the corresponding *ortho*-olefinated products in good yield. Intriguingly, olefination of biphenyl benzamide **1l** occurs at the remote aryl ring, which is in marked contrast to the selective functionalization of the same substrate at the proximal *ortho*-C–H bond with a Rh(III) catalyst.[14h]

Having established conditions for the olefination of Weinreb amide substrates, we proceeded to test the feasibility of employing phenylacetyl esters as directing groups in this transformation. Although benzoates have been applied in C–H functionalization reactions using various transition metals, phenylacetyl esters are rarely used in these transformations.[10b,c] After a brief reaction optimization we found that desired olefinated products can be obtained by increasing the amount of silver carbonate and lengthening the reaction time, which implies that phenylacetyl esters are less reactive than the corresponding Weinreb amide substrates (Table 2). These

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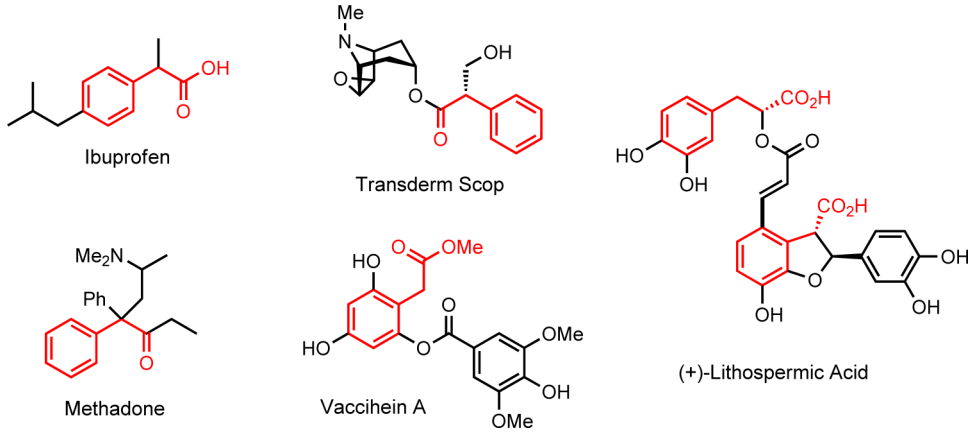
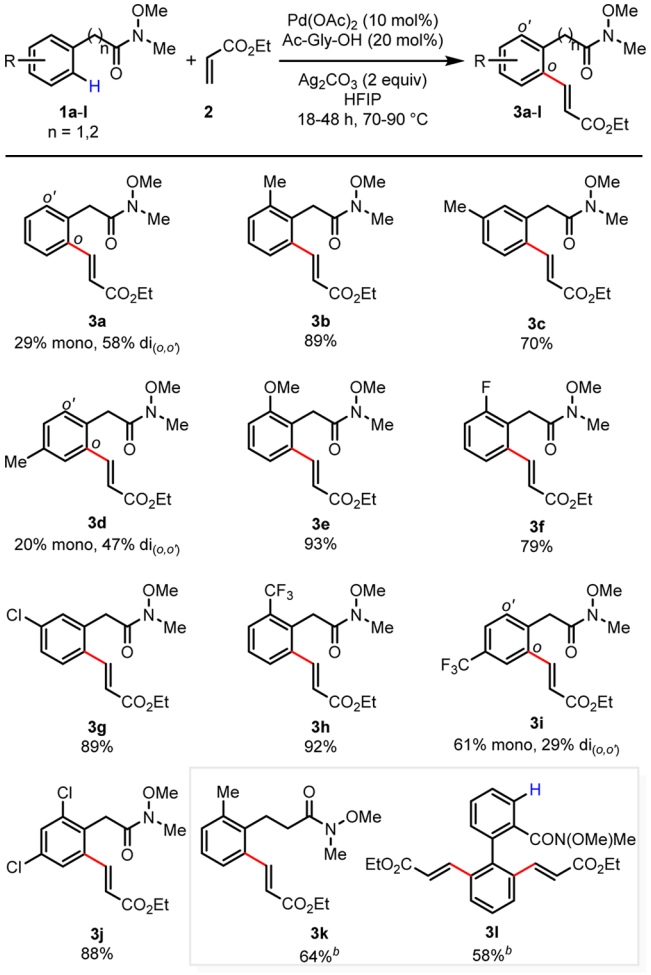


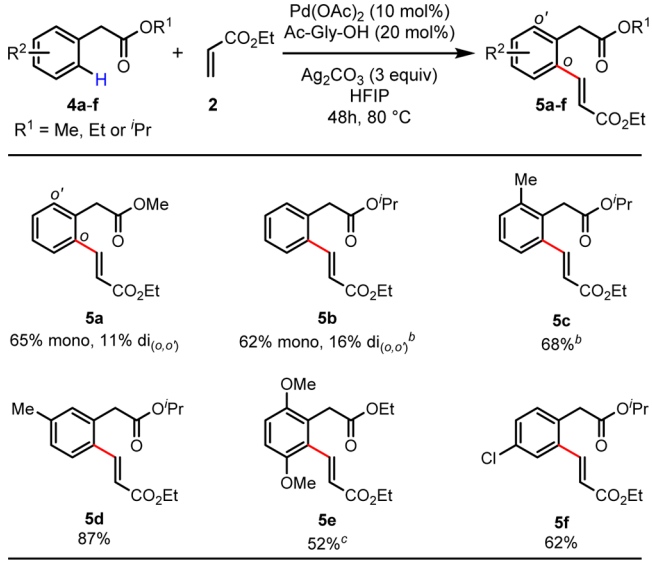
Figure 3. Natural products and pharmaceuticals featuring the phenylacetyl scaffolds.

Table 1. Pd(II)-Catalyzed *Ortho*-Olefination of Weinreb Amides[a]



[a]Conditions: **1** (0.2 mmol), **2** (1.25−1.5 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), Ag_2CO_3 (2 equiv), HFIP (2 mL), 18−48 h, 70−90 °C, in 35 mL sealed tube. Isolated yields were reported; see Supporting Information for details. [b]Ag_2CO_3 (3 equiv) was added.

Table 2. Pd(II)-Catalyzed *Ortho*-Olefination of Phenylacetyl Esters[a]



[a]Conditions: **1** (0.2 mmol), **2** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), Ag_2CO_3 (3 equiv), HFIP (2 mL), 48 h, 80 °C, in 15 mL sealed tube. Isolated yields were reported; see Supporting Information for details. For substrates **4a−c** minor amount of other isomers was also observed. [b]**2** (1.25 equiv) was added. [c]The reaction was run at 90 °C for 60 h.

reaction conditions are compatible with both methyl ester and isopropyl ester substrates (**5a** and **5b**). Although a range of electron-rich substituents (**4c−e**) is tolerated in this transformation, electron-deficient phenylacetyl esters afford poor yields except for para-chloro-substituted **4f**, which gave the desired product in synthetically useful yield (**5f**). In contrast to the olefination of phenylacetyl Weinreb amides, the olefination of phenylacetyl esters displayed high monoselectivity, presumably due to the fast off-rate of the less coordinative products.

We further sought to apply this reactivity to the olefination of dialkyl ketones. To the best of our knowledge the reactivity of these substrates in C−H functionalization has not yet been reported (Table 3). To our delight, our reaction conditions developed for the olefination of phenylacetyl ester substrates are also applicable for the olefination of phenylacetone derivatives. Although a low yield was obtained with the parent phenylacetone (**6a**), the reaction of benzyl ethyl ketone **6b** provided the desired olefinated product in excellent combined yield (**7b**). It is possible that Pd(II) coordinates to the carbonyl on the same side of the less hindered methyl group in **6a** and results in a loss of reactivity. This reaction proceeds for arylacetone derivatives with both electron-donating (**7c−e**) and

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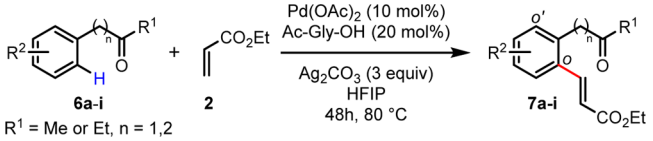
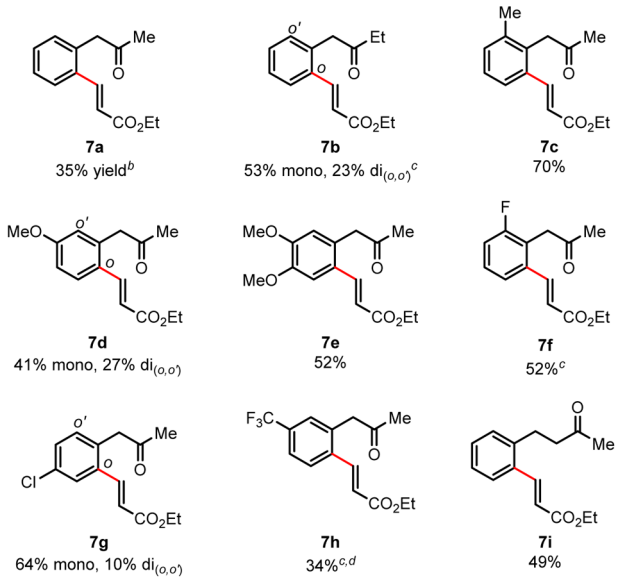
Table 3. Pd(II)-Catalyzed *Ortho*-Olefination of Phenylacetone Derivatives[a]



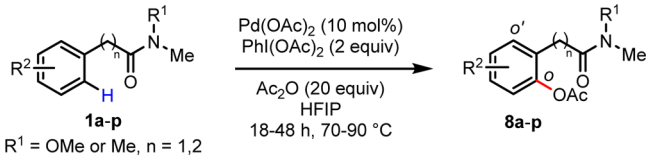


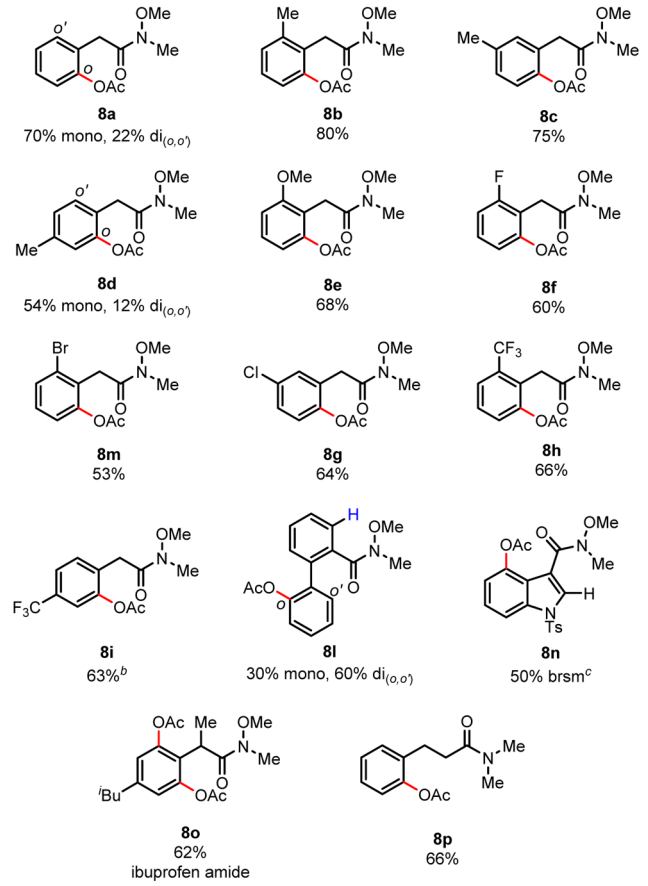
[a]Conditions: **1** (0.2 mmol), **2** (1.25−2 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), Ag_2CO_3 (3 equiv), HFIP (2 mL), 48 h, 80 °C, in 10−35 mL sealed tube. Isolated yields were reported; see Supporting Information for details. For substrates **6i** some diolefinated and minor amount of other isomers was also observed. [b]Ag_2CO_3 (2 equiv) was added. [c]The reaction was run at 90 °C. [d]HFIP (1 mL) was added as solvent.

electron-withdrawing substitutents (**7f−g**) to provide the corresponding products in moderate to good yield, albeit the reaction with highly electron-deficient substrate **6h** afforded low yield of desired product (**7h**). The reaction of 4-phenyl-2-butanone (**6i**) also provides a moderate yield of the mono-olefinated product **7i**.

2.2. Acetoxylation of Weinreb Amides. In order to probe the efficacy of weak chelating substrates in a variety of C−H functionalization reactions with different redox manifolds, we explored the application of our Weinreb amide substrates in a Pd(II)/Pd(IV) acetoxylation reaction. We recognized that this transformation might be challenging since benzylic methylenes are often unstable to strongly oxidizing reaction conditions. We were pleased to find that the desired oxidized product **8a** could be obtained in 92% of acetoxylated products (mono/di =3.2/1) by treatment of Weireb amide **1a** with $PhI(OAc)_2$[5b,17] and Ac_2O in the presence of 10 mol % $Pd(OAc)_2$ in HFIP at 70 °C for 18 h (Table 4). The addition of 20 equiv of Ac_2O was found to improve the efficiency of the reaction and prevent alkoxylation with HFIP. Similar effects of Ac_2O have also been observed in Pd-catalyzed C−H oxygenation with tert-butyl peroxyacetate ($MeCOOO^tBu$).[18] Substrates with either electron-donating (**8b−e**) or electron-withdrawing groups (**8f-i, m**) reacted to afford the corresponding products in moderate to good yield. An *ortho*-bromo-substituent is compatible with this reaction, which provided an opportunity for further product derivatization (**8m**). The

Table 4. Pd(II)-Catalyzed *Ortho*-Acetoxylation of Amides[a]





[a]Conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2 equiv), Ac_2O (20 equiv), HFIP (2 mL), 18−48 h, 70−90 °C, in 35 mL sealed tube. Isolated yields were reported; see Supporting Information for details. [b]Ac_2O (10 equiv) and HFIP (1 mL) were added. [c]The reaction was run at 0.15 mmol scale, minor amount of other isomers was observed; brsm: based on recovered starting material.

biphenyl Weinreb amide (**1l**) was regioselectively acetoxylated at the remote *ortho*-C−H bond to provide **8l**. Interestingly, acetoxylation of a 3-indole Weinreb amide proceeded selectively at C4, rather than C2, to afford indole **8n**, presumably due to the steric hindrance of the *N*-tosyl protecting group. Treatment of the Weinreb amide **1o**, derived from ibuprofen, with our standard conditions provided the corresponding diacetoxylated product in 62% yield. Additionally, the weakly coordinating *N,N*-dimethyl hydrocinnamic amide **1p** also underwent the desired acetoxylation at the distal remote *ortho*-C−H bond. We also found that the inexpensive oxidant ($60 per mole), tert-butyl peroxyacetate ($MeCOOO^tBu$), was similarly effective for acetoxylation as previously reported in the asymmetric acetoxylation of sp^3 C−H bonds (Scheme 1),[18] with slightly longer reaction times.

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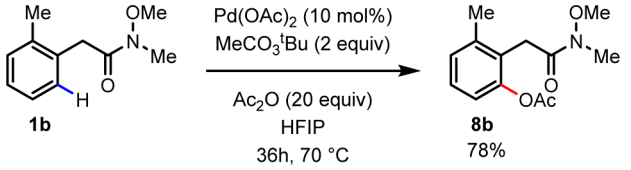
Scheme 1. *Ortho*-C−H Acetoxylation of Weinreb Amides with Inexpensive Peroxides



3. CONCLUSION

In summary, we have developed *ortho*-C(sp^2)−H olefination and acetoxylation of commonly used phenylacetyl Weinreb amides, esters, and ketones without installing a additional directing group. The interplay between the weak coordination and the ligand-acceleration has also enabled distal C−H functionalization reactions via a seven-membered cyclopalladation. Functionalizations of *ortho*-C−H bonds in hydrocinammoyl ketones and Weinreb amides are exemplary. Notably, both Pd(II)/Pd(0)and Pd(II)/Pd(IV) redox catalysis are shown to be compatible with these weakly coordinating directing groups. It is our anticipation that other C−H activation transformations of diverse range of synthetically relevant substrates will continue to be discovered through the interplay between the weak coordination of substrates and ligand on the metal centers.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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