Dehydrogenation of Inert Alkyl Groups via Remote C−H Activation: Converting a Propyl Group into a π-Allylic Complex

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Summary: Pd(OAc)$_2$-mediated dehydrogenation of an alkyl group to a double bond or a η^3-allylic complex via sp^3 C−H bond activation and allylic oxidation is reported. A novel redox is proposed for this double oxidation under oxidant-free conditions. A catalytic protocol using benzoquinone as the stoichiometric oxidant has also been developed for the dehydrogenation of cyclopentylcarboxamides.

Metal-catalyzed C−H bond activation has received considerable attention in recent years.[1] In particular, palladium has been extensively used in sp^2 and sp^3 C−H bond functionalizations.[2] While direct hydrocarbon C−H functionalization remains a significant challenge,[3] the chelation-assisted activation of inert sp^3 C−H bonds is relatively well-established.[4] Heteroatom-assisted C−H cleavages, such as those directed by oximes,[5] oxazolines,[6] pyridines,[7] and amides,[8] have been extensively explored. Simple functionalities such as *Boc*,[9] carboxyl,[10,11] and amino[12] groups have also been shown to be effective in directing Pd(II) insertions into C−H bonds. These chelates share a common mechanistic theme of forming a five-membered palladacycle.[13] We have recently characterized by X-ray crystallography a number of such C(sp^3)−Pd complexes.[6d] Herein we report a Pd(OAc)$_2$-mediated dehydrogenation of an alkyl group into a double bond or a π-allylic C(sp^3)−Pd complex using oxazolylamide as a directing group. A catalytic protocol has also been developed for the dehydrogenation of cyclopentylcarboxamides.

β-Hydride elimination is one of the fundamental events in C−H bond activation.[14] Such a process can be harnessed to construct a useful synthetic target using a stoichiometric amount of a cationic Pt complex (L_2PtMeOTf).[15] Transfer dehydrogenation using dihydrido iridium PCP pincer complexes (PCPIrH_2)[3b,16] has been developed into an elegant synthetic process, whereby a hydrocarbon is dehydrogenated. Dehydrogenation of carbonyl compounds to α,β-unsaturated systems using organoselenium,[17] iodine(V),[18] and Pd(OAc)$_2$[19] have found broad utility in

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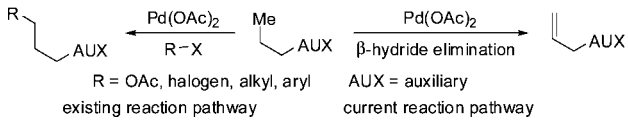
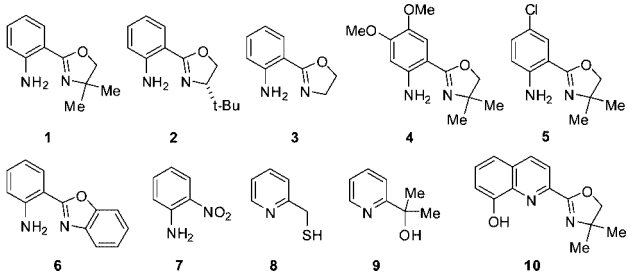
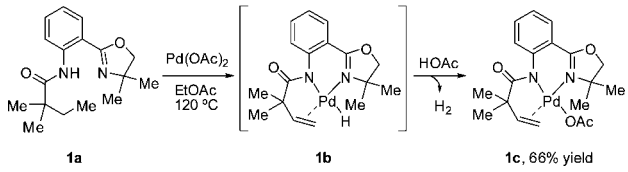
Scheme 1. $Pd(OAc)_2$-Catalyzed Dehydrogenative Pathway



Scheme 2. Various Auxiliaries for Carboxylic Acids



Scheme 3. Dehydrogenation via an Oxidant-Free Catalysis



synthesis. Direct dehydrogenation of inert alkyl groups[20] using Pd(II)/Pd(0) catalysis and cheap oxidants would be highly valuable in broadening the synthetic utility of the dehydrogenation reaction.

The different directing groups mentioned earlier have been widely used in a variety of Pd-catalyzed reactions such as oxidation,[5c,6d] halogenation,[6a,c] alkylation,[7a] and arylation[10a] of sp^3 C−H bonds. We began to investigate if the C−H insertion intermediates in such reactions could undergo β-hydride elimination in the absence of organic electrophiles or nucleophiles (Scheme 1).

Using $Pd(OAc)_2$ as the reagent, we screened various auxiliaries (Scheme 2) for sp^3 C−H bond activation in carboxylic acids. Amide and ester substrates were prepared from 2,2-dimethylbutyric acid and the corresponding auxiliaries **1**−**10**.

We found that both an amide and an oxazoline moiety in tandem directed the activation of the sp^3 C−H bond at the ethyl group and generated a dehydrogenation product after subsequent β-hydride elimination. Thus, heating a stoichiometric mixture of $Pd(OAc)_2$ and the substrate **1a** in ethyl acetate at 120 °C afforded the dehydrogenated palladium complex **1c** in 66% yield (Scheme 3). This came as a surprise to us, since C−H insertion at the α-methyl group via a five-membered cyclopalladation was the predominant reaction in our previous studies of similar substrates.[6c,d] It appears that either the α-methylene or the β-methyl group was activated in this case. Furthermore, the previously reported analogous substrates in which an amide linkage was attached to a pyridine moiety did not follow the

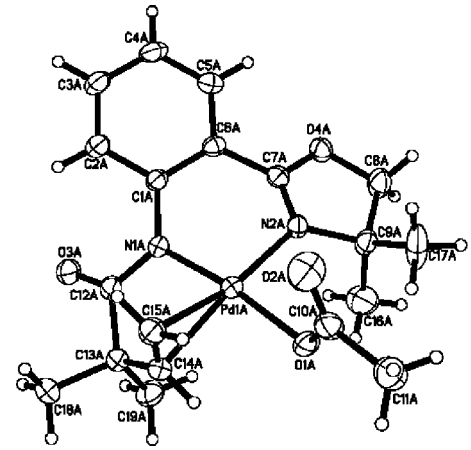


Figure 1. Molecular structure of **1c**. Pertinent bond lengths (Å) and angles (deg): Pd1A−N1A, 1.980(3); Pd1A−N2A, 2.049(3); Pd1A−C15A, 2.155(4); Pd1A−C14A, 2.137(4); Pd1A−O1A, 2.019(3); N1A−Pd1A−N2A, 89.83(13); N1A−Pd1A−C14A, 82.07(16); N1A−Pd1A−C15A, 86.91(17); C14A−Pd1A−O1A, 91.30(16); C15A−Pd1A−O1A, 90.03(17); N2A−Pd1A−O1A, 94.88(13).

β-hydride elimination pathway.[7e] Other auxiliaries, such as nitroaniline (**7**), thiopyridyl (**8**) and hydroxypyridyl (**9** and **10**), were not effective for the dehydrogenation reaction.

The complex **1c** was crystallized from CH_2Cl_2/hexane (1:10) as a golden yellow, parallelepiped-shaped crystal, and its molecular structure was confirmed by X-ray crystallography (Figure 1). The amido palladacycle **1c** maintains a monomeric structure, with the intramolecular terminal alkene acting as the fourth ligand trans to the oxazoline to prevent it from forming a μ-acetato-bridged dimer.[21] The palladium center adopts a slightly distorted square planar geometry with the following angles (in deg): N1A−Pd1A−N2A = 89.83(13), N1A−Pd1A−C14A = 82.07(16), N1A−Pd1A−C15A = 86.91(17), C14A−Pd1A−O1A = 91.30(16), C15A−Pd1A−O1A = 90.03(17), and N2A−Pd1A−O1A = 94.88(13). The distortion about the palladium center is imposed by the nonplanar disposition of the aryl and oxazoline rings, which forces the six-membered amido palladacycle to adopt a half-chair conformation. The N−Pd bond distance in the amido palladium complex **1c** falls in the expected range (1.980(3) Å).[7e] However, the Pd−O bond distance in the monomeric acetate complex **1c** is shorter (2.019(3) Å) by 0.039 Å than the Pd−O bond distance in the analogous μ-acetato-bridged dimeric amido palladacycle (2.058(16) Å).[7e]

Palladium hydrides are known to be oxidized in reactions with molecular oxygen to palladium oxo intermediates.[22] However, the dehydrogenation of the ethyl group in substrate **1a** was still observed in 57% yield, as determined by ^{1}H NMR, when the reaction was carried out in a sealed NMR tube in ethyl acetate-d_8 under an oxygen-free atmosphere (glovebox). We believe that the acetic acid generated after the C−H cleavage protonates the transient Pd hydride intermediate **1b** and the acetate complex **1c** is formed with the evolution of H_2 (Scheme 3). It is also possible that the transient RCONPdH reductively eliminates the N−H bond while the Pd(0) still remains three-

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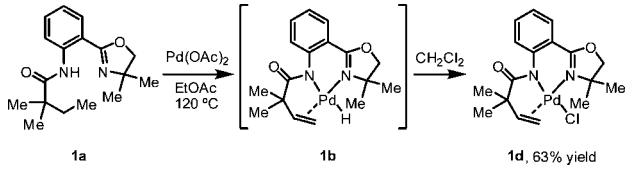
Table 1. $Pd(OAc)_2$-Mediated Dehydrogenation of 2,2-Dimethylbutyric Acid using Various Auxiliaries[a]

entry	auxiliary	yield (%)[b]	entry	auxiliary	yield (%)[b]
1	**1**	66	4	**4**	62
2	**2**	35	5	**5**	40
3	**3**	90[c]	6	**6**	10[d]

[a] Conditions: substrate (0.1 mmol), $Pd(OAc)_2$ (1 equiv), ethyl acetate (1 mL), 120 °C, 30 min. [b] Isolated yields. [c] 100 °C. [d] Determined by ^1H NMR.

Scheme 4. Dehydrogenation of 2,2-Dimethylbutyric Acid using Auxiliary 1 with CH_2Cl_2 as an Additive



coordinated to the product through amide, oxazoline, and the alkene chelation. Such $Pd(0)L_n$ complexes are known to reversibly form Pd(II) hydride by the oxidative addition of HOAc.[23] The $HPd^{II}OAcL_n$ intermediate formed thereafter can further cleave the N−H bond with the evolution of H_2, thereby generating the observed acetate complex **1c**.

Steric and electronic factors have a significant effect on the current dehydrogenation reaction. A poor yield was obtained when the oxazoline auxiliary was switched from *gem*-dimethyl (**1**) to *tert*-butyl (**2**), while complete removal of the steric bulkiness from the oxazoline auxiliary by replacing *gem*-dimethyl (**1**) with hydrogens (**3**) not only dramatically increased the product yield from 66% to 90% but also allowed the reaction to occur at a lower temperature (100 °C) (Table 1, entry 3). Substitution of the aryl ring with an electron-donating group (**4**) showed little effect on the product yield (Table 1, entry 4). An electron-withdrawing group (**5**), however, decreased the product yield (Table 1, entry 5). Similarly, the use of the aminobenzoxazole auxiliary **6**, in which the oxazoline C═N is conjugated with the aryl ring, drastically decreased the product yield to 10% (Table 1, entry 6).

Substrate **1a** produced the dehydrogenated palladium chloride complex **1d** in the presence of CH_2Cl_2 in 63% yield (Scheme 4). We believe that the initially formed transient Pd hydride complex, RCONPdH (**1b**), readily abstracts a chloride from CH_2Cl_2 during the reaction. Since the acetate complex **1c** was not converted to its chloride derivative **1d** when it was heated with CH_2Cl_2 as an additive under similar reaction conditions, it seems unlikely that the anion exchange process occurred via the intermediacy of the acetate complex **1c**. However, no hydride intermediate was observed by ^1H NMR when the reaction was carried out in ethyl acetate-d_8 under an argon atmosphere.[24]

The complex **1d** was crystallized from CH_2Cl_2/hexane (1:10) as a reddish yellow crystal, and its molecular structure was confirmed by X-ray crystallography (Figure 2). The complex **1d** is analogous to the complex **1c**. The amido N−Pd (1.9942(13) Å) and Pd−Cl (2.3125(4) Å) bond distances[25] fall in the expected range.

Auxiliary **11** was effective for the dehydrogenation of ethyl groups at a milder temperature. Substrate **11a** was dehydrogenated with $Pd(OAc)_2$ at 80 °C in CH_2Cl_2 or toluene, providing the acetate complex **11b** in 88% yield (Scheme 5). The complex **11b** was characterized by ^1H and ^{13}C NMR. Interestingly, a similar auxiliary, **12**, was ineffective for the dehydrogenation reaction.

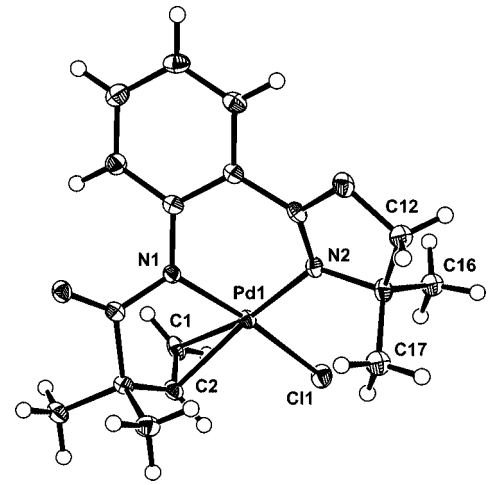
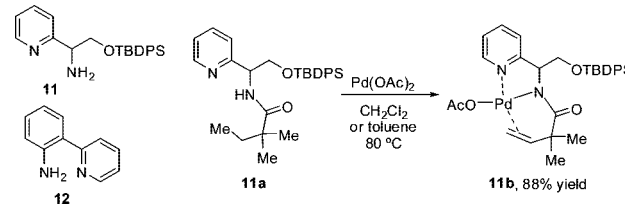
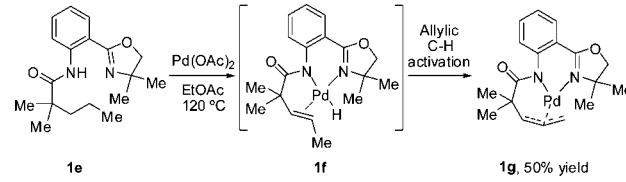


Figure 2. Molecular structure of **1d**. Pertinent bond lengths (Å) and angles (deg): Pd1−N1, 1.9942(13); Pd1−N2, 2.0731(13); Pd1−C1, 2.1735(16); Pd1−C2, 2.1370(16); Pd1−Cl1, 2.3125(4); N1−Pd1−N2, 88.70(5); N1−Pd1−C1, 85.86(6); N1−Pd1−C2, 81.95(6); C1−Pd1−Cl1, 88.04(5); C2−Pd1−Cl1, 91.77(5), N2−Pd1−Cl1, 97.76(4). Disorder arising from two ring orientations affects atoms C12, C16, and C17 and the associated H atoms; only the major component (present at 57(2)% occupancy) is shown.

Scheme 5. Dehydrogenation of 2,2-Dimethylbutyric Acid using Auxiliary 11



Scheme 6. Dehydrogenation of 2,2-Dimethylvaleric Acid using Auxiliary 1



To investigate the possibility of activating a remote δ-C−H bond through this pathway, reaction of the substrate **1e**, derived from 2,2-dimethylvaleric acid, was carried out with a stoichiometric amount of $Pd(OAc)_2$. Under the standard reaction conditions, the Pd allyl complex **1g** was formed after double C−H activation in 50% yield (Scheme 6).[26] The complex **1g** was also formed in 42% yield, as determined by ^1H NMR, when the reaction was carried out in a sealed NMR tube in ethyl acetate-d_8 under oxygen-free conditions (glovebox). We believe that the allylic hydrogen in the intermediate complex **1f** is further activated by the transient Pd hydride species.[27] However, the

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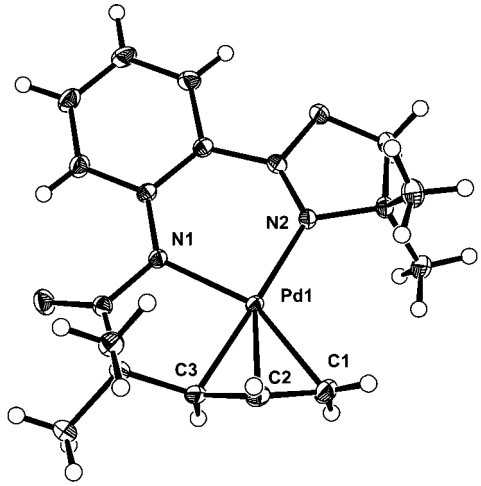


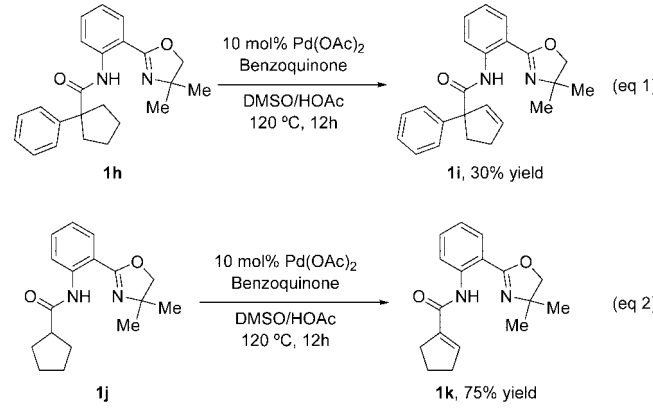
Figure 3. Molecular structure of **1g**. Pertinent bond lengths (Å) and angles (deg): Pd1−N1, 2.0593(10); Pd1−N2, 2.0381(9); Pd1−C1, 2.1618(14); Pd1−C2, 2.0887(12); Pd1−C3, 2.0538(12); C1−C2, 1.4158(18); C2−C3, 1.4094(18); N1−Pd1−N2, 92.99(4); N1−Pd1−C3, 84.42(4); C3−Pd1−C1, 69.78(5).

possibility that the hydride is exchanged with an acetate before the allylic C−H bond is activated can also not be ruled out at this moment on the basis of our experimental results with the substrate **1a**.

The complex **1g** was crystallized from CH_2Cl_2/hexane (1:10) as a reddish yellow crystal, and its molecular structure was confirmed by X-ray crystallography (Figure 3). The amido palladacycle **1g** maintains a monomeric η^3-allyl structure with Pd1−C1 (2.1618(14) Å), Pd1−C2 (2.0887(12) Å), Pd1−C3 (2.0538(12) Å), C1−C2 (1.4158(18) Å), and C2−C3 (1.4094(18) Å) bond distances which fall in the expected range for η^3-allyl complexes.[28] The amido N−Pd bond distance (2.0593(10) Å) in the η^3-allyl complex **1g** is longer by 0.0793 Å than the amido N−Pd bond distance in the amido palladacycle **1c**.

The dehydrogenation reaction can also be carried out catalytically with cyclopentylcarboxamides **1h** and **1j**. The substrate **1h** was dehydrogenated at the methylene group with 10 mol % $Pd(OAc)_2$ in DMSO in the presence of benzoquinone to afford the alkene **1i** in 30% isolated yield (Scheme 7, eq 1). Dehydrogenation of the carboxamide substrate **1j** with an α-hydrogen proceeds much more quickly with a higher product yield (75%)

Scheme 7. $Pd(OAc)_2$-Catalyzed Dehydrogenation of Cyclopentylcarboxylic Acids using Auxiliary 1



(Scheme 7, eq 2). Surprisingly, however, the catalytic version of the current dehydrogenation reaction proved difficult with the open-chain carboxamides **1a** and **1e** under various conditions. The reaction ceases to proceed catalytically under various oxidizing conditions, and the palladium complexes **1c** and **1g** were consistently observed in the crude reaction mixture.

In summary, we have established reaction conditions for the dehydrogenation of ethyl and propyl groups in carboxylic acid derivatives using $Pd(OAc)_2$ as the catalyst. An oxidant-free pathway for Pd(II) catalysis is proposed. A number of monomeric amido Pd complexes after dehydrogenation have been characterized by X-ray crystallography. Despite the limited substrate scope, the catalytic dehydrogenation protocol for cyclopentylcarboxamides could prove useful in synthesis.

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Supporting Information Available: Text and figures giving experimental procedures and characterization data for all new compounds and CIF files giving crystal data for **1c**,**d**,**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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