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Diastereoselective Synthesis of Cyclopropane Amino Acids Using Diazo Compounds Generated in Situ

Luke A. Adams, Varinder K. Aggarwal,* Roger V. Bonnert,† Bettina Bressel, Russell J. Cox,* Jon Shepherd, Javier de Vicente, Magnus Walter,‡ William G. Whittingham,‡ and Caroline L. Winn

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K.

v.aggarwal@bristol.ac.uk; r.j.cox@bris.ac.uk

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A simple and high-yielding method for the preparation of cyclopropane amino acids is described. The novel method involves the one-pot cyclopropanation of readily available dehydroamino acids using aryl and unsaturated diazo compounds generated in situ from the corresponding tosylhydrazone salts. It was found that thermal 1,3-dipolar cycloaddition followed by nitrogen extrusion gave the cyclopropane amino acid derivatives with good *E* selectivity, while reactions in the presence of *meso*-tetraphenylporphyrin iron chloride gave predominantly the corresponding *Z* isomers. The synthetic utility of this process was demonstrated in the synthesis of (±)-(*Z*)-2,3-methanophenylalanine [(±)-(*Z*)-**1**], the anti-Parkinson (±)-(*E*)-2,3-methano-*m*-tyrosine [(±)-(*E*)-**2**], and the natural product (±)-coronamic acid [(±)-**3**].

Introduction

The biological study of new amino acids, as well as their effect on the structure of peptides and in proteins, is a central goal in drug discovery.[1,2] These compounds are also used as a source of chiral materials,[3] food additives,[4] and agrochemicals. Cyclopropane amino acids, especially α-2,3-methanoamino acids, have recently found wide application in peptidomimetics due to their rigid conformation. The presence of the strained cyclopropane ring in an amino acid based drug may also lead to new interactions with an enzyme active site (or to a receptor), resulting in biological activity.[5] Enhanced specific binding can also be gained by "preorganization" of the amino acid side chain by attachment to the cyclopropane moiety. This then leads to issues of diastereoselectivity that must be addressed during synthesis.

The α-2,3-methanoamino acids are the most common analogues of the naturally occurring amino acids including 2,3-methanophenylalanine (**1**) and 2,3-methano-*m*-tyrosine (**2**) (Figure 1). The 1*R*,2*S* enantiomer of the latter amino acid is the most potent competitive inhibitor

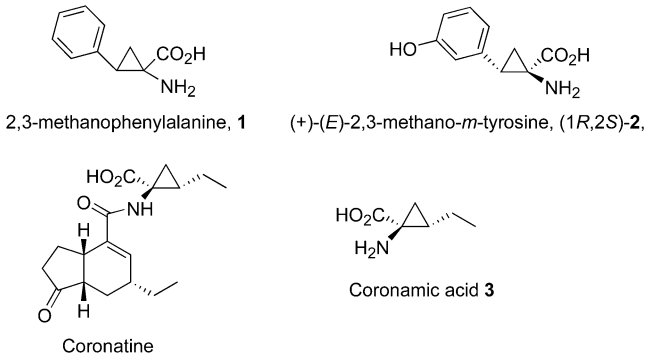

FIGURE 1. α-2,3-Methanoamino acids.

of L-aromatic amino acid decarboxylase (dopa decarboxylase, DDC), a pyridoxal 5′-phosphate (PLP) dependent enzyme which catalyzes the decarboxylation of L-dopa and 5-hydroxy-L-tryptophan, thus playing a critical role in the biosynthesis of the important neurotransmitters ephedrine, norephedrine, and serotonin.[6] DDC inhibitors are used in the treatment of Parkinson's disease.[7] Cyclopropane amino acids such as coronamic acid (**3**) can also be found in nature, isolated after hydrolysis of the bacterial toxin coronatine from *Pseudomonas syringae*.[8]

The synthesis of cyclopropane amino acids has attracted much curiosity.[9−12] The synthetic challenge in the

* To whom correspondence should be addressed.
† AstraZeneca R&D Charnwood, Medicinal Chemistry, Bakewell Rd., Loughborough, Leics LE11 5RH, U.K.
‡ Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6ET, U.K.

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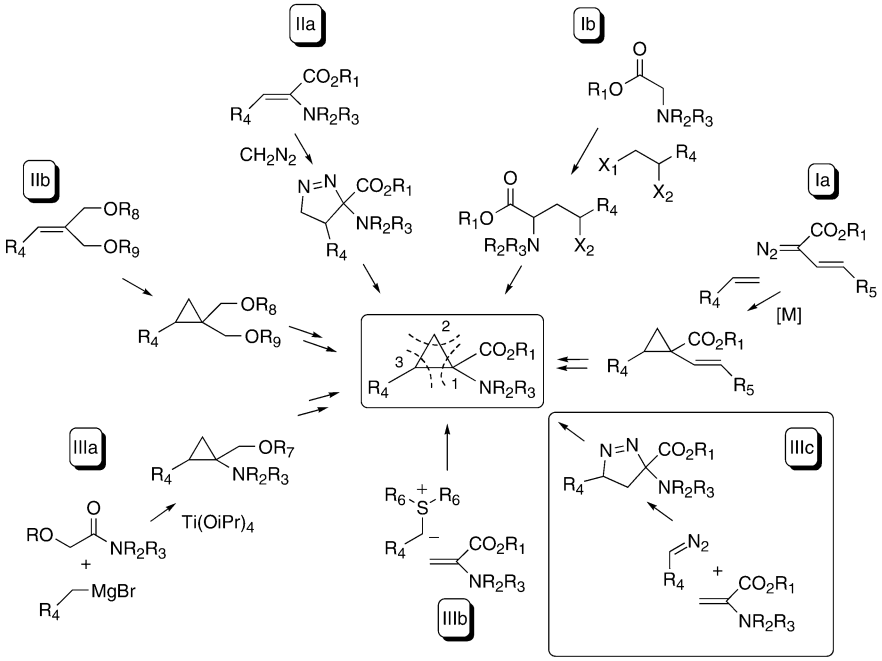
SCHEME 1. Synthetic Routes to Cyclopropane Amino Acids



preparation of such cyclopropanes has normally been the diastereoselective formation of the trisubstituted carbocyclic three-membered ring. The reported syntheses of cyclopropane amino acids can be classified according to the last carbon unit assembled (C-1, C-2, or C-3) in the cyclopropane ring formation step. This leads, therefore, to three different synthetic strategies (I−III, Scheme 1) involving seven well-known synthetic methods for the preparation of cyclopropanes.

The quaternary carbon unit (C-1) of cyclopropane amino acids can be installed via transition-metal-catalyzed cyclopropanation of alkenes using a vinyldiazoacetate (route Ia).[13,14] The amino group is then installed by oxidative cleavage of the double bond to the corresponding acid followed by Curtius rearrangement. A related method involves the metal-catalyzed reaction between α-nitro-α-diazo carbonyl compounds and olefins, followed by reduction of the nitro group to yield the desired cyclopropane amino acid.[15] The dialkylation of glycine equivalents (route Ib) is another convenient method for the preparation of cyclopropane amino acids in which the amino and acid functional groups are already present in the starting material.[16−18] The classical 1,3-dipolar cycloaddition of diazomethane (route IIa)[19−21] and Simmons−Smith reaction(route IIb)[22] with alkenes are effective cyclopropanation methods for the introduction of the methylene carbon unit (C-2) in cyclopropane amino acids. Alternatively, cyclopropanes can be prepared by the addition of alkyl Grignard reagents to amides in the presence of methyltitanium triisopropoxide in a convenient adaptation of the Kulinkovich reaction (route IIIa).[23] Finally, the formation of cyclopropane amino acids can be accomplished by the addition of dipoles or ylides to dehydroamino acids (routes IIIb and IIIc). While the Michael addition of sulfur ylides to dehydroamino acids leads directly to cyclopropane amino acids (route IIIb),[7,24,25] the 1,3-dipolar cycloaddition of diazo compounds onto dehydroamino acids furnishes the desired cyclopropane after extrusion of nitrogen from the pyrazoline intermediate (route IIIc).[26,27]

The 1,3-dipolar cycloaddition of diazo compounds onto dehydroamino acids is one of the best methods for the preparation of cyclopropane amino acids (route IIIc, Scheme 1) because dehydroamino acids are easily accessible. Furthermore, there is no requirement for functional group modification to access the final amino acid. However, the main limitation of this method is the need to synthesize and handle diazo compounds, which are toxic and potentially explosive.[28] The hazards associated with handling diazo compounds limit the practicality of the process and its scaleup.

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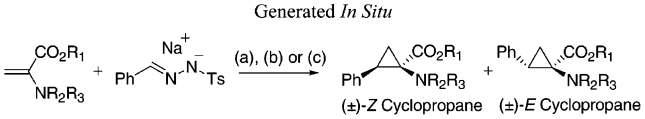
We recently reported a method for the generation of aryldiazomethanes from stable tosylhydrazone derivatives.[29] This procedure has proven to be a highly effective and safe alternative to handling aryldiazomethanes directly and has been employed in the sulfur ylide mediated synthesis of epoxides from carbonyl compounds,[29] sulfur ylide mediated aziridination of imines,[25] homologation of aldehydes to ketones,[30] cyclopropanation of alkenes,[31] Wittig olefination of aldehydes using phosphorus ylides generated from phosphites,[32] and 1,3-dipolar cycloaddition of diazo compounds with alkynes to give pyrazoles.[33] We were therefore keen to examine whether this process could be applied in the 1,3-dipolar cycloaddition approach to cyclopropane amino acids (route IIIc). Cyclopropane amino acids could also be furnished by the transition-metal-catalyzed cyclopropanation of dehydroamino acids using diazo compounds generated in situ. This metal carbene transfer process to a dehydroamino acid has never been explored as the metal-catalyzed process is normally only efficient when electron-rich alkenes and diazo carbonyl compounds are employed as substrates.[34] Indeed, a number of reports have indicated that no cyclopropane adducts were formed during the metal-catalyzed intermolecular reactions between diazoesters and electron-deficient alkenes.[35,36] Of course, dehydroamino acids bear both an electron-donating group and an electron-withdrawing group and so could, in principle, be sufficiently nucleophilic. Literature precedent,[37] however, was not in our favor as it had been reported that methyl *N*-acetyldehydroalaninate (**7**) reacted with diazoesters in the presence of $Rh_2(OAc)_4$ to give only a 10% yield of the desired cyclopropane as a 2:1 (*E*/*Z*) mixture of isomers. Aryldiazomethanes would be expected to perform less well than diazoesters as they have a greater tendency to dimerize in the absence of nucleophilic alkenes.[38,39] Nevertheless, if our reported procedure for the transition-metal-catalyzed cyclopropanation of alkenes using aryldiazomethanes generated in situ from tosylhydrazones salts[31] could be extended to the use of dehydroamino acids, it would provide a new and direct route to cyclopropane amino acids. In this paper, we report our success in achieving these goals and the development of a new, straightforward, one-pot method for the selective preparation of *either diastereomer* of cyclopropane amino acids from easily accessible dehydroamino acids and tosylhydrazone salts.

Results and Discussion

We began our studies by testing the easily accessible dehydroamino acid **4** as dipolarophile in the 1,3-dipolar cycloaddition of phenyldiazomethane generated in situ from benzaldehyde tosylhydrazone sodium salt in the presence of the phase-transfer catalyst benzyltriethylammonium chloride (condition a). This gave a good yield of the cyclopropyl amino acid **8** with a diastereomeric ratio strongly in favor of the *E* isomer (Table 1, entry 1). Interestingly, the pyrazoline cycloadduct was never detected in this or subsequent thermal reactions. While there is an example in the literature of this pryazoline cycloadduct having been isolated from the addition of phenyldiazomethane to dihydroamino acid **5**, the reaction was conducted at −15 °C, and presumably, the pyrazoline was stable enough to be characterized at room temperature.[27] On heating at 90 °C in toluene, elimination of nitrogen occurred to yield cyclopropane amino acid **9**. In our case, transformation to the cyclopropane must have occurred under the prolonged thermal conditions required for the decomposition of the tosylhydrazone salt (40 °C for 60 h).

TABLE 1. Optimization of the Cyclopropanation of Dehydroamino Acids Using Diazo Compounds Generated in Situ



Reagents and conditions: (a) $BnEt_3NCl$ (0.05 eq.), toluene, 40°C, 60h; (b) $Rh_2(OAc)_4$, $BnEt_3NCl$ (0.1 eq.), 1,4-dioxane, 30°C, 60h; (c) ClFeTPP, $BnEt_3NCl$ (0.05 eq.), toluene, 40°C, 60h.

entry	dehydroamino acid		cond.[a]	catalyst (mol %)	yield[b] (%)	*E*:*Z*[c]	product
1			(a)	-	68	94:6	**8**
2			(b)	1	12	49:51	**8**
3	CO_2Me	**4**	(b)	10	35	17:83	**8**
4	$NHBOC$		(c)	1	79	36:64	**8**
5			(c)	10	53	36:64	**8**
6	CO_2PNB	**5**	(a)	-	50	95:5	**9**
7	$NHBOC$		(c)	1	73	43:57	**9**
8	CO_2Me	**6**	(a)	-	traces	64:36	-
9	$N(BOC)_2$		(c)	1	-	-	-
10			(a)	-	48	85:15	**10**
11	CO_2Me	**7**	(c)	1	84	19:81	**10**
12	$NHAc$		(c)	10	84	16:84	**10**

[a] A 2-fold excess of dehydroamino acid was employed. [b] Isolated yields. [c] Determined by ^1H NMR (see the text for details). Abbreviations: BOC = *tert*-butoxycarbonyl, PNB = *p*-nitrobenzyl.

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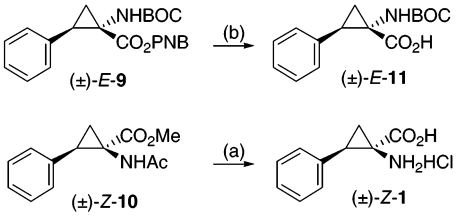
We then decided to investigate whether the addition of a transition-metal catalyst to the reaction could switch the reaction pathway to a metal carbene transformation (Table 1, entries 2−5). $Rh_2(OAc)_4$ (rhodium(II) acetate dimer) and ClFeTPP (*meso*-tetraphenylporphyrin iron(III) chloride) have previously been shown to be highly effective catalysts for the catalytic cyclopropanation of alkenes using diazo compounds.[31] In our experiments, the iron complex proved to be a more efficient catalyst than $Rh_2(OAc)_4$ (Table 1, compare entries 2 and 4 and entries 3 and 5). Interestingly, in these reactions, the *Z* isomer (*Z*)-**8** was favored.

We then explored the use of a range of other protected dehydroamino acids (**5**−**7**)[40] with diverse electronic and steric properties under both thermal and ClFeTPP-catalyzed conditions. Substrates **5** and **7** gave the corresponding protected cyclopropane amino acids (products **9** and **10**, respectively), in moderate to good yields. However, poor yields were obtained when olefin **6** was used. This was thought to be due to both the additional steric hindrance and also the reduction in nucleophilicity of the olefin, caused by having a second BOC group on the nitrogen (Table 1, entries 8 and 9).

The relative stereochemistry of the 2-phenyl-substituted cyclopropanes was assigned by comparison with the corresponding literature data, except for the PNB-protected cyclopropanes (Table 2, entries 6 and 7). The relative stereochemistry of these compounds was assigned by correlation with the known acid (*E*)-**11**, prepared by treatment of (*E*)-**9** with activated zinc (Scheme 2). Acid hydrolysis of (*E*)-**10** provided the known hydrochloride salt of (±)-(*Z*)-2,3-methanophenylalanine [(±)-(*Z*)-**1**] in 84% yield (Scheme 2).

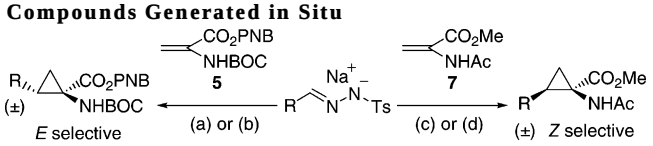
SCHEME 2. Chemical Correlation of 2-Arylcyclopropane Amino Acids[a]



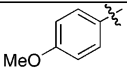
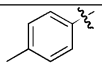
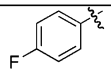
[a] Reagents and conditions: (a) Zn dust, THF, 0.35 M phosphate aq buffer (pH 6), 16 h, 74%; (b) 4 N HCl, reflux, 16 h, 84%.

In all cases, the non-metal-catalyzed reactions which occurred via 1,3-dipolar cycloaddition were *E* selective (Table 1, entries 1, 6, 8, and 10), while reactions catalyzed by ClFeTPP were *Z* selective (Table 1, entries 4, 5, 7, 11, and 12). Changing the ester substituent on the mono-BOC-protected alkene seemed to have little effect on the diastereoselectivity of the reaction (compare entries 4 and 7). In contrast, the preference for formation of the *Z* isomer was increased under both reaction pathways by replacing the *N*-BOC group by an *N*-acetyl group (compare entries 1 and 10 and entries 4 and 11). The loading of the metal catalyst was also studied with alkenes **4** and **7**. The amount of the rhodium catalyst employed had a dramatic effect on the diastereoselectivity of the reaction (Table 1, entries 2 and 3), which indicated that a significant amount of non-rhodium-mediated cyclopropanation was occurring at low catalyst loadings. However, reactions carried out with 10 mol % ClFeTPP gave results nearly identical to those using 1 mol % catalyst, reflecting the high efficiency of the iron porphyrin in promoting the metal carbene pathway (Table 1, compare entries 4 and 5 and entries 11 and 12).

TABLE 2. Yields and Ratios of Cyclopropane Amino Acids Formed from Dehydroamino Acids Using Diazo Compounds Generated in Situ



Reagents and conditions:
(a) $BnEt_3NCl$ (0.05 eq.), toluene, 40°C, 60 h;
(b) starting with RCH=NNHTs; (i) LiHMDS, THF, -78°C to rt;
(ii) $BnEt_3NCl$ (0.05 eq.), toluene, 40°C, 60 h.
(c) ClFeTPP (0.01 eq.), $BnEt_3NCl$ (0.05 eq.), toluene, 40°C, 60 h.
(d) starting with RCH=NNHTs;(i) LiHMDS, THF, -78°C to rt;
(ii) ClFeTPP (0.01 eq), PTC (0.05 eq), toluene, 40°C.

entry	R	cond.[a]	yield (%)[b]	*E*:*Z*[c]	product
1		(a)	50	95:5	**9**
2		(c)	84	19:81	**10**
3		(a)	72	95:5	**12**
4	MeO	(c)	52	12:88	**13**
5		(a)	52	89:11	**14**
6		(c)	49	14:86	**15**
7		(a)	62	87:13	**16**
8	F	(c)	82	15:85	**17**
9		(a)	76	66:34	**18**
10	Ph Ph	(c)	82	8:92	**19**
11		(b)	47	96:4	**20**
12	OTBS	(d)	44	16:84	**21**
13		(b)	36	72:28	**22**

[a] A 2-fold excess of dehydroamino acid was employed. [b] Isolated yields. [c] Determined by ^1H NMR.

The newly developed method for the preparation of cyclopropane amino acids was extended to the use of a range of hydrazone salts (Table 2; see the Supporting Information for details of their preparation). Initially, dehydroamino acid **4** was chosen as a test substrate because it had given high *E* selectivity and good yields in the 1,3-dipolar cycloaddition reaction (Table 1, entry 1). Several aromatichydrazones and vinylhydrazones were tested under the previously optimized reaction conditions. Unfortunately, alkene **4** unexpectedly polymerized under the cyclopropanation conditions, and the reaction became irreproducible. It had been reported that **4** could be stabilized by the addition of hydroquinone and

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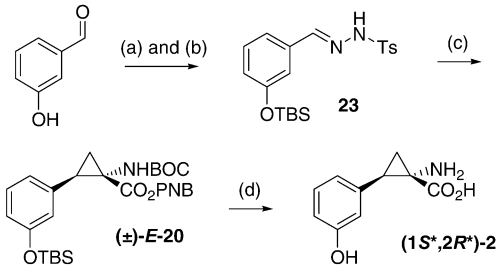
(40) The dehydroamino acids were easily prepared on a large scale by dehydratation of the corresponding protected serine derivative (see the Experimental Section). Methyl 2-(acetylamino)acrylate (7) is also commercially available.

stored as a solution in CH_2Cl_2 at −15 °C,[41] but attempts at cyclopropanation reactions in the presence of hydroquinone as polymerization inhibitor were also unsuccessful. Hence, dehydroamino acid **5**, a crystalline, nonpolymerizable compound that had also displayed good levels of *E* selectivity in the initial studies, was studied instead, and good yields with good to high *E* selectivities of the protected amino acids were achieved (Table 2, entries 1, 3, 5, 7, and 9).

The *N*-acetyldehydroamino acid **7**, which had previously given good results in the metal-catalyzed reaction, was tested in the presence of ClFeTPP with several aromatichydrazones. In these examples, the *Z*-protected cyclopropane amino acids were formed with high levels of diastereoselectivity (Table 2, entries 2, 4, 6, 8, and 10).

It had been previously shown that tosylhydrazone salts could be generated in situ from the corresponding tosylhydrazone and base[30] for use in epoxidation reactions. It was demonstrated in this case that the conditions were compatible with our cyclopropanation process (Table 2, entries 11−13). This procedure has been shown to be very useful in those cases where the tosylhydrazone salts were unstable, for example, during the synthesis of **22** (Table 2, entry 13).

SCHEME 3. Synthesis of (±)-(*E*)-2[a]

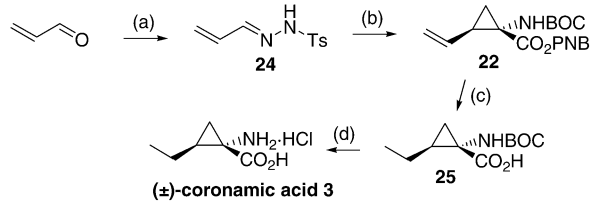


[a] Reagents and conditions: (a) (TBS)Cl (1.15 equiv), imidazole (1.2 equiv), DCM, rt, 19 h, 97%; (b) $TsNH_2NH_2$ (1.15 equiv), MeOH, rt, 10 min, 84%; (c) (i) LiHMDS (1 equiv), THF, −78 °C to rt; (ii) $BnEt_3NCl$ (0.05 equiv), **5** (2 equiv), toluene, 40 °C, 60 h, 50%; (d) (i) 4 N HCl aq, 1,4-dioxane, rt, 16 h; (ii) 4 N HCl aq, 1,4-dioxane, reflux, 6 days, 87%.

An application of the newly developed technology for the synthesis of aromatic α-2,3-methanoamino acids was illustrated by the efficient synthesis of the dopa decarboxylase inhibitor (±)-(*E*)-2,3-methano-*m*-tyrosine [(±)-(*E*)-**2**] (Scheme 3). Hydrazone **23** was prepared in high yield by TBS protection of *m*-hydroxybenzaldehyde followed by condensation with tosylhydrazide. The salt derived from hydrazone **23** was found to be unstable (vide supra), and so was prepared in situ by deprotonation with LiHMDS. The salt was then allowed to react with olefin **5** under the standard, 1,3-dipolar addition conditions, to afford the corresponding cyclopropane in 47% yield as a 96:4 mixture in favor of the *E* isomer (Table 2, entry 12). Treatment of (*E*)-**20** with aq 4 M HCl in dioxane at rt for 16 h provided the PNB-protected amino acid hydrochloride salt, which could be fully deprotected by continuing the acid hydrolysis at reflux for 6 days. Finally, ion exchange purification afforded the dopa decarboxylase inhibitor (±)-(*E*)-**2** in 87% yield.

(41) Flynn, G. A.; Beight, D. W. *Tetrahedron Lett.* **1984**, *25*, 2655−2658.

SCHEME 4. Synthesis of (±)-3[a]

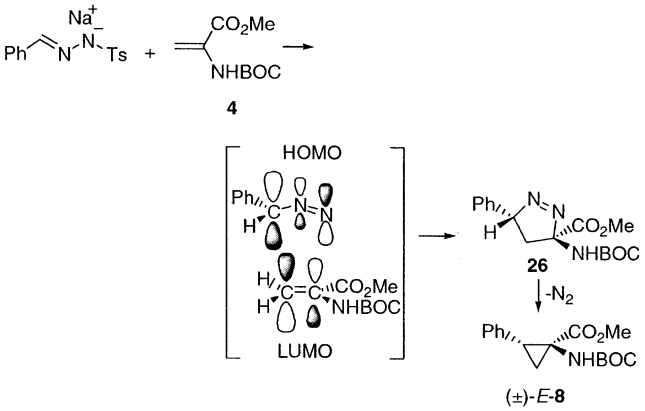


[a] Reagents and conditions: (a) $TsNH_2NH_2$ (1.15 equiv), MeOH, rt, 10 min, 68%; (b) (i) LiHMDS (1 equiv), THF, −78 °C to rt; (ii) $BnEt_3NCl$ (0.05 equiv), **4** (2 equiv), toluene, 40 °C, 60 h. 36%; (c) H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt, 79%; (d) 1 N HCl, MeOH, rt, 44 h, 89%.

The scope of the process has been further explored in the preparation of the natural product (±)-coronamic acid [(±)-**3**] (Scheme 4). Tosylhydrazone **24** was prepared by condensation of acrolein with tosylhydrazide. In situ deprotonation with LiHMDS followed by reaction with **5** in the presence of a phase-transfer catalyst gave the cyclopropane **22** in 36% yield as a 72:28 mixture in favor of the required *E* isomer (Table 2, entry 13). Treatment of cyclopropane (*E*)-**22** with $Pd(OH)_2$ on carbon under an atmosphere of hydrogen allowed removal of the PNB group and hydrogenation of the olefin to occur in a single synthetic step. Finally, amine deprotection in acidic media gave (±)-coronamic acid. This compound was spectroscopically identical to the reported natural product.[5]

Stereochemical Course of Cyclopropanation Reactions. The mechanism of the formation of cyclopropanes in the non-metal-catalyzed reactions is postulated to proceed via diastereoselective construction of a pyrazoline (e.g., **26**) followed by extrusion of nitrogen with retention of the configuration of the pyrazoline's stereocenters (Scheme 5).[42,43] The favored parallel approach of

SCHEME 5. Mechanism of Cyclopropane Formation under the 1,3-Dipolar Cycloaddition Pathway



phenyldiazomethane to the alkene, in which the biggest substituents of both molecules are *anti* to one another, determines the *E* selectivity of cyclopropane formation. The regioselectivity of the 1,3-dipolar cycloaddition reaction is likely to be determined by the dominant HOMO

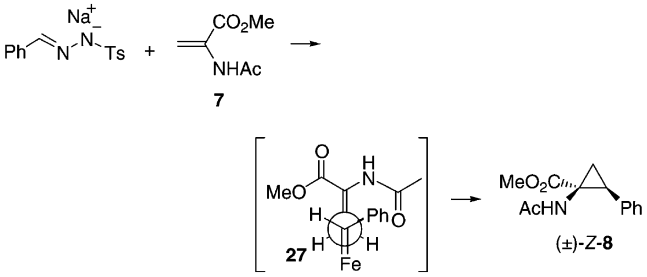
(42) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vol. I.

(43) Nakano, Y.; Hamaguchi, M.; Nagai, T. *J. Org. Chem.* **1989**, *54*, 1135−1144.

(phenyldiazomethane)−LUMO (acrylic ester) interaction, which favors the combination of the large atomic orbital lobes.[42]

In the metal-catalyzed cyclopropanation of dehydroamino acid **7**, the iron carbene, formed from the phenyldiazomethane generated in situ, reacts directly with the alkene (Scheme 6). The unusual reactivity of the dehydroamino acid toward electrophilic carbene addition can be explained by the electron-donating effect of the monoacetylated amino group balancing out the electron-withdrawing effect of the conjugated ester substituent. The diastereoselectivity of the carbene transfer process may be accounted for by the parallel approach[44] of the alkene **7** to the iron carbene. As the (*Z*)-cyclopropane **8** is formed predominantly, the alkene must approach the iron carbene with the amide *cis* to the phenyl group (**27**). As indicated above, the amide donates electron density into the alkene and the developing positive charge may be stabilized by the polarizable π system of the aromatic ring. This could account for the observed *cis* selectivity.

SCHEME 6. Proposed Mechanism of Cyclopropane Formation Catalyzed by ClFeTPP



In conclusion, we have developed a simple method for the preparation of 2,3-methanoamino acids through coupling of dehydroamino acid with tosylhydrazone salts with or without an iron porphyrin catalyst. These reactions occur via diazo compounds that are generated and used in situ. Considerable variation in diastereoselectivity was observed in relation to the reaction pathway: while cyclopropanations with the commercially available dehydroamino acid **7** catalyzed by the iron porphyrin catalyst ClFeTPP afforded (*Z*)-cyclopropanes, thermal reactions with dehydroamino acid **5** gave (*E*)-cyclopropanes. Thus, using either thermal conditions or iron catalysis, complementary diastereoselectivity could be achieved in all cases.[45] Thermal reactions occur through a 1,3-dipolar cycloaddition of the diazo compound to the dehydroamino acid followed by nitrogen extrusion, while reactions with the iron porphyrin involve addition of an electrophilic metal carbene to the dehydroamino acid. The latter process was surprisingly efficient as the alkene in the dehydroamino acid is not very nucleophilic, and under such circumstances diazo dimerization often dominates.[34]

The thermal process for the synthesis of (*E*)-cyclopropyl amino acids was successfully used in the synthesis of the dopa decarboxylase inhibitor (±)-(*E*)-**2** and the natural product (±)-**3**. It is worth noting that racemic mixtures of cyclopropane amino acids can be easily resolved by fractional recrystallization of their diastereomeric quinine quaternary salts,[7] but as an alternative, we are developing a novel approach for the asymmetric synthesis of cyclopropane amino acids mediated by chiral porphyrin-type catalysts.

Experimental Section

Representative Procedure for the Preparation of Tosylhydrazones. Benzaldehyde (2.36 mL, 23.30 mmol) was added dropwise to a rapidly stirred suspension of *p*-toluenesulfonyl hydrazide (5.0 g, 26.79 mmol) in anhydrous MeOH (10 mL) under nitrogen at rt. A mildly exothermic reaction ensued, and the hydrazide dissolved. Within 5−10 min the tosylhydrazone began to precipitate. After approximately 30 min, the mixture was cooled to 0 °C and the product removed by filtration, washed with a small quantity of cold MeOH, and then crystallized from hot MeOH to afford benzaldehyde tosylhydrazone (5.81 g, 91%) as colorless needles: mp 127−128 °C (MeOH) (lit.[46] mp 128−129 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (3H, s, C*H*$_3$), 7.29−7.36 (5H, m, aryl H), 7.52−7.57 (2H, m, aryl H), 7.78 (1H, s, C*H*N), 7.89 (2H, d, J = 8.3 Hz, aryl H), 8.29 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (q), 127.3 (2d), 127.9 (2d), 128.6 (2d), 129.7 (2d), 130.4 (d), 133.1 (s), 135.2 (s), 144.3 (s), 147.9 (d).

Representative Procedure for the Preparation of Tosylhydrazone Sodium Salts. A 1 M sodium methoxide solution in MeOH was prepared by adding sodium (423 mg, 18.39 mmol) to anhydrous MeOH (19 mL) at 10 °C under nitrogen. Once all of the metal was dissolved, benzaldehyde tosylhydrazone (4.80 g, 17.51 mmol) was added and the mixture stirred until all of the solid dissolved. After the mixture was stirred for a further 15 min, the MeOH was removed under reduced pressure (without external heating). The last traces of MeOH were removed under high vacuum (0.1 mmHg). The resultant salt was then ground using a mortar and pestle, and dried again under high vacuum to afford benzaldehyde tosylhydrazone sodium salt[47] (5.21 g, 99%) as a pink solid: ^{1}H NMR (400 MHz, D_2O) δ 2.17 (3H, s, C*H*$_3$), 7.15−7.23 (5H, m, aryl H), 7.35−7.40 (2H, m, aryl H), 7.60 (2H, d, J = 8.4 Hz, aryl H), 7.83 (1H, s, C*H*N); ^{13}C NMR (100 MHz, D_2O) δ 20.7 (q), 126.6 (2d), 126.7 (2d), 128.8 (2d), 129.5 (2d), 129.6 (d), 135.8 (s), 139.2 (s), 142.8 (s), 145.9 (d); MS *m*/*z* (FAB) 297 ([MH]$^+$, 84). The product was stored in a cool dry place in absence of direct light.

Representative Procedure for the Cyclopropanation of 5 Using Diazo Compounds Generated from Tosylhydrazone Sodium Salts in Situ (Table 1, Entry 6, and Table 2, Entry 1). See Table 1, Method a, and Table 2, Method a. A mixture of benzaldehyde tosylhydrazone sodium salt (445 mg, 1.5 mmol), benzyltriethylammonium chloride (17 mg, 0.075 mmol), **5** (604 mg, 3 mmol), and anhydrous toluene (5 mL) was vigorously stirred for 60 h at 40 °C. Water (10 mL) was added to the mixture, which was then washed with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were dried over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure to give the crude material, which was purified by column chromatography (petroleum ether/EtOAc, 10:1) to afford (*E*)-**9** (293 mg, 47%) and (*Z*)-**9** (15 mg, 3%). Data for (*E*)-**9**: colorless solid; eluent petroleum ether/EtOAc, 3:1; R_f = 0.35; mp 116−117 °C (EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (9H, s, C(C*H*$_3$)$_3$), 1.67 (1H, dd, J = 9.7 and 5.5 Hz, C*H*HCCO$_2$), 2.21 (1H, dd, J = 8.4 and 5.5 Hz,

(44) Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194−9199.

(45) The assignment of the *cis* and *trans* isomers of the unknown 2-arylcyclopropanes synthesized was determined by analogy to the confirmed stereochemistry of the 2-phenylcyclopropanes. The relative stereochemistry of the 2-(2,2-diphenylvinyl)-1-cyclopropanecarboxylic acids prepared was determined by X-ray crystallography. The crystallographic data are reported in the Supporting Information.

(46) McMahon, R. J.; Abelt, C. J.; Chapman, O. L.; Johnson, J. W.; Kreil, C. L.; LeRoux, J. P.; Mooring, A. M.; West, P. R. *J. Am. Chem. Soc.* **1987**, *109*, 2456−2469.

(47) Creary, X. *Org. Synth.* **1986**, *64*, 207−216.

C*H*HCCO$_2$), 2.93 (1H, dd, J = 9.7 and 8.4 Hz, C*H*Ph), 4.87 and 4.96 (2H, AB system, J_{AB} = 13.2 Hz, COOCH_2), 5.37 (1H, br s, N*H*), 7.06 (2H, d, J = 8.8 Hz, aryl *H*), 7.21−7.33 (3H, m, aryl *H*), 7.33 (2H, br d, J = 8.8 Hz, aryl *H*), 8.06 (2H, d, 8.8 Hz, aryl *H*); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.1 (t), 28.4 (3q), 35.7 (d), 41.0 (s), 65.3 (t), 80.3 (s), 123.5 (2d), 127.2 (d), 128.2 (2d), 128.2 (2d), 129.4 (2d), 135.2 (s), 142.9 (s), 147.6 (s), 155.9 (s), 170.0 (s); IR ν_{max}/cm^{-1} 3386, 1714, 1605, 1509, 1346, 1250, 1151, 1061, 923, 734, 696; MS *m*/*z* (EI) 413 ([MH]$^+$, 20), 357 (32), 313 (14), 220 (14), 176 (65), 159 (24), 137 (28), 130 (30), 104 (29), 78 (26), 57 (100). Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 63.88; H, 5.87; N, 6.49. Data for (*Z*)-**9**: colorless solid; eluent petroleum ether/EtOAc, 3:1; R_f = 0.30; mp 157−158 °C (EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (9H, s, C(CH_3)$_3$), 1.78 (1H, dd, J = 8.8 and 4.8 Hz, C*H*HCCO$_2$), 2.16 (1H, dd, J = 8.8 and 4.8 Hz, C*H*HCCO$_2$), 3.03 (1H, t, J = 8.8 Hz, C*H*Ph), 4.64 (1H, br s, N*H*), 5.26 and 5.34 (2H, AB system, J_{AB} = 13.6 Hz, COOCH_2), 7.20 (2H, d J = 7.0 Hz, aryl *H*), 7.26−7.35 (3H, m, aryl *H*), 7.54 (2H, d, J = 8.4 Hz, aryl *H*), 8.22 (2H, d, J = 8.4 Hz, aryl *H*); ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.0 (t), 28.2 (3q), 33.3 (d), 39.8 (s), 65.8 (t), 80.2 (s), 123.8 (2d), 127.4 (d), 128.1 (2d), 128.4 (2d), 129.8 (2d), 134.2 (s), 143.2 (s), 147.8 (s), 155.7 (s), 172.2 (s); IR ν_{max}/cm^{-1} 3375, 2972, 1720, 1687, 1607, 1505, 1339, 1286, 1241, 1160, 844, 698. Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 63.72; H, 6.13; N, 6.87.

Representative Procedure for the Cyclopropanation of 7 Using Diazo Compounds Generated fromTosylhydrazone Sodium Salts in Situ (Table 1, Entry 11). See Table 1, Method c, and Table 2, Method c. A mixture of benzaldehyde tosylhydrazone sodium salt (445 mg, 1.5 mmol), benzyltriethylammonium chloride (17 mg, 0.075 mmol), ClFeTPP (10 mg, 0.015 mmol), **7** (429 mg, 3 mmol), and anhydrous toluene (5 mL) was vigorously stirred for 60 h at 40 °C. Water (10 mL) was added to the mixture, which was then washed with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were dried over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure to give the crude material, which was purified by column chromatography (petroleum ether/EtOAc, 10:1) to afford (*E*)-**10** (56 mg, 16%) and (*Z*)-**10** (237 mg, 68%). Data for (*E*)-**10**: colorless solid; eluent ether/MeOH, 99:1; R_f = 0.20; mp 146−148 °C (EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (1H, dd, J = 9.8 and 5.6 Hz, C*H*HCCO$_2$), 2.04 (3H, s, CH_3CONH), 2.24 (1H, dd, J = 8.3 and 5.6 Hz, CH*H*CCO$_2$), 2.84 (1H, dd, J = 9.8 and 8.3 Hz, C*H*Ph), 3.32 (3H, s, OCH_3), 6.84 (1H, br s, N*H*), 7.21−7.35 (5H, m, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (t), 23.2 (q), 34.7 (d), 40.7 (s), 51.9 (q), 127.1 (d), 128.0 (2d), 129.3 (2d), 135.3 (s), 170.2 (s), 171.4 (s); MS *m*/*z* (EI) 234 ([MH]$^+$, 62), 201 (82), 190 (99), 159 (79), 130 (100), 115 (48), 103 (64), 91 (48), 77 (55); HRMS *m*/*z* found 233.1052, $C_{13}H_{15}NO_3$ requires 233.1052. Data for (*Z*)-**10**: colorless solid; eluent ether/MeOH, 99:1; R_f = 0.25; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.73 (1H, dd, J = 7.9 and 6.0 Hz, C*H*HCCO$_2$), 1.81 (3H, s, CH_3CONH), 2.18 (1H, dd, J = 9.7 and 6.0 Hz, CH*H*CCO$_2$), 2.95 (1H, dd, J = 9.7 and 7.9 Hz, C*H*Ph), 3.73 (3H, s, OCH_3), 5.57 (1H, br s, N*H*), 7.14−7.36 (5H, m, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (t), 23.0 (q), 32.6 (d), 39.1 (s), 52.8 (q), 127.6 (d), 128.6 (2d), 128.7 (2d), 134.3 (s), 171.3 (s), 172.1 (s); MS *m*/*z* (EI) 233 (M$^+$, 46), 215 (47), 201 (51), 190 (83), 159 (69), 130 (100), 115 (33), 104 (58), 91 (28), 84 (49) 77 (41); HRMS *m*/*z* found 233.1055, $C_{13}H_{15}NO_3$ requires 233.1052.

Representative Procedure for the Catalytic Cyclopropanation of 5 via in Situ Generation of Diazo Compounds from Tosylhydrazones (Table 2, Entry 11, and Schemes 3 and 4). See Table 2, Method b. To a solution of 3-(*tert*-butyldimethylsilyloxy)benzaldehyde tosylhydrazone (**23**) (404.6 mg, 1 mmol) in anhydrous THF (4 mL) at −78 °C was added under nitrogen a solution of 1 M LiHMDS in THF (1 mL, 1 mmol). After being stirred at −78 °C for 15 min, the mixture was warmed to rt, and the solvent was evaporated under reduced pressure. To the resultant salt were added benzyltriethylammonium chloride (11 mg, 0.05 mmol), **5** (645 mg, 2 mmol), and anhydrous toluene (4 mL). The mixture was vigorously stirred for 60 h at 40 °C. Water (10 mL) was added to the mixture, which was then washed with DCM (3 × 25 mL). The organic layer was separated and dried over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure to give a residue. The crude material was purified by flash chromatography (eluent petroleum ether/EtOAc, 6:1) to afford (*E*)-**20** (242 mg, 45%) and (*Z*)-**20** (13 mg, 2%). Data for (*E*)-**20**: colorless oil; EtOAc/petroleum ether, 1:6; R_f = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (6H, s, Si(CH_3)$_2$), 0.96 (9H, s, SiC(CH_3)$_3$), 1.47 (9H, s, COOC(CH_3)$_3$), 1.64 (1H, dd, J = 6.8 and 5.4 Hz, C*H*HCCO$_2$), 2.18 (1H, dd, J = 8.3 and 5.4 Hz, C*H*HCCO$_2$), 2.85 (1H, dd, J = 8.3 and 6.8 Hz, ArC*H*), 4.89 and 4.97 (2H, AB system, J_{AB} = 13.7 Hz, COOCH_2), 5.44 (1H, br s, N*H*), 6.69 (1H, d, J = 8.3 Hz, aryl H), 6.81 (1H, s, aryl H), 6.93 (1H, d, J = 5.9 Hz, aryl H), 7.09 (1H, dd, J = 8.3 and 5.9 Hz, aryl H), 7.10 (2H, d, J = 8.8 Hz, aryl H), 8.07 (2H, d, J = 8.8 Hz, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4 (2q), 18.2 (s), 21.1 (t), 25.7 (3q), 28.4 (3q), 35.3 (d), 41.2 (s), 65.3 (t), 80.4 (s), 119.0 (d), 121.2 (d), 122.4 (d), 123.6 (2d), 128.2 (2d), 129.1 (d), 136.7 (s), 142.8 (s), 147.6 (s), 155.7 (s), 155.8 (s), 169.9 (s); IR ν_{max}/cm^{-1} 2931, 2859, 1722, 1604, 1583, 1523, 1486, 1347, 1251, 1146, 1107, 1053, 1004, 917, 831, 779, 737, 692; MS *m*/*z* (EI) 543 ([MH]$^+$, 10), 385 (30), 306 (35), 289 (50); HRMS ([M − Boc]$^+$) *m*/*z* found 441.1857, $C_{23}H_{29}N_2O_5Si$ requires 441.1846. Anal. Calcd for $C_{28}H_{38}N_2O_7Si$: C, 61.97; H, 7.06; N, 5.16. Found: C, 62.33; H, 7.02; N, 5.23. Data for (*Z*)-**20**: colorless oil characterized from an enriched mixture of both diastereoisomers; EtOAc/petroleum ether, 1:6; R_f = 0.15; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (6H, s, Si(CH_3)$_2$), 0.98 (9H, s, SiC(CH_3)$_3$), 1.35 (9H, s, COOC(CH_3)$_3$), 1.72 (1H, dd, J = 7.8 and 5.4 Hz, C*H*HCCO$_2$), 2.17 (1H, dd, J = 9.8 and 5.4 Hz, C*H*HCCO$_2$), 2.94 (1H, dd, J = 9.8 and 7.8 Hz, ArC*H*), 5.22 and 5.36 (2H, AB system, J_{AB} = 14.2 Hz, COOCH_2), 6.63 (1H, s, aryl H), 6.76 (1H, d, J = 7.8 Hz, aryl H), 6.82 (1H, d, J = 7.8 Hz, aryl H), 7.18 (1H, t, J = 7.8 Hz, aryl H), 7.54 (2H, d, J = 8.8 Hz, aryl H), 8.22 (2H, d, J = 8.8 Hz, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.3 (2q), 18.3 (s), 22.3 (t), 25.7 (3q), 29.8 (3q), 35.3 (d), 39.6 (s), 65.8 (t), 80.2 (s), 119.3 (d), 120.1 (d), 122.4 (d), 123.8 (2d), 128.1 (2d), 129.4 (d), 135.7 (s), 143.1 (s), 147.8 (s), 155.8 (s), 155.8 (s), 172.2 (s).

Representative Procedure for the Catalytic Cyclopropanation of 7 via in Situ Generation of Diazo Compounds from Tosylhydrazones (Table 2, Entry 12). See Table 2, Method d. To a solution of **23** (606.9 mg, 1.5 mmol) in anhydrous THF (5 mL) at −78 °C was added, under nitrogen, a 1 M solution of LiHMDS in THF (1.5 mL, 1.5 mmol). After being stirred at −78 °C for 15 min, the mixture was warmed to rt, and the solvent was evaporated under reduced pressure. To the resultant salt were added benzyltriethylammonium chloride (17 mg, 0.075 mmol), ClFeTPP (11 mg, 0.015 mmol), **7** (429 mg, 3 mmol), and anhydrous toluene (5 mL). The mixture was vigorously stirred for 3 days at 40 °C. Water (10 mL) was added to the mixture, which was then washed with DCM (3 × 25 mL) and dried over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure to give a residue, which was purified by flash chromatography (eluent petroleum ether/EtOAc, 1:1) to afford methyl (1*R**,2*S**)- and (1*R**,2*R**)-1-(acetylamino)-2-(3-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxyphenyl)-1-cyclopropanecarboxylate (**21**). Data for (*E*)-**21**: colorless oil (7% yield); EtOAc/petroleum ether, 1:1; R_f = 0.15; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (6H, s, Si(CH_3)$_2$), 0.97 (9H, s, SiC(CH_3)$_3$), 1.59 (1H, dd, J = 9.9 and 5.5 Hz, C*H*HCCO$_2$), 2.05 (3H, s, CH_3CONH), 2.21 (1H, dd, J = 8.4 and 5.5 Hz, CH*H*CCO$_2$), 2.77 (1H, dd, J = 9.9 and 8.4 Hz, ArC*H*), 3.34 (3H, s, COOCH_3), 6.33 (1H, br s, N*H*), 6.73 (1H, dd, J = 8.1 and 1.8 Hz, aryl H), 6.83 (1H, d, J = 1.8 Hz, aryl H) 6.92 (1H, d, J = 7.7 Hz, aryl H), 7.12 (1H, dd, J = 8.1 and 7.7 Hz, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.3 (2q), 18.3 (s) 20.5 (t), 23.3 (q), 25.8 (3q), 34.4 (d), 40.7 (s), 51.9 (q), 118.9 (d), 121.1 (d), 122.3 (d), 129.0 (d), 136.8 (s), 155.5 (s), 170.0 (s), 171.1 (s);

IR ν_{max}/cm^{-1} 3289, 2931, 2858, 1737, 1662, 1532, 1487, 1436, 1334, 1277, 1151, 1005, 918, 833, 779, 693; MS *m*/*z* (EI) 363 (M$^+$, 63), 306 (92), 245 (100), 232 (100), 204 (90); HRMS *m*/*z* found 363.1854, $C_{19}H_{29}NO_4Si$ requires 363.1866. Data for (*Z*)-**21**: colorless solid (37% yield); EtOAc/petroleum ether, 1:1; R_f = 0.25; mp 110−112 °C (EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (6H, s, Si(C*H*$_3$)$_2$), 0.98 (9H, s, SiC(C*H*$_3$)$_3$), 1.68 (1H, dd, *J* = 8.0 and 6.0 Hz, C*H*HCCO$_2$), 1.86 (3H, s, C*H*$_3$CONH), 2.22 (1H, dd, *J* = 9.5 and 6.0 Hz, CH*H*CCO$_2$), 2.88 (1H, dd, *J* = 9.5 and 8.0 Hz, ArC*H*), 3.75 (3H, s, COOC*H*$_3$), 5.31 (1H, br s, N*H*), 6.63 (1H, d, *J* = 8.1 Hz, aryl H), 6.77 (2H, m, aryl H), 7.19 (1H, t, *J* = 7.9 Hz, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.3 (2q), 18.2 (s) 21.3 (t), 22.9 (q), 25.7 (3q), 32.3 (d), 39.0 (s), 52.7 (q), 119.2 (d), 120.4 (d), 121.9 (d), 129.5 (d), 135.9 (s), 155.9 (s), 171.2 (s), 172.1 (s); IR ν_{max}/cm^{-1} 3299, 2959, 1742, 1665, 1602, 1542, 1489, 1270, 1249, 1159, 971, 921, 834, 781, 687; MS *m*/*z* (EI) 363 (M$^+$, 32), 304 (100), 245 (72), 232 (71), 204 (70); HRMS *m*/*z* found 363.1862, $C_{19}H_{29}NO_4Si$ requires 363.1866. Anal. Calcd for $C_{19}H_{29}NO_4Si$: C, 62.78; H, 8.04; N, 3.85. Found: C, 62.63 H, 8.39; N, 4.00.

Synthesis and Characterization of Compounds in Schemes 2−4. (1*S,2*R**)-1-[(*tert*-Butoxycarbonyl)amino]-2-phenylcyclopropane-1-carboxylic Acid [(*E*)-11].**[24] Freshly activated zinc dust (300 mg) was added to a mixture of (*E*)-**9** (28 mg, 0.067 mmol), THF (1.5 mL), and 0.35 M phosphate buffer solution (pH 6, 4.5 mL). After being stirred vigorously at rt for 16 h, the mixture was filtered and washed several times with EtOAc. The aq layer was adjusted to pH 3, and the organic layer was separated and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure to give (*E*)-**11** (14 mg, 74%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (9H, s, C(C*H*$_3$)$_3$), 1.51 (1H, m, C*H*HCO$_2$), 2.08 (1H, m, C*H*HCO$_2$), 2.84 (1H, m, C*H*Ph), 5.29 (1H, br s, N*H*), 7.10−7.30 (5H, m, aryl H).

(1*R,2*R**)-1-Amino-2-phenyl-1-cyclopropanecarboxylic Acid Hydrochloride [(*Z*)-1].**[13] A mixture of (*Z*)-**10** (90 mg, 0.38 mmol) and a 4 N aq solution of HCl (5 mL) was stirred at reflux for 16 h. The solvent was evaporated under reduced pressure to give (*Z*)-**1** (69 mg, 84%) as a pale yellow solid: ^{1}H NMR (400 MHz, D_2O) δ 1.82 (1H, dd, *J* = 8.8 and 6.8 Hz, C*H*HCCO$_2$), 1.97 (1H, dd, *J* = 10.0 and 6.8 Hz, C*H*HCCO$_2$), 3.19 (1H, dd, *J* = 10.0 and 8.8 Hz, C*H*Ar), 7.30−7.39 (5H, m, aryl H); ^{13}C NMR (100 MHz, D_2O) δ 17.0 (d), 23.4 (t), 39.3 (s), 128.9 (d), 129.4 (2d), 130.0 (2d), 132.0 (s), 172.8 (s).

(1*S,2*R**)-1-Amino-2-(3-hydroxyphenyl)-1-cyclopropanecarboxylic Acid [(*E*)-2].**[7] A 4 N aq solution of HCl (3 mL) was added to a solution of (*E*)-**20** (230 mg, 0.42 mmol) in 1,4-dioxane (10 mL). After the mixture was stirred at rt for 16 h, the solvent was evaporated under reduced pressure to give the ammonium salt as a pale yellow solid: ^{1}H NMR (400 MHz, MeOD) δ 1.77 (1H, dd, *J* = 10.7 and 6.8 Hz, C*H*HCCO$_2$), 2.15 (1H, dd, *J* = 8.8 and 6.8 Hz, C*H*HCCO$_2$), 2.92 (1H, dd, *J* = 10.7 and 8.8 Hz, C*H*Ar), 492 and 4.96 (2H, AB system, J_{AB} = 13.2 Hz, CO$_2$C*H*$_2$PNB), 6.55−6.61 (2H, m, aryl OH), 6.66 (1H, d, *J* = 7.8 Hz, aryl OH), 6.96 (1H, m, aryl OH), 6.96 (2H, dd, *J* = 8.3 Hz, ArNO$_2$), 7.98 (2H, dd, *J* = 8.3 Hz, ArNO$_2$); ^{13}C NMR (100 MHz, MeOD) δ 16.3 (t), 31.0 (d), 40.0 (s), 66.2 (t), 114.5 (d), 115.8 (d), 119.9 (d), 123.1 (2d), 128.6 (2d), 129.3 (d), 134.8 (s), 141.8 (s), 147.7 (s), 157.5 (s), 167.2 (s).

A 4 N aq solution of HCl (3 mL) was added to a solution of the ammonium salt in 1,4-dioxane (10 mL). After the mixture was stirred at reflux for 160 h, the solvent was evaporated under reduced pressure. The residue was dissolved in a 2% aq solution of HCl (10 mL) and washed with CH_2Cl_2 (20 mL) and then EtOAc (20 mL). The aq phase was evaporated under reduced pressure to give the crude material, which was passed through a Dowex 50 anionic exchange resin. The solvent in the fraction containing the free amino acid was evaporated under reduced pressure to give (*E*)-**2** (70 mg, 87%) as a pale yellow solid: mp 192−202 °C (MeOH) (lit.[7] mp 195−205 °C); ^{1}H NMR (400 MHz, 5% DCl in D_2O) δ 1.96 (1H, dd, *J* = 10.3 and 7.1 Hz, C*H*HCCO$_2$), 2.19 (1H, dd, *J* = 9.1 and 7.1 Hz, C*H*HCCO$_2$), 3.16 (1H, dd, *J* = 10.3 and 9.1 Hz, C*H*Ar), 6.79−6.99 (3H, m, aryl H), 7.26 (1H, t, *J* = 7.7 Hz, aryl H); ^{13}C NMR (100 MHz, 5% DCl in D_2O) δ 16.9 (t), 30.7 (d), 39.6 (s), 114.6 (d), 115.7 (d), 121.0 (d), 129.6 (d), 135.2 (s), 155.7 (s), 169.6 (s): IR ν_{max}/cm^{-1} 2994, 1597, 1505, 1452, 1403, 1215, 890, 871, 695; MS *m*/*z* (CI with CH_4) 191 ([M − 2H]$^+$, 45), 148 ([M − CO_2H]$^+$.

(1*S,2*R**)-1-[(*tert*-Butoxycarbonyl)amino]-2-ethylcyclopropane-1-carboxylic Acid [(*E*)-25].**[5] To a solution of (*E*)-**22** (339 mg, 936 μmol) in MeOH (8 mL) was added $Pd(OH)_2$ (38 mg, 20 wt % Pd on carbon). The solvent was briefly degassed (1 mmHg, 25 °C), and hydrogen was added via a balloon. This mixture was then stirred at rt for 5 h. The reaction mixture was filtered through Celite and washed with EtOAc (3 × 20 mL). The organic washings were combined, and water (50 mL) was added. The pH of the aq layer was adjusted to 1 with a 2 M aq solution of HCl. The layers were separated, and the aq layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure to afford the crude material, which was partially purified by column chromatography (eluent EtOAc/petrol, 50:50) to afford a solid. This residue was dissolved in EtOAc (10 mL) and added to a saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). EtOAc (10 mL) was added to the aqueous phase, which was then acidified to pH 1 with an 11.8 M aqueous solution of HCl. The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure to afford (*E*)-**25** (169 mg, 79%) as a colorless solid: mp 127−128 °C (lit.[5] mp 126−127 °C); ^{1}H NMR (300 MHz at 55 °C, CD_3OD) δ 0.99 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.15 (1H, dd, *J* = 8.6 and 4.2 Hz, C*H*HCO$_2$), 1.34−1.42 (1H, m, C*H*HCO$_2$), 1.42−1.48 (1H, m, CH_3CH_2CH), 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.58 (2H, q, *J* = 7.4 Hz, C*H*$_2$CH$_3$); IR ν_{max}/cm^{-1} 3254, 3093, 2975, 2934, 2877, 2577, 1697, 1651, 1478, 1455, 1394, 1367, 1305, 1195, 1158.

(1*S,2*R**)-1-Amino-2-ethyl-1-cyclopropanecarboxylic Acid Hydrochloride [(±)-Coronamic Acid, (±)-3].**[5] (*E*)-**25** (98 mg, 427 μmol) was dissolved in a 1 M aqueous solution of HCl in MeOH (17.1 mL, 17.1 mmol) at 0 °C. The clear yellow solution was slowly allowed to warm to rt and subsequently stirred for 44 h. The solvent was removed under reduced pressure. The residue was washed with EtOAc (3 × 10 mL), filtered, and dried under reduced pressure to afford (±)-**3** (63 mg, 89%) as a colorless solid: mp 199−200 °C (lit. (free amino acid),[5] sublimes at >185 °C); ^{1}H NMR (300 MHz, D_2O) δ 0.82 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 1.35−1.54 (3H, m, C*H*$_2$CH$_3$ and C*H*HCN), 1.54−1.68 (2H, m, C*H*HCN and CH_3CH_2CH); IR ν_{max}/cm^{-1} 2957, 1720, 1590, 1500, 1462, 1402, 1308, 1191, 1164.

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Supporting Information Available: Characterization data of all the compounds synthesized and X-ray crystallographic data of 2-(2,2-diphenylvinyl)-1-cyclopropanecarboxylic acids. This material is available free of charge via the Internet at http://pubs.acs.org.

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