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Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds

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Deuterium- and tritium-labeled pharmaceutical compounds are pivotal diagnostic tools in pharmaceutical drug discovery research, providing vital information about the biological fate of drugs and drug metabolites. Herein, we demonstrate that a photoredox-mediated hydrogen atom transfer (HAT) protocol can efficiently and selectively install deuterium and tritium at α -amino sp^3 C–H bonds in a single step, using isotopically labeled water (D_2O or T_2O) as the source of hydrogen isotope. In this context, we also report a convenient synthesis of T_2O from T_2 , providing access to high specific activity T_2O . This protocol has been successfully applied to the high incorporation of deuterium and tritium in 18 drug molecules, which meet the requirements for use in ligand binding assays and absorption, distribution, metabolism and excretion (ADME) studies.

An essential component of the drug discovery and development process is the thorough elucidation of a drug molecule's action and toxicity (1–9). Despite rapid advancements in analytical techniques over the past 20 years, the introduction of isotopic labels, which integrates a unique signal into a molecule without drastically altering its function, remains the most effective method to detect and quantify drugs and drug metabolites in both in vivo and in vitro studies (1–6). Recently, the ability to introduce hydrogen isotopes at non-labile C–H moieties has seen the emergence of deuterium (2H) and tritium (3H) as cheaper and more readily accessible alternatives to ^{13}C and ^{14}C for the synthesis of isotopically labeled drug analogs, especially when high isotopic incorporation is desired (1–6). In particular, highly deuterated analogs of drug molecules are used in absorption, distribution, metabolism and excretion (ADME) studies, where they are ideal internal standards for mass spectrometry-based quantification in animal and human samples, as they negate matrix effects which can interfere with accurate quantification (10, 11). On the other hand, high specific activity tritium analogs are critical for the accurate quantification of nanomolar ligand binding affinity studies, as well as the imaging of in vivo compound distribution via autoradiography (7–9).

Currently, a large majority of deuterium- and tritium-labeled pharmaceutical compounds are synthesized via multi-step procedures involving the reduction of halogenated or unsaturated drug precursors (1–6). However, advances in transition metal-catalyzed C–H activation have allowed for the direct hydrogen isotope exchange (HIE) of C–H bonds for

deuterium or tritium, enabling the synthesis of labeled compounds in a single step without the need for resynthesis (12–14). This straightforward approach has recently found widespread application in the pharmaceutical industry, where the increasing impact of early-stage ligand binding assays and ADME studies on drug discovery has led to a rising demand for the efficient synthesis of isotopically labeled pharmaceutical compounds (2).

Currently, transition metal-catalyzed HIE reactions at aromatic $C(sp^2)$ –H moieties are well established (Fig. 1A). For example, cationic iridium(I) complexes have long been used to selectively label sites ortho to directing groups on aromatic rings (12, 13). More recently, Chirik and co-workers reported the use of an iron catalyst for the deuteration and tritiation of pharmaceutical drugs at aromatic C–H moieties without the need for a directing group, enabling orthogonal site selectivity relative to the iridium catalyst (14). In contrast, the direct HIE at aliphatic $C(sp^3)$ –H moieties remains a challenge in the field (15–20). With over 50% of the top selling commercial drugs containing at least one alkyl amine moiety (21), the development of an HIE reaction targeting α -amino $C(sp^3)$ –H bonds could potentially provide a general method for the isotopic labeling of the aliphatic positions of a drug molecule. Indeed, the site of the isotopic label can be of vital importance depending on the nature of the study and the metabolic pathways of the substrate of interest (1–6). In addition, the inherently larger number of exchangeable hydrogens at α -amino C–H moieties relative to aromatic C–H moieties enables high incorporation of the desired isotopic label, which

is often necessary for the labeled compound to be of practical use in pharmaceutical studies. Therefore, the development of a mild and efficient HIE reaction targeting α -amino C(sp³)-H bonds is particularly attractive for the pharmaceutical industry.

Visible light-mediated photoredox catalysis has emerged in recent years as an enabling platform to access new organic transformations through single-electron transfer events (22–24). In particular, our laboratory and others have demonstrated that tertiary amines can be activated via single-electron oxidation to give an amine radical cation, which can undergo facile α -deprotonation to yield carbon-centered α -amino radicals. The synthetic utility of α -amino radicals has been showcased by its ability to couple with various electrophilic partners (25–27). On this basis, we questioned if we could exploit α -amino radicals to access α -deuterated or α -tritiated products (Fig. 1B). Specifically, we hypothesized that, instead of trapping the α -amino radical with a carbon electrophile, the use of an appropriate hydrogen atom transfer (HAT) catalyst in equilibrium with D₂O or T₂O could facilitate the abstraction of deuterium or tritium to yield labeled products. We recognized that the choice of the HAT catalyst would be heavily influenced by thermodynamic factors, in particular the bond dissociation energy (BDE) relative to that of the α -amino C-H bond, as well as its pK_a relative to water (Fig. 1B) (28–30). With these considerations in mind, we postulated that thiols, which have been demonstrated to be good hydrogen atom donors (31), would be suitable HAT catalysts for this transformation. Herein, we describe the direct HIE of α -amino C(sp³)-H bonds mediated by the synergistic merger of photoredox and HAT catalysis. This methodology was readily applied to the program-scale deuteration (32) and high specific activity tritiation of 18 representative drugs and drug candidates.

A proposed mechanism for the photoredox and HAT catalyzed HIE of α -amino C(sp³)-H bonds is shown in Fig. 2A (33). Initial photoexcitation of the iridium (III) photocatalyst Ir(F-Meppy)₂(dtbbpy)PF₆ [F-Meppy = 2-(4-fluorophenyl)-5-(methyl)pyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine] (**1**) would generate the long lived (τ = 1.1 μ s) triplet excited state Ir^{III} complex **2** (34). This species is a strong single-electron oxidant ($E_{1/2}^{\text{red}}$ [*Ir^{III}/Ir^{II}] = +0.94 V vs. SCE in acetonitrile) (34) and can oxidize amine **3**, which undergoes facile deprotonation at the α -position to give α -amino radical **4**. At the same time, a thiol HAT catalyst (**6**) would undergo exchange with T₂O to give the tritiated thiol **7**, which would serve as the source of tritium. In addition to the reported BDE for typical α -amino C-H and thiol S-H bonds, we reasoned that HAT can proceed between the polarity matched (35) nucleophilic α -amino radical **4** and tritiated thiol **7**, which would furnish α -tritiated amine product **8** and the electrophilic thiol radical **9** (α -amino C-H BDE = 93.0 kcal mol⁻¹ (36)

vs S-H BDE = 87.0 kcal mol⁻¹ (37)). Both catalytic cycles can then converge to undergo a second single-electron transfer between **5** and **9** to regenerate photocatalyst **1** and tritiated thiol **7** via protonation of thiol anion **10** ($E_{1/2}^{\text{red}}$ [Ir^{III}/Ir^{II}] = -1.50 V vs. SCE in acetonitrile (31), $E_{1/2}^{\text{red}}$ [thiol] = -0.85 V vs. SCE for cysteine) (38).

We began our investigations into the proposed isotopic labeling protocol by first examining the deuteration of clomipramine (**11**) hydrochloride (Anafranil), a commercially available antidepressant. For the application of deuterated compounds as internal standards in pharmaceutical studies, each compound should ideally have an isotopic incorporation of more than 4.0 deuteriums per molecule, with less than 0.1% of the unlabeled compound remaining, so as to avoid peak overlaps on the mass spectrum to allow for accurate quantification (11). In addition, to facilitate long term studies, the program-scale synthesis of a uniformly deuterated batch of compound is also highly desirable (Fig. 2B, left). A variety of photoredox catalysts and thiol catalysts, as well as their respective loadings were evaluated, using *N*-methyl-2-pyrrolidone (NMP) as solvent (see figs. S1 and S2). In our preliminary studies conducted at 0.1 mmol scale, we were delighted to observe that the use of 2 mol % of organic photocatalyst, 4Cz-IPN (**12**) (4Cz-IPN = 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene, excited state τ = 5.1 μ s, $E_{1/2}^{\text{red}}$ [*4Cz-IPN/ 4Cz IPN] = +1.35 V, $E_{1/2}^{\text{red}}$ [4Cz-IPN/ 4Cz IPN] = +1.21 V) (39) and 30 mol % triisopropylsilanethiol **13** along with 1.2 equivalents of lithium carbonate afforded the corresponding deuterated product in 79% yield with 9.2 deuteriums incorporated per molecule and less than 0.1% of unlabeled compound remaining. Scaling the reaction up resulted in a comparable efficiency of deuterium incorporation, enabling the program-scale synthesis of [²H]**11** with 7.2 deuteriums per molecule, no detectable unlabeled compound remaining and an isolated yield of 76% as its HCl salt (1.06 g) (Fig. 2B, left). The use of the sterically hindered triisopropylsilanethiol was critical to prevent a deleterious thiol-substrate coupling pathway (see fig. S2). Control experiments also revealed that, light, photoredox catalyst, and thiol are all essential for deuteration to proceed (see table S1).

Next, we sought to extend this HIE protocol to the high specific activity tritiation of amine-containing drugs with T₂O. In contrast to the deuterium HIE reactions, the analogous tritium HIE reactions are predominantly run on micromolar scale as i) the tritium isotope is easily detectable and only a small amount of radioactive product is required, and ii) safety and cost concerns favor limiting the amount of tritium used to 1.0 Ci (17.2 μ mol) per reaction. An additional complication is that commercially available T₂O is typically highly diluted with natural abundance H₂O to prevent the decomposition of T₂O via autoradiolysis (Fig. 2C) (3). To overcome this issue, we set out to establish a convenient process

to synthesize high specific activity T₂O using only 1 Ci of T₂ gas, which could be performed in a common laboratory setting and used immediately in our tritium HIE reaction. Industrially, neat T₂O is produced in bulk from the reaction between T₂ and PtO₂ before being distilled and diluted (40). To facilitate the transfer of micromolar scale T₂O into our photoredox reaction mixture, we proposed to adapt this procedure for the generation of T₂O in a potential reaction solvent. Among the solvents evaluated, we were pleased to observe that the use of NMP as the reaction solvent enabled the formation of high specific activity tritiated water in 61% yield (0.51 Ci, 8.8 μmol) from 1.0 Ci T₂ gas and PtO₂ (see fig. S3).

With this convenient method to access T₂O in hand, we proceeded to optimize the proposed photoredox-HAT catalyzed tritium labeling protocol. In general, high specific activity tritium labeled compounds are required to have a specific activity of at least 15 Ci mmol⁻¹ (equivalent to an incorporation of 0.5 tritiums per molecule), and are isolated in an appreciable radiochemical yield of at least 10 mCi (Fig. 2B, right). Under the dilute micromolar conditions (using approximately 4.4 equivalents of T₂O), we observed that the use of **11** in its free base form, along with increased loadings of the photoredox (4 mol %) and thiol (60 mol %) catalysts, and the use of the integrated photoreactor developed at Merck & Co., Inc. (41) as the visible light source greatly enhanced the incorporation of tritium, yielding [³H]**11** with a high specific activity of 40.2 Ci mmol⁻¹ and isolated yield of 39.8 mCi (Fig. 2B, right).

With the above optimized conditions in hand, we explored the generality of the photoredox-mediated deuteration and tritiation protocols with a library of commercially available drugs containing a variety of alkyl amine scaffolds. For the deuteration of these substrates (Fig. 3), the best conditions were found to be substrate dependent, given a choice of two photocatalysts, Ir(F-Meppy)₂(dtbbpy)PF₆ (**1**) and 4-CzIPN (**12**), two thiols (**13** and **14**) and two light sources, a 34 W blue LED or the integrated photoreactor (see the supplementary materials). Acyclic trialkyl amines ([²H]**15**–[²H]**17**) worked well, as did piperidine ([²H]**18**, [²H]**19**) and piperazine rings ([²H]**20**–[²H]**24**). The reaction also showed good tolerance for a variety of functional groups. Aryl fluoride ([²H]**16**) and aryl chloride ([²H]**18**, [²H]**22**) substituents were well tolerated under the reaction conditions. Carboxylic acid ([²H]**21**), ester ([²H]**17**), amide ([²H]**20**, [²H]**22**, [²H]**24**) and nitrile ([²H]**15**, [²H]**16**) functionalities were also amenable to the photoredox conditions, as were free hydroxyl groups ([²H]**23**, [²H]**25**, [²H]**26**). In addition, chiral centers away from the reactive sites were unperturbed during the reaction ([²H]**16**, [²H]**17**, [²H]**21**). Our deuteration protocol was also applicable to macrolide drugs like azithromycin ([²H]**25**) and clarithromycin ([²H]**26**).

These high molecular weight macrocycles with no C(sp²)-H bonds are particularly challenging substrates for HIE via conventional transition metal catalysis. The preparation of deuterated azithromycin would have previously involved a multi-step sequence and the use of costly deuterated reagents (42). In contrast, our photoredox protocol enables access to [²H]**25** in a single step using D₂O, a readily available source of deuterium. Remarkably, stereochemistry was retained even when H/D exchange occurred at chiral centers on these macrocycles, likely due to substrate control in the HAT process. In addition to α-amino positions, benzylic and β-amino positions were also deuterated in certain instances ([²H]**15**, [²H]**16**, [²H]**18**, [²H]**22**), see figs. S4 and S5). In summary, all substrates gave excellent deuterium incorporations on program-scale, with incorporations of more than 5.0 deuteriums per molecule, and importantly, less than 0.1% of the unlabeled compound, meeting the minimum requirement for their use as internal standards.

With the same library of 13 pharmaceutical drugs, we were able to demonstrate similar functional group tolerance for the photoredox-mediated tritium HIE protocol (Fig. 4). As with the deuteration reaction, the best conditions were substrate dependent, and combinations of the two photocatalysts, **1** and **12**, and the two thiols, triisopropylsilanethiol (**13**) and methyl thioglycolate (**14**) were used. Despite the smaller excess of T₂O in the reaction, the presence of acidic hydrogens from carbamate ([³H]**19**), amide ([³H]**22**, [³H]**24**), carboxylic acid ([³H]**21**) and alcohol ([³H]**23**, [³H]**25**, [³H]**26**) functionalities did not have a major impact on tritium incorporation. Again, we were pleased to see high tritium incorporations with the high molecular weight macrocycles azithromycin ([³H]**25**) and clarithromycin ([³H]**26**), as these substrates have no aromatic rings and cannot be tritiated using existing HIE protocols. For [³H]**22**, when the amount of T₂ gas used was increased to 2 Ci, specific activity was boosted from 11.5 to 14.6 Ci mmol⁻¹, with a large increase in yield (8.6 mCi to 19.6 mCi), demonstrating the tunability of our protocol with respect to the amount of T₂ used, enabling single step tritiation even for particularly recalcitrant substrates. We were delighted to achieve high specific activities for all substrates, meeting the typical standards for the preparation of high specific activity pharmaceutical drugs in appreciable yield for their use in ligand binding studies.

In addition to the library of commercially available drug molecules, we further evaluated the utility of this photoredox-catalyzed tritiation with a series of potential GPR40 agoPAMs (Fig. 4) developed in the research laboratories of Merck & Co., Inc. (43). The characterization of GPCR allostery is critical to advancing this agoPAM chemical class. Augmentation of binding in the presence of orthosteric ligands has been previously demonstrated using radiolabeled analogs in radioligand binding assays, and subsequently visualized in the GPR-

40 ternary crystal structure (44). As such, we envision that the radiolabeling methodology described herein might be used to enable metabolite identification both in vitro and in vivo, as well as the elucidation of the extent of covalent protein binding in human hepatocytes to derisk any bioactivation toward reactive electrophiles (45).

Initially, photoredox-mediated decarboxylation of the aliphatic carboxylic acid moiety in the drug candidates was observed. However, this was overcome by using a less oxidizing photocatalyst, Ir(ppy)₂(dtbbpy)PF₆ ($E_{1/2}^{\text{red}}[*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +0.66$ V vs. SCE in acetonitrile) (34) or a Lewis acid additive (see the supplementary materials). We were also pleased to observe that sterically hindered amines (**[³H]27** and **[³H]28**) and azetidine rings (**[³H]29**) were also amenable substrates for this protocol. Tritiation was also observed at a C(sp²)-H moiety in **[³H]27**, possibly due to conjugation of the benzylic α -amino radical. For **[³H]31**, epimerization likely occurred at the chiral center adjacent to nitrogen as a result of the introduction of tritium (46). All 5 compounds were satisfactorily labeled and met the requirements for use in preclinical candidate selection studies.

We anticipate that the facile access to highly deuterated and tritiated compounds based on the method described herein will enable accelerated and broader interrogation of the biological activity of molecules in the pursuit of the development of new molecular therapies.

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Supplementary Text

Figs. S1 to S5

Tables S1 and S2

NMR Spectra

References (47–54)

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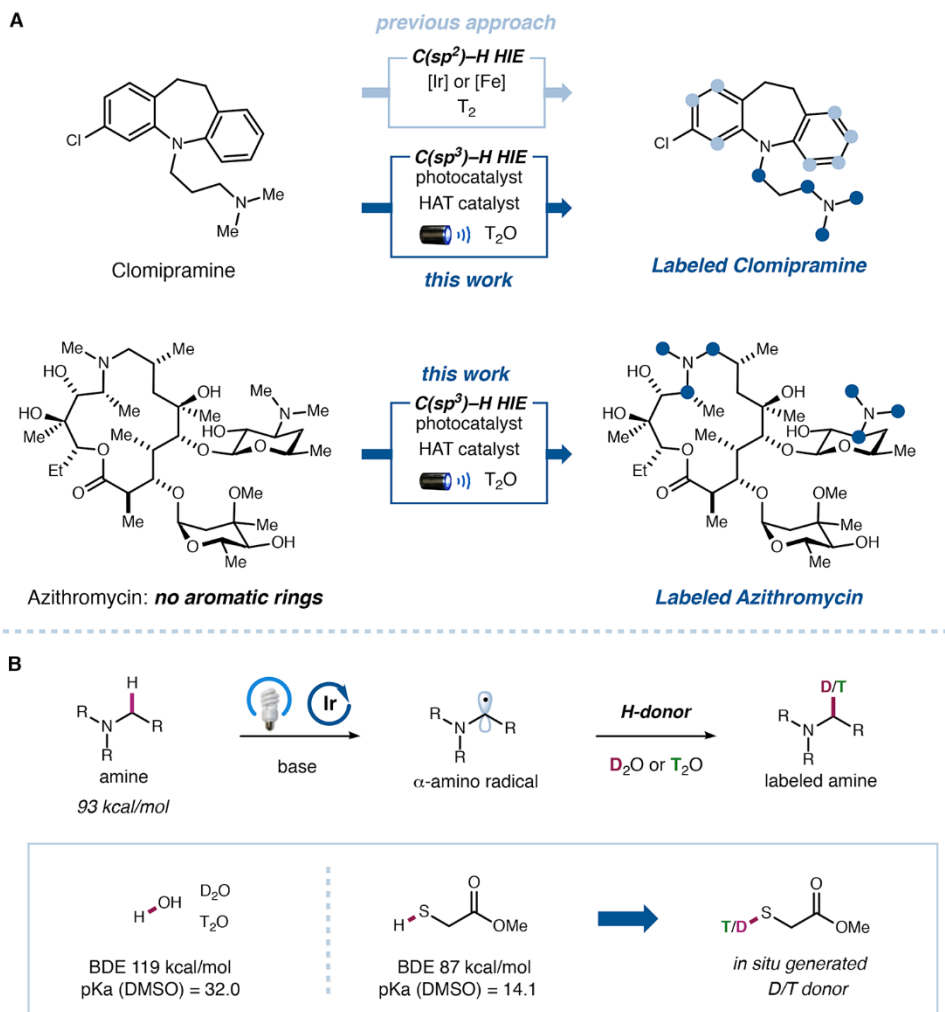


Fig. 1. Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds. (A) The merger of photoredox and hydrogen atom transfer (HAT) catalysis enables α -amino $C(sp^3)$ -H selective HIE of alkylamine-based drugs. (B) Hypothesis for the proposed photoredox-catalyzed deuteration and tritiation.

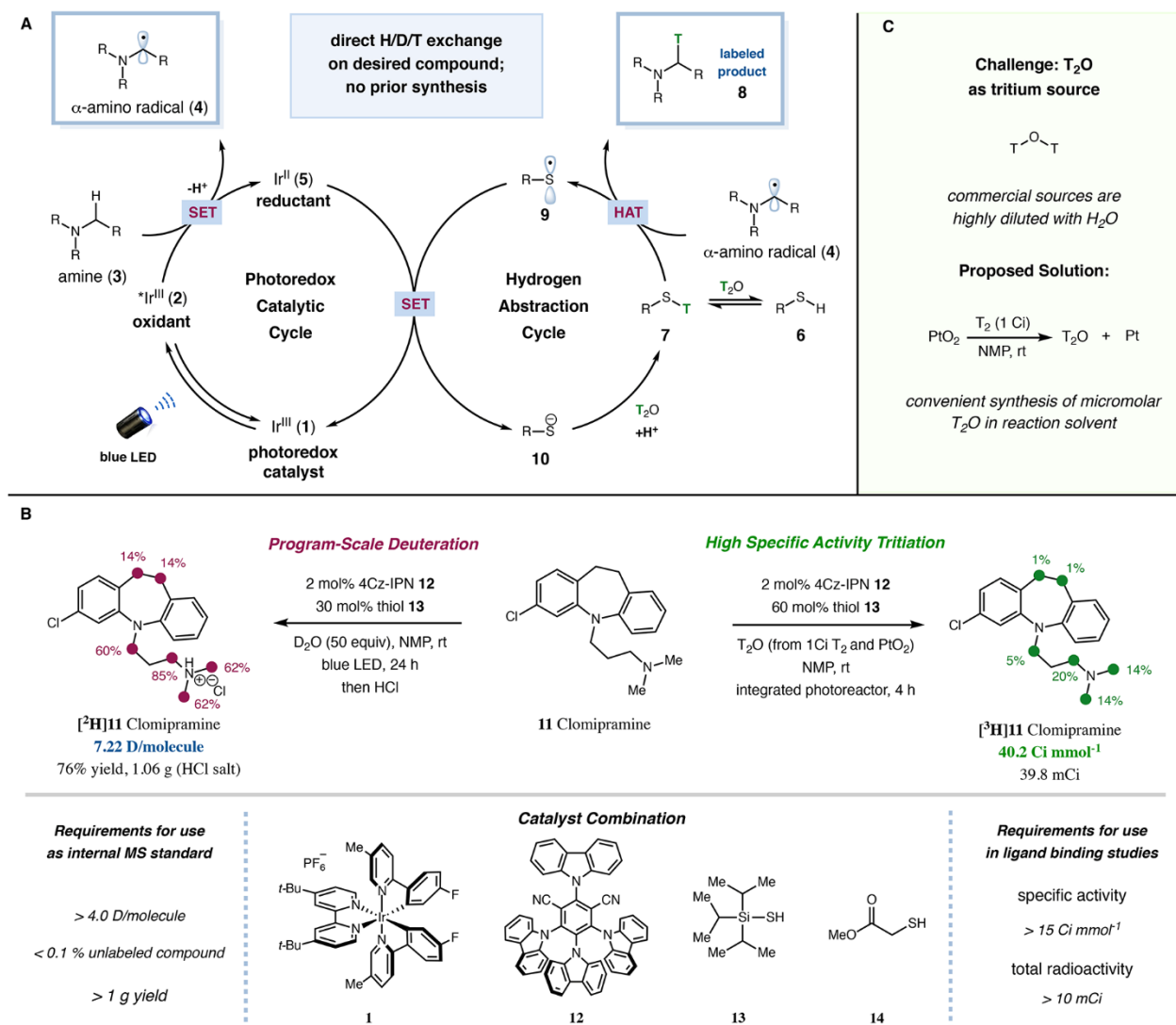


Fig. 2. Reaction development. (A) Proposed catalytic cycle for the photoredox-catalyzed HAT protocol is shown. SET, single-electron transfer; HAT, hydrogen atom transfer; LED, light-emitting diode. (B) Procedures and requirements for program-scale deuteration and high specific activity tritiation. The colored dots (maroon or green) and numbers denote the positions of the C–H bonds that are labeled and the % incorporation of the hydrogen isotope, respectively. NMP, *N*-methyl-2-pyrrolidone; rt, room temperature (C) High specific activity T_2O is accessible from T_2 and PtO_2 at micromolar scale and can be used for photoredox-catalyzed tritiation in a one-pot procedure.

Program-Scale Deuteration

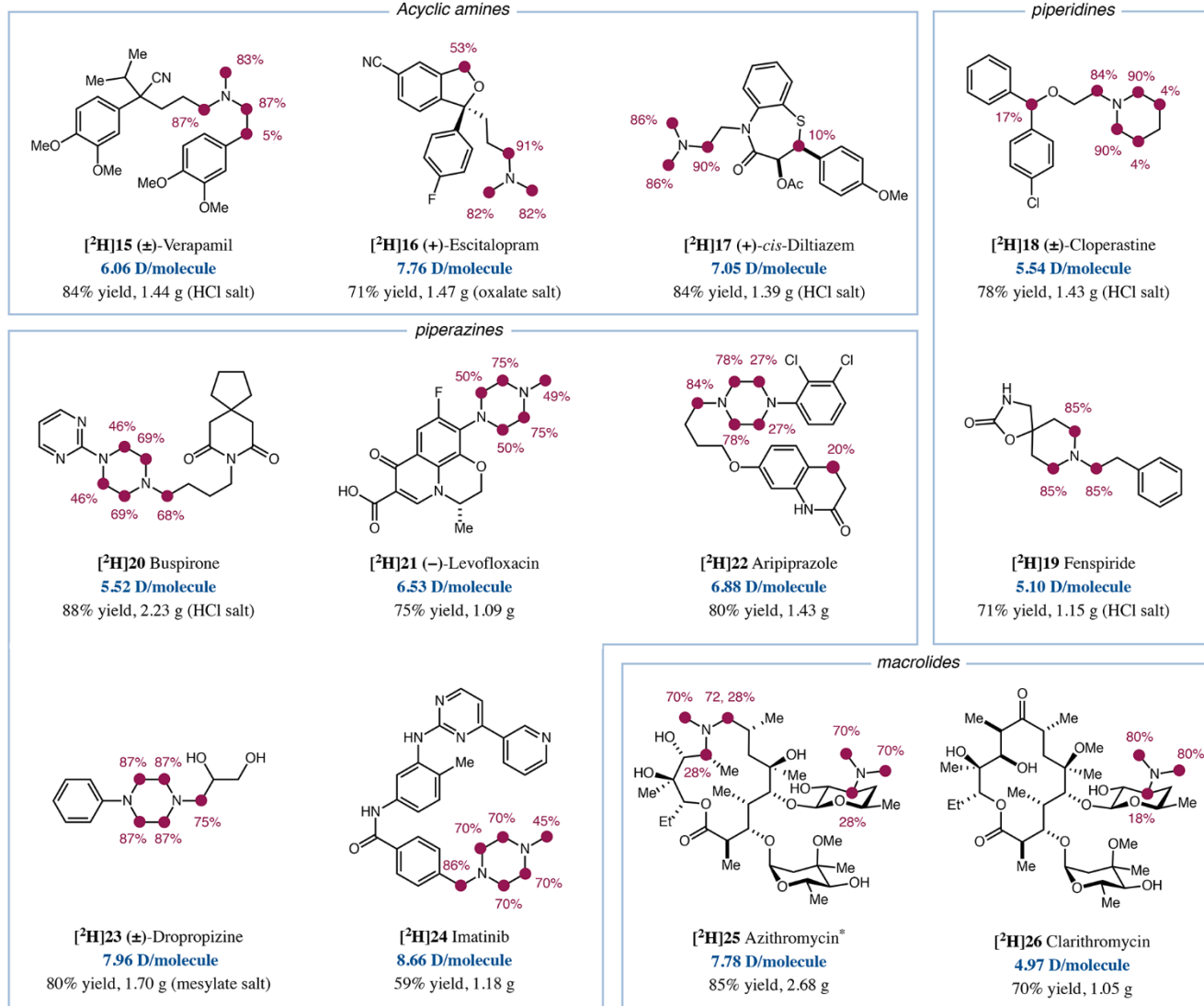


Fig. 3. Scope of program-scale deuteration. Reaction conditions: photoredox catalyst **1** or **12** (2 mol %), triisopropylsilanethiol **13** (30 mol %), D₂O (50 equiv.), Li₂CO₃ (1.2 equiv., added when substrate is used as its acid salt) NMP, room temperature, 34W blue LED or integrated photoreactor. The products were isolated as the appropriate acid salts shown in the parentheses. Ac, acetyl group. *The two protons at the α-amino methylene position are diastereotopic and are labeled to different extents.

High Specific Activity Tritiation

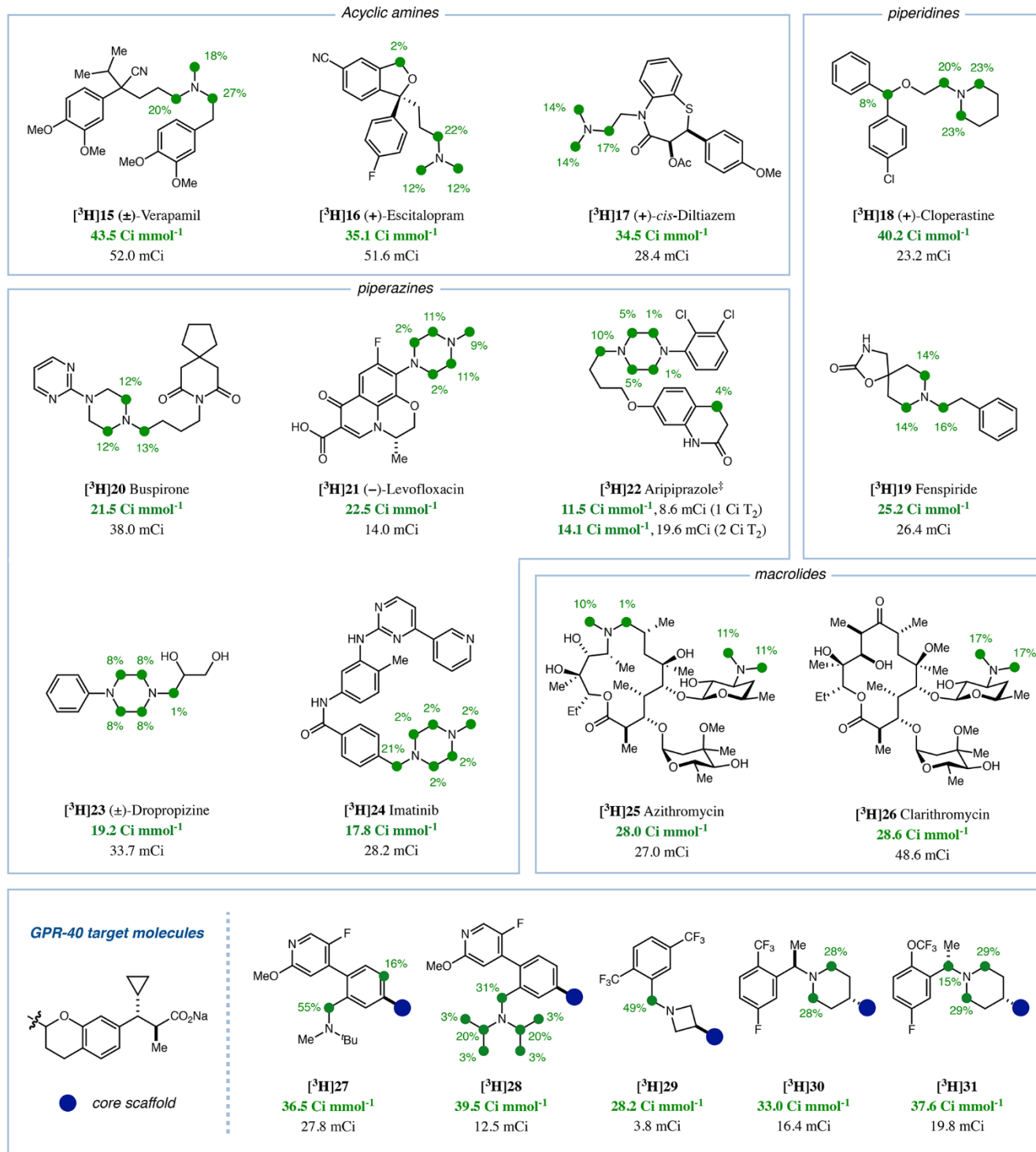


Fig. 4. Scope of high specific activity tritiation. Reaction conditions: substrate (2 μmol), photoredox catalyst **1** or **12** (4 mol %), thiol catalyst **13** or **14** (60 mol %), T₂O (preformed from 1Ci T₂ and PtO₂), NMP, room temperature, 34W blue LED or integrated photoreactor. ^tBu, *tert*-butyl group. [‡]Incorporation depicted is for the 2 Ci reaction with [³H]22.

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