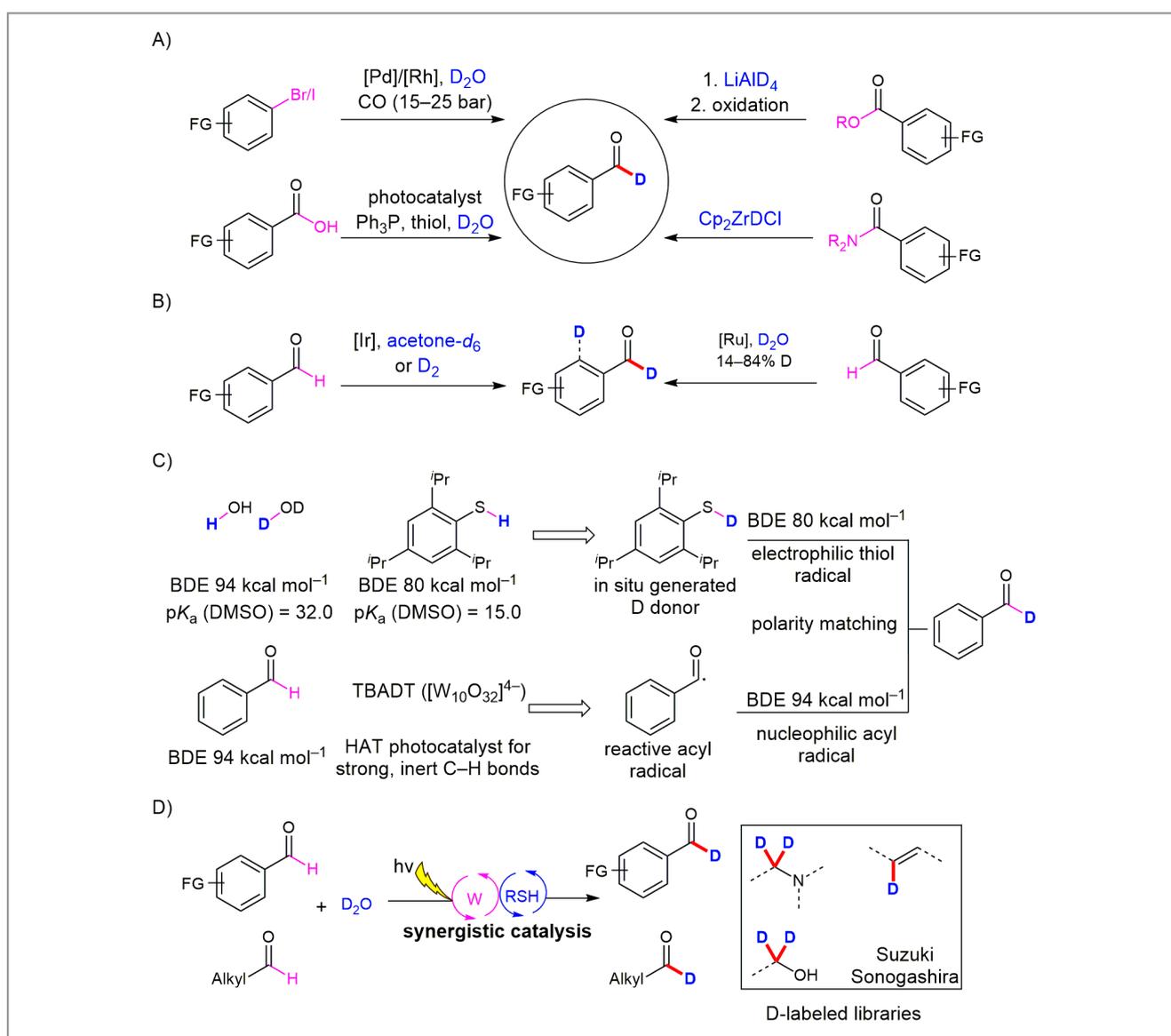


# Formyl-Selective Deuteration of Aldehydes with D<sub>2</sub>O via Synergistic Organic and Photoredox Catalysis

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In recent years, interest in the incorporation of deuterium atoms into patented drugs and drug candidates to enhance their metabolism and pharmacokinetic properties has bur-

geoned. "In 2017, the US Food and Drug Administration approved the first deuterated drug, deutetrabenazine (Austedo), and the increasing demand for new deuterium-labeled drugs



**Scheme 1** Strategies for synthesizing deuterated aldehydes. A) Previous methods to produce formyl-deuterated aldehydes through FG transformation. B) Hydrogen isotope exchange (HIE) to produce deuterated aldehydes. C) Hypothesis for the proposed deuteration. D) This work.

has motivated the development of efficient deuteration methods,” said Professor Qingmin Wang, from the State Key Laboratory of Elemento-Organic Chemistry, College of Chemistry, Nankai University (P. R. of China).

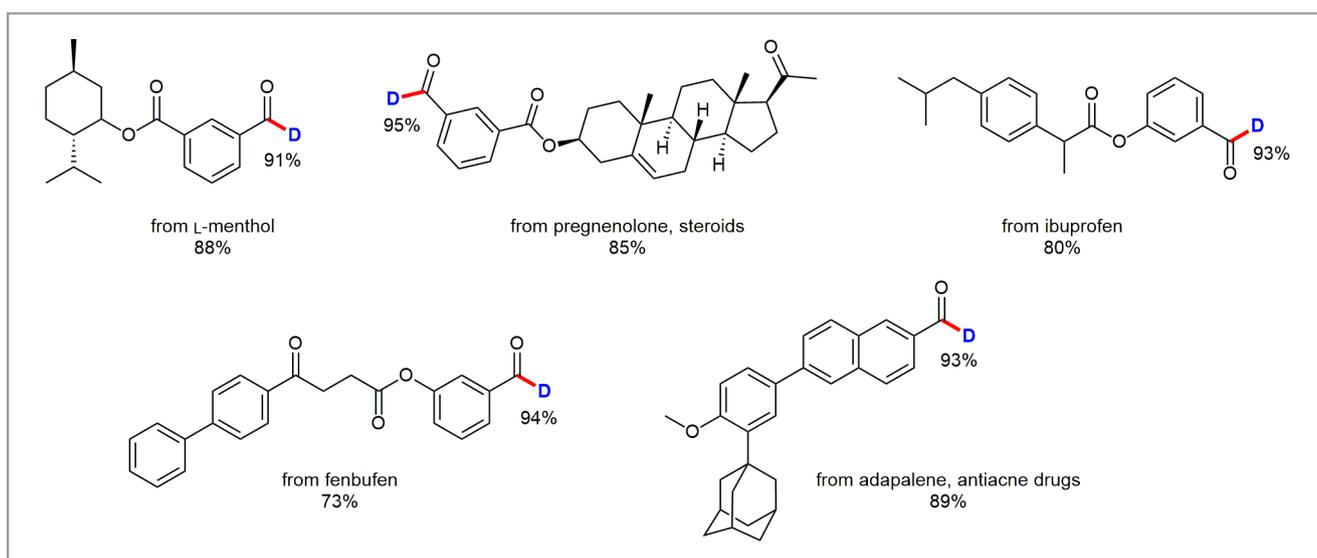
“The development of an efficient protocol for constructing formyl-deuterated aromatic aldehydes can be expected to increase the availability of deuterated lead compounds,” said Professor Wang. Aromatic aldehydes selectively labeled at the formyl position are traditionally produced from (1) the corresponding esters by means of reduction with  $\text{LiAlD}_4$  followed by oxidation, (2) from the corresponding amides by reaction with deuterated Schwartz’s reagent, (3) from aryl halides via Pd/Rh-cocatalyzed reductive carbonylation or (4) from carboxylic acids via deoxygenative deuteration (Scheme 1A, for references see the original paper). A few protocols for Ir- and Ru-catalyzed hydrogen isotope exchange (HIE) at the formyl moiety have been reported, although there is an intrinsic difficulty in controlling the reactivity of aryl ring moiety and formyl moiety (Scheme 1B). Recently, MacMillan’s group reported direct HIE at  $\alpha$ -amino  $\text{C}(\text{sp}^3)\text{-H}$  bonds via a pathway involving abstraction of a deuterium atom from a deuterium-labeled thiol catalyst by an  $\alpha$ -amino radical. “We hypothesized that generation of acyl radicals from aldehydes by a hydrogen atom transfer (HAT) photocatalyst in the presence of  $\text{D}_2\text{O}$  and a thiol catalyst would produce deuterated aldehydes,” said co-author Dr. Jianyang Dong.

Professor Wang continued: “Decatungstate anion ( $[\text{W}_{10}\text{O}_{32}]^{4-}$ ), an efficient HAT photocatalyst, has bond dissociation energies (BDE) of up to 100  $\text{kcal mol}^{-1}$  (for cyclohexane).

To our knowledge, visible-light polyoxometalate-facilitated HAT has not previously been synergistically merged with thiol catalysis. Because aldehydes have relatively low BDEs (94  $\text{kcal mol}^{-1}$ ), we envisioned that such a combination of catalytic processes would afford access to a considerable variety of acyl radicals and deuterated aldehydes from abundant aldehyde feedstocks (Scheme 1C). Moreover, owing to the gaps between the BDEs of  $\text{C}(\text{=O})\text{H}$  bonds (94  $\text{kcal mol}^{-1}$ ), aryl  $\text{C-H}$  bonds (113  $\text{kcal mol}^{-1}$ ), and  $\text{S-H}$  bonds (80–88  $\text{kcal mol}^{-1}$ ), decatungstate anion would be unable to abstract a hydrogen atom from the aryl  $\text{C-H}$  bond, allowing us to achieve formyl labeling without the formation of aryl-labeled by-products (Scheme 1C).” The group recognized that the choice of a suitable thiol catalyst would be heavily influenced by thermodynamic factors, particularly the BDE of the thiol bond relative to that of the acyl  $\text{C-H}$  bond, as well as its  $\text{p}K_a$  relative to that of water.

Professor Wang emphasized that this general strategy for formyl-selective deuteration of aldehydes with  $\text{D}_2\text{O}$  mediated by the synergistic combination of light-driven, polyoxometalate-facilitated HAT and thiol catalysis has a broad substrate scope, excellent functional group tolerance and selectivity (Scheme 1D). “We provided a practical method for late-stage modification of synthetic intermediates in medicinal chemistry and for generating libraries of deuterated compounds (Figure 1). We hope that this method can help the development of novel deuterium-labeled drugs,” concluded Professor Wang.

*Matthew Fenske*



**Figure 1** Structurally complex deuterated aldehydes prepared by using the alkylation protocol

## About the authors



Prof. Q. Wang

the design, synthesis, and structure–activity relationships of pesticides and drugs.



J. Dong



X. Wang

**Qingmin Wang** is currently a professor at the State Key Laboratory of Elemento–Organic Chemistry, Nankai University (P. R. of China). He obtained his B.Sc. (1994) from Lanzhou University (P. R. of China) and Ph.D. (2000) from Nankai University under the supervision of Prof. Runqiu Huang. His research interests mainly focus on the isolation, total synthesis, structural optimization, and bioactivity research of natural products and

**Jiayang Dong** obtained his B.S. (2016) under the supervision of Prof. Jianhan Huang at Central South University (P. R. of China). He then pursued a Master's degree in 2016 under the supervision of Prof. Qingmin Wang at Nankai University (P. R. of China) and in 2018 he began his PhD studies. His research focuses on photoredox-catalyzed radical chemistry.

**Xiaochen Wang** obtained her B.Sc. (2017) at Changchun University of Science and Technology (P. R. of China). She then started her M.Sc. studies under the supervision of Prof. Qingmin Wang at Nankai University (P. R. of China) in 2018. Her research focuses on photoredox-catalyzed radical chemistry.



Z. Wang

**Zhen Wang** obtained his B.Sc. (2017) under the supervision of Prof. Kunxian Shu at Chongqing University of Posts and Telecommunications (P. R. of China) before starting his current M.Sc. studies under the supervision of Prof. Qingmin Wang at Nankai University (P. R. of China). His research focuses on photoredox-catalyzed radical chemistry.



Dr. H. Song

**Hongjian Song** obtained his B.S. in 2008 at Qufu Normal University (P. R. of China). He then obtained his M.S. (2011) and Ph.D. (2014) under the supervision of Prof. Qingmin Wang at Nankai University (P. R. of China), majoring in organic chemistry. Currently he is a lecturer at Nankai University. His research focuses on natural pesticide discovery.



Prof. Y. Liu

**Yuxiu Liu** obtained her B.Sc. (1994), Master's (1997) and Ph.D. (2003) from Nankai University (P. R. of China). She is currently an associate professor at the State Key Laboratory of Elemento–Organic Chemistry, Nankai University. Her research interests mainly focus on the isolation, total synthesis, structural optimization, and bioactivity research of natural products.