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Palladium-Catalyzed Remote *meta*-C−H Bond Deuteration of Arenes Using a Pyridine Template

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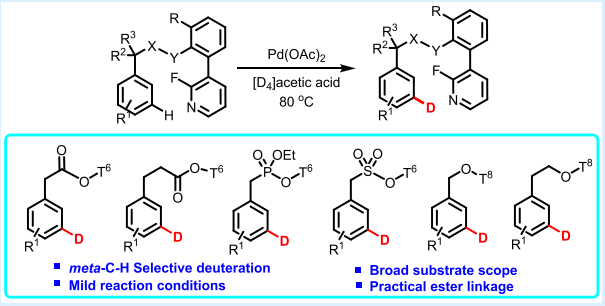
Supporting Information

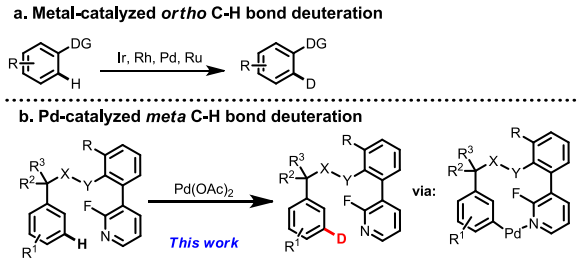
ABSTRACT: Palladium-catalyzed *meta*-selective C−H deuteration of a series of substrates, including phenylacetic acids, hydrocinnamic acid, benzylphosphonate, benzylsulfonate, and benzyl and phenyl ethyl alcohol ester, is developed by using a pyridine-based directing template. The template is installed into the substrate through a practical ester linkage. Under mild reaction conditions, a variety of phenylacetic acids containing alkyl, methoxyl, and halo substituents are compatible in the reaction, resulting in high levels of D-incorporation at the *meta* position.



Incorporation of deuterium atoms to generate valuable deuterium-labeled compounds is of high importance for their utility in mass spectrometry and mechanistic and metabolic studies.[1] Especially, in the pharmaceutical industry, incorporation of deuterium paves a way to alter and explore the ADME properties of existing drug candidates.[2] In 2017, the FDA approved the first deuterated drug Austedo (deutetrabenazine).[2g] The wide applications of deuterium-labeled compounds in these areas demand a suite of synthetic methods to install the deuterium atoms in specific positions. However, how to regioselectively introduce deuterium atoms remains a challenging synthetic problem. Metal-catalyzed C−H activation has allowed for the direct hydrogen isotope exchange (HIE) in the molecular substrate, thus circumventing the need for the multistep synthetic processes. In contrast with a heterogeneous metal catalyst, homogeneous metal-catalyzed HIE methods are typically more site selective.[1a,b] Assisted by a directing group, Ir,[3] Rh,[4] Pd,[5] and Ru[6] catalysts have been adopted in deuteration of *ortho*-C−H of aromatic compounds (Scheme 1a). Complementary to the directing group approach, Chirik and co-workers reported the Fe-catalyzed C−H bond deuteration and tritiation at sterically unencumbered positions.[7] However, the realization of the regioselective *meta*-C−H deuteration still remains a challenge.[8]

Compared to *ortho*-C−H activation of arene, directed remote C−H activation has drawn more and more attention in recent years.[9] The distance and geometry of a directing group are key recognition parameters to activate remote C−H bonds. In 2012, we first reported template-directed Pd-catalyzed *meta*-C−H activation of toluene derivatives and hydrocinnamic acids through a cyclophane-like pretransition state.[9m] This approach made it possible to recruit a metal catalyst to the remote position and override the governance of electronic properties and steric biases of the substituents. Since then, we and others have developed many templates that can direct remote *meta*- and even *para*-C−H activation, including olefination,[9a,b,e,g−j] arylation,[9a] acetoxylation,[9b,h] silylation,[9f] germanylation,[9f] cyanation,[9b,d] and iodination.[9a,g] Prompted by our recently developed palladium-catalyzed *ortho*-deuteration of phenylacetic acids, benzoic acid, and benzamide substrates through protonolysis of weakly coordinated unstable palladacycles,[5c] we envisioned that assisted by a directing template we could install deuterium at the *meta*-positions of

Scheme 1. Directed C−H Deuteration



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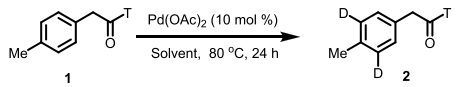
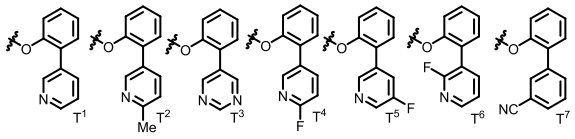
phenylacetic acids through protonolysis of cyclophane-like palladacycles (Scheme 1b).

A pyridine-containing template has been utilized to realize *meta*-C−H activation in recent years by taking advantage of the σ-coordinating property of the nitrogen atom.[9a,b,d,g] From a practical perspective, the directing group should be easily installed and readily removed for late-stage modification of pharmaceuticals and bioactive compounds. Thus, we began our initial studies by installing different pyridine-containing templates into phenylacetic acids through an ester linkage.[9f,d,i,k] As shown in Table 1, when the template containing a simple

Table 1. Optimization of the Reaction Conditions for *meta*-C−H Deuteration[a]



entry	template	T (°C)	time (h)	solvent	deuterium incorporation (%)[b]	yield (%)[c]
1	T^1	80	24	[D_4]acetic acid	0	0
2	T^2	80	24	[D_4]acetic acid	0	0
3	T^3	80	24	[D_4]acetic acid	0	0
4	T^4	80	24	[D_4]acetic acid	62	30
5	T^5	80	24	[D_4]acetic acid	0	0
6	T^6	80	24	[D_4]acetic acid	94, 0[d], 88[e]	75, 0[d], 72[e]
7	T^7	80	24	[D_4]acetic acid	0	0
8	T^6	80	24	$CDCl_3$	0	0
9	T^6	80	24	[D_4]methanol	0	0
10	T^6	80	24	D_2O	0	0
11	T^6	80	24	[D_1]acetic acid	88	75
12	T^6	40	24	[D_4]acetic acid	0	0
13	T^6	60	24	[D_4]acetic acid	25	93
14	T^6	80	6	[D_4]acetic acid	69	90
15	T^6	80	12	[D_4]acetic acid	81	82

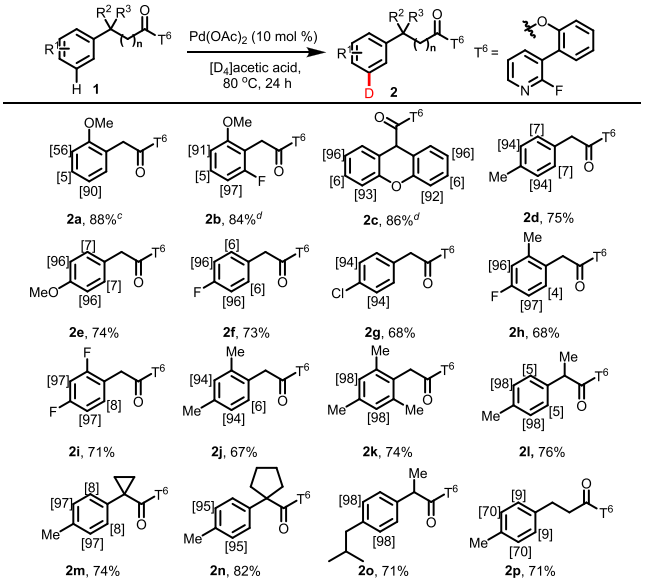


[a]Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), solvent (1 mL), 80 °C, 24 h. [b]Deuterium incorporation was determined by ^{1}H NMR spectroscopic analysis. [c]Isolated yield. [d]Without $Pd(OAc)_2$. [e]5 mol % $Pd(OAc)_2$.

pyridyl moiety in substrate **1** was subjected to *meta*-C−H deuteration, no D-incorporation was observed in the reaction (entries 1 and 2). It is possible that the strong coordination of pyridine with Pd(II) deactivates the catalyst in the reaction. To modulate the coordination ability, we introduced an electron-withdrawing fluoro group into the pyridine ring, which has been shown to be an efficient method to improve the yield and selectivity in Pd-catalyzed *meta*-C−H activation.[9a,g] To our delight, the fluoro-substituted pyridine templates improved the D-incorporation (entries 4−6). The template containing 2-fluoro-3-pyridyl (**T^6**) was the most efficient and gave the desired product in 75% yields with 94% deuterium incorporation. Both nitrile-containing template and the pyrimidine-based auxiliary have been shown to be efficient directing groups in Pd-catalyzed *meta*-C−H activation of arenes;[9] however, they did not work in *meta*-C−H deuteration under the standard reaction conditions (entries 3 and 7). No D-incorporation is observed in the absence of $Pd(OAc)_2$, indicating the Pd catalyst is indispensable in the reaction (entry 6). Different deuterium-containing solvents (D_2O, [D_4]-methanol, and $CDCl_3$) were also investigated, but no deuterated product was found under these conditions (entries 8−10). When [D_1]-acetic acid was used in the reaction, the deuterated product could be obatained in 75% yield with 88% *meta*-deuterium incorporation (entry 11). Decreasing the reaction temperature, lowering the catalyst loading, or shortening the reaction time led to a lower degree of deuteration (entries 6 and 12−15).

The established template was then attached to a variety of phenylacetic acids to test *meta*-C−H deuteration (Scheme 2).

Scheme 2. Scope of Phenylacetic Acids Derivatives for *meta*-C−H Deuteration[a,b]



[a]Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), [D_4]acetic acid (1 mL), 80 °C, 24 h. [b]Deuterium incorporation determined by ^{1}H NMR spectroscopic analysis is shown in square brackets. [c]2 h. [d]3 h.

Regardless of the steric hindrance and electronic properties of the substituents, methyl-, methoxy-, fluoro-, and chloro-substituted phenylacetic acids were compatible in the reaction to give the corresponding *meta*-C−H deuterated products with >90% deuterium incorporation (**2a**−**2k**). Under the mild reaction conditions, the benzylic positions of phenylacetic acids were not deuterated according to the ^{1}H NMR spectroscopic analysis.[5c] The halide groups in products provide a useful handle for further structural elaborations. Substrates with alkyl substitution at benzylic positions afforded the deuterated product with high regioselectivity and deuterium incorporation (**2l**−**2n**). Notably, the *meta*-deuterated ibuprofen derivative could be obtained in 71% yields with >98% *meta*-deuterium incorporation (**2o**). The regioselectivity of product **2o** was determined by NOE analysis. The template can also be effectively implemented to the hydrocinnamic acid ester scaffold, giving the *meta*-deuterated product **2p**.

Phosphonate and sulfonate are useful synthons in the synthetic chemistry and could be converted to the alkenyl product by Horner−Wadsworth−Emmons reactions[10] and Julia olefination.[9f,i,11] To demonstrate the great flexibility of

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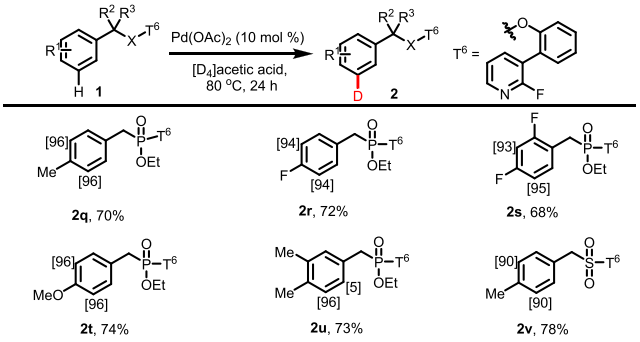
this template, we subjected the benzylphosphonate and benzylsulfonate substrates to *meta*-C−H deuteration conditions. Gratifyingly, the template $\mathbf{T}^6$ could overcome the limitation of *ortho*-C−H activation directed by P(O)(OEt) and to effectively realize the *meta*-C−H deuteration (Scheme 3).[10b,12]

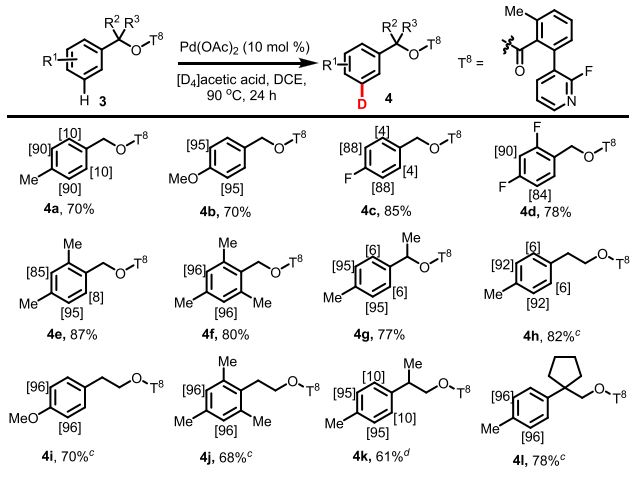
Scheme 3. Scope of Benzylphosphonate and Benzylsulfonate for *meta*-C−H Deuteration[a,b]



[a]Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), [D_4]acetic acid (1 mL), 80 °C, 24 h. [b]Deuterium incorporation determined by ^{1}H NMR spectroscopic analysis is shown in square brackets.

Alcohols are prevalent in the in natural products and drug molecules. Previously, our group first adapted the strong coordination of pyridine template ($\mathbf{T}_8$) to realize the *meta*-C−H bond olefination and iodination of benzyl and phenyl ethyl alcohols.[9g] We wondered whether this pyridine template could be used in the *meta*-C−H bond deuteration of alcohols. To our delight, methyl-, methoxy-, and fluoro-substituted benzyl alcohols could be smoothly deuterated at the *meta*-position. As shown in Scheme 4, substrates with electron-donating groups showed better reactivity with higher *meta*-deuterium incorporation (**4a**−**4d**). Steric hindrance has little effect in the reaction (**4e**, **4f**). Deuteration of secondary benzyl alcohols **3g**

Scheme 4. Scope of Alcohols for *meta*-C−H Deuteration[a,b]

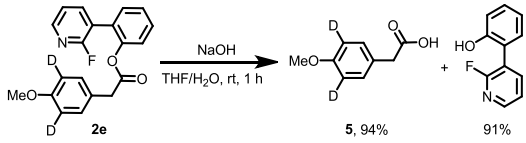


[a]Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), [D_4]acetic acid (0.5 mL), DCE (0.5 mL), 90 °C, 24 h. [b]Deuterium incorporation determined by ^{1}H NMR spectroscopic analysis is shown in square brackets. [c][D_4]acetic acid (1.0 mL), 80 °C. [d][D_4]acetic acid (1.0 mL), 90 °C.

provided similar results to that of primary benzyl alcohols. By increasing the chain length from benzyl alcohols to phenylethyl alcohols, the template also showed high selectivity with >92% *meta*-C−H deuteration (**4h**−**4l**).

Finally, the template could be easily removed by hydrolysis of **2e** under basic conditions, giving the *meta*-deuterated phenylacetic acids **5** and the directing group in good yields (Scheme 5).

Scheme 5. Removal of the Directing Template



In conclusion, we have developed Pd-catalyzed template-assisted *meta*-selective C−H deuteration of phenylacetic acid scaffolds. The pyridine-based template was anchored to the substrate via a practical ester linkage. A variety of phenylacetic acids containing electron-donating and -withdrawing substituents are compatible in the reaction. Assisted by the pyridine template, other substrate types, including benzylphosphonate, benzylsulfonate, and benzyl and phenyl ethyl alcohol ester, could also be *meta*-C−H deuterated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01784.

Experimental procedures, characterizations of new compounds, NMR spectra data (PDF)

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Notes

The authors declare no competing financial interest.

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