Visible-light mediated catalytic asymmetric radical deuteration at non-benzylic positions

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Site- and enantioselective incorporation of deuterium into organic compounds is of broad interest in organic synthesis, especially within the pharmaceutical industry. While catalytic approaches relying on two-electron reaction manifolds have allowed for stereoselective delivery of a formal deuteride (D–) or deuteron (D+) at benzylic positions, complementary strategies that make use of one-electron deuterium atom transfer and target non-benzylic positions remain elusive. Here we report a photochemical approach for asymmetric radical deuteration by utilizing readily available peptide- or sugar-derived thiols as the catalyst and inexpensive deuterium oxide as the deuterium source. This metal-free platform enables four types of deuterofunctionalization reactions of exocyclic olefins and allows deuteration at non-benzylic positions with high levels of enantioselectivity and deuterium incorporation. Computational studies reveal that attractive non-covalent interactions are responsible for stereocontrol. We anticipate that our findings will open up new avenues for asymmetric deuteration.

Deuterium is a stable and non-radioactive isotope of hydrogen and deuterium-labeled compounds are widely used in a broad range of disciplines1–6. While some applications need deuterated compounds with high overall deuterium content without considering site- and stereoselectivity, others require deuteration at a distinct position and/or in a stereoselective manner. In the pharmaceutical industry, for example, site- and enantioselective incorporation of deuterium into drug molecules can slow down drug metabolism and potential epimerization of stereocenters, among other benefits, thereby improving drug efficacy7. Approval of the first deuterated drug, deutetrabenazine, by the US Food and Drug Administration in 2017 has further spurred the development of novel deuteration methods. While considerable progress has been made on regioselective non-asymmetric deuteration8–11, asymmetric deuteration remains underexplored. In this regard, protocols employing enantioenriched starting materials have emerged, allowing for stereoretentive hydrogen isotope exchange12–14 and highly diastereoselective deuteration12,13. In contrast, catalytic asymmetric deuteration approaches using prochiral or racemic substrates are still limited, mainly due to the challenges associated with identifying a chiral catalyst capable of binding with the commonly used deuterating reagents such as deuterium gas, deuterium oxide, and deuterated solvents. While the use of chiral transition metal complexes14–17, enzymes18–20, and small-molecule catalysts such as chiral phosphoric acids21–23 have met with some success, deuterations are mostly restricted to benzylic positions in these studies. Moreover, from a mechanistic perspective, the deuteration event in the existing approaches typically proceeds through a two-electron manifold where the deuterium atom is introduced to stereocenters as a formal deuteride (D–) or deuteron (D+) (Fig. 1a), with notable exceptions being disclosed recently in the deuteration labeling experiments of Hyster’s18,19 and Jiang’s23 work, where a radical deuteration pathway is operative when a deuterated enzyme cofactor or deuterated Hantzsch ester is utilized as the deuterium source.
Motivated by the growing interest in merging asymmetric organocatalysis with photocatalysis and in view of the paucity of practical methods for asymmetric radical deuterations, we recently questioned whether a photocatalytic radical deuteriation could be achieved in a highly enantioselective and cost-effective fashion. In particular, we hypothesized that a combination of chiral thiols with deuterium oxide (D₂O) might be a potential solution, given the widespread use of achiral thiols as a catalyst for non-asymmetric radical deuteration and the encouraging stereocontrol that chiral thiol catalysts exerted in a handful of prior work. Additionally, the following features make this strategy promising: 1) uncatalyzed background deuteriation—a common issue when carbon anions are involved—would be inhibited as prochiral carbon radicals are virtually unreactive towards D₂O due to the high bond dissociation energy (BDE) of the O–D bond (119 kcal/mol for HO–H bond); 2) deuterium atom transfer would be covalently bonded to the chiral thiol catalyst through facile in-situ hydrogen/deuterium exchange, thereby enhancing enantiofacial discrimination for the deuteration event. If successful, this strategy would not only introduce a complementary and mechanistically distinct approach to construct deuterated stereocenters, but also enable asymmetric deuteriation in a metal-free manner, a feature that would be appealing to the pharmaceutical industry.

Herein, we report a photochemical approach for catalytic, asymmetric radical deuteriation at non-benzylic positions in the context of deuteroboration, deuterolysilation, deuterophosphinoylation, and deuterodifluoralkylation of exocyclic olefins using inexpensive D₂O and readily available thiol catalysts derived from peptides or sugars (Fig. 1b).

**Results and discussion**

**Reaction development**

During our investigations on photoinduced hydroalkylation of olefins under the joint catalysis of Lewis base-borane and thiol, we serendipitously observed the addition of N-heterocyclic carbene (NHC)–BH₃ complex onto olefins. While photoinduced hydroboration of olefins using NHC–BH₃ complexes have been disclosed recently by several groups, asymmetric version of the reaction remains unexplored. We thus chose the reaction of 1a and exocyclic olefin 2a as a model reaction to evaluate our hypothesis using chiral thiols that are readily available thiol catalysts derived from inexpensive D₂O and readily available thiol catalysts. While Roberts have shown that sugar-derived thiols such as 5a are competent catalysts for radical hydroxylation of olefins under thermal conditions, only a single product with high enantiomeric ratio (97.5:2.5 er) was obatained using a sterically very demanding substrate, with low to moderate enantioselectivity for all the other substrates. We started our investigation by using 5a as the deuterium atom transfer (DAT) catalyst and readily available 4DPAIPN as the organophotocatalyst in a binary solvent mixture of toluene and D₂O (3:1) at 10°C. While the desired product 3a was obtained in 56% yield with 96% D upon isolation, a very low er was observed (entry 1). Other chiral pool-derived thiols such as 5b–5e also provided the product in almost racemic form (entries 2–4). To our delight, when cysteine-derived β-turn-containing peptidic thiol 5f, which was recently developed by Miller and Knowles for the derecemicization of ureas, was tested under our conditions, 3a was obtained in 67% yield with 93:7 er and high levels of deuterium incorporation (94% D) at the α–N position (entry 5). Thiol 5g with a leucine unit gave same er but lower yield of 3a while thiol 5h with a cyclopropane moiety provided slightly lower er (entries 6 and 7). We then examined the influence of D₂O on the reactivity and enantioselectivity of the reaction. Increasing the amount of D₂O (toluene:D₂O = 1:1) significantly lowered the yield of 3a but increased the deuterium incorporation to 97% (entry 8). In contrast, decreasing the amount of D₂O (toluene:D₂O = 4:1) had negligible influence on the reaction yield but diminished the deuterium incorporation to 90% (entry 9). Interestingly, the enantioselectivity remained the same under these conditions. However, when the reaction was carried out in the absence of D₂O, the er dropped to 88:12, although the reaction efficiency was maintained (entry 10). Extending the reaction time to 72 h further improved the yield of 3a to 73% (entry 11). Importantly, control experiments confirmed that the photocatalyst, visible light, and the thiol are essential for the reaction (entries 12–14).

**Reaction scope**

With the optimized conditions in hand, the scope and limitations of the deuteroboration reaction was explored (Fig. 2a). NHC boranes with various substituents on nitrogen and 1,2,4-triazol-5-ylidene borane all underwent the reaction smoothly, providing the desired products 3a–3h in good yields with high levels of deuterium incorporation and with er ranging from 89:11 to 94:6. Other Lewis base-borane complexes such as Ph₃P–BH₃ and DMAP–BH₃ were evaluated but no reactivity was observed under the current conditions. In addition to 2-oxazolidinone-based olefins, exocyclic olefins on 2-piperidinones and 2-pyrolidinones are also viable substrates, furnishing the corresponding products 3i–3p in 57-74% yield with er up to 97:3. Interestingly, high resolution mass spectra (HRMS) analysis indicated that the BH₂ moieties in all these products were also partially deuterated. We also briefly examined the deuterosilylation pathway. This work, enantioselective deuterofunctionalization of olefins using a chiral thiol catalyst and deuterium oxide (D₂O), PC photocatalyst, LED light-emitting diode.
Table 1 | Reaction optimization

| Entry | R*SH | Solvent                  | Yield /%<sup>b</sup> | D /%<sup>c</sup> | er<sup>d</sup> |
|-------|------|--------------------------|----------------------|-----------------|---------------|
| 1     | S1   | toluene:D<sub>2</sub>O (3:1) | 56                   | 96              | 48:52         |
| 2     | S2   | toluene:D<sub>2</sub>O (3:1) | 79                   | 90              | 51:49         |
| 3     | S3   | toluene:D<sub>2</sub>O (3:1) | 42                   | 90              | 53:47         |
| 4     | S4   | toluene:D<sub>2</sub>O (3:1) | 50                   | 95              | 56:42         |
| 5     | S5   | toluene:D<sub>2</sub>O (3:1) | 67                   | 94              | 93:7          |
| 6     | S6   | toluene:D<sub>2</sub>O (3:1) | 49                   | 96              | 93:7          |
| 7     | S7   | toluene:D<sub>2</sub>O (3:1) | 68                   | 94              | 92:8          |
| 8     | S5   | toluene:D<sub>2</sub>O (1:1) | 43                   | 97              | 93:7          |
| 9     | S5   | toluene:D<sub>2</sub>O (4:1) | 71                   | 90              | 93:7          |
| 10    | S5   | toluene                  | 73                   | –               | 88:12         |
| 11<sup>e</sup> | S5 | toluene:D<sub>2</sub>O (3:1) | 73                   | 94              | 93:7          |
| 12<sup>f</sup> | S5 | toluene:D<sub>2</sub>O (3:1) | N.D.                 | –               | –             |
| 13<sup>g</sup> | S5 | toluene:D<sub>2</sub>O (3:1) | N.D.                 | –               | –             |
| 14<sup>h</sup> | – | toluene:D<sub>2</sub>O (3:1) | N.D.                 | –               | –             |

er = enantiomeric ratio. N.D. = Not detected.

<sup>a</sup>Unless otherwise noted, all reactions were carried with 1a (0.2 mmol), 2a (0.1 mmol), 4DPAIPN (1 mol%), R*SH (15 mol%), toluene (0.75 mL), D<sub>2</sub>O (0.25 mL) under 10 °C for 48 h with irradiation from a 30 W blue LED.

<sup>b</sup>Isolated yield of 3a.

<sup>c</sup>Determined by <sup>1</sup>H NMR analysis of the isolated product.

<sup>d</sup>Determined by chiral HPLC analysis.

<sup>e</sup>Reaction time: 72 h.

<sup>f</sup>No photocatalyst.

<sup>g</sup>Without light irradiation.

<sup>h</sup>No thiol catalyst.
reactions given that Roberts’ early studies on the hydrosilylation reaction under thermal conditions mostly gave low to moderate enantioselectivities. Under room temperature, the reaction of triphenylsilane with 2a in the presence of S5 afforded the desired product 4a in 85% yield with 89% D and 88:12 er (Fig. 2b). The er was improved to 92:8 upon using S7 as the thiol catalyst. To demonstrate the practicality of the reaction, we scaled up the reaction with lower catalyst loadings and 1.08 gram of 4a was obtained with comparable results as that of the small scale reaction. By comparison, the reaction using Roberts’ optimal thiol S1 under otherwise identical conditions provided 4a in 70% yield with 96% D but with very low enantioselectivity (46:54 er). Replacing the phenyl group on nitrogen with n-butyl group produced 4b with a decreased er (82:18) while the use of 2-piperidinone-based olefins afforded 4c and 4d in moderate yields with good enantioselectivities. Other silanes such as diphenylmethylsilane, tris(trimethylsilyl)silane, and diphenylmethylsilane were also tolerated (4e–4g). γ-Lactone-based olefin afforded the product 4h in good yield with modest levels of enantioselectivity. 1,1-Disubstituted olefins in acyclic systems were tested but typically gave low selectivity of acyclic radicals. The absolute configurations of the deuterated stereocenters were determined by X-ray crystallographic analysis to be R and S for products 3c and 4a, respectively. At the end of the reactions, the D2O can be recovered using a separatory funnel for products 3a, 3b, and 4a. At the end of the reactions, the D2O can be recovered using a separatory funnel.
For deuterophosphinoylation and deuterodi-
fluoroalkylation reactions, the substitu-
tes at the allylic positions were found to be
very important as much lower conver-
sions and enantioselectivities were observed
using an olefin devoid of such substituents
(Supplementary Fig. 3). The reason behind
this observation remains unknown and is
currently under investigation.

Having demonstrated the generality of this
enantioselective deuterofunctionalization
strategy for introducing heteroatoms to
olefins, we sought to extend it to alkene
deuteralkylation. We chose α-bromodifluoroacetamides as alkyl radical precursors
given their widespread applications in
radical chemistry and the importance of
difluoroalkylated compounds. To our delight,
using thiol S8 as the DAT catalyst and Hantzsch ester (HE) as an electron donor,
photo-reductive deuterodi-fluoroalkylation reactions occurred smoothly to
furnish gem-difluoro- and deuterium-containing products 6a–6e in
modest to good yields with high levels of enantioselectivity and deu-
terium incorporation (Fig. 3b).

Product derivatization
The deuterated products obtained in this study can be easily elabo-
rated to provide versatile chiral building blocks without erosion of
enantipurity and deuterium content (Fig. 4). For example, NHC-
borane 3a was treated with 2M HCl and pinacol to provide

![Fig. 3 | Sugar-derived thiol-catalyzed enantioselective deuterofunctionalization of exocyclic olefins. a Enantioselective deuterophosphinoylation. b Enantioselective deuterodifluoroalkylation. See Supplementary Note 2.3 for experimental details.](Image)
The rate. While the oxidation potential of ni-
mentary Figs. 13 and 14), the quenching rate of thiol increased sig-
4DPAIPN were largely unchanged in the presence of water (Supple-
of the photoredox catalyst 4DPAIPN \(E_{1/2}(PC*/PC_s)\) but not by the NHC
Sus SCE) but not by the NHC
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Hydrolysis under basic conditions afforded valuable
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| \(E_{1/2}(PC*/PC_s)\) | \(+0.90\text{V vs SCE}\)|
| \(E_{1/2}(PC*/PC_s)\) | \(+1.41\text{V vs SCE}\)|
| \(E_{1/2}(PC*/PC_s)\) | \(+0.76\text{V versus SCE}\)|

although reductive quenching by 1a is thermodynamically more
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Mechanistic studies

Subsequently, preliminary mechanistic studies were carried out to
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and 2a was much faster in the presence of D\(_2\)O than in its absence
( Supplementary Table 7). Finally, the quantum yield of the reaction of
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and 2a was determined to be 0.76%, indicating that a radical chain-
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While further mechanistic investigations for the other three types of reactions are currently underway in our
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labatory, a plausible mechanism was proposed based on prior work44,56,59 and our experimental observations (Fig. 5c).
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Photoscien-
tation of the photocatalyst (PC) with visible light would produce the
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the excited stated PC*, which oxidizes a thiol catalyst to generate an
trophilic thiyl radical I via a PCET process. A polarity-matched hydro-
gen atom transfer (HAT) event then occurs between the thyl radical
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and a hydric \(R-H\) ( \(R=B, Si\) or \(P\) ) bond of the substrate40,41. Subsequent radical addition to the olefin furnishes a prochiral and nucleophilic
carbon-centered radical III, which undergoes polarity-matched and

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selective DAT with the in-situ generated deuterated chiral thiol
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(RSD) to deliver the desired deuterated product and regenerate the

thyl radical. Finally, single-electron reduction of the thyl radical by
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the reduced state of the photocatalyst (PC\(^*\)) would regenerate the ground-

state photocatalyst and the deuterated thiol after protonation.
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Computational studies

To elucidate the origin of enantioselectivity for the DAT step, we
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performed density functional theory (DFT) calculations at the

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CPCM(Toluene) B3LYP/6-311++G(3d,2p)//\(\omega\)B97X-D/6-31+G(d,p) level

of theory using thiol S6 as the catalyst for the reaction of 1a and 2a

(Fig. 5d, see Supplementary Information for computational details).

After conformation analysis of the peptide catalyst based on Miller’s

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pioneering studies on \(\beta\)-turn-containing tetrapeptides56,57, it was

found that the approach of the radical adduct in the transition state

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(TS) is dictated by the C=O···H-N interaction in the backbone

(highlighted with blue dash lines). Moreover, the SI and Re faces of

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the carbon radical interact differently with the peptide thiol in the

transition states due to non-covalent dispersion interactions64,65,

with TS-SI displaying strong C-H···\(\pi\) interactions between the pro-

line and the phenyl ring of the radical adduct. In contrast, only weak

C-H···\(\pi\) interactions are identified in TS-Re. As depicted in the NCI

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plot and quantified in the distortion/interaction analysis66, the

interaction between the radical adduct and the thiol catalyst is

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stronger by 1.6 kcal/mol in TS-SI. In addition, the overall activation

energy difference considering entropic contributions is calculated
to be 1.3 kcal/mol (\(\Delta\DeltaG\)), corresponding to a theoretical er of 91:9

at 10°C in favor of R enantiomer, which is in close agreement with the

experimentally observed sense and magnitude of enantioin-
duction (93:7 er).

In summary, by merging organocatalysis with photoredox cata-
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lysis, highly enantioselective radical deuteration at non-benzylic

positions has been achieved using peptide- or sugar-derived thiol

catalysts and D\(_2\)O. This metal-free approach is uniformly effective for
differentiation of theory using thiol

S6 as the catalyst for the reaction of 1a and 2a

(Fig. 5d, see Supplementary Information for computational details).

After conformation analysis of the peptide catalyst based on Miller’s

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duction (93:7 er).

Methods

General procedure for the deuteroboration of olefins

To an oven-dried 16 × 60 mm vial containing a dry Teflon stir bar
were charged with 4DPAIPN (0.8 mg, 0.001 mmol), thiol catalyst S5
(9.0 mg, 0.015 mmol), and NHCl–BH\(_3\) 1a (22.2 mg, 0.2 mmol). After
sequential addition of dry toluene (0.75 mL), D\(_2\)O (0.25 mL), and
olefin 2a (17.5 mg, 0.1 mmol), the reaction mixture was flushed with
nitrogen gas for two minutes and then the vial was sealed with a cap
and parafilm. The vial was placed in a cooling station and a 30 W
blue LED (\(\lambda_{\text{max}} = 441\text{nm}\)) was then placed at the top of the cooling
station, which is connected to a chiller to maintain the temperature

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of the cooling water at 10 °C. The reaction mixture was stirred at 10 °C under irradiation with a stirring rate of 400 r/min for 72 h. When the reaction is complete as monitored by thin layer chromatography and gas chromatography–mass spectrometry, CH₂Cl₂ (10 mL) and H₂O (5 mL) were added, the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄. After filtration and evaporation, the residue was purified by chromatography on silica gel to afford the desired product.

Data availability
All data generated or analyzed during this study are included in this Article and the Supplementary Information and Supplementary Data files. Details about materials and methods, experimental procedures, mechanistic studies, characterization data, computational details, NMR and HPLC spectra are available in the Supplementary Information. Calculated coordinates are available in the Supplementary Data file. Crystallographic data for compounds 3c, 4a, and 5a are available free of charge from the Cambridge Crystallographic Data Centre (CCDC) under reference number 2143290, 2106903, and 2106903, respectively (https://www.ccdc.cam.ac.uk/structures).

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Author contributions

J.Y. conceived and directed the project. Q.S., M.X., R.C., and D.R. performed the experiments and analyzed the data. B.P. and I.F.A. carried out the computational studies. J.Y. and I.F.A. wrote the manuscript with input from all authors.

Competing interests

A patent application by J.Y., Q.S., and M.X. detailing part of this research was filed through the Patent Office of the People’s Republic of China (November 2021). J.Y., Q.S., and M.X. declare no other competing interests. The other authors declare no competing interests.

Additional information

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