UDC 546.26-162: 541.13:549.21 doi: 10.33609/2708-129X.91.10.2025.27-71

CUTTING-EDGE STRATEGIES IN THE ASYMMETRIC SYNTHESIS OF α-AMINOCYCLOPROPANE CARBOXYLIC ACIDS: ESSENTIAL SCAFFOLDS FOR DRUG DISCOVERY.

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α-Aminocyclopropanecarboxylic acid (ACC) and its derivatives are widely distributed in the plant kingdom, fulfilling diverse roles ranging from regulation of plant life cycles to defensive mechanisms. The sterically constrained structure of ACC has proven invaluable in the design of numerous drugs, particularly hepatitis C virus (HCV) NS3/4A protease inhibitors. Indeed, ACC has been instrumental in the development of multiple generations of potent HCV treatments, with ongoing efforts focused on further improvements and refinements. The inherent steric constraints of these derivatives present a significant challenge for their synthesis, especially in enantiomerically pure form. This article provides a comprehensive overview of synthetic methodologies reported in the literature for the preparation of ACC and its derivatives. The synthetic strategies discussed herein are organized based on key transformations, including dialkylation of nucleophilic glycine equivalents, cyclopropanation of carbenoid glycine equivalents, and addition reactions to dehydroamino acids. Particular emphasis is placed on asymmetric approaches that enable the preparation of these tailor-made amino acids in enantiomerically pure form. Furthermore, aspects of Self-Disproportionation of Enantiomers (SDE) relevant to enantioselective catalysis are highlighted. By compiling these methodologies, we aim to provide a comprehensive resource and a source of inspiration for researchers in synthetic and medicinal chemistry, as well as drug discovery.

Key words: Amino Acids, Pharmaceuticals, Cyclopropane, Chirality, Synthesis, Nucleophilic Glycine Equivalents, Carbenoid Glycine Equivalents, Dehydroamino Acids, Self-Disproportionation of Enantiomers (SDE).

INTRODUCTION.

Amino acids represent a pinnacle of molecular design. Their orthogonal amino and carboxylic acid functionalities enable virtually infinite polymeric peptide structures, while diverse side chains can introduce a vast array of additional functional groups, facilitating non-bonding electrostatic or lipophilic/hydrophilic interactions. Furthermore, the inherent chiral stereogenic center adds another dimension of molecular complexity in three-dimensional space. Early pharmaceutical applications of amino acids primarily involved dietary supplements and medical nutrition therapy for conditions such as malnutrition and metabolic disorders [1–4]. However, with advancements in biochemical research, amino acids became central to the development of hormonal therapies, exemplified by insulin synthesis, which revolutionized diabetes treatment. Moreover, peptide-based drugs, derived from amino acids, pioneered new classes of antibiotics, enzyme inhibitors, and vaccines [5–8].

In contemporary pharmaceutical science, amino acids play a pivotal role in biologic drugs (biopharmaceuticals), targeted therapies, and synthetic medicinal compounds (small-molecule pharmaceuticals). A significant breakthrough, representing a paradigm shift in drug design, has been the strategic utilization of modified, tailor-made amino acids in place of their natural counterparts [9–15]. These custom-engineered amino acids can be rationally designed to enhance drug stability, solubility, and absorption, thereby optimizing biological efficacy and enabling more precise targeted delivery [15–21].

The asymmetric synthesis of α-amino acids (α-AAs) remains an exciting and crucial area of research, fueled by ever-evolving scientific and practical imperatives [22–41]. Within this broad field, sterically constrained α-AAs are of particular pharmaceutical significance, as their restricted side-chain chi(χ)-dihedral angles afford exquisite control over molecular interactions with biological target receptors [42–51]. A prominent class within this category is the α,β-methano-α-AAs family (Fig. 1), characterized by an α-quaternary carbon atom embedded within a highly rigid cyclopropane ring. This unique structural motif represents the apex of steric and conformational constraint among α-AAs [52, 53]. Notably, certain members of this family are naturally occurring compounds (*vide infra*) [54–58]. For instance, 1-aminocyclopropanecarboxylic acid (ACC) (**1**), along with its 2-methyl (**2**, **3**) and 2-ethyl (**4**, **5**) derivatives, have been identified as constituents of plant proteins [59–62]. The intriguing biological properties of the ethyl derivatives **4** and **5** have spurred the development of even more conformationally restricted tailor-made 2-vinyl analogues, such as compound **6**. Intriguingly, despite being stereochemically equivalent to **5**, compound **6** exhibits a (1*R*,2*R*) absolute configuration as dictated by CIP priority rules [63, 64].

Currently, 1-amino-2-vinylcyclopropane-1-carboxylic acids have emerged as crucial pharmacophoric elements in the design of next-generation hepatitis C virus (HCV) NS3/4A protease inhibitors [65]. As detailed in the corresponding section (*vide infra*), vinyl derivatives of 1-aminocyclopropanecarboxylic acids have profoundly impacted the HCV pharmaceutical landscape, contributing to the development of over a dozen therapeutic agents. Given the significant and ongoing socioeconomic impact of 1-aminocyclopropanecarboxylic acids on the pharmaceutical industry, a comprehensive review of the available synthetic methodologies

is both timely and essential. A critical analysis of these approaches will facilitate the assessment of their respective advantages and limitations, thereby guiding future advancements in this important field. Considering the inherently multidisciplinary nature of the chemistry, biological properties, and pharmaceutical applications of cyclopropane-derived α-amino acids, this review is anticipated to be of broad interest to graduate students and professionals across diverse disciplines, including organic, bioorganic, and medicinal chemistry, biochemistry, pharmacology, virology, and drug design, as well as process chemists within the pharmaceutical and chemical industries, and clinical researchers.

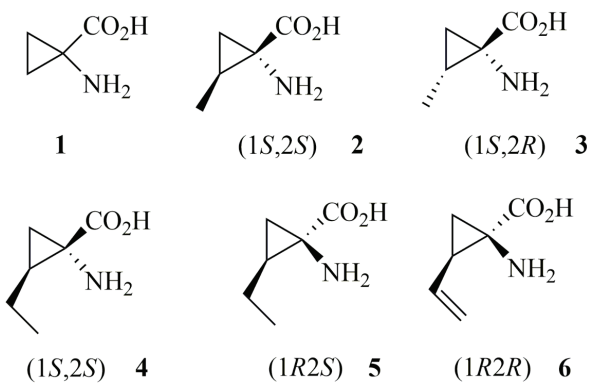


Fig. 1. Family of 1-aminocyclopropane carboxylic acids.

Naturally occurring 1-aminocyclopropanecarboxylic acids and their derivatives.

As discussed in the previous section, ACC **1** (Fig. 1), norcoronamic acid (**2**), allo-norcoronamic acid (**3**), allo-coronamic acid (**4**), and coronamic acid (**5**) are widely distributed in the proteins of higher plants, where they play specific defensive roles [54–62, 66–69]. ACC **1** is particularly notable for its role in the in vivo production of ethylene, a vital plant hormone that regulates key processes throughout the plant's seasonal life cycle. Ethylene influences germination, growth, leaf and flower senescence, fruit ripening, and the plant's response to various environmental stresses, ensuring adaptability and survival.

As shown in Fig. 2, ACC **1** serves as a key structural unit in natural products such as polycyclic alkaloids, including norcoronatine (**7**, R = Me) and coronatine (**8**, R = Et). These compounds, isolated from certain pathovars of *Pseudomonas syringae*, play a crucial role in plant-pathogen interactions. Norcoronatine **7** and coronatine **8** exhibit significant biological activity, primarily as jasmonate mimics. They can interfere with plant hormone signaling pathways, contributing to the pathogen's virulence by suppressing plant defense responses and promoting disease development [70–73].

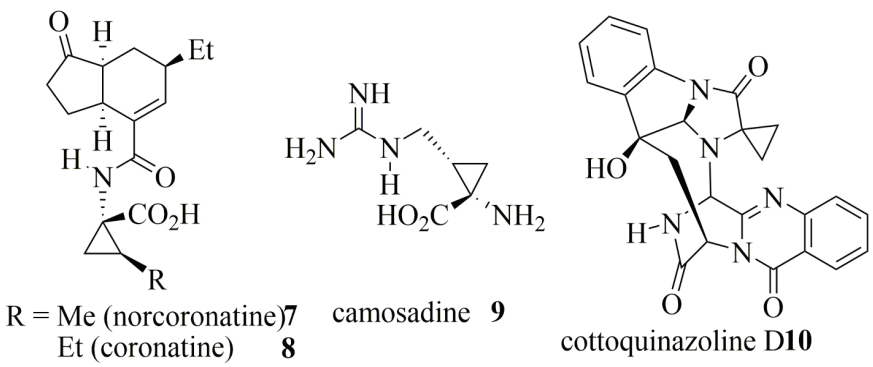


Fig. 2. Natural products containing residue of ACC **1**.

Carnosadine **9**, a guanidino-substituted derivative of ACC **1**, isolated from the red alga *Grateloupia carnosa*, represents an interesting divergence from other ACC-derived natural products like norcoronatine **7** and coronatine **8**. This naturally occurring compound is notable for its structural uniqueness, specifically the incorporation of a guanidine substituent, which introduces a strongly basic center and the potential for different types of molecular interactions compared to the alkyl-substituted cyclopropanes. While its full functional profile is still being elucidated, the presence of a guanidino group suggests its involvement in various biochemical pathways, potentially influencing enzyme activity and physiological regulation in ways distinct from other ACC derivatives. [74, 75].

Cottoquinazoline D **10**, a complex quinazoline alkaloid containing a residue of ACC **1**, belongs to the fumiquinazoline family, a significant class of natural products primarily isolated from marine and fungal sources known for their structural diversity and biological activities. Cottoquinazoline D **10** itself has demonstrated promising antimicrobial, cytotoxic, and enzyme-inhibitory properties, aligning with the broader pharmaceutical interest in fumiquinazolines as a source of bioactive compounds. The presence of the ACC **1** unit within this polycyclic scaffold underscores the importance of this constrained amino acid in the biosynthesis of structurally complex and biologically active natural products [76–78].

1-Aminocyclopropanecarboxylic Acid Derivatives: Essential Pharmacophores for Next-Generation HCV NS3/4A Protease Inhibitors.

Viral infectious diseases pose significant challenges to treatment. Recent high-profile examples include the COVID-19 pandemic and the Ebola virus epidemic in West Africa [79–81]. While the hepatitis C virus (HCV) may not currently dominate alarming headlines, its impact on global health remains significant, causing substantial liver-related morbidity and mortality. The World Health Organization estimates that nearly 170 million individuals worldwide are living with chronic HCV infection, with approximately 3.5 million new cases occurring annually and 350,000 to 500,000 deaths each year attributed to HCV-related liver diseases [82]. A crucial turning point in HCV treatment was the development of the first generation of direct-acting antiviral drugs, including the tailor-made α-amino acid-derived NS3/4A protease inhibitors boceprevir **11** [83] and telaprevir **12** [84] (Figure 2). These drugs marked a significant step forward in combating this persistent viral infection. The first-generation direct-acting antiviral drugs boceprevir **11** and telaprevir **12**, although a significant step forward in their time, were voluntarily withdrawn from the market by Merck and Vertex in 2015. This decision reflected the clinical superiority and improved tolerability of subsequently developed all-oral direct-acting antiviral regimens, which have fundamentally altered the landscape of Hepatitis C treatment.

Boceprevir **11** and telaprevir **12** are all-tailor-made amino acid-based drugs, specifically a tri- and tetrapeptide, respectively. Interestingly, both feature cyclopropane rings, a structural motif that also connects them to the second-generation direct-acting ACC **1** containing antiviral drugs asunaprevir **13** (Fig. 4) [85], simeprevir **14** [86], paritaprevir **15** [87], and vaniprevir **16** [88], all of which received FDA approval for HCV treatment around 2015.

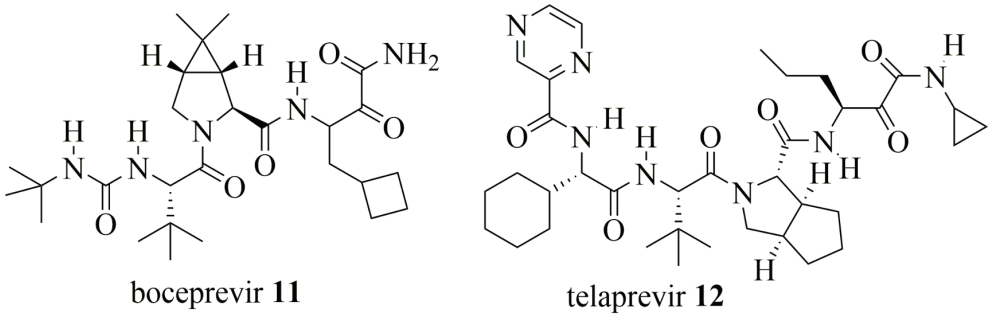


Fig. 3. The first-generation direct-acting antiviral drugs boceprevir **11** and telaprevir **12**.

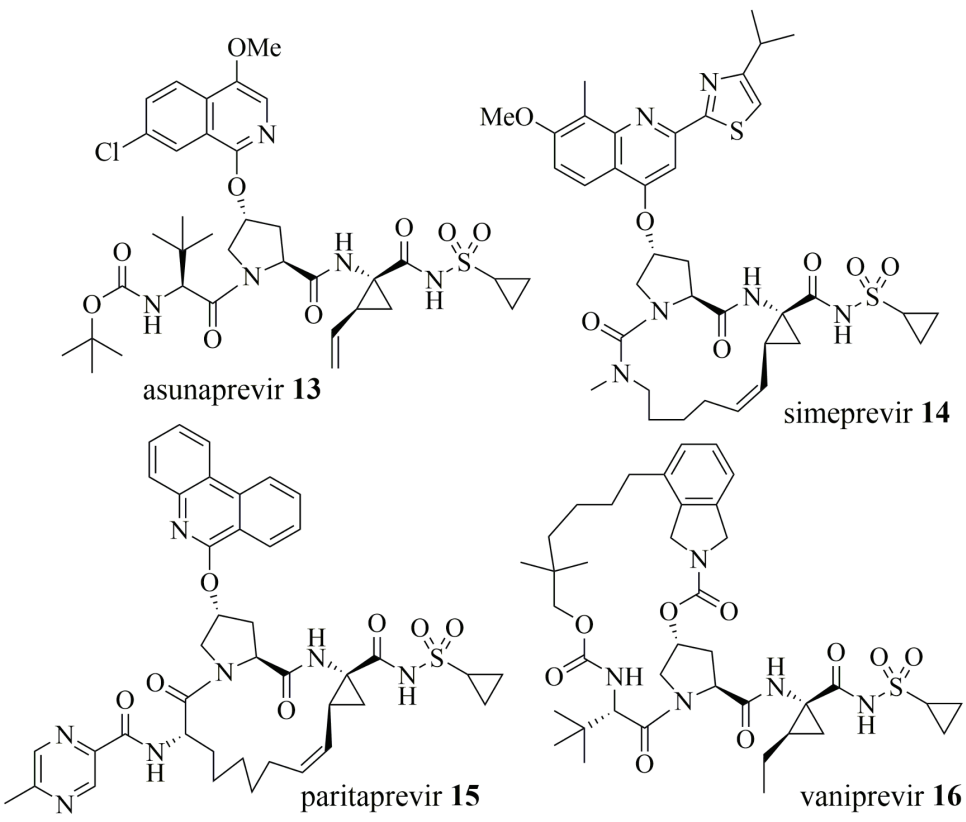


Fig. 4. The second-generation ACC **1** derived antiviral drugs.

While these compounds **13**-**16**, being di- or tripeptides, share some structural similarities with the earlier drugs boceprevir **11** and telaprevir **12**, a key distinguishing feature in their design is the significant conformational constraint imposed by the residue of ACC **1** often integrated within three distinct types of macrocyclic motifs [89]. The rapid and successful development of these four drugs **13**-**16** represents a remarkable achievement in a relatively short timeframe, underscoring the power of rational drug design. However, the full pharmaceutical potential of ACC **1** and its diverse array of derivatives remains largely untapped

and ripe for further exploration. The unique steric and conformational properties imparted by the cyclopropane ring in ACC **1** offer a powerful tool for modulating molecular interactions and pharmacokinetic profiles, suggesting a wealth of opportunities for the design of novel therapeutics beyond HCV treatment.

What is particularly noteworthy is the current development pipeline, featuring numerous novel drug candidates incorporating the ACC **1** moiety. To illustrate the chemical architecture of current-generation HCV treatment drugs, we have selected neceprevir **17** [90], danoprevir **18** [91], glecaprevir **19** [92], and GS-9256 **20** [93]. Chemically, these compounds are peptidomimetics that share a central hydroxyproline core and ACC **1** as key structural elements. Additional steric constraints, enabling more precise biological interactions, are introduced through macrocyclic bridges and bulky aromatic groups. Furthermore, these structures are stereochemically complex, possessing an average of five or more stereogenic centers and existing as single enantiomers [94], highlighting the critical importance of the precise three-dimensional positioning of all functional groups. Notably, these structures also strategically incorporate fluorine [95–97] for fine-tuning their biopharmaceutical properties and metabolic stability, underscoring the significant role of fluorine in modern pharmaceutical design [98–100]. Finally, as exemplified by GS-9256 **20**, the application of phosphorus analogs of carboxylic acids represents a growing trend in drug design [101–103].

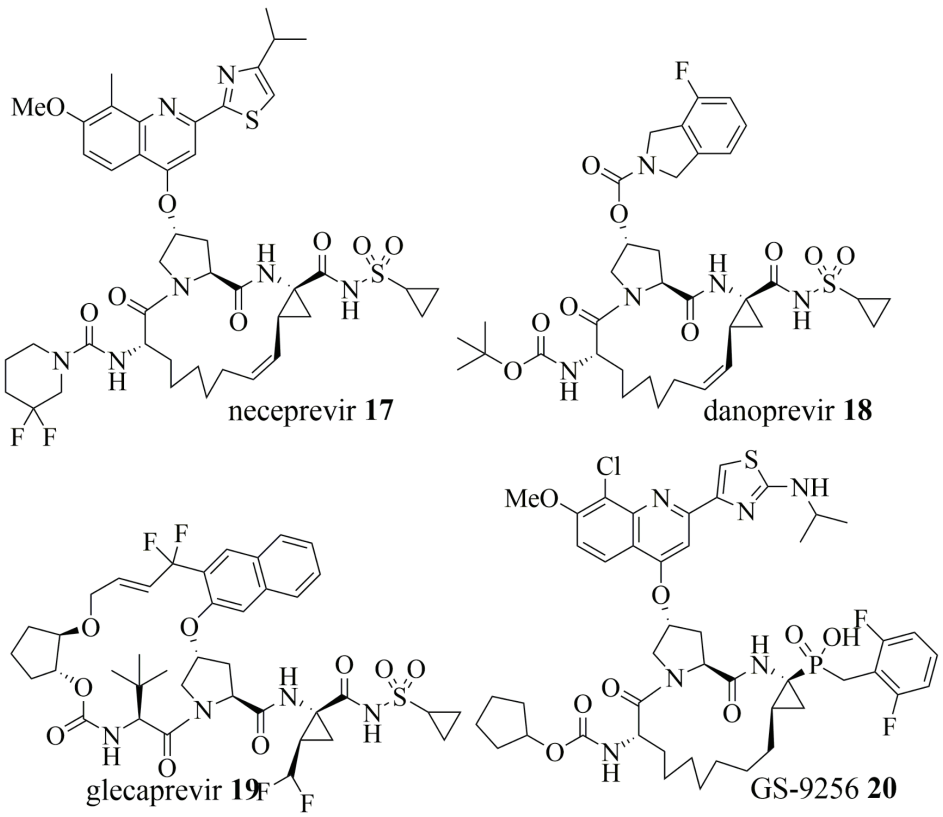
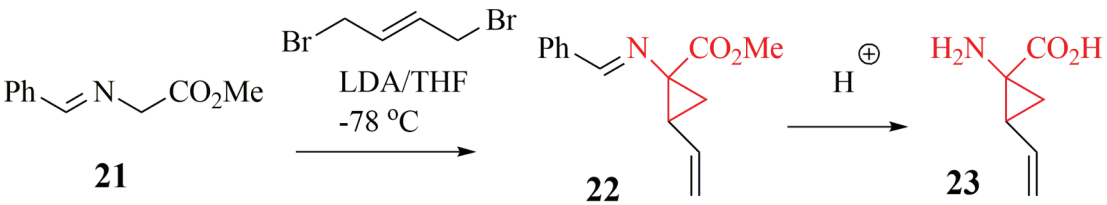


Fig. 5. Recent antiviral drugs incorporating ACC **1** and fluorine substitution.

Given the widespread occurrence of ACC and its derivatives in natural products, coupled with the remarkable success of ACC-based compounds in the design of numerous HCV drugs, it is reasonable to expect that the synthesis of ACC has garnered significant attention. The extensive body of synthetic methodologies will be classified in the subsequent sections based on the mode of ACC skeleton construction.

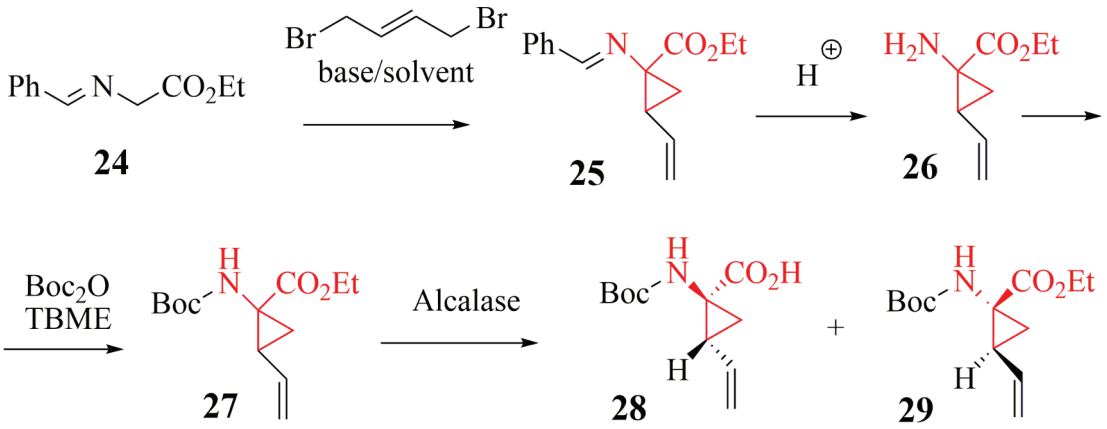
Successive di-alkylation of nucleophilic glycine equivalents

The first synthesis of racemic vinyl-ACC **23** was reported in 1981 by a group of biochemists studying the biological mechanism of ethylene production in plants [104]. The procedure was based on the alkylation of the starting Schiff base **21**, derived from glycine methyl ester and benzaldehyde (Scheme 1). The vinyl-cyclopropane ring was formed in a key step, involving an intermolecular S_N2 alkylation followed by intramolecular S_N2' cyclization of glycine Schiff base **21** with *trans*-1,4-dibromo-2-butene. A notable aspect of this approach is the high stereochemical control: the S_N2–S_N2' dialkylation of glycine derivative **21** proceeded with complete relative stereochemistry, yielding the diastereomerically pure intermediate **22**, which was then converted to the free amino acid **23** via acidic hydrolysis. The reactions were conducted under homogeneous conditions using a strong base (LDA) in THF at low temperature. This S_N2–S_N2' dialkylation sequence proved to be a synthetically general and concise route to the vinyl-ACC skeleton, and has been employed in many subsequent studies.



Scheme 1. Synthesis of vinyl-ACC **23** via S_N2–S_N2' dialkylation of Schiff base **21**.

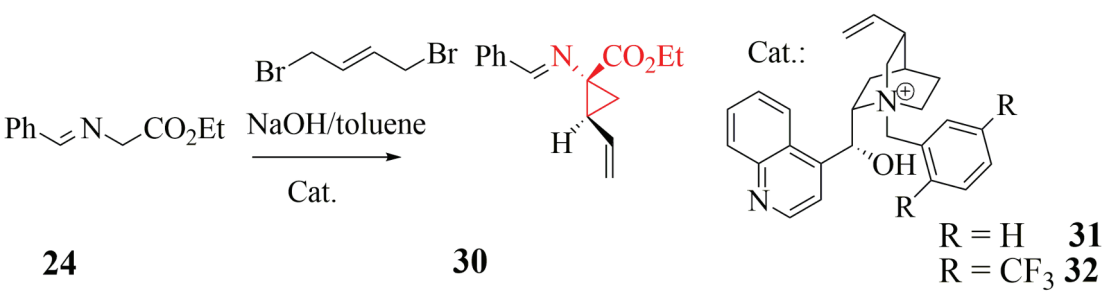
This approach was thoughtfully designed for large-scale synthesis, with careful consideration of the cost structure [105], reaction simplicity, and operational convenience [106–108]. For the construction of the vinyl-ACC framework, the authors selected the straightforward S_N2–S_N2' dialkylation sequence. The reaction of glycine ethyl ester Schiff base **24** (Scheme 2) with *trans*-1,4-dibromo-2-butene was systematically studied using a variety of bases and solvents. It was found that aprotic solvents were essential for high diastereoselectivity. In particular, the reaction conducted in toluene with lithium *tert*-butoxide as a base yielded the desired cyclopropane **25** with virtually complete diastereomeric purity. After Schiff base deprotection and simple purification by several extractions, diastereomerically pure racemic **26** was converted into Boc-protected vinyl-ACC ethyl ester **27** in 65–70% overall yield. Enzymatic resolution of diastereomerically pure ethyl ester **27** using Alcalase proceeded with very high enantioselectivity, producing a mixture of (1*S*,2*R*)-**28**, as a free acid, and (1*R*,2*S*)-**29**, as an ethyl ester.



Scheme 2. Enzymatic approach for preparation of enantiomerically pure derivatives **28** and **29**.

In general, enzymatic resolutions of sterically constrained α-amino acids are challenging [109–111] as most natural enzymes are sterically sensitive and adapted to the typical structure of α-unsubstituted amino acids.

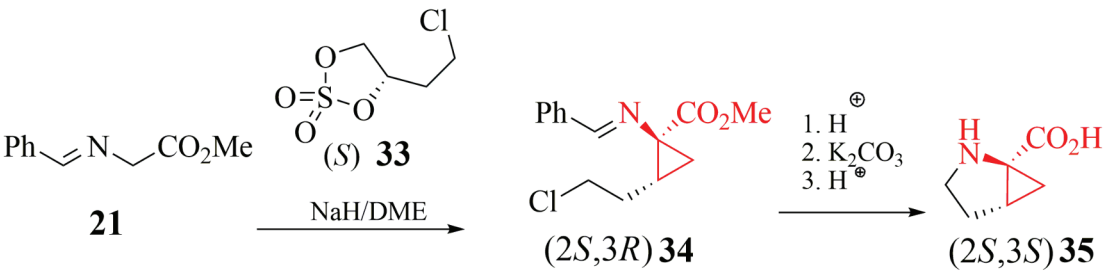
Enantioselective adaptation of the S_N2–S_N2' dialkylation sequence strategy, employing a chiral phase transfer catalyst (Scheme 3) [112, 113]. Extensive efforts to refine the catalyst's structure ultimately led to the breakthrough discovery of the catalyst **32**, with the benzylic moiety substitution proving essential—its unsubstituted benzyl counterpart **31** delivered a mere 2% ee of **30**. With catalyst 32, the synthesis of **30** achieved an impressive 77% enantiomeric excess (ee) and 78% yield, marking a significant advancement. However, meticulous control over reaction conditions was crucial—water content and sodium hydroxide selection played pivotal roles in minimizing undesirable byproducts, particularly ester saponification. Notably, pin-milled NaOH with fine particle size (~30 μm) ensured complete conversion within 24 hours at 0°C, whereas commercial powdered NaOH led to extended reaction times and diminished yields. These findings underscored the profound impact of precise reagent selection and process optimization in achieving superior synthetic outcomes.



Scheme 3. Enantioselective synthesis of vinyl-ACC **30** under PTC conditions.

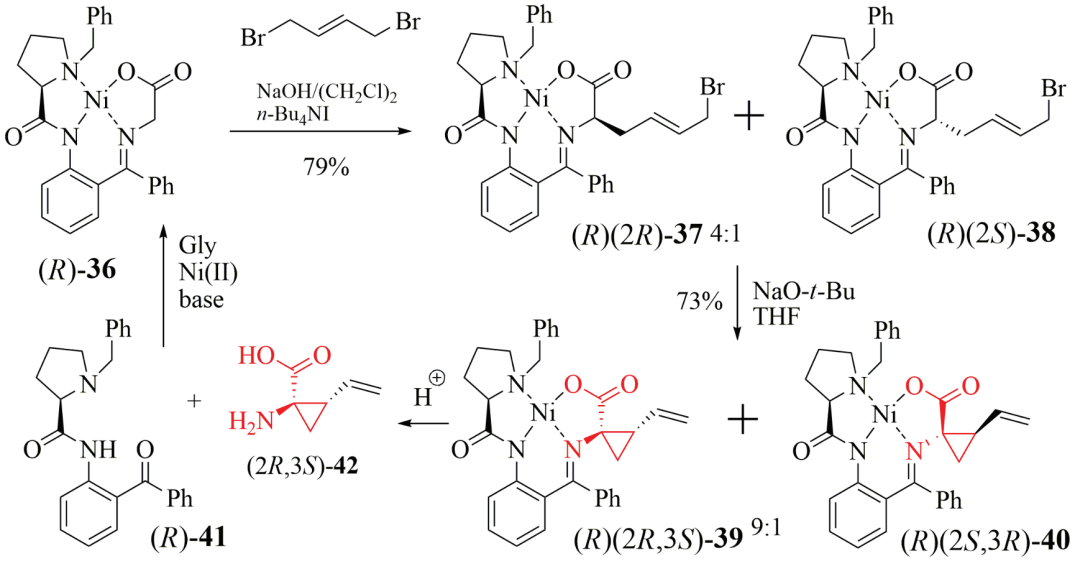
It is important to note that the isolation and purification of product **30** in this study relies on column chromatography procedures, which are known to be associated with the phenomenon of Self-Disproportionation of Enantiomers (SDE)—a widely reported occurrence in chiral amines and amino acid derivatives subjected to achiral column chromatography [114–116]. As a result, unless a dedicated SDE study on compound **30** is conducted, the reported stereochemical outcome [112, 113] should be regarded as tentative.

The elegant chemical transformation of glycine ethyl ester Schiff base **21** with alkylating reagent **33** is illustrated in Scheme 4 [117]. The four-carbon framework of **33** contains three electrophilic sites with distinct reactivity, enabling a stepwise alkylation cascade. The reaction proceeds under operationally convenient conditions, employing NaH as the base. The first two alkylation steps follow a typical S_N2–S_N2' sequence, yielding intermediate **34**. Subsequent neutralization of the reaction medium, followed by re-exposure to basic conditions using K_2CO_3, initiates the third and final alkylation, culminating in the formation of the sterically constrained bicyclic architecture **35**. Most notably, the use of enantiomerically pure (*S*)-**33** efficiently transmits stereochemical information, directing the configuration of two newly formed stereogenic centers. As a result, the process affords the diastereomerically pure intermediate (2*S*,3*R*)-**34**, ultimately leading to the final product (2*S*,3*S*)-**35** with exceptional stereochemical fidelity.



Scheme 4. Asymmetric synthesis of bicyclic ACC derivative **35**.

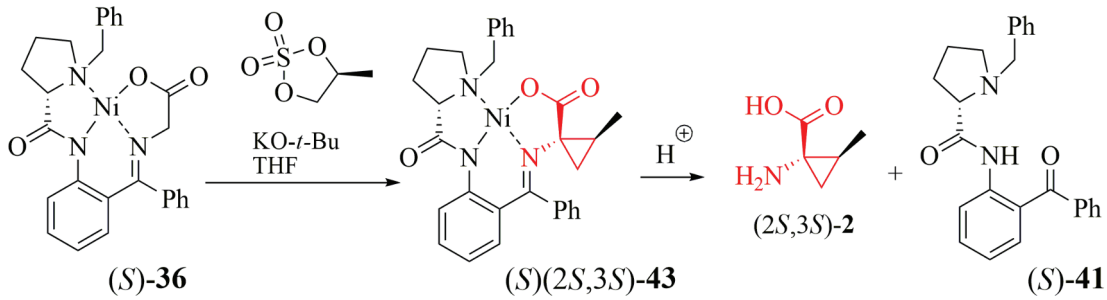
Asymmetric synthesis of α-amino acids via Ni(II) complexes of glycine Schiff bases, such as those of type **36**, represents a well-established and widely used methodology (Scheme 5) [118–121]. Homologation of the glycine moiety within chiral Schiff base **36** can be achieved through various reactions, including aldol [122–125], Michael [126–129], and Mannich [130–132] additions, as well as alkyl halide alkylation [133, 134], including reactions with sterically constrained derivatives [135, 136], dialkylation [137–139], and bisalkylation [140] reactions. Therefore, the application of the Ni(II) complex **36** holds significant potential for the preparation of ACC derivatives. In this context, the Ni(II) complex of Schiff base (*R*)-**36**, readily prepared from glycine, Ni(II) acetate or chloride, and an (*R*)-proline-derived ligand **41** [141, 142], was reacted with *trans*-1,4-dibromo-2-butene under solid-liquid phase-transfer catalysis (PTC) conditions [143, 144], using solid NaOH in the presence of tetrabutylammonium iodide (TBAI). This PTC alkylation yielded a mixture of monoalkylated products **37** and **38** in a 4:1 ratio, with an overall yield of 79% [145, 146].



Scheme 5. Asymmetric synthesis of vinyl-ACC **42** via proline-derived chiral Schiff base **36**.

The relatively low diastereoselectivity at this stage was inconsequential, as both diastereomers **37** and **38** were utilized in the subsequent intramolecular alkylation. The S_N2' alkylation was accomplished by treating the resulting mixture with sodium *tert*-butoxide, affording the target vinylcyclopropanes **39** and **40** in a 9:1 ratio and a 73% yield. Notably, the direct one-pot sequential S_N2–S_N2' dialkylation of **36** under homogeneous conditions in *N,N*-dimethylformamide (DMF) did not produce the desired products **39** and **40**, suggesting that these conditions are too harsh for the reagents and intermediates, which possess multiple reactive centers. Following chromatographic separation, the diastereomerically pure major product **39** was treated with 1 *N* HCl, resulting in the decomplexation of the Ni(II) complex and the formation of chiral ligand **41**, along with the desired vinyl-ACC **42**. The chiral ligand **41** was recycled and used to generate new batches of the starting glycine Schiff base Ni(II) complex **36**. The target vinyl-ACC **42** was isolated using a cation exchange resin.

Chiral glycine Schiff base Ni(II) complex **36** was also employed in the highly diastereoselective synthesis of norcoronamic acid (**2**) (Scheme 6) [147]. A key feature of this reaction is that both starting compounds—the Ni(II) complex of Schiff base **36** and the corresponding ester—are chiral and possess matching (*S*) absolute configurations. This double asymmetric induction leads to complete diastereoselectivity in the formation of the cyclopropane ring. Consequently, the product **43** required no additional purification before being disassembled to yield the target norcoronamic acid (**2**) and chiral ligand **41**. Interestingly, attempts to use the racemic sulfate resulted in a 1:1 ratio of the corresponding diastereomers, indicating no significant kinetic resolution in the alkylating reagent. It should be noted that noticeable kinetic resolution was observed in the alkylation of chiral Schiff base Ni(II) complexes of type **36** with racemic α-alkylbenzyl bromides [49, 148].



Scheme 6. Asymmetric synthesis of norcoronamic acid (**2**) via chiral Schiff base **36**.

The synthetic potential of Ni(II) complexes derived from glycine chiral Schiff bases in the field of asymmetric AA synthesis has driven the development of next-generation derivatives designed for large-scale preparation of tailor-made AAs with enhanced efficiency [149–151]. For example, informed by extensive crystallographic data [152], Ni(II) complex **44** (Fig. 6) was strategically engineered with chlorine atoms to optimize its performance in asymmetric transformations [153, 154]. This complex has demonstrated remarkable efficiency in dynamic kinetic resolution of racemic AAs [155, 156]. Similarly, Ni(II) complex **45**, featuring two elements of chirality, has shown exceptional selectivity in alkylation and aldol addition reactions, benefiting from double asymmetric induction, where central and axial chirality are stereochemically matched [121]. Meanwhile, Ni(II) complex **46** [157, 158] has emerged as the most effective catalyst in processes governed by second-order asymmetric transformation control [159], further expanding the potential of Ni(II)-based systems in complex synthetic applications.

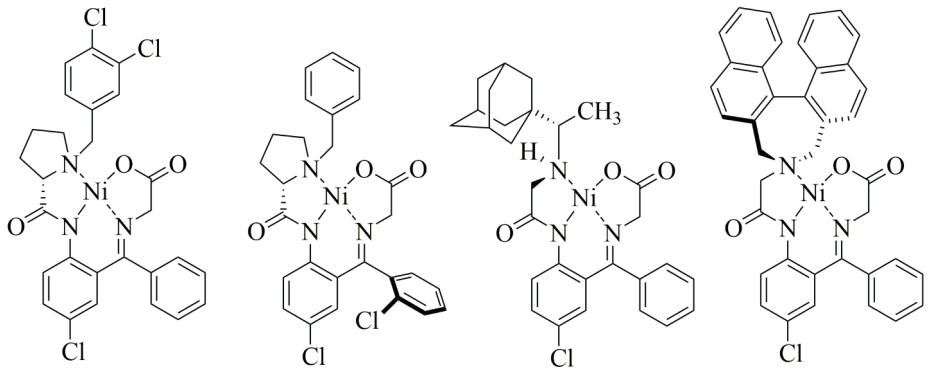


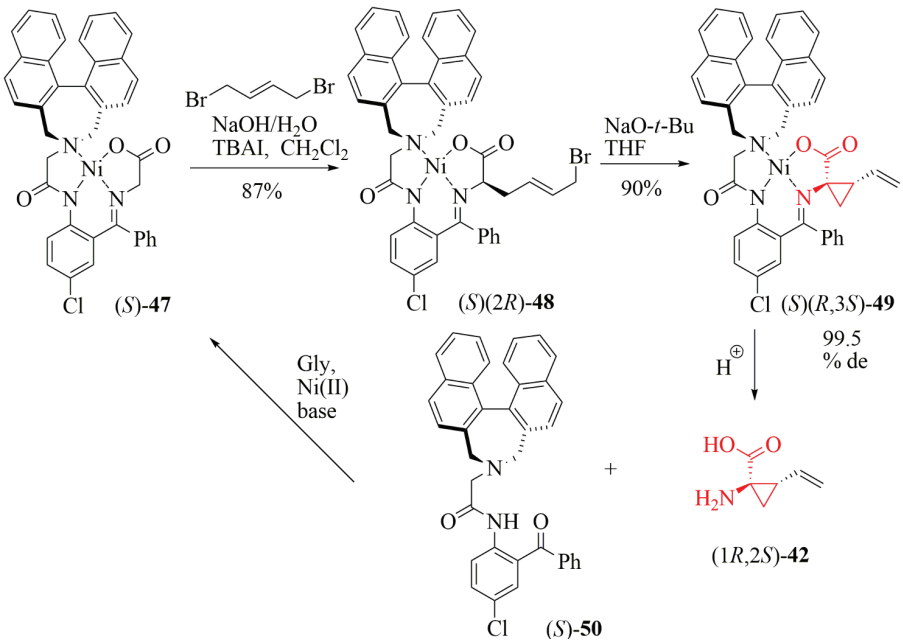
Fig. 6. New generation Ni(II) complexes of chiral nucleophilic glycine equivalents.

Ni(II) complex **47**, derived from C_2-symmetric bis(naphthyl)amine [160–162], holds significant potential for the asymmetric synthesis of AAs. Its application in the synthesis of vinyl-ACC derivatives is illustrated in Scheme 7 [163].

After extensive experimentation, it was determined that the two-step S_N2–S_N2' dialkylation of the glycine moiety in **47** was best carried out using a two-step approach. First, the reaction was performed under phase transfer catalysis (PTC) conditions with the corresponding dibromide, employing 30% aqueous NaOH in the presence of TBAI, yielding product **48** as the major diastereomer (70:30 ratio). Without purification, the diastereomeric mixture was then treated with sodium tert-butoxide, leading to the cyclopropane-cyclized Ni(II) complex **49** with an 83% overall yield and exceptional diastereoselectivity (99.5% de)—highlighting the superior stereocontrolling properties of **47** compared to the proline-derived complex **36**.

Product **49**, without further purification, was subsequently disassembled by treatment with 1*N* HCl, affording free vinyl-ACC **42** and chiral ligand **50**, which were efficiently separated via simple extraction. Vinyl-ACC **42** was further purified using a cation exchange resin.

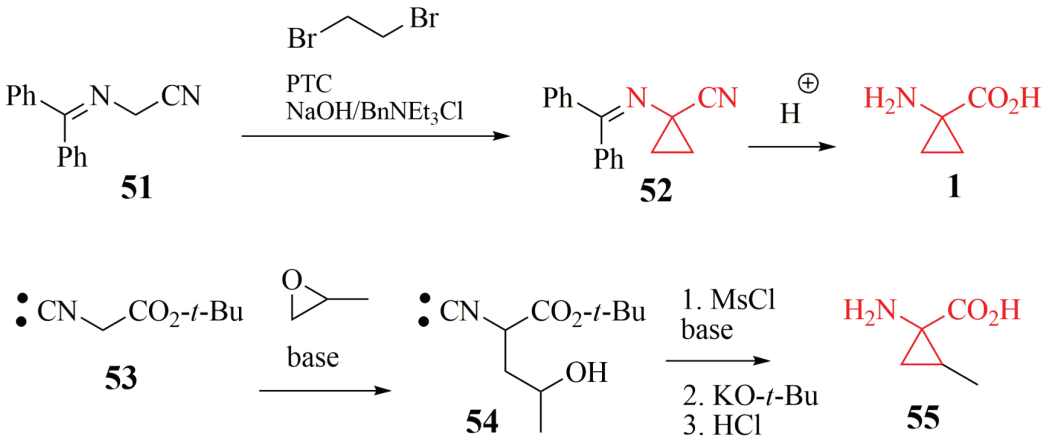
Notably, ligand **50** is highly stable and not prone to racemization under typical organic synthesis conditions, making it virtually indefinitely recyclable and reusable. In this regard, the application of ligand **50** presents a more economical and practical approach—even surpassing the efficiency of enantioselective catalysis.



Scheme 7. Asymmetric synthesis of vinyl ACC **42** via Ni(II) complex of Schiff base derived from axially chiral ligand **50**.

This synthetic sequence was carried out using 33 g of Ni(II) complex **47**, yielding 4.5 g of vinyl-ACC **42**. The process demonstrates a virtually complete stereochemical outcome, a fully recyclable chiral source, and operational simplicity, ensuring convenient and efficient reaction conditions. Moreover, the proven scalability of Ni(II) complex chemistry further supports its potential for broad synthetic applications.

(Diphenylmethylene)aminoacetonitrile **51** represents another type of nucleophilic glycine equivalent, utilized in the synthesis of ACC **1** via a dialkylation sequence. The cyclopropane ring was efficiently formed under PTC conditions using 1,2-dibromoethane as the electrophilic agent, in the presence of sodium hydroxide as a base [164–166]. Subsequent acidic hydrolysis removed the Schiff base and CN protecting groups in **52**, yielding the target compound ACC **1**. Notably, this approach is remarkably straightforward and well-suited for large-scale synthesis.

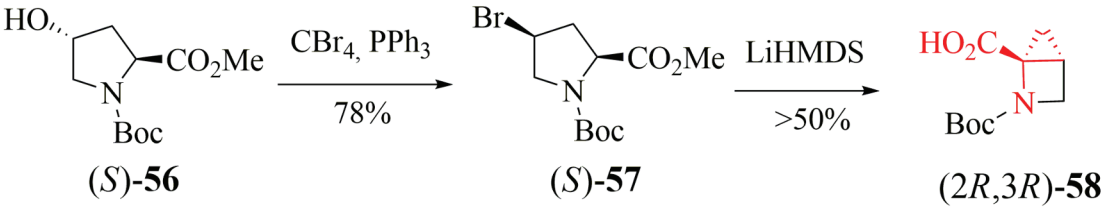


Scheme 8. Preparation of ACC **1** *via* dialkylation of (diphenylmethylene)aminoacetonitrile **5** and synthesis of *allo*-norcoronamic acid **55** via dialkylation of isocyanoacetate **53**

Isocyanoacetates are highly versatile reagents in amino acid synthesis, exhibiting unique reactivity due to their electron-withdrawing isocyanide and ester functional groups. Their ability to serve as nucleophilic glycine equivalents makes them particularly valuable for the tailored construction of amino acids via alkyl halide alkylations and various addition reactions [167–171]. For example, the alkylation of isocyanoacetate **53** with propene oxide proceeds efficiently in the presence of butyl lithium at −78 °C, yielding product **54** with an excellent yield (>90%). Subsequent mesylation of the hydroxyl group in **54** is followed by a second alkylation step that induces cyclopropane ring formation. A final hydrolytic cleavage of the isonitrile and ester protecting groups affords ACC **55** with an overall yield of approximately 50%. Notably, this cyclization protocol strongly favors the stereochemistry of *allo*-norcoronamic acid, with the major diastereomer comprising over 85% of the product [172,173].

An intriguing example of intramolecular alkylation within the proline framework is illustrated in Scheme 9. Naturally occurring and properly protected hydroxyproline **56** was treated with CBr_4/PPh_3, facilitating the stereoselective substitution of the hydroxyl group with a bromine atom. The resulting intermediate **57** was then exposed to harsh reaction conditions, utilizing an excess of a strong base in THF at −78 °C, forcing the formation of an extremely sterically constrained bicyclic system **58**, consisting of four- and three-membered rings. Remarkably, despite significant

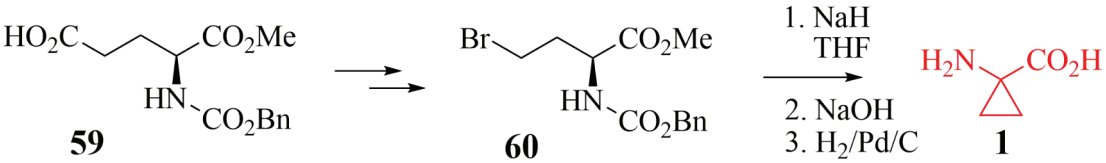
steric strain, the process achieved a respectable yield. Most notably, this cyclization reaction proceeded in a highly stereoselective manner, converting (*S*)-configured hydroxyproline **56** into the (2*R*,3*R*)-bicyclic system **58** with impressive selectivity [174].



(*S*)-**56** (*S*)-**57** (2*R*,3*R*)-**58**

Scheme 9. Preparation of bicyclic ACC **58** from hydroxy proline **56**.

Another example of intramolecular cyclization of amino acid derivatives, resulting in the formation of a cyclopropane ring, is presented in Scheme 10. In this case, the ω-carboxy group in properly protected glutamic acid **59** was substituted with a bromine atom, and the resulting compound **60** underwent intramolecular cyclization. The formation of the three-membered ring was achieved using NaH in THF at –78 °C. It should be noted that the application of two equivalents of NaH was necessary, as one mole of the base was used to ionize the N-H bond. The cyclization proceeded cleanly at the α-carbon, with no products of *N*-alkylation observed. Following cyclization, hydrolysis of the ester group and deprotection of CO_2Bn using hydrogen over a palladium catalyst afforded the target compound, ACC **1** [175–178].

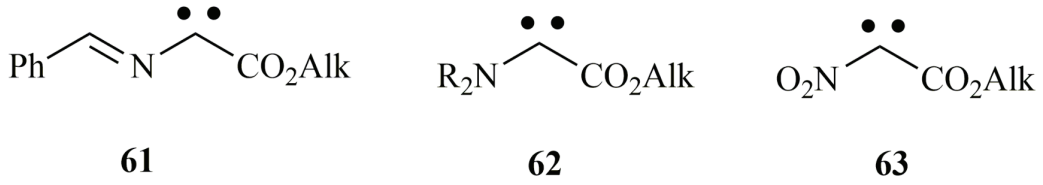


59 **60** **1**

Scheme 10. Preparation of ACC **1** via intramolecular cyclization of glutamic acid derivative **60**.

Alkyl 2-nitroacetates as carbenoid glycine equivalents.

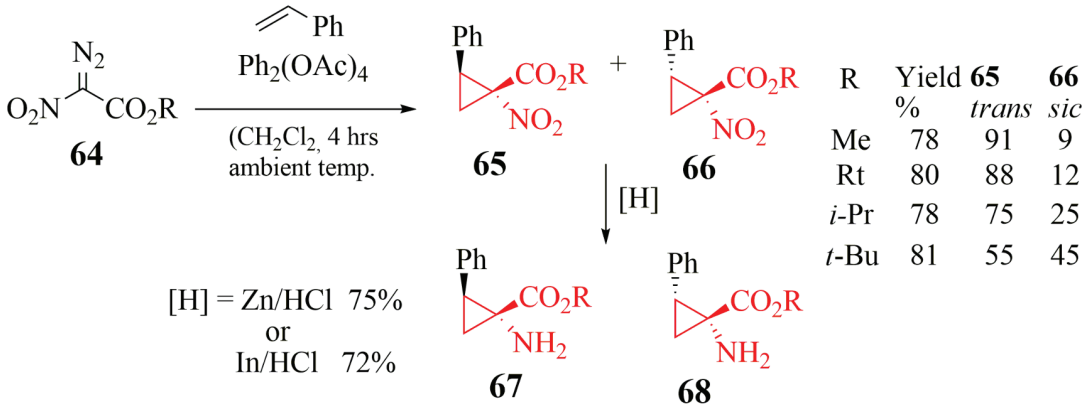
Reactions between carbenes and alkenes represent one of the most widely utilized approaches for constructing cyclopropane rings [179]. In this context, compounds **61** and **62** (Fig. 7), each contributing a single carbon atom to the three-membered ring and carrying amino and carboxyl groups, can be regarded as suitable carbenoid glycine equivalents for the synthesis of tailor-made ACC derivatives. However, the precursors of carbenes **61** and **62**—such as the corresponding diazo compounds—are highly unstable, requiring strongly electron-withdrawing or aromatic substituents directly attached to the carbene carbon. Consequently, nitroacetates **63** may serve as generalized carbenoid glycine equivalents. The synthesis of ACC derivatives via carbenes **63** will thus necessitate an additional step involving chemo-selective reductive transformation of the nitro group into the requisite amino group [180, 181].



61 **62** **63**

Fig. 7. Carbenoid glycine equivalents.

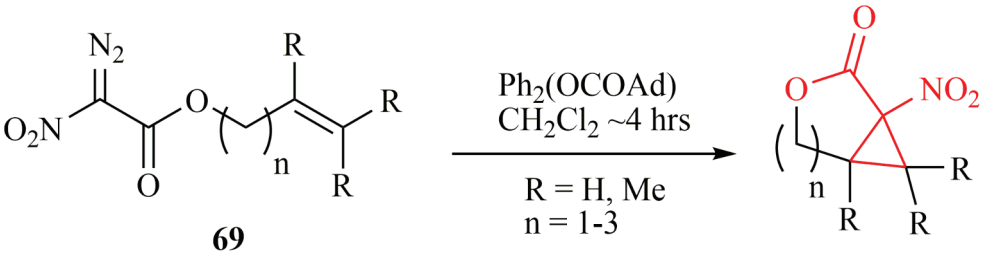
For example, the cyclopropanation reaction has been extensively studied using various diazoesters **64** (Scheme 11). The yields are generally high, while the diastereoselectivity varies significantly and is strongly influenced by the nature of the alkyl ester group [182]. The formation of the *trans* isomer **65** is typically favored over the *cis* diastereomer **66**, though the ratio is clearly dependent on the steric bulk of the ester alkyl group—highest for methyl and lowest for *tert*-butyl. The nitro group was efficiently reduced to the corresponding amino functionality using either zinc or indium in the presence of hydrochloric acid [183]. Notably, this procedure can be carried out on a scale exceeding 250 g without any loss in yield or stereoselectivity.



R	Yield %	65 *trans*	66 *sic*
Me	78	91	9
Rt	80	88	12
i-Pr	78	75	25
t-Bu	81	55	45

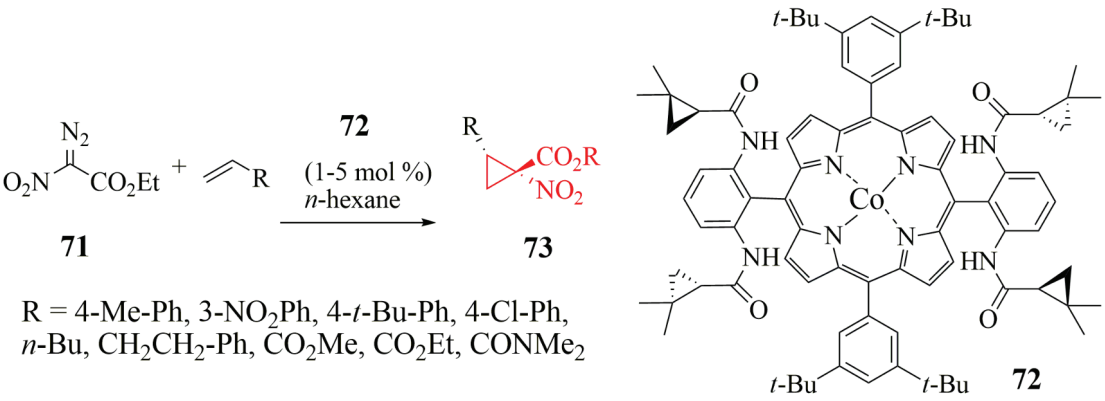
Scheme 11. Rh-catalyzed cyclopropanation of nitrodiazoesters with styrene, followed by the reduction of the nitro group to an amino group.

Intramolecular cyclopropanation of molecules containing both unsaturated and α-nitrodiazoester functionalities has been successfully carried out (Scheme 12) [184]. Rhodium complexes derived from bulky carboxylate ligands, such as rhodium *bis*(1-adamantanecarboxylate) dimer ($Rh_2(OCOAd)_4$), achieved the highest yields of cyclopropanation products. Treatment of nitrodiazoester **69**, bearing a substituted unsaturated moiety, with a catalytic amount (0.5%) of rhodium catalyst prepared with adamantyl carboxylate in dichloromethane at mild heating (40°C) for about four hours resulted in the formation of a bicyclic product **70** with good isolated yields. As expected, higher yields (95%) were observed for products with minimal steric hindrance and ring strain (n = 3, R = H). Notably, in all cases studied, only a single diastereomer containing NO_2 and R in the bridged position was isolated.



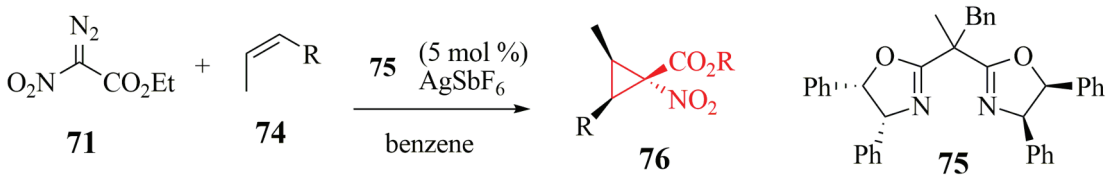
Scheme 12. Rh-catalyzed intramolecular cyclopropanations.

Cyclopropanation via nitrodiazoacetate reactions, as precursors to carbenoid glycine equivalents, can be successfully carried out in a catalytic enantioselective manner. As shown in Scheme 13, the enantioselective cyclopropanation of ethyl α-nitrodiazoacetate **71** with terminal olefins is efficiently catalyzed by the chiral porphyrin-based cobalt(II) complex **72** [186–188]. The reaction proceeds in normal hexane at temperatures ranging from 0 °C to ambient conditions over a 24-hour period. This process enables the enantioselective formation of the corresponding *cis* isomer **73**, wherein the nitro group and R are positioned *cis* relative to each other. While yields and enantioselectivities are generally high, the stereochemical outcomes were not confirmed via SDE tests. Specifically, enantioselectivity data was obtained after product purification by column chromatography, followed by high-vacuum drying—potentially allowing for SDE effects via achiral chromatography [189–191] and sublimation [192–194]. Notably, when R is an aryl substituent, enantioselectivity reaches approximately 90% ee, whereas alkyl and carbonyl derivatives exhibit enantioselectivities in the range of 75–88% ee. Reported yields vary significantly, ranging from 42% to 92%, highlighting the need for a more precise and systematic study of these cyclopropanation reactions.



Scheme 13. Enantioselective chiral Co-complex catalyzed cyclpropanation reactions.

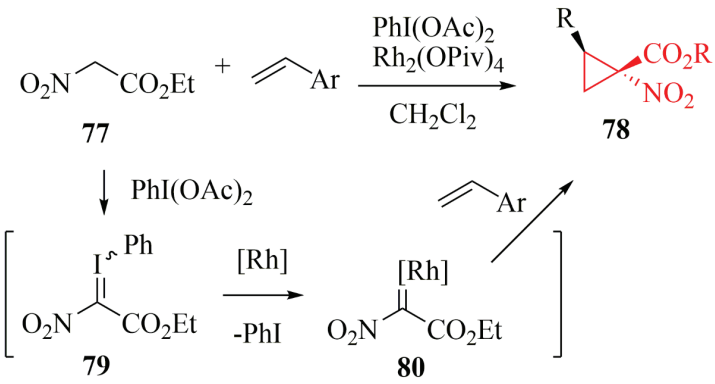
Another example of enantioselective cyclopropanation, specifically involving (*Z*)-1,2-disubstituted olefins and nitrodiazoacetates, is presented in Scheme 14 [195]. The catalyst used in this synthesis, *bis*-oxazoline **75**, features two distinct substituents (Me and Bn) on the carbon bridging the two moieties and has been demonstrated as a preferred catalyst for enantioselective cyclopropanation of disubstituted olefins with diazoesters [196]. Treatment of (*Z*)-olefins **74** and ethyl nitrodiazoacetate **71** with copper complexes of *bis*-oxazoline **75** resulted in the formation of products **76**, with moderate yields and exhibiting excellent diastereoselectivity (>99:1) and enantioselectivity. Medium-range chemical yields combined with high enantioselectivity often indicate the manifestation of SDE effects [197–199]. This method is quite versatile, as the substituent R can be either an aryl group or an olefinic residue and can be further extended to cyclic alkenes. The only notable limitation of this approach is the requirement for the corresponding (*Z*)-olefins.



R	Ph	4-Br-Ph	4-Me-PhPh	b-styryl
yield (%)	56	59	59	65
ee (%)	95	97	97	85

Scheme 14. Chiral Cu-complex catalyzed enantioselective cyclopropanation using nitrodiazoacetates and (*Z*)-1,2-disubstituted olefins.

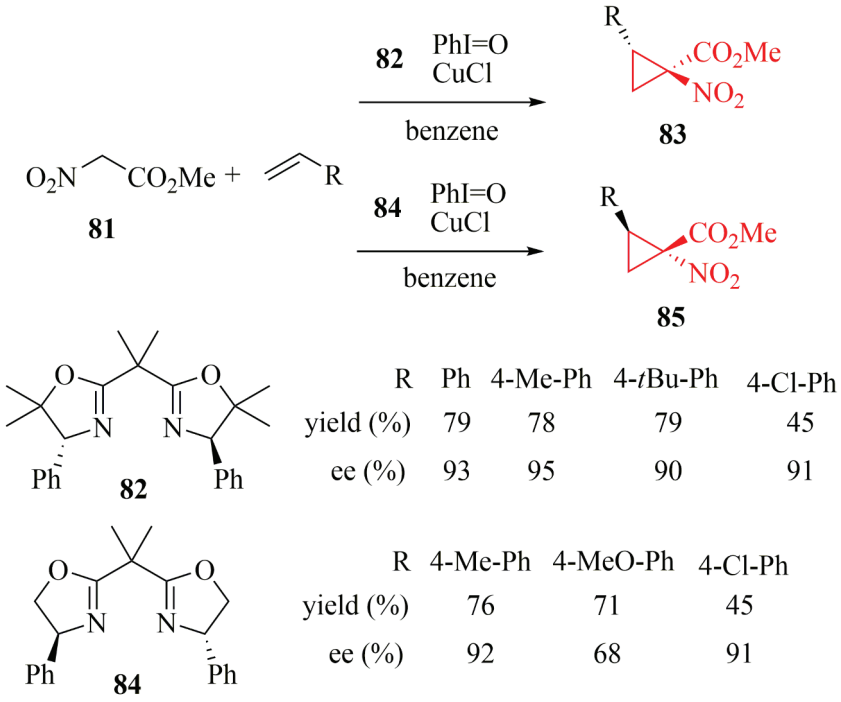
As noted above (*vide supra*), diazo compounds rapidly decompose under standard conditions in the absence of stabilizing electron-withdrawing substituents [200]. As discussed in this text, nitrodiazoacetates serve as excellent reagents for various cyclopropanation reactions. The search for alternative approaches led to the discovery of a method utilizing the corresponding phenyliodonium derivatives [201], which are formed in situ from nitroesters and phenyliodonium acetate [202–204]. This approach exhibits reactivity remarkably similar to Rh-catalyzed cyclopropanation with nitrodiazoacetates, suggesting the intermediate formation of identical metal–carbene species. As illustrated in Scheme 15, ethyl nitroacetate **77** and an excess (5 eq.) of olefin are treated with $PhI(OAc)_2$ (1.1 eq.) and $Rh_2(Piv)_4$ (0.5 eq.) in dichloromethane at ambient temperature, yielding cyclopropanation products **78** with good yields (>80%). These reactions are highly robust and can be performed in near-open-air conditions, underscoring the practicality of this approach. The Ar group can be either a substituted phenyl or a naphthyl moiety, and the methodology extends to *cis*-disubstituted and cyclic olefins, further enhancing its versatility and synthetic value. It is proposed that the reaction proceeds via *in situ* formation of phenyliodonium derivatives **79**, followed by the generation of ruthenium–carbene species **80**.



Scheme 15. Rh-Catalyzed approach for cyclopropanation reaction of nitroacetates and olefines via phenyliodonium derivatives.

The enantioselective catalytic version of this reaction can be achieved using chiral bisoxazoline ligands in combination with copper(I) as the metal catalyst. As illustrated in Scheme 16 [205–207], methyl nitroacetate **81** reacts with an excess (5 eq.) of terminal olefin in the presence of PhI=O (1.1 eq.), $AgSbF_6$ (2.4 mol%), Na_2CO_3 (2.3 eq.), CuCl (2 mol%), and either chiral bisoxazoline **82** or **84**, leading to the formation of cyclopropanation products **83** or **85**, respectively. The reactions are carried out in benzene at ambient temperature for approximately two hours. The reported chemical yields and stereochemical outcomes are generally favorable. The substituent R on the olefin counterpart can be a mono-substituted phenyl or naphthyl ring, or a vinyl group. Unfortunately, SDE tests were not conducted [208–210], and the enantiomeric purity values were obtained only after product isolation, purification via column chromatography, and subsequent drying under high vacuum. Interestingly, the variability in the reported enantioselectivity is difficult to rationalize based on differences in the electronic or steric properties of substituents such as Me, MeO, Cl, or even *t*-Bu groups situated in the remote para-position of the phenyl ring, far from the reaction center. However, these substituents do contribute to variations in the physicochemical properties of the products, affecting their SDE profiles under achiral chromatography conditions and their volatility (sublimation) [211–213].

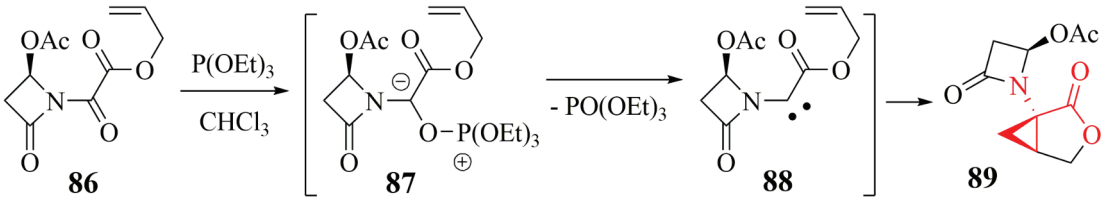
An alternative approach for generating an in situ carbenoid glycine equivalent is presented in Scheme 17. In this method, the oxalic acid-derived compound **86**, which contains an activated carbonyl group, reacts with $P(OEt)_3$ in chloroform under reflux conditions, yielding cyclopropanation product **89** with moderate efficiency and reasonably good diastereoselectivity governed by the stereogenic center of the starting azetidinone **86** [214]. The reaction proceeds via interaction between the amide carbonyl of **86** and $P(OEt)_3$, leading to the formation of betaine intermediate **87**. This intermediate stabilizes through the elimination of $PO(OEt)_3$, generating free carbene **88**, which subsequently undergoes intramolecular cyclopropanation by reacting with terminal olefin residues. The resulting diastereomeric mixture of products can be separated via column chromatography, affording the major diastereomer with a yield of 42%. Despite the relatively low-to-moderate yields, this methodology has been employed for the synthesis of various carbacepham analogs [215].



R	Ph	4-Me-Ph	4-*t*Bu-Ph	4-Cl-Ph
yield (%)	79	78	79	45
ee (%)	93	95	90	91

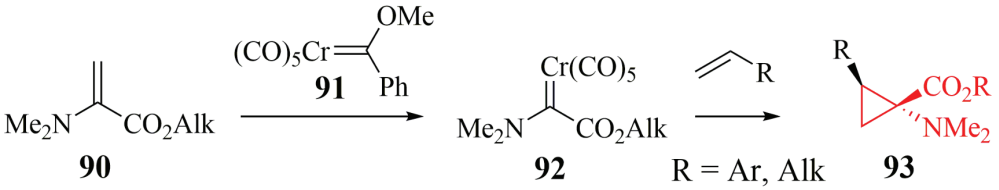
R	4-Me-Ph	4-MeO-Ph	4-Cl-Ph
yield (%)	76	71	45
ee (%)	92	68	91

Scheme 16. Cu-Catalyzed enantioselective catalytic cyclopropanation of nitroacetates and olefines via phenyliodonium derivatives.



Scheme 17. Cyclopropanation reaction via in situ generation of carbenoid glycine equivalent using $P(OEt)_3$.

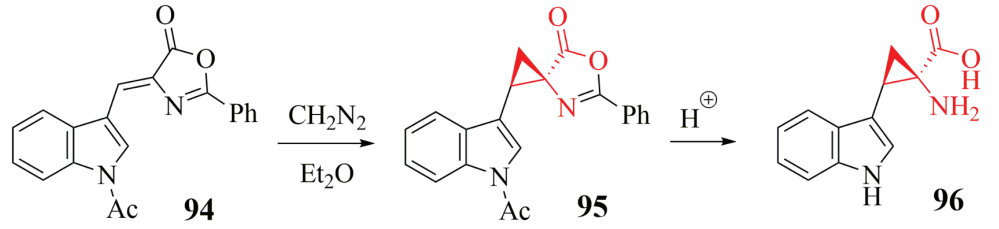
Fischer dialkylaminocarbenes are known to react with olefins to form cyclopropane rings [216]. The application of these reagents as carbenoid glycine equivalents for the synthesis of ACC derivatives is illustrated in Scheme 18 [217]. First, the Fischer dialkylaminocarbene complex **92** is prepared from alkyl 2-(dimethylamino)acrylate, a dehydroalanine derivative **90**, and reagent **91**. Next, the Fischer complex **92** is treated with an excess (4 eq.) of terminal olefin in refluxing toluene, yielding cyclopropane product **93** with variable efficiency (40–70%) but consistently high diastereoselectivity (~95/5). However, the primary limitation of this approach is that it only allows for the preparation of ACC derivatives featuring a dimethylamino group.



Scheme 18. Application of Fisher dialkylaminocarbene complex in cyclopropanation reactions with olefines.

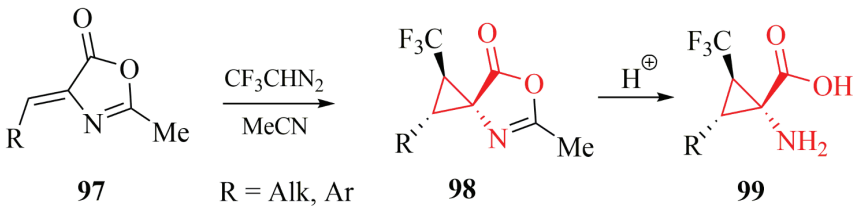
Cyclopropanation of dehydroamino acids.

As discussed in Scheme 18, dehydroalanine derivatives can be transformed into corresponding carbenoid glycine equivalents, contributing one carbon atom in cyclopropanation reactions with alkenes. This strategy can also be reversed, allowing dehydroalanine to act as an olefin, contributing two carbon atoms in reactions with carbenes [218–220]. A simple example of this alternative approach is the reaction shown in Scheme 19, where properly protected (*Z*)-dehydrotryptophan **94** reacts with diazomethane to yield the spiro cyclopropanation product **95** as a single diastereomer, albeit with a relatively low yield (34%). The reaction proceeds overnight at ambient temperature in diethyl ether. The use of (*E*)-dehydrotryptophan also affords the corresponding diastereomer of **95** with excellent diastereoselectivity. Cycloaddition product **95** can be conventionally converted into free amino acid **96** via acidic hydrolysis [221]. Notably, tailor-made tryptophan derivatives are particularly useful for studying peptide folding and peptide–peptide interactions [222–224].



Scheme 19. Cyclopropanation of dehydrotryptophane with diazomethane.

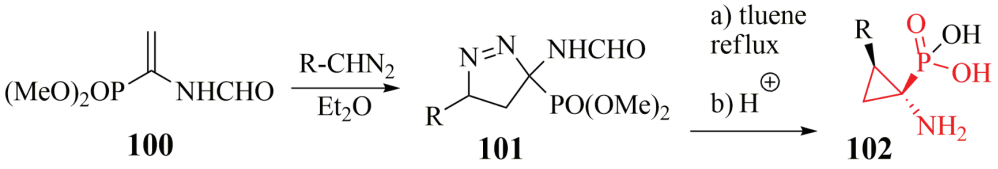
This method can be extended to the use of substituted diazomethanes for the synthesis of ACC derivatives featuring multiple substituents on the cyclopropane ring. One noteworthy example is illustrated in Scheme 20 [225]. In this approach, trifluoromethyldiazomethane reacts with a series of dehydroamino acids **97**, enabling the preparation of various tailor-made β-amino acids **99** constrained by a trifluoromethylcyclopropane moiety [226]. The reactions of dehydroamino acids **97** with 2,2,2-trifluorodiazoethane are conducted in acetonitrile at 80 °C over two days, yielding cyclopropanated products **98** with efficiencies ranging from 47% to 87% and excellent diastereoselectivity (>95/5). The substituent R on the cyclopropane ring can be either an alkyl or aryl group, highlighting the versatility of this approach. Free amino acids **99** are obtained from products **98** via simple conventional hydrolysis.



Scheme 20. Cyclopropanation of dehydroamino acids with 2,2,2-trifluorodiazoethane.

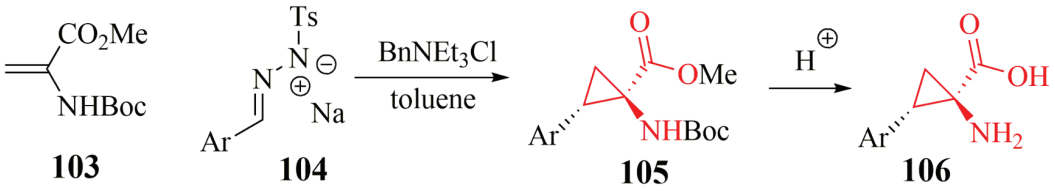
Mechanistically, the reactions of dehydroamino acids with diazomethane derivatives proceed via a [3+2] cycloaddition, resulting in 1-pyrazoline intermediates. The subsequent ring contraction is facilitated by electron-withdrawing groups and, in some cases, requires heating of the reaction mixture [227,228].

For example, the cyclopropanation of the phosphorus analog of dehydroalanine **100** with substituted diazomethanes leads to the formation of unusually stable pyrazoline intermediates **101**, which are reported as solid compounds that can be stored at low temperatures (5 °C) for months without signs of decomposition [229]. However, upon heating in refluxing toluene, compounds **101** undergo the expected ring contraction, ultimately yielding the target aminocyclopropanephosphonic acids **102** after subsequent hydrolysis. This approach is broadly applicable, as the substituent R on the starting diazomethane can be either an alkyl or aryl group. The yields range from 63% to 90%, with excellent diastereoselectivity (>99/1) for aryl derivatives but low (~55/45) for aliphatic ones. The synthesis of tailor-made aminophosphonic acids has attracted significant attention due to their diverse applications in medicinal chemistry, enzyme inhibition, and peptide engineering [230–233].



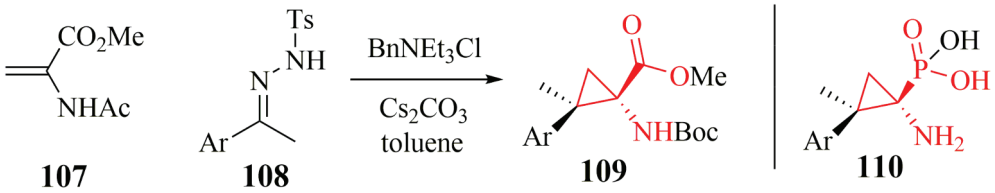
Scheme 21. Synthesis of aminocyclopropanephosphonic acids.

While diazo compounds are highly effective reagents for cyclopropanation reactions, their preparation and handling present inherent challenges. This has driven the need for safer and more efficient alternatives, leading scientists to develop new reagents. One such discovery is tosylhydrazones, which have proven particularly successful in cycloaddition reactions with dehydroamino acids [234]. In this approach, properly protected dehydroalanine **103** (Scheme 22) reacts with metalated tosylhydrazone **104** in the presence of a catalytic amount of a phase-transfer catalyst [235], yielding cyclopropane **105** with high diastereoselectivity. The major stereoisomer features aryl and amine groups positioned *trans* to each other. The reaction is conducted in toluene at 40 °C for 60 hours with 5 mol% of $BnNEt_3Cl$ as the phase-transfer catalyst, producing 105 with yields ranging from 50% to 72%. The target ACC 106 is obtained via simple hydrolysis of the cyclization products **105**.



Scheme 22. Cyclopropanation of dehydroamino acids using diazo compounds generated from metalated tosylhydrazone.

This approach, initially utilizing metalated tosylhydrazones as precursors to diazo compounds, was modified to incorporate non-metalated tosylhydrazones derived from ketones, as illustrated in Scheme 23. In these reactions, protected dehydroalanine derivatives **107** are treated with aromatic ketone-derived tosylhydrazones **108** in the presence of 20 mol% of a phase-transfer catalyst in toluene. A key distinction from previous conditions is the requirement for a strong base, Cs_2CO_3 (2 eq.), and an elevated reaction temperature (90 °C). The resulting cyclopropanation products **109** are obtained with good yields (~80%) and high stereoselectivity (~85/15) [236]. Given the strong interest in synthesizing phosphorus analogs of tailor-made amino acids [237–239], this approach was further applied to the preparation of phosphonate derivatives **110** using 2-aminophosphonates **100** (Scheme 21) and ketone-derived tosylhydrazones **108**. The corresponding phosphonates 110 were isolated with similar yields but of significantly lower diastereomeric purity 52/48.



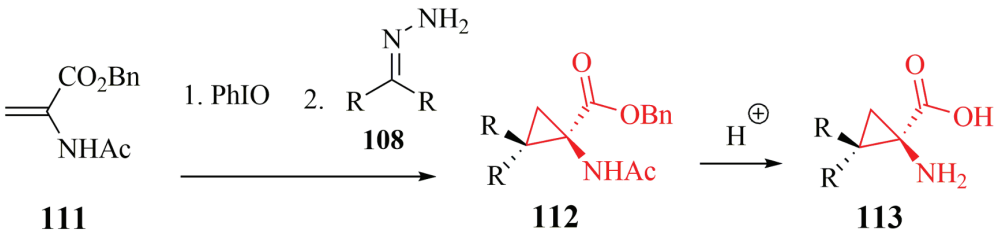
Scheme 23. Cyclopropanation reactions using non-metalated ketone-derived tosylhydrazones.

This methodology, cyclopropanation of dehydroamino acids using in situ generated diazo compounds from tosylhydrazones can be applied for catalytic enantioselective synthesis of ACC derivatives. For example, application of porphyrin-based Co(II) catalyst type of **72** (Scheme 13) [240]. The reported stereochemical outcome is rather variable with diastereoselectivity in the range of 70/30 and enantioselectivity being even more disperse between 40 and 90% most likely as a result of the SDE [241–243].

The application of nonactivated hydrazones for the cyclopropanation of dehydroamino acids is illustrated in Scheme 24 [244]. In this method, hydrazone **108** is added dropwise to a solution of PhIO at ambient temperature, generating the corresponding diazo compound in situ. This reactive intermediate subsequently undergoes cyclopropanation with protected dehydroalanine **111**, yielding ACC derivatives **112** in nearly quantitative amounts.

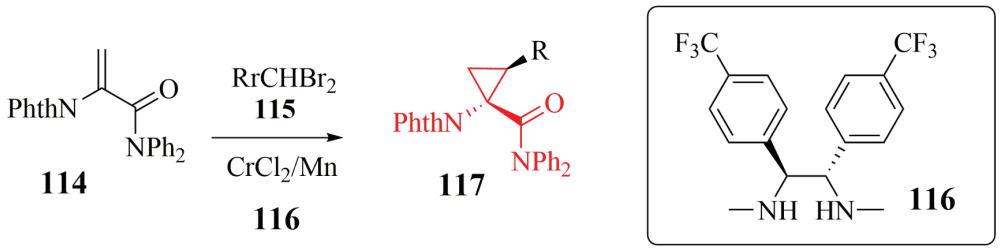
For unsymmetrical hydrazones **108**, the diastereoselectivity of product **112** formation is

moderate, with a ratio ranging between 4:1 and 5:1. Nonetheless, this approach is entirely metal-free, offering remarkable safety and enhancing its synthetic value as a viable alternative to metal-mediated methodologies.



Scheme 24. Cyclopropanation of dehydroamino acid derivatives using diazoalkanes generated in situ from nonactivated hydrazones.

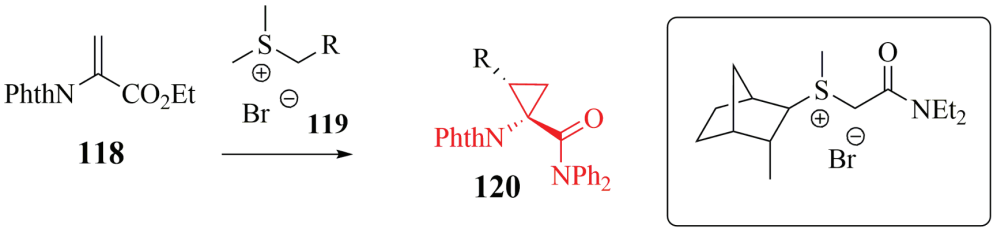
1,1-Dihaloalkanes are well-established as one-carbon unit donors in the cyclopropanation with dehydroamino acids mediated by chromium salts [245, 246]. The reactions of dehydroamino acid derivatives **114**, illustrated in Scheme 25, are typically carried out in ether using 10 mol% Cr(II) salts and 1.5 eq. Mn, maintained at 0 to -10 °C for 24 hours. To induce enantioselectivity, chiral diamine ligands **116** capable of metal chelation are employed. The substituent R can be a *para*-substituted phenyl, naphthyl, or alkyl group. When comparing dichloroalkanes with dibromo derivatives **115**, the former exhibit slower reaction rates but yield products **117** with high efficiency (~90%). Diastereoselectivity strongly favors the formation of products **117** with R and amino groups positioned *cis* to each other, achieving excellent selectivity (>20/1) in most reported cases [247]. The enantioselectivity of these reactions varies, ranging from 73% to 94% ee. However, the SDE tests [248–250] have not been conducted to validate the reported stereochemical data.



Scheme 25. Catalytic enantioselective cyclopropanation of dehydroalanine derivatives with 1,1-dihaloalkanes.

Substituted sulfonium ylides can also serve as effective one-carbon unit donors in the cyclopropanation of dehydroamino acids. As illustrated in Scheme 26, dehydroalanine derivative **118** undergoes reaction with ylides **119** in a highly polar solvent such as acetonitrile or DMF [251]. To generate the reactive species from carbonyl-stabilized ylides **119**, potassium carbonate has been found to provide excellent yields (>90%) and diastereoselectivity (>99/1)

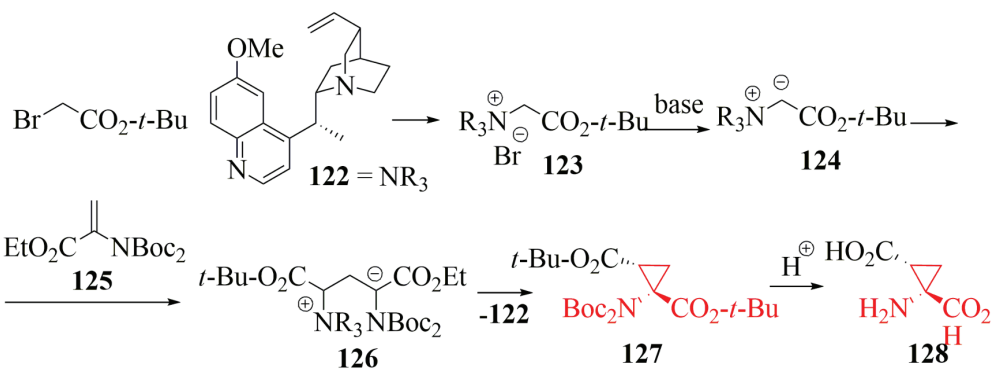
for cyclopropanation products **120**. For ylides **119** semi-stabilized by aromatic groups, cesium carbonate proved more effective, yielding products with a stereochemical outcome similar to that of carbonyl-stabilized ylides **119**. In contrast, ylides **119** stabilized by alkene groups require *t*BuOK as a base, resulting in lower yields (79%) and compromised diastereoselectivity (9.3/1). The reaction can also be conducted using chiral sulfonium ylide **121** in acetonitrile with *t*BuOK, providing access to scalemic products **120** with high diastereoselectivity (up to 90%) and yields (80%).



R = $CONEt_2$, CO_2Et, COPh; Ph, 4-NO_2-Ph, 4Me-Ph, CH=CH-$SiMe_3$

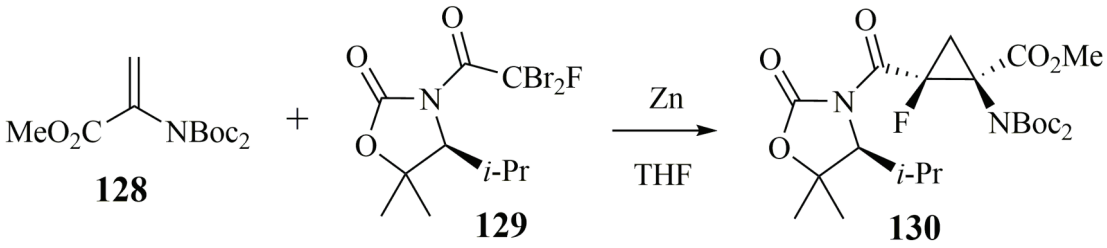
Scheme 26. Application of stabilized sulfonium ylides for cyclopropanation of dehydroalanine derivatives.

An interesting example of the use of bromoacetates as one-carbon unit donors in the cyclopropanation of dehydroamino acids is illustrated in Scheme 27 [252, 253]. The process begins with the quaternization of the tertiary nitrogen in chiral amine **122** via reaction with the corresponding bromoacetate. The resulting quaternary salt **123** is then treated with Cs_2CO_3 to remove hydrogen bromide, generating ylide **124**, which subsequently engages in a Michael addition-type reaction with dehydroalanine **125** to form the stabilized intermediate **126**. The ensuing cyclization of intermediate **126** yields the amino diester **127**, while regenerating chiral amine **122**, allowing it to re-enter the reaction cycle. Tertiary amine is employed in amounts ranging from 1 to 20 mol%. The reactions are conducted in acetonitrile at 80 °C for 24 hours. The chemical yields and enantioselectivity of this cyclopropanation exceed 90%; however, the SDE tests were not performed [254].



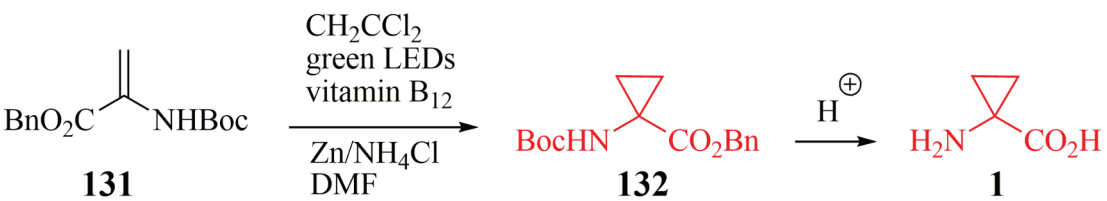
Scheme 27. Application of bromoacetates as one-carbon unit donors in the cyclopropanation of dehydroalanine.

Another method for the asymmetric synthesis of fluorinated ACC is illustrated in Scheme 28 [255]. This approach is based on the Reformatsky reaction of fluorodibromoacetate **129** with properly protected dehydroalanine **128**. The reaction is conducted in THF at -20 °C, yielding ACC derivative **130**, with the fluorine atom positioned *beta* to the amino group. The process begins with the formation of the Reformatsky reagent [256], where one of the bromine atoms in **129** is substituted with Zn, stabilizing it as an enolate. This intermediate then undergoes Michael-type addition to dehydroalanine **128**, followed by cyclization, which involves substitution of the second bromine atom. Chiral oxazolidinones are preferred chiral auxiliaries in asymmetric synthesis, known for providing exceptional stereocontrol in Michael addition reactions [257–259]. As a result, the diastereoselectivity of this addition–cyclization sequence is excellent, exceeding 9:1, with diastereomers readily separable by column chromatography.



Scheme 28. Synthesis of ACC derivatives via Reformatsky-Michael-cyclization sequence.

Finally, an example of photocatalyzed cyclopropanation is illustrated in Scheme 29. This photocatalyzed radical addition–ring-closing sequence of alkyl halide-derived radicals provides a general method for synthesizing functionalized cyclopropanes [260–262]. To generate the corresponding radical from dichloromethane, the reaction is performed in DMF under green LED light (525 nm), with zinc (3 eq.) as the reducing agent, NH_4Cl (1 eq.), and vitamin B_{12} as the photocatalyst. Under these conditions, the dehydroalanine derivative **131** undergoes clean cyclopropanation, yielding product **132** with 92% efficiency. Subsequent acidic hydrolysis of **132** affords the target ACC **1** [263].



Scheme 29. Photocatalyzed cyclopropanation of dehydroalanine with dichloromethane.

CONCLUSIONS. The synthesis of α-aminocyclopropane carboxylic acids (ACC) has evolved into a well-established and sophisticated field. The extensive body of research offers a diverse range of methodologies, providing multiple approaches for tailoring ACC derivatives to meet specific physicochemical, reactivity, and functional versatility requirements. While some of the methods reviewed here hold historical significance, others represent groundbreaking advancements in modern synthetic strategies developed over the past decade. Despite this progress, certain ACC derivatives still pose considerable synthetic challenges. Notably, ACC variants with multiple substitutions on the cyclopropane ring remain underexplored in existing literature. The strategies discussed in this work center around the amino acid core and methods for constructing the cyclopropane ring around it. The key pathways for increasing structural complexity include: dialkylation of nucleophilic glycine equivalents, cyclopropanation of carbenoid glycine equivalents, and addition reactions to dehydroamino acids. These routes comprehensively cover all documented methodologies and are relatively balanced in their representation across published studies.

ACC derivatives are an exceptional subclass of tailor-made amino acids, seamlessly integrating the unique electronic and steric properties of their highly constrained cyclopropane ring. Beyond their presence in biologically significant natural compounds, their role in drug design continues to expand, solidifying their importance in medicinal chemistry. Given that pharmaceutical applications demand enantiomerically pure derivatives, asymmetric synthesis remains a central focus in this field. Several promising methodologies—such as chiral auxiliary-assisted asymmetric synthesis and catalytic enantioselective approaches—offer operational convenience and high stereochemical fidelity, making them viable for large-scale preparation of enantiomerically pure ACC derivatives. However, one aspect that remains insufficiently explored is the self-disproportionation of enantiomers (SDE) in ACC compounds. Based on comparisons with other amino acids, ACC derivatives are expected to exhibit a significant degree of SDE, particularly under achiral chromatography conditions. As a result, integrating simulated moving bed (SMB) chromatography with SDE principles represents the most practical solution for obtaining enantiomerically pure compounds [94, 264]. Furthermore, given the regulatory importance of chiral drug characterization, investigating the SDE behavior of biologically active compounds [249, 265–267] is essential for meeting US FDA requirements for chiral drug submissions [268–270]. Since sterically constrained amino acids serve as fundamental building blocks in biological, medicinal, and pharmaceutical sciences, synthetic advancements in ACC derivatives are expected to grow substantially in the coming years.

ACKNOWLEDGMENTS:
We gratefully acknowledge the financial support from ikerbasque, basque foundation for science (for soloshonok). the authors acknowledge the assistance of microsoft copilot and google gemini with ukrainian translation.

ПЕРЕДОВІ СТРАТЕГІЇ АСИМЕТРИЧНОГО СИНТЕЗУ α-АМІНО-ЦИКЛОПРОПАН-КАРБОНОВИХ КИСЛОТ: КЛЮЧОВІ СТРУКТУРНІ ЕЛЕМЕНТИ ДЛЯ РОЗРОБЛЕННЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ.

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α-Аміноциклопропанкарбонова кислота (ACC) та її похідні широко поширені в рослинному царстві, виконуючи різноманітні функції — від регуляції життєвих циклів рослин до механізмів захисту. Стерично обмежена структура ACC виявилася надзвичайно корисною у розробленні численних лікарських засобів, зокрема інгібіторів протеази NS3/4A вірусу гепатиту С (HCV), і зіграла ключову роль у створенні кількох поколінь ефективних препаратів проти HCV, із тривалими дослідженнями щодо їхнього подальшого вдосконалення. Властиві ACC стеричні обмеження створюють значні труднощі у їхньому синтезі, особливо у енантіомерно чистій формі, що робить асиметричні методи центральною темою досліджень. У цій статті представлено комплексний огляд синтетичних методологій для отримання ACC та її похідних, згрупованих за ключовими перетвореннями, зокрема діалкілування нуклеофільних похідних гліцину, циклопропанування карбеноїдних еквівалентів гліцину та реакції приєднання до дегідроамінокислот. Окремий акцент зроблено на енантіоселективних стратегіях, що дозволяють отримувати ці специфічні амінокислоти у високій чистоті. Крім того, розглянуто аспекти самодиспропорціонування енантіомерів (SDE), які відіграють важливу роль в enantioselective catalysis. Об'єднуючи ці методології, ми прагнемо надати вичерпний ресурс для дослідників у синтетичній та медичній хімії, а також у галузі розроблення лікарських препаратів, сприяючи подальшому прогресу в цій важливій сфері.

Ключові слова: амінокислоти, фармацевтика, циклопропан, хіральність, синтез, нуклеофільні еквіваленти гліцину, карбеноїдні еквіваленти гліцину, дегідроамінокислоти, самодиспропорціонування енантіомерів (SDE).

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Стаття надійшла 05.05.2025.