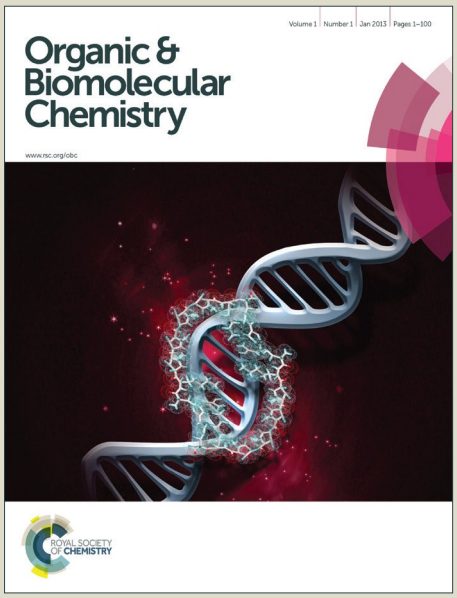
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. Peruncheralathan and M. Janni, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB00193A.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

View Article Online
DOI: 10.1039/C6OB00193A

Journal Name

ARTICLE

Catalytic Selective Deuteration of Halo(hetero)arenes

Manojkumar Janni[a] and S. Peruncheralathan[a*]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Deuterium labeled aromatic and heteroaromatic compounds are synthesized in good to excellent yields with >98% deuterium purity via palladium catalyzed deuterodehalogenation reaction using commercially available and inexpensive reagents. Selective deuteration of bromoaniline is also demonstrated without H/D exchange in amino N—H group.

Introduction

Deuterated compounds are effectively utilized in studying reaction mechanism (Kinetic Isotopic Effects), catalysts pathways, for elucidation of biosynthetic pathways, as analytical standards, and for altering selectivity in total synthesis.[1] Further, these compounds are realized as potential drug candidates because of their unique ability of altering the therapeutic profile and metabolic fate of the drug thereby retaining its biochemical potency and selectivity.[2] For example deuterated analogues of tetrabenazine (SD-809) and lisofylline (CTP-499) are in clinical trials for treatment of chorea associated with Huntingdon's disease and diabetic nephropathy respectively (Chart 1).[3] Very recently, DeWitt *al* found that differentiation of anti-inflammatory and antitumorigenic properties of deuterium stabilized enantiomers of thalidomide analogs (CC-122) in in vitro and in vivo efficacy models (Chart 1).[4] These findings open up a new window to improve therapeutic properties of other racemic drugs.[4] Hence, the deuterated drugs are increasingly in high demand in pharmaceutical industries.[2e] Therefore, deuteration of organic compounds especially drugs have a great potential to generate new drugs with high therapeutic values.

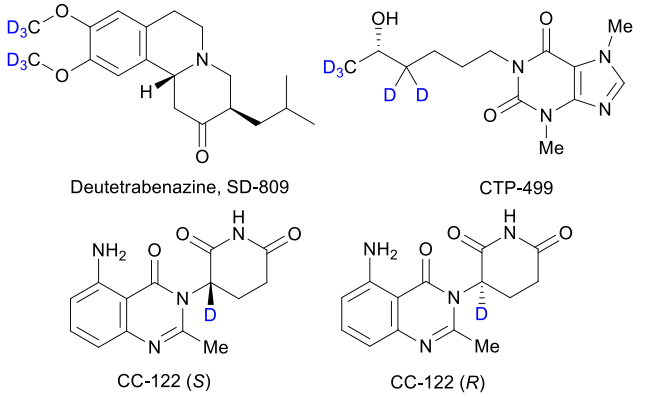


Chart 1. Selected Deuterated Drugs in Clinical Trials

Deuteration of aromatic compounds by traditional methods such as H/D exchange processes and metal-halogen exchange process suffer from selectivity, strong basic conditions and less functional group tolerances.[5] Hence, several alternative methods were developed to overcome those drawbacks.[6] For example: (i) immobilized triazene precursors were used for selective D-incorporation into arenes;[7] (ii) aromatic acids were transformed into deutero aromatic compounds via copper and silver mediated decarboxylative deuteration procedures;[8] (iii) α,α-dideutero alcohols were synthesized from carboxylic acids by using SmI_2 and D_2O as deuterium source[9] and (iv) palladium catalyzed *ortho*-deuteration of arenes bearing weakly coordinated directing groups was also developed.[10] Despite excellent selectivities and high D-incorporation, each of these individual protocols has its own limitations owing to multi-step synthesis of starting materials, use of large excess deuterated solvents, excess of metal salts, higher catalyst loading & less heterocyclic substrates. Therefore, developing a simple and catalytic method for synthesis of deuterated compounds is always needed.

The cross-coupling between aryl halides and aliphatic alcohols represents a direct approach to synthesize alkyl aryl ethers.[11] During this process, a reduced arene (Ar–H) is usually formed as by-product particularly primary and secondary alcohols are used as nucleophiles. To suppress undesired reduced product, Buchwald, Beller and other groups individually developed new protocols by changing phosphine ligands and palladium precatalysts.[11,12] However, few groups cleverly demonstrated usefulness of this process for dehalogenation of arenes especially polychlorinated aromatic

[a]*School of Chemical Sciences, National Institute of Science Education and Research (NISER), Bhimpur-Padanpur (PO), Jatni (via), Khurda – 752050, Odisha, India. Fax: +91-674-2494004; Tel: +91-674-2494173; E-mail: peru@niser.ac.in*

†Electronic Supplementary Information (ESI) available: [Copies of ^1H & ^{13}C NMR Spectra]. See DOI: 10.1039/x0xx00000x

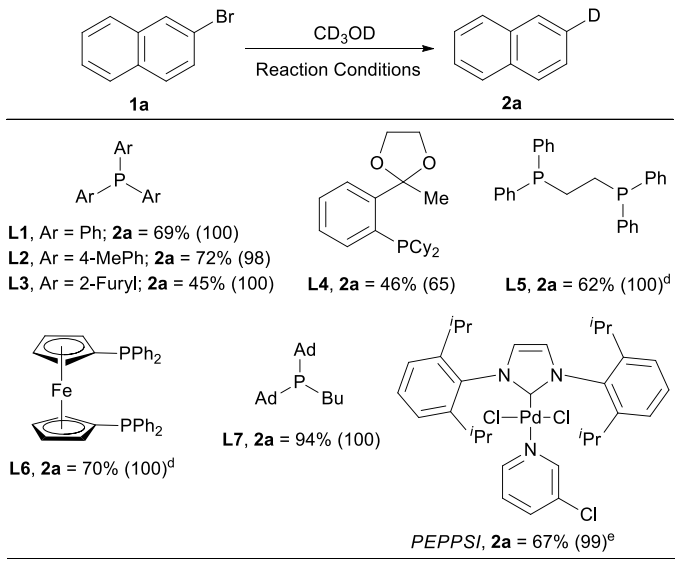
compounds.[13-15] Further, deuterated alcohols are used to establish mechanistic pathway of hydrodehalogenation reaction by Helquist,[14] Nolan[15c] and recently McIndoe.[16] To our surprise, high demand in deuterated organic compounds, no attempts has been made to use this process for a general synthetic protocol to access deuterated aromatic compounds from aryl halides.[17] Herein we report a first catalytic method for selective deuteration of aryl and heteroaryl halides by using 1 mol% of $Pd(OAc)_2$ and 2 mol% of Ad_2P^nBu and CD_3OD as deuterium source affording deuterated arenes and heteroarenes good to excellent yields with >98% deuterium incorporation.

Results and Discussion

Recently, we reported the first general and efficient method for trideuteromethoxylation of aryl/heteroaryl halides with CD_3OD using a commercially available ^{t}BuXPhos ligand.[18] During this study, we observed that few ligands gave a mixture of deutero and trideuteromethoxy aromatic compounds. To accomplish an exclusive deuterated product, we started the optimization studies with a set of commercially available ligands **L1-L7** for deuteration of aryl halides (Table 1). Thus, the reaction of 2-bromonaphthalene (**1a**) with CD_3OD was investigated as a model system in the presence of 5 mol% $Pd(OAc)_2$ and 5-10 mol% ligands **L1**-**L6** (Table 1). In most of the cases, the reaction was completed within 12 hours, however yield of the product **2a** was ranging from 45 to 72%. Gratifyingly, an experiment performed in the presence of *cataCXium®A* (**L7**) ligand provided an improved yield of 94%. On the other hand, with *PEPPSI,* a carbene based ligand, gave a lower yield as compared to ligand **L7**.[19] For further fine tuning of this process, other palladium precursors such as $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3$ were screened and found to be less beneficial when compared with $Pd(OAc)_2$. However, in case of bases, K_3PO_4 gave better yield as compared with KOH, Et_3N, K_2CO_3 and Cs_2CO_3. Interestingly, we obtained quantitative yield of **2a** when the catalyst loading was reduced from 5 mol% to 1 mol% and reaction was completed within 16 hours.

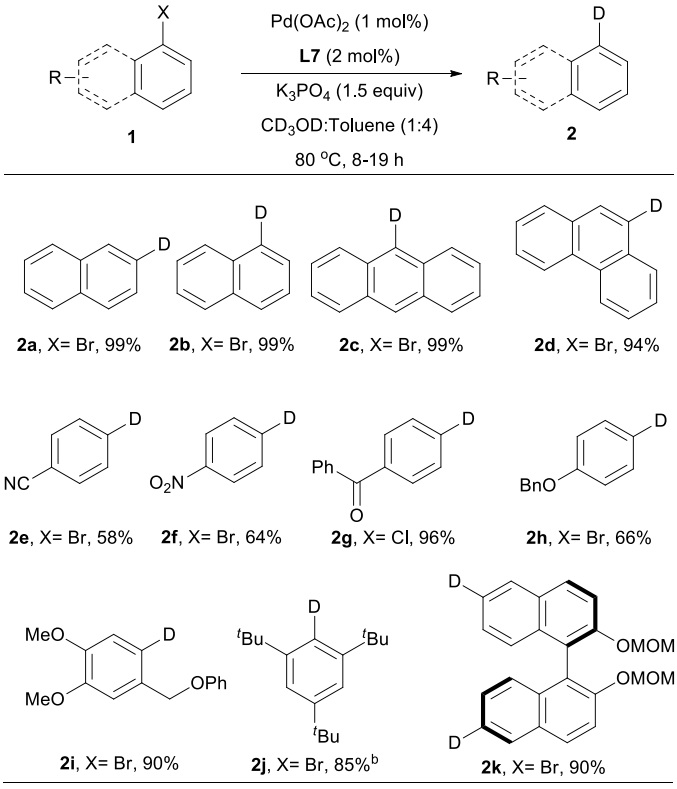
The optimized conditions in our hand, we examined a series of polyaromatic bromides for deuteration reaction. These bromides were effectively deuterated furnishing the corresponding deutero polyaromatic compounds **2a-d** in excellent yields (Table 2, **2a-d**). Next, we performed the deuteration of the aryl halides having electron withdrawing group at para-position. Thus, 4-cyano and 4-nitro bromobenzenes gave the corresponding deuterated 4-nitro and 4-cyanobenzenes only in moderated yields (Table 2, **2e-f**). On the other hand, benzoyl substituted phenyl chloride was smoothly converted to 4-deuterobenzophenone (**2g**) in excellent yield. Whereas the alkoxy substituted bromide 1h gave only 66% of deuterated compound **2h**. However, ortho substituted bromide **1i** afforded the corresponding product **2i** in excellent yield (90%). Similarly, the deuteration of sterically hindered substrate 1-bromo-2,4,6-tri^{t}butylbenzene gave the corresponding deuterated product **2j** in 85% yield. Interestingly, 6,6'-dibromo-MOM-protected *R*-BINOL **1k** was transformed into the corresponding deuterated product **2k** in 90% of yield (Table 2).

Table 1. Ligand Screening for Deuteration of 2-Bromonaphthalene[a-e]



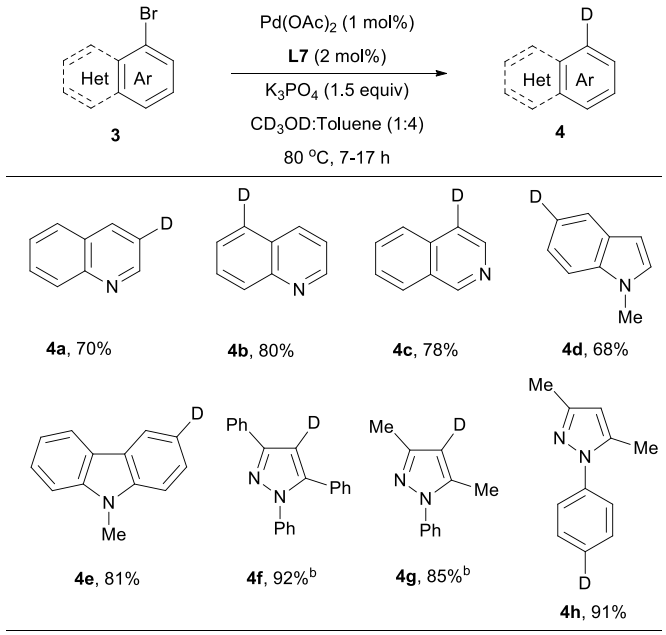
[a] Reaction Conditions: 2-Bromonaphthalene (0.5 mmol), $Pd(OAc)_2$ (5 mol%), **L1 - L4**, **L7** (10 mol%), Cs_2CO_3 (0.75 mmol), CD_3OD/Toluene (1:4), 80 °C, 12 h; [b] Conversions are inside the parenthesis; [c] GC yield; [d] **L5 - L6** (5 mol%); [e] Without $Pd(OAc)_2$.

Table 2. Catalytic Deuteration of Aryl Halides[a]



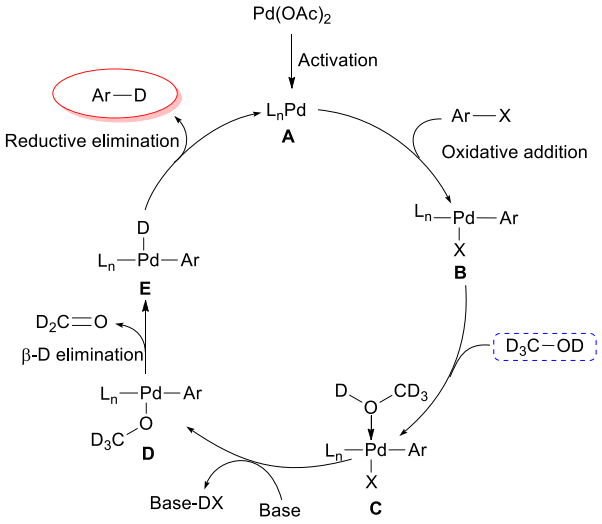
[a] Isolated yields; [b] 5 mol% $Pd(OAc)_2$ & 10 mol% **L7** were used.

Table 3. Catalytic Deuteration of Heteroaryl Bromides[a]

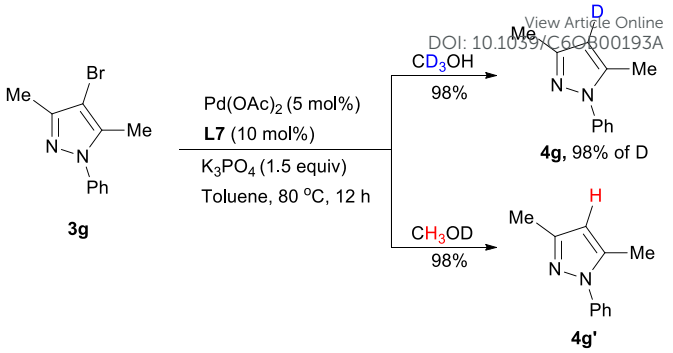


[a] Isolated yields; [b] 5 mol% $Pd(OAc)_2$ & 10 mol% **L7** were used.

We next turned our attention towards to the synthesis of deuterated heterocycles by applying our established synthetic methodology. Thus, 3- and 5-bromoquinolines were smoothly converted into the corresponding deuterated quinolines in good to very good yields (Table 3, **4a-b**). This process could also be successfully applied to 4-bromoisoquinoline yielding 78% of **4c**. Further, other heteroaryl bromides like 5-bromo-*N*-methylindole and 4-bromo-*N*-methylcarbazole proved to be suitable substrates for this process to deliver deuterated products in 68% & 81% yields respectively (Table 3, **4d-e**). Interestingly, bromosubstituted pyrazoles **3f-h** were transformed into the corresponding deuterated products **4f-h** in very good to excellent yield (Table 3).



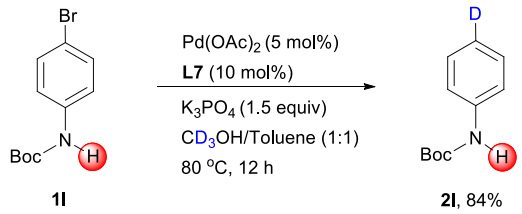
Scheme 1. Mechanism of Deuteration of Aryl and Heteroaryl Halides



Scheme 2. Deuteration of 4-Bromopyrazole **3g** with CD_3OH & CH_3OD

As shown in Scheme 1, we propose a mechanism which involves a palladium catalytic cycle. The first-step is the $Pd(OAc)_2$ in the presence of strong *σ*-donating ligand **L7**, accelerating the oxidative addition of the catalyst **A** to form **B**. This step is most commonly believed to be the rate determining step. The displacement of the halide (**C**) by using base (K_3PO_4), *β*-D-elimination of **D** and reductive elimination of **E** to regenerate the Pd(0) species (**A**). To validate the proposed cycle, we performed two separate experiments with CD_3OH and CH_3OD respectively (Scheme 2). The first experiment gave exclusively deuterated product **4g** whereas the second experiment did not give a trace amount of **4g**, instead formed **4g'** (Scheme 2). These experiments clearly support that the D/H transfer occurs from the CD_3/CH_3. However, mechanistic investigation of deuterodehalogenation of aryl iodide in presence of CH_3OD gave mixture of products which was proposed by McIndoe *et al*. Interestingly our methodology provides a highly selective product depending upon methanol (CD_3OH vs CH_3OD).[16, 20]

To see if this methodology is reasonable, we performed an experiment with Boc protected 4-bromoaniline. We obtained exclusively 4-deuteroaniline **2l** without exchange of acidic proton (Scheme 3). Hence, we believe that there is no H/D exchange during reaction and deuterium incorporation occurs from reductive elimination process.



Scheme 3. Selective Deuteration of 4-Bromoaniline **1l** with CD_3OH

Conclusions

In conclusion, we have described the first general catalytic method for deuteration of aryl and heteroaryl halides with 1 mol% of $Pd(OAc)_2$/2 mol% of Ad_2P^nBu. The present protocol is simple and straight forward providing a variety of deuterium

View Article Online
DOI: 10.1039/C6OB00193A

labeled aryl/heteroaryl compounds in good to excellent yields with 98% deuterium purities from readily available reagents. The potential application of the protocol was also demonstrated by the bromoaniline without H/D exchange in amino N—H group. Further studies directed towards understanding the mechanism of this reaction and extending the application of selective incorporation of D moiety in the existing drugs are underway.

Acknowledgements

This work was supported by the Department of Atomic Energy, Government of India.

Experimental

All reactions were performed by using standard vial technique with rubber septum. All solids were weighed in air. CD_3OD, CD_3OH and CH_3OD used as received (without adding any drying agent) from Acros. Toluene, Cs_2CO_3, K_3PO_4, KOH, K_2CO_3 and Et_3N were purchased from Aldrich, Acros, Merck or Alfa-Aesar and used as received. $Pd(PPh_3)_4$, $Pd(CH_3CN)_2Cl_2$ and $Pd(OAc)_2$ were purchased from Aldrich. Aryl and heteroaryl bromides and chlorides were purchased from Aldrich, Acros, Afla-Aesar and Spectrochem. Tri-(*o*-tolyl)-phosphine, tri-(2-furyl)-phosphine, 1,1'-bis(diphenylphosphino)ferrocene, di-(1-adamantyl)-n-butyl phosphine, [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-*i*Pr), 2′-(dicyclohexylphosphino)-acetophenone ethylene ketal, ethylene bis-(diphenylphosphine), triphenylphosphine were purchased from Aldrich. All other reagents were purchased from common suppliers and used without further purification. Flash chromatography was performed using Merck Silica gel (230-400 mesh). Fractions were monitored by thin-layer chromatography on precoated silica gel 60 F254 plates (Merck & co.) and were visualized by UV. NMR data were recorded on Bruker ARX 400 spectrometers. ^{13}C and ^{1}H NMR spectra were recorded in $CDCl_3$ and were referenced accrording to signals of deutero solvent. Gas chromatography analysis was performed on ThermoFisher ITQ 900 instrument with a FID detector and HP-5 capillary column (polydimethylsiloxane with 5% phenyl groups, 30 m, 0.32 mm i.d., 0.25 µm film thickness) using helium as carrier gas. Gas chromatography-Mass analysis was carried out on Thermo Fisher ITQ 900 instrument (EI) and TG-SQC capillary column using helium carrier gas. ESI and APCI HR-MS measurements were performed on Bruker micro TOF-Q-II mass-spectrometer.

Procedure for the Optimization of Palladium-Catalyzed Deuteration of 2-Bromonaphthalene with CD_3OD

An oven-dried 8 mL reaction vial was charged with $Pd(OAc)_2$(5 mol-%), ligand (10 mol%), base (1.5 equiv), 2-Bromonaphthalene (0.5 mmol), hexadecane (50 mg) and toluene (1.0 mL). The reaction mixture was stirred at 80 °C for 12 h. The reaction was monitored by TLC or GC/MS analysis. The yield and conversion of the reactions were calculated from GC using hexadecane as internal standard.

General Procedure for the Palladium-Catalyzed Deuteration of Aryl Halides and Heteroaryl Halides with CD_3OD

An oven-dried 8 mL reaction vial was charged with $Pd(OAc)_2$(1-5 mol-%), ligand **L7**(2-10 mol-%) and K_3PO_4 (0.75 mmol), respective aryl/heteroaryl halide (0.5 mmol) in CD_3OD (0.25 mL) and toluene (2.0 mL) was stirred at 80 °C for 7-19 h. The reaction mixture was stirred at 80 °C and was monitored by TLC or GC/MS analysis. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

2-Deuteronaphthalene (2a)[21]: Reaction time: 16 h. Yield: 99%, as a white colour solid. Melting point: 64 – 66 °C. R_f: 0.40 in petroleum ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 – 7.87 (m, 4H), 7.52 – 7.49 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 133.6, 128.0, 127.9, 125.95, 125.8, 125.7 (t, *J* = 24 Hz). MS (EI, 70eV): m/z (%) = 129 (100).

1-Deuteronaphthalene (2b)[21]: Reaction time: 16 h. Yield: 98%, as a colourless solid. Melting point: 71 – 73 °C. R_f: 0.50 in hexane. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85 – 7.88 (m, 3H), 7.48 – 7.52 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 133.6, 133.5, 128.0, 127.9, 127.7 (t, *J* = 23 Hz), 125.9, 125.8. MS (EI, 70eV): m/z (%) = 129 (100).

9-Deuteroanthracene (2c)[22]: Reaction time: 16 h. Yield: 99%, as a white colour solid. Melting point: 198 – 201 °C. R_f: 0.32 in petroleum ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.44 (s, 1H), 8.03 – 8.01 (m, 4H), 7.49 – 7.47 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 131.8, 131.7, 128.3, 128.2, 126.3, 126.00 (t, *J* = 24 Hz), 125.5 (2C). HR-MS (APCI): Calcd. for $C_{14}H_9D$ (M+H): 180.0918, found: 180.0928.

9-Deuterophenanthrene (2d)[23]: Reaction time: 16 h. Yield: 94%, as a white colour solid. Melting point: 88 – 90 °C. R_f: 0.30 in petroleum ether. IR (KBr): ν (cm^{-1}) = 3050, 2925, 2368, 1638, 1428, 1006, 771, 754. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.72 (d, *J* = 8.2 Hz, 2H), 7.92 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.76 (s, 1H), 7.70 – 7.60 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 132.2, 132.1, 130.4, 128.71, 128.66, 126.9, 126.74 (t, *J* = 24 Hz), 126.70, 122.8. HR-MS (APCI): Calcd. for $C_{14}H_9D$ (M+H): 180.0918, found: 180.0926.

4-Deuterobenzonitrile (2e) [8a]: Reaction time: 10.5 h. Yield: 58%, as a colourless oily liquid. R_f: 0.36 in 10% diethyl ether in Petroleum ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 – 7.64 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 132.6 (t, *J* = 25 Hz), 132.2, 129.1, 118.9, 112.5. MS (EI, 70eV): m/z (%) = 104 (100), 77 (20).

4-Deuteronitrobenzene (2f) [24]: Reaction time: 18 h. Yield: 64%, as a brown colour oily liquid. R_f: 0.32 in 5% ethyl acetate in petroleum ether. IR (as film in CCl_4): ν (cm^{-1}) = 2921, 2360, 1657, 1310, 1276, 938. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.24 – 8.21 (m, 2H), 7.55 (dd, *J* = 7.6, 0.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.3, 134.4 (t, *J* = 25 Hz), 129.3, 123.6.

4-Deuterobenzophenone (2g)[25]: Reaction time: 10.5 h. Yield: 96%, as a pale yellow oily liquid. R_f: 0.35 in 10% diethyl ether in petroleum ether. IR (as film in CCl_4): ν (cm^{-1}) = 3060, 2920, 2423, 2264, 1659, 1651, 1599, 1513, 1472, 1447, 1408, 1311, 1277, 1175, 1149, 1108, 1076, 1026. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.82 – 7.80 (m, 4H), 7.61 – 7.57 (m, 1H), 7.50 – 7.46 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.8, 137.7, 132.5, 132.2 (t, *J* = 25 Hz), 130.2, 128.4, 128.3. HR-MS (APCI): Calcd. for $C_{13}H_9DO$ (M+H): 184.0867, found: 184.0870.

4-Benzyloxy-1-deuterobenzene (2h): Reaction time: 8 h. Yield: 66%, as a white colour solid. Melting point: 36 – 38 °C. R_f: 0.29 in hexane. IR (KBr): ν (cm^{-1}) = 3035, 2907, 2867, 2373, 1590, 1467, 1377, 1293, 1245, 1170, 1107, 1022. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 – 7.46 (m, 2H), 7.44 – 7.40 (m, 2H), 7.37 – 7.33 (m, 3H), 7.03 – 7.00 (m, 2H), 5.09 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 137.2, 129.5, 128.7, 128.1, 127.6, 120.8 (t, *J* = 24 Hz), 114.9, 70.0. MS (EI, 70eV): m/z (%) = 185 (25), 91(100). HR-MS (APCI): Calcd. for $C_{13}H_{11}DO$ (M^+): 185.0954, found: 185.0915.

6-Benzyloxy-3,4-dimethoxy-1-deuterobenzene (2i): Reaction time: 8 h. Yield: 90%, as a pale yellow colour solid. Melting point: 67 – 70 °C. R_f: 0.33 in 20% ethyl acetate in hexane. IR (KBr): ν (cm^{-1}) = 2997, 2961, 2937, 2835, 1595, 1508, 1402, 1376, 1340, 1229, 1159, 1080.^1H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.28 (m, 2H), 7.02 – 6.96 (m, 4H), 6.88 (s, 1H), 5.00 (s, 2H), 3.90 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.8, 149.2, 148.9, 129.5, 129.47, 120.9, 120.0 (t, *J* = 25 Hz), 114.9, 111.0 (2C), 69.9, 55.96, 55.90. HR-MS (ESI): Calcd. for $C_{15}H_{15}DO_3$ (M^+): 245.1157, found: 245.1166.

2,4,6-Tri-*t*-butyldeuterobenzene (2j)[26]: Reaction tme: 18 h. Yield: 85%, as a colourless solid. Melting point: 55 – 58 °C. R_f: 0.71 in *n*-Pentane. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.26 (s, 2H), 1.34 (s, 27H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.1, 150.0, 119.6, 35.1, 31.7. MS (EI, 70eV): m/z (%) = 247 (25), 232 (100), 204 (20), 176 (5), 57 (15).

6,6'-Dibromo-2,2'-bis (methoxymethoxy)-1,1'-binaphthalene (2k): Reaction time: 19 h. Yield: 94%, as a white colour solid. Melting point: 93 – 96 °C. R_f: 0.27 in 20% diethyl ether in petroleum ether. IR (KBr): ν (cm^{-1}) = 3055, 3026, 2998, 2952, 2901, 2846, 2824, 1620, 1586, 1499, 1463, 1347, 1298, 1241, 1196, 1147, 1094, 1075, 1039, 1026. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8.8 Hz, 2H), 7.88 (s, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.18 (dd, *J* = 8.4, 0.4 Hz, 2H), 5.09 (d, *J*= 6.8 Hz, 2H), 4.99 (dd, *J* = 6.8, 0.4 Hz, 2H), 3.158 (s, 3H), 3.156 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.8, 134.2, 130.0, 129.5, 127.9, 126.3, 125.7, 123.9 (t, *J* = 23 Hz) 121.4, 117.4, 95.3, 55.9. HR-MS (ESI): Calcd. for $C_{24}H_{20}D_2O_4$ (M^+): 376.1638, found: 376.1640.

3-Deuteroquinoline (4a)[27]: Reaction time: 7 h. Yield: 70%, as a brown colour oily liquid. R_f: 0.26 in 20% diethyl ether in petroleum ether. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.91 (s, 1H), 8.15 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.69 (m, 1H), 7.56 – 7.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.3, 148.2, 136.2, 129.6, 129.4, 128.4, 127.9, 126.7, 120.9 (t, *J* = 25 Hz). HR-MS (ESI): Calcd. for C_9H_6DN (M+H): 131.0714, found: 131.0716.

5-Deuteroquinoline (4b)[28]: Reaction time: 8 h. Yield: 80%, as a colourless liquid. R_f: 0.24 in 10% ethyl acetate in hexane. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.89 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.14 – 8.09 (m, 2H), 7.70 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.52 (dd, *J* = 6.8, 0.8 Hz, 1H), 7.37 (dd, *J* = 8.2, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.4, 148.2, 136.2, 129.6, 129.4, 128.3, 127.5 (t, *J* = 25 Hz), 126.5, 121.1. HR-MS (ESI): Calcd. for C_9H_6DN (M+H): 131.0714, found: 131.0725.

4-Deuteroisoquinoline (4c)[29]: Reaction time: 17 h. Yield: 78%, as a brown colour oily liquid. R_f: 0.28 in 20% ethyl acetate in petroleum ether. IR (as film in CCl_4): ν (cm^{-1}) = 2926, 2345, 2372, 1626, 1583, 1493, 1381, 1260, 1230, 1162, 941. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.24 (s, 1H), 8.51 (s, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.81 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.61 – 7.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5, 142.9, 135.8, 130.5, 128.7, 127.7, 127.4, 126.5, 120.3 (t, *J* = 25 Hz). HR-MS (APCI): Calcd. for C_9H_6DN (M+H): 131.0714, found: 131.0732.

5-Deutero-*N*-methylindole (4d): Reaction time: 7 h. Yield: 68%, as a colourless oily liquid. R_f: 0.32 in 5% ethyl acetate in petroleum ether. IR (as film in CCl_4): ν (cm^{-1}) = 3100, 3046, 2943, 2816, 2264, 1870, 1610, 1513, 1471, 1442, 1422, 1382, 1333, 1288, 1243, 1194, 1148, 1107, 1079, 1018. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.69 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.09 – 7.08 (m, 1H), 6.55 – 6.54 (m, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.8, 128.9, 128.6, 121.5, 120.9, 119.1 (t, *J* = 24 Hz), 109.3, 100.9, 32.9. HR-MS (APCI): Calcd. for C_9H_8DN (M+H): 133.0871, found: 133.0887.

3-Deutero-9-methyl-9*H*-carbazole (4e): Reaction time: 16 h. Yield: 81%, as a white colour solid. Melting point: 80 – 83 °C. R_f: 0.41 in 3% ethyl acetate in hexane. IR (KBr): ν (cm^{-1}) = 3049, 2888, 2823, 2352, 2320, 2267, 1623, 1596, 1476, 1457, 1423, 1350, 1331, 1285, 1246, 1142. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.15 – 8.13 (m, 2H), 7.54 – 7.50 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.28 (m, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.1, 125.8, 125.7, 122.9, 120.4, 120.3, 118.9, 118.7 (t, *J* = 24 Hz), 108.5, 29.1. HR-MS (ESI): Calcd. for $C_{13}H_{10}DN$ $(M)^+$: 182.0949, found: 182.0923.

4-Deutero-1,3,5-triphenyl-1*H*-pyrazole (4f): Reaction time: 10.5 h. Yield: 92%, as a white colour solid. Melting point: 132 – 136 °C. R_f: 0.38 in 10% diethyl ether in Petroleum ether. IR (KBr): ν (cm^{-1}) = 3061, 2352, 2332, 1596, 1498, 1479, 1455, 1366, 1358, 1311, 1178, 1159, 1001. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.96 – 7.93 (m, 2H), 7.47 – 7.43 (m, 2H), 7.41– 7.28 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.0, 144.5, 140.2, 133.1, 130.7, 129.0, 128.9, 128.8, 128.6, 128.4, 128.1, 127.6, 125.9, 125.4, 105.1 (t, *J* = 25 Hz). HR-MS (ESI): Calcd. for $C_{21}H_{15}DN_2$ (M+H): 298.1449, found: 298.1440.

4-Deutero-3,5-dimethyl-1-phenyl-1*H*-pyrazole (4g): Reaction time: 8 h. Yield: 85%, as a pale yellow liquid. R_f: 0.35 in 10% ethyl acetate in hexane. IR (as film in CCl_4): ν (cm^{-1}) = 3067, 2926,

2362, 1598, 1542, 1504, 1458, 1415, 1381, 1364, 1140, 1072, 1047, 1024, 911. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.40 (m, 4H), 7.36 – 7.30 (m, 1H), 2.30 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.9, 139.9, 139.3, 129.0, 127.3, 124.8, 106.7 (t, *J* = 26 Hz), 13.5, 12.4. HR-MS (APCI): Calcd. for $C_{11}H_{11}DN_2$ (M+H): 174.1136, found: 174.1132.

1-(4-Deuterophenyl)-3,5-dimethyl-1*H*-pyrazole (4h): Reaction time: 10.5 h. Yield: 91%, as a pale yellow liquid. R_f: 0.40 in 10% ethyl acetate in petroleum ether. IR (as film in CCl_4): ν (cm^{-1}) = 2924, 2367, 1595, 1556, 1500, 1415, 1382, 1366, 1133, 1104, 1025, 977. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 – 7.41 (m, 4H), 6.00 (s, 1H), 2.30 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.0, 139.9, 139.5, 128.9, 127.0 (t, *J* = 25 Hz), 124.9, 107.0, 13.6, 12.5. HR-MS (APCI): Calcd. for $C_{11}H_{11}DN_2$ (M+H): 174.1136, found: 174.1154.

Procedure for the Palladium-Catalyzed Deuteration of 4-Bromopyrazole/4-Bromoaniline derivatives with CD_3OH or CH_3OD

An oven-dried 8 mL reaction vial was charged with $Pd(OAc)_2$ (5 mol-%), **L7** (10 mol-%) and K_3PO_4/KO^{t}Bu (1.5 equiv), bromo derivative (0.5 mmol) in CD_3OH/CH_3OD (0.5 mL) in toluene (0.5 mL). The reaction mixture was stirred at 80 °C for 3-12 h. The reaction mixture was monitored by TLC or GC/MS analysis. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

4-Deutero-3,5-dimethyl-1-phenyl-1*H*-pyrazole (4g): Reaction time: 12 h. Yield: 98%, as a pale yellow liquid. R_f: 0.35 in 10% ethyl acetate in hexane. IR (as film in CCl_4): ν (cm^{-1}) = 3067, 2926, 2362, 1598, 1542, 1504, 1458, 1415, 1381, 1364, 1140, 1072, 1047, 1024, 911. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.40 (m, 4H), 7.36 – 7.30 (m, 1H), 2.30 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.9, 139.9, 139.3, 129.0, 127.3, 124.8, 106.7 (t, *J* = 26 Hz), 13.5, 12.4. HR-MS (APCI): Calcd. for $C_{11}H_{11}DN_2$ (M+H): 174.1136, found: 174.1132.

3,5-Dimethyl-1-phenyl-1*H*-pyrazole (4g')[30]: Reaction time: 3-12 h. Yield: 98%, as a pale yellow liquid. R_f: 0.30 in 10% ethyl acetate in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.41 (m, 4H), 7.36 – 7.31 (m, 1H), 5.99 (s, 1H), 2.30 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.99, 139.97, 139.46, 129.05, 127.30, 124.82, 106.98, 13.56, 12.42. HR-MS (ESI): Calcd. for $C_{11}H_{12}N_2(M+H)$: 173.1073, found: 173.1085.

***N*-Boc-4-deuterophenylamine (2l)**: Reaction time: 10 h. Yield: 84%, as a white colour solid. Melting point: 124 – 126 °C. R_f: 0.40 in 10% ethyl acetate in hexane. IR (KBr): ν (cm^{-1}) = 3305, 2984, 2372, 1689, 1522, 1407, 1312, 1297, 1243, 1155, 1060. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.51 (s, 1H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.9, 138.5, 128.9, 122.9(t, *J* = 25 Hz), 118.7, 80.6, 28.5. ^{1}H NMR (400 MHz, $CDCl_3$) (D_2O shake) δ = 7.35 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 1.52 (s, 9H). HR-MS (ESI): Calcd. for $C_{11}H_{14}DNO_2$ $(M)^+$: 194.1160, found: 194.1134.

Notes and references

1 a) E. V. Anslyn and D. A. Dougherty, in Modern Physical Organic Chemistry; University Science Books: Sausalito, 2006; b) T. Matsuda, M. Shigeno and M. Murakami, J. Am. Chem. Soc. 2007, 129, 12086; c) E. M. Simmons and J. F. Hartwig, Angew. Chem., Int. Ed. 2012, 51, 3066; d) S. Seo, M. Slater and M. F. Greaney, *Org. Lett*. 2012, **14**, 2650; e) J. Atzrodt and V. J. Derdau, Labelled Compd. Radiopharm. 2010, 53, 674; f) K. W. Quasdorf, A. D. Huters, M. W. Lodewyk, D. J. Tantillo, and N. K. Garg, *J. Am. Chem. Soc.* 2012, **134**, 1396; g) M. Miyashita, M. Sasaki, I. Hattori, M. Sakai and K. Tanino, *Science*, 2004, **305**, 495.

2 a) T. G. Gant, *J. Med. Chem*., 2014, **57**, 3595; b) N. A. Meanwell, *J. Med. Chem*., 2011, **54**, 2529; c) S. L. Harbeson, R. D. Tung, *Annual Reports in Medicinal Chemistry*, J. E. Macor; Ed. Elsevier, 2011, Vol. 46. p. 403; d) K. Sanderson, *Nature*, 2009, ***458***, 269; e) For example: In 2009, Auspex's deuterated Effexor® and CoNCERT's deuterated Paxil® demonstrate the potential success of deuterating known drugs.

3 A. Katsnelson, *Nature Med.,* 2013, **19**, 656.

4 V. Jacques, A. W. Czarnik, T. M. Judge, L. H. T. Van der Ploeg and S. H. DeWitt , Proc. *Natl. Acad. Sci. U.S.A.*, 2015, **112**, E1471.

5 a) J. Azrodt, V. Derdau, T. Fey and J. Zimmermann, *Angew. Chem. Int. Ed.* 2007, **46**, 7744; b) T. Junk and W. J. Catallo, *Chem. Soc. Rev*. 1997, **26**, 401; selected examples: c) C. M. Yung, M. B. Skaddan and R. G. Bergman, *J. Am. Chem. Soc.*, 2004, **126**, 13033; d) R. CorberáN, M. Sanáu and E. Peris, *J. Am. Chem. Soc*., 2006, **128**, 3974; e) S. H. Lee, S. I. Gorelsky and G. I. Nilkonov, *Organometallics*, 2013, **32**, 6599; f) M. H. G. Prechtl, M. Hoelscher, Y. Ben-David, N. Theyssen, R. Loschen, D. Milstein and W. Leitner, *Angew. Chem. Int. Ed*., 2007, **119**, 2319; g) F. Alonso, I. P. Beletskaya and M. Yus, *Chem, Rev*. 2002, **102**, 4009; h) T. Kurita, F. Aoki, T. Mizumoto, T. Maejima, H. Esaki, T. Maegawa, Y. Monguchi and H. Sajiki, *Chem. Eur. J.*, 2008, **14**, 3371; j) H. Esaki, R. Ohtaki, T. Maegawa, Y. Monguchi and H. Sajiki, *J. Org. Chem*., 2007, **72**, 2143.

6 Recent examples: a) E. Khaskin and D. Milstein, *ACS Catal.*, 2013, **3**, 448; b) F. Perez, Y. Ren, T. Boddaert, J. Rodriguez and Y. Coquerel, *J. Org. Chem.,* 2015, **80**, 1092; c) S. H. M. Mehr, K. Fukuyama, S. Bishop, F. Lelj and M. J. MacLachlan, *J. Org. Chem.,* 2015, **80**, 5144; d) B. Chatterjee and C. Gunanathan, *Org. Lett*., 2015, **17**, 4794; e) T. Yamada, K. Park, Y. Monguchi, Y. Sawama and H. Sajiki *RSC Adv*. 2015, **5**, 92954.

7 S. Vanderheiden, B. Bulat, T. Zevaco, N. Jung and S. Bräse, *Chem. Commun.*, 2011, **47**, 9063.

8 a) M. Rudzki, A. Alcalde-Aragonés, W. I. Dzik, N. Rodríguez and L. J. Gooßen, *Synthesis* 2012, **44**, 184; b) R. Grainger, A. Nikmal, J. Cornella and I. Larrosa, *Org. Biomol. Chem.*, 2012, **10**, 3172.

9 M. Szostak, M. Spain and D. J. Procter, *Org. Lett.,* 2014, **16**, 5052.

10 S. Ma, G. Villa, P. S. Thuy-Boun, A. Homs and J.-Q, Yu, *Angew. Chem. Int. Ed*. 2014, **53**, 734.

11 a) C. W. Cheung and S. L. Buchwald, *Org. Lett*., 2013, **15**, 3966; b) K. E. Torraca, X. Huang, C. A. Parrish and S. L. Buchwald, *J. Am. Chem. Soc*. 2001, **123**, 10770; c) M. Palucki, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc*. 1997, **119**, 3395; d) S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann and M. Beller, *J. Am. Chem. Soc.* 2010, **132**, 11592;

View Article Online
DOI: 10.1039/C6OB00193A

e) S. Gowrisankar, H. Neumann and M. Beller, *ChemCatChem,* 2011, **3**, 1439; f) J. F. Hartwig, *Angew. Chem. Int. Ed.* 1998, **37**, 2046; g) J. D. Prim, J.-M. Campagne, D. Joseph and B. Andrioletti, *Tetrahedron* 2002, **58**, 2041; h) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.* 2004, 2337; i) R. B. Bedford, C. S. J. Cazin and D. Holder, *Coord. Chem. Rev.* 2004, 2283; j) A. R. Muci and S. L. Buchwald, "*Practical Palladium Catalysts for C—N and C—O Bond Formation*, in *Topics in Current Chemistry*; N. Miyaura, Ed.; Springer-Verlag: Berlin, Germany, 2001; Vol. 219, 131-209. K) S. Enthaler and A. Company, *Chem. Soc. Rev*. 2011, **40**, 4912; l) P. E. Maligres, J. Li, S. W. Krska, J. D. Schreier and I. T. Raheem, *Angew. Chem. Int. Ed*., 2012, **51**, 9071.

12 *tert*-BippyPhos *Adamantyl*-BippyPhos, BrettPhos-Pd-G3 GTcapsule, ^{t}BuBrettPhos, RockPhos, ^{t}BuXPhos, CyPF-^{t}Bu were used as ligands in palladium catalysed C—O cross coupling reactions.

13 Selected Examples: a) M. L. Buil, M. A. Esteruelas, S. Niembro, M. Olivan, L. Orzechowski, C. Pelayo and A. Vallribera, *Organometallics*, 2010, **29**, 4375; b) A. A. Peterson, K. A. Thoreson and K. McNeill, *Organometallics*, 2009, **28**, 5982; c) H. Sajiki, A. Kume, K. Hattori and K. Hirota, *Tetrahedron Lett.,* 2002, **43**, 7247; d) P. P. Cellier, J. F. Spindler, M. Taillefer and H. J. Cristau, *Tetrahedron Lett.,* 2003, **44**, 7191; e) N. Hirasawa, Y. Takahashi, E. Fukuda, O. Sugimoto and K. I. Tanji, *Tetrahedron Lett.,* 2008, **49**, 1492; f) K. A. Cannon, M. E. Geuther, C. K. Kelly, S. Lin and A. H. Roy MacArthur, *Organometallics,* 2011, **30**, 4067; g) S. T. Handy, H. Bregman, J. Lewis, X. Zhang and Y. Zhang, *Tetrahedron Lett.,* 2003, **44**, 427; h) C. Desmarets, S. Kuhl, R. Schneider and Y. Fort, *Organometallics,* 2002, **21**, 1554; i) M. E. Logan and M. E. Oinen, *Organometallics,* 2006, **25***,* 1052; j) J. Moon and S. Lee, *J. Organomet. Chem.,* 2009, **694**, 473; k) J. Chen, Y. Zhang, Z. Yang, J. Liu, L. Li, and H.Zhang, H. *Tetrahedron* 2007, **63**, 4266.

14 A. Zask and P. Helquist, *J. Org. Chem*., 1978, **43**, 1619.

15 a) M. S. Viciu, G. A. Grasa and S. P. Nolan, *Organometallics,* 2001, **20***,* 3607; b) O. Navarro, H. Kaur, P. Mahjoor and S. P. Nolan, *J. Org. Chem*. 2004, **69**, 3173; c) O. Navarro, M. Marion, Y. Oonishi, R. A. Kelly III and S. P. Nolan, *J. Org. Chem.* 2006, **71**, 685.

16 Z. Ahmadi and J. S. McIndoe, *Chem. Commun*., 2013, 49, 11488.

17 Y. Miura, H. Oka, E. Yamano and M. Morita, J. Org. Chem., 1997, 62, 1188. This method involves large excess of toxic sodium amalgam, inert atmosphere and tedious work-up.

18 P. Dash, M. Janni and S. Peruncheralathan, *Eur. J. Org. Chem*., 2012, 4914.

19 Nolan et al found ^{i}PrOH is a better solvent for PEPPSI catalysed dehalogenation of aryl halides. Whereas MeOH gave poor yield of reduced product.

20 We performed the reaction under similar basic conditions (KOtBu as base). No trace amount of deuterated product 4g was observed.

21 Y. Miura, H. Oka, E. Yamano and M. Morita, *J. Org. Chem*., 1997, **62**, 1188.

22 R. Radtke and A. Heesing, *Chem. Ber*., 1990, **123**, 621.

23 M. Tobisu, K. Yamakawa, T. Shimasaki and N. Chatani*, Chem. Commun*., 2011, **47**, 2946.

24 B. Stefane and S. Polanc, *Synlett*, 2008, 1279.

25 J. D. Revell and A. Ganesan, *Chem. Comm*., 2004, **17**, 1916.

26 J. A. Murphy, J. Garnier, S. R. Park, F. Schoenebeck, S. Zhou and A. T. Turner*, Org. Lett*., 2008, **10**, 1227.

27 T. Mutsumi, H. Iwata, K. Maruhashi, Y. Monguchi and H. Sajiki, *Tetrahedron*, 2011, **67**, 1158.

28 A. Albert and G. Catterall, *J. Chem. Soc. C*., 1967, 1533.

29 W. R. Schleigh, *J. Heterocyclic Chem*., 1972, **9**, 675.

30 H. J. Cristau, P. P. Cellier, J. F. Spindler and M. Taillefer, *Eur. J. Org. Chem.*, 2004, 695.