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Catalytic Allylic C−H Acetoxylation and Benzoyloxylation via Suggested (η^3-Allyl)palladium(IV) Intermediates

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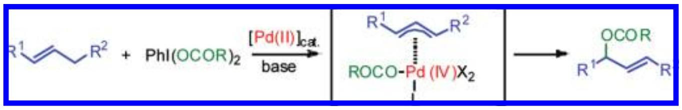
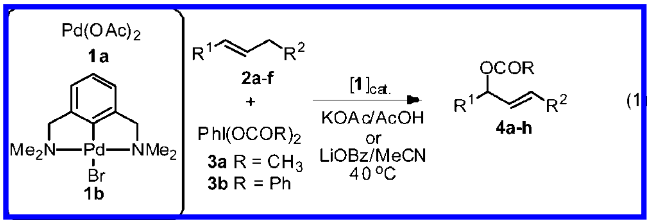
ABSTRACT



Palladium-catalyzed allylic acetoxylations and benzoyloxylations were carried out using iodonium salts. The reactions proceed under mild conditions with high regio- and stereoselectivity. The catalysis can be performed under both acidic and nonacidic conditions without use of BQ or other external oxidants and activator ligands. Deuterium labeling experiments clearly show that the catalytic reaction proceeds through (η^3-allyl)palladium intermediates. A stoichiometric study with one of the catalysts provided evidence for the formation of a Pd(IV) species.

Palladium-catalyzed allylic acetoxylation is one of the most efficient procedures for C−H functionalization of alkenes.[1,2] Åkermark,[2a,b] Bäckvall,[2c,d] White,[2e,f] and others[2g,h] have presented many excellent applications for preparation of allylic acetates via palladium-catalyzed acetoxylation of the allylic C−H bond in various alkenes.

In the vast majority of these studies, benzoquinone (BQ) was used as a crucial additive. According to in-depth mechanistic studies, BQ plays a dual role in the acetoxylation reactions: (i) reoxidation of Pd(0) to Pd(II) to maintain the catalytic cycle and (ii) activation of the Pd(II) intermediate for selective nucleophilic attack.[3] Although these two important features render BQ an almost indispensible component in allylic acetoxylation reactions,[1c] there are a couple of disadvantages as well. For example, the oxidation potential of BQ is pH dependent, as protonation is involved in the redox process generating hydroquinone. As a result, in most catalytic applications acidic conditions have to be applied, which reduce the nucleophilicity of the acetate component.[2]



In this paper, we disclose our results of a conceptually new method for allylic C−H acetoxylation/benzoyloxylation reactions, which can be performed without BQ (eq 1, Table 1). Our basic idea is replacement of the traditional Pd(0)/Pd(II) catalytic cycle with a Pd(II)/Pd(IV) cycle.[4] Iodonium salts **3a**,**b** are applied as oxidants for allylic C−H functionalization of alkenes **2a**−**f** in the presence of palladium catalysts **1a** or **1b** (eq 1).

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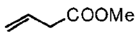
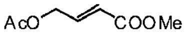
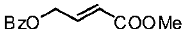
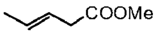
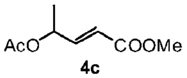
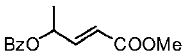
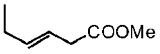
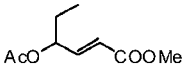
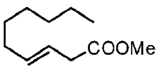
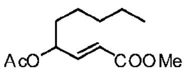
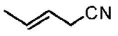
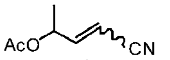
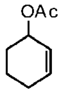
Table 1. Pd-Catalyzed C−H Acetoxylation and Benzoyloxylation of Alkenes with Iodonium Salts[a]

entry	substrate	cat.	$PhI(OCOR)_2$	solv.	product	yield [%][b]
1	 **2a**	1a	3a	AcOH	 **4a**	59
2	**2a**	1b	3a	AcOH	**4a**	60
3	**2a**	1b	3a	MeCN	**4a**	46
4	**2a**	1a	3b	MeCN	 **4b**	64
5	 **2b**	1a	3a	AcOH	 **4c**	62
6	**2b**	1a	3b	MeCN	 **4d**	61
7	 **2c**	1a	3a	AcOH	 **4e**	61
8	 **2d**	1a	3a	AcOH	 **4f**	70
9	 **2e**	1a	3a	AcOH	 **4g**	52[c]
10	 **2f**	1a	3a	AcOH	 **4h**	66

[a] Alkene **2** (0.3 mmol), iodonium salt **3** (0.6 mmol), catalyst **1** (5 mol %), and KOAc (0.3 mmol) or LiOBz (0.3 mmol) were dissolved/suspended in the indicated solvent (1 mL), and the reaction mixture was stirred at 40 °C for 18 h. KOAc and LiOBz were used with oxidants **3a** and **3b**, respectively. [b] Isolated yield. [c] *Cis* and *trans* isomers formed in a 1:1 ratio.

Under our conditions, alkene **2** (0.3 mmol), iodonium salt **3** (0.6 mmol), catalyst **1** (5 mol %), and the appropriate carboxylate salt base were reacted in AcOH or MeCN. Potassium acetate was used with $PhI(OAc)_2$ (**3a**), while lithium benzoate was used with $PhI(OBz)_2$ (**3b**). The reactions were conducted under mild conditions (40 °C) for 18 h. Palladium acetate **1a** and pincer complex **1b** proved to be equally efficient catalysts for model substrate **2a** (cf. entries 1 and 2). For this reason, and because of its commercial availability, the majority of the reactions were performed using **1a**. However, the fact that **1b** readily catalyzed the process provided a handle for the exploration of some important mechanistic aspects of the reaction (vide infra). Most of the acetoxylation reactions (entries 1, 2, 5, and 7−10) were performed in acetic acid with **3a** in the presence of KOAc.

The benzoyloxylation reactions (entries 4 and 6) were conducted with **3b** as oxidant in the presence of LiOBz in MeCN solvent. Thus, the catalytic C−H benzyloxylation could be performed under slightly basic conditions, which is not possible with BQ as oxidant (vide supra). We found that the acetoxylation reaction can also be performed under similar nonacidic conditions (entry 3).

The catalytic reactions proceeded smoothly with both terminal (**2a**) and internal (**2b**−**f**) alkenes. In the case of carboxylates **2a**−**d** we did not observe isomerization reported for the classical Pd(0)/Pd(II) reactions, in which BQ pentyl nitrite or $CuCl_2$ were used as oxidants.[2h] Our conditions gave exclusively one regio- and stereoisomer of each product. The only exception was the acetoxylation of **2e** in which the *cis* and *trans* products were formed in a 1:1 ratio. In the case of **2b**−**d**, the alkyl chain length did not influence the selectivity of the reaction. Acetoxylation of cyclohexene (**2f**) was performed with high regioselectivity without formation of the vinyl-substituted product (entry 10).

We were particularly interested in exploring two basic mechanistic aspects of the catalytic process: (1) the mechanism of the nucleophilic attack and (2) the oxidation state of the palladium under the reaction conditions. The nucleophilic attack of the C−H acetoxylation reaction can proceed by two different mechanisms.[2c,d] One possibility is the formation of an (η^3-allyl)palladium (such as **5**, eq 2) followed by nucleophilic attack of the acetate. The other possibility is an acetoxy-palladation (through intermediates such as **6**, eq 3), followed by β-hydride elimination to give the final product. To differentiate between these two mechanisms, we carried out an isotope labeling study with monodeuterated cyclohexene (**2f**-1d). Using this substrate two different (η^3-allyl)palladium complexes (**5a** and **5b**, eq 2) may be expected to form, each of which could react with the nucleophile at either of the terminal positions. This would give three allylic acetoxy products, **4h**-1d, **4h**-2d, and **4h**-3d, in an expected 1:2:1 ratio. Alternatively, if the palladium complex undergoes acetoxy-palladation, two insertion complexes may form: **6a** and **6b** (eq 3). Subsequent β-hydride elimination would give two allylic acetates **4h**-1d and **4h**-2d in a 1:1 ratio. In this case, formation of **4h**-3d (in which

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(3) (a) Bäckvall, J. E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619. (b) Bäckvall, J.-E.; Gogoll, A. *Tetrahedron Lett.* **1988**, *29*, 2243. (c) Szabó, K. J. *Organometallics* **1998**, *17*, 1677.

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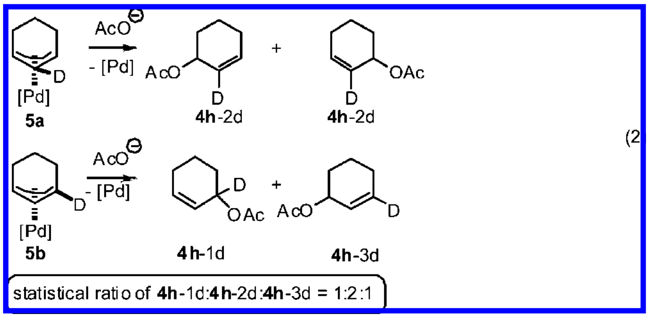
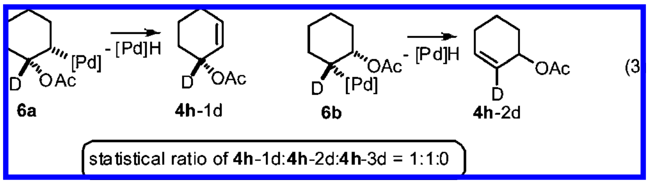
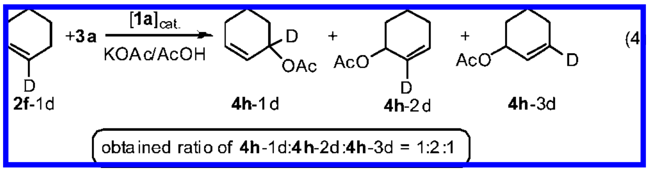
(6) Stang, P. J.; Boehshar, M.; Wingert, H.; Kitamura, T. *J. Am. Chem. Soc.* **1988**, *110*, 3272.

the deuterium and the acetate group are separated by three carbon atoms) is not expected to occur.





When we performed the catalytic acetoxylation of **2f**-1d under our standard conditions (entry 10), we obtained three deuterated products (**4h**-1d, **4h**-2d, and **4h**-3d, eq 4) in a 1:2:1 ratio, as determined by ^{2}H NMR spectroscopy.



Thus, we conclude that the acetoxylation of **2f** involves an (η^3-allyl)palladium intermediate, and very probably the rest of the substrates (**2a**−**e**) react via analogous intermediates. Interestingly, previous studies on the Pd(0)/Pd(II)-based catalytic acetoxylation using BQ also showed evidence of (η^3-allyl)palladium intermediates.[2c,d]

A further important mechanistic question concerns the oxidation state of palladium. It is known that iodonium salts are able to oxidize Pd(II) species to Pd(IV).[4,5] Sanford and co-workers have shown that benzoyloxy iodonium salts (e.g., **3a**,**b**) readily oxidize Pd(II) complexes to form stable Pd(IV) species.[5c,d]

This process provided the evidence for the intermediacy of Pd(IV) species in directed C−H acetoxylation of heteroaromatics and related substrates.[4e] Furthermore, van Koten and co-workers demonstrated that NCN pincer complex **1b** reacts with $PhICl_2$ to form a Pd(IV) species, which was observed by ^{1}H NMR spectroscopy.[5a] In addition, Canty and co-workers have reported that pincer complex **1b** can undergo oxidative addition with an alkynyl iodonium salt to give the corresponding Pd(IV) species.[5b]

Similarly, we attempted to generate Pd(IV) intermediates starting from pincer complex **1b**, which we found to be as active a catalyst for our acetoxylation protocol as **1a** (cf., entries 1 and 2). In our investigation, NCN complex **1b** was reacted with iodonium salt **3a** in $CDCl_3$ and the progress of the reaction was monitored by ^{1}H NMR spectroscopy (Figure 1). The signals for the CH_2 and CH_3 protons of the side arms of **1b** appear as singlets resonating at 4.04 and 3.01 ppm, respectively.[5a,b] This arises from the fast inversion of the nitrogen atoms of the side arms, lending a time-averaged C_{2v} symmetry to the complex. Addition of 3 equiv of **3a** to the $CDCl_3$ solution of **1b** led to a color change from pale yellow to amber. Notable changes in the ^{1}H NMR spectrum were (i) the splitting of the CH_3 signals into two distinct sharp singlets resonating at 2.88 and 3.24 ppm and (ii) the emergence of two doublets (J = 14 Hz) at 4.46 and 4.38 ppm. (We also observed the formation of iodobenzene, indicating removal of the acetate groups from **3a**.) Canty and co-workers reported similar characteristic changes in the ^{1}H NMR spectrum for the reaction of NCN complex **1b** and an ethynyl iodonium salt.[4a,b,5b] A reasonable explanation for the observed changes in the NMR signals is the expansion of the palladium coordination sphere from tetracoordinated (**1b**) to hexacoordinated (**7**) species, due to oxidation of the palladium atom from Pd(II) to Pd(IV). The change of the coordination number hinders the ring inversion process in the side arms and reduces the NMR time-scale averaged symmetry of the complex from C_{2v} to C_s. Consequently, the chemical environment of the two CH_2 side arm protons will be different, giving rise to a geminal coupling pattern. Similarly, the chemical environments of the CH_3 groups will also become different, and therefore, these groups resonate as two distinct singlets. These results suggest that under the applied catalytic conditions the palladium atom of the catalyst may be oxidized to Pd(IV) by the iodonium salts **3**.

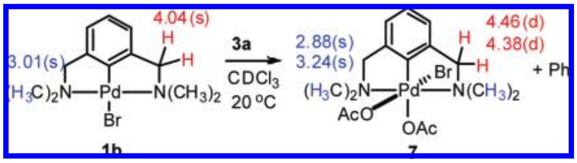


Figure 1. Oxidation of the Pd(II) central atom of **1b**. The ^{1}H NMR shifts are given in ppm values.

On the basis of these results, we propose the catalytic cycle shown in Figure 2. The suggested initial step is the oxidative addition of the Pd(II) complex with the iodonium salt (**3a** or **3b**) to give Pd(IV) complex **8**. The coordination of alkene **2** affords the complex **9** and subsequent deprotonation generates the (η^3-allyl)palladium complex **10**, in accordance with the results of our deuterium labeling study (eqs 2−4).

Alternatively, the (η^3-allyl)palladium(II) complex may be formed first in the case of **1a**, followed by oxidation of the palladium by the iodonium salt. However, an (η^3-allyl)palladium(II) complex cannot be formed from **1b** directly, as in **1b** only a single coordination site is available on the metal center. We assume that formation of (η^3-allyl)palladium(IV) complex **10** from **9** is thermodynamically favorable with the efficient π-donor allyl moiety stabilizing the electron-poor palladium(IV) center.

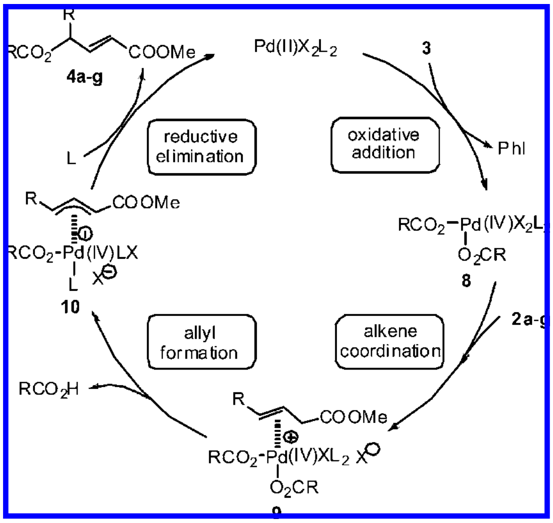


Figure 2. Proposed catalytic cycle for the allylic C−H acetoxylation/benzoyloxylation reaction.

In the final step of the cycle, reductive elimination gives products **4** and regenerates the Pd(II) catalyst. This does not require external activation, as the driving force is the reduction of Pd(IV) to Pd(II). In contrast, reactions via the Pd(0)/Pd(II) catalytic cycle require the presence of an activator ligand. The (η^3-allyl)palladium(II)acetate and chloride complexes are known to be stable for reductive elimination or external nucleophilic attack, unless an activator ligand (such as BQ) is present in the reaction mixture.[3] Significantly, the reductive elimination from the (η^3-allyl)palladium(IV) complex (such as **10**) appears to be inherently facile, obviating the need for BQ or other activator ligands. The regioselectivity of the nucleophilic attack is the same as the regioselectivity in the corresponding Pd(0)/Pd(II) process.[2h]

The carboxylate nucleophile of complex **10** does not necessarily arise from the employed iodonium salts (**3a** or **3b**). When the catalytic reaction of **2a** and acetoxy iodonium salt **3a** (entry 3) was repeated with LiOBz as an additive in place of KOAc, a mixture of **4a** and **4b** formed. This indicates that the carboxylate groups may undergo exchange either in the iodonium salt[6] (i.e., **3a** is converted to **3b**) or in complexes **8**−**10**. New synthetic applications based on this principle are underway in our laboratory.

In summary, we have presented a new catalytic allylic C−H functionalization process and evidence for the formation of (η^3-allyl)palladium(IV) intermediates. The reactions are suitable for selective acetoxylation and benzoyloxylation of various terminal and internal alkenes using iodonium salts as oxidants. This catalytic process is regio- and stereoselective, and it can be performed under mild conditions. Unlike some of the Pd(0)/Pd(II) acetoxylation methods,[2h] the present procedure does not induce rearrangement of the reagents or products. Thus, the presented procedure is complementary to the existing Pd(0)/Pd(II) methods, when rearrangements or isomerizations have to be avoided or application of nonacidic conditions is required. The presented process is also very interesting mechanistically. As far as we know, this is the first catalytic process in which an (η^3-allyl)palladium(IV) complex is suggested as the key intermediate in iodonium salt mediated oxidation reactions. Thus, the presented procedure significantly broadens the scope of palladium-catalyzed processes proceeding via a presumed Pd(II)/Pd(IV) redox cycle.[4,5]

Acknowledgment. A postdoctoral stipend by the Carl Tryggers Stiftelse for L.T.P. and the support of the Swedish Research Council is greatly acknowledged.

Supporting Information Available: Experimental procedures and spectroscopic data for **4a**−**h** as well as details of the mechanistic studies are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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