Asymmetric Catalysis

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# Pd-Catalyzed Stereoselective Oxidation of Methyl Groups by Inexpensive Oxidants under Mild Conditions: A Dual Role for Carboxylic Anhydrides in Catalytic C–H Bond Oxidation**

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The selective oxidation of unactivated C–H bonds is a significant research goal because of its importance in synthesis and the chemical industry.[1] In the past few years, the development of stoichiometric σ-chelation directed C–H activation processes in catalytic reactions has met with remarkable success.[2] This approach has also yielded fruitful

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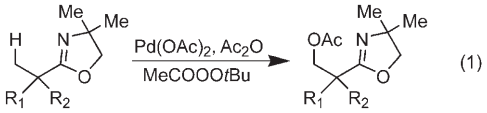
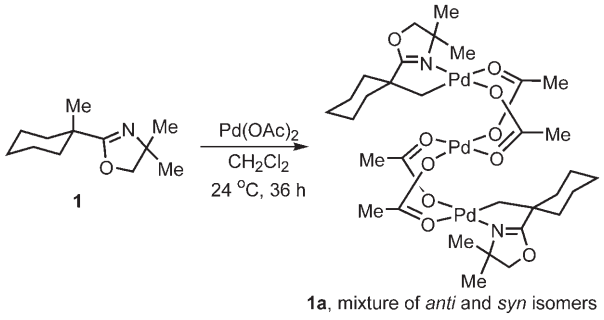
results in the oxidation of methyl groups catalyzed by transition-metal species.[3–5] Despite this significant progress, the development of practical catalytic methods to oxidize methyl groups using inexpensive oxidants under mild conditions remains an important task.

We have recently reported the use of a chiral oxazoline as the chelating group to iodinate prochiral $sp^3$ and $sp^2$ C–H bonds diastereoselectively.[6] The importance of the direct oxidation of methyl groups in synthesis turned our attention to the development of a catalytic system using inexpensive oxidants.[7] Pyridine and *O*-methyl oxime directed palladium-catalyzed acetoxylation has been recently reported using $PhI(OAc)_2$ as an oxidant.[8] Herein, we disclose a Pd-catalyzed oxidation of unactivated methyl groups using the peroxyester MeCOOO*t*Bu as the stoichiometric oxidant and $Ac_2O$ as a crucial promoter [Eq. (1)]. Preliminary results on the diastereoselective oxidation of methyl groups using lauroyl or benzoyl peroxide as the stoichiometric oxidant are also described.




Our efforts began with the characterization of a Pd–alkyl complex formed from oxazoline directed C–H activation. The reaction of substrate **1** with 1.5 equivalents of $Pd(OAc)_2$ in $CH_2Cl_2$ at 24 °C for 36 h afforded a mixture of *anti* and *syn* trinuclear C($sp^3$)–Pd complexes in a 3:2 ratio (Scheme 1).




***Scheme 1.*** Formation of trinuclear C($sp^3$)–Pd complex **1a**.

The molecular structure of the *anti* isomer **1a** determined by X-ray diffraction is related to a recently obtained C($sp^2$)–Pd ferrocene derivative[9] and confirms earlier proposals based on $^1H$ NMR spectroscopic analysis (Figure 1).[6,10]

We envisioned that *tert*-butyl hydroperoxide (TBHP) would oxidize the Pd–C($sp^3$) bond in **1a** to give Pd–OR complex **1b**, as TBHP/[$VO(acac)_2$] (acac = acetylacetonate) is known to insert an oxygen atom into the Pd–C($sp^2$) bond of dimeric Pd–aryl complexes (Scheme 2).[11] We found that the reaction of **1a** with five equivalents of TBHP in $CH_2Cl_2$ at 24 °C for 36 h, followed by reduction with $NH_2NH_2$, afforded the hydroxylated product **1c** in 35 % yield of isolated product (Scheme 2).

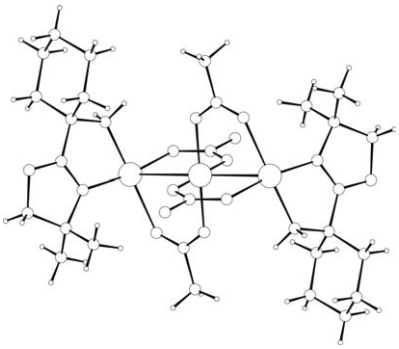
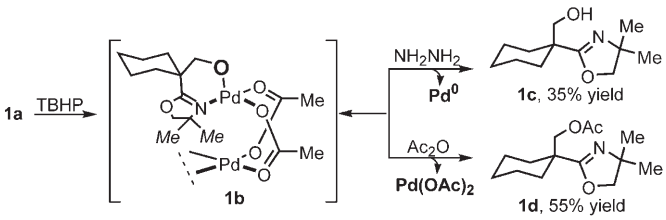


***Figure 1.*** X-ray crystal structure of **1a**.




***Scheme 2.*** Stoichiometric acetoxylation of methyl groups.

We further hypothesized that $Ac_2O$ would acetylate the Pd–OR complex **1b** and regenerate $Pd(OAc)_2$, thereby rendering this reaction catalytic. Following the treatment of **1a** with TBHP in $CH_2Cl_2$ , addition of $Ac_2O$ to the reaction mixture was found to give the product in the form of acetate **1d** and regenerate $Pd(OAc)_2$ (Scheme 2).

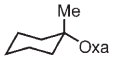
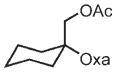
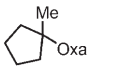
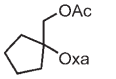
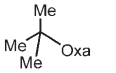
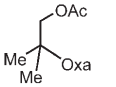
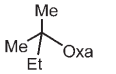
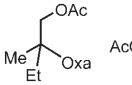
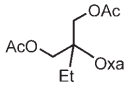
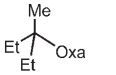
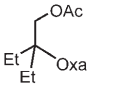
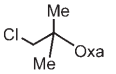
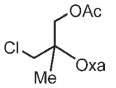
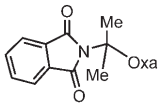
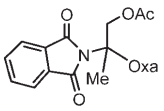
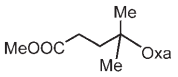
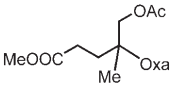
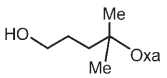
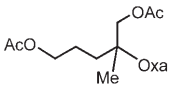
Carrying out this reaction with only a catalytic amount of $Pd(OAc)_2$ led us to discover that peroxyester MeCOOO*t*Bu, generated from the reaction of TBHP with $Ac_2O$, is an efficient oxidant for the oxidation of methyl groups. A combination of $Pd(OAc)_2$ (5 mol %) and MeCOOO*t*Bu (2 equiv) in $Ac_2O$ was able to yield acetoxylate **1** in 71 % yield.[12] A wide range of substrates are oxidized in good yields (Table 1): polar functional groups, such as ketals, imides, esters, and chlorides, are tolerated. Substrate **9** was used directly without protection of the hydroxy group, which was acetylated in the reaction. This oxidation protocol is potentially useful in the laboratory as MeCOOO*t*Bu is a cheap oxidant (TBHP: 5–6 M in hydrocarbon, $\$154\,mol^{-1}$; MeCOOO*t*Bu, 5–6 M in hydrocarbon, $\$14\,mol^{-1}$).[13]

Next, we attempted to extend this protocol to diastereoselective oxidation using a chiral oxazoline. MeCOOO*t*Bu is not compatible with a chiral oxazoline containing a hydrogen atom α to the nitrogen atom, as this hydrogen atom is readily oxidized, thus leading to the formation of an oxazole. We were delighted to find that this side reaction can be prevented by using inexpensive benzoyl or lauroyl peroxide as the oxidants (Table 2). Moderate diastereoselectivity (12–82 % *de*) was observed with substrates containing prochiral methyl groups.

A chiral trinuclear C($sp^3$)–Pd complex **16a** has also been obtained and characterized by X-ray studies (Figure 2). In sharp contrast to the 2:3 mixture of *syn* and *anti* complexes formed from nonchiral oxazoline **1** (Scheme 1), only the

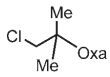
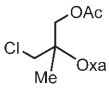
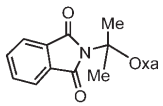
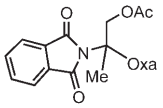
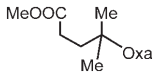
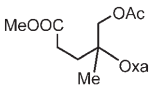
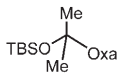
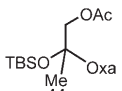
  

***Table 1:*** $Pd(OAc)_2$-catalyzed oxidation of methyl groups by MeCOOO*t*Bu.[a]

| Entry | Substrate | Product | Yield [%] |
|---|---|---|---|
| 1 |  **1** |  **1d** | 71 |
| 2 |  **2** |  **2a** | 62 |
| 3 |  **3** |  **3a** | 69 |
| 4 |  **4** |  **4a**  **4b** | 89 |
| 5 |  **5** |  **5a** | 90 |
| 6 |  **6** |  **6a** | 68 |
| 7 |  **7** |  **7a** | 50 |
| 8 |  **8** |  **8a** | 70 |
| 9 |  **9** |  **9a** | 50 |

[a] Oxa = 2-substituted 4,4-dimethyloxazoline. Reaction conditions: entries 1–5, $Pd(OAc)_2$ (5 mol%), $Ac_2O$, MeCOOO*t*Bu (2 equiv), 65°C, 48–72 h; entries 6–9, $Pd(OAc)_2$ (10 mol%). In the absence of air or pure $O_2$, the reaction stopped at 30–40% conversion and the precipitation of $Pd^0$ was observed. [b] **4a**/**4b** = 1:1.

***Table 2:*** $Pd(OAc)_2$-catalyzed diastereoselective oxidation of methyl groups by lauroyl peroxides.[a]

| Entry | Substrate | Product | Yield [%] | *de* [%] |
|---|---|---|---|---|
| 1 |  **10** |  **10a** | 67 | 18 |
| 2 |  **11** |  **11a** | 66 | 38 |
| 3 |  **12** |  **12a** | 38 | 12 |
| 4 |  **13** |  **13a** | 73 | 24 |
| 5 |  **14** |  **14a** | 43 | 62 |
| 6 |  **15** |  **15a** | 49 | 82 |

[a] Oxa = 2-substituted 4-*tert*-butyloxazoline. Reaction conditions: $Pd(OAc)_2$ (5 mol%), $Ac_2O$, lauroyl peroxide (2 equiv), 50°C, 48 h. The presence of air or pure $O_2$ increases the conversion rate.

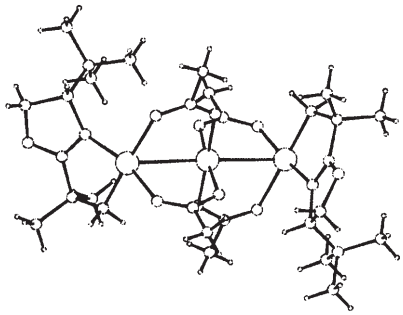
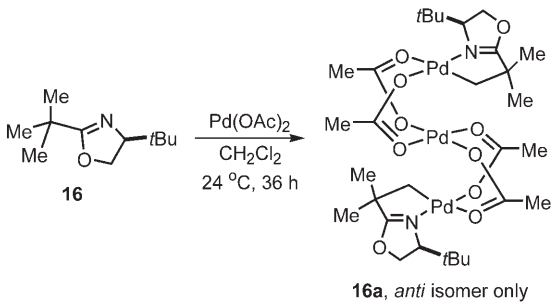


***Figure 2.*** X-ray crystal structure of **16a**.

*anti* isomer was obtained from the chiral substrate **16** (Scheme 3). This result suggests that the asymmetric center on the oxazoline is crucial in the control of the geometry of the trinuclear complex. The exclusive formation of the *anti* isomer could be important for the rationalization of the observed stereoselectivity in the C–H activation step, as the *syn* isomer has a different symmetry and steric environment and could generate asymmetric centers of the opposite configuration in the C–H activation step. In future work, the crystal structures of $C(sp^3)$–Pd complexes derived from prochiral substrates, such as **15**, will be obtained and will shed further light on the stereoselectivity of the C–H activation step.

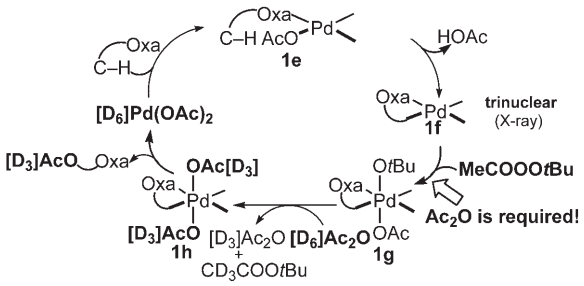
As reported previously, a mixture of $AcOH/Ac_2O$ has been used as the reaction media for $Pd^{II}$-catalyzed C–H activation reactions.[8,14] To the best of our knowledge, the role




**16a**, *anti* isomer only

***Scheme 3.*** Formation of chiral trinuclear $C(sp^3)$–Pd complex **16a**.

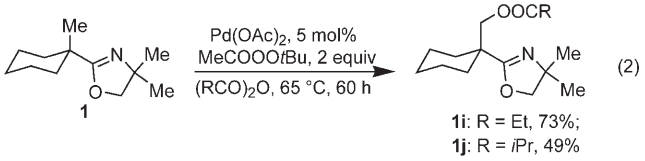
of $Ac_2O$ remains obscure in C–H bond oxidation reactions. Isolation of the complex **1f** prompted us to investigate the influence of $Ac_2O$ on the elementary steps of the reaction. Although no compelling evidence for the involvement of a $Pd^{IV}$ species has been obtained in our experiments, previous characterization of a $Pd^{IV}$ species formed upon the oxidative addition of benzoyl peroxide or aryl transfer from diphenyliodonium triflate to 2,2′-bipyridine-coordinated $Pd^{II}$ and $Pt^{II}$ centers allows the proposal of a plausible pathway (Scheme 4).[15] The formation of **1f** in $CH_2Cl_2$ was monitored




***Scheme 4.*** Proposed catalytic cycle.

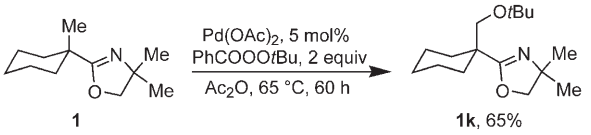
by $^1H$ NMR spectroscopy in the absence and presence of various amounts of $Ac_2O$ (see the Supporting Information). The results showed that the rate was not affected by $Ac_2O$. The oxidative-addition step, however, was shown to require $Ac_2O$ as no reaction of **1f** with MeCOOO*t*Bu was observed in $CH_2Cl_2$ at 50 °C. However, it is also possible that **1g** is in equilibrium with **1f**, largely in favor of the latter, and $Ac_2O$ could scavenge $tBuO^-$ ions in **1g** to form **1h**, which undergoes reductive elimination.

We have also made a number of other observations that may be relevant to the mechanistic understanding of this catalytic reaction. The bridging acetate in complex **1f** undergoes rapid degenerate acetate exchange with $[D_6]Ac_2O$. The exchange process requires breaking of the μ-acetate bridge in the trinuclear complex **1f**, which could be related to the acceleration of the oxidative addition. The use of $[D_6]Ac_2O$ as a solvent also shows that the acetate or acetyl group from acetic anhydride, rather than from the oxidant, is incorporated predominantly into the product. The use of other anhydrides, such as propionic and isobutyric anhydrides, consistently affords the corresponding carboxylates [Eq. (2)].




(2)

This result further suggests that the acetate ligand at the apical position of the octahedral $Pd^{IV}$ complex **1g** also rapidly exchanges with carboxylic anhydrides to give **1i** or **1j** prior to reductive elimination. Interestingly, when PhCOOO*t*Bu is used as an oxidant, the ether product **1k** was formed predominantly [Eq. (3)], which could be explained by assuming that the $PhCOO^-$ ion is less labile than the $tBuO^-$ ion in the octahedral intermediate analogous to **1g**.




(3)

The use of lauroyl peroxide or benzoyl peroxide as the oxidant has led us to identify a second role for $Ac_2O$. The reaction of **1f** with both peroxides proceeds to give the acetoxylated products in the absence of $Ac_2O$. However, the presence of $Ac_2O$ is essential for the catalytic turnover. Measurement of the reaction rate by GC using 20 mol% $Pd(OAc)_2$ shows that the reaction in the first 10% conversion is not influenced by the addition of $Ac_2O$, but does not proceed further after 15% conversion in the absence of $Ac_2O$. This result suggests that $Ac_2O$ is crucial for the regeneration of the reactive $Pd(OAc)_2$, as shown in Scheme 4.

In summary, the inexpensive oxidant MeCOOO*t*Bu is shown to oxidize unactivated methyl groups in the presence of a catalytic amount of $Pd(OAc)_2$ under mild conditions. The diastereoselective oxidation of methyl groups is also achieved in moderate diastereoselective excess (*de*) by using lauroyl or benzoyl peroxide as the oxidant. Investigations into the reactivity of the characterized trinuclear Pd–alkyl complex indicated a crucial dual role for anhydrides in C–H bond oxidation. Further efforts are being directed towards the characterization of crystal structures of $C(sp^3)$–Pd complexes derived from prochiral substrates to explain the stereoselectivity shown.

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