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Chemical Synthesis

Liu *et al. Chem. Synth.* **2026**, *6*, 67 **DOI:**10.20517/cs.2025.51

CO_2 shuttling in organic synthesis

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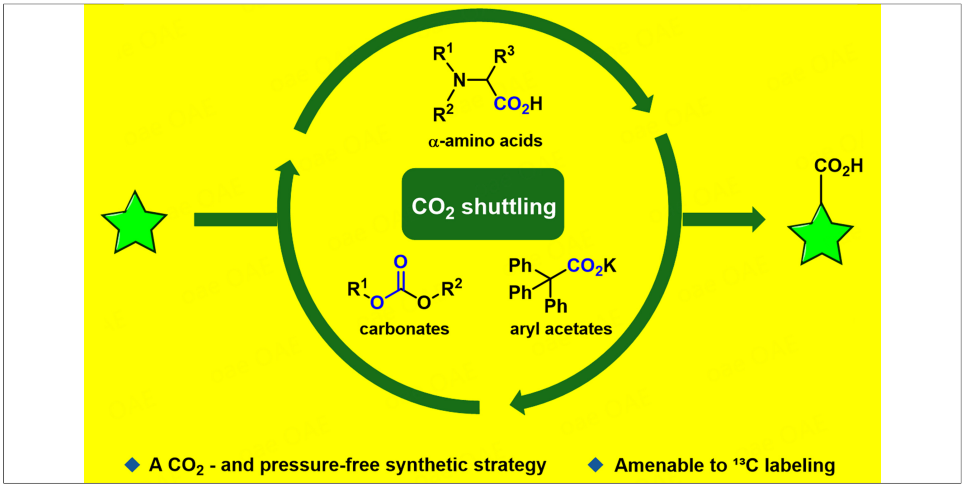
Citation: Liu, X.; Wang, H.; Kong, D. CO_2 shuttling in organic synthesis. *Chem. Synth.* **2026**, *6*, 67. https://dx.doi.org/10.20517/cs.2025.51

Received: 9 Apr 2025
First Decision: 2 Jul 2025
Revised: 4 Jul 2025
Accepted: 15 Jul 2025
Published: 17 Aug 2026

Academic Editor: Da-Gang Yu
Copy Editor: Ting-Ting Hu
Production Editor: Ting-Ting Hu



INTRODUCTION

Carboxylic acids are prevalent functional groups found in numerous biologically active molecules and natural compounds[1,2]. Beyond their significance in bioactive compounds, carboxylic acids also serve as valuable synthetic linchpins in organic chemistry, providing functional handles for a wide range of useful transformations[3,4]. Compared to traditional synthetic methods for carboxylic acid formation[5-7], the use of CO_2 as a carboxyl source has attracted considerable interest due to its low toxicity, affordability, and renewability[8,9]. Many strategies for converting CO_2 into carboxylic acids rely on excess CO_2 gas or high-pressure conditions to drive the reaction forward[10,11]. Additionally, the high thermodynamic stability and low reactivity of CO_2 often necessitate sensitive organometallic reagents (e.g., organolithium and Grignard reagents) or other preactivated substrates to form C–CO_2H bonds[12,13]. However, as carboxylic acid derivatives become increasingly complex for applications in materials science, biomedicine, and drug discovery[14], new synthetic routes must be developed to minimize both the length and cost of synthesis.

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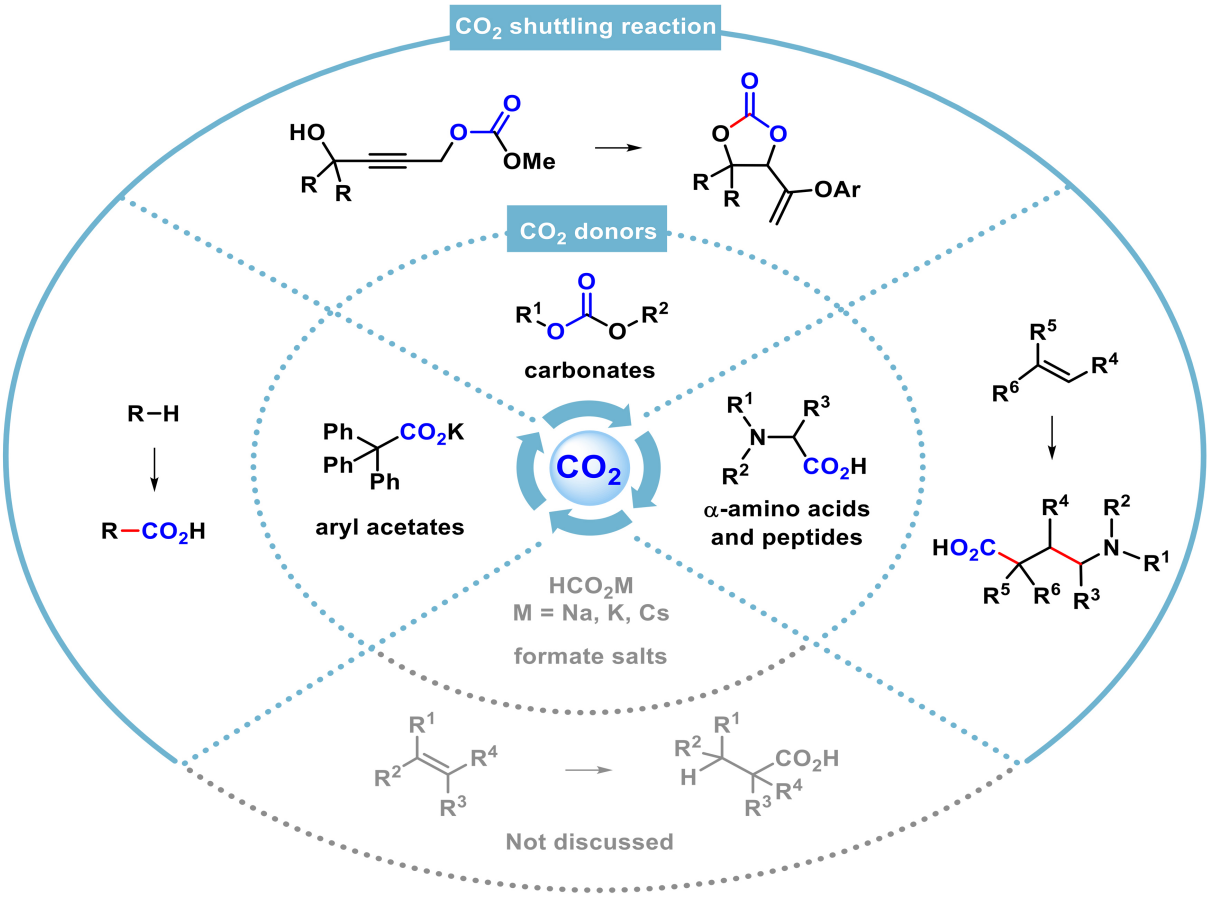

Figure 1. CO_2 shuttling reactions.

Recently, the ready availability of carboxylic acids has led to the development of decarboxylative coupling reactions, in which carboxylic acids function as user-friendly cross-coupling partners[15]. In these reactions, the released CO_2 is typically considered as a waste. Catalytic reversible transfer reactions, such as alkene metathesis[16,17] and transfer hydrogenation[18,19], are key transformations in modern organic chemistry. Building on these foundational techniques, researchers have developed shuttle catalysis processes that transfer functional groups between donor and acceptor molecules[20]. In this context, CO_2 shuttling, where CO_2 is transferred from a readily available carboxylic acid or its derivative to an acceptor molecule, has emerged as a promising method for generating new molecules. Several CO_2 shuttling systems have recently been reported, utilizing carboxylic acids (R_1CO_2H) or their derivatives ($R_1CO_2R_2$) as CO_2 donors instead of excess CO_2 gas [Figure 1][21-35].

Notably, formate salts (R_1CO_2M, R_1 = H; M = Na, K, Cs) have recently gained prominence in organic chemistry as $CO_2^{\bullet-}$ sources for accessing valuable carboxylic acids. For example, Hendy *et al.* and Alektiar *et al.* developed alkene hydrocarboxylation reactions mediated by $CO_2^{\bullet-}$, which was generated via hydrogen atom transfer (HAT) from formate salts[21,22]. Since then, numerous studies and reviews have summarized carboxylation reactions involving HAT of formate salts[23], so further discussion will not be provided here. Additionally, amino acids (AAs) and organic acids have proven to be attractive reactants in CO_2 shuttling reactions, serving multiple roles as reaction substrates, bases, and CO_2 donors[24-35]. This approach circumvents the need for excess CO_2 or pressurized vessels, offering a more versatile and safer method for functional group interconversion.

This Perspective summarizes recent advances in CO_2 shuttling that exploit carboxylic acids and their derivatives ($R_1CO_2R_2$, $R_1 \neq H$) as potential CO_2 donors, including carbonates, α-amino acids (α-AAs), and organic carboxylates. We also explore potential future developments in CO_2 shuttling strategies.

RECENT ADVANCES

Carbonates (e.g., OCO_2Me or $OCO_2{}^tBu$) are among the most commonly used leaving groups in substitution reactions, where their cleavage releases CO_2 gas while simultaneously generating an alkoxide anion[24-31]. Efficient re-fixation of the resulting CO_2 into organic molecules aligns with the principle of carbon economy,

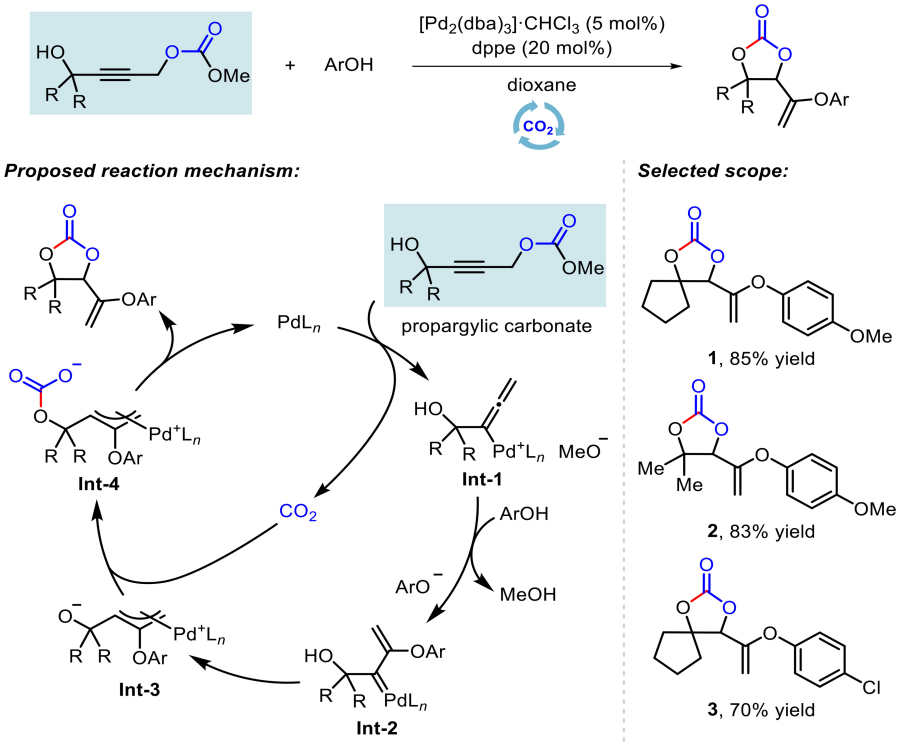

Figure 2. Cyclic carbonates synthesis using propargylic carbonates via CO_2 shuttling.

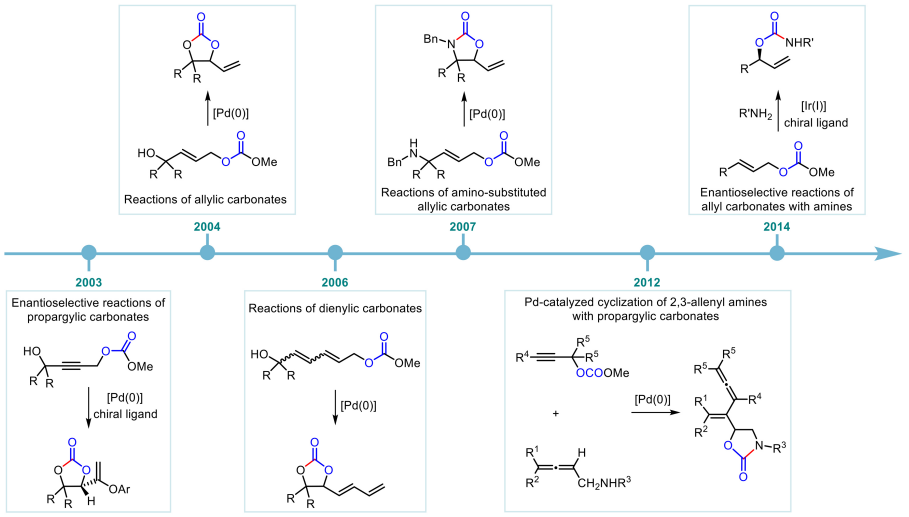

Figure 3. Other works involving CO_2 elimination-fixation of carbonates.

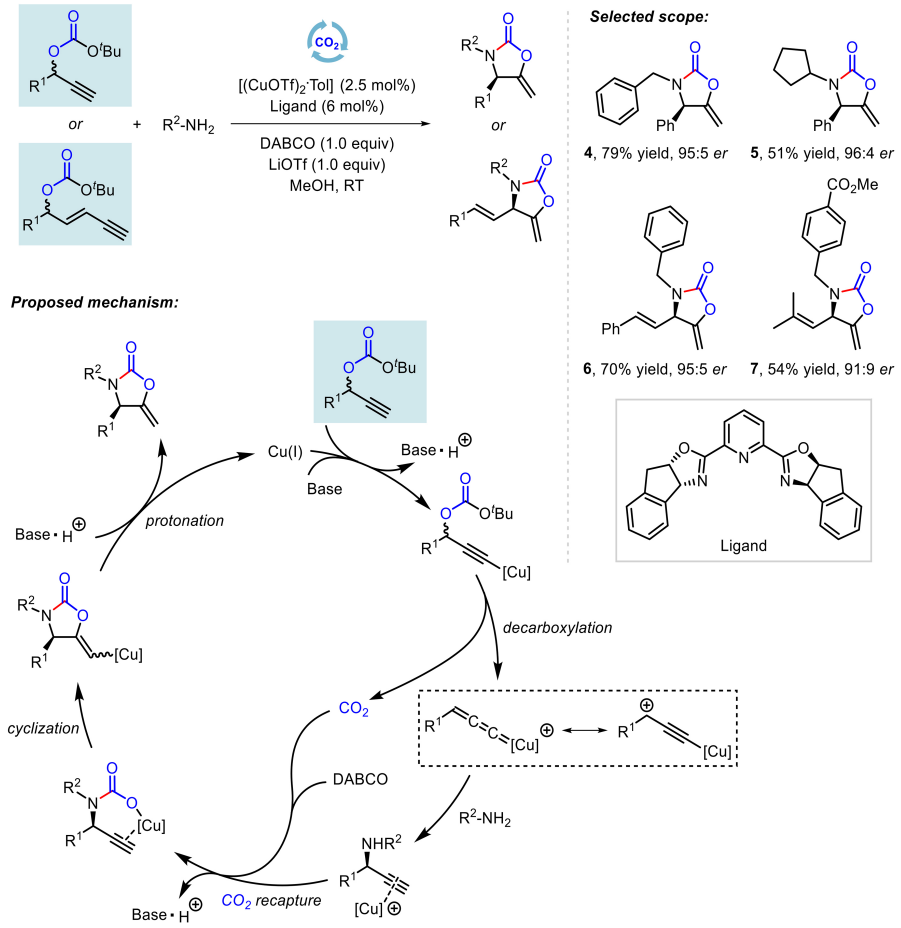

Figure 4. Asymmetric multicomponent propargylations via CO_2 shuttling.

making the development of such methods highly desirable. In 2001, Yoshida *et al.* introduced the concept of CO_2 recycling to develop a novel approach for synthesizing cyclic carbonates. As shown in Figure 2, their proposed mechanism involved sequential CO_2 elimination and fixation. In this process, a palladium catalyst promoted the decarboxylation of a propargylic carbonate, generating allenylpalladium methoxide intermediate (**Int-1**) and CO_2. Deprotonated phenols then underwent nucleophilic attack on **Int-1**, forming the π-allylpalladium complex (**Int-3**), which subsequently re-fixed CO_2 to yield carbonate species **Int-4**. Cyclization of this intermediate produced aryloxy-substituted cyclic carbonates[24]. This is the first reported example of efficient CO_2 re-fixation from carbonate decarboxylation reactions. Since then, numerous reactions based on the CO_2 elimination-fixation process have been developed, enabling the synthesis of chiral cyclic carbonates, vinyl-substituted cyclic carbonates, 1,3-dienyl-substituted cyclic carbonates, oxazolidinones, allenic oxazolidin-2-ones, and branched allyl carbamates [Figure 3][25-30].

In 2024, Li *et al.* introduced Cu-catalyzed stereoselective propargylation and alkynylallylic substitution strategies that integrate CO_2 shuttling and fixation. In these reactions, a variety of alkynyl carbonates underwent decarboxylation and then asymmetric propargylation or alkynylallylic substitution with primary amines in sequence. The resulting propargyl amines then captured CO_2 released from decarboxylation. Experimental and computational mechanistic studies indicated that the reaction proceeded via a CO_2 shuttling pathway as depicted in Figure 4. Additionally, DABCO was proposed to facilitate the capture of low-concentration CO_2, while the cyclization process likely involved a rate-limiting step[31].

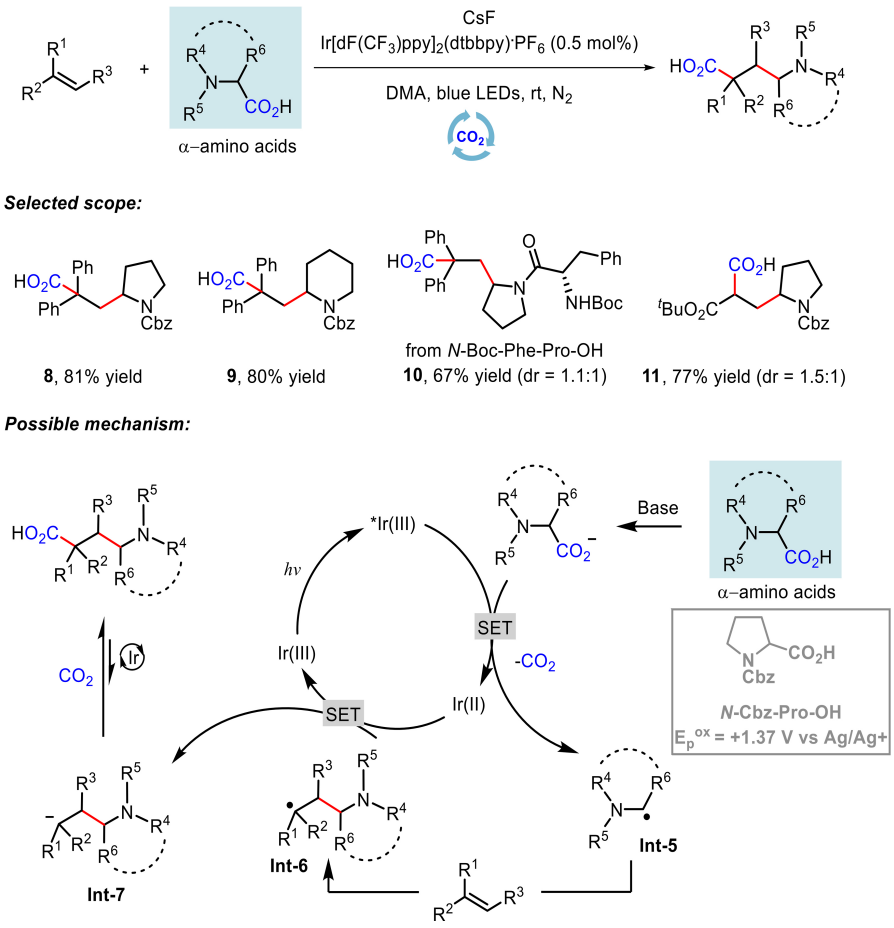

Figure 5. CO_2 shuttling between alkenes and α-amino acids.

AAs, particularly the readily available and inexpensive α-AAs, are essential and widely occurring carboxylic acids that play a crucial role in nature. Recently, Liao *et al.* reported an elegant approach to alkene carboxylation using α-AAs as CO_2 surrogates. The proposed photocatalytic radical mechanism, which incorporated CO_2 shuttling, was depicted in Figure 5. Upon irradiation, single-electron transfer (SET) occurred between the photoexcited Ir(III) catalyst and the α-AA salt, which formed *in situ* upon deprotonation of the α-AA in the presence of a base. Cyclic voltammetry (CV) experiments revealed that the carboxylate form is more readily oxidized than the corresponding carboxylic acid during the SET process, highlighting the critical role of the base. For example, when *N*-Cbz-Pro-OH was tested in the presence of CsF, a distinct oxidative peak was observed at +1.37 V. In contrast, no oxidative peak appeared in the absence of CsF. This SET process generated the α-amino alkyl radical (**Int-5**) and CO_2. The radical then added to the alkene, forming intermediate **Int-6**, which underwent another SET with the Ir(II) photocatalyst to yield the key carbanion intermediate (**Int-7**). In this system, the CO_2 produced *in situ* at low concentration was efficiently recaptured by **Int-7**, leading to the desired carboxylated product[32]. Luminescence quenching experiments demonstrated that the quenching rate for product is much slower than that of substrate in presence of CsF, which might be the reason for more facile decarboxylation of substrate than product under the reaction conditions[32]. In stark contrast to conventional carboxylation methods that require high pressure and/or excess CO_2 gas, this strategy offers an efficient and sustainable alternative by utilizing CO_2 shuttling with near-stoichiometric amounts of α-AAs as CO_2 donors.

Wang *et al.* recently demonstrated the carboxylation of heteroarenes, electron-deficient arenes and terminal alkynes using triphenylacetic acid potassium salt as a bifunctional reagent, acting as both a base and a CO_2

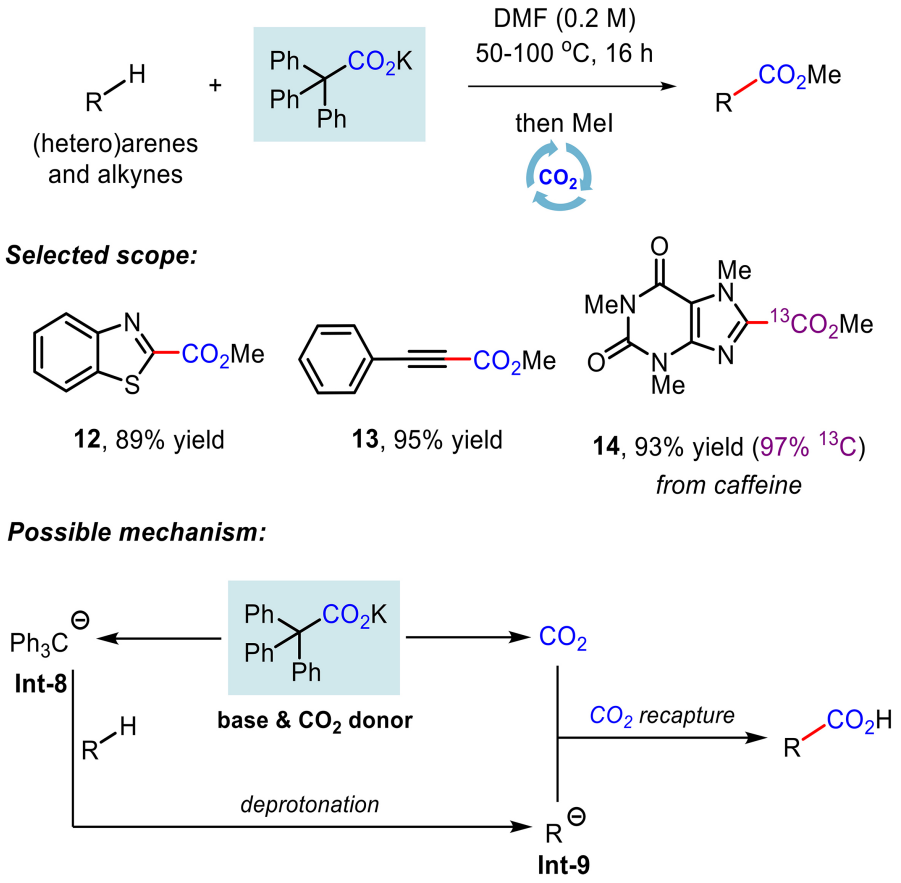

Figure 6. CO_2 shuttling between heteroarenes/alkynes and organic carboxylates.

donor. The proposed mechanism was outlined in Figure 6. This strategy relied on the decarboxylation of triphenylacetic acid potassium salt to generate CO_2 and the trityl anion (**Int-8**). Due to its high basicity (pKa of Ph_3CH = 30.6 in DMSO)[36], the trityl anion could efficiently deprotonate substrates, forming alkyl carbanion (**Int-9**), which subsequently recaptured the *in situ* generated CO_2 to yield the desired carboxylated product. Notably, this reaction system enables CO_2 shuttling carboxylation of certain acidic C–H bonds and provides a convenient route for synthesizing ^{13}C-labeled molecules[34].

Similarly, in 2024, Liu *et al*. reported a sequential approach for synthesizing α-keto acids by integrating umpolung reactivity with CO_2 shuttling, utilizing triphenylacetic acid potassium salt as a formal CO_2 donor. The reaction began with the umpolung activation of carbonyl compounds using thiol, facilitating the carboxylation of aldehydes. The subsequent CO_2 shuttling process was key to obtaining α-keto acids. This transition-metal-free shuttle carboxylation method effectively transfers CO_2 from triphenylacetic acid potassium salt to dithioacetals, eliminating the need for pressurized CO_2 gas or specialized equipment. Moreover, this approach has been extended to achieve complete ^{13}C labeling of α-keto acid derivatives with biological and pharmacological relevance [Figure 7][35].

CONCLUSION AND OUTLOOK

CO_2 shuttling has emerged as a promising strategy for sustainable carboxylation reactions, enabling efficient CO_2 utilization without requiring excess gaseous CO_2 or high-pressure conditions. In recent years, significant progress has been made in this field through the development of diverse carboxylic acid derivatives - such as carbonates, AAs, and triphenylacetic acids - as CO_2 donors within various reaction models. These advances

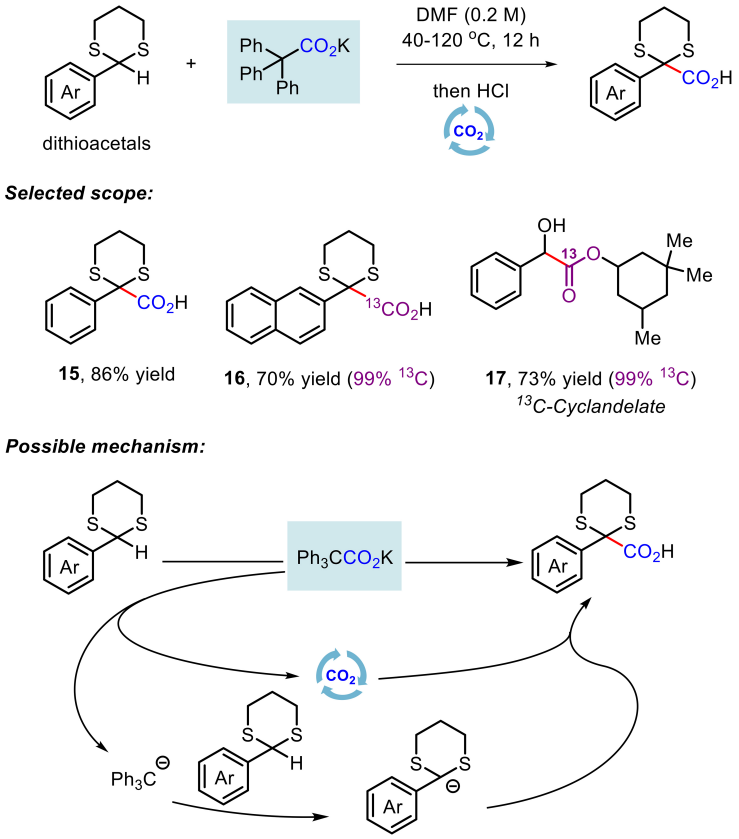

Figure 7. CO_2 shuttling between dithioacetals and organic carboxylates.

underscore the potential of CO_2 shuttling as a carbon-economical and sustainable synthetic tool, offering new opportunities for functional group interconversion and isotope labeling in organic chemistry. Despite these achievements, key challenges remain. While CO_2 shuttling strategies have enabled the carboxylation of heteroarenes and electron-deficient arenes, the direct carboxylation of electron-rich arenes remains unresolved. Additionally, the selective C(sp^3)-H carboxylation of simple linear alkanes via CO_2 shuttling remains elusive. Another critical frontier is the design of novel and stereoselective carboxylating agents for constructing chiral carboxylic acid derivatives. Advancing these methodologies could significantly expand the synthetic utility of CO_2 shuttling and warrants further intensive research.

Beyond synthetic applications, CO_2 shuttling holds particular promise for carbon isotope labeling, which is essential in nuclear medicine and drug discovery. The high cost of carbon isotope-labeled building blocks makes efficient synthetic methods highly valuable. Carbon isotopic CO_2 has recently emerged as an attractive primary isotope source; however, the need for large excesses and high-pressure conditions presents economic and safety concerns. An ideal approach would involve stoichiometric isotopic CO_2 precursors that release CO_2 gradually, enabling more controlled and efficient labeling. This CO_2 shuttling paradigm could pave the way for the complete ^{13}C labeling of carboxylic acids, further broadening its applicability in synthetic and pharmaceutical chemistry.

DECLARATIONS

Authors' contributions

Prepared the manuscript: Liu, X.
Designed and revised the manuscript: Wang, H.; Kong, D.
All authors contributed to the discussion and preparation of the manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

Not applicable.

Financial support and sponsorship

This work is supported by the National Natural Science Foundation of China (22471011), the Beijing Municipal Natural Science Foundation (2232015), and the Beijing Nova Program (20230484447).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Ertl, P.; Altmann, E.; McKenna, J. M. The most common functional groups in bioactive molecules and how their popularity has evolved over time. *J. Med. Chem.* **2020**, *63*, 8408-18. DOI PubMed
2. Bhutani, P.; Joshi, G.; Raja, N.; et al. U.S. FDA approved drugs from 2015-June 2020: a perspective. *J. Med. Chem.* **2021**, *64*, 2339-81. DOI PubMed
3. Walker, S. D.; Borths, C. J.; Divirgilio, E.; et al. Development of a scalable synthesis of a GPR40 receptor agonist. *Org. Process. Res. Dev.* **2011**, *15*, 570-80. DOI
4. Ji, C. L.; Lu, Y. N.; Xia, S.; et al. Photoinduced late-stage radical decarboxylative and deoxygenative coupling of complex carboxylic acids and their derivatives. *Angew. Chem. Int. Ed. Engl.* **2025**, *64*, e202423113. DOI PubMed
5. Kraus, G. A.; Roth, B. Synthetic studies toward verrucarol. 2. Synthesis of the AB ring system. *J. Org. Chem.* **1980**, *45*, 4825-30. DOI
6. Ma, S.; Liu, J.; Li, S.; et al. Development of a general and practical iron nitrate/TEMPO-catalyzed aerobic oxidation of alcohols to aldehydes/ketones: catalysis with table salt. *Adv. Synth. Catal.* **2011**, *353*, 1005-17. DOI
7. Jiang, X.; Liu, J.; Ma, S. Iron-catalyzed aerobic oxidation of alcohols: lower cost and improved selectivity. *Org. Process. Res. Dev.* **2019**, *23*, 825-35. DOI
8. Williams, C. M.; Johnson, J. B.; Rovis, T. Nickel-catalyzed reductive carboxylation of styrenes using CO_2. *J. Am. Chem. Soc.* **2008**, *130*, 14936-7. DOI PubMed PMC
9. Huang, K.; Sun, C. L.; Shi, Z. J. Transition-metal-catalyzed C–C bond formation through the fixation of carbon dioxide. *Chem. Soc. Rev.* **2011**, *40*, 2435-52. DOI PubMed
10. Pimparkar, S.; Dalvi, A. K.; Koodan, A.; et al. Recent advances in the incorporation of CO_2 for C–H and C–C bond functionalization. *Green. Chem.* **2021**, *23*, 9283-317. DOI
11. Shigeno, M.; Hanasaka, K.; Tohara, I.; et al. Direct C-H carboxylation forming polyfunctionalized aromatic carboxylic acids by combined Brønsted bases. *Org. Lett.* **2022**, *24*, 809-14. DOI PubMed
12. Chen, Y.; Xu, X.; Zhang, K.; et al. Transition-metal-catalyzed carboxylation of organic halides and their surrogates with carbon dioxide. *Synthesis* **2018**, *50*, 35-48. DOI
13. Tortajada, A.; Juliá-Hernández, F.; Börjesson, M.; Moragas, T.; Martin, R. Transition-metal-catalyzed carboxylation reactions with carbon dioxide. *Angew. Chem. Int. Ed. Engl.* **2018**, *57*, 15948-82. DOI PubMed
14. Zhang, M.; Guo, D.; Zhou, X.; Zhou, D.; Zhu, Y.; Huang, S. Synthesis and application of poly(amidoamine) functional biomedical materials in the field of biomedicine over the past decade. *J. Chinese. Chemical. Soc.* **2025**, *72*, 72-82. DOI
15. Sun, S.; Nicholls, B. T.; Bain, D.; et al. Enantioselective decarboxylative alkylation using synergistic photoenzymatic catalysis. *Nat. Catal.* **2024**, *7*, 35-42. DOI
16. Schrock, R. R.; Hoveyda, A. H. Molybdenum and tungsten imido alkylidene complexes as efficient olefin-metathesis catalysts. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 4592-633. DOI PubMed

17. Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. A general model for selectivity in olefin cross metathesis. *J. Am. Chem. Soc.* **2003**, *125*, 11360-70. DOI PubMed
18. Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. Catalytic carbonyl addition through transfer hydrogenation: a departure from preformed organometallic reagents. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 34-46. DOI PubMed PMC
19. Corma, A.; Navas, J.; Sabater, M. J. Advances in one-pot synthesis through borrowing hydrogen catalysis. *Chem. Rev.* **2018**, *118*, 1410-59. DOI PubMed
20. Bhawal, B. N.; Morandi, B. Shuttle catalysis-new strategies in organic synthesis. *Chem. Eur. J.* **2017**, *23*, 12004-13. DOI PubMed
21. Hendy, C. M.; Smith, G. C.; Xu, Z.; Lian, T.; Jui, N. T. Radical chain reduction via carbon dioxide radical anion ($CO_2^{\bullet-}$). *J. Am. Chem. Soc.* **2021**, *143*, 8987-92. DOI PubMed PMC
22. Alektiar, S. N.; Wickens, Z. K. Photoinduced hydrocarboxylation via thiol-catalyzed delivery of formate across activated alkenes. *J. Am. Chem. Soc.* **2021**, *143*, 13022-8. DOI PubMed
23. Xiao, W.; Zhang, J.; Wu, J. Recent advances in reactions involving carbon dioxide radical anion. *ACS. Catal.* **2023**, *13*, 15991-6011. DOI
24. Yoshida, M.; Ihara, M. Palladium-catalyzed domino reaction of 4-methoxycarbonyloxy-2-butyn-1-ols with phenols: a novel synthetic method for cyclic carbonates with recycling of CO_2. *Angew. Chem. Int. Ed.* **2001**, *40*, 616-9. DOI PubMed
25. Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. A novel methodology for the synthesis of cyclic carbonates based on the palladium-catalyzed cascade reaction of 4-methoxycarbonyloxy-2-butyn-1-ols with phenols, involving a novel carbon dioxide elimination-fixation process. *J. Am. Chem. Soc.* **2003**, *125*, 4874-81. DOI PubMed
26. Yoshida, M.; Ohsawa, Y.; Ihara, M. Palladium-catalyzed carbon dioxide elimination-fixation reaction of 4-methoxycarbonyloxy-2-buten-1-ols. *J. Org. Chem.* **2004**, *69*, 1590-7. DOI PubMed
27. Yoshida, M.; Ohsawa, Y.; Ihara, M. Palladium-catalyzed carbon dioxide elimination-fixation reaction of 6-methoxycarbonyloxy-2,4-hexadien-1-ols. *Tetrahedron* **2006**, *62*, 11218-26. DOI
28. Yoshida, M.; Ohsawa, Y.; Sugimoto, K.; Tokuyama, H.; Ihara, M. Synthesis of vinyloxazolidinones by palladium-catalyzed CO_2-recycling reaction of 4-(benzylamino)-2-butenyl carbonates. *Tetrahedron. Letters.* **2007**, *48*, 8678-82. DOI
29. Ye, J.; Li, S.; Ma, S. Palladium-catalyzed cyclization reactions of 2,3-allenyl amines with propargylic carbonates. *Org. Lett.* **2012**, *14*, 2312-5. DOI PubMed
30. Zheng, S. C.; Zhang, M.; Zhao, X. M. Enantioselective transformation of allyl carbonates into branched allyl carbamates by using amines and recycling CO2 under iridium catalysis. *Chem. Eur. J.* **2014**, *20*, 7216-21. DOI PubMed
31. Li, Z.; Ma, J.; Lu, H.; Lin, G.; He, Z. Asymmetric multicomponent propargylations via carbon dioxide shuttling and fixation. *ACS. Catal.* **2024**, *14*, 11646-56. DOI
32. Liao, L. L.; Cao, G. M.; Jiang, Y. X.; et al. α-amino acids and peptides as bifunctional reagents: carbocarboxylation of activated alkenes via recycling CO_2. *J. Am. Chem. Soc.* **2021**, *143*, 2812-21. DOI
33. Zhou, C.; Li, M.; Sun, J.; Cheng, J.; Sun, S. Photoredox-catalyzed α-aminomethyl carboxylation of styrenes with sodium glycinates: synthesis of γ-amino acids and γ-lactams. *Org. Lett.* **2021**, *23*, 2895-9. DOI PubMed
34. Wang, S.; Larrosa, I.; Yorimitsu, H.; Perry, G. J. P. Carboxylic acid salts as dual-function reagents for carboxylation and carbon isotope labeling. *Angew. Chem. Int. Ed. Engl.* **2023**, *62*, e202218371. DOI PubMed
35. Liu, X.; Cao, S.; Zhang, C.; Jiang, Y.; Kong, D. Integrating umpolung and CO_2 shuttling strategies for the synthesis of ^{12}C- and ^{13}C-α-ketoacids from aldehydes. *Org. Lett.* **2024**, *26*, 8967-72. DOI PubMed
36. Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; et al. Equilibrium acidities of carbon acids. VI. Establishment of an absolute scale of acidities in dimethyl sulfoxide solution. *J. Am. Chem. Soc.* **1975**, *97*, 7006-14. DOI