Palladium-catalyzed Br/D exchange of arenes: Selective deuterium incorporation with versatile functional group tolerance and high efficiency

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Cite this: DOI:

DOI:

www.rsc.org/chemicalscience

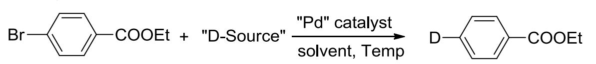
A facile method for introducing one or more deuterium atoms onto an aromatic nucleus via Br/D exchange with high functional group tolerance and high incorporation efficiency is disclosed. Deuterium-labeled aryl chlorides and aryl borates which could be used as cross-coupling substrates to construct more complicated deuterium-labeled compounds can also be synthesized by this method.

Selectively–deuterated compounds have been increasingly attracting attention and interest in areas such as metabolic or pharmacokinetic (PK) probes both *in vitro* and *in vivo*, drug discovery and development, and exploring advanced functional materials[1-3]. Deuteration is also a powerful method in the study of structure and dynamics in soft matters through neutron scattering.[3a-3b] The synthesis of selectively deuterium-labeled compounds often requires multiple steps sometimes under harsh conditions, such as strong acid or base, and high temperature and/or high pressure, particularly in H/D and H/Br exchange reactions.[4,5] Accordingly, functional group tolerances has been a major challenge. Furthermore, achieving high efficient deuterium incorporation is another challenge in deuteration[4a]. Therefore, development of a general method to efficiently introduce deuterium at a selected position with versatile functional group tolerance is highly demanded.

We are interested in exploring the deuteron effect on the properties of materials through development of selectively deuterium-labeled compounds.[6] Deuteration can be achieved either through reactions involving deuterium gas, or with deuterium cations or anions. Although introducing deuteron through deuterium cation and deuterium gas has been well developed,[4,5] the deuterium anion was rarely employed in deuteration reactions other than reduction of carbonyl groups.[7] It is well known that in order to obtain high efficient deuterium incorporation, a large excess of deuterium gas or deuterium cation is often required to overcome the influence of active hydrogen generated from the substrate, solvent, catalyst or the reaction. In contrast, high atom percent deuterium incorporation could be achieved in the reduction of carbonyl groups using equimolar amounts of deuterium anion as deuterium source.[7] Based on the consideration that a deuterium anion reagent such as sodium formate-d is compatible with a wide-array of functional groups,[8] we envisioned that such weak deuterium anion could be a mild reagent to introduce deuterium with high functional group tolerance. Herein we report the results of our investigation into palladium catalyzed Br/D exchange reactions using deuterium anion as deuterium source to produce a wide variety of deuterium-labeled compounds.

Our study began with the Br/D exchange reaction with palladium acetate as the catalyst and sodium formate-d (D-COONa) as the deuterium source. We found the deuterium-labeled product formed with 20% conversion and 94% deuterium incorporation, which indicated most of the deuterium involved in the reaction was from DCOONa (entry 1 in Table 1). Based on the consideration that DCOONa is the only deuterium source in this reaction system and the reduced deuterium incorporation could be caused by the hydrogen from catalyst, ligand or solvent, several palladium catalyst and phosphine ligand combinations were examined to determine the effect of conversion and deuterium incorporation (entries 1-6 in Table 1). We found the combination of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$)/*t*-Bu_3P especially effective, with 100% conversion and 94% deuterium incorporation. Since the deuterium-labeled compounds and related non-deuterium-labeled compounds are very difficult to separate, further improvement in the atom percent level of deuterium incorporation was still necessary. The similar level of deuterium incorporation obtained from different combinations of palladium catalyst and ligands also indicated that the palladium catalyst and ligands were not the reason for less than full deuterium incorporation (entries 1-6). Therefore, we next examined the effect of different solvents (entries 7-10) for the $Pd_2(dba)_3$/*t*-Bu_3P combination. As shown in Table 1, dioxane and THF (entries 8 and 9) were inefficient with no conversion, probably due to the poor solubility of DCOONa. DMSO (entry 10) gave the best result with 100% conversion and >98% deuterium incorporation. Entry 11 shows the importance of the *t*-Bu_3P ligand, as $Pd_2(dba)_3$ alone only provide 25% conversion. We next varied the reagent conditions for the deuterium source, and found that *in situ* generated DCOOK or DCOONa (entries 12 and 13) were also good deuterium reagents for this reaction. Other common deuterium sources such as CD_3OD, D_2O (entries 14-15) afforded no conversion. These results indicated that strong polar aprotic solvent, such as DMSO, A key finding was that the acid form DCOOD (entry 16) also afforded no conversion, highlighting the importance of the salt form (DCOOM) of the deuterated formate as the D-source for this Br/D exchange reaction (see mechanism discussion below).

Table 1 Optimization of reaction conditions for the Br/D exchange of ethyl 4-bromobenzoate

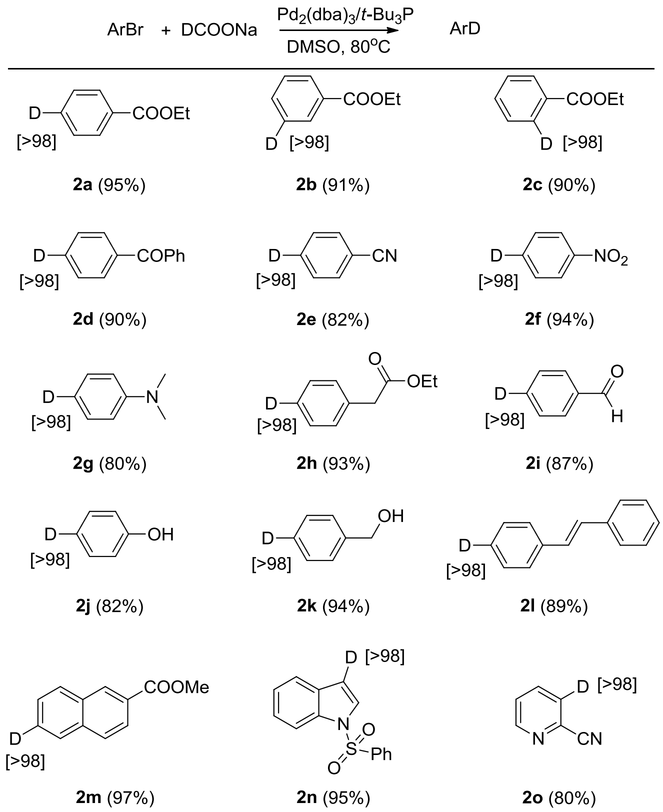


Entry	"Pd" catalyst	Temp	solvent	"D-Source"	Conv.[a]	D incorporation[b]
1	$Pd(OAc)_2$	80	DMF	DCOONa	20	94
2	$Pd(OAc)_2$ +XPhos	80	DMF	DCOONa	38	94
3	$Pd(OAc)_2$ +S-Phos	80	DMF	DCOONa	50	94
4	$Pd(OAc)_2$ + t-Bu_3P	80	DMF	DCOONa	50	94
5	$Pd_2(dba)_3$ + t-Bu_3P	80	DMF	DCOONa	100	94
6	$Pd_2(dba)_3$ +S-Phos	80	DMF	DCOONa	80	93
7	$Pd_2(dba)_3$ + t-Bu_3P	80	DMA	DCOONa	100	88
8	$Pd_2(dba)_3$ + t-Bu_3P	80	Dioxane	DCOONa	0	-
9	$Pd_2(dba)_3$ + t-Bu_3P	80	THF	DCOONa	0	-
10	$Pd_2(dba)_3$ + t-Bu_3P	80	DMSO	DCOONa	100	98
11	$Pd_2(dba)_3$	80	DMSO	DCOONa	25	98
12[c]	$Pd_2(dba)_3$ + t-Bu_3P	80	DMSO	DCOOD	100	98
13[d]	$Pd_2(dba)_3$ + t-Bu_3P	80	DMSO	DCOOD	100	98
14	$Pd_2(dba)_3$ + t-Bu_3P	80	DMSO	CD_3OD	0	-
15	$Pd_2(dba)_3$ + t-Bu_3P	80	DMSO	D_2O	0	-
16	$Pd_2(dba)_3$ + t-Bu_3P	80	DMSO	DCOOD	0	-

[a]Coversion was determined by GC/MS or ^1H NMR [b]The deuterium incorporation was determined by GC/MS or ^1H NMR. [c]2 equiv. K_3PO_4 was used. [d]2 equiv. Na_2CO_3 was used

With the optimized condition of $Pd_2(dba)_3$/*t*-Bu_3P with DCOOM in DMSO (entries 10, 12-13 in Table 1) in hand, several aryl bromide compounds with versatile functional groups were examined for this Br/D exchange reaction. As shown in Table 2, we found that aryl bromide compounds containing ester, ketone, nitrile, nitro, amine, aldehyde, alkene, or sulfonamide functional groups successfully afforded the deuterium-labeled products in good yields without degradation of the functional group. Several aryl bromide compounds containing active hydrogen (e.g., hydroxyl) were also suitable substrates, when 3 equivalent of DCOONa was used (**2h, 2j, 2k**). Usually, high atom percentage deuterium incorporation for these types of substrates could only be achieved by using a large excess of deuterium reagent or extremely strong base.[9] The active hydrogen in the substrate did not affect the deuterium incorporation and the deuterium anion did not react with active hydrogen (such as **2h**, **2j**, **2k**), which means DCOONa is a very mild deuterium source.[4i,10] It is noteworthy to mention that functional groups such as alkene, aldehyde, and nitro which are sensitive to reducing conditions also showed high stability with the optimized reaction conditions. When other deuteration methods are employed,[4,5] these types of deuterium-labeled compounds would require several protection/deprotection steps to prepare. Several heterocyclic bromide compounds were also examined and they also afforded the deuterium-labeled compounds in good yields. Under the optimized reaction conditions all the functionalized deuterium-labeled compounds were obtained with >98% deuterium incorporation using only 2-3 equivalent of sodium formate-D as deuterium reagent.

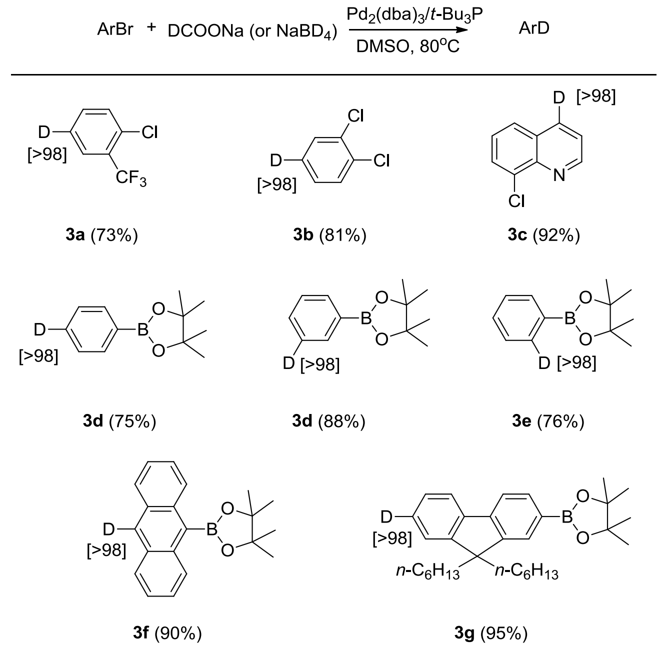
Table 2 Synthesis of functionalized Deuterium-labeled compounds **2** via Br/D exchange [a,b,c]



[a]Conditions for Palladium-catalyzed Br/D exchange reaction: aryl bromide (1 mmol), Pd_2dba_3 (2 mol%), t-Bu_3P (6 mol%), DCOONa (2 mmol), DMSO (1 mL), 80°C. [b]Isolated yield is shown in parentheses. [c]A Deuterium incorporation determined by ^{1}H NMR spectroscopic analysis is shown in square brackets.

Aryl chlorides and boronic acid esters are very important building blocks since they are widely used in different cross coupling reactions in synthetic organic chemistry to build more complicated compounds.[11] To further explore the scope of this Br/D exchange reaction, a number of different aryl bromides containing chloride or boronic acid ester functionality were examined for Br/D exchange under the optimized reaction conditions. Though the combination of $Pd_2(dba)_3$/t-Bu_3P has been well reported for the cross-coupling of aryl chlorides in THF,[12] we found that this catalyst/ligand combination used under the optimized reaction conditions afforded deuterium-labeled aryl chlorides in good yield in DMSO, with no degradation of carbon chloride bond being observed even after 16 hours (Table 3). However, when 3-bromobenzene boronic acid ester was employed as the substrate, the self-coupling dimer and trimer products were observed. Based on this observation, we considered that competition between the boronic acid ester and deuterium ion in the transmetalation step of the reaction could be the reason for the self-coupling products.[11a,11b] To suppress this self-coupling reaction, 2 equivalents of the more reactive sodium borohydride-d_4 were employed as the deuterium source. Several deuterium-labeled boronic acid esters were thus obtained in good yields and excellent deuterium incorporation using sodium borohydride-d_4 as deuterium source.

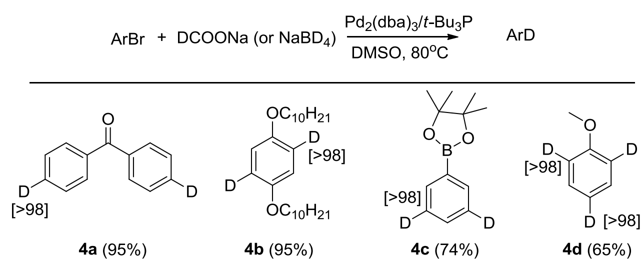
Table 3 Synthesis of Deuterium-labeled aryl chloride and boronic acid ester **3** via Br/D exchange [a,b,c,d]



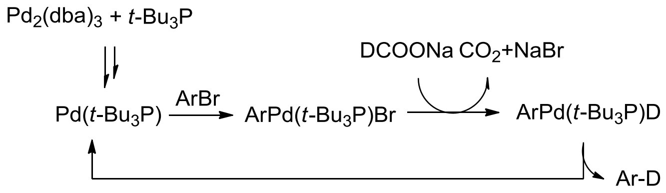
[a]Conditions for deuterium-labeled aryl chloride (**3a-3c**) : aryl bromide (1 mmol), Pd_2dba_3 (2 mol%), t-Bu_3P (6 mol%), DCOONa (2 mmol), DMSO (1 mL), 80°C. [b]Conditions for deuterium-labeled aryl boronic acid ester (**3d-3g**): aryl bromide (1 mmol), Pd_2dba_3 (2 mol%), t-Bu_3P (6 mol%), $NaBD_4$ (2 mmol), DMSO (2 mL), 80°C. [c]Isolated yield is shown in parentheses. [d]A Deuterium incorporation determined by ^{1}H NMR spectroscopic analysis is shown in square brackets.

After testing the scope of the functional group compatibility, we turned our attention to deuteration of di- and tri-bromoarenes. A number of functionalized arenes with two bromides and one with three bromides were also examined for Br/D exchange. As shown in Table 4,all of these substrates afforded the deuterated products in good yields and with excellent deuterium incorporation. Compound **4b** is an important building block for preparing conjugated polymers which are widely employed as optical and electronic materials.[13]

Table 4 Synthesis of di- or tri- deuterium-labeled arenes **4** via Br/D exchange [a,b,c,d]

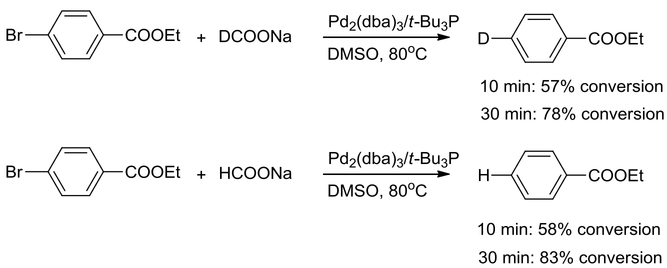


[a]Conditions for **4a**, **4b, 4d**: aryl bromide (1 mmol), Pd_2dba_3 (2 mol%), t-Bu_3P (6 mol%), DCOONa (2 equivalent to bromide), DMSO (2 mL), 80°C. [b]Conditions for **4c**: aryl bromide (1 mmol), Pd_2dba_3 (2 mol%), t-Bu_3P (6 mol%), $NaBD_4$ (4 mmol), DMSO (4 mL), 80°C. [c]Isolated yield is shown in parentheses. [d]A Deuterium incorporation determined by ^{1}H NMR spectroscopic analysis is shown in square brackets.



Scheme 1 Mechanism for Palladium catalyzed Br/D exchange

The proposed reaction mechanism is shown in Scheme 1. Based on the observation that only the deuterium anion as deuterium source could afford high conversion in this Br/D exchange reaction we believe the deuterium anion is essential to replace the bromide in ArPd(II)LBr complex. This is also the reason for high atom percent deuterium incorporation, since active (cationic) hydrogen present in the substrate did not impact the Br/D replacement step.



Scheme 2 Kinetic isotope effect study

The parallel reactions with sodium formate-H and sodium formate-D were performed to examine the kinetic isotope effect. As shown in Scheme 2, comparable levels of conversion were achieved in both cases after reaction times of 10 and 30 minutes. The results indicated that formation and breaking of a carbon-hydrogen/carbon-deuterium bond is not involved in the rate-limiting step. Therefore, the oxidative addition step could be the rate-limiting step of this Br/D exchange reaction.

In summary, we have demonstrated that the commercially available deuterium-labeled formate salt can serve as a mild deuterium reagent in a palladium catalyzed Br/D exchange reaction. Our method provides introduction of deuterium at selected positions of arenes in high atom percent deuterium incorporation with high tolerance of a wide range of functional groups. This will facilitate the synthesis of more complicated deuterium-labeled compounds through further modification of the functional groups. We believe this method will be a powerful tool to provide deuterium-labeled compounds for various applications. Further extension to substrates other than aryl bromides in this palladium catalyzed Br/D exchange reaction is now under investigation.

Acknowledgements

This research was conducted at the Center for Nanophase Materials Sciences, which is a DOE Office of Science User Facility

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details of Br/D exchange, identification of products. See DOI: 10.1039/c000000x/

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