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Catalytic, Regioselective Hydrocarbofunctionalization of Unactivated Alkenes with Diverse C−H Nucleophiles

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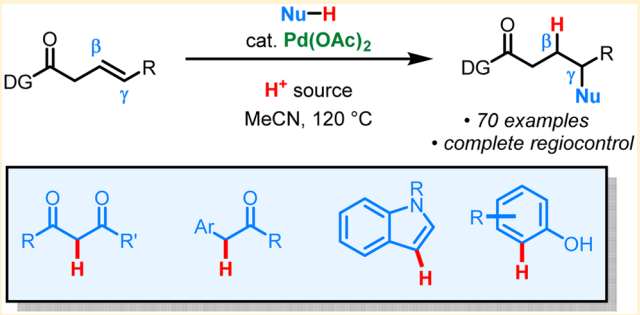
Supporting Information

ABSTRACT: Reactions that forge carbon−carbon (C−C) bonds are the bedrock of organic synthesis, widely used across the chemical sciences. We report a transformation that enables C−C bonds to be constructed from two classes of commonly available starting materials, alkenes and carbon−hydrogen (C−H) bonds. The reaction employs a palladium(II) catalyst and utilizes a removable directing group to both control the regioselectivity of carbopalladation and enable subsequent protodepalladation. A wide range of alkenes and C−H nucleophiles, including 1,3-dicarbonyls, aryl carbonyls, and electron-rich aromatics, are viable reaction partners, allowing Michael-type reactivity to be expanded beyond α,β-unsaturated carbonyl compounds to unactivated alkenes. Applications of this transformation in drug diversification and natural product total synthesis are described. Stoichiometric studies support each of the proposed steps in the catalytic cycle.



INTRODUCTION

Carbon−carbon (C−C) bonds link together to form the skeletal backbones of all organic molecules. Hence, the development of new methods for C−C bond formation is of central importance to the field of organic synthesis, providing improved routes to valuable compounds ranging from pharmaceutical agents to functional polymers.[1] Alkenes are among the most abundant classes of organic molecules, available in bulk quantities from petrochemical feedstocks and renewable resources. The widespread availability of alkenes combined with their unique reactivity profile has made alkene functionalization reactions staples in organic synthesis.[2] Nevertheless, despite its obvious attractiveness in terms of synthetic strategy for C−C bond formation, the regioselective delivery of a hydrogen and carbon atom across an alkene, hydrocarbofunctionalization, remains a tremendous challenge (Figure 1).

While many approaches have been pursued to accomplish alkene hydrocarbofunctionalization,[3] those employing simple C−H bonds as reaction partners are especially appealing due to their inherent atom economy. Traditional methods for alkene hydrocarbofunctionalization with C−H coupling partners, however, generally employ harsh reaction conditions and have limited substrate scope. For example, the Conia-ene reaction, the sigmatropic addition of enols to unactivated alkenes, requires temperatures in excess of 350 °C and can typically only be performed intramolecularly.[4] The venerable Michael reaction, one of the most reliable and efficient methods for C−C bond formation, constitutes the formal hydrocarbofunctionalization of α,β-unsaturated carbonyl compounds.[5] However, though the Michael reaction is known to proceed with a diverse range of carbon nucleophiles, it is limited to alkenes containing an electron-withdrawing group in conjugation with the alkene. Breaking this paradigm and achieving Michael-type reactivity with unactivated alkenes would offer exciting new possibilities in organic synthesis.

Transition-metal catalysis has been pursued as a strategy to overcome existing limitations in alkene hydrocarbofunctionalization with C−H coupling partners. Two general approaches have been explored: (1) oxidative addition of a low-valent metal center to a C−H bond, followed by hydrometalation and C−C reductive elimination, and (2) π-Lewis acid activation of the alkene to enable attack of a C−H nucleophile (e.g., a carbonyl compound reacting as the corresponding enol or enolate), followed by protonation of the resultant carbon−metal (C−M) bond. While significant advances have been made using the former approach, the overall scope and practical utility remain limited due to challenges in effecting C−H bond cleavage with diverse substrate classes and in controlling the regioselectivity of the hydrometalation step with internal alkenes.[6] The second approach is attractive because it does not necessitate a transition-metal-mediated C−H cleavage step and would thus potentially function with a broad range of C−H nucleophiles under a common set of reaction conditions, but the realization of a catalytic, regioselective, intermolecular variant has thus far proven elusive.[7] Key challenges in developing the proposed transformation include: (1) controlling the regioselectivity of the carbopalladation step, and (2) achieving the desired protodepalladation event in preference to β-hydride elimination. Herein, we describe the discovery and development of a

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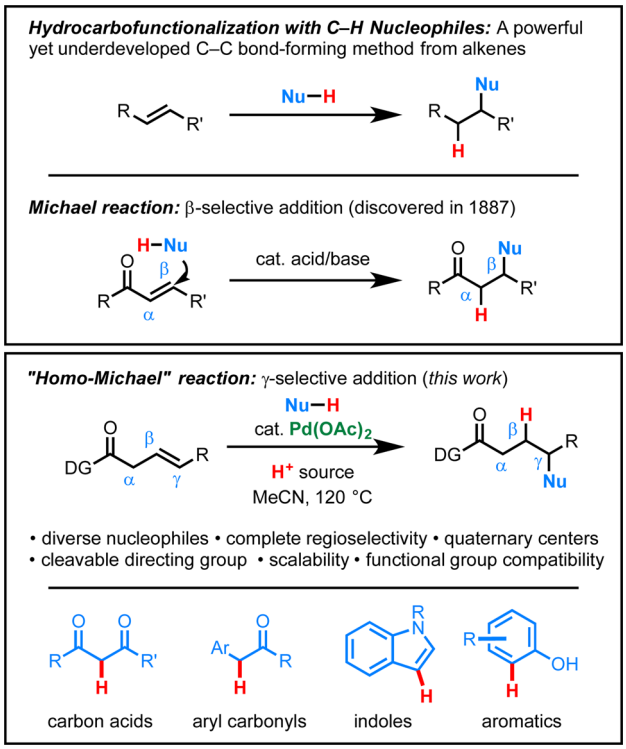

Figure 1. Development of a Pd(II)-catalyzed alkene hydrocarbofunctionalization reaction.

palladium(II)-catalyzed alkene hydrocarbofunctionalization reaction that proceeds with several different categories of C−H nucleophiles and is compatible with internal alkenes. The reaction takes advantage of a removable bidentate auxiliary and accomplishes a "homo-Michael" γ-selective addition to unsaturated carboxylic acid derivatives.

Our group recently reported a method for palladium(II)-catalyzed hydroamination of unactivated alkenes using a removable bidentate directing group.[8] In this catalytic cycle, the regiochemical course of aminopalladation is controlled by the directing group, which also subsequently stabilizes the resulting palladacycle, preventing β-hydride elimination and enabling protodepalladation with a weak Brønsted acid.[9] For the present investigation, we hypothesized that we could adjust this catalytic cycle to accommodate C−H nucleophiles, thereby enabling alkene hydrocarbofunctionalization to take place. While less studied than their N−H and O−H counterparts, C−H nucleophiles have been examined in Wacker-type carbopalladation[10] since 1965, when Takahashi and Tsuji reported the nucleophilic addition of malonate salts to cyclooctadiene in the presence of stoichiometric $PdCl_2$ (Figure 2).[11] Holton later took advantage of a dialkylamine directing group in carrying out regioselective carbopalladation of allylic amines upon activation with stoichiometric Li_2PdCl_4.[12] Hegedus demonstrated a two-step formal hydroalkylation of unactivated alkenes involving carbopalladation and hydrogenolysis with H_2 (g).[13] In 2001, Widenhoefer reported a pioneering example of intramolecular palladium(II)-catalyzed cyclization of diketones with alkenes to form cyclohexanones.[14] Although the authors anticipated catalyst turnover via protodepalladation of the alkylpalladium(II) intermediate formed upon carbopalladation, they later found that β-hydride elimination and a series of alkene isomerizations occur before eventual protonation of a palladium enolate.[15] This result underscores the difficulty of intercepting a nucleopalladated

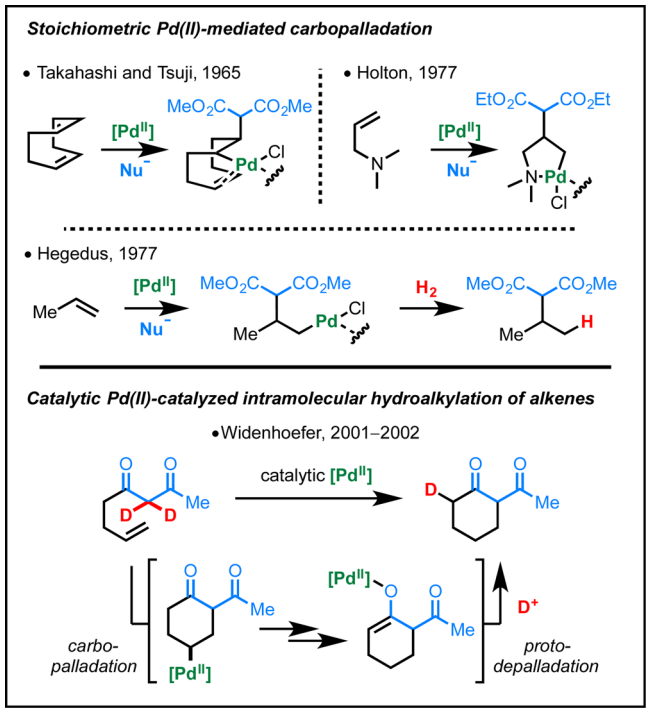

Figure 2. Key precedents for carbopalladation.

alkylpalladium(II) intermediate with a proton. Generally, palladium-catalyzed alkene hydrocarbofunctionalization with C−H nucleophiles is limited to intramolecular cyclizations or reactions involving activated or electronically biased alkenes (e.g., allenes, 1,3-dienes, and acrylates).[16] Furthermore, most studies have employed only simple 1,3-diketone C−H nucleophiles, while expansion to other C−H nucleophiles, particularly those that are less acidic, is underexplored. We envisioned that these historical limitations in palladium(II)-catalyzed alkene hydrocarbofunctionalization could be addressed using a removable directing group strategy.

RESULTS AND DISCUSSION

To initiate our investigation, we elected to use 2,4-pentanedione, a carbon acid with significant enol content, as our pilot C−H nucleophile in an attempt to achieve a formal intermolecular Conia-ene reaction. For the alkene, we selected 3-butenoic acid masked as its 8-aminoquinoline (AQ) amide (**1**), and we were delighted to observe excellent formation of hydroalkylation product **2** when the dione and alkene were heated to 120 °C in a sealed vial with 5 mol % $Pd(OAc)_2$, AcOH cocatalyst, and acetonitrile solvent (Table 1A).[17] Under these conditions, we were pleased to find that a wide array of different acidic methylene compounds, including cyclic and acyclic diketones, acetoacetates, malonates, and cyanoacetates, were efficient coupling partners, providing good yields of desired anti-Markovnikov hydroalkylated products **3**−**7**. Other activated methylene compounds including malononitrile, phosphonates, and sulfones were also reactive, but gave products **8**−**10** in reduced yields. Remarkably, this reaction also proved effective in forming tetrasubstituted carbon centers bearing heteroatoms; activated methine compounds including acetamidomalonates, nitropropanoates, 2-fluoroacetoacetates, and even amino acid surrogates were all successful in furnishing desired products **11**−**14**. Sterically hindered α-alkyl 1,3-dicarbonyl nucleophiles were similarly effective, providing access to products **15**−**19** containing all-carbon

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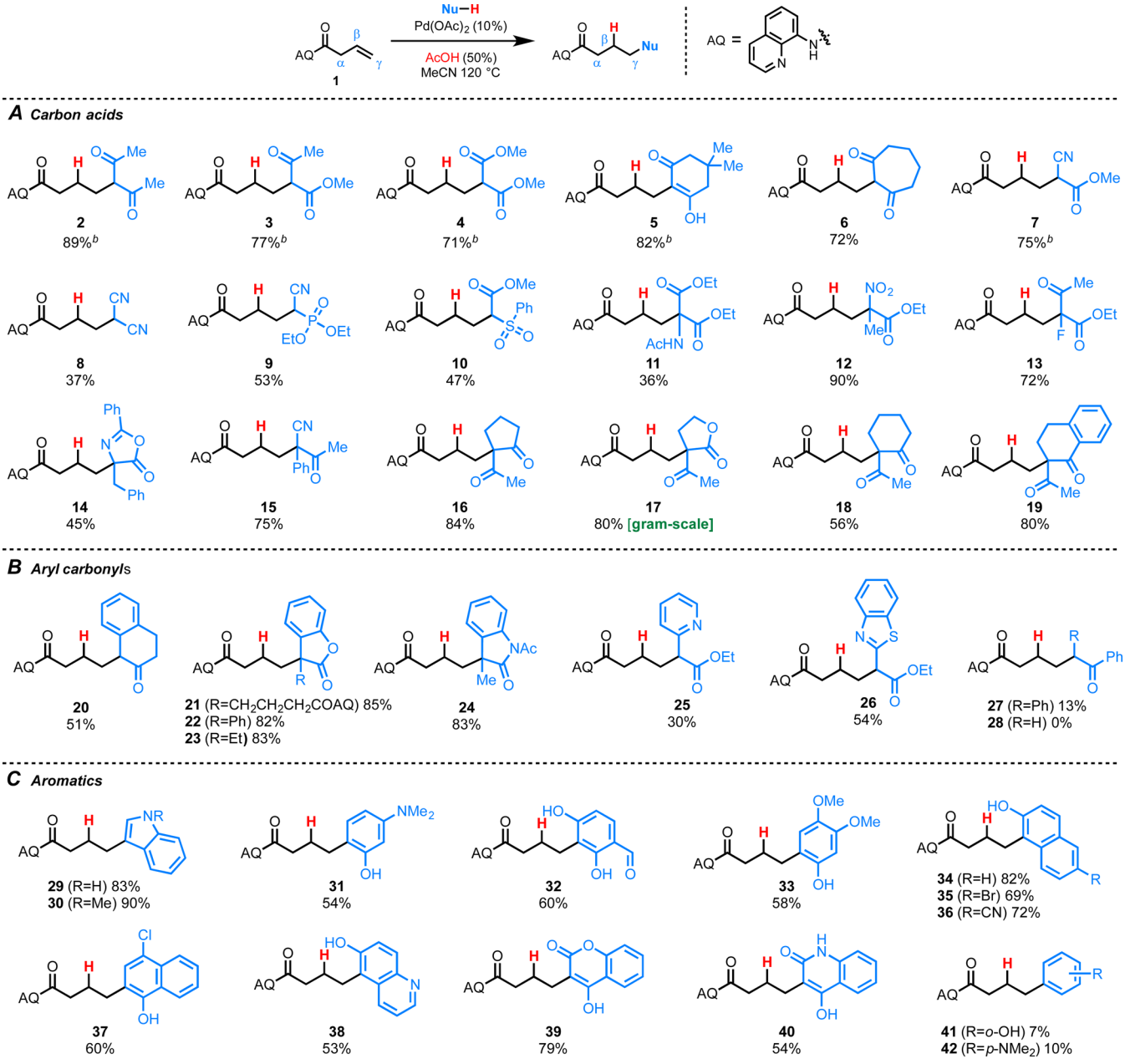
Table 1. Nucleophile Scope for Hydrocarbofunctionalization[a]



[a]All percentages correspond to isolated yields. Reaction conditions: Alkene **1** (0.2 mmol), nucleophile (0.3 mmol), AcOH (0.1 mmol), and $Pd(OAc)_2$ (10 mol %) in MeCN (0.05–0.1 mL), 120 °C, 4–36 h. [b]5 mol % $Pd(OAc)_2$.

quaternary centers. To demonstrate the scalability of the reaction, >1 g of **17** was synthesized under the standard reaction conditions.

In order to assess the potential limitations of this catalytic reaction, less acidic carbon nucleophiles were examined. We found aryl carbonyls were competent nucleophiles (Table 1B). For example, β-tetralone gave desired product **20** in 51% yield. For reasons that are currently unclear, reaction of 2-coumaranone led to the unexpected formation of diaddition product **21**. Thus, we employed 3-substituted coumaranones and oxindoles to furnish the corresponding quaternary products **22**–**24** in excellent yields. Nucleophiles containing heterocycles commonly found in small molecule pharmaceuticals (pyridine or benzothiazole) were also tolerated in the reaction. We reasoned that these nitrogen heterocycles could be protonated, promoting enolization of the carbonyl (**25** and **26**). Poor yield was obtained when 2-phenylacetophenone was used, while no product was detected with acetophenone (**27** and **28**). Collectively, these experiments reveal that nucleophiles within the pK_a range of approximately 10–18 in DMSO are potential reaction partners.

Reasoning that under the reaction conditions carbonyl-type C–H nucleophiles likely react as the corresponding enols, we next turned to alternative electron-rich C–H nucleophiles with similar structures. Gratifyingly, electron-rich aromatics were also highly reactive, allowing for anti-Markovnikov Friedel–Crafts alkylation with unactivated alkenes (Table 1C). Indoles proved highly reactive at the C3 position, providing hydroarylated products **29** and **30**. Strongly electronically activated arenes containing free hydroxyl groups were excellent coupling partners (**31**–**33**). Additionally, a variety of substituted naphthols

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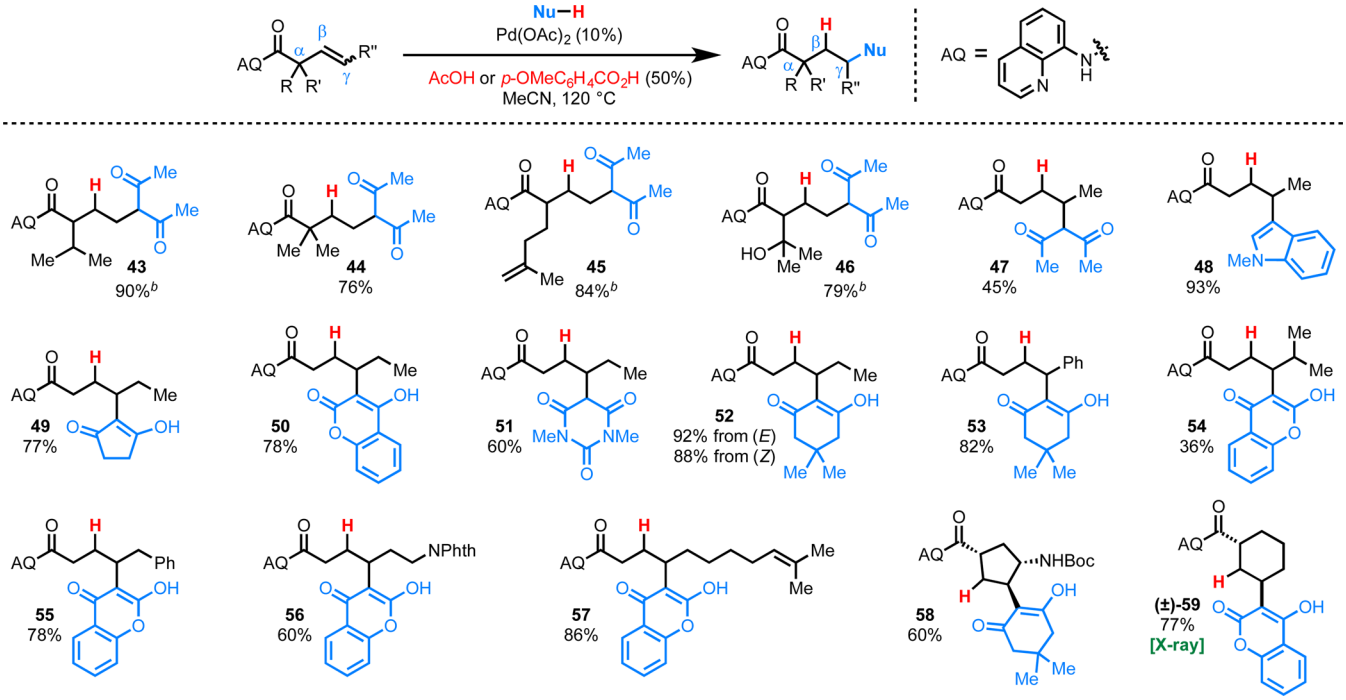
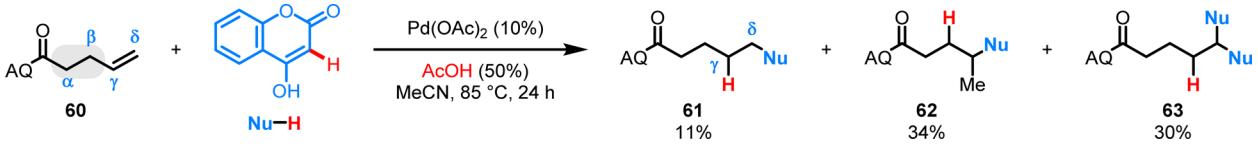
Table 2. Alkene Scope for Hydrocarbofunctionalization[a]



[a]All percentages correspond to isolated yields. Reaction conditions: Alkene (0.2 mmol), nucleophile (0.3 mmol), acid (0.1 mmol), and $Pd(OAc)_2$ (10 mol %) in MeCN (0.1 mL), 4–28 h. [b]5 mol % $Pd(OAc)_2$ and 50 mol % AcOH.

Scheme 1. Expansion to Larger Six-Membered Palladacycle



proved to be sufficiently electronically activated to give high yields (**34**–**37**).[18] Interestingly, the presence of a hydroxyl group on the arene was found to be essential for good yields, and products were typically functionalized *ortho* to the hydroxyl group. Other electron-rich aromatics including hydroxycoumarins and hydroxyquinolines were also tolerated in the reaction (**38**–**40**). A survey of other aromatic nucleophiles revealed poor performance when simpler aromatics, such as phenol or dimethylaniline, were used (**41** and **42**). The results of this regioselective Friedel–Crafts alkylation lie in sharp contrast to Brønsted or Lewis acid activation, which typically follow Markovnikov's rule, favoring formation of the branched product.[19]

An evaluation of the alkene substrate scope followed. With 2,4-pentanedione as a standard nucleophile, alkene substrates containing substituents at the α-position of the amide were reactive, and a free alcohol or a more distal and more highly substituted alkene were tolerated at this position (**43**–**46**) (Table 2). Internal alkenes also participated in the hydrocarbofunctionalization reaction, though they required the use of more reactive C–H nucleophiles. For example, while 2,4-pentanedione displayed markedly lower reactivity with internal alkenes, *N*-methylindole performed superbly (**47** and **48**).[20] A survey of several nucleophiles revealed that the best results were obtained when cyclic nucleophiles such as dimedone, barbituric acid, and hydroxycoumarin were employed (**49**–**52**). As expected, the *Z*- and *E*-configured internal alkenes performed similarly (**52**). An assortment of other internal alkenes, including a styrenyl alkene and various alkyl-substituted alkenes bearing isopropyl and benzyl groups, as well as distal functional groups, also proceeded to provide products **53**–**59**. Rigid cyclic alkenes offered a probe to examine the relative stereochemistry of the product, which sheds light on the nature of the carbopalladation step. A crystal structure of product **59** revealed that the directing group and nucleophile are *trans* to one another, consistent with *anti*-carbopalladation.[8] While less reactive, internal alkenes are still completely regioselective for addition at the γ position via the five-membered palladacycle. Given that α-alkylation of carbonyl compounds with secondary alkyl halides is typically problematic due to competitive E2 elimination, the present method is a powerful complementary approach.

Encouragingly, we have obtained preliminary data suggesting that this removable directing group approach will be amenable to different substrate classes that proceed via larger metallacycles (Scheme 1). Reacting ethylene-spaced alkene **60** with 4-hydroxycoumarin, we observed formation of a mixture of products including the desired hydroarylation product **61**, regioisomer **62**, and 1,1-difunctionalized **63**, with the latter two byproducts likely stemming from preceding isomerization and β-hydride elimination from the less stable six-membered metallacycle, respectively (see Supporting Information).

With diene substrates **64** and **65**, we hypothesized that nucleophilic attack would potentially occur at the ε position rather than the γ position (Table 3). Indeed, reaction with 2-naphthol gave adduct **66**, in which the starting diene had undergone a formal

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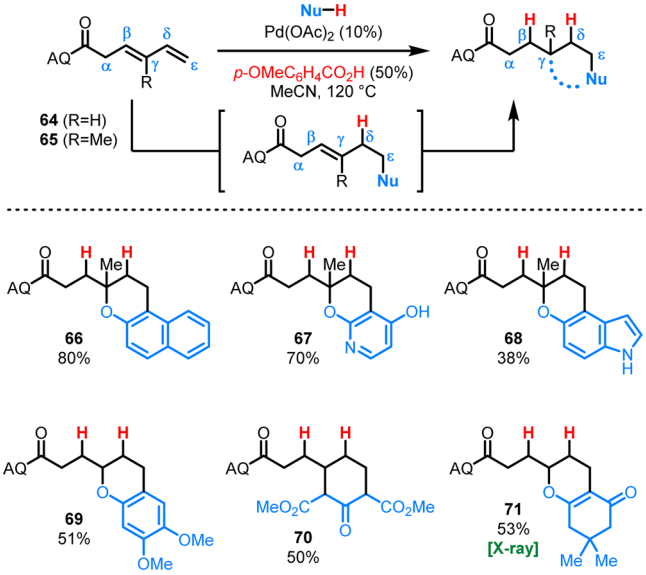
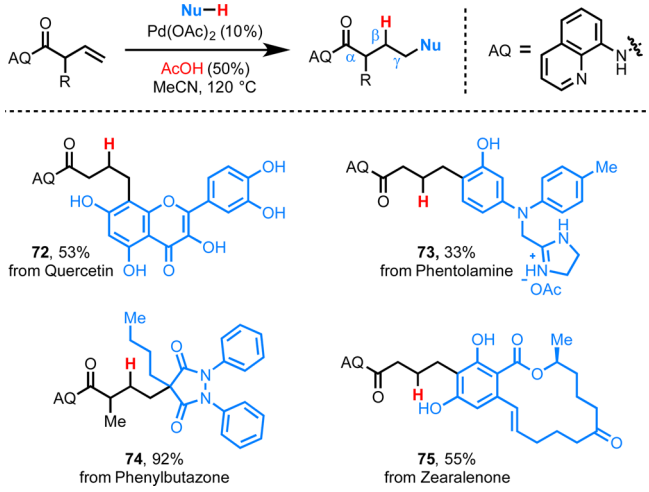
Table 3. Sequential Hydrofunctionalization: Formal [3 + 3] Cycloaddition of 1,3-Dienes[a]



[a]All percentages correspond to isolated yields. Conditions: Alkene (0.2 mmol), nucleophile (0.3 mmol), *p*-$OMeC_6H_4CO_2H$ (0.1 mmol), and $Pd(OAc)_2$ (10 mol %) in MeCN (0.1 mL), 120 °C, 4 h.

Table 4. Late-Stage Functionalization: Appendage of a Butyric Acid Derivative[a]



[a]All percentages correspond to isolated yields. Conditions: Alkene (0.1 mmol), nucleophile (0.1 mmol), AcOH (0.05 mmol), and $Pd(OAc)_2$ (10 mol %) in MeCN (0.1–0.2 mL), 120 °C, 4–6 h.

[3 + 3] cycloaddition via two consecutive hydrofunctionalization events. This transformation appears to proceed via an initial nucleophilic addition to the ε position of the alkene, followed by a δ-selective protonation of the subsequent π-allyl species.[21] The resulting β,γ-unsaturated amide presumably undergoes a second intramolecular hydrofunctionalization reaction to provide the cyclized product. A series of formal [3 + 3] cycloadditions were carried out with phenols, indoles, hydroxypyridines, diketones, and even a tricarbonyl containing oxoglutarate, which allowed the formation of two C–C bonds in succession, providing products **67**–**71**.

In order to demonstrate the practical utility and functional group tolerance of this hydrocarbofunctionalization method, we sought to utilize it for late-stage functionalization of biologically relevant molecules (Table 4). Quercetin, a densely oxygenated flavonoid with *in vitro* pharmacological activities, reacted regioselectively to provide monoalkylated product **72** as the sole product despite the fact that the starting material contains many distinct electron-rich sites. Likewise, the α-adrenergic antagonist phentolamine, which contains an imidazolinium salt, reacted to provide the *ortho*-alkylated product **73** in modest yield. Phenylbutazone, an anti-inflammatory, and zearalenone, an estrogenic mycotoxin, both similarly reacted to provide C–H alkylated products **74** and **75** in good yields. To illustrate the utility of this reaction in offering novel disconnections in retrosynthetic analysis, the first total synthesis of (±)-euparvic acid, a related compound to the immunosuppressant drug mycophenolic acid, was carried out in a one-pot procedure from resorcinol **77** to provide nearly 1 g of the natural product (**78**) (Scheme 2).[22] Notably, the AQ directing group could be conveniently cleaved to the free acid in this telescoped sequence.

A series of mechanistic experiments were performed to further clarify the reaction pathway. Treatment of styrenyl alkene **79** with stoichiometric $Pd(OAc)_2$ verified the formation of π-complex **80**, as confirmed by X-ray crystallography (Scheme 3).[23] When terminal alkene **1** was treated with stoichiometric $Pd(OAc)_2$ and 4-hydroxycoumarin in acetonitrile at room temperature, a yellow precipitate was collected to provide 89% yield of alkylpalladium(II) complex **81**, indicating a facile carbopalladation (Scheme 4). Crystals of alkyl palladium complex **81** were grown in DMF to reveal a square planar complex in which an oxygen atom from the nucleophile serves as an anionic ligand, causing the organic fragment to adopt an overall tetradentate coordination mode. Exposure of complex **81** to the standard reaction conditions confirmed the formation of desired product **39**. Alkene **60** similarly proceeded to form the alkylpalladium complex **82** in excellent yield, demonstrating that carbopalladation occurs to form larger six-membered palladacycles (Scheme 5). In order to probe the reversibility of the protodepalladation step, product **48** was heated in the presence of catalytic $Pd(OAc)_2$ in tetradeuteroacetic acid, which led to 77% deuterium incorporation at the β position of species **83** after 3 h, indicating that protodepalladation and C–H activation are reversible (Scheme 6).[24] Importantly, no deuterium incorporation is observed at the α position, ruling out the intermediacy of a palladium enolate species. To determine the possibility of reversible carbopalladation, **17** was treated with standard reaction conditions with the addition of 2 equiv of *N*-methylindole. After 24 h, 10% of the desired indole-containing product **30** was formed along with expulsion of the dicarbonyl compound. No product was detected if palladium was omitted in the reaction, supporting the notion that carbopalladation is also reversible, akin to reports of reversible oxy- or amino-palladation reactions.[25,26] Collectively, these experiments support the proposed mechanism for the hydrocarbofunctionalization of alkenes and illustrate how a directing group approach enables isolation and characterization of catalytically relevant organometallic species such as **81** (Scheme 7).

CONCLUSION

In summary, we have developed a catalytic, regioselective hydrocarbofunctionalization of unactivated alkenes with diverse C–H nucleophiles using a directing group approach. We expect that this method will find immediate use in the preparation of γ-functionalized carbonyl compounds. More broadly, we believe this work will stimulate interest in

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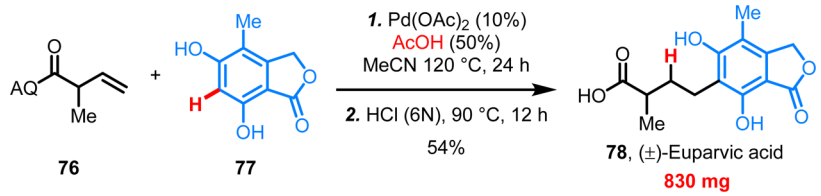
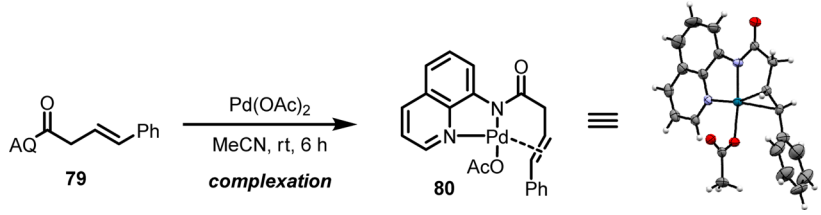
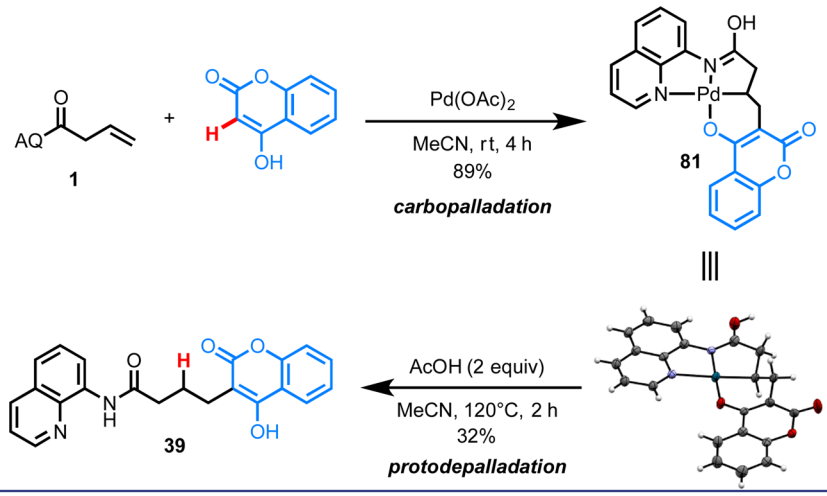
Scheme 2. Natural Product Synthesis: Scalable Route to (±)-Euparvic Acid



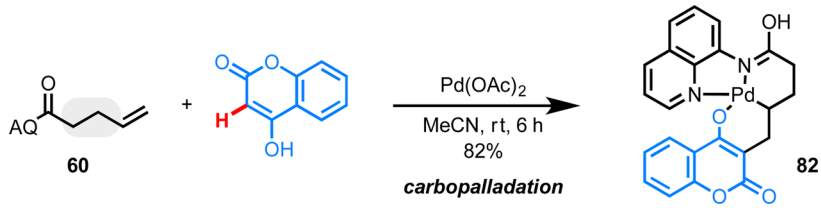
Scheme 3. Stoichiometric Formation of Palladium π-Complex 80



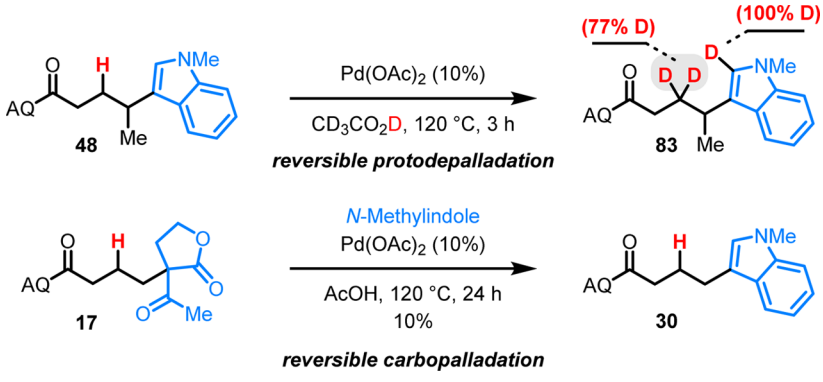
Scheme 4. Stoichiometric Carbopalladation and Protodepalladation



Scheme 5. Stoichiometric Formation of Six-Membered Palladacycle 82



Scheme 6. Catalytic Studies on Reaction Reversibility



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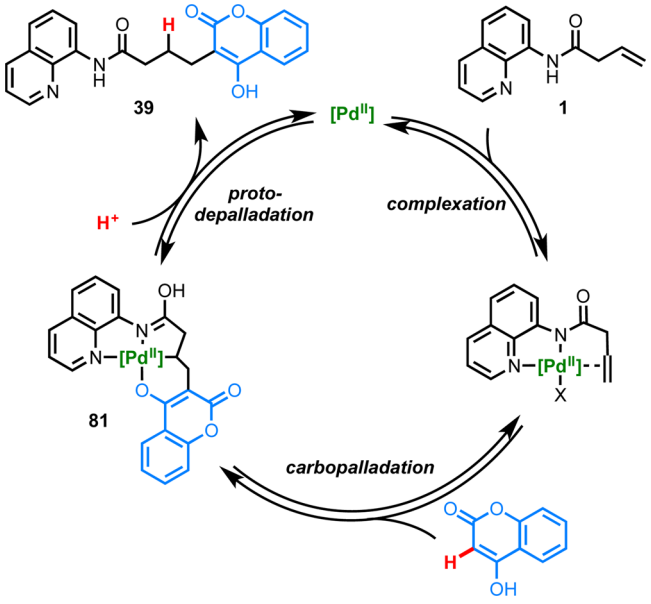
Scheme 7. Proposed Mechanism for Pd(II)-Catalyzed Hydrocarbofunctionalization of Alkenes



developing a future generation of directed and nondirected alkene functionalization reactions that have heretofore proven elusive.

EXPERIMENTAL SECTION

General Procedure for Hydrocarbofunctionalization of Unactivated Alkenes. To a 1 dram (4 mL) vial equipped with a magnetic stir bar were added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol or 4.4 mg, 0.02 mmol), alkene **1** (42.4 mg, 0.2 mmol), acetic acid (6.0 mg, 0.1 mmol), carbon nucleophile (0.3 mmol), and MeCN (0.1 mL). The vial was sealed with an unpunctured TFE septum-covered screw cap and placed in a heating block that was preheated to 120 °C. After the designated reaction time, the dark reaction mixture was purified directly by flash column chromatography to provide the desired product. Full experimental details can be found in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08850.

Experimental details and data (PDF)
Compound **59** (CIF)
Compound **71** (CIF)
Compound **80** (CIF)
Compound **81** (CIF)

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Notes

The authors declare no competing financial interest.

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