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Introduction

Amides are ubiquitous functional groups, pervading both natural and synthetic realms. They are foundational components of organic chemistry, material science, and drug discovery.¹ The exceptional robustness of the amide bond is a key factor in its prevalence within biological systems. This functional group remains the most common motif in medicinal chemistry literature and blockbuster drugs, with over 40% of bioactive molecules incorporating this structural feature (Scheme 1a).²

The widespread importance of amides has stimulated the development of methods to incorporate stable and radioactive isotopes into this privileged functional group.^{3,4} (Radio) tracers, organic molecules containing one or more (radioactive) isotopes, are invaluable tools for tracking and studying the behavior of these compounds. Their detection capabilities enable researchers to elucidate the fate of these molecules in various systems.^{5,6} Carbon-14 (¹⁴C), a long-lived beta-emitter with a half-life of 5730 years, is a fundamental tool in drug and agrochemical development. Its incorporation into compounds facilitates critical studies such as quantitative whole-body autoradiography (QWBA)⁷ and the determination of pharmacokinetic (PK) and pharmacodynamic (PD) properties of lead compounds, as well as assessing the safety profile of drug candidates.⁸ While carbon isotope labeling introduces greater synthetic complexity and often increases resource and cost demands,⁹ the inherent stability of the C–C bond compared to

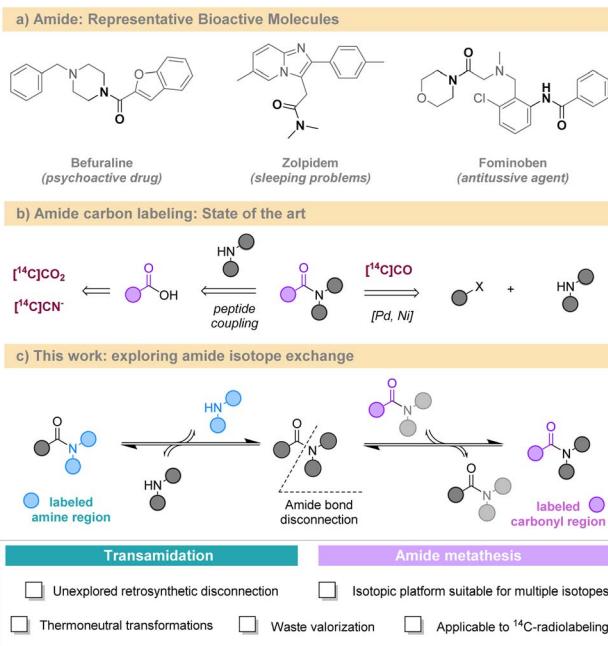
Base-promoted dynamic amide exchange: efficient access to isotopically enriched tertiary amides[†]

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Amide isotope labeling is a crucial tool in drug discovery and development. However, current methods label the desired peptide bond in a multi-step fashion. This study presents novel strategies for amide isotope exchange through transamidation and amide metathesis. By optimizing reaction conditions and exploring substrate scope, we achieved direct labeling of both amine and carbonyl moieties. These findings pave the way for more sustainable isotope labeling technologies. Furthermore, preliminary examples of isotope-containing waste recycling demonstrate a crucial step towards a greener future for isotope chemistry.

the C–H bond offers superior metabolic stability, a critical advantage for human absorption, distribution, metabolism, and excretion (h-ADME) studies.^{10,11}

The ¹⁴C-labeling of the amide bond at the carbonyl position offers a routine approach to trace the metabolic fate of organic compounds. The traditional bottom-up strategy involves the initial incorporation of the ¹⁴C-label into the carboxylic acid moiety, followed by conversion to the target C-labeled amide (Scheme 1b).¹² The carboxylation step, employing Mg and Li organometallic reagents, often exhibits poor functional group



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tolerance when using [¹⁴C]CO₂.¹³ This limitation restricts radioisotope incorporation to moderately functionalized building blocks, necessitating subsequent multi-step and waste-intensive decoration processes.¹⁴ Alternatively, the ¹⁴C-cyanation of alkyl or aryl halides *via* SN₂¹⁵ or metal catalyzed cross-coupling reactions¹⁶ and subsequent nitrile hydrolysis and amide bond formation might grant access to labeled amides.

In this context, the advent of low-pressure metal-catalyzed amino-carbonylative cross-couplings have significantly broadened the landscape for amide labeling.¹⁷ Despite the reported instability of [¹⁴C]CO to radiolysis, *in situ* generation of this ¹⁴C-labeled gas has mitigated this challenge.^{18–20} While attractive, these strategies demand *ad hoc* precursors suitable for the carbonylation, namely the corresponding aromatic halides. Furthermore, the need for gaseous radioactive isotope reagents presents a challenge in countries with strict emission regulations, rendering previous [¹⁴C]CO-based technologies very challenging to implement.^{18b,21} An ideal top-down approach would target directly the amide itself as a starting precursor, which in presence of an adequate isotope source, would enable the crucial labeling step through dynamic exchange, *i.e.* the disassembly and reassembly of the amide bond. This approach would complement the state of the art and help streamline the radio-synthesis process by simultaneously deconstructing and reconstructing the desired amide bond, thus providing an unexplored retro-synthetic disconnection.²² In addition, the amide could be labeled either at the carbonyl or at the amine region.

Amide exchange (or metathesis)²³ has been explored in the area of polymer chemistry in polyamides,²⁴ usually under harsh thermal conditions (>270 °C). In the early 2000s, pioneering works from Gellman and Stahl conceptualized this transformation for small organic molecules both on secondary²⁵ as well as tertiary amides.²⁶ Starting from two distinct amides, it was possible to reach the thermodynamic equilibrium, given the optimized set of conditions. While these groundbreaking reports moved forward the boundaries of dynamic covalent chemistry,²⁷ the utilization of such concept have been essentially overlooked since then. A significant drawback of amide metathesis is its propensity to yield a statistic mixture of four amides, thereby complicating downstream purification efforts.

Seeking to explore amide isotope exchange, we identified amide bond metathesis as a promising strategy. Herein, we present our preliminary findings in this area (Scheme 1c). We disclose a base-promoted transamidation reaction that enables direct exchange of the amine partner, yielding the desired labeled amide. Building upon these findings, we developed a complementary strategy targeting amide bond metathesis. By employing a non-volatile isotope carrier, we explored the potential for labeling the carbonyl moiety of an amide. Furthermore, we also illustrate its potential for radioactive labeling with ¹⁴C, offering an unexplored platform for future human ADME research. Considering the cardinal importance of unactivated *N,N*-disubstituted amides in isotope labeling, we anticipate that this preliminary study will find applications and inspire future efforts in the area.

Results and discussion

Transamidation: labeling the amine region

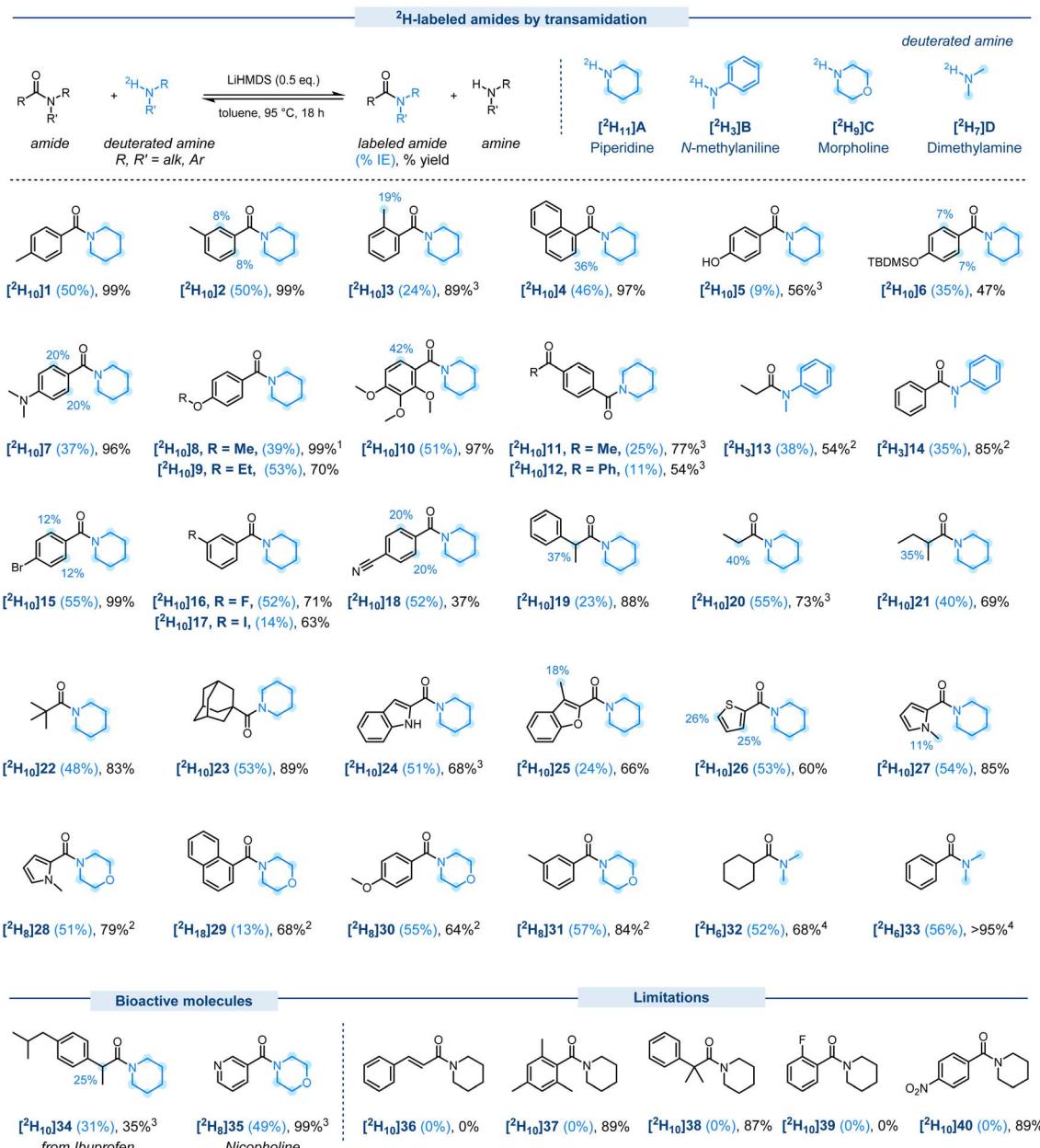
Initially, we explored amide isotope exchange focusing on labeling the amine moiety. Carboxamides exhibit enhanced stabilization of their carbonyl carbon compared to other carbonyl compounds. It is textbook knowledge that, unlike acyl halides, anhydrides and esters, amides are notoriously unreactive toward nucleophilic addition.²⁸ Transamidations are inherently difficult due to the stability and robustness of the amide C–N bond, resulting in kinetically unfavorable and typically thermoneutral reactions. This challenge is exacerbated in tertiary amides by the steric hindrance around the C–N bond and the absence of an activation site on the nitrogen atom.²⁹ Common strategies to overcome these difficulties are the use of sterically or electronically biased tertiary amides,³⁰ namely unconventional activated and twisted amides have been broadly studied.³¹ Otherwise, the reaction with primary amines will facilitate the formation of a stable amidate anion, which provides a thermodynamic driving force for the overall transformation.³² Lacking a driving force, transamidation of tertiary amides is governed by amide stability, typically yielding a mixture of thermodynamic products.³³

While typically detrimental, we took advantage of the thermoneutral nature of transamidation to access amide isotope exchange by employing an isotopologue secondary amines. To start the investigation, we identified tertiary amide **1** and per-deuterated piperidine [²H₁₁]A as model substrates. After optimization (Table 1), an efficient exchange was observed using 0.25 equiv. of LiHMDS as base, 1.0 equiv. of labeled amine, at 95 °C for 18 h in toluene with almost perfect equilibration and

Table 1 Optimization of transamidation between substrate **1** and deuterium-labeled amine [²H₁₁]A

Transamidation optimization				
Entry	Deviation from initial cdtns	Yield (%)	[² H ₁₀]1/[¹ H]1 ratio	
1	None	88%	48/52	
2	0.75 equiv. of LiHMDS	41%	51/49	
3	0.50 equiv. of LiHMDS	85%	51/49	
4	0.10 equiv. of LiHMDS	97%	0/100	
5	NaHMDS instead of LiHMDS	79%	0/100	
6	KHMDS instead of LiHMDS	78%	0/100	
7	<i>n</i> BuLi instead of LiHMDS	44%	45/55	
8	THE instead of toluene	91%	37/63	
9	Chloroform instead of toluene	70%	0/100	
10	CH ₃ CN instead of toluene	75%	0/100	
11	55 °C	97%	51/49	
12	25 °C	96%	0/100	
13	6 h at 55 °C	96%	45/55	
14	2 h at 55 °C	88%	26/74	





[²H₁₀]1 (50%), 99%

[²H₁₀]2 (50%), 99%

[²H₁₀]3 (24%), 89%³

[²H₁₀]4 (46%), 97%

[²H₁₀]5 (9%), 56%³

[²H₁₀]6 (35%), 47%

[²H₁₀]7 (37%), 96%

[²H₁₀]8, R = Me, (39%), 99%¹

[²H₁₀]9, R = Et, (53%), 70%

[²H₁₀]10 (51%), 97%

[²H₁₀]11, R = Me, (25%), 77%³

[²H₁₀]12, R = Ph, (11%), 54%³

[²H₁₀]13 (38%), 54%²

[²H₃]14 (35%), 85%²

[²H₁₀]15 (55%), 99%

[²H₁₀]16, R = F, (52%), 71%

[²H₁₀]17, R = I, (14%), 63%

[²H₁₀]18 (52%), 37%

[²H₁₀]19 (23%), 88%

[²H₁₀]20 (55%), 73%³

[²H₁₀]21 (40%), 69%

[²H₁₀]22 (48%), 83%

[²H₁₀]23 (53%), 89%

[²H₁₀]24 (51%), 68%³

[²H₁₀]25 (24%), 66%

[²H₁₀]26 (53%), 60%

[²H₁₀]27 (54%), 85%

[²H₈]28 (51%), 79%²

[²H₁₈]29 (13%), 68%²

[²H₈]30 (55%), 64%²

[²H₈]31 (57%), 84%²

[²H₆]32 (52%), 68%⁴

[²H₆]33 (56%), >95%⁴

Bioactive molecules

Limitations

[²H₁₀]34 (31%), 35%³

from Ibuprofen

[²H₈]35 (49%), 99%³

Nicopoline

[²H₁₀]36 (0%), 0%

[²H₁₀]37 (0%), 89%

[²H₁₀]38 (0%), 87%

[²H₁₀]39 (0%), 0%

[²H₁₀]40 (0%), 89%

Scheme 2 Amide isotope exchange, scope of the transamidation. Standard conditions: amide (0.2 mmol), deuterated amine (0.2 mmol), LiHMDS (0.1 mmol) in dry toluene (2.0 mL) under N_2 at 95 °C for 18 h. Isotopic enrichment measured by HRMS.¹ 55 °C, 25% LiHMDS,² 1.0 equiv. LiHMDS,³ 1.5 equiv. LiHMDS,⁴ 3.0 equiv. LiHMDS. Blue colored circles denote the positions of the D atoms labeled.

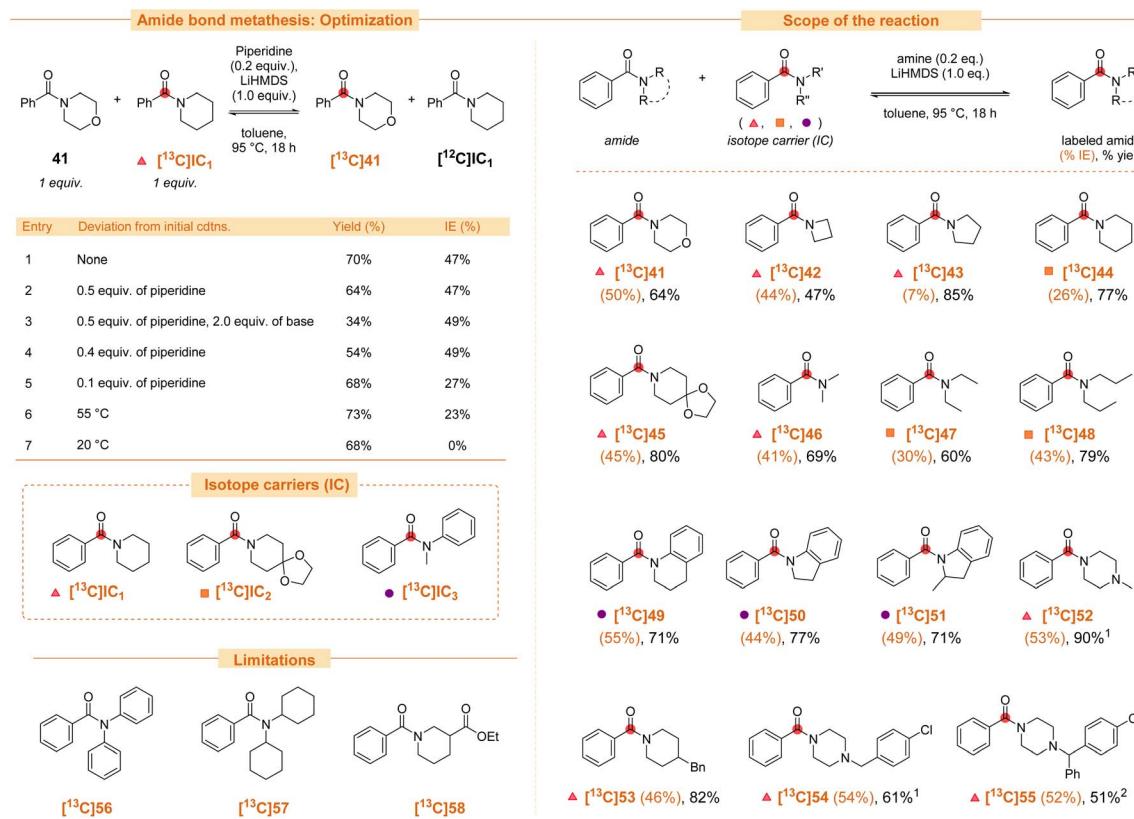
48% IE (isotope enrichment, *i.e.* ratio of labeled/unlabeled amide: 48/52) and 88% yield. Deviation from these optimized conditions proved generally detrimental, especially in terms of isotope incorporation. Optimization of the base loading (Table 1, entries 2–4) revealed that increasing the base amount to 0.50 equiv. did not significantly impact product yield, whereas 0.75 equiv. led to a substantial decrease in amide recovery. Conversely, reducing the base to 0.10 equiv. suppressed the labeling process.

LiHMDS was the most effective base (Table 1, entries 5–7), while *n*-BuLi provided similar labeling efficiency, it resulted in a lower overall yield. THF was identified as the alternative

solvent, surpassing chloroform and acetonitrile (Table 1, entries 8–10). Temperature and reaction time studies indicated that 55 °C for 18 hours produced the best results. Shorter times compromised labeling efficiency, although a reasonable 45 : 55 ratio was achieved after 6 hours.

While the 6 h reaction at 55 °C proved effective for substrate 1 (entry 13), initial substrate scope exploration indicated a need for more stringent conditions. To broaden applicability, the temperature was increased to 95 °C, and the reaction time extended to 18 h.

With such conditions in hand, we explored the scope of the isotope transamidation reaction (Scheme 2). A primary finding



Scheme 3 Optimization and substrate scope of the amide bond metathesis, reaction conditions: amide (0.05 mmol), isotope carrier (0.05 mmol), the selection of carrier is indicated for each substrate next to the yield), LiHMDS (0.05 mmol), amine (0.01 mmol, correspond to the amine moiety of the isotope carrier) in dry toluene (1 mL) under N_2 , at 95 °C for 18 h. Isotopic enrichment measured by HRMS. ¹LiHMDS 2.0 equiv., ²LiHMDS 4.0 equiv. red colored circles denote the positions of the ¹³C atoms labeled.

was the sensitivity of the exchange process to steric hindrance on the aromatic ring. While *meta* and *para*-methyl substituents had negligible impact ([²H₁₀]1 and 2), an *ortho* methyl group [²H₁₀]3 significantly impeded isotope exchange, limiting incorporation to 24% and necessitating base increase, from 0.5 to 1.5 equiv. On the other hand, 1-naphthoic and 2,3,4-trimethoxybenzoic amide derivatives 4 and 10 have been successfully labeled in the process. We then demonstrated the tolerance of the method to common functional groups including silyl ether (6), halogens (15–17), tertiary amine (7), nitrile (18), and ketones (11–12), even if in the last case, the base amount had to be increased to 1.5 equivalent. A low isotopic enrichment of 9% was also obtained using a phenol derivative [²H₁₀]5, still showcasing the tolerance of this group. We then studied the impact of replacing the aromatic ring with alkyl- or heteroaromatic patterns (13, 20–28, 32). In most cases, the IE reached the theoretical maximum with good isolated yields, except in the case of 3-methylbenzofuran-2-carboxylic amide [²H₁₀]25, probably due to the steric proximity of the methyl group. The use of 2-phenylpropionic derivative [²H₁₀]19 also led to a low 23% IE, presumably due to the presence of a proton in benzylic position. To note, minor deuteration was observed due to the presence of a labile N-D on [²H₁₁]A.³⁴ Acidic positions like benzylic (²H₁₀]3 and [²H₁₀]25) or in alpha of the carbonyl

([²H₁₀]19, [²H₁₀]20 and [²H₁₀]34) were labeled (see ESI† for details). The versatility of the method was demonstrated by successfully employing various labeled amines, including *N*-methylaniline [²H₃]B, morpholine [²H₉]C and dimethylamine [²H₇]D. Finally, nicopholine [²H₈]35, an anti-trypanosomal agent, has been successfully labeled, as well as an amide derived from ibuprofen [²H₁₀]34. Some limitations were encountered during scope evaluation: the presence of nitro-group (40) was detrimental for the reaction and having multiple methyl groups near the reaction site inhibited the exchange (37, 38). Secondary reactions have also been observed, such as 1,4-addition in the case of an amide derived from cinnamic acid (36), or as aromatic substitution of fluorine-substitution aromatic cycle (39).

Amide bond metathesis: labeling the carbonyl region

Having established an effective transamidation method for amine exchange, we shifted our focus to developing a complementary strategy for isotope exchange of the carbonyl motif. To ensure a sustainable process, a non-volatile and readily accessible isotopic carrier (IC) was designed.³⁵ Aryl carboxamides, compatible with amide metathesis, were identified as suitable ICs based on these criteria (Scheme 3). Unfortunately, initial attempts made on model carboxamide 41 and [¹³C]IC₁ using



tetrakis(dimethylamido) zirconium(IV) $Zn(NMe_2)_4$ or tris(dimethylamino) aluminium dimer $Al_2(NMe_2)_6$ were unproductive in our hands (see ESI† for details).^{25,26} The unsuccessful results and the demanding handling requirements of these sensitive reagents under anhydrous conditions persuaded us to explore alternative, more practical approaches.

Capitalizing on our transamidation findings, we devised a strategy to exploit the equilibrium nature of the reaction for carboxylate exchange. We hypothesized that *in situ* generated lithium piperide^{37,38} would react unselectively with both substrate **41** and labeled carrier $^{[13]C}IC_1$. While transamidation onto $^{[13]C}IC_1$ would be unproductive, the reaction with **41** would generate the unlabeled isotopologue of the carrier $^{[12]C}IC_1$ and the desired lithium morpholide. This lithium amide would then promote amide isotope exchange through subsequent transamidation with $^{[13]C}IC_1$. We predicted that compared to previously reported amide metathesis reactions, this protocol would offer notable advantages in terms of simplicity and reaction composition, involving only two amides and their respective isotopologues. Gladly, initial attempts were encouraging and after some optimization we established the optimized conditions, based on the use of 1.0 equiv. of $^{[13]C}IC_1$ and LiHMDS, 20 mol% of piperidine, in toluene at 95 °C for 18 h. With these conditions, we were glad to observe that a labeled amide $^{[13]C}41$ was obtained with a good 70% yield and 47% IE.

Variations of some parameters, including the amount of piperidine, equivalents of base, and temperature were then tested, but did not improve the outcome of the reaction (Scheme 3). Increasing the amount of piperidine reduced the yield of labeled recovered amide. On the other hand, a reduction to 0.1 equivalent of piperidine was detrimental, with a reduced IE of 27%. Regarding the temperature, a reduced IE of 23% has been obtained at 55 °C and no reaction was observed at room temperature. We then decided to keep our initial conditions for the scope evaluation.

Careful selection of the isotope carriers was crucial to facilitate the subsequent purification. Three carriers were evaluated, including amides bearing piperidine $^{[13]C}IC_1$ and 4-piperidone cyclic ketal $^{[13]C}IC_2$. Employing these carriers, carbonyl labeling was successfully achieved for a range of tertiary amides, including derivatives of azetidine $^{[13]C}42$, pyrrolidine $^{[13]C}43$, 4-benzylpiperidine $^{[13]C}53$, *N*-methylpiperazine $^{[13]C}54$, and dialkyl amines (dimethyl, diethyl, and dipropyl) $^{[13]C}46$ – 48 . However, when anilides were submitted to amide exchange no reaction was observed, with both labeled-**IC₁** and **IC₂**. As previously reported by Hong, Szostak and co-workers, who charted the selectivity in transamidation of unactivated amides, anilides are generally more reactive toward the rate-limiting nucleophilic addition step compared to *N,N*-dialkyl amides.³² To unlock the reactivity of these derivatives, it was mandatory to adapt the carrier/amine couple and use a *N*-methylanilide moiety. Gratifying, using $^{[13]C}IC_3$ amide exchange proceeded on anilides **49**–**51** with 71 to 77% yield and 44 to 55% IE. As expected, limitations of the reaction were also identified. Amides bearing hindered, bis-aromatic or electrophilic *N*-substitutions were unsuitable substrates for the transamidation process.

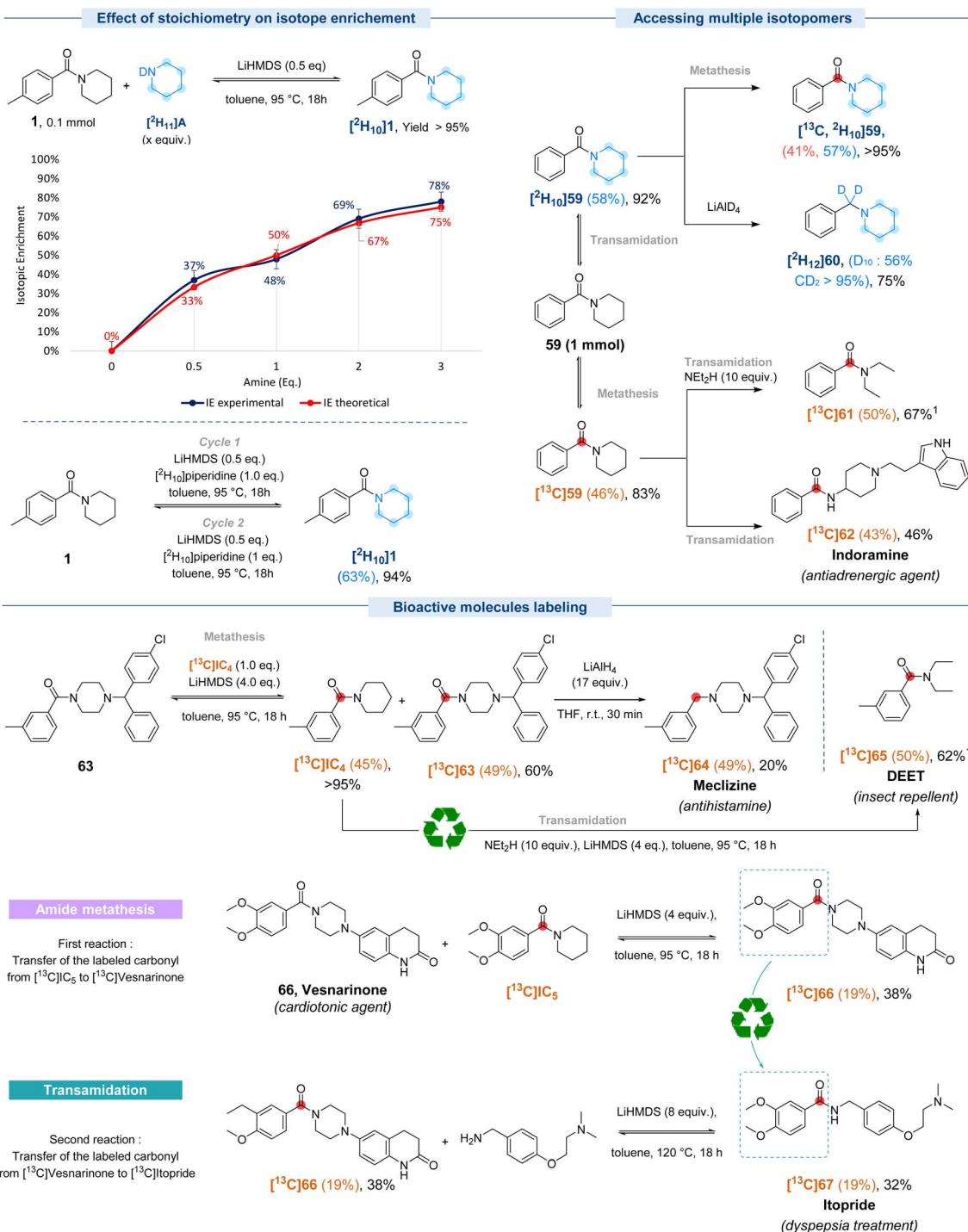
Applications of amide transamidation and metathesis

Since the isotope enrichment of a labeled molecule can affect its application, we examined the variation of the stoichiometry of the amine on the transamidation on our model substrate (Scheme 4, top left). By varying the amount of deuterated amine from 0.5 equivalents to 3 equivalents, the experimental enrichments obtained were well in line with the theoretical maximum enrichments. Alternatively, repeating the transamidation twice in a sequential method, the enrichment could be increased using less isotope carrier. Furthermore, the scale of both transamination and amide metathesis were increased by a 5-fold scale without any drop in yield or isotopic enrichment (Scheme 4, top right). It was shown that this platform offers access to multiple isotopomers in a straightforward manner. Three isotopomers of **59** [$^{[13]C}$, $^{[2]H_{10}}$] and [$^{[13]C}$, $^{[2]H_{10}}$] were within reach by simple alternation of the conditions and $^{[2]H_{10}}$ **59** could be reduced in presence of $LiAlD_4$ to give 12-fold deuterated *N*-benzylpiperidine $^{[2]H_{12}}\mathbf{60}$, with unique isotopic signature and 95% enrichment of the benzylic position and 56% on the piperidine moiety.

Waste management is a significant yet overlooked issue in isotope chemistry, particularly given the high value, especially in the case of radioactive materials. While stoichiometric control, as advocated by Derdau,³⁹ is a crucial step, the ultimate goal of waste valorisation and recycling remains elusive due to its inherent complexity. In this context, we sought to take full advantage from the transamidation and attempt isotope waste valorization. Indeed, from ^{13}C -labeled amide $^{[13]C]59}$, the amine moiety could be transferred further by transamidation with a secondary amine (in 10 eq. excess) to push the equilibrium towards the formation of $^{[13]C]61}$. In addition, in presence of a primary amine, the antiadrenergic agent indoramine $^{[13]C]62$ could be assembled. Both transformations didn't influence the ^{13}C -enrichment of the carbonyl moiety and allowed to valorize compound **59**. As a corollary, examples of bioactive molecules were labeled. The antihistamine agent meclizine was successfully labeled with ^{13}C by a first metathesis step in presence of $^{[13]C]IC_4$ with an IE of 47% and 60% yield. A reduction step in presence of $LiAlH_4$ gave the labeled meclizine $^{[13]C]64}$ in 20% yield and consistent IE.⁴⁰ Interestingly, the remaining isotopic carrier $^{[13]C]IC_5$ was recovered in over 95% yield and 45% IE and recycled by transamidation with excess of diethylamine to obtain the insect repellent diethyltoluamide (DEET) in 63% yield and ^{13}C -labeled at 50%. Similarly, cardiotonic agent Vesnarinone (**66**) was labeled by metathesis to obtain $^{[13]C]66}$ in 38% yield and 19% IE. In a subsequent transamidation reaction, the newly labeled carbonyl moiety of $^{[13]C]66$ was transferred into biologically active itopride $^{[13]C]67}$ with comparable yield and IE.

Our primary goal was to explore the feasibility of using this strategy for radioactive carbon-14 labeling. Given the encouraging results achieved with Vesnarinone ^{13}C -labeling, we chose this substrate in conjunction with the amide $^{[14]C]IC_5}$. The latter was synthesized in a previous project and had been stored as waste. Utilizing this waste for Vesnarinone labeling offers a valuable opportunity to repurpose it into a useful



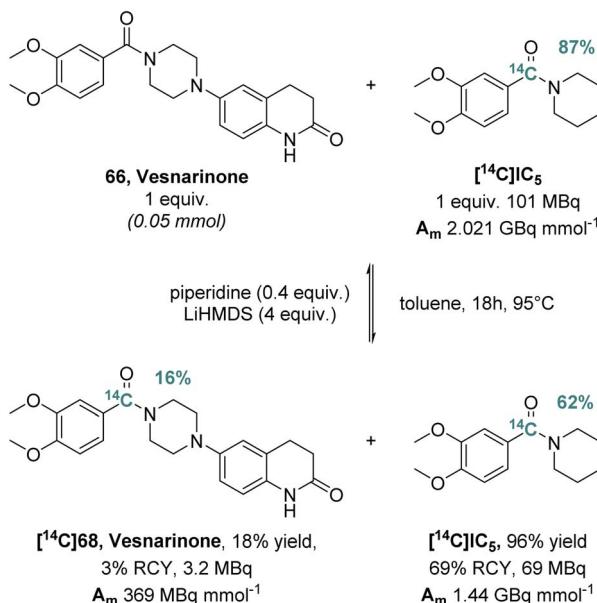


Scheme 4 Applications of amide transamidation and metathesis. Transamidation conditions: LiHMDS (0.5–10.0 equiv.) amine (1.0 equiv. for secondary deuterated amine or 2.0 equiv. for primary amine), toluene, 95 °C, 18 h; metathesis conditions (^{13}C labeling): amide (0.05 mmol), isotopic carrier (1.0 equiv., see ESI† for more details), LiHMDS (2.0–4.0 equiv.), piperidine (20 mol%), toluene dry (0.1 M), 95 °C, 18 h; amide reduction: amide (0.05–0.10 mmol), LiAlH₄ or LiAlD₄ (20.0 equiv.), THF (0.05 M), RT, 30 min. In light blue: deuterium isotopic enrichment. In red: carbon-13 isotopic enrichment; $^{1\text{H}}\text{-NMR}$ ratio product/starting material. Blue and red colored circles denote the positions of the ^2H and ^{13}C atoms labeled, respectively.

radiolabeling reagent. As shown in Scheme 5, despite a low enrichment of 16% and a yield of 18%, the molar activity (A_m) of 369 MBq mmol⁻¹ renders $[\text{^14C}]68$ Vesnarinone suitable for biological applications, including AMS, biodistribution

studies.⁴¹ We speculate that the low yield is a consequence of the presence of an unprotected lactone and a challenging purification of the highly polar radioactive compounds. Nevertheless, the possibility to use a previous radioactive waste for

Carbon-14 Radiolabeling



Scheme 5 Radioactive carbon-14 labeling of Vesnarinone.

the ¹⁴C-labeling of a bioactive compounds has been demonstrated, the remaining [¹⁴C]IC₅ carrier was recovered (62% IE, 1.44 GBq mmol⁻¹) and could be recycled for further radio-labeling transfer.

Conclusion

Driven by the pursuit of sustainable isotope labeling, this study focused on developing efficient methods for amide isotope exchange. By investigating transamidation and amide metathesis, we successfully established strategies for labeling both the amine and carbonyl functionalities of amides. This method offers an alternative to conventional techniques and complies with regulations against radioactive gaseous waste release. Although waste management remains a critical challenge, the presented protocols provide a foundation for advancing isotope chemistry toward greater sustainability. We anticipate that this preliminary study will serve as a starting point for a wide range of applications and inspire future advancements in the field.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Q. L. and R. B. contributed equally to the investigation performing all non-radioactive experiments and to the writing of the original draft. A. S. performed all radioactive experiments. T. D. measured all isotopic enrichments, provided and reviewed all analytical data. F. T. helped to supervise the project. D. A.

conceptualized the project, supervised the project and participated in the writing of the original draft.

Conflicts of interest

There are no conflicts of interest to declare.

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