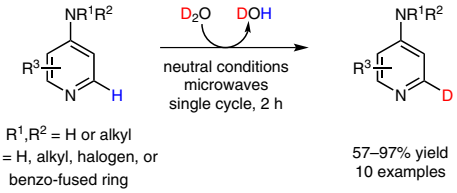
Synlett M. C. Bagley et al. Letter

Rapid Protium–Deuterium Exchange of 4-Aminopyridines in Neutral D_2O under Microwave Irradiation

Mark C. Bagley*
Ayed Alnomsy
Hussein I. Sharhan

Department of Chemistry, School of Life Sciences, University of Sussex, Falmer, Brighton, East Sussex, BN1 9QJ, UK
m.c.bagley@sussex.ac.uk



R^1,R^2 = H or alkyl
R^3 = H, alkyl, halogen, or benzo-fused ring

57–97% yield
10 examples

Received: 11.05.2016
Accepted after revision: 25.06.2016
Published online: 03.08.2016
DOI: 10.1055/s-0035-1562479; Art ID: st-2016-d0334-l

Abstract 4-Aminopyridines undergo surprisingly rapid and highly selective H/D exchange at C-2 and C-6 in neutral D_2O upon microwave irradiation at only 190 °C for two hours in a sealed vessel. This method contrasts and complements acid-mediated H/D exchange, requires no catalyst, and is appropriate for the synthesis of deuterium isotopologues of N- and C-substituted 4-aminopyridines and a benzofused (quinoline) analogue.

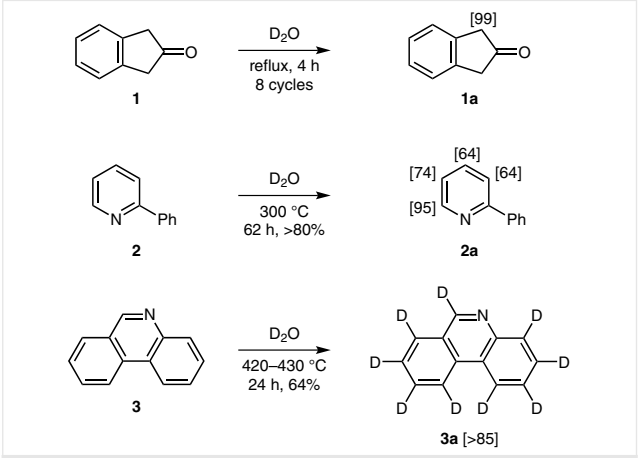
Key words deuteration, heterocycles, microwave synthesis

The demand for compounds multiply labeled with stable isotopes has increased dramatically in recent years.[1,2] Deuterated derivatives are valuable as internal standards for quantifying human and animal pharmacokinetic and metabolism experiments in drug development, as well as for mechanistic probes to determine reaction pathways. Generally speaking, deuterated standards exhibit similar physical and chemical properties to their nondeuterated isotopologues, such as ionization behavior and LC retention times, but differ on account of their mass difference. If this is large enough to separate signals from natural isotope patterns, quantitative analysis is possible.[3] Furthermore, deuterated drug isotopologues may be unexpectedly nonobvious in patent law,[4] differentiating these compounds from prior art and thus making them essential targets for study.

A number of strategies are available for the preparation of compounds bearing multiple deuterium labels.[5–7] Firstly, it may be most appropriate to carry out the synthesis using isotopically labelled precursors. This has the advantage of being predictable, by comparison to the 'natural' isotopologue, but can be time consuming and may require expensive reagents and/or the development of additional sequences. An alternative approach, protium–deuterium exchange of the target molecule or late-stage intermediate, has the potential to be more rapid, efficient, and cost-effective. This method removes the need for further developmental work, but must be capable of introducing multiple deuterium atoms in an efficient and predictable fashion.[3] H/D exchange is a valuable analytical tool in its own right in protein dynamics[8,9] and can serve as a useful model for analytical techniques involving protium–tritium exchange.[1,10,11]

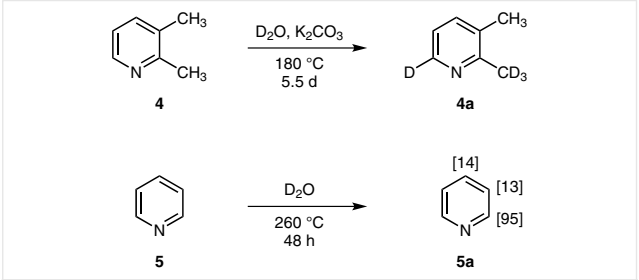
As a synthetic tool, H/D-exchange experiments received intensive study in the 1960s and 1970s,[5,6] leading to a number of advances in pH-dependent and metal-catalyzed processes.[12] With the recent development of higher performance mass spectrometers, and a renaissance of interest in C–H bond activation,[13] a plethora of H/D-exchange methods has now emerged, some using C–H activation technology.[14] Whilst for some substrates, metal-mediated methods are required,[2] for others it is possible to use the autoprotolytic equilibrium of D_2O in the absence of any catalyst. However, this approach often requires multiple cycles [for example in the synthesis of indanone-d_4 (**1a**)],[15] prolonged reaction times,[16] or extreme conditions, such as the use of an autoclave in supercritical media at 420–430 °C for the synthesis of phenanthridine (**3a**, Scheme 1).[17] Interestingly, H/D exchange of 2-phenylpyridine (**2**) at 300 °C incorporates D to a degree in **2a** at all pyridine positions, but is most rapid at C-6.[16]

H/D exchange at the α-position of a number of pyridine derivatives was first observed by Zoltewicz,[18] but has also been described recently. When dimethylpyridine **4** was heated under basic conditions at 180 °C in D_2O for 5.5 days (Scheme 2), exchange at C-6 occurred more rapidly than at the other ring positions, but very forcing conditions were still required.[19] Similarly, pyridine (**5**), when heated to 260 °C for 48 hours in D_2O underwent H/D exchange, in high re-



Scheme 1 Percentage D incorporation (in parentheses) under forcing conditions using neutral D_2O[15–17]

gioselectivity for the α-position, to give dideuterated **5a**. The same process carried out at 200 °C for 24 hours gave only 15% D incorporation at this position.[16] Many recent efforts have been directed towards the efficient H/D exchange of pyridine derivatives.[20–27] A highly site-selective one-step α-labelling of pyridines and N-heteroaromatic compounds has been described using deuterium gas and a rhodium or ruthenium catalyst.[28] Furthermore, it has been remarked that a 4-pyrrolidino group accelerates H/D exchange at all pyridine positions.[16] With this precedent, we set out to establish a simple one-step method for site-selective protium–deuterium exchange using neutral D_2O that would proceed under microwave irradiation, in a commercial instrument using readily automated conditions in the absence of any catalyst.



Scheme 2 D incorporation (percentage in parentheses) in pyridines using D_2O[16,19]

We started by reviewing the H/D exchange of 2-aminopyridine (**6**), 3-aminopyridine (**7**), and 4-aminopyridine (**8**) in neutral D_2O under microwave irradiation at 190 °C for just 2 hours in a commercial instrument, comparing the results to H/D exchange of aniline (**9**) under the same conditions (Table 1). Considerable differences were noted in the efficiency of H/D exchange at different positions across this small series of substrates. For 2-aminopyridine (**6**), exchange was poorly efficient at all positions under these relatively mild conditions, as might be expected. The reaction of 3-aminopyridine (**7**) under these conditions was much more selective, with good incorporation at C-2 and yet very low levels of H/D exchange at all other positions, including at C-6. Unfortunately, increasing the reaction time gave no further improvement in D incorporation at C-2 (80%). Remarkably, 4-aminopyridine (**8**) underwent rapid H/D exchange at the α-positions, even at this relatively low temperature, indicating its unusual high reactivity in the process. By means of comparison, aniline (**9**) was found to undergo low levels of H/D exchange at ring positions under the experimental conditions. It is noteworthy that contrasting behaviour has been described by Zoltewicz in a study of H/D exchange of 4-amino-2,6-dimethylpyridine, with respect to 2,6-lutidine, under neutral and acidic conditions.[18e]

Table 1 %D Incorporation[a] after Microwave Irradiation in Neutral D_2O (190 °C, 2 h)

Product	C-2	C-3	C-4	C-5	C-6	Yield (%)[b]
2-aminopyridine (**6a**)	–	54	52	53	56	72
3-aminopyridine (**7a**)	80	–	6	3	12	66
4-aminopyridine (**8a**)	98	50	–	50	98	57
4-aminopyridine (**8c**)[c]	39	5	–	5	39	52
4-aminopyridine (**8d**)[c]	67	17	–	17	67	57
aniline (**9a**)	17	14	24	14	17	49[d]

[a] As determined by ^{1}H NMR spectroscopic analysis after introduction of an internal standard by acetylation (AcCl, K_2CO_3, acetone, r.t., 3 h), followed by aqueous workup.
[b] Yield refers to the isolated yield (%) of product after microwave irradiation of the substrate in D_2O in a sealed Pyrex™ tube at 190 °C, unless stated otherwise, for 2 h (hold time) by moderation of the initial magnetron power (300 W), followed by cooling and an acid–base workup.
[c] Microwave irradiation was at a temperature of 170 °C (for **8c**) or 180 °C (for **8d**).
[d] Isolated yield (%) of the product after an aqueous workup.

In order to understand these phenomena, and the high reactivity of 4-aminopyridine (**8**) towards α-exchange under relatively mild conditions, the study was repeated, but, this time, in the presence of DCl (Table 2). It was anticipated that this would provide a basis for understanding the site-selectivity of proton–deuteron exchange by electrophilic aromatic substitution and provide comparison with Zoltewicz's mechanistic studies. Under acid-mediated conditions, 2-aminopyridine (**6b**) showed D incorporation to a similar degree at C-4 and C-6, but positions activated towards electrophilic aromatic substitution (C-3 and C-5) exhibited a dramatic increase in D incorporation (both 94%), as expected. The same phenomenon was observed in the deuteration of 3-aminopyridine (**7**), with an increase in incorporation at the activated α-positions of **7b** (96% at C-2), making it a useful synthetic procedure. Aniline (**9**), under these conditions, showed increased incorporation at the *ortho* and *para* positions of **9b**, also as expected, and yet es-

sentially the same %D incorporated at *meta* positions. The observation most worthy of note was that H/D exchange of 4-aminopyridine (**8**) completely reversed under acidic conditions, with high levels of incorporation now observed at C-3 and C-5 (positions activated to electrophilic aromatic substitution) and yet minimal incorporation at the pyridine α-carbons of **8b**. This demonstrated that mechanisms operating in neutral D_2O (Table 1) were distinct from the electrophile-mediated process (Table 2) for this substrate and so were worthy of further optimization as a site-selective method for D incorporation. Carrying out the H/D exchange in neutral D_2O at lower temperatures (170 °C or 180 °C) gave 4-aminopyridine (**8c** or **8d**) with much less efficient D incorporation at all positions (Table 1) and so reaction at 190 °C under microwave irradiation in neutral D_2O was adopted as the method of study.

Table 2 %D Incorporation[a] after Microwave Irradiation in D_2O (190 °C, 2 h) in the Presence of DCl

Product	C-2	C-3	C-4	C-5	C-6	Yield (%)[b]
2-aminopyridine (**6b**)	–	94	54	94	54	70
3-aminopyridine (**7b**)	96	–	15	3	34	60
4-aminopyridine (**8b**)	9	92	–	92	9	56
aniline (**9b**)	57	12	45	12	57	61[c]

[a] As determined by ^{1}H NMR spectroscopic analysis after introduction of an internal standard by acetylation (AcCl, K_2CO_3, acetone, r.t., 3 h), followed by aqueous workup.
[b] Yield refers to the isolated yield (%) of product after microwave irradiation of the substrate in D_2O in the presence of DCl (4 equiv) in a sealed Pyrex™ tube at 190 °C for 2 h (hold time), by moderation of the initial magnetron power (300 W), cooling, and an acid–base workup.
[c] Isolated yield (%) after aqueous workup.

Given the high site-selectivity for H/D exchange of 4-aminopyridine (**8**) in neutral D_2O, a range of substrates was investigated under the newly found set of conditions[29] (microwave irradiation at 190 °C, 2 h) to establish the scope of the method, changing the nature of the substituent, its position, and even the heterocycle (Table 3). For some substrates, reaction in both the presence and absence of DCl was investigated to see if a reversal of the regioselectivity was observed. It was found that *N*-alkyl groups exhibited minimal side-chain exchange under these conditions (entries 3–7) and their presence slightly retarded H/D exchange at C-3 and C-5, presumably as a consequence of steric effects. Excellent incorporation at C-2 and C-6 (95–98%) was observed for **10**–**12** under neutral conditions, also with high levels of regiocontrol (entries 3, 5, and 6). 4-Aminoquinoline (**13**) showed similar behavior (entry 8), although the efficiency of incorporation at C-2 in **13a** (89%) was reduced slightly with respect to its pyridine counterpart **8a** (98%). D incorporation in 4-pyrrolidinopyridine (**12b**) and 4-aminoquinoline (**13b**) was seen to reverse by carrying out the procedure in the presence of DCl (entries 7 and 9), demonstrating that this method proceeds by a contrasting mechanism and complements acid-mediated exchange. For quinoline products **13a** and **13b**, minimum exchange was noted in the carbocyclic ring under both sets of conditions. Efficient incorporation was only affected marginally (89%) by the presence of a methyl group, at C-3 in **14a** (entry 10) or at C-2 in **15a** (96%) – the latter also showing efficient incorporation (97%) at C-1′ (entry 11). The effect of halogen substituents (**16**–**18**) did vary with position: with a halogen at C-3 high efficiency (98%) and regioselectivity for C-2 was observed (entries 12 and 13), but the 2-chloride **18** did not exchange efficiently (entry 14) perhaps as a consequence of its reduced basicity. Interestingly, the 3-iodide **17a** exhibited relatively high D incorporation at both α-positions (entry 13; 98% and 75%) whereas the 3-bromide did not (entry 12; 98% and 34%). Finally, exchange in both 4-aminopyrimidine (**19a**) and 2-aminopyrazine (**20a**) was less rapid (entries 15 and 16), the corresponding substrates postulated as being less reactive in the process as a consequence of their reduced basicity (cf. pK_{aH} 2-aminopyridine 6.86; 4-aminopyrimidine 5.7l; 2-aminopyrazine 2.96; 4-aminopyridine 9.17).[30] In cases for which H/D exchange was efficient and highly selective the isolated yield of the product was of preparative value (57–97% yield).[31]

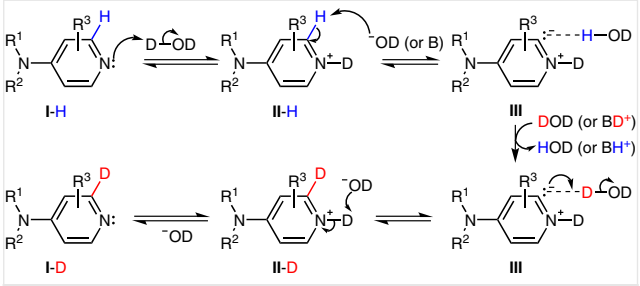
The fast kinetics of H/D exchange of 4-aminopyridines under neutral conditions, and the high regioselectivity of the process, complements acid-mediated exchange[32] and could be attributed to the distinct nature of the operating mechanism. In accordance with the kinetic and mechanistic studies by Zoltewicz on base-catalyzed H/D exchange of N-substituted pyridinium ions,[18d] and exchange of methylpyridines in dilute acid,[18e] we believe this method could be a specific acid-general base-catalyzed process which may be influenced by internal return (Scheme 3). The equilibrium almost certainly involves protonation of the substrate **I** by the solvent (D_2O), giving a pyridinium conjugate acid **II**, which can then be deprotonated by the lyate anion (or substrate B) to give pyridinium ylide **III**. Under this premise, the efficiency of the exchange process for 4-aminopyridines would be attributed to the increased pyridine basicity in general base catalysis, increased stability of the pyridinium ylides **III** upon deprotonation, or a shift from general base catalysis to an internal return limited process, with no significant general base catalysis and slow dissociation of a hydrogen-bonded ylide **III**–conjugate acid complex, as a consequence of the reduced acidity of the pyridinium conjugate acid.[18d] A profile of reactivity dependent upon aminopyridine basicity and proceeding in equilibrium via pyridinium ylide **III** would, broadly speaking, explain the trends observed in this work (Table 3), such as reduced exchange in 4-amino-2-chloropyridine (**18**), 4-aminopyrimidine (**19**), and 2-aminopyrazine (**20**), but clearly other factors are involved. For example, D incorporation at C-2 (80%) vs. C-6 (12%, Table 1) of 3-aminopyridine (pK_{aH} 5.98) indicates a role of ylide **III** stability, which could also be in evi-

Table 3 %D Incorporation[a] of Substituted 4-Aminopyridines and Related Heterocycles after Microwave Irradiation in D_2O (190 °C, 2 h) in the Presence or Absence of DCl

Entry	Substrate	DCl present	Product	C-2	C-3	C-5	C-6	C-7	C-8	C-1′	C-2′	C-3′	Yield (%)[b]
1	4-aminopyridine (**8**)	×	**8a**	98	50	50	98	–	–	–	–	–	57
2	4-aminopyridine (**8**)	√	**8b**	9	92	92	9	–	–	–	–	–	56
3	4-(methylamino)pyridine (**10**)	×	**10a**	98	22	22	98	–	–	<4	–	–	91
4	4-(methylamino)pyridine (**10**)	√	**10b**	<4	96	96	<4	–	–	<4	–	–	82
5	4-(dimethylamino)pyridine (**11**)	×	**11a**	97	6	6	97	–	–	<4	–	–	97
6	4-pyrrolidinopyridine (**12**)	×	**12a**	95	9	9	95	–	–	–	<4	<4	96
7	4-pyrrolidinopyridine (**12**)	√	**12b**	<4	74	74	<4	–	–	–	<4	<4	97
8	4-aminoquinoline (**13**)	×	**13a**	89	23	9	<4	<4	9	–	–	–	69
9	4-aminoquinoline (**13**)	√	**13b**	19	98	10	<4	<4	10	–	–	–	74
10	4-amino-3-methylpyridine (**14**)	×	**14a**	94	–	8	93	–	–	<4	–	–	97
11	4-amino-2-methylpyridine (**15**)	×	**15a**	–	5	8	96	–	–	97	–	–	84
12	4-amino-3-bromopyridine (**16**)	×	**16a**	98	–	17	34	–	–	–	–	–	82
13	4-amino-3-iodopyridine (**17**)	×	**17a**	98	–	25	75	–	–	–	–	–	93
14	4-amino-2-chloropyridine (**18**)	×	**18a**	–	42	30	30	–	–	–	–	–	98
15	4-aminopyrimidine (**19**)	×	**19a**	64	–	22	58	–	–	–	–	–	26
16	2-aminopyrazine (**20**)	×	**20a**	–	52	17	17	–	–	–	–	–	61

[a] As determined by ^{1}H NMR spectroscopic analysis, after introduction of an internal standard (entries 1–3, 7–15) by acetylation (AcCl, K_2CO_3, acetone, r.t., 3 h), followed by aqueous workup and purification by column chromatography on silica if required; or by reference to a known quantity of dioxane as an external standard (entries 4–6).
[b] Yield refers to the isolated yield (%) of product after microwave irradiation of the substrate in D_2O in a sealed Pyrex™ tube at 190 °C for 2 h (hold time) in the presence or absence of DCl (4 equiv), by moderation of the initial magnetron power (300 W), cooling, and an acid–base workup.

dence with the high C-2 selectivity for D incorporation in 3-bromide **16a** and low D incorporation (56%) at C-6 for 2-aminopyridine (pK_{aH} 6.86)[30] (**6**; Table 1); alternative mechanisms could also be in competition. However, no matter what alternative mechanisms might be operating, this relatively mild method under neutral conditions would seem to tolerate a range of 4-aminopyridine basicities, gives quite predictable outcomes, and is well suited to this particular core heterocyclic motif, and a benzo-fused counterpart.



Scheme 3 Possible mechanism of D incorporation in 4-aminopyridine **I**-H involving H/D-exchange equilibria of pyridinium ylide **III**

In conclusion, we have demonstrated that 4-aminopyridines undergo rapid H/D exchange at the α-position upon microwave irradiation in D_2O at 190 °C in only 2 hours. These neutral conditions tolerate a range of functionality, proceed in a single cycle, and require no specialist equipment or added catalyst to provide deuterated isotopologues in reasonable yield. For these substrates the method contrasts from acid-mediated exchange reactions, proceeds via a distinct mechanism (or mechanisms) and provides complementary isotopomers or isotopologues for further study.

Acknowledgment

We thank the EPSRC-BBSRC-MRC sponsored network SMS-Drug (EP/I037229/1; award to MCB), Saudi Cultural Bureau (support for AA), and the R M Phillips Trust (award to MCB) for support of this work and Dr. Alaa Abdul-Sada at the University of Sussex for mass spectra.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562479.

References and Notes

(1) Junk, T.; Catallo, W. J. *Chem. Soc. Rev.* **1997**, *26*, 401.
(2) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 7744.
(3) Blom, K.; Schuhardt, J.; Munson, B. *Anal. Chem.* **1985**, *57*, 1986.

(4) Buteau, K. C. *J. High Tech. L.* **2009**, *10*, 22.
(5) Hanson, J. R. In *The Organic Chemistry of Isotopic Labelling*; The Royal Society of Chemistry: Cambridge, **2011**.
(6) Thomas, A. F. In *Deuterium Labeling in Organic Chemistry*; Appleton-Century-Crofts, Educational Div., Meredith Corp: New York, **1972**.
(7) Murray, A. III.; Williams, D. L. In *Organic Synthesis with Isotopes. Part II: Organic Compounds Labeled with Isotopes of the Halogens, Hydrogen, Nitrogen, Oxygen, Phosphorus and Sulfur*; Interscience Publishers: New York, **1958**.
(8) Hvidt, A.; Nielsen, S. O. *Adv. Protein Chem.* **1966**, *21*, 287.
(9) For recent reviews, see: (a) Percy, A. J.; Rey, M.; Burns, K. M.; Schriemer, D. C. *Anal. Chim. Acta* **2012**, *721*, 7. (b) Majumdar, R.; Middaugh, C. R.; Weis, D. D.; Volkin, D. B. *J. Pharm. Sci.* **2015**, *104*, 327.
(10) Lockley, W. J. S. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 256.
(11) Elander, N.; Jones, J. R.; Lu, S.-Y.; Stone-Elander, S. *Chem. Soc. Rev.* **2000**, *29*, 239.
(12) Garnett, J. L. *Catal. Rev.* **1971**, *5*, 229.
(13) Labinger, J. A.; Bercaw, J. E. *Nature (London, U.K.)* **2002**, *417*, 507.
(14) The area has been reviewed recently (ref. 2 and 5). Notable examples of acid-mediated methods include: (a) Vaidyanathan, S.; Surber, B. W. *Tetrahedron Lett.* **2005**, *46*, 5195. (b) Fodor-Csorba, K.; Galli, G.; Holly, S.; Gács-Baitz, E. *Tetrahedron Lett.* **2002**, *43*, 3789. (c) Boix, C.; Poliakoff, M. *Tetrahedron Lett.* **1999**, *40*, 4433. (d) Lockley, W. J. S. *Tetrahedron Lett.* **1982**, *23*, 3819. Notable examples of metal-mediated methods include: (e) Sajiki, H.; Ito, N.; Esaki, H.; Maesawa, T.; Maegawa, T.; Hirota, K. *Tetrahedron Lett.* **2005**, *46*, 6995. (f) Derdau, V.; Atzrodt, J.; Zimmermann, J.; Kroll, C.; Brückner, F. *Chem. Eur. J.* **2009**, *15*, 10397. (g) Sajiki, H.; Aoki, F.; Esaki, H.; Maegawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 1485. (h) Cioffi, E. A.; Bell, R. H.; Le, B. *Tetrahedron: Asymmetry* **2005**, *16*, 471. (i) Cioffi, E. A. *Tetrahedron Lett.* **1996**, *37*, 6231. (j) Cioffi, E. A.; Alston, K. E.; Patel, A. M. *Tetrahedron Lett.* **2002**, *43*, 8985. (k) Sawama, Y.; Yamada, T.; Yabe, Y.; Morita, K.; Shibata, K.; Shigetsura, M.; Monguchi, Y.; Sajiki, H. *Adv. Synth. Catal.* **2013**, *355*, 1529. (l) Maegawa, T.; Fujiwara, Y.; Inagaki, Y.; Esaki, H.; Monguchi, Y.; Sajiki, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5394. (m) Derdau, V.; Atzrodt, J. *Synlett* **2006**, 1918. (n) Hardacre, C.; Holbrey, J. D.; Jane McMath, S. E. *Chem. Commun.* **2001**, 367.
(15) Edlund, U.; Bergson, G. *Acta Chem. Scand.* **1971**, *25*, 3625.
(16) Werstiuk, N. H.; Ju, C. *Can. J. Chem.* **1989**, *67*, 5.
(17) Junk, T.; Catallo, W. J. *Tetrahedron Lett.* **1996**, *37*, 3445.
(18) For Zoltewicz's original studies, see: (a) Zoltewicz, J. A.; Smith, C. L. *J. Am. Chem. Soc.* **1967**, *89*, 3358. (b) Zoltewicz, J. A.; Kauffman, G. M.; Smith, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 5939. (c) Zoltewicz, J. A.; Kauffman, G. M. *J. Org. Chem.* **1969**, *34*, 1405. (d) Zoltewicz, J. A.; Helmick, L. S. *J. Am. Chem. Soc.* **1970**, *92*, 7547. (e) Zoltewicz, J. A.; Kandetzki, P. E. *J. Am. Chem. Soc.* **1971**, *93*, 6562.
(19) Kebede, N.; Pavlik, J. W. *J. Heterocycl. Chem.* **1997**, *34*, 685.
(20) Sullivan, J. A.; Flanagan, K. A.; Hain, H. *Catal. Today* **2008**, *139*, 154.
(21) Guy, K. A.; Shapley, J. R. *Organometallics* **2009**, *28*, 4020.
(22) Beringhelli, T.; Carlucci, L.; D'Alfonso, G.; Ciani, G.; Proserpio, D. M. *J. Organomet. Chem.* **1995**, *504*, 15.
(23) Prechtl, M. H. G.; Hölscher, M.; Ben-David, Y.; Theyssen, N.; Loschen, R.; Milstein, D.; Leitner, W. *Angew. Chem. Int. Ed.* **2007**, *46*, 2269.
(24) Eguillor, B.; Esteruelas, M. A.; García-Raboso, J.; Oliván, M.; Oñate, E. *Organometallics* **2009**, *28*, 3700.
(25) Piola, L.; Fernández-Salas, J.; Manzini, S.; Nolan, S. P. *Org. Biomol. Chem.* **2014**, *12*, 8683.
(26) McAuley, B.; Hickey, M. J.; Kingston, L. P.; Jones, J. R.; Lockley, W. J. S.; Mather, A. N.; Spink, E.; Thompson, S. P.; Wilkinson, D. J. *J. Labelled Compd. Radiopharm.* **2003**, *46*, 1191.
(27) Esaki, H.; Ito, N.; Sakai, S.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* **2006**, *62*, 10954.
(28) Alexakis, E.; Jones, J. R.; Lockley, W. J. S. *Tetrahedron Lett.* **2006**, *47*, 5025.
(29) **General Procedure for H/D Exchange of 4-Aminopyridines**
A solution of the substrate in D_2O (5 mL) was irradiated in a sealed Pyrex tube at 190 °C for 2 h (hold time) using a CEM Explorer microwave synthesizer (maximum pressure 150 psi) by moderation of the initial microwave power (300 W). The mixture was cooled in a stream of compressed air and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated in vacuo.
(30) (a) Barlin, G. B.; Pfleiderer, W. *J. Chem. Soc. B* **1971**, 1425. (b) Collot, A.-G.; Courtney, M.; Coyne, D.; Eustace, S. E.; More O'Ferrall, R. A. *J. Org. Chem.* **2009**, *74*, 3356.
(31) See Supporting Information for detailed experimental procedures and characterization data.

4-Aminopyridine-d_2 (8a)
Compd **8a** was prepared as a colorless solid; mp 157 °C. IR (neat): 3433, 3144, 3036, 2967, 2262, 1686, 1616, 1583, 1519, 1368, 1299, 1279, 1005, 891, 756 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 7.95 (0.04 H, d, *J* = 5 Hz, 2,6-H), 6.55 (1 H, s, 3,5-H). ^{13}C NMR (125 MHz, CD_3OD): δ = 155.3 (s, C-N), 148.4 (s, CH isotopologue), 148.1 (t_D, *J* = 26 Hz, CD), 108.9 (s, CH). MS (EI): *m/z* (%) = 96 (100) [$M^{+\cdot}$], 69 (25), 41 (35).

4-(Methylamino)pyridine-d_2 (10a)
Compd **10a** was prepared as a colorless solid; mp 125 °C. IR (neat): 3396, 3323, 3269, 3030, 2497, 2402, 2232, 1909, 1635, 1564, 1460, 1301, 1250, 1153, 1042, 914 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 7.99 (0.04 H, d, *J* = 7 Hz, 2,6-H), 6.51 (1.56 H, s, 3,5-H), 2.80 (3 H, s, Me). ^{13}C NMR (125 MHz, CD_3OD): δ = 155.5 (s, CN), 147.9 (t_D, *J* = 27 Hz, CD), 106.7 (s, CH), 27.8 (s, Me). MS (EI): *m/z* (%) = 111 (52), 110 (100) [$M^{+\cdot}$], 109 (69).

4-(Dimethylamino)pyridine-d_2 (11a)
Compd **11a** (300 mg, 2.45 mmol) was prepared as a colorless solid; mp 113–114 °C. IR (neat): 3286, 3250, 3179, 3045, 2922, 2819, 2236, 1579, 1498, 1350,1308, 1225, 1068, 993, 750 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 8.06 (0.07 H, m, 2,6-H), 6.63 (1.88 H, s, 3,5-H), 3.03 (6 H, s, 2Me). ^{13}C NMR (125 MHz, CD_3OD): δ = 155.0 (s, CN), 147.7 (t_D, *J* = 25 Hz, CD), 106.3 (s, CH), 37.7 (s, Me). MS (EI): *m/z* (%) = 124 (86) [$M^{+\cdot}$], 123 (100), 107 (6), 96 (24), 80 (54), 52 (81), 42 (42). HRMS: *m/z* [M + H] calcd for $C_7H_8D_2N_2$: 125.1042; found: 125.1043.

4-Pyrrolidinopyridine-d_2 (12a)
Compd **12a** (300 mg, 2.02 mmol) was prepared as a colorless solid; mp 59 °C. IR (neat): 3074, 2961, 2910, 2845, 2230, 1583, 1532, 1478, 1361, 1286, 1246, 1154, 997, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.20 (0.10 H, d, *J* = 5 Hz, 2,6-H), 6.36 (1.82 H, s, 3,5-H), 3.29 (4 H, t, *J* = 6 Hz, 2′,5′-H), 2.02 (4 H, t, *J* = 6 Hz, 3′,4′-H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.4 (s, CN), 147.5 (t_D, *J* = 27 Hz, CD), 106.7 (s, CH), 46.7 (s, CH_2), 24.8 (s, CH_2). MS (EI): *m/z* (%) = 150 (85) [$M^{+\cdot}$], 149 (100), 121 (15). HRMS: *m/z* [M + H] calcd for $C_9H_{10}D_2N_2$: 151.1199; found: 151.1199.

4-Aminoquinoline-d_1 (13a)
Compd **13a** was prepared as an orange solid; mp 155 °C. IR (neat): 3443, 2968, 1683, 1528, 1475, 1339, 1316, 1245, 1009, 917, 751 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 8.25 (0.11 H, s, 2-H), 8.06 (0.91 H, d, *J* = 8 Hz, 5- or 8-H), 7.81 (0.91 H, d, *J* = 8 Hz,

5- or 8-H), 7.64 (1 H, t, *J* = 8 Hz, 6- or 7-H) 7.43 (1 H, t, *J* = 8 Hz, 6- or 7-H), 6.62 (0.77 H, s, 3-H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.6 (s, CN), 149.2 (t_D, *J* = 26 Hz, CD), 147.9 (s, CN), 129.2 (s, CH), 127.4 (s, CH), 124.0 (s, CH), 121.4 (s, CH), 118.6 (s, C), 102.2 (s, CH). MS (EI): *m/z* (%) = 145 (100) [M$^{•+}$], 144 (15), 118 (13). HRMS: *m/z* [M + H] calcd for $C_9H_7DN_2$: 146.0823; found: 146.0824.

4-Amino-3-methylpyridine-*d*$_2$ (14a)

Compd **14a** was prepared as a colorless solid; mp 106 °C. IR (neat): 3345, 3311, 3164, 2536, 2404, 2367, 2288, 2237, 2194, 1631, 1553, 1436, 1264, 1197, 1042, 877 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.87 (0.06 H, s, 2-H), 7.71 (0.07 H, d, *J* = 7 Hz, 6-H), 6.57 (0.92 H, s, 5-H), 2.08 (2.96 H, s, Me). ^{13}C NMR (125 MHz, CD_3OD): δ = 153.5 (s, CN), 148.3 (s, CH isotopologue), 146.4 (s, CH isotopologue), 146.1 (t_D, *J* = 25 Hz, CD), 116.7 (s, CC), 108.3 (s, CH), 12.7 (s, Me). MS (EI): *m/z* (%) = 110 (100) [M$^{•+}$], 109 (33), 81 (29).

4-Amino-2-methylpyridine-*d*$_4$ (15a)

Compd **15a** was prepared as a colorless solid; mp 98 °C. IR (neat): 3324, 3065, 2911, 2848, 2366, 1638, 1602, 1559, 1495, 1345, 1297, 1261, 985, 705 cm^{-1}. ^{1}H NMR (500 MHz; CD_3OD): δ = 7.84 (0.04 H, d, *J* = 6 Hz, 6-H), 6.43 (0.95 H, d, *J* = 2 Hz, 3-H), 6.39 (0.92 H, d, *J* = 2 Hz, 5-H), 2.27 (0.08 H, m, 1′-H). ^{13}C NMR (125 MHz, CD_3OD): δ = 157.3 (s, CN), 155.7 (s, CC), 147.5 (t_D, *J* = 26 Hz, CD), 108.0 (s, CH), 106.6 (s, CH), 21.4 (sept$_D$, *J* = 19 Hz, CD_3). MS (EI): *m/z* = 112 (%) [M$^{•+}$], 111 (22), 110 (11), 83 (22), 69 (23), 41 (25).

4-Amino-3-bromopyridine-*d*$_1$ (16a)

Compd **16a** was prepared as an orange solid; mp 70 °C. IR (neat): 3448, 3149, 2925, 2536, 2156, 1707, 1628, 1589, 1502, 1419, 1339, 1270, 1184, 1074, 1013, 823 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ = 8.20 (0.02 H, s, 2-H), 7.90 (0.66 H, d, *J* = 6 Hz, 6-H), 6.70 (0.83 H, d, *J* = 6 Hz, 5-H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.3 (s, CN), 149.6 (t_D, *J* = 27 Hz, CD), 147.0 (s, CH), 109.5 (s, CH), 105.4 (s, C). MS (EI): *m/z* (%) = 174 (60) [M$^{•+}$], 94 (30), 67 (29).

4-Amino-3-iodopyridine-*d*$_2$ (17a)

Compd **17a** was prepared as an orange oil; mp 99 °C. IR (neat): 3421, 3294, 3038, 1639, 1581, 1491, 1412, 1337, 1267, 1185, 820, 725 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ = 8.38 (0.01 H, s, 2-H), 7.92 (0.25 H, d, *J* = 6 Hz, 6-H), 6.68 (0.75 H, s, 5-H). ^{13}C NMR (125 MHz, CD_3OD): δ = 155.4 (t_D, *J* = 28 Hz, CD), 154.8 (s, CN), 147.7 (s, CH), 108.7 (s, CH), 79.8 (s, C). MS (EI): *m/z* (%) = 222 (100) [M$^{•+}$], 221 (30) 127 (15), 95 (23), 67 (22), 40 (20).

(32) Di Giuseppe, A.; Castarlenas, R.; Oro, L. A. *C. R. Chim.* **2015**, *18*, 713.