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Late-Stage Isotopic Exchange of Primary Amines

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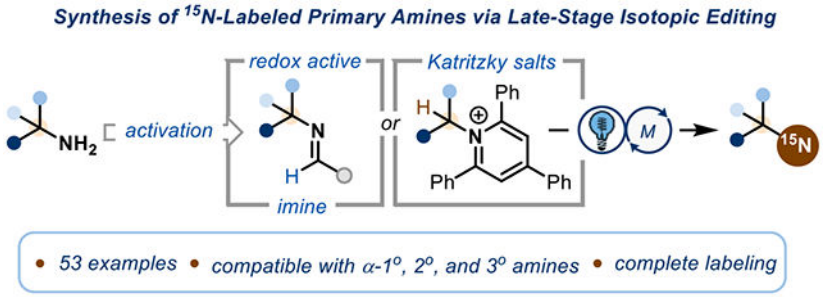
Abstract

Stable isotopes such as ^{2}H, ^{13}C, and ^{15}N have important applications in chemistry and drug discovery. Late-stage incorporation of uncommon isotopes via isotopic exchange allows for direct conversion of complex molecules into their valuable isotopologues without requiring a *de novo* synthesis. While synthetic methods exist for the conversion of hydrogen and carbon atoms into their less abundant isotopes, a corresponding method for accessing ^{15}*N*-primary amines from their naturally occurring ^{14}*N*-analogues has not yet been disclosed. We report an approach to access ^{15}*N*-labeled primary amines via late-stage isotopic exchange using a simple benzophenone imine as the ^{15}N source. By activating α-1° and α-2° amines to Katritzky pyridinium salts and α-3° amines to redox-active imines, we can engage primary alkyl amines in a deaminative amination. The redox-active imines proceed via a radical-polar-crossover mechanism, whereas the Katritzky salts are engaged in copper catalysis via an electron donor-acceptor complex. The method is general for a variety of amines, including multiple drug compounds, and results in complete and selective isotopic labeling.

Graphical Abstract



Keywords

Isotope; labeling; photoredox catalysis; radical-polar crossover; copper catalysis

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The authors declare a conflict of interest: A provisional patent has been filed on this work.

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org

Experimental procedures, optimization tables, compound characterization data

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INTRODUCTION

The incorporation of isotopes into organic molecules is of paramount interest across many areas of science. Stable isotopes such as ^{2}H, ^{13}C, and ^{15}N have had important applications in elucidating chemical mechanisms[1-5] and in drug discovery as tracers for metabolic studies.[6-13] In addition, ^{13}C and ^{15}N-labeled amino acids have been extensively used as labeling tracers in quantitative proteomics (SILAC).[14,15] More specialized uses, such as in hyperpolarized NMR,[16] are also emerging, increasing the demand for reliable syntheses of these labeled materials. As molecules for these advanced applications become more complex, new synthetic routes to prepare isotopically enriched materials must advance to minimize the length and cost of synthesis.[17] Selective replacement of an atom for its isotope through late-stage functionalization is attractive because it obviates the need for a costly and time consuming *de novo* synthesis. However, such a realization requires very mild reaction conditions and ideally complete isotopic exchange.

Significant efforts towards late-stage atom exchange[18] of hydrogen- and carbon-containing molecules have been previously described. Installing ^{2}H in organic frameworks has been achieved by exploiting the inherent acidity of many C-H bonds, or by using isotopically enriched metal-hydrides or hydrogen-atom-transfer reagents (Scheme 1A).[19] Although powerful, the C-H functionalization step is often in equilibrium between the labeled and unlabeled substrate, which can lead to incomplete labeling. Strategies aiming to incorporate carbon isotopes, specifically via carbon atom exchange, have been developed largely using decarboxylative carboxylation with $^{13}CO_2$ (Scheme 1B).[20-25] This strategy again relies on the reversibility of the decarboxylation process, which makes it challenging to obtain high levels of the desired isotopic enrichment without biasing the system, often by using large excess of labeled starting material.[26]

In contrast, due to the strength of C-N bonds, as well as the inherent nucleophilicity and poor leaving group ability of amines, direct exchange of a nitrogen atom for its isotope is a non-trivial transformation. The unique properties of ^{15}N, such as wide chemical shift range and optimal relaxation lifetime, makes it an ideal nucleus for emerging biological imaging techniques.[16] The current technology for obtaining an ^{15}N-labeled primary amine requires a *de novo* synthesis of the desired molecule,[27-30] precluding fast and modular diversification of existing medicinally relevant or naturally abundant nitrogen containing molecules for their ^{15}N counterparts.[31-33] In addition, some of these examples also result in incomplete labeling. Herein, we present strategies for direct conversion of a broad range of primary amines to their isotopic counterparts (Scheme 1C). Judicious choice of reaction conditions renders the reaction feasible for α-primary, -secondary, and -tertiary amines, including many pharmaceutical compounds. The isotope is introduced using ^{15}N-labeled benzophenone imine, easily synthesized from ^{15}N-ammonium chloride, the most economic and abundant form of ^{15}N. The isotopically labeled products are isolated with complete labeling, as the unreacted ^{14}N-starting material is functionalized and separated. The reaction proceeds under mild conditions, making it amenable to many complex drug targets.

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RESULTS AND DISCUSSION

We envisioned that we could utilize existing amine activation strategies (Scheme 2A) to engage primary amines in isotopic editing. State-of-the-art amine activation for α-1° and αa-2° amines relies on the formation of Katritzky pyridinium salts, which can undergo single-electron reduction via transition metal (TM) catalysis[34] or photoredox catalysis[35] to generate a primary or secondary carbon-centered radical. For sterically hindered α-3° amines, Katritzky salt formation is not possible due to steric clash of the 2,6-phenyl substitution and the α-3° amine. Instead, the use of redox-active imines that engage in a single-electron oxidation enables the formation of a tertiary alkyl radical.[36,37] We posited that these radical species could be further oxidized and trapped with a ^{15}N-labeled nucleophile in a radical-polar-crossover (RPC) mechanism. RPC has gained traction over the years as a reliable method for coupling nucleophiles to sterically hindered electrophiles via a carbocation intermediate.[38-45]

It became immediately apparent that using the redox-active imines for RPC posed several significant challenges: a sacrificial oxidant is needed for photocatalyst turnover and radical oxidation; the alkyl radical could be reduced via hydrogen-atom-transfer; the carbocation trapping could be outcompeted by water (hydration product) or by elimination to form an alkene. Extensive optimization (see Supporting Information for full optimization efforts) led us to suitable conditions to minimize these deleterious pathways and successfully form the isotopically labeled amines, showing a clear trend with respect to yield and carbocation stability. We found that irradiating the redox-active imines with 456 nm light in combination with an oxidizing iridium photocatalyst, potassium persulfate as a sacrificial oxidant, potassium phosphate tribasic, and ^{15}N-benzophenone imine in pivalonitrile (Condition A) provides good yields of the desired ^{15}N-labeled α-3° amines (Scheme 2B). The reaction tolerates acyclic α-3° amines **(3a-e)** with myriad protected functionalities, such as alcohols **(3d)** and amines **(3e)**. Cyclic α-3° amines with various ring sizes are also competent coupling partners in the reaction conditions **(3f-m)**, including an example with an unprotected alcohol **(3m)**. Benzylic α-3° amines **(3n, 3o)** give higher yields of desired product, likely due to the stability of both the radical and carbocation intermediates, which mitigates undesired reactivity. However, electron-deficient benzylic α-3° amines are not suitable coupling partners, instead forming the homodimer of the radical species as the major product (see SI).

In an effort to engage α-1° and α-2° amines in isotopic exchange, we turned to Katritzky salts for a redox-neutral RPC. The oxidized photocatalyst after radical generation can be reduced by the resulting radical, generating the desired carbocation intermediate. We found that a reducing ruthenium photocatalyst and ^{15}N-benzophenone imine as the nucleophile (Condition B) affords labeled primary benzylic amines in high yields **(4a-c)**. Electron-rich benzylic amines are good coupling partners, while electron neutral ones lead to a drop in yield **(4d, 4e)** and electron-deficient ones result in trace yields **(4f, 4g)**, likely due to the challenging generation of the carbocation intermediate. In addition, using nonbenzylic Katritzky salts in the RPC system results in trace yields of desired product. It was apparent that the dependence on carbocation stability limited this system to electron-rich α-primary amines.

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To address this limitation, we sought a method suitable for isotopic exchange of unactivated α-1° and α-2° amines by functionalizing the intermediate radical through a divergent pathway that does not involve carbocation formation (Scheme 3). Radicals generated from Katritzky salts are known to interact with a wide variety of electrophilic coupling partners because of the polarity match with the nucleophilic carbon-centered radical.[46] To instead encourage coupling with nucleophilic amine sources, we turned to copper catalysis as a viable approach for a C–N cross coupling given recent precedent using benzophenone imine as a coupling partner.[47,48] In this approach, we hypothesized that a photoredox catalyst could reduce the Katritzky salt to the corresponding radical, which can be subsequently trapped by a copper catalyst.

We were pleased to find that this approach proved effective for performing isotopic exchange on α-secondary amines. However, control studies revealed that omitting photocatalyst has little effect on the yield of the reaction, but light is necessary for productive reactivity (see SI for optimization and control studies). Therefore, we propose that the single-electron transfer event occurs with the copper catalyst and the Katritzky salt through a transiently formed electron donor-acceptor (EDA) complex,[49,50] enabling formation of the desired radical and the oxidized Cu(II) catalyst (Scheme 3A). Alternatively, the Cu(I)(TMHD)imido species, which would be formed if benzophenone imine exchanged with Br, can still form an EDA complex with the Katritzky salt (see Figure S1 in SI). Ligand exchange and radical trapping (or vice versa) results in the formation of a Cu(III) species that is poised to undergo reductive elimination to yield the desired product. UV-Vis studies confirm that upon mixing the copper catalyst with the Katritzky salt in the presence of base, a new complex is formed that can absorb light. This complex can then undergo photoinduced single-electron transfer, allowing isotopic exchange for unactivated α-secondary amines (Scheme 3B).

Interestingly, replacing Katritzky salt **A** for Katritzky salt **B** containing an α-1° amine disrupts the EDA complex with a concomitant loss of reactivity (Scheme 3C and 3D). Because the redox potentials of **A** and **B** differ by around 50 mV (see SI for cyclic voltammetry data), we wondered if this loss in yield was due to the slight shift in electronics. However, utilizing an α-1° Katritzky salt with electron-deficient aryl substituents, thus shifting the redox potential past that of **A**, also results in low yield (see SI). Therefore, we mainly attribute this loss of reactivity to steric differences between the two pyridinium salts. In the case of **A**, the α-2° amine is twisted out of plane, creating a rigid complex for the copper catalyst to interact with and twisting the pyridinium ring out of planarity. Conversely, **B** has more degrees of freedom and less steric clash, resulting in a more planarized pyridinium ring and possibly affecting the manner in which it interacts with the Cu(I)(TMHD) catalyst.[51] Redesigning the Katritzky salt[52] and installing ethylene bridges between the triphenyl core to rigidify the structure (Katritzky salt **C**) results in the formation of a new EDA complex while restoring reactivity and yield (Scheme 3D).

Having established a viable strategy for isotopic exchange of unactivated primary amines, we proceeded to examine the scope of amines for the transformation (Scheme 4). Cyclic α-2° amines containing various functionalities provide good yields, including six- **(5a-5d)**, five- **(5e, 5f)**, four- **(5g)**, and seven-membered rings **(5h)**. Linear α-2° amines

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are also competent coupling partners **(5i, 5j)**. Excitingly, amino acid motifs **(5k, 5l)** are successful coupling partners in this transformation, affording valuable ^{15}N-labeled amino acid derivatives[53,54] and complimenting recent carbon isotope exchange methodologies on amino acids.[55]

Utilizing Pyr**2** allows for isotopic exchange of a wide variety of α-1° amines. Various heterocycles are tolerated, including furans **(6c, 6e)**, indoles **(6g)**, pyrazoles **(6h)**, imidazoles **(6i)**, and thiazoles **(6j)**. Protected lysine **6d** undergoes desired coupling efficiently, showcasing the ability to label either nitrogen of this amino acid. Lastly, electron-deficient arenes that were low yielding under the radical-polar crossover conditions can be efficiently converted in the Cu catalytic system **(6l, 6m)**.[56]

Lastly, we sought to demonstrate the versatility and applicability of our reaction conditions by labeling a variety of drug-like molecules (Scheme 5). Amine functionality is one of the most prevalent functional groups in pharmaceutical targets,[57] with primary amines occurring in a variety of market drugs or being used as late-stage intermediates (see **7b)** towards substituted amine and amide containing drugs.[58] Installing an isotopic label as the last step in a complex molecule synthesis is ideal, as the yield of the isotopically enriched substrate is maximized and there is minimal isotopically labeled waste.

Utilizing α-1° amines such as Mosapride intermediate **7b** and Boc-Histamine **7c** give the desired product in moderate to good yields. Drug derivatives containing α-2° amines such as Mexilitene **7a,** Tamiflu **7e,** DL-DOPA **7g,** and Alogliptin also give desired isotopic exchange product in synthetically useful yields, while demonstrating the feasibility of deprotection to the primary amine **(7h)**. In addition, α-3° amines such as Namenda **7d** and Phentermine **7f** also perform well in the isotopic exchange.

CONCLUSIONS

In conclusion, we have developed a general method for the synthesis of ^{15}N-labeled primary amines. This expands the range of isotopic labeling to include nitrogen-isotope exchange of primary amines, complementary to hydrogen- and carbon-isotope exchange methodologies. By condensing α-1° and -2° amines to the Katritzky pyridinium salt and α-3° amines to redox-active imines, we have developed the first isotopic-exchange conditions suitable for all three categories of primary alkyl amines. The reaction tolerates a variety of functionality and is amenable to the isotopic exchange of late-stage drug derivatives. We hope that unlocking this new approach to the synthesis of ^{15}N-labeled materials will broaden their already prevalent uses in mechanistic studies, amino acid labeling, hyperpolarization probes, and labels in clinical pharmacology.

Supplementary Material

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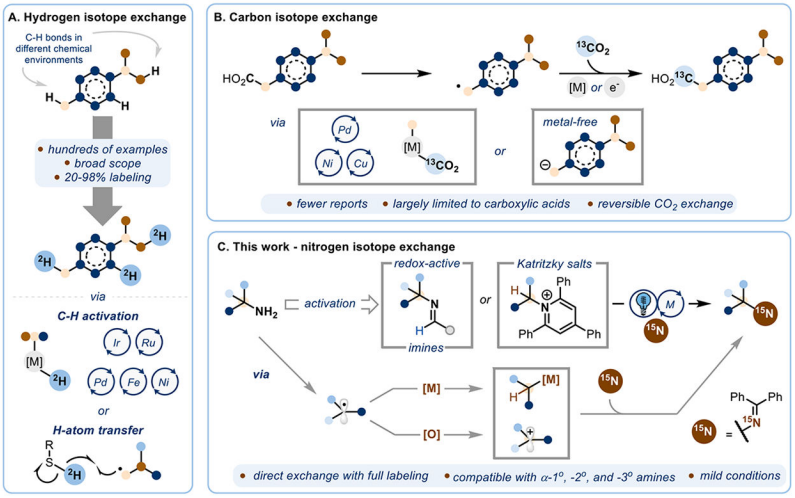

Scheme 1.
Overview of Late-Stage Stable Isotope Incorporation.

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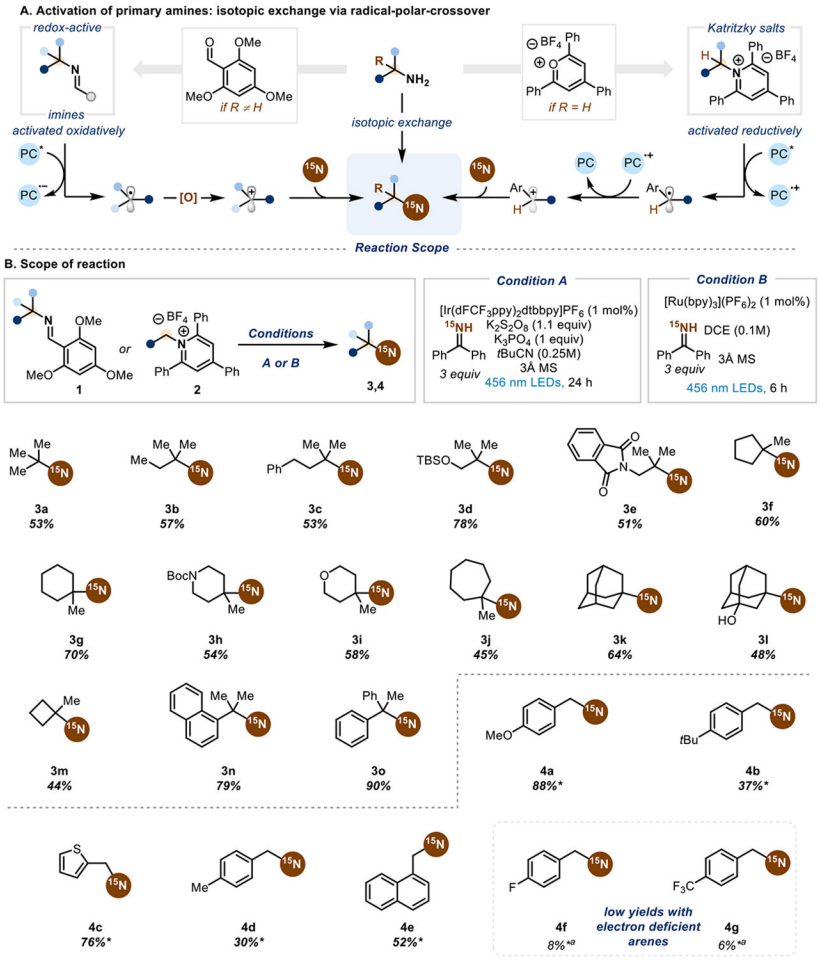

Scheme 2. Reaction Design and Scope.

All yields are isolated yields with >99% ^{15}N labeling. Compounds without an asterisk indicates that the reaction was conducted with coupling partner **1** and Condition A. An asterisk indicates that the reaction was conducted with coupling partner **2** and Condition B. (a) NMR yield with mesitylene as an internal standard.

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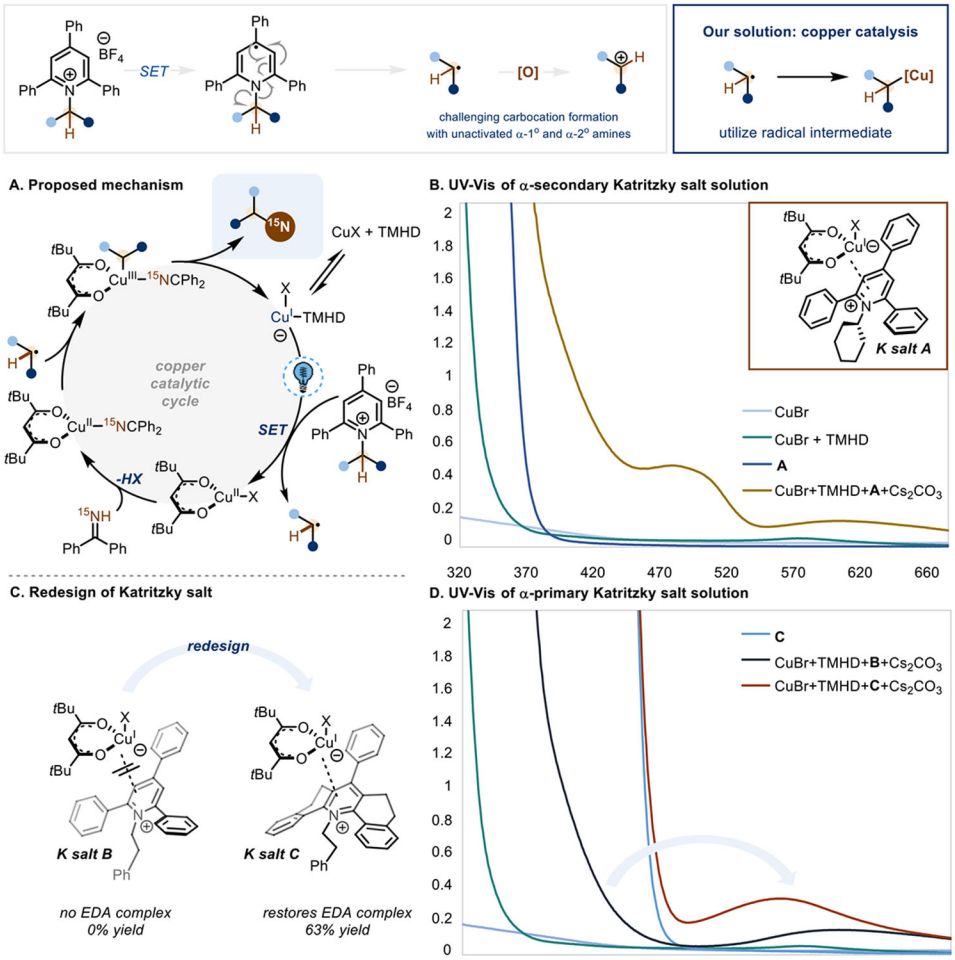

Scheme 3.

Activating Amines for Isotopic Exchange via Copper Catalysis.

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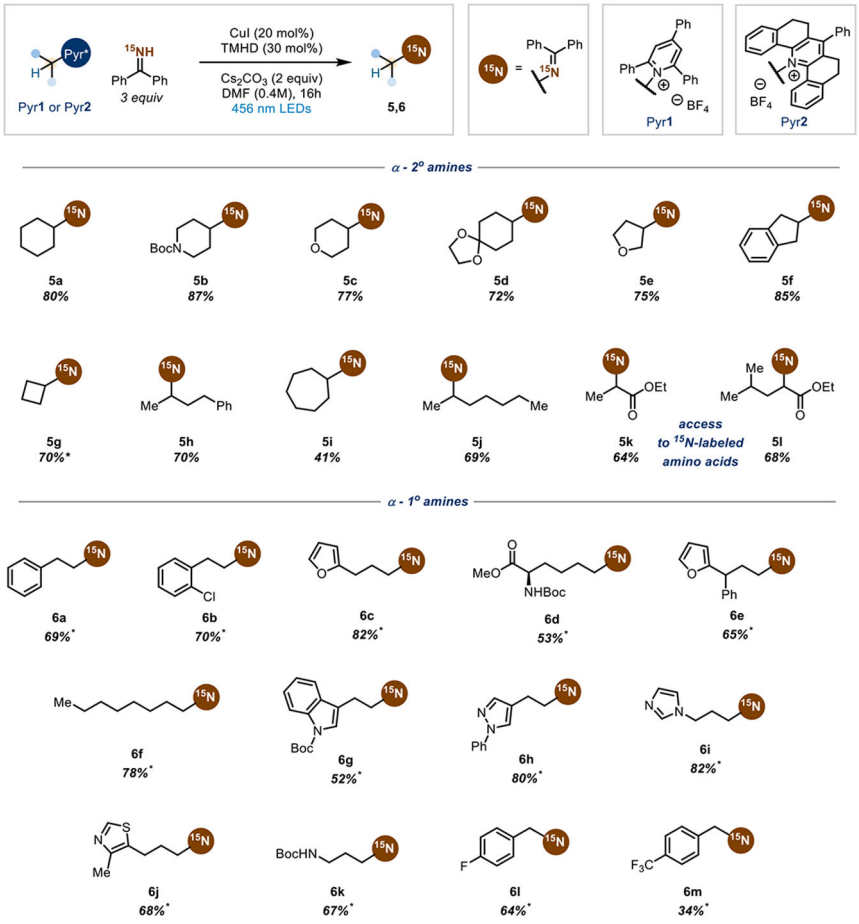

Scheme 4. Scope of Amines for Isotopic Exchange with Cu Catalysis.

All yields are isolated yields with >99% ^{15}N labeling. Compounds without an asterisk indicates that the reaction was conducted with Pyr**1**. An asterisk indicates the reactions conducted with Pyr**2**.

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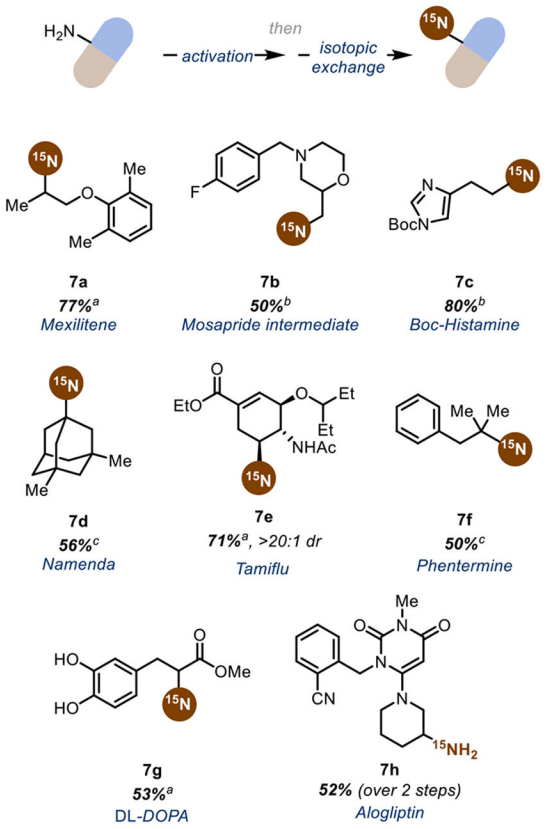

Scheme 5. Scope of Reaction Conditions with Drug-Like Molecules.

All yields are isolated yields with >99% ^{15}N labeling. (a) 1 equiv Pyr**1**, 20 mol% CuI, 30 mol% TMHD, 2 equiv Cs_2CO_3, 3 equiv *^{15}N*-benzophenone imine, DMF (0.4M), 456 nm LED irradiation for 16 hours. (b) Reaction conditions are the same as in (a) but with 1 equiv Pyr**2** instead of Pyr**1**. (c) 1 equiv redox-active imine, 1 mol% $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$,2 equiv potassium persulfate, 1 equiv potassium phosphate tribasic, 3 equiv *^{15}N*-benzophenone imine, ~25 mg 3Å MS in pivalonitrile (0.25M) with 456 nm irradiation for 24 hours.