A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Room-temperature Palladium-Catalyzed Deuterogenolysis of Carbon Oxygen Bonds towards Deuterated Pharmaceuticals

Authors: Wei Ou, Xudong Xiang, Ru Zou, Qing Xu, Kian Ping Loh, and Chenliang Su

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202014196

Link to VoR: https://doi.org/10.1002/anie.202014196

WILEY-VCH

10.1002/anie.202014196

WILEY-VCH

Room-temperature Palladium-Catalyzed Deuterogenolysis of Carbon Oxygen Bonds towards Deuterated Pharmaceuticals

Wei Ou,[a] Xudong Xiang,[a] Ru Zou,[a] Qing Xu,[b] Kian Ping Loh,[c] Chenliang Su*[a]

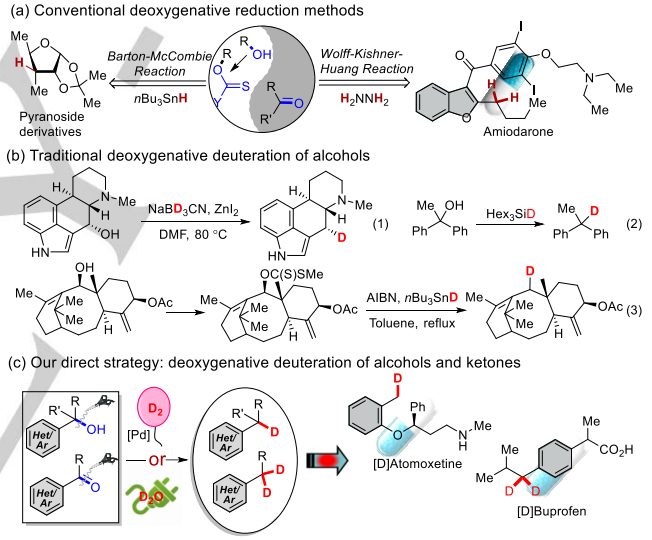
[a] Dr. Wei Ou, Xudong Xiang, Ru Zou, and Prof. Dr. Chenliang Su
International Collaborative Laboratory of 2D Materials for Optoelectronic Science & Technology, Engineering Technology Research Center for 2D Materials Information Functional Devices and Systems of Guangdong Province, Institute of Microscale Optoelectronics, Shenzhen University, Shenzhen, 518060, China
[b] Prof. Dr. Qing Xu
College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang, China
[c] Prof. Dr. Kian Ping Loh
Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore.

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Abstract: Site-specific incorporation of deuterium into drug molecules to study and improve their biological properties is crucial for drug discovery and development. Herein, we describe a palladium-catalyzed room-temperature deuterogenolysis of carbon-oxygen bonds in alcohols and ketones with D_2 balloon for practical synthesis of deuterated pharmaceuticals and chemicals with benzyl-site (sp^3 C-H) D-incorporation. The highlights of this deoxygenative deuteration strategy are mild conditions, broad scope, practicability and high chemoselectivity. To enable the direct use of D_2O, electrocatalytic D_2O-splitting is adapted to *in-situ* supply D_2 on demand. With this system, the precise incorporation of deuterium in the metabolic position (benzyl-site) of ibuprofen is demonstrated in a sustainable and practical way with D_2O.

Deuterium labeling techniques are widely utilized as efficient tools in synthetic chemistry, quantitative LC–MS/MS analysis as well as pharmaceutical discovery and development.[1-3] In 2017, the first deuterated drug, deutetrabenazine (Austedo, SD-809) was approved by FDA,[4] which led to a rising demand for the practical synthesis of deuterated drugs as well as their key building blocks. Traditional strategies for introducing deuterium to pharmaceuticals are the stoichiometric alkylation of nucleophilic *N*, *O* with expensive and highly toxic deuterium reagents (such as CD_3I), and the C–H/C–D exchanges promoted by transition metals, acid/base, *N*-heterocyclic carbenes, or photocatalysts.[5] However, site-specific deuterium labeling of pharmaceuticals with controllable deuterium atoms remains a major challenge. Defunctionalization-deuteration (DFD) reactions refer to the conversion of a specific functional group into deuterium by using a low cost and readily available deuterium source such as D_2O, CD_3OD and D_2. The advantages of DFD strategy have allowed the precise deuterium labeling at target sites. Very recently, a variety of strategies involving the reductive deuteration of halides, [6] alkenes and alkynes,[7] unsaturated carboxylic acid derivatives [8], deuterium methylation of nitroarenes [9] etc, have been developed via DFD strategy by us and other research groups.

Deoxygenation of alcohols, [10] aldehydes or ketones [11] to the corresponding alkanes is very important in the construction of drugs, natural products and their key intermediates. Barton-McCombie deoxygenation, Wolff-Kishner-Huang reduction and their various modifications are the classical methods for deoxygenative reduction of alcohols and aldehydes or ketones to synthesize drugs and their intermediates (Scheme 1a).[12] Traditional deoxygenative deuteration of carbon-oxygen bonds (i. e. alcohols) usually require the use of corresponding deuterated reducing reagents such as $NaBD_3CN$, nBu$_3$SnD, Hex$_3$SiD etc. (Scheme 1b), which are generally expensive and highly volatile, causing poor-functionalities tolerance, high costs and waste production. There is thus a need to develop mild, selective and direct deoxygenative deuteration strategy that utilizes readily available alcohols and ketones.



Scheme 1. DFD strategy for deoxygenative reduction of alcohols and ketones.

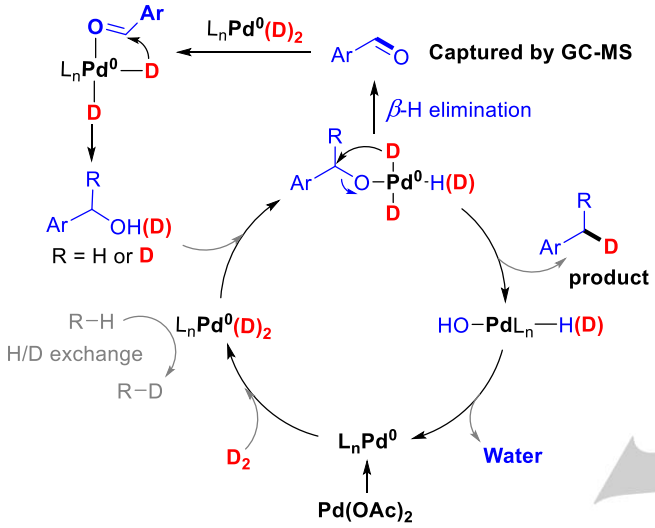
Herein, we reported the Pd-catalyzed room-temperature deuterogenolysis of benzylic alcohols and aromatic ketones using D_2 or D_2O as the deuterium source (Scheme 1c). This strategy exhibits broad reaction scopes, excellent functionalities tolerance, high chemo-selectivity and efficiency. In addition, a variety of deuterated drug intermediates and drugs including atomoxetine, tesmilifene etc. are constructed in good-excellent yields with high D-incorporation at the specific benzyl-site (sp^3 C-H). Since D_2O is the most ideal deuterium source, an electrocatalytic D_2O splitting coupled with the mild Pd-catalyzed deuterogenolysis system is designed, in which the D_2 gas could be *in-situ* generated and supplied on-demand. Gram-scale production of metabolic position D-labeled ibuprofen has been achieved, attesting to the practicability of this synergistic system.

Our initial investigations were focused on screening proper catalysts and additives for hydrogenolysis of aryl alcohol and optimization of the reaction conditions. We used commercially available $Pd(OAc)_2$ catalyst, as it could be easily converted to

This article is protected by copyright. All rights reserved.

Accepted Manuscript

highly reactive Pd(0) species under reductive atmosphere. Encouragingly, the hydrogenolysis of 1-phenylethan-1-ol occurred smoothly in the presence of the $Pd(OAc)_2$ (10 mol %) under 1 bar H_2 at room temperature in chlorobenzene, affording ethylbenzene product in 61% GC yield in 2 h. Nearly quantitative yield was achieved in the presence of strong base (*t*-BuOK, 1.2 equiv.). Encouraged by these results, Pd-catalyzed deuterogenolysis of benzyl alcohol was performed and optimized under D_2 atmosphere (see SI for detailed). For primary alcohols, the best conditions is the use of $Pd(OAc)_2$ (10 mol%) in D_2O/PhCl (0.2 mL/1 mL) under 1 atm D_2 at room temperature; For the second and tertiary benzylic alcohols, additional 20 mol% of *t*-BuOK is required to achieve good yields.



Scheme 2. Working mechanistic proposal.

The reaction mechanism is currently the subject of detailed investigation. The reaction-rate analysis conforms that there was an induction period in the initial stage of the reaction, suggesting the *in-situ* generation of reactive Pd(0) species from palladium acetate under reductive atmosphere (Figure S1). Deuterium could be easily activated by Pd(0) to form Pd-$(D)_2$ reductive species. It is believed that the coordination of alcohols with Pd(0) occurs, followed by C-O cleavage reaction by Pd-$(D)_2$, furnishing the desired deuterated compounds. A side reaction, β-elimination of benzyl alcohols to produce aldehyde was observed, verifying the interaction of alcohols with reactive Pd(0) species. The aldehyde intermediate could be reduced by Pd-$(D)_2$ to form deuterium-incorporated benzyl alcohols, which underwent deoxygenative deuteration, furnishing the corresponding product with two-deuterium atoms on the benzyl site (scheme 2). Consistently, a mixture of undeuterated, mono- di- and trideuterated products (more than 100% D-atom incorporation) were observed for some special substrates (scheme 3).

Next, the generality and practicality of this strategy was investigated to synthesize valuable deuterated chemicals and pharmaceuticals (scheme 3). A wide range of substituted primary benzyl alcohols were amenable to our strategy, producing the corresponding deuterated products (**2a-2l**) in 61-99% yields with high D incorporation (>90%). This protocol exhibited excellent functional groups tolerance, including boronic esters (**2c**), sulfonyl (**2j**), ester (**2k**), hydroxy (**2l**) as well as heterocycles such as benzofuran (**2h**) and indole derivatives (**2i**). Cyclic or chain secondary benzyl alcohols were also found to be competent substrates, providing the deuterated products (**2m-2r**) in high yields with moderate to high D incorporation. Deuterogenolysis of a series of chain or ring (6, 7 or 12 membered) tertiary alcohols was also smoothly achieved, indicating the little impact of the steric effect and re-confirming the university of this strategy. Interestingly, this mild protocol could be further extended to epoxide substrate, producing the deuterated product **2aa** in 94% yield with excellent D-incorporation under the mild conditions.

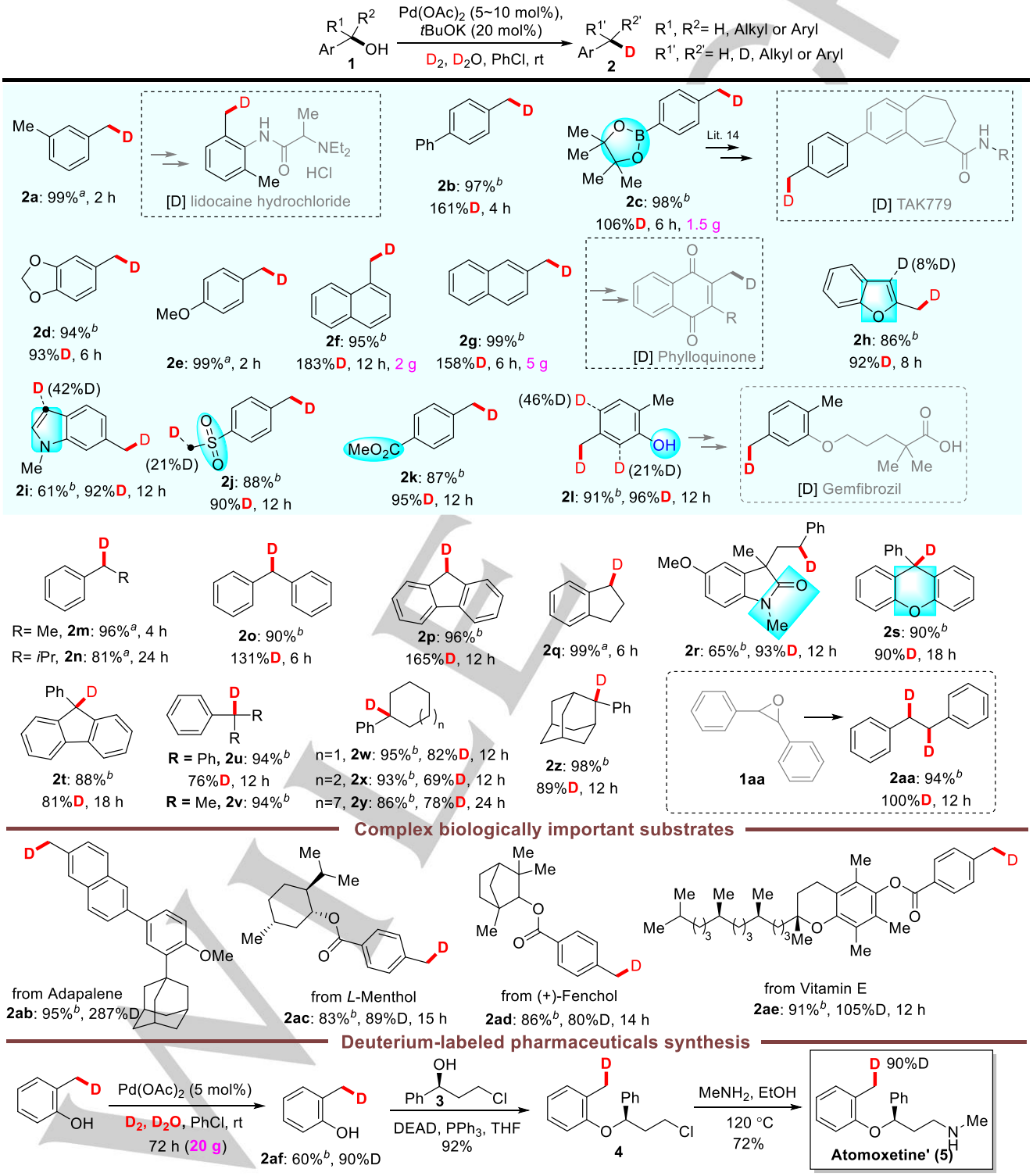
Benzyl sites are typical oxidative metabolic positions present in many important drugs, such as tolbutamide, buprofen etc., while the classical iridium-catalyzed H/D exchange method generally introduce D-atom at the aromatic rings.[13] Deuterium substitution of groups at benzyl sites is therefore highly desired to study the metabolic process as an important diagnostic tool, providing vital information about the drug metabolites. Owing to the mild process, the protocol enabled facile access to a variety of benzyl butsite-specifically labeled key intermediates of drugs, including Lidocaine (**2a**), Phylloquinone (**2g**), Gemfibrozil (**2l**) and the D-labeled TAK779 (**2c**). [14] The late-stage functionalization of complex biologically active molecules such as Adapalene derivatives (product **2ab**), *L*-Methol (product **2ac**), (+)-Fenchol (product **2ad**), and Vitamin E (product **2ae**) were also achieved readily with 83-95% yield with high D incorporations. Next, gram-scale production of drugs intermediates was evaluated. As a result, 1.5 g of **2c** and 5.0 g of **2g**, the building blocks for construction of TAK779 and Phylloquinone, had been achieved in 98%, 99% yield with uniformly high D-incorporations. Atomoxetine **5** is an important marketed drug for treatment of attention deficit/hyperactivity disorder in children. Utilizing our strategy, a 20 gram-scale production of key intermediate **2af** of deuterated atomoxetine was demonstrated from commercially available 2-hydroxybenzyl alcohol, allowing the rapid and low-cost access to deuterated atomoxetine in high overall yields. Wolff-Kishner-Huang reduction reactions offer a powerful approach to methylene from ketones. However, their application in construction of deuterated building blocks and drugs had been hindered due to the lack of commercially available deuterated reagents. We propose that the mechanism in our protocol involves the Pd-catalysed deuterogenolysis/hydrogenolysis of aldehydes or ketones that were generated from the β-elimination of substituted benzyl alcohols probably. This was verified by the more than 100% D-atom incorporation in deuterogenolysis of several substituted benzyl alcohols. On this basis, we became interested in the room-temperature Pd-catalytic deuterogenolysis of ketones for construction of valuable deuterated building blocks and drugs. To our delight, the use of 10 mol% $Pd(OAc)_2$ and 20 mol% of *t*BuOK for catalytic deuterogenolysis of acetophenone with D_2 at room-temperature produced the desired product deuteron-ethylbenzene **7a** in almost quantitative yield. Based on this protocol, we tested a variety of structurally diverse ketones, affording the corresponding deuterated products (**7a-7n**) in good to excellent yields with high D-incorporations. Consistently, this protocol shows good functionality-tolerance. For example, aromatic ketones bearing ester groups (**7j**, **7k**), cyano (**7l**) and hydroxyl (**7m**), furnished the corresponding products with good D incorporation (59-84%) and in 63-92% isolated yields. Deuterogenolysis of heteroaromatic ketone deserves comment as heterocyclic motifs are widespread in many natural products, medicinal agents and their key intermediates. The room temperature deuterogenolysis of 1-(benzofuran-2-yl)butan-1-one was evaluated, affording the corresponding deuterated 2-butylbenzofuran **7n** in 93% yield. Here, the H/D exchange on the side chain of product **7n** catalyzed by Pd(0) can be observed,

This article is protected by copyright. All rights reserved.

Accepted Manuscript

owing to the reactive α-position of ketones. With the deuterated building-block **7n** in hand, we turned our efforts to synthesize deuterium-labeled Amiodarone. Subjecting **7n** and 4-methoxybenzoyl chloride **8** to Friedel-Crafts acylation and demethoxylation cascade reaction under the $AlCl_3$-Lewis acid condition successfully afforded the deuterated building block **9** in 67% yield. Subsequently, the iodination of **9** with iodine and potassium carbonate, followed by alkylation of the phenol unit, afforded the targeted deuterium-labeled Amiodarone **12** in 64% total yields with 73% D incorporation.

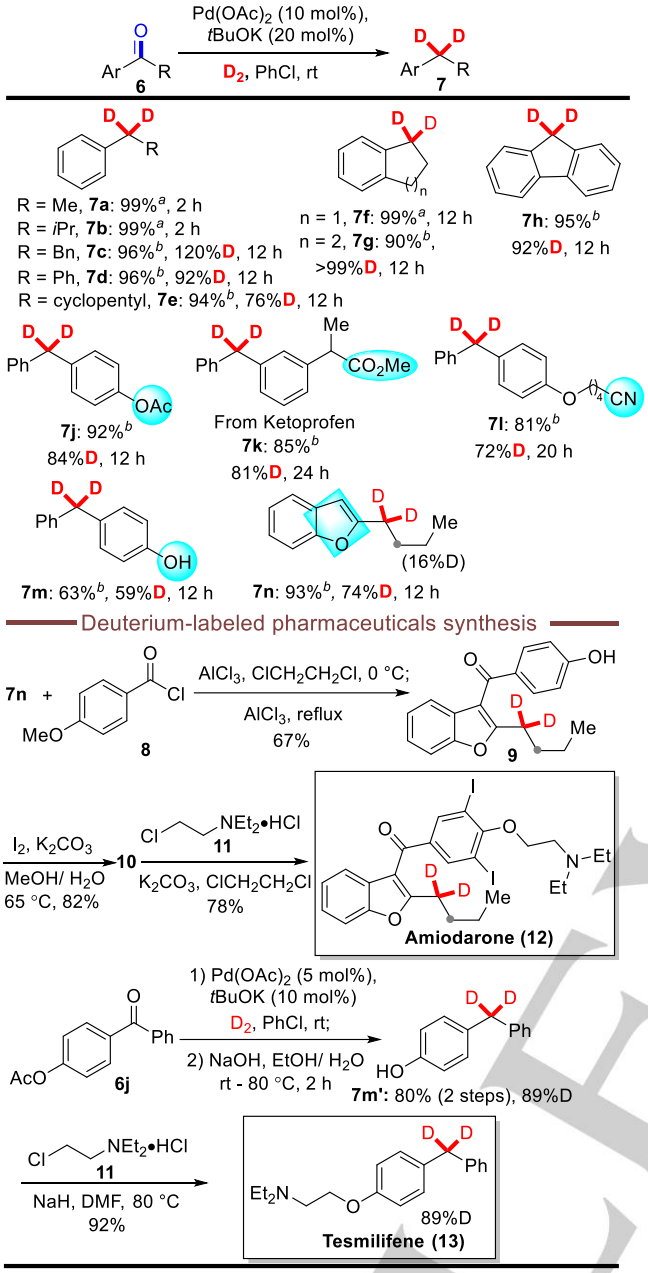
Diarylmethane skeletons are ubiquitous in pharmaceutically important molecules and medicinal agents such as antihistamines (i. e. Diphenhydramine), anticancer drugs (i. e. Tesmilifene), hypolipidemic drugs (i. e. Beclobrate), etc. Here, Tesmilifene was selected as a model drug to test the effectiveness and practicability of our strategy in construction



Scheme 3. Alcohol scope (see the Supporting Information for detailed reaction conditions). the D content was determined by ^{1}H NMR spectroscopy. [a] GC-MS yield using anisole as an internal standard. [b] Isolated yield.

This article is protected by copyright. All rights reserved.

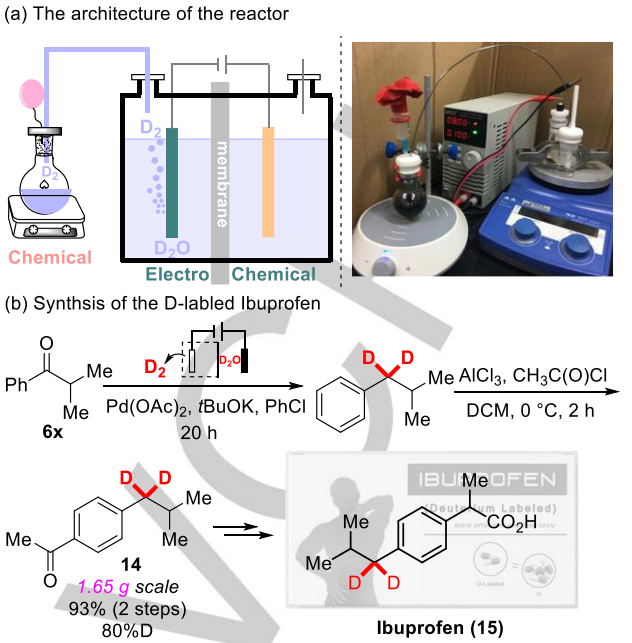
Accepted Manuscript



Scheme 4. Ketone scope (see the Supporting Information for detailed reaction conditions). the D content was determined by ^{1}H NMR spectroscopy. [a] GC-MS yield using anisole as an internal standard. [b] Isolated yield. *i*Pr = Isopropyl, Bn = benzyl.

of deuterated diarylmethane pharmaceuticals. Under the optimized conditions, diaryl ketone **6j** smoothly underwent deuterogenolysis followed by ester hydrolysis, providing the corresponding aryl phenol **7m'** in 80% yield (2 steps) with 89% D incorporation. Alkylation of **10** with aminoalkyl chloride **11** yielded the desired deuterium-labeled Tesmilifene **13** in 92% yield.

Electrocatalytic water-splitting is a well-established technology to produce hydrogen from water.[15] Here, to avoid using the flammable D_2 gas, an ideal way is to *in-situ* supply D_2 by electrocatalytic D_2O-splitting. To this end, a reactor consisting of a chemical compartment and electrochemical compartment connected with a cannula was designed, in which deuterium produced at cathode cell could be utilized for Pd-catalytic deuterogenolysis reaction at the chemical compartment. To test the practicability of this synergistic system, the precise



Scheme 5. Concept of electrolysis of D_2O to provide deuterium source.

incorporation of deuterium in the metabolic position (benzyl-site) of ibuprofen was performed (scheme 5). Firstly, the electrocatalytic D_2O-splitting occurred at electrochemical compartment, which continuously supplied D_2 gas for the room temperature deuterogenolysis of **6x**. As a result, 5 mmol of **6x** was successfully converted into D-labeled **7b**, which further underwent Friedel-Crafts acylation with acetyl chloride, affording the key building block **14** in 93% yield with 80% D incorporation (2 steps). Next, the *α*-D-labled buprofen could be obtained smoothly following the literature method.[16] Since *α*-oxidation is a key step in ibuprofen metabolism, precise deuteration of the metabolic position is a useful way to study and improve its biological properties.

In summary, we have developed a room-temperature palladium-catalyzed deuterogenolysis of alcohols and ketones for the practical synthesis of deuterated pharmaceuticals and chemicals with benzyl-site D-incorporation. This strategy also allows the precise-controlling the deuterium atom number at the benzyl-site by changing the substrates of alcohols and ketones. The mild conditions, high chemoselectivity and scalability of this protocol enable its application to the practical construction of valuable deuterated pharmaceuticals and chemicals for synthetic mechanism study as well as LC/MS quantification. Further mechanistic studies are ongoing in our lab.

Acknowledgements ((optional))

This work was financially supported by the National Natural Science Foundation of China (21972094 and 21672163), Guangdong Special Support Program, Pengcheng Scholar program, and Shenzhen Innovation Program (JCYJ20190808142001745).

Keywords: deoxygenative • deuteration • electrocatalysis • reduction • drug

This article is protected by copyright. All rights reserved.

Accepted Manuscript

[1] B. Belleau, J. Burba, M. Pindell, J. Reiffenstein, *Science* **1961, *133*,** 102.
[2] A. E. Mutlib, *Chem. Res. Toxicol.* **2008**, *21*, 1672.
[3] a) J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 1758-1784; b) J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 3022-3047; c) V. Zachleder, M. Vítová, M. Hlavová, Š.Moudříková, P. Mojzeš, H. Heumann, J. R. Becher, K. Bišová, *Biotechnol. Adv.* **2018**, *36*, 784–797.
[4] a) A. Mullard, *Nat. Rev. Drug Discov.* ***2017**, 16,* 305-305.
[5] a) J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, *Angew. Chem. Int. Ed.* **2007**, *46*, 7744 – 7765; b) R. P. Yu, D. Hesk, N. Rivera, I. Pelczer, P. j. Chirik, *Nature*, **2016**, *529*, 195-199; c) Y. Loh, K. Nagao, A. J. Hoover, D. Hesk, N. R. Rivera, S. L. Colletti, I. W. Davies, D. W. C. MacMillan, *Science* **2017**, *358*, 1182; d) T. R. Puleo, A. J. Strong, J. S. Bandar, *J. Am. Chem. Soc.* **2019**, *141*, 1467-1472; e) W. Liu, L.-L. Zhao, M. Melaimi, L. Cao, X. Xu, J. Bouffard, G. Bertrand, X. Yan, *Chem* **2019**, *5*, 2484–2494; f) H. Geng, X. Chen, J. Gui, Y. Zhang, Z. Shen, P. Qian, J. Chen, S. Zhang, W. Wang, *Nat. Cat.* **2019**, *2*, 1071–1077; g) Y. Chang, A. Yesilcimen, M. Cao, Y. Zhang, B. Zhang, J. Z. Chan, M. Wasa, *J. Am. Chem. Soc.* **2019**, *141*, 14570-14575; h) J. Dong, X. Wang, Z. Wang, H. Song, Y. Liu, Q. Wang, *Chem. Sci.* **2020**, *11,* 1026-1031.
[6] a) X. Ling, Y. Xu, S. Wu, M. Liu, P. Yang, C. Qiu, G. Zhang, H. Zhou, C. Su, *Sci China Chem*, **2020**, *63*, 386; b) V. Soulard, G. Villa, D. P. Vollmar, P. Renaud, *J. Am. Chem. Soc.* **2018**, *140*, 155; c) X. Wang, M.-H. Zhu, D. P. Schuman, D. Zhong, W.-Y. Wang, L.-Y. Wu, W. Liu, B. M. Stoltz, W.-B. Liu, *J. Am. Chem. Soc.* **2018**, *140*, 10970; d) C. Liu, Z. Chen, C. Su, X. Zhao, Q. Gao, G.-H. Ning, H. Zhu, W. Tang, K. Leng, W. Fu, B. Tian, X. Peng, J. Li, Q.- H. Xu, W. Zhou, K. P. Loh, *Nat. Commun.* **2018**, *9*, 80.
[7] a) S. P. Cummings, T. Le, G. E. Fernandez, L. G. Quiambao, B. J. Stokes, *J. Am. Chem. Soc.* **2016**, *138*, 6107-6110; b) C. Qiu, Y. Xu, X. Fan, D. Xu, R. Tandiana, X. Ling, Y. Jiang, C. Liu, L. Yu, W. Chen, C. Su, *Adv. Sci.* **2018**, 1801403.
[8] a) T. Patra, S. Mukherjee, J. Ma, F. Strieth-Kalthoff, F. Glorius, *Angew. Chem. Int. Ed.* **2019**, *58*, 10514 – 10520; b) M. Szostak, M. Spain, D. J. Procter, *Org. Lett.* **2014**, *16*, 5052-5055; d) M. Zhang, X.-A. Yuan, C. Zhu, J. Xie, *Angew. Chem. Int. Ed.* **2019**, *58*, 312 –316; e) B. Zhang, H. Li, Y. Ding, Y. Yan, J. An, *J. Org. Chem.* **2018**, *83*, 6006−6014.
[9] L. Wang, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2019**, *58*, 5417 – 5421.
[10] a) X.-J. Dai, C.-J. Li, *J. Am. Chem. Soc.* **2016**, *138*, 5433-5440; b) J. O. Bauer, S. Chakraborty, D. Milstein, *ACS Catal.* **2017**, *7*, 4462-4466; c) S. Yang, W. Tang, Z. Yang, J. Xu, *ACS Catal.* **2018**, *8*, 9320-9326; d) E. E. Stache, Alyssa B. Ertel, T Rovis, A. G. Doyle, *ACS Catal.* **2018**, *8*, 11134-11139; e) R. T. Larson, A. Samant, J. Chen, W. Lee, M. A. Bohn, D. M. Ohlmann, S. J. Zuend, F. D. Toste, *J. Am. Chem. Soc.* **2017**, *139*, 14001-14004.
[11] R. J. Rahaim, R. E. Maleczka, *Org. Lett.* **2011**, *13*, 584-587.
[12] a) T. R. R. Pettus, M. Inoue, X.-T. Chen, S. J. Danishefsky, *J. Am. Chem. Soc.* **2000**, *122*, 6160-6168; b) M. E. Furrow, A. G. Myers, *J. Am. Chem. Soc.* **2004**, *126*, 5436–5445; c) D. A. Spiegel, K. B. Wiberg, L. N. Schacherer, M. R. Medeiros, J. L. Wood, *J. Am. Chem. Soc.* **2005**, *127*, 12513-12515; d) G. Zhao, L.-Z. Yuan, M. Alami, O. Provot, *Adv. Synth. Catal*. **2018**, *360*, 2522–2536.
[13] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; b) J. Liu, Q. Yuan, F. D. Toste, M. S. Sigman, *Nat. Chem.* **2019**, *11*, 710-715; c) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359; d) M. Valero, D. Becker, K. Jess, R. Weck, J. Atzrodt, T. Bannenberg, V. Derdau, M. Tamm, *Chem. Eur. J.* **2019**, *25*, 6517–6522.
[14] H. Konno, S. Aimoto, S. O. Smith, K. Nosaka, K. Akaji, *Bioorg. Med. Chem.* **2009**, *17*, 5769–5774.
[15] a) R. Chen, S.-F. Hung, D. Zhou, J. Gao, C. Yang, H. Tao, H. B. Yang, L. Zhang, L. Zhang, Q. Xiong, H. M. Chen, B. Liu, *Adv. Mater.* **2019**, 1903909; b) I. M. Mándity, T. A. Martinek, F. Darvas, F. Fülöp, *Tetrahedron Lett.* **2009**, *50*, 4372-4374; c) E. R. M. Habraken, P. Haspeslagh, M. Vliegen, T. Noël, *J. Flow Chem.* **2015**, *5*, 2-5.
[16] N. F. Badham, W. L. Mendelson, A. Allen, A. M. Diederich, D. S. Eggleston, J. J. Filan, A. J. Freyer, L. B. Killmer, C. J. Kowalski, L. Liu, V. J. Novack, F. G. Vogt, K. S. Webb, J. Yang, *J. Org. Chem.* **2002**, *67*, 5440-5443.

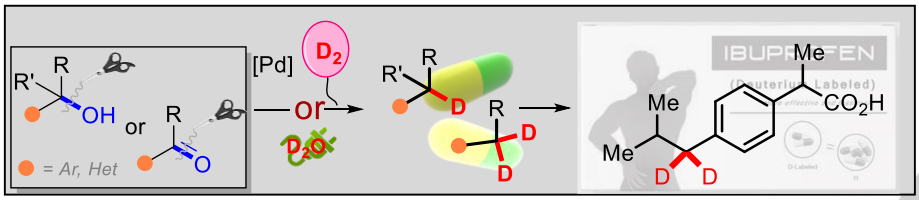
This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/anie.202014196

Entry for the Table of Contents

Insert graphic for Table of Contents here. ((Please ensure your graphic is in **one** of following formats))



We developed an operationally simple and easily scale-up protocol for deuterogenolysis of carbon oxygen bonds, which leads to a practical approach to synthetically valuable benzyl-deuterated building blocks and deuterium medicines, including atomoxetine, tesmilifene, amiodarone, ibuprofen. Combining the *in situ* electrocatalytic heavy water-splitting, this protocol enables the direct utilization of D_2O for construction of high value-added deuterated chemicals and pharmaceuticals from low cost and easily available alcohols and ketones.

Institute and/or researcher Twitter usernames: ((optional))

WILEY-VCH

Accepted Manuscript

This article is protected by copyright. All rights reserved.