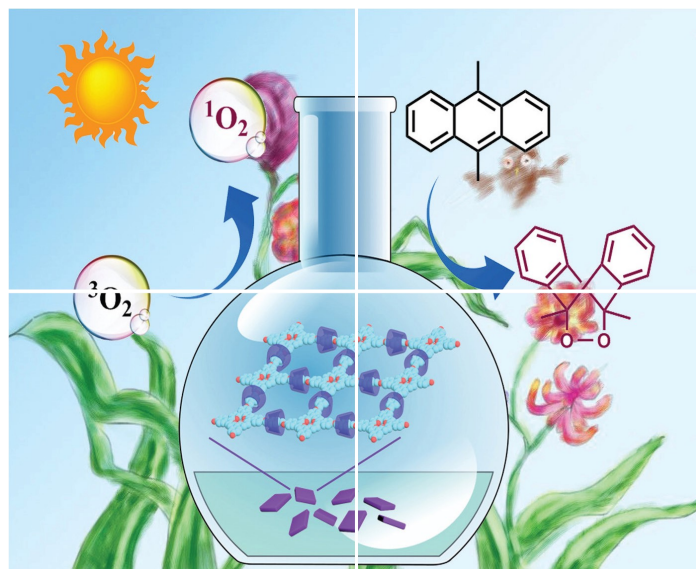


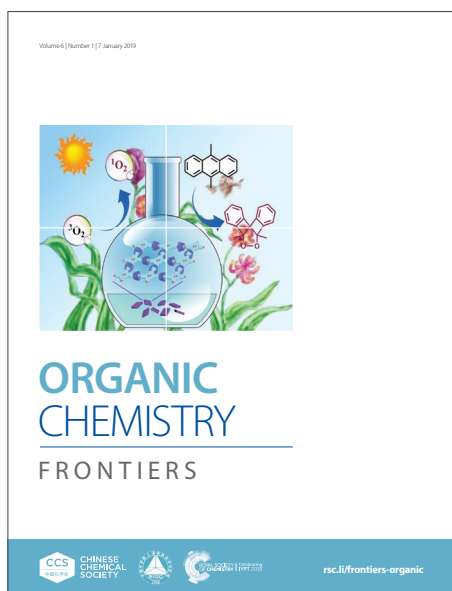
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Tutorial Review

Carbon Isotope Exchange and Transfer Reactions Involving CO₂Grace Beaver,^{1a} Katherine E. Marris,^{1a} Daniel J. Ryder Mahoney,^{1a} Dimitrios Ioannis Tzaras,^{1a} Ryan A. Bragg,^b Charles S. Elmore,^c Gregory J. P. Perry*^aReceived 00th January 20xx,
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Carboxylation reactions are fundamental transformations in organic chemistry, enabling the synthesis of diverse and valuable compounds, including polymers, pharmaceuticals, and agrochemicals. In recent years, carboxylation processes proceeding via carbon isotope exchange or CO₂ transfer have received significant interest. These processes offer intriguing decarboxylation/carboxylation reactivity and enhance existing carboxylation pathways, in particular by delivering efficient and sustainable solutions for carbon isotope labelling. This review compares and contrasts the related fields of carbon isotope exchange and transfer reactions involving CO₂. We detail early developments to the most recent advancements and discuss the advantages and limitations of each approach, in particular with regard to the efficiency of each strategy.

1. Introduction

Isotope chemistry represents a unique and essential field with broad relevance in both academic research and industrial applications. In particular, the pharmaceutical and agrochemical sectors rely heavily on isotopically labelled compounds.^{1,2} More specifically, ¹¹C isotopes play a critical role in therapeutic research, as the high sensitivity enables high-resolution imaging and tracking using positron emission tomography (PET) for biodistribution, pharmacokinetic and receptor binding studies. The radioactivity facilitates the detection and mapping of various cancers.³ On the other hand, ¹³C labelling, in addition to applications in structural elucidation and mechanistic studies, has become a powerful bioanalytical tool for investigating metabolic pathways, including studies of cancer metabolism.⁴ Meanwhile, ¹⁴C-labelled compounds are extensively used in in vivo metabolic (ADME) and pharmacokinetic (DMPK) studies.⁵ The long half-life (t_{1/2} = 5730 years) and low-energy β-decay provide a safer and higher-resolution alternative to other isotopes.⁶ Furthermore, isotopic labelling is also valuable in agrochemical development, enabling detailed metabolic profiling and assessment of potential human and environmental exposure.⁷

Carboxylation is a cornerstone transformation in organic chemistry, underpinning the preparation of various molecules, including polymers, pharmaceuticals, and agrochemicals.⁸ Although all labelled reagents are relatively costly compared to their non-labelled counterparts, labelled CO₂ gases (¹³CO₂, ¹⁴CO₂) are the least expensive or the easiest to prepare (¹¹CO₂).⁹

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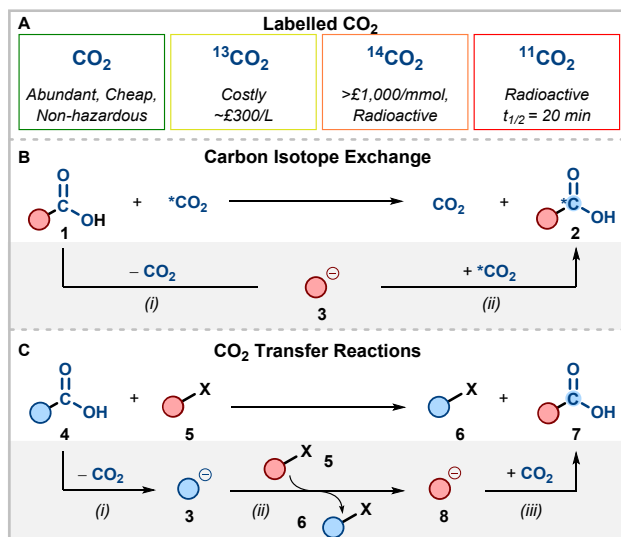
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Thus, carboxylation technologies often present an ideal method for introducing carbon isotopes. However, some distinct considerations must be made when performing a process with labelled CO₂ in comparison to a standard carboxylation reaction (Scheme 1A), namely; 1) labelled CO₂ gas is significantly more expensive than non-labelled CO₂, thus, maximizing the yield relative to CO₂ is critical. 2) ¹⁴CO₂ is radioactive, therefore, methods using equimolar amounts of the labelled reagent are preferred to avoid waste. The development of non-gaseous CO₂ surrogates may also aid the handling of these hazardous reagents and obviate the need for specialised gas handling manifolds. 3) ¹¹CO₂ is a short-lived isotope (t_{1/2} = 20 min), thus, short reaction times are required. Recent years have seen the emergence of carbon isotope exchange and transfer reactions with CO₂ as useful strategies that satisfy these considerations and will be the focus of this review (Scheme 1B and 1C). These processes have the potential to directly label complex carboxylic acids via single step synthetic routes, avoiding de novo synthesis and thereby minimising waste and handling steps. CO₂ transfer additionally offers bench-weightable surrogates and near-quantitative incorporation, providing a green and practical option for isotope labelling.

In carbon isotope exchange, the unlabelled carboxylic acid **1** functionality is swapped with labelled CO₂ gas to provide the labelled carboxylic acid **2** (Scheme 1B). A simplified description of this process involves decarboxylation of **1** to remove the unlabelled carboxyl group (step i), followed by carboxylation of the reactive intermediate **3**¹⁰ with labelled CO₂ (step ii). Key advantages of this process include 1) switching one isotope for another presents a simple yet effective approach for installing isotope labels. 2) The process can be applied in late-stage isotope labelling. For example, complex molecules can theoretically be selectively labelled at the carboxylic acid group, whilst leaving the rest of the molecule untouched. This allows the molecule to be labelled directly and avoids lengthy de novo

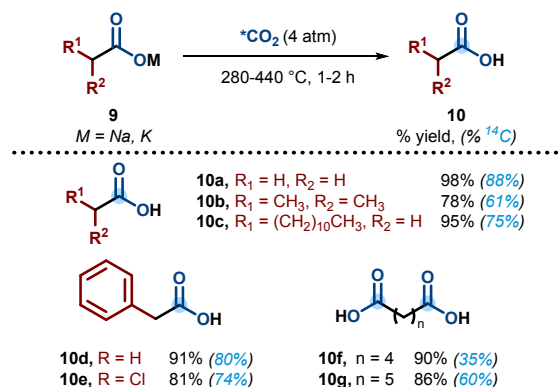
synthesis, thereby improving the overall greenness of the process. 3) If the carbon-isotope exchange is fast, it can be used for ^{13}C isotope labelling. A limitation of this method is that an excess of labelled CO_2 is required to deliver high levels of isotopic enrichment. This is because, upon decarboxylation, the intermediate **3** can react with the unlabelled CO_2 that has just been expelled (giving back the starting material **1**) or react with the desired labelled CO_2 . An excess of labelled CO_2 is therefore required to favour the desired isotope exchange, but this can add significant expense and waste. To improve the greenness of this process, the excess/unused labelled gas could be recycled, however, this is rarely demonstrated in the literature.¹¹ Lower equivalents of labelled CO_2 gas can be used, but at the expense of lower isotope incorporations. Although highly enriched isotopically labelled compounds are often not required, if the exchange is particularly inefficient, the isotope level may not meet the levels required for purpose. In this review, we focus our discussion on carbon isotope exchange reactions involving CO_2 to allow comparison with related CO_2 transfer reactions. For carbon isotope exchange more broadly, we direct the readers to several expert reviews.^{9,12-14}



Scheme 1. A) Comparison of labelled vs unlabelled CO_2 . B) Overview of carbon isotope exchange reactions. C) Overview of CO_2 transfer reactions.

The other strategy that will be discussed in this review is CO_2 transfer, sometimes referred to as CO_2 shuttling (Scheme 1C).¹⁵ A simplified description of this process involves the release of CO_2 from decarboxylation of a carboxylic acid-containing molecule **4** (step i), followed by the capture of the CO_2 by another species **5** via intermediate **8**¹⁰ to deliver the desired carboxylated product **7** (step iii). As will be discussed in more detail below, the intermediate **3**¹⁰ can also play a key role in the reaction, for example by acting as a base/metalating agent (step ii). We limit our discussion to CO_2 transfer reactions that are isodesmic, i.e. the types of bonds that are made in forming the products are the same as those which are broken in the

reactants.¹⁶ More specifically, reagent **4** contains a $\text{C}-\text{CO}_2$ bond to deliver a $\text{C}-\text{CO}_2$ bond in product **7** (Scheme 1C). This allows us to better compare the related areas of carbon-isotope exchange and CO_2 transfer.¹⁷ CO_2 transfer presents several benefits in comparison to traditional carboxylation pathways including 1) the use of stable and weighable CO_2 surrogates. This improves the practicality of the procedure as it avoids the handling of gaseous reagents. This also presents safety benefits, for example by avoiding the use of high-pressure apparatus and the possibility of asphyxiating gas leaks. In addition, high vacuum transfers that are used when performing isotope labelling, including the liberation of $^{14}\text{CO}_2$ from labelled barium carbonate and subsequent condensation with liquid nitrogen, are avoided. 2) As the reagent can be weighed on the bench, it allows the equivalents of the labelled reagent to be easily controlled, thereby minimising costs and waste. 3) Due to inherent differences in the mechanisms, transfer reactions lead to higher (often full) isotope incorporation over carbon-isotope exchange. 4) We have largely described the benefits of CO_2 transfer reactions in the context of carbon isotope labelling, however, these methods can also find use in carboxylation reactions more generally as they provide practical and easy-to-handle CO_2 surrogates. Drawbacks include the need to prepare the carboxylating agent, which can add steps on to the synthesis whilst increasing costs and waste. Similarly, this can prevent applications in ^{11}C labelling due to the short lifetime of this isotope, however automated processes, may offer solutions to this problem.¹⁸ The atom economy of the process is also lower in comparison to using CO_2 gas, however, these drawbacks can be offset by practicality and cost benefits, especially when performing isotope labelling.



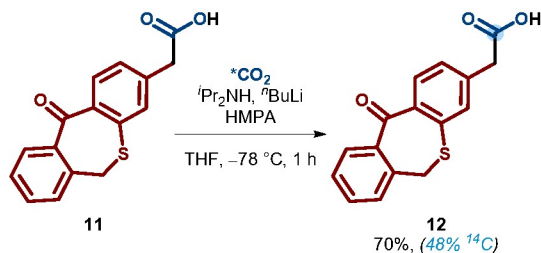
Scheme 2. Thermally induced ^{14}C isotope exchange of carboxylic salt **9**.¹⁹

2. Carbon Isotope Exchange Reactions

2.1. Early reports on carbon isotope exchange

One of the earliest examples of carbon isotope exchange via carboxylation dates back to 1974 when Szammer and co-workers postulated a process driven by thermal exchange for incorporating ^{14}C isotopes (scheme 2).¹⁹ Preliminary references to such transformations can be found in works led by Nakai and

Darensbourg,^{20,21} however Szammer provided the first detailed account and scope, specifically describing the process as isotope exchange. A range of labelled carboxylic acids, **10a-g**, were generated from the corresponding Na or K salt **9**, and obtained in high yields with generally high isotopic enrichment. Although exceedingly high temperatures (280-440 °C) and high pressures (4 atm) were required, this work clearly provided inspiration for more recent developments.



Scheme 3. Synthetic ¹⁴C isotope exchange on aryl acetic acid **11**.²²

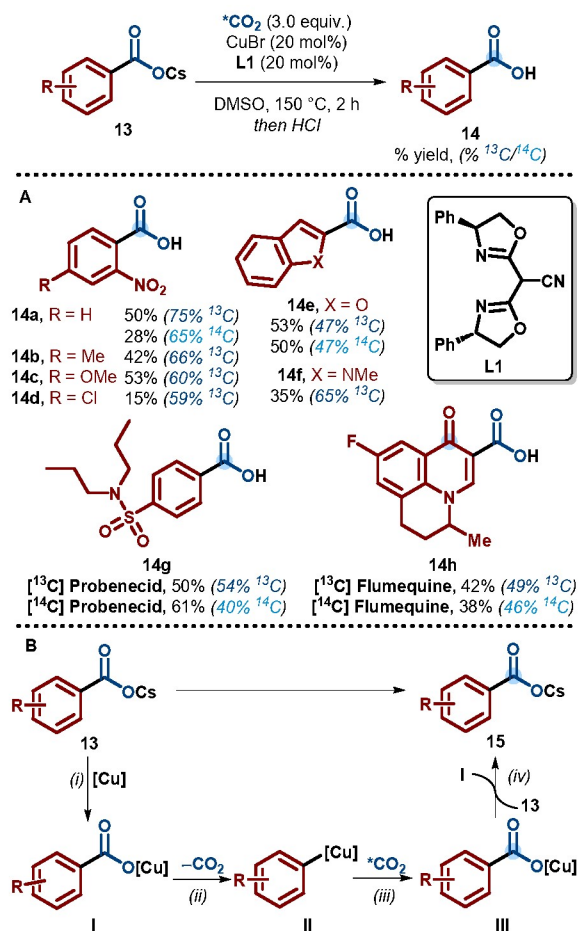
A few years later, Parnes reported a related strategy for the ¹⁴C labelling of an aryl acetic acid (Scheme 3).²² Though only a single example of isotope exchange was reported, the manuscript included an engaging discussion on mechanisms and concepts for carbon isotope exchange that have been built on in more recent years.

2.2. Transition metal-promoted carbon isotope exchange

Recent years have seen a significant growth in the development of carbon isotope exchange strategies involving CO₂. This area garnered newfound interest through a series of reports published between 2018 and 2019 by the groups of Audisio, Baran and Martin on transition metal catalysed carbon isotope exchange.²³⁻²⁵

Audisio and co-workers reported a copper catalysed carbon isotope exchange of aromatic and benzopyrone derived carboxylic acids (Scheme 4).²³ Use of the cesium salt of the acid was necessary to limit competing protodecarboxylation. The conditions and scope of the process reflected related copper promoted decarboxylations of aromatic acids,²⁶ namely that relatively high temperatures (>150 °C) were required and aromatic substrates bearing ortho substituents showed the greatest reactivity. As three equivalents of labelled CO₂ gas was used, the highest possible enrichment at equilibrium is 75%. In general, the isotopic enrichment varied between substrates, with a slight trend that more sterically hindered substrates showed lower isotopic incorporation. The procedure was also applied to the late-stage ¹³C and ¹⁴C isotope labelling of biologically relevant molecules such as probenecid **14g** and flumequine **14h**. Although mechanistic studies were not conducted, the authors were able to suggest a possible mechanism based on previous knowledge (Scheme 4B).²⁶ Firstly, salt exchange with the copper catalyst (step i) followed by decarboxylation (step ii) provided the aryl copper species **II**. The labelled CO₂ was then trapped by intermediate **II** to deliver carboxylate **III** (step iii). Another salt exchange with the cesium

salt **13** delivered the labelled carboxylate **15** (step iv) and regenerated the unlabelled copper carboxylate **I** to close the catalytic cycle. At the end of the process, the mixture of cesium and copper carboxylates **III** and **15** were protonated to deliver the isotope enriched carboxylic acids **14** shown in Scheme 4A.

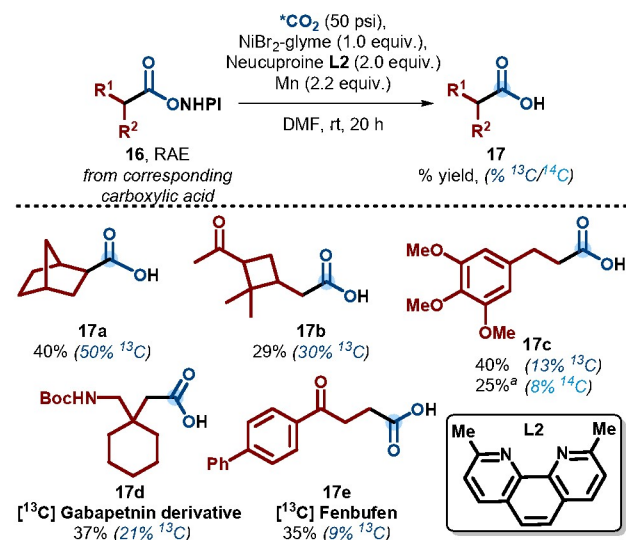


Scheme 4. A) Cu catalysed ¹³C/¹⁴C Isotope Exchange on carboxylic salt **13**. B) Proposed mechanism for catalytic cycle of Cu mediated Carbon Isotope Exchange.²³

In 2019, Baran and co-workers demonstrated a nickel mediated carbon isotope exchange of aliphatic carboxylic acids (Scheme 5).²⁴ This process made use of the known reactivity of *N*-hydroxyphthalimide derived redox active esters **16** as an effective strategy for carboxylic acid activation. The procedure was applicable to a range of primary and secondary carboxylic acids, however, tertiary carboxylic acids were incompatible. A range of medically-relevant substrates underwent carbon isotope exchange (e.g. see **17d** and **17e**) and the process was also applied to ¹³C and ¹⁴C labelling. The isotope enrichment/specific activity was relatively low, however, the authors reasoned that the levels obtained in this study were still of use in early-stage development.

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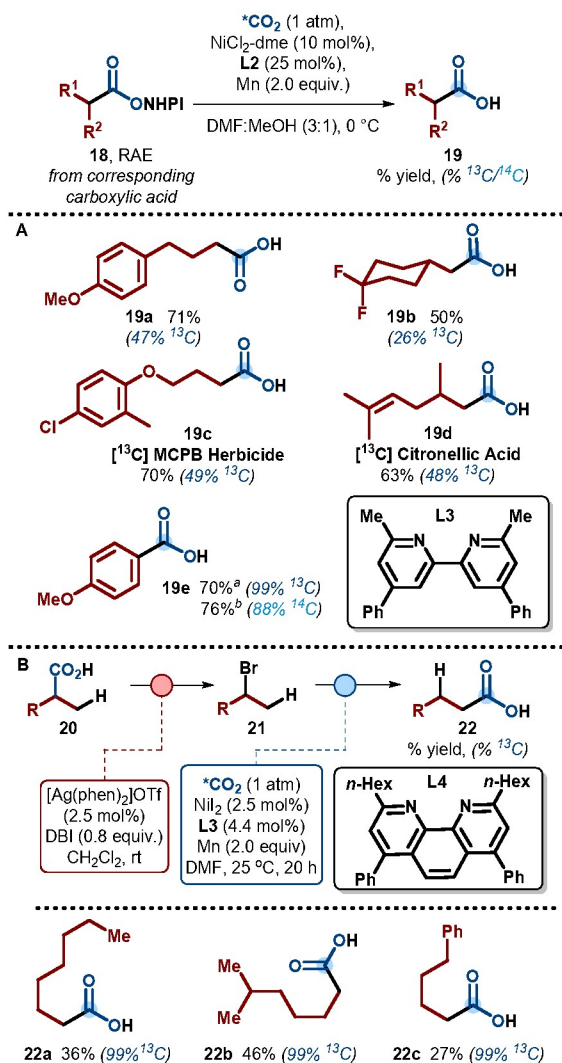
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Scheme 5. Ni mediated carbon isotope exchange of aliphatic redox active esters **16**.²⁴ ^aAlternative reaction conditions for ¹⁴C labelling of ¹⁴CO₂ (1 atm), DMF (0.05M), -25 °C (1 h) to room temperature (20 h).

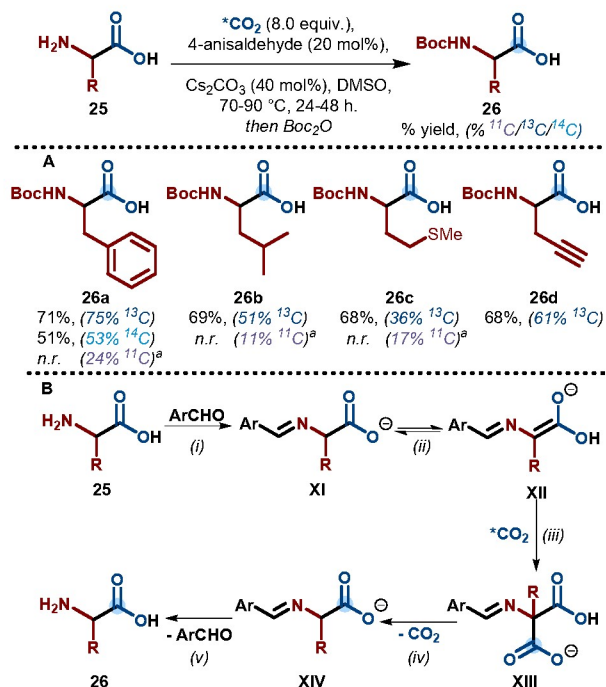
Following on from the work by Baran and co-workers, a related process was reported in the same year by the Martin group (Scheme 6).²⁵ A key development in this study was the ability to use catalytic quantities of the nickel catalyst, rather than the stoichiometric amounts that had previously been required. The isotope incorporation was also generally higher in this report, though consistently high values were unachievable, as is often encountered in carbon isotope exchange processes. To get around this problem, the authors developed an alternative formal CO₂ exchange through a sequence of decarboxylative halogenation and C–X carboxylation.²⁷ This led to complete isotope incorporation in all cases, though the yields were lower. The authors also demonstrated the preparation of the ¹³C and ¹⁴C labelled benzoic acid **19e** from the corresponding aryl bromide.²⁸ Finally, the authors revealed the application of this carbon isotope exchange strategy in chain-walking carboxylation reactions (Scheme 6B).²⁹ This process was initiated by conversion of the carboxylic acid **20** to the alkyl bromide **21**. Upon exposure to a nickel catalyst, substrates **21** underwent a chain-walking process towards functionalisation at the terminal position of the alkyl chain. Thus, in the presence of ¹³CO₂ the labelled products **22** were formed with good isotopic enrichment, albeit in relatively low yields. Overall, the authors described several strategies for delivering isotope labelled aliphatic and aromatic acids, including medically relevant molecules, through formal carbon isotope exchange processes. Neither report by the Baran group or Martin group discussed the mechanism in detail, which is reasonable as the intricacies of these nickel catalysed processes are somewhat disputed.³⁰ In order to inform the reader, we provide simplified mechanisms for these processes, however, we leave our discussion deliberately vague due to the uncertainty surrounding these details (Scheme 7). We suggest that the role of the manganese

was to reduce the nickel precatalyst to an active nickel species **IV** (step i),^{31,32} which could promote decarboxylation of the redox active ester **18** to provide the nucleophilic intermediate **V** (step ii). The labelled CO₂ was then captured by intermediate **V** to give nickel carboxylate **VI** (step iii).^{33,34} Under Baran's conditions, which used stoichiometric nickel, carboxylate **VI** would then deliver the desired carboxylic acid **19** upon workup (step iv).²⁴ In the case of Martin and co-workers, the nickel catalyst **IV** would be regenerated from the reaction between nickel carboxylate **VI** and manganese metal (step v).²⁵ The manganese carboxylate generated in this step would then lead to the carboxylic acid product **19** upon workup.



Scheme 6. A) Ni catalysed carbon isotope exchange of carboxylic acid derivatives **18**.²⁵ **19e** was synthesised from the corresponding aryl bromide using alternative conditions: ^aNiBr₂.dme (10 mol%), neocuproine (20 mol%) in DMA at 50 °C, ^bNiL₂ (2.5 mol%), L₃ (4.4 mol%), DMF at 25 °C. B) Ni catalysed carbon isotope exchange via chain-walking. DBI = dibromoisocyanuric acid.

imine **XI** (step i). Tautomerisation (or deprotonation) and carboxylation then delivered the imino malonate derivative **XIII** (steps ii and iii). Finally, subsequent decarboxylation (step iv) and hydrolysis (step v) delivered the desired labelled amino acid **26** and regenerated the aldehyde catalyst (Scheme 9C).

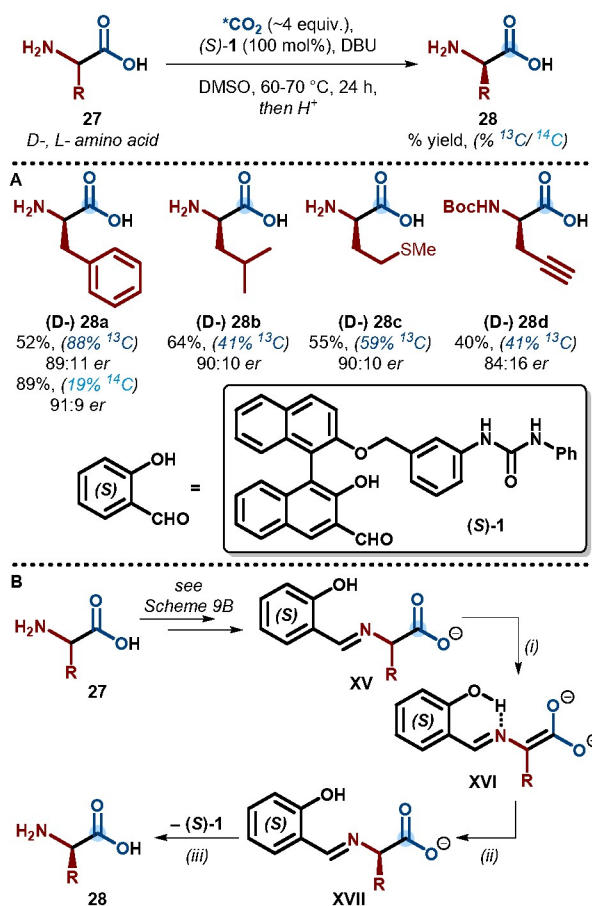


Scheme 9. A) Carbon isotope exchange of amino acids **25**.^{37 a 1} PhCHO (1.0 equiv.), Cs₂CO₃ (0.50 equiv.), MeOH, 70 °C, 2) ¹¹CO₂ (7-10 GBq), DMSO, 90 °C, 10 min, then HCl. % incorporation for ¹¹C is based on radiochemical yield: an amount calculated from isotopic purity and corrected for decay. n.r. = not reported. B) Mechanistic proposal for carbon isotope exchange of amino acids.

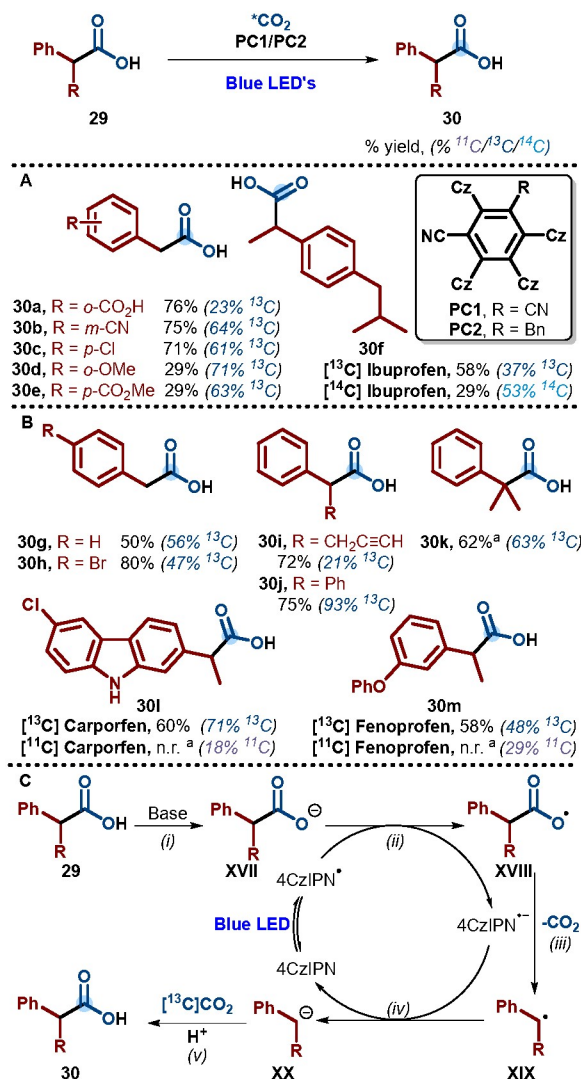
During their studies on the carbon isotope exchange of amino acids (Scheme 9), Lundgren, Rotstein and co-workers noted the drawback that, unless subsequent resolution was performed, access to enantiopure labelled amino acids was not possible.³⁷ To address this limitation, Lundgren, Derdau and colleagues presented a related carbon isotope exchange for accessing enantioenriched labelled amino acids (Scheme 10).³⁸ The overall strategy involved combining their work on aldehyde-promoted carbon isotope exchange with a chiral aldehyde-promoted stereoconversion of amino acids previously reported by Chin, Kim and co-workers.³⁹ The chiral aldehyde **(S)-1** was found most suitable for promoting isotope exchange and controlling the stereochemistry of the product. The authors attempted to use catalytic amounts of chiral aldehyde **(S)-1**, but ultimately these attempts were fruitless. The reaction was applicable to a variety of natural and non-natural amino acids and both ¹³C and ¹⁴C labelling was achieved, though the scope seemed less general in comparison to their previous racemic approach (c.f. Scheme 9). As has become standard in CO₂ exchange processes, the level of isotope incorporation varied between substrates. Due to the lack of methods for generating chiral labelled amino acids, this chemistry demonstrated a

particularly elegant solution. However, the enantiomeric ratios of the products were often not ideal (generally <90:10 e.r.), thus the authors reverted to resolution techniques for delivering products with high enantiomeric ratios.

The authors proposed that the CO₂ exchange and stereochemical induction processes proceed in separate steps. Firstly, condensation with the chiral aldehyde **(S)-1** provided an imine intermediate that could undergo carbon isotope exchange in a similar fashion to that described in Scheme 9B. This would provide the labelled imine intermediate **XV** (Scheme 10B, c.f. **XIV** Scheme 9B). In agreement with the reports by Chin, Kim and co-workers,³⁹ the authors suggested that deprotonation of chiral imine **XV** provided intermediate **XVI** (step i), which is then susceptible to a diastereoselective reprotonation to give the enantioenriched compound **XVII** (step ii). Subsequent hydrolysis then delivered the enantioenriched labelled amino acid **28** (step iii).



Scheme 10. A) Chiral aldehyde-promoted carbon isotope exchange of amino acids. B) Proposed diastereoselective mechanism for formation of **28**.³⁸



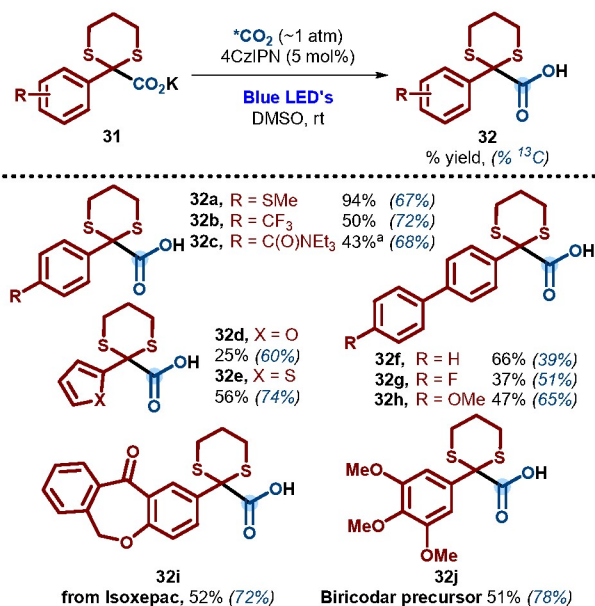
Scheme 11. Photocatalyzed carbon isotope exchange of carboxylic acid **29** from: A) Audisio and co-workers.⁴⁰ Standard conditions: *CO_2 (3.0 equiv.), **PC1** (6 mol%), K₃PO₄ (1.0 equiv.), DMF, 6 h, then HCl. ^a **PC2** used instead of **PC1**. B) Lundgren, Rotstein and co-workers.⁴¹ Standard conditions: *CO_2 (7.0 equiv.), **PC1** or **PC2** (5 mol%), Cs₂CO₃ (1.0 equiv.), DMA or DMSO, rt. % incorporation for ^{13}C is based on Radiochemical yield: an amount calculated from isotopic purity and corrected for decay. n.r. = not reported. C) Proposed mechanism for photocatalyzed carbon isotope exchange of carboxylic acid **29**.

2.4. Light mediated carbon isotope exchange

In 2021, the groups of Audisio, and Lundgren and Rotstein reported related photoredox catalysed carbon isotope exchange processes in unison.^{40,41} The general conditions for both processes were a photoredox catalyst (either 4-CzIPN (**PC1**) or 4-CzBnBN (**PC2**)), a base (K₃PO₄ or Cs₂CO₃), a polar aprotic solvent (DMF, DMA or DMSO) under blue light irradiation (Scheme 11). Both groups realised that 4-CzIPN was converted to 4-CzBnBN under the reaction conditions, in agreement with previous reports.³⁷ Thus, whereas 4-CzIPN (**PC1**) was used in many cases, 4-CzBnBN (**PC2**) provided a more

reliable and efficient exchange process for more complex substrates, as it was less prone to side reactions. This was of note for Lundgren and Rotstein, who discovered that 4-CzBnBN (**PC2**) could facilitate ^{13}C transfer when 4-CzIPN (**PC1**) failed. A clear advantage of these processes in comparison to the thermally induced methods (up to 190 °C, see Scheme 8) is the ability to perform exchange at room temperature. Both groups demonstrated reactivity with various phenylacetic acids with known bioactivity (**30f**, **30l**, **30m**) and Audisio and coworkers also applied the process in exchange with $^{14}CO_2$ (**30f**).⁴⁰ Realising that this photoredox catalysed process proceeded much faster than the thermally induced version, Lundgren, Rotstein and co-workers nicely demonstrated the suitability of the reaction in ^{13}C isotope exchange (**30l**, **30m**).⁴¹

Both groups provided similar mechanistic proposals, with the Audisio group conducting some informative mechanistic studies to support their suggestions (Scheme 11C).⁴⁰ Previous studies on the photoredox catalysed decarboxylation of phenylacetic acids were also used as support for the proposed mechanisms.⁴² Under basic reaction conditions, the carboxylic acid **29** was initially deprotonated to give carboxylate **XVII** (step i). Oxidation of the carboxylate by the photoredox catalyst then provided the carboxyl radical **XVIII** (step ii), which was prone to decarboxylation towards carbon centred radical **XIX** (step iii). Single electron transfer from the reduced photoredox catalyst to the radical species **XIX** would then provide the nucleophile **XX** (step iv), which was able to capture the labelled CO₂ gas towards the desired product **30** (step v). In contrast to the mechanistic proposals for thermally induced carbon isotope exchange in which a malonate intermediate was proposed (c.f. intermediate **IX** in Scheme 8 and **XIII** in Scheme 9), the direct capture of labelled CO₂ gas by the benzyl anion **XX** (step v) was suggested in this study.

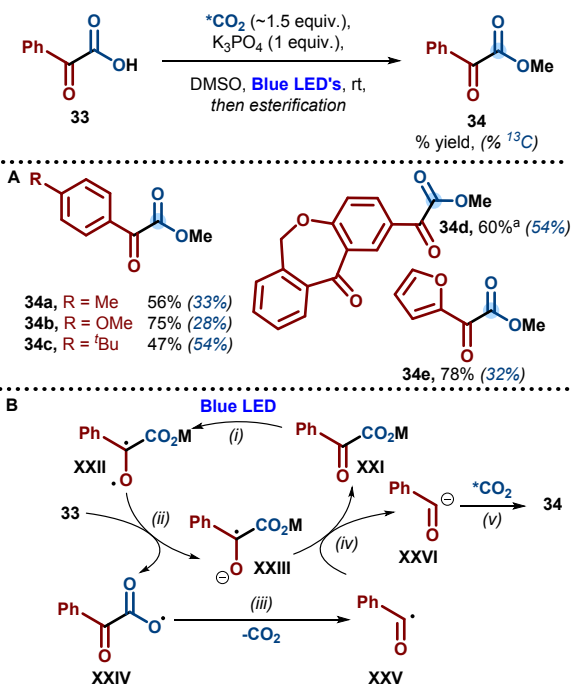


Scheme 12. Photocatalysed carbon isotope exchange of protected α -keto acids. ^aIsolated as the corresponding methyl ester.⁴³

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Following these reports, Kong and co-workers expanded the methodology towards a formal carbon isotope exchange of α -keto acids via thioketal acid salts **31** (Scheme 12).⁴³ The reaction was applied to a range of substrates, with the yields and levels of isotope enrichment consistent with the efficiencies observed in related photoredox catalysed isotope exchanges (c.f. Scheme 11).^{40,41} The preparation of isotope-labelled drug derivatives (**32i**, **32j**) was also demonstrated. Mechanistic studies, including Stern-Volmer quenching experiments, supported a mechanistic pathway like that shown in Scheme 11C.



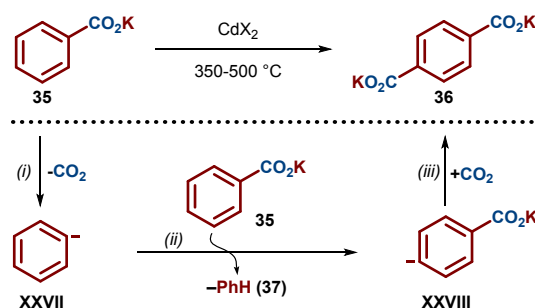
Scheme 13. A) Direct carbon isotope exchange of α -keto acids. $^{13}\text{CO}_2$ (3.0 equiv.), CuCN/BINAP (20 mol%). B) Mechanistic proposal.⁴⁴

The Kong group were then able to demonstrate a direct carbon isotope exchange of α -ketoacids, foregoing the steps of thioketal installation and removal, that were previously required (Scheme 13).⁴⁴ The reactivity was once again demonstrated on a range of substrates, though overall the scope, yields and isotope enrichment were diminished in comparison to their previous report. Nonetheless, by developing both an indirect but general (Scheme 12) and a more direct yet less efficient (Scheme 13) CO_2 exchange, a flexible approach to labelled α -ketoacids was demonstrated. Interestingly, this photoinitiated process did not require a photoredox catalyst. Through several preliminary experiments, the authors tentatively proposed the mechanism described in Scheme 13B. They suggested irradiation with light forms the excited state of the α -keto carboxylate **XXII** (step i), which was able to undergo single electron transfer with the ground state of another molecule of α -ketoacid **33** (step ii). Decarboxylation

of intermediate **XXIV** would generate the radical species **XXV** (step iii), which could then undergo single electron transfer with **XXIII** to provide the acyl anion **XXVI** (step iv) and regenerate the ground state α -keto acid **XXI** to maintain the catalytic cycle. Carboxylation of the acyl anion **XXVI** then would deliver the labelled α -keto ester **34** (step v). Further studies would better delineate the mechanism of this interesting process.

3. CO_2 Transfer Reactions3.1. Early reports on CO_2 transfer reactions

The earliest documentation of a CO_2 transfer reaction was outlined by Henkel in 1958 (Scheme 14).⁴⁵ The process involved a disproportionation reaction of potassium benzoate **35** into terephthalate **36** and benzene **37** (Scheme 14). This type of disproportionation reaction is sometimes referred to as the Henkel or Raecke reaction. The method required heating to very high temperatures (350–500 °C), often in the presence of a cadmium catalyst. The harsh conditions limit the generality of the process, but it has found interest in the preparation of bulk chemicals, such as terephthalic acid and furan-2,5-dicarboxylic acid.^{46,47} The mechanism has not been well studied, but it is proposed that heating promotes decarboxylation of the benzoic acid salt **35** to give the anionic species **XXVII** (step i). The intermediate **XXVII** then deprotonates another molecule of the aromatic acid salt **35**. This produces benzene **37** and the intermediate **XXVIII** which is able to capture the CO_2 that was expelled during the first decarboxylation step. Though an impressive transformation, the harsh conditions have prevented the widespread use of this chemistry. In addition, many of the processes also required the addition of (pressurised) CO_2 , thus a true CO_2 transfer process is not in operation.⁴⁸



Scheme 14. The Henkel process.⁴⁵

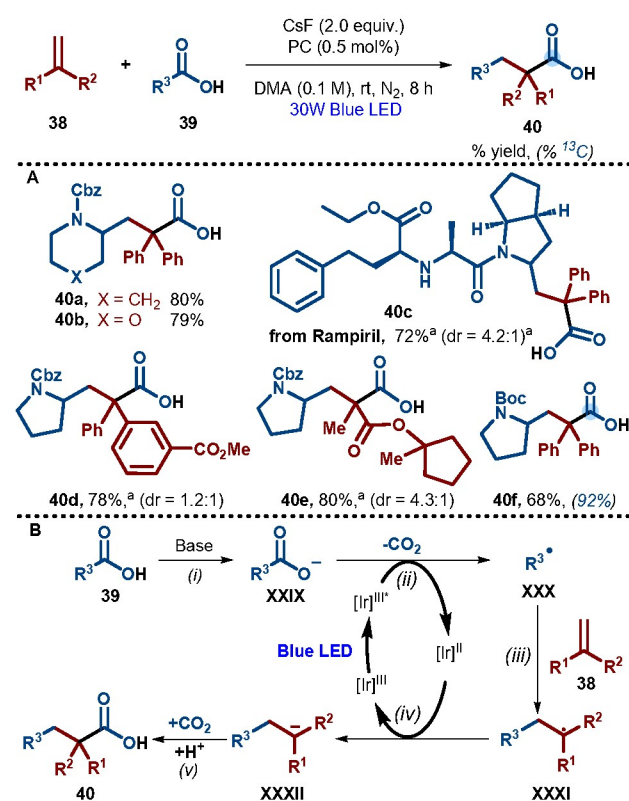
3.2. CO_2 transfer via addition across alkenes

An impressive example of CO_2 transfer was reported by Yu and co-workers in 2021 (Scheme 15A).⁴⁹ The process involved the addition of the C– CO_2H bond in amino acids across the C=C double bond of activated alkenes. Importantly, the work demonstrated the efficient transfer of CO_2 under mild reaction conditions. The reaction was generally performed using cyclic amino acids and styrene derivatives (see **40a**, **40b** and **40d**), though extending the reactivity to natural amino acid derivatives and other alkenes (see **40e**) was also possible.

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The reaction with several drug derivatives (see **40c**) was also demonstrated. The labelled product **40f** was prepared using the corresponding labelled amino acid. Though this was used as a mechanistic experiment, it does offer a possible route to apply this method in isotope labelling.

Several other mechanistic studies were conducted to support the proposed mechanism of this photoredox catalysed process (scheme 15B), which the authors suggested to involve an initial oxidation of the carboxylate **XXIX** by the excited state of the photoredox catalyst (step ii). This provided a carboxyl radical which was prone to decarboxylation, leading to the alkyl radical **XXX**. Addition to the alkene **38** then afforded the radical species **XXXI** (step iii), which could undergo single electron transfer with the reduced state of the photoredox catalyst to give the anionic species **XXXII** and close the catalytic cycle (step iv). Finally, the intermediate **XXXII** would capture the in situ generated CO₂ to provide the desired product **40** after protonation.



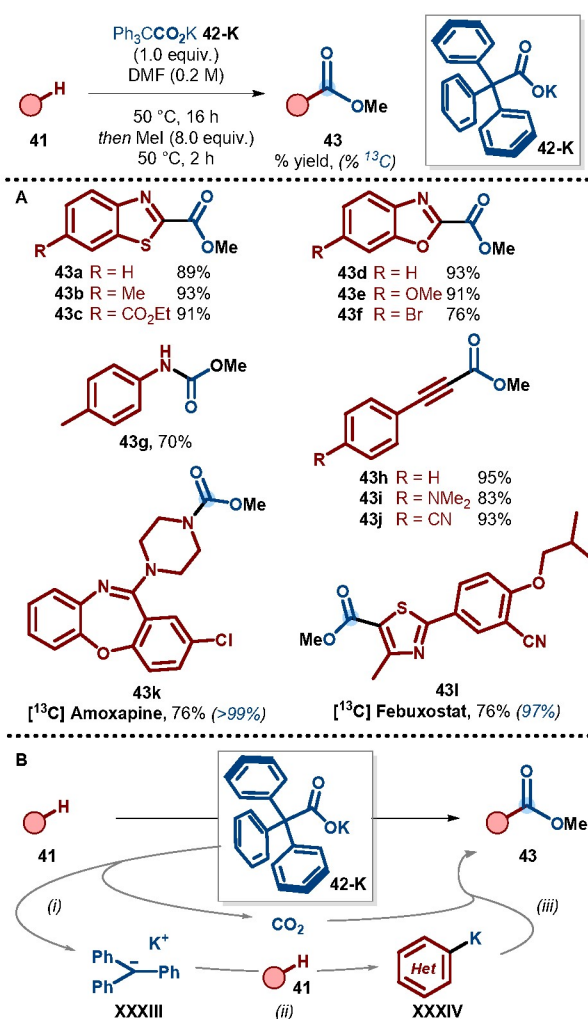
Scheme 15. CO₂ transfer from amino acids across alkenes. ^a CsF (3.0 equiv.).⁴⁹

3.3. CO₂ transfer via deprotonation

A general strategy for CO₂ transfer was reported by Yorimitsu, Perry and co-workers who developed the salt of triphenylacetic acid **42-K** for the transfer of CO₂ to a range of compounds, including (hetero)arenes, alkynes and amines (Scheme 16A).⁵⁰ By using the labelled analogue of reagent **42-K**, the process was also extended to the isotope labelling of some biologically relevant molecules (see **43k**, **43l**). Importantly, all labelled

products were isolated with high isotope enrichment, a general advantage of transfer reactions over carbon isotope exchange. Interestingly, reagent **42-K** provided the source of base and CO₂ for the reaction, leading the authors to describe these compounds as dual-function reagents.

With the support of mechanistic studies (Scheme 16B), they proposed that reagent **42-K** initially underwent decarboxylation to provide CO₂ and the relatively strong base **XXXIII** (step i, pK_a of Ph₃CH = 30.6 in DMSO).⁵¹ This enabled the deprotonation of the substrate **41** to provide the intermediate **XXXIV** (step ii), which was then able to capture the in situ generated CO₂ and deliver the carboxylated product **43** after alkylation (step iii). In general, substrates containing a C–H bond with a pK_a of 30.6 or less (in DMSO) were able to undergo an efficient carboxylation, reflecting the basicity of the intermediate **XXXIII**.



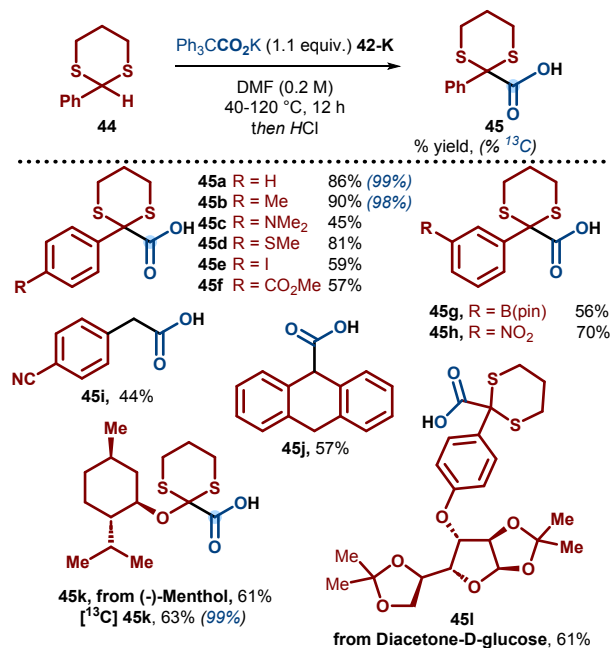
Scheme 16. CO₂ transfer via decarboxylative metalation.⁵⁰

Building on the work by Perry and Yorimitsu (Scheme 16)⁵⁰ and their earlier reports on the formation of labelled α-ketoacids (Scheme 12),⁴⁴ Kong and co-workers revealed the application of this reactivity in a CO₂ transfer with benzaldehyde-derived dithianes **44** (Scheme 17).⁵² A variety of functional groups were compatible (**45a-h**) and the

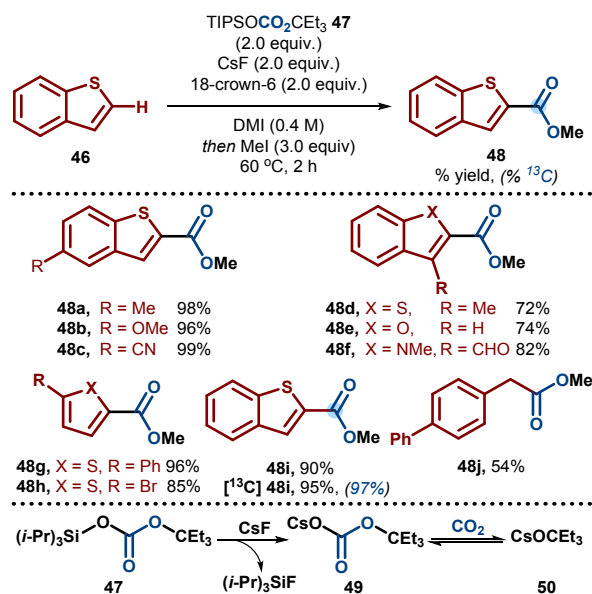
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reactivity was extended to the carboxylation of selected toluene derivatives (**45i**). Various drug derivatives (**45k**, **45l**) also performed well in this CO₂ transfer and the extension of this method to isotope labelling (**45a**, **45b** and **45k**) was demonstrated. As generally seen in CO₂ transfer reactions, the level of isotope incorporation was high in all cases. The mechanism for the process likely proceeds in a similar fashion to that shown in Scheme 16B.



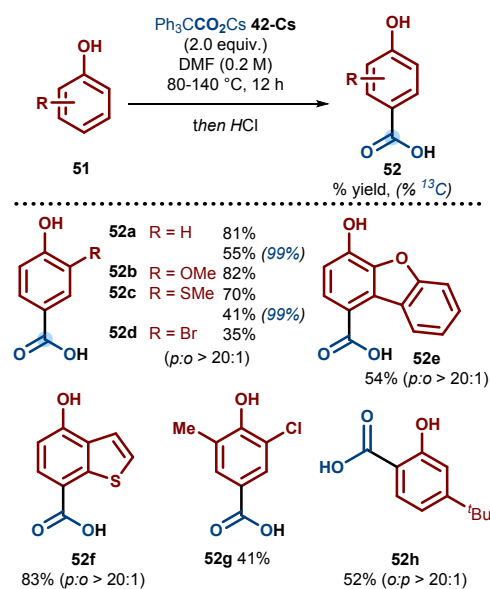
Scheme 17. CO₂ transfer with benzaldehyde-derived dithianes.⁵²



Scheme 18. CO₂ transfer reaction utilizing silicon-based reagents. ^aTIPSOCO₂CET₃ (2.0 equiv.).⁵³

Shigeno and co-workers have developed an alternative silicon-based reagent **47** for CO₂ transfer reactions (Scheme 18).⁵³ This work built

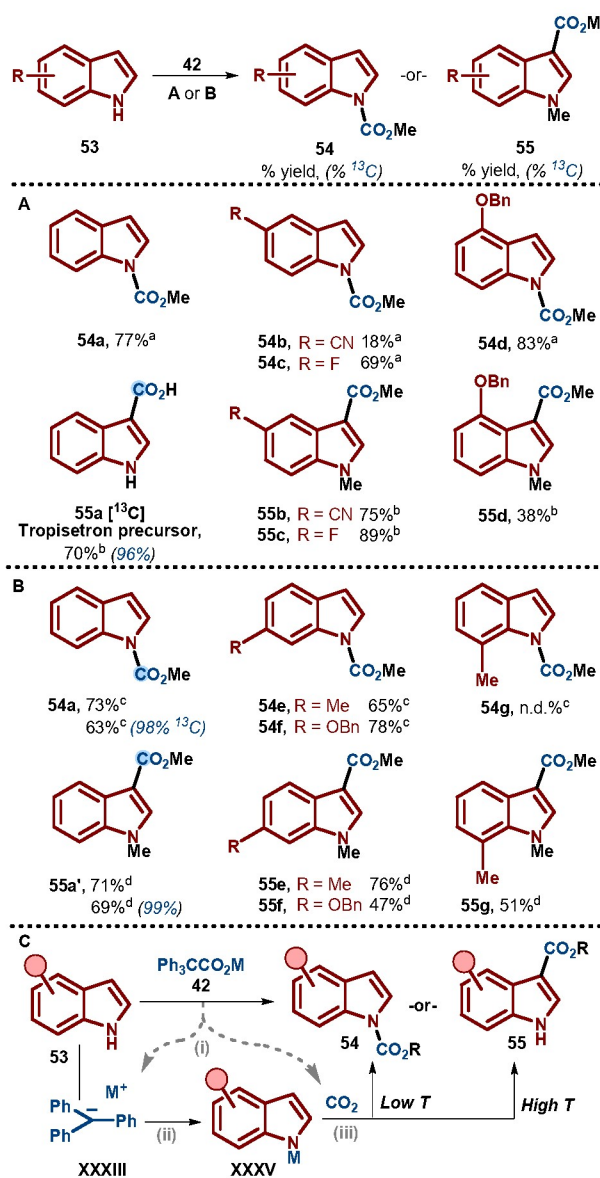
on their/Kondo's previous work in carboxylation chemistry⁵⁴ by applying it to the arena of CO₂ transfer. The reaction was demonstrated on the C–H carboxylation of (hetero)arenes (**48a-i**) and in benzylic carboxylation (**48j**). As the base (Et₃COCs, **50**; pK_a of *t*-BuOH = 32.2 in DMSO)⁵¹ generated during this process is more reactive than that formed in the method reported by Yorimitsu and Perry (Ph₃CK, **42-K**; pK_a of Ph₃CH = 30.6 in DMSO; Scheme 16)⁵¹ it has the potential to offer wider substrate scope, however, at present, the scope of each process is relatively similar. By using the isotope labelled reagent **47**, the procedure was also used to prepare the isotope labelled compound **48i**. In addition to the carboxylating agent **47**, CsF and 18-crown-6 were also required to promote the reaction. The reaction mechanism was suggested to proceed in a similar fashion to that shown in Scheme 16, except that the CO₂ and active base (Et₃COCs, **50**) were proposed to form upon desilylation of the reagent **47** with CsF via intermediate **49** (Scheme 18B).



Scheme 19. Para-selective Kolbe-Schmitt reaction.⁵⁵

To further illustrate the power of dual-function reagents in carboxylation reactions, Perry, Kong and co-workers have recently described a Kolbe-Schmitt-type carboxylation of phenols (Scheme 19).⁵⁵ The procedure overcame some of the longstanding challenges associated with Kolbe-Schmitt type reactivity, such as excessive temperatures and pressures. Interestingly, by using the cesium salt of the carboxylating agent **42-Cs** (and in some cases the potassium salt **42-K**) unique para-selectivity was observed. The sodium salt of the carboxylating agent **42-Na**, provided ortho-carboxylation in line with classical Kolbe-Schmitt-type reactivity, however, the yield of this process was low (38%). Access to a range of substituted 4-hydroxybenzoic acids was demonstrated with high para-selectivity (**52a-52g**). Ortho-carboxylation was observed in some cases, but only when the para-position was blocked or sterically encumbered (see **52h**). Owing to the ability to use near-stoichiometric quantities of the carboxylating reagent, this

approach offered a practical and efficient route to ^{13}C -labelled 4-hydroxybenzoic acid derivatives (**52a**, **52c**).

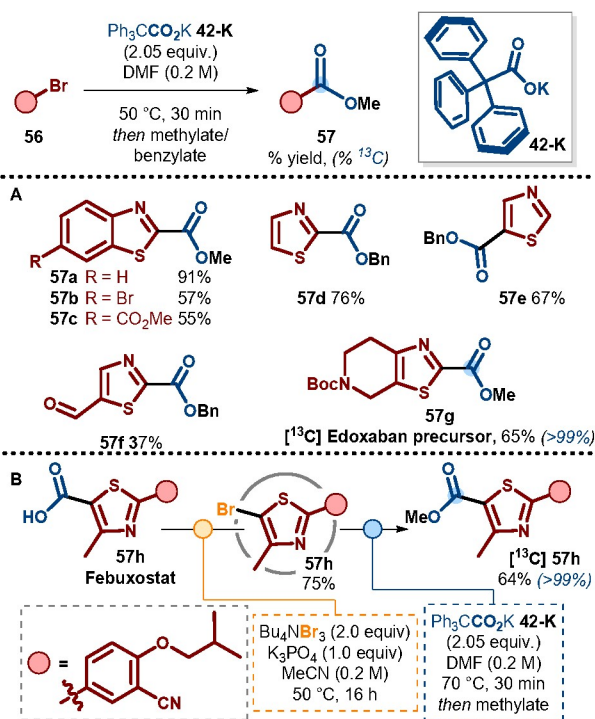


Scheme 20. Switchable N–H and C3–H CO_2 transfer on indoles by: A) Perry and co-workers.⁵⁴ ^aStandard conditions: **42-K** (1.1 equiv.), DMF (0.2 M), 50 °C, 4 h, then alkylation. ^b**42-K** (2.0 equiv.), 140 °C. B) Kong and co-workers.⁵⁵ ^cStandard conditions: **42-Cs** (1.1 equiv.), DMF (0.2 M), 40 °C, 12 h, then alkylation. ^d**42-Cs** (2.2 equiv.), 120 °C C) Agreed mechanism for switchable reactivity.

Recently, the Perry and Kong groups concurrently reported the application of CO_2 transfer reactions in regiodivergent indole functionalization (Scheme 20).^{56,57} Both groups found that N–H carboxylation occurred at lower temperatures (40–50 °C) whereas C3–H carboxylation was possible at higher temperatures (120–140 °C). In addition, the equivalents of the carboxylating agent **42-K** or **42-Cs** were increased when switching between N–H (1.1 equivalents) and C3–H carboxylation (2.0–2.2 equivalents). The Perry group used the

potassium salt of triphenylacetic acid ($\text{Ph}_3\text{CCO}_2\text{K}$, **42-K**, Scheme 20A), whereas the Dong group opted for the cesium salt ($\text{Ph}_3\text{CCO}_2\text{Cs}$, **42-Cs**, Scheme 20B), but overall, there was no significant difference in reactivity between the two salts. Both groups presented a detailed scope representing switchable N–H vs C3–H carboxylation on a range of indoles, **54/55a-g**, with applications in late-stage ^{13}C labelling and the carboxylation of biologically relevant compounds, **55a**. Perry and co-workers also demonstrated a series of related transformations with indoles and the N–H carboxylation of other amines. Both groups offered similar mechanistic hypotheses following the types of steps described in Scheme 16. Here (Scheme 20C), upon generation of the trityl anion **XXXIII**, the indole is deprotonated to provide the intermediate **XXXV**. The N–H carboxylated product **54** can then be accessed when conducting the experiment at low temperatures and lower equivalents of the carboxylating agent **42-K/42-Cs**. Alternatively, by increasing the reaction temperature and the number of equivalents of the carboxylating agent **42-K/42-Cs** the C3–H carboxylated product **55** is produced.

3.4. CO_2 transfer via decarboxylative metal-halogen exchange



Scheme 21. CO_2 transfer via decarboxylative metal-halogen exchange.⁵⁸

Until this point, the CO_2 transfer reagents described in Schemes 16–20 promoted carboxylation through a sequence of deprotonation and carboxylation. To further illustrate the abilities of these reagents, Perry, Yamazaki and co-workers developed a C–X carboxylation of (hetero)aromatic halides (Scheme 21A).⁵⁸ The reaction was applicable to either heteroaryl bromides or iodides, however, chlorides were unreactive under the reaction conditions. Through a series of

experimental and computational studies, the authors suggested a mechanism similar to that shown in Scheme 16B in which the dual-function reagent **42-K** acts as the source of CO₂ and metalating agent. A key advancement in this work was that the metalated intermediate **XXXIV** was generated through metal-halogen exchange, rather than deprotonation (c.f. Scheme 16B, step ii). Noteworthy features included: 1) the site of carboxylation was governed by the position of the C–X bond, for example, 2- and 5-brominated thiazoles **56d** and **56e** gave the 2- and 5-carboxylated products **57d** and **57e**. 2) through examination of the reaction scope and a robustness screen,⁵⁹ the reaction was shown to be tolerant of various functional groups that are usually incompatible with traditional metal-halogen exchange processes, such as aldehydes (**57f**), ketones, amides, alkyl chlorides and nitriles. 3) The process was applied in the isotope labelling of some biologically relevant molecules, for example the Edoxaban precursor **57g**. Finally, the authors demonstrated a formal carbon isotope exchange (Scheme 21B). In this process the drug molecule Febuxostat **57h** was first converted into the aryl bromide **57h** via decarboxylative bromination,⁶⁰ followed by C–X carboxylation under the standard reaction conditions.

4. Conclusions

Recent years have seen the rise of carbon isotope exchange and CO₂ transfer reactions as effective strategies in the field of carboxylation. These methods advance the current-state-of-the-art, in particular towards the development of efficient carbon isotope labelling processes. We have provided a thorough review covering early studies to the latest developments in these areas and highlighted the advantages and limitations of each strategy. Developments in both areas have uncovered novel reactivity that has advanced the field of carboxylation. Further development of these processes is highly anticipated, owing to the key role carbon isotope labelling has in the pharmaceutical and agrochemical fields. Expanding the generality in both carbon isotope exchange and transfer reactions with CO₂ is required to make these processes more general and reliable. In particular, further application of CO₂ transfer reactions in late-stage-functionalization of complex molecules is anticipated. The robustness of carbon isotope exchange reactions could also be improved as many examples often give low chemical yields, even if % isotope incorporation is satisfactory. Both processes could be made more amenable to ¹¹C isotope labelling. The application of CO₂ transfer in ¹¹C isotope labelling seems distant at present due to the need to prepare these reagents and the short lifetime of the ¹¹C isotope, however, advancements in automation may aid this area.¹⁸ Although some examples of ¹¹CO₂ incorporation via carbon isotope exchange are known they often result in low molar activity which limits possible applications. The inherent nature of the process (a direct competition for carboxylation with either labelled or non-labelled CO₂, see Scheme 1B) is somewhat to blame for this, however, solutions to this problem, such as faster reactions and greater levels of exchange, would greatly improve applicability. Overall, we hope this review

informs the community of the benefits and limitations of carbon isotope exchange and CO₂ transfer reactions and encourages others to consider these strategies when planning their own carboxylation or carbon isotope labelling reactions.

Conflicts of interest

“There are no conflicts to declare”.

Acknowledgements

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11. A handful of reports on carbon isotope exchange comment on the capture of excess CO₂. However, quantifying the amount of recovered CO₂ has not been described. We quote directly from the original reports: Ref 14 - “The ¹⁴CO₂

- pressure was about 4-5 atm at the reaction temp. The system was opened and $^{14}\text{CO}_2$ recovered in the form of $\text{Ba}^{14}\text{CO}_3$. Ref 19 – In the SI: “Question 14: Can unreacted $^{14}\text{CO}_2$ in the reaction flask be recaptured for use in other reactions? Answer: Efforts to capture $^{14}\text{CO}_2$ from the side-arm flask into base solution had limited success. No attempt to capture the $^{14}\text{CO}_2$ by recondensation with liquid nitrogen was attempted. HPLC analyses of crude reaction mixtures with radioactivity detection does suggest that a significant portion of the unreacted $^{14}\text{CO}_2$ remains bound to the nickel catalyst. Ref 32 - In the SI: “After stirring for 17 hours, the excess $^{13}\text{C}\text{CO}_2$ was transferred into a separate flask (flask 3) filled with an aqueous 2% BaOH solution (15 mL), while being cooled with liquid nitrogen.”
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Data Availability Statement

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No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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