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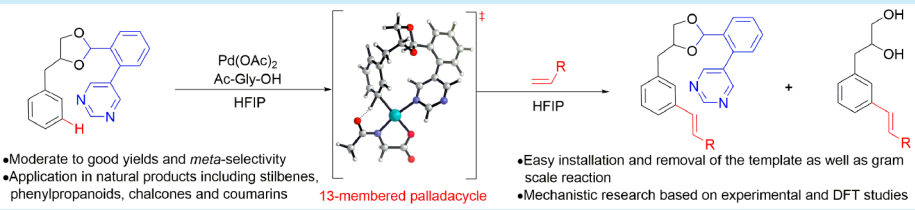
Palladium-Catalyzed *meta*-C−H Olefination of Arene-Tethered Diols Directed by Well-Designed Pyrimidine-Based Group

Siqiang Fang, Xiaobing Wang,* Fucheng Yin, Pei Cai, Huali Yang, and Lingyi Kong*

Jiangsu Key Laboratory of Bioactive Natural Product Research and State Key Laboratory of Natural Medicines, School of Traditional Chinese Pharmacy, China Pharmaceutical University, 24 Tong Jia Xiang, Nanjing 210009, People's Republic of China

Supporting Information



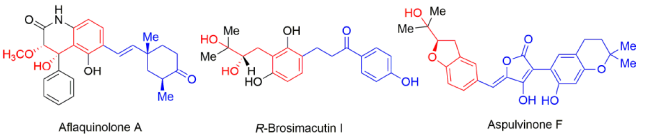
ABSTRACT: The palladium-catalyzed *meta*-olefination of arene-tethered diols attached to a well-designed pyrimidine moiety is presented. Applications of the protocol are illustrated by the synthesis of various diol-based natural products, such as coumarins, phenylpropanoids, stilbenes, and chalcones. Advantages of this method are demonstrated through the easy removal of the template and a gram-scale olefination reaction. Finally, experimental verification, including ^{1}H NMR, ESI-MS and IR, and DFT studies are undertaken to elucidate the mechanistic complexity.

Recently, carbon−hydrogen (C−H) functionalization has shown great potential to dramatically streamline synthetic efforts in total synthesis, semisynthesis, and the late-stage diversification of natural products and pharmaceuticals.[1] However, it is difficult to distinguish small differences in C−H bonds in different locations and achieve specific selectivity. With the introduction of a manifold of well-designed directing groups (DGs) that can assist transition metals in differentiating omnipresent C−H bonds, significant achievements were made in transition-metal catalyzed C−H bond functionalization.[2,3] Since carbonyl groups as DGs were presented,[4,5] *ortho*-C−H functionalization of arenes has gained momentum via steady cyclometalation.[6,7] Nevertheless, selective distal C−H bond activation is still in its infancy owing to an unstable macrocyclic transition state (TS) and intricate properties of substrates. Despite undisputable achievements in the development of the catalysis of remote C_{sp^2}−H activation reactions,[8,9] the efficiency and scope of those reactions via metal insertion are far from enabling broad applications. In this domain, it is crucial to strike a proper balance between the stability and chelate ring size of a macrocyclic TS.[10]

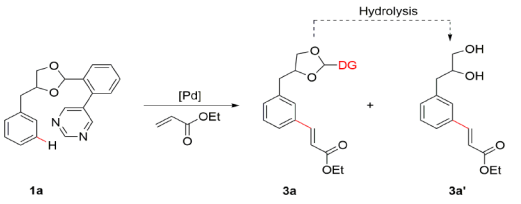
Since the *meta*-olefination of alcohol compounds was pioneered by Yu et al. using linear "end-on" coordinating nitrile groups,[11] the remote C−H functionalization of a variety of alcohol has gradually evolved.[12] Nevertheless, investigation of the remote C−H functionalization of arene-tethered diols has remained rare. Given the widespread occurrence of 1,2-diol compounds in drug compounds and bioactive natural products (Scheme 1a),[13] the distal *meta*-C−H olefination of 3-phenylpropane-1,2-diol has long been the focus of our research. Initially, we envisioned that a template-based strategy could potentially provide a route for our aim (Scheme 1b).

Scheme 1. Outline of the Research

a) Natural products with styrene scaffolds



b) The outline of this work



Through the fine-tuning of DGs and reaction conditions, we found $Pd(OAc)_2$, Ac-Gly-OH, AgF, Na_2CO_3, and pyrimidine as the DG were essential for achieving high yields and selectivity (Tables S1−S5 from the SI). The subtle impact of substrate chiralities on total yields was observed from Table S6 (SI). Next, the olefination of a variety of substituted arenes was undertaken (Scheme 2). Exclusive *meta*-products were founded for *ortho*-, *meta*-, and *para*-substituted substrates with total isolated yields of 56−92% (**1b**−**1r**), and the reaction showed good compatibility to electron-withdrawing groups as well as electron-donating groups. For **1a**, **1s**, and **1t**, which have no substituted groups, some *ortho*- or *para*-products

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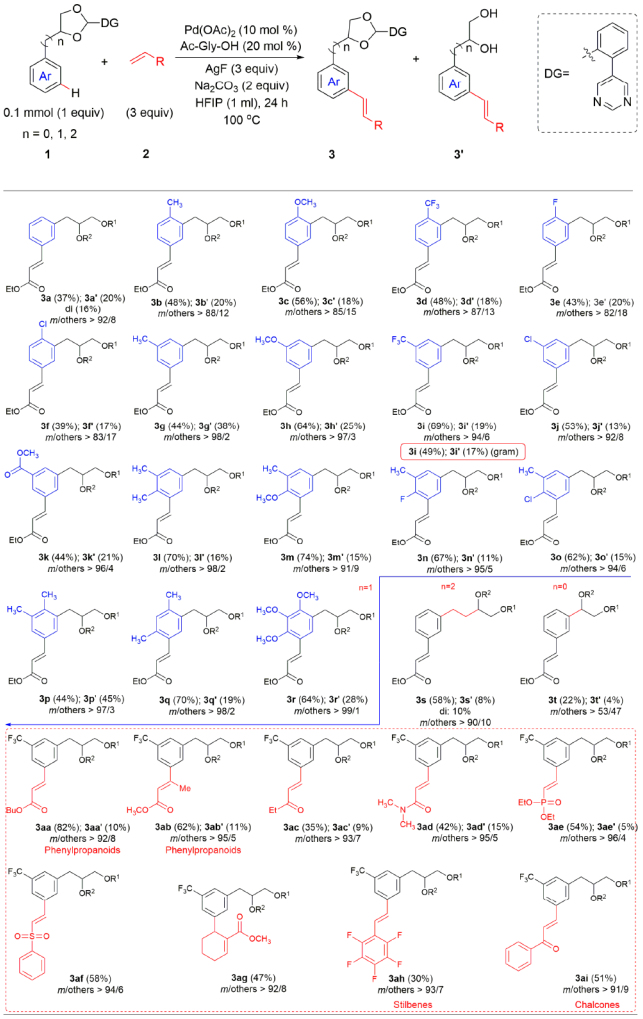
Scheme 2. Scope of Functionalized Arenes and Olefin Coupling Partners[a,b,c]



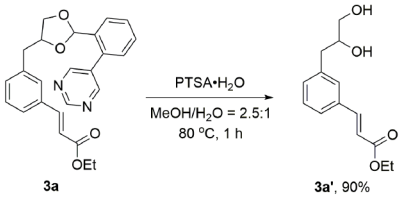
[a]*meta*-C−H Olefinations were all undertaken on 0.1 mmol. [b]Data were reported as isolated yields. [c]Others refer to *ortho*- or *para*-products, and *m*/others values were determined by ^{1}H NMR.

emerged. Next, a gram-scale experiment was performed to demonstrate the utility of this protocol. With **1i** of **1g**, the reaction was scalable in normal reaction equipment and gave the olefinated products with a total yield of 66%. Gratifyingly, the pyrimidine template was also available for the *meta*-C−H olefination of **1s** and **1t** with different chain lengths, although decreasing the aliphatic chain length distinctly reduced the yield, possibly due to an increase in steric hindrance. In addition, we further investigated whether the protocol could be applied to a wide range of olefin coupling partners. As expected, butyl acrylate, ketone, amide, and phosphonate (**3aa**, **3ac**, **3ad**, and **3ae**, respectively) could all be effectively tolerated with moderate to good yields. This reaction was also suitable for the 1,2-disubstituted olefin (**3ab**). Notably, phenyl vinyl sulfone, cyclohexene, phenyl ketene, and styrene gave no hydrolysis products (**3af**−**3ai**). It might be attributed to spatial or electronic effects.

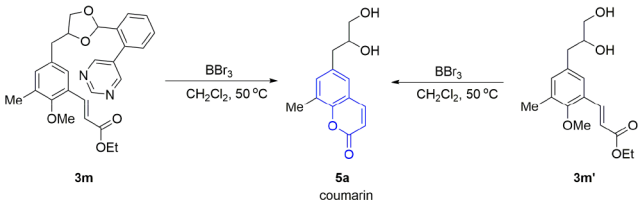
Next, as shown in Scheme 3a, another major advantage of this method is the easy removal of the template by a hydrolysis step. Substrate **3a** was readily converted to *meta*-olefinated free benzyl diol **3a′** in 90% yield under acidic conditions. In

Scheme 3. Utility of This Method

a) Removal of the directing template



b) Synthesis of the coumarin analogue **5a**



addition, to explore the elaboration of this approach, we used the alkenylated product **3m** or **3m′** as the reactant and thereby achieved the synthesis of **5a**, a coumarin analogue, by a ring-closing reaction (Scheme 3b).

To elucidate the reaction mechanism, deuterium-labeling experiments were performed. Two parallel experiments with **1a** and *D*-**1a** provided a k_H/k_D value of 1.17. Furthermore, an intermolecular competition experiment was carried out and gave a P_H/P_D value of 1.78 (Scheme 4a). This result suggests that C−H activation is not the rate-limiting step, and the mechanism may be related to radicals.[14] Next, radical trapping experiments were explored. The reaction still proceeded with the addition of the radical scavengers TEMPO and BHT, and there was no remarkable dropoff of the yield. These results eliminate the possibility of a radical process (Scheme 4b). To develop a better understanding of the reaction mechanism, the reaction was monitored using real-time online ^{1}H NMR.[15] The ^{1}H NMR analysis experiments were carried out in the same clean NMR tube in a continuous sequence. For this experiment, For-Gly-OH was used instead of Ac-Gly-OH. As shown in Scheme 4c, upon the addition of the MPAA ligand followed by the addition of substrate **1a**, the absolute integral of the acetyl (-Ac) peak gradually decreased and inversely the acetic acid (AcOH) peak increased, which indicates the release of the acetyl group from $Pd(OAc)_2$ and then the formation of the acetic acid. These results suggest the process from the intermediate **II′** to the intermediate **III′**. Meanwhile, this process was also confirmed by the ESI-MS (Scheme 4d). In addition, the formation of the interaction between the palladium and substrate **1a** was also proved by IR analysis (see Figure S4 from the SI).

According to the above mechanistic studies and related reports,[16] a detailed description of our proposed mechanism for this reaction is outlined in Scheme 5. Under standard conditions, the interaction of $Pd(OAc)_2$, HFIP, and Ac-Gly-OH forms intermediate **II**. In the presence of **1a**, the intermediate **II** undergoes substrate binding to form intermediate **III**, which leads to the formation of intermediate **IV**, a 13-membered palladacycle. Subsequently, olefin coordination, 1,2-migratory insertion, *β*-hydride elimination, and finally reductive elimination produce desired *meta*-olefinated products, which may generate the hydroxylated compound

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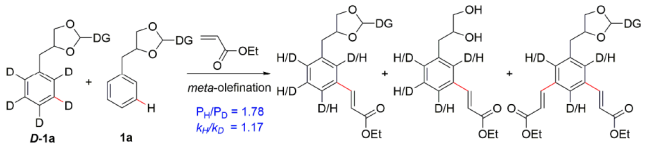
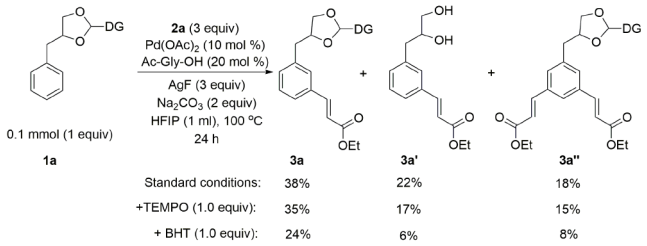
Scheme 4. Mechanistic Studies

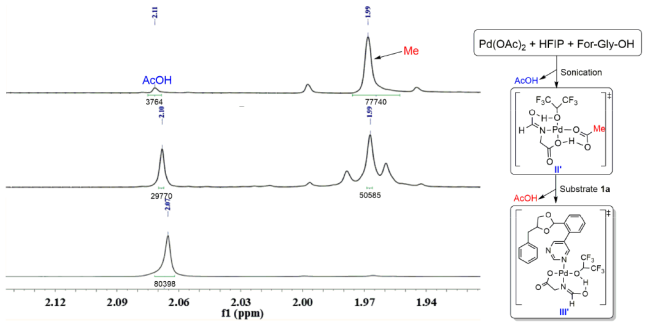
a) KIE experiments



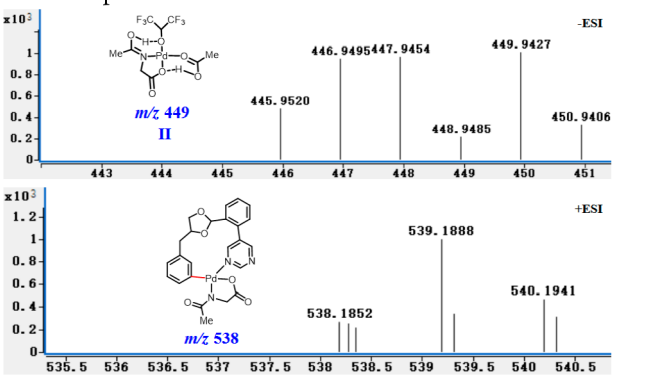
b) Radical trapping experiments



c) Real-time on-line ^{1}H NMR monitoring of Pd-ligand-substrate interaction



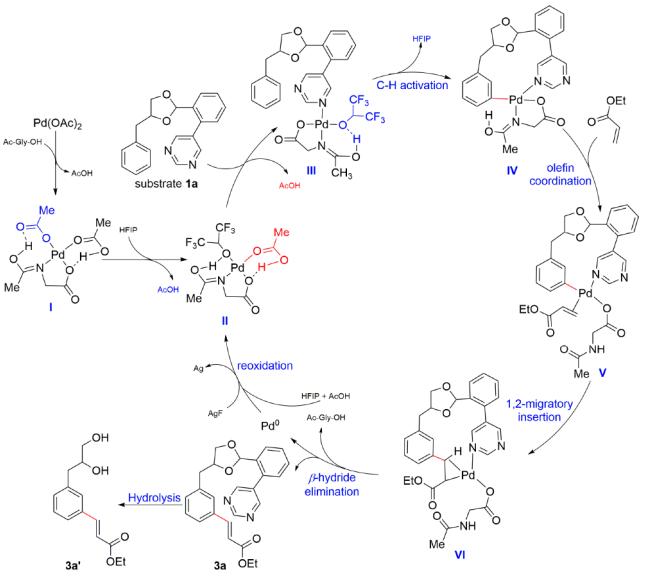
d) ESI-MS studies to detect the monomeric Pd-Gly-HFIP and Pd-arene complex



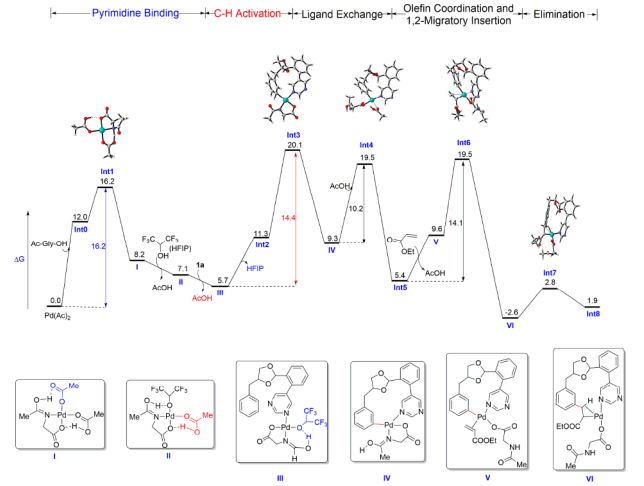
through acid catalyzed hydrolysis in the case of HFIP. Meanwhile, the Pd^0 intermediate regenerates Pd^{II} by reoxidation, which completes the mechanistic cycle.

To further illuminate this mechanism, DFT studies were carried out (Scheme 6). The proposed initiation of the mechanism is the formation of the monomeric Pd-Gly complex **I**. At the same time, bidentate coordination between Ac-Gly-OH and palladium may facilitate ligand exchange of the acetate with HFIP. As shown in Scheme 6, the change from intermediate **I** to **II** is exergonic, which indicates that HFIP may act as an active ligand leading to coordination of the substrate **1a**. The ^{1}H NMR and ESI-MS experiments shown in

Scheme 5. A Plausible Mechanistic Cycle



Scheme 6. Free Energy Profile for the Mechanistic Cycle



Scheme 4c and Scheme 4d can also lay a solid foundation for HFIP intervention. Obviously, the deprotonation of **1a** by the amide of Ac-Gly-OH as an intramolecular base is significantly endergonic,[17] which illuminates why lower temperatures do not enable this reaction to proceed. Notably, C−H activation may occur through the concerted-metalation-deprotonation (CMD) pathway.[18]

In conclusion, we have disclosed the Pd^{II}-catalyzed *meta*-C−H olefination of arene-tethered diols attached to a pyrimidine template. Electron-withdrawing and electron-donating groups are tolerated at all positions on the 3-phenylpropane-1,2-diol framework. The site-selective olefination of arene-tethered diols across different linker lengths and a broad coupling partner scope can enable the rapid adoption of this methodology in the pursuit of bioactive natural products including phenylpropanoids, stilbenes, chalcones, and coumarins. Easy removal of the template and gram-scale reaction demonstrated the utility of this protocol. Finally, experimental and computational studies provide the basis of the reaction mechanism. Further applications of this protocol to natural compounds are underway.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00433.

Detailed experimental and computational procedures and compound characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: cpu_lykong@126.com.
*E-mail: xbwang@cpu.edu.cn.

ORCID

Xiaobing Wang: 0000-0001-5044-3721
Lingyi Kong: 0000-0001-9712-2618

Notes

The authors declare no competing financial interest.

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