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C−H Functionalization via Remote Hydride Elimination: Palladium Catalyzed Dehydrogenation of *ortho*-Acyl Phenols to Flavonoids

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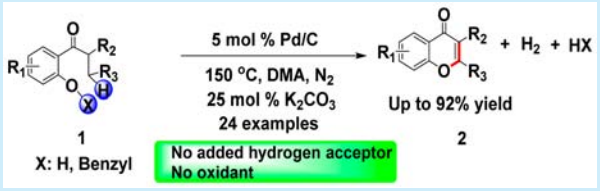
Supporting Information

ABSTRACT: Although deprotonation of electron-poor C−H bonds to carbon anions with bases has long been known and widely used in organic synthesis, the hydride elimination from electron-rich C−H bonds to carbon cations or partial carbocations for the introduction of nucleophiles is a comparatively less explored area. Here we report that the carbonyl β-C(sp^3)−H bond hydrogens of *ortho*-acyl phenols could be substituted by intramolecular phenolic hydroxyls to form O-heterocycles, followed by dehydrogenation of the O-heterocycle into flavonoids. The cascade reaction is catalyzed by Pd/C without added oxidants and sacrificing hydrogen acceptors.



Carbon−heteroatom (O, S, N, and P) bond formation is a fundamental reaction in chemical synthesis. Traditionally, the construction of carbon−heteroatom bonds relies mainly on the transformation of functional groups except for the direct oxidation/halogenation of C−H bonds; thus, these reactions require a substrate containing pre-existing functional groups, such as halides, carbonyls, alcohols or alkenes, or additional synthetic steps for introduction of functional groups into the substrates. A streamlined approach for carbon−heteroatom bond construction is direct installation of functional groups at C−H bonds. Recent progress in this field shows that a large and varied number of functionalization methods have been developed for site-selective and stereoselective C−H functionalization in a variety of molecular contexts.[1] However, most successful methodologies for C−H functionalization often require C−H bond coupling partner prefunctionalization (most for C−H bond alkylation), e.g. preoxidation, prehalogenation, and prediazotization,[2] use of stoichiometric strong chemical oxidants, or sacrificial hydrogen acceptors.[3]

Alternatively, direct transformation of C−H bonds into carbon−heteroatom bonds may be realized through patterns of replacement of C−H bond hydrogens by heteroatom-containing nucleophiles, in which prefunctionalization of C−H bond coupling partners, oxidants, or hydrogen acceptors would not be needed. Such protocols have the potential to substantially streamline the process of precision installation of functional groups at C−H bonds. For now, however, direct replacement of C−H bond hydrogens with nucleophiles is largely a thought experiment and reports on this particular subject remain extremely limited.

Herein, we describe the discovery, development, and study of reactions that achieve this goal. Specifically, in the one-step synthesis of flavonoids from *ortho*-acyl phenols or phenyl benzyl ethers, we developed a palladium(0)-catalyzed dehydrogenation system where the β-C−H bond hydrogens of ketones were directly and selectively replaced by the intramolecular phenolic hydroxyls or phenyl benzyl ethers to form O-heterocycles, followed by dehydrogenation of the O-heterocycle into target flavonoid molecules without any added oxidants and sacrificing hydrogen acceptors. The phenolic hydroxyl coupling with the β-C−H bonds to form a ring in the reaction results in a hydrogen atom that is nucleophilically substituted, so we refer to this class of reactions as hydrogen substitution C−H functionalization (HSCHF).

Our strategy for HSCHF was inspired by a substitution reaction. We reasoned that if C−H bond hydrogens could be substituted by nucleophilic heteroatom functional groups, a HSCHF reaction without added oxidants and hydrogen acceptors would be realized. While HSCHF is an intuitively appealing idea, we soon realized that the practical execution of this synthetic strategy is a formidable task, needing to overcome two fundamental challenges: (i) finding which hydrogen of C−H bonds can be replaced by nucleophiles in complex molecules and (ii) how can we allow the hydrogen of nonpolarized C−H bonds to be nucleophilically substituted.

Fortunately, the deprotonation of C−H bonds in organic molecules provides very good enlightenment to address the first challenge. The C−H bonds bonded to electron-withdrawing groups are known to benefit the C−H bond deprotonation with bases; thus, we foresee that the electron-rich C−H bonds, which are bonded to electron-donating groups or aryl groups, should have the potential to eliminate the hydrides from the C−H bonds to generate the corresponding carbon cations or partial carbocations for nucleophilic reactions. Hence the electron-rich C−H bonds can potentially be functionalized by nucleophiles.

To the second major challenge, although C−H bond hydrogens are exceedingly poor leaving groups, there are still

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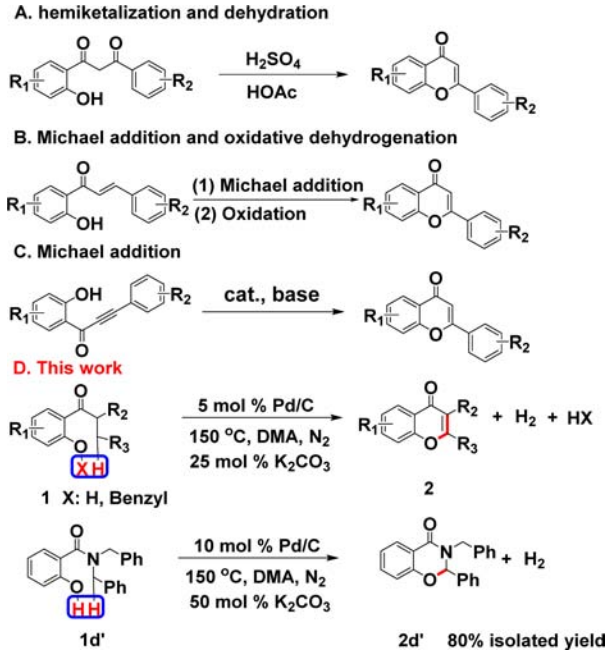
some specific C−H bonds that can eliminate the hydride by transition metal catalysis. For example, recently emerging acceptorless dehydrogenation of alcohols to the carbonyl compounds showed that some transition metal complexes in combination with hydroxyl groups of alcohols were capable of β-C−H bond hydride elimination to form a C═O bond and H_2.[4] These metal complex β-hydride elimination methods for acceptorless dehydrogenation of alcohols educe an illuminative clue for the design and development of an HSCHF reaction. However, the existing examples of hydride elimination are still primarily confined to adjacent β-hydride elimination to form a double bond. Metal complex hydride elimination from a remote C−H bond (more than two atomic centers away) to form a new single bond remains to be proven. As a consequence, we questioned whether it would be possible to utilize metal insertion into a hydrogen(carbon)−heteroatom bond to accomplish hydride elimination from a remote electron-rich C−H bond to form a carbon−heteroatom bond and H_2 release. If such a remote hydride elimination occurs indeed, an HSCHF reaction without added oxidants and hydrogen acceptors would be realized. With these design principles in mind, we focused our efforts on finding the metal catalyst that is able to achieve this goal. Recently, we discovered the palladium(0) has the ability to dehydrogenate organic compounds without oxidants or hydrogen acceptors.[5] The findings suggest that palladium(0) would serve as the effective catalyst for the designated HSCHF reactions. We hypothesize that metal palladium insertion in O−H bonds may eliminate the hydride from distant electron-rich C−H bonds (e.g., hydride elimination from ζ-position C−H bonds to form C(ζ)−O bonds and H_2 release) to realize a HSCHF reaction. Thus, we selected flavonoid synthesis as the research subject and used Pd/C as the palladium(0) catalyst to develop an HSCHF method for streamlined synthesis of flavonoids.

Flavonoids are a class of plant secondary metabolites and found to have a wide range of biological and pharmacological activities.[6] The commonly used methods for flavonoid synthesis typically require a key C−O bond formation step, in which the phenolic hydroxyl is coupled with a pre-existing intramolecular functional group such as a carbonyl,[7] alkene,[8] or alkyne[9] group to form the O-heterocycle (Scheme 1) .

It was intriguing to see if the phenolic hydroxyl could directly couple with the intramolecular β-C−H bonds of the ketone to form the C−O bond without intermediate conversion steps (prior functionalization of the C−H bonds), oxidants, or hydrogen acceptors. Toward this end, we devised an HSCHF protocol for the C−O bond formation and applied it in flavonoid synthesis, which is outlined below (Figure 1).

In the HSCHF approach design for flavonoid synthesis, the C(β)−H of **3** was considered as a latent functional group which has the potential to eliminate hydrides from themselves due to the enol hydroxyl groups which can donate an electron to the C(β)−H bonds (Figure 1). Thus, the hydrogen of C(β)−H bonds of **3** would be eliminated and replaced by the nucleophilic intramolecular phenolic hydroxyl groups according to our hypothesis. On the basis of our previous studies on palladium-catalyzed acceptorless dehydrogenations, we employed Pd/C to implement the reaction. The palladium(0) insertion into the O−X bond formed intermediate **4**. We hypothesized the palladium(II) in **4** would abstract hydrides from the remote ζ-position C−H bonds to form **5** and HPdX (the process is termed ζ-hydride elimination). The procedure is essentially similar to β-hydride elimination, but varies in β-

Scheme 1. Synthetic Approaches to Flavonoids



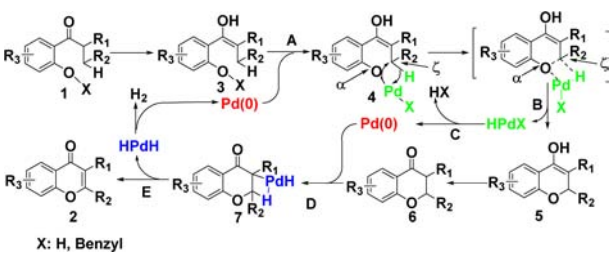


Figure 1. Working hypothesis regarding a HSCHF strategy for flavonoid synthesis. R_1, R_2, R_3: alkyl, aryl, and benzyl. (A) Oxidative addition; (B) ζ-hydride elimination; (C) reductive elimination; (D) oxidative addition; (E) β-hydride elimination.

hydride elimination forming one new bond between the α- and β-position (resulting in a double bond formation) while ζ-hydride elimination forms one new single bond between the α- and ζ-position. The HPdX regenerates Pd(0) and HX by reductive elimination. The conversion of **6** to **2** would be realized via successive oxidative addition and β-hydride elimination processes. This successive process should be feasible according to our previous studies on palladium-catalyzed acceptorless dehydrogenation and aromatization.[5]

To begin our study we used Pd/C as the palladium(0) catalyst, *N*,*N*-dimethylacetamide (DMA) as the solvent, 1 atm of N_2 (as a N_2 balloon), and 150 °C for investigation of the reactivity. Using 5 mol % of Pd, 0.5 mL of DMA, 50 mol % Cs_2CO_3, and a 12 h reaction time, we observed a 68% conversion of **1a** into flavonoid **2a** with 98% selectivity (Table 1, entry 1). This result clearly indicated the assumptive HSCHF for flavonoid synthesis was feasible and inspired us to further optimize the reaction conditions. A variety of additives were screened for their ability to promote the reaction. The acidic additives have proved deleterious to the reaction. In contrast, most alkaline additives provide excellent product yields. The reaction remained almost unreactive in the absence of both acids and bases (Table 1, entry 3). The effect of different solvents was also evaluated. Strong polar aprotic solvents are

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Table 1. Reaction Optimization for the Dehydrogenation of *ortho*-Acyl Phenol to Flavonoids

entry	conditions	conv/select/yield (%)[a]
1	DMA/5% Pd/50% Cs_2CO_3/150 °C/N_2	68/98/67
2	DMA/5% Pd/50% CH_3COOH/150 °C/N_2	NR/NR/NR
3	DMA/5% Pd/150 °C/N_2	3/50/2
4	DMA/5% Pd/75% K_2CO_3/150 °C/N_2	80/94/75
5	**DMA/5% Pd/25% K_2CO_3/150 °C/N_2**	**99/99/98**
6	DMA/5% Pd/25% K_2CO_3/140 °C/N_2	93/98/91
7	DMA/5% Pd/25% K_2CO_3/150 °C/O_2	83/54/45

[a]Determined by GC analysis using n-dodecane as the internal standard.

generally effective for conversion of the substrates to the desired flavonoids. We were surprised to discover that molecular oxygen not only does not promote the reaction conversion but also reduces the reaction selectivity greatly compared with the reaction under N_2 (Table 1, entry 5 vs 7). Using 5 mol % Pd, 25 mol % K_2CO_3, 1 atm of N_2, and 150 °C reaction conditions, we observed that 98% **1a** was converted into flavonoid **2a** with 98% selectivity (Table 1, entry 5).

With these optimized conditions in hand (Table 1, entry 5), we next set out to explore the scope of this new reaction. The results shown in Figure 3 demonstrated that the newly developed protocol was effective in the preparation of a number of substituted flavornoid derivatives. A wide range of different functional groups were tolerated under the optimized conditions. Substrates with aryl, naphthyl, and benzyol groups on the carbon β of the carbonyl afforded high yields of the desired flavonoids. Varying substituent groups including methyl, aryl, and benzyl groups on the carbon (α) of ketones had little effect on the outcome of the reaction. The β-C−H bonds of substrate **1t** and **1u** are generally regarded as being less reactive for functionalization because of the absence of functional groups on the β carbons. It is noteworthy that these two substrates were also very smoothly converted into the desired products in moderate yields (Figure 3, **2t**, **2u**). A nitrogen-containing substrate seldom interfered with the catalytic reaction and also gave excellent yields (Figure 3, **2q**). For substrate **1e**, the reaction isolated yield was up to 92% (Figure 3, **2e**). This result arises because the methoxyl electron effect was conducive to *para*-benzyl hydride elimination.

The reaction would produce H_2 according to our working hypothesis (see Figure 1), but attempts to determine the H_2 product with GC analysis did not provide positive results, likely due to the very low concentration of H_2 in the reaction gas atmosphere. To facilitate the detection of the substituted hydrogen in the hydrogen substitution reaction step, we modified the working hypothesis; namely, the hydrogen of the phenolic hydroxyl was replaced by benzyls (Figure 1, X: benzyls), so that the substituted hydrogen would be converted into liquid/solid toluene derivatives (HX) rather than H_2 gas. As can be expected, we clearly detected 4-chlorotoluene in the reaction mixture with GC-MS analysis when substrates were *ortho*-acyl phenyl 4-chlorobenzyl ethers (the phenolic hydroxyl hydrogen of substrates was replaced by 4-chlorobenzyl). The hydrogen of β-C−H bonds of the ketones was transferred to the 4-chlorobenzyl. These *ortho*-acyl phenyl benzyl ethers as the reaction substrates also obtained moderate isolated yields of flavonoids (Figure 3, **2a′**−**2c′**). Ethers are seldom used as C−H bond coupling reaction partners or nucleophilic reagents for

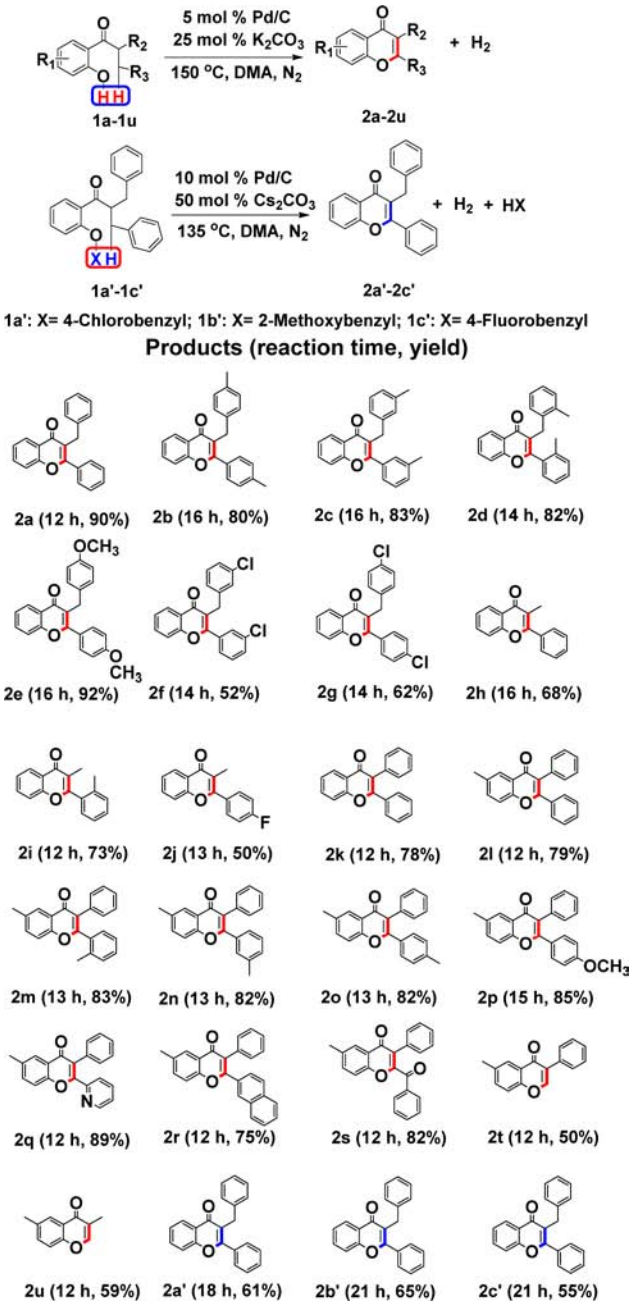

Figure 3. Palladium-catalyzed dehydrogenation of o-acyl phenols/phenyl benzyl ethers to flavonoids.

nucleophilic substitution. It is noteworthy that, in this protocol, C−H functionalization could be implemented using ethers as the coupling partners.

The C−O bond formation step is central to the reaction. The mechanism described in Figure 1 provides a possible pathway for the C−O bond formation to generate the intermediate **6**. However, another pathway for formation of intermediate **6** is also possible; namely, the reaction undergoes a stepwise process involving carbonyl α-C−H palladation, β-hydrogen elimination to the enones, and the phenolic hydroxyl Michael addition. Key to the second mechanism is the enone formation. For the substrates that exhibited difficulty in generating the enone intermediate, the reaction preferred to proceed via the first mechanism. To prove that the C−O bond formation does not have to undergo the second mechanism, we carried out the

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reaction with a salicylamide compound as the substrate. The salicylamide demonstrated difficulty in forming the enone intermediate in the reaction, but it does not hinder forming the C−O bond, providing an up to 80% isolated yield of the cyclized product (see Scheme 1D). This reaction has been reported by the Maiti group using a Cu/O_2 catalytic system, but it failed to proceed under N_2.[10]

The results presented clearly show that the hydrogen of electron-rich C−H bonds may be viewed as leaving group equivalents and can be substituted by nucleophilic reagents in the presence of palladium(0). These findings provide new access to C−H functionalization directly through C−H bond hydrogen substitution without oxidants, hydrogen acceptors, and substrate prefunctionalization. Furthermore, these reactions being without oxidants and hydrogen acceptors circumvent the intrinsic reaction complications normally associated with oxidative C−H functionalization and also avoid the byproducts from oxidants, hydrogen acceptors, and C−H bond coupling partners. The novel use of palladium(0) in place of high valence state palladium as the catalyst and the realization of ζ-hydride elimination play crucial roles in this transformation. These reactions for flavonoid synthesis exhibit high isolated yields, functional-group tolerance, and atom economy. Taken together, the broad substrate scope and applications and the use of minimum quantities of additives as well as a simple and recycled catalyst in these transformations make the substitution C−H functionalization strategy for organic synthesis intrinsically easy for industrial applications. As an effective complement to the current dehydrogenative synthetic methods, the protocol represents a significant step forward in the constant search for more streamlined and greener chemical synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03652.

Experimental details for chemical synthesis of all compounds, materials, supplementary text, and NMR spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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