A Platform for Multiple Isotope Labeling via Carbon-Sulfur Bond Exchange

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Abstract: Isotopes are at the foundation of applications in life science such as nuclear imaging and are essential tools for the determination of pharmacokinetic and dynamic profiles of new pharmaceuticals. However, the insertion of an isotope into an organic molecule remains challenging and current technologies are element-specific. Despite the ubiquitous presence of sulfur in many biologically active molecules, sulfur isotope labeling is an underexplored field and sulfur isotope exchange has been overlooked. In this work, we explore a nickel-catalyzed reversible carbon-sulfur (C-S) bond activation strategy to achieve selective sulfur isotope exchange. This approach enables to move beyond standardized element-specific procedures and was applied to multiple isotopes, including deuterium, carbon-13, sulfur-34 and radioactive carbon-14. These results provide a unique platform for multiple isotope labeling and are compatible with a wide range of substrates, including pharmaceuticals. In addition, this technology proved its potential as isotopic encryption device of organic molecules.

Since the seminal communication of Frederick Soddy in 1913,[1] recognized by the Nobel Prize in chemistry in 1921, isotopes have provided incomparable benefits to our society. The word "isotope" comes from the Greek roots "isos" (equal) and "topos" (place), and it refers to atoms of the same element but with different atomic masses. Isotopes have been instrumental in many of the most important discoveries of the 20th century, including nuclear fission and fusion, radiocarbon dating, nuclear medicine and the determination of how plants utilize carbon dioxide in photosynthesis.

Stable and radioactive isotopes play a fundamental role in life science. The insertion of a radioisotope into an organic compound generates a tracer, which can be closely tracked to unveil information, essential to establish safety profiles of pharmaceuticals and agrochemicals.

However, isotope labeling is a difficult task. Isotopic sources and primary building blocks are limited and precious, as they must either be generated artificially or by separation/fractionation from natural abundant elements, using energy-intensive processes. Chemists have devised countless strategies for labeling organic molecules, with the goal of maximizing the efficiency of the process, reducing the number of linear steps and minimizing isotopic waste. Isotope exchange is a powerful concept that can be used to achieve these goals. Based on dynamic processes, isotope exchange allows cleaving reversibly a bond such as C-H and replacing it with an identical isotopologue, as C-D (deuterium) and C-T (tritium). This technology has exquisite inherent advantages. It is a method that can be applied directly on the compound of interest and it does not require the preparation of over-engineered chemical precursors.

Hydrogen isotope exchange (HIE, Fig. 1) is by far the best-established technology, as it is utilized on a daily bases in pharmaceutical industry.[2] Recently, carbon isotope exchange (CIE) was recognized as a modern tool for late-stage labeling with ^{11}C, ^{13}C and ^{14}C.[3] In addition, fluorine exchange (FIE, for positon emitter ^{18}F)[4] and examples of iodine exchange (IIE) have been described, as well.[5] A general pitfall of these technologies is that they are element-specific, meaning they are optimized for one single element. This is because they exploit the intrinsic chemical reactivity of the corresponding C-X bonds, where X can be hydrogen, carbon, fluorine, or iodine.

Sulfur is the 15th most abundant element in the Earth's crust and is found in a wide variety of compounds, including many pharmaceuticals.[6] Organosulfur molecules are ubiquitous in nature and possess high synthetic versatility. They are found in a wide variety of compounds, including drugs, pesticides, and food additives.[7]

Although sulfur isotope labeling is well-recognized, sulfur isotope exchange (SIE) has essentially been neglected. SIE has been limited to mere scientific curiosity and has been specifically focused on the thiocarbonyl functional group (C=S) exchange, in the presence of elemental sulfur, under generally harsh conditions.[8,9,10] The invention of a sulfur isotope exchange strategy capable of selectively replacing C-S bonds would provide a crucial step forward in exchange technologies and a milestone in the field of SIE. In addition, the nature of sulfur presents a unique opportunity to accommodate, for the first time, a platform suitable for multiple isotope incorporation.

Herein, we disclose a solution to this challenge and report a successful Ni-catalyzed reversible Csp^2-S bond activation to achieve SIE. This platform, which is based on the versatile phenyl alkyl sulfide scaffold, is the first to formally allow multiple isotope exchange of hydrogen (^2H), carbon (^{13}C), and sulfur (^{34}S). We also demonstrate its use for radioactive labeling with ^{14}C, thus providing concrete foundation for applications in human ADME studies.

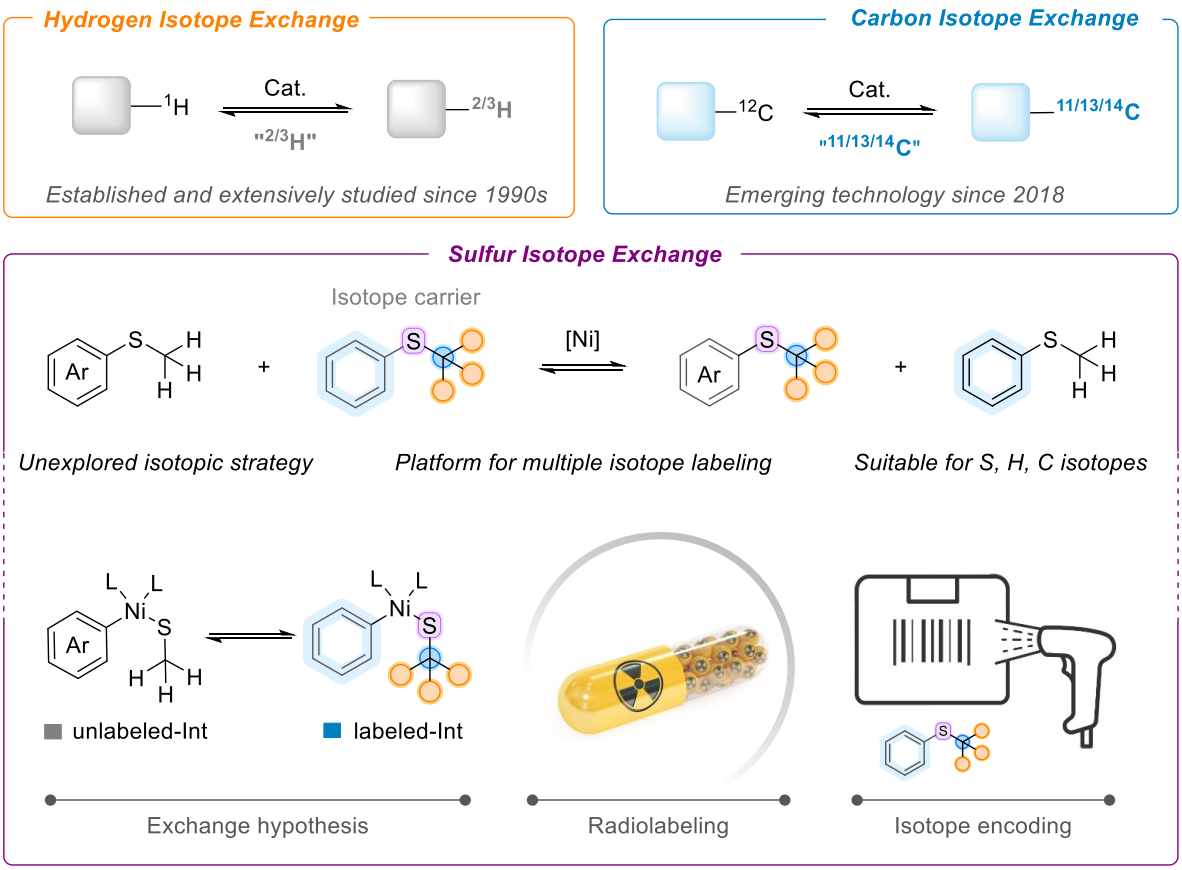


***Fig. 1*. State of the art in isotope exchange reactions.** Top: Hydrogen and carbon isotope exchange represent state of the art technology in the field of labeling. Middle: Sulfur isotope exchange, an unreported opportunity for multiple isotope labeling. Bottom: Applications of this technology. Blue colored circles denote the positions of the

^{13}C atoms labeled. Purple colored circles denote the positions of the ^{34}S atoms labeled. Orange colored circles denote the positions of the D atoms labeled.

With the ambition to rejuvenate sulfur labeling in a safe and sustainable way, we anticipated the following strategic considerations. The Csp^2-SCH_3 motif was identified as ideal, because this functional group is commonly found in biologically active compounds and the activation of this sigma bond in cross-coupling reactions has been reported.[11] We reasoned that for sustainable and safe SIE, the (radio)isotopic labeled source (i.e. isotope carrier, IC) should not be volatile and ideally be in the solid state under ambient conditions. Consequently, methanethiol and its corresponding thiolates were excluded due to obvious practical reasons.[12] Finally, IC had to be easily accessible from the commercially available isotopic sources of multiple elements. With these observations in mind, methyl aryl sulfanes were selected as IC.

From a mechanistic perspective, we conceived that in presence of a defined IC, activation of the labeled Csp^2-*SMe in presence of a transition metal catalyst (TM^n) would provide a corresponding TM^{n+2} intermediate (labeled-Int), which should exchange the labeled-*SMe unit with a second unlabeled-Int, formed in concomitance. While appealing, a sequence of possible pitfalls were expected. Thiolate additives should be excluded from the reaction mixture, to avoid undesired isotopic dilution and complex mixtures of products. The functional group tolerance of the reaction was questioned, as methyl phenyl sulfanes have been reported to undergo aryl transfer onto Ar-CN, Ar-Br, Ar-Cl, Ar-COOAr' and Ar-OR (R = Ts, Piv, Boc) by the groups of Walsh,[13] Morandi[14,15] and Yamaguchi.[16] With such challenges in mind, we started seeking proof-of-concept to validate our hypothesis, utilizing deuterated methyl phenyl sulfane **2-*d*$_3$** as IC and in presence of model substrate **1** (Fig. 2).

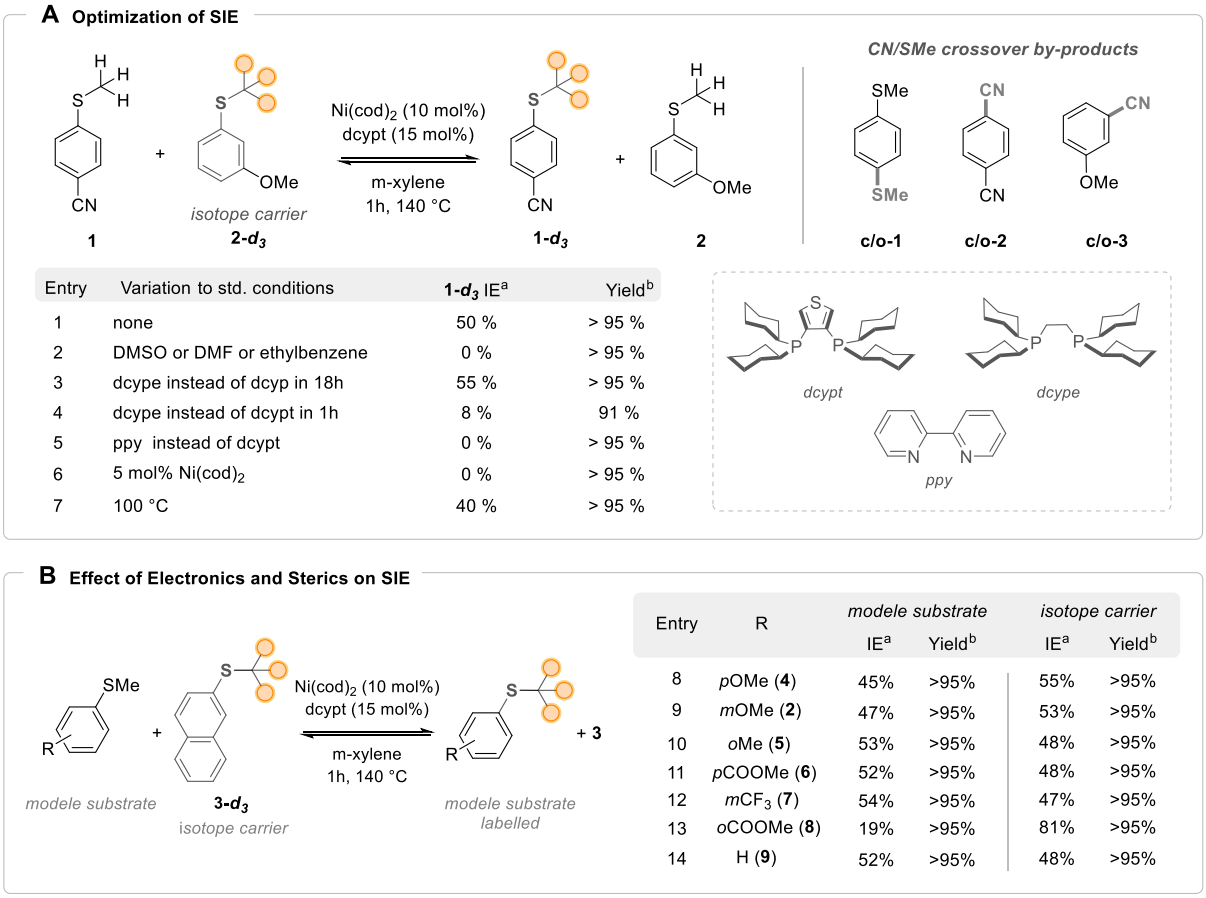
While palladium catalysis proved ineffective,[17,18,19] nickel showed productive catalytic activity and the desired labeled **1-*d*$_3$** was observed (SI, Table 1). After optimization, it was found that using 1 equiv. of **1** and **2-*d*$_3$,** in presence of $Ni(cod)_2$ (10 mol%) and dcypt (15 mol%) in *m*-xylene at 140 °C in 1 hour, **1-*d*$_3$** was isolated in excellent 95% yield and quantitative SCH_3/SCD_3 exchange between both partners was obtained as illustrated by the theoretically maximal isotopic enrichment of 50% (IE).

Substrate **1** was selected for the optimization at it bears inherent challenges. Morandi and co-workers showed that functional group metathesis between aryl nitriles and aryl thioethers occurs under similar reaction conditions, and at the outset a complex mixture of crossover by-products was expected (**c/o-1**, **c/o-2** and **c/o-3**).[14] We were delighted to observe that under

optimized conditions, effective SIE occurred while **c/o-1**, **2** and **3** accounted for less than 5% (NMR yield, see SI Fig. 2-3). The exquisite selectively of the process is in agreement with the lower bond dissociation energies of the Csp^2-SMe bond (~85 kcal/mol) compared to Csp^2-CN bond (~130 kcal/mol).[20]

Variation from the standard conditions afforded lower isotope incorporation (Figure 1A and SI Fig. 5). SIE appeared to be a ligand dependent transformation. Only the thiophene-bridged bidentate phosphine dcypt was found effective. Bidentate dcpe afforded similar SIE, but after a much longer reaction time (18 hours, entry 3), while proved almost ineffective in 1 h reaction (entry 4). Comparative kinetic studies between dcpe and dcypt confirmed that dcypt was more efficient, and maximal IE was reached in 30 minutes (SI Fig 4). Switching the solvent to DMSO, DMF or ethylbenzene proved ineffective (Figure 1A entry 2), while when the reaction was performed at 100 °C lower IE was observed (Figure 1A, entry 7).

Next, we investigated the effects of electronics and sterics on the exchange in presence of electron neutral IC **3-*d*$_3$** (Figure 1B). Surprisingly, except for substrate **8**, no significant effects were observed with both electron-donating and -withdrawing groups in *ortho*, *meta* or *para* position in respect to the SMe group (entries 8-12 and 14). Both IC and substrates were recovered after the reaction in high yields and IE close to 50%. The lower IE obtained in the case of **8** (entry 13) could be explained by the increased steric hindrance of the methyl ester, with a more challenging oxidative addition step taking place in *ortho* position to the bulky substituent.



Entry	Variation to std. conditions	1-d_3 IE[a]	Yield[b]
1	none	50 %	> 95 %
2	DMSO or DMF or ethylbenzene	0 %	> 95 %
3	dcype instead of dcyp in 18h	55 %	> 95 %
4	dcype instead of dcypt in 1h	8 %	91 %
5	ppy instead of dcypt	0 %	> 95 %
6	5 mol% $Ni(cod)_2$	0 %	> 95 %
7	100 °C	40 %	> 95 %

Entry	R	*modele substrate* IE[a]	*modele substrate* Yield[b]	*isotope carrier* IE[a]	*isotope carrier* Yield[b]
8	*p*OMe (**4**)	45%	>95%	55%	>95%
9	*m*OMe (**2**)	47%	>95%	53%	>95%
10	*o*Me (**5**)	53%	>95%	48%	>95%
11	*p*COOMe (**6**)	52%	>95%	48%	>95%
12	*m*CF_3 (**7**)	54%	>95%	47%	>95%
13	*o*COOMe (**8**)	19%	>95%	81%	>95%
14	H (**9**)	52%	>95%	48%	>95%

***Fig. 2*. Development of a platform for sulfur isotope exchange.** General conditions: IC (1.0 equiv., 0.20 mmol), aryl thioether (1.0 equiv., 0.20 mmol) , $Ni(cod)_2$ (10 mol%), dcypt (15 mol%) heated at 140 °C for 1h. A) Optimizaton of the reaction. B) Study of the electronic and steric effects on the transformation. [a] Isotopic enrichments determined by NMR and/or HRMS. [b] Yields determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene or dibromomethane as internal standard. Orange colored circles denote the positions of the D atoms labeled.

We next explored the scope of the reaction using 2 equiv. of the isotopic carriers **2-*d*$_3$** or **3-*d*$_3$**, selected for their different polarity on chromatography. Pleasingly, electron-withdrawing groups such as nitrile **1** aldehyde **10**, ketones **11** and **12**, esters **6** and **8** and sulfone **13** were tolerated, and the desired labeled products were isolated with yield spanned from 72% to 96%. Good results were obtained with substrates bearing electron neutral groups **14**, **15**, and **16**. Unprotected anilines in *para*- **18** or *ortho*- **19** positions were tolerated with excellent IE of 60% and 61%, while *para*-phenol **20** provided lower 10% IE. Double incorporation was even possible in the case of substrate **21** and **22**. Hetero-aromatics, often found in pharmaceutical products, were good substrates providing maximal IE **23-28-*d*$_3$**. For recalcitrant substrates, the reaction time and the catalytic charge were increased to improve IE (**4**, **25**, **27**, **28**, **35**). To

evaluate its robustness, the reaction was challenged towards a series of substrates reported for aryl exchange by Yamaguchi.[16] We found that no Csp^2-OR bond activation was observed with aryl pivalate **30**, carbonate **31** or carbamate **32**, even though these patterns were suitable for SMe exchange under harsher reaction conditions (150 °C, 24 h). Pleasingly, even the presence of a Csp^2-Cl bond **33** was compatible, though the reaction time had to be reduce to 30 minutes. Finally, biologically active Thioridazine **36** an anti-psychotic drug,[21] coumarine **34** reported for its anti-HBV activity[22] and Probenecid derivative **35** were labeled with IE spanning from 45 to 74%. As limitations, we account the presence of benzyl bromine **37**, carboxylic acid **38**, the *o,o'*-methyl substitution **39** and benzothiazole **40** which failed to provide the desired products.

We further explored ^{13}C-labeling, using 1 equiv. of isotope carrier **[^{13}C]3** under otherwise identical reactions conditions (Figure 4). Pleasingly, ^{13}C-enriched products were obtained in satisfying yields and IE. The coumarin **[^{13}C]34,** Thioridazine **[^{13}C]36**, and Metitepine **[^{13}C]41**[23] were labeled with excellent isotopic enrichment of 56%, 56% and 48%, respectively. Interestingly, **[^{13}C]36** was oxidized to provide mesoridazine **[^{13}C]42**[24] as a diastereomeric mixture.

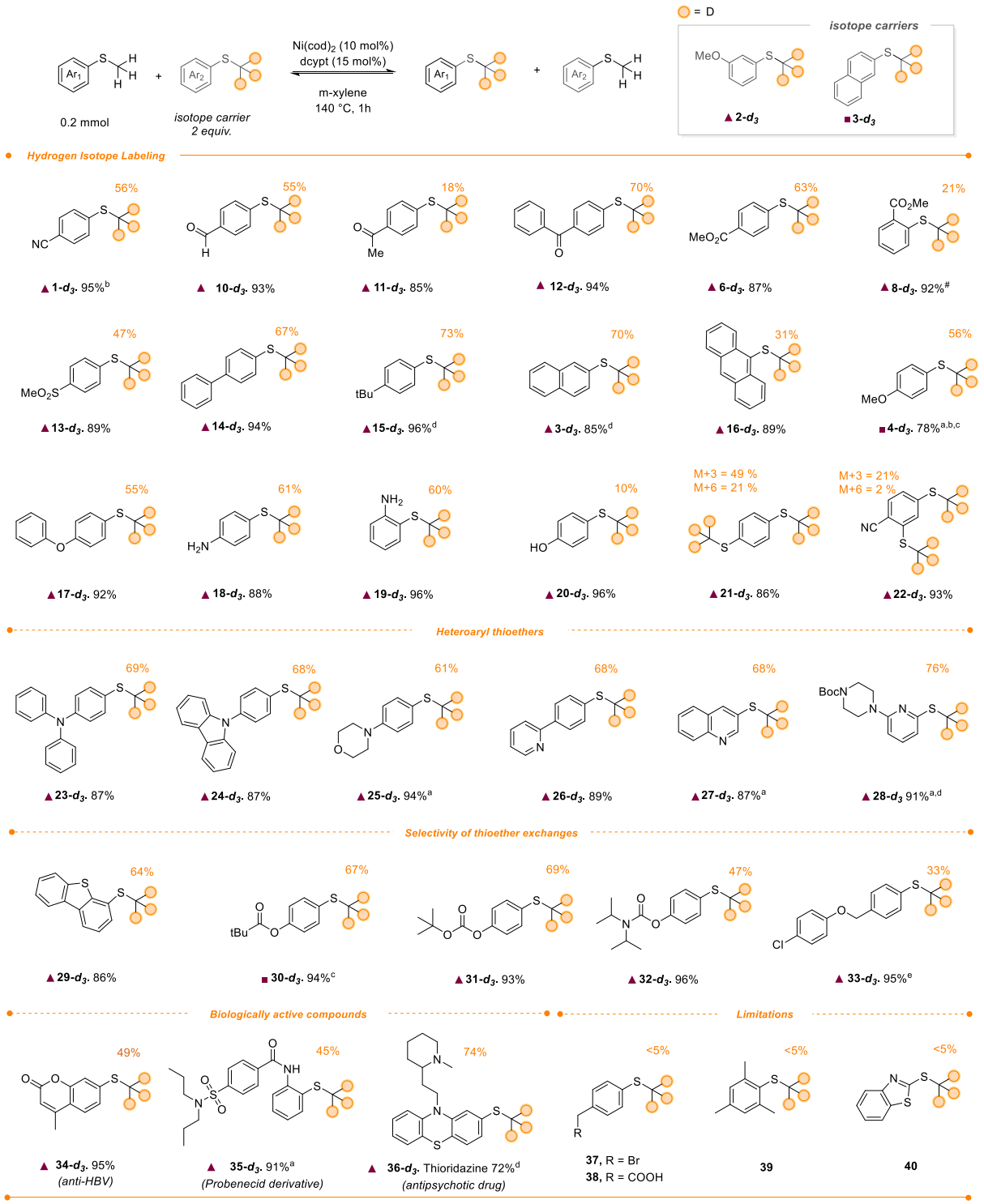


Fig. 3. Hydrogen isotope labeling of aryl thioethers. General conditions: IC (2.0 equiv., 0.40 mmol), aryl thioether (1.0 equiv., 0.20 mmol), $Ni(cod)_2$ (10 mol%), dcypt (15 mol%) heated at 140 °C for 1h. [a] $Ni(cod)_2$ (15 mol%), dcypt (15 mol%) in *m*-xylene heated for 16h at 140 °C. [b] IC (1.0 equiv., 0.20 mmol). [c] ^{1}H-NMR yield calculated with dibromomethane as internal standard. [d] 3 equiv. of IC. [e] heated for 30 min at 140°C. Orange colored circles denote the positions of the D atoms labeled, orange colored % are IE values. [#] In presence of 1 equiv. IC **2-*d*$_3$** 19% IE was obtained.

While HIE and CIE are established, methods for sulfur exchange are virtually unknown. ^{34}S-labeled IC **[^{34}S]3, [^{34}S]43** and **[^{34}S]44** were synthesized in one step from primary isotopic source [^{34}S]S_8 (SI, general procedure 6). Pleasingly, in presence of 1 equiv. of **[^{34}S]3**, ketone **[^{34}S]12** was easily labeled in 85% yield and 39 % IE. Interestingly, when thioethers with diverse length of the aliphatic chain successfully underwent SIE. *n*-Propyl and *n*-butyl derivatives [**^{34}S]45**, [**^{34}S]46** and [**^{34}S]47** were labeled by C-S bond exchange in maximal IE and isolated yields over 71%. Albendazole, a commercial anti-helmintic agent, was labeled with ^{34}S in 93% yield and though in lower 11% IE.

Given the versatility of the isotopic platform, we reasoned that the dynamic nature of the nickel-catalyzed C-S bond cleavage might provide unprecedented opportunity for isotope labeling of the aromatic carbon moiety. Indeed, [$^{2}H_5$] and [$^{13}C_6$]benzene are the simplest labeled aromatics available. Their use for synthesis of stable isotopically labeled (SIL) internal standards is routine in pharmaceutical and agrochemical industries. D and ^{13}C-carriers **49-*d*$_5$, 50-*d*$_5$** and [**^{13}C$_6$]50** were synthetized in one-step from the corresponding labeled iodobenzene, *via* palladium-catalysed coupling in excellent yields. Pleasingly, productive exchange reactions allowed labeling a series of substrates in good yields and IE. 55% incorporation was obtained with pentyl(phenyl)sulfane **51-*d*$_5$** with an aliphatic chain. A coordination on the double bond and the PEG could explain the lower isotopic incorporation seen in the case of **52-*d*$_5$** and **53-*d*$_5$** with 24% and 35% IE, respectively. In presence of an amide or an ester, excellent isotopic enrichments were observed with the compounds **54-*d*$_5$**, **50-*d*$_5$** and **55-*d*$_5$** of 61%, 42% and 48%, respectively. Double labeling of the phenyl was obtained in the case of phenyl sulphide **57**, this could be explained by the recommitment of the mono-benzene-d_6 labeled product in the catalytic cycle, thus providing an incorporation between mono- and di-benzene-d_6 labeled product of 47% and 13%.

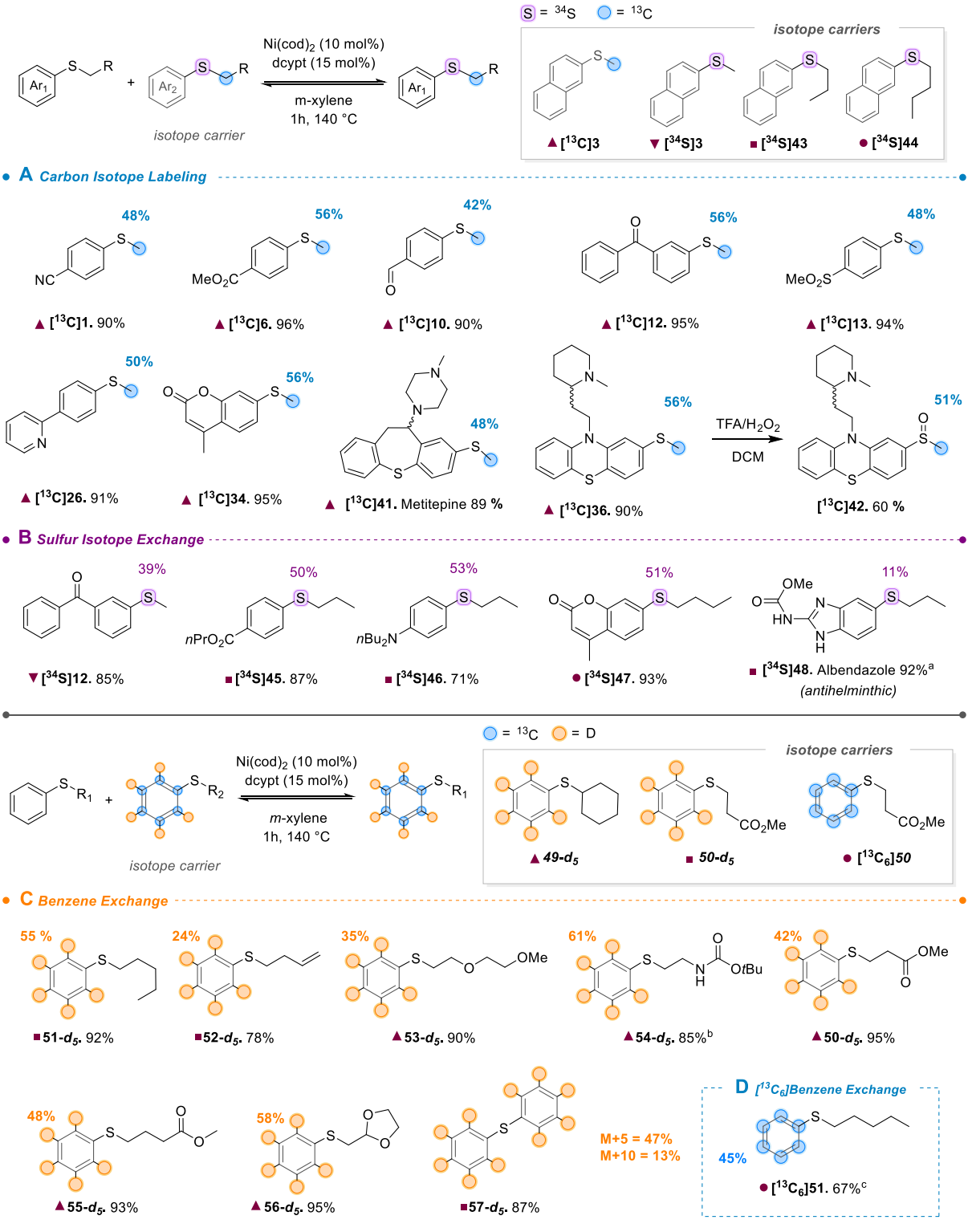


***Fig. 4*. Platform for multiple isotope labeling. A) Carbon labeling. B) Sulfur isotope Exchange. C) Labeled benzene exchange.** General conditions: isotope carrier (1.0 equiv., 0.20 mmol), aryl thioether (1.0 equiv., 0.20 mmol), $Ni(cod)_2$ (10 mol%), dcypt (15 mol%) in m-xylene (1 mL) heated at 140 °C for 1h. [a] $Ni(cod)_2$ (15 mol%), dcypt (15 mol%) heated for 16h at 140 °C. [b] 2 equiv. of the IC. [c] aryl thioether and IC (1.0 equiv., 0.10 mmol). Blue colored circles denote the positions of the ^{13}C atoms labeled. Purple colored circles denote the positions of the ^{34}S atoms labeled. Orange colored circles denote the positions of the D atoms labeled.

Inspired by the work of La Clair,[25] Huc and Kotschy[26] on the use of isotopic labeling in the regulation of matter, we leveraged this platform to develop a tool for molecular encryption that would help to track and trace valuable goods. By inserting a distinctive isotopic signature into the material before it is commercialized, regulatory authorities could track it and verify its authenticity, using routine mass spectrometry analysis. Thioridazine **36** was selected as the template for isotopic encoding. In a preliminary experiment, **36** was reacted with both **[^{34}S]3** (1 equiv.) and **3-*d*$_3$** (1 equiv.), resulting in a peculiar isotopic signature consisting of **36, [^{34}S]36** and **36-*d*$_3$** isotopologues in a 37/35/24 ratio (Fig. 5A). Likewise, by using 1 equiv. of each carrier, **[^{13}C]3**, **[^{34}S]3** and **3-*d*$_3$**, a second, unique signature was detected by MS. By further modifying the ratio of the IC, a multitude of unprecedented MS signatures could be encoded at will, providing a simple yet effective encryption device.

As a corollary, the unique potential of the technology towards radioactive labeling was demonstrated. Starting from high molar activity **[^{14}C]3** (A_m = 2.18 GBq mmol^{-1}), under standard catalytic conditions, we could effectively label bioactive coumarin **34**. Within 85 minutes, the radioactivity was equally distributed onto the desired product **[^{14}C]34** with 46% IE (A_m = 1.07 GBq mmol^{-1}) and the recovered IC in 48% IE (**[^{14}C]3'**,A_m = 1.11 GBq mmol^{-1}). After purification, **[^{14}C]34** was isolated in 69% yield and 34% radiochemical yield (RCY). The overall transformation accounts for a formal CIE, thus adding an unprecedented opportunity in the carbon-14 toolbox.[27,28,29] Importantly, both **[^{14}C]34** and recovered **[^{14}C]3'** could be utilized and recycled for further radioactivity transfer, an approach which is conceptually novel in the state of the art for isotope exchange and radiolabeling.

Aiming to gain concrete evidence on the mechanism of the transformation, the oxidative addition **complex-1** and **-2** were prepared (Fig. 5C). The choice of ^{13}C-labeled **complex-2** was made to observe a resonance coupling in both ^{31}P- and ^{13}C-NMR (SI, Fig. 10). When a toluene-d_8 solution of **complex-1** and **[^{13}C]complex-2** was heated at 70 °C, dynamic isotope exchange between the complexes was detected by ^{31}P-NMR spectroscopy and complete equilibration between these species was achieved within 270 min. By further increasing the temperature, the formation of the corresponding thioethers **[^{13}C]1** and **[^{13}C]6** were observed in 45% and 46% IE (SI, Fig. 16). These observations and additional experimentations (SI, Fig 19 and 21) support the mechanism and will be useful for further developments in the area.

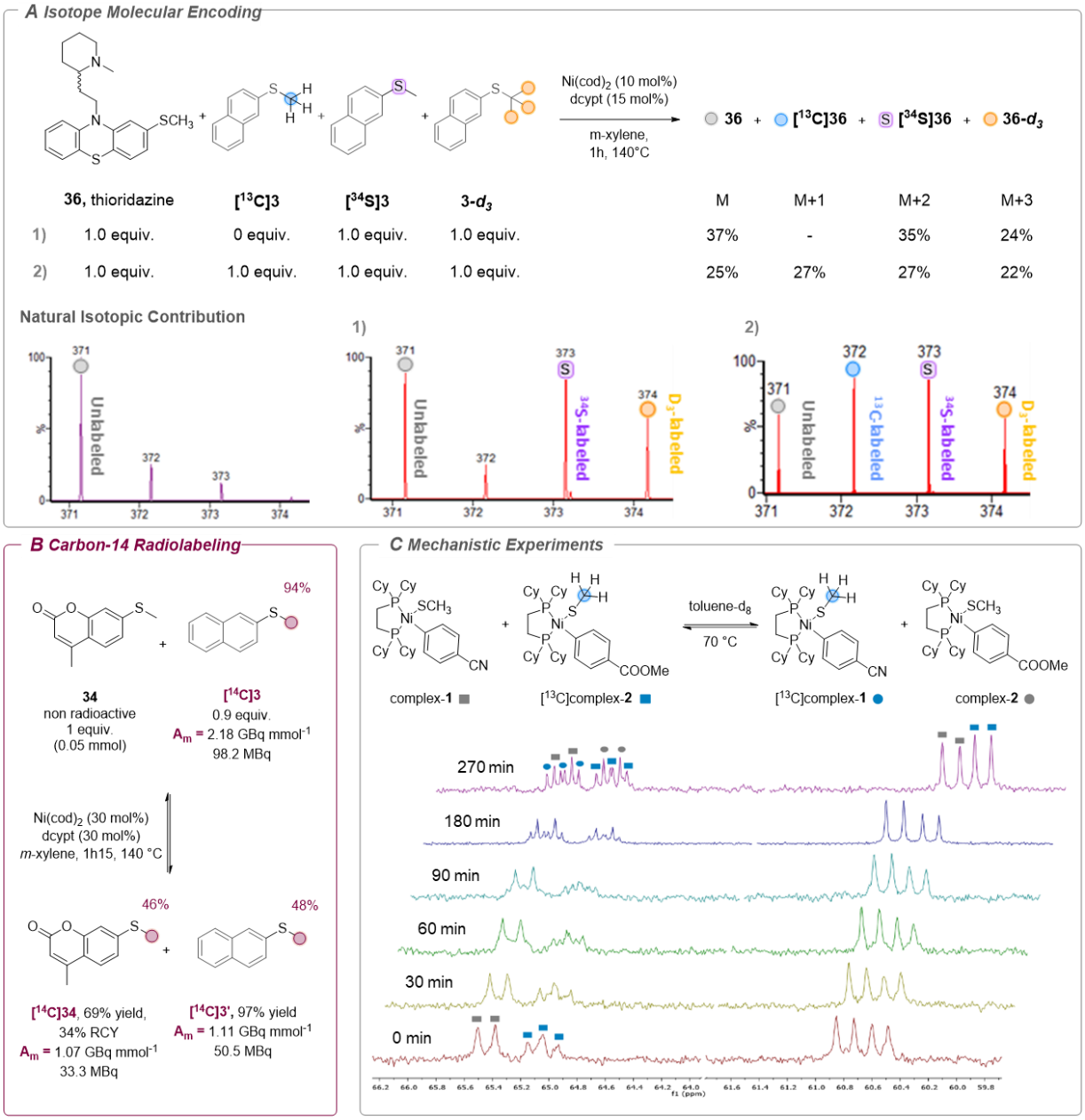


***Fig. 5*. Applications and mechanistic studies of the SIE platform.** A) Development of isotope molecular encoding device. B) Radioactive carbon-14 labeling. C) Mechanistic investigation of the isotope exchange reaction. ^{31}P-NMR of the mixture of **Complex-1** and **-2**, over time.

This study presents a solution to access labeled molecules by SIE, based on a nickel-catalyzed reversible carbon-sulfur (C-S) bond activation. The technology conceptualizes a new avenues in the field of isotope labeling, which prospects to move beyond standardized element-specific procedures and was applied for the first time to multiple isotopes, including deuterium, carbon-13 and sulfur-34. This versatile tool has been applied to radioactive carbon-14 labeling, displaying concrete evidences for applications in ADME studies for the development of

pharmaceuticals. This technology has also proved its potential as isotopic encryption device of organic compounds, useful to track and trace valuable goods.

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Author contributions:

B.M. M.N. performed the experiments, synthesized and characterized the molecules, analyzed the data discussed the results. J.G. synthetized and prepared the starting materials. F.T. discussed the results. A.S. performed the carbon-14 labeling. D.A. conceived and directed the project. D.A. prepared the manuscript with contributions from all authors.

Competing interests:

The authors declare no competing interests.

Data and materials availability:

Experimental procedures and characterization data are provided in the supplementary materials. Correspondence and requests for materials should be addressed to D.A.

References and Notes:

[1] F. Soddy, Intra-atomic Charge. *Nature* **92**, 399-400 (1913).

[2] S. Kopf, F. Bourriquen, W. Li, H. Neumann, K. Junge, M. Beller, Recent Developments for the Deuterium and Tritium Labeling of Organic Molecules. *Chem. Rev.* **122**, 6634-6718 (2022).
10.1021/acs.chemrev.1c00795.

[3] A. Labiche, A. Malandain, M. Molins, F. Taran, D. Audisio, Modern Strategies for Carbon Isotope Exchange. *Angew. Chem. Int. Ed.* e202303535 (2023). 10.1002/anie.202303535.

[4] T. Wang, S. Lv, Z. Mou, Z. Zhang, T. Dong, Z. Li, Isotope Exchange-Based ^{18}F-Labeling Methods. *Bioconj. Chem.* **34**, 140-161 (2023). 10.1021/acs.bioconjchem.2c00530.

[5] J.-M. Chezal, J. Papon, P. Labarre, C. Lartigue, M.-J. Galmier, C. Decombat, O. Chavignon, J. Maublant, J.-C. Teulade, J.-C. Madelmont, N. Moins, Evaluation of Radiolabeled (Hetero)Aromatic Analogues of N-(2-diethylaminoethyl)-4-iodobenzamide for Imaging and Targeted Radionuclide Therapy of Melanoma. *J. Med. Chem.* **51**, 3133-3144 (2008). 10.1021/jm701424g.

[6] M. Feng, B. Tang, H. S. Liang, X. Jiang, Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry. *Curr. Top. Med. Chem.* **16**, 1200-1216 (2016).

[7] K. A. Scott, J. T. Njardarson, Analysis of US FDA-Approved Drugs Containing Sulfur Atoms. *Top. Curr. Chem.* **376**, 5 (2018). 10.1007/s41061-018-0184-5.

[8] C. Choitan, I. Zamfir, Labelling of thioxanthine, thioguanine and 2-thio-uracil with 35S by isotopic exchange. *J. Label. Compd* **4**, 356-360 (1968). https://doi.org/10.1002/jlcr.2590040412)

[9] S. Yamada, D. Wang, S. Li, M. Nishikawa, E. W. Qian, A. Ishihara, T. Kabe, Characterization of sulfur exchange reaction between polysulfides and elemental sulfur using a 35S radioisotope tracer method. *Chem. Commun.* 842-843 (2003) 10.1039/B212438F.

[10] J. Cífka, V. Vinš, Preparation of ^{35}S-labelled xanthates and ^{35}S-labelled carbon disulphide by exchange reactions. *J. Labelled Compd* **1**, 189-194 (1965). https://doi.org/10.1002/jlcr.2590010305.

[11] S. Huang, M. Wang, X. Jiang, Ni-catalyzed C–S bond construction and cleavage. *Chem. Soc. Rev.* **51**, 8351-8377 (2022). 10.1039/D2CS00553K).

[12] T. Delcaillau, A. Bismuto, Z. Lian, B. Morandi, Nickel-Catalyzed Inter- and Intramolecular Aryl Thioether Metathesis by Reversible Arylation. *Angew. Chem. Int. Ed.* **59**, 2110-2114 (2020). https://doi.org/10.1002/anie.201910436).

[13] J. Mao, T. Jia, G. Frensch, P. J. Walsh, Palladium-Catalyzed Debenzylative Cross-Coupling of Aryl Benzyl Sulfides with Aryl Bromides: Synthesis of Diaryl Sulfides. *Org. Lett.* **16**, 5304-5307 (2014).
10.1021/ol502470e.

[14] T. Delcaillau, P. Boehm, B. Morandi, Nickel-Catalyzed Reversible Functional Group Metathesis between Aryl Nitriles and Aryl Thioethers. *J. Am. Chem. Soc.* **143**, 3723-3728 (2021).
10.1021/jacs.1c00529.

[15] P. Boehm, P. Müller, P. Finkelstein, M. A. Rivero-Crespo, M.-O. Ebert, N. Trapp, B. Morandi, Mechanistic Investigation of the Nickel-Catalyzed Metathesis between Aryl Thioethers and Aryl Nitriles. *J. Am. Chem. Soc.* **144**, 13096-13108 (2022).
10.1021/jacs.2c01595.

[16] R. Isshiki, M. B. Kurosawa, K. Muto, J. Yamaguchi, Ni-Catalyzed Aryl Sulfide Synthesis through an Aryl Exchange Reaction. *J. Am. Chem. Soc.* **143**, 10333-10340 (2021).
10.1021/jacs.1c04215.

[17] Z. Lian, B. N. Bhawal, P. Yu, B. Morandi, Palladium-catalyzed carbon-sulfur or carbon-phosphorus bond metathesis by reversible arylation. *Science* **356**, 1059-1063 (2017).
doi:10.1126/science.aam9041.

[18] M. A. Rivero-Crespo, G. Toupalas, B. Morandi, Preparation of Recyclable and Versatile Porous Poly(aryl thioether)s by Reversible Pd-Catalyzed C–S/C–S Metathesis. *J. Am. Chem. Soc*. **143**, 21331-21339 (2021).
10.1021/jacs.1c09884.

[19] S. Yang, X. Yu, A. Poater, L. Cavallo, C. S. J. Cazin, S. P. Nolan, M. Szostak, Buchwald–Hartwig Amination and C–S/S–H Metathesis of Aryl Sulfides by Selective C–S Cleavage Mediated by Air- and Moisture-Stable [Pd(NHC)(μ-Cl)Cl]$_2$ Precatalysts: Unified Mechanism for Activation of Inert C–S Bonds. *Org. Lett.* **24**, 9210-9215 (2022).
10.1021/acs.orglett.2c03717.

[20] Y.-R. Luo Editor *Comprehensive Handbook of Chemical Bond Energies* (Taylor and Francis group, ed. 12007)

[21] R. H.K. Thanacoody, Thioridazine: The Good and the Bad. *Recent Patents on Anti-Infective Drug Discovery* **6**, 92-98 (2011).
10.2174/157489111796064588.

[22] Y. Chen, J. Zhou, H. Wang, Y. Xia, Z. Y. Yang, P. Xia, Synthesis and anti-HBV activity of S-substituted 7-mercapto-4-methylcoumarin analogs. *Chin. Chem. Lett.* **19**, 925-927 (2008). 10.1016/j.cclet.2008.05.043.

[23] M. A. Monachon, W. P. Burkard, M. Jalfre, W. Haefely, Blockade of central 5-hydroxytryptamine receptors by methiothepin. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **274**, 192-197 (1972).
10.1007/BF00501854.

[24] R. S. Vardanyan, V. J. Hruby, in *Synthesis of Essential Drugs*, R. S. Vardanyan, V. J. Hruby, Eds. (Elsevier, Amsterdam, 2006), pp. 83-101.

[25] J. J. La Clair, Encoding matter with regiospecific $^{12}C/^{13}C$ isotopic labels. *Chem. Commun*. **54**, 2611-2614 (2018).
10.1039/C8CC00080H.

[26] M. Zwillinger, L. Fischer, G. Sályi, S. Szabó, M. Csékei, I. Huc, A. Kotschy, Isotope Ratio Encoding of Sequence-Defined Oligomers. *J. Am. Chem. Soc.* **144**, 19078-19088 (2022).
10.1021/jacs.2c08135.

[27] D. Kong, P. J. Moon, E. K. J. Lui, O. Bsharat, R. J. Lundgren, Direct reversible decarboxylation from stable organic acids in dimethylformamide solution. *Science* **369**, 557-561 (2020).
10.1126/science.abb4129)

[28] O. Bsharat, M. G. J. Doyle, M. Munch, B. A. Mair, C. J. C. Cooze, V. Derdau, A. Bauer, D. Kong, B. H. Rotstein, R. J. Lundgren, Aldehyde-catalysed carboxylate exchange in α-amino acids with isotopically labelled CO_2. *Nat. Chem.* **14**, 1367-1374 (2022).

10.1038/s41557-022-01074-0.

[29] S. Monticelli, A. Talbot, P. Gotico, F. Caillé, O. Loreau, A. Del Vecchio, A. Malandain, A. Sallustrau, W. Leibl, A. Aukauloo, F. Taran, Z. Halime, D. Audisio, Unlocking full and fast conversion in photocatalytic carbon dioxide reduction for applications in radio-carbonylation. *Nat. Commun.* **14**, 4451 (2023).
10.1038/s41467-023-40136-w.