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DISSERTATION

SYNTHESIS AND UTILIZATION OF FERROCENE CHIRAL AUXILIARIES

Submitted by

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In partial fulfillment of the requirements for

the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Fall 2002

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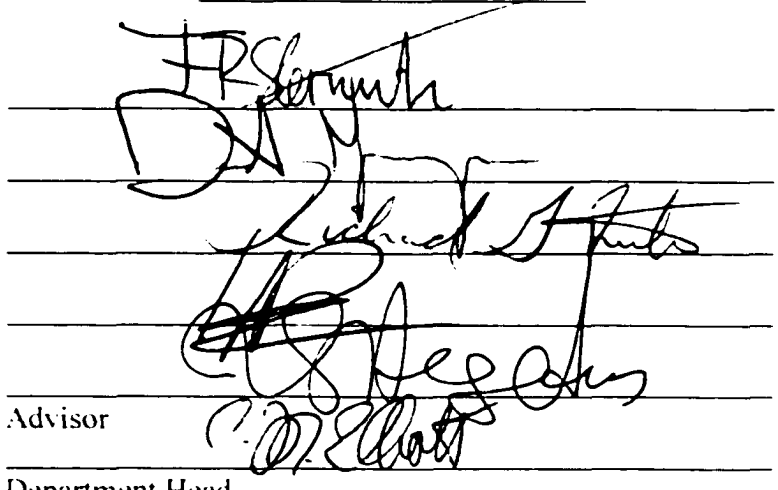
FEBRUARY 8, 2002

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY JEREMY A. WEITGENANT ENTITLED SYNTHESIS AND UTILIZATION OF FERROCENE CHIRAL AUXILIARIES BE ACCEPTED AS FULFILLING IN PART REQUIRMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work



Advisor

Department Head

ABSTRACT OF DISSERTATION

SYNTHESIS AND UTILIZATION OF FERROCENE CHIRAL AUXILIARIES

With the goal to produce β-amino acids in an asymmetric fashion, *S*-(1-ferrocenyl-2-methylpropyl)amine was condensed with ethyl acetoacetate, which provided a novel ferrocenyl enamine ester. Two consecutive alkylation reactions in the α-position gave low or no enantioselectivity.

The above result led to the synthesis of a novel chiral ferrocenyl enamide that underwent a formal [2+2] cycloaddition with (methyl)(methoxy)chromium carbene complex that resulted in the formation of a cyclobutanone as a single diastereomer. Ring expansion followed by cleavage of the novel ferrocenyl auxiliary gave an amine-substituted cyclopentanone and allowed for the recycling of the chiral auxiliary.

The success of the above example allowed for the synthesis of a novel ferrocenyl lactam that when alkylated with ethyl bromoacetate followed by two consecutive alkylations in the α-position gave disubstituted ferrocenyl esters in diastereomeric ratios of ~4.9:1 to >25:1 in moderate to high yields. Cleavage of the ferrocenyl auxiliary gave

α,α-disubstituted α-amino esters in enantiomeric excesses of 65% to 96% in moderate yields and once again allowed for the recycling of the auxiliary.

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ACKNOWLEDGEMENTS

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I would like to thank everyone that I met at Colorado State University but I would also like to thank a few individuals that helped me learn about chemistry and about myself as well. Throughout my stay in the Hegedus group I was fortunate enough to work with some wonderful postdocs, namely Andrew Riches, Lisa Reeder, and Todd Brugel. They were all great examples of what Ph. D.'s should be and they were able to pass some of their vast knowledge on to me and for that I will always be grateful. Thanks also to postdocs outside of my group such as Jeff Kahl and Dave Hennings, both of which were also wonderful resources and great personalities as well. I was also fortunate enough to have excellent people in classes above me that helped me learn about chemistry and were also some of the best people to be around such as, Brian Brown, Brad Herberich, Steve Wenglowski, Tom Wynn, and Mike Frohn.

Starting graduate school in 1996, however, was the best thing that could of happened to me. The group of individuals that started graduate school with me that year was truly amazing and I could not have hoped for a better group of people to be associated with. These people became very good friends and I will never forget the help that Jon Lorenz, Holly Norling, Paul Sebahar, Shawn Sapp, Brady Clappsaddle, Matt Odom, and Ted Judd gave me whether it was advise on how to run a reaction or letting me know what fly the trout were hitting on.

The classes below me, however, also provided me with support as well as the occasional diversion to distract me from my trials. I would like to thank Lisa Geisler, Duane DeMong, Louise White, Jory Wendling, Katie Hervert, Matt Havighurst, Corey Bloom, Ryan Looper, Nate Guz, Carl Evenson, Karl Manske, as well as so many others that I don't have room to name.

I would also like to thank a very important person in my graduate school career, Prof. Hegedus. I would like to thank him for his patience and his guidance and for allowing me to work on a project that I found extremely interesting. I learned a considerable amount of chemistry from him and will always remember the lessons that he taught me.

I would also like to thank the two living things on the face of this planet that were always happy to see me and immediately forgot that I had neglected them if I gave them something as simple as a chewy. My two dogs Lundi and Bernie are the best friends that I could ever ask for and I know that they will never understand how much they make the world a better place for me to live in.

Lastly and most importantly I would like to thank my beautiful wife Jennifer. When I told her that I wanted to quit my well paying job and move halfway across the United States to go back to school she never questioned why. She believed in me when I didn't believe in myself and challenged me to be the best person that I could be. Not just the best chemist but also the best all-around person. She listened to my problems, and helped me get through them. She made me laugh and feel better when I was down and gave me the courage to go on when things were not going well. She went on countless walks with me when I felt down and forced me to see things in a different light. To her I owe the most thanks of all and I know that I will never be able to repay her for all of the wonderful things that she did for me. To Jennifer I give the greatest thanks of all. Thank you for never allowing me to live an ordinary life.

Table of Contents

ABBREVIATIONS

Ac	acetyl
Ar	aryl
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
t-Bu	*t*-butyl
Bz	benzoyl
CBz	benzyloxycarbonyl
DMAP	dimethylaminopyridine
ee	enantiomeric excess
Et	ethyl
Fc	ferrocene
c-Hex	cyclohexyl
HMPA	hexamethylphosphoric triamide
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
Me	methyl

Ms	methane sulfonyl
NaHMDS	sodium hexamethyldisilazide
PMP	*p*-methoxyphenyl
i-Pr	*i*-propyl
TFA	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
p-TsOH	*p*-toluenesulfonic acid

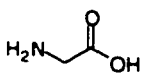
Chapter One

Asymmetric Synthesis of α,α-Disubstituted β-Amino Acids

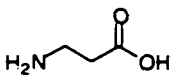
Introduction

As the search for new drug candidates becomes more competitive in both academia and industry, new approaches to drug design must be examined. One of the newest classes of compounds currently being investigated are β-amino acids. β-Amino acids (**2**) are similar to α-amino acids **1**, but they have an additional carbon linking the amine functionality to the carboxylic acid group (Figure 1.1).

Figure 1.1



α-aminoacid
1

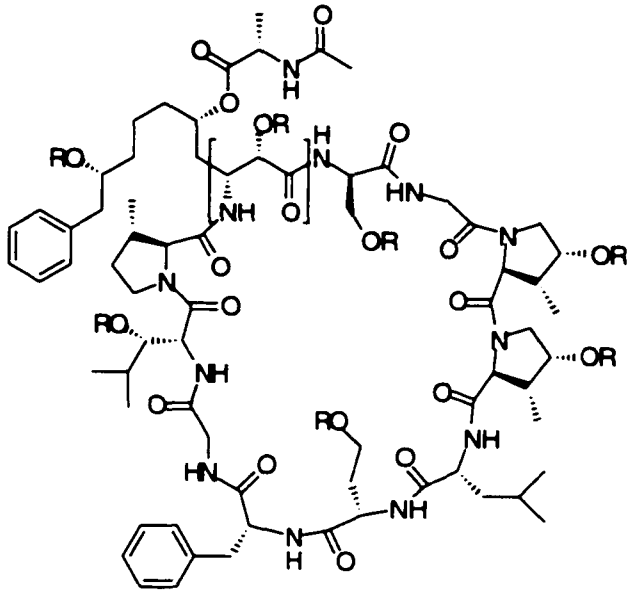


β-aminoacid
2

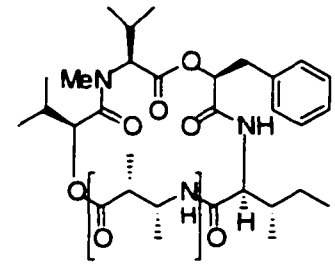
Although β-amino acids are found individually in natural products including peptides, the structures are not found in proteins. Examples of compounds containing a β-amino acid group include, scytonemin (**3**), a calcium antagonist that was isolated from a

blue-green alga[1], and dolastatin D (**4**), a 16 membered macrocycle that possesses cytotoxic activity (Figure 1.2).[2] β-Amino acids are also found in other natural products such as Paclitaxel[3], bestatin[4] and amastatin.[5]

Figure 1.2



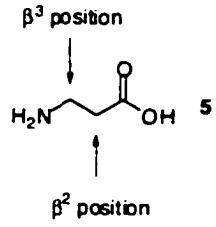
3

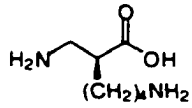


4

It is important to understand the nomenclature that has been adopted for naming α– or β–substituted β–amino acids first used by Seebach. If the substitution occurs in the α–position then that is described as a β^2 substitution and if the substitution occurs in the β–position it is described as a β^3 substitution. This can be seen in β^2-Hlys **6** and β^3-Hlys **7** (Figure 1.3).

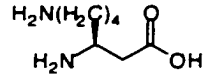
Figure 1.3





β²-HLys

6

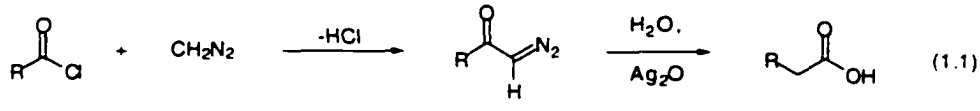


β³-HLys

7

Syntheses of β–amino acids

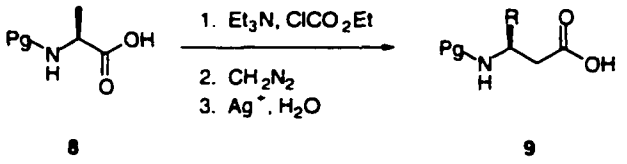
There are numerous methods for the production of β–amino acids[6]. Seebach, one of the leaders in the field of β–amino acid chemistry, uses Arndt-Eistert homologations[7], modified oxazolidinones[8], and hydropyrimidines[9]; all to stereoselectively produce β–amino acids. The Arndt-Eistert reaction involves the homologation of acid chlorides by one carbon (equation 1.1).[10]



(1.1)

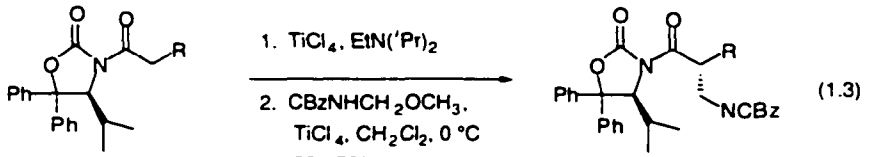
When there is a stereocenter in the α–position of the acid chloride the reaction occurs without racemization. Seebach carried out this homologation on existing α–amino

acids, which resulted in the stereoselective formation of β–substituted β–amino acids.[7] The drawback to this reaction is that it does not allow for the synthesis of α–substituted β–amino acids (equation 1.2).



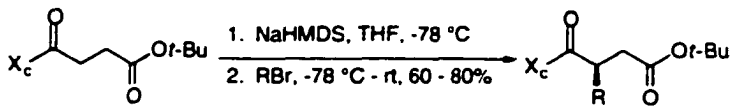
8 9 (1.2)

In order to form α–substituted β–amino acids Seebach used a modified oxazolidinone that was allowed to react with various acid chlorides to produce acyloxazolidinones.[8] Alkylation with *N*-methoxymethyl benzyl carbamate gave α–substituted β–amino acids upon hydrolysis of the oxazolidinone (equation 1.3).



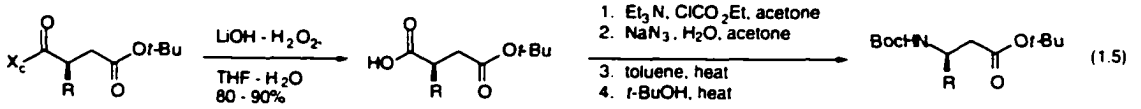
10 11 (1.3)

Sibi has also used chiral oxazolidinones for the formation of β–substituted β–amino acids.[11] Alkylation of dicarboxylic acid derivatives that have been functionalized with a chiral oxazolidinone provides the alkylation product **13** (equation 1.4).



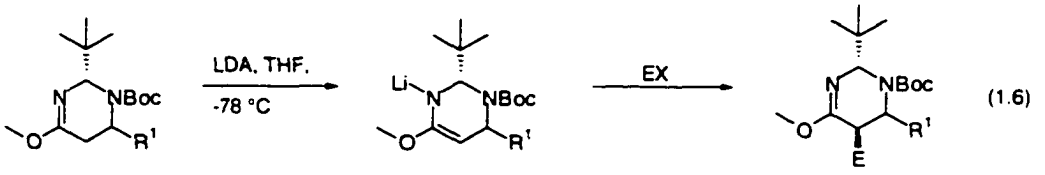
12 13

Curtius rearrangement of acid **15** in the presence of *t*-BuOH provides the Boc protected β–substituted β–amino acid **16**. This procedure is limited because it only provides for monosubstitution in the β–position.



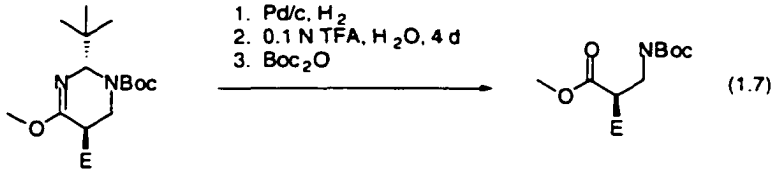
14 15 16

In a different approach Seebach used chiral hydropyrimidines **17** to furnish α–substituted β–amino acids.[9] Deprotonation of **17** and addition of electrophiles to the enolate **18**, results in enantiomerically enriched products **19**.



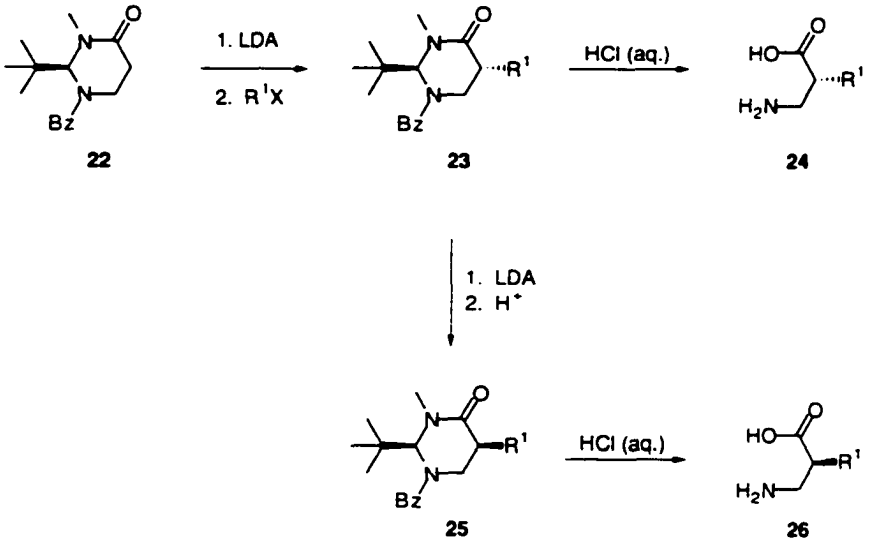
17 18 19

Removal of the Boc group and cleavage of the hydropyrimidine rings furnishes α–substitued β–amino acids **21** after reprotection (equation 1.7).



28 29

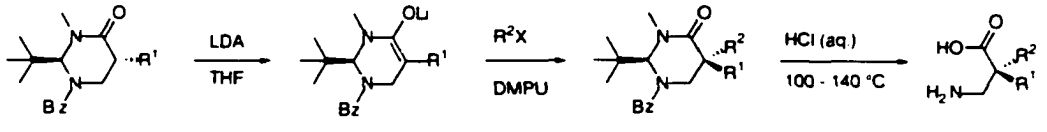
This method is very similar to a strategy employed by Juaristi (equation 1.8).[12] This technique involves alkylation of *N,N*-acetal pyrimidinones **22**. Once again, deprotonation and addition of electrophiles afforded the α–substituted β–amino acids **24** upon hydrolysis. Subjecting the alkylated pyrimidinones **23** to another deprotonation and then quenching the resultant enolate with water results in the other diastereomer **25**.



22 **23** **24** **25** **26**

(1.8)

α,α–Disubstitued β–amino acids **27** were also generated stereoselectively through a second alkylation of **23** followed by hydrolysis (equation 1.9). The major drawback to this procedure is the need of harsh conditions for removal of the *t*-butyl group that is controlling the stereoselectivity.

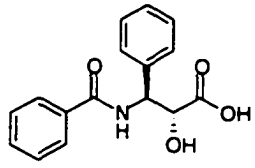


23 **27**

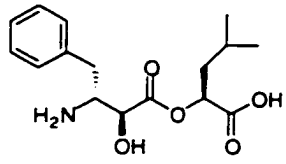
(1.9)

α–Hydroxy-β–amino acids are an important subgroup of β-amino acids found in natural products such as the side chain of Paclitaxel[3] **28**, an anticancer drug currently undergoing clinical trials (Figure 1.4) as well as bestatin[4] **29** and amastatin[5] **30**, which are aminopeptidase inhibitors. The syntheses mentioned previously do not allow for the synthesis of these types of compounds.

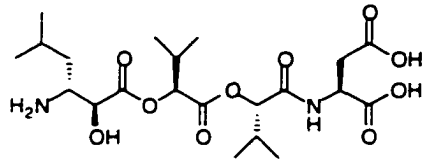
Figure 1.4



Paclitaxel side chain
28

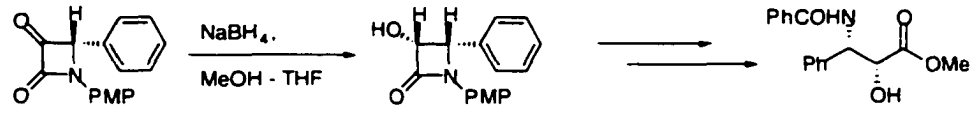


Bestatin
29



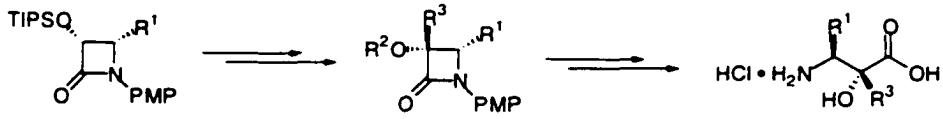
Amastatin
30

Several groups including those of Palomo and Ojima have synthesized these types of compounds. Palomo racemically synthesized the side chain for Paclitaxel by selectively reducing the previously synthesized azetidine-2,3-dione **31** (equation 1.10).[13] Protecting group manipulation and opening of the lactam ring provided the methyl ester of the Paclitaxel side chain **28**.



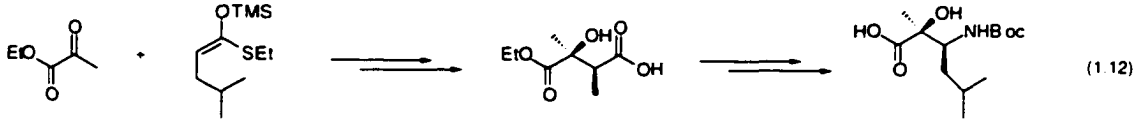
31 **32** **28** (1.10)

Ojima started his synthesis of α–hydroxy β–amino acids from the previously synthesized enantiopure (3*R*,4*S*)-1-PMP-3-TIPSO-β–lactams **33** (equation 1.11).[14] Stereoselective alkylation and lactam ring opening provided the α–substituted α–hydroxy β–amino acids **35**.



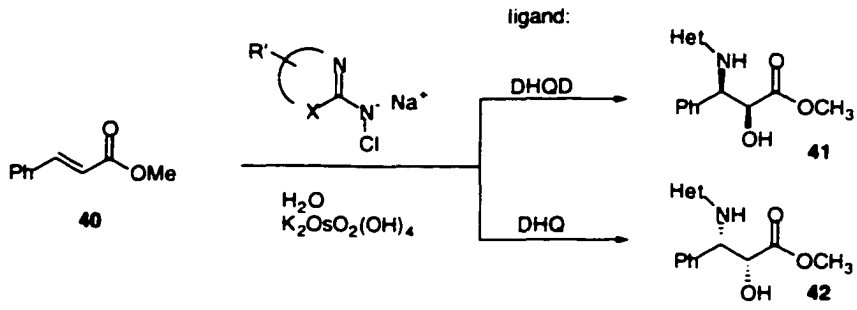
33 **34** **35**

Verdine also carried out the synthesis of α–substituted α–hydroxy β–amino acids.[15] Catalytic aldol reaction[16] between ester **36** and TMS enol ether **37** followed by Curtius rearrangement of acid **38** gave the desired tertiary α–hydroxy β–amino acids (equation 1.12).



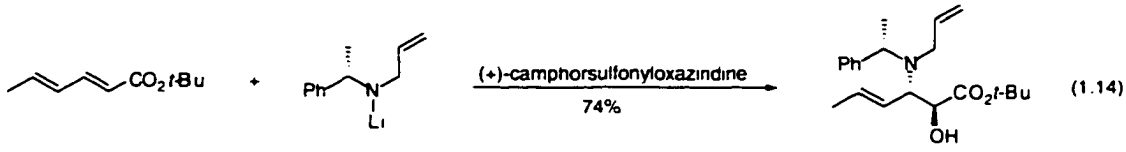
36 **37** **38** **39**

Sharpless has also provided a route to these valuable compounds through his aminohydroxylation reaction (equation 1.13).[17] α–Hydroxy β–amino acids **41** and **42** are produced in one step from readily available α,β–unsaturated esters **40**.



40 (1.13)

Davies has used α,β–unsaturated esters **43** as well in his syntheses of α–hydroxy β–amino acids (equation 1.14).[18] Conjugate addition of chiral amine **44** followed by oxidation of the resulting enolate with (+)-camphorsulfonyloxaziridine stereoselectively produces α–hydroxy β–amino acids **45**.



43 **44** **45** (1.14)

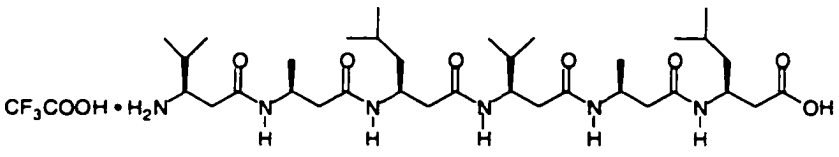
Interest in β–amino acids is increasing, however, and these are only a few representative examples of all the chemistry that is currently being investigated by groups all over the world. This, once again, shows the importance of developing better ways to stereoselectively synthesize new and interesting β–amino acids.[19]

Importance of β–amino acids

The uses of β–amino acids are quite extensive. As shown above, β–amino acids are integral parts of natural products that are under investigation as pharmaceutical targets (Figures 1.2 and 1.4). They can also be used for their ability to enforce predictable secondary structure such as α–helices, β–sheets, and β–turns[20] through the formation of β–peptides. β–Peptides are comprised entirely of β–amino acids. Incorporation of β–amino acids into peptides made up of naturally occurring α–amino acids can also facilitate the formation of secondary structure.[21]

Simple β–peptides form stable α–helices that turn in either direction and are different sizes.[22] Peptide **46**, for instance, contains 3 residues per turn, has a pitch of 5.0 Å, and turns in a left-hand fashion (Figure 1.5).[23] For comparison, α–peptides, consisting of normal α–amino acid residues, contain 3.6 residues per turn, have a pitch of 5.6 Å, and turn in a right-hand manner.

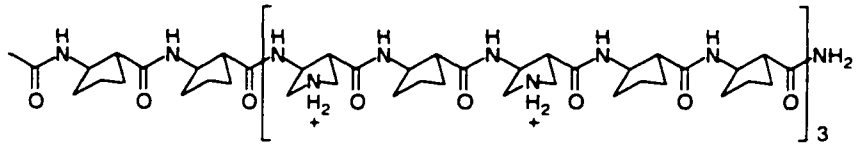
Figure 1.5



β-peptide
46

Both Gellman and Seebach have shown the importance of secondary structure in their application of β–peptides for pharmaceutical targets. A β–peptide synthesized by Gellman that forms an amphiphilic helix was shown to have antibiotic activity against *Enterococcus faecium* A463 and *Staphylococcus aureus* 5332.[24] The β–peptide is thought to mimic magainins, a class of peptides that also form amphiphilic helices that are used by organisms for protection against bacteria. Gellman has synthesized other β–peptides that form amphiphilic helices as well.[25]

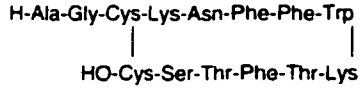
Figure 1.6



47

Seebach synthesized β–peptide **49** in order to mimic somatostatin **48** (Figure 1.7), a hormone that possesses important biological functions such as the regulation for the release of growth hormone as well as the regulation of insulin.[26] Somatostatin's activity hinges on it adopting a β–turn conformation.

Figure 1.7

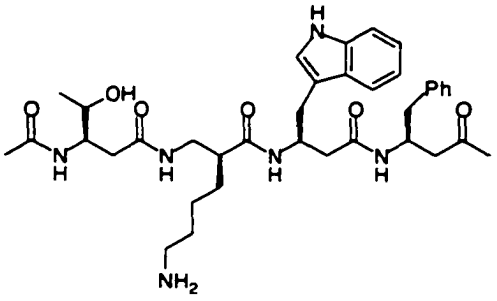


Somatostatin
48

Seebach's β–peptide **49** also adopts a similar β–turn and binds to the same receptors targeted by somatostatin (Figure 1.8). Seebach has also focussed on other

pharmaceutical areas as well such as using β–peptides to regulate the absorption of cholesterol.[27] Gellman has also put a considerable effort into using β–peptides in order to produce predictable β–turns.[21]

Figure 1.8



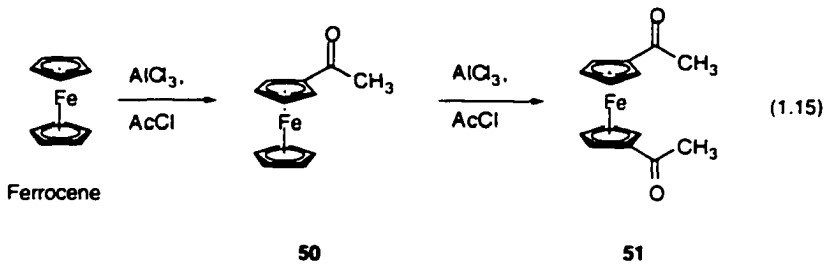
β[3]-HThr-β[2]-HLys-β[3]-HTrp-β[3]HPhe-NH2
49

In most cases, the use of β-peptides provides lower efficacy than normal peptides being tested, but when exposed to enzymatic degradation their stability is outstanding. Peptides formed from β-amino acids are stable for over 48 hours under enzymatic conditions that degrade normal peptides formed from α-amino acids in minutes.[23,28] This provides a distinct advantage of using β-amino acids in biological systems over natural peptides.

Properties of Ferrocene

The discovery of ferrocene was reported in 1951.[29] Its existence as an iron (II) atom sandwiched between two cyclopentadienes quickly followed in 1952.[30]

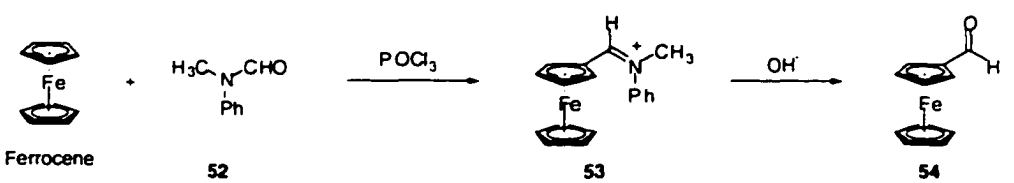
Ferrocene is a very robust compound that is stable to air, moisture, and heat.[31] Most importantly it behaves similarly to phenol in organic reactions, allowing it to undergo Friedel-Crafts acylation 10^6 times faster than benzene.[32] Ferrocene is such an electron-rich system that even acetylferrocene (**50**), which possesses an electron-withdrawing substituent, still undergoes Friedel-Crafts acylation (equation 1.15).



(1.15)

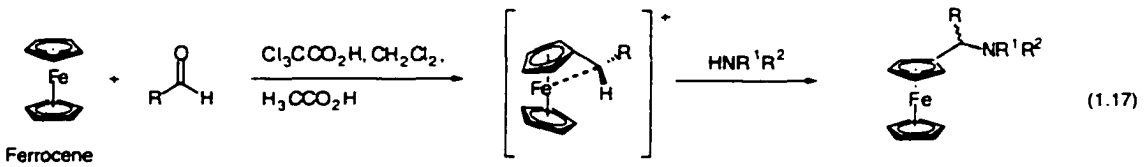
In general the acylations are carried out using aluminum chloride and acetyl chloride although $SnCl_4$, BF_3, H_3PO_4, and HF have been used in conjunction with acetyl chloride as well.[32]

Ferrocene's electron-rich system also reacts with the Vilsmeier reagent to produce ferrocene aldehyde **54** (equation 1.16). Formylation of ferrocene with *N*-methylformanilide **52** in the presence of phosphorous oxychloride gives iminium salt **53**, which is hydrolyzed to give the ferrocene aldehyde **54**.[32,33] Only one formylation results no matter how large of an excess of reagents is used.[32]



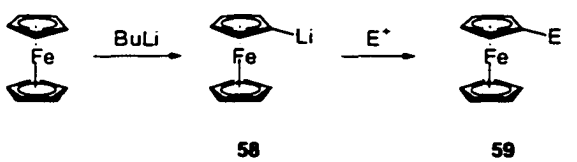
(1.16)

Ferrocenylalkylamines **57** can be directly synthesized through Friedel-Crafts reactions (equation 1.17).[34] Dissolving ferrocene in a mixture of acetic acid, trichloroacetic acid, and methylene chloride, in the presence of an aldehyde **55** results in an attack of ferrocene on the aldehyde. Trapping of the formed carbocation **56** with amines produces ferrocenylalkylamines. Ugi developed the resolution of these ferrocenylalkylamines, so enantiomerically pure compounds could be isolated.

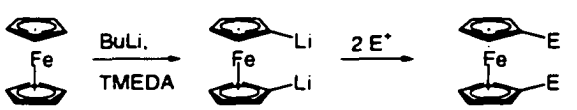


Ferrocene **55** **56** **57** (1.17)

Reaction of ferrocene with alkyllithium bases generates lithioferrocenes (equation 1.18).[35] Addition of *n*-butyllithium to ferrocene causes monolithiation to occur. Trapping of lithioferrocene **58** by an electrophile provides the substituted ferrocenyl derivative **59**. Lithiation with *n*-butyllithium in conjunction with tetramethylethylenediamine gives the dilithioferrocene **60**, which can be trapped with electrophiles to produce the disubstituted ferrocenyl derivative **61**.[36]



58 **59** (1.18)



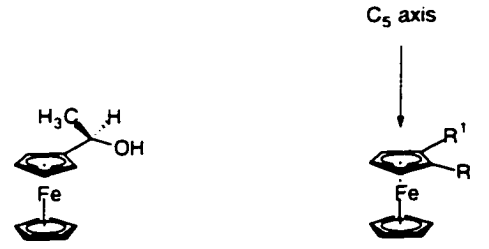
60 **61**

These reactions are comparable to lithiations of aromatic systems. It will be shown later that substituents on the ring can direct ortho-lithiation as well.

Chirality of Ferrocene

An interesting aspect of ferrocenyl compounds is the stereochemistry that defines them.[37] Since ferrocene is constructed of two cyclopentadiene rings, two types of stereochemistry can exist. In the case of the ferrocenes with chirality removed from the cyclopentadienyl ring system, as in ferrocenyl alcohol **62**, central chirality exists. When the cyclopentadiene ring itself is substituted in more than one position as in **63**, however, then planar chirality exits (Figure 1.9).

Figure 1.9



Central Chirality
62

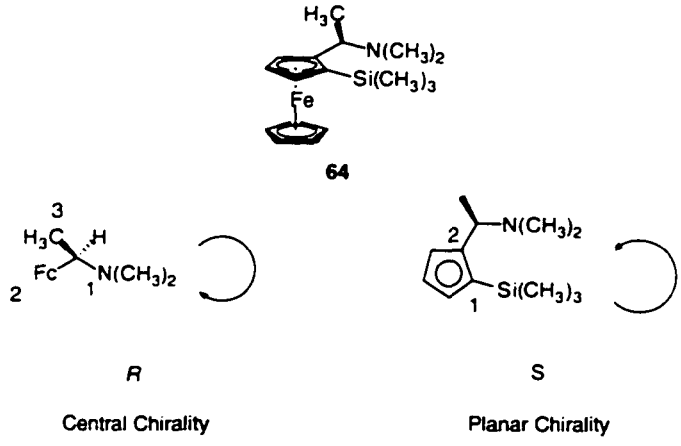
Planar Chirality
63

The Cahn-Ingold-Prelog system for determining the configuration applies in both situations. Central chirality is assigned as usual. Planar chirality is determined by assigning the substituent with the highest priority and then assigning the next highest group on the ring. The *R* or *S* configuration can then be determined by looking down the C5 axis of the molecule. If going from the substituent with the highest priority to the next

highest in the shortest distance proceeds in a clockwise fashion then the compound is assigned *R*. If it proceeds in a counter clockwise fashion, then it is assigned as *S*. If there is multiple substitution on both of the cyclopentadiene rings, then the ring with the substituent with the highest priority is first assigned and then the entire system is flipped over and the other ring is assigned. The assignments are always determined from the top of the molecule while looking down at it.

If there is central and planer chirality in a molecule then the assignment of the central chirality is written first followed by the assignment for planar chirality (Figure 1.10). This can be seen in (*R*,*S*)-α–[2-trimethylsilylferrocenyl]ethyldimethylamine **64**.

Figure 1.10



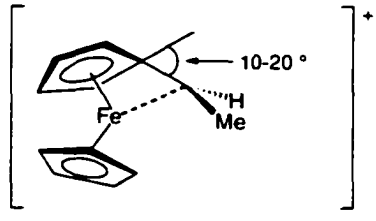
In this case the chirality in the α–position is designated as *R* because the highest priority is assigned to the amine, the second highest is the ferrocene group and the third highest is the methyl group. The planar chirality on the cyclopentadienyl ring is designated as *S* because the highest priority is the silyl group and the next highest is the

methine group. The shortest path between these two groups is in a counter clockwise direction. Also from this example it can be seen that the central designation comes before the planar designation in the name of the molecule.

Carbocation Stability

Generation of cations in the α-position of alkylferrocenes occurs quite readily and these cations are quite stable for long periods of time (Figure 1.11).[38] It is interesting that the cyclopentadienyl rings actually bend 4-5 ° away from their normal parallel configuration.[39] The alkyl substituent also bends out of the plane of the cyclopentadienyl ring 10-20 ° towards the iron molecule in the complex. This was predicted theoretically[40] as well as observed experimentally

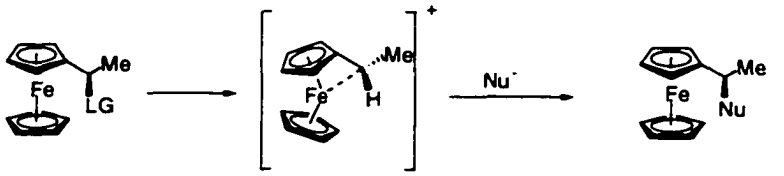
Figure 1.11



65

Reaction of these cations with various nucleophiles has led to a variety of substituted ferrocenyl compounds. Interestingly, these S_N1 type reactions are executed without loss of stereochemistry at the α-position in contrast to typical S_N1 reactions. For instance, the functional group in **66** can be induced to leave to provide the cation **65**. Nucleophilic attack generates the new compound **67** without racemization (equation

1.19). Charge delocalization from the iron atom in the ferrocene complex not only stabilizes the cation but also hinders its rotation.[41]

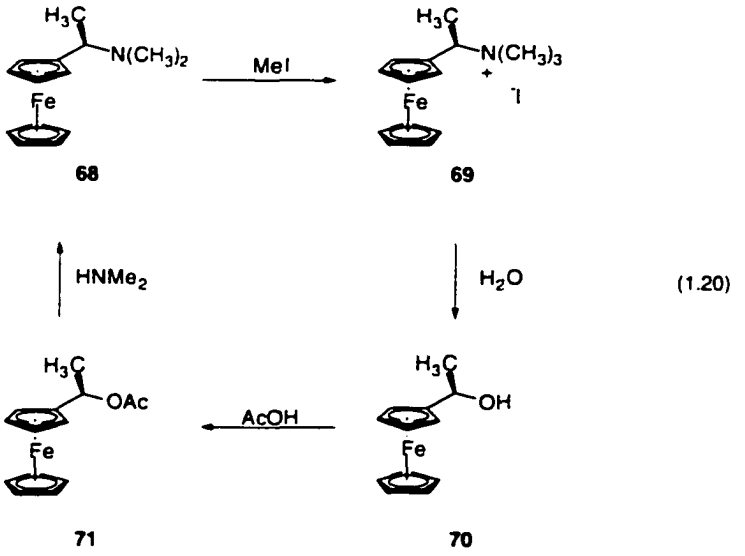


(1.19)

66 65 67

Watts reported that the barrier to rotation was $\Delta H^{\ddagger} \approx 80$ KJ/mole for these types of cationic systems demonstrating how resistant these systems are to racemization.[41]

The term that is used when referring to these types of reactions is retentive S_N1. Switching functional groups in the α–position of chiral ferrocenes through S_N1 reactions allowed Ugi to observe if the compound's optical rotations changed at all (equation 1.20).[42]



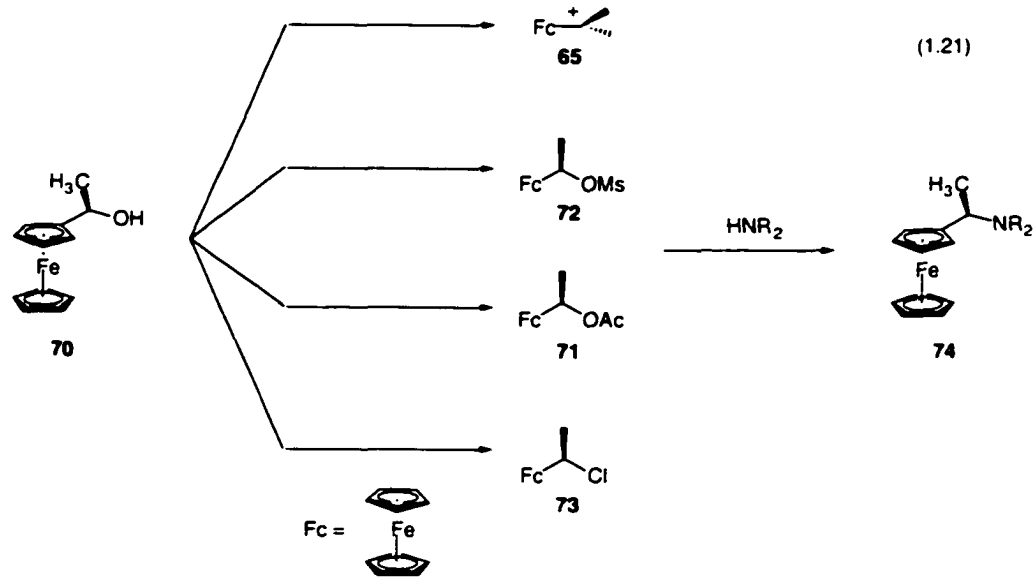
68 69 71 70

(1.20)

Quaternization of the amine **68** to **69** and then conversion to alcohol **70** and then conversion back to amine **68** through acetate **71**, resulted in no loss of optical purity. In doing this Ugi proved that functionality can be replaced in the α–position without loss of stereochemistry. This makes alkyl ferrocenes very useful as chiral catalysts and chiral auxiliaries.

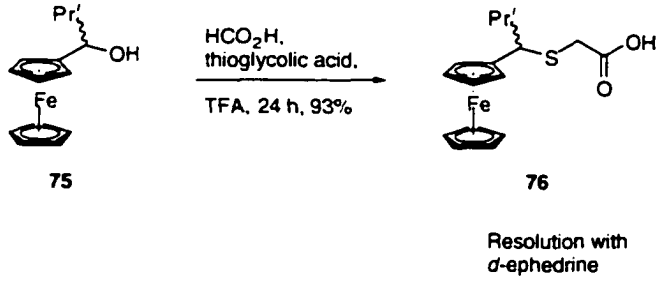
Substitution Reactions

There are also a few different methods for changing the functionality in the α–position. A general starting material for most of these transformations is ferrocenylethanol **70**. Friedel-Crafts acylation followed by reduction conveniently provides this alcohol.[43] The versatility of the hydroxyl group in the α–position provides for the synthesis of ferrocenylalkylamines **74**, for instance. Simple transformation can be carried out a number of ways (equation 1.21). Protonation forms the α–carbocation **65**.[44] The hydroxyl can also be converted into a leaving group through mesylation **72**[45] or acylation **71**[42b] and the α–chloride **73** can be formed by treatment with phosgene.[46] The important aspect of all of these conversions is to transform the alcohol into a good leaving group. Addition of an amine nucleophile, which in-turn displaces the functionalized hydroxyl group, provides ferrocenylalkylamines **74**. Ugi also provided many resolution methods so that the amines could be isolated enantiomerically pure.[47]



(1.21)

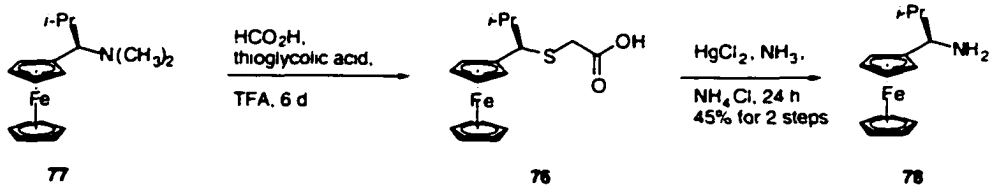
Substitution also occurs using thioglycolic acid under acidic conditions (equation 1.22).[48] Ugi carried out this reaction with racemic ferrocenylalcohol **75** and was then able to resolve the enantiomers of the resulting thiol **76** as the *d*-ephedrine salt.



(1.22)

A more useful and much more important use of thioglycolic acid, however, is for the displacement of amines[42a,48] which was developed for use in the Ugi reaction (4 component coupling reaction). In the simplest example of this, Ugi forms the thiol-substituted ferrocene **76** by dissolving dimethylamine **77** with thioglycolic acid in formic acid and trifluoroacetic acid. Treatment of the thiol **134** with mercuric chloride in the

presence of ammonia and ammonium chloride provides the primary amine **76** with no loss of stereochemistry.

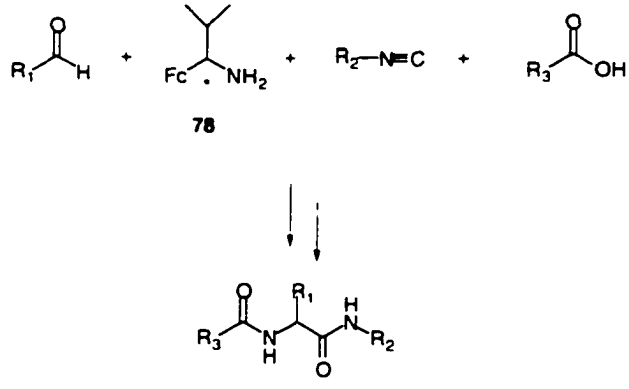


77 **76** **78** (1.23)

Uses of Ferrocenylalkylamines

In the 1970's, Ugi employed chiral α-ferrocenylalkylamine compounds as auxiliaries for the synthesis of α-amino acids[49] (Figure 1.12).

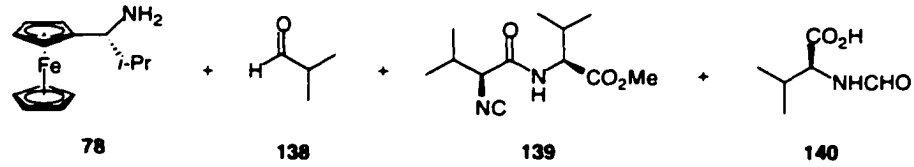
Figure 1.12



78

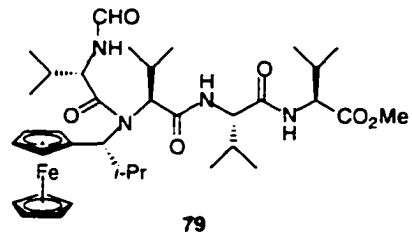
The reaction was termed the four component coupling (4CC) reaction and the purpose of it was to quickly produce α-amino acids. The reaction involved an aldehyde, an isocyanide, a carboxylic acid, and an amine **78**. When Ugi used enantiomerically pure α-ferrocenylalkylamines, the resulting product was an enantiomerically enhanced α-amino acid.

In one of the more important examples of this chemistry, Ugi showed that ferrocenyl compounds could be used to induce asymmetry in the 4 component condensation reaction to give peptide bond formation in high enantiomeric purity (equation 1.24).[50]



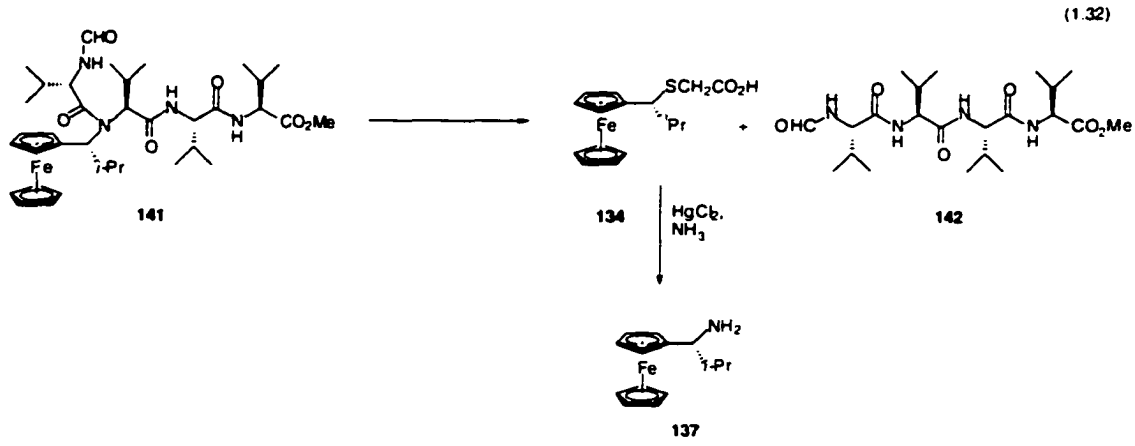
78 138 139 140

(1.24)



79

Cleavage of the ferrocenyl system from the peptide occurs leaving the amino functionality behind. Treating the resultant thiol **76** with mercuric chloride in the presence of ammonia yields amine **78**, which can be used once again in the 4CC reaction (equation 1.25).[51]

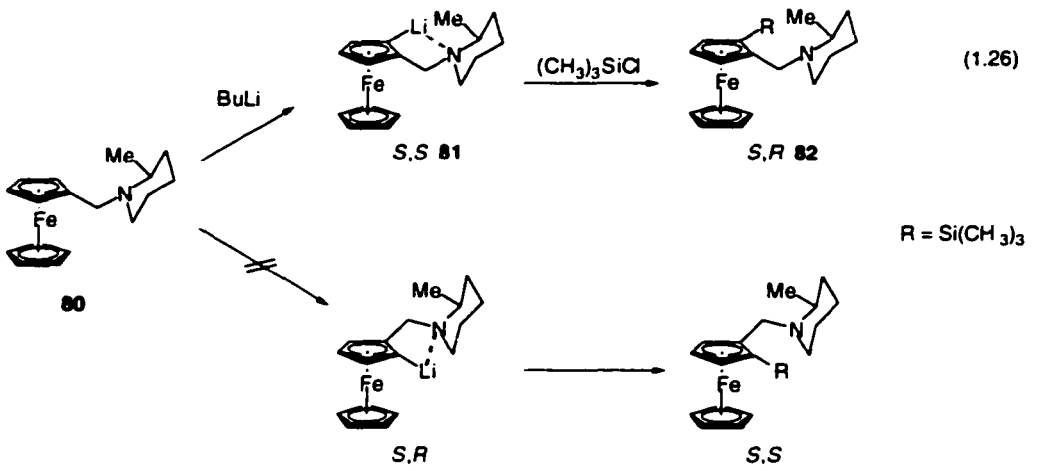


(1.32)

Directed ortho-lithiations

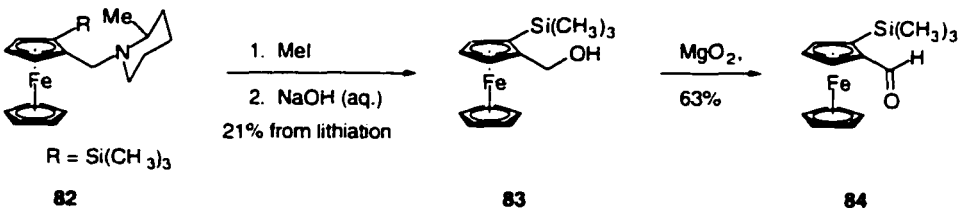
Directing ortho-lithiation is one of the more important aspects of the ferrocenylalkylamines. Directed ortho-lithiations are well documented in aromatic systems and are not exclusive to ferrocenyl compounds.[52] When ferrocenyl alkyl amines are lithiated, the nitrogen group directs the lithiation to the ortho position of the cyclopentadienyl ring. If the alkyl amine is substituted or if something chiral is attached to it, then the lithiation can be directed to one ortho position over the other.

Aratani first showed this in 1969.[53] Lithiation of ferrocenylamine **80** gave rise to the *S,S* configuration of the compound **81** (equation 1.26). Reaction of **81** with chlorotrimethylsilane gave the stable silyl compound **82** in the *S,R* configuration.



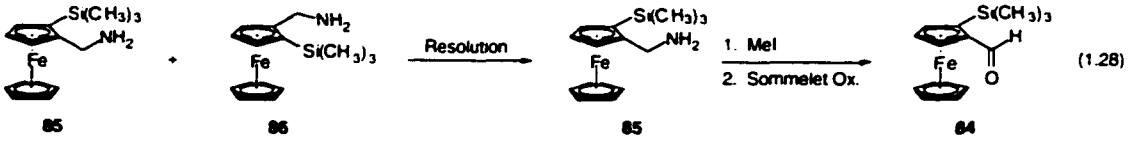
(1.26)

Conversion of **82** to aldehyde **84** allowed for the determination of optical rotation which was given as +130 °. Aratani reported that the aldehyde was obtained as one stereoisomer (equation 1.27).

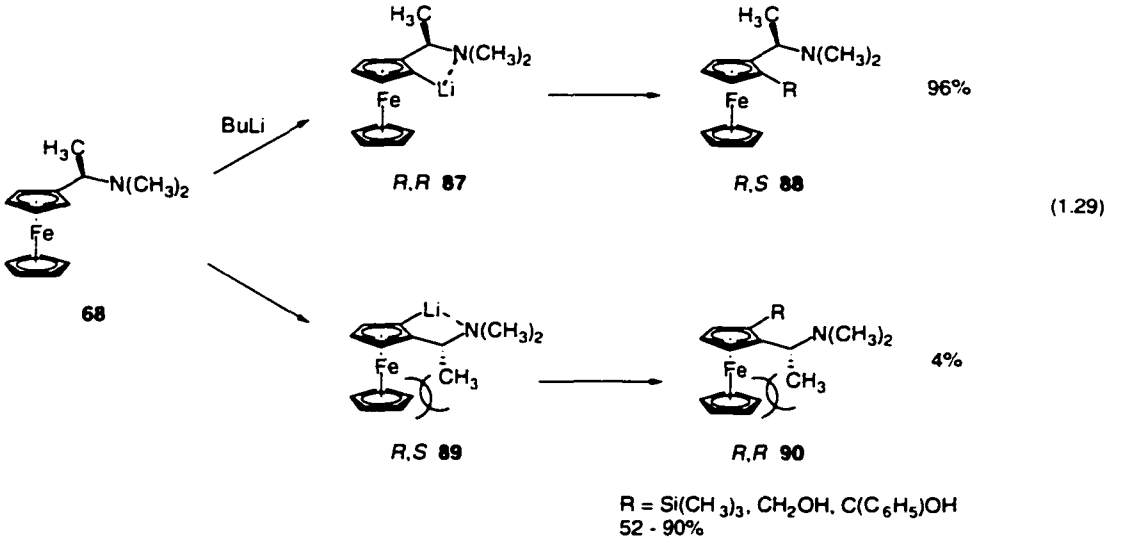


(1.27)

This claim of only forming one diastereomer was refuted by Ugi the following year.[54] Synthesis of the silyl amine (**85**,**86**) had previously been carried out and this amine had been resolved as well (equation 1.28). Quaternization of the amine and Sommelet oxidation provided the aldehyde **94**. The optical rotation that Ugi reported was +194 ° showing that the method that was used by Aratani was only 67% diastereoselective.



Ugi improved on directing ortho-lithiations in ferrocenyl systems using ferrocenealkylamines with substitution in the α–position. Lithiation of α–*N,N*-dimethylaminoethylferrocene **68** gave the two substituted ferrocenes **88** and **90** in a diastereomeric ratio of 96 to 4, due to more steric bias between the alkyl group and the cyclopentadienyl ring system (equation 1.29)[46].

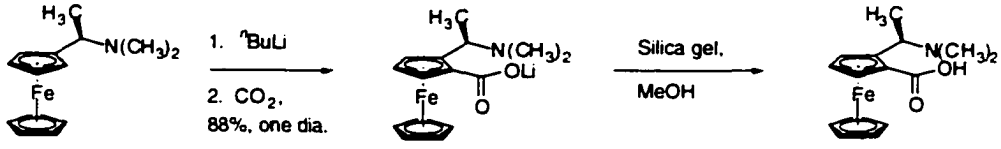


High selectivity is believed to result from the interaction between the large methyl group and the cyclopentadienyl ring system. Little interaction occurs in the *R,R* species **87** because the smaller hydrogen is forced to interact with the cyclopentadienyl ring system. This is yet another very important aspect of ferrocenyl systems because

directed ortho-lithiations allow for the generation of disubstituted ferrocenes in a stereoselective fashion.

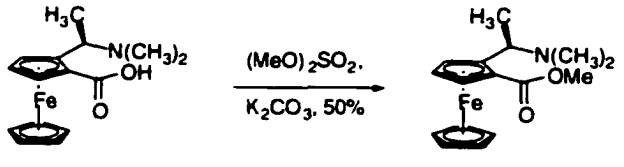
Another example of the directed lithiations of ferrocenes generates disubstituted ferrocenyl carboxyl compounds.[55] Utilizing the ortho-lithiation technique developed by Ugi, Cullen showed that carboxyl-substituted ferrocenylalkylamines could be made diastereoselectively (equation 1.30).

Ortho-lithiation of α–*N,N*-dimethylaminoethylferrocene **68** with *n*-butyllithium followed by addition of solid CO_2 gave carboxyl ferrocene lithium salt **92** as one diastereomer in 88% yield.

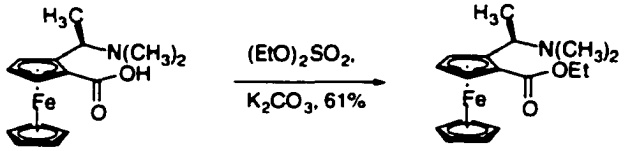


68 **91** **92** (1.30)

Purification of the lithiate salt **91** by silica gel column chromatography using methanol as the eluent provided the free acid **92**. Conversion of the acid into either the methyl ester **93** or the ethyl ester **94** using dimethyl sulfate or diethyl sulfate respectively was also reported (equation 1.31). The yields of these conversions were low, but until this paper these transformations had not been carried out.[55]

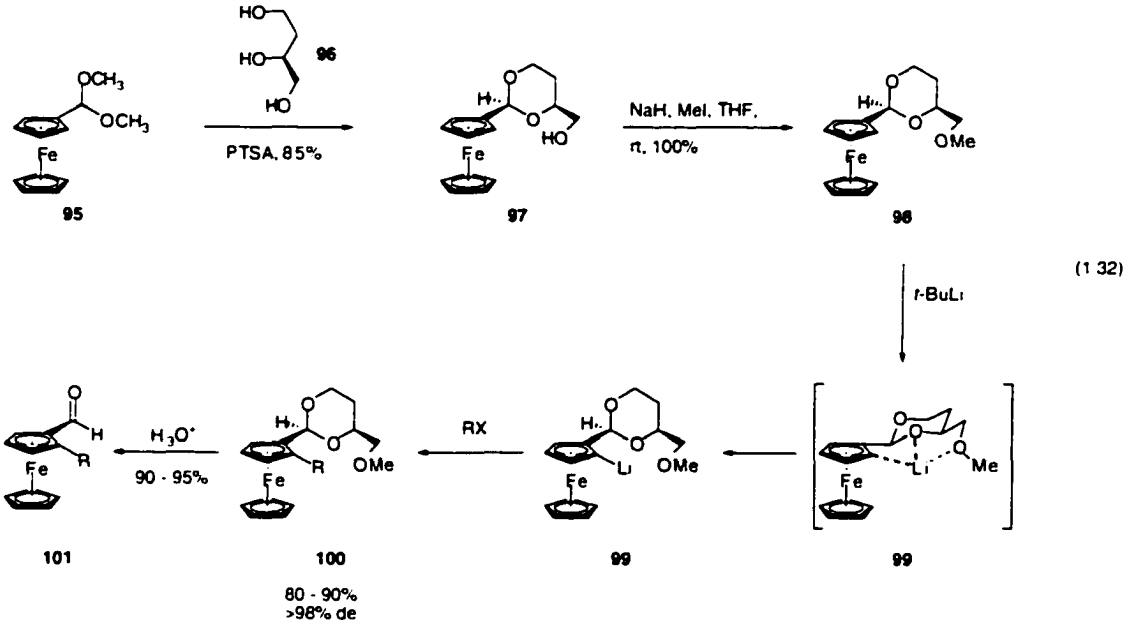


92 93 (1.31)



92 94

Directed ortho-lithiations of functionalized aldehydes have been shown as well (equation 1.32).[56] Transacetylization of known acetal **95** with chiral alcohol **96** forms the chiral 1,3-dioxarane **97**. Etherification of the free alcohol and lithiation using *t*-BuLi gives lithium species **99** which is reacted with a variety of compounds to produce the disubstituted ferrocenes **100** with de's greater than 98%.



(1.32)

R = TMS, $SnBu_3$, PPh_2, CO_2Me, I, C≡C-TMS, C≡C-Ph

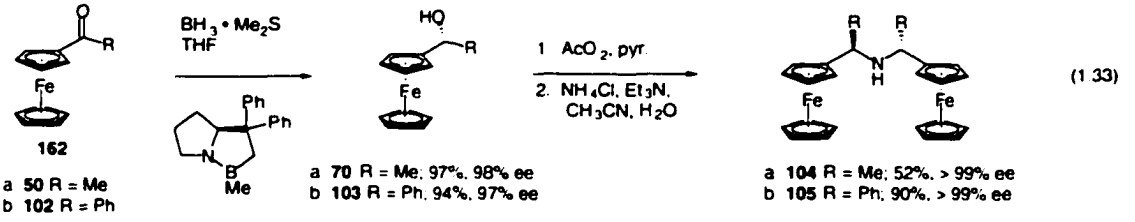
Hydrolysis with aqueous acid produces the chiral ferrocenyl aldehydes **101** in good yields (90 - 95%).

Once again the ability to direct ortho-lithiation is a very important property of ferrocenyl compounds. Being able to generate these disubstituted molecules in a stereoselective fashion lends itself to the creation of a diverse array of compounds that can be used in the future as chiral catalysts or chiral auxiliaries.

With such an array of chemical properties it is not surprising that ferrocenyl compounds are used in very diverse chemical reactions. The use of ferrocenes that is currently getting the most attention is in the area of chiral catalysis.[57] The focus of this discussion, however, is on their recent use as chiral auxiliaries.

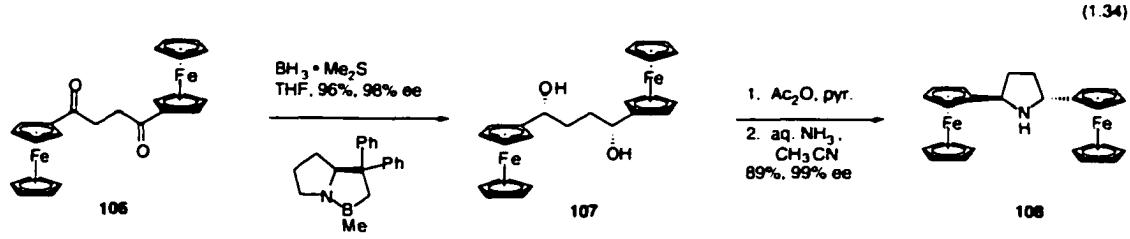
Recent Uses of Chiral Ferrocenes

Knochel synthesized three new chiral ferrocenyl amines in 1997 to be used as chiral auxiliaries for diastereoselective alkylations as well as bases for stereoselective deprotonations.[58] Reduction of ketones **50** and **102** followed by coupling of the alcohols with ammonium chloride gave ferrocenyl compounds **104** and **105** (equation 1.33).

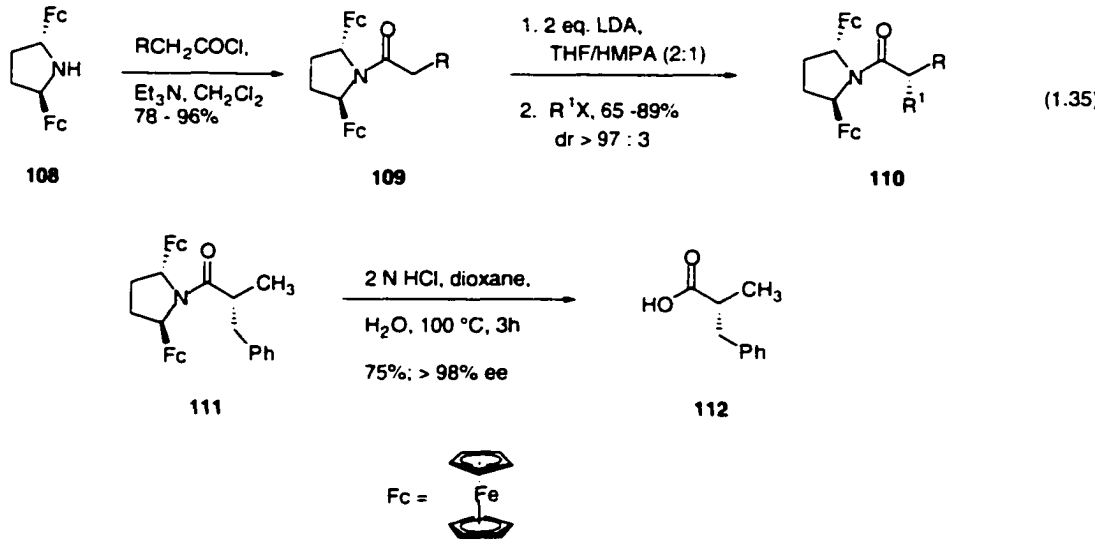


(1.33)

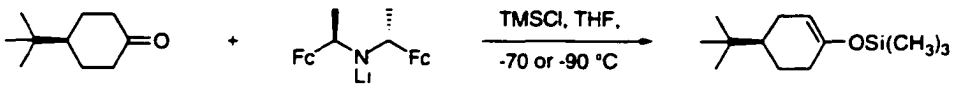
The cyclic amine was formed in a similar manner. Reduction of diketone **106** to the diol **107** and addition of ammonia yielded amine **108** (equation 1.34).



Cyclic amine **108** was used for carrying out stereoselective alkylations. Reaction between acid chlorides and cyclic amine **108** gave amides **109**. Deprotonation with LDA followed by addition of various electrophiles produced monoalkylated products **110** with yields of 65 - 89% with diastereomeric ratios of 97 : 3. Cleavage of the auxiliary on benzyl compound **111** gave the carboxylic acid **112** in 75% yield and greater than 98% enantiomeric excess.



The linear chiral ferrocenyl amine **104** was used for enantioselective deprotonations (equation 1.36). Addition of the lithium amide **114** to ketone **113** in the presence of trimethylsilylchloride generated the silyl enol ether **115** in upwards of 62% ee.

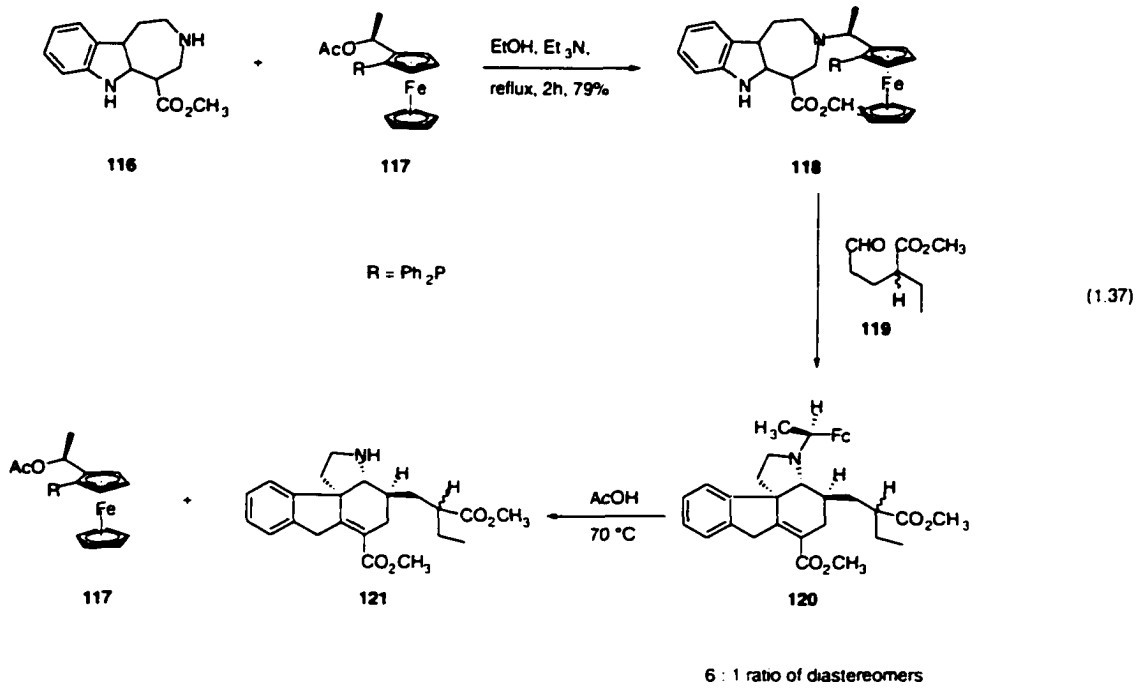


(1.36)

113 **114** **115**

up to 62% ee

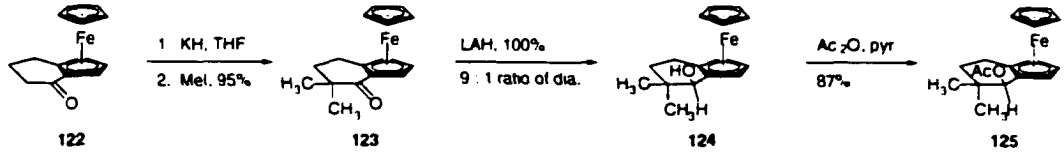
Chiral ferrocene auxiliaries can also be seen in the stereoselective synthesis of a variety of *Aspidosperma*, *Iboga*, and *Strychnos* alkaloid analogs carried out by Kuehne.[59] Coupling of ferrocene auxiliary **117** with indolazepine **116** followed by addition of aldehyde **119** produced a Diels-Alder intermediate that cyclized *in situ* to provide tetracyclic core **120** in a 6 to 1 ratio of diastereomers (equation 1.37).



(1.37)

Cleavage of the chiral ferrocenyl auxiliary **117** with acetic acid yielded the tetracyclic core **121**. The use of a larger cyclic ferrocenyl compound as a chiral auxiliary was also investigated.[60] The related chiral auxiliary used for the same reaction was synthesized in the follow manner (equation 1.38). Dialkylation of ferrocenyl ketone **122** followed by reduction with lithium aluminum hydride gave a 9:1 ratio of diastereomers of the ferrocenyl alcohol **124**.

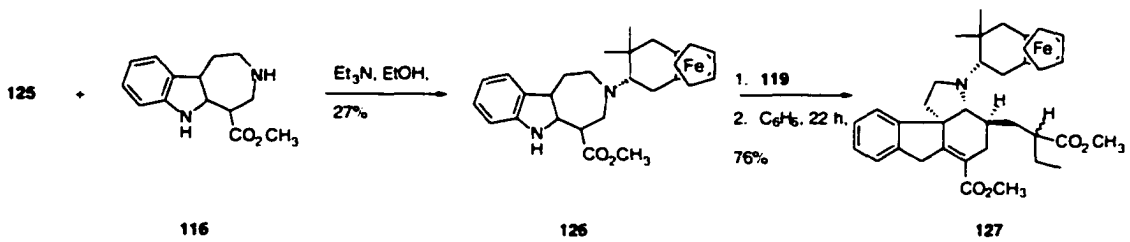
(1.38)



Coupling of acetate **125**, formed from alcohol **124**, to indoloazepine **116** (equation 1.39). Addition of aldehyde **119** and ensuing Diels-Alder reaction provided a 97 : 3 ratio

of diastereomers of the desired tetracycle **127**. The auxiliary could then be cleaved through the same process shown previously.

(1.39)

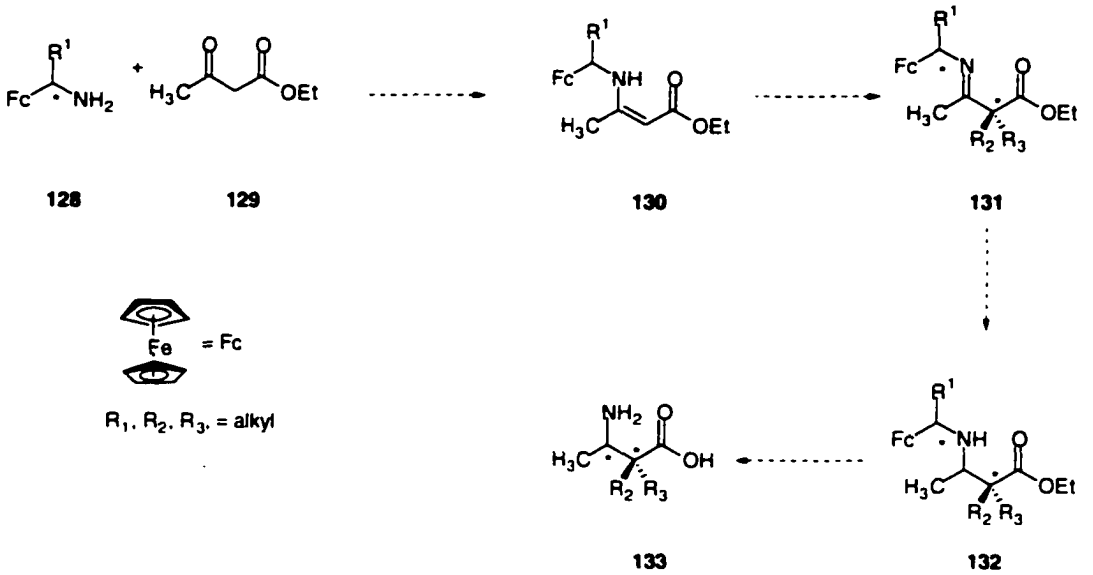


Rationale

Ferrocenyl compounds have proven to be excellent sources of recyclable chiral auxiliaries that can induce stereoselectivity in various reactions. It was decided to utilize these favorable properties to stereoselectively produce α,α–disubstituted β–amino acids. It was, therefore, hypothesized that a chiral ferrocenyl amine could be developed as a recyclable chiral auxiliary for the synthesis of α,α-disubstituted β-amino acids from acetoacetates.

The synthetic approach involves condensing chiral ferrocene derivative **129** with ethyl acetoacetate **129** (Figure 1.13). Two sequential alkylations might then be carried out on the chiral enaminone **130**, followed by reduction of the imine **131**, and cleavage of the auxiliary to generate the α,α-disubstituted β-amino acid **132**.

Figure 1.13



128 129 130 131 132 133

Reduction of the imine **131** has been previously shown to occur stereospecifically in similar reactions.[61]

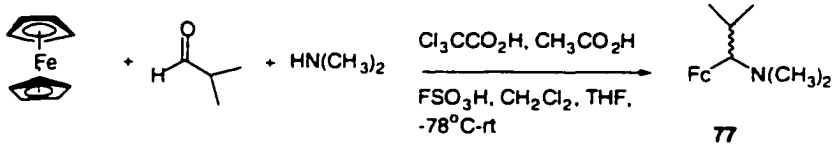
Results and Discussion

The first step in developing a method for the stereoselective synthesis of αα-disubstituted β-amino acids was to generate a chiral α-ferrocenylalkylamine. For preliminary investigations, (1-ferrocenyl-2-methylpropyl)amine **78** was chosen because both the *R* and *S* enantiomers of this compound could be isolated and used as chiral auxiliaries for the subsequent alkylations (Figure 1.14). These compounds were

Figure 1.14

78

synthesized using the method first developed by Ugi.[48] A Friedel-Crafts alkylation was carried out on ferrocene, using isobutyraldehyde as the electrophile. The resulting alcohol was further protonated, facilitating elimination to form the α-cation, which could then be quenched with dimethylamine, forming both *R* and *S*-(1-ferrocenyl-2-methylpropyl)dimethylamine (**77**) in 72% yield (equation 1.40).

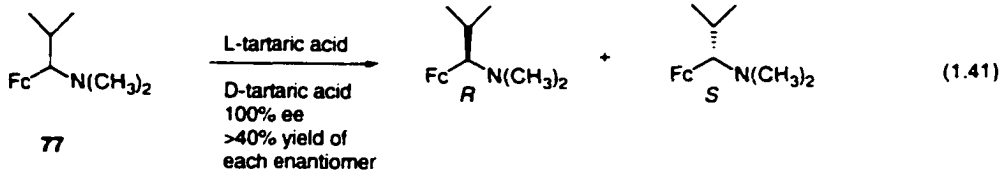


77

72%

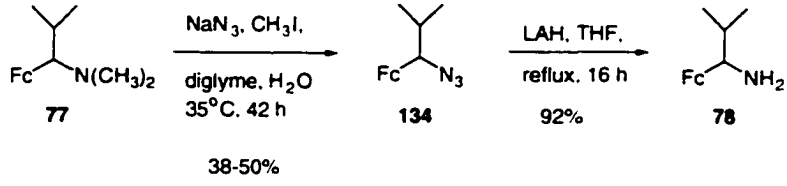
(1.40)

Resolution utilizing D and L-tartaric acid provides the *S* and *R* compounds respectively. The tartrate salts of the enantiomers were crystallized from water to give enantiomerically pure *R* and *S*-(1-ferrocenyl-2-methylpropyl)dimethylamine **77** in yields greater than 40% of each enantiomer (equation 1.41). The enantiomer excesses were determined by comparison of the previously reported optical rotations.[48]



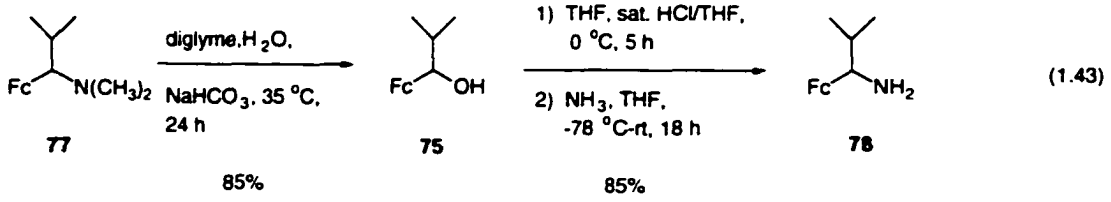
(1.41)

The chiral (1-ferrocenyl-2-methylpropyl)dimethylamine **77** was converted to the amine **78** utilizing a procedure developed by Ugi.[47] This procedure required that the dimethylamine group first be quaternized by iodomethane in the presence of sodium azide. This process gave the azido compound **134**, which was then reduced to the primary amine **78** using lithium aluminum hydride (LAH) (equation 1.42).



(1.42)

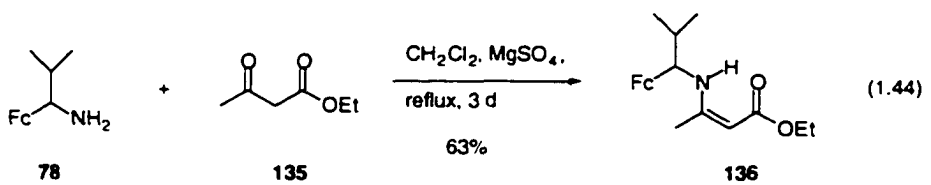
Although the second step in this process gave 92% yield of the primary amine **78**, generating the azido compound **134** was time consuming and gave low and variable yields. While attempting to optimize the reaction conditions given in the literature procedure, a major side product was isolated and found to be the alcohol **75**. The reaction conditions were then changed to drive the reaction solely to the alcohol. The reaction was run using diglyme, water and sodium carbonate, and iodomethane was added to this mixture dropwise (equation 1.43). This provided the alcohol in 85% yield. Acid hydrolysis of alcohol **75** to the cation was followed by quenching with ammonia, which furnished amine **78** in 85% yield.



(1.43)

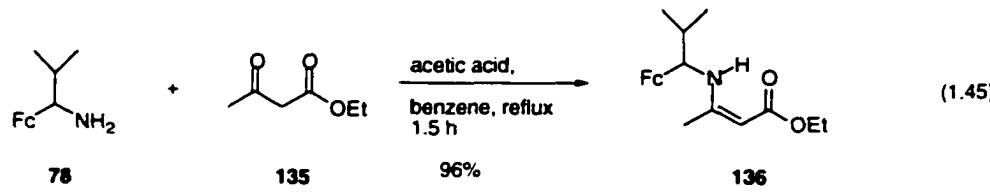
This route to the primary amine **78** was faster and gave higher yields. Going through the alcohol **75** also alleviated any problems brought on by using large excesses of sodium azide because of its explosive nature and its tendency to form hydrazoic acid. The new reaction conditions also seem to be better if larger scale reactions are required.

Condensation of the amine **78** with ethyl acetoacetate (**135**) led to the enaminone **136** (equation 1.44).



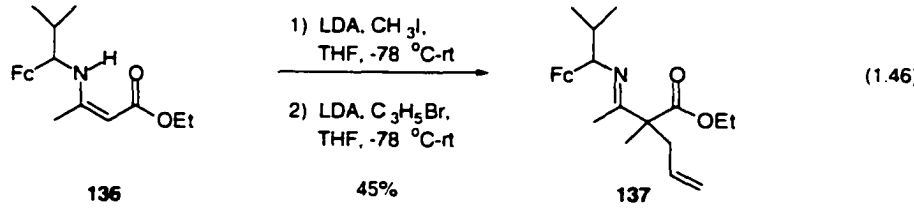
(1.44)

This reaction was slow and did not reach completion, which caused low yields. Various reaction conditions were tried and the optimum conditions that were found utilized a Dean-Stark trap, which removed the water from the refluxing acetic acid/benzene solution. These reaction conditions afforded the enaminone **136** in 96% yield (equation 1.45).



(1.45)

Alkylation in the α-position of the enaminone **136** was carried out using lithium diisopropylamide (LDA) at -78 °C with iodomethane as the electrophile. This alkylation provided the mono-substituted enaminone in a pure enough form that it could be immediately taken on to the next reaction without further purification. The second alkylation was carried out, once again using LDA at -78 °C but employing allyl bromide as the electrophile (equation 1.46).

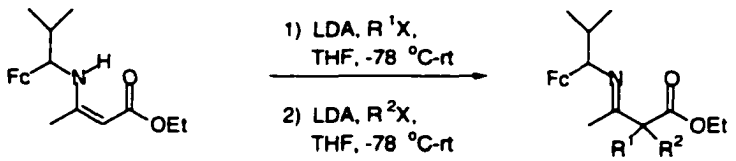


(1.46)

The two sequential alkylation reactions led to the α,α-dialkylated imine **137** in 45% yield. The condensation and alkylation reactions were carried out using the racemic ferrocenyl auxiliary and then employing the *R* and *S* chiral auxiliaries once the reaction conditions were optimized so that the stereoselectivity could be examined.

The dialkylations were carried out repeatedly using the same synthetic technique in order to produce a variety of disubstituted ferrocenyl compounds (Table 1.1).

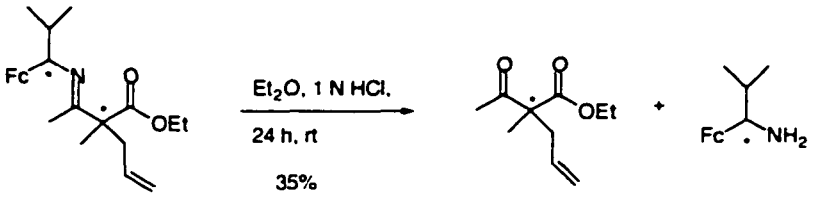
Table 1.1 Dialkylation of ferrocenyl enamine **136**



136 45%

R^1	R^2	Yield over 2 steps
CH_3	$CH_2C_6H_5$	51% (**138**)
C_2H_5	$CH_2C_6H_5$	52% (**139**)
C_3H_7	$CH_2C_6H_5$	51% (**140**)
C_2H_5	CH_2OCH_3	50% (**141**)

Hydrolysis of the imine **137** to the disubstituted ethyl acetoacetate **142** was carried out so that the stereoselectivity of the alkylation reactions could be determined prior to the reduction of the imine (equation 1.54). The reaction was carried out using a two phase system consisting of diethyl ether and aqueous HCl.[62] The imine **137** was first dissolved in the organic phase and 1N aqueous HCl was added to this and the resulting two phase system was stirred at room temperature for 24 hours.



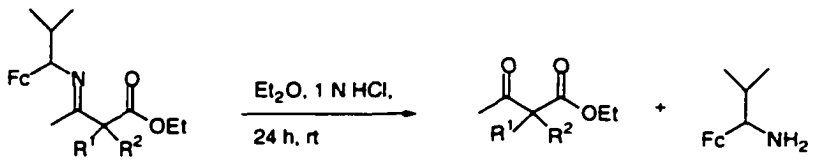
(1.47)

137 **142** **78**

2:1 Mixture of enantiomers

The chiral ferrocenyl amine auxiliary was recovered by separating the two phases of the reaction. The disubstituted ethyl acetoacetate **142** stayed in the organic layer of the reaction and the HCl salt of the amine **78** went into the water layer or precipitated out of the solution. The hydrolysis of the imine was carried out several times but the yields always remained low. The best yield of the product **142** was 35% starting from the enaminone **136**. It was thought that the purification of the imine **137** was causing a loss of yield, so it was carried on without purification to the hydrolysis reaction. This improved the yield but only slightly. The hydrolysis reaction was also carried out on the other disubstituted imines that were generated (Table 1.2).

Table 1.2 Hydrolysis of dialkylated amines



R^1	R^2	Yield over 2 steps
CH_3	$CH_2C_6H_5$	31% (**143**)
C_2H_5	$CH_2C_6H_5$	30% (**144**)
C_3H_7	$CH_2C_6H_5$	30% (**145**)
C_2H_5	CH_2OCH_3	29% (**146**)

Determination of the dialkylation stereoselectivity by chiral G.C. analysis revealed that the chiral ferrocene derivatives resulted in modest asymmetric induction. The ratio of enantiomers of **142** was ~2:1. This result showed potential. Any promise of using this system for the stereoselective synthesis of α,α-disubstituted β-amino acids was quelled, however, when the four other dialkylated β-ketoesters were resolved by chiral HPLC. All of the rest of the compounds synthesized were shown to be racemic when analyzed by chiral HPLC.

Conclusion

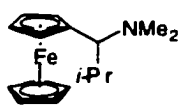
Although initial attempts to asymmetrically synthesize α,α-disubstituted β-amino acids through the use of chiral ferrocenylalkylamines proved to be less selective

than anticipated, the results helped to clarify how few restrictions were placed on these systems conformationally. The proposed hypothesis, therefore, was not valid for the specific auxiliary used to carry out the stereoselective syntheses. The revised hypothesis, therefore, became can a more rigid ferrocenyl amine be used to influence the stereoselectivity of future reactions as well as be recovered in high yields without loss of stereochemistry?

Experimental

General Procedures: All NMR spectra (300 MHz for ^{1}H NMR and 75 MHz. for ^{13}C NMR) were recorded in $CDCl_3$ and chemical shifts were given relative to TMS (0.00 for ^{1}H) and $CDCl_3$ (77.23 for ^{13}C) unless otherwise stated. The 300 MHz ^{1}H NMR and 75.5 MHz ^{13}C NMR were taken on a Varian Inova–300 spectrometer and 400 MHz ^{1}H NMR and 100.6 ^{13}C NMR were taken on a Varian Inova-500 spectrometer. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR. THF was distilled from sodium-benzophenone ketyl; CH_2Cl_2 was distilled from CaH; MeOH was distilled from CaH. Column chromatography was performed with ICN 32-63 nm, 60 Å silica gel. Chiral HPLC was carried out using an OJ Column (Column No. OJ00CE-HC029). (1-Ferrocenyl-2-methylpropyl)dimethylamine **77** was synthesized and resolved according to literature methods.[48]

(1-Ferrocenyl-2-methylpropyl)dimethylamine 77



In a 250 ml round bottom three neck flask was placed a solution consisting of 42 g (0.257 mole) of trichloroacetic acid and 9 ml of glacial acetic acid, which was cooled to 0 °C. To this then was added 9 ml (0.099 mole) of isobutyraldehyde and 9 g (0.048 mole) of ferrocene. This mixture was stirred briefly and to it was added 3 ml (0.052 mole) of fluorosulfonic acid that had been dissolved in 7 ml of dichloromethane. The solution was added all at once. The reaction mixture was then allowed to stir at 0 °C for 2 hrs. During this time, 27 g (0.6 mole) of dimethylamine was condensed into 80 ml of anhydrous THF at -78 °C in a 500 ml round bottom three neck flask. After the ferrocene mixture had stirred for 2 hrs. at 0 °C it was added to the dimethylamine solution being stirred at -78 °C. The addition was carried out via cannulae over a 45 minute period. The reaction was allowed to slowly warm up to room temperature overnight, over which time the solution had turned a homogeneous red color. The reaction was partitioned between ether and an excess of 50:50 saturated sodium bicarbonate in water/water solution. The ether layer was isolated and washed several more times with water and extracted with 8.5% phosphoric acid solution (300 ml total). The acid extracts were combined and washed with ether until the extracts were colorless and made basic using an excess of solid sodium hydroxide. The basic solution was extracted until there was no more color left in the aqueous layer. The ether extracts were combined and washed with saturated NaCl/water solution, dried over magnesium sulfate

and then concentrated under reduced pressure.[48] Yield of **77** was 52.8 g (72%) of an orange oil.

^{1}H NMR ($CDCl_3$) δ 4.14 (m, 3H), 4.12 (s, 5H), 4.07 (m, 1H), 3.14 (d, *J*= 6.2 Hz, 1H), 2.16 (m, 1H), 2.09 (s, 6H), 1.14 (dd, *J*= 44.5, 7.0 Hz, 6H).

The residual oil was then resolved into the *R* and *S* enantiomers in the following manner.

Resolution of *R* and *S* (1-ferrocenyl-2-methylpropyl)dimethylamine (77)

General Procedure[48]

Racemic (1-ferrocenyl-2-methylpropyl)dimethylamine (**77**) was dissolved in ether and extracted with a 3% L-tartaric acid solution in water. A solid formed during this process. The aqueous layer along with the solid was separated from the ether solution and the ether solution was extracted two more times with the 3% tartaric acid solution. The aqueous extracts were combined and allowed to sit at room temperature overnight, filtered, and the solid was washed with small amounts of water and ether. The acid layer was then extracted with ether and the extracts were discarded. The acid layer was made basic using an excess of solid sodium hydroxide and extracted with ether. The ether extracts were combined and washed with a saturated NaCl/water solution, dried over magnesium sulfate, and concentrated under reduced pressure. The residual oil was partially resolved **77***S*. The solid recovered as the insoluble L-tartrate salt was partially resolved **77***R*. This was then set free from the L-tartrate salt by treatment with NaOH.

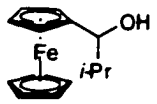
The enantiomers were then completely resolved using L-tartaric acid and D-tartaric acid respectively using the following procedure.

Partially resolved **77*R*** (2.85 g, 10 mmoles) was dissolved in 20 ml of diethyl ether. To this solution was then slowly added a solution consisting of 1.5 g (10 mmoles) of L-tartaric acid in 35 ml of water so that the two layers were not vigorously mixed together. Seed crystals were added to the two phase system and the mixture was then allowed to stand overnight at room temperature. The crystals that had formed were filtered, washed with small amounts of ether and water, and then allowed to air dry. More crystals were recovered by repeating this process and scaling down all of the components in reference to the amount of **77*R*** being resolved. The other enantiomer **77*S*** was resolved in the same fashion, but instead of using L-tartaric acid, D-tartaric acid was used.

The respective tartrate salts were stable at room temperature and were also not sensitive to air or light. The free **77**, however, decomposed upon standing at room temperature. A yield of >40% of each enantiomer could be achieved through the recrystallization process.

The reported optical rotation for **77*R*** and **77*S*** are -191.5° and 192.8° respectively (c=1.000, benzene, sodium lamp). The optical rotations obtained matched these reported values.[48] The tartrate salts were recovered as orange solids.

Alcohol 75



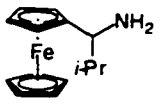
In a 50 ml round bottom three neck flask equipped with a dropping funnel was placed a solution consisting of 285 mg (1 mmole) of (1-ferrocenyl-2-methylpropyl)dimethylamine (**77**) and 15 ml of diglyme. This was stirred and to it was added 525 mg of sodium carbonate that had been dissolved in 10 ml of water. The solution became cloudy as the sodium carbonate precipitated out of solution. The reaction was stirred and the temperature was brought up to 35 °C. After stirring at this temperature for 30 min., 0.31 ml of iodomethane that had been dissolved in 4 ml of diglyme was added to the reaction dropwise over a 30 min. period and it was allowed to stir at 35 °C for 18 hrs. Upon cooling to room temperature the reaction was partitioned between hexane and water. The layers were separated and the water layer was washed with hexane (2 X 20 ml) which were combined and washed with water and finally with saturated NaCl/water solution. The hexane solution was further dried over magnesium sulfate and concentrated under reduced pressure. The crude oil was purified by column chromatography (silica gel, 20:1 hexane/EtOAc). The reaction yielded 220 mg (85%) of the pure alcohol **75** as an orange oil.[48]

^{1}H NMR 4.2 (m, 9H), 4.07 (d, 1H), 2.13 (d, 1H), 1.743 (m, 1H), 0.858 (dd, 6H).

^{13}C NMR 77.421, 77.000, 76.579, 75.107, 69.122, 68.815, 68.184, 67.489, 64.723, 34.749, 18.687

IR 3569.5, 3489.4, 3091.2, 2957.9, 1650.3

(1-Ferrocenyl-2-methylpropyl)amine (78)

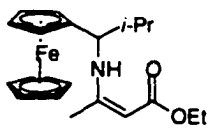


In a 50 ml round bottom three neck flask was placed a solution consisting of 220 mg (0.85 mmole) of alcohol **75** and 20 ml of anhydrous THF, which was cooled to 0 °C. To this was added 2 ml of saturated HCl in THF. The reaction was allowed to stir at 0 °C for 4 hours and to it was added an excess of ammonia that had been condensed into THF at -78 °C. The addition was carried out via double ended needle over a period of 30 min. The reaction was then allowed to stir for 18 hrs. over which time the reaction was allowed to slowly warm up to room temperature. The reaction was then partitioned between ether and water and the water layer was washed with ether (2 X 30 ml), which were combined and washed with water (4 X 30 ml). The ether solution was then extracted with 8.5% phosphoric acid until no more colored material was going into the aqueous solution. The acid layers were combined and made basic using solid NaOH and the solution was extracted with ether (3 X 30 ml). The ether extracts were washed with water and finally with saturated NaCl/water solution. The ether solution was then further dried over magnesium sulfate and was then concentrated under reduced pressure. The yield of the desired amine **78**[18] was 185 mg (85%) of an orange oil. For *R*$[\alpha]^{20}_{D}$ = -79° (c=1, benzene),

S$[a]^{20}_{D}$ = +79 (c=1, benzene)

^{1}H NMR ($CDCl_3$) δ 4.17 (s, 5H), 4.11 (m, 3H), 3.48 (d, *J*= 5.1 Hz, 1H), 1.63 (m, 3H), 0.82 (dd, *J*= 17.9, 7.0 Hz, 6H)

Enaminone 136

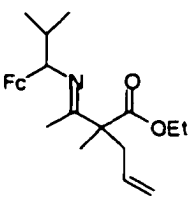


In a 25 ml round bottom one neck flask was placed a solution consisting of 100 mg (0.39 mmole) of (*S*) amine **78** and 6 ml of benzene was stirred and to it was added 0.2 ml of ethyl acetoacetate and 0.2 ml of glacial acetic acid. The vessel was then equipped with a Dean-Stark trap and the reaction was warmed to reflux for 1.5 hrs. The reaction was allowed to cool to room temperature and concentrated under reduced pressure. The crude oil was purified by column chromatography (Florisil, 20:1 hexane/EtOAc). The yield of the desired enaminone **136** was 137 mg (96%).

^{1}H NMR ($CDCl_3$) δ 9.2 (bd, 1H), 4.5 (s, 1H), 4.15 (m, 11H), 2.07 (s, 3H), 1.82(m, 1H), 1.28 (t, 3H), 0.833 (dd, 6H).

^{13}C NMR ($CDCl_3$) δ 170.64, 160.45, 89.98, 81.58, 77.42, 76.98, 76.56, 68.59, 68.41, 68.36, 68.28, 67.97, 67.62, 66.83, 65.81, 58.26, 57.92, 35.60, 19.63, 18.80, 18.21, 14.69

Imine 187

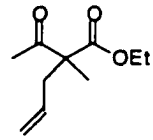


In a 50 ml round bottom three neck flask was placed a solution consisting of 0.308 ml of diisopropylamine and 15 ml of anhydrous THF at 0 °C and to this was added 1.3 ml of 1.6 M *n*-butyllithium in hexane. The solution was allowed to stir for 10 minutes at 0 °C, and was cooled to -78 °C and 192 mg of (*S*) **136** dissolved in 8 ml of anhydrous THF was added to the reaction

dropwise over a 15 minute period. The reaction was allowed to stir at -78 °C for an additional 10 minutes and to the reaction was then added 0.16 ml of iodomethane that had been dissolved in 4 ml of anhydrous THF. The addition was dropwise over a 15 minute period. The reaction was allowed to stir for another 2 hrs. at -78 °C and was then allowed to slowly warm up to room temperature. The reaction was stirred for another 0.5 hr. at room temperature, over which time the reaction became cloudy. The reaction was then partitioned between water and ether and the water layer was extracted with ether. The ether extracts were washed with water and finally with saturated NaCl/water and then further dried over magnesium sulfate and concentrated under reduced pressure. The above procedure was then repeated using the crude oil but instead of using iodomethane in the reaction, allyl bromide (0.22 ml, 2.5 mmoles) was used. Yield of **137** was 98.6 mg (45% over two steps) as an orange oil. The reaction was carried on without further purification to the next step.

This procedure was repeated to form compounds **138**, **139**, **140**, **141**.

β-ketoester 137

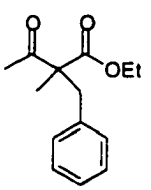


In a 25 ml round bottom three neck flask was placed a solution consisting of 120 mg (0.28 mmole) of (*S*) imine **137** and 10 ml of ether and to this was added 7 ml of 1N HCl. This two phase system was allowed to stir for 17 hrs. at room temperature. The reaction was filtered and then placed in a separatory funnel. The layers were separated and the water layer was extracted with ether (3 X 10

ml). The ether extracts were combined and washed with saturated NaCl/water solution. The ether solution was further dried over magnesium sulfate and concentrated under reduced pressure. The residual orange oil was purified by column chromatography (silica gel, 20:1 hexane/EtOAc). Yield of the purified disubstituted ethyl acetoacetate **142**[63] was 18.5 mg (35%). The enantiomeric excess was determined to be 33% by chiral GC analysis. This procedure was repeated to form compounds **143**[63], **144**[63], **145**[64], **146**.

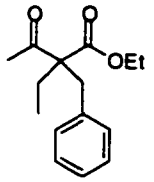
^{1}H NMR ($CDCl_3$) δ 5.66 (m, 1H), 5.1 (m, 2H), 4.20 (q, J = 7.2 Hz, 2H), 2.68 (dd, J = 7.0, 14.2 Hz, 1H), 2.54 (dd, J = 7.6, 14.2 Hz, 1H) 2.158 (s, 3H), 1.338 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 206.389, 172.485, 132.612, 118.992, 77.421, 77.000, 76.563, 61.342, 39.295, 26.225, 18.865, 14.045; IR ν 3079.1, 2982.1, 2938.4, 1712.8, 1640.8

β-ketoester 143



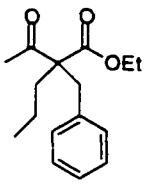
^{1}H NMR ($CDCl_3$) δ 7.24 (m, 3H), 7.09 (m, 2H), 4.19 (m, 2H), 3.17 (dd, J= 65.6, 13.9 Hz, 2H), 2.18 (s, 3H), 1.3 (s, 3H) 1.26 (t, J= 7.3 Hz, 3H). The enantiomeric excess was determined to be 0% by chiral HPLC.

β-ketoester 144



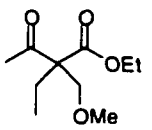
^{1}H NMR ($CDCl_3$) δ 7.24 (m, 3H), 7.06 (m, 2H), 4.18 (m, 2H), 3.17 (q, *J*= 14.3 Hz, 2H), 2.12 (s, 3H), 1.86 (q, *J*= 7.7 Hz, 2H), 1.25 (t, *J*= 7 Hz, 3H), 0.88 (t, *J*= 7.3 Hz, 3H). The enantiomeric excess was determined to be 0% by chiral HPLC.

β-ketoester 145



^{1}H NMR ($CDCl_3$) δ 7.24 (m, 3H), 7.04 (m, 2H), 4.18 (m, 2H), 3.18 (q, *J*= 14.3 Hz, 2H), 2.12 (s, 3H), 1.72 (dd, *J*= 9.52, 7.7 Hz, 2H), 1.25 (m, 5H), 0.94 (t, *J*= 7.3 Hz, 3H). The enantiomeric excess was determined to be 0% by chiral HPLC.

β-ketoester 146



^{1}H NMR ($CDCl_3$) δ 4.97 (q, *J*= 7 Hz, 2H), 3.46 (s, 3H), 1.99 (d, *J*= 1.1 Hz, 3H), 1.83 (q, *J*= 0.7 Hz, 3H), 1.29 (t, *J*= 7Hz, 3H). The enantiomeric excess was determined to be 0% by chiral HPLC.

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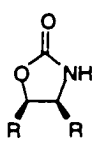
Chapter Two

Synthesis and Utilization of a Novel Ferrocene Chiral Auxiliary

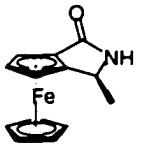
Introduction

The ability to control asymmetry in reactions has always posed a challenge. One very important method for inducing asymmetry is through the use of a chiral auxiliary. Chiral auxiliaries have been used for a long time and the most useful ones provide high selectivity and can be recycled as well. One of the best-known chiral auxiliaries used today is Evan's oxazolidinone (**1**) (Figure 2.1). This chiral auxiliary is able to induce selectivity in a wide variety of reactions and can be recycled.[1] One limitation with chiral oxazolidinones, however, is that if the amine functionality is to remain on the compound that it is influencing, the chiral auxiliary is destroyed.[2] With this in mind, it was decided to synthesize a chiral auxiliary that could induce asymmetry, donate functionality in compounds that it was attached to, and be recycled as well. The compound that was chosen to accomplish this was ferrocenyl lactam **2**.

Figure 2.1



1



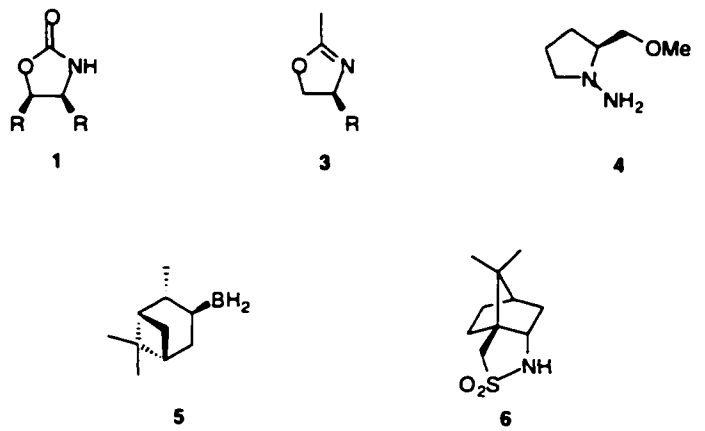
2

Chiral Oxazolidinones in Asymmetric Synthesis

Chiral auxiliaries have always been very powerful tools in asymmetric synthesis.[3] The ability to develop a chiral auxiliary depends on how well it lends itself to various synthetic conditions. A chiral auxiliary must posses a number of properties in order for it to gain acceptance as a useful compound. Chiral catalysts have several advantages over auxiliaries because they are generally used in small quantities in reactions and are easily recovered. Chiral auxiliaries, however, must be used stoichiometrically and must actually be attached to the compounds that are being influenced. The most desirable situation in producing a chiral auxiliary is to synthesize it efficiently from inexpensive starting materials. The auxiliary must also be attached to the molecule in high yields as well as be removed in high yields.

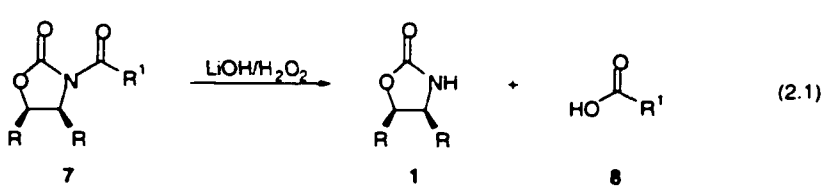
Chiral auxiliaries exist in a wide variety of structures to produce different results in different reactions.[3] Some examples include oxazolidinones **1**[1], oxazolines **3**[4], (*S*)-1-amino-2-(methoxymethyl)-pyrrolidine (SAMP) **4**[5], isopinocamphenylborane **5**[6], and camphorsultams **6**[7] (Figure 2.2).

Figure 2.2



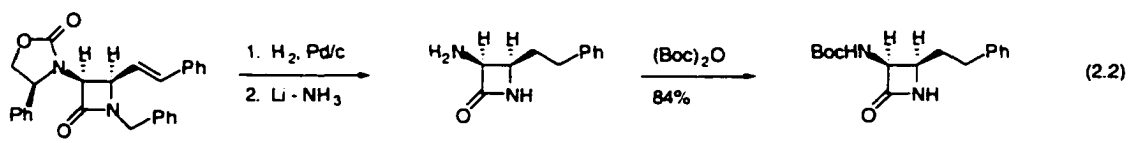
All of these auxiliaries can be used to provide high stereoselectivity in a wide variety of reactions. The group that has received the most attention, however, is the chiral oxazolidinone **1**.

The chemistry of chiral oxazolidinones **1** (Evans chiral auxiliary) is very diverse. It can be used in aldol reactions, C-alkylations, α-aminations, Michael additions, and pericyclic reactions.[1] The reactions generally give products with high enantiomeric excesses in high yields. After the stereoselectivity is induced, the oxazolidinone is usually cleaved. Typically the chiral auxiliary exists as an *N*-acyloxazolidinone **7** making exocyclic cleavage rather straight forward (equation 2.1).[8]



(2.1)

Oxazolidinones can also be cleaved in an endocyclic fashion (equation 2.2).[2] These cleavages are usually performed when the compound is not an *N*-acyloxazolidinone and it is desired to have the amine functionality stay attached to the target compound. When this is carried out, however, the chiral auxiliary is destroyed and cannot be recycled.[2]



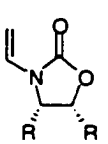
9 10 11 (2.2)

This is a limitation of oxazolidinones. If the amine functionality is to remain on the compound it is attached to, then the oxazolidinone is completely lost in the process.

Ene-carbamates

Chiral oxazolidinones can be functionalized with a vinyl substituent as well. These compounds are generally termed ene-carbamates **12** (Figure 2.3).

Figure 2.3

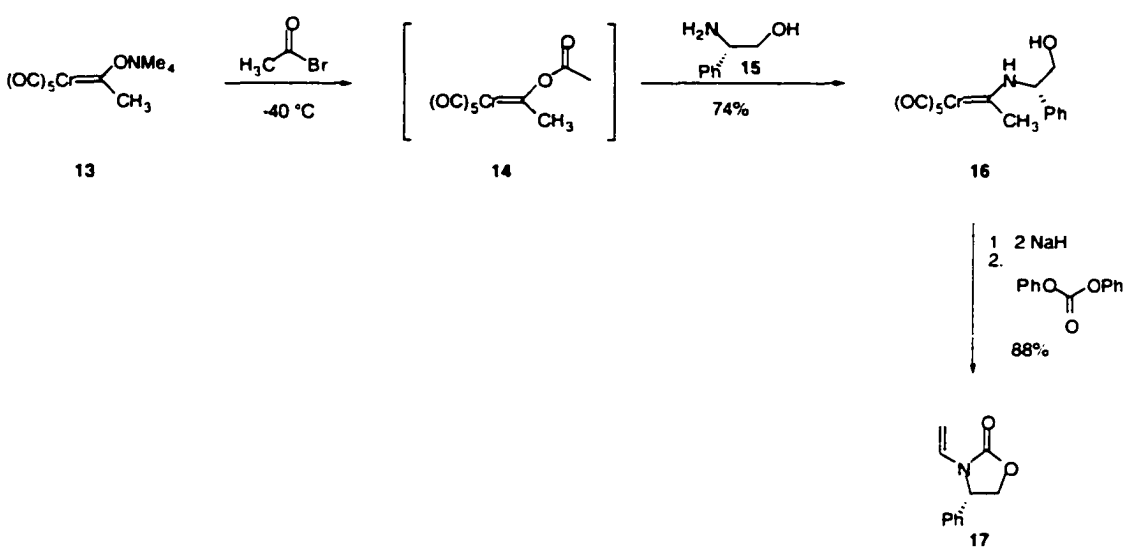


12

Syntheses of Ene-carbamates

The initial synthesis of chiral ene-carbamates was carried out by Hegedus in 1990.[9] Acylation of chromium carbene complex **13** with acetyl bromide provided acetoxycarbene complex **14** (equation 2.3). Displacement with (*S*)-phenylglycinol **15** resulted in aminocarbene complex **16**. Deprotonation with two equivalents of sodium hydride followed by diphenyl carbonate gave the desired ene-carbamate **17**.

(2.3)

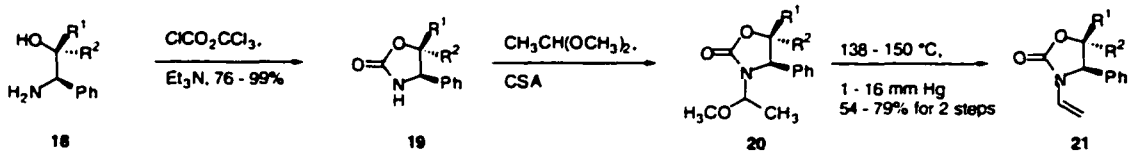


13 14 16 17

The synthesis of ene-carbamates was also performed without the use of chromium carbene complexes as demonstrated by Terashima.[10] A number of ene-carbamates were synthesized from readily available (*R*)-2-phenylaminoethanols **18** by treatment with trichloromethyl chloroformate to give the oxazolidinones **19** (equation 2.4). Heating with acetaldehyde dimethyl acetal with a catalytic amount of camphorsulfonic acid afforded

the methoxyoxazolidinones **20**. Subjecting the methoxyoxazolidinone to high temperatures under vacuum caused elimination of the methoxyl group forming the ene-carbamates **21**.

(2.4)

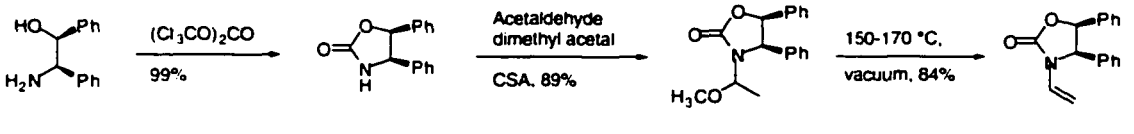


18 **19** **20** **21**

a) R^1 = Ph, R^2 = H, b) R^1 = R^2 = H, c) R^1 = R^2 = Ph

This method was improved on through cyclization of (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**22**) with triphosgene to provide oxazolidinone **23** (equation 2.5). Addition of acetaldehyde in the presence of (±)-camphorsulfonic acid gave methoxyoxazolidinone **24**, which when heated in the presence of ammonium chloride under vacuum yielded desired ene-carbamate **25**.[11]

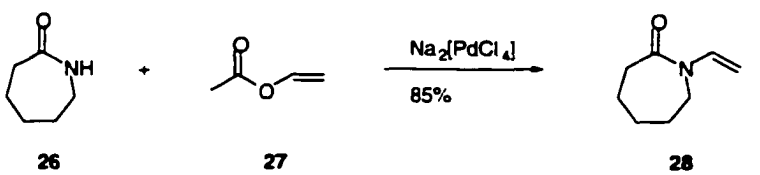
(2.5)



22 **23** **24** **25**

The synthesis of structurally related *N*-vinyl lactams **28** has been carried out as well using vinyl acetate (**27**) and sodium tetrachloropalladate (equation 2.6).

Transvinylation of lactam **26** resulted in the desired *N*-vinyl lactam **28**.[12] When δ-valerolactam was used as the starting material the reaction resulted in only 20% yield of the desired *N*-vinyl lactam.[13]

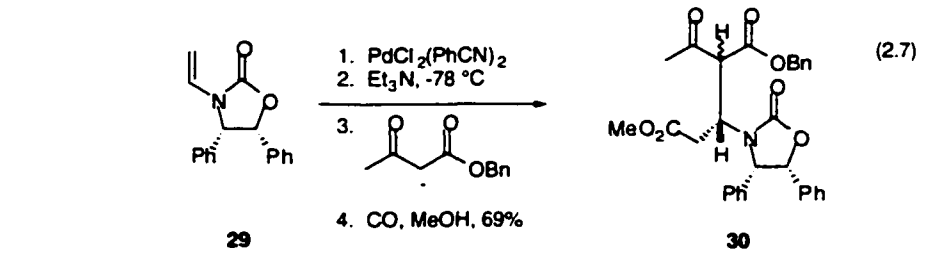


26 **27** **28** (2.6)

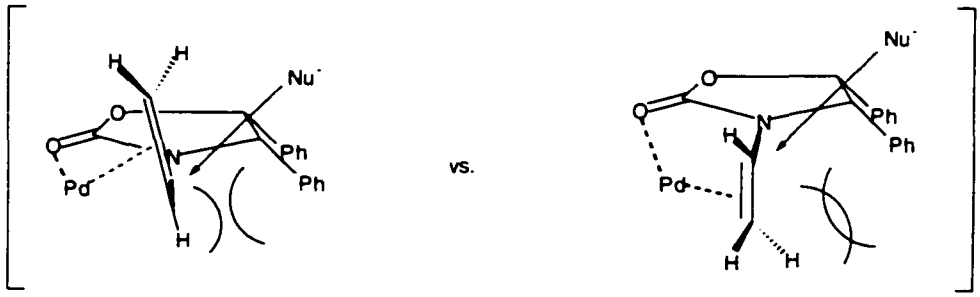
Uses of Ene-carbamates

Ene-carbamates have been used in palladium-assisted alkylations, and asymmetric cyclopropanations, as well as in the formation of α-amino acids and cyclobutanones in a stereoselective manner.

Palladium-assisted alkylations using ene-carbamates have led to the production of natural products such as a key relay to (+)-thienamycin by treatment of ene-carbamate **29** with $PdCl_2(PhCN)_2$ (equation 2.7).[9] Addition of triethylamine and sodium benzyl acetoacetate at -78 °C followed by addition of carbon monoxide and methanol provided ester **30**. The palladium forms a chelate with the carbonyl oxygen and the π-electrons of the vinyl group. The observed stereochemistry is due to nucleophilic attack from the face opposite of this palladium chelate on the sterically-favored olefin complex **31**. Futher manipulation provided the key relay to (+)-thienamycin as a single diastereomer.



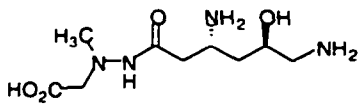
29 30



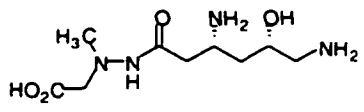
31 32

Asymmetric palladium-assisted alkylation was also used to synthesize the natural products (+)-negamycin **33** and (-)-5-*epi*-negamycin **34** in a stereoselective fashion (Figure 2.4).[14] Ene-carbamate **29** was subjected to $PdCl_2(MeCN)_2$ followed by

Figure 2.4



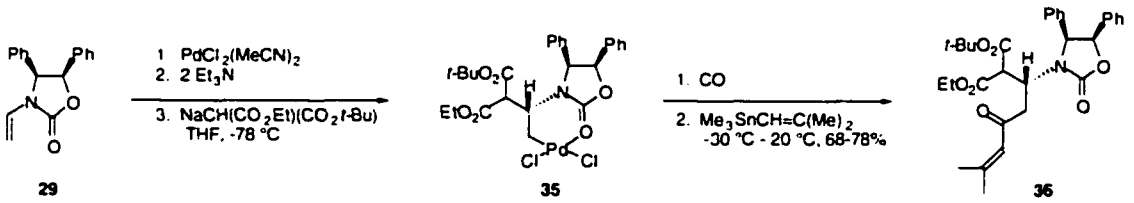
(+)-negamycin
38



(-)-5(*S*)-*epi*-negamycin
39

triethylamine and finally the sodium anion of *t*-butyl ethyl malonate at -78 °C (equation 2.8). Addition of carbon monoxide and isobutenyltrimethylstannane provided the unsaturated ketone **36** in a 1:1 mixture of diastereomers of the malonates but isomerically pure at the amine carbon. The stereochemical outcome was the same as that observed in the synthesis of the key relay to (+)-thienamycin. Attack of the nucleophile once again occurred from the face opposite of the metal chelate on the sterically favored olefin isomer. After further manipulation of the molecule, the desired (-)-5-*epi*-negamycin **34** was provided in a 20% yield in 12 steps. The synthesis of (+)-negamycin **33** was also carried out in the same manner which was afforded in 13% overall yield in 15 steps.

(2.8)

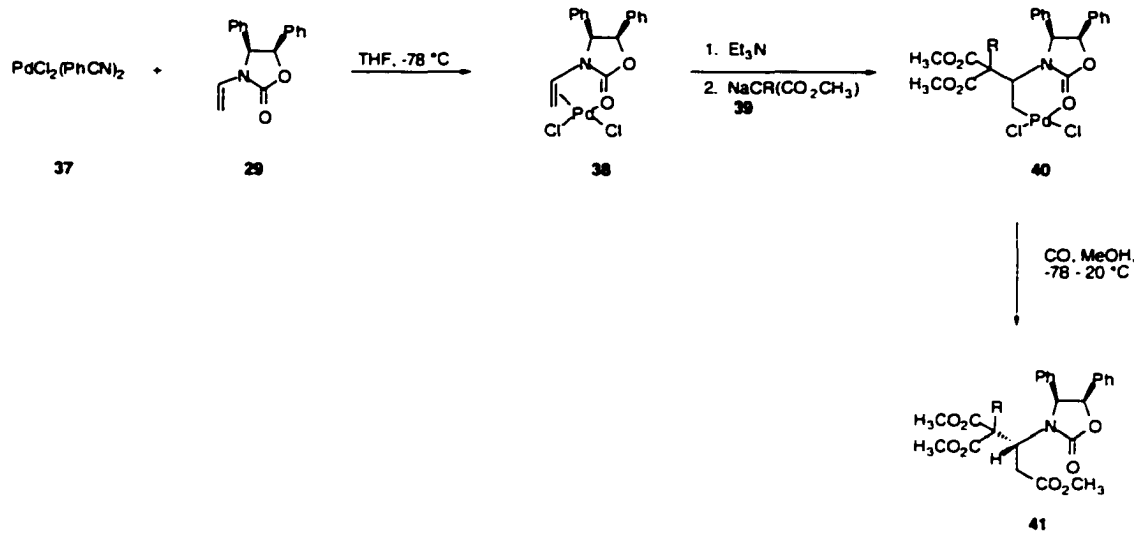


29 **35** **36**

Substituted malonate esters were also formed by quenching σ-alkylpalladium intermediate with carbon monoxide and methanol in yields of 50-85% as a single diastereomer (equation 2.9).[15] The alkylations were carried out using (bis)benzonitrile palladium chloride **37**, triethylamine, and the anion of substituted malonates **39**. The

observed stereochemistry was the same as that shown for the syntheses of the previous palladium assisted alkylations.

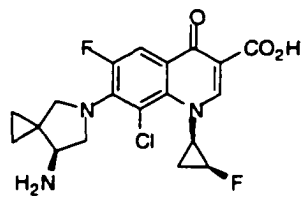
(2.9)



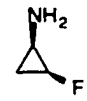
37 29 38 40 41

Ene-carbamates can also be used in the stereoselective synthesis of cyclopropanes such as (1*R*,2*S*)-2-fluorocyclopropylamine (**43**) which is a component of DU-6859 (**42**) (Figure 2.5).[10] DU-6859 (**42**) is a quinolonecarboxylic acid that was shown to possess antibacterial activity while at the same time exhibiting few side effects.

Figure 2.5



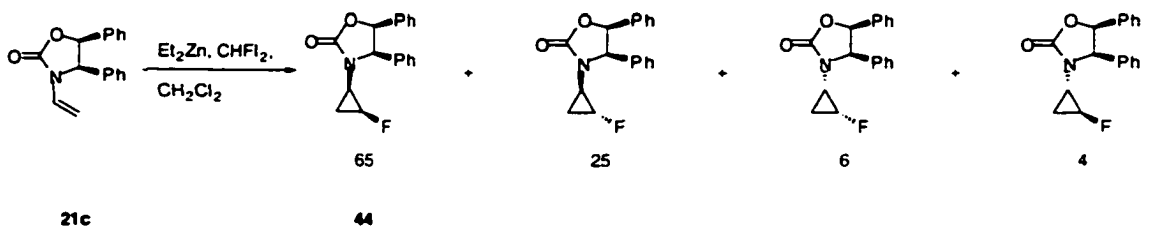
DU-6859
42



(1 *R*,2*S*)-2-fluorocyclopropylamine
43

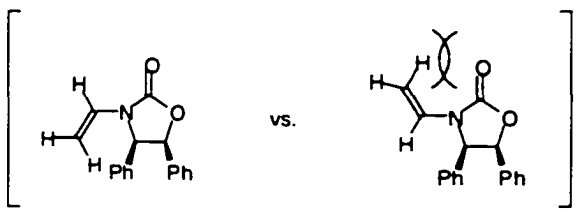
Cyclopropanation of ene-carbamate **21c** in the presence of fluorodiiodomethane and diethylzinc in methylene chloride gave a 65:25:6:4 ratio of the possible diastereomers with the desired diastereomer **44** being the major product (equation 2.10). The

(2.10)

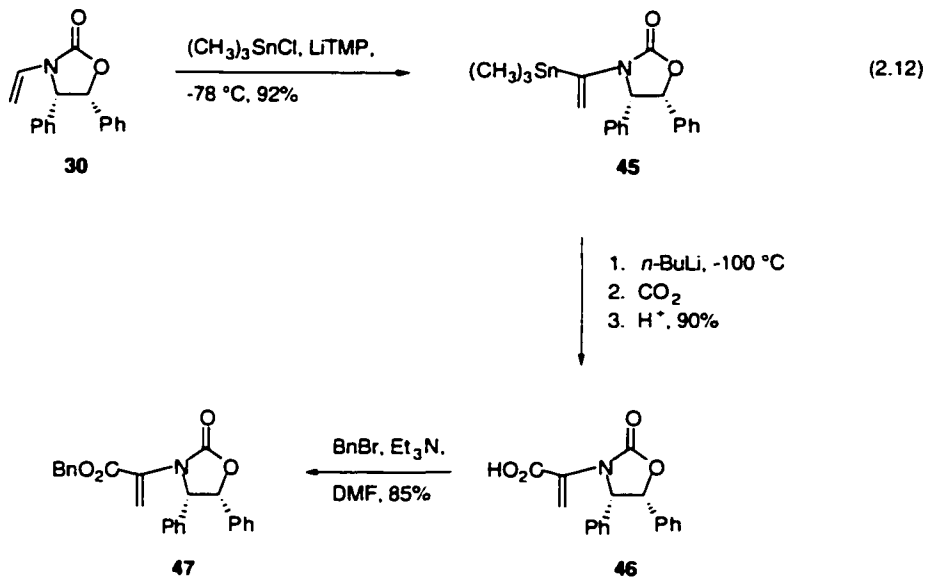


stereochemistry was explained to arise from the lowest energy conformation of oxazolidinones without the formation of a metal chelate. Zinc chelating to oxygen would result in low yields though loss of the vinyl group's electron donating ability, which was not observed. The stereochemistry was instead dictated by the preferred conformation of the vinyl group (equation 2.11). Approach of the zinc-monofluorocarbenoid on the sterically-favored conformation from the face opposite of the large phenyl groups resulted in the observed stereoselectivity.

(2.11)



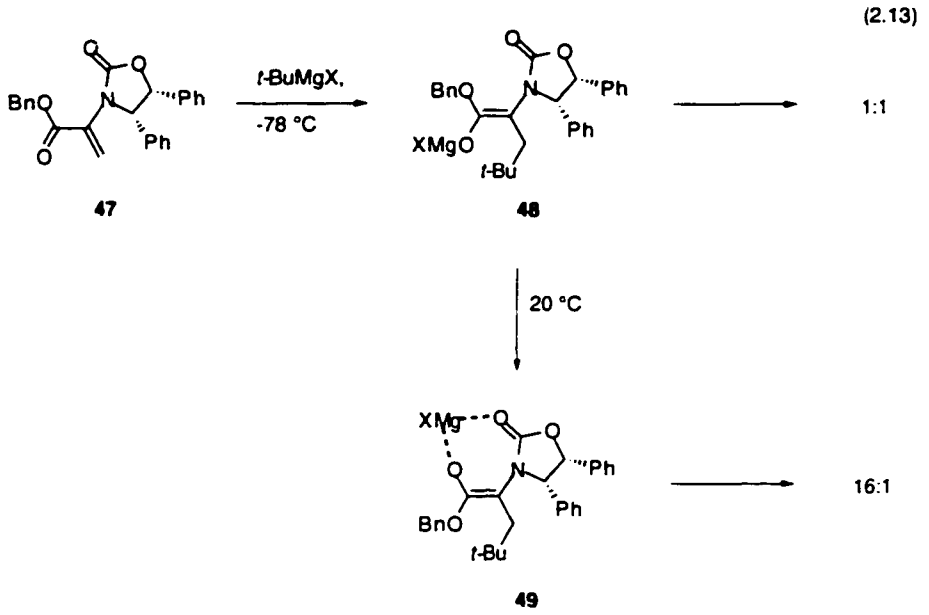
α-Amino acids have been synthesized through the use of chiral ene-carbamates as well.[16] This asymmetric synthesis was carried out through copper-catalyzed conjugate additions to carbamatoacrylates **47** that are derived from ene-carbamate **29** (equation 2.12). Treatment of the ene-carbamate **29** with trimethyltin chloride and lithium 2,2,6,6-tetramethy piperidide (Li(TMP)) gave the stanylated ene-carbamate **45**. Lithiation with *n*-butyllithium and addition of carbon dioxide provided the carboxylic acid **46**. Esterification with benzyl bromide yielded the desired dehydroalanine **47** in 75 - 80% overall yield from ene-carbamate **29**.



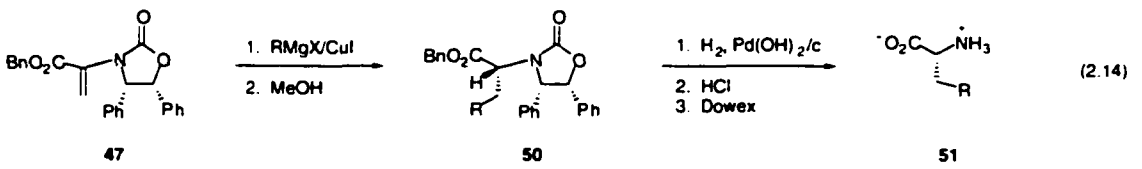
(2.12)

Reaction of the dehydroalanine with various Grignard reagents in the presence of copper iodide followed by addition of methanol gave the addition products **50**. The observed stereochemistry resulted from the stereoselective protonation of the formed seven membered magnesium chelate (equation 2.13). Equilibration of the kineticically favored *E*-enolate **48** to the *Z*-enolate **49** at 20 °C resulted in the formation of this

magnesium chelate which was protonated from the face opposite of the phenyl groups. When the reaction was not allowed to warm to room temperature, the *E*-enolate **48** did not equilibrate to the *Z*-enolate **49**, required for the formation of the chelate, which resulted in a 1:1 ratio of diastereomers.



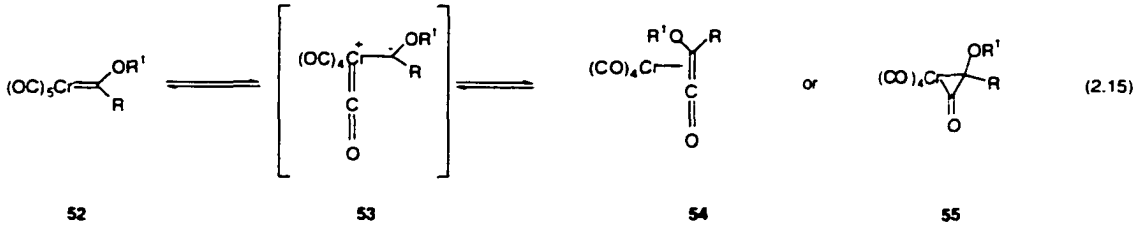
Removal of the auxiliary using Pearlman's catalyst provided the monosubstituted α-amino acids **51** in yields of 89 to 98% in enantiomeric excess of 73 to 97% (equation



2.14). These are all very good examples of the synthetic diversity of ene-carbamates. The use of ene-carbamates in [2+2] photochemistry with chromium carbenes has also undergone a considerable amount of investigation.[17]

Photolysis Reactions

One of the more useful applications of ene-carbamates is in conjunction with the photolysis of chromium carbenes in order to form cyclobutanones in a stereoselective fashion.[17] The synthesis of cyclobutanones is a one step process involving the reaction of chromium carbene complexes and ene-carbamates. The syntheses of these compounds have been studied quite thoroughly. The initial step of the reaction is thought to be the generation of a chromium bound ketene **54.** which occurs through irradiation into a metal-to-ligand charge transfer (MLCT) absorption band of the chromium complex (350 - 450nm) (equation 2.15).[18]



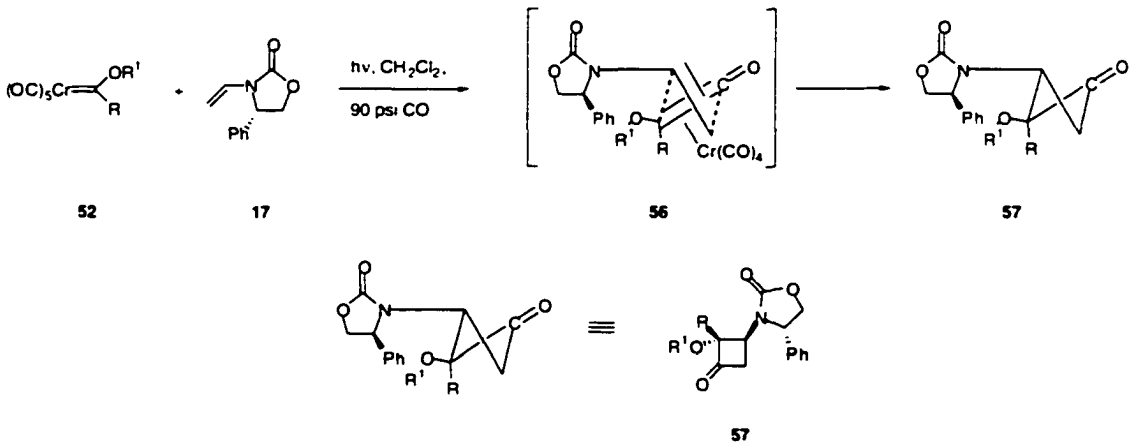
52 53 54 55 (2.15)

Promotion of an electron from chromium to the carbene carbon results in a formal oxidation of the metal center which allows for reversible carbonyl insertion. which is thought to lead to either a chromium-bound ketene **54** or a metallocyclopropanone chromium complex **55**. Neither of these species has been directly observed. but their

postulated existence is based on their pattern of reactivity.[19] Due to the reversibility of this reaction, the ketene species is present in small amounts so no dimer product is formed, which is typically seen when using conventional ketenes.[21]

The chromium bound ketene is now reactive towards the ene-carbamate and the reaction is thought to proceed through a $[{}_{\pi}2_s + ({}_{\pi}2_s + {}_{\pi}2_a)]$ mechanism.[21] The steroechemistry is dictated by the chiral ene-carbamate **17** (equation 2.16).[22] The chromium-bound ketene **54** approaches the face opposite of the phenyl substituent. Also the alkoxy group has less steric interaction with the ene-carbamate so it is on the side closest to the oxazolidinone ring. The result is the formation of the desired cyclobutanone ring in a stereoselective manner. This chemistry provided a very short and convenient way of forming cyclobutanones as well as compounds derived from these four membered rings such as lactones and cyclopentanones.

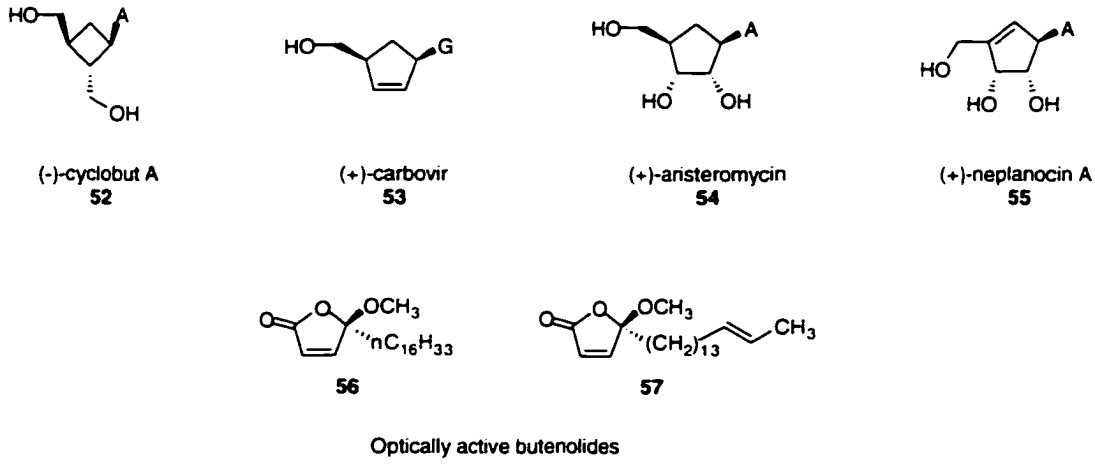
(2.16)



Initial studies on this type of reaction provided a variety of cyclobutanones using the same ene-carbamate to induce stereoselectivity.[22] Reaction of the ene-carbamate with

the chromium carbenes in the presence of light under a carbon monoxide atmosphere gave various cyclobutanones in yields from 50 to 67% and diastereomeric excesses ranging from 86 to >97%. The chemistry behind these photolysis reactions has allowed for the production of a wide variety of significant products including, (-)-cyclobut-A (**58**)[23], (+)-carbovir (**59**)[24], (+)-aristeromycin (**60**)[24], (+)-neplanocin A (**61**)[25], as well as natural products such as optically active butenolides **62** and **63**[26] isolated from the marine sponge *Plakortis lita* (Figure 2.6).

Figure 2.6

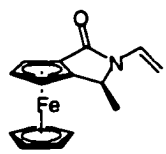


Rationale

Oxazolidinone containing ene-carbamates have proven to be efficient chiral substrates for a wide range of reaction types, however, the synthesis of products which must retain the nitrogen of the auxiliary precludes their recycling. In contrast, an appropriate ferrocenyl derived equivalent could provide all of the advantages of oxazolidinone chiral auxiliaries, including a high degree of asymmetric induction, and

applicability across a wide range of reaction types, with the additional advantages of being recyclable while allowing the product to retain the nitrogen. Attempts to develop such a ferrocenyl based equivalent in the contexts of ene-carbamate cycloaddition chemistry is described below. The target compound chosen for this initial investigation was chiral ferrocenyl enamide **64** (Figure 2.7).

Figure 2.7



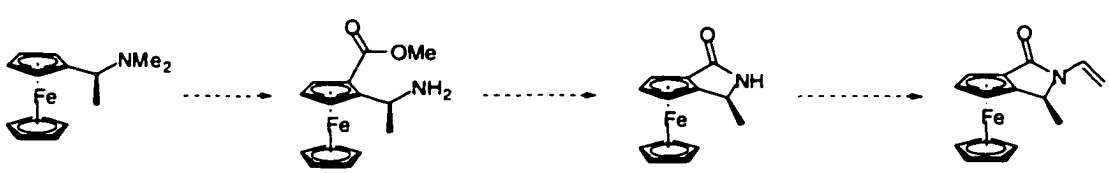
64

Results and Discussion

Synthesis of Enamide 64

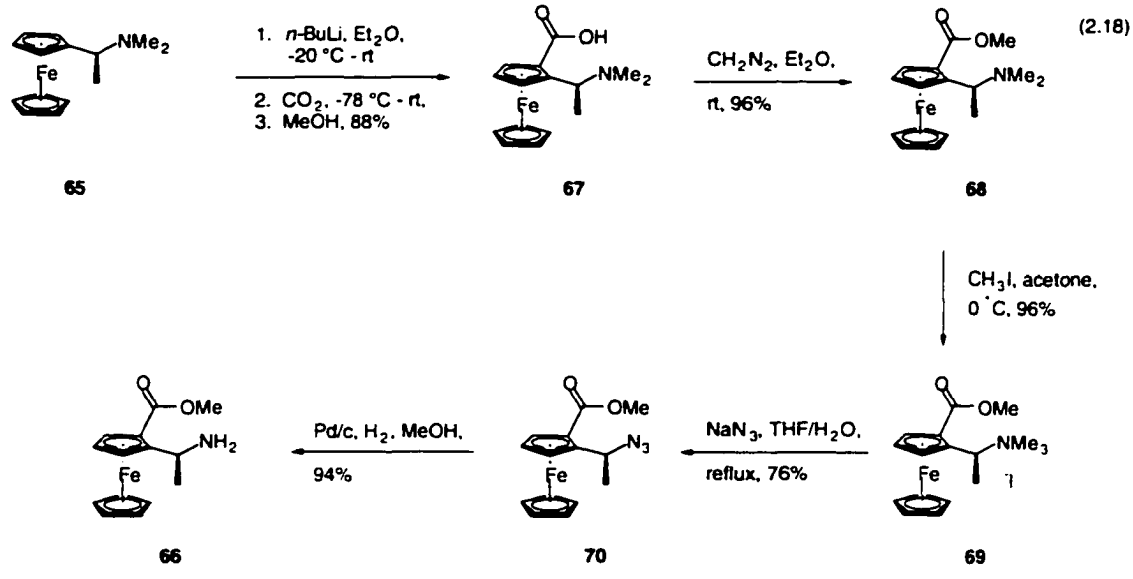
The first approach to **64** was patterned on that used to synthesize ene-carbamate **29** and involved the vinylation of ferrocenyl lactam **2**.[13] This, in turn, should be accessible from the known (*S*)- α-N,N-dimethylaminoethylferrocene **65** (equation 2.17)

(2.17)



65 **66** **2** **64**

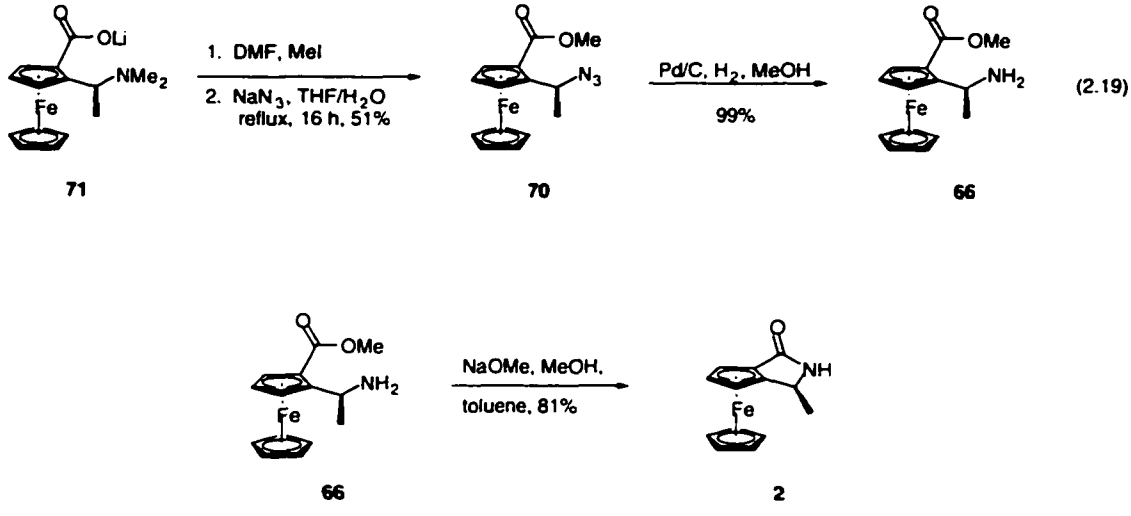
Directed ortho-lithiation using *n*-butyllithium provided the desired lithioferrocene with a diastereoselectivity of 10:1.[27] Addition of solid carbon dioxide formed the lithiate salt of the carboxylic acid, which upon silica gel column chromatography with methanol as the eluant gave acid **67**. Esterification of acid **67** into methyl ester **68** using diazomethane followed by alkylation with iodomethane provided the quaternary amine **69**. Displacement of the quaternary amine with sodium azide provided azide **70**, which was reduced to give amine **66** (equation 2.18).



(2.18)

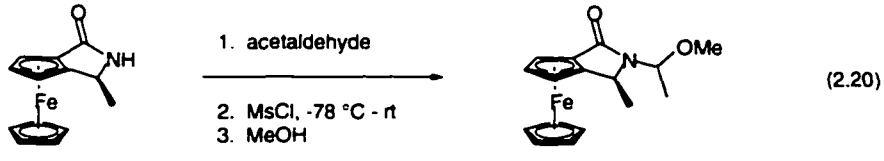
Subsequently, a shorter route involving the methylation of both the carboxylate and the amine groups of **71** with iodomethane, followed by displacement of the quaternary amine with sodium azide in THF/water at reflux gave the azide **70** (equation 2.19). Reduction of the azide with palladium on carbon provided the primary amine **66**.

Treatment of the amine **66** with 1N NaOMe in methanol in toluene at reflux yielded the desired amide **2**. The distillation of methanol drove the reaction to completion.



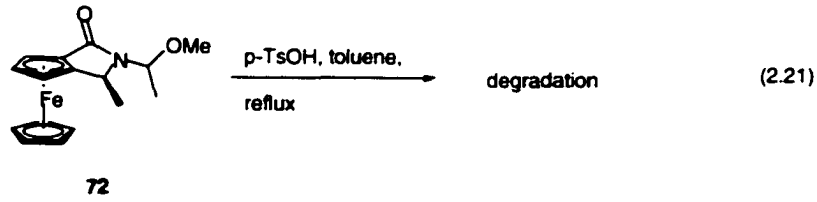
71 70 66 66 2 (2.19)

N-vinylation of amide **2** with acetaldehyde failed to produce the desired enamide but the methoxy amide **72** was formed using acetaldehyde with mesyl chloride followed by methanol (equation 2.20). Attempted conversion of methoxy amide **72** into the

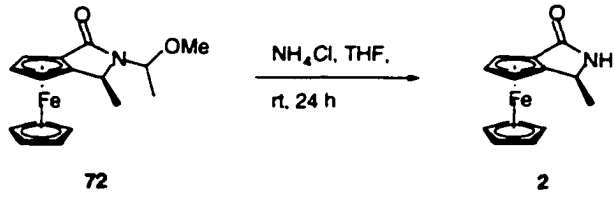


2 72 (2.20)

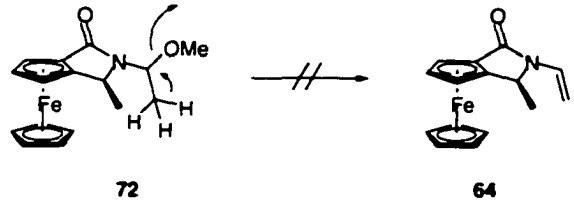
desired enamide (equation 2.21) resulted in degradation or recovery of amide **2**. Recovery of amide **2** suggested that the system was not biased enough to cause only



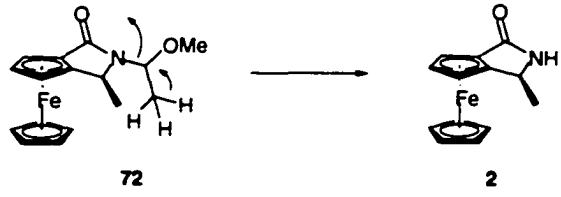
(2.21)



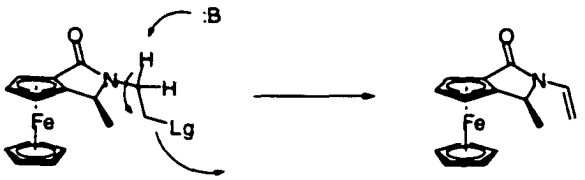
elimination of the methoxy group and the amide was being eliminated instead (equation 2.22). The molecule was changed to cause elimination to occur away from the amide



(2.22)

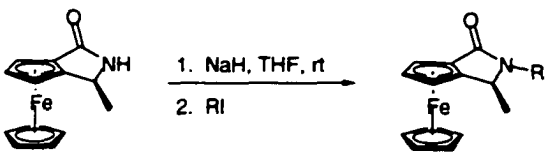


through the addition of an ethyl group with a leaving group opposite of the amide (equation 2.23).



73 64 (2.23)

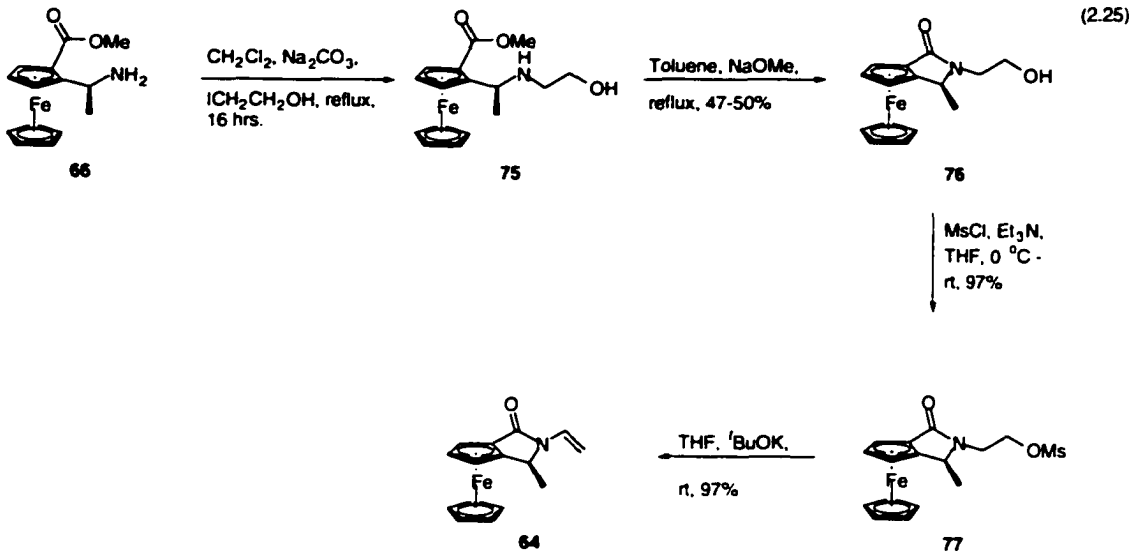
Alkylation of amide **2** with iodomethane occurred to give the methyl amide **74** but alkylation with either iodoethanol or diiodoethane, electrophiles with the requisite leaving group in the correct position, did not produce the desired alkyl amide (equation 2.24). Since the desired ethyl groups could not be added to the amide they were added to



2 (2.24)

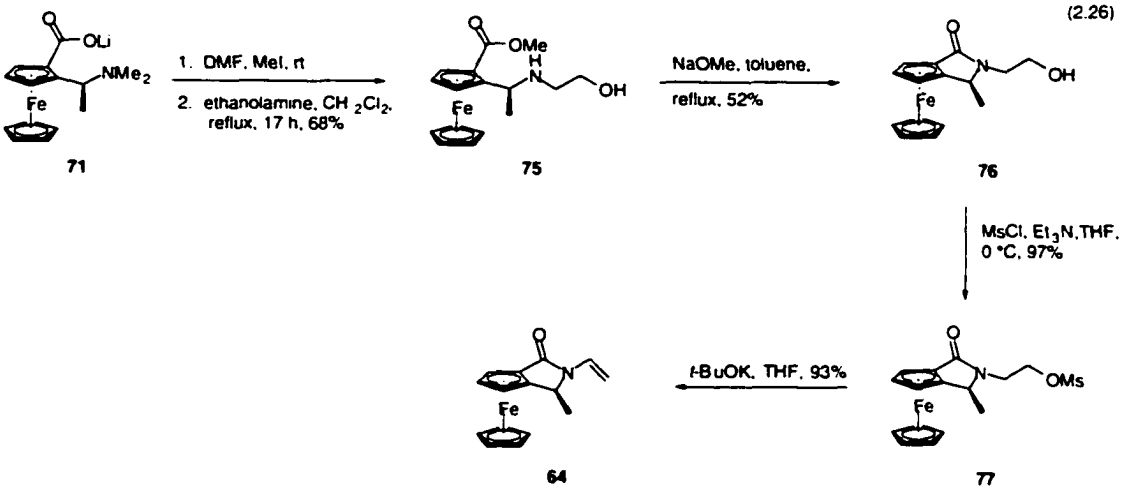
R = Me, 80% **74**
R = CH_2CH_2OH, no alkylation
R = CH_2CH_2I, no alkylation

amine **66** before ring closure. Treatment of amine **66** with iodoethanol in the presence of sodium carbonate gave alkylated amine **75** along with a mixture of dialkylated and non-alkylated compounds. Cyclization of amine **75** was carried out using sodium methoxide in toluene at reflux. Mesylation of alcohol **76** and elimination using potassium *t*-butoxide formed the desired enamide **64** (equation 2.25).



(2.25)

To eliminate over-alkylation of amine **66**, the desired functionality was introduced through displacement of the quaternary amine with ethanolamine in refluxing methylene chloride to produce amino alcohol **75**, which in-turn, was cyclized with 1N sodium methoxide in toluene at reflux. Mesylation of alcohol **76** and elimination formed the desired enamide **64** (equation 2.26).

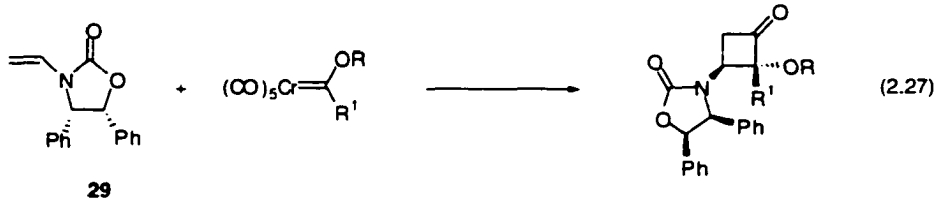


(2.26)

Utilization of Enamide 64

The first reaction type that was chosen to investigate the use of the chiral ene-amide **64** was the [2+2] chromium carbene photoreaction. The importance of cyclobutanones and compounds derived from these cyclic compounds has been shown extensively in literature making them targets for new and interesting asymmetric syntheses.[28]

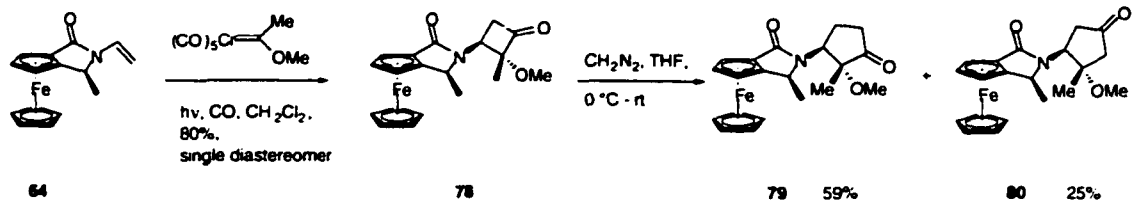
In photolysis reactions, the stereoselectivity is controlled by ene carbamate **29** (equation 2.27).[20] During further synthetic transformations, however, the chiral auxiliary is either destroyed leaving amino functionality behind, or eliminated completely from the molecule which exemplifies the need to develop chiral auxiliaries that can be recycled.



(2.27)

Enamide **64** was allowed to react with (methyl)(methoxy)chromium carbene to produce the desired cyclobutanone **78** as a single diastereomer (equation 2.28). Ring expansion of cyclobutanone **78** using diazomethane formed cyclopentanones **79** and **80**.

(2.28)

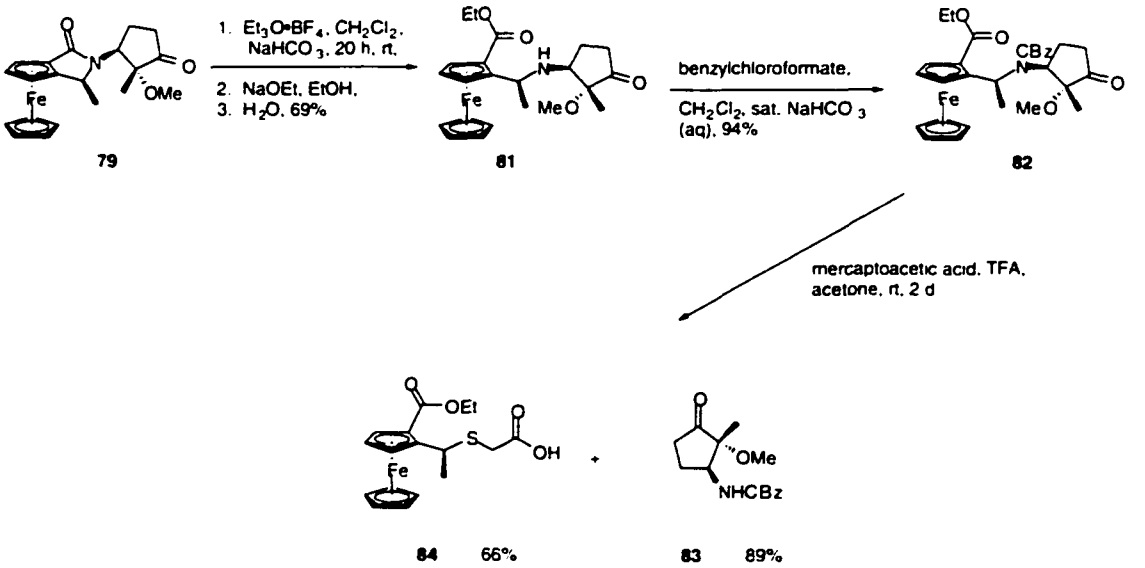


64 78 79 59% 80 25%

The absolute stereochemistry of **79**, determined by X-ray crystallography (Figure 2.8), was the same as that produced by ene carbamate **29**.

Cleavage of the auxiliary by treatment of amide **79** with triethyloxonium tetrafluoroborate at room temperature for 17 hours followed by cooling to 0 °C and addition of sodium ethoxide in ethanol followed immediately with water provided the secondary amine **86**.[29] Protection of the amine provided carbamate **82** and cleavage using mercaptoacetic acid and trifluoroacetic acid gave the desired cyclopentanone **83** as well as the ferrocenyl thiol **84** (equation 2.29).

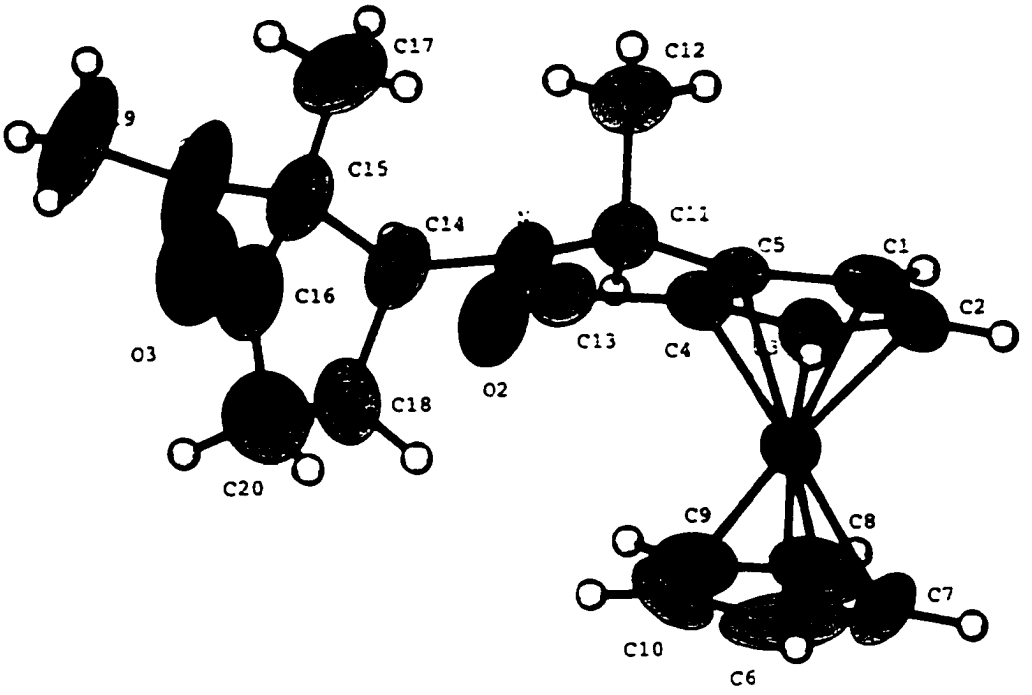
(2.29)



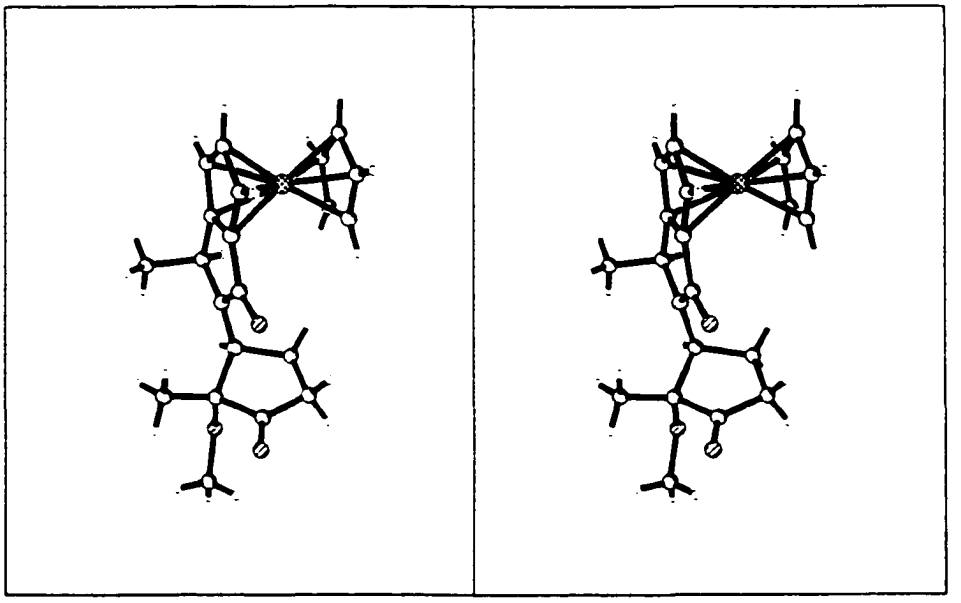
79 81 82

84 66% 83 89%

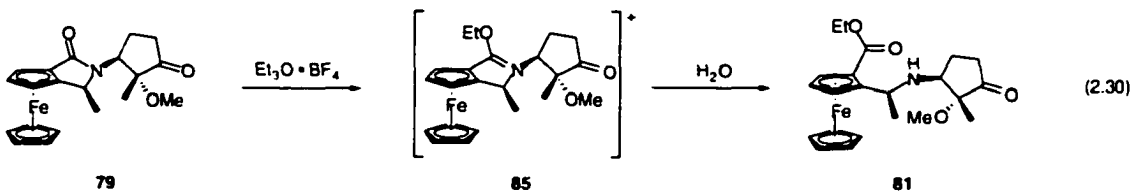
Figure 2.8 – X-ray of



Stereoview of 79

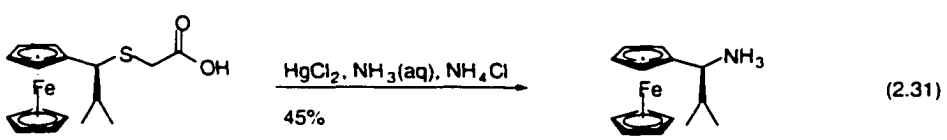


The mechanism of the lactam cleavage proceeds through iminium ester **85** that is hydrolyzed to provide ester **81** (equation 2.28). Both compounds **83** and **84** were isolated as only one diastereomer, demonstrating that no racemization occurred during the cleavage reaction.



79 **85** **81** (2.30)

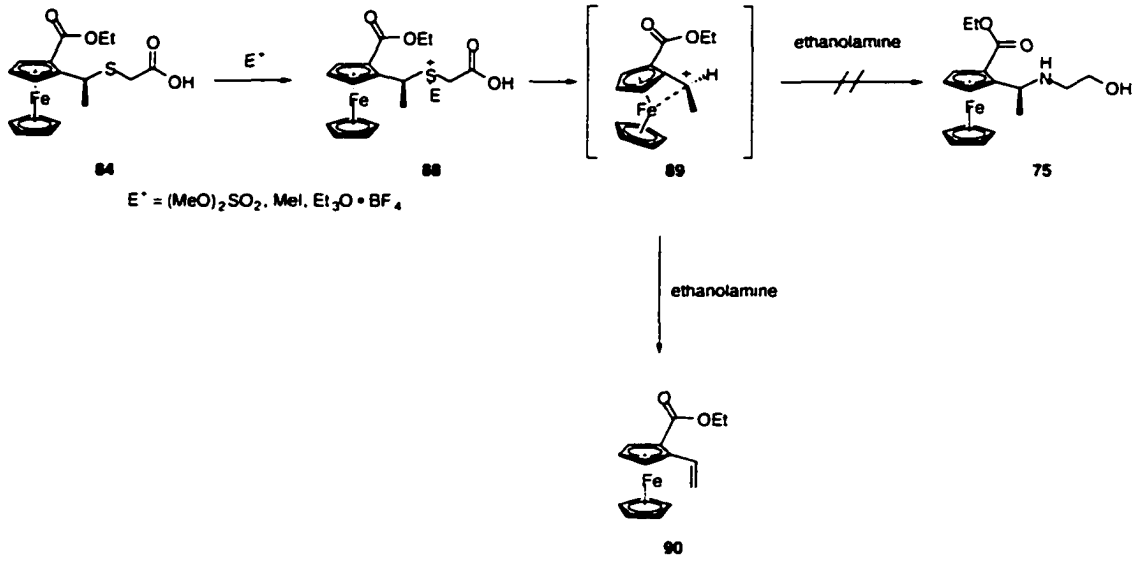
The technique used to convert the related thiol **86** back to amine **87** utilized mercuric chloride in aqueous ammonia (equation 2.31).[30] Thiol **84** was converted into



86 **87** (2.31)

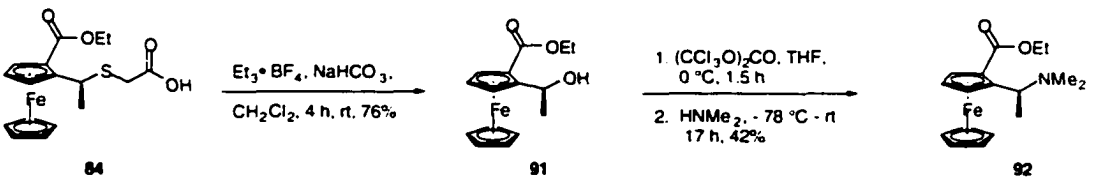
the sulfonium **88** with electrophiles to eliminate the use of mercury but when the reaction was quenched with ethanolamine, elimination occurred forming **90** (equation 2.32).

(2.32)



Alkylation of thiol **84** with triethyloxonium tetrafluoroborate in the presence of solid $NaHCO_3$ and water, formed alcohol **91** (equation 2.33). Addition of triphosgene to alcohol **91** followed by dimethylamine provided the amine **92**, which can be used to form the enamide **64** showing that the auxiliary can indeed be recycled.

(2.33)



Conclusion

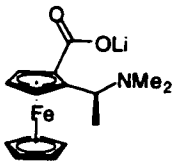
The hypothesis that a ferrocenyl-based analog of the oxazolidinone ene-carbamate could provide high asymmetric induction in [2+2] the photocycloaddition and that the

auxiliary could be cleaved leaving the nitrogen in the product was confirmed. Recyclability of the auxiliary was demonstrated as well, but the process as developed lacked efficiency. Optimization of both the synthesis of the ferrocenyl auxiliary as well as the recycling of the auxiliary will be required before the system becomes generally useful.

Experimental

General Procedures: All NMR spectra (300 MHz for ^{1}H NMR and 75 MHz, for ^{13}C NMR) were recorded in $CDCl_3$ and chemical shifts were given relative to TMS (0.00 for ^{1}H) and $CDCl_3$ (77.23 for ^{13}C) unless otherwise stated. The 300 MHz ^{1}H NMR and 75.5 MHz ^{13}C NMR were taken on a Varian Inova–300 spectrometer and 400 MHz ^{1}H NMR and 100.6 ^{13}C NMR were taken on a Varian Inova-500 spectrometer. IR spectra were recorded on an Avatar 320 FT-IR by Nicolet. THF was distilled from sodium-benzophenone ketyl; CH_2Cl_2 was distilled from CaH; MeOH was distilled from CaH. Column chromatography was performed with ICN 32-63 nm, 60 Å silica gel. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. (*S*)-α-N,N-Dimethylaminoferrocene was synthesized and resolved according to literature methods.[27]

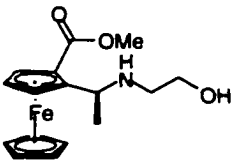
Lithium salt 71



71

In a 500 ml round bottom three neck flask under argon was placed a solution of 1.25g (4.86 mmoles) of (*S*)-α-N,N-dimethylaminoethylferrocene (**65**) dissolved in 50 ml of anhydrous diethyl ether. This was cooled to 0 °C and to it was slowly added 8 ml (13.6 mmoles) of 1.7 M *n*-butyllithium in hexanes. The reaction was allowed to stir for 1 hour at 0 °C and was then slowly warmed to room temperature. After stirring at room temperature for 17 hours, the reaction was cooled to –78 °C and an excess of solid CO_2 was carefully added to the reaction. The reaction was allowed to stir at –78 °C for 2 hours and was then slowly warmed to room temperature. The reaction was filtered under argon and the solid was rinsed with diethyl ether. The solid was then dissolved in methanol, filtered and concentrated under reduced pressure. Yield of the desired product (**71**) was 1.21g (81%) of an orange solid. Analytical data reported for acid.[27] Mp = decomposition > 150 °C; $[\alpha]^{20}_{D}$ = +201.5 ° (c = 1, ethanol): ^{1}H NMR: ($CDCl_3$) δ 5.067 (q, *J* = 1.5 Hz, 1H), 4.58 (q, *J* = 7.0 Hz, 1H), 4.33 (m, 3H), 4.24 (s, 5H), 2.61 (bs, 3H), 2.09 (bs, 3H), 1.46 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.0, 83.3, 77.7, 77.2, 76.8, 75.1, 71.0, 69.2, 68.7, 59.5, 8. IR (thin film): ν 3415, 1579, 1446 cm^{-1}. MS (LSIMS) $(M + 1)^{+}$ = 302.1

Ester 75

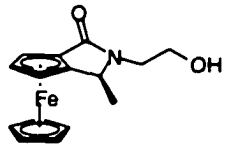


75

In a 250 ml round bottom one neck flask under argon was suspended 945 mg (3.08 mmoles) of **71** partially dissolved in 6 ml of DMF and to this was added 1 ml (16.1 mmoles) of iodomethane. The reaction was allowed to stir for 30 minutes and was then concentrated under reduced pressure. The residual oil was dissolved in methylene chloride, filtered, concentrated under reduced pressure and placed under high vacuum. The residual dark brown oil was then dissolved in 20 ml of methylene chloride and to this was added 1 ml (16.6 mmoles) of ethanolamine. The reaction was heated to reflux for 16 hr. At the end of this time another 1 ml of ethanolamine was added to the reaction and it was refluxed for an additional hour, cooled to room temperature, and was then partitioned between methylene chloride and water. The layers were separated and the water layer was extracted with methylene chloride (2 x 30 ml). The organic layers were combined, washed several times with water (5 x 30 ml), rinsed with brine, and dried over anhydrous magnesium sulfate. The orange solution was concentrated under reduced pressure. Silica gel flash chromatography (methanol) provided 692 mg of **75** as an orange solid (68% over two steps). Mp = 110-112 °C; $[\alpha]^{20}_{D}$ = +43.3 ° (c = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 4.81 (m, 1H), 4.49 (t, J = 2.3 Hz, 1H), 4.44 (q, J = 6.6 Hz, 1H), 4.37 (t, J = 2.6 Hz, 1H), 4.17 (s, 5H), 3.82 (s, 3H), 3.65 – 3.71 (m, 1H), 3.50 – 3.55 (m, 1H), 2.70 (m, 2H), 2.3 (bs, 1H), 1.54 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.3, 93.6, 77.7, 77.2, 76.8, 71.8, 70.6, 70.5, 70.0, 68.7, 60.8, 51.9, 49.5, 47.3, 18.8; IR (thin film) ν 3095, 1708 cm^{-1}; MS

(LSIMS) M^+ = 331.1; Anal. Calcd for $C_{16}H_{21}FeNO_3$: C, 58.02; H, 6.39; N, 4.23; Found: C, 58.18; H, 6.44; N, 4.25.

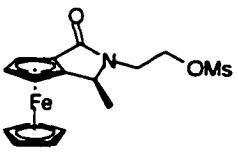
Alcohol 76



76

In a 250 ml round bottom one neck flask under argon was placed a solution of 4.5g (13.59 mmoles) of **75** dissolved in 90 ml of dry toluene and to this was added 19 ml (19 mmoles) of 1N NaOMe in methanol. The reaction was warmed to reflux and the methanol was distilled off of the reaction, which was then concentrated under reduced pressure. The residual oil was redissolved in methylene chloride and filtered. This solution was then once again concentrated and silica gel flash chromatography (20:1 methylene chloride/methanol) provided 2.13 g of **76** (52%) of an orange solid. Mp = 147 – 152 °C; $[\alpha]^{20}_D$ = - 916 ° (c = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 4.66 (q, J = 6.6 Hz, 1H), 4.61 (d, J = 2.6, 1H), 4.48 (d, J = 2.2 Hz, 1H), 4.22 (t, J = 2.2 Hz, 1H), 4.16 (s, 5H), 3.83 – 3.87 (m, 2H), 3.69 (t, J = 4.4 Hz, 1H), 3.29 – 3.34 (m, 1H), 1.31 (d, J = 6.6, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 96.6, 77.8, 77.7, 77.2, 76.8, 72.2, 70.7, 69.8, 63.1, 62.6, 62.0, 56.7, 44.8, 20.6; IR ν 3373, 1654 cm^{-1}; HRMS (LSIMS) m/z calculated for $C_{15}H_{17}FeNO_2$ (M + 1) 300.0692; found 300.0686; Anal. Calcd for $C_{15}H_{17}FeNO_2$: C, 60.22; H, 5.73; N, 4.68; Found: C, 60.41; H, 5.85; N, 4.64.

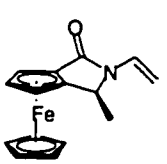
Mesylate 77



77

In a 50 ml round bottom one neck flask under argon was placed a solution of 183 mg (0.61 mmole) of **76** and 20 ml of anhydrous THF. This was cooled to 0 °C and to it was added 0.1 ml (1.3 mmoles) of methane sulfonyl chloride and 0.18 ml (1.3 mmoles) of triethylamine. A precipitate formed immediately and the reaction was allowed to stir for 10 minutes at 0 °C. The reaction was then partitioned between water and ether. The layers were separated and the water layer was extracted with ether (2 x 20 ml). The ether layers were combined, washed with brine, and further dried over anhydrous magnesium sulfate. Concentration under reduced pressure and silica gel flash chromatography (20:1 methylene chloride/methanol) provided 200 mg of **77** (97%) as an orange oil. $[\alpha]^{20}_{D}$ = -758.98 ° (c = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 4.73 (q, J = 6.6 Hz, 1H), 4.62 (d, J = 2.2 Hz, 1H) 4.40 – 4.54 (m, 3H), 4.24 (t, J = 2.2 Hz, 1H), 4.17 (s, 5H), 4.08 (dt, J = 15.4, 4.8 Hz, 1H), 3.43 (m, 1H), 3.07 (s, 3H), 1.31 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.2, 96.8, 77.7, 77.4, 77.2, 76.8, 72.2, 70.7, 68.3, 63.1, 61.9, 56.2, 40.4, 37.8, 20.4; IR ν 3419, 1670 cm^{-1}; MS (LSIMS) M^{+} = 377.0.

Enamide 64

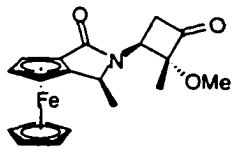


64

In a 50 ml round bottom one neck flask under argon was placed a solution of 190 mg (0.504 mg) of **77** and 20 ml of anhydrous THF. To this was added 68 mg of *t*-BuOK and the reaction was allowed to stir at

room temperature for 10 minutes and was then partitioned between ether and water. The layers were separated and the water layer was extracted with ether (1 x 15 ml). The ether layers were combined and washed with water (3 x 20 ml), brine, and further dried over anhydrous magnesium sulfate. Concentration under reduced pressure and column chromatography (1:1, hex/EtOAc, florisil) provided 132 mg (93%) of enamide **70** as a solid. Mp = 123-125 °C; $[\alpha]^{20}_D$ = -1836 ° (c = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 7.16 (dd, J = 9.5, 16.1 Hz, 1H), 4.83 (q, J = 6.6 Hz, 1H), 4.70 (d, J = 2.2 Hz, 1H), 4.54 (d, J = 2.2 Hz, 1H), 4.47 (d, J = 9.2 Hz, 1H), 4.38 (d, J = 16.5 Hz, 1H) 4.32 (t, J = 2.6 Hz, 1H), 4.17 (s, 5H), 1.40 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.0, 96.6, 92.7, 77.6, 77.2, 76.9, 73.1, 70.8, 70.0, 63.2, 62.6, 53.6, 20.7; IR ν 1699, 1627 cm^{-1}; MS M^+ = 281.1. Anal. Calcd for $C_{15}H_{15}FeNO$: C, 64.08; H, 5.38; N, 4.98; Found: C, 63.76; H, 5.60; N, 4.81.

Cyclobutanone 78

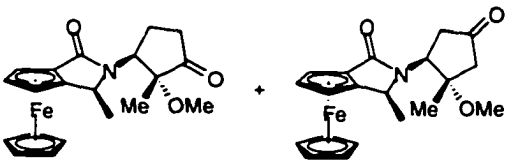


78

A solution consisting of 1.4 g (5 mmoles) of **64**, 1.9 g (7.6 mmoles) of (methyl)(methoxy)chromium carbene, and 50 ml of methylene chloride, were place in a Pyrex pressure tube. The reaction was degassed, placed under 80 psi of CO, and irradiated (450 W Hg vapor lamp) at 35 °C for 22 hours. The reaction was concentrated under reduced pressure and excess $Cr(CO)_6$ was removed by sublimation. The residual solid was purified by silica gel flash chromatography (7:3 hexane/ethyl acetate) to yield 1.47 g (80%) of **78** as an orange solid. Mp = 130-132 °C; $[\alpha]^{20}_D$ = -607 ° (c = 0.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$)

δ 4.58 (d, J = 2.1 Hz, 1H), 4.53 (m, 2H), 4.47 (d, J = 2.1 Hz, 1H), 4.24 (t, J = 2.1 Hz, 1H), 4.15 (s, 5H), 4.02 (dd, J = 8.3, 10.4 Hz, 1H), 3.09 (dd, J = 10.4, 17.9 Hz, 1H), 1.48 (s, 3H), 1.35 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 207.2, 172.3, 96.6, 96.2, 78.7, 77.7, 77.2, 76.2, 72.2, 70.8, 70.6, 70.4, 62.9, 61.9, 59.3, 53.1, 52.6, 42.5, 22.0, 14.7; IR ν 1783, 1673 cm^{-1}; MS M^+ = 367.1; Anal. Calcd for $C_{19}H_{21}FeNO_3$: C, 62.14; H, 5.76; N, 3.82; Found: C, 62.30; H, 6.00; N, 3.80.

Cyclopentanone 79

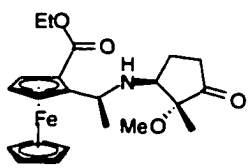


79 59% **80** 25%

In a large test tube was placed a solution of 1 g (2.72 mmoles) of **78** dissolved in 20 ml of THF. This was cooled to 0 °C and diazomethane that had been generated from 8.5 g (39.7 mmoles) of Diazald was bubbled through the solution. The reaction was allowed to sit for 17 hours, over which time the reaction had slowly warmed to room temperature. Argon was then bubbled through the reaction in order to remove any excess diazomethane still in solution. The reaction was concentrated under reduced pressure and the residual solid was purified by silica gel flash chromatography (1:1 hexane/ethyl acetate) yielding 59% of the desired expansion product **79** as an orange solid. Mp = 192-194 °C; $[\alpha]^{20}_D$ = -446.8 (c = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 4.57 (m, 2H), 4.49 (d, J =

2.2 Hz, 1H), 4.27 (t, J = 2.2 Hz), 4.17 (s, 5H), 3.60 (d, J = 7.6 Hz, 1H), 3.21 (s, 3H), 2.80 (m, 1H), 2.65 - 2.40 (m, 2H), 2.00 (m, 1H), 1.37 (d, 6.6 Hz, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 209.6, 171.8, 97.0, 81.9, 78.1, 77.7, 77.2, 76.8, 72.2, 70.4, 63.1, 61.9, 61.8, 57.8, 51.6, 35.1, 25.9, 21.3, 12.3; IR ν 1743, 1673 cm^{-1}, MS $(M + 1)^+$ = 382.2. Anal. Calcd. for $C_{20}H_{23}FeNO_3$: C, 63.00; H, 6.08; N, 3.67; Found: C, 63.00; H, 6.04, N, 3.68.

Ester 81

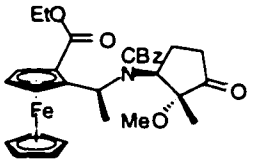


81

In a 100 ml round bottom one neck flask under argon was placed a solution of 196 mg (0.51 mmole) of **79** and 40 ml of methylene chloride and to this was added 1 g (11.9 mmoles) of solid sodium bicarbonate. This was suspended at room temperature and to it was added 300 mg (1.58 mmoles) of triethyloxonium tetrafluoroborate. The reaction was allowed to stir at room temperature for 20 hours. The reaction was cooled to 0 °C and 1 N NaOEt was added to the reaction dropwise until the solution turned from a dark red color to yellow. An excess of water was added immediately and the reaction was placed in a separatory funnel shaken vigorously. The layers were separated and the organic layer was washed with water until the aqueous layers became clear and colorless, washed with brine, and dried over anhydrous magnesium sulfate. The methylene chloride solution was then concentrated under reduced pressure and purified by silica gel flash chromatography (40:1 methylene chloride/methanol) yielding 150 mg (69%) of the purified compound **81** as an orange oil as well as 25 mg of recovered starting material **79**. ^{1}H NMR ($CDCl_3$) δ 4.80 (dd, J = 1.7, 2.7 Hz, 1H), 4.48 (m, 2H), 4.28 (m, 3H), 4.17 (s,

5H), 3.31 (dd, J = 6.4, 9.0 Hz, 1H), 3.11 (s, 3H), 2.35 (m, 1H), 2.34 - 2.06 (m, 2H), 1.69 (bs, 1H), 1.60 (m, 1H), 1.55 (d, J = 6.8 Hz, 3H), 1.37 (t, J = 7, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 217.4, 177.4, 172.3, 95.1, 84.2, 77.5, 77.2, 76.8, 71.5, 70.7, 70.6, 69.6, 69.2, 60.3, 56.8, 51.6, 49.0, 34.4, 25.3, 20.2, 14.8, 14.7; IR ν 2977, 1745, 1742 cm^{-1}, MS $(M+1)^+$ = 428.1

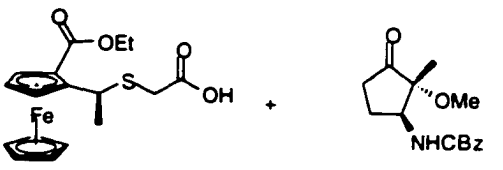
CBz-protected amine 82



82

In a 10 ml round bottom one neck flask was placed a solution of 33 mg (0.077 mmole) of **81** dissolved in 2 ml of methylene chloride was stirred at room temperature and to it was added 2 ml of saturated sodium bicarbonate. This mixture was stirred vigorously, cooled to 0 °C, and to it was added 0.1 ml (0.7 mmole) of benzyl chloroformate. The reaction was allowed to stir briefly at 0 °C and the ice bath was then removed. After stirring at room temperature for 17 hours the reaction was partitioned between methylene chloride and water. The layers were separated and the organic layer was washed with saturated sodium bicarbonate (4 x 15 ml) and dried over anhydrous magnesium sulfate. The organic solution was concentrated under reduced pressure and the residual oil was pushed through a silica gel plug using 1:1 hexane/ethyl acetate. The solution was then once again concentrated and placed under high vacuum for 24 hours. This residual oil was then purified by silica gel flash chromatography (7:3 hexane/ethyl acetate). Yield of the purified oil **87** was 40.7 mg (94%).

Cylcopentanone 83 and Thiol 84



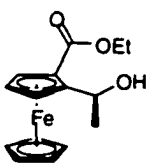
84 66% **83** 89%

In a 10 ml round bottom one neck flask under argon was placed a solution of 45 mg (0.0801 mmole) of **82** dissolved in 3 ml of acetone and to this were added 0.16 ml (2.3 mmoles) of mercaptoacetic acid and 0.12 ml (1.56 mmoles) of trifluoroacetic acid. The reaction was completely covered with aluminum foil and allowed to stir at room temperature. After 41 hours of stirring the reaction was partitioned between sat. $NaHCO_3$ (aq) and methylene chloride. The layers were separated and the methylene chloride layer was extracted with sat. $NaHCO_3$ (aq) and finally with water. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residual oil was purified by silica gel flash chromatography (6:4 hexane/ethyl acetate). Yield of the protected cyclopentanone **83** was 19.7 mg (89%) of a clear colorless oil. The basic aqueous extract was extracted once with methylene chloride, made acidic using 8.5% phosphoric acid, and extracted with methylene chloride (3 x 30 ml), which were combined and washed with water (3 x 30 ml). The organic solution was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residual oil was purified by silica gel flash chromatography (10:1 methylene chloride/methanol). Yield of the purified oil **84** was 20 mg (66%) of an orange oil. Analytical data for **84**. $[\alpha]^{20}_{D} = +134°$ (c = 0.97, ethanol); ^1H

NMR ($CDCl_3$) δ 4.84 (dd, J = 1.5, 2.6 Hz, 1H), 4.75 (q, J = 7.1 Hz, 1H), 4.46 (m, 1H), 4.40 (t, J = 2.7 Hz, 1H), 4.23 - 4.36 (m, 2H), 4.18 (s, 5H), 3.24 (s, 2H), 1.78 (d, J = 7.1 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.1, 172.3, 93.3, 77.6, 77.2, 76.8, 71.3, 71.2, 70.7, 70.2, 70.1, 70.0, 69.9, 68.4, 60.5, 38.0, 37.9, 33.1, 21.2, 14.79, 14.76. IR ν 3095, 1704 cm^{-1}; MS M^+ = 376.1; HRMS (LSIMS) m/z calculated for $C_{17}H_{20}FeSO_4$ M^+ 376.0427; found 376.0432.

Analytical data for **83** $[\alpha]^{20}_D$ = -55.3° (c = 0.84, ethanol); ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 5H), 5.16 (m, 2H), 4.78 (bs, 1H), 4.48 (bq, J = 8 Hz, 1H), 2.41 (m, 2H), 2.27 (m, 1H), 1.62 (m, 1H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 214.9, 156.0, 136.3, 128.8, 128.6, 128.5, 83.3, 77.6, 77.2, 76.9, 67.4, 53.0, 52.0, 34.5, 24.9, 15.2; IR ν 3330, 1747, 1716 cm^{-1}, HRMS (LSIMS) m/z calculated for $C_{15}H_{19}NO_4$ M^+ 277.1317; found 277.1314.

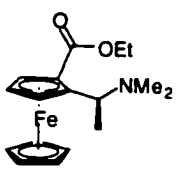
Alcohol 91



In a 10 ml round bottom one neck flask under argon was placed a solution of 11 mg (0.0292 mmole) of **84** dissolved in 2 ml of CH_2Cl_2 and to this was added 150 mg of solid $NaHCO_3$ followed by 25 mg (0.13 mmole) of $Et_3O \bullet BF_4$. The reaction was allowed to stir for 4 hours at room temperature, and was partitioned between water and methylene chloride. The organic layer was washed with water (2 x 20 ml) and with sat. $NaHCO_3$ (aq) (2 x 20 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was purified by silica gel flash chromatography (9:1, hex/EtOAc). Yield of the residual orange oil **91** was 6.7 mg (76%) of an orange oil. $[\alpha]^{20}_D$ = +21° (c = 0.3, EtOH) ^{1}H NMR ($CDCl_3$) δ 5.0 (m, 1H), 4.80

(dd, J = 1.5, 2.7 Hz, 1H), 4.53 (d, J = 5.9 Hz, 1H), 4.47 (dd, J = 1.8, 2.6 Hz, 1H), 4.28 - 4.38 (m, 3H), 4.22 (s, 5H), 1.52 (d, J = 6.6 Hz, 3H), 1.40 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.3, 95.2, 77.6, 77.2, 76.9, 72.2, 71.2, 70.8, 69.8, 69.1, 65.5, 61.0, 22.1, 14.8, IR ν 3095, 1683 cm^{-1}; MS M^+ = 302.1. HRMS (LSIMS) m/z calculated for $C_{15}H_{18}FeNO_3$ M^+ 302.0605; found 302.0616.

Amine 92



92

In a 10 ml round bottom one neck flask was placed solution consisting of 18 mg (0.0625 mmole) of **91** dissolved in 4 ml of anhydrous THF. This was cooled to 0 °C and to it was added 6.8 mg (0.029 mmole) of triphosgene and the reaction was allowed to warm to room temperature. After 1.5 hours the reaction was slowly added to 1 g (22 mmoles) of dimethylamine that had been condensed into 10 ml of anhydrous THF at -78 °C. This was then allowed to stir for 17 hours, over which time the reaction had slowly warmed to room temperature, and was partitioned in ether and water. The organic layer was washed with water (3 x 30 ml) and extracted with 8.5% phosphoric acid (1 x 40 ml) and once with 40 ml of water. The aqueous layers were made basic using saturated $NaHCO_3$ (aq) and extracted with ether. The organic solution was extracted with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Yield of **92** was 8 mg (42%) of an orange oil. ^{1}H NMR ($CDCl_3$) δ 4.79 (m, 1H), 4.54 (q, J = 7 Hz, 1H), 4.41 (m, 1H), 4.38 (m, 1H), 4.25 (m, 2H), 4.13 (s, 5H), 2.12 (s, 6H), 1.55 (d, J = 7 Hz, 3H), 1.35 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 89.8, 77.6, 77.2, 76.8, 71.2, 70.8, 70.7, 69.7, 69.6, 60.1, 55.4, 40.6, 16.3, 14.8; IR

ν 1708 cm^{-1}, MS (LSIMS) $(M + 1)^+ = 330.2$. HRMS (LSIMS) m/z calculated for $C_{17}H_{23}FeNO_2$ $(M + 1)^+$ 330.1156; found 330.1159.

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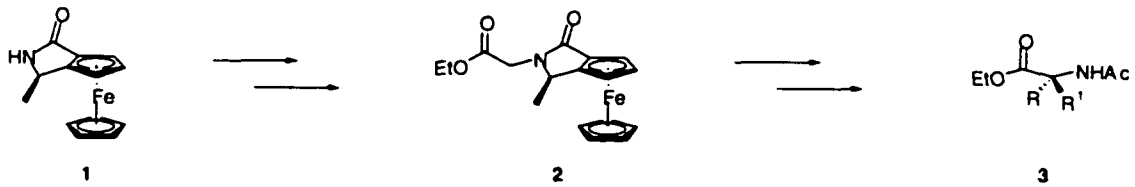
Chapter Three

Asymmetric Synthesis of α,α-Disubstituted α-Amino Esters

Introduction

Having demonstrated, in principal, that the ferrocene system developed above could act as a recyclable chiral auxiliary for the introduction of nitrogen into substrates, additional applications for this methodology were sought. A system where this auxiliary could induce stereoselectivity in the α–position of an ester followed by removal of the auxiliary in a way that leaves the amine functionality behind could be used to asymmetrically synthesize α–substituted α–amino esters (Figure 3.1). These esters could then lead to α,α–disubstituted α–amino acids.

Figure 3.1



1 2 3

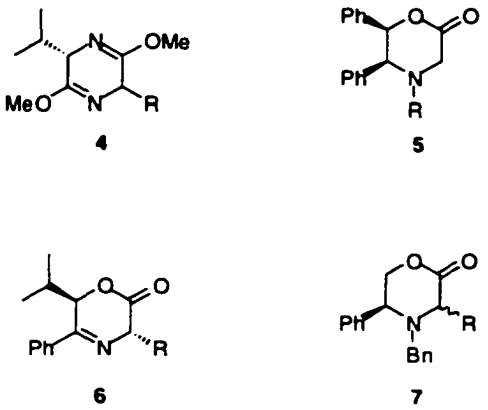
α,α–Disubstituted α–amino acids have received a great deal of attention within the past few decades in the area of biomimetics,[1] primarily because of their ability to force peptides into specific secondary structures.

Syntheses of α,α–Disubstituted α–Amino Acids

The ability to synthesize α,α–disubstituted α–amino acids has been a challenge for decades.[1] The amount of attention that has been paid to this area of asymmetric synthesis shows its importance to the fields of chemistry and biochemistry. The synthetic strategies used to form α,α–disubstituted α–amino acids are quite extensive and include alkylations of cyclic lactones and lactams,[1-5] alkylations of monosubstituted α–amino acids through the self-regeneration of the stereogenic center,[6-8] alkylation of acyclic chiral esters,[9-11] rearrangement reactions,[12] alkylation of β–lactams,[13] and many others. The synthetic chemistry involved with the generation of these compounds is important and a small set of examples involving some of these techniques can be seen below.

The synthesis of α,α–disubstituted α–amino acids through the alkylation of cyclic lactams and lactones has proved to be an efficient strategy (Figure 3.2). The cyclic lactams and lactones include Schöllkopf's bis-lactam ethers (**4**),[2] William's diphenyloxazinones (**5**),[1d,3] as well as oxazinones developed by Najera (**6**)[4] and Ma (**7**)[5].

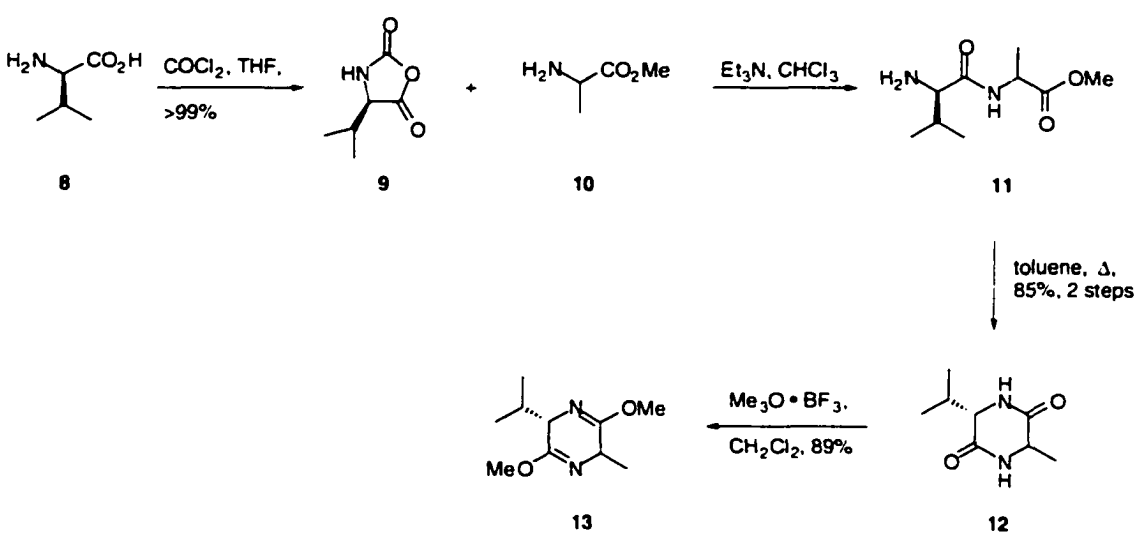
Figure 3.2



4 5 6 7

Schöllkopf generated the bis-lactam ether **13** by first forming Leuch's anhydride **9** of L-valine **8** which was added to L-alanine methyl ester **10** to give peptide **11** which provided the diketopiperazine **12** upon heating (equation 3.1).[2] Treatment with methyl Meerwein reagent gave the desired bis-lactam ether **13**.

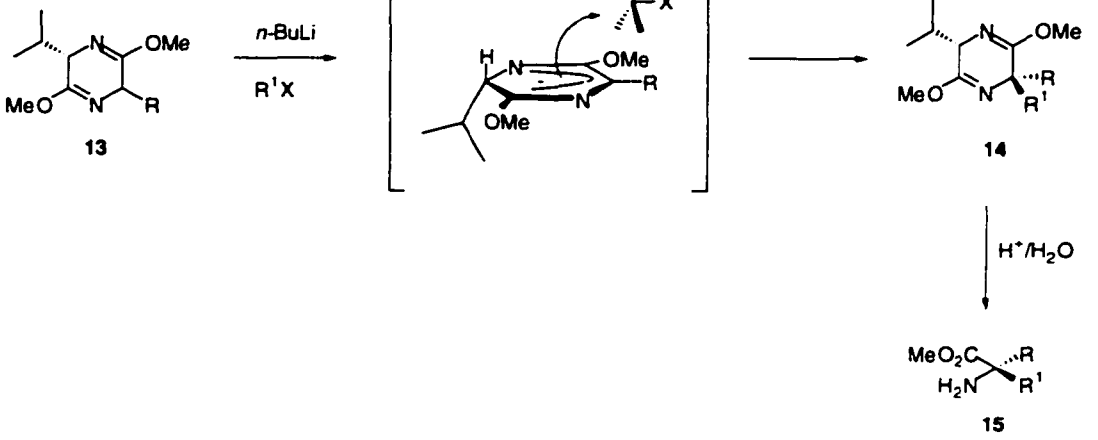
(3.1)



8 9 10 11 12 13

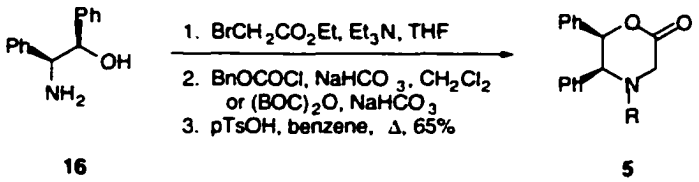
When treated with *n*-butyllithium followed by the addition of an electrophile the alkylation product **14** formed which, when hydrolyzed, gave the desired α,α–disubstituted α–amino acids (**15**). The chiral auxiliary, however, is lost during the cleavage process. The stereocontrol is due to attack on the electrophile from the face opposite of the bulky isopropyl group (equation 3.2).

(3.2)



The Williams' diphenyloxazinones **5** are generated through alkylation of the readily available diphenyl amino alcohol **16** with ethyl bromoacetate, acylation with di-*t*-butyl dicarbonate or benzylchloroformate (equation 3.3).[1d,3] Cyclization in benzene at reflux in the presence of p-toluene sulfonic acid provides the desired diphenyloxazinone **5**.

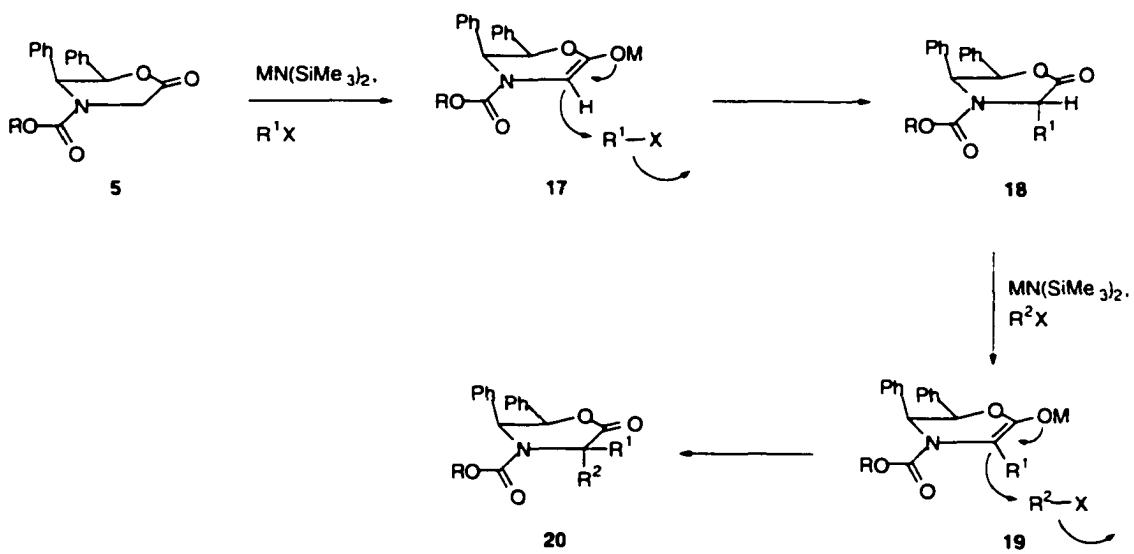
(3.3)



16 5

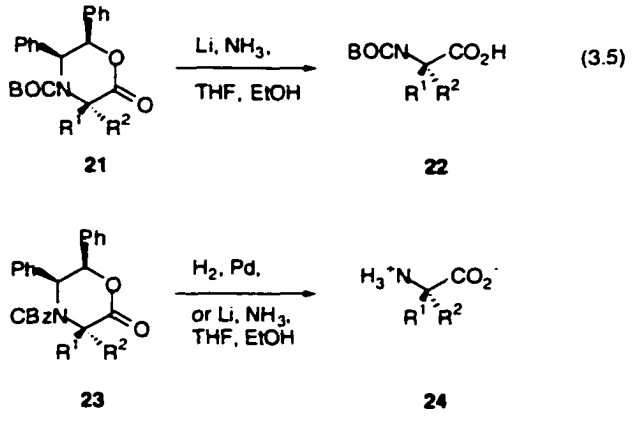
α,α–Disubstituted α–amino acids are then generated from the chiral diphenyloxazinones through two consecutive alkylation reactions using hindered amide bases (equation 3.4). The stereoselectivity of these reactions is very high and results from attack on the electrophile from the face opposite of the phenyl groups.

(3.4)



5 17 18 19 20

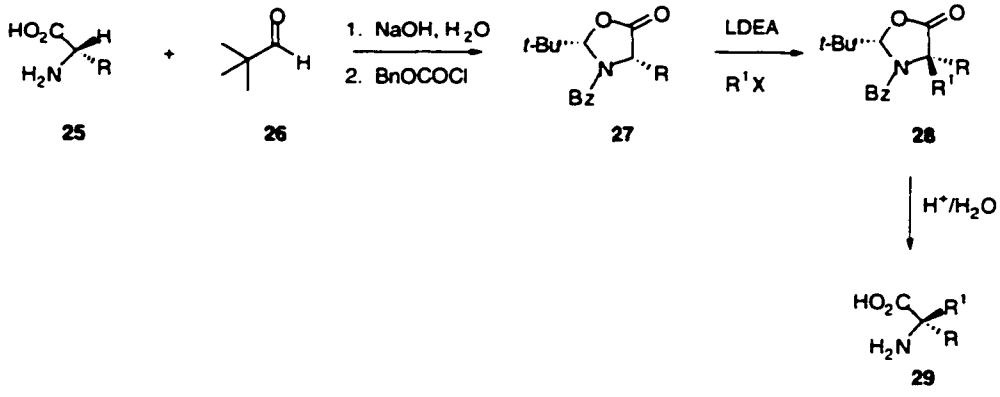
Reduction of the diphenyloxazinones by lithium in ammonia or with palladium and hydrogen produces the desired α,α–disubstituted α–amino acids (**22** and **24**) in yields of 60-95% in 100% enantiomeric excess (equation 3.5). Once again in this example the auxiliary is unrecoverable.



(3.5)

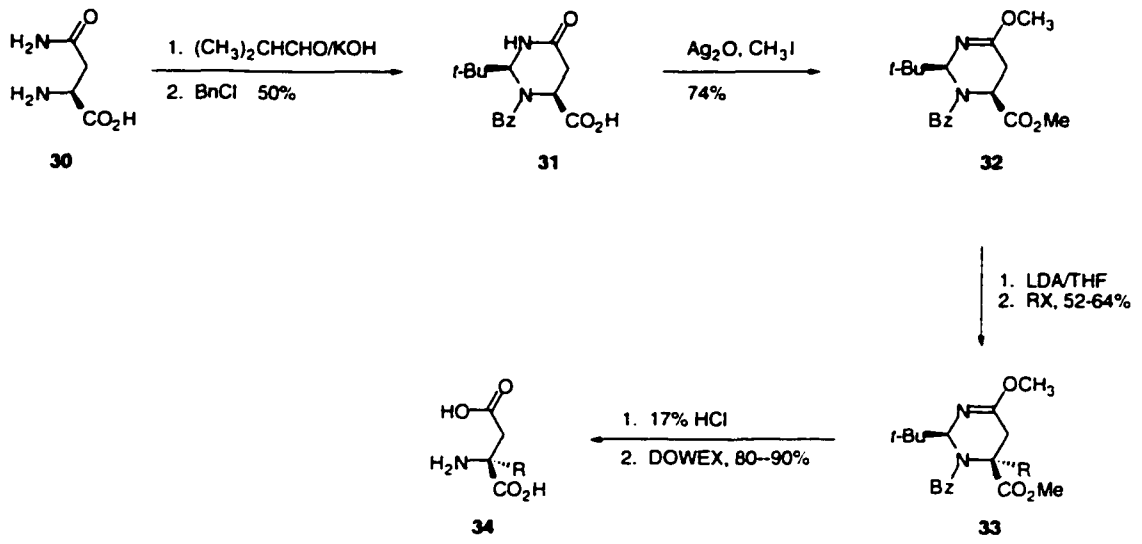
The technique known as the self-regeneration of stereogenic centers developed by Seebach has also been used to produce α,α–disubstituted α–amino acids in an asymmetric fashion.[6] The origins of self-regeneration involved the addition of achiral aldehydes to chiral substrates that resulted in a chiral product. For instance, condensation of pivalaldehyde **26** with chiral α–amino acids **25** resulted in the formation of chiral oxazolidinones **27** (equation 3.6). Deprotonation with lithium diethylamide which destroys the initial stereocenter and subsequent addition of electrophiles provided the disubstituted oxazolidinones **28** in yields of 85-95% and in distereoselective excesses of >90%. Stereoselectivity was directed by attack of the electrophile from the face opposite of the *t*-butyl group. Hydrolysis of the auxiliary provided the α,α–disubstituted α–amino acid **29**.

(3.6)



Another example of the use of self-regeneration of a stereogenic center stemmed from Juaristi's work on the asymmetric synthesis of β–amino acids.[7] Condensation of (*S*)-asparagine **30** with pivalaldehyde followed by *O*-methylation provided the desired imino ether **32** (equation 3.7). Deprotonation with LDA followed by addition of electrophiles provided the substituted compounds **33** in 52-64% yields in diastereomeric excesses of >97%. Hydrolysis of the compounds provided the substituted aspartic acids in yields of 80-95%. Stereoselectivity was once again due to addition from the face opposite of the *t*-butyl group.

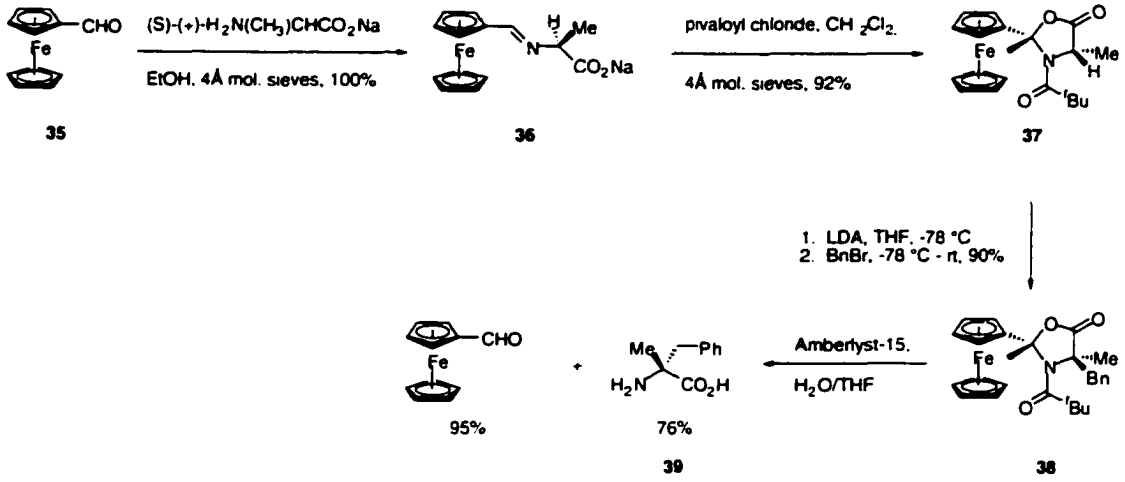
(3.7)



Ferrocene derivatives were shown to also be useful for the self-regeneration of stereogenic centers in a technique developed by Davies (equation 3.8).[8] Condensation of ferrocene carboxaldehyde **35** with (*S*)-alanine followed by treatment with pivaloyl chloride, gave the ferrocenyl oxazolidinone **37**, which upon treatment with LDA followed by benzyl bromide yielded the disubstituted oxazolidinone **38** in 90% in a diastereomeric excess of >98%. Hydrolysis provided the α,α–disubstituted α–amino acid **39** in a 76% yield in an enantiomeric excess of >98%. The stereoselectivity resulted from the attack on the electrophile from the face opposite of the cyclopentadienyl ring system.

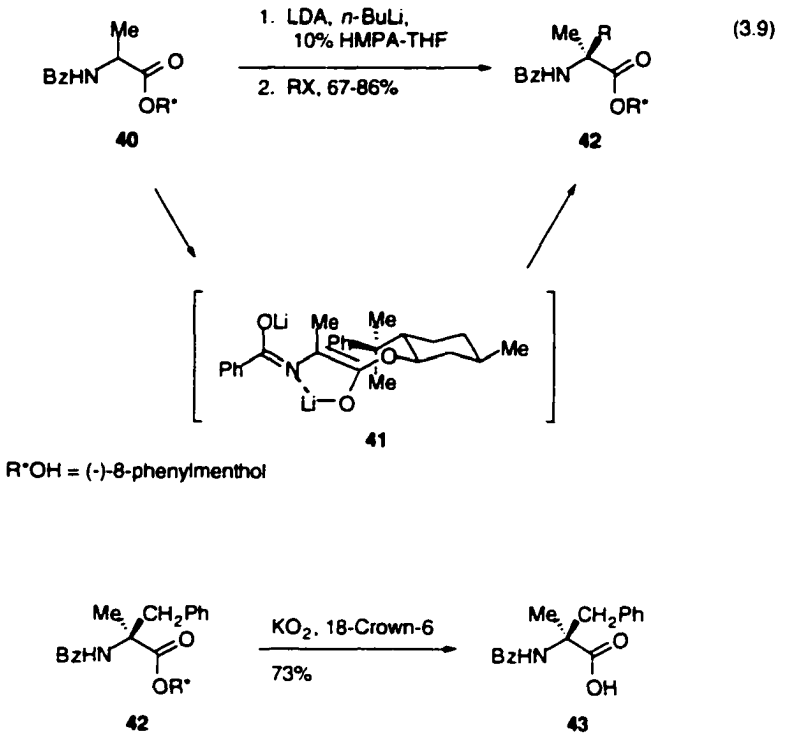
In self-regeneration, the auxiliary was recovered as the initial aldehyde, which possesses no stereocenter. The auxiliary, therefore, has to be once again added to a compound that has a stereocenter present in the molecule.

(3.8)



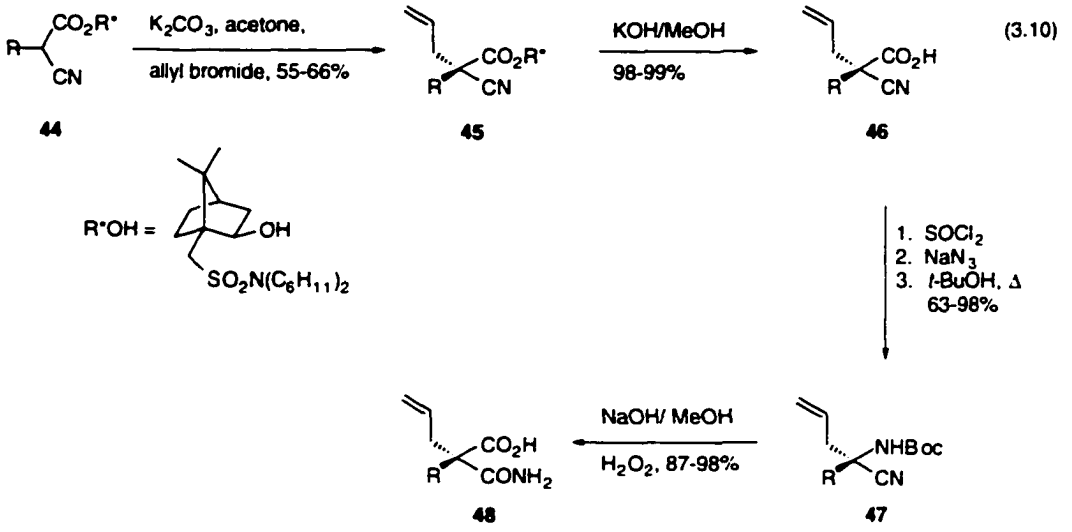
35 36 37 39 38

The above examples show the utility of cyclic systems for the generation of α,α–disubstituted α–amino acids but acyclic systems have also been shown to be useful in the generation of these quaternary compounds, through the use of chiral auxiliaries. In one example Berkowitz synthesized the hindered (-)-8-phenylmenthol ester of *N*-benzoylalanine (**40**).[9] Deprotonation with LDA followed by addition of electrophiles resulted in the α,α–disubstituted α–amino esters **42** in 67-86% yields and diastereomeric excesses of 78-88% (equation 3.9). Cleavage of the auxiliary provided the α,α–disubstituted α–amino acids **43** in yields of 43-73%. Diastereoselectivity was due to the preference of the lithiated compound to adopt a chain-extended conformation **41** which the phenyl group blocks the *re* face of the dianion which allowed for attack on the electrophile to occur from the *si* face.



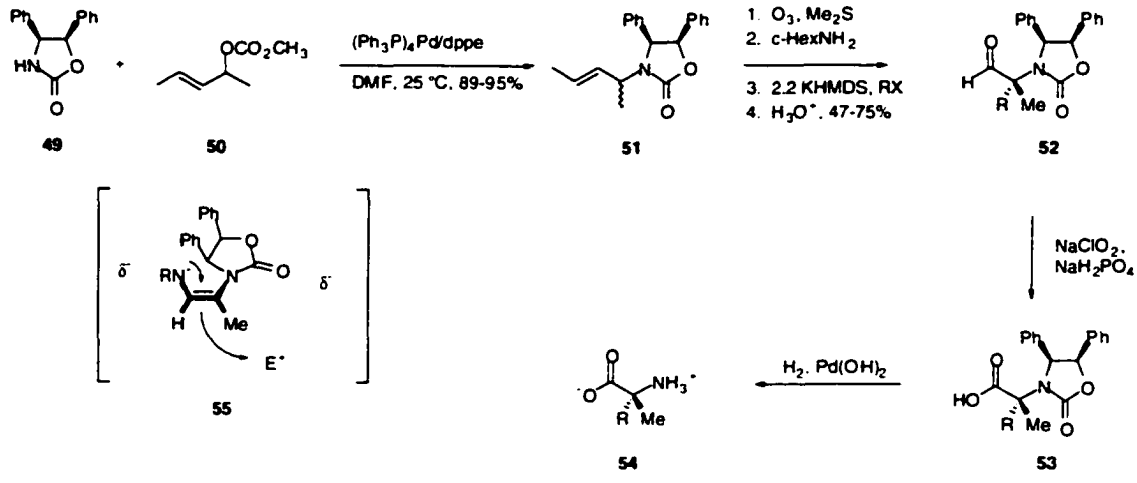
Cativiela also used a chiral ester approach to stereoselectively form α–allyl substituted amino acids (equation 3.10).[10] Alkylation of (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-alkyl-2-cyanoacetates **44** with allylbromide afforded the quaternary cyano compounds **45** in yields of 97-99% in diastereomeric excesses of 50-90%. Hydrolysis of the chiral ester **45** followed by Curtius rearrangement and subsequent treatment with hydrogen peroxide under basic conditions provided the desired α,α-disubstituted α-amino amides **48** in yields of 57-84% over three steps.

As is the case for all uses of chiral esters, the chiral auxiliary is recovered at the end of the synthesis but these chiral auxiliaries are unable to donate functionality to the systems they are attached to.



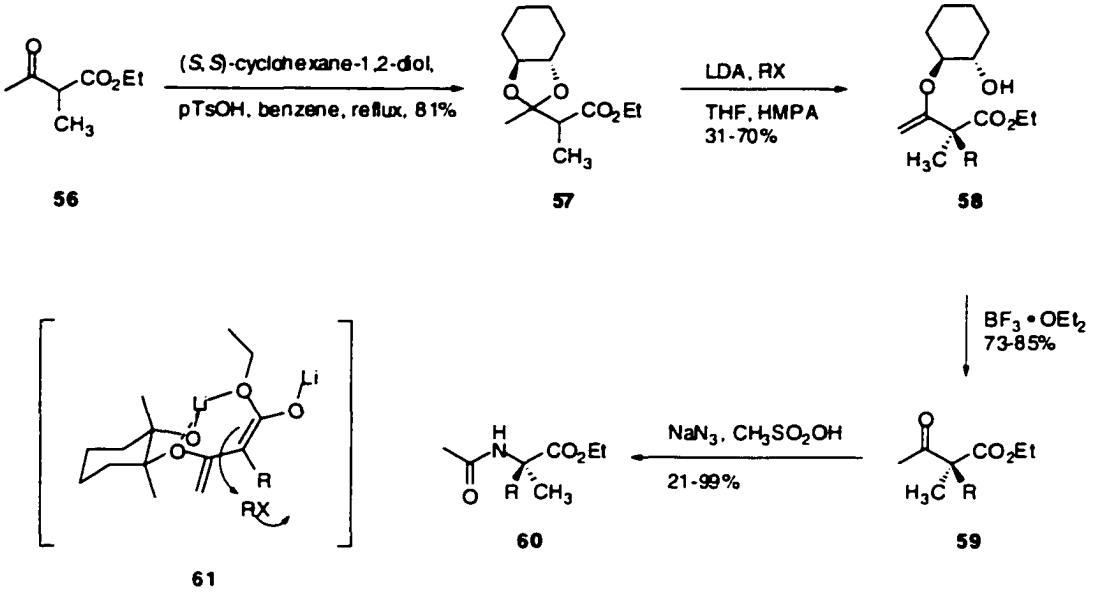
α,α–Disubstituted α–amino acids have also been generated through the use of chiral oxazolidinones in acyclic systems in a method developed by Hegedus (equation 3.11).[11] Addition of oxazolidinone **49** to carbonate **50** through Pd(0)-catalyzed allylic amination followed by oxidative cleavage of the double bond to the aldehyde followed by condensation with cyclohexylamine provided the imine, which was deprotonated in the presence of an electrophile to give the desired aldehyde **52** upon hydrolysis in yields of 47-75% in diastereomeric excesses of 80-95%. The stereoselectivity was due to attack on the electrophile from the face opposite of the phenyl groups on the oxazolidinone when the anionic compound **55** was in the most favorable conformation. Oxidation of the aldehydes **52** to acids **53** followed by reductive cleavage of the oxazolidinone resulted in the desired α,α–disubstituted α–amino acids **54** in 84-92% yields. The reductive cleavage destroys the chiral oxazolidinone in order for the compounds to retain the nitrogen functionality.

(3.11)



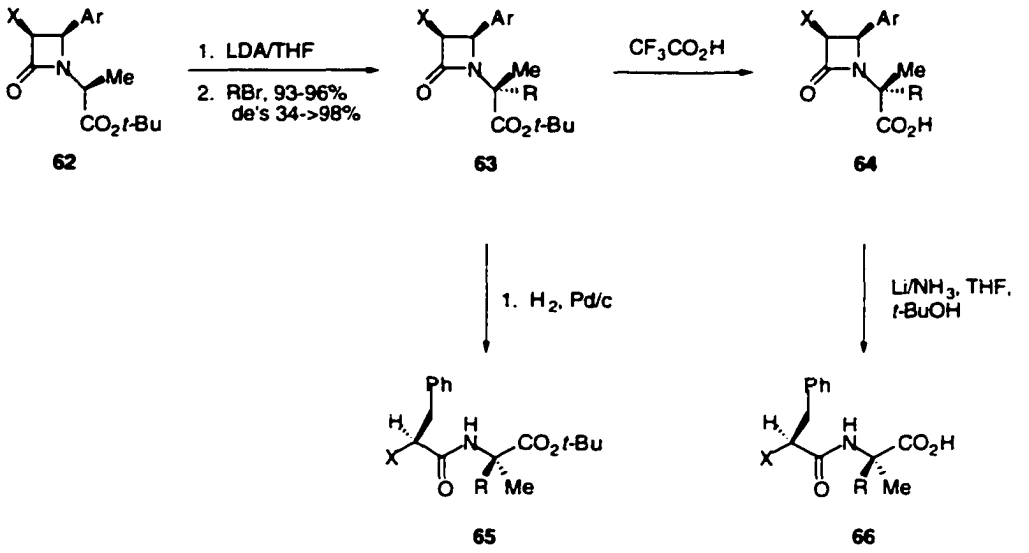
Alkylation of modified β–keto esters and then subsequent rearrangement is another method for producing α,α–disubstituted α–amino acids.[12] Suemune recently demonstrated this technique by converting ethyl 2-methylacetoacetate **56** to chiral acetal **57** by treatment with (*S*,*S*)-cyclohexane-1,2-diol (equation 3.12).[12a] Deprotonation followed by addition of an electrophile provided the disubstituted enol ethers **58** in yields of 31-70% in diastereomeric excesses of 92-95%. Removal of the chiral auxiliary gave the desired β–keto esters **59** in yields of 73-85%. Diastereoselectivity was proposed to occur through the lithium chelated structure **61**. Attack on the electrophile occurred away from the chiral auxiliary. Schmidt rearrangement provided the desired α,α–disubstituted α–amino esters as the acetamides **60**. Once again the chiral auxiliary was removed from the compound intact, but the auxiliary did not donate any functionality to the substrate.

(3.12)



β-Lactams can also be used for the generation of α,α–disubstituted α–amino acids.[13] Ojima demonstrated this by forming the ester enolates of β–lactams **62** using LDA followed by addition of electrophiles, which generated the α,α–dialkylated products **63** that could then be hydrolyzed to the acids **64** or taken on as the esters **65** (equation 3.13).[13a] Cleavage of the lactam ring using either hydrogenolysis conditions (H^2, Pd/c) or dissolving metal conditions (Li/NH_3, THF, *t*-BuOH) provided the desired disubstituted compounds **65** and **66**. In this case the β-lactam was used as the molecule influencing the stereochemical outcome of the reactions. The β-lactam, therefore, was transformed into the desired compound, which prohibited its recovery.

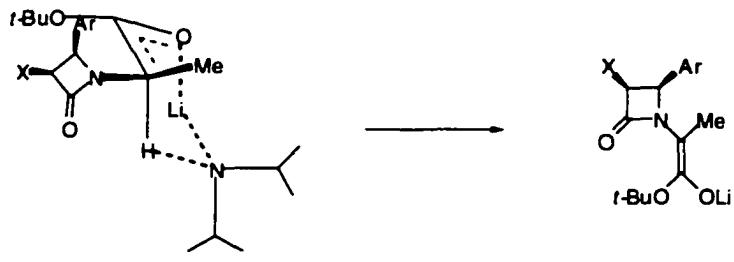
(3.13)



The alkylation reactions gave yields of 93 to 96% with diastereomeric excesses that range from 34 to >98%. An interesting aspect of this chemistry is the rationalization of the stereochemical outcome.

When the enolate is generated at -78 to -95 °C the ratios of the two diastereomers were only 2:1 to 3:1, but when the reactions were carried out between 0 to -5 °C the diastereoselectivities were very good as can be seen by the above examples. Ojima proposed the reason for this was kinetic enolate formation verses thermodynamic enolate formation based on the Ireland model for kinetic enolate formation (Figure 3.3).[13a] At colder temperatures, the kinetic enolate **68** would be nonchelated.

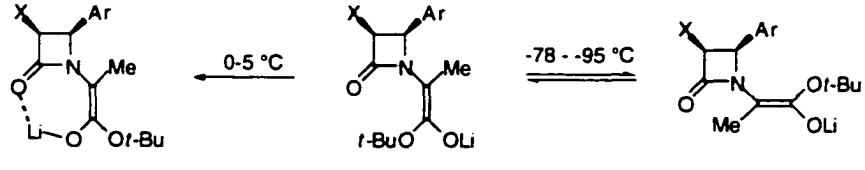
Figure 3.3



67 68

At the colder temperatures the enolate cannot equilibrate to the thermodynamic enolate **69** which forms a stable 7 membered lithium chelated ring, which would allow the enolate to adopt other conformations that lead to the other diastereomer. At the warmer temperature, however, the thermodynamic enolate **69** can form readily and once this is locked into place, the system is rigid and does not allow any other conformations of the enolate, which leads to much higher diastereoselectivities (Figure 3.4).

Figure 3.4

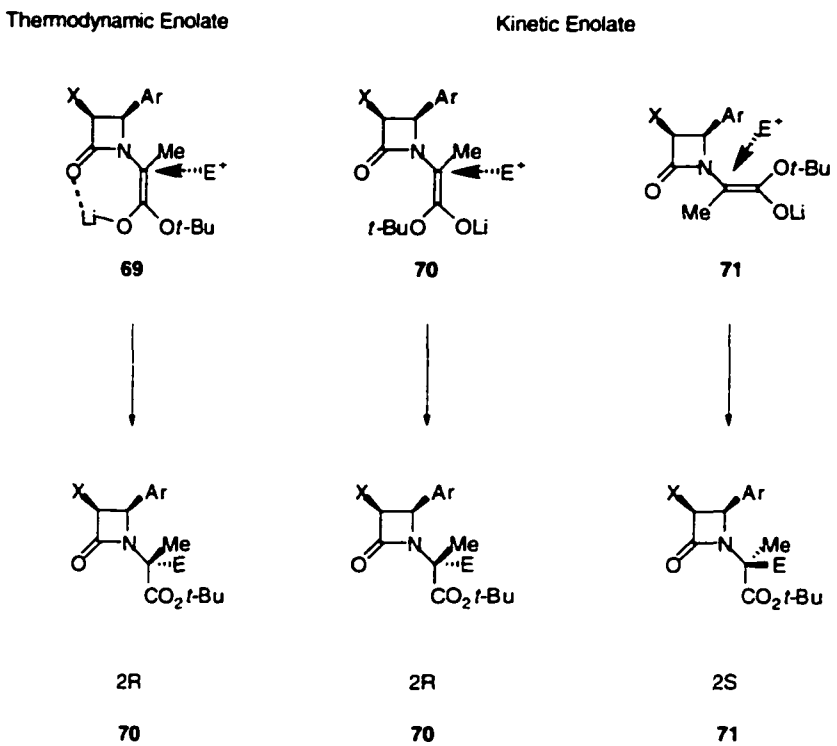


69 68 68

The lithium chelated enolate **69** forms a majority of one diastereomer **70** whereas the kinetic enolate **68** can give rise to both diastereomers **70** and **71** due to its lack of

rigidity (Figure 3.5). By controlling the temperature of the reaction, Ojima was able to produce the desired quaternized compounds in a diastereoselective fashion.[13a]

Figure 3.5



Once again these are just a few examples of the chemistry that has been done to produce α,α–disubstituted α–amino acids asymetrically, which shows how important these compounds are to the field of chemistry. These examples also lack in the area of using recyclable chiral auxiliaries to induce stereoselectivity.

Uses of α,α–Disubstituted α–Amino Acids

The importance of being able to control the secondary and tertiary structure of proteins was discussed previously with regard to β–amino acids. α,α–Disubstituted α–amino acids have also been shown to force predictable secondary structure.[1a] The activity of any given protein is linked to its three dimensional shape. Being able to design proteins and peptides that can adopt a predetermined shape is a very powerful tool in the area of biomimetic research. Restriction of the rotational freedom around the quaternary α–carbon in α,α–disubstituted α–amino acids places conformational constraints on peptide backbones. For instance, α–methylalanine[14] can be used to induce helices, α–methylvaline[15] induces β–turns as well as right handed helices, and α–methylphenylalanine[16] can induce β–turns and helices as well.

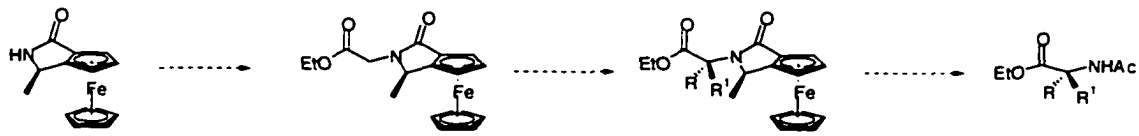
Another important aspect of α,α–disubstituted α–amino acids is their pharmacological activity. α–Methyltryptophan, for instance, inhibits tryptophan hydrolase[17] and α–methylaspartic acid inhibits aspartate amino transferase.[18] α–Methylserine has also been incorporated into peptides for the purpose of determining their activity towards opioid receptors[19] and α,α–dialkylated glycyl residues have been introduced into peptides to probe therapeutic treatments for extrapyramidal motor disorders and depression.[20]

The area of peptide design for the specific purpose of creating tertiary structure is a field of chemistry and biochemistry that is growing very rapidly. Discovering new ways to asymmetrically synthesize α,α–disubstituted α–amino acids is, therefore, very important in the area of synthetic chemistry.

Rationale

The amount of synthetic work that has been done on producing α,α-disubstituted α-amino acids asymmetrically attests to the interest in developing new and better ways to generate these types of compounds. The chiral ferrocenyl lactam developed in chapter 2 proved highly efficient for inducing stereoselectivity in the ene-carbamate photo-cyclization developed therein. It was hypothesized that appending this same auxiliary to ethyl bromoacetate might provide a platform for the efficient synthesis of α,α-dialkylamino acids while retaining the ability to induce high diastereoselectivity, install nitrogen functionality into the desired targets, and be recycled (Figure 3.6). The results of the experiments addressing this issue are detailed below.

Figure 3.6



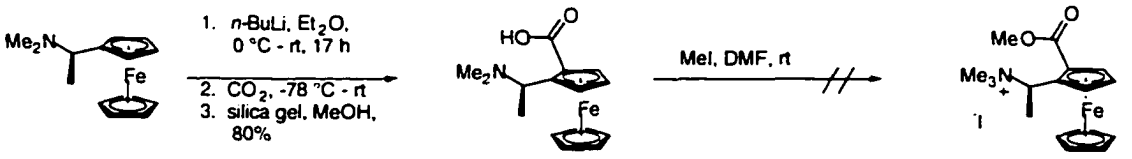
1 2 73 3

Results and Discussion

The synthesis of **1** was carried out in a manner similar to that of the ferrocenyl enamide shown in Chapter 2. Directed ortho-lithiation of known (*R*)-α-N,N-

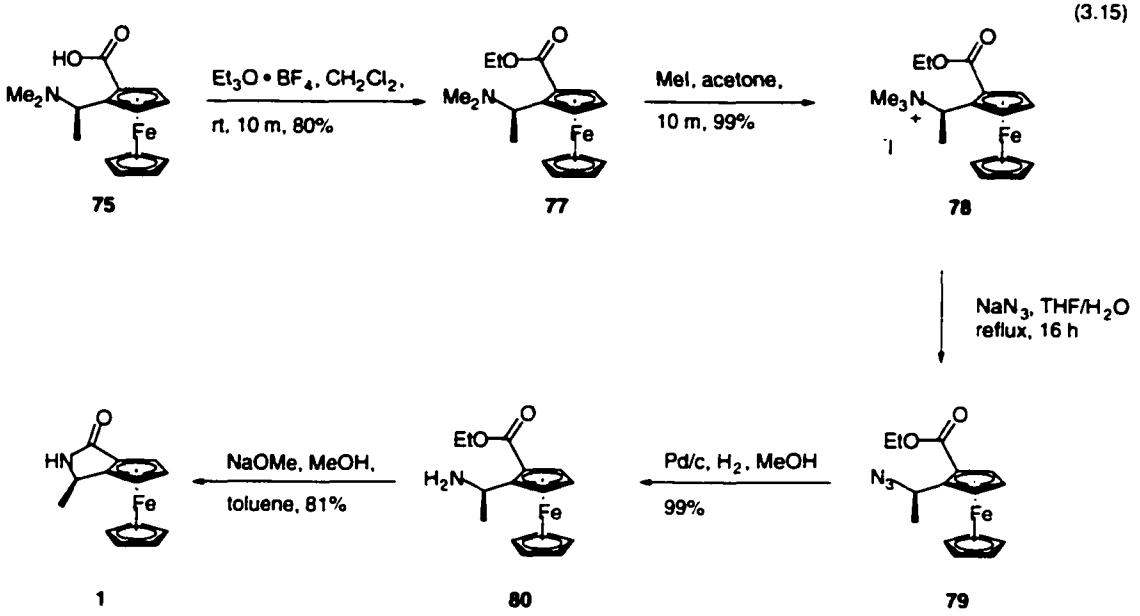
dimethylaminoethylferrocene **74** followed by addition of solid carbon dioxide provided the lithium salt, which when treated with silica gel and methanol gave carboxylic acid **75** (equation 3.14). Recrystallization with methylene chloride and hexane resulted in recovery of a single diastereomer of acid **75**. Attempts to form the methyl ester and the quaternary amine **76** in the same reaction using iodomethane in DMF, resulted in decomposed starting material. Addition of an excess of potassium carbonate to the reaction in order to facilitate the formation of the carboxylate salt, also resulted in decomposed starting material.

(3.14)



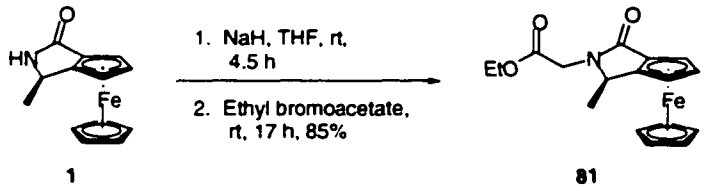
74 **75** **76**

The esterification and quaternization were carried out in two separate steps instead. Addition of triethyloxonium tetrafluoroborate to acid **75** yielded ethyl ester **77**, which was purified by acid/base extraction. Alkylation of the amine with iodomethane resulted in the quaternary amine **78** that required no further purification.



(3.15)

Displacement of the quaternary amine with sodium azide followed by reduction of azide **79** with 10% Pd/C under a H_2 atmosphere yielded amine **80** which was cyclized with 1N NaOMe in methanol in toluene at reflux gave desired amide **1**. The reaction was driven by the removal of methanol by distillation. Deprotonation of amide **1** with sodium hydride followed by addition of ethyl bromoacetate generated α–amido ester **81** (equation 3.16) which could now undergo alkylation reactions.

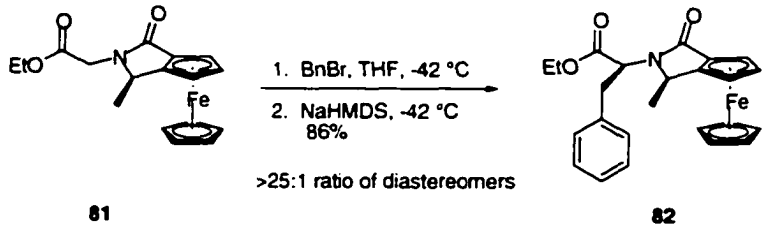


(3.16)

Generation of the enolate followed by addition of an electrophile to the reaction resulted in mixtures of non-alkylated, monoalkylated, and dialkylated products.

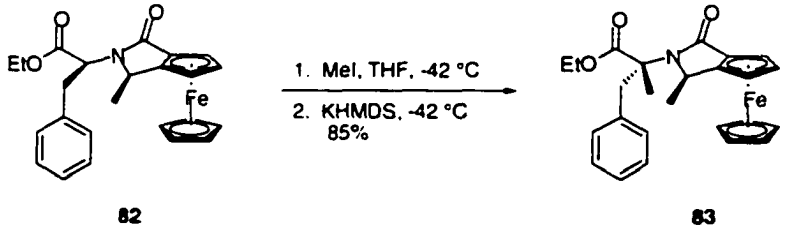
Variation of time, temperatures, and bases to push the reaction towards complete monoalkylation also resulted in unacceptable amounts of monoalkylated products.

Pre-mixing the ester and benzyl bromide at -42 °C followed by addition of 1N sodium hexamethyldisilazane (NaHMDS) followed by quenching in water, provided the monoalkylated product **82** in 85% yield and in a diastereomeric ratio of >25:1 (equation 3.17).



81 **82** (3.17)

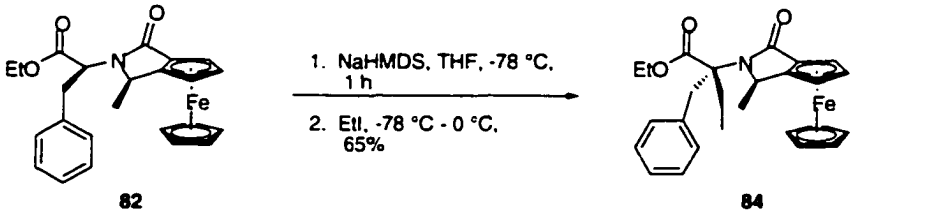
The second alkylation was attempted through the same procedure. Pre-mixing the ester with iodomethane at -42 °C, followed by the addition of 1N NaHMDS in THF followed by the addition of water, provided only starting material. Pre-mixing the ester and iodomethane at -42 °C followed by the addition of 0.5 M potassium hexamethyldisilazane (KHMDS) in toluene followed by addition of water resulted in the desired dialkylated ester **83** in 85% yield and a diastereomeric ratio of >25 to 1 (equation 3.18).



82 **83** (3.18)

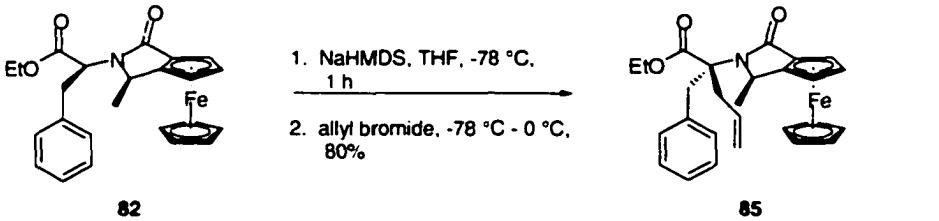
With this example worked out further alkylations were carried out. Pre-mixing the benzylated ester **82** with iodoethane followed by addition of 0.5 M KHMDS in toluene followed by quenching with water gave a 1:1 mixture of diastereomers. Deprotonation of the benzylated ester **82** with 1N NaHMDS at -78 °C followed by addition of iodoethane and gradual warming to 0 °C where the reaction was kept for 15 hours followed by the addition of water provided the disubstituted ester **84** in a 9:1 ratio of diastereomers, which could not be separated. The allyl substituted benzyl ester **85** was synthesized in the same fashion to give a 5:1 ratio of diastereomers, which also could not be separated by silica gel flash chromatography.

(3.19)



82 **84**

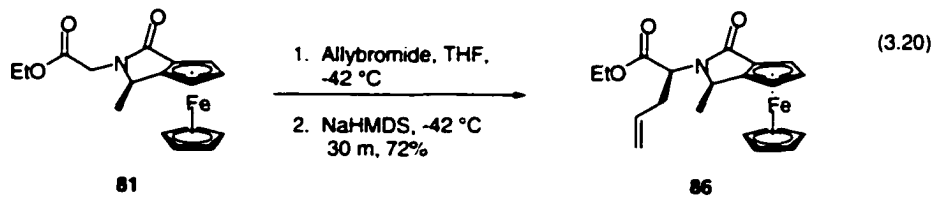
9:1 ratio of diastereomers



82 **85**

5:1 ratio of diastereomers

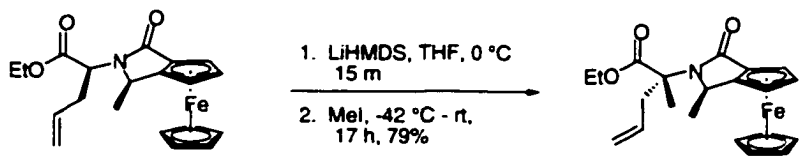
Pre-mixing ester **81** with allyl bromide followed by addition of 1N NaHMDS in THF followed by addition of water provided the monosubstituted allyl ester **86** in 72% yield in >25:1 ratio of diastereomers. Pre-mixing allyl ester **86** with iodomethane followed by addition of 0.5N KHMDS in toluene gave the disubstituted ester in a 1:1 ratio of diastereomers. Deprotonation of the allyl ester **86** at -78 °C with 1N NaHMDS in THF followed by addition of iodomethane also provided a 1:1 ratio of diastereomers. Deprotonation of the allyl ester **86** at 0 °C with 1N lithium hexamethyldisilazane (LiHMDS) in THF for 15 minutes followed by cooling to -42 °C and addition of iodomethane provided the disubstituted ester ester **87** in a 11:1 ratio of diastereomers upon slow warming to room temperature and addition of water (equation 3.20). The diastereomers could be partially separated by silica gel flash chromatography. The ethyl-substituted ester **88** was formed in the same fashion providing a 6:1 ratio of diastereomers, which could not be separated by silica gel flash chromatography.



81 86

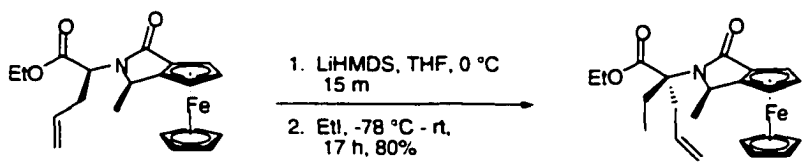
(3.20)

>25:1 ratio of diastereomers



86 87

11:1 ratio of diastereomers



86 88

6:1 ratio of diastereomers

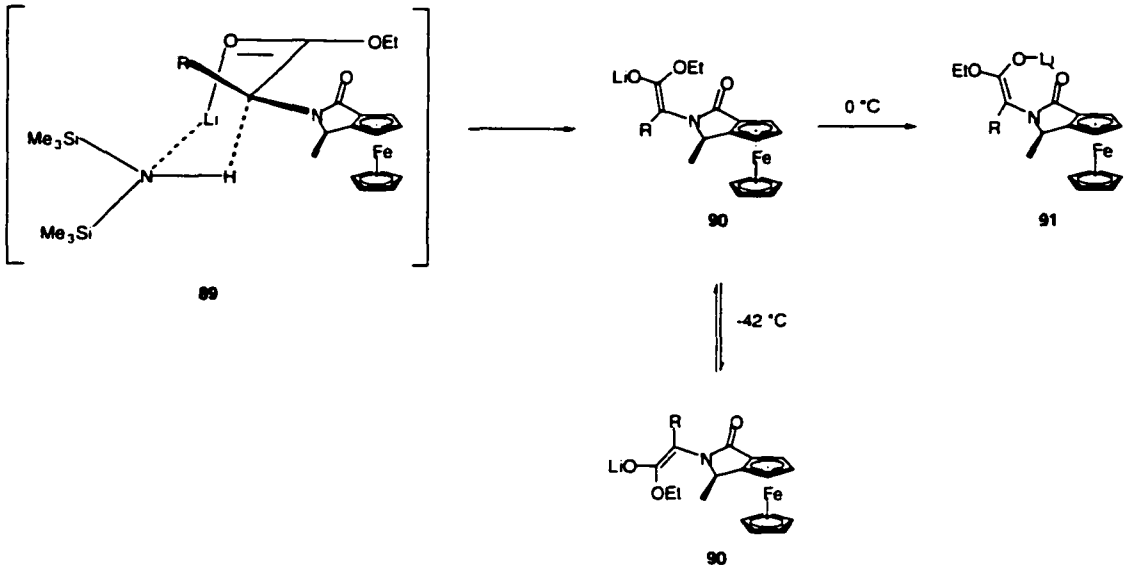
The results of the diastereoselectivities of the reactions followed the diastereoselectivity observed by Ojima[13a] for the alkylation of β–lactams that was discussed previously. For the first alkylation, where R = H, both benzyl bromide and allyl bromide reacted with the initially formed kinetic enolate **90**, shown by the Ireland model **89**, forming the monoalkylated products **82** and **86** in high diastereomeric ratios (Figure 3.7). When the second alkylation was carried out, though, the system was less reactive so the alkylations did not proceed as quickly and the enolate was free to rotate. In the case of the benzyl substituted ester **82** the enolate must have had a preferred conformation because of the bulky phenyl group which lead to the selectivity. With the

smaller allyl ester **86** the enolate was free to rotate, which resulted in a mixture of diastereomers. When the deprotonations were carried out with LiHMDS at 0 °C the enolate was free to equilibrate to the thermodynamic enolate **91** which could form a rigid 7 membered ring lithium chelate, which is not free to rotate and therefore led to the higher diastereoselectivities observed (Figure 3.7).

The use of lithium cation as the counter ion verses sodium cation or potassium cation has a major influence on enolate formation. The Li-O bond that is formed in the generation of the enolate is more covalent in nature and the Na-O bond and the K-O bond are more ionic. Using LiHMDS for generating the enolate, therefore, results in the formation of a relatively covalent Li-O bond which in-turn allows the lithium to chelate the carbonyl group of the amide, which leads to the rigid intermediate **91**. Using NaHMDS or KHMDS as the base to generate the enolate does not allow for the generation of a rigid 7 membered ring because the ionic characteristics of the Na-O and the K-O bond. This ionic character also allows for NaHMDS and KHMDS to be stronger bases than LiHMDS and these bases can be used to fully deprotonate systems quickly at temperatures lower than those required for lithium bases.[21]

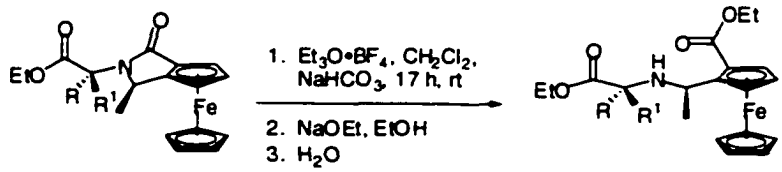
The absolute stereochemistry was determined through comparison of optical rotations of known α,α-disubstituted α-amino esters (vide infra).

Figure 3.7



The ferrocene auxiliaries now needed to be cleaved from the disubstituted esters. The lactams were cleaved in the following manner. Addition of triethyloxonium tetrafluoroborate in the presence of sodium bicarbonate followed by addition of 1N sodium ethoxide and then water provided the amino esters **92**, **93**, **94**, **95**, and **96** (Table 3.1).

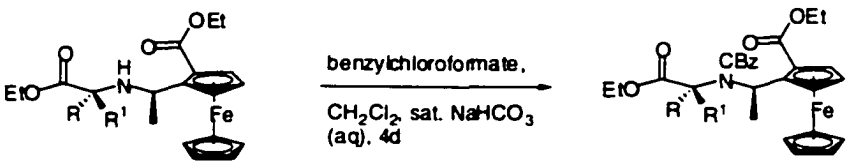
Table 3.1 Cleavage of amide bond



R	R^1	Yield	Comp. #
$C_6H_5CH_2$	CH_3	69%	**92**
$C_6H_5CH_2$	C_2H_5	65%	**93**
$C_6H_5CH_2$	CH_2CHCH_2	75%	**94**
CH_2CHCH_2	CH_3	77%	**95**
CH_2CHCH_2	C_2H_5	64%	**96**

Protection of the amine with benzylchloroformate proved to be slow for the disubstituted esters **92** and **95** yielding the CBz-protected amines **97** and **98** (Table 3.2), so the disubstituted esters **93**, **94**, and **95** were cleaved without protection.

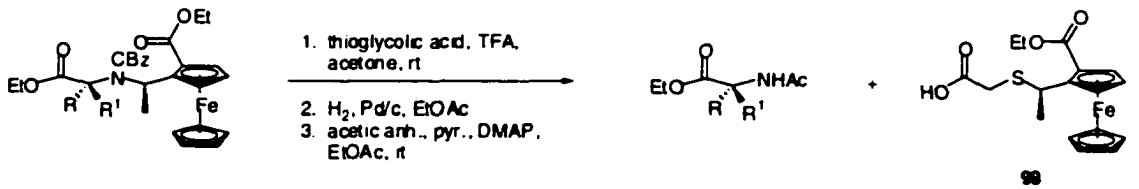
Table 3.2 CBz protection



R	R^1	Yield	Comp. #
$C_6H_5CH_2$	CH_3	70%	**97**
CH_2CHCH_2	CH_3	51%	**98**

Cleavage of the protected amines **97** and **98** using thioglycolic acid and trifluoroacetic acid provided the protected amines which were reductively deprotected and reprotected using acetic anhydride to provide the disubstituted amino ester **100** and **101** (Table 3.3). Enatiomeric excesses were determined by chiral HPLC. Extraction of the reaction with aqueous sodium bicarbonate solution after the first step of the reaction sequence provided ferrocenyl thiol **99**.

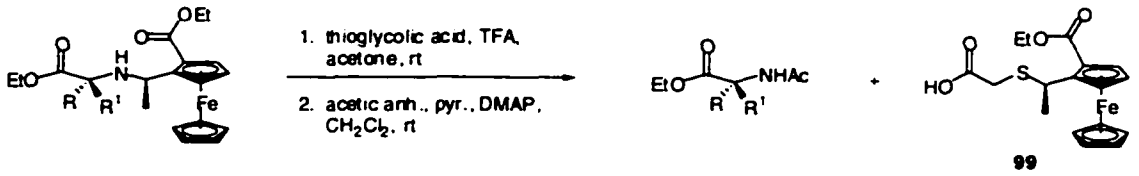
Table 3.3 Cleavage of auxiliary



R	R^1	Yield	ee's	Comp. #
$C_6H_5CH_2$	CH_3	78%	96%	**100**
$CH_3CH_2CH_2$	CH_3	69%	91%	**101**

Cleavage of amines **93**, **94**, and **96** using thioglycolic acid and trifluoroacetic acid provided the amino esters, which were protected using acetic anhydride to give the protected disubstituted amino esters **102**, **103**, and **104** (Table 3.4). Enantiomeric excesses were determined by chiral HPLC. Once again, extraction of the reaction with aqueous sodium bicarbonate solution after the first step of the reaction sequence provided ferrocenyl thiol **99**.

Table 3.4 Cleavage of auxiliary



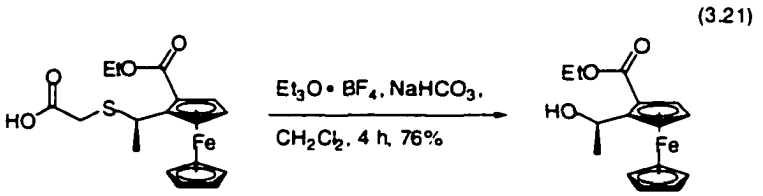
R	R^1	Yield	ee's	Comp. #
$C_6H_5CH_2$	C_2H_5	75%	78%	**102**
$C_6H_5CH_2$	CH_2CHCH_2	85%	66%	**103**
CH_2CHCH_2	C_2H_5	50%	71%	**104**

The absolute stereochemistry of the reactions was determined by comparing the optical rotations of the final products **100**, **101**, and **102** to known literature values and shown to be *R* at the α-position.[12a, 22] These three examples represent the three different methods used to carry out the second alkylation showing that the stereochemistry of **103** and **104** was *R* as well.

The observed optical rotation for (*R*)-*N*-acetyl-α-methylphenylalanine ethyl ester (**100**) is $[\alpha]^{20}_D$ = -52.2° (c = 0.36, chloroform). The reported value is $[\alpha]^{20}_D$ = -47.8° (c = 1, chloroform) for an enantiomeric excess of >95%.[22] The observed optical rotation for (*R*)-*N*-acetyl-α-methylpropylglycine ethyl ester (**101**) is $[\alpha]^{20}_D$ = -12.0° (c = 0.78, chloroform). The reported value is $[\alpha]^{23}_D$ = -12.6° (c = 1.10, chloroform).[12a] The observed optical rotation for (*R*)-*N*-acetyl-α-ethylphenylalanine ethyl ester (**102**) is $[\alpha]^{20}_D$

= -69.3° (c = 0.14, chloroform). The reported value is $[\alpha]^{30}_D$ = -107.2° (c = 1.40, chloroform).

Treatment of the recovered ferrocenyl thiol with triethyloxonium tetrafluoroborate provided the alcohol **105** which was can be converted to various amine substituted ferrocenes by the technique developed in the previous chapter, demonstrating the recyclability of the ferrocene chiral auxiliaries (equation 3.21).



(3.21)

99 **105**

Conclusion

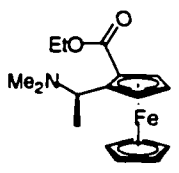
Once again the ferrocene chiral auxiliary provided stereoselective induction while at the same time donating its amine functionality. In this instance, the ferrocenyl amide was used to stereoselectively synthesize α,α–disubstituted α–amino esters. The ferrocenyl auxiliary was also once again cleaved in a way that allows it to be reused as a chiral auxiliary for future synthetic procedures. The synthetic example shown in Chapter Two and the example provided in this chapter definitely show the potential of these ferrocenyl compounds to become useful auxiliaries in the field of organic synthesis. The hypothesis proposed that the auxiliary should posses the ability to induce high stereoselectivities in the synthesis of α,α-disubstituted α-amino acids in high

enantiomeric excesses was confirmed. However, recyclability remained inefficient and requires further optimization before the process becomes generally useful.

Experimental

General Procedures: All NMR spectra (300 MHz for ^{1}H NMR and 75 MHz, for ^{13}C NMR) were recorded in $CDCl_3$ and chemical shifts were given relative to TMS (0.00 for ^{1}H) and $CDCl_3$ (77.23 for ^{13}C) unless otherwise stated. The 300 MHz ^{1}H NMR and 75.5 MHz ^{13}C NMR were taken on a Varian Inova–300 spectrometer and 400 MHz ^{1}H NMR and 100.6 ^{13}C NMR were taken on a Varian Inova-500 spectrometer. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR. THF was distilled from sodium-benzophenone ketyl; CH_2Cl_2 was distilled from CaH; MeOH was distilled from CaH. Column chromatography was performed with ICN 32-63 nm, 60 Å silica gel. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Enantiomeric excesses were determined by chiral HPLC (Chiralpak OD #OD00CE-JA001). (*R,S*)-2'-(N,N-dimethylaminoethylferrocene)carboxylic acid **75** was synthesized according to literature methods.[23] Compounds **100**, **101**, and **102** were previously synthesized by Suemune.[12a] Compound **103** was previously synthesized by Speckamp.[24]

Ethyl ester 77

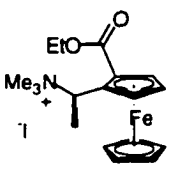


77

In a 250 ml round bottom one neck flask under argon was placed a solution consisting of 100 ml of CH_2Cl_2 and 2.91 g (9.66 moles) of (*R,S*)-2'-(*N,N*-dimethylaminoethylferrocene)carboxylic acid **75**, which

was stirred at room temperature. To this was added 3 g of solid $NaHCO_3$ and after stirring briefly, 2.02 g (10.63 mmoles) of triethyloxonium tetrafluoroborate was added to the solution and it was allowed to stir for 10 min. The reaction was then poured into saturated $NaHCO_3$ (aq.) and partitioned. The layers were separated and the organic layer was washed with water (1 X 50 ml), extracted with 8.5% phosphoric acid (aq.) (2 X 60 ml) and once with 60 ml of water. The aqueous layers were combined and extracted with CH_2Cl_2 (2 X 50 ml), diluted to twice the original volume and neutralized with solid $NaCO_3$. The aqueous layer was extracted with CH_2Cl_2 (4 X 60 ml) and the organic layers were combined and washed once with water, brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Ethyl ester **77** was isolated as an orange oil. Yield = 2.83 g (89%). $[\alpha]^{20}_D$ = -68.5° (c = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 4.79 (m, 1H), 4.54 (q, J = 7 Hz, 1H), 4.41 (m, 1H), 4.38 (m, 1H), 4.25 (m, 2H), 4.13 (s, 5H), 2.12 (s, 6H), 1.55 (d, J = 7 Hz, 3H), 1.35 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 89.8, 77.6, 77.2, 76.8, 71.2, 70.8, 70.7, 69.7, 69.6, 60.1, 55.4, 40.6, 16.3, 14.8; IR ν 1708 cm^{-1}, MS (LSIMS) $(M + 1)^+$ = 330.2

Ammonium salt 78

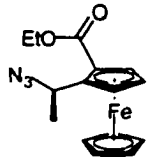


78

In a 250 ml round bottom three neck flask under argon was placed a solution consisting of 100 ml of acetone and 2.73 g (8.29 mmoles) of ester **77**. This was stirred at room temperature and to the solution was added 1 ml (16.06 mmoles) of iodomethane. The reaction was allowed to stir for 10 min. and was then concentrated under reduced pressure. Quaternary amine

78 was isolated as an orange glassy foam. Yield = 3.88 g (99%). ^{1}H NMR ($CDCl_3$) δ 5.35 (q, J = 7 Hz, 1H), 4.99 (m, 1H), 4.91 (m, 1H), 4.71 (t, 2.6 Hz, 1H), 4.33 (m, 1H), 4.27 (s, 5H), 4.24 (m, 1H), 3.21 (s, 9H), 2.11 (d, J = 7 Hz, 3H), 1.38 (t, J = 7 Hz, 3H); ^{13}C NMR δ 172.1, 82.6, 77.6, 77.2, 76.8, 73.5, 72.7, 72.5, 72.0, 70.1, 69.8, 61.2, 51.6, 17.5, 14.8; IR ν 1697 cm^{-1}; MS (LSIMS) (M – 126.9 (I$^-$)) = 344.1

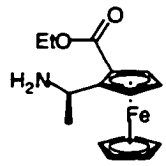
Azide 79



79

In a 250 ml round bottom one neck flask was placed a solution consisting of 50 ml of water 50 ml of THF and 3.2 g (6.8 mmoles) of salt **78**. The solution was stirred at room temperature and to it was added 0.88 g (13.6 mmoles) of NaN_3. The reaction was stirred briefly and warmed to reflux for 17 hours and was allowed to cool to room temperature and was partitioned with CH_2Cl_2. The layers were separated and the water layer was extracted with CH_2Cl_2 (1 x 50 ml). The organic layers were combined and washed with water (3 x 60 ml), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by silica gel flash chromatography (9:1, hex/EtOAc). Yield of azide **79** was 1.75 g (79%) of an orange oil. $[\alpha]^{20}_D$ = -229.5° (c = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 5.29 (q, J = 7 Hz, 1H), 4.90 (dd, J = 2.6, 1.5 Hz, 1H), 4.50 (t, J = 1.5 Hz), 4.44 (t, J = 2.9 Hz, 1H), 4.32 (m, 2H), 4.19 (s, 5H), 1.65 (d, J = 7 Hz, 3H), 1.38 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.8, 89.4, 77.6, 77.2, 76.9, 72.0, 70.8, 70.3, 69.7, 69.5, 60.5, 55.0, 19.5, 14.8; IR ν 2096, 1706 cm^{-1}; MS (LSIMS) M^+ = 327.1 HRMS (LSIMS) m/z calculated for $C_{15}H_{17}FeN_3O_2$ M^+ 327.0670; found 327.0672.

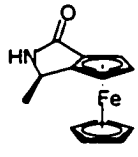
Amine 80



80

In a 100 ml round bottom one neck flask was placed a solution consisting of 20 ml of methanol and 200 mg of azide **79**. This was stirred at room temperature and to it was added 50 mg of 10% Pd/C. The solution was stirred and placed under a H_2 atmosphere and after stirring for 17 hours the reaction was filtered and concentrated under reduced pressure. The residual oil was dissolved in CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Yield of amine **80** 178 mg (97%) of an orange oil. $[\alpha]^{20}_D$ = -69.2° (c = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 4.81 (m, 1H), 4.44 - 4.24 (m, 6H), 4.15 (s, 5H), 1.82 (bs, 1H), 1.51 (d, J = 6.8 Hz, 3H), 1.38 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.6, 97.2, 77.6, 77.2, 76.9, 72.0, 70.5, 69.5, 69.3, 69.1, 60.4, 45.3, 21.8, 14.8; IR ν 3369, 1700 cm^{-1}; MS (LSIMS) $(M + 1)^+$ = 302.1

Lactam 1

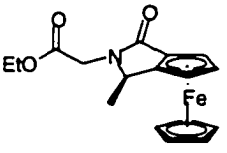


1

In a 100 ml round bottom one neck flask under argon was placed a solution of 916 mg (3.19 mmoles) of amine **80** dissolved in 50 ml of dry toluene which was stirred at room temperature. To this was added 10 ml (10 mmoles) of 1N sodium methoxide in methanol and this was warmed to reflux and the methanol was distilled off of the reaction. Once the methanol was

completely gone the reaction was concentrated under reduced pressure and purified by column chromatography (20:1 methylene chloride/methanol). The residual orange oil solidified. Yield of amide **1** was 530mg (65%). $[\alpha]^{20}_{D}$ = +902.6 (c = 1, ethanol); mp = 145 - 148 °C; ^{1}H NMR ($CDCl_3$) δ 6.2 (bs, 1H), 4.71 (q, J = 6.4 Hz, 1H), 4.62 (s, 1H), 4.5 (s, 1H), 4.24 (s, 1H), 4.18 (s, 5H), 1.33 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.5, 99.2, 77.5, 77.2, 76.9, 72.6, 70.7, 63.2, 61.8, 51.9, 23.1; IR ν 3230, 1683 cm^{-1}; MS (LSIMS) M^+ = 255.0; Anal. Calcd. for $C_{13}H_{13}FeNO$: C, 61.20; H, 5.14; N, 5.49; Found: C, 61.08; H, 5.22, N, 5.44.

Ester 81

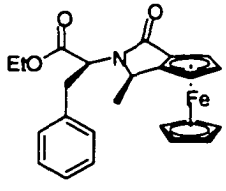


81

In a 100 ml round bottom one neck flask under argon, a solution of 358mg (1.4 mmoles) of amide **1** dissolved in 40 ml of anhydrous THF was stirred at room temperature and to it was added 112 mg (2.8 mmole) of 60% sodium hydride in mineral oil. The reaction was allowed to stir at room temperature for 4 hours and at this time then 1.55 ml (14 mmoles) of ethyl bromoacetate was added to the reaction. After stirring at room temp for 17 hours the reaction was partitioned between methylene chloride and water. The layers were separated and the water layer was extracted once with methylene chloride. The organic layers were combined and washed with water (3 X 50 ml) and finally with brine. The solution was dried over magnesium chloride and concentrated under reduced pressure. The residual oil was purified by silica gel flash chromatography (1:1 hexanes/ethyl acetate). The purified oil solidified. Yield of ester **81** was 440 mg (92%) of an orange

solid. $[\alpha]^{20}_D$ = +777.8° (c = 1, ethanol); mp = 100 - 102 °C; ^{1}H NMR ($CDCl_3$) δ 4.77 (q, J = 6.6 Hz, 1H), 4.71 (d, J = 17.9 Hz, 1H), 4.64 (d, J = 2.2 Hz, 1H), 4.50 (d, J = 1.8 Hz, 1H), 4.26 (m, 8H), 3.67 (d, J = 17.9 Hz, 1H), 1.33 (t, J = 7.0 Hz, 3H), 1.28 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.5, 96.7, 77.6, 77.4, 77.2, 76.9, 72.2, 70.9, 63.0, 62.0, 61.5, 55.1, 41.6, 19.9, 14.5; IR ν 1745, 1687 cm^{-1}; MS (LSIMS) M^+ = 341.1; Anal. Calcd. for $C_{17}H_{19}FeNO_3$: C, 59.84; H, 5.61; N, 4.11; Found: C, 59.84; H, 5.77, N, 4.08.

Benzyl ester 82

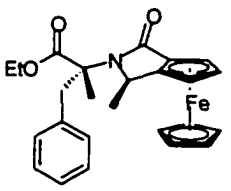


82

In a 100 ml round bottom one neck flask under argon was placed a solution of 350 mg (1.03 mmoles) of ester **81** dissolved in 40 ml of anhydrous THF which was cooled to –42 °C. To this was added 0.36 ml (3 mmoles) of benzyl bromide and after stirring briefly, 2.6 ml (2.6 mmoles) of 1N NaHMDS was added to the reaction. After stirring at –42 °C for 20 minutes, the reaction was poured into an ether/water mixture and the layers were partitioned and separated and the ether layer was washed with water (3 X 20 ml) and finally with brine. The solution was further dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was purified by silica gel flash chromatography (1:1 hexanes/ethyl acetate). Yield of the benzyl ester **82** was 354 mg (80%) of an orange solid. $[\alpha]^{20}_D$ = +513.4° (c = 1, ethanol); Mp = 112 - 116 °C; ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 3H), 7.17 (m, 2H), 4.94 (dd, J = 11.85, 4.8 Hz, 1H), 4.56 (d, J = 2.2 Hz, 1H), 4.50 (q, J = 6.6 Hz, 1H), 4.32 (d, J = 1.5, 1H), 4.22 (m, 2H), 4.15 (s, 1H), 3.88 (s, 5H), 3.6 (dd, J = 15.2, 4.8 Hz, 1H), 3.34 (dd, J = 15.2, 11.7 Hz, 1H), 1.29 (t, J = 7.3 Hz, 3H), 1.01 (d, J

= 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.3, 171.5, 137.9, 129.0, 127.2, 96.8, 78.3, 77.6, 77.2, 76.9, 71.8, 70.5, 62.4, 61.8, 55.2, 55.1, 34.9, 20.7, 14.4; IR ν 1733, 1683 cm^{-1}, MS (LSIMS) M^+ = 431.1; HRMS (LSIMS) m/z calculated for $C_{24}H_{25}FeNO_3$ M^+ 431.1183; found 431.1180.

Methylbenzyl ester 83

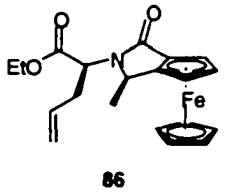


83

In a 10 ml round bottom round bottom one neck flask under argon was placed a solution of 50 mg (0.116 mmoles) of **82** dissolved in 4 ml of anhydrous THF that was cooled to –42 °C. To this was added 0.1 ml (1.6 mmoles) of iodomethane and after stirring briefly, 0.46 ml (0.23 mmole) of potassium bis(trimethylsilyl) amide was added to the reaction. After stirring for 80 minutes at –42 °C, the reaction was quenched with methanol and poured into water. The water was extracted with ether (2 X 15 ml). The ether layers were combined and washed with water (3 X 20 ml) and finally with brine. The solution was dried over magnesium sulfate and concentrated under reduced pressure. The residual solid was purified by silica gel flash chromatograhy (40:1 methylene chloride/methanol). Yield of the purified orange solid **83** was 44.8 mg (87%). $[\alpha]^{20}_D$ = +453.6° (c = 0.5, ethanol); Mp = 180 - 183 °C; ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 3H), 7.23 (m, 2H), 4.95 (q, J = 6.2 Hz, 1H), 4.55 (d, J = 2.1 Hz, 1H), 4.41 (d, J = 2.1 Hz, 1H), 4.28 (s, 5H), 4.18 (m, 2H), 4.03 (m 1H), 3.38 (d, J = 12.1 Hz, 1H), 3.20 (d, J = 12.1 Hz, 1H), 1.48 (d, J = 5.8 Hz, 6H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.5, 171.3,

135.1, 130.7, 128.3, 127.4, 97.1, 77.5, 77.2, 76.9, 71.9, 70.7, 63.8, 62.3, 62.0, 61.1, 54.3, 43.4, 25.2, 21.8, 14.2; IR ν 1743, 1677 cm^{-1}; MS (LSIMS) M^+ = 445.1

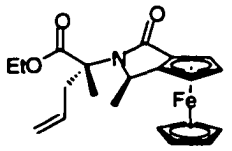
Allyl ester 86



86

In a 10 ml round bottom one neck flask under argon was placed a solution consisting of 2 ml of anhydrous THF and 30 mg (0.088 mmole) of ester **81** that was cooled to –42 °C. To this was added 0.05 ml (0.58 mmole) of allyl bromide and after stirring briefly, 0.22 ml (0.22 mmole) of 1N NaHMDS in THF was added to the reaction and it was allowed to stir for 35 min. at –42 °C. The reaction was then poured into an ether/water mixture and partitioned. The layers were separated and the ether layer was washed with water (3 x 20 ml), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by silica gel flash chromatography (1:1, hex/EtOAc). Yield of allyl ester **86** was 24 mg (72%) of an orange solid. $[\alpha]^{20}_D$ = +482.3° (c = 1, ethanol); Mp = 108 - 111 °C; ^1H NMR ($CDCl_3$) δ 5.85 (m, 1H), 5.20 (m, 2H), 4.74 (dd, J = 10.8, 4.8 Hz, 1H), 4.64 (bs, 2H), 4.44 (d, J = 1.5 Hz, 1H), 4.23 (s, 1H), 4.19 (s, 7H), 3.00 (dt, J = 15.4, 4.8 Hz, 1H), 2.74 (m, 1H), 1.26 (t, J = 7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 172.0, 171.5, 134.8, 118.0, 96.6, 78.4, 77.6, 77.3, 76.9, 72.0, 62.7, 62.0, 61.7, 54.9, 54.0, 33.3, 21.4, 14.4; IR ν 1727, 1677 cm^{-1}; MS (LSIMS) M^+ = 381.2; HRMS (LSIMS) m/z calculated for $C_{20}H_{23}FeNO_3$ M^+ 381.1027; found 381.1031.

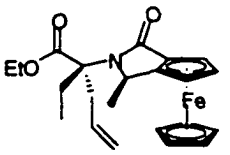
Methylallyl ester 87



87

In a 10 ml round bottom one neck flask under argon was placed a solution consisting of 24 mg (0.063 mmole) of allyl ester **86** dissolved in 2 ml of anhydrous THF that was cooled to 0 °C. To this solution was added 0.4 ml (0.4 mmole) of 1N LiHMDS in THF and after 15 minutes at 0 °C, the reaction was cooled to -42 °C and to it was added 0.05 ml (0.8 mmole) of iodomethane. The reaction was allowed to stir for 17 hours over-which time it gradually warmed to room temperature. The reaction was partitioned between methylene chloride and water and the organic layer was washed with water (3 x 20 ml), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by silica gel flash column chromatography (1:1, hex, EtOAc). Yield of disubstituted ester **87** as a single diastereomer was 19.6 mg (79%) of an orange oil. Major diastereomer: $[\alpha]^{20}_D$ = +561.3° (c = 0.97, ethanol); ^{1}H NMR ($CDCl_3$) δ 5.79 (m, 1H), 5.20 (m, 2H), 4.83 (q, J = 6.6 Hz, 1H), 4.57 (d, J = 2.2 Hz, 1H), 4.40 (d, J = 1.8 Hz, 1H), 4.31 (m, 2H), 4.24 (s, 5H), 4.21 (m, 1H), 2.81 (d, J = 7.3 Hz, 2H), 1.56 (s, 3H), 1.43 (d, J = 6.2 Hz, 3H), 1.33 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 171.3, 132.4, 119.6, 97.4, 77.6, 77.3, 76.9, 72.1, 70.6, 62.4, 62.3, 62.0, 61.4, 54.4, 41.8, 25.1, 22.3, 14.6; IR ν 1735, 1683 cm^{-1}; MS (LSIMS) M^+ = 395.1

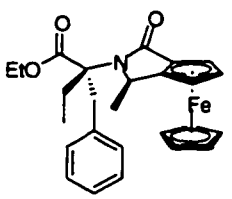
Ethylallyl ester 88



88

In a 10 ml round bottom one neck flask under argon was placed a solution of 22 mg (0.0577 mmole) of allyl ester **86** dissolved in 2 ml of anhydrous THF was cooled to 0 °C and to it was added 0.4 ml (0.4 mmole) of 1N LiHMDS in THF. After stirring for 15 minutes the reaction was cooled to -78 °C and to it was added 0.05 ml (0.63 mmole) of iodoethane and the reaction was allowed to stir for 17 hours over-which time the reaction gradually warmed to room temperature. The reaction was partitioned between methylene chloride and water and the organic layer was washed with water (3 x 20 ml), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by silica gel flash column chromatography (1:1, hex, EtOAc). Yield of disubstituted ester **88** as an inseparable mixture of diastereomers was 18.8 mg (80%) of an orange oil. Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 5.76 (m, 1H), 5.18 (m, 2H), 4.88 (q, J = 6.4 Hz, 1H), 4.58 (d, J = 2.2 Hz, 1H), 4.38 (d, J = 2.1 Hz, 1H), 4.34 (m, 1H), 4.25 (s, 5H), 4.21 (m, 2H), 2.84 (m, 2H), 2.37 (m, 1H), 1.82 (m, 1H), 1.43 (d, J = 6.4 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.6, 172.0, 132.4, 119.3, 97.4, 78.1, 77.6, 77.2, 76.9, 70.5, 66.3, 62.0, 61.8, 61.2, 54.8, 39.5, 27.4, 25.6, 25.2, 14.6, 8.9; IR ν 1736, 1686 cm^{-1}; MS (LSIMS) M^+ = 409.2.

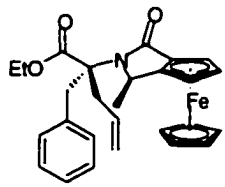
Ethylbenzyl ester 84



84

In a 10 ml round bottom one neck flask under argon was placed a solution consisting of 49 mg (0.11 mmole) of benzyl ester **82** dissolved in 4 ml of anhydrous THF that was cooled to -78 °C. To it was added 0.55 ml (0.55 mmole) of 1N NaHMDS in THF and after stirring at -78 °C for 1 hour, 0.1 ml (1.25 mmoles) of iodoethane was added to the reaction and it was allowed to slowly warm to 0 °C and kept at this temperature for 15 hours followed by partitioned between water and methylene chloride. The organic layer was washed with water (3 x 20 ml), brine, dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel flash chromatography (1:1, hex/EtOAc) furnished 31 mg (65%) of disubstituted ester **84** as an inseparable mixture of diastereomers as an orange oil. Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 3H), 7.19 (m, 2H), 5.08 (q, J = 6.6 Hz, 1H), 4.59 (d, J = 2.6 Hz, 1H), 4.43 (d, J = 2.2 Hz, 1H), 4.32 (s, 5H), 4.24 (m, 2H), 4.02 (m, 1H), 3.35 (dd, J = 27.5, 12.1 Hz, 2H), 2.4 (m, 1H), 1.75 (m, 1H), 1.45 (d, 6.6 Hz, 3H), 1.18 (t, J = 7 Hz, 3H), 0.99 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.5, 172.3, 135.4, 130.7, 128.3, 127.3, 97.2, 78.2, 77.6, 77.2, 76.9, 70.7, 67.9, 62.2, 61.9, 61.0, 54.8, 41.5, 26.6, 24.9, 14.2, 9.4; IR ν 1740, 1686 cm^{-1}; MS (LSIMS) M^+ = 459.1

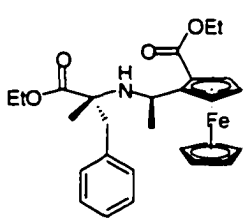
Allylbenzyl ester 85



85

Allylbenzyl ester **85** was synthesized using the same procedure as that used for ethylbenzyl ester **84**. Starting with 51 mg (0.12 mmoles of benzyl ester **82**, 44.7 mg of was yielded as an inseparable mixture of diastereomers as an orange oil. Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 3H), 7.19 (m, 2H), 5.08 (q, J = 6.6 Hz, 1H), 4.59 (d, J = 2.6 Hz, 1H), 4.43 (d, J = 2.2 Hz, 1H), 4.32 (s, 5H), 4.24 (m, 2H), 4.02 (m, 1H), 3.35 (dd, J = 27.5, 12.1 Hz, 2H), 2.4 (m, 1H), 1.75 (m, 1H), 1.45 (d, J = 6.6 Hz, 3H), 1.18 (t, J = 7.0 Hz, 3H), 0.99 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.5, 172.3, 135.4, 130.7, 128.3, 127.3, 97.2, 78.2, 77.6, 77.2, 76.9, 70.7, 67.9, 62.2, 61.9, 61.0, 54.8, 41.5, 26.6, 24.9, 14.2, 9.4; IR ν 1739, 1685 cm^{-1}; MS (LSIMS) M^+ = 459.1.

Amino ester 92

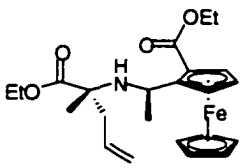


92

In a 10 ml round bottom one neck flask under argon was placed a solution consisting of 5 ml of CH_2Cl_3 and 39.8 mg (0.089 mmole) of disubstituted ester **83** which was stirred at room temperature. To this was added 200 mg of solid $NaHCO_3$ followed by 67 mg (0.352 mmole) of triethyloxonium tetrafluoroborate. The reaction was covered with foil and allowed to stir at room temperature for 17 hours over which time the reaction had changed from yellow to dark red. The reaction was cooled to 0 °C and 1N NaOEt in EtOH was added to the reaction until it changed from dark red to

yellow. Immediately after the color change an excess of water was added to the reaction and it was partitioned between CH_2Cl_2 and water. The layers were separated and the CH_2Cl_2 layer was washed with water (3 x 20 ml), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by silica gel flash chromatography (8:2, hex/EtOAc), which provided 30.5 mg (69%) of amine **92** as an orange oil. $[\alpha]^{20}_D$ = -53.4° (c = 0.59, ethanol) ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 3H), 7.09 (m, 2H), 4.76 (dd, *J* = 2.5, 1.5 Hz, 1H), 4.51 (t, *J* = 2.5 Hz, 1H), 4.40 (q, *J* = 6.6 Hz, 1H), 4.33 (m, 1H), 4.20 (m, 3H), 4.14 (s, 5H), 4.07 (q, *J* = 7.0 Hz, 2H), 2.81 (q, 9.2 Hz, 2H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.32 (t, *J* = 7.3 Hz, 3H), 1.27 (s, 3H), 1.21 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 177.2, 171.8, 136.5, 130.5, 128.0, 126.7, 97.4, 77.7, 77.2, 76.8, 70.9, 70.7, 70.5, 69.3, 68.7, 62.4, 60.9, 60.1, 48.0, 46.6, 22.3, 20.0, 15.0, 14.4; IR ν 1708 cm^{-1}; MS (LSIMS) $(M + 1)^+$ = 492.2

Amino ester 95

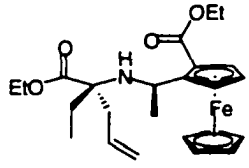


95

Amino ester **95** was synthesized using the same procedure for that of amino ester **92**. Starting with 51 mg (0.13 mmole) of methylallyl ester **87**, 44.1 mg (77%) of amino ester **95** was yielded as a single diastereomer as an orange oil. $[\alpha]^{20}_D$ = -35.8° (c = 0.4, ethanol): ^{1}H NMR ($CDCl_3$) δ 5.68 (m, 1H), 5.02 (m, 2H), 4.75 (m, 1H), 4.51 (s, 1H), 4.41 (q, *J* = 6.8 Hz, 1H), 4.31 (m, 3H), 4.15 (s, 5H), 4.07 (q, *J* = 7.0 Hz, 2H), 2.29 (d, *J* = 7.2 Hz, 2H), 1.79 (bs, 1H), 1.50 (d, *J* = 6.6 Hz, 3H), 1.38 (t, *J* = 7 Hz, 3H), 1.29 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) 177.2, 172.1, 133.4, 118.7,

97.4, 77.5, 77.2, 76.9, 70.9, 70.6, 70.5, 69.4, 68.7, 61.2, 60.8, 60.2, 46.2, 45.5, 22.7, 21.0, 14.9, 14.4; IR ν 3079, 1709 cm^{-1}; MS (LSIMS) $(M + 1)^+ = 442.2$

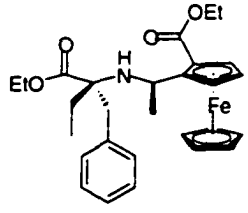
Amino ester 96



96

Amino ester **96** was synthesized using the same procedure as that of amino ester **92**. Starting with 44 mg (0.11 mmole) of ethylallyl ester **88**, 32 mg (64%) of amino ester **96** was yielded as an inseparable mixture of diastereomers as an orange oil. Major diastereomer: ^1H NMR ($CDCl_3$) δ 5.65 (m, 1H), 5.03 (m, 2H), 4.73 (m, 1H), 4.50 (s, 1H), 4.46 (q, J = 6.7 Hz, 1H), 4.34 (t, J = 2.6 Hz, 1H), 4.30 (q, J = 7 Hz, 2H), 4.15 (s, 1H), 3.84 - 3.99 (m, 2H), 2.48 (dd, 14.6, 7 Hz, 1H), 2.26 (dd, J = 14.6, 7.2 Hz, 1H), 1.61 (m, 3H), 1.38 (t, J = 7 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H), 0.72 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.0, 172.1, 134.0, 117.8, 98.5, 77.6, 77.2, 76.9, 70.7, 70.6, 69.6, 68.4, 64.6, 60.6, 60.2, 44.4, 37.9, 28.3, 25.4, 14.9, 14.3, 8.0; IR ν 3076, 1726, 1709 cm^{-1}. MS (LSIMS) $(M + 1)^+ = 456.1$.

Amino ester 93

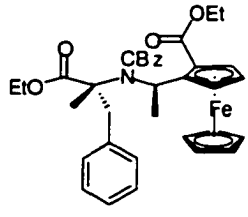


93

Amino ester **93** was synthesized using the same procedure as that of amino ester **92**. Starting with 31 mg (0.067 mmole) of ethylallyl ester **88**, 22.3 mg (65%) of amino ester **93** was yielded

as an inseparable mixture of diastereomers as an orange oil. Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 3H), 7.11 (m, 2H), 4.75 (dd, J = 2.6, 1.6 Hz, 1H), 4.53 (m, 2H), 4.36 (t, J = 2.6 Hz, 1H), 4.28 (q, J = 7 Hz, 2H), 4.17 (s, 5H), 3.90 (m, 2H), 2.8 (dd, J = 97.9, 13.9 Hz, 2H), 1.62 (m, 6H), 1.37 (t, J = 7 Hz, 3H), 1.12 (t, 7.2 Hz, 3H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.2, 172.2, 137.4, 130.4, 128.1, 126.5, 98.6, 77.6, 77.2, 76.9, 70.9, 70.7, 69.7, 69.5, 68.5, 65.9, 60.6, 60.2, 45.0, 40.7, 26.3, 25.0, 14.9, 14.2, 8.2; IR ν 1706 cm^{-1}; MS (LSIMS) $(M + 1)^+$ = 506.1.

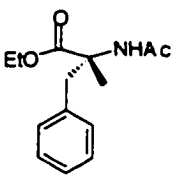
CBz-protected amine 97



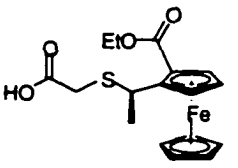
97

In a 10 ml round bottom one neck flask was placed a solution consisting of 13.3 mg (0.027 mmole) of amine ester **92**, 1 ml of CH_2Cl_2, and 1 ml of sat. $NaHCO_3$ (aq) and to this was added 0.1 ml (0.7 ml) of benzyl chloroformate. The reaction was stirred vigorously for 44 hours and another 0.5 ml of sat $NaHCO_3$ (aq) and 0.05 ml (0.35 mmole) of benzyl chloroformate was added. After stirring another 17 hours the reaction was partitioned between sat. $NaHCO_3$ (aq) and CH_2Cl_2 and the organic layer was washed with sat. $NaHCO_3$ (aq) (4 x 20 ml), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was placed under high vacuum and purified by silica gel flash column chromatography (8:2, hex/EtOAc) yielding 11.8 mg (70%) of CBz protected amine **97** as an orange oil. CBz protected amine **98** was synthesized using the same procedure as above. Starting with 44.1 mg (0.1 mmole) of amine ester **95**, 29.4 mg (51%) of CBz protected amine **98** was yielded as an orange oil.

(*R*)-*N*-Acetyl-α-methylphenylalanine ethyl ester (100)



100



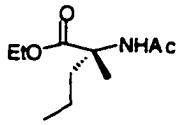
99

In a 10 ml round bottom one neck flask under argon was placed a solution of 24.7 mg (0.0395 mmole) of CBz protected amine **97** dissolved in 2 ml of acetone. To this was added 0.1 ml (1.4 mmoles) of mercaptoacetic acid followed by 0.8 ml (1.0 mmole) of trifluoroacetic acid and the reaction was covered with aluminum foil. After stirring at room temperature for 17 hours the reaction was partitioned between sat. $NaHCO_3$ (aq) and methylene chloride. The organic layer was washed with sat. $NaHCO_3$ (3 x 30 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by silica gel flash column chromatography (8:2, hex/EtOAc). Yield of the CBz-protected amine was 12.1 mg (90%) as a clear colorless oil and this was taken on to the next step in the reaction sequence. The ferrocenyl thiol **99** was recovered by acidification of the aqueous basic extractions with 8.5% phosphoric acid followed by extraction with methylene chloride until no more colored material remained in the aqueous layer. The organic layer was washed with water (6 x 30 ml) and brine, dried over $MgSO_4$, concentrated under reduced pressure, and placed under high vacuum. Yield = 11.15 mg (75%) of an orange oil. Analytical data for thiol **99**. $[\alpha]^{20}_D$ = -132° (c = 0.3, ethanol); ^1H NMR ($CDCl_3$) δ 4.84 (dd, J = 2.6, 1.5 Hz, 1H), 4.75 (q, J = 7.1 Hz, 1H), 4.46 (m, 1H),

4.40 (t, J = 2.7 Hz, 1H), 4.23 - 4.36 (m, 2H), 4.18 (s, 5H), 3.24 (s, 2H), 1.78 (d, J = 7.1 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.1, 172.3, 93.3, 77.6, 77.2, 76.8, 71.3, 71.2, 70.7, 70.2, 70.1, 70.0, 69.9, 68.4, 60.5, 38.0, 37.9, 33.1, 21.2, 14.79, 14.76. IR ν 3095, 1704 cm^{-1}; MS (LSIMS) M^+ = 376.1. HRMS (LSIMS) m/z calculated for $C_{17}H_{20}FeSO_4$ M^+ 376.0427; found 376.0432.

The protected amine was then converted to (*R*)-*N*-acetyl-α-methylphenylalanine ethyl ester (**100**) in the following manner. In a 10 ml round bottom one neck flask under argon was placed a solution consisting of 9.8 mg (0.0287 mmole) of protected amine, 2 ml of ethyl acetate, and 10mg of 10% Pd/c that was placed under an H_2 atmosphere. After 17 hours, the reaction was filtered, rinsed with EtOAc, and concentrated to ~2 ml of solution and to this was added 0.05 ml (0.53 mmole) of acetic anhydride, 0.05 ml of pyridine, and a catalytic amount of DMAP. After 17 hours the reaction was partitioned between 1N HCl (aq) and methylene chloride and the organic layer was washed once more with 1N HCl (aq) and with sat. $NaHCO_3$ (aq) (2 x 30 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by silica gel flash column chromatography (1:1, hex/EtOAc). Yield of the purified (*R*)-*N*-acetyl-α-methylphenylalanine ethyl ester (**100**) was 6.2 mg (87%) of a clear colorless oil. $[\alpha]^{20}_D$ = -52.2° (c = 0.36, chloroform). Analytical data compared to literature values.[12a]

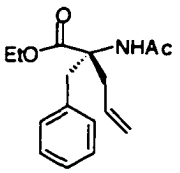
(*R*)-*N*-Acetyl-α-methylpropylglycine ethyl ester (101)



101

(*R*)-*N*-Acetyl-α-methylpropylglycine ethyl ester (**101**) was prepared in the same manner as (*R*)-*N*-acetyl-α-methylphenylalanine ethyl ester (**100**). Starting with 29.4 mg (0.0511 mmole) of CBz protected amine **98**, 12.2 mg (82%) of the CBz protected amine was isolated as a clear colorless oil. This was then deprotected and reacted with acetic anhydride as above to give 7 mg (84%) of (*R*)-*N*-acetyl-α-methylpropylglycine ethyl ester (**101**) as a clear colorless solid. $[\alpha]^{20}_{D}$ = -12.5° (c = 0.78, chloroform). Analytical data compared to literature values.[12a]

(*R*)-*N*-Acetyl-α-allylphenylalanine ethyl ester (103)

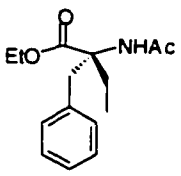


103

In a 10 ml round bottom one neck flask under argon was placed a solution consisting of 34.2 mg (0.0661 mmole) of ester amine **94** dissolved in 3 ml of acetone and to this was added 0.1 ml (1.4 mmoles) of mercaptoacetic acid and 0.08 ml of trifluoroacetic acid. The reaction was covered with aluminum foil and allowed to stir at room temperature for 4 days and was then partitioned between sat. $NaHCO_3$ (aq) and methylene chloride. The organic layer was washed with sat. $NaHCO_3$ (aq) (3 x 30 ml), dried over $MgSO_4$, and concentrated down to ~2 ml. To the solution was then added 0.05 ml (0.53 mmole) of acetic anhydride, 0.05 ml (0.62 mmole) of pyridine, and a catalytic amount of DMAP and after 17 hours the

reaction was partitioned between 1N HCl (aq) and methylene chloride. The organic layer was washed once more with 1N HCl (aq) and with sat. $NaHCO_3$ (aq) (3 x 30 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash column chromatography (6:4, hex/EtOAc) provided 15.5 mg (85%) of (*R*)-*N*-acetyl-α-allylphenylalanine ethyl ester (**103**) as a clear colorless oil. Analytical data compared to literature values.[22]

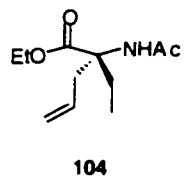
(*R*)-*N*-Acetyl-α-ethylphenylalanine ethyl ester (102)



102

(*R*)-*N*-Acetyl-α-ethylphenylalanine ethyl ester (**102**) was synthesized in the same manner as above. Starting with 22.3 mg (0.0441 mmole) of ester amine **93**, 8.7 mg (75%) of (*R*)-*N*-acetyl-α-ethylphenylalanine ethyl ester (**102**) was yielded as a clear colorless oil. $[\alpha]^{20}_D$ = -69.3° (c = 0.14, chloroform). Analytical data compared to literature values.[12a]

(*R*)-*N*-Acetyl-α-allylethylglycine ethyl ester (104)



104

(*R*)-*N*-Acetyl-α-allylethylglycine ethyl ester (**104**) was synthesized in the same manner as above. Starting with 28 mg (0.0615 mmole) of ester amine **95**, 6.6 mg (50%) of (*R*)-*N*-acetyl-α-allylethylglycine ethyl ester (**104**) was yielded as a clear colorless oil. ^{1}H NMR ($CDCl_3$) δ 6.35 (bs, 1H), 5.59 (m, 1H), 5.05 (m, 2H), 4.24 (q, *J* = 7.3 Hz, 2H), 3.25 (dd, 7.3, 13.9 Hz, 1H), 2.50 (m,

2H), 2.02 (s, 3H), 1.78 (m, 1H), 1.31 (t, J = 7.3 Hz, 3H), 0.76 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.9, 169.3, 132.8, 118.9, 77.6, 77.2, 76.9, 65.5, 62.1, 39.3, 28.2, 24.4, 14.5, 8.6; IR ν 3293, 1735, 1654 cm^{-1}; HRMS (LSIMS) m/z calculated for $C_{11}H_{19}NO_3$ $(M + 1)^+$ 214.1443; found 214.1443.

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APPENDIX I

X-ray Crystal Data for Compound **79**

Table 1. Crystal data and structure refinement for sadlsh38.

Identification code	sadlsh38
Empirical formula	$C_{20}H_{23}FeNO_3$
Formula weight	381.24
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.61710(10) Å alpha = 90° b = 7.5171(2) Å beta = 90° c = 37.4031(4) Å gamma = 90°
Volume, Z	1860.48(6) $Å^3$, 4
Density (calculated)	1.361 Mg/m^3
Absorption coefficient	0.828 mm^{-1}
F(000)	800
Crystal size	0.02 x 0.28 x 0.63 mm
θ range for data collection	2.18 to 23.17°
Limiting indices	$-7 \le h \le 7$, $-7 \le k \le 7$, $-41 \le l \le 11$
Reflections collected	3895
Independent reflections	2198 (R_{int} = 0.0351)
Completeness to θ = 23.17°	91.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2198 / 0 / 228
Goodness-of-fit on F^2	0.901
Final R indices [I>2σ(I)]	R1 = 0.0473, wR2 = 0.1204
R indices (all data)	R1 = 0.0689, wR2 = 0.1388
Absolute structure parameter	0.00(5)
Extinction coefficient	0.0000(10)

Largest diff. peak and hole	**0.252 and -0.223 eÅ^{-3}**

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for sadlsh38. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Fe	2555(2)	8025(1)	1912(1)	50(1)
N	1025(7)	6732(8)	1040(1)	47(1)
C(1)	3570(12)	10118(11)	1609(2)	65(2)
C(2)	2129(13)	10712(9)	1871(2)	65(2)
C(3)	275(12)	9789(9)	1809(2)	55(2)
C(4)	591(10)	8646(9)	1507(2)	46(2)
C(5)	2629(11)	8854(8)	1389(1)	42(1)
C(6)	1910(20)	6650(20)	2360(3)	127(5)
C(7)	3860(30)	7466(15)	2395(3)	144(7)
C(8)	4997(15)	6715(16)	2110(3)	103(4)
C(9)	3830(18)	5547(13)	1935(3)	86(3)
C(10)	1961(18)	5525(13)	2077(3)	90(3)
C(11)	2981(9)	7678(9)	1063(2)	49(2)
C(12)	3414(12)	8772(11)	725(2)	73(2)
C(13)	-370(10)	7244(9)	1291(2)	49(2)
C(14)	870(10)	5091(10)	835(2)	56(2)
C(15)	-996(10)	4947(11)	593(2)	60(2)
C(16)	-2531(13)	3925(10)	820(2)	71(2)
C(17)	-1734(12)	6647(12)	423(2)	85(3)
C(18)	770(11)	3394(10)	1069(2)	73(2)
C(19)	-1858(11)	2924(16)	97(2)	118(4)
C(20)	-1442(13)	2822(13)	1088(3)	91(3)
O(1)	-326(7)	3664(10)	328(1)	99(2)
O(2)	-2066(6)	6577(7)	1321(1)	70(2)
O(3)	-4360(8)	3957(10)	775(2)	96(2)

Table 3. Bond lengths [Å] and angles [°] for sadlsh38.

Fe-C(10)	2.016(9)	Fe-C(2)	2.045(7)
Fe-C(6)	2.015(9)	Fe-C(4)	2.050(6)
Fe-C(8)	2.033(9)	Fe-C(5)	2.054(5)
Fe-C(1)	2.052(7)	Fe-C(7)	2.048(9)
Fe-C(9)	2.046(9)	Fe-C(3)	2.046(7)
N-C(13)	1.372(7)	N-C(14)	1.456(8)
N-C(11)	1.479(8)	C(1)-C(5)	1.402(9)
C(1)-C(2)	1.440(10)	C(2)-C(3)	1.428(10)
C(3)-C(4)	1.435(9)	C(4)-C(5)	1.428(9)
C(4)-C(13)	1.471(9)	C(5)-C(11)	1.523(8)
C(6)-C(10)	1.354(15)	C(6)-C(7)	1.434(19)
C(7)-C(8)	1.422(18)	C(8)-C(9)	1.341(13)
C(9)-C(10)	1.345(14)	C(11)-C(12)	1.535(8)
C(13)-O(2)	1.234(7)	C(14)-C(15)	1.534(9)
C(14)-C(18)	1.548(10)	C(15)-O(1)	1.455(8)
C(15)-C(17)	1.509(10)	C(15)-C(16)	1.530(11)
C(16)-O(3)	1.223(9)	C(16)-C(20)	1.487(11)
C(18)-C(20)	1.527(11)	C(19)-O(1)	1.443(8)

C(10)-Fe-C(2)	156.4(4)	C(10)-Fe-C(6)	39.3(4)
C(2)-Fe-C(6)	122.6(5)	C(10)-Fe-C(4)	108.4(4)
C(2)-Fe-C(4)	68.5(3)	C(6)-Fe-C(4)	126.7(5)
C(10)-Fe-C(8)	65.9(4)	C(2)-Fe-C(8)	128.0(4)
C(6)-Fe-C(8)	67.4(5)	C(4)-Fe-C(8)	152.2(5)
C(10)-Fe-C(5)	125.4(4)	C(2)-Fe-C(5)	68.5(2)
C(6)-Fe-C(5)	162.4(6)	C(4)-Fe-C(5)	40.7(3)
C(8)-Fe-C(5)	118.5(4)	C(10)-Fe-C(1)	161.3(4)
C(2)-Fe-C(1)	41.1(3)	C(6)-Fe-C(1)	157.2(5)
C(4)-Fe-C(1)	67.9(3)	C(8)-Fe-C(1)	108.3(4)
C(5)-Fe-C(1)	39.9(3)	C(10)-Fe-C(7)	67.7(5)
C(2)-Fe-C(7)	109.0(4)	C(6)-Fe-C(7)	41.3(5)
C(4)-Fe-C(7)	165.2(7)	C(8)-Fe-C(7)	40.8(5)
C(5)-Fe-C(7)	153.4(7)	C(1)-Fe-C(7)	120.5(6)
C(10)-Fe-C(9)	38.7(4)	C(2)-Fe-C(9)	163.5(4)
C(6)-Fe-C(9)	65.4(4)	C(4)-Fe-C(9)	120.0(3)
C(8)-Fe-C(9)	38.4(4)	C(5)-Fe-C(9)	107.9(3)
C(1)-Fe-C(9)	125.9(4)	C(7)-Fe-C(9)	66.5(4)
C(10)-Fe-C(3)	121.2(4)	C(2)-Fe-C(3)	40.9(3)
C(6)-Fe-C(3)	109.5(4)	C(4)-Fe-C(3)	41.0(2)
C(8)-Fe-C(3)	165.7(4)	C(5)-Fe-C(3)	69.0(3)
C(1)-Fe-C(3)	68.9(3)	C(7)-Fe-C(3)	127.6(5)
C(9)-Fe-C(3)	154.5(4)	C(13)-N-C(14)	123.4(6)
C(13)-N-C(11)	114.5(5)	C(14)-N-C(11)	119.9(5)
C(5)-C(1)-C(2)	108.4(7)	C(5)-C(1)-Fe	70.1(4)
C(2)-C(1)-Fe	69.2(4)	C(3)-C(2)-C(1)	107.9(6)
C(3)-C(2)-Fe	69.6(4)	C(1)-C(2)-Fe	69.7(4)
C(4)-C(3)-C(2)	107.1(6)	C(4)-C(3)-Fe	69.7(4)
C(2)-C(3)-Fe	69.6(4)	C(5)-C(4)-C(3)	108.4(6)
C(5)-C(4)-C(13)	108.5(5)	C(3)-C(4)-C(13)	142.9(6)
C(5)-C(4)-Fe	69.8(3)	C(3)-C(4)-Fe	69.3(4)
C(13)-C(4)-Fe	121.1(4)	C(4)-C(5)-C(1)	108.2(6)
C(4)-C(5)-C(11)	109.1(5)	C(1)-C(5)-C(11)	142.6(7)
C(4)-C(5)-Fe	69.5(3)	C(1)-C(5)-Fe	70.0(3)
C(11)-C(5)-Fe	126.1(4)	C(10)-C(6)-C(7)	108.5(11)

C(10)-C(6)-Fe	70.4(5)	C(7)-C(6)-Fe	70.6(7)
C(6)-C(7)-C(8)	103.7(8)	C(6)-C(7)-Fe	68.1(5)
C(8)-C(7)-Fe	69.1(5)	C(9)-C(8)-C(7)	108.7(11)
C(9)-C(8)-Fe	71.4(5)	C(7)-C(8)-Fe	70.2(6)
C(10)-C(9)-C(8)	110.2(10)	C(10)-C(9)-Fe	69.5(6)
C(8)-C(9)-Fe	70.3(6)	C(9)-C(10)-C(6)	108.8(10)
C(9)-C(10)-Fe	71.9(6)	C(6)-C(10)-Fe	70.3(6)
N-C(11)-C(5)	101.1(5)	N-C(11)-C(12)	111.9(5)
C(5)-C(11)-C(12)	112.1(5)	O(2)-C(13)-N	124.1(6)
O(2)-C(13)-C(4)	129.4(6)	N-C(13)-C(4)	106.6(6)
N-C(14)-C(15)	115.3(6)	N-C(14)-C(18)	113.8(5)
C(15)-C(14)-C(18)	103.9(6)	O(1)-C(15)-C(17)	111.7(6)
O(1)-C(15)-C(14)	101.8(5)	C(17)-C(15)-C(14)	116.7(6)
O(1)-C(15)-C(16)	104.4(6)	C(17)-C(15)-C(16)	116.4(6)
C(14)-C(15)-C(16)	104.1(6)	O(3)-C(16)-C(20)	125.8(8)
O(3)-C(16)-C(15)	124.7(8)	C(20)-C(16)-C(15)	109.4(7)
C(14)-C(18)-C(20)	107.5(6)	C(16)-C(20)-C(18)	106.0(8)
C(19)-O(1)-C(15)	116.8(5)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for sadlsh38.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
Fe	66(1)	39(1)	45(1)	2(1)	-5(1)	-3(1)
N	37(3)	62(4)	43(3)	-13(3)	3(2)	4(3)
C(1)	70(5)	58(6)	65(4)	22(4)	-9(4)	-12(4)
C(2)	103(6)	33(5)	58(4)	-2(3)	-8(5)	6(5)
C(3)	71(5)	41(5)	54(4)	-8(3)	-1(3)	13(4)
C(4)	51(4)	40(5)	47(3)	0(3)	3(3)	10(3)
C(5)	54(4)	34(3)	38(3)	5(2)	-3(4)	3(4)
C(6)	190(14)	133(12)	57(6)	46(7)	37(7)	48(10)
C(7)	289(19)	58(8)	84(7)	-11(6)	-114(11)	12(10)
C(8)	80(6)	86(9)	143(9)	60(8)	-59(7)	-20(6)
C(9)	115(8)	63(7)	81(6)	13(5)	-21(7)	29(6)
C(10)	109(9)	48(6)	114(8)	23(5)	-13(6)	-12(5)
C(11)	41(4)	53(5)	53(3)	0(3)	-1(3)	2(3)
C(12)	82(5)	84(6)	51(4)	8(4)	15(4)	-3(5)
C(13)	44(4)	54(5)	48(3)	-4(3)	-3(3)	14(4)
C(14)	33(3)	79(6)	56(4)	-24(4)	2(3)	8(4)
C(15)	34(4)	89(6)	56(4)	-25(4)	-2(3)	5(4)
C(16)	44(4)	86(5)	84(4)	-31(4)	-2(5)	2(6)
C(17)	64(5)	115(8)	76(5)	4(5)	-13(4)	20(5)
C(18)	61(5)	51(5)	108(6)	-18(5)	-29(4)	18(4)
C(19)	56(5)	204(12)	94(6)	-82(7)	-9(4)	4(6)
C(20)	79(6)	83(7)	112(7)	-8(6)	-2(5)	12(5)
O(1)	42(3)	157(6)	96(4)	-83(4)	-10(3)	11(3)
O(2)	34(3)	101(4)	75(3)	-29(3)	8(2)	1(3)
O(3)	36(3)	133(6)	118(5)	-45(4)	2(3)	-2(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for sadlsh38.

	x	y	z	U(eq)
H(1A)	4976	10515	1589	77
H(2A)	2377	11590	2060	78
H(3A)	-981	9922	1945	66
H(6A)	747	6852	2517	152
H(7A)	4314	8304	2579	172
H(8A)	6412	6984	2055	124
H(9A)	4258	4850	1727	104
H(10A)	836	4784	1994	108
H(11A)	4082	6836	1108	59
H(12A)	3664	7983	528	109
H(12B)	4579	9507	764	109
H(12C)	2268	9509	672	109
H(14A)	2072	5003	683	67
H(17A)	-656	7177	288	127
H(17B)	-2170	7458	605	127
H(17C)	-2845	6387	266	127
H(18A)	1283	3641	1307	88
H(18B)	1581	2457	963	88
H(19A)	-1248	2093	-66	177
H(19B)	-2490	3863	-37	177
H(19C)	-2856	2323	239	177
H(20A)	-1576	1568	1032	110
H(20B)	-1980	3028	1326	110

Table 6. Hydrogen bonds for sadlsh38 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)