JOC The Journal of Organic Chemistry

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Selective Ru(0)-Catalyzed Deuteration of Electron-Rich and Electron-Poor Nitrogen-Containing Heterocycles

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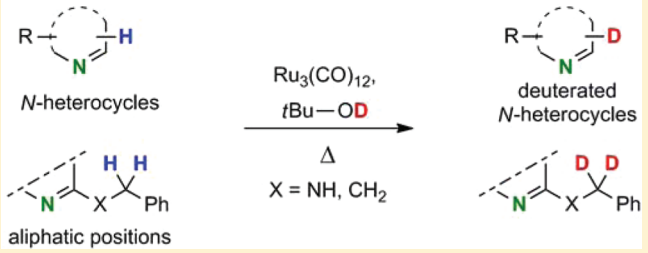
Supporting Information

ABSTRACT: A highly selective $Ru_3(CO)_{12}$-catalyzed deuteration method using *t*-BuOD as deuterium source is reported. Electron-rich and electron-poor N-heteroarenes such as indoles, azaindoles, deazapurines, benzimidazole, quinolines, isoquinolines, and pyridines were efficiently deuterated at specific positions with high selectivity; in most cases, deuterium incorporation was close to the theoretically possible values. To further increase deuteration degrees, several cycles of the reaction protocol can be carried out which gave superior deuteration degrees employing a much lower excess of deuterating agent compared to established protocols. It was proved that the same protocol can in principle be applied to tritiation reactions important for radioactive labeling of bioactive molecules.



Nitrogen-containing heterocycles are considered to be privileged structures because of their occurrence in many natural products and synthetic compounds with interesting biological activity.[1] Deuterated derivatives thereof are of high interest for mechanistic investigations leading to a better understanding of synthetic transformations and enabling the development of more efficient reaction conditions.[2] Various methods for the incorporation of deuterium were reported previously,[3] and the topic was recently reviewed.[4] In addition, tritiated compounds are of increasing importance for radiolabeling of bioactive compounds in medicinal chemistry applications.[5,6] Hence, facile, fast, and efficient protocols for the deuteration and tritiation[5,6] of indole and pyridine derivatives are of great value. A novel method to conduct such transformations is reported in this contribution.

Transition metal catalyzed H−D/T exchange reactions are a most attractive option. Pioneering examples for deuteration of (hetero)arenes or alkanes were reported by the groups of Garnett,[7] Shilov,[8] and Biddiscombe et al.[9] using either gaseous D_2O,[9] D_2,[10] or liquid D_2O in combination with Fe, Co, Ni, Ru, Rh, Pd, Ir, and Pt catalysts.[7] Several examples for deuterations of N-heterocycles were reported utilizing catalytic systems such as Raney nickel,[11] Pd/PVP (poly-*N*-vinylpyrolidone) colloid catalyst systems,[12] Crabtree's catalyst,[13] $NaBD_4$-activated Rh, Pt, or Pd catalysts,[14] Pd or Pt metal surfaces,[15] or CuI.[16] Deuterium incorporation up to 95% was achieved in positions 1 and 3 of indole by heating indoles in D_2O upon repetitive application of the developed deuteration protocol.[17] However, it was not reported how many repetitive cycles had to be applied to reach this high deuterium content.

Published protocols often suffer from certain limitations in order to achieve high degrees of deuteration: (i) a large excess of the deuteration reagent is required (>50 equiv);[11−13] (ii) basic or acidic additives are needed;[16] (iii) long reaction times are required;[11,14] (iv) high catalyst loadings and/or expensive or difficult to access catalysts are used;[12] (v) there is a narrow substrate scope;[16] and (vi) unselective deuteration leads to different deuteration degrees (DDs) in the different positions.[11,13−15] Hence, a more economic and generally applicable method to obtain deuterated or tritiated N-heterocycles is of high interest. Within this paper, we disclose a protocol which works under neutral conditions, reduces the amount of deuteration reagent required, proceeds relatively fast, and shows high selectivity in most cases. Unfortunately, relatively high catalyst loading (of a commercially available catalyst) and elevated temperatures (115 °C) are still required.

Based on a recent report indicating the capability of $Ru_3(CO)_{12}$ to insert into pyridine C−H bonds even though in an unselective manner,[18] we hypothesized that successful H−D exchange could be implemented with this catalyst by concomitantly employing a protic deuterated solvent. Indole and isoquinoline were chosen as first prototype systems for electron-rich and electron-poor heterocycles. Initially, 5 mol % of $Ru_3(CO)_{12}$ and 5 equiv of *t*-BuOD[19] per exchangeable proton were used under argon atmosphere at 115 °C.[20] After 3 h, selective incorporation of deuterium into positions 1 and 3 was observed with a DD of 77% and 80%, respectively (determined via ^1H NMR), an extent very close to the theoretically possible values when employing the specified amount of D source[21] (Table 1, entry 1). Additionally, no side products were observed. Decreasing the reaction temperature led to a lower DD (see the Supporting Information). Other deuterium sources such as D_2O or MeOD led only to trace

Received: January 31, 2012
Published: April 12, 2012

Table 1. Optimization of Deuteration Conditions on Indole and Isoquinoline (Time = 3 h, $Ru_3(CO)_{12}$)

				%D	
entry	equiv per H	cat. (%)	T (°C)	indole	isoquinoline
1	5	5	115	77	80
2	5	2.5	115	76	24
3	1.25	5	115	52	30
4	2.5	5	115	63	60
5	3.75	5	115	71	73
6	10	5	115	83	85

amounts of deuterated products with indole as well as with isoquinoline as substrate.

Lowering the catalyst loading to 1 mol % did not affect the DD on indole; with this substrate, a DD of 37% was obtained even without catalyst (data not shown). In the isoquinoline series, deuteration was significantly more susceptible to changes of catalyst loading: 2.5 mol % gave only 24% of deuterated isoquinoline (entry 2). In general, the best results were obtained when 5 mol % of catalyst was applied. In addition, the amount of deuteration reagent was optimized. Increasing the amount to 10 equiv of *t*-BuOD led to 85% deuteration on isoquinoline and 83% on indole (entry 6). Further lowering the amount of the deuterium source (entries 3−5) expectedly led to lower DDs; however, in all cases, the observed deuterium incorporation was close to the theoretically possible values.[21] For subsequent reactions, 5 equiv of *t*-BuOD was as a compromise between high deuterium incorporation and economics.

The results of the substrate scope investigation are summarized in Table 2. A reaction time of 30 min turned out to be sufficient for indole and isoquinoline; however, deuteration of substituted derivatives required longer times (up to 3 h). Products were obtained in quantitative isolated yield after purification in all cases (Table 2).

In the case of indoles (compounds **1**−**8**), 7-azaindole (compound **9**) and deazapurine (compound **10**) H−D exchange takes place in β-position to the ring nitrogen, representing the most electron-rich site. In the case of benzimidazole, deuteration commences at position 2 (compound **11**). Introduction of methyl substituents into indoles in positions 1 (compound **7**) and 2 (compound **8**) led to lower DDs. In the case of nitroindoles (5- and 7-nitroindole), decomposition and formation of a black tar was observed, and no deuterated products were isolated. An additional N-atom in the ring system had no significant effect on deuterium incorporation (compounds **9** and **10**).

The deuteration of electron-poor compounds (compounds **12**−**17**) generally occurs in the α-position to the nitrogen atom, again representing the most electron-rich site. Best results were obtained on isoquinoline and pyridine (compounds **12** and **15**). 4-Aminopyridine showed significantly lower D-incorporation, possibly due to the free amino group competing with the ring nitrogen for complexation of the catalyst (compound **14**). Introducing a methyl group (3-methylisoquinoline) led again to a lower DD (compound **16**). In this case, the steric bulk of the methyl group might disfavor Ru−N complexation. Interestingly, other N-heterocycles such as pyrimidine, pyrazole, pyridazine, and pyrrole were not deuterated at all under these conditions. As expected, (benzo)thiophene and (benzo)furan were not substrates for this protocol.

The outlined deuteration protocol can be carried out in repetitive cycles in order to reach higher DDs. After the first deuteration reaction, the deuteration reagent was removed, and fresh *t*-BuOD and catalyst were added. Simple exchange of the deuterium source for fresh material did not improve deuteration grades, indicating catalyst inactivation after a reaction cycle. The theoretical DD is 96.8% for a two-cycle process with 5 equiv of *t*-BuOD in each cycle.[21] This is significantly higher compared to a single-step process using 10 equiv of deuteration reagent where a maximum of 90.9% DD can be obtained. Two examples of this protocol were performed (Table 2, compounds **1** and **15**, conditions B). A D-incorporation of 90% (indole) and 93% (isoquinoline) was observed, closely approaching the theoretical value.

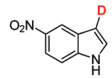
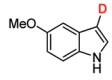
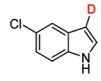
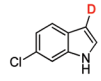
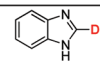
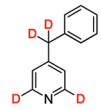
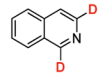
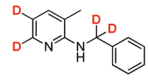
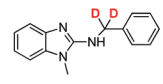
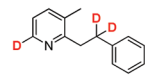
In an attempt to expand the methodology to aliphatic carbon centers, we found that benzylic positions attached to an N-heterocycle could be deuterated with high DDs (compounds **17**−**19**) under slightly altered reaction conditions. The capability of such systems to form a 5-membered metallacycle intermediate after C−H activation was a critical requirement (Scheme 1, lower part). In compounds **17** and **19**, an exchangeable pyridine position was present which was also deuterated, but to a lesser extent compared to the benzylic positions. This shows that on the investigated substrates aliphatic C−H activation is preferred over aromatic (pyridine) C−H activation. Interestingly, the 5-position on the pyridine ring was also deuterated in compound **17**, even to a higher extent (51%) than the 6-position (22%), which was not observed with any other pyridine derivatives.

Reactions were also carried out under microwave irradiation (Table 2, conditions C). An excess of 10 equiv of *t*-BuOD per deuteration position was identified as optimum for the microwave-assisted protocol (see the Supporting Information for details). Interestingly, electron-deficient compounds could not be deuterated efficiently under these conditions even after extensive optimization efforts (e.g., conditions C compound **15**). The reason for the failure in these cases remains unclear. In contrast, deuteration of electron-rich substrates proceeded very well, and reaction times could be shortened to 15 min. With the shorter microwave protocol, 5-nitroindole could be deuterated with 45% DD, but only 25% of product was obtained due to decomposition which required purification of the crude material by column chromatography. Still, under conventional heating this product was not obtained at all. For benzimidazole, a decreased DD of 40% was obtained, and with 6-Cl-7-deazapurine no H−D exchange was observed at all, even after 1 h in the microwave. These two substrates and the deuterated electron-deficient compounds can be obtained using the protocol where conventional heating is applied.

Finally, we investigated the possibility of using the presented methodology for tritiation reactions based on the high importance of radiolabeled compounds for medicinal applications.[5,6] For that purpose, it is necessary to enable access to *t*-BuOT. According to literature reports, CF_3COOT was employed in the synthesis of chiral methyl groups.[5c] We hypothesized that CF_3COOT would react with *t*-BuONa leading to the more stable salts CF_3COONa and *t*-BuOT. As proof of principle, the corresponding reaction using commercially available CF_3COOD instead of CF_3COOT was carried out, and *t*-BuOD was formed successfully in a high DD. The so formed *t*-BuOD was successfully applied in our deuteration protocol (for details, see the Supporting Information). Since the corresponding reaction works analogously using tritium

dx.doi.org/10.1021/jo300219v | J. Org. Chem. 2012, 77, 4432−4437

Table 2. Substrate Scope of Deuterated Heterocycles

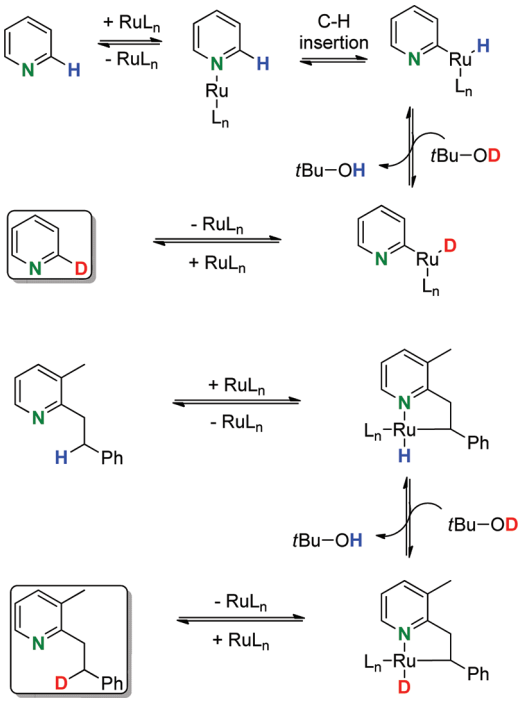
Compound	Product	Method and %DD
1[e]		A[a] 77 B[b] 90 C[c] 88
2[e]		A 0 C 45
3[e]		A 50 C 84
4[e]		A 69 C 85
5[e]		A 77 C 87
6[e]		A 77 C 86
7		A 66 C 85
8[e]		A 50 C 70
9[e]		A 70 C 80
10[e]		A 78 C 0
11[e]		A 71 C 40
12		A 79
13		A 50 (Pyr) 84 (Bn) C 0
14[e]		A 50 C 0
15		A 80 B 93 C 30(1), 20(3)
16		A 58 C 0
17[e]		D[d] 51 (Pyr-5) 22 (Pyr-6) 89 (Bn)
18[e]		D 88
19		D 42 (Pyr) 87 (CH_2)

dx.doi.org/10.1021/jo300219v | J. Org. Chem. 2012, 77, 4432−4437

Table 2. continued

[a]Method A: batch, T = 115 °C, time = 3 h, *t*-BuOD = 5 equiv/deuteration position, $Ru_3(CO)_{12}$ = 5 mol %. [b]Method B: application of two cycles of method A. [c]Method C: microwave irradiation, T = 115 °C, time = 15 min, *t*-BuOD = 10 equiv/deuteration position, $Ru_3(CO)_{12}$ = 5 mol %. [d]Method D: batch, T = 140 °C, time = 24 h, *t*-BuOD = 5 equiv/deuteration position, $Ru_3(CO)_{12}$ = 5 mol %. [e]Initially, the NH in these compounds are exchanged for ND. However, in presence of small amounts of water (e.g., water in the NMR solvent) re-exchange to NH occurs.

Scheme 1. Proposed Mechanism



instead of deuterium, this demonstrates the principal feasibility of tritiation reactions.

A plausible mechanism of the deuteration process is displayed in Scheme 1 for a pyridine deuteration (upper part) as well as for the deuteration of an aliphatic position (lower part). Initially, the catalyst is coordinated by the pyridine nitrogen in both cases, which was already reported previously in the literature.[22] With pyridines as substrate, the metal insertion takes place in the closest C–H bond, which is located in position 2 since there is no possibility for the formation of a usually favored 5-membered ruthenacycle. For the aliphatic substrate in the lower part of Scheme 1, the insertion takes place in the benzylic position giving rise to a favorable 5-membered ruthenacycle.[30] Then hydrogen is exchanged for deuterium originating from the solvent (eventually via reversible HD formation and alkoxide coordination). Finally, reductive elimination leads to the deuterated target compound. All of the steps are reversible, and an equilibrium of deuterated and nondeuterated compounds is established.

In case of indole substrates, a different mechanism must be operable since initial N-coordination of catalyst should rather lead to insertion into the C2 C–H bond. However, insertion takes obviously place in position 3. At this moment, we cannot explain this unusual selectivity. Further mechanistic studies will be carried out to elucidate this mechanism.

In conclusion, we have developed a protocol for selective Ru(0)-catalyzed deuteration of both electron-rich and electron-deficient N-heteroarenes as well as benzylic CH_2 groups under conventional heating; in addition, a very effective microwave-promoted protocol for electron-rich N-heterocycles was also elaborated. DDs of above 80% could often be achieved within 15 min employing only 5 or 10 equiv of *t*-BuOD as deuterium source. Additionally, it was demonstrated that DDs above 90% can be achieved by repeating the deuteration step. In principal, the presented methodology can also be extended to the corresponding tritiation reactions, which is important for the synthesis of radiolabeled compounds for medicinal applications.

EXPERIMENTAL SECTION

Deuteration on sp^2-Systems. General Procedure for the Preparation of Deuterated Compounds in Batch. Heteroarene (0.5 mmol), $Ru_3(CO)_{12}$ (16 mg, 0.025 mmol), and *t*-BuOD (5 equiv/deuteration position) were added to a reaction vial with a screw cap septum. The vial was flushed with argon several times. The reaction mixture was then heated to 115 °C and stirred at this temperature for 3 h. After the mixture was cooled to rt, 10 mL of *n*-hexane was added, and the resulting solvent mixture was evaporated (azeotropic distillation of *t*-BuOH/*n*-hexane). Deuteration degrees were determined via ^{1}H NMR.

In the case where multiple cycles were applied, the same amounts of $Ru_3(CO)_{12}$ and *t*-BuOD were added after the evaporation step again, and the reaction was repeated.

Because of the existence of several isotopomers by incomplete deuteration and their interactions, signals in ^{13}C spectra can split or decrease in intensity. Since the assignment of the split signals to the corresponding isotopomers is not trivial, only the chemical shift of the most intense signal is reported, and these signals are marked with an asterisk.

1,3-Dideutero-6-chloro-7-deazapurine (**10**): prepared via conventional heating; amount of *t*-BuOD applied: 376 mg, 5 mmol = 5equiv/D-position; ^{1}H NMR (DMSO-d_6) 6.33 (d, J = 3.13 Hz), 7.42 (s), 8.34 (s), 12.31 (s); ^{13}C NMR (DMSO-d_6): 99.7*, 117.5*, 129.2*, 151.2, 151.4*, 152.7.

1,2-Dideuterobenzimidazole (**11**):[23] prepared via conventional heating; amount of *t*-BuOD applied: 376 mg, 5 mmol = 5equiv/D-position; ^{1}H NMR (DMSO-d_6): 7.11–7.28 (m), 7.52–7.66 (m), 8.27 (s); ^{13}C NMR (DMSO-d_6): 116.0, 122.7, 142.9*.

1,2-Dideuteropyridine (**12**):[24] prepared via conventional heating; amount of *t*-BuOD applied: 376 mg, 5 mmol = 5 equiv/D-position; ^{1}H NMR ($CDCl_3$): 7.07 (d, J = 7.63 Hz), 7.46 (t, J = 7.63 Hz) 8.29–8.36 (m).

4-(Dideutero(phenyl)methyl)-1,5-dideuteropyridine (**13**):[15] prepared via conventional heating; amount of *t*-BuOD applied: 376 mg, 5 mmol = 5 equiv/D-position; ^{1}H NMR (DMSO-d_6): 4.00 (s), 6.89–8.00 (m), 8.65–8.99 (m); ^{13}C NMR (DMSO-d_6): 125.0, 127.3, 129.5, 129.8, 140.4, 150.5*.

4-N,N-Dideuteroamino-1,5-dideuteropyridine (**14**): prepared via conventional heating; amount of *t*-BuOD applied: 752 mg, 10 mmol, 5 equiv/D-position; ^{1}H NMR (DMSO-d_6) 6.03 (s), 6.49 (s), 8.00 (d, J = 5.48 Hz); ^{13}C NMR (DMSO-d_6): 110.3, 153.0, 156.0.

1,3-Dideuteroisoquinoline (**15**):[15] prepared via conventional heating using two subsequent steps; amount of *t*-BuOD applied: 2 × 376 mg, 5 mmol, 5 equiv/D-position; purification via column chromatography (PE:EtOAc 10:1) ^{1}H NMR ($CDCl_3$) 7.38–8.18 (m), 8.53 (d, J = 5.67 Hz), 9.22–9.29 (m); ^{13}C NMR ($CDCl_3$): 120.6, 126.2, 126.7*, 127.7*, 128.9, 130.6*, 136.1, 143.3, 152.8.

1-Deutero-3-methylisoquinoline (**16**): prepared via conventional heating; amount of *t*-BuOD applied: 188 mg, 2.5 mmol, = 5 equiv/D-position; ^{1}H NMR ($CDCl_3$) 2.69 (s), 7.41–7.56 (m), 7.89 (d, J = 8.02 Hz), 9.15 (s); ^{13}C NMR ($CDCl_3$): 24.4, 118.6, 126.1, 126.4, 127.0, 127.6, 130.4, 136.7, 151.8, 152.1.

dx.doi.org/10.1021/jo300219v | J. Org. Chem. 2012, 77, 4432–4437

General Procedure for the Preparation of Deuterated Compounds in the Microwave. Heteroarene (0.5 mmol), $Ru_3(CO)_{12}$ (16 mg, 0.025 mmol), and *t*-BuOD (10 equiv/deuteration position) were added to a microwave vial. The vial was sealed and subsequently flushed with argon. The reaction mixture was then heated in a Biotage Initiator Sixty microwave to 115 °C for 15 min. The temperature was measured by an external IR-sensor. After the mixture was cooled to rt, 10 mL of *n*-hexane was added (azeotropic distillation of *t*-BuOH/*n*-hexane), and the resulting solvent mixture was evaporated. Deuteration degrees were determined via ^{1}H NMR.

*1,3-Dideuteroindole (**1**):*[25] prepared via microwave protocol; amount of *t*-BuOD applied 752 mg, 10 mmol = 10 equiv/D-position; ^{1}H NMR ($CDCl_3$) 6.53 (d, J = 2.93 Hz), 7.01−7.36 (m), 7.57−7.70 (m); deuterium NMR ($CHCl_3$) 6.53 (s), 8.16 (s); ^{13}C NMR ($CDCl_3$) 102.9*, 111.4*, 120.1, 121.0*, 122.2, 124.3*, 128.0*, 136.0*.

*1,3-Dideutero-5-nitroindole (**2**):* prepared via microwave protocol; amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv/D-position; ^{1}H NMR ($CDCl_3$) 6.69−6.79 (m), 7.31−7.52 (m), 8.12 (dd, J = 9.00 Hz, J = 2.35 Hz), 8.62 (d, J = 2.15 Hz); ^{13}C NMR ($CDCl_3$): 105.5*, 111.4, 118.1, 118.4*, 127.6, 127.7*, 139.1, 142.3*.

*1,3-Dideutero-5-methoxyindole (**3**):* prepared via microwave protocol; amount of *t*-BuOD applied: 752 mg, 10 mmol = 10equiv/D-position; ^{1}H NMR ($CDCl_3$) 3.99 (s), 6.62 (d, J = 2.54 Hz), 7.01 (dd, J = 8.70 Hz, J = 2.45 Hz), 7.20−7.42 (m), 8.17 (s); ^{13}C NMR ($CDCl_3$) 56.1, 102.4*, 102.5*, 112.1*, 112.5, 125.2*, 128.4*, 131.2*, 154.3.

*1,3-Dideutero-5-chloroindole (**4**):*[26] prepared via microwave protocol; amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv/D-position; purification via column chromatography (PE:EtOAc 5:1); ^{1}H NMR ($CDCl_3$) 6.47 (d, J = 3.13 Hz), 7.06−7.24 (m), 7.61 (d, J = 1.76 Hz), 8.03 (s); ^{13}C NMR ($CDCl_3$): 102.6*, 112.3, 120.3, 122.5, 125.6*, 125.8*, 129.1*, 134.2*

*1,3-Dideutero-6-chloroindole (**5**):* prepared via microwave protocol; amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv/D-position; ^{1}H NMR ($CDCl_3$) 6.56 (d, J = 2.93 Hz), 7.07−7.23 (m), 7.37 (d, J = 1.76 Hz), 7.58 (d, J = 8.41), 8.05 (s); ^{13}C NMR ($CDCl_3$): 103.0*, 111.2*, 120.8*, 121.8, 125.0*, 126.6*, 128.1, 136.4*.

*1,3-Dideutero-7-Chloroindole (**6**):* prepared via microwave protocol; amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv/D-position; purification via column chromatography (PE:EtOAc 5:1); ^{1}H NMR ($CDCl_3$) 6.62 (d, J = 3.13 Hz), 7.01−7.32 (m), 7.23 (d, J = 3.33 Hz), 8.34 (s); ^{13}C NMR ($CDCl_3$): 104.0*, 116.9, 119.6, 120.9, 121.6, 125.0*, 129.5*, 133.4*.

*3-Deutero-1-methylindole (**7**):*[27] prepared via microwave protocol; amount of *t*-BuOD applied: 752 mg, 10 mmol =10 equiv/D-position; ^{1}H NMR ($CDCl_3$) 3.73 (s), 6.44 (d, J = 2.93 Hz), 6.95−7.31 (m), 7.58 (d, J = 7.43 Hz); Deuterium-NMR ($CHCl_3$): 6.44 (s); ^{13}C NMR ($CDCl_3$): 33.1, 101.2, 109.5, 119.5, 121.2, 121.8, 128.8, 129.1*, 137.0.

*1,3-Dideutero-2-methylindole (**8**):*[28] prepared via microwave protocol; amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv/D-position; ^{1}H NMR ($CDCl_3$) 2.44 (s), 6.26 (m), 7.10−7.34 (m), 7.50−7.66 (m); ^{13}C NMR ($CDCl_3$): 14.0, 100.7, 110.5, 119.9, 121.2, 129.4, 135.4, 136.3.

*1,3-Dideutero-7-azaindole (**9**):*[29] prepared via microwave protocol; amount of *t*-BuOD applied: 752 mg, 10 mmol =10 equiv/D-position; purification via column chromatography (PE:EtOAc 10:1); ^{1}H NMR ($CDCl_3$) 6.49 (d, J = 3.52 Hz), 7.01−7.17 (m), 7.38 (s), 7.96 (d, J = 7.83 Hz), 8.35 (d, J = 3.91 Hz), 12.02 (s); ^{13}C NMR ($CDCl_3$): 100.5*, 115.7, 120.6*, 125.4*, 129.1, 142.2, 148.8.

Deuteration on sp^3-Systems. General Procedure. Substrate (0.5 mmol), $Ru_3(CO)_{12}$ (16 mg, 0.025 mmol), and *t*-BuOD (5 equiv/deuteration position) were added to a reaction vial with a screw cap septum. The vial was flushed with argon several times. The reaction mixture was then heated to 140 °C and stirred at this temperature for 24 h. After the mixture was cooled to rt, 10 mL of *n*-hexane was added, and the resulting solvent mixture was evaporated (azeotropic distillation of *t*-BuOH/*n*-hexane). Deuteration degrees were determined via ^{1}H NMR.

*N-(Dideutero(phenyl)methyl)-N,5,6-trideutero-3-methylpyridin-2-amine (**17**):*[30] prepared via conventional heating; amount of *t*-BuOD applied: 940 mg, 12.5 mmol, = 5 equiv/D-position; ^{1}H NMR ($CDCl_3$) 1.96 (s), 4.26 (s), 4.50−4.63 (m), 6.41−6.55 (m), 7.05−7.38 (m), 7.83−8.02 (m); ^{13}C NMR ($CDCl_3$): 17.2, 133.1, 116.7, 127.4, 128.1, 128.8, 137.0*, 140.2, 145.7*, 156.9.

*N-(Dideutero(phenyl)methyl)-N-deutero-1-methyl-1H-benzo[d]-imidazol-2-amine (**18**):*[31] prepared via conventional heating; amount of *t*-BuOD applied; 564 mg, 7.5 mmol, = 5 equiv/D-position; ^{1}H NMR ($CDCl_3$) 3.38 (s), 4.60−4.71 (m), 4.78−4.95 (m), 5.26 (s), 6.82−7.65 (m); ^{13}C NMR ($CDCl_3$): 28.4, 107.3, 116.4, 119.8, 121.4, 127.7, 128.1, 128.8*, 135.3, 138.8*, 142.3, 154.7.

*2-(1,1-Dideutero-2-phenylethyl)-6-deutero-3-methylpyridine (**19**):*[32] prepared via conventional heating; amount of *t*-BuOD applied: 564 mg, 7.5 mmol = 5 equiv/D-position; ^{1}H NMR ($CDCl_3$) 2.46 (s), 3.06 (s), 6.95−7.44 (m), 8.44 (d, J = 3.91 Hz); ^{13}C NMR ($CDCl_3$): 19.0, 35.3*, 121.6*, 126.2, 128.8, 128.9, 131.5, 137.9, 142.3, 147.1*, 159.8.

Synthesis of t-BuOD via CF_3COOD. A mixture of sodium *tert*-butoxide (480 mg, 5 mmol) and CF_3COOD (575 mg, 5 mmol) was stirred at room temperature for 1 h. The product was purified via Kugelrohr distillation and obtained in 31% yield (147 mg).

■ ASSOCIATED CONTENT

Supporting Information

Reaction optimization and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding for this research by the Austrian Science Fund (FWF, project P21202-N17) is gratefully acknowledged

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(20) Equivalents of *t*-BuOD are always calculated as equivalents per exchangeable position. For details, see the Supporting Information.
(21) Theoretically possible DDs: 10 equiv of *t*-BuOD/exchangeable proton = 90.9%, 5 equiv = 83.3%, 3.75 equiv = 78.9%, two cycles 5 equiv each = 96.8%. For calculations, see the Supporting Information.
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