ADVANCEMENTS IN ISOTOPIC LABELING: H/D EXCHANGE ON *N*-HETEROCYCLES AND THE DEVELOPMENT OF A $^{13}CO_2$ GENERATOR

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INTRODUCTION

Isotopically labeled compounds play a crucial role in material sciences, physical organic chemistry, and in pharmaceutical research, especially for the identification and quantification of metabolites during drug development. The most compelling approach for preparing isotopically labeled compounds is through direct isotope exchange, as it allows practitioners to perform the labelling without the need for pre-functionalization.

X-Chem is the pioneer of DNA-encoded library (DEL) technology and a leader in small molecule drug discovery. We combine proven DEL and medicinal chemistry expertise with groundbreaking AI/ML solutions and expert custom synthesis. We bring the most modern and powerful synthetic methodologies to bear, including asymmetric catalysis, photoredox, and flow chemistry. Herein, we present our latest results in the fields of H/D exchange and ^{13}C labeling.

H/D exchange. We present a continuous flow Raney nickel-catalyzed hydrogen isotope exchange process that boasts compatibility with a wide spectrum of nitrogen-containing heterocycles and pharmaceutical compounds.

^{13}C labeling. We describe a practical and economical chemical generator for CO_2. When used with ^{13}C-labeled Na_2CO_3, the generator provides alternative to expensive $^{13}CO_2$ cylinders.

HYDROGEN ISOTOPIC EXCHANGE (HIE)

- Labeling reactions were carried out in an H-Cube Pro™ flow reactor.
- Five heterogenous catalysts were evaluated (10% Pt/C, 10% Pd/C, 2.5-2.5% Pd-Pt/C, 5% Ru/C, Raney nickel), with Raney nickel demonstrating the most optimal results.
- Flow reactions provided superior results compared to batch.

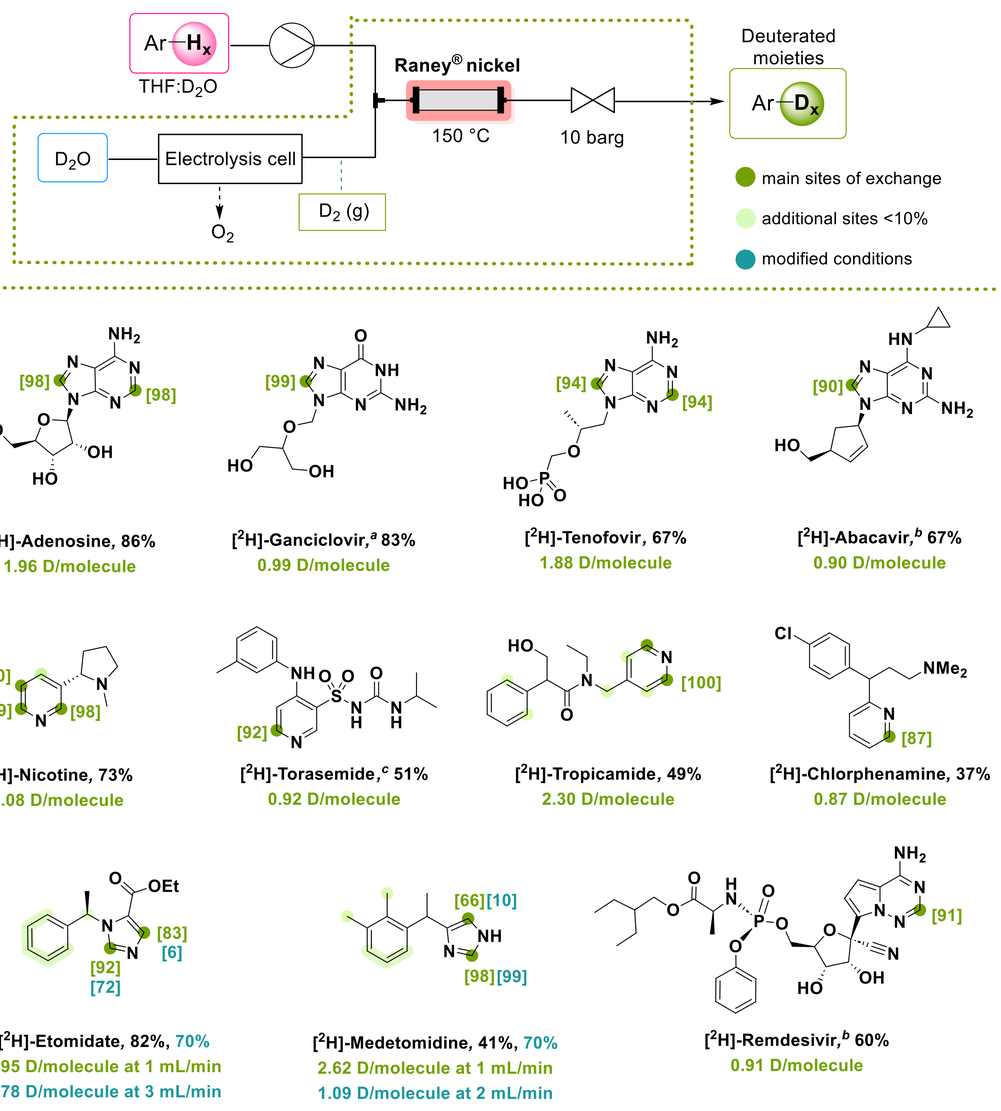
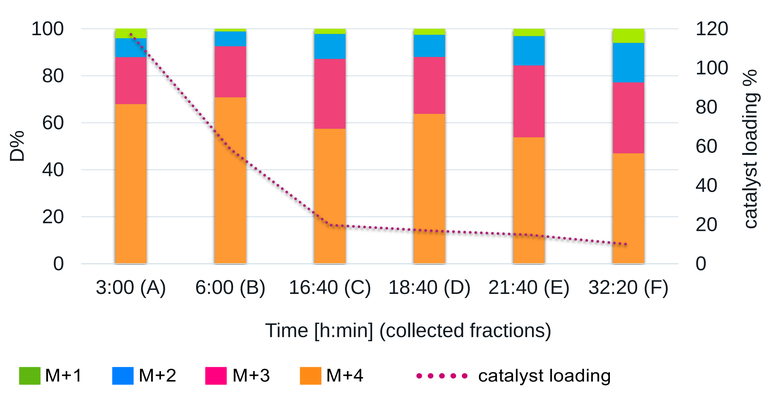
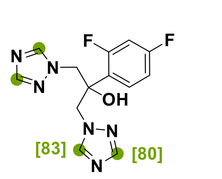


Figure 1. Labeling of APIs. Sites of deuterium incorporation were determined by ^1H NMR spectroscopy. General conditions: substrate (1 mmol) in THF:D_2O = 95:5 (0.01 M), 30 mm RaNi CatCart, 150 °C, 10 bar, 3% D_2, 0.3 - 2 mL/min. *a* 0.05 M; *b* without D_2; *c* 130 °C.

GRAM SCALE HIE IN FLOW





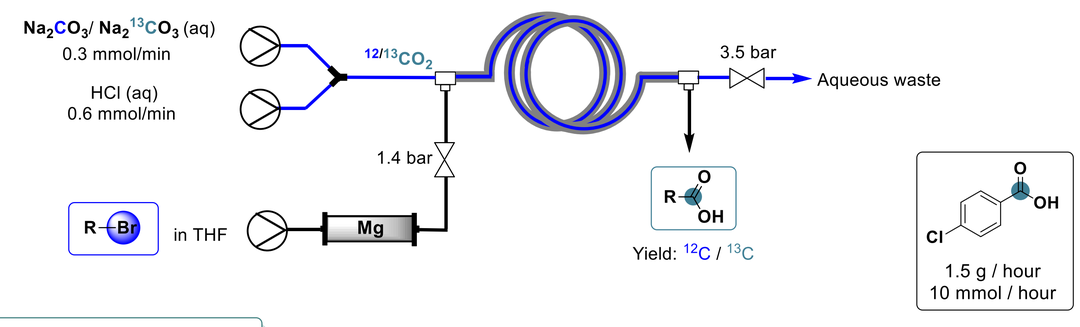
[2H]-Fluconazole, 98%
3.25 D/molecule

20 mmol scale
~6 g labeled compound

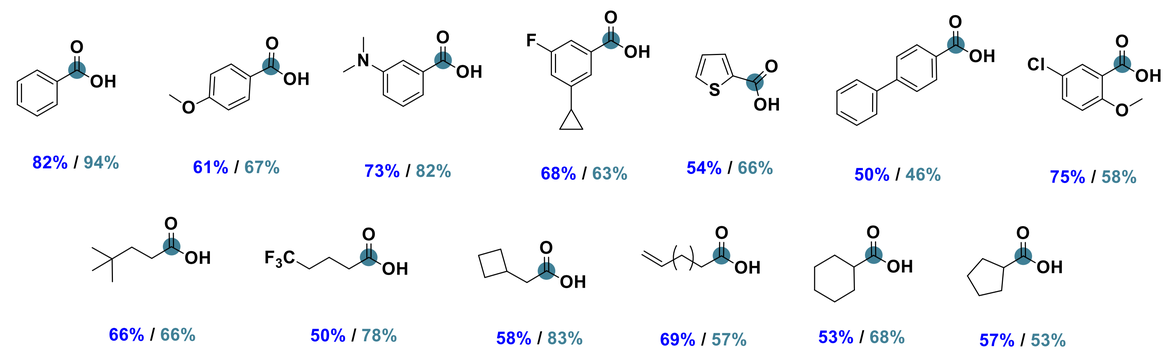
Figure 2. Gram scale synthesis of [^2H]-Fluconazole

$^{13}CO_2$ GENERATION AND LABELING

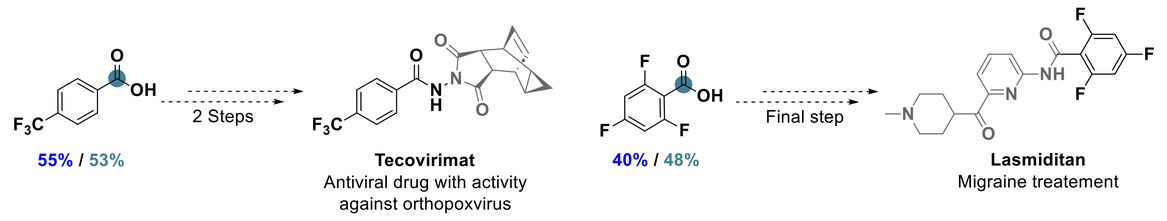
On-demand $^{13}CO_2$ generator: The setup consists of tube-in-tube reactor and utilizes $Na_2{}^{13}CO_3$ as an easily available precursor. As a proof of concept, the on-demand generated $^{13}CO_2$ was reacted with Grignard intermediates to form ^{13}C-labeled carboxylic acids.



Aromatic/Aliphatic substrates



Building blocks for APIs



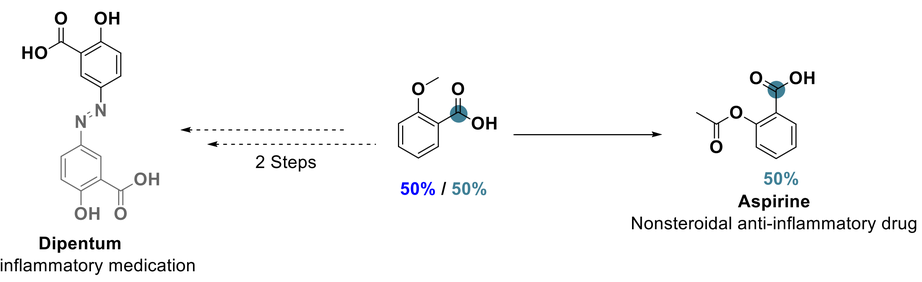
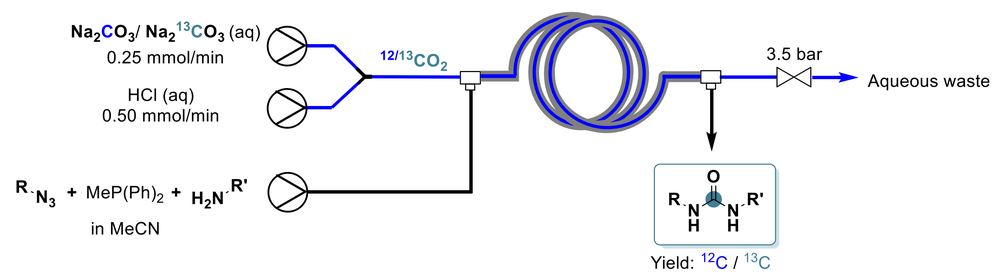


Figure 3. On-demand CO_2 generation. General conditions: substrate (3.5 mmol, 1 equiv), $Na_2{}^{12}CO_3/Na_2{}^{13}CO_3$ (0.8 equiv), THF (6 mL), room temperature, 15 min reaction time, 0.5 mL/min.

SYNTHESIS OF ^{13}C-LABELED ASYMMETRIC UREAS

The CO_2 generator was also utilized for the synthesis of both ^{12}C- and ^{13}C-labeled biologically active asymmetric ureas through the Staudinger/aza-Wittig sequence.



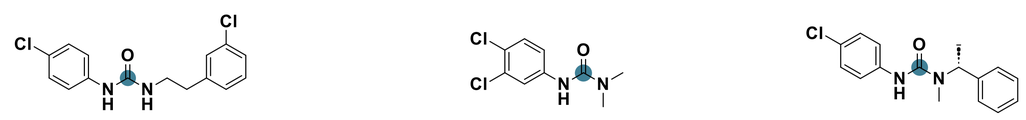


Figure 4. Synthesis of asymmetric urea compounds. General conditions: amine (0.3 mmol, 1 equiv), azide (0.3 mmol, 1 equiv), $MeP(Ph)_2$ (0.3 mmol, 1 equiv), $Na_2{}^{12}CO_3/Na_2{}^{13}CO_3$ (1.75 equiv), MeCN (3 mL), room temperature, 3 min reaction time, 750 µL/min.

SUMMARY

- We described a continuous flow Raney nickel-catalyzed hydrogen isotope exchange process. The broad applicability of the method was demonstrated through successful labeling of various purine bases, imidazoles, pyridines, and active pharmaceutical ingredients.
- We developed a practical and economical CO_2 generator which utilizes Na_2CO_3 as a readily available precursor. The CO_2 generator was employed in the synthesis ^{13}C-labeled carboxylic acids and non-symmetrical urea compounds.

References: [1] HIE: G. Sipos *et al. ChemRxiv*, **2024**, doi:10.26434/chemrxiv-2024-tk50j-v2; [2] Chemical generators: Kappe *et al. Acc. Chem. Res.* **2020**, *53*, 1330–1341; [3] Urea synthesis in flow: Audisio *et al. Asian J. Org. Chem.* **2023**, *12*, e202200640

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FLIX FLow chemistry for Isotopic eXchange

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