Stereoselectivity in Cyclopropanation of Amino Acid-derived Enones

by
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Abstract:

An efficient synthesis of cyclopropyl peptidomimetics was developed by Dunlap et. al.; the key step of this synthesis is the cyclopropanation of amino-acid derived enones to access both nitrocyclopropyl and estercyclopropyl peptidomimetics. However, the key cyclopropanation step suffers from a lack of stereoselectivity. The goal of this study is to improve stereoselectivity in the cyclopropanation step using Gaunt's quinine and quinidine-based catalysts. Prior work using Gaunt's quinine methyl ether catalyst has shown improved diastereoselectivity for the *syn* isomer of some amino acids. Current efforts to improve diastereoselectivity using Gaunt's quinine and quinidine benzyl ether catalysts are reported here. The catalysts are selective for opposing diastereomers and improve diastereoselectivity for a wider range of amino acids.

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Chapter 1: Introduction

Peptidomimetics

Peptidomimetics are a class of compounds whose structures resemble peptides, but the structure is modified to make it more suitable as a medication compared to the original peptide. In general, peptides are poor drugs due to their hydrolysis *in vivo* by peptidases. Peptidomimetics can mimic peptide substrates and serve as enzyme inhibitors, and there are multiple different types of modifications that can be done to their structure. One such modification is the substitution of the amide bond in the peptide backbone with a hydroxyethylene core (Figure 1). The hydroxyethylene core is found in drugs such as HIV protease inhibitors ritonavir and lopinavir (Figure 1).[1]

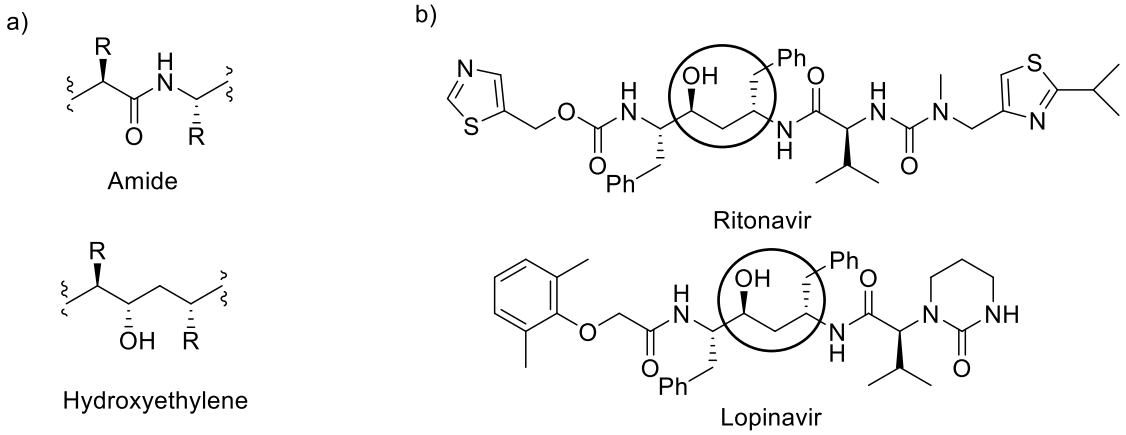
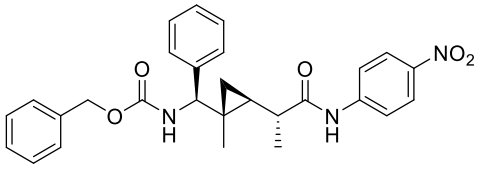
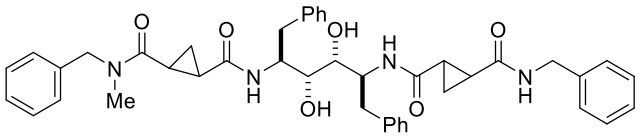


Figure 1: a) Comparison of amide and hydroxyethylene core and b) examples of drugs containing hydroxyethylene core (circled).

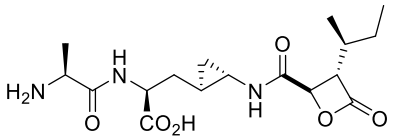
Another possible modification is the addition of a cyclopropyl group; the addition of a cyclopropyl group makes the peptidomimetic more rigid. Examples of cyclopropyl peptidomimetics include Wipf's cyclopropane dipeptide isostere and Martin's pseudopeptide HIV-1 inhibitors..[2,3] A backbone cyclopropyl is also seen in belactosin A, a naturally occurring proteasome inhibitor and anti-tumor compound. As such, belactosin A is a potential lead for future cyclopropyl peptidomimetics that may act as proteasome inhibitors.



Wipf's cyclopropane dipeptide isostere



Martin's pseudopeptide inhibitor



belactosin A

Figure 2: Examples of peptidomimetics containing a cyclopropyl motif.

Cyclopropyl Peptidomimetic Synthesis

In 2011, a three-step synthesis of cyclopropyl hydroxyethylene peptidomimetics was published by Dunlap et al (Figure 3).[4] The synthesis began with conversion of the Weinreb amides (1) of Cbz-protected amino acids to enones (2) *via* a Grignard reaction with vinylmagnesium bromide. The enone then undergoes cyclopropanation (3) using the

sulfur ylide EDSA; the mechanism for this is a Michael Induced Ring Closure (MIRC). The final step of the synthesis is the reduction of the ketone to an alcohol using $NaBH_4$ to form a cyclopropyl peptidomimetic (4).

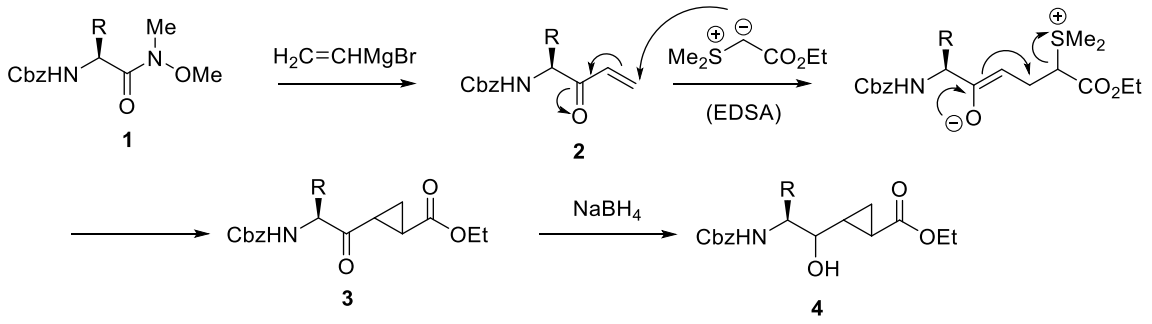


Figure 3: Three-step synthesis of cyclopropyl peptidomimetcs.

A flaw of the synthesis is the lack of stereoselectivity in the cyclopropanation and reduction steps of the synthesis.[4] Though the cyclopropanation reaction will produce a *trans* ring with respect to its substituents as seen in Figure 3, it also forms a 1:1 ratio of *syn:anti* diastereosomers (Figure 4). This lack of stereoselectivity is most likely due to the distance of the R group from where the cyclopropanation reaction occurs. The distance from where the reaction takes place minimizes any directing effect the R group could have in the reaction. Furthermore, the subsequent reduction step only has mild stereoselectivity, forming a 2:1 mixture of the 4R and 4S isomers of compound **4** respectively. Due to this deficiency in both steps, efforts have been made to improve stereoselectivity for both steps. The focus of this research is on improving stereoselectivity for the cyclopropanation step.

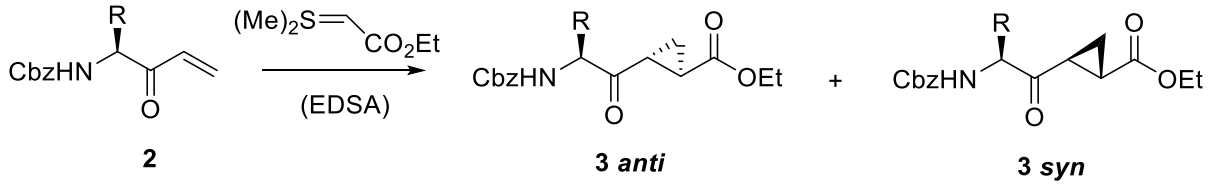


Figure 4: Stereosisomers formed in cyclopropanation step.

Sulfonium Ylide-Directed Cyclopropanation

There are numerous studies that have used chiral catalysts in directing a cyclopropanation reaction. Three were of particular interest, all using natural products as a source of chirality. The first of these, Aggarwal's studies, used sulfonium ylide catalysts derived from camphor to direct the cyclopropanation reaction (Figure 5).[5-7] These are similar to the EDSA cyclopropanation; however the dimethyl sulfide is replaced with a bicyclic sulfide linked to a chiral camphor (compound **6**). A weakness is that it requires four steps to make compound **6** from camphor sulfonyl chloride (**5**), although stereoselectivity with the catalyst is usually high.

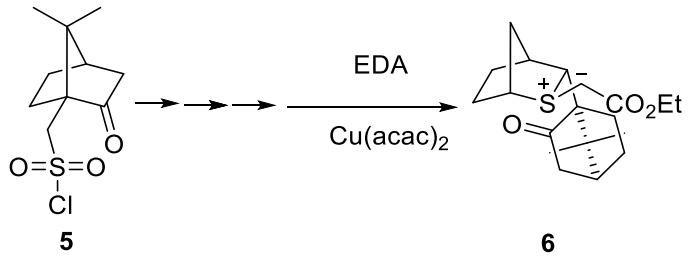


Figure 5: Synthesis of Aggarwal's chiral sulfide and ylide (EDA is ethyl diazoacetate).

Some examples of the use of Aggarwal's catalyst are described here. One study's goal was to carry out a one-step stereoselective cyclopropanation reaction using cyclic enones as a starting point and the sulfonium ylides as catalysts. This describes a general framework for how stereoselectivity occurred in sulfonium ylide mediated cyclopropanation though equilibration of the betaine intermediate (Figure 6a). When the reaction was metal-catalyzed, under neutral conditions, and under elevated temperatures, the reaction had little diastereoselectivity, irreversibly forming a 1:1 ratio of the two betaine intermediates and hence the *endo* and *exo* diastereosmers., but high enantioselectivity. However, under basic conditions, while betaine intermediates irreversibly formed a 1:1 ratio, due to equilibration the reaction had high diastereoselectivity for the *exo* isomer, but as a consequence, there is also lowered enantioselectivity. Aggarwal speculated that using acyclic enones in the reaction would provide greater diastereoselectivity. In fact, he has many examples where high stereoselectivity is achieved with acyclic enones, with a few examples shown in Figure 6b.

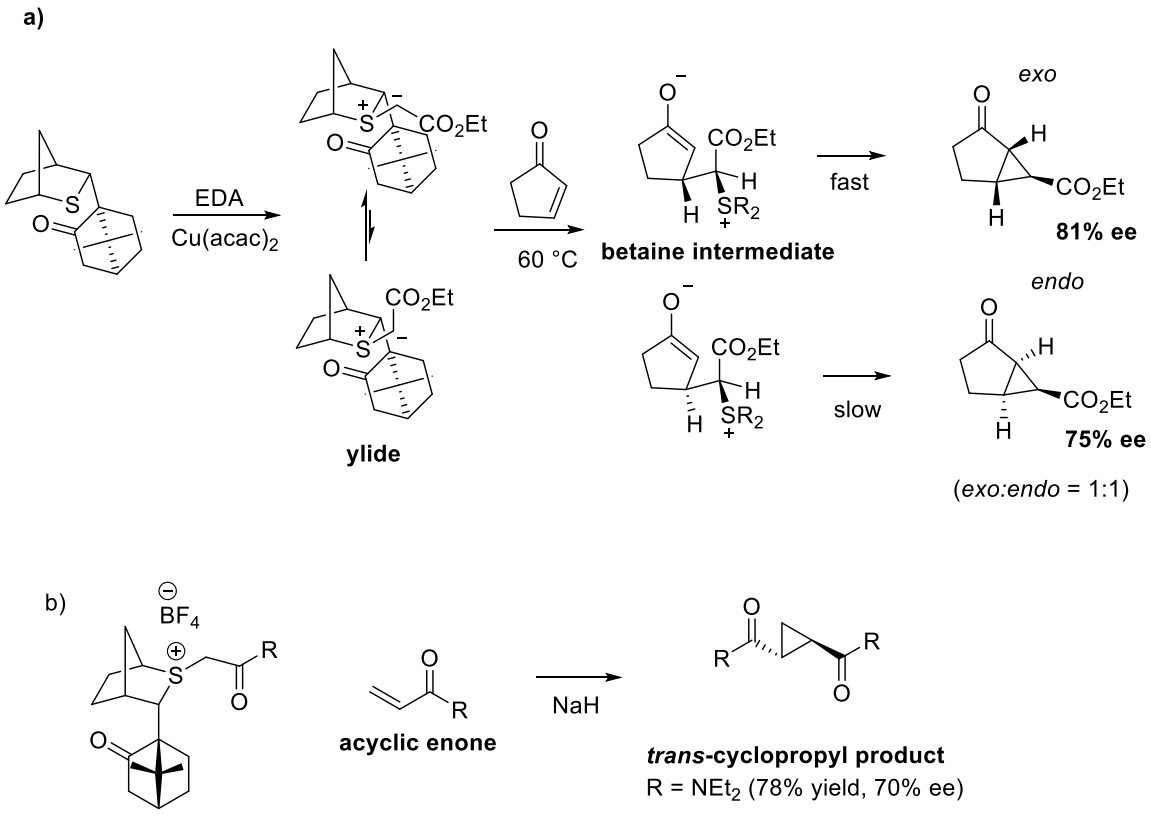


Figure 6: Cyclopropanation of cyclic and acyclic enones using chiral sulfide catalsyts (a) cyclic enone example (b) acylic enone example.[5,7]

Nitrocyclopropanation

A second study by Ley used a pyrrodinyl tetrazole catalyst to direct a nitrocyclopropanation reaction.[8] The catalyst affords both high yields and good enantioselectivity for cyclic and acyclic enones (Figure 7). Multiple changes to conditions were made including optimizing solvent and reagent conditions such as doubling the amount of bromonitromethane and tripling the amount of morpholine used.

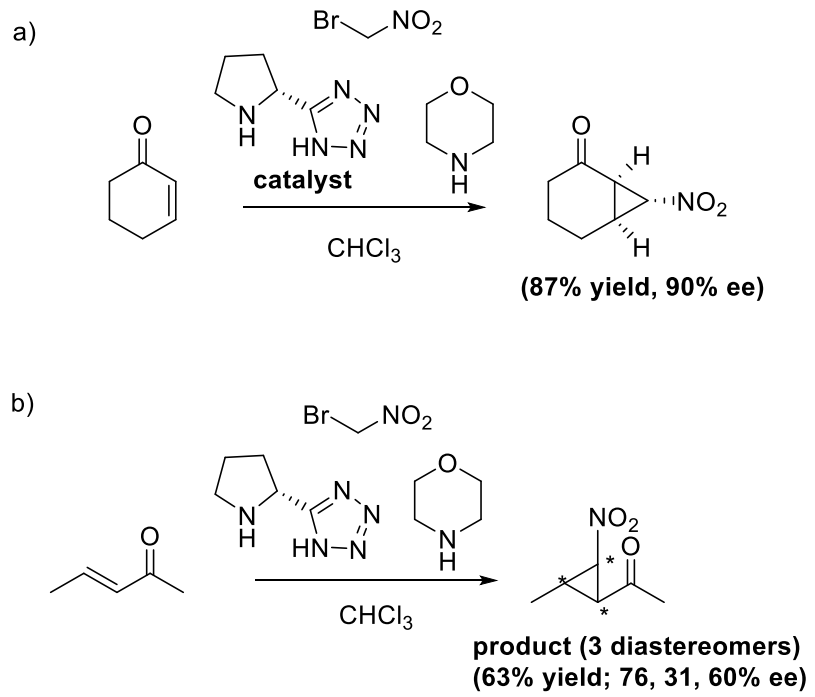


Figure 7: Nitrocyclopropanation of cyclic and acyclic enones with proline-derived catalyst a) cyclic enone example b) acyclic enone example.[8]

Though this new approach produced overall high yields and enantioselectivity for cyclic and acyclic enones, there are certain conditions needed when using acyclic enones. When the R_1 group of the enone was a methyl group, the results showed high yields and enantioselectivity (Table 1). However, when the methyl was replaced by a bulkier group such as an ethyl or phenyl group, the results instead showed low yields and enantioselectivity (Table 1).

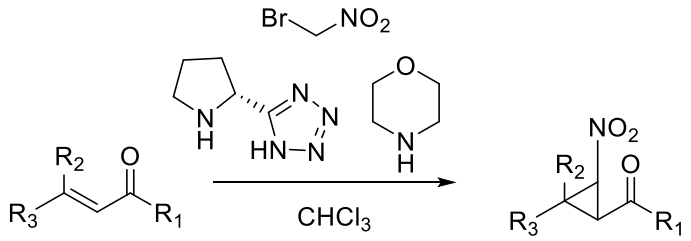
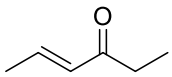
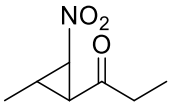
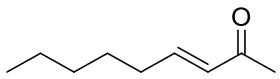
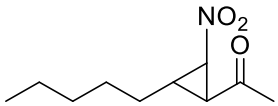
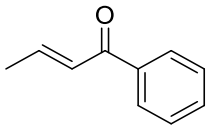
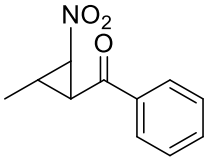


Table 1: Nitrocyclopropanation of acyclic enones.[8]

Enone	Product	Yield (%)	ee (%)
		47	63,37
		84	70,37,61[a]
		42	42,29[a]

a) Multiple ee values of acyclic enones are due to formation of diastereomers.

Ammonium Ylide-Directed Cyclopropanation

The most promising of these studies was Gaunt's use of cinchona-based catalysts to direct an ammonium-ylide based cyclopropanation to afford ester-cyclopropyl compounds.[9-11] These catalysts are derived from cinchona alkaloids, the natural products quinine and quinidine. In the proposed catalytic cycle, the catalyst, a tertiary amine, covalently bound itself to the α-bromo ketone to give an intermediate chiral ammonium

ylide. This allows the catalyst to direct the reaction towards a specific stereoisomer (Figure 8).

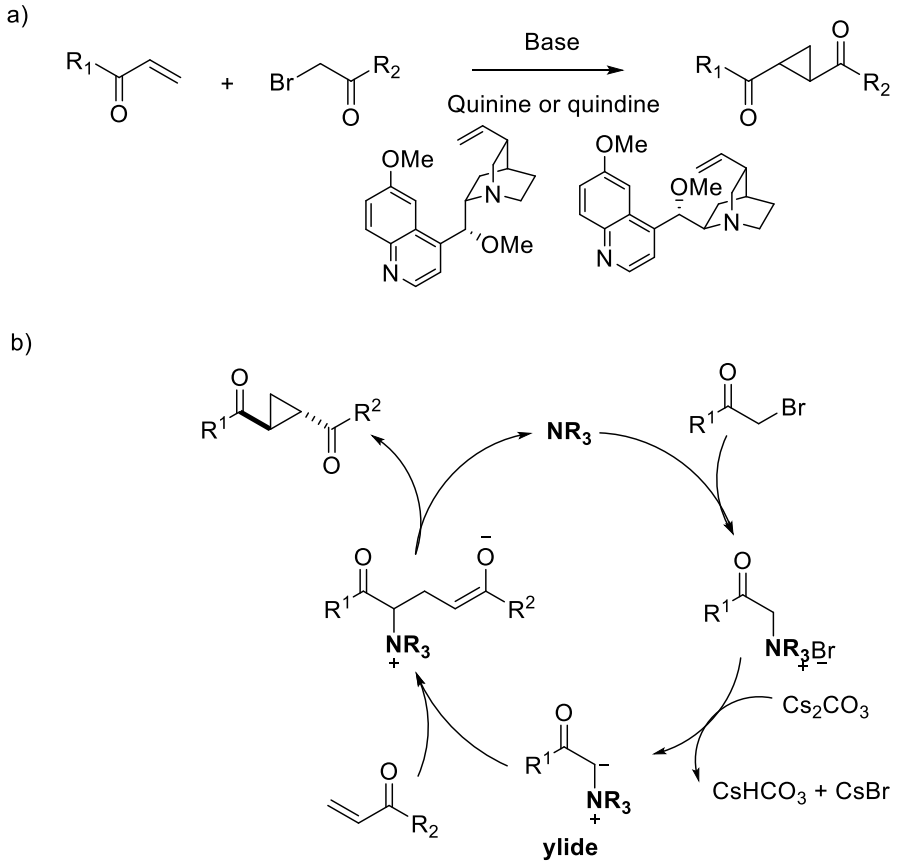
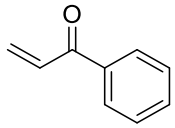
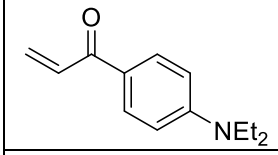
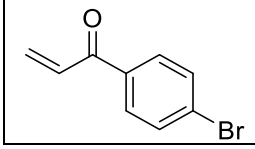


Figure 8: Cyclopropanation using cinchona-based catalysts a) general reaction and b) proposed catalytic cycle.

The results of the studies showed that the catalysts provided high stereoselectivity and good yields when tested (Table 2). Although similar to Ley's tetrazole catalyst in that there is an intermediate ammonium ylide, these results showed improvement with enones with large α-alkyl substituents. The catalysts were easy to prepare, and the reagents,

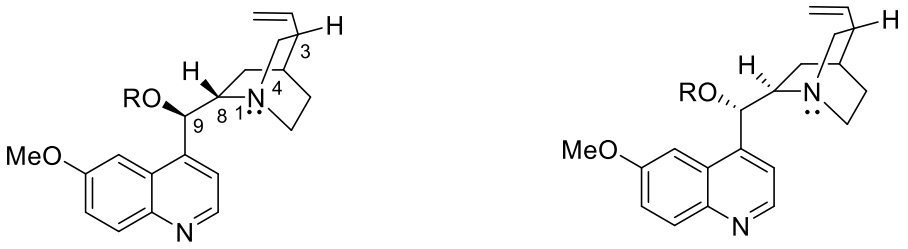
similar to Ley's, are commercially available. As such, Gaunt's catalysts were considered as a potential solution for our problem.

Table 2. Cinchona-catalyzed cyclopropanation using bromo tert-butylacetate.[9]

Alkene	Catalyst	Yield (%)	ee(%)
	Quinine methyl ether Quinidine methyl ether	96% 92%	86 (+) 88 (-)
	Quinine methyl ether Quinidine methyl ether	73% 73%	84 (+) 84 (-)
	Quinine methyl ether	83%	85 (+)

Quinine and Quinidine

Of Gaunt's cinchona-based catalysts, the quinine and quinidine-derived catalysts are the focus of this study (Figure 10). Quinine and quinidine are diastereomers, with only two different chiral centers; however, though they are diastereomers, their structures are nearly mirror images of one another (Figure 10).[12] As a result, though they are diastereomers, they behave as enantiomers and quinine and quinidine are considered to be "pseudoenantiomers" as a result of this unique relationship. One area where they would behave as enantiomers would be their capability to act as chiral catalysts. Due to quinine and quinidine's relationship as "pseudoenantiomers", Gaunt's quinine and quinidine-derived catalysts were chosen for our studies.



(1S, 3R, 4S, 8S, 9R) **(1S, 3R, 4S, 8R, 9S)**

Figure 8: Structures of quinine (left) and quinidine (right) ethers (R = methyl or benzyl)

Initial Studies with Methyl Ethers.

This study is a continuation of prior work done in Dr. Dunlap's lab testing Gaunt's quinine and quinidine-derived catalysts, specifically the methyl ether derivatives. When the quinine methyl ether derivative was used for the cyclopropanation of amino acid derived enones, the reaction afforded 100% *syn* isomer. However, this result was only seen with with α-branched amino acids such as valine and isoleucine (Table 3). Furthermore, the use of the quinidine methyl ether did not provide stereoselectivity to the reaction towards the *anti* isomer, producing a 1.0:1.0 ratio of *syn* to *anti* isomer. Due to deficiency in stereoselectivity afforded by the methyl ether derivatives, attention was turned to Gaunt's benzyl ether derivatives, the focus of this study. As the use of the methyl ether derivatives provided either limited stereoselectivity or no stereoselectivity, we speculated that by substituting the methyl group for a larger benzyl group, the benzyl ether catalysts would show greater stereoselectivity than the methyl ether catalysts.

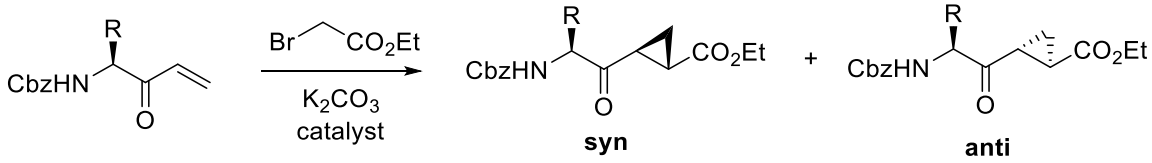
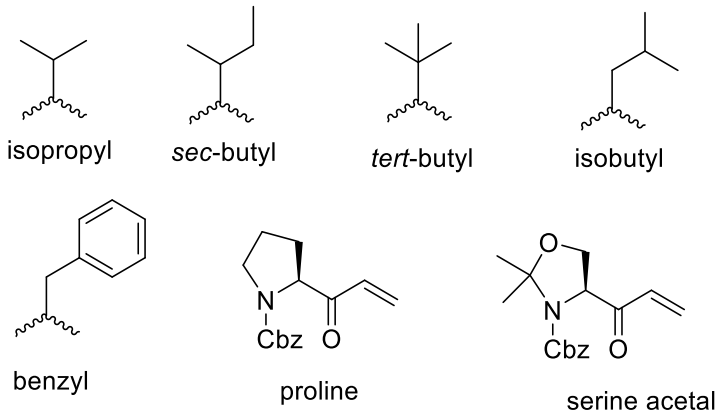


Table 3: Ratios of Cyclopropanation With and Without Quinine OMe from a) ^{1}H-NMR or b) HPLC

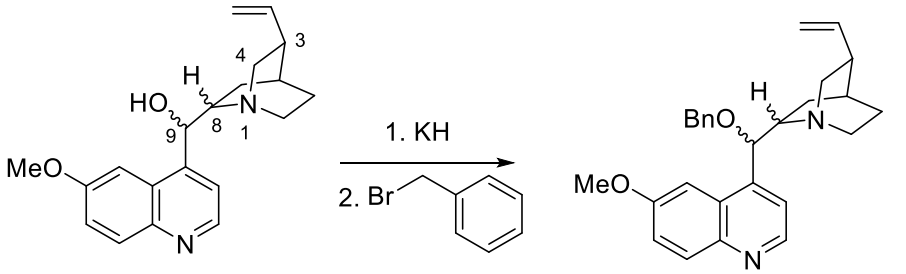
Amino acid	**R group**	**With Quinine OMe**	**(no catalyst)**
		syn/anti	**syn/anti**
valine	isopropyl	100/0[b]	1.0/1.5[b]
isoleucine	*sec*-butyl	100/0	1.5/1.0
(Boc) *tert*-butylglycine	*tert*-butyl	100/0	1.0/2.0
leucine	isobutyl	1.0/1.0[a]	1.0/1.0[a]
phenylalanine	benzyl	1.0/1.0[a]	1.0/1.1[a]
proline	-ring-	1.0/1.0	1.0/1.0
serine acetal	-ring-	2.0/1.0	2.0/1.0



Chapter 2: Materials and Methods

Catalyst Preparation

The catalysts were synthesized using a Williamson ether synthesis (Scheme 1). To form each catalyst, quinine or quinidine was added to a suspension of KH at 0 °C and heated to reflux for 30 minutes under argon. Afterward, the benzyl bromide was added to the solution, and the crude product was purified using flash column chromatography. The catalysts were identified using NMR spectroscopy and were identical to those reported in the literature.[7]



Quinine (1S, 3R, 4S, 8S, 9R)
Quinidine (1S, 3R, 4S, 8R, 9S)

benzyl ether catalyst

Figure 9: Catalyst preparation.

Enone Preparation

A two-step procedure outlined by Dunlap et al. was used to produce the enones as substrates for the cyclopropanation reaction (Scheme 2).[4] The first step was the conversion of commercially available Cbz-protected amino acids into Weinreb amides. The Weinreb amides were then converted into enones *via* a Grignard reaction using vinylmagnesium bromide (Scheme 2). In both steps, the crude product was purified by chromatography and the structure verified using NMR spectroscopy.

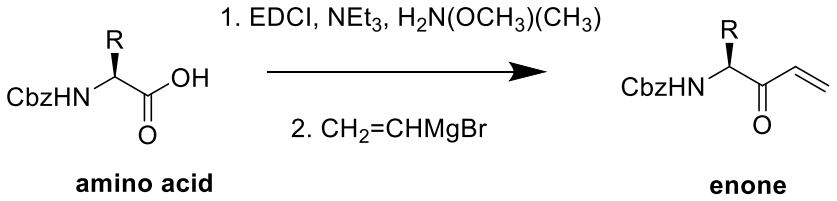


Figure 10: Enone preparation.

Cyclopropanation

The procedure used by Papageorgiou et. al. was used for the cyclopropanation reaction (Scheme 3).[9-11] The reagents were dissolved in acetonitrile and the resulting mixture was heated to reflux for at least 24 hours. To ensure the reaction went to completion, one equivalent of bromoethyl acetate was added to the mixture every two hours, up to four hours into the reaction. The product was purified by chromatrography and ^{1}H-NMR was used to verify the products. The ratio of *syn:anti* isomers were determined using HPLC and ^{1}H-NMR.

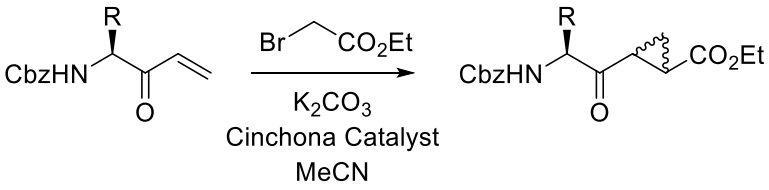
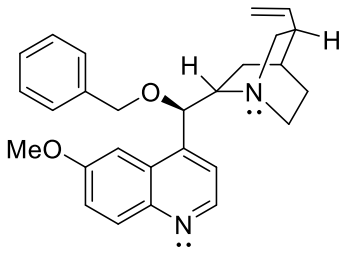


Figure 11: General cyclopropanation procedure.

Experimental Section

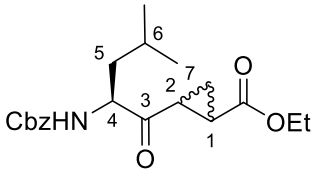
NMR data was collected using a JEOL ECA 500 NMR spectrophotometer with $CDCl_3$ as the NMR solvent. HPLC data was collected using a Waters 1525 Binary HPLC Pump using a normal phase Waters Spherisorb column (10 x 250 mm). Reagents and solvents were purchased from Sigma-Aldrich and used without further purification; acetonitrile (MeCN) was anhydrous. All compounds made are known compounds and ^{1}H-NMR was identical to previously reported data.[4,9-11] The quinidine benzyl ether is not reported here; it was prepared in the same manner as the quinine benzyl ether.

Quinine Benzyl Ether



Quinine (324 mg, 1 mmol) was added to a suspension of potassium hydride (72 mg, 1.8 mmol) in 8 mL of dry THF at 0°C. The solution was heated to reflux for 30

minutes under argon. To the solution, benzyl bromide (118 μL, 1.0 mmol) was added slowly, over 5 minutes, and the resulting solution was stirred at room temperature for 2 hours. The solution was poured into water and extracted twice with ethyl acetate. The organic layer was dried using anhydrous magnesium sulfate, filtered, and evaporated. The crude product was purified using flash column chromatography on silica gel, eluting with CH_2Cl_2, 1:20 MeOH/CH_2Cl_2, and 1:10 MeOH/CH_2Cl_2 to afford 532.3 mg (100%) of OBn quinine.



Leucine-derived cyclopropyl ester 3a: Ethyl 2-(((benzyloxy)carbonyl)leucyl)cyclopropane-1-carboxylate)

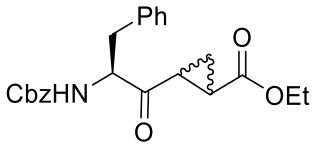
Cyclopropanation with quinine OBn: To a solution of quinine benzyl ether (25 mg, 0.060 mmol) in 1 mL acetonitrile, freshly ground potassium carbonate (40 mg, 0.29 mmol) was added and the resulting solution was heated to reflux. To the mixture, a solution of enone (50 mg, 0.18 mmol) and bromo ethylacetate (21.5 μL, 0.19 mmol) in 1 mL acetonitrile was added and the solution was refluxed overnight. Every 2 hours, bromo ethylacetate (21.5 μL, 0.19 mmol) was added up to a total of four equivalents after 6 hours. The solution was poured into brine and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated. The crude

was purified by CombiFlash, eluting with ethyl acetate/hexanes to afford 47 mg (75%) of cyclopropyl ketone (3.8:1.0 *syn:anti* isomers).

The isomers were analyzed by HPLC, eluting with an initial solvent ratio of 80/20 hexanes-ethyl acetate (EA) for 5 min, then 70/30 over 17 min for a total run time of 25 min, with a flow rate of 2.0 mL/min. The peaks were integrated to a 3.8:1.0 ratio of *syn:anti* isomers. Retention times were 16.004 min (*syn*) and 16.793 min (*anti*).

Cyclopropanation with quinidine OBn: Freshly ground potassium carbonate (32 mg, 0.24 mmol) was weighed into a 10 mL round bottom flask. The enone (50 mg, 0.18 mmol) and quinidine benzyl ether (25 mg, 0.060 mmol) were dissolved in 1.0 mL acetonitrile each and added to the flask; both were rinsed with 0.25 mL acetonitrile and added to the flask. Bromo ethylacetate (19 μL, 0.17 mmol) was syringed into the flask and the solution was heated to reflux for 24.5 hours. Every 2 hours, 1 equivalent of bromo ethylacetate (19 μL, 0.17 mmol) was added up to a total of three equivalents after 4 hours. The solution was poured into brine and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated. The crude was purified by CombiFlash, eluting with ethyl acetate/hexanes to afford 42.0 mg (67%) of cyclopropyl ketone (1.0:5.53 *syn:anti* isomers).

The isomers were analyzed by HPLC, eluting with an initial solvent ratio of 80/20 hexanes-ethyl acetate for 5 min, then 70/30 over 17 min for a total run time of 25 min, with a flow rate of 2.0 mL/min. The peaks were integrated to a 1.0:5.53 ratio of *syn:anti* isomers. Retention times were 16.330 min (*syn*) and 17.450 min (*anti*).



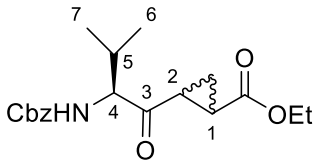
Phenylalanine (3b): ethyl-2-(((benzyloxy)carbonxyl)phenylalanyl)cyclopropane-1-carboxylate

Cyclopropanation with quinine OBn: To a solution of quinine benzyl ether (25 mg, 0.060 mmol) in 1 mL acetonitrile, freshly ground potassium carbonate (40 mg, 0.29 mmol) was added and the solution was heated to reflux for 10 minutes. To the mixture, a solution of enone (50 mg, 0.16 mmol) and bromo ethylacetate (17.9 μL, 0.16 mmol) in 1 mL acetonitrile was added and the resulting solution was refluxed overnight. Every 2 hours, bromo ethylacetate (17.9 μL, 0.16 mmol) was added to the solution, up to a total of three equivalents after 4 hours. The solution was poured into brine and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated. The crude was purified by CombiFlash, eluting with ethyl acetate/hexanes to afford 27.6 mg (43%) of cyclopropyl ketone (3.1:1.0 *syn:anti* isomers).

The isomers were analyzed by HPLC, eluting with an initial solvent ratio of 80/20 hexanes-ethyl acetate for 5 min, then 70/30 over 17 min for a total run time of 25 min, with a flow rate of 2.0 mL/min. The peaks were integrated to a 3.1:1.0 ratio of *syn:anti* isomers. Retention times were 19.503 min (*syn*) and 20.431 min (*anti*).

Cyclopropanation with quinidine OBn: To a solution of quinidine benzyl ether (25 mg, 0.060 mmol) in 1 mL acetonitrile, freshly ground potassium carbonate (40 mg, 0.29 mmol) was added and the solution was heated to reflux for 10 minutes. To the mixture, a solution of enone (50 mg, 0.16 mmol) and bromo ethylacetate (17.9 μL, 0.16 mmol) in 1 mL acetonitrile was added and the resulting solution was refluxed overnight. Every 2 hours, bromo ethylacetate (17.9 μL, 0.16 mmol) was added to the solution, up to a total of three equivalents after 4 hours. The solution was poured into brine and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated. The crude was purified by CombiFlash, eluting with ethyl acetate/hexanes to get 50.8 mg (79%) of cyclopropyl ketone (1.0:2.2 *syn:anti* isomers).

The isomers were analyzed by HPLC, eluting with an initial solvent ratio of 80/20 hexanes-ethyl acetate for 5 min, then 70/30 over 17 min for a total run time of 25 min, with a flow rate of 2.0 mL/min. The peaks were integrated to a 1.0:2.2 ratio of *syn:anti* isomers. Retention times were 19.090 min (*syn*) and 20.016 min (*anti*).



Valine (3c): ethyl 2-(((benyloxy)carbonyl)valyl)cyclopropane-1-carboxylate

Cyclopropanation with quinine OBn: To a solution of quinine benzyl ether (25 mg, 0.060 mmol) in 1 mL acetonitrile, freshly ground potassium carbonate (40 mg, 0.29 mmol) was added and the solution was heated to reflux for 10 minutes. To the mixture, a solution of enone (50 mg, 0.19 mmol) and bromo ethylacetate (21 μL, 0.19 mmol) in 1

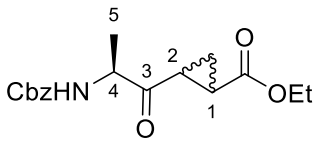
mL acetonitrile was added and the resulting solution was refluxed overnight. Every 2 hours, bromo ethylacetate (21 μL, 0.19 mmol) was added to the solution, with a total of three equivalents being used after 4 hours. The solution was poured into brine and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated. The crude was purified by CombiFlash, eluting with ethyl acetate/hexane to afford 59.1 mg (88.6%) of cyclopropyl ketone (10.8:1.0 *syn:anti* isomers).

The isomers were analyzed by ^{1}H-NMR. The signals for the C^{2} hydrogen were integrated to a 10.8:1.0 ratio of *syn:anti* isomers.

Cyclopropanation with quinidine OBn: To a solution of quinidine benzyl ether (25 mg, 0.060 mmol) in 1 mL acetonitrile, freshly ground potassium carbonate (40 mg, 0.29 mmol) was added and the solution was heated to reflux for 10 minutes. To the mixture, a solution of enone (50 mg, 0.19 mmol) and bromo ethylacetate (21 μL, 0.19 mmol) in 1 mL acetonitrile was added and the resulting solution was refluxed overnight. Every 2 hours, bromo ethylacetate (21 μL, 0.19 mmol) was added to the solution, up to a total of three equivalents after 4 hours. The solution was poured into brine and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated. The crude was purified by CombiFlash twice, eluting with ethyl acetate/hexanes to get 8.2 mg (12.3%) of cyclopropyl ketone (1.0:9.5 *syn:anti* isomers).

The isomers were analyzed by HPLC, eluting with an initial solvent ratio of 80/20 hexanes-ethyl acetate for 5 min, then 70/30 over 17 min for a total run time of 25 min,

with a flow rate of 2.0 mL/min. The peaks were integrated to a 1.0:9.5 ratio of *syn:anti* isomers. Retention times were 17.708 min (*syn*) and 18.471 min (*anti*).



Alanine (3d): ethyl 2-(((benzyloxy)carbonxyl)alanyl)cyclopropane-1-carboxylate

Cyclopropanation with quinine OBn: To a solution of quinine benzyl ether (25 mg, 0.060 mmol) in 1 mL acetonitrile, freshly ground potassium carbonate (40 mg, 0.29 mmol) was added and the solution was heated to reflux for 10 minutes. To the mixture, a solution of enone (50 mg, 0.21 mmol) and bromo ethylacetate (24 μL, 0.21 mmol) in 1 mL acetonitrile was added and the resulting solution was refluxed overnight for 26 hours. Every 2 hours, bromo ethylacetate (24 μL, 0.21 mmol) was added to the solution, up to a total of three equivalents after 4 hours. The solution was poured into brine and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated. The crude was purified by flash column chromatography, eluting with 1:10 ethyl acetate/hexanes and 1:6 ethyl acetate/hexanes to afford 10.6 mg (16.2%) of cyclopropyl ketone (1.1:1.0 *syn:anti* isomers).

The isomers were analyzed by ^{1}H-NMR, as they are inseparable by HPLC. The signals for the C^{2} hydrogen were integrated to a 1.1:1.0 ratio of *syn:anti* isomers.

Cyclopropanation with quinidine OBn: To a solution of quinidine benzyl ether (25 mg, 0.060 mmol) in 1 mL acetonitrile, freshly ground potassium carbonate (40 mg, 0.29 mmol) was added and the solution was heated to reflux for 10 minutes. To the mixture, a solution of enone (50 mg, 0.21 mmol) and bromo ethylacetate (24 μL, 0.21 mmol) in 1 mL acetonitrile was added and the resulting solution was refluxed overnight for 26.5 hours. Every 2 hours, bromo ethylacetate (24 μL, 0.21 mmol) was added to the solution, up to a total of three equivalents after 4 hours. The solution was poured into brine and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated. The crude was purified by CombiFlash, eluting with ethyl acetate/hexanes to get 30.6 mg (46.7%) of cyclopropyl ketone (1.0:2.9 *syn:anti* isomers).

The isomers were analyzed by ^{1}H-NMR, as they were inseparable by HPLC. The signals for the C^{2} hydrogen were integrated to a 1.0:2.9 ratio of *syn:anti* isomers.

Chapter 3: Results and Conclusions

Data from HPLC and ^{1}H-NMR revealed a trend when using quinine benzyl ether or quinidine benzyl ether as catalysts. Use of the quinine benzyl ether showed a preference for the *syn* isomer to form during the reaction; on the other hand, use of the quinidine benzyl ether showed a preference for the *anti* isomer to form (Table 4). This trend extends to amino acids such as leucine and phenylalanine, which were unaffected by the quinine and quinidine methyl ether catalysts tested prior to this study. The alanine enone was unaffected by the quinine benzyl ether, though the quinidine benzyl ether afford some selectivity.

Table 4: Cyclopropanation results using quinine OBn and quinidine OBn using a) HPLC or b) ^{1}H-NMR

Amino Acids	**R Group**	**Quinine OBn Yield (%)**	**Quinine OBn *syn:anti ratio***	**Quinidine OBn Yield (%)**	**Quinidine OBn *syn:anti ratio***
Leucine	**isobutyl**	**75**	**3.8:1[a]**	**67**	**1.0:5.53[a]**
Phenylalanine	**benzyl**	**43**	**3.1:1.0[a]**	**79**	**1.0:2.2[a]**
Alanine	**methyl**	**16.2**	**1.1:1.0[b]**	**46.7**	**1.0:2.9[b]**
Valine	**Isopropyl**	**88.6**	**10.8:1.0[b]**	**12.3**	**1.0:9.5[a]**

The selectivity of the quinine benzyl ether for the *syn* isomer and quinidine benzyl ether for the *anti* isomer may be related to their conformations. Prior studies done by Caner et al. and Dijkstra et al. have studied the conformations of cinchona alkaloids,

including quinine and quinidine.[13,14] These studies have shown that quinine and quinidine both naturally exist in a conformation called *anti-closed-α*; the naming refers to the rotation about three major bonds in quinine and quinidine: the $C^{4'}$-C^9 bond, the C^9-C^8 bond, and the C^9-O^9 bond (Figure 11).

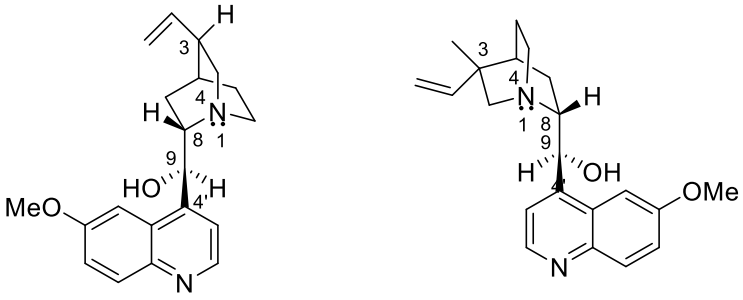


Figure 12: Preferred conformations of quinine (left) and quinidine (right)[13]

In Gaunt's proposed catalytic cycle for the ammonium ylide cyclopropanation, the tertiary amine chiral catalyst binds to the α-bromo ketone (in this case, ester) and remains bound until the formation of the cyclopropyl ring. When bound, the catalysts may be shielding one face, or side, of the intermediate, preventing the formation of one isomer and favoring the formation of another; the faces of the enone are designated *si* and *re* in reference to whether the 1S, 2S (*syn*) or 1R, 2R (*anti*) cyclopropyl forms. The quinine catalysts may approach the *si* face of the enone, making the *syn* isomer more likely to form. On the other hand, the quinidine catalysts may approach the *re* face of the enone, allowing for the formation of the *anti* isomer.

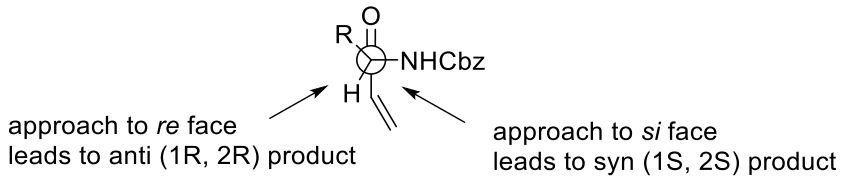


Figure 13: Two faces of enone where approach to ammonium ylide leads to product.

Conclusions

Prior to this study, an efficient three-step synthesis for cyclopropyl hydroxyethylene peptidemimetics was developed; a major flaw in the synthesis is a lack of diastereoselectivity. Though cyclopropyl peptidomimetics are potential bioactive compounds, only one stereoisomer in general is bioactive. As a result, a synthesis able to selectively form the *syn* or *anti* isomers without having to separate them would be valuable.

Though the initial studies with quinine methyl ether afforded selectivity for the *syn* isomer, this selectivity was limited to α-branched amine acids such as valine and alanine. Furthermore, the quinidine methyl ether didn't show any selectivity for either isomer. The current study addresses these issues *via* the benzyl ether derivatives. Quinine benzyl ether, though selective for the *syn* isomer like quinine methyl ether, affords the *syn* isomer for a wider range of amino acid enones, including leucine and phenylalanine.

Quinidine benzyl ether, unlike quinidine methyl ether, is selective for the *anti* isomer, and shows a similar range to quinine benzyl ether for affected amino acid enones.

With the exception of alanine, the *syn* or *anti* stereoisomers of amino acid enones can be afforded with good selectivity. As a result, the synthesis will be invaluable when synthesizing new bioactive compounds, including analogs of belactosin A.

References

1) Ghosh A.K., Bilcer G., and Schiltz G. Syntheses of FDA Approved HIV Protease Inhibitors. *Synthesis (Stuttg*) **2001**, *15*, 2203-2229.

2) Wipf P.; Xiao J.; and Geib S. J. Imine Additions of Internal Alkynes for the Synthesis of Trisubstituted (*E*)-Alkene and Cyclopropane Peptide Isosteres. *Adv. Synth. Catal.* **2005**, *347*, 1605-1613.

3) Martin S. F.; Dorsey G. O.; Gane T.; Hillier M. C.; Kessler H.; Baur M.; Mathä B.; Erickson J. W.; Bhat T. N.; Munchi S.; Gulnik S. V.; and Topol I. A. Cyclopropane-Derived Peptidomimetics. Design, Synthesis, Evaluation, and Structure of Novel HIV-1 Protease Inhibitors. *J. Med. Chem.* **1998**, *41*, 1581-1597.

4) Dunlap N., Lankford K. R., Pathiranage A. L., Taylor J., Nikhil R., Gouger, D., Singer P., Griffin K., and Reibenspies J. Three-Step Synthesis of Cyclopropyl Peptidomimetics. *Org. Lett.* **2011**, *18*(13), 4879-4881.

5) Aggarwal V. K., and Grange E. Asymmetric Sulfonium Ylide Mediated Cyclopropanation: Stereocontrolled Synthesis of (+)-LY354740. *Chem. Eur. J.* **2006**, *12*, 568-575.

6) Aggarwal V. K.; Alonso E.; Hynd G.; Lydon K. M.; Palmer M. J.; Porcelloni M.; and Studley J. R. Catalytic Asymmetric Synthesis of Epoxides from Aldehydes Using Sulfur Ylides with In Situ Generation of Diazocompounds. *Angew. Chem. Int. Ed.* **2001**, *40*(8), 1430-1433.

7) Riches S. L.; Saha C.; Filgueira N. F.; Grane E.; McGarrigle E. M.; and Aggarwal V. K. On the Mechanism of Ylide-Mediated Cyclopropanations: Evidence for a Proton-

Transfer Step and its Effect on Stereoselectivity. *J. Am. Chem. Soc.* **2010**, *132*, 7626-7630.

8) Wascholowski V., Hansen H. M., Longbottom D. A., and Ley S. V. A General Organocatalytic Enantioselective Nitrocyclopropanation Reaction. *Synthesis* **2008**, *8*, 1269-1275.

9) Gaunt M. J. and Johansson C. C. C. Recent Developments in the Use of Catalystic Asymmetric Ammonium Enolates in Chemical Synthesis. *Chem Rev.* **2007**, *107*, 5596-5605.

10) Papageorgiou C. D., Cubillo de Dios M. A., Ley S. V. and Gaunt M. J. Enantioselective Organocatalytic Cyclopropanation via Ammonium Ylides. *Angew. Chem. Int. Ed.* **2004**, *43*, 4641-4644.

11) Papageorgiou C. D.; Ley S. V.; and Gaunt M. J. Organic-Catalyst Mediated Cyclopropanation Reaction. *Angew. Chem. Int. Ed.* **2003**, *42*(7), 828-831.

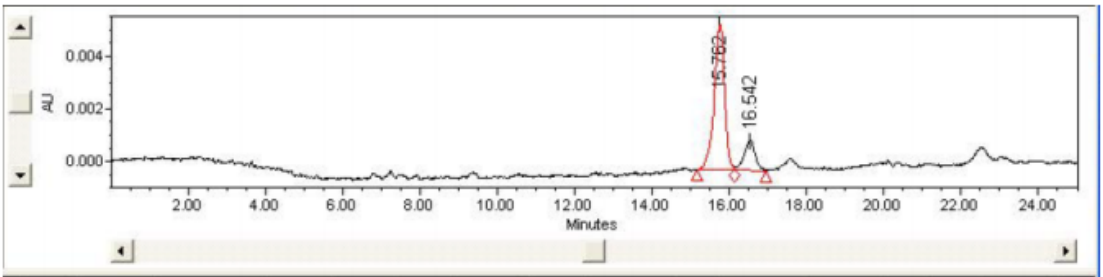
12) Sen A., Lepere V., Barbu-Debu K. L., and Zehnacker A. How do Pseudoenantiomers Structurally Differ in the Gas Phase? An IR/UV Spectroscopy Study of Jet-Cooled Hydroquinine and Hydroquinidine. *ChemPhysChem* **2013**, *14*, 3559-3568.

13) Canar, H.; Biedermann, P. U.; and Agranat, I. Conformational Spaces of Cinchona Alkaloids. *Chirality* **2003**, *15*, 637-645.

14) Dijkstra, G. D. H.; Kellogg R. M.; Wynberg H; Svendsen J. S.; Marko I.; and Sharpless K. B. Conformational Study of Cinchona Alkaloids. A Combined NMR, Molecular Mechanics, and X-Ray Approach. *ACS* **1989**, *111*(21), 8069-8076.

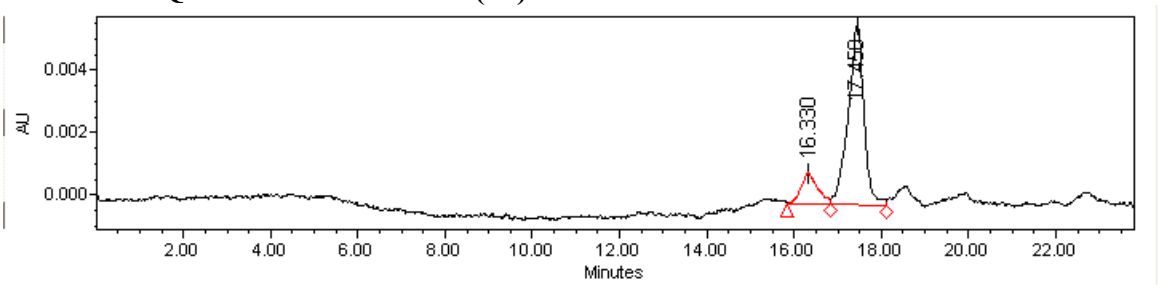
Appendix: HPLC Chromatograms of Cyclopropanation Products

Leucine with Quinine OBn HPLC (3a)



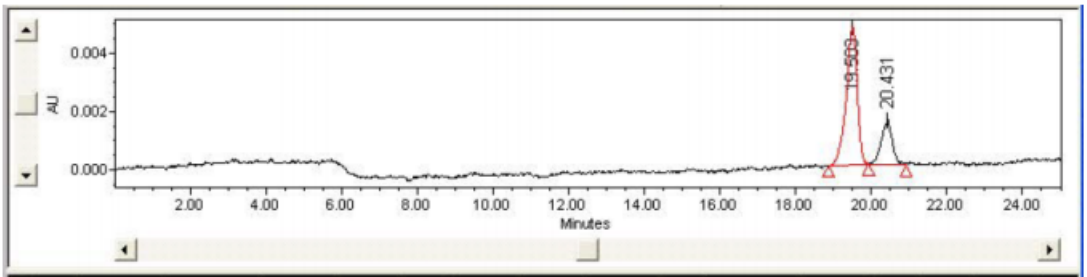
	Name	Retention Time (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Amount	% Amount	Units	Integration Type	Relative RT (min)	RT Ratio	Peak Level	Control Amount	% De
1		15.762	Unknown	103832	81.73	5542	82.79				BV					
2		16.542	Unknown	23208	18.27	1152	17.21				VB					

Leucine w/ Quinidine OBn HPLC (3a)



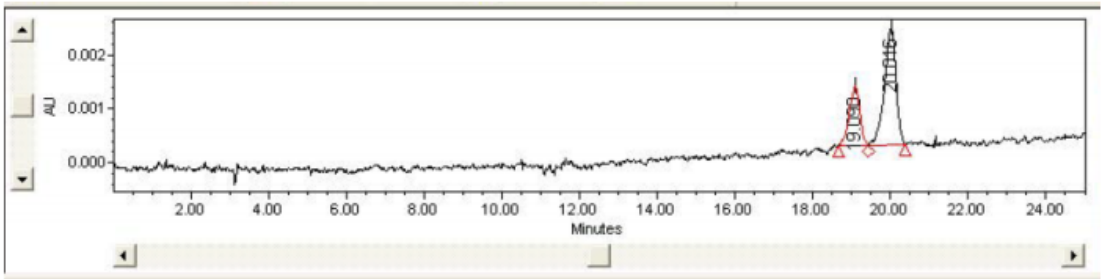
Name	Retention Time (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Amount	% Amount	Units	Integration Type	Relative RT (min)	RT Ratio	Peak Level	Cont Amo
	16.330	Unknown	26516	15.31	1002	14.85				BV				
	17.450	Unknown	146718	84.69	5744	85.15				VV				

Phenylalanine w/ Quinine OBn HPLC (3b)



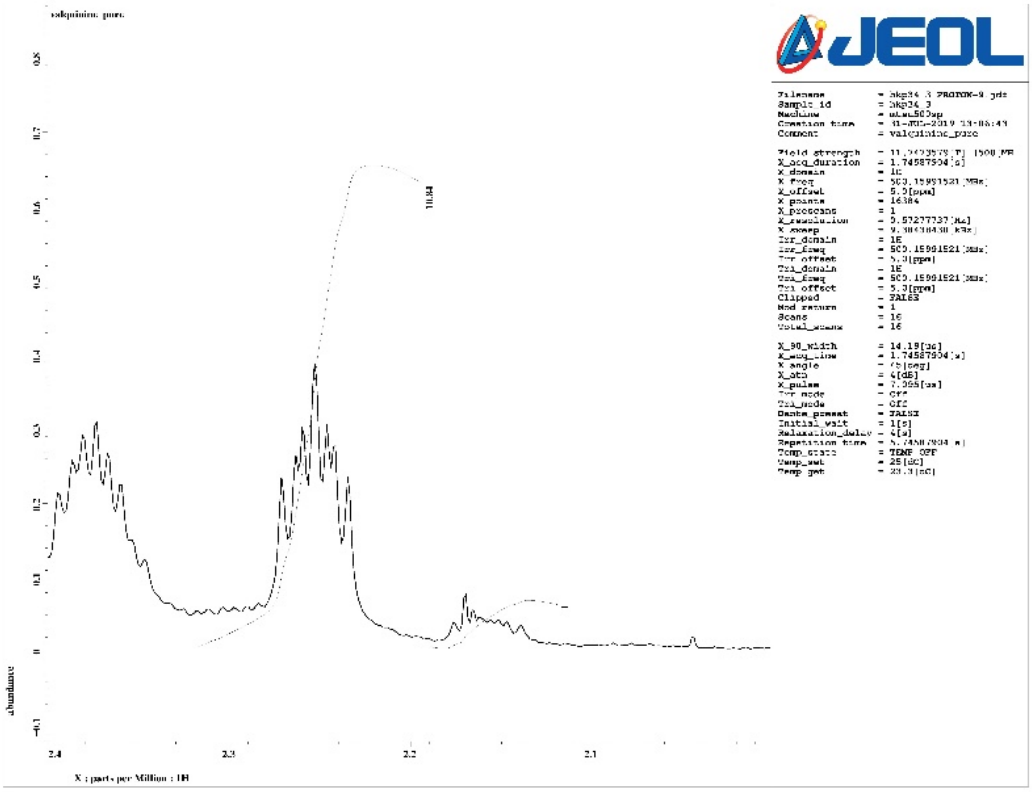
	Name	Retention Time (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Amount	% Amount	Units	Integration Type	Relative RT (min)	RT Ratio	Peak Level	Control Amount	% De
1		19.503	Unknown	96466	75.64	4725	75.52				BB					
2		20.431	Unknown	31060	24.36	1532	24.48				BB					

Phenylalanine w/ Quinidine OBn HPLC (3b)

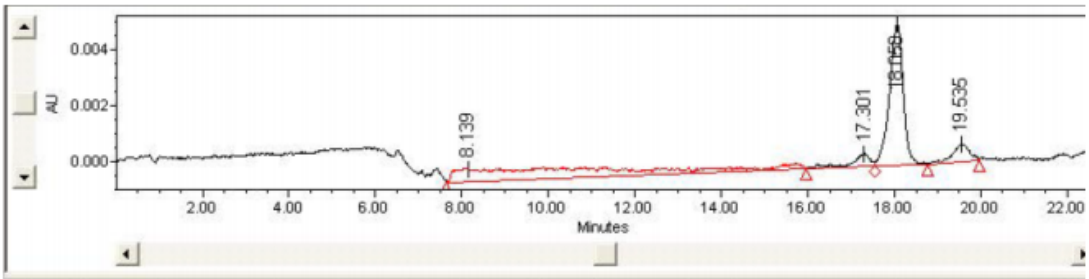


	Name	Retention Time (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Amount	% Amount	Units	Integration Type	Relative RT (min)	RT Ratio	Peak Level	Control Amount	% De
1		19.090	Unknown	20840	31.74	1110	33.78				BV					
2		20.016	Unknown	44824	68.26	2176	66.22				VB					

Valine C^2 Hydrogen (Left: *syn*, Right: *anti*) w/ Quinine OBn ^{1}H-NMR (3c)

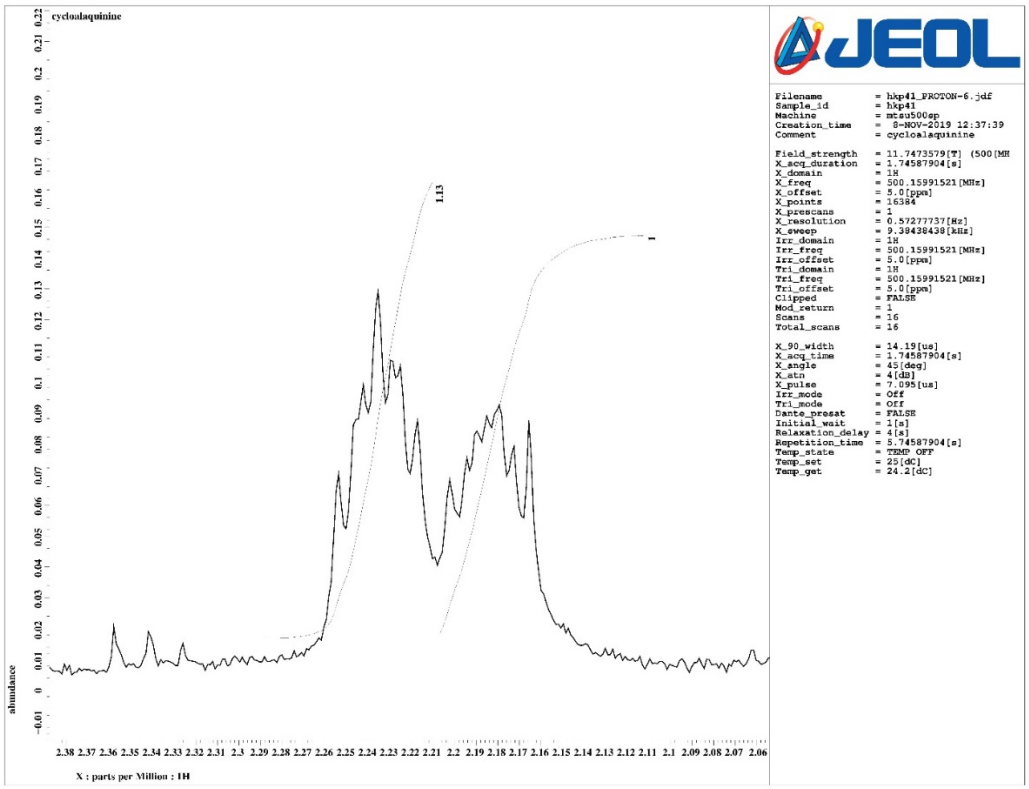


Valine w/ Quinidine OBn HPLC (3c)



	Name	Retention Time (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Amount	% Amount	Units	Integration Type	Relative RT (min)	RT Ratio	Peak Level	Control Amount
1		8.139	Unknown	108402	43.93	465	7.09				BB				
2		17.301	Unknown	12804	5.19	447	6.81				BV				
3		18.058	Unknown	109392	44.33	5037	76.76				VB				

Alanine C^2 Hydrogen (Left: *syn*, Right: *anti*) w/ Quinine OBn ^{1}H-NMR (3d)



Alanine C^2 Hydrogen (Left: *syn*, Right: *anti*) w/ Quinidine OBn ^{1}H-NMR (3d)