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FULL PAPER

Directed C−H Bond Oxidation of Bridged Cycloalkanes Catalyzed by Palladium(II) Acetate

Marta Larrosa,[a] Benjamin Zonker,[a] Jannis Volkmann,[a] Felix Wech,[a] Christian Logemann,[b] Heike Hausmann,[a] and Radim Hrdina*[a]

Abstract: We have developed a synthesis of 1,2-substituted adamantane carboxylic acids and further bridged cycloalkanes (cage compounds) by palladium acetate-catalyzed C−H bond oxidation. Acetoxylation of cycloalkane framework was performed using picolylamide as a directing group. Modification of the substrate, ligand design and variation of reaction conditions enabled us to study the mechanism of acetoxylation of aliphatic compounds. Post-functionalization reactions and cleavage of the directing group were developed. For the first time the synthesis and characterization of a β-C_3-*tri*-substituted adamantane derivatives was achieved.

Introduction

Several methods for the synthesis of β-hydroxy carboxylic acids of alkanes and non-bridged cycloalkanes have been described in the literature utilizing the reactivity of a C=C double bond or precursors derived from alkenes, such as Michael addition of oxygen nucleophiles to acrylic acid derivatives,[1] carboxymethoxylation of epoxides,[2] carboxylation of ketones[3] and its reduction (β-keto carboxylic acid derivatives).[4]
However, bridgehead (Bredt)[5] compounds do not undergo these types of reactivity (unstable C=C double bond at the bridgehead position) and new approaches to β-substitution pattern have to be developed. Namely for bi-or-tricyclic compounds such as terpenes[6] or diamondoids present in natural products and commercial drugs.[5b,7] Previously, for the latter class of compounds, the synthesis of 2-hydroxy-1-carboxylic acids involved skeletal rearrangements[8] of the hydrocarbon framework, or the framework was constructed *de novo*.[9]
Recently, an approach to β-hydroxy (relative to the functional group) aliphatic compounds by C−H bond oxidation was introduced using a covalently bound directing group (DG).[10] One of the first C−H oxidation of alkane chains was done with oxime amide as DG and with stoichiometric amounts of palladium.[11] Subsequently, a similar oxime derived DG was extensively studied by Sanford and co-workers.[12] Corey and co-workers presented the first quinoline amide directed oxidation of amino acids (Figure 1, A).[13] Dong and co-workers reported the palladium-catalyzed oxidation of C(sp^3)−H bonds using hydrazone-based *exo*-DG.[14] Sahoo and co-workers developed a new directing group (*S*-methyl-*S*-2-pyridyl-sulfoximine) for the acetoxylation of carboxylic acid derivatives[15] (Figure 1, A). Rao and co-workers developed a Pd-catalyzed C−H alkoxylation of cyclic cycloalkanes using quinoline amide as DG.[16] Chen and co-workers reported the first γ-activation of an alkylamine in a [2.2.1] bicyclic compounds using picolinamide as DG.[17]
To the best of our knowledge, there are only two studies that employ C–H bond oxidation in the β-position (to the DG) on bridged compounds (Figure 1, B). Mei and co-workers performed the electrochemical oxidation of adamantane derivatives using an oxime as DG and palladium acetate as catalyst.[18] Dong and co-workers reported the first acetoxylation reaction of norbornyl-derived alcohols using oxime based exo-DG.[19]

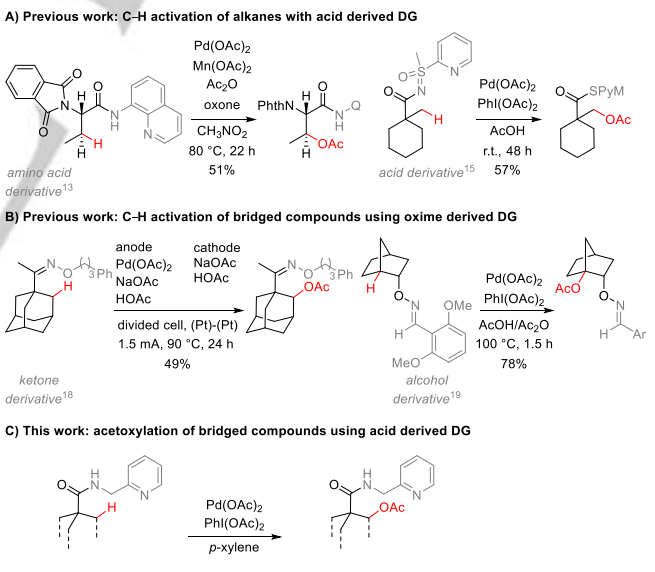

Figure 1. Synthetic methods for the directed acetoxylation of aliphatic compounds.

Here we report a *C–H bond functionalization of bridged carboxylic acids* using picolylamide as a directing group, palladium acetate as a catalyst and $PhI(OAc)_2$ as an oxidant. This reaction leads to preparation of β-hydroxy carboxylic acid derivatives.

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Results and Discussion

1-Adamantanecarboxylic acid was selected as the model substrate. Inspired by the works of Rao[16] and Dong,[19] a number of directing groups were screened using $Pd(OAc)_2$ as catalyst, $PhI(OAc)_2$ as oxidant and toluene as solvent (Figure 2).

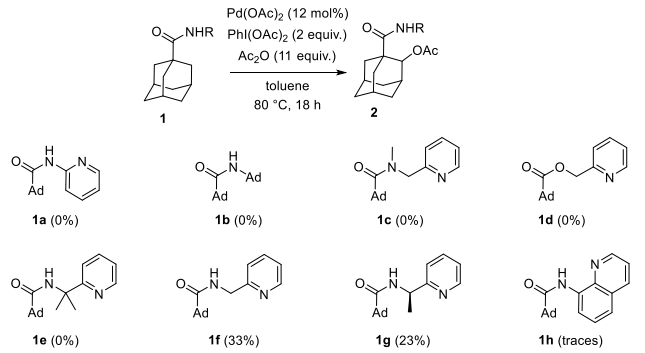
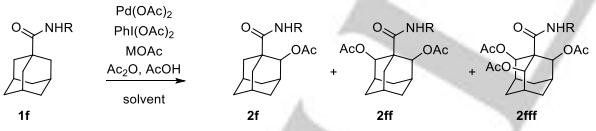


Figure 2. Screening of directing groups, yield of **2** in parentheses. Ad = adamantane.

Acetoxylation reaction was observed in the β-position (with respect to the DG) of the adamantane framework only when bidentate directing groups were used (Figure 2). The best yield was obtained with picolylamide (33%) as directing group (**1f**).
In the case of adamantane framework, there are six C–H bonds adjacent to the directing group, potentially leading to a mixture of *mono*-, *di*-, and *tri*-acetoxylated products (Scheme 1). Optimization of the reaction conditions for the desired *mono*-acetoxylation was performed by varying temperature, loading and concentration of corresponding compounds and screening of solvent, oxidant and additives. The highest conversion to the *mono*-acetoxylated compound **2f** was obtained when $PhI(OAc)_2$ was used as oxidant, *p*-xylene as solvent, with 6 equivalents of acetic anhydride, 1 equivalent of acetic acid, and 0.5 equivalents of potassium acetate (Table 1).



Scheme 1. Acetoxylation of adamantane with directing group (**1f**). R = CH_2Py.

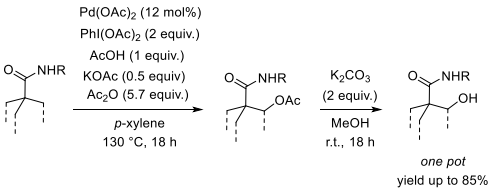
During the screening of conditions, it was found that the yield of **2f** depends on the presence of metal acetates (Table 2). As such, a number of acetate bases were screened in order to increase the conversion of starting material and to increase the selectivity for *mono*-acetoxylation (Scheme 1). The best yield for compound **3f** was obtained using KOAc (Table 2, entry 3), the best selectivity was obtained using $Mn(OAc)_2$ where just *mono*-alcohol **3f** was obtained (Table 2, entry 8).

Table 1. Optimization of the palladium(II)-catalyzed C−H acetoxylation[a]

Entry	Oxidant	AcOH (equiv.)	MOAc	Solvent	Conversion of **1f** (%)
1	$PhI(OAc)_2$	-	-	toluene[b]	46%
2	$PhI(OAc)_2$	2	-	toluene[b]	67%
3	$PhI(OAc)_2$	2	LiOAc	toluene	70%
4	$PhI(OAc)_2$	2	LiOAc	*p*-xylene	74%
5	$PhI(OAc)_2$	2	KOAc	*p*-xylene	74%
6	$PhI(TFA)_2$	2	KOAc	*p*-xylene	decomp.
7	oxone	2	KOAc	*p*-xylene	no reaction
8	$PhI(OAc)_2$	2	KOAc	*p*-xylene	72%[c]
9	$PhI(OAc)_2$	-	KOAc	*p*-xylene	49%[c]
10	Dess-Martin	1	KOAc	*p*-xylene	30%[c]
11	IBX	1	KOAc	*p*-xylene	20%[c]
12	$PhI(OAc)_2$	2	KOAc	*p*-xylene	69%[c]
13	$PhI(OAc)_2$	1	KOAc	HFIP	32%[c]
14	$PhI(OAc)_2$	1	KOAc	*p*-xylene	82%[c]
15	$PhI(OAc)_2$	as solvent	-	-	19%[c]

[a] All reactions were carried out with 11 equiv. of Ac_2O, 2 equiv. of oxidant and 0.5 equiv. of base on a 0.18 mmol scale in *p*-xylene (2 mL) at 130 °C for 18 h under argon unless otherwise specified. [b] 110 °C. [c] 5.7 equiv. of Ac_2O. Entry 6: decomp.= decomposition

To facilitate the separation of the main product from the side products, **2f** was hydrolyzed to the alcohol **3f** in one pot (Scheme 2). A mixture of *mono*-, *di*-, and *tri*-alcohols **3f**, **3ff**, **3fff** was separated by silica gel flash column chromatography.



Scheme 2. One pot reaction conditions: acetoxylation to **2** and subsequent hydrolysis to **3**; R= CH_2Py.

Table 2. Screening of metal and organic acetates.

Entry	Acetate salt	Yield *mono*-**3f** (%)	Yield *di*-**3ff** (%)
1	LiOAc	44	16
2	NaOAc	38	18
3	KOAc	60	16
4	CsOAc	35	21
5	$Ca(OAc)_2$	52	14
6	$Ba(OAc)_2$	24	0
7	$Sc(OAc)_2$	34	0
8	$Mn(OAc)_2$	45	0
9	$Fe(OAc)_2$	23	0

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10	$Co(OAc)_2$	0	0
11	CuOAc	0	0
12	$Cu(OAc)_2$	0	0
13	$Zn(OAc)_2$	32	12
14	AgOAc	32	0
15	NH_4OAc	36	0

With the optimized reaction conditions in hand, we explored the scope of the C(sp^3)–H oxidation reaction on various adamantane derivatives (Figure 3).

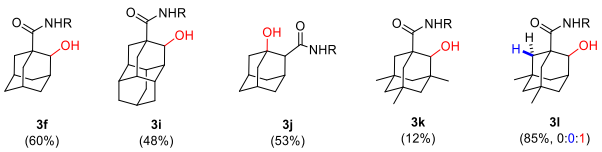

Figure 3. Scope of adamantane derivatives, yield of isolated products **3** in parentheses (color code used for regioselectivity); R= CH_2Py.

Adamantane carboxylic acid derivative **1f** reacts to give **3f** in 60% yield, with a ratio of *mono*-**3f**: *di*-**3ff** (3.7:1) and less than 5 % of *tri*-**3fff**. Diamantane **1i**, as a higher adamantane congener, displays similar reactivity (48% yield for **3i**), the ratio *mono*-/*di*-/*tri*- is (2:1:traces). Having the directing group in a secondary position of adamantane framework **1j** enables the oxidation of the tertiary C–H bond to **3j** in 53% yield with traces of *di*-**3jj**. The derivative **1k** with three methyl groups in the tertiary position of the adamantane framework reacts to **3k** in a low 12% yield. Dimethyl derivative **1l** provides product **3l** in 85% yield with absolute selectivity for *mono*-oxidation. The regioselective formation of **3l** shows that electronic and steric effects play an important role.
To study the electronic effects of substituents on reactivity and regioselectivity additional starting materials were tested (Figure 4). The conversion of the 3-chloroadamantane-1-carboxylic acid derivative **1m** to the *mono*-hydroxy **3m** is moderate and a 1:1 mixture of epimers was obtained with an isolated yield of 50% (ratio of *mono*-**3m**:*di*-**3mm**:*tri*-**3mmm** 1:0.7:0). For the following derivatives the ratios of *mono*- versus *di*- versus *tri*- were not recorded. In the case of the bromo derivative **1n**, a 1:1 mixture of epimers **3n** was obtained in 66%. Similar conversion and same regioselectivity for methylcarboxylate derivative **1o** was obtained in 68% isolated yield. Derivative **1p** with an oxo group in position 4 of the adamantane framework provides the *mono*-hydroxy **3p** in 70% yield as a mixture of all regioisomers. Noradamantane derivative **1q** provides a mixture of epimers **3q** in ratios 1:1, the tertiary C–H bond, due to the strain in noradamantane cage (reduced sp^3 character) remained unreacted. A mixture of geometrical isomers of the chloro derivative **1r** provides corresponding isomers **3r** in 46% isolated yield (the isomers of **1r** are separable by preparative HPLC and conversion was confirmed by performing the reaction with individual isomers, see SI page 25).

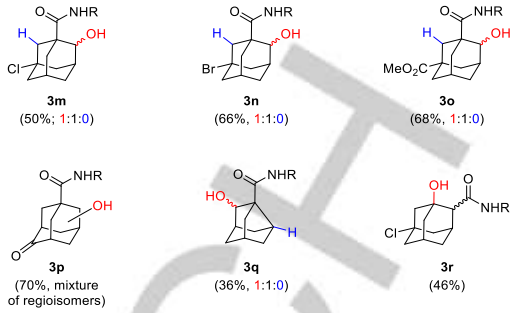

Figure 4. Scope of substituted adamantane derivatives, conversion of **3** and ratios of epimers in parenthesis using color code; R= CH_2Py.

The optimized conditions were applied on further bicyclic compounds with a focus on isolation and characterization of *mono*-hydroxy products (Figure 5). The bicyclo[2.2.2]octane derivative (**1s**) provided **3s** in 42% isolated yield. Deoxoketopinic acid derivative **1t** provided *mono*-alcohol **3t** in 48% yield and ketopinic acid derivative **1u** in 50% yield with absolute regioselectivity for the exo product **3u**. Since all assignments have been verified by the spectra mentioned in SI, we use the NOESY information for the assignment of the diastereotopic methylene protons. For this, these protons are labeled *exo* and *endo* (see SI page 68). The bicyclo[2.2.1]heptane derivative **1v** with -CO_2Me group in position 4 of the bicyclic framework provided mixture of all regioisomers of *mono*-alcohols **3v** in 54% yield. In the case of bicyclo[1.1.1]pentane derivative **1w**, the oxidation of the C−H bond does not occur. This may reflect the fact that the bond dissociation energy for C–H bond in such strained cycloalkane is higher than 107 kcal/mol.[20]

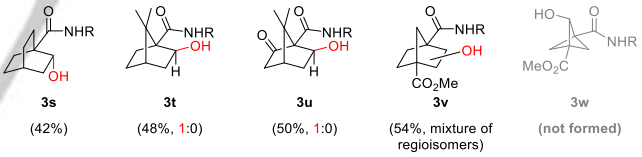

Figure 5. Scope of bicyclic derivatives **1**, yields of **3** and ratios of epimers in parenthesis using color code; R= CH_2Py.

Based on the literature reports for similar substrates[21] and similar directing groups[22] we propose that the catalytic cycle contains two consecutive steps (Scheme 3). C−H bond activation with palladium acetate to give a palladacycle intermediate; followed by transformation of carbon palladium bond (presumably through Pd^{IV} intermediate)[23] to carbon oxygen bond. Following mechanistic study combines the information from obtained results with additional experiments.

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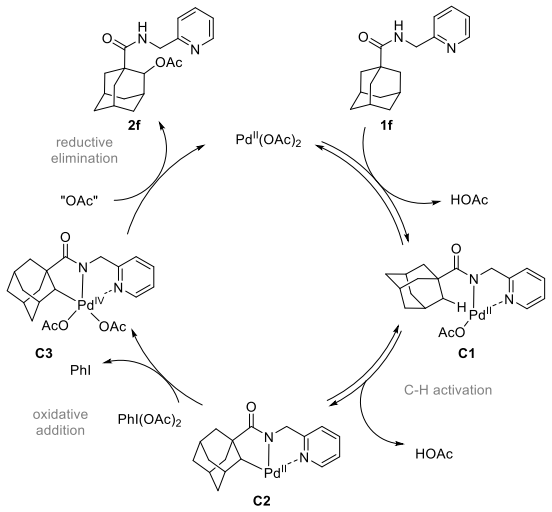


Scheme 3. Proposed catalytic cycle for the directed C−H acetoxylation (the role of MOAc and Ac_2O were omitted, as well as ligands to describe 16 and 18 electron complexes).

As in our previous study[24] dealing with the C−H bond arylation of the same molecule **1f**, the properties of the directing group were tested (Figure 6). The structural arrangement of two five membered rings in the palladacycle intermediate does not play a role and in the same manner it is possible to acetoxylate methylene amine derivatives on the adamantane framework to get the compound **4** in 37% yield. This supports the hypothesis that the interplay of the directing group and ligands (acetate) in the C−H activation step is similar as in the C−C bond formation reactions.

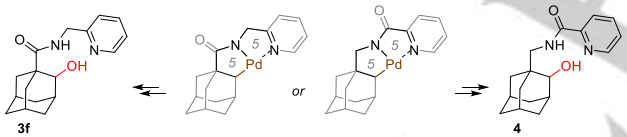
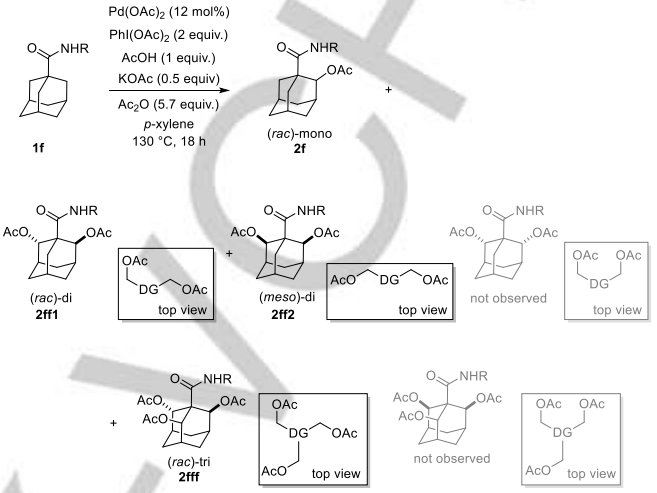


Figure 6. Properties of the directing group, oxidation of acid derivatives or methylene amine derivatives.

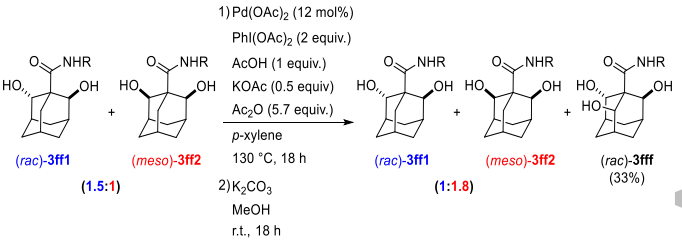
The strong dependence of conversion on the presence of metal acetates[25] (Table 2) indicates that metal cations synergistically facilitate the C−H activation step and C−O bond formation step.[17] Presumably by coordinating to the carbonyl group of the substrate providing optimal conformations for the C−H bond palladium insertions[25c,26] and by influencing electronically the ligand exchange processes (trans effect).[27]

From the results summarized in Figures 3, 4 and 5, it can be deduced that oxidation of the C−H bond is dependent not only on C−H bond electron densities (**1m**), but also on steric effects (**1k**). This fact should be reflected by the number of isomers formed in the over oxidation of the adamantane framework (Scheme 4). If two equivalents of the oxidant $PhI(OAc)_2$ are used, a mixture of isomers is formed. A detailed analysis of the reaction mixture showed that just 4 isomers can be detected by ^1H and ^{13}C NMR. From the fact that just one isomer of *tri*-acetoxy **2fff** was formed and just two isomers of **2ff** were detected, we deduce that two C−O bonds never face each other on the adamantane framework.



Scheme 4. Stereoisomers detected in the acetoxylation reaction.

In 1964 Schleyer and co-workers designed *tri*-substituted adamantane derivative with central chirality[28] and in 1974, Červinka and Hájíček achieved the first synthesis of optically pure adamantane derivative of such type.[29] To the best of our knowledge, we herein describe the first synthesis of a 2,8,9-*tri*-substituted chiral adamantane derivative with C_3-symmetry.This molecule was proposed in the work focused on the synthesis of the smallest organic triol with C_3-symmetry by Haufe group.[30] The exclusive formation of the (*rac*)-**2fff** isomer is remarkable. In the next experiment a mixture of two isomers, (*rac*)-**3ff1** and (*meso*)-**3ff2**, was separated and subjected to the acetoxylation reaction conditions. The (*rac*)-**3fff** was formed as a single C_3-symmetrical isomer in 33% isolated yield (Scheme 5). Analysis of the starting material after the reaction revealed that the ratio of isomers (*rac*)-**3ff1** and (*meso*)-**3ff2** had changed from 1.5:1 to 1:1.8, indicating that just (*rac*)-**3ff1** provides the product (*rac*)-**3fff** (See SI page 91).



Scheme 5. Acetoxylation of mixture of isomers (*rac*)-**3ff1** and (*meso*)-**3ff2**; (color code for ratios).

Furthermore, **1f** was subjected to an excess of oxidant (6 equiv.) keeping the same reaction conditions (Scheme 6). This resulted

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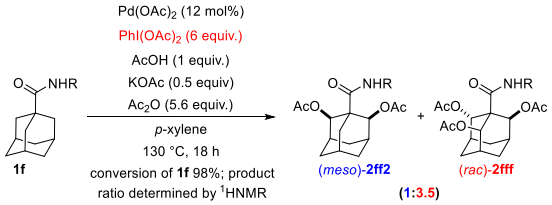
in a mixture of two products, the *di*- and the *tri*-acetylated compounds (*meso*)-**2ff2** and (*rac*)-**2fff**. They are formed in a ratio of 1:3.5 (See SI page 91).



Scheme 6. Acetoxylation of **1f** with excess of oxidant; (color code for product ratios).

The formation of the palladacycle was examined with deuterium labeling experiments. The starting material was exposed to standard conditions, but instead of 1 equivalent AcOH, various amounts of AcOD-d_4 were used and the oxidant was omitted (see SI page 93). Depending on the ratio of AcOD to the starting material, different ratios of incorporated deuterium versus hydrogen were detected (in the first experiment all additives and reagents were used, in the latter were conducted with AcOD and solvent only). When 10 equivalents of AcOD were used, one to one ratio of hydrogens versus deuteriums in the β-position was observed. Increasing the amount to 20 equivalents of AcOD resulted in 1:2 isotopic ratio. These experiments confirm that the C−Pd bond formation is reversible. When the experiment is carried out at a lower temperature (80 °C), only the methylene (acidic) hydrogens in the directing group were exchanged for deuterium.

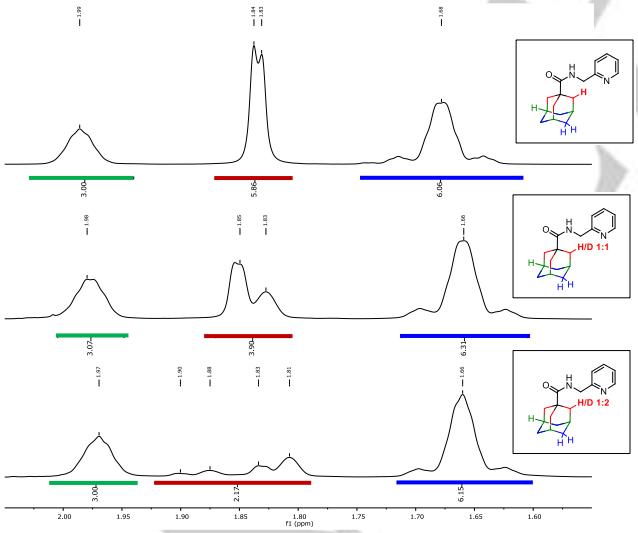
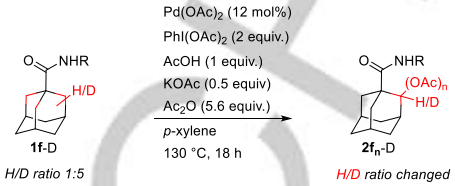


Figure 7. Directed deuterium isotope exchange in β-position to the DG.

Almost fully deuterated product **1f** (βD/βH = 5:1) in the β-position was synthesized (see SI page 93) and subjected to the oxidation reaction (Scheme 7). The ratio of βD/βH on the oxidized carbon changed to a lower ratio, which indicates that the acidolysis of the palladacycle competes with the oxidation step. The degree of exchange was not determined due to overlap of the signals for *mono*-, *di*- and *tri*-acetoxylated products.



Scheme 7. Oxidation of C–D derivative **1f-D** and H/D ratio in the oxidized position of **2f-D**.

Additional deuterium exchange experiments were conducted with compounds **1t** and **1u** (see SI page 93), the results showed that the palladacycle can be formed in both the *exo*- and *endo*-position (red-colored, Figure 8). However, the acetoxylations of **1t** and **1u** proceeds only in the *exo*-position (Figure 5). This result indicates that the transition state for *exo*-C−O bond formation is substantially lower than for the endo-pathway.

Figure 8. Deuterium incorporation experiments with **1t** and **1u**; red: acidolysis of palladacycle; blue: enolizable position.

To determine if the product formation is kinetically controlled (C−O bond is formed irreversibly in the catalytic cycle and no further substitution reactions are involved), the following experiment was designed. *Mono*-acetylated **2f** was subjected to the reaction conditions this time with pivalic anhydride and pivalic acid (instead of potassium acetate, the potassium carbonate was used). No substitution reaction of acetoxy group occurred, starting material was fully recovered (see SI page 95).

From the results obtained (adamantane framework **3j**, **2fff** and ketopinic framework **3t**, **3u**) we may also conclude that the C−O bond formation has reductive elimination character[10d,31] (retention of configuration during the C−O bond formation step, Figure 9).

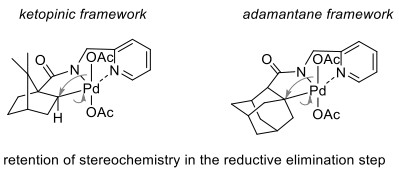


Figure 9. C−O bond formation *via* reductive elimination.

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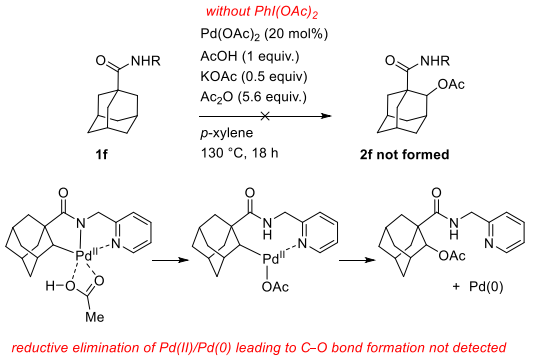
In order to disclose the Pd(II)/Pd(0) reaction pathway (C−O bond formation by reductive elimination of Pd(II) complexes), an experiment without oxidant and under inert conditions was performed with 20 mol% of $Pd(OAc)_2$ (Scheme 8). Acetoxylated compound **2f** was not formed, which was confirmed by ^{1}H-NMR and more sensitive HRMS analysis.



Scheme 8. Acetoxylation attempt of **1f** without oxidant.

In the next step we focused on the role of the acetate salt (MOAc) and of the acetic anhydride.

Both additives do not change the reaction outcome, regioselectivity and stereoselectivity (see SI page 96), but strongly influence the reaction speed. In the case of metal acetates,[25] which were chosen to be oxophylic, interaction between the oxygen of the directing group and the metal cation is proposed to facilitate ligand exchange processes and change of electron densities on palladium, which influences the oxidative addition/reductive elimination steps (Figure 10, I). Acetic anhydride is proposed to modulate the ligation properties of nucleophilic pyridine nitrogen (ligand exchange processes) by forming reversibly acylium intermediates (Figure 10, II). In order to prove such intermediate, alcohol **3ff** was subjected to the reaction conditions. Fully acetylated product (*rac*)-**2fff** was formed (see SI page 91).

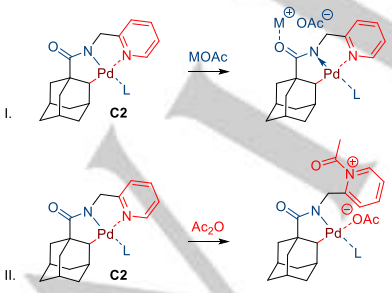
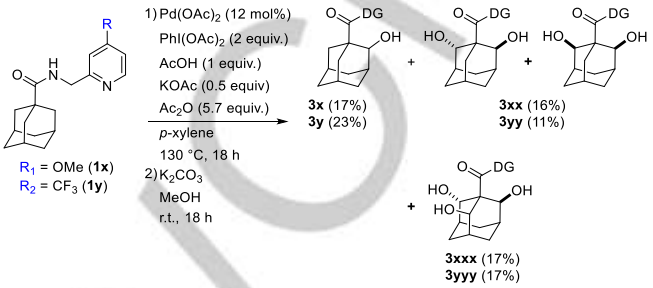


Figure 10. Proposed modulation of electronic density on palladium by MOAc and Ac_2O; depicted on complex **C2** using color code.

Derivatives **1x** and **1y** were synthesized in order to study the influence of the electronic properties of the directing group[32] on the reaction outcome and kinetics of the reaction. The obtained results show slightly higher conversions for the derivative OMe-**1x**, significant impact of R group in the para position of the pyridine ring on the product distribution was not observed (Scheme 9). In the competitive experiment between **1x** and **1y**, derivative **1x** was consumed faster than **1y**.



Scheme 9. Electronic modification of the directing group on the pyridine ring (DG).

To summarize the mechanistic investigation we have proven that the catalytic cycle can be divided in two consecutive steps: reversible C−H activation[33] to palladacycle **C2** and irreversible oxidation to complex **C4**, which proceeds with retention of configuration. The nature of the oxidation step is not yet proven[34a,17,10d,10e,14,34b,21,10g] (two plausible pathways are proposed: concerted demetalation-oxidation[35] or oxidation of Pd^{II} complexes to Pd^{IV}) (Figure 11).

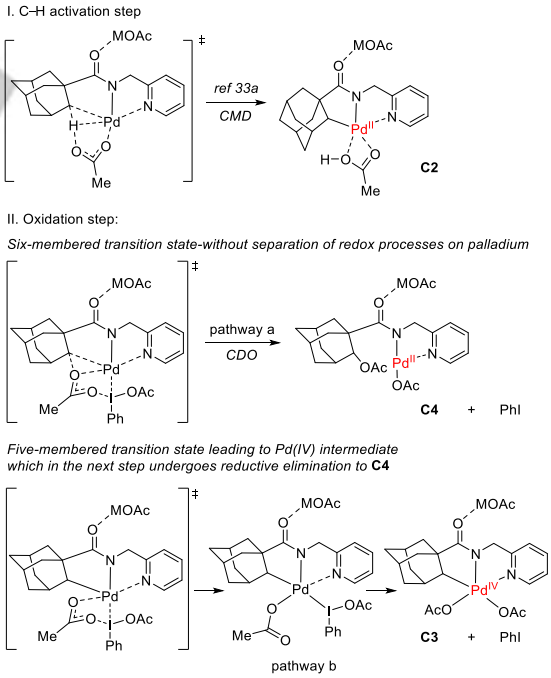


Figure 11. Proposed pathways for C−H activation (CMD- concerted metalation-deprotonation), and oxidation step (CDO- concerted demetalation-oxidation versus Pd(II)/Pd(IV) oxidation).

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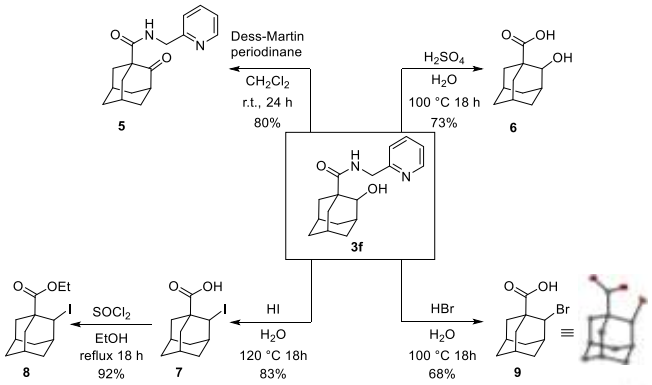
The synthetic utility of our protocol is demonstrated by the preparation of several β-substituted adamantane carboxylic acids (Scheme 10). The oxidation of the alcohol **3f** with Dess-Martin periodinane proceeds in 80% yield to give the keto derivative **5**. Hydrolysis of the **3f** occurs under strongly acidic conditions and gives the corresponding carboxylic acid **6**[36] in good yields. HI or HBr were used for the cleavage of the directing group and as nucleophilic agents for the corresponding substitution reactions providing halogenated acid derivatives **7**[37] and **9**[38]. Esterification of acids **7** gives compound **8** which can be used for various further transformations.



Scheme 10. Post-functionalization reactions of **3f**.

Conclusions

In summary, we have developed the first Pd(II)-catalyzed acetoxylation of C(sp^3)−H bond adjacent to the carboxylic acid moiety on bridged cage compounds. Cleavage of the directing group and hydrolysis of the acetyl group provides access to 2-hydroxy-1-carboxylic acid derivatives. This method has a good functional group tolerance and a broad scope of substrates. Additionally, we were able to synthesize C_3-symmetric 2,8,9-*tri*-substituted adamantane derivative. Current effort is focused on the application of the products formed using this reaction and getting further information concerning the mechanism of the acetoxylation reaction.

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Keywords: C−H activation • palladium acetate • acetoxylation • cage compounds • diamondoids

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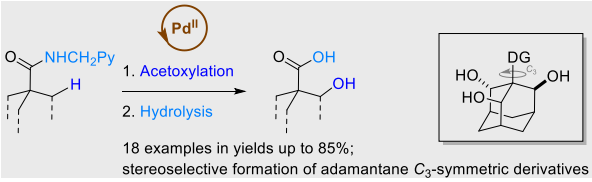

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