

Enantioselective Incorporation of CO₂:

Status and Potential

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ABSTRACT: CO₂ is a promising and sustainable carbon feedstock for organic synthesis. New catalytic protocols for efficient incorporation of CO₂ into organic molecules are continuously reported. However, little progress has been made in the enantioselective conversion of CO₂ to form enantioenriched molecules. In order to allow CO₂ to become a versatile carbon source in academia, and in the fine chemical and pharmaceutical industries, the development of enantioselective approaches is essential. Here we discuss general strategies for CO₂ activation and for generation of enantioenriched molecules, alongside selected examples of reactions involving asymmetric incorporation of CO₂. Main product classes considered are carboxylic acids and derivatives (C-

CO₂ bonds), and carbonates, carbamates, and polycarbonates (C-OCO bonds). Similarities to asymmetric hydrogenation are discussed, and some strategies for developing novel enantioselective CO₂ reactions are outlined.

KEYWORDS: Enantioselectivity, CO₂, Catalysis, Asymmetric synthesis, Carboxylic acid, Carbonate, Carbamate

1. Introduction

The quality of modern life is dependent on organic molecules such as plastics, paints, agrochemicals, and pharmaceuticals. The synthesis of these molecules requires carbon-based starting materials, which typically originate from fossil sources such as oil, natural gas, and coal. However, fossil resources are finite, making it important to identify alternative sources of carbon that can be used in the synthesis of organic molecules. In analogy to natural photosynthetic processes, it has been proposed that CO₂ could be used as an alternative carbon source in organic synthetic reactions. Multiple features make CO₂ a promising carbon feedstock: it is widely abundant, non-toxic, non-flammable and sustainable - there is no indication that CO₂ resources can become depleted. Human activity alone generates ~33 billion metric tons of CO₂ per year, which is far beyond the amount needed if all chemical industry was based on CO₂ (estimated to some hundred million tons per year).¹ In fact, the large amounts of circulating CO₂ are causing environmental concerns, because CO₂ accumulation in the atmosphere leads to an increase in the global temperature. Some of the circulating CO₂ could instead be captured and transformed to organic molecules. The transformation could be driven by renewable energies, with the potential to make the overall process sustainable. An interesting example is the Icelandic company *Carbon Recycling International*, which employs geothermal energy for reduction of CO₂ to methanol.²

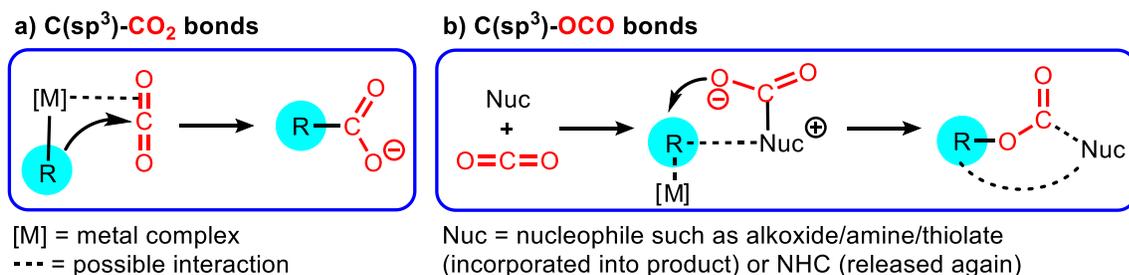
Usage of CO₂ in chemical synthesis will not provide a significant reduction of greenhouse gases,¹ but it is still relevant to use CO₂, or C₁/C₂-products derived from CO₂ (e.g. methanol³), as a sustainable carbon source. The number of efficient protocols for incorporation of CO₂ is steadily growing,^{4,5,6,7,8} however, little work has been devoted to making *enantioselective* reactions with CO₂ [a general review of this area has been provided by Kleij and coworkers (2013)⁹ and Lu (2016)¹⁰, and a specific review of stereoselective polymerization by Coates and coworkers (2014)¹¹]. It can be noted that both the carbon and the oxygen atoms of CO₂ can be involved in the generation of novel chiral centres. Especially for C-CO₂ bond formation, reported reactions are mostly symmetric and provide racemic mixtures.^{12,13,14,15,16,17} If CO₂-based syntheses are to replace known industrial processes, e.g. for synthesis of pharmaceuticals and fine chemicals, it is important that catalytic CO₂ incorporation can be made enantioselective.

Here we discuss general strategies for C(sp³)-CO₂ and C(sp³)-OCO bond formation (section 2.1) and for synthesis of enantioenriched molecules from CO₂ (section 2.2), followed by a selection of reported enantioselective CO₂ reactions and resulting products, including mechanistic aspects (section 2.3). Finally, a summary of the current status and a future outlook on strategies for development of enantioselective CO₂ reactions is presented (section 2.4).

2.1 Strategies for Bond Formation to CO₂

Incorporation of CO₂ into another molecule is a more desirable form of CO₂ fixation than its multi-electron reduction to e.g. methane, which is energetically more costly. However, in order to be feasible, bond formation reactions should be catalytic. A variety of comprehensive reviews on catalytic synthesis of organic molecules from CO₂ have emerged in recent years, including metal-based and organic catalysis.^{4,5,6,11,18,19,20,21,22,23,24,25,26,27,28} There are two catalytic approaches that

have found widespread use for activation of the rather inert CO₂ molecule (Scheme 1); both approaches involve incorporation of the entire CO₂ molecule, which is our main focus here. In the first approach (Scheme 1a), C-CO₂ bonds are primarily formed through insertion of CO₂ into reactive metal-carbon bonds; in these reactions CO₂ acts as an electrophile.¹⁸ Typical products are carboxylic acids, including α -amino acids or α -methoxy derivatives. Alternatively, in the second approach (Scheme 1b), CO₂ reacts with oxygen- or nitrogen-based nucleophiles, which enhance the nucleophilicity of CO₂, making it able to react with a carbon-based electrophile to form C-OCO bonds. Typical products are carbonates and carbamates. Nucleophiles that are incorporated into the final product include alkoxides formed from epoxides or alcohols,^{29,30,31,32,33} amines,³⁴ aziridines,³⁵ (and also thiolates^{36,37}), whereas nucleophiles that are released again include *N*-heterocyclic carbenes (NHCs).^{38,39}



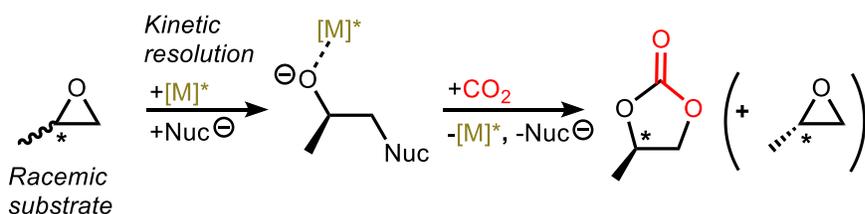
Scheme 1. Formation of **a) C(sp³)-CO₂** bonds through insertion into metal-R bonds and **b) C(sp³)-OCO** bonds through activation of CO₂ with a nucleophile (Nuc).

2.2 Strategies for Formation of Enantioenriched Molecules from CO₂

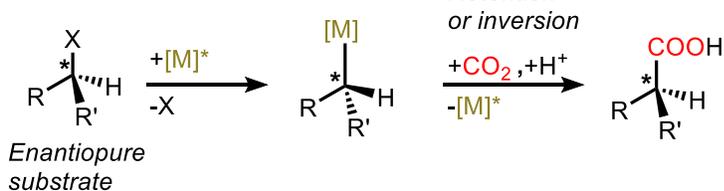
There are three main strategies to synthesize chiral molecules in an enantioenriched fashion (Scheme 2): Strategy I involves **deracemization** of a racemic starting material through use of a chiral catalyst, e.g. kinetic resolution and enantioconvergent synthesis (including dynamic kinetic resolution). The number of chiral centres remains unchanged, but the product is enantioenriched. Strategy II implies **chirality transfer** from an enantiopure starting material, without the use of

enantiopure additives or catalysts. No novel chiral centres are formed, but the configuration of the product is determined by the configuration of the substrate. Strategy III involves **enantioselective synthesis**, implying the formation of a novel element of chirality in an asymmetric fashion through the use of an enantiopure chiral catalyst or additive.⁴⁰ Strategy III may set out from a variety of starting materials, e.g. unsaturated prochiral compounds, saturated achiral substrates (e.g. in enantioselective deprotonation), symmetric prochiral or *meso* compounds (e.g. in enantioselective desymmetrization) or enantiopure starting materials (e.g. in diastereoselective synthesis).

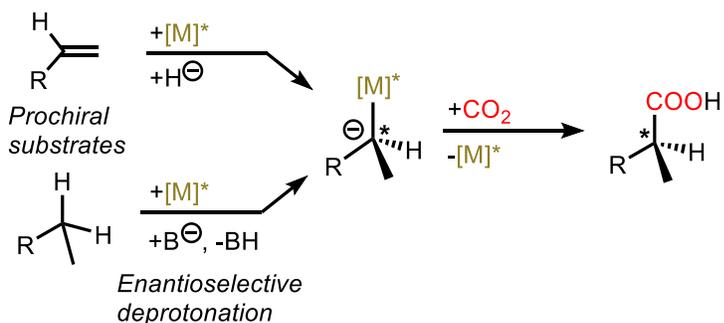
I. Deracemization



II. Chirality transfer



III. Enantioselective synthesis



[M] = metal or organocatalyst, Nuc = nucleophile

Scheme 2. Strategies for forming enantioenriched products, illustrated with CO₂-based reactions.

The strategies I-III have been applied in varying degrees to form enantioenriched molecules from CO₂. For formation of C-CO₂ bonds, examples in the literature involve deracemization (Strategy I), e.g. dynamic kinetic resolution to convert configurationally labile α -sulfenyl carbanions to enantioenriched α -thiomethoxy acids,⁴¹ and chirality transfer (Strategy II), e.g. formation of enantioenriched α -amino acids from enantioenriched α -amino organostannanes and α -amido silanes.^{42,43,44} Asymmetric deprotonation (Strategy III) has been employed for formation of α -methoxy acids from achiral substrates and CO₂.^{45,46} Surprisingly, only very few examples of enantioselective incorporation of CO₂ into unsaturated starting materials such as alkenes or ketones have been reported: a nickel-catalyzed ring-closing carboxylation of prochiral bis-1,3-dienes with CO₂ (from 2004),⁴⁷ an asymmetric electrocarboxylation of acetophenone with CO₂ employing cinchonidine as catalyst (from 2009),⁴⁸ and a rhodium-catalyzed enantioselective hydrocarboxylation of prochiral α,β -unsaturated esters with CO₂ (from 2016).⁴⁹

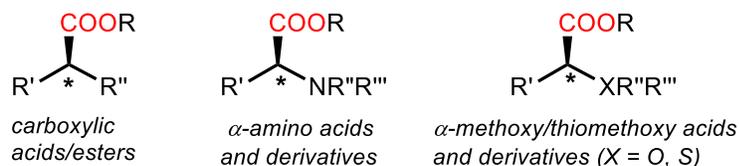
Formation of C-OCO bonds and synthesis of enantioenriched carbonates and polycarbonates mainly relies on kinetic resolution (Strategy I),^{9,29,30,31,32} and desymmetrization of achiral and meso-compounds (Strategy III).^{50,51,52,53} Enantioenriched carbamates rely on chirality transfer, e.g. from aziridines (Strategy II).^{35,54} Only a few approaches for enantioselective formation of C-OCO bonds from unsaturated compounds are known, e.g. a palladium-BINAP-mediated conversion of achiral propargylic carbonates (from 2003),⁵⁵ and an organocatalytic conversion of achiral homoallylic alcohols (from 2015).²⁹

2.3 Major Product Classes and Selected Examples of Enantioselective CO₂ Incorporation

Examples of products formed through enantioselective incorporation of CO₂ are given in Fig. 1. C-CO₂ bond formation provides chiral carboxylic acids, such as α -amino and α -methoxy acids, and their derivatives. C-OCO bond formation provides chiral carbonates, polycarbonates and

carbamates. In the following, we give examples of reactions reported for all product classes in Fig. 1, including relevant mechanisms, which serve to provide insight into the CO₂ bonding step.

Chiral C(sp³)-CO₂ bonds:



Chiral C(sp³)-OCO bonds:

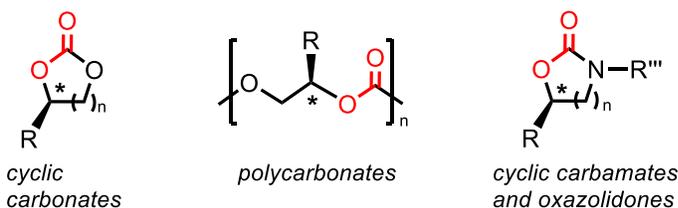


Figure 1. Examples of enantioenriched products synthesized from CO₂.

2.3.1 Examples of Asymmetric C-CO₂ Bond Formation

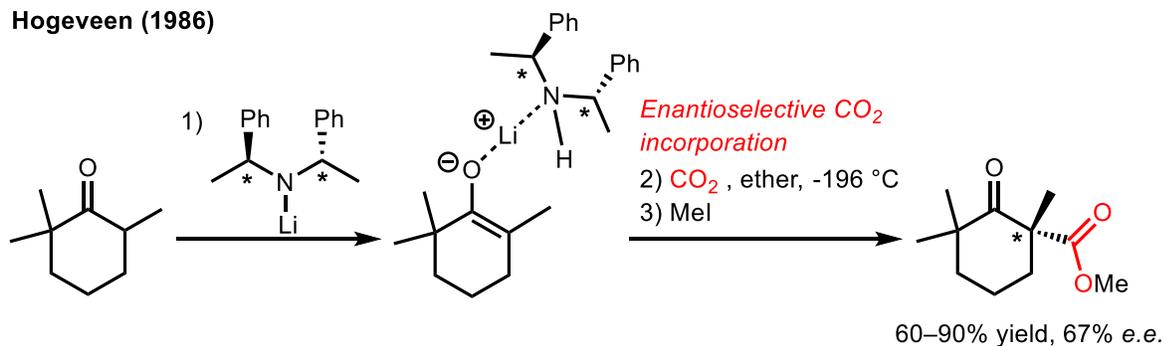
Carboxylic acids and derivatives are important in fine chemical, agrochemical, and pharmaceutical synthesis.^{6,20,22,56} Here we give examples of diverse carboxylic acids formed in an enantioenriched manner from CO₂.

Carboxylic Acids through Asymmetric Carboxylation: In 1986, the Hogeveen group explored the carboxylation of a lithium enolate, formed by deprotonation of 2,2,6-trimethylcyclohexanone with the chiral base lithium (*S,S*)- α,α' -dimethyldibenzylamide.⁵⁷ Carboxylation and methylation gave the ester in up to 67% *e.e.* (Scheme 3). In this enantioconvergent reaction, the enantioselective incorporation of CO₂ into the pro-chiral enolate is mediated by an enantioenriched amine.

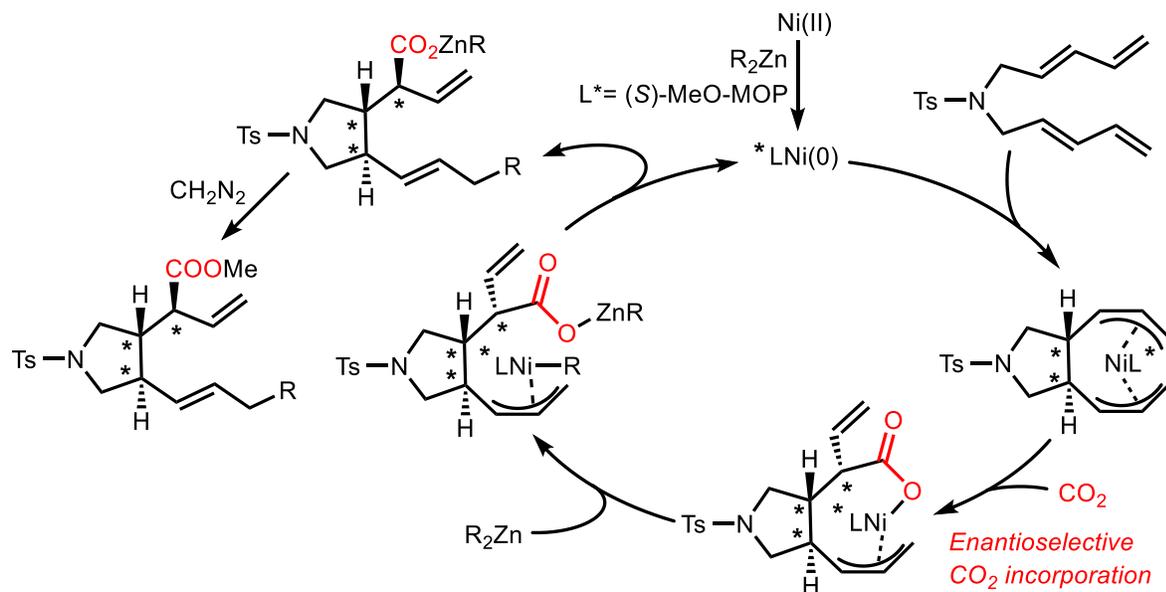
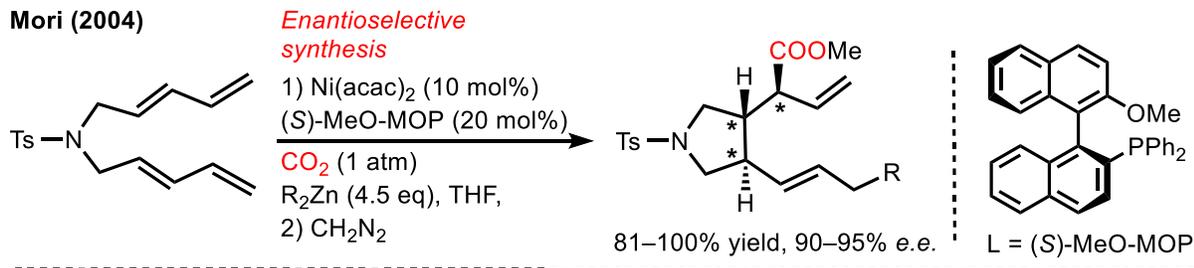
The Mori's group developed an interesting metal-catalyzed carboxylative cyclization, which in a single operation can generate three new chiral centres by addition of bis-1,3-dienes, CO₂, 10 mol % [Ni(acac)₂], chiral phosphines, and diethylzinc (Scheme 4).⁴⁷ With 2-

diphenylphosphino-2'-methoxy-1,1'-binaphthyl (MeO-MOP) as chiral ligand, *e.e.*'s of up to 95% were reported.^{47a} The active Ni(0) phosphine catalyst reacts with the diene to give a bis-allyl species, which inserts CO₂ in an enantioselective manner. Transmetalation of the resulting Ni-carboxylate with R₂Zn followed by treatment with CH₂N₂ afforded methyl carboxylates.

Hogeveen (1986)

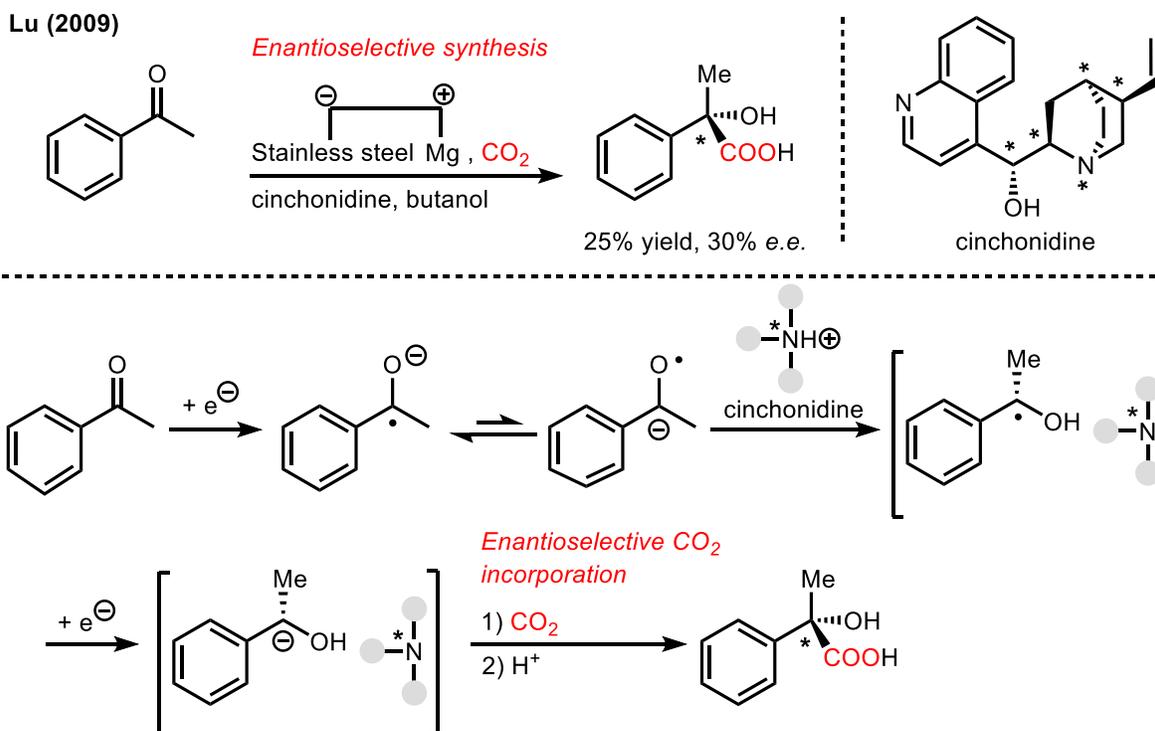


Scheme 3. Enantioconvergent carboxylation (and esterification) of trimethyl cyclohexanone.⁵⁷



Scheme 4. Nickel-catalyzed asymmetric carboxylation.⁴⁷

In 2009, Lu and coworkers explored asymmetric electrocarboxylation of the prochiral substrate acetophenone using platinum or stainless electrode materials for the synthesis of the pharmaceutical intermediate 2-hydroxy-2-phenylpropionic acid using cinchonidine or cinchonine as a chiral catalyst (Scheme 5).⁴⁸ Initially, butanol protonates the chiral amine catalyst, whereas acetophenone receives an electron from the cathode to form a ketyl radical anion. Then, selective proton transfer from the chiral protonated alkaloid to the ketyl radical anion yields an alcohol radical, which after receiving another electron from the cathode generates an α -hydroxy anion. This intermediate incorporates CO_2 in an enantioselective fashion to give 2-hydroxy-2-phenylpropionic acid with up to 30% e.e. .



Scheme 5. Asymmetric electrocarboxylation of prochiral acetophenone.⁴⁸

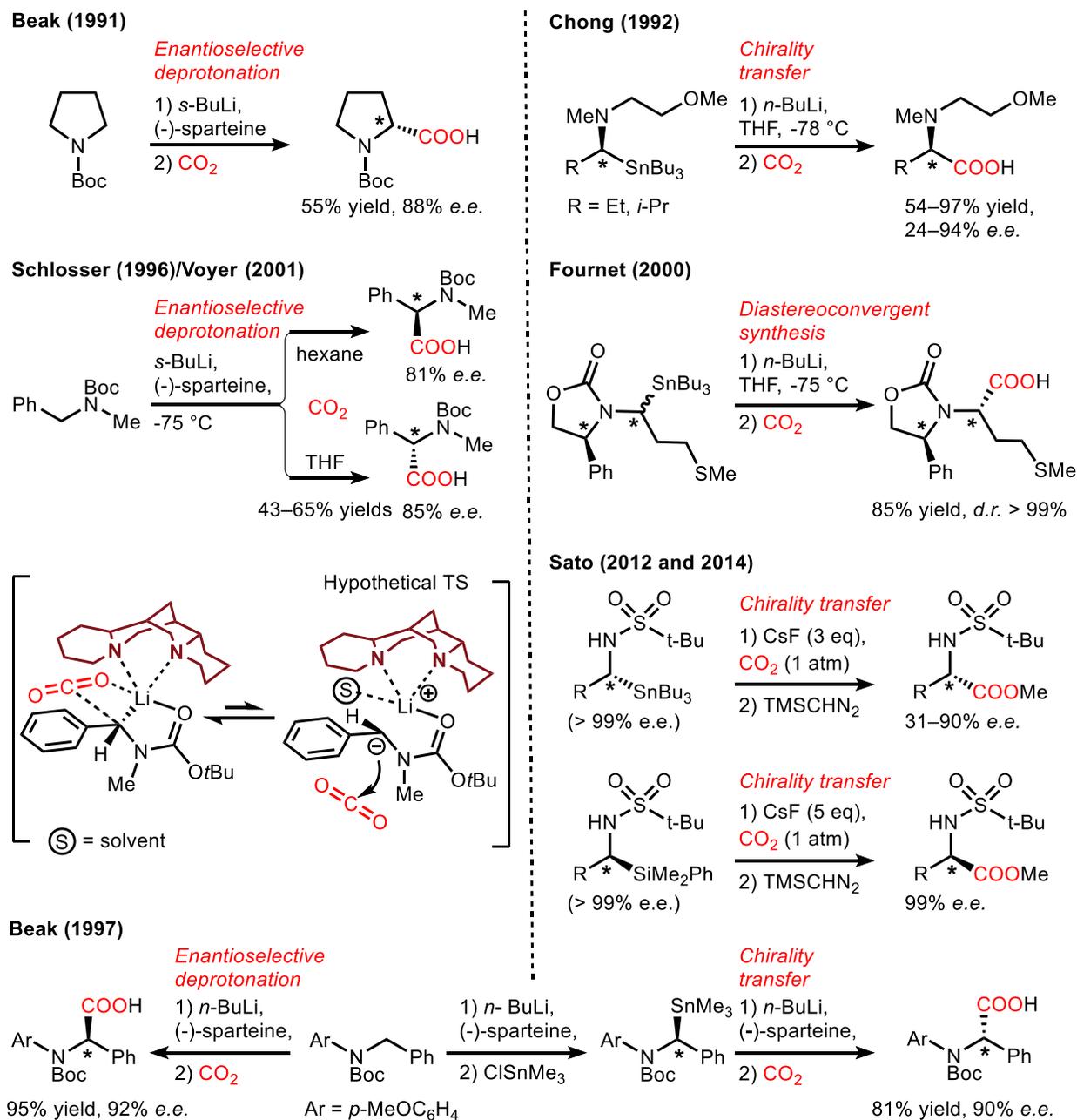
The first catalytic asymmetric hydrocarboxylation of prochiral α,β -unsaturated esters with CO₂ was reported by the Mikami group in 2016, involving a cationic rhodium catalyst with the chiral diphosphine (*S*)-(-)-4,4'-bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphine) [SEGP₂OS], resulting in carboxylated products of up to 66% *e.e.* (Scheme 6).⁴⁹ Catalytic amounts of AgSbF₆ provided best results. The active Rh-H species is formed from ZnEt₂ and inserts into an α,β -

the same amino acid derivative with 81 % yield and 90 % *e.e.*, with inversion of configuration. The groups of Schlosser⁶⁰ and Voyer⁶¹ reported a sparteine-mediated asymmetric deprotonation and enantioselective carboxylation of achiral precursors to synthesize *N*-Boc-protected phenyl glycine derivatives. The Schlosser group also studied the effect of solvent on the carboxylation of *N*-Boc-*N*-methylbenzylamine.⁶⁰ In hexane or diethyl ether, (*R*)-amino acid derivatives are formed with *e.e.*'s of 81% and 67%, respectively, but when the same reaction is carried out in THF, the (*S*)-product was obtained with 85% *e.e.*. It was hypothesized that CO₂ incorporation is affected by the interaction of the sparteine-organolithium intermediate with the solvent (Scheme 7).

In a study by Chong and co-workers,⁴² α -amino organostannanes underwent chirality transfer via Sn-Li exchange to generate secondary amino organolithiums, which were trapped by electrophiles (Scheme 7). The α -aminoorganostannanes contained a methoxyethyl group that was crucial to stabilize enantioenriched α -amino organolithiums generated *in situ*, which trapped CO₂ to furnish amino acid derivatives with up to 94% *e.e.*. The same group subjected enantioenriched *N*-Boc-protected α -aminoorganostannanes to lithiation with *n*-butyl-lithium. The resulting intermediate was then trapped by CO₂ yielding amino acids with up to 94% *e.e.*.

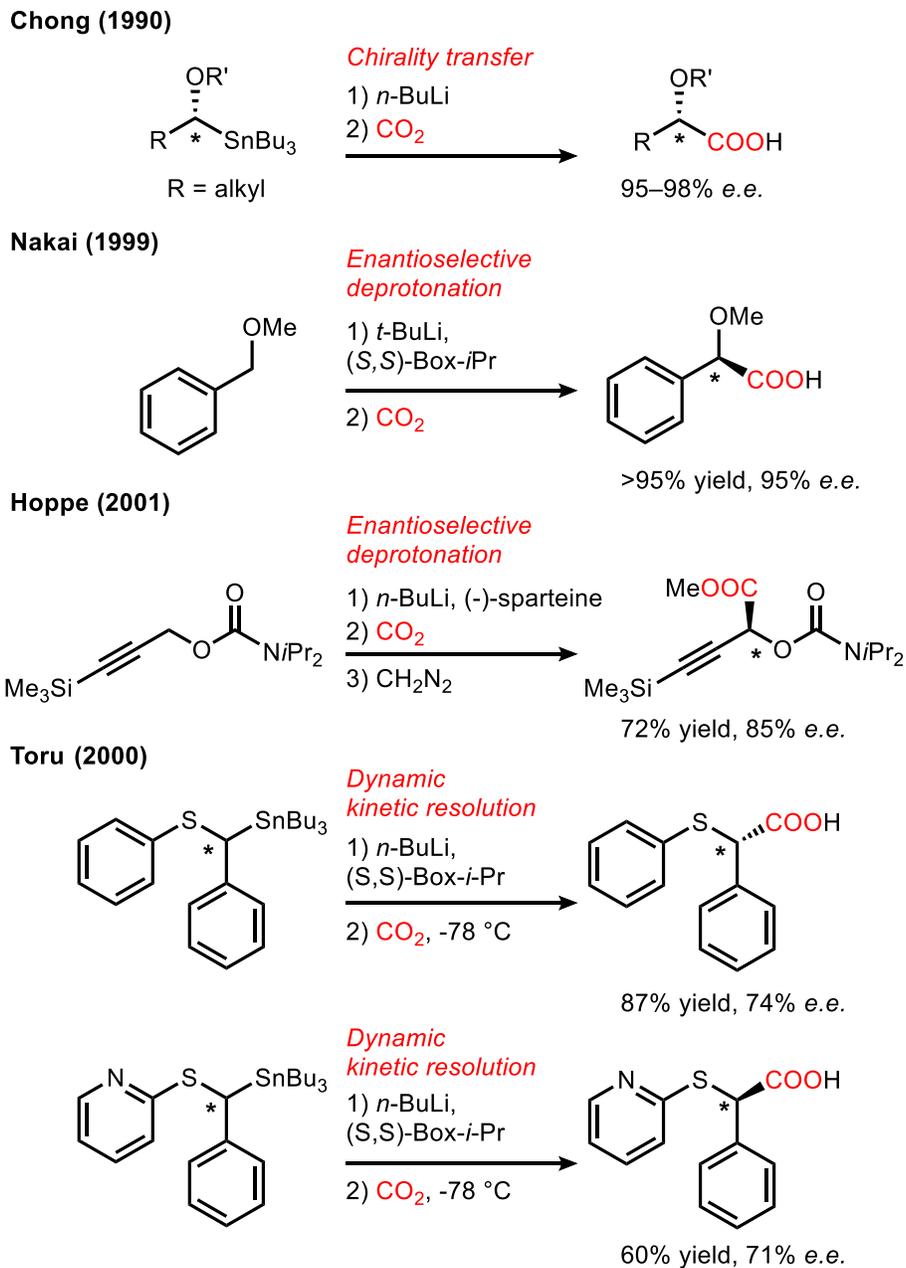
In 2000, Fournet and co-workers prepared various amino acids in good yields and *e.e.*'s up to 95% through diastereoconvergent carboxylation of *N*-(α -stannylalkyl)oxazolidinones (Scheme 7).⁶² The complete carboxylation process requires short reaction times (35-40 min), implying that this method can be used to synthesize 1-[¹¹C] amino acids, which can be useful as positron emission tomography tracers. In 2012, the Sato group prepared asymmetric amino and mandelic acid derivatives from α -amido and α -acetoxy stannanes, respectively, using CsF as a tin-activator.⁴⁴ The chirality of (*S*)-*N*-tert-butylsulfonyl- α -amido stannanes was transferred (with retention of

configuration⁴³) and gave *N*-sulfonyl amino acids with up to 90% *e.e.*. The same group used enantioenriched α -amido silanes for the synthesis of α -amino acid derivatives with 99% *e.e.*.⁴³



Scheme 7. Synthesis of enantioenriched α -amino acid derivatives with CO_2 , involving enantioselective deprotonation (left side) or chiral starting materials (right side).^{43,44,58,59,60,61,62}

α -Methoxy and α -Thiomethoxy Acid Derivatives by Asymmetric Carboxylation: The strategies developed for synthesis of enantioenriched α -amino acid derivatives (asymmetric deprotonation by enantioenriched bases and enantiospecific transformation of organostannanes) were successfully transferred to the synthesis of α -methoxy acids and esters (Scheme 8). The Chong⁶³ group applied chirality transfer via Sn-Li transmetallation followed by CO₂ fixation for the synthesis of α -alkoxy acids in high *e.e.* (95 – 98%) with retention of configuration (Scheme 8). In 1999, the Nakai group synthesized mandelic acid derivatives in 95% *e.e.* by asymmetric deprotonation of achiral benzyl methyl ether with a *tert*-butyl-lithium/chiral bis(oxazoline) complex followed by carboxylation.⁴⁶ Interestingly, the asymmetric induction occurs at the post-lithiation step, which was proven by deuterium-labelling on the benzylic position of benzyl methyl ether. Hoppe and coworkers carried out asymmetric deprotonation of propargylic carbamate with (–)-sparteine and n-butyllithium at –78 °C followed by carboxylation, which afforded the corresponding acid derivatives in up to 85% *e.e.* (Scheme 8).⁴⁵ Also thioethers underwent α -carboxylation with good yields and high *e.e.*. In 2000, the Toru group studied the enantioconvergent carboxylation of thioorganostannyls using n-butyllithium/chiral bis(oxazoline) followed by CO₂ addition.⁴¹ Carboxylation of α -lithio benzyl 2-pyridyl sulfides gave products with reverse stereochemistry to that obtained with benzyl phenyl sulfide (Scheme 8).



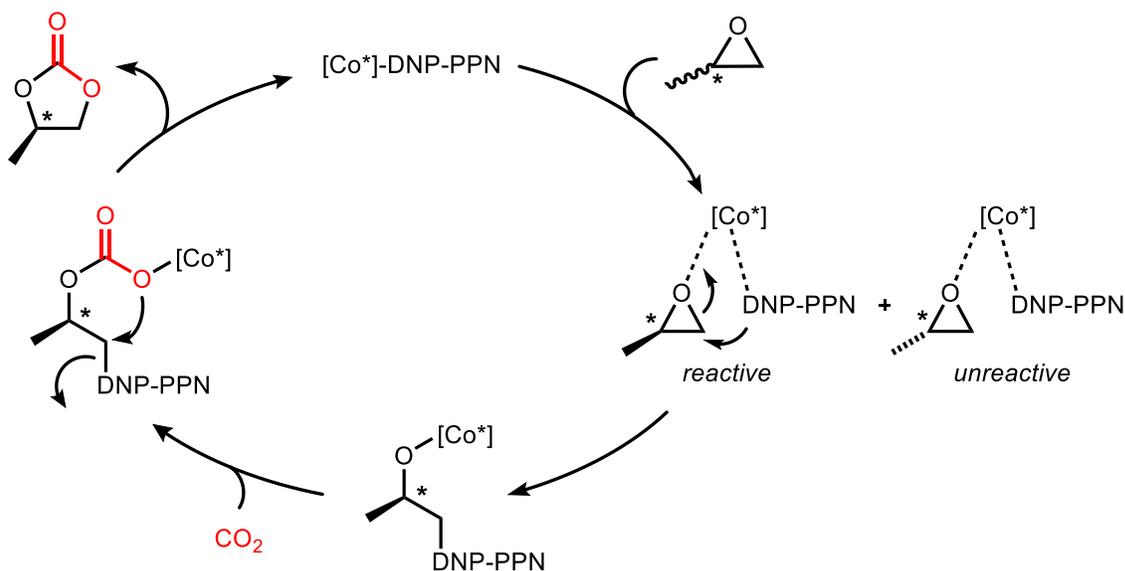
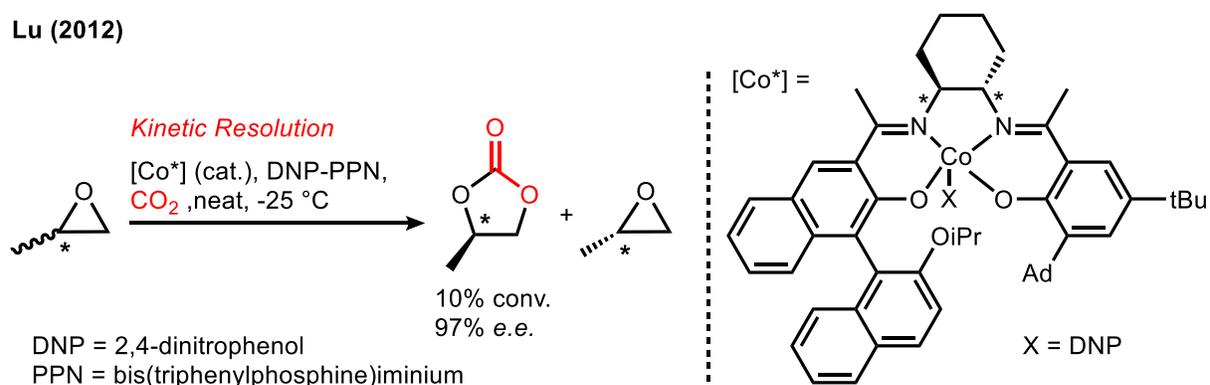
Scheme 8. Synthesis of enantioenriched α -methoxy and α -thiomethoxy acid derivatives.^{41,45,46,63}

2.3.2 Examples of Asymmetric C-OCO Bond Formation

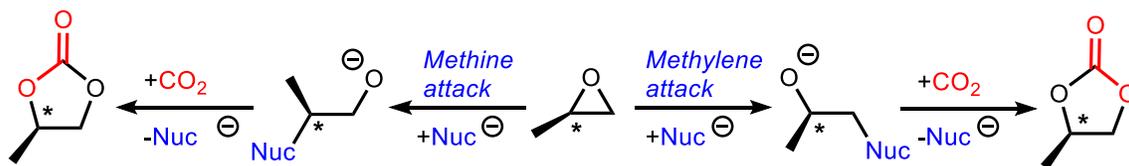
Enantioenriched products involving C-OCO bonds include linear and cyclic carbonates, polycarbonates, and carbamates such as oxazolidinones.

Cyclic Carbonates from CO₂: Cyclic carbonates represent a multibillion dollar industry and are used as solvents and starting materials for polycarbonates.⁶⁴ Most examples of stereo-enriched material come from kinetic resolution.^{29,30,31,32} The group of Lu used a chiral cobalt-salen catalyst for insertion of CO₂ into a racemic mixture of propylene oxide to form cyclic carbonates.³² This system relies on a co-catalyst, 2,4-dinitrophenol (DNP) with the organic soluble cation bis(triphenylphosphine)iminium (PPN) in 200 times excess in order to suppress polycarbonate formation. However, only 10 % conversion was observed, albeit with 97% *e.e.* of the (*S*)-propylene carbonate (Scheme 9). Higher temperature gave higher conversion, but reduced enantioselectivity. In this reaction, CO₂ is not incorporated at the chiral centre, implying that the asymmetry of the product comes from the fact that mainly the (*R*)-epoxide reacts. It can be noted that for monosubstituted epoxides, the site of CO₂ incorporation depends on the initial nucleophilic attack – if it is at the methylene (β) carbon, the stereocentre at the methine (α) carbon is retained; attack at the methine carbon is required for bonding of CO₂ to the chiral centre (Scheme 10).

Lu (2012)



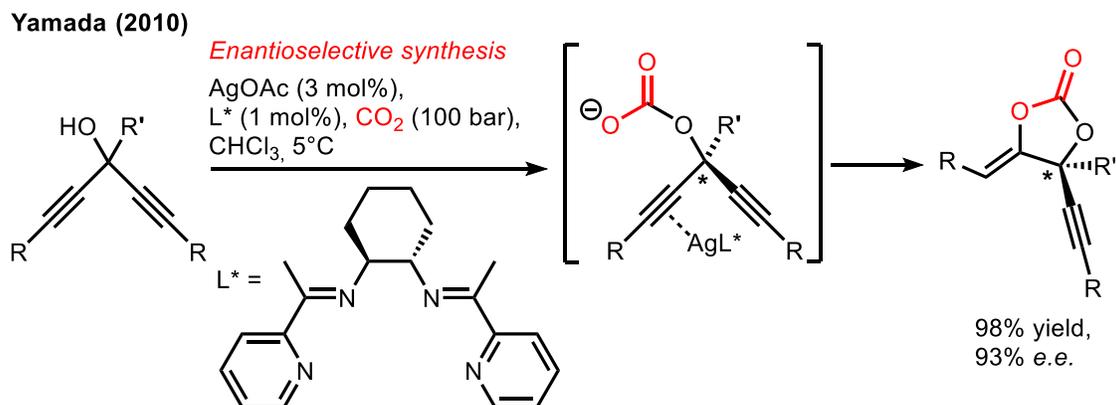
Scheme 9. Kinetic resolution of epoxides for the generation of cyclic carbonates.³²



Scheme 10. Different modes of CO₂ incorporation into mono-substituted epoxides.

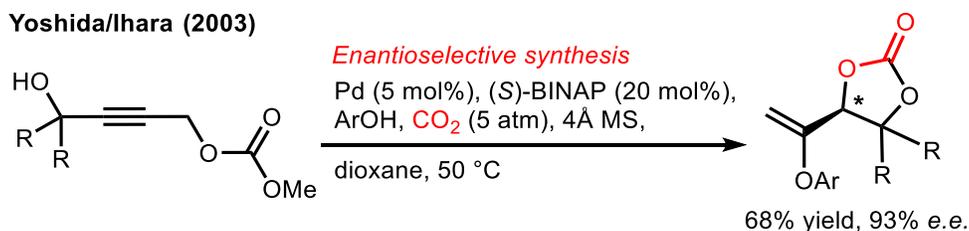
Chiral cyclic carbonates have been made without relying on kinetic resolution of epoxides; for example the silver-mediated desymmetrization of a bispropargylic alcohol provided excellent yields and 93% *e.e.* (Scheme 11).⁵⁰ The configuration appears to be determined by the

conformation of the cyclization transition state (TS), but note that CO₂ does not become bound to the chiral centre.

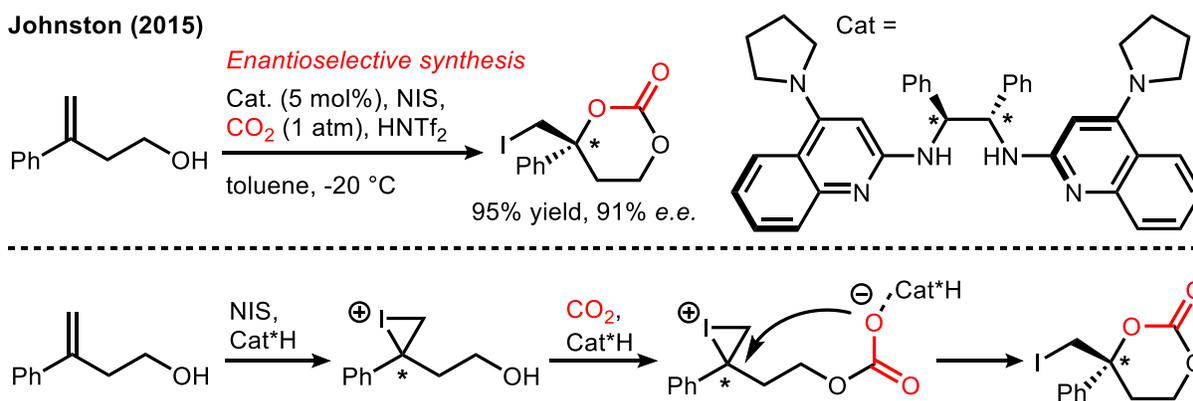


Scheme 11. Desymmetrization of a bispropargylic alcohol with CO₂.⁵⁰

Two examples involving enantioselective CO₂ incorporation into unsaturated substrates can be given. Yoshida *et al.* reported in 2003 an asymmetric synthesis of cyclic carbonates from achiral propargylic carbonates (Scheme 12).⁵⁵ Formally, it is a CO₂ re-fixation process, as the initial linear carbonate is eliminated and then added to another site. The starting material forms an allene-Pd complex that reacts with the external aryl alcohol to form a Pd allyl complex, which is attacked by the newly formed tertiary alkylcarbonate to give the cyclic carbonate in *e.e.*'s of up to 93%. The product is useful as a synthon for α -hydroxyketones. Of general use is also the reported enantioselective cyclization of prochiral (homo)allylic alcohols giving 5- or 6-membered cyclic carbonates (Scheme 13).³³ In this case, CO₂ forms a transient monoalkylcarbonate anion that is stabilized by hydrogen bonds to the Brønsted acid/chiral base catalyst. The resulting cyclic carbonates are useful chiral intermediates that may undergo a range of transformations.



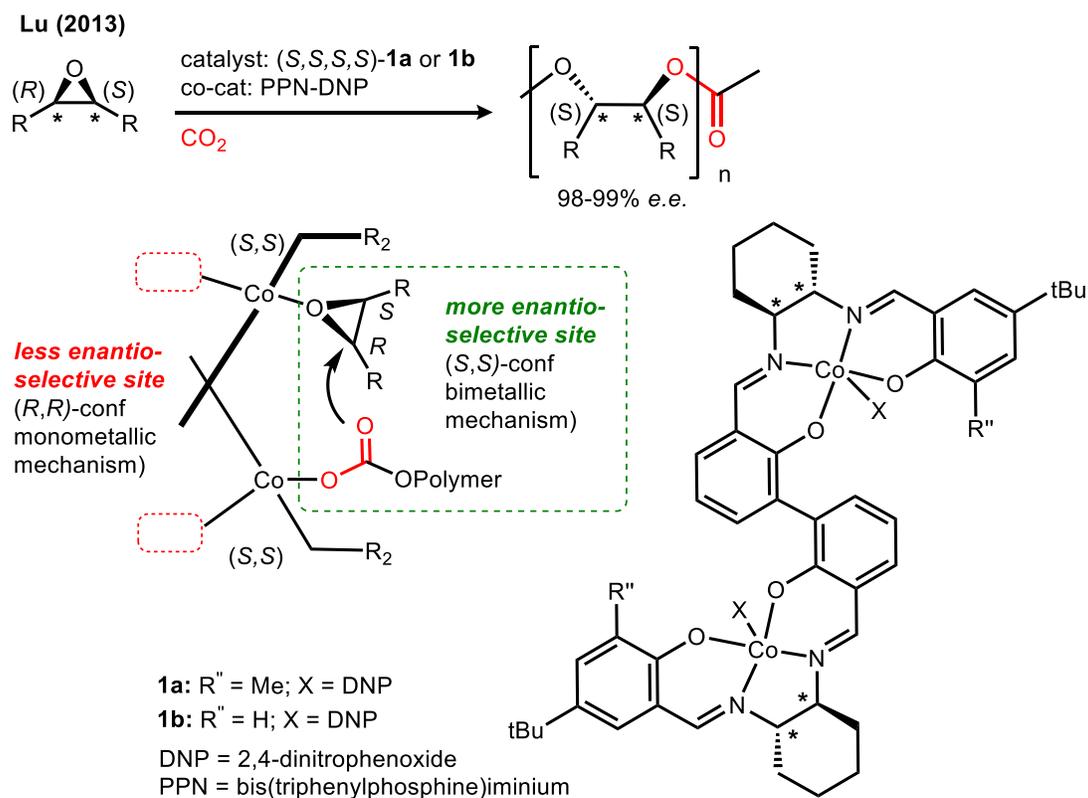
Scheme 12. Conversion of achiral propargylic carbonates to chiral cyclic carbonates.⁵⁵



Scheme 13. Formation of chiral carbonates from achiral homoallylic alcohols and CO₂.³³

Polycarbonates from CO₂: A successful process for CO₂ utilization is the catalytic production of polycarbonates, which has found industrial applications.⁶⁵ The synthesis of polycarbonates with CO₂ and involved mechanisms have been reviewed in detail (see in particular Coates and coworkers¹¹ for stereoselective aspects, but also Lu,^{10,66} Rieger and coworkers,⁶⁷ and Darensbourg⁶⁸) and is only touched upon briefly here. The stereochemistry of the polymer can be determined by the growing polymer chain (chain-end-control) or by a chiral metal catalyst (enantiomorphic site control); most reported systems exhibit the latter form for stereo-control.¹¹ Formation of polycarbonates with well-defined repetition of stereocentres is essential, due to their superior properties compared to racemic polymers.⁶⁹ A high degree of stereoregularity gives higher melting temperatures and increased crystalline behavior, something that is desired.

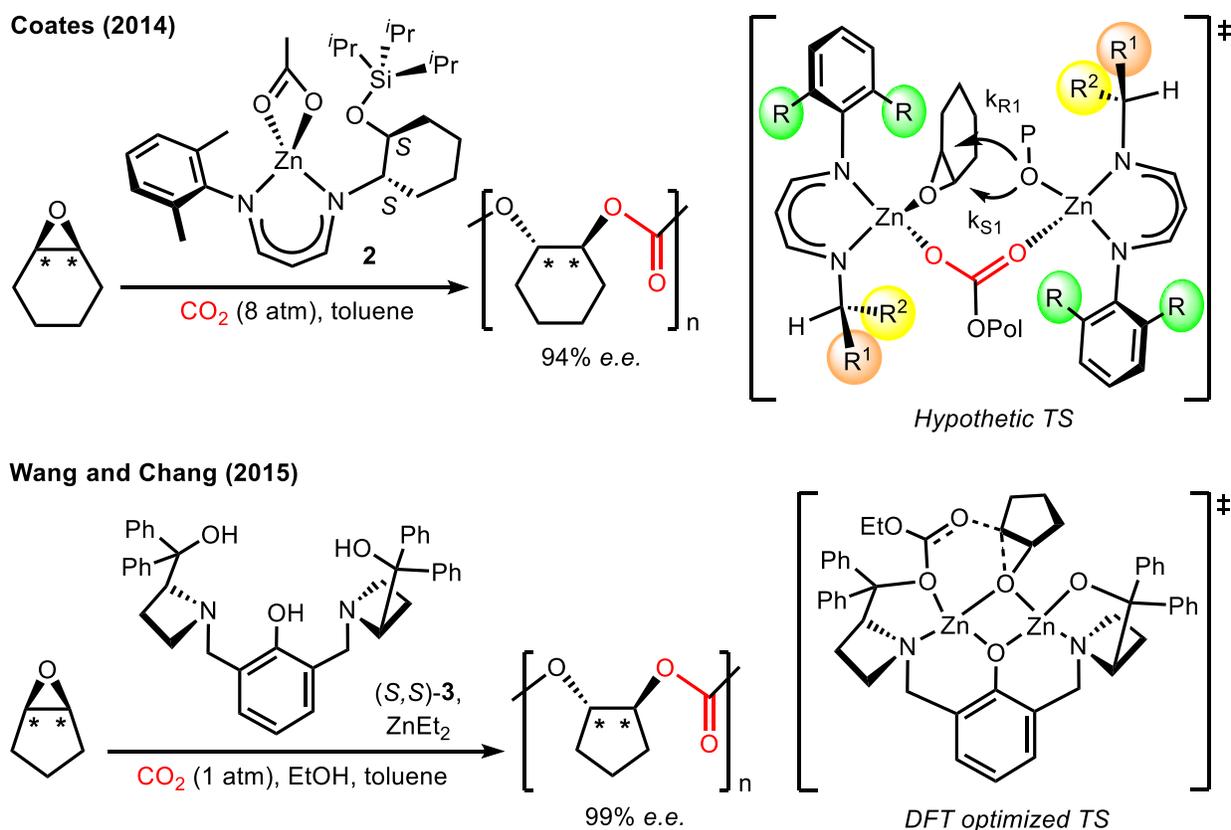
Both mononuclear and dinuclear catalysts have been developed for copolymerization reactions, however in both cases usually bimetallic mechanisms are proposed.¹¹ Recent studies by the group of Lu⁵¹ on the copolymerization of different meso-epoxides with CO₂ showed that by using chiral dinuclear Co(III) catalysts (**1a** or **1b**, Scheme 14), the activity and enantioselectivity significantly increased from previous mononuclear systems.⁷⁰ A mechanistic investigation showed that the initiation and chain growth can either occur in the inside or in the outside cleft of the catalyst (in green and red, respectively in Scheme 14). The former is the more enantioselective site and all conditions enhancing this pathway will benefit the enantioselectivity.



Scheme 14. Copolymerization of CO₂ and meso-epoxides by dinuclear Co(III) complexes with PPN-DNP cocatalyst and schematic representation of the polymer chain growth.⁵¹

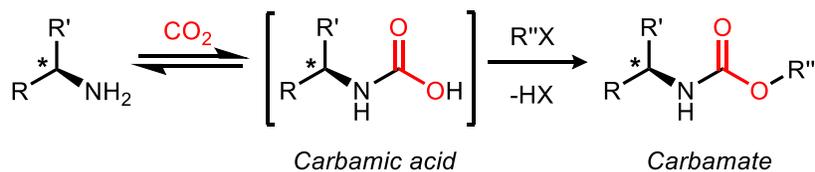
Zinc complexes have also been shown to be efficient catalysts for asymmetric polymerization of cyclic epoxides. The group of Coates designed a variety of C₁-symmetric catalysts able to favor a TS, in which the two Zn complexes involved in the ring opening are located *anti* to each other (Scheme 15, top).⁵² The best catalyst (**2**) provided polycyclohexane carbonate with *e.e.*'s. up to 94%. A different strategy was followed by Wang and Chang, who used the chiral ligand (*S,S*)-**3** to copolymerize cyclopentene oxide with CO₂ with 99% *e.e.* (Scheme 15, bottom).⁵³ In this case, the excess of (*R,R*)-product was predicted by DFT optimization of the *re* and *si*-TSs.

Copolymerization of CO₂ and linear epoxides are more challenging, given their tendency to “back-bite” and form monomeric cyclic carbonate, but examples have been reported, such as the stereoselective polypropylene carbonate (PPC) synthesis by the Coates group using a cobalt-salen catalyst and a PPN co-catalyst.⁷¹ The use of racemic propylene oxide provided iso-enriched PPC with high turnover numbers and very little cyclic carbonate from back-biting.



Scheme 15. Copolymerization of CO₂ and cyclic epoxides via Zn catalysts.^{52,53}

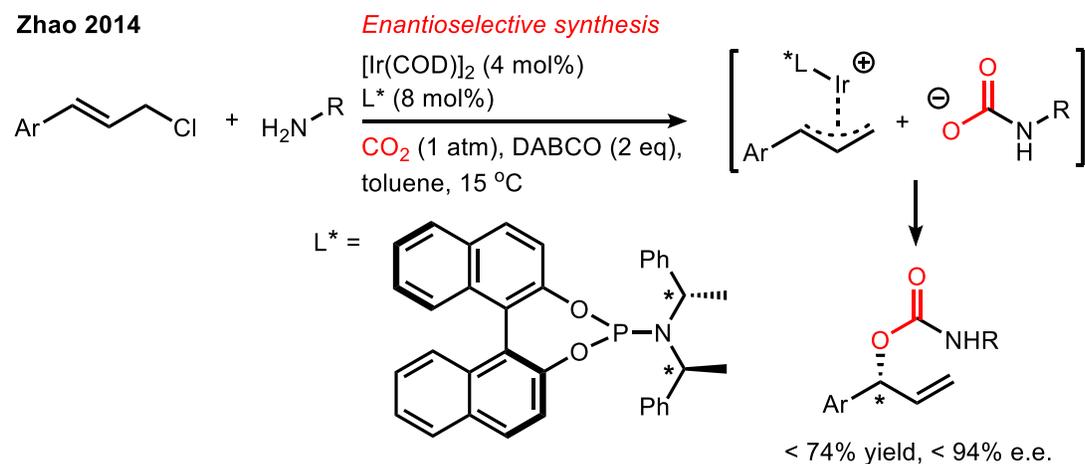
Linear Carbamates from CO₂: Amines react reversibly with CO₂ to produce carbamic acids, which can then be trapped by alkyl halides,⁷² or alcohols under dehydrogenative,⁷³ or Mitsunobu conditions⁷⁴ to give chiral linear carbamates (Scheme 16). An alternative approach is to bind CO₂ as carbonates, which form carbamates upon treatment with primary or secondary amines.⁷⁵



Scheme 16. General synthesis of carbamates

In 2014, Zhao *et al.* reported enantioselective iridium-catalyzed formation of allyl

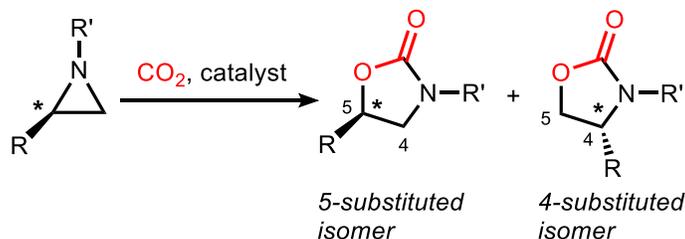
carbamates from cinnamic chlorides and CO₂ under mild reaction conditions (Scheme 17).⁷⁶ This three component reaction follows a similar reaction pathway as the previously reported palladium-catalyzed ring-opening of vinylaziridines and subsequent CO₂ fixation followed by intramolecular cyclization.⁷⁷



Scheme 17. Iridium-catalyzed enantioselective synthesis of allyl carbamates.⁷⁶

Cyclic Carbamates from CO₂: Cyclic carbamates, particularly five-membered oxazolidinones, are of great interest as they are used as chiral auxiliaries (Evans' type).⁷⁸ Their synthesis from CO₂ has been reviewed in 2013.²³ Oxazolidinones can be prepared from CO₂ in manners similar to cyclic carbonates, but there are no reported methods for their asymmetric synthesis from achiral substrates. Formation of enantioenriched oxazolidinones instead relies on the use of enantiopure starting materials. In notable reports by the group of Muñoz, α- and/or β-substituted enantiopure amino-alcohols were carbonylated with CO₂ employing different electrophiles and organic bases.⁷⁹ Only the C=O of CO₂ is retained in the oxazolidinone product. The chirality is preserved, except for ephedrine derivatives, which give a β-inverted byproduct, especially with SOCl₂ as electrophile. This suggests that the stereoselectivity can be tuned through the choice of

electrophile. Cyclization of enantiopure aminoalcohols with catalytic Cs_2CO_3 or fluoride has also been reported.⁸⁰

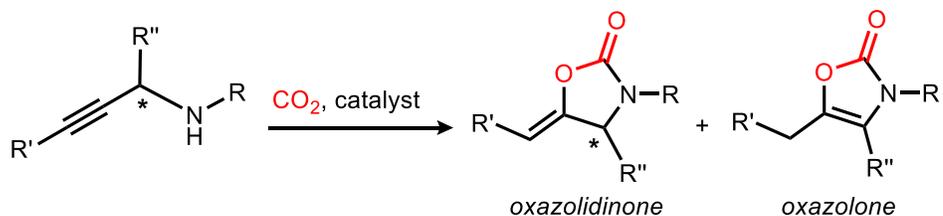


Scheme 18. General synthesis of oxazolidinones by carboxylation of aziridines.

Aziridines are another major substrate class for the synthesis of oxazolidinones. Chirality transfer from enantiopure aziridines provides enantioenriched products.^{35,54} This transformation can give two different isomers (Scheme 18), but ionic liquids,⁸¹ NHCs,⁸² Cr-salen,⁸³ and Al-salen/ammonium salt,³⁵ favour the 5-substituted isomer (if the nitrogen is substituted and $\text{R}' = \text{Ph}$). Adhikari *et al.*⁸⁴ observed no racemization, suggesting that the regioselectivity originates from an incipient carbocation intermediate rather than a true carbocation. The 4-substituted isomer is available through metal-halide catalysis with aziridines without nitrogen substituent.⁸⁵

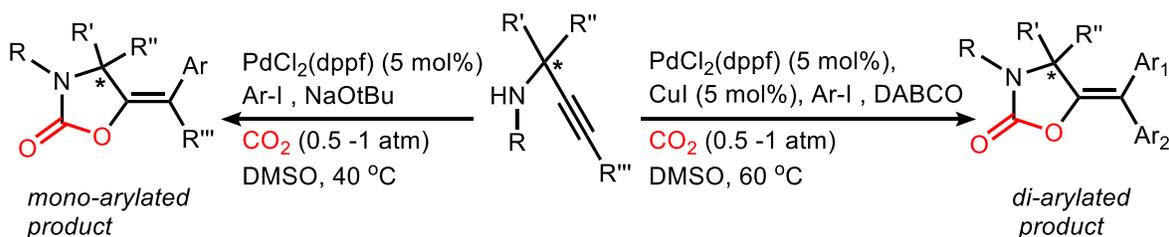
Propargylic amines are a third substrate class used for synthesis of cyclic carbamates. They react analogously to propargylic alcohols (Scheme 11) and give unsaturated oxazolidinones (Scheme 19). This transformation can be catalyzed by noble metals, e.g. Ag-acetate,⁸⁶ Au-NHC,⁸⁷ or a Pd-SCS pincer complex;⁸⁸ the latter offers the broadest substrate scope to date. Other methods involve catalysis by ionic liquid,⁸⁹ organic bases^{90,91} or NHCs.⁹² The *in-situ* tautomerization of oxazolidinones to oxazolones (Scheme 19) was reported with ionic liquid or a NHC catalyst.^{93,94} Nevado and coworkers have reported a Pd-catalyzed carboxylation of propargylic amines and aryl iodides, giving mono-arylated oxazolidinones with complete *E*-selectivity (Scheme 20).⁹⁵ Also

homodiarlylated ($Ar^1 = Ar^2$) and heterodiarlylated products ($Ar^1 \neq Ar^2$) can be obtained by changing the reactions conditions. Note that any chiral products were prepared as racemic mixtures only.



Scheme 19. Synthesis of oxazolidinones and oxazolones from propargylic amines.

Nevado 2016

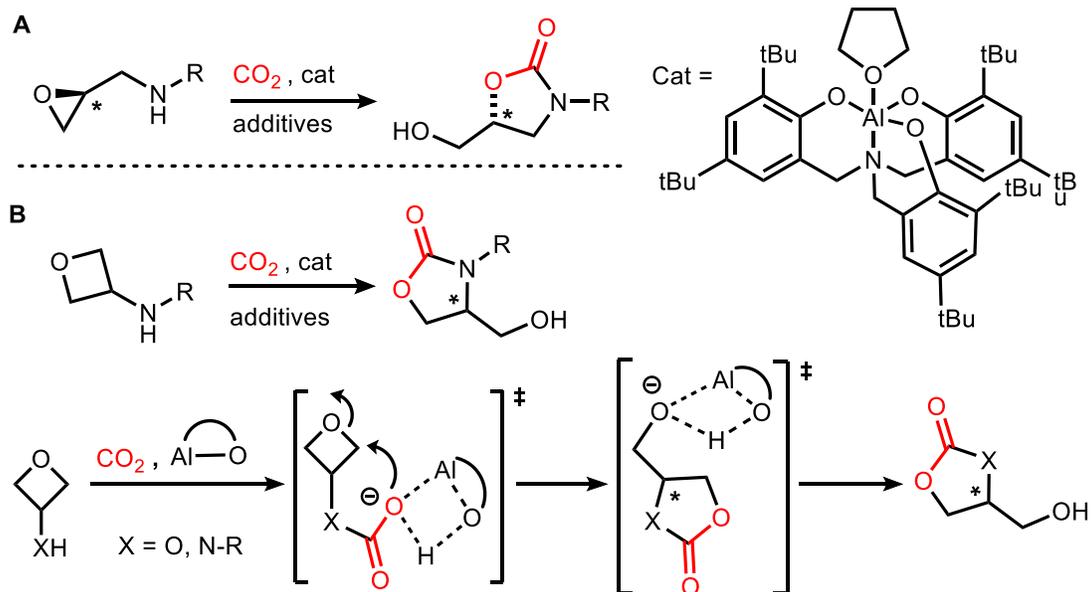


Scheme 20. Mono- and diarylsubstituted oxazolidinones from propargylic amines and CO_2 .⁹⁵

Other interesting substrates have been used for oxazolidinone synthesis, but not enantioselectively. In 2014, Repo and coworkers³⁴ reported 5- and 6-membered cyclic carbamates from racemic cyclization of various β - and γ -haloamines with CO_2 , and Soldi *et al.*⁹⁶ reported intramolecular carboxylative cyclization of allylamines. Yu *et al.*⁹⁷ reported CuI-catalyzed cyclization of primary amine carbamate salts with aldehydes and aromatic terminal alkynes. In 2015, Kleij and coworkers⁹⁸ reported the synthesis of racemic oxazolidinones from epoxy amines (Scheme 21A). A mechanistic investigation with an enantiopure epoxy alcohol showed chirality inversion at the β -carbon, implying that the reaction likely proceeds through an intramolecular attack at the β -carbon. Also CO_2 incorporation into amino- and hydroxyl-oxetanes has been reported (Scheme 21B), which provided racemic oxazolidinones and carbonates, respectively.⁹⁹ 3-

substituted oxetanes are prochiral, implying that they offer great potential as substrates in asymmetric catalysis.

Kleij 2015/2016



Scheme 21. CO₂ incorporation into epoxy amines (A) and amino-oxetanes (B).⁹⁹

2.4. Summary of Status and Future Outlook

The previous sections highlight the different strategies that have been employed for asymmetric incorporation of CO₂. Kinetic resolution (Strategy I, Scheme 2) may involve loss of up to 50% of the starting materials, whereas chirality transfer can appear inconvenient, because it depends on the access to enantiopure substrates (Strategy II). The most-atom economical and convenient strategy may be synthesis of enantioenriched molecules from unsaturated prochiral starting materials and CO₂ (Strategy III),⁵ but only a handful of this type of transformations has been reported, with varying selectivities.^{29,47,48,49,55} Such reactions may be difficult to make enantioselective, although conceptually, they are related to the asymmetric hydrogenation of unsaturated starting materials; a field that has brought forward numerous highly enantioselective

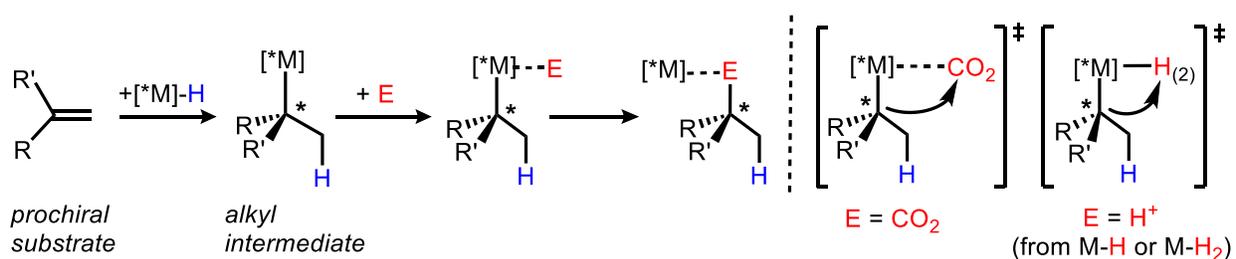
reactions.^{100,101,102} Here we compare enantioselective hydrogenation and hydrocarboxylation reactions in order to highlight the similarities and differences between these, followed by a more general discussion of strategies for development of novel enantioselective CO₂ reactions.

2.4.1 Asymmetric Hydrocarboxylation vs. Asymmetric Hydrogenation

Hydrocarboxylation of alkenes appears to be a conceptually interesting approach for formation of C-C bonds with CO₂. Several alkene hydrocarboxylations have been reported, including some that provide chiral molecules, however, all but one yield racemic mixtures.^{12,13,14,16,49,103} A particular challenge is the need for additives that promote catalyst regeneration and product release.^{12,13,14,49} These additives may interfere with the ability to make reactions enantioselective: for example, known iron-based hydrocarboxylation catalysts depend on Grignard reagents,^{13,14} which can be expected to scramble any induced asymmetry upon formation of configurationally labile carbon-metal bonds. The only reported asymmetric hydrocarboxylation of alkenes is the rhodium-based Mikami system⁴⁹ which involves ZnEt₂ as an additive (Scheme 6), but asymmetric conversion is solely reported with α,β -unsaturated esters (*e.e.*'s of 66%), which can be considered functionalized alkenes. Currently, the status of asymmetric hydrocarboxylation with CO₂ is reminiscent of the beginning of asymmetric hydrogenation: during the first decades (1960's to 80's), best results were obtained with rhodium catalysts and functionalized alkenes.^{104,105} After ~50 years of development in this field, such systems are still in use,¹⁰² but have been complemented with a variety of catalysts that can hydrogenate unfunctionalized alkenes (and imines and ketones) with very high *e.e.*'s, up to >99%.^{100,101,106} In contrast, hydrocarboxylation reactions are in their infancy: Stoichiometric hydrocarboxylation of alkenes is known since the 1980's,¹⁰⁷ but catalytic reactions have been developed for only ~10 years,¹² with the first asymmetric reaction reported last year.⁴⁹

Interestingly, from a mechanistic point of view, metal-catalyzed hydrogenation and

hydrocarboxylation of alkenes show similarities (assuming an inner sphere mechanism¹⁰⁸): initially the alkene inserts into a metal-hydride bond to form a metal-alkyl intermediate (Scheme 22).^{49,109,110,111,112} The nucleophilic alkyl can then react with an electrophile, which would be a proton in hydrogenation and a CO₂ molecule in hydrocarboxylation reactions. However, H⁺ and CO₂ have different electrophilicities, and their mode of interaction with the metal at the bond formation step may differ substantially. Whereas the proton donor (an H₂ molecule, or a metal- or ligand-bound hydrogen) in general is in close proximity to the metal, the nature of the interaction between CO₂ and metal is much less understood. A computational study evaluating rhodium catalysts with 38 different achiral pincer ligands showed that at the C-CO₂ bonding step, the CO₂ molecule might be located 2.1 to 4.9 Angstrom from the metal.¹⁰⁹ During bond formation in asymmetric reactions, CO₂ might thus experience less of the chiral catalyst environment than a proton, which normally originates from a tightly-bound ligand. Note that the formed products (alkane vs. carboxylate) have profoundly different abilities to complex to the metal. Although complexation of carboxylates may inhibit product release, this should not affect enantioselectivities.

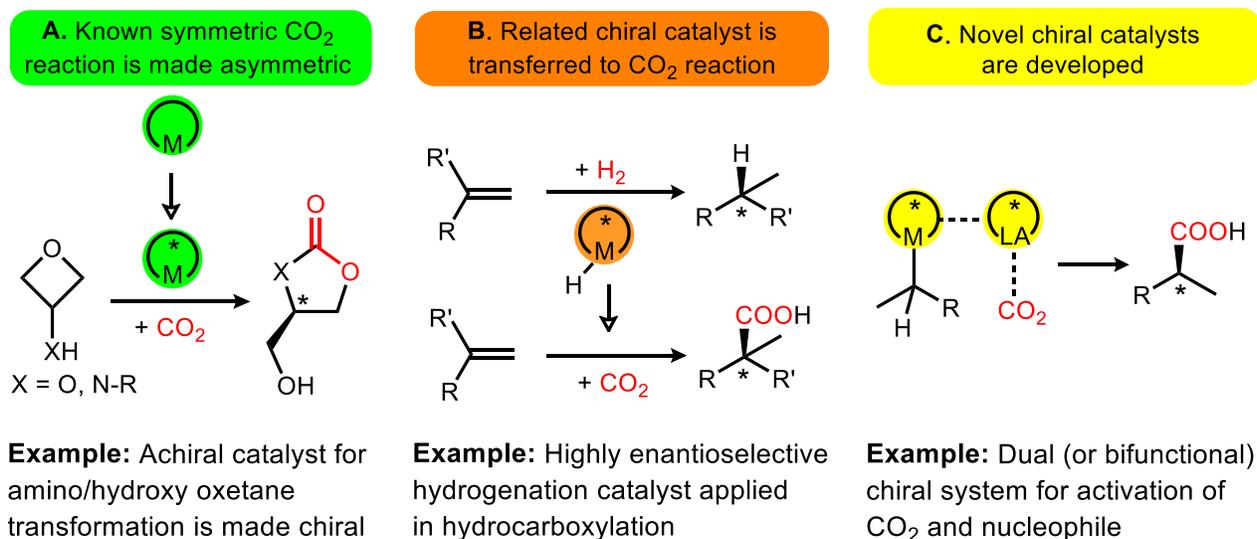


Scheme 22. Mechanistic similarities between hydrocarboxylation (E = CO₂)^{49,109} and hydrogenation (E = H⁺).^{109,111,112} The regioselectivity may differ from the example shown here.

2.4.2 Approaches for development of novel enantioselective CO₂ reactions

Novel asymmetric CO₂ reactions may be based on already existing reactions and catalysts, or

involve development of novel systems. We suggest here three possible approaches (Scheme 23). The most straightforward strategy may be to start out from already known *symmetric* CO₂ reactions yielding racemic products, and to modify involved catalysts such that they become chiral. For example, asymmetric NHCs¹¹³ and salen complexes¹¹⁴ are attractive to develop catalysts for enantioselective CO₂ incorporation to form cyclic carbamates. The transformation of prochiral amino- and hydroxyl-oxetanes to carbamates and carbonates (Scheme 21B)⁹⁹ is an example of a symmetric reaction that may be made asymmetric through introduction of a chiral catalyst (Scheme 23A). A strategy for making chiral C-CO₂ bonds may rely on the similarities between hydrogenation and hydrocarboxylation (section 2.4.1). For example, one may identify a highly enantioselective hydrogenation catalyst for an unsaturated substrate and then apply the same catalyst and substrate in an asymmetric hydrocarboxylation reaction (Scheme 23B). The most challenging approach will be the design of entirely new asymmetric systems. One strategy for C-CO₂ bond formation may be the development of dual chiral (or bifunctional) catalyst systems, where one catalyst interacts with the carbon-based nucleophile while the other interacts with CO₂ (Scheme 23C). The CO₂-binding co-catalyst should be tuned such that the electrophilicity of CO₂ is enhanced. Activation of CO₂ with Lewis acids such as aluminium salts has been reported for carboxylation of aromatics and allylsilanes.^{18,115,116} Further exploration of this approach may provide an interesting entry to enantioselective transformations of CO₂, given the waste number of chiral Lewis acid catalysts known.¹¹⁷



Scheme 23. Tentative strategies for design of enantioselective CO₂ reactions on basis of A) known symmetric reactions, B) known related enantioselective catalysts, or C) development of novel systems (M = Metal, LA = Lewis Acid).

Conclusions

CO₂ is a rather inert molecule and current research efforts are mostly focusing on making CO₂ conversion efficient. However, in order for CO₂ to become an important carbon source in organic synthesis, enantioselective processes need to be developed, especially carbon-carbon bond formation reactions that are based on achiral starting materials. The development of enantioselective CO₂ reactions may rely on already known symmetric transformations and may build on the insights obtained from other types of enantioselective conversions, such as asymmetric hydrogenation. Ideally, the focus should also be on sustainable methods, i.e. not on the use of precious metals. However, as with asymmetric hydrogenation, the use of precious metals might be needed to bring the field forward.

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