C–H Activation

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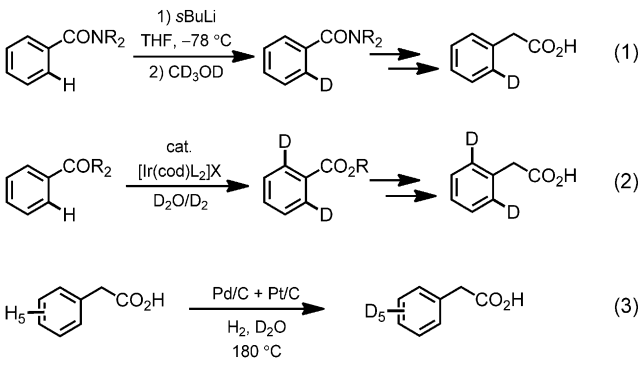
Palladium-Catalyzed *ortho*-Selective C–H Deuteration of Arenes: Evidence for Superior Reactivity of Weakly Coordinated Palladacycles**

*Sandy Ma, Giorgio Villa, Peter S. Thuy-Boun, Anna Homs, and Jin-Quan Yu**

Abstract: *We disclose a protocol for the palladium-catalyzed ortho-selective C–H deuteration of arenes. Phenylacetic acids and benzoic acids are suitable substrates for this reaction. This reaction offers a catalytic route to ortho-deuterated phenylacetic acids and benzoic acids and demonstrates the sharp difference in reactivity of palladacycle intermediates held together by weak and strong coordination.*

Deuterium-labeled compounds are widely used in mass spectrometry as well as in mechanistic and metabolic studies.[1,2] Furthermore, there is growing interest in selective deuteration because deuterium incorporation can improve the overall therapeutic and metabolic profile of a drug.[3] Owing to the prevalence of the phenylacetic acid moiety in drug molecules,[4] the directed *ortho*-deuteration of phenylacetic acids would be an attractive step-economical route, as current methods for accessing the same scaffold either require multistep synthetic routes or are nonselective for the *ortho* position [Eqs. (1)–(3)]. The first possible method is to use the selective *ortho*-deuteration of benzamide derivatives through directed stoichiometric *ortho*-metalation (DoM)[5,6] followed by one-carbon homologation [Eq. (1)]. An alternative approach is to use catalytic, cationic iridium complexes, such as the Crabtree catalyst,[7] to *ortho*-metalate/deuterate benzoic acid derivatives [Eq. (2); cod = 1,5-cyclooctadiene]. This protocol has been widely used to *ortho*-deuterate benzamides, benzoic acid derivatives, and acetanilides in high yields;[1b,8] however, this route still requires a one-carbon-homologation step to access *ortho*-deuterated phenylacetic acids. The third possible method is to use hetereogeneous mixed-transition-metal catalysts and D_2 to afford the deuterated phenylacetic acids, albeit in a nonselective manner [Eq. (3)].[9] This reductive protocol may not be compatible with functional groups that are prone to hydrogenation.

Inspired by our previous successes in the use of palladium catalysts for the selective *ortho*-functionalization of arenes,[10]

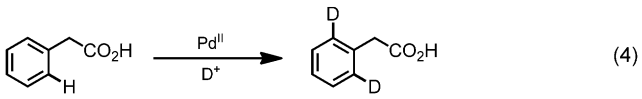


(1)

(2)

(3)

we were eager to develop a palladium-catalyzed *ortho*-selective deuteration protocol for phenylacetic acids and other arene derivatives [Eq. (4)]. Despite extensive studies on palladium-catalyzed *ortho*-directed C–H activation reactions, catalytic deuteration through cyclopalladation has not yet been developed, largely because the stable palladacycles held together by strong coordination do not readily undergo protonolysis.[11] We envisioned that the recently established reactivity of phenylacetic acids towards *ortho*-C–H activation through weak coordination[12] with palladium(II) catalysts could enhance the protonolysis, thus leading to deuteration. Herein, we report the palladium-catalyzed *ortho*-deuteration of phenylacetic acids through protonolysis of palladacycles held together by weak coordination. This catalytic protonolysis pathway is mechanistically distinct from the D-exchange processes based on the use of a metal and D_2. Comparative studies with 2-phenylpyridine and 2-benzylpyridine substrates further illustrate that weakly coordinated palladacycles are significantly more reactive in C–H functionalization reactions.



(4)

Our initial efforts towards a palladium-catalyzed *ortho*-selective C–H deuteration commenced with the treatment of (2-trifluoromethylphenyl)acetic acid (**1a**) with $Pd(OAc)_2$ (5 mol%) in deuterated acetic acid. However, heating of the reaction mixture at 120 °C for 12 h led to 0% deuterium incorporation (Scheme 1). In contrast, when Li_2CO_3 was added under the same reaction conditions, *ortho*-deuterated phenylacetic acid **2a** was obtained with 99% deuterium incorporation. More thorough screening revealed that inor-

[*] Dr. S. Ma, Dr. G. Villa, P. S. Thuy-Boun, A. Homs, Prof. Dr. J.-Q. Yu
Department of Chemistry, The Scripps Research Institute (TSRI)
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
E-mail: yu200@scripps.edu
Homepage: http://www.scripps.edu/chem/yu

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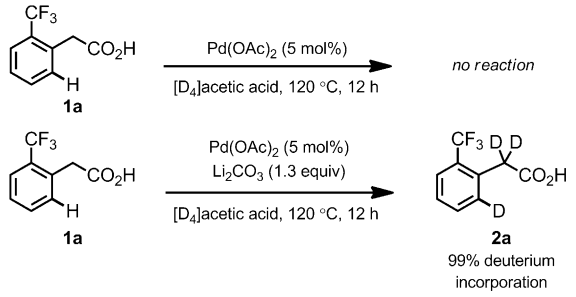
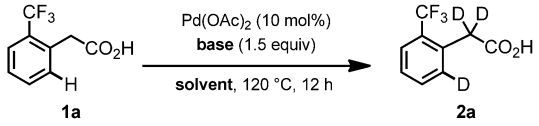


Scheme 1. Initial results.

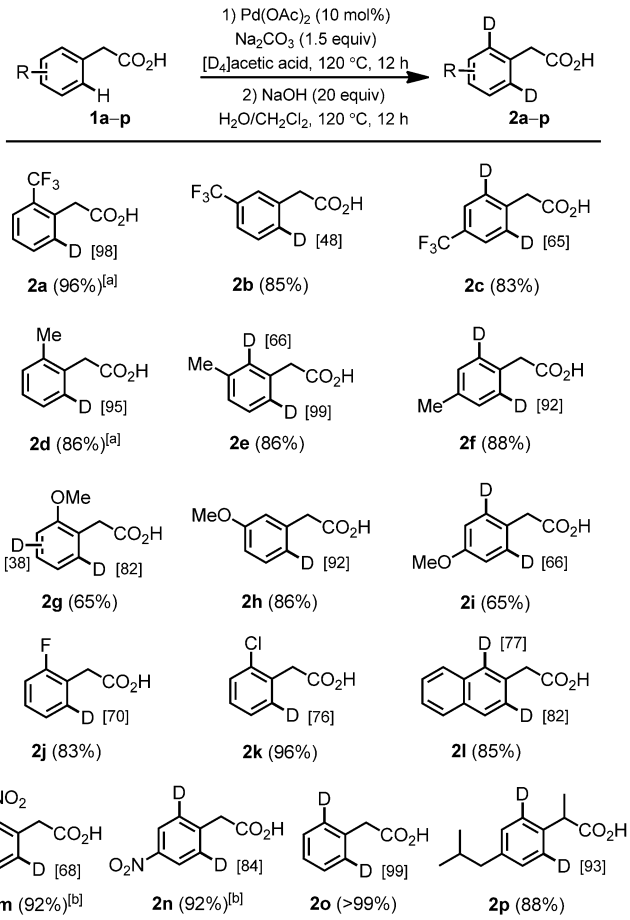
ganic bases were crucial for the observed reactivity (Table 1). This result was consistent with our previous findings that the presence of sodium or potassium cations promotes the *ortho*-palladation of benzoic and phenylacetic acids.[10b,13] However, no reaction was observed with sodium chloride.[14]

Table 1: Optimization of the reaction conditions.[a]



Entry	Base	Solvent	Deuterium incorporation [%][b]
1	Li_2CO_3	[D_4]acetic acid	99
2	Na_2CO_3	[D_4]acetic acid	99
3	K_2CO_3	[D_4]acetic acid	99
4	LiOAc	[D_4]acetic acid	99
5	NaOAc	[D_4]acetic acid	99
6	KOAc	[D_4]acetic acid	99
7	NaCl	[D_4]acetic acid	0
8	LiF	[D_4]acetic acid	80
9	KHF_2	[D_4]acetic acid	80
10	Na_2CO_3	D_2O	0
11	Na_2CO_3	[D_4]methanol	0
12	Na_2CO_3	[D_1]TFA	0
13	Na_2CO_3	$CDCl_3$	0

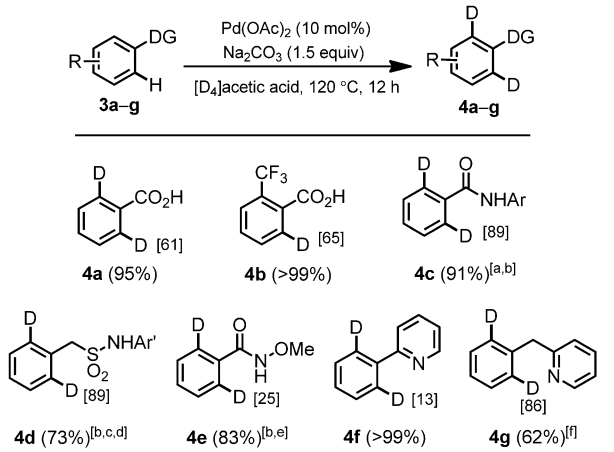
[a] Reaction conditions: **1a** (0.5 mmol), base (0.75 mmol), $Pd(OAc)_2$ (10 mol%), solvent (5 mL), 120°C, 12 h. The reactions were carried out in a 50 mL sealed tube. [b] Deuterium incorporation at the aromatic position was determined by ^{1}H NMR spectroscopy. TFA = trifluoroacetic acid.



Scheme 2. Palladium-catalyzed *ortho*-deuteration of phenylacetic acids. Conditions for *ortho*-deuteration (in a 50 mL sealed tube): **1** (0.5 mmol), Na_2CO_3 (0.75 mmol), $Pd(OAc)_2$ (10 mol%), [D_4]acetic acid (5 mL), 120°C, 12 h. Conditions for α-reprotonation (in a 50 mL sealed tube): crude **1** (0.5 mmol), NaOH (10 mmol), H_2O (2 mL), CH_2Cl_2 (2 mL), 120°C, 12 h. Deuterium incorporation determined by ^{1}H NMR spectroscopic analysis after the first step is shown in square brackets.[21] The yield of the isolated product after two steps is shown in parentheses. Deuteration at the α-position was observed after the first step, which necessitated the use of NaOH for reprotonation. [a] Deuterium incorporation was determined by ^{1}H NMR spectroscopic analysis of the corresponding methyl ester derivative (see the Supporting Information for details). [b] The yield of the isolated product after the first step is given owing to product decomposition upon treatment with NaOH. Deuterium incorporation at the α-position has been omitted for clarity.

Different deuterium-containing solvents (D_2O, [D_4]methanol, and [D_1]TFA) were also tested, but no product was observed in these reactions. Reaction times and temperatures were also briefly examined, which led to the identification of our optimized reaction conditions: treatment of the substrate with $Pd(OAc)_2$ (10 mol%) and Na_2CO_3 (1.5 equiv) in [D_4]acetic acid at 120°C for 12 h.

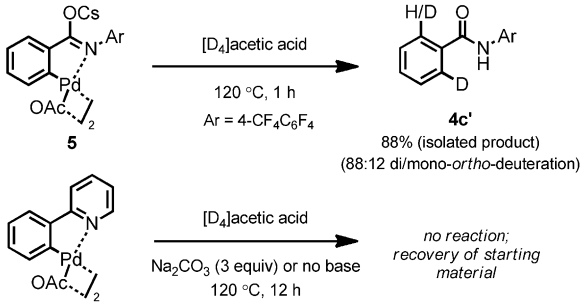
A variety of substituted phenylacetic acids were examined, including both electron-deficient and electron-rich substrates (Scheme 2). ^{1}H NMR spectroscopic analysis showed that the benzylic positions were also deuterated. The yields of the *ortho*-deuterated phenylacetic acids were determined after subsequent reprotonation at the α-position under basic conditions. Trifluoromethyl-, methyl-, and methoxy-substituted phenylacetic acids with *ortho*, *meta*, and *para* substitution were examined. Nonselective over-deuteration was observed for (2-methoxyphenyl)acetic acid (**1g**), but *ortho*-selective deuteration was observed for (3-methoxyphenyl)acetic acid (**1h**). Nitro-substituted phenylacetic acids **1m** and **1n** as well as the nonsubstituted phenylacetic acid **1o** were also suitable substrates for selective *ortho*-deuteration. Notably, the *ortho*-deuterated product derived from ibuprofen (**2p**) was isolated in 88% yield with 93% deuterium incorporation.



Scheme 3. Palladium-catalyzed *ortho*-deuteration of arenes. Conditions for *ortho*-deuteration (in a 50 mL sealed tube): **3** (0.5 mmol), Na_2CO_3 (0.75 mmol), $Pd(OAc)_2$ (10 mol%), [D_4]acetic acid (5 mL), 120°C, 12 h. Deuterium incorporation as determined by ^{1}H NMR spectroscopic analysis is shown in square brackets.[16] The yield of the isolated product is shown in parentheses. [a] Ar = 4-$CF_3C_6F_4$. [b] The reaction was performed on a 0.2 mmol scale. [c] The product of *ortho*-deuteration was subjected to α-reprotonation conditions (yield of the isolated product after two steps). [d] Ar′ = C_6F_5. [e] The reaction was performed at 80°C for 18 h. [f] Deuterium incorporation at the α-position has been omitted for clarity. DG = directing group.

Substrates other than phenylacetic acids were also studied (Scheme 3). The deuteration of benzoic acid (**3a**) and 2-trifluoromethylbenzoic acid (**3b**) yielded the *ortho*-deuterated acids with 61 and 65% deuterium incorporation, respectively. We were pleased to find that deuteration of the benzoic acid derived benzamide **3c** afforded the *ortho*-deuterated product **4c** in 91% yield with 89% deuterium incorporation. The pharmaceutically important sulfonamide **3d** was also transformed into the *ortho*-deuterated product **4d** with 89% deuterium incorporation and in 73% yield. Notably, the deuteration of *N*-methoxybenzamide **3e** and 2-phenylpyridine (**3f**) proceeded in low yield, although these two substrates are known to undergo facile cyclopalladation.[15] The poor reactivity of the *N*-methoxybenzamide remains to be elucidated; however, the low deuterium incorporation observed with 2-phenylpyridine suggests that weakly coordinated palladacycle intermediates are more reactive towards protonolysis through an electrophilic-cleavage pathway. This understanding is reinforced by the results obtained with 2-benzylpyridine (**3g**), which was *ortho*-deuterated to give **4g** with 86% D incorporation in total, thus suggesting that the less stable six-membered palladacycle is more reactive towards functionalization with electrophilic protons.

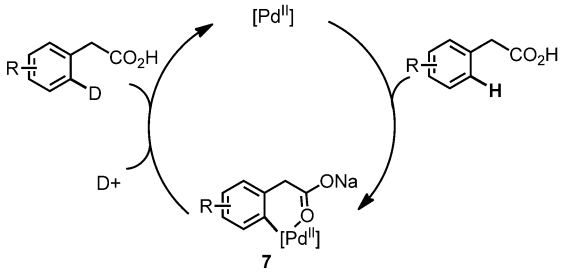
In light of our observation that substrates that are typically thought to coordinate strongly to the palladium metal center, such as 2-phenylpyridine (**3f**), undergo deuteration in low yields, we wanted to elucidate whether weak coordination was operative during the C–H insertion step and was responsible for the observed reactivity under our deuteration conditions. To compare the reactivity of palladacycles held together by either weak or strong coordination, we



Scheme 4. *ortho*-Deuteration with palladacycles.

evaluated the reactivity of palladacyles **5** and **6** under our deuteration conditions (Scheme 4). We used palladacycle **5**, which contains the cesium imidate derived from benzamide **3c** weakly coordinated to the palladium metal center, as a probe for investigating the reactivity of a palladacycle held together by weak coordination under deuteration conditions.[16,17] The treatment of complex **5** with deuterated acetic acid at 120°C for 1 h afforded the *ortho*-deuterated benzamide, which was isolated in 88% yield as an 88:12 mixture of di-*ortho*-deuterated and mono-*ortho*-deuterated products.[18] Thus, the deuteration of palladacycle **5** gave mainly the di-*ortho*-deuterated product, which suggests that the Pd^{II} species formed after protonolysis remained bound to the imidate and further cleaved the second *ortho*-C–H bond. In contrast, the treatment of palladacycle **6** with deuterated acetic acid at 120°C for 12 h promoted no reaction in either the presence or absence of a base. These results suggest that palladacycles that are derived from weak coordination are more reactive towards electrophiles and imply that a weak coordination mode between the substrate and the palladium metal center is responsible for the observed reactivity under our deuteration conditions.

We tentatively speculate that our deuteration proceeds first by C–H activation to generate an aryl–palladium(II) complex **7** (Scheme 5).[13a] This intermediate can then react with D^+ to give the deuteration product and the Pd^{II} catalyst. Reports on the interception of aryl–palladium(II) intermediates of type **7** by electrophiles, such as ketones, aldehydes, and nitriles, are still rare.[19] We have reported previously that aryl–palladium(II) complexes generated by C–H activation can react with alkyl halides through an electrophilic-cleavage pathway.[20] Our deuteration protocol suggests that under Pd^{II}



Scheme 5. Proposed catalytic cycle.

catalysis, the scope of reacting partners may be expanded to other electrophilic species. However, a mechanism that involves the formation of an [ArPd^{IV}D] intermediate cannot be disproved at this time.

In conclusion, we have developed an *ortho*-selective deuteration of phenylacetic acids with palladium(II) catalysts. Related benzoic acid derivatives were also suitable substrates for this reaction. These results offer an attractive one-step method to access *ortho*-deuterated phenylacetic acid compounds. The observed catalytic deuteration provides further evidence that palladacycles derived from weak coordination are more reactive. The facile protonation also reveals their potential reactivity towards other electrophiles.

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[14] The chloride anion might be detrimental to reactivity. The treatment of (2-trifluoromethylphenyl)acetic acid (**1a**) with $PdCl_2$ (10 mol%), Na_2CO_3 (1.5 equiv), and [D_4]acetic acid yielded the deuterated product with only 49% conversion.

[15] In the absence of a base, the *ortho*-deuteration of 2-phenylpyridine only proceeded to give trace amounts of the desired product.

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[21] Because deuterium incorporation was determined by ^{1}H NMR spectroscopic analysis, there exists the possibility of an unknown mixture of the mono-/di-*ortho*-deuteration product for *para*-substituted and unsubstituted arenes.

