

Pd(II)-Catalyzed Hydroxyl-Directed C–H Olefination Enabled by Monoprotected Amino Acid Ligands

Yi Lu, Dong-Hui Wang, Keary M. Engle, and Jin-Quan Yu*

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

Received March 6, 2010; E-mail: yu200@scripps.edu

Abstract: A novel Pd(II)-catalyzed *ortho*-C–H olefination protocol has been developed using spatially remote, unprotected tertiary, secondary, and primary alcohols as the directing groups. Mono-*N*-protected amino acid ligands were found to promote the reaction, and an array of olefin coupling partners could be used. When electron-deficient alkenes were used, the resulting olefinated intermediates underwent subsequent Pd(II)-catalyzed oxidative intramolecular cyclization to give the corresponding pyran products, which could be converted into *ortho*-alkylated alcohols under hydrogenolysis conditions. The mechanistic details of the oxidative cyclization step are discussed and situated in the context of the overall catalytic cycle.

1. Introduction

Paramount in modern organic synthesis are transition metal-catalyzed reactions that forge carbon–carbon bonds, including the Pd(0)-catalyzed coupling of olefins and aryl halides,¹ first reported in the early 1970s in independent work by Heck² and Mizoroki.³ An attractive complement to this chemistry is the direct coupling of unactivated aryl carbon–hydrogen bonds with olefins (Figure 1), the earliest example of which was reported in 1967 by Fujiwara and Moritani.^{4–6} Though the initial reports concerning Pd(II)-catalyzed aryl C–H olefination were roughly contemporaneous to those of the Mizoroki–Heck reaction, the development of the former as a practical synthetic tool has been far slower than that of the latter. In this respect, two pervasive limitations have historically hampered Pd(II)-catalyzed C–H olefination: (1) excess arene (as solvent) has generally been needed to give high yields, and (2) intractable mixtures of

positional isomers are generally obtained when a substituted arene (e.g., toluene) is used.^{5c} During the past several years, these problems have partially been overcome using electron-rich heterocycles,⁷ chelating functional groups (or “directing groups”),⁸ and external ligands^{7b,8h,9–11} to control the selectivity and improve the reactivity.¹² Indeed, using electron-rich pyrrole and indole substrates, C–H olefination with stoichiometric^{13a–d} and catalytic^{13e,f} Pd(II) has found a number of remarkable examples in natural products total synthesis.

Generally speaking, the directing group strategy has been instrumental in enabling a diverse array of Pd-catalyzed C–H activation reactions during the past several decades.¹⁴ However, many of the common directing groups in C–H activation, such as pyridine, oxazoline, and acetanilide, can be highly disad-

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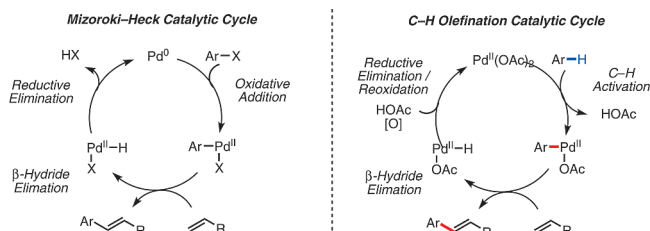


Figure 1. Comparison of Mizoroki–Heck chemistry (left) with arene C–H olefination (right).

vantageous, as they often leave behind undesired chemical “footprints”. Converting a directing group to the requisite functionality for a given synthetic need could require several extra steps or be impossible altogether. Moreover, many directing groups only effect C–H activation of proximate bonds via five-membered palladacycles, which restricts the range of carbon skeletons that can be accessed and constrains further potential synthetic elaboration.

Inspired by the power of other substrate-directable reactions in organic synthesis,¹⁵ including catalytic, hydroxyl-directed epoxidation reactions,^{16,17} we envisioned that the directing group limitations in the area of C–H activation could be largely alleviated by using a range of simple, commonly encountered functional groups to direct C–H insertion, and by developing tactics to activate remote C–H bonds (those located 5–6 bonds away from the directing atom).¹⁸ Taken together, these advancements will not only enable functionalization of C–H bonds in multiple locations of a given molecule using available adjacent functional groups but also allow chemists to plan synthetic sequences in which the directing group is indeed the precise functional group needed for the following steps.

To implement this strategy, we have focused on developing C–H activation reactions with three major classes of synthetically useful substrates: carboxylic acids, amines, and alcohols.

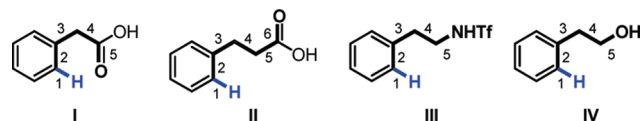


Figure 2. Remote C–H activation directed by common functional groups.

Moreover, we have sought to achieve reactivity through relatively remote coordination, rather than via five-membered cyclometalation.^{8a,19} Despite the realization of these goals with phenylacetic acids (I),²⁰ 3-phenylpropionic acids (II),^{8h} and phenethylamines (III),^{8f} Pd(II)-catalyzed C–H activation of alcohols (IV) has not been reported to date.^{21,22} Herein, we report an example of hydroxyl-directed C–H olefination (Figure 2) promoted by monoprotected amino acid ligands.

2. Results

2.1. Initial Studies and Reaction Optimization. At the outset, we were aware of several potential difficulties that we could encounter in using alcohols to direct C–H palladation. First, σ -chelation of alcohols with Pd(II) is known to be weak, and prior to our experimental work, we questioned whether the palladium alkoxide (Pd-OR) species would be electrophilic enough for C–H activation. Second, Pd(II) is known to oxidize primary and secondary alcohols²³ and decompose tertiary alcohols.²¹ Despite these concerns, we set forth to develop this chemistry, beginning our investigation by undertaking a rigorous, systematic evaluation of viable reaction conditions.

In light of the facile oxidation of primary and secondary alcohols by Pd(II), tertiary alcohol **1** was selected as the screening substrate. Our first approach was to promote *in situ* formation of a [Pd(II)-OR] species using strong bases such as *t*-BuOLi in accordance with a literature report.²⁴ However, attempts to perform C–H olefination failed to give any of the desired product in the presence of *t*-BuOLi, *t*-BuONa, and CH₃ONa. Subsequently, we hypothesized that we could exploit another coordination mode between Pd(II) and the alcohol, with the latter serving as a neutral ligand (Figure 3).²⁴ Through extensive screening of solvents and bases, we found that the combination of nonpolar aromatic solvents, such as toluene and α,α,α -trifluorotoluene, and weaker bases, such as Li₂CO₃, was promising. However, under these conditions we observed concomitant, undesired Pd(II)-catalyzed olefination of the arene solvent. This finding later prompted us to examine C₆F₆ as a potential solvent, which we hypothesized would be similarly

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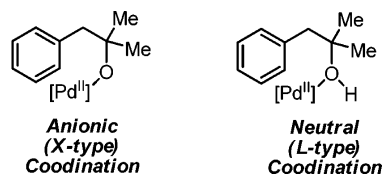


Figure 3. The two potential coordination modes of an alcohol with Pd(II).

Table 1. Initial Examination of Oxidants with Optimal Solvent and Base for C–H Olefination of **1**

| entry | oxidant | % yield ^a |
|-------|---------------------------------|----------------------|
| 1 | O ₂ (1 atm) | 16 |
| 2 | Cu(OAc) ₂ (2 equiv) | 5 |
| 3 | PhI(OAc) ₂ (2 equiv) | 0 |
| 4 | Ag ₂ O (2 equiv) | 0 |
| 5 | AgOAc (2 equiv) | 22 |

^aThe yield was determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as the internal standard.

nonpolar but would also be incapable of undergoing palladation. Gratifyingly, we found that the reaction of 1 equiv of **1** with 1 equiv of ethyl acrylate in the presence of 10 mol % Pd(OAc)₂, 20 mol % 1,4-benzoquinone (BQ), 1 equiv of Li₂CO₃ in C₆F₆ under 1 atm O₂ at 100 °C gave **1a'** in 16% yield after 24 h (Table 1, entry 1). Among a range of co-oxidants tested, AgOAc was found to increase the yield of **1a'** to 22% (Table 1, entry 5), with the major competing side reaction being Wacker-type oxidation of the olefin to vinyl acetate.

With this preliminary result in hand, we began to test if monoprotected amino acid ligands could enhance the desired C–H activation/olefination reaction.^{8h,25} Indeed, we were pleased to find that this class of ligands had a substantial influence (Table 2). (+)-Menthyl(O₂C)-Leu-OH was found to be the most effective ligand, affording the benzopyran **1a** in 52% yield (Table 2, entry 11). Apparently, after initial C–H olefination, the resulting intermediate **1a'** had undergone subsequent Pd(II)-catalyzed oxidative intramolecular cyclization to give **1a**.^{6c,26} It is worth noting here that the formation of uncyclized product **1a'** under the previous, less catalytically efficient conditions provides evidence that the reaction pathway for pyran formation proceeds via two discrete steps: initial C–H olefination, followed by oxidative intramolecular cyclization of the resulting intermediate (for a detailed discussion, see section 2.3). In light of the fact that the olefination step and the oxidative cyclization step should theoretically each require 2 equiv of AgOAc oxidant, we increased the loading of AgOAc to 4 equiv, which further improved the isolated yield to 85% (entry 12).

2.2. Substrate Scope for Hydroxyl-Directed C–H Olefination. Under the optimized conditions, various methyl- and methoxy-substituted arenes were olefinated to give the corresponding cyclized products in good to excellent yields (Table 3, **1a–9a**), while chlorinated and fluorinated arenes afforded

Table 2. Ligand Screening for C–H Olefination of **1**

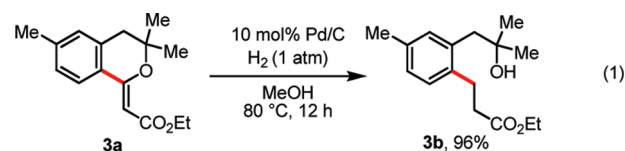
| entry | Ligand | % yield ^a |
|-----------------|--------------------------------------|----------------------|
| 1 | Boc-Ala-OH | 23 |
| 2 | Boc-Val-OH | 37 |
| 3 | Boc-β-Cl-Ala-OH | <5 |
| 4 | Formyl-Ile-OH | <5 |
| 5 | PhSO ₂ -Pro-OH | 19 |
| 6 | Boc-Leu-NHOMe | 0 |
| 7 | Boc-tert-Leu-OH | 17 |
| 8 | Boc-Leu-OH | 21 |
| 9 | Boc ₂ -Leu-OH | 33 |
| 10 | formyl-Leu-OH | 22 |
| 11 | (+)-Menthyl(O ₂ C)-Leu-OH | 52 |
| 12 ^b | (+)-Menthyl(O ₂ C)-Leu-OH | 88 (85) |

^aThe yield was determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as the internal standard. Isolated yield is shown in parentheses. ^b 4 equiv of AgOAc.

moderate yields (**10a–12a**), brominated and trifluoromethylated arenes gave low yields (**13a**, **14a**). More hindered tertiary alcohol substrates were also tolerated (**15a**, **16a**).

We were pleased to find that a variety of electron-deficient olefins were compatible with this reaction protocol (**9b–f**). Notably, **9d** possesses an olefin that is not in conjugation with the aromatic ring. This is due to the geometric requirements of the syn-β-hydride elimination event: following C–H activation and carbopalladation across the cyclopentene ring, the [Pd(II)-R] species is forced to undergo coplanar β-hydride elimination away from the aromatic ring. The resulting carbon–carbon double bond is oriented in a spatially remote location relative to the alcohol, thereby precluding oxidative cyclization. Interestingly, **9f** was also found not to undergo cyclization, and **9e** was found to undergo cyclization very slowly.

Although the cascade olefination/oxidative cyclization affords synthetically useful pyran products, the uncyclized olefinated precursors and analogues thereof are potentially more versatile synthons. Treatment of benzopyran **3a** with 1 atm H₂ in the presence of Pd/C afforded the alkylated product **3b** in quantitative yield, thus providing another avenue for further synthetic applications (eq 1). In addition, dehydration of **3b** could also lead to synthetically useful styrene derivatives.

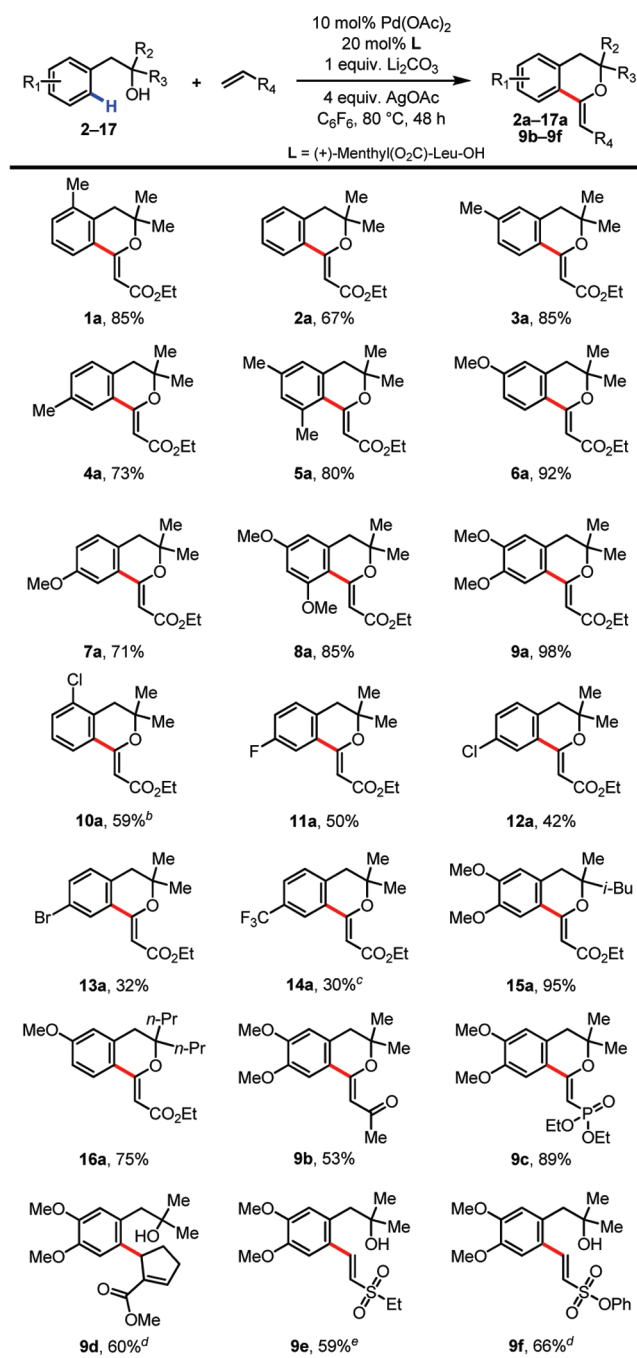


We were also pleased to find that olefination with styrenes and simple olefins gave only the olefinated products without further cyclization (Table 4), presumably because the oxidative 1,4-addition is less facile when the olefin is less electrophilic. Notably, in all cases in which the products do not undergo oxidative cyclization, only 2 equiv of AgOAc was needed. In these cases, additional AgOAc was not found to improve the yield.

Next, a number of primary and secondary alcohol substrates were also subjected to the standard reaction conditions, representative examples of which are shown in Table 5. Though the

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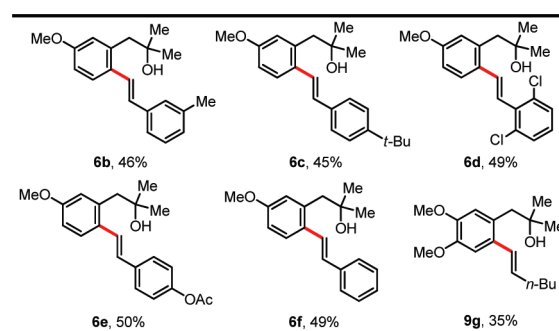
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Table 3. C–H Olefination of Tertiary Alcohol Substrates **1–16**^a

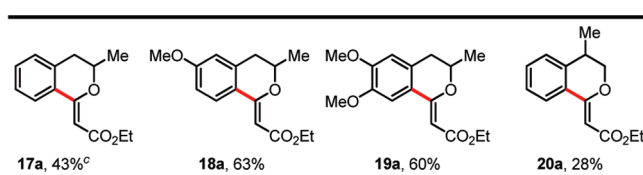
^a Isolated yield. ^b 100 °C. ^c 20 mol % Pd(OAc)₂, 40 mol % L. ^d 2 equiv of AgOAc. ^e Cyclized C–H olefination product **9e** was also isolated in 26% yield.

yields with secondary alcohols tended to be low, electron-rich substrates **18** and **19** were found to be more reactive, giving **18a** and **19a** in 63% and 60% yield, respectively. We were also able to obtain encouraging results with primary alcohol **20**, which could be olefinated to give **20a** in 28% yield.

The lower observed reactivity with these substrates can be attributed to several factors. First, in contrast to the case with tertiary alcohols, where the conformational freedom is restricted and there is bond angle compression between the benzylic carbon atom and the hydroxyl group (the Thorpe–Ingold

Table 4. C–H Olefination with Electron-Neutral Olefins^{a,b}

^a Reaction conditions: 10 mol % Pd(OAc)₂, 20 mol % (+)-Menthyl(O₂C)-Leu-OH, 1 equiv of Li₂CO₃, 2 equiv of AgOAc, C₆F₆, 80 °C, 48 h. ^b Isolated yield.

Table 5. C–H Olefination of Primary and Secondary Alcohols **17–20**^{a,b}

^a Reaction conditions: 10 mol % Pd(OAc)₂, 20 mol % (+)-Menthyl(O₂C)-Leu-OH, 1 equiv of Li₂CO₃, 4 equiv of AgOAc, C₆F₆, 80 °C, 48 h. ^b Isolated yield. ^c 15 mol % Pd(OAc)₂, 30 mol % (+)-Menthyl(O₂C)-Leu-OH, 72 h.

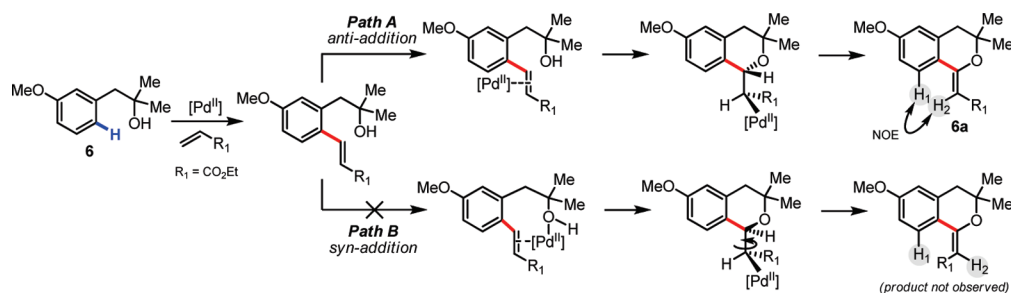
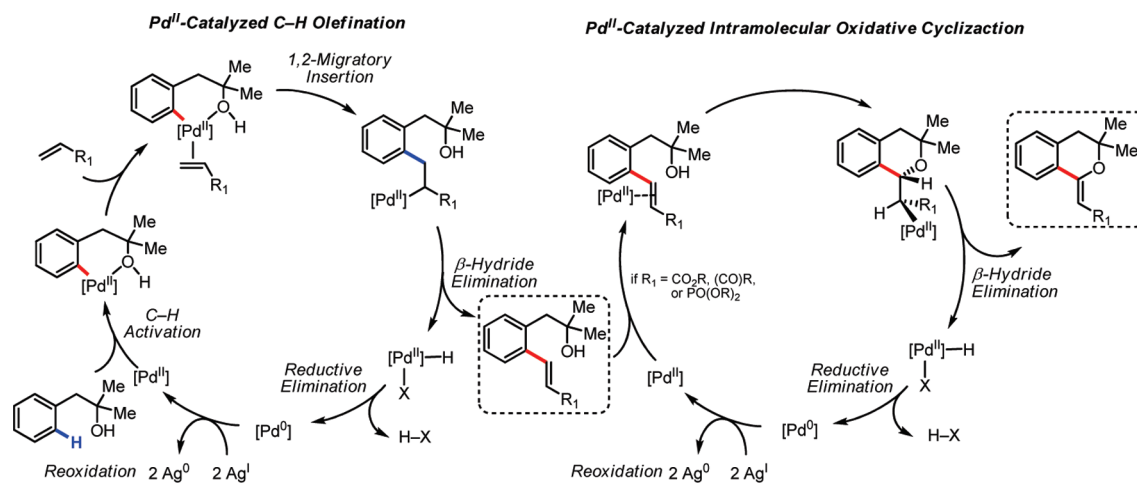
effect),²⁷ C–H insertion by Pd using secondary and primary alcohol directing groups is less kinetically favorable. Second, though we typically observed minimal formation of the anticipated oxidized ketone and aldehyde byproducts after 48 h (normally less than 5% by ¹H NMR), none of the starting material remained in the reaction mixture in the case of **17–19** and only approximately 20% in the case of **20** (as observed by ¹H NMR). This observation suggests that under our reaction conditions, competitive decomposition, presumably through the fragmentation at the benzylic carbon atom, is a problem in the case of substrates where palladation is sluggish.

2.3. Mechanistic Considerations and Catalytic Cycle. Two possible mechanistic pathways exist for the oxidative cyclization reaction following the initial C–H olefination event, as alkoxy-palladation can presumably occur via either anti- or syn-addition (paths A and B, respectively, Scheme 1). Because these two paths would lead to different olefin geometries in the resulting products, with path A leading to the *Z*-isomer and path B leading to the *E*-isomer, determination of the stereochemistry would provide strong evidence for the operative mechanism.

To address this question, we determined the stereochemistry of a representative cyclized product (**6a**). We observed an NOE between H₁ and H₂, consistent with the *Z*-stereoisomer and with path A. From this result, anti-alkoxypalladation seems to be operative.

Thus, the overall catalytic cycle is proposed to proceed as follows (Scheme 2). Following hydroxyl-directed insertion of Pd(II) into the *ortho*-C–H bond, the resulting [Pd(II)-Ar] species coordinates with an olefin. This intermediate undergoes 1,2-migratory insertion, followed by β-hydride elimination to

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Scheme 1. Two Mechanistic Pathways for the Oxidative Cyclization Event**Scheme 2.** Overall Depiction of the Catalytic Cycle for C–H Olefination/Oxidative Cyclization

generate the uncyclized intermediate. Pd(0), which is presumably stabilized by the monoprotected amino acid ligand, is then reoxidized to Pd(II) by two atoms of Ag(I), at which point it re-enters the catalytic cycle.

Following olefination, if the alkene of the resulting intermediate is nonelectrophilic, such as those in **6b–f** and **9g** (Tables 2 and 3), subsequent cyclization will not occur. If the newly installed olefin contains an electron-withdrawing group (i.e., R₁ = CO₂R, (CO)R, or PO(OR)₂ in Scheme 2), the aforementioned Pd(II)-catalyzed oxidative cyclization takes place, generating the cyclized product with Z geometry and producing Pd(0), which requires reoxidation by an additional 2 equiv of Ag(I) to re-enter the catalytic cycle.

At this point, it remains unclear whether the alcohol directing group coordinates as a neutral ligand or as an anionic ligand during the C–H activation. (In Scheme 2, for simplicity we depict the alcohol as coordinating as a neutral ligand, but anionic coordination cannot be ruled out at this time.) Studies to investigate this mechanistic question and to extend the range Pd(II)-catalyzed C–H activation reactions that can be performed using alcohol directing groups are currently underway in our laboratory.

3. Summary

In summary, we have developed an unprecedented alcohol-directed olefination reaction. The use of monoprotected amino acids to promote the reaction represents a rare example of a ligand-promoted C–H activation reaction. The coordination mode of the alcohol directing group with Pd(II) in the C–H activation step poses an intriguing question for mechanistic investigation. We anticipate that further advances in ligand

design will improve the yields of these reactions, particularly in the case of secondary and primary alcohols.

4. Experimental Section

4.1. General Information. All solvents were used as received from commercial sources without further purification. Anhydrous solvents were prepared according to standard methods.²⁸ Olefin coupling partners and reagents used to prepare the alcohol substrates were purchased from Acros, Sigma-Aldrich, TCI, and Alfa-Aesar and were used as received without further purification. Palladium acetate was purchased from Sigma-Aldrich and used without further purification. Hexafluorobenzene was purchased from Oakwood and used without further purification. ¹H NMR and ¹³C NMR spectra were recorded on Bruker-AV (400 and 100 MHz, respectively) and Bruker-DRX (500 and 125 MHz, respectively) instruments internally referenced to SiMe₄ or chloroform signals. High-resolution mass spectra were recorded at the Center for Mass Spectrometry, The Scripps Research Institute.

4.2. General Procedure for the Preparation of Alcohol Substrates. Substrates **1**, **3–9**, **15**, and **16** were prepared according to a literature procedure.²⁹ A benzyl magnesium bromide (50 mmol) solution in diethyl ether was added dropwise to a solution of ketone (55 mmol) in diethyl ether at room temperature over a 1 h period, and the resulting solution was then heated at reflux for 4 h. Subsequently, the reaction mixture was cooled to 0 °C in an ice–water bath, and 40 g of crushed ice was carefully added. Concentrated HCl was then added dropwise until all of the resulting precipitate had dissolved. The organic layer was separated, and the aqueous layer was further extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄.

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The solution was filtered, and the solvent was removed *in vacuo* to give the crude product which was purified by flash column chromatography on silica gel (using hexanes/ethyl acetate as the eluent).

Substrates **10–14** were prepared according to a literature procedure.²⁹ A three-necked flask, equipped with a magnetic stir bar, an addition funnel, and a reflux condenser, was flame-dried and then placed under an N₂ environment. To the flask were added phenylacetone (50 mmol) and anhydrous diethyl ether (50 mL). A methylmagnesium bromide solution (55 mmol, 3 N, 18 mL) was added at a rate such that the reaction mixture refluxed smoothly. When the Grignard reagent had been fully added, the reaction mixture was heated at reflux for 6 h. The reaction mixture was cooled to 0 °C in an ice–water bath, and 40 g of crushed ice was added carefully. The resulting magnesium salt precipitate was dissolved by adding concentrated hydrochloric acid. The ether layer was separated, and the aqueous layer was further extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried over Na₂SO₄. The solution was filtered, and the solvent was removed *in vacuo* to give the crude product which was purified by column chromatography on silica gel (using hexanes/ethyl acetate as the eluent).

Substrate **17** was prepared as follows. To a flame-dried 250 mL two-necked flask equipped with a reflux condenser and under an N₂ environment were added 3,4-dimethoxyphenylacetone (9.7 g, 50 mmol) and 50 mL of methanol. NaBH₄ (4.6 g, 120 mmol) was then added batch-wise at room temperature. The resulting reaction mixture was then heated at reflux for 12 h. After the reaction mixture had cooled to 0 °C in an ice–water bath, 2 N HCl was added to acidify the solution to pH 2 (as monitored by pH paper). The mixture was then extracted with diethyl ether (3 × 50 mL), and the combined organic layers were dried over anhydrous Na₂SO₄. The solution was filtered, and the solvent was removed *in vacuo* to give the crude product which was purified by column chromatography on silica gel (hexanes:ethyl acetate = 8:1).

4.3. General Procedure for Hydroxyl-Directed C–H Olefination. To a 50 mL Teflon-capped sealed tube equipped with a magnetic stir bar were added the alcohol substrate (0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol %), (+)-Menthyl(O₂C)-Leu-OH (11.2 mg, 0.04 mmol), Li₂CO₃ (14.8 mg, 0.2 mmol), AgOAc (133.5 mg, 0.8 mmol), hexafluorobenzene (1.5 mL), and the olefin coupling partner (0.2 mmol). The tube was sealed, and

the reaction mixture was stirred at 80 °C for 48 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to afford the crude product, which was then purified by flash column chromatography on silica gel to give the pure product.

4.4. Hydrogenation of the C–H Olefination Product. To a 50 mL Teflon-capped sealed tube equipped with a magnetic stir bar were added 2-methyl-1-(*m*-tolyl)propan-2-ol (32.8 mg, 0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol %), (+)-Menthyl(O₂C)-Leu-OH (11.2 mg, 0.04 mmol), Li₂CO₃ (14.8 mg, 0.2 mmol), AgOAc (133.5 mg, 0.8 mmol), hexafluorobenzene (1.5 mL), and ethyl acrylate (20.0 mg, 0.2 mmol). The tube was sealed, and the reaction mixture was stirred at 80 °C for 48 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The crude C–H olefination product was dissolved in methanol (3 mL) and transferred to a 50 mL Schlenk-type sealed tube equipped with magnetic stir bar. The tube was charged with hydrogen (balloon, 1 atm) and 10 wt % Pd/C (21.2 mg, 10 mol %) and then sealed with a Teflon cap. The reaction mixture was stirred at 80 °C overnight. After the reaction mixture had cooled to room temperature, the solution was filtered through a small pad of Celite, and the filtrate was concentrated *in vacuo*. The resulting residue was purified by silica gel flash column chromatography (hexanes:ethyl acetate = 8:1) to give the corresponding product, **3b** (44 mg, 83% yield).

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Supporting Information Available: 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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