



HAL
open science

Superacid-Mediated Late-Stage Aromatic Polydeuteration of Pharmaceuticals

Emeline Appert, Agnès Martin-Mingot, Omar Karam, Fabien Zunino, Bastien Michelet, Fodil Bouazza, Sébastien Thibaudeau

► **To cite this version:**

Emeline Appert, Agnès Martin-Mingot, Omar Karam, Fabien Zunino, Bastien Michelet, et al.. Superacid-Mediated Late-Stage Aromatic Polydeuteration of Pharmaceuticals. *Chemistry - A European Journal*, 2022, 28 (49), pp.e202201583. 10.1002/chem.202201583 . hal-03769665

HAL Id: hal-03769665

<https://hal.science/hal-03769665>

Submitted on 5 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Superacid-Mediated Late-Stage Aromatic Polydeuteration of Pharmaceuticals

Emeline Appert,^{[a],[b]} Agnès Martin-Mingot,^[a] Omar Karam,^[b] Fabien Zunino,^[b] Bastien Michelet,^{*[a]} Fodil Bouazza^[b] and Sébastien Thibaudeau^{*[a]}

[a] E. Appert, Dr. A. Martin-Mingot, Dr. B. Michelet, Prof. S. Thibaudeau
Superacid Group – Organic Synthesis Team,
IC2MP, Université de Poitiers, UMR-CNRS 7285,
4 rue Michel Brunet, TSA 51106, 86073 Poitiers Cedex 9, France
E-mail: sebastien.thibaudeau@univ-poitiers.fr

[b] Dr. O. Karam, Dr. F. Zunino, Dr. F. Bouazza
@rtMolecule, 1 rue Georges Bonnet, Bâtiment B37, 86000 Poitiers, France

Supporting information for this article is given via a link at the end of the document.

Abstract: The field of medicinal chemistry is currently witnessing a *deuterium rush* owing to the remarkable properties of this element as bioisoster of hydrogen atom. Aromatic hydrogen isotope exchange (HIE) is one of the most studied strategies nowadays as it promises to access deuterium-modified drugs directly from their non-labeled parents. While most of the recent studies focus on metal-catalyzed C–H activation strategy, the use of superacidic conditions has been largely overlooked. Here, we show that the use of TfOD as reaction medium allows the late-stage polydeuteration of a broad library of pharmaceuticals bearing a wide array of functional groups, complementing existing procedures.

Introduction

The applications of deuterium-labeled compounds in the pharmaceutical industry have been growing considerably over the last decades,^[1] especially for their use as stable isotopically-labeled standards for mass spectrometry analyses of biological samples in toxicological and metabolism studies.^[1c,2] Deuterium-modified drugs also benefit from the greater stability of the C–D bond (in particular towards oxidative process) usually improving their pharmacokinetics while retaining biochemical potency and selectivity.^[1a,b] Deuterium isosteric replacement can also have a favorable effect on the reduction of toxicity or on the stereoisomeric stability of pharmaceuticals.^[1a] Since 2017 and the first FDA approval of a D-containing drug (deutetrabenazine),^[1d] deuterium is thus expected to play a major role in the emergence of new drug candidates.^[1a] For all these reasons, the development of new methods to directly insert deuterium atoms into organic molecules with high D-incorporation has recently received a considerable attention.^[3] Amongst them, aromatic hydrogen isotope exchange (HIE) has been particularly investigated owing to the remarkable progress made in the field of metal-catalyzed C(sp²)–H activation over the last two decades.^[3a,3,3] Selective deuteration can be achieved in high yields by using temporary or native directing groups (DGs) but these methods usually fail to incorporate deuterium atoms at distal positions of the DGs and are of limited interest for the preparation of labeled standards with high overall D-content.^[4] Heterogeneous transition metal catalysis allows multisite H/D exchange without the requirement of a dedicated DG but such approaches usually necessitate the use of

harsh reaction conditions which might hamper their application for the labeling of fragile polyfunctionalized molecules.^[3],5] Only recently has the multisite aromatic HIE under heterogeneous^[5h,i] or homogeneous^[6] catalysis been successfully shown as a general method for the labeling of pharmaceuticals. Methods using hydrogen isotop gas are particularly well-suited to mediate late-stage tritiation, affording high specific activities with good radiochemical yields, although the overall rate of HIE remains highly substrate-dependent.^[6a-c] On the other hand, the use of iron or manganese nanoparticles with D₂O under hydrogen pressure allows for the labeling of electron-rich (hetero)arenes with substantially higher degree of deuteration (Figure 1A).^[5h,i] Multisite homogeneous Pd-catalyzed H/D exchange was also successfully achieved via the design of dedicated amide ligands but this method can suffer from low deuterium incorporation at sterically hindered positions or from catalyst poisoning by nitrogen-containing substrates (Figure 1B).^[6d]

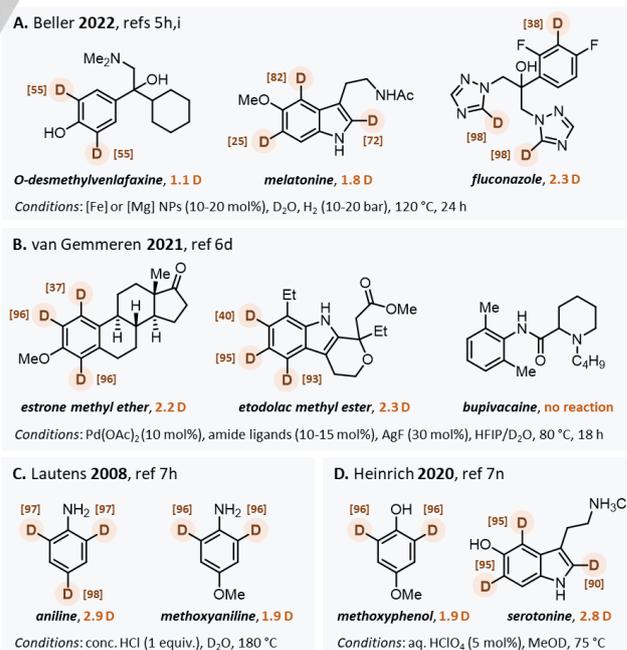


Figure 1. Representative examples of the different strategies recently used for the multisite H/D exchange of arenes.

COMMUNICATION

The main alternative to these C(sp²)–H activation methods mostly rely on acid-mediated S_EAr-type H/D exchange which benefits notably from low sensitivity to steric factors and ease of setup.^[7] However, this approach is mainly restricted to the deuteration of electron-rich positions and is poorly efficient for the labeling of substrates containing several basic functional groups^[7h] (Figures 1C–D). In addition, when deuterated aqueous solutions of mineral acids are used, unwanted hydrolysis of functional groups can occur which could limit their applications for the labeling of elaborated compounds. Our group has recently demonstrated that anhydrous superacids^[8] can be used to characterize long-lived polycationic species derived from polyfunctionalized substrates^[9] and to directly functionalize complex natural alkaloids and steroids,^[10] benefiting from the protection of the functional groups by protonation^[11] and from the spectator role of the weakly-basic counter-anions. A superacid is conventionally defined as being more acidic than pure sulfuric acid,^[8] which can be quantified by using the Hammett acidity function H_0 .^[12] A more practical definition could be its ability to fully protonate low-basic arenes such as toluene, the acidity of toluenium ions lying at the edge of the superacidity border ($H_0 = -12$) (Figure 2).^[13]

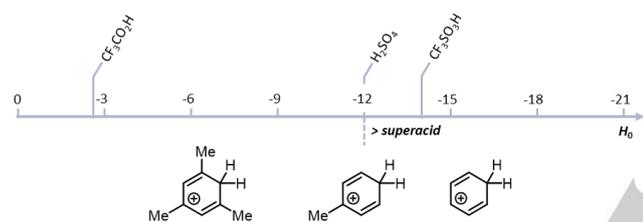


Figure 2. Relative acidities of protonated arenes on the Hammett acidity scale.

This implies that deuterated superacids should act as powerful reagents for aromatic H/D exchange and should be compatible with a broad range of substrate. Very recently, the group of Oestreich has reported a method for aromatic H/D exchange using a superelectrophilic silylium ion catalyst with success on aryl halides.^[14] On the other hand, the use of superacidic media to promote aromatic deuteration is very scarce in the literature and only a handful of substrates were polydeuterated with neat TfOD.^[7i,7j] Herein, we describe the first general study on superacid-mediated polydeuteration of arenes including a broad range of relevant natural compounds and pharmaceuticals, showing the efficiency of superacid-promoted late-stage reactions on classically recalcitrant deactivated aromatic compounds.

Results and Discussion

Aromatic amines being ubiquitous in medicinal chemistry, *N*,3-dimethylacetanilide **1** which displays four aromatic protons with different steric and electronic environment was selected as a model substrate to evaluate our hypothesis (Table 1). With aqueous deuterium chloride solution or deuterated trifluoroacetic acid, no significant deuterium incorporation was observed after 20 hours of reaction at room temperature (Table 1, entries 1–2). While only traces of deuterium were detected in the product using a 74% aqueous solution of D₂SO₄, carrying out the reaction with concentrated D₂SO₄ allows to obtain **1-d** with a moderate degree of deuteration (Table 1, entries 3–4). The poorly nucleophilic position 5 remained however unreactive under these conditions. Switching to deuterated trifluoromethanesulfonic acid (TfOD),

compound **1-d** was isolated with a good deuterium incorporation (Table 1, entry 5). More importantly, 12% deuteration was observed in position 5 demonstrating the superior activity of TfOD in promoting H/D exchange of unactivated C–H bonds. While the use of stoichiometric amount of main group or transition metal Lewis acids along with TfOD did not prove beneficial to the conversion,^[15] raising the temperature to 80 °C eventually led to the isolation of **1-d** in 86% yield with a good overall D content in all aromatic positions and higher temperature had no major effect on the outcome of the reaction (Table 1, entries 7 and 8).

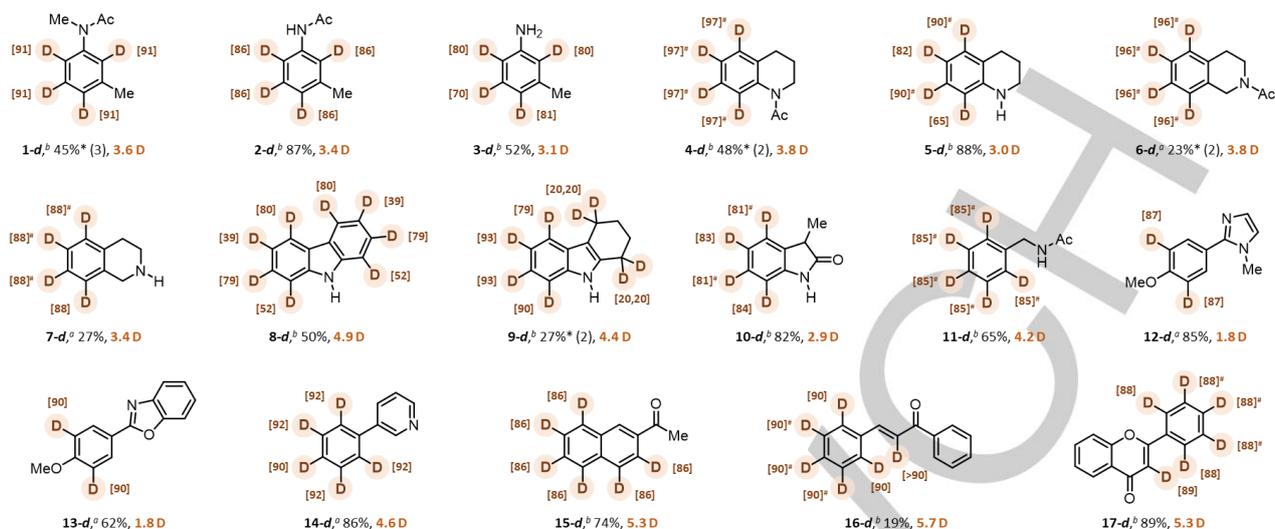
Table 1. Preliminary studies on acid-mediated C–H deuteration of *N*,3-dimethylacetanilide **1**.

| Entry | Acid- <i>d</i> (H_0) | T (°C) | Yield (%) ^[a] | D content (%) ^[b] | | | | Total D content ^[d] |
|-------|---|----------|--------------------------|------------------------------|----|----|----|--------------------------------|
| | | | | 2 | 4 | 5 | 6 | |
| 1 | DCl 20% (-2.2) ^[d] | 20 | 99 | - | - | - | - | <0.05 |
| 2 | CF ₃ CO ₂ D (-2.7) ^[e] | 20 | 91 | - | - | - | - | <0.05 |
| 3 | D ₂ SO ₄ 74% (-6.4) ^[f] | 20 | 78 | <5 | 7 | <5 | - | 0.2 |
| 4 | D ₂ SO ₄ 98% (-10.4) ^[f] | 20 | 96 | 15 | 52 | <5 | 5 | 0.8 |
| 5 | CF ₃ SO ₃ D (-13.7) ^[e] | 20 | 89 | 80 | 90 | 12 | 77 | 2.7 |
| 6 | CF ₃ SO ₃ D (-13.7) ^[e] | 40 | 91 | 86 | 87 | 35 | 86 | 2.9 |
| 7 | CF ₃ SO ₃ D (-13.7) ^[e] | 80 | 86 | 83 | 85 | 86 | 83 | 3.4 |
| 8 | CF ₃ SO ₃ D (-13.7) ^[e] | 120 | 83 | 85 | 86 | 86 | 84 | 3.4 |

[a] Yield of the isolated product. [b] Estimated by ¹H-NMR analysis. [c] Determined by HRMS analysis of the pure product. [d] From ref. 12b. [e] From ref. 12c. [f] From ref. 12d.

We next moved to the study of the scope and limitations of this superacid-mediated aromatic H/D exchange starting with the screening of model arenes exhibiting scaffolds frequently encountered in drugs (Figure 3, top).^[16] We first focused on aromatic amines owing to the lack of general and efficient methods for their labeling despite their importance in pharmacology.^[4ac,5h-i,6c,7h,17] Following the optimized procedure, aniline **1-d** was obtained with 91% deuterium incorporation in all four exchangeable positions after three runs in TfOD at 80 °C. Under similar conditions, acetanilide **2** and aniline **3** were efficiently converted to their deuterated analogues **2-d** and **3-d**, demonstrating the applicability of the method to free anilines. Tetrahydroquinolines and tetrahydroisoquinolines **4–7** were also smoothly polydeuterated, competing nicely with the most recent procedure employing heterogeneous catalysis,^[5h-i] although greater yields and D-incorporation were obtained when the amine was protected with an acetyl group. This might be explained by the in-situ formation of a strongly electron-withdrawing ammonium moiety from the free amine which decreases the nucleophilicity of the aromatic ring.

Reaction scope on model arenes



Reaction scope on bioactive compounds

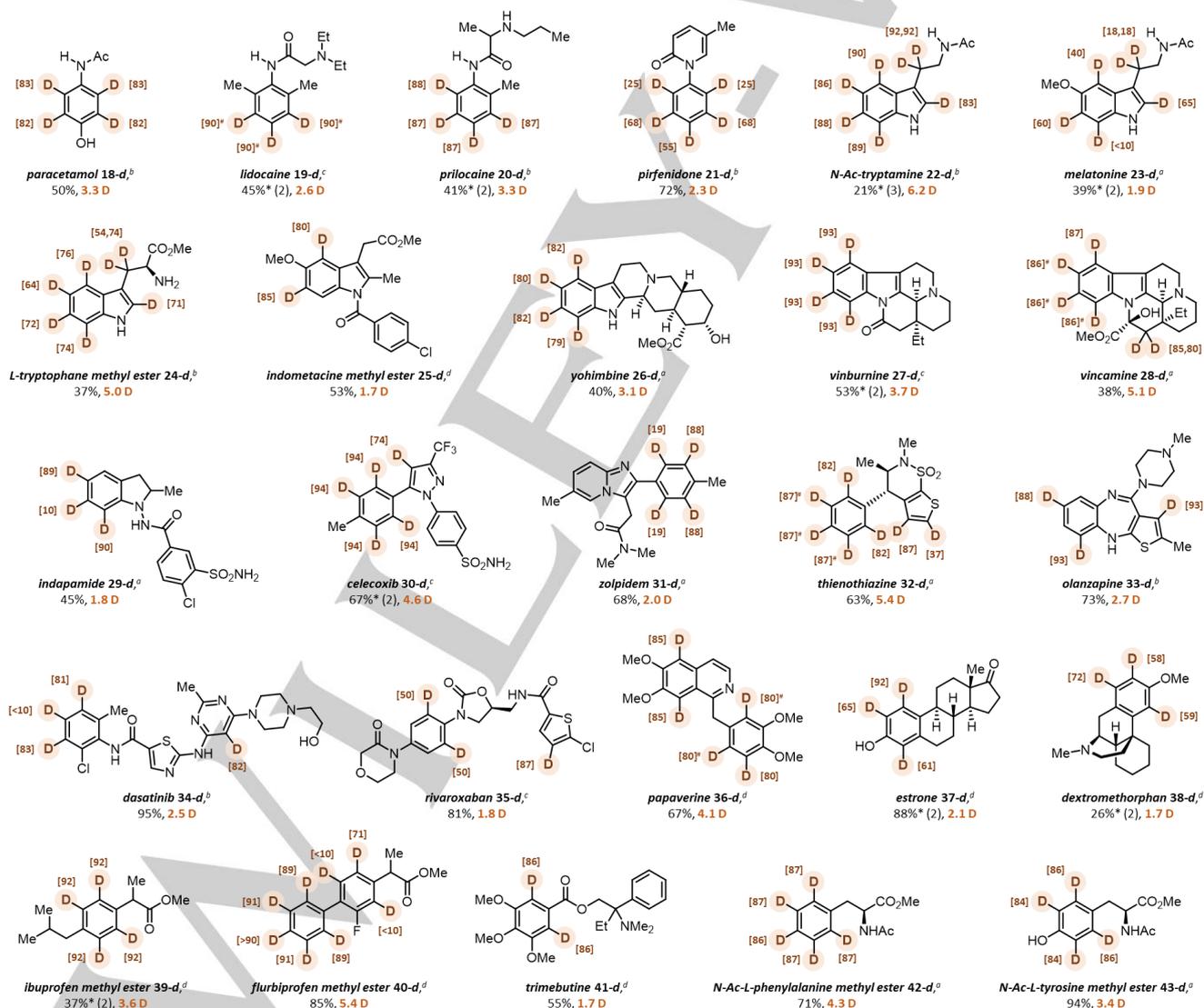


Figure 3. Scope of the superacid-mediated polydeuteriation of arenes. Isolated yields. * Successive runs were performed: the yield correspond to the overall yield (number of iterations indicated in parenthesis). The %D incorporation (in brackets) on each position was estimated by ¹H-NMR analysis and the overall D incorporation was determined by HRMS analysis of the pure product. # Indistinguishable by ¹H-NMR: the %D incorporation is an average value of the marked positions. Reaction conditions: neat TfOD (12 equiv. per aromatic C–H bond), ^a 20 °C, 20 h; ^b 80 °C, 20 h; ^c 80 °C, 40 h; ^d –20 °C, 20 h.

COMMUNICATION

Free carbazole 8-*d* and tetrahydrocarbazole 9-*d* could nevertheless be obtained with high overall D-incorporation, also with deuteration in activated aliphatic position for the latter. Oxindole 10 and benzylamide 11 were deuterated evenly on every aromatic positions with high efficiency. This method also tolerates the presence of heteroaromatic pharmacophores as exemplified by the partial deuteration of compounds 12-14. Phenylpyridine 14-*d* illustrates well the complementarity of this method to recent C–H activation procedures which are more selective of the pyridyl moiety.^[6b,6c] Nitrogen-free aromatic drug precursors also readily undergo H/D exchange with TfOD as shown by the isolation of acetonephthone 15-*d*, chalcone 16-*d* and flavone 17-*d* with very high overall D-content. For the latter two compounds, it is worth noting that the challenging α,β -unsaturated ketone function was also deuterated in each case, highlighting the potency of this superacid-mediated procedure. We next moved to the evaluation of our method for the late-stage polydeuteration of bioactive molecules including synthetic drugs and natural products (Figure 3, bottom). As expected, anilides 18-21 were converted to their deuterated analogues with good to excellent efficiency. The common indole residue^[16] found at the core structure of tryptamine 22, melatonin 23, tryptophane 24, indometacine 25 and vinca alkaloids 26-28 was labeled on every free aromatic positions unless it was substituted by a methoxy group on C5 as in 23 and 25 for which the inactivated C7–H bond remained untouched. These results are yet in striking contrast to those obtained from recent C–H activation procedures on similar substrates which hardly allow to exchange more than two aromatic C–H bonds.^[5h,6c] Interestingly, in the case of tryptamine derivatives 22-24, the indolylic protons were also substituted by deuterons suggesting that the C3-carbocation generated upon C2-protonation is in equilibrium with the formation of an exocyclic double bond under these conditions. The lower rate of HIE for melatonin 23 is a result of the softer conditions used in this case, extensive degradation being observed at higher temperature. Also, the 80% methylenic deuteration obtained for vincamine 28-*d* indicates that the hemiaminal function most likely undergoes dehydration under these acidic conditions, resulting in an iminium/enamine equilibrium which converts back to vincamine upon aqueous work-up. Interestingly, indapamide 29 which displays a sensitive hydrazide function was well tolerated under these conditions affording analogue 29-*d*. This method can also be applied to a broad range of heteroaromatic-containing active ingredients as illustrated by the isolation of celecoxib 30-*d*, zolpidem 31-*d*, thienothiazine 32-*d*,^[18] olanzapine 33-*d*, dasatinib 34-*d*, rivaroxaban 35-*d* and papaverine 36-*d*. To complete the scope of this study, a selection of bioactive molecules composed of electron-rich arenes were subjected to this superacid-mediated H/D exchange including estrone 37, dextromethorphan 38, ibuprofen and flurbiprofen derivatives 39-40, trimebutine 41 and amino acid derivatives 42-43. They all tolerated the superacidic conditions and yielded the corresponding deuterated analogues with moderate to good overall D-content even at low temperature. Unexpectedly, the benzylamine subunit of trimebutine 41 did not undergo H/D exchange but this might be explained by the low temperature necessary to avoid degradation of the molecule and by the in situ formation of an ammonium at proximity of the phenyl moiety disfavoring the generation of a cationic charge within the benzene ring. This scope study demonstrates the large functional group compatibility of this procedure despite the superacidic

nature of TfOD. Moreover, this method is technically very simple as it is solvent, catalyst and additive free.

An eventual limitation could be that TfOD – whose commercial availability varies over time – is a relatively expensive source of deuterium that would hamper its applicability on larger scale.^[3a] To address this issue, we designed an alternative procedure^[19] to prepare in situ TfOD directly from D₂O, one of the cheapest and most convenient sources of deuterium. After reacting an equimolar mixture of D₂O and triflic anhydride for three hours at 80 °C, the reaction was conducted as before. This new procedure was evaluated on a selection of eight molecules requiring various reaction temperatures for efficient labeling and afforded the corresponding labeled molecules with consistent degrees of deuteration (Figure 4). In particular, this one-pot protocol could be applied to the gram-scale labeling of vinburnine to furnish 0.82 g of 27-*d* using only 1.5 mL of D₂O.

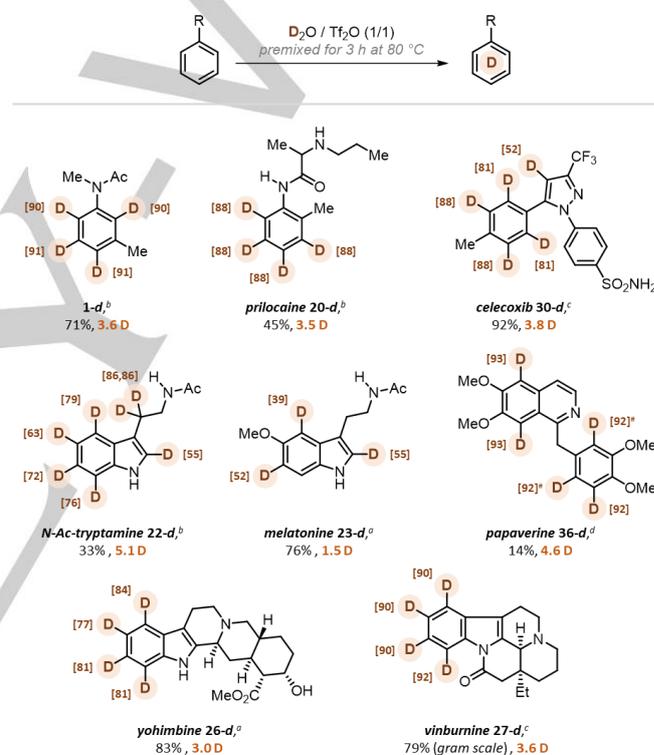


Figure 4. Scope of deuterated arenes using *in situ* prepared TfOD. The %D incorporation (in brackets) on each position was estimated by ¹H-NMR analysis and the overall D incorporation was determined by HRMS analysis of the pure product. # Indistinguishable by ¹H-NMR: the %D incorporation is an average value of the marked positions. Reaction conditions: Tf₂O:D₂O 1:1 (12 equiv. TfOD per aromatic C–H bond), 80 °C, 3 h followed by addition of substrate and then ^a 20 °C, 20 h; ^b 80 °C, 20 h; ^c 80 °C, 40 h; ^d -20 °C, 20 h.

Conclusion

In summary, previously used with great success in organic synthesis, superacid activation has been underestimated as an efficient tool to perform late-stage H/D exchange on elaborated compounds. This strategy allows to insert deuterium atoms in positions that are hard to reach by other strategies. This easy-to-setup procedure could be considered as a useful method for the preparation of high D-content bioactive compounds. From a more fundamental perspective, we believe that this study will pave the way for the emergence of new superacid-oriented strategies for

late-stage functionalization in the growing field of superacid catalysis.^[20,21]

Experimental Section

TfOD-mediated aromatic polydeuteration (Figure 3): the arene 1-43 (1 equiv.) was added to TfOD (12 equiv. per aromatic C-H bond) at 0 °C (unless stated otherwise, see SI) in an Ace pressure tube. The tube was sealed with a Teflon screw cap and the resulting mixture was then stirred at the appropriate temperature for the indicated time. The mixture was then hydrolyzed on ice and neutralized with a saturated aq. solution of Na₂CO₃. The aqueous phase was extracted thrice with DCM or EtOAc. The combined organic layers were dried over MgSO₄, filtrated and concentrated under reduced pressure. The crude residue was purified by flash column chromatography.

Aromatic polydeuteration using *in situ* prepared TfOD (Figure 4): D₂O (6 equiv. per aromatic C-H bond) was added to Tf₂O (6 equiv. per aromatic C-H bond) at 0 °C under argon in an Ace pressure tube. The resulting mixture was stirred at 80 °C for 3 h. The arene was added at 0 °C (unless stated otherwise, see SI). The resulting mixture was then stirred at the appropriate temperature for the indicated time. The mixture was then hydrolyzed on ice and neutralized with a saturated aq. solution of Na₂CO₃. The aqueous phase was extracted thrice with DCM or EtOAc. The combined organic layers were dried over MgSO₄, filtrated and concentrated under reduced pressure. The crude residue was purified by flash column chromatography.

Acknowledgements

E. Appert thanks ANRT and @rtMolecule society for a PhD grant. A. Martin-Mingot, B. Michelet and S. Thibaudeau thank the University of Poitiers and the CNRS. The authors acknowledge the financial support from Région Nouvelle Aquitaine (Isotop project). The authors also thank the French fluorine network (GIS-FLUOR).

Keywords: Alkaloids • Deuterium • Isotop labeling • Late-stage functionalization • Superacid

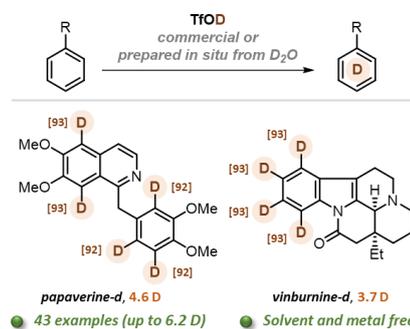
- [1] For selected reviews, see: a) T. Pirali, M. Serafini, S. Cargnin, A. A. Genazzani, *J. Med. Chem.* **2019**, *62*, 5276–5297; b) S. Cargnin, M. Serafini, T. Pirali, *Future Med. Chem.* **2019**, *11*, 2039–2042; c) J. Atzrodt, V. Deraud, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2017**, *57*, 1758–1784; d) C. Schmidt, *Nat. Biotechnol.* **2017**, *35*, 493–494; e) T. G. Gant, *J. Med. Chem.* **2014**, *57*, 3595–3611.
- [2] J. Atzrodt, V. Deraud, *J. Label. Compd. Radiopharm.* **2010**, *53*, 674–685.
- [3] For selected reviews, see: a) S. Kopf, F. Bourriquen, W. Li, H. Neumann, K. Junge, M. Beller, *Chem. Rev.* **2022**, *122*, 6634–6718; b) Q.-K. Kang, H. Shi, *Synlett* **2021**, *32*, A–J; c) R. Zhou, L. Ma, X. Yang, J. Cao, *Org. Chem. Front.* **2021**, *8*, 426–444; d) P. Ranjan, S. Pillitteri, E. V. Van der Eycken, U. K. Sharma, *Green Chem.* **2020**, *22*, 7725–7736; e) H. Yang, D. Hesk, *J. Label. Compd. Radiopharm.* **2020**, *63*, 296–307; f) W. J. Kerr, G. J. Knox, L. C. Paterson, *J. Label. Compd. Radiopharm.* **2020**, *63*, 281–295; g) M. Valero, V. Deraud, *J. Label. Compd. Radiopharm.* **2020**, *63*, 266–280; h) D. Hesk, *J. Label. Compd. Radiopharm.* **2020**, *63*, 247–265; i) Y. Sawama, K. Park, T. Yamada, H. Sajiki, *Chem. Pharm. Bull.* **2018**, *66*, 21–28; j) J. Atzrodt, V. Deraud, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 3022–3047; k) D. Munz, M. Webster-Gardiner, R. Fu, T. Strassner, W. A. Goddard III, T. B. Gunnoe, *ACS Catal.* **2015**,

5, 769–775; l) J. Atzrodt, V. Deraud, T. Frey, J. Zimmermann, *Angew. Chem. Int. Ed.* **2007**, *46*, 7744–7765; m) T. Junk, W. J. Catalo, *Chem. Soc. Rev.* **1997**, *26*, 401–406.

- [4] For representative examples of directing-group oriented aromatic H/D exchange including pharmaceuticals, see: a) D. Hesk, P. R. Das, B. Evans, *J. Label. Compd. Radiopharm.* **1995**, *36*, 497–502; b) A. R. Kennedy, W. J. Kerr, R. Moir, M. Reid, *Org. Biomol. Chem.* **2014**, *12*, 7927–7931; c) A. R. Cochrane, C. Idziak, W. J. Kerr, B. Mondal, L. C. Paterson, T. Tuttle, S. Andersson, G. N. Nilsson, *Org. Biomol. Chem.* **2014**, *12*, 3598–3603; d) G. Pieters, C. Taglang, E. Bonnefille, T. Gutmann, C. Puente, J.-C. Berthet, C. Dugave, B. Chaudret, B. Rousseau, *Angew. Chem. Int. Ed.* **2014**, *53*, 230–234; e) L. Piola, J. A. Fernández-Salas, S. Manzinia, S. P. Nolan, *Org. Biomol. Chem.* **2014**, *12*, 8683–8688; f) J. A. Brown, A. R. Cochrane, S. Irvine, W. J. Kerr, B. Mondal, J. A. Parkinson, L. C. Paterson, M. Reid, T. Tuttle, S. Andersson, G. N. Nilsson, *Adv. Synth. Catal.* **2014**, *356*, 3551–3562; g) A. Modvig, T. L. Andersen, R. H. Taaning, A. T. Lindhardt, T. Skrydstrup, *J. Org. Chem.* **2014**, *79*, 5861–5868; h) J. Atzrodt, V. Deraud, W. J. Kerr, M. Reid, P. Rojahn, R. Weck, *Tetrahedron* **2015**, *71*, 1924–1929; i) R. Giles, G. Ahn, K. W. Jung, *Tetrahedron Lett.* **2015**, *56*, 6231–6235; j) W. J. Kerr, M. Reid, T. Tuttle, *ACS Catal.* **2015**, *5*, 402–410; k) P. W. Cross, J. M. Herbert, W. J. Kerr, A. H. McNeill, L. C. Paterson, *Synlett* **2016**, *27*, 111–115; l) W. J. Kerr, R. J. Mudd, P. K. Owens, M. Reid, J. A. Brown, S. Campos, *J. Label. Compd. Radiopharm.* **2016**, *59*, 601–603; m) W. J. Kerr, D. M. Lindsay, M. Reid, J. Atzrodt, V. Deraud, P. Rojahn, R. Weck, *Chem. Commun.* **2016**, *52*, 6669–6672; n) K. Jess, V. Deraud, R. Weck, J. Atzrodt, M. Freytag, P. G. Jones, M. Tamm, *Adv. Synth. Catal.* **2017**, *359*, 629–638; o) A. Burhop, R. Weck, J. Atzrodt, V. Deraud, *Org. Chem.* **2017**, *1418–1424*; p) W. J. Kerr, D. M. Lindsay, P. K. Owens, M. Reid, T. Tuttle, S. Campos, *ACS Catal.* **2017**, *7*, 7182–7186; q) H. Yang, C. Zarate, W. N. Palmer, N. Rivera, D. Hesk, P. J. Chirik, *ACS Catal.* **2018**, *8*, 10210–10218; r) E.-C. Li, G.-Qi Hu, Y.-X. Zhu, H.-H. Zhang, K. Shen, X.-C. Hang, C. Zhang, W. Huang, *Org. Lett.* **2019**, *21*, 6745–6749; s) M. Valero, A. Mishra, J. Blass, R. Weck, V. Deraud, *ChemistryOpen* **2019**, *8*, 1183–1189; t) M. Valero, D. Becker, K. Jess, R. Weck, J. Atzrodt, T. Bannenberg, V. Deraud, M. Tamm, *Chem. Eur. J.* **2019**, *25*, 6517–6522; u) A. Palazzolo, S. Feuillastre, V. Pfeifer, S. Garcia-Argote, D. Bouzouita, S. Tricard, C. Chollet, E. Marcon, D.-A. Buisson, S. Cholet, F. Fenaille, G. Lippens, B. Chaudret, G. Pieters, *Angew. Chem. Int. Ed.* **2019**, *58*, 4891–4895; v) P. Eisele, F. Ullwer, S. Scholz, B. Plietker, *Chem. Eur. J.* **2019**, *25*, 16550–16554; w) S. Bag, M. Petzold, A. Sur, S. Bhowmick, D. B. Werz, D. Maiti, *Chem. Eur. J.* **2019**, *25*, 9433–9437; x) V. Pfeifer, M. Certiat, D. Bouzouita, A. Palazzolo, S. Garcia-Argote, E. Marcon, D.-A. Buisson, P. Lesot, L. Maron, B. Chaudret, S. Tricard, I. del Rosal, R. Poteau, S. Feuillastre, G. Pieters, *Chem. Eur. J.* **2020**, *26*, 4988–4996; y) V. Müller, R. Weck, V. Deraud, L. Ackermann, *ChemCatChem* **2020**, *12*, 100–104; z) G.-Qi Hu, E.-C. Li, H.-H. Zhang, W. Huang, *Org. Biomol. Chem.* **2020**, *18*, 6627–6633; aa) M. Valero, T. Kruissink, J. Blass, R. Weck, S. Güssregen, A. T. Plowright, V. Deraud, *Angew. Chem. Int. Ed.* **2020**, *59*, 5626–5631; ab) W. Liu, L. Cao, Z. Zhang, G. Zhang, S. Huang, L. Huang, P. Zhao, X. Yan, *Org. Lett.* **2020**, *22*, 2210–2214; ac) M. Valero, D. Bouzouita, A. Palazzolo, J. Atzrodt, C. Dugave, S. Tricard, S. Feuillastre, G. Pieters, B. Chaudret, V. Deraud, *Angew. Chem. Int. Ed.* **2020**, *59*, 3517–3522; ad) A. Tlahuext-Aca, J. F. Hartwig, *ACS Catal.* **2021**, *11*, 1119–1127; ae) S. Kopf, F. Ye, H. Neumann, M. Beller, *Chem. Eur. J.* **2021**, *27*, 9768–9773.
- [5] For representative examples of aromatic H/D exchange including pharmaceuticals under heterogeneous catalysis conditions, see: a) H. Sajiki, H. Esaki, F. Aoki, T. Maegawa, K. Hirota, *Synlett* **2005**, *9*, 1385–1388; b) V. Deraud, J. Atzrodt, *Synlett* **2006**, *12*, 1918–1922; c) H. Esaki, F. Aoki, M. Umemura, M. Kato, T. Maegawa, Y. Monguchi, H. Sajiki, *Chem. Eur. J.* **2007**, *13*, 4052–4063; d) N. Ito, H. Esaki, T. Maesawa, E. Imamiya, T. Maegawa, H. Sajiki, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 278–286; e) V. Deraud, J. Atzrodt, J. Zimmermann, C. Kroll, F. Brückner, *Chem. Eur. J.* **2009**, *15*, 10397–10404; f) N. Modutlwa, T. Maegawa, Y. Monguchi, H. Sajiki, *J. Label. Compd. Radiopharm* **2010**, *53*, 686–692; g) H. Shen, Y. Liu, X. Tian, X. Zhang, Y. Zhang, *ChemistrySelect* **2018**, *3*, 8724–8728; h) W. Li, J. Rabeah, F. Bourriquen, D. Yang, C. Kreyenschulte, N. Rockstroh, H. Lund, S. Bartling, A.-E. Surkus, K.

- Junge, A. Brückner, A. Lei, M. Beller, *Nat. Chem.* **2022**, *14*, 334–341; i) F. Bourriquen, N. Rockstroh, S. Bartling, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2022**, *59*, 21114–21120, doi: 10.1002/anie.202202423.
- [6] a) R. Pony Yu, D. Hesk, N. Rivera, I. Pelczer, P. J. Chirik, *Nature* **2016**, *529*, 195–199; b) C. Zarate, H. Yang, M. J. Bezdek, D. Hesk, P. J. Chirik, *J. Am. Chem. Soc.* **2019**, *141*, 5034–5044; c) M. Daniel-Bertrand, S. Garcia-Argote, A. Palazzolo, I. Mustieles Marin, P.-F. Fazzini, S. Tricard, B. Chaudret, V. Deraud, S. Feuillastre, G. Pieters, *Angew. Chem. Int. Ed.* **2020**, *59*, 21114–21120; d) M. Farizyan, A. Mondal, S. Mal, F. Deufel, M. van Gemmeren, *J. Am. Chem. Soc.* **2021**, *143*, 16370–16376.
- [7] For representative examples of acid-mediated aromatic H/D exchange, see: a) G. J. Köves, *J. Label. Compd. Radiopharm.* **1994**, *34*, 255–262; b) S. Rasku, K. Wähälä, J. Koskimies, T. Hase, *Tetrahedron* **1999**, *55*, 3445–3454; c) P. S. Kiuriu, K. Wähälä, *Tetrahedron Lett.* **2002**, *43*, 3411–3412; d) G. Heinkele, T. E. Mürdter, *J. Label. Compd. Radiopharm.* **2005**, *48*, 457–461; e) O. Soidinsalo, K. Wähälä, *J. Label. Compd. Radiopharm.* **2006**, *49*, 973–978; f) U. Hakala, K. Wähälä, *J. Org. Chem.* **2007**, *72*, 5817–5819; g) E. Leppälä, M. Pohjoispää, J. Koskimies, K. Wähälä, *J. Label. Compd. Radiopharm.* **2008**, *51*, 407–412; h) A. Martins, M. Lautens, *Org. Lett.* **2008**, *10*, 4351–4353; i) Z. Jian, T. Ray, A. Wu, L. Jones, *J. Label. Compd. Radiopharm.* **2012**, *55*, 84–87; j) Y. Murai, L. Wang, K. Masuda, Y. Sakihama, Y. Hashidoko, Y. Hatanaka, M. Hashimoto, *Eur. J. Org. Chem.* **2013**, *23*, 5111–5116; k) M. Pohjoispää, R. Mera-Adasme, D. Sundholm, S. Heikkinen, T. Hase, K. Wähälä, *J. Org. Chem.* **2014**, *79*, 10636–10640; l) L. Wang, Y. Murai, T. Yoshida, M. Okamoto, K. Masuda, Y. Sakihama, Y. Hashidoko, Y. Hatanaka, M. Hashimoto, *Biosci. Biotechnol. Biochem.* **2014**, *78*, 1129–1134; m) W. Li, M.-M. Wang, Y. Hu, T. Werner, *Org. Lett.* **2017**, *19*, 5768–5771; n) O. Fischer, A. Hubert, M. R. Heinrich, *J. Org. Chem.* **2020**, *85*, 11856–11866.
- [8] G. A. Olah, G. K. S. Prakash, A. Molnar, J. Sommer, *Superacid Chemistry*, Wiley, New York, **2009**.
- [9] A. Martin, A. Arda, J. Désiré, A. Martin-Mingot, N. Probst, P. Sinaÿ, J. Jimenez-Barbero, S. Thibaudeau, Y. Blériot, *Nat. Chem.* **2016**, *8*, 186–191.
- [10] For selected examples, see: a) N. Bhuma, L. Lebedel, H. Yamashita, Y. Shimizu, Z. Abada, A. Ardá, J. Désiré, B. Michelet, A. Martin-Mingot, A. Abou-Hassan, M. Takumi, J. Marrot, J. Jiménez-Barbero, A. Nagaki, Y. Blériot, S. Thibaudeau, *Angew. Chem.* **2021**, *133*, 2064–2069; *Angew. Chem. Int. Ed.* **2021**, *60*, 2036–2041; b) A. Mamontov, A. Martin-Mingot, B. Métayer, O. Karam, F. Zunino, F. Bouazza, S. Thibaudeau, *Chem. Eur. J.* **2020**, *26*, 10411–10416; c) L. J. C. Bonazaba Milandou, H. Carreyre, S. Alazet, G. Greco, A. Martin-Mingot, C. Nkounkou Loumpangou, J.-M. Ouamba, F. Bouazza, T. Billard, S. Thibaudeau, *Angew. Chem.* **2017**, *129*, 175–178, *Angew. Chem. Int. Ed.* **2017**, *56*, 169–172; d) J. Fahy, A. Duflos, J.-P. Ribet, J.-C. Jacquesy, C. Berrier, M.-P. Jouannetaud, F. Zunino, *J. Am. Chem. Soc.* **1997**, *119*, 8576–8577.
- [11] I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193–205.
- [12] a) L. H. Hammett, A. J. Deyrup, *J. Am. Chem. Soc.* **1932**, *54*, 2721–2739; b) M. A. Paul, F. A. Long, *Chem. Rev.* **1957**, *57*, 1–45; c) S. Saito, S.-i. Saito, T. Ohwada, K. Shudo, *Chem. Pharm. Bull.* **1991**, *39*, 2718–2720; d) M. J. Jorgenson, D. R. Hartter, *J. Am. Chem. Soc.* **1963**, *85*, 878–883.
- [13] C. A. Reed, *Chem. Commun.* **2005**, 1669–1677.
- [14] T. He, H. F. T. Klare, M. Oestreich, *J. Am. Chem. Soc.* **2022**, *144*, 4734–4738.
- [15] See supporting information for complete optimization.
- [16] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.
- [17] W. Liu, L. Cao, Z. Zhang, G. Zhang, S. Huang, L. Huang, P. Zhao, X. Yan, *Org. Lett.* **2020**, *22*, 2210–2214.
- [18] Thienothiazine **32** is a selective hCAXII enzyme inhibitor (unpublished results from our group). For its synthesis, see: B. Michelet, U. Castelli, E. Appert, M. Boucher, K. Vitse, J. Marrot, J. Guillard, A. Martin-Mingot, S. Thibaudeau, *Org. Lett.* **2020**, *22*, 4944–4948.
- [19] Adapted from: R. J. Smith, R. M. Pagni, *J. Org. Chem.* **1981**, *46*, 4307–7309.
- [20] H. F. T. Klare, M. Oestreich, *J. Am. Chem. Soc.* **2021**, *143*, 15490–15507.
- [21] S. A. Schwengers, C. Kanta De, O. Grossmann, J. A. A. Grimm, N. R. Sadlowski, G. G. Gerosa, B. List, *J. Am. Chem. Soc.* **2021**, *143*, 14835–14844.

Entry for the Table of Contents



The simpler the better: while most of the recent studies on late-stage aromatic polydeuteration focus on the design of metal-catalyzed C–H activation procedures, we developed an easy-to-setup and broadly applicable method based on the use of superacidic TfOD that opens new perspectives for the preparation of deuterated drugs.