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Selective Carbon-Carbon Bond Formation: Catalysis, Mechanism, and Asymmetric Induction

presented by

Nancy Sue Barta

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Ph. D. degree in Chemistry

John R Stille
Major professor

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SELECTIVE CARBON-CARBON BOND FORMATION: CATALYSIS, MECHANISM, AND ASYMMETRIC INDUCTION

By

Nancy Sue Barta

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ABSTRACT

SELECTIVE CARBON-CARBON BOND FORMATION: CATALYSIS, MECHANISM, AND ASYMMETRIC INDUCTION

By

Nancy Sue Barta

One of the most significant challenges faced by synthetic organic chemists is the selective formation of carbon-carbon bonds. The following work describes the selectivity of carbon-carbon bond formation from three different perspectives. Catalysis and regioselectivity of bond formation is examined through the 3-aza-Cope rearrangement. Ziegler-Natta polymerization models are used as tools for investigation of the activation of transition-metal-carbon bonds toward olefin insertion in the formation of five- and six-membered carbocycles. Lastly, the extent of asymmetric induction in the formation of quaternary carbon centers was determined for the aza-annulation of β-enamino esters with acrylate derivatives.

The [3,3] sigmatropic rearrangement of *N*-alkyl-*N*-allyl enamines was accelerated through the use of a number of Lewis acids. Organoaluminum reagents provided the most efficient rearrangement, and the yields of the rearranged and reduced δ,ε-unsaturated amines ranged from 59 to 99%. The rearrangement of both phenyl and alkyl substituted *N*-alkyl-*N*-allyl enamines occurred exclusively through a [3,3] sigmatropic shift for either protic or Lewis acid catalysis.

Intramolecular olefin insertion in the selective formation of five- and six-membered rings was used as a model for Ziegler-Natta polymerization of α-olefins. Both α- and β-deuterium isotope effects were shown for the first time in a titanium system modeling α-olefin polymerization. Promotion of the intramolecular olefin insertions with methylaluminoxane resulted in inverse alpha kinetic isotope effects (k_H/k_D=0.88 and 0.95 ±0.03) and normal isotope effects for the beta position (k_H/k_D=1.06 ±0.03). These findings were compared with the MgX_2 promoted cyclizations which resulted in alpha effects of k_H/k_D=1.22 and 1.28 ±0.03 and beta effects of k_H/k_D=1.09 and 1.10 ±0.03. The intramolecular olefin insertion reaction was also utilized to show the existence of chain transfer/ligand transposition processes, and to provide evidence for the intramolecular nature of these processes in titanium systems.

Stereoselective carbon-carbon bond formation was effectively illustrated through the aza-annulation of β-keto esters with a variety of acrylate derivatives. Annulated products were obtained in yields ranging from 43 to 87% with 84-96% de, and the effects of solvent, temperature, reaction time and chiral auxiliary were examined.

FOR MOM, DAD, AND JOHN

Thank you for all of your love and support throughout the years. I never could have gotten to this point -or past it- without the three of you in my life. All my love.

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Dunbar-thanks for your encouragement and support, I really appreciate your concern for my scientific development. Dr. Nocera-thanks for your help and your letters of recommendation. Dr. Funkhouser-I could never thank you enough for all you have done for me and for the Stille group as a whole. Best wishes always.

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LIST OF ABBREVIATIONS

Ac	Acetyl ($CH_3C(O)$)
Bn	Benzyl
nBu	n-Butyl
n-BuLi	n-Butyllithium
C_6H_6	Benzene
Cp	Cyclopentadienyl
Cp*	Pentamethyl Cyclopentadienyl
D	Deuteron (^2H)
DIPA	Diisopropylamine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl Acetate
EWG	Electron withdrawing group
GLC	Gas liquid chromatography
LAD	Lithium aluminum deuteride
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
MAO	Methylaluminoxane

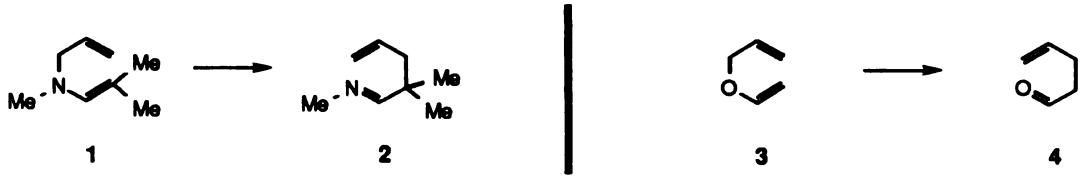
Me	Methyl
MgX_2	Magnesium dihalide (X=Br or Cl)
NBS	N-Bromosuccinimide
Ph	Phenyl
nPr	n-Propyl
iPr	Isopropyl
TEA	Triethylamine
THF	Tetrahydrofuran
pTsOH	para-Toluene sulfonic acid

CHAPTER I

LEWIS ACID ACCELERATION OF THE 3-AZA-COPE REARRANGEMENT

BACKGROUND AND SIGNIFICANCE

The research described herein involving the 3-aza-Cope rearrangement (**1** to **2**, Figure 1) parallels much of the reported findings for the well known Claisen rearrangement (**3** to **4**, Figure 1),[1] the oxygen analog of the 3-aza-Cope rearrangement. The Claisen rearrangement is an extremely useful reaction in organic synthesis because it is a carbon-carbon bond forming process that can selectively generate as many as two new stereocenters as well as establish double bond geometry.



1 2 3 4

Figure 1. [3,3] Sigmatropic Rearrangements

The Claisen rearrangement is a concerted and nonsynchronous process, which proceeds through a well defined six-membered transition state in either a boat- or chair-like conformation.[2] The chair conformation has been reported as the preferred transition state by Schmid and coworkers.[2] As illustrated in Figure 2, the stereochemical outcome of the rearrangement depends upon several factors. The first factor is the geometry of the olefins of both the allyl and the vinyl substituents, and the second major factor is the transition

state conformation: boat *vs.* chair. In addition, the C-4 stereochemistry can influence the outcome of this sigmatropic rearrangement. The thermal Claisen rearrangement is known to proceed predominantly through a chair-like transition state in which a substituent in the allylic position occupies a pseudo-equatorial orientation (**8**, Figure 2).[1b,g-i] As a result of the equatorial orientation of the allylic substituent, the resultant double bond predominantly has the *E* configuration. The concerted nature of this reaction and the rigidity of the six-membered chair transition state work together to define the orientation of the two new stereogenic centers (**9**) based on the olefin geometry of the rearrangement precursor. Failure to control double bond geometry in the allyl vinyl ether substrate for the Claisen rearrangement results in incomplete selectivity of the vicinal stereocenters in the rearrangement product.

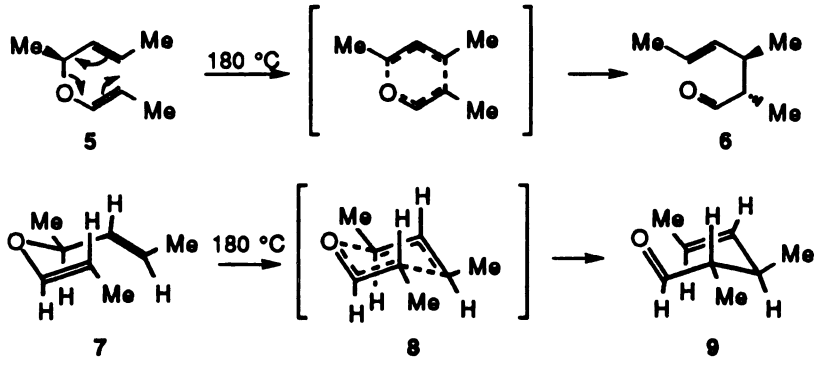


Figure 2. Transition States For the Thermal Claisen Rearrangement

Simple comparisons of the bond energies involved in the Claisen and the 3-aza-Cope rearrangements are shown in Schemes I and II. The Claisen rearrangement (**3**→**4**, Scheme I) has ΔE=-24 kcal/mol, with the formation of the carbon-oxygen double bond being the strongest driving force. Similarly, the energy difference in the 3-aza-Cope rearrangement (**10**→**11**, Scheme I) is ΔE=-21 kcal/mol. The overall difference between the two rearrangement processes is 3 kcal/mol. This energy difference arises from the

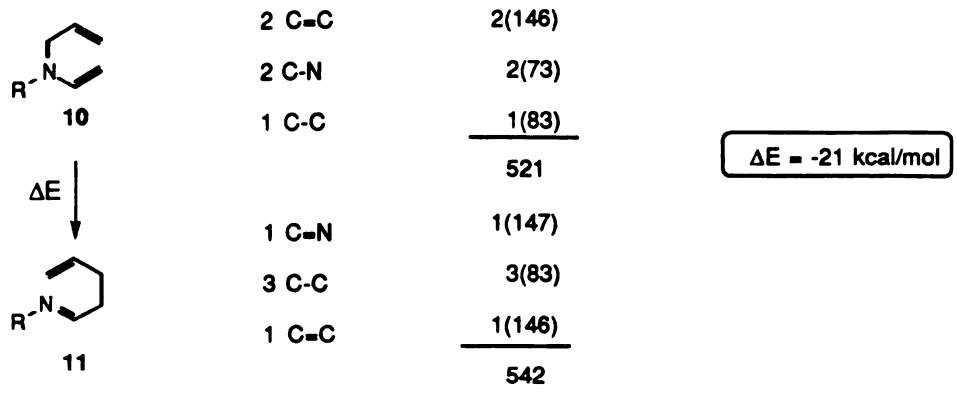
more favorable formation of a carbon-oxygen double bond in the Claisen rearrangement relative to formation of the carbon-nitrogen double bond in the 3-aza-Cope rearrangement. Therefore, the thermal [3,3] Claisen rearrangement occurs at lower temperatures than the 3-aza-Cope rearrangement as has been previously reported.[1,3] Accordingly, thermal 3-aza-Cope rearrangements have attenuated synthetic utility due to the high temperatures required for complete conversion of starting material to product. Many important functional groups present in natural products are too sensitive to withstand the reaction conditions required for the thermal 3-aza-Cope rearrangement.[3] Therefore, this rearrangement is restricted to early incorporation in synthetic pathways, prior to introduction of sensitive functional groups. In addition to the potentially destructive high temperatures required for rearrangement, isolation of the resulting imine can be difficult, so the product is typically hydrolyzed to the corresponding aldehyde or ketone. This hydrolysis provides a δ,ε-unsaturated carbonyl compound, which is the same product that can be obtained from the Claisen rearrangement of the corresponding allyl vinyl ether. Acceleration of the 3-aza-Cope rearrangement and development of a means of isolation that does not require hydrolysis of the rearrangement product are both essential in order for this reaction to become synthetically useful.

Scheme I. Energetics of the Claisen Rearrangement.

BONDS	ENERGY (kcal/mol)
2 C=C	2(146)
2 C-O	2(86)
1 C-C	1(83)
	547
1 C=O	1(176)
3 C-C	3(83)
1 C=C	1(146)
	571

ΔE = -24 kcal/mol

Scheme II. Energetics of the 3-Aza-Cope Rearrangement.



Several features of the 3-aza-Cope rearrangement, however, provide potential for increased synthetic utility in comparison to the related Claisen rearrangement. Olefin geometry is more effectively controlled during enamine formation than during allyl vinyl ether formation.[1g] Also, the presence of the *N*-alkyl group potentially facilitates asymmetric induction through the use of allyl enamines derived from amino acid sources.[4] Since a wide variety of *N*-alkyl-*N*-allyl enamines are accessible,[5] and due to the number of potential applications of δ,ε-unsaturated imines, acceleration of the 3-aza-Cope rearrangement is of synthetic interest. An alternative to isolation of the sensitive imine is reduction of the rearrangement product to yield δ,ε-unsaturated amines which are also synthetically valuable since such amines can be cyclized *via* a number of known pathways to nitrogen containing heterocycles (Figure 3).[6]

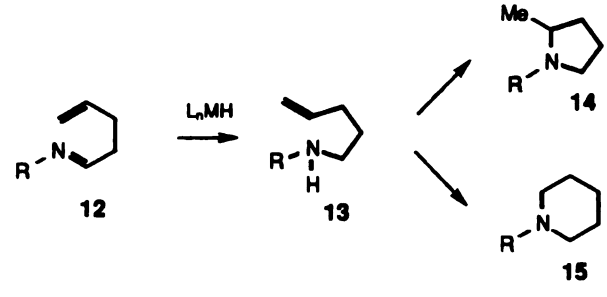
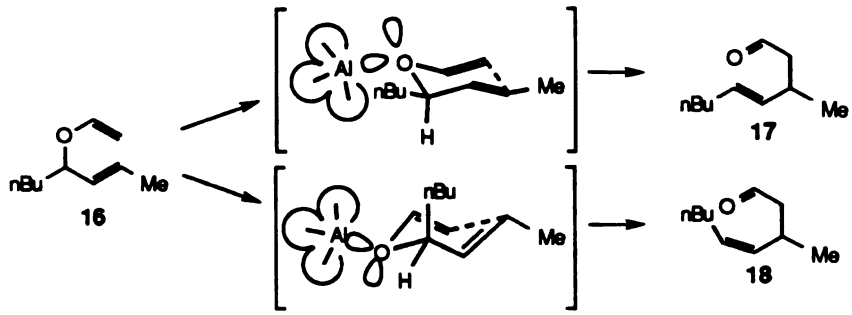


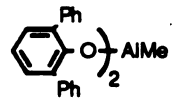
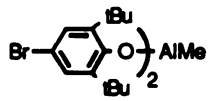
Figure 3. Reduction and Heterocycle Formation.

Acceleration of the Claisen Rearrangement. There have been a number of reports in which the Claisen rearrangement was accelerated through the use of Lewis acids.[7,1i,j] Lewis acids such as $TiCl_4$, $Et_2O{:}BF_3$, $SnCl_4$, and $ZnBr_2$ were not effective for acceleration of the [3,3] sigmatropic shift. To date, the only Lewis acid complexes that have shown promise for acceleration of the Claisen rearrangement have been organoaluminum complexes.[8] Takai, *et al.* have reported that Et_2AlSPh and Et_2AlCl/PPh_3 give δ,ε-unsaturated aldehydes from allyl vinyl ethers at room temperature.[8] However, this acceleration process was not catalytic, as 2.2-2.5 equivalents of aluminum were required to effect rearrangement. Both *i*-Bu_3Al and *i*-Bu_2AlH drive rearrangement, but *in situ* reduction of the resulting carbonyl functionality could not be avoided.[8] $AlMe_3$ was also an effective rearrangement promoter, but addition of a methyl group to the carbonyl carbon always followed rearrangement.[7a,8a]

Recently, Yamamoto reported the rearrangement of allyl vinyl ethers (**16**→**17**+**18**, Scheme III) at temperatures as low as -78 °C using a number of bulky aryloxy aluminum reagents.[9] In addition to remarkable acceleration of the Claisen rearrangement, Yamamoto's work has generated great interest due to the different olefin geometry selectivity available based on the steric demands of the aluminum complex (Scheme III). For bis-(2,6-diphenylphenoxy) methyl aluminum (Reagent **A**), rearrangement resulted in the same product mixture as the thermal rearrangement. However, variation in the steric constraints and the electronic contribution of the aluminum reagent, through the use of Reagent **B** (bis-(2,6-di-t-butyl-4-bromo)phenoxy) methyl aluminum) instead of Reagent **A**, changed the conformation of the chair transition state. In order to accommodate the more sterically demanding Lewis acid, the allylic *n*-butyl group was forced into a pseudo-axial position rather than the normal equatorial position.[2] This conformation change resulted in the preferential formation of **18**.[9]

Scheme III. Acceleration of the Claisen Rearrangement *via* Organoaluminum Complexes



	REAGENT	TEMPERATURE	RATIO (17:18)
	None	250 °C	92:8
A		-20 °C (15-30 min)	99:1
B		-78 °C (15 min)	16:84

Yamamoto's evidence for variable transition states in the Lewis acid promoted Claisen rearrangement[9] prompted further investigation into the mechanism of carbon-carbon bond formation in the analogous 3-aza-Cope rearrangement. There are two mechanistic extremes possible for this six-atom rearrangement (Figure 4). The first possible path is an ionic transition state in which bond breakage precedes bond formation. An ion pair transition state of this nature can potentially give rise to both [1,3] and [3,3] rearrangement products. A second mechanistic extreme is described as a concerted transition state in which bond breakage and bond formation occur simultaneously. The concerted transition state only allows for the formation of [3,3] rearrangement products.

As seen for the Claisen rearrangement, various means of reaction acceleration favor different mechanistic pathways.[9] Therefore, it is necessary to define the limits of [1,3] *vs.* [3,3] regioselectivity for the Lewis acid promoted 3-aza-Cope rearrangement.

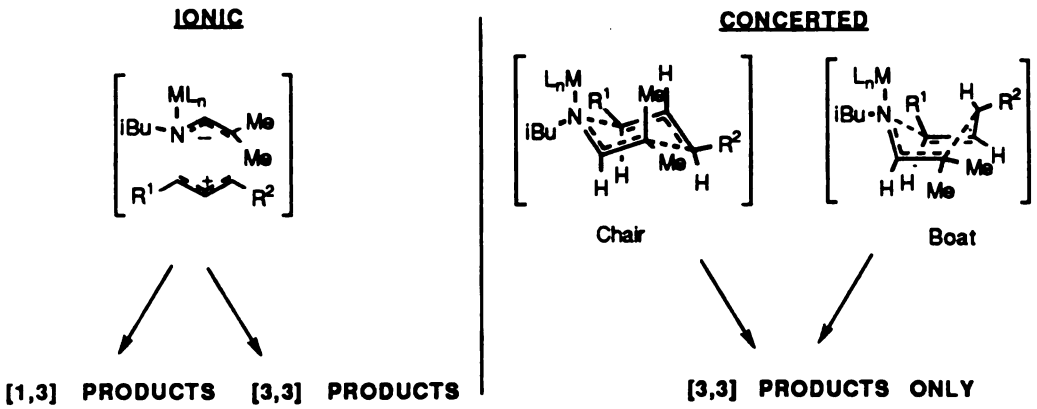
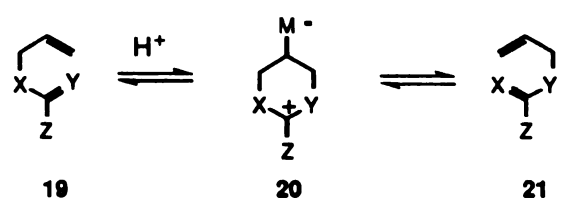


Figure 4. Possible Aza-Cope Transition States.

Both [1,3][10] and [3,3][11] rearrangements of allyl vinyl ethers are possible through palladium catalysis. As shown by Bosnich, in the case of the [1,3] rearrangement, the reaction is reported to proceed through a π-allyl palladium intermediate following oxidative addition to the Pd(0) species.[12] The [3,3] rearrangement is presumed to proceed through a cyclic zwitterionic intermediate for Pd(II) catalysis (**48**, Scheme IV).[12]

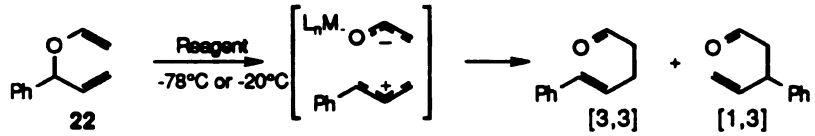
Scheme IV. Pd(0) Catalyzed [3,3] Rearrangement.

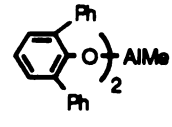
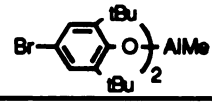


Murahashi has shown that palladium (0) complexes, in the presence of protic acid cocatalysts, are effective in transforming enamines to imines; a process which on the surface is similar to the 3-aza-Cope rearrangement.[13] However, the palladium catalyzed rearrangement proceeded through a (π-allyl)palladium complex that resulted from oxidative addition of palladium to the protonated enamine.[13] Both [1,3] and [3,3] rearrangement products were obtained during this process, therefore, the palladium catalyzed reaction is not a sigmatropic process, but rather proceeds through an ionic intermediate.

Interestingly, Yamamoto also observed the formation of [1,3] rearrangement products using the complexes **A** and **B** when the allyl vinyl ether had a phenyl substituent in the allylic position (**22**, Scheme V).[9] The presence of both [1,3] and [3,3] rearrangement products implied the intervention of an ionic intermediate rather than a concerted chair-like transition state.[9]

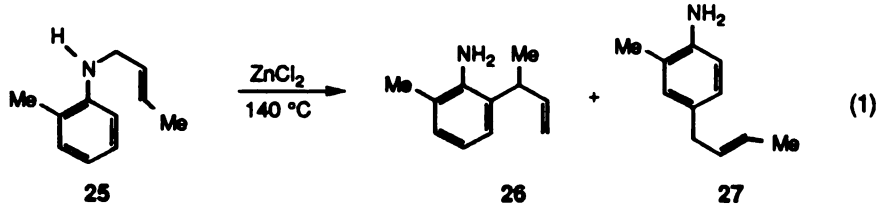
Scheme V. Regioselectivity of the Claisen Rearrangement.



REAGENT	[3,3]	[1,3]
A 	45%	13%
B 	31%	49%

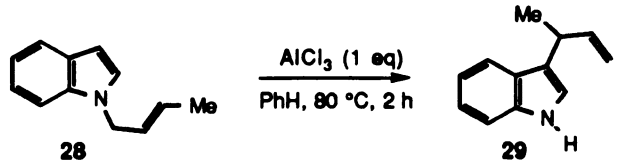
Acceleration of the Aromatic 3-Aza-Cope Rearrangement. Investigations into acceleration of the 3-aza-Cope rearrangement has lagged considerably behind those pertaining to the Claisen rearrangement. The majority of reported studies describe acceleration of the aromatic 3-aza-Cope rearrangement. Jolidon and Hansen have shown that the thermal rearrangements of aromatic enamines were accomplished at temperatures of 200-350 °C, and that these carbon-carbon bond forming processes were, in fact, [3,3] sigmatropic shifts that exhibited a preference for a chair-like transition state.[14] Attempts to decrease the required temperature for the 3-aza-Cope rearrangement included the use of both protic and Lewis acids.[14] Acceleration of this rearrangement has been accomplished at temperatures as low as 50-70 °C for α,α-dimethyl substituted allyl enamines with the aid of protic acids such as H_2SO_4, H_3PO_4, CF_3CO_2H and HCl.[1i] For monosubstituted systems, the required temperatures remained above 100 °C.[14]

Both $ZnCl_2$ and $Et_2O{:}BF_3$ were effective in promoting the aromatic 3-aza-Cope rearrangement.[15] For the rearrangement of *N*-allylaniline, 0.7 equivalents of $ZnCl_2$ in refluxing xylene gave a 42% yield of *o*-allylaniline.[10] $Et_2O{:}BF_3$ appeared to be more efficient in promoting the rearrangement of the same substrate, as a 73% yield of *o*-allylaniline was obtained.[15] The [3,3] nature of this rearrangement was clearly seen from the lack of inversion of a substituted allyl group with $ZnCl_2$ as the catalyst (Equation 1).[15] Enamine **25** rearranged to give a mixture of amines **26** and **27** (78:12 ratio), and the noninverted crotyl group of amine **27** resulted from two consecutive [3,3] rearrangements.[16]



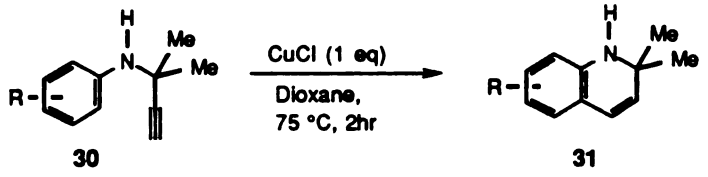
25 **26** **27** (1)

Other Lewis acids examined for acceleration of the aromatic 3-aza-Cope rearrangement include $AlCl_3$, $TiCl_4$, $SbCl_5$, and CuCl.[17] $AlCl_3$, $TiCl_4$, $SbCl_5$ and $ZnCl_2$ were used for promoting rearrangement in indole systems (Equation 2).[17] $AlCl_3$ was the only remotely efficient catalyst in these systems giving a 43% isolated yield of **29** from **28**.



(2)

Copper chloride has shown marginal promise for catalysis of the acetylenic 3-aza-Cope rearrangement (**30**→**31**, Equation 3), giving yields of 25-66% depending on the substitution pattern of the aromatic ring.[18]



(3)

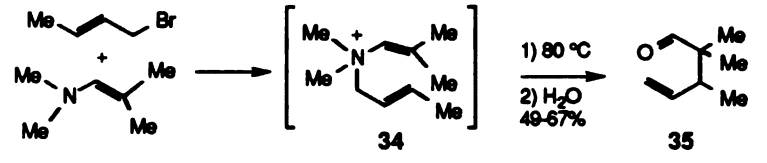
Work from these labs has recently provided a systematic study of the Lewis acid acceleration of *N*-alkyl-*N*-allylanilines.[19] This investigation revealed that rearrangement of such aromatic systems was possible at temperatures between 111 and 140 °C. $AlCl_3$, $ZnCl_2$, and $Et_2O{:}BF_3$ (1.2 equiv. each) were shown to be the Lewis acids of choice to provide rearrangement within 48 hours.[19]

Acceleration of the Aliphatic 3-Aza-Cope Rearrangement. Very few attempts have been reported for acceleration of the aliphatic 3-aza-Cope rearrangement. Initially, variation of the C(2) substituent (Y) was examined as a means of rearrangement

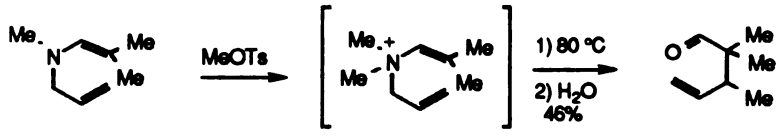
acceleration (Equation 4).[20,21] By placing an electron donating alkoxy substituent at this position, the rearrangement was accomplished at 190 °C.[21] The use of a dialkylamino substituent gave rearrangement at 200 °C,[22] but the rearrangement of *N*-allyl amide enolates was successful at 135 °C.[23]

32 33 (4)

Another approach to rearrangement acceleration was to decrease the electron density on nitrogen through the formation of quaternary nitrogen centers. Brannock has shown that the 3-aza-Cope rearrangement was promoted at temperatures as low as 80 °C by first allylating an *N,N*-dimethylenamine with allyl bromide (**34**, Equation 5).[24] The rearrangement also proceeded at 80 °C following methylation of an allyl enamine (**37**) with methyl tosylate (Equation 6).[24] Although these methods are effective, symmetrical allyl groups must be used due to the competitive nature of C versus N allylation. In addition, the resultant imines were not isolated, but rather hydrolyzed to the corresponding δ,ε-unsaturated carbonyl compounds.[24]



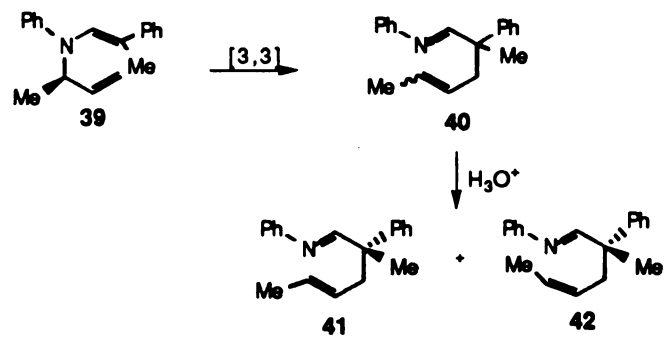
34 35 (5)



36 37 38 (6)

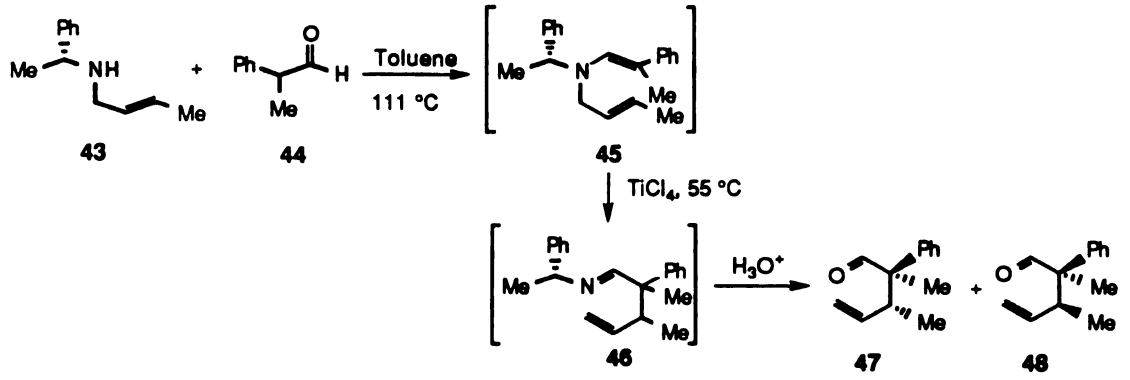
Prior to this investigation, Lewis acid catalysis of the aliphatic 3-aza-Cope rearrangement had only been reported on two occasions.[25,26] In 1978, Hill reported that $TiCl_4$ could be used to catalyze enamine formation, and these enamines (if allylic) rearranged to imines in refluxing benzene, and even to a significant extent at room temperature.[25] Hill was able to show that the $TiCl_4$ catalyzed rearrangement also exhibited chair-like character in the transition state and gave selectivity comparable to that obtained for the thermal process.[3] For example, rearrangement of enamine **39** gave the same ratio of **41**:**42** (90:10) for both thermal and catalyzed rearrangement, and the asymmetric induction was also the same (67%) (Scheme VI).[25]

Scheme VI. Selectivity of the 3-Aza-Cope Rearrangement.



As recently as 1989, Bailey reported the use of $TiCl_4$ for the preparation of aldehydes **47** and **48** having excesses of 90% and 98% respectively (Scheme VII).[26] Chiral amine **43** was condensed with 2-phenylpropionaldehyde (**44**) in refluxing toluene to give enamine **45**, which was not isolated. *In situ* treatment of **45** with $TiCl_4$ at 55 °C, followed by hydrolysis gave aldehydes **47** and **48**. In contrast to the remarkable selectivities, the overall yields were quite low, (16-56%). Reaction times and catalyst concentrations were not reported.[26]

Scheme VII. Preparation of 47 and 48 *Via* the 3-Aza-Cope Rearrangement.



The myriad of readily available Lewis acids lends a great deal of flexibility to the development of the 3-aza-Cope rearrangement as a synthetic tool. The undertaking of this study was anticipated to provide some of the missing information, and increase the synthetic utility of this selective carbon-carbon bond forming process.

EXPERIMENTAL GOALS

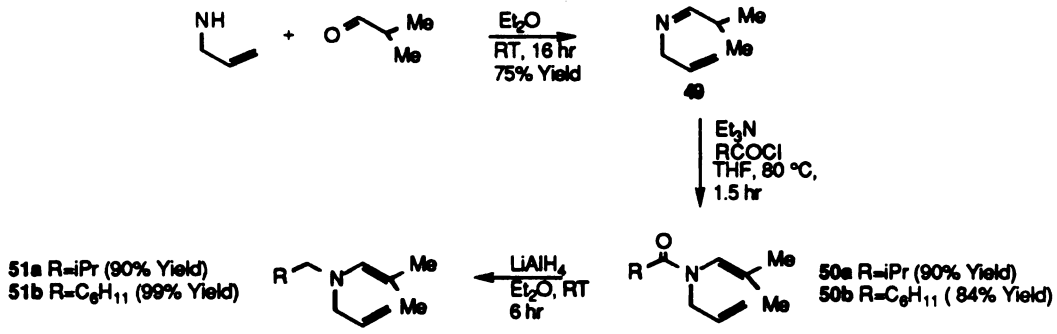
The goals of this work were to systematically define the range of Lewis acids that can be used to efficiently accelerate the sigmatropic rearrangement of *N*-alkyl-*N*-allyl enamines.[27] The benefits of Lewis acid promotion with respect to decreased reaction time, reduced reaction temperature and ease of product isolation were explored. In addition, the regioselectivity of the aza-Cope rearrangement under Lewis acid promotion conditions was investigated.

EXPERIMENTAL DESIGN

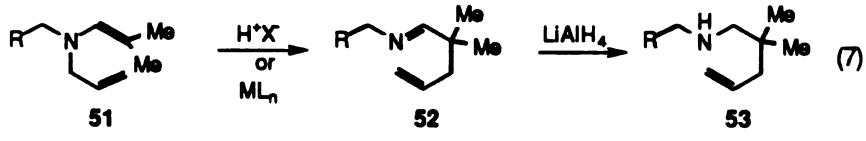
Optimization of Lewis acid promoted rearrangement conditions began with the preparation of enamine **51** from allyl amine and isobutyraldehyde (Scheme VIII). Imine

49 was isolated in 75% yield, and acylation with the appropriate acid chloride gave enamides **50a** and **50b** in good yield. The enamides were very stable and easily purified by column chromatography. Therefore, the substrates were stored as the enamides and reduced just prior to use to give enamines **51a** and **51b** in high yields.

Scheme VIII. Preparation of Rearrangement Substrates.



Due to comparative costs and availability of the required acid chlorides, initial optimization of rearrangement conditions, as monitored by GC, were performed with enamine **51a**. For isolated yields, however, an increase in molecular weight was desirable, so enamine **51b** was used. The sigmatropic rearrangement and reduction process is shown in Equation 7. Since this method does not require hydrolysis of the imine, isolated yields are reported for the rearranged and reduced δ,ε-unsaturated amine **53b**. The limiting parameters set for this rearrangement study were a maximum reaction time of 24 hours and maximum temperature of 111 °C (refluxing toluene).



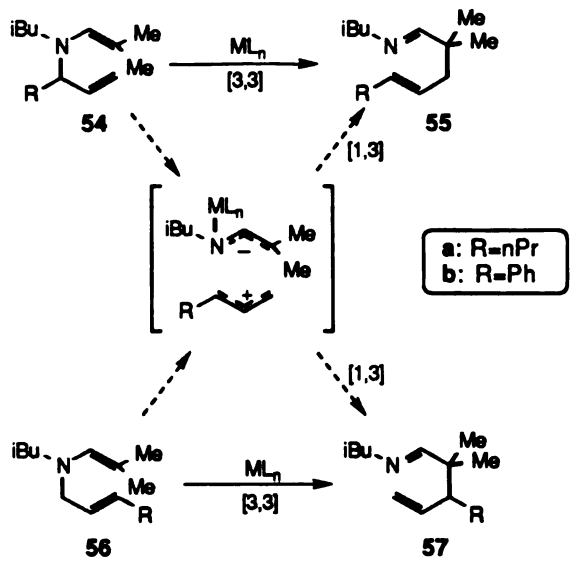
(7)

In order to elucidate the mechanistic pathway, experiments were designed in which the rearrangement of unsymmetrically substituted allyl enamines was examined. This strategy is illustrated in Scheme IX.

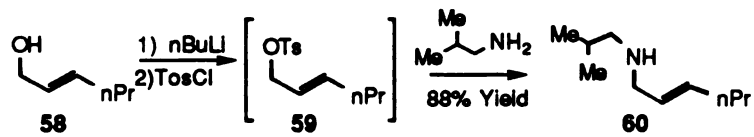
The formation of a single product from each reaction would be expected (**54**→**55**, **56**→**57**) if the reaction proceeded exclusively *via* a concerted [3,3] pathway. If, however, the pathway was ionic in nature, both the [1,3] and [3,3] rearrangement products would be observed (**54**→**55+57**, **56**→**55+57**) for each reaction. Two classes of substrates were examined (**54** and **56**), so that variation in charge stabilization ability could also be used to probe the propensity for the formation of ionic intermediates.

Yamamoto's studies discussed previously showed intervention of an ionic intermediate for substrates with an allylic phenyl substituent.[9] This allylic phenyl substituent could, potentially, provide sufficient charge stabilization for the formation of a cationic fragment which would allow formation of the [1,3] rearrangement product. A terminal phenyl substituent on the allyl fragment would not be expected to provide such effective stabilization during the bond breaking process. An alkyl substituent in either position would also be less effective than the allylic phenyl substituent for charge stabilization. For these reasons, the first class of substrates was substituted with an alkyl group (**54a**, R=nPr; **56b**, R=nPr) and the second was substituted with a phenyl group (**54b**, R=Ph; **56b** , R=Ph). Both phenyl substrates (**69** and **73**) as well as alkyl substrate **61** were originally prepared by Ms. Meg Landis, and the details are given in the Experimental Section for completeness.[28] Amine **60** was prepared from *trans*-2-cyclohexen-1-ol (**58**) *via* the tosylate and subsequent reaction with isobutyl amine as shown in Scheme X.

Scheme IX. Regioselectivity Study Strategy.



Scheme X. Preparation of Secondary Amine 56.



RESULTS AND DISCUSSION

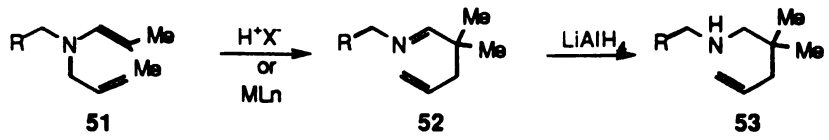
The results for protic acid (HCl) and several non-aluminum metal halide promoted rearrangements are given in Table I.[29] Although the rearrangement of **51a** was complete within 6 hours at 111 °C using only 0.3 equivalents of HCl, the isolated yield was maximized at 85% by using 0.5 equivalents. Lower temperatures with 0.5 equivalents did not increase the yield even with increased reaction times. As $TiCl_4$ has been reported to be effective for similar transformations,[25] its use was examined under a variety of conditions. Using more than 0.1 to 0.2 equivalents was not beneficial, perhaps due to increased substrate oligomerization, however, a respectable isolated yield (73%) could be obtained

via $TiCl_4$ catalysis with 0.1 equivalents. $TiCl_4$, therefore, was more effective for promotion of the aliphatic 3-aza-Cope rearrangement than it was for promotion of the Claisen rearrangement.[7,1i,j] An attempt to modify the Lewis acidity of $TiCl_4$ was made by exchanging two chloride ligands with 2,6-diphenylphenoxide ligands. This catalyst gave comparable GC yields, but slightly decreased isolated yields due to difficulties in separating the final δ,ε-unsaturated amine from the 2,6-diphenylphenol.

$Et_2O{:}BF_3$ gave good GC results for the rearrangement at 111°C with 0.5 equivalents of the Lewis acid, however, the isolated yields did not reflect this level of efficiency. The effectiveness of $Et_2O{:}BF_3$ in promotion of the 3-aza-cope rearrangement is in contrast to the results reported for acceleration of the Claisen rearrangement, but parallels the results reported for acceleration of the aromatic 3-aza-Cope rearrangement.[15]

Both $SnCl_4$ and $ZnCl_2$ were also examined, and even at 111 °C for 48 hours, $SnCl_4$ was only able to affect 84% conversion, and gave an extremely low yield (14%). Although $ZnCl_2$ gave complete conversion with 1.0 equivalent at 111 °C within 24 hours, 10-15% of an unidentified side product was formed in each case. Further exposure to the reaction conditions resulted in degradation of the rearrangement product. Despite the fact that $SnCl_4$ and $ZnCl_2$ are good catalysts for the aromatic 3-aza-Cope rearrangement, the results for the accelerations of the aliphatic 3-aza-Cope were not as good.[15,17]

Table I. Catalytic Acceleration of the 3-Aza-Cope Rearrangement.[a]



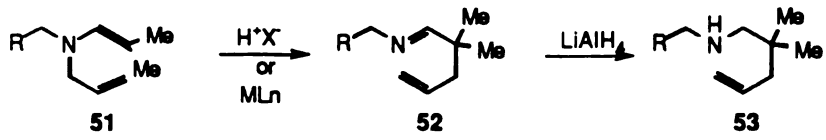
				YIELDS	
CATALYST	EQUIV	TIME	TEMP	GLC[b]	ISOLATED[c]
HCl	0.3	6 hr	111 °C	70%	
	0.5	3 hr	111 °C	82%	85%
	0.5	6 hr	80 °C	64%	
	0.8	6 hr	111 °C	82%	
$TiCl_4$	0.1	24 hr	111 °C	83%	73%[d]
	0.3	24 hr	111 °C	64%	
	0.5	24 hr	111 °C	56%	
	0.5	24 hr	80 °C[e]	8%	
$(ArO)_2TiCl_2$	0.5	24 hr	111 °C	80%	71%
	0.5	48 hr	111 °C	87%	
$Et_2O{:}BF_3$	0.5	24 hr	111 °C	82%	59%
	0.5	24 hr	80 °C[f]	59%	
	1.0	9 hr	111 °C	75%	
	1.5	5 hr	111 °C	70%	
$SnCl_4$	0.1	48 hr[g]	111 °C	14%	
$ZnCl_2$	1.0	12 hr	111 °C	86%	
	1.0	24 hr	111 °C	74%	

[a] All reactions were run 0.2 M in toluene. [b] Rearrangement of **51a** to **52a** (R=iPr) was performed on a 1.0 mmol scale. Yields were determined by capillary gas chromatographic (GLC) analysis of the quenched reaction mixture (10% w/v MeONa/MeOH) using internal standards and correcting for detector response. Values were based on reaction substrate. [c] Isolated yields of **53a** (R=cyclohexyl) after rearrangement of **51b** (5 mmol) and reduction of **52b**. [d] 0.2 equiv of catalyst required on 0.5 mmol scale. [e] 18% conversion. [f] 97% conversion. [g] 84% conversion.

Since aluminum catalysts have been successfully utilized to accelerate the Claisen rearrangement,[8] a series of aluminum complexes were studied for their effectiveness for promotion of the transformation of **51** to **53**. As reported for promotion of the Claisen rearrangement with Et_2AlSPh and Et_2AlCl/PPh_3,[8] all of the aluminum catalysts examined promoted the rearrangement, but only when employed in stoichiometric amounts (Table II). This is clearly seen from the results of $ClAlMe_2$ where 0.2 equivalents and 0.5 equivalents gave a maximum of 19% and 60% conversion of **51a** to **53a** respectively.

As expected, increasing the Lewis acidity of the aluminum complex lowered the temperature required for complete conversion of substrate to product. Both $ClAlMe_2$ and Cl_2AlMe promoted the rearrangement at 50 °C with isolated yields of 91% and 87% respectively. These results represented a decrease of 200 °C in reaction temperature for the 3-aza-Cope rearrangement. In addition, promotion of the 3-aza-Cope rearrangement with $AlMe_3$, $ClAlMe_2$, or Cl_2AlMe did not result in ligand addition as reported for the Claisen rearrangement of allyl vinyl ethers.[7a,8a] $AlCl_3$ was also examined as a potential catalyst, however, yields of the rearranged product were unacceptably low (63% at 80 °C) despite the fact that $AlCl_3$ was one of the only Lewis acids to efficiently promote the 3-aza-Cope rearrangement in indole systems.[19] Lastly, bis-(2,6-diphenylphenoxy) methyl aluminum was employed to affect the rearrangement. The aryloxy aluminum reagent was quite effective for promotion of the 3-aza-Cope rearrangement which parallels the Claisen rearrangement results reported by Yamamoto.[9] Yields for the 3-aza-Cope rearrangement of *N*-alkyl-*N*-allyl enamines were optimum with the aryloxy aluminum catalyst after 24 hours at 40 °C (87% GC, 80% isolated).

Table II. Studies of [3,3] Rearrangement Promoted by Aluminum Reagents.[a]



51 52 53

				YIELD	
CATALYST	EQUIV	TIME	TEMP	GLC[b]	ISOLATED[c]
$AlMe_3$	0.5	12 hr	111 °C	100%	
	1.0	12 hr	111 °C	100%	99%
	1.5	6 hr	111 °C	100%	
	1.5	24 hr	80 °C	100%	
$ClAlMe_2$	0.2	24 hr	111 °C	50%[d]	
	0.5	24 hr	80 °C	71%[e]	
	1.0	24 hr	25 °C	54%	
	1.0	24 hr	40 °C	67 %	
	1.0	24 hr	50 °C	88%	91%
	1.0	9 hr	60 °C	83%	
	1.0	5 hr	80 °C	96%	96%
Cl_2AlMe	1.0	24 hr	50 °C	79%	87%
	1.0	12 hr	80 °C	91%	84%
$(ArO)_2AlMe$	1.0	24 hr	40 °C	87%	80%
	1.0	12 hr	60 °C	84%	
Cl_3Al	1.0	24 hr	50 °C	36%	
	1.0	24 hr	80 °C	63%	

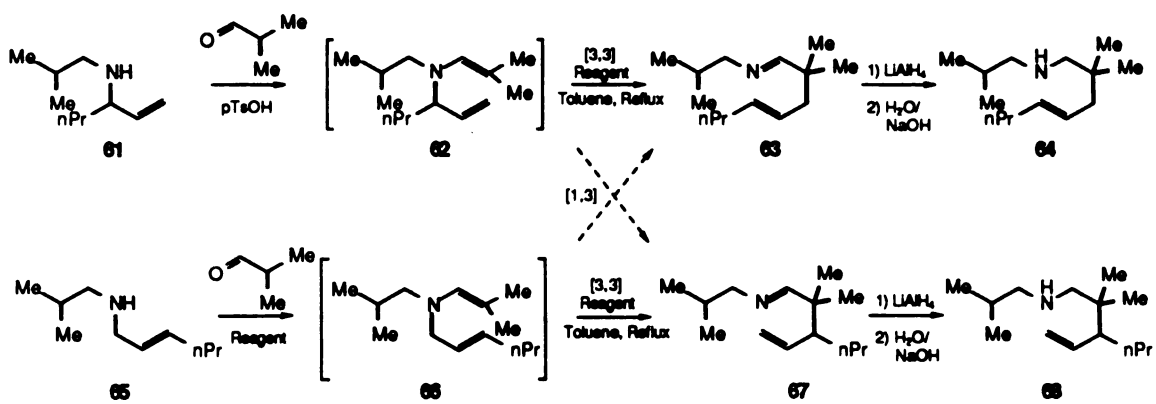
[a] All reactions were run 0.2 M in toluene. [b] Rearrangement of **51a** to **52a** (R=iPr) was performed on a 1.0 mmol scale. Yields were determined by capillary gas chromatographic (GLC) analysis of the quenched reaction mixture (10% w/v MeONa/MeOH) using internal standards and correcting for detector response. Values were based on reaction substrate. [c] Isolated yields of **53b** (R=cyclohexyl) after rearrangement of **51b** (5 mmol) and reduction of **52b**. [d] 19% conversion to product. [e] 60% conversion.

Table III illustrates the condensation, rearrangement and reduction process for the alkyl substituted enamines **62** and **66**, and summarizes the findings of the regioselectivity study.[30] The catalysts examined were a protic acid (HCl, 0.5 equiv.), the metal halide $TiCl_4$ (0.2 equiv.), and two organoaluminum complexes $AlMe_3$ and bis(2,6-diphenylphenoxy)methyl aluminum (1.0 equiv. each), all of which have previously been shown to efficiently promote the 3-aza-Cope rearrangement.[23] For each reagent, it is clear that the rearrangement was a [3,3] sigmatropic process, as the products of [1,3] rearrangement were not observed. For amine **61**, condensation with isobutyraldehyde was easily accomplished with *p*-toluenesulfonic acid in refluxing benzene. The reaction was driven to completion by azeotropic removal of the water with a modified Dean-Stark trap designed in these labs.[31] Enamine **62** was not isolated, rather, the benzene was simply removed by rotary evaporation, replaced with toluene, and the rearrangement promotion complex was added. When enamine **62** was treated with HCl in refluxing toluene for 6 hours, and then reduced with $LiAlH_4$, **64** was isolated in 69% yield as the only reaction product. Similar treatment using $TiCl_4$ for 24 hours at reflux resulted in a single rearrangement product which was isolated in 79% yield. $AlMe_3$ also gave exclusively [3,3] rearrangement, and **64** was isolated in 80% yield. Contrary to the findings of Yamamoto regarding the use of bis(2,6-diphenylphenoxy)methyl aluminum for the rearrangement of allyl vinyl ethers, **64** was isolated in 61% yield without evidence for formation of **68**.[8] In all cases, only the E alkene isomer of the final amine was observed, as shown by the presence of the characteristic E alkene absorption at 970 cm^{-1}, and the absence of the Z alkene absorption in the region of 690 cm^{-1}.[32]

Amine **65** could not be easily condensed with isobutyraldehyde in the presence of *p*-toluenesulfonic acid. As a result, a "one-pot" procedure for the condensation, rearrangement and reduction was developed for the formation of imine **67** with HCl and $TiCl_4$. Enamine **66** was isolated for rearrangement with $AlMe_3$. It is important to note that *p*-toluenesulfonic acid would not promote rearrangement of **62** or **66** even in refluxing

toluene. For the rearrangement of **65**, again only [3,3] rearrangement was observed, with isolated yields ranging from 76-87%.

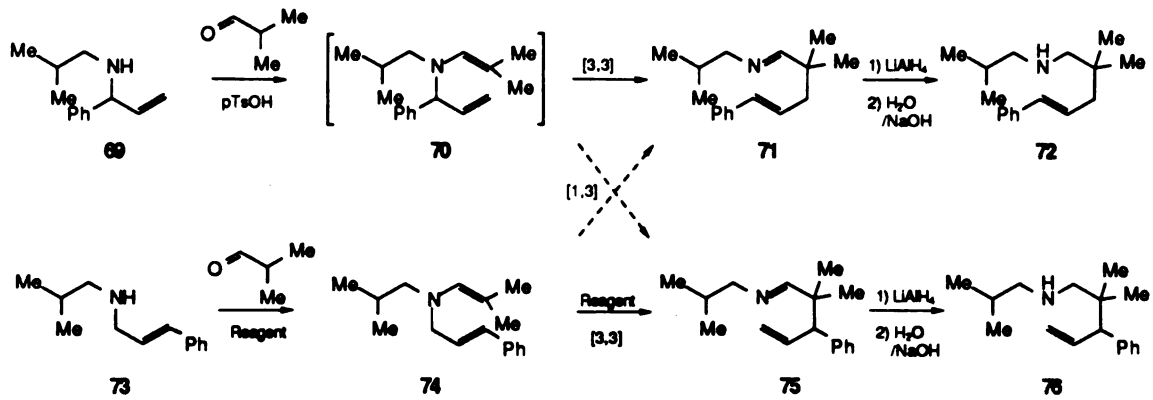
Table III. 3-Aza-Cope Rearrangement and Imine Reduction.



ENAMINE[a]	REAGENT[b]	CONDITIONS Time(h)/ Temp(•C)[c]	PRODUCT RATIO (64:68)[d]	YIELD[e]
62	HCl	6/111	>99:1	69%
	$TiCl_4$	24/111	>99:1	79%
	$AlMe_3$	24/111	>99:1	80%
	$(ArO)_2AlMe$[f]	24/111	>99:1	61%
66	HCl	30/111	1:>99	76%
	$TiCl_4$	30/111	1:>99	78%[g]
	$AlMe_3$	8/111	1:>99	87%
	$(ArO)_2AlMe$[f]	30/111	1:>99	85%

[a]Enamines were generated *in situ* by condensation of the corresponding allyl amine with isobutyraldehyde in either benzene or toluene. [b]Reagent (equiv.): HCl (0.5), pTsOH (0.05), $TiCl_4$ (0.2), $AlMe_3$ (1.1), and $(ArO)_2AlMe$ (1.1). [c]Rearrangements were run 0.2 *M* at reflux in toluene (111 °C) or benzene (80 °C). [d]In each case, the product of [1,3] rearrangement was not detected by ^1H NMR or capillary GC. [e]Overall isolated yield of condensed, rearranged, and reduced products. [f]ArO=2,6-diphenyl phenoxy. [g]Destruction of starting material. [i]Formation of **64** or **68** was not observed.

Table IV. 3-Aza-Cope Rearrangement and Imine Reduction.



ENAMINE[a]	REAGENT[b]	CONDITIONS Time(h)/ Temp(°C)[c]	PRODUCT RATIO (72:76)[d]	YIELD[e]
70	HCl	48/80	>99:1	81%
	pTsOH	48/80	>99:1	80%
	$TiCl_4$	48/80	>99:1	80%
74	HCl	24/111		*h*
	$TiCl_4$	24/111		*i*
	$AlMe_3$	5/111	1:>99	56%
	$(ArO)_2AlMe$[f]	18/111	1:>99	55%

[a]Enamines were generated *in situ* by condensation of the corresponding allyl amine with isobutyraldehyde in either benzene or toluene. [b]Reagent (equiv.): HCl (0.5), pTsOH (0.05), $TiCl_4$ (0.2), $AlMe_3$ (1.1), and $(ArO)_2AlMe$ (1.1). [c]Rearrangements were run 0.2 *M* at reflux in toluene (111 °C) or benzene (80 °C). [d]In each case, the product of [1,3] rearrangement was not detected by ^1H NMR or capillary GC. [e]Overall isolated yield of condensed, rearranged, and reduced products. [f]ArO=2,6-diphenyl phenoxy. [h]Destruction of starting material. [i]Formation of **72** or **76** was not observed.

The results for the rearrangement of the phenyl substituted enamines are shown in Table IV. The presence of a phenyl substituent in the allylic position accelerated rearrangement to the extent that *p*-toluenesulfonic acid was sufficiently strong to promote complete rearrangement in refluxing toluene. Since enamine **70** rearranged under condensation conditions, recourse to the previously described "one-pot" method was necessary. Again, only [3,3] rearrangement products were formed during the rearrangement process with HCl, *p*-toluenesulfonic acid and $TiCl_4$. Because enamine **70** could not be isolated, rearrangement with each of the two aluminum complexes could not be investigated. The rearrangement of enamine **70** was quite facile perhaps due to charge stabilization from the phenyl substituent. While this ability to stabilize positive charge facilitated rearrangement, it was not sufficient to allow intervention of a cationic intermediate. Therefore, [1,3] rearrangement products were not observed.

Amine **73** was easily condensed in the presence of *p*-toluenesulfonic acid, but would not rearrange with this catalyst. The use of HCl or $TiCl_4$ only destroyed the enamine, perhaps due to the stryene-like nature of the vinylic phenyl substituent. Fortunately, the rearrangement could be effected with the aluminum complexes, and only [3,3] rearrangement was observed giving 55% and 56% yields of amine **76** for the two aluminum complexes.

CONCLUSIONS

As indicated by the results of this study, the initial premise that the 3-aza-Cope rearrangement can be efficiently accelerated through the use of both protic and Lewis acids was correct. A variety of reagents could be used for this rearrangement, and in most cases conditions were found for isolation of the desired products in good yields. The utilization of aluminum reagents allowed for a decrease of 200 °C from the temperature required for

uncatalyzed rearrangement. This study also showed that isolation of the rearrangement product after subsequent reduction provided an avenue for the efficient selective preparation of δ,ε-unsaturated amines.

Due to the decreased temperatures now required for complete rearrangement, the fact that the Lewis acid promoted aza-Cope rearrangement was completely selective for the [3,3] pathway, and the efficiency of isolation of the δ,ε-unsaturated amines, the synthetic utility of the 3-aza-Cope rearrangement has now been increased significantly.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out performing standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of either nitrogen or argon. Benzene, toluene, tetrahydrofuran (THF), and Et_2O were distilled from sodium/benzophenone immediately prior to use. Triethylamine was heated at reflux over calcium hydride for a minimum of 12 h and then distilled immediately prior to use. Solutions of HCl (1.0 *M* in Et_2O), $LiAlH_4$ (1.0 *M* in THF), and Cl_2AlMe (1.0 *M* in hexanes) were obtained from Aldrich Chemical Co. Solutions of $AlMe_3$ and $ClAlMe_2$ (1.0 *M* in toluene) were prepared from neat organoaluminum compounds obtained from Aldrich Chemical Co. Cyclohexanecarbonyl chloride, isobutyryl chloride, allyl amine, $TiCl_4$, and $Et_2O{:}BF_3$ were distilled prior to use. Additions were made with gas tight syringes, or via cannula transfer under nitrogen. Unless specified, concentration of solutions after workup was performed on a Büchi rotary evaporator.

Gas chromatographic (GLC) analyses were carried out on a Perkin-Elmer 8500 instrument with a 50 m RSL-200 capillary column (5% methyl phenyl silicone) and an FID detector at a 220 °C injector temperature, and a 300 °C detector temperature. Helium gas pressure was set at 15 psi with a flow rate of 2 mL/min. NMR spectra were obtained on Varian Gemini 300 or VXR-300 spectrometers with $CDCl_3$ as solvent. Data are reported as follows: chemical shift relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet), integration, and coupling. Infrared spectra were recorded on a Nicolet 42 FT-IR instrument.

***N*-Allylisobutylideneamine (49):** Allylamine (3.54 g, 62 mmol) was added to a flask containing 100 mL of Et_2O and 14 g of 4Å molecular sieves. Over the period of 10 min, isobutyraldehyde (4.47 g, 62 mmol) was added dropwise at 25 °C. After being stirred at ambient temperature overnight, the solution was filtered and the remaining solids were washed with two 50 mL portions of Et_2O. The mixture then was distilled under nitrogen at atmospheric pressure to give **49** (5.13 g, 46.0 mmol) in 75% yield (bp 112-114 °C): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.05 (d, 6 H, J = 6.9 Hz), 2.42 (dsept, 1 H, J = 4.9, 6.9 Hz), 3.95 (d, 2 H, J = 5.6 Hz), 5.05 (dd, 1 H, J = 1.8, 10.3 Hz), 5.10 (dd, 1 H, J = 1.8, 17.2 Hz), 5.93 (ddt, 1 H, J = 10.3, 17.2, 5.6 Hz), 7.51 (d, 1 H, J = 4.9 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.3, 34.1, 63.2, 115.5, 136.1, 170.9; IR (neat) 3083, 3013, 2967, 2932, 2874, 2824, 2674, 1466, 1456, 1437, 1366, 1103, 1019, 995, 916 cm^{-1}.

Synthesis of 50a by Acylation of 49: To 50 mL of dry THF were added **6** (3.34 g, 30 mmol) and NEt_3 (3.54 g, 33 mmol). The solution was cooled to 0 °C and isobutyryl chloride (3.50 g, 33 mmol) in 20 mL of THF was added dropwise over a 30 min period. After being heated at reflux for 1.5 h, the solution was cooled to ambient temperature and filtered through a pad of silica on a glass frit, and the solids were washed with two portions of Et_2O. The solvents were removed under reduced pressure, and the crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - 50:50 Et_2O:petroleum ether). The solvents were evaporated and the enamide was isolated via Kugelrohr distillation under vacuum to give **50a** (4.88 g, 27 mmol) in 90% yield (bp 55-65 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.02 (d, 6 H, J = 6.8 Hz), 1.57 (s, 3 H), 1.70 (s, 3 H), 2.65 (sept, 1 H, J = 6.8 Hz), 3.89 (d, 2 H, J = 6.2 Hz), 5.04 (dd, 1 H, J = 1.6, 11.3 Hz), 5.06 (dd, 1 H, J = 1.6, 16.0 Hz), 5.74 (ddt, 1 H, J = 11.3, 16.0, 6.2 Hz), 5.85 (s, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.3, 18.8, 21.5, 30.9, 50.0,

116.9, 123.5, 133.4, 135.9, 177.7; IR (neat) 3083, 2975, 2936, 2876, 1653, 1472, 1404, 1242, 1208, 1092, 993, 920 cm^{-1}. Anal. Calcd for $C_7H_{15}N$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.43; H, 13.69; N, 12.21.

Reduction of 50a to 51a: To a flask containing $LiAlH_4$, (2.51 g, 66 mmol) was added 300 mL of Et_2O, and the suspension was cooled to 0 °C. Amide **50a** (10.87 g, 60 mmol) in 30 mL of Et_2O was added dropwise over a 45 min period. The solution was warmed to room temperature and stirred for six hours. After the solution was cooled to 0 °C, the reaction was quenched by addition of 2.5 mL of H_2O, followed by 2.5 mL of 15% aqueous NaOH, and then again by 7.5 mL of H_2O. The solution was stirred for 1.5 h and then dried with K_2CO_3. The solids were removed by filtration, and the solvent was removed under reduced pressure. Enamine **51a** was isolated via Kugelrohr distillation: (bp 54-55 °C, 8 mmHg, 9.84 g, 98% yield). ^1H NMR (300 MHz) ($CDCl_3$) δ 0.83 (d, 6 H, J = 6.6 Hz), 1.58 (d, 3 H, J = 1.3 Hz), 1.58 (tsept, 1 H, J = 7.3, 6.6 Hz), 1.65 (d, 3 H, J = 1.3 Hz), 2.25 (d, 2 H, J = 7.3 Hz), 3.15 (dt, 2 H, J = 1.6, 1.6, 6.2 Hz), 5.02 (ddt, 1 H, J = 2.0, 10.2, 1.6 Hz), 5.08 (ddt, 1 H, J = 2.0, 17.2, 1.6 Hz), 5.22 (qq, 1 H, J = 1.3, 1.3 Hz), 5.81 (ddt, 1 H, J = 10.2, 17.2, 6.2 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.4, 20.4, 22.0, 27.4, 59.6, 63.1, 115.9, 122.8, 135.8, 136.9; IR (neat) 3081, 3009, 2955, 2926, 2870, 2803, 1676, 1644, 1468, 1449, 1377, 1337, 1194, 1117, 1101, 995, 916 cm^{-1}.

General Procedure for Rearrangement of 51a to 52: All flasks used in rearrangement studies were heated under vacuum for 20-30 minutes and then purged with argon for 10 minutes. A solution containing **51a** (0.167 g, 1 mmol), *o*-xylene (0.121 mL, 1 mmol, internal GLC standard) and 5 mL of toluene was cooled to -78 °C. After an initial gas chromatograph was taken, the Lewis acid reagents (see Tables I and II for equiv.) were added at -78°C or the HCl was added at 0°C. For Cl_3Al and $(ArO)_2AlMe$ accelerated

reactions, a solution of **51a** was added to the catalyst in 25 mL of toluene via cannula at -78°C. All aliquots for analysis were removed from the reaction vessel via cannula, quenched in Et_2O with 10% w/v solution of NaOMe in MeOH, and was dried over Na_2SO_4 or K_2CO_3 prior to GLC analysis.

Preparation of 50b by Acylation of 49: Imine **49** (2.44 g, 22 mmol) and NEt3 (3.69 mL, 26.4 mmol) were taken up in 150 mL of THF and cooled to 0°C. Cyclohexanecarbonyl chloride (3.50 g, 24 mmol) in 35 mL of THF was added dropwise over a 2 h period. The reaction was allowed to warm to room temperature during the addition, and then was brought to reflux for 2.5 h. After cooling the solution to ambient temperature, solids were removed by filtration through a pad of silica on a glass frit, and then washed with two portions of Et_2O. The solvents were removed via rotary evaporation, and the remaining oil was purified by column chromatography (silica, 230-400 mesh; eluent: 30:70 Et_2O:petroleum ether) and isolated via Kugelrohr distillation to give **50b**: (75-100°C, <1 mmHg, 3.35 g, 69% yield). ^1H NMR (300 MHz) ($CDCl_3$) δ 1.21 (m, 4 H), 1.43 (m 2 H), 1.61 (m, 4 H), 1.60 (s, 3H), 1.75 (s, 3H), 2.38 (m, 1H), 3.96 (d, 1 H, J= 6.2 Hz), 5.02 (d, 1 H, J=11.5 Hz), 5.04 (d, 1 H, J= 15.8 Hz), 5.72 (ddt, 1 H, J= 11.5, 15.8, 6.2 Hz), 5.82 (s, 1 H). ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.6, 21.8, 25.7, 28.9, 41.5, 50.0, 116.7, 123.3, 133.3, 135.9, 176.0. IR (neat) 3101, 2930, 2855, 1653, 1451, 1427, 1342, 1256, 1206, 1123, 990, 918, 895, 831 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.54; H, 10.28; N, 7.72.

Two-Step Synthesis of 50b from Allylamine: Allylamine (2.20 g, 30.0 mmol) and isobutyraldehyde (1.74 g, 30.0 mmol) were taken up in 85 mL of benzene. A Dean-Stark trap was fitted on the apparatus and the solution was heated to reflux to azeotropically remove the resulting water. After being heated 19-22 h, the water was

removed, 4Å molecular sieves were added to the Dean-Stark trap, and reflux was continued for 2 h. The solution was cooled to ambient temperature and NEt_3 (3.03 g, 30.0 mmol) and cyclohexanecarbonyl chloride (4.40 g, 30.0 mmol) were added, sequentially, and then heated at reflux for 3 h. After benzene was removed under reduced pressure, the crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent: 30:70 Et_2O:petroleum ether). The solvents were evaporated and the enamide was distilled under vacuum to give 4.53 g **50b** (20.5 mmol, 68% yield). Spectroscopic data was identical to that reported for the product obtained by acylation of isolated **49**.

Reduction of 50b to 51b: Enamide **50b** (4.71 g, 21.0 mmol) in 40 mL of Et_2O was added dropwise to a suspension of $LiAlH_4$ (0.89 g, 23.0 mmol) in 300 mL of Et_2O at 0°C over a 1 h period. The reaction mixture was warmed to room temperature and then stirred for 5 h. The $LiAlH_4$ was quenched at 0 °C through slow addition of 0.9 mL of H_2O, 0.9 mL of 15% NaOH, and then 2.7 mL of H_2O. After being stirred for 1 h, the solids were removed by filtration, and the solvents were removed via rotary evaporation to give an oil. The oil was isolated via Kugelrohr distillation to give 4.15 g **51b**: (70-80°C, 5 mmHg, 95% yield). ^1H NMR (300 MHz) ($CDCl_3$) δ 0.83 (m, 2 H), 1.15 (m 4 H), 1.30 (m, 1 H), 1.59 (s, 1H), 1.65 (s, 3H), 1.75 (s, 3H), 2.30 (d, 2 H, J= 7.2 Hz), 3.14 (d, 2 H, J= 6.1 Hz), 5.02 (dd, 1 H, J=10.2, 2.0 Hz), 5.09 (dd, 1 H, J= 17.3, 2.0 Hz), 5.22 (s, 1 H), 5.81 (ddt, 1 H, J= 17.3, 10.2, 6.1). ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.6, 22.3, 26.2, 26.9, 31.6, 37.1, 59.6, 61.9, 115.7, 122.0, 135.7, 136.8. IR (neat) 3091, 2923, 2851, 2797, 1650, 1600, 1449, 1374, 1337, 1283, 1263, 1178, 1123, 993, 9163, 843 cm^{-1}.

Representative Procedure for Charge-Accelerated 3-Aza-Cope Rearrangement and Reductive Workup (51b to 53b): All flasks used in rearrangement studies were heated under vacuum for 20-30 minutes and purged with argon

for 10 minutes. The electrophilic reagents (see Tables I and II for equiv.) were added to a solution containing **51b** (1.04 g, 5.0 mmol) in 25 mL of toluene to give a final concentration of 0.2 *M* of **51b**. Lewis acids were added at -78°C, and HCl was added at 0°C. For Cl_3Al and $(ArO)_2AlMe$ accelerated reactions, a solution of **51b** was added to the catalyst in 25 mL of toluene via cannula at -78°C. The reaction mixture was heated until complete conversion of **51b** to **52b** had occurred (see Tables I and II for temperatures and reaction times). Following rearrangement, the reaction was placed in an ice bath and 5.5 mL of 1.0 M $LiAlH_4$ solution was added. After 3 h, the reduction was quenched at 0 °C through slow addition of 0.2 mL of H_2O, 0.2 mL of 15% NaOH, and then 0.6 mL of H_2O. The solids were removed by filtration through sodium sulfate on a glass frit. Solvents were removed by rotary evaporation and the oil was isolated via Kugelrohr distillation to give **53b**.

53b: (bp 70-80°C, < 1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.89 (s, 6 H), 1.31 (m 4 H), 1.40 (m, 1 H), 1.72 (m, 6H), 1.96 (d, 2H, J= 7.5 Hz), 2.28 (s, 2H), 2.37 (d, 2 H, J= 6.8 Hz), 4.97 (d, 1 H, J=16.6 Hz), 4.98 (d, 1 H, J= 12.2 Hz), 5.78 (ddt, 1 H, J= 16.6, 12.2, 7.5 Hz). ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 25.5, 26.1, 26.8, 31.4, 37.6, 44.7, 57.8, 60.5, 116.6, 135.7. IR (neat) 3350, 3074, 2923, 2853, 2807, 2753, 1639, 1462, 1447, 1364, 1127, 995, 913 cm^{-1}. Anal. Calcd for $C_{14}H_{27}N$: C, 80.31; H, 13.00; N, 6.70. Found: C, 79.00; H, 12.49; N, 6.85.

53a: (bp 50-60 °C, 8 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.85 (s, 6 H), 0.86 (d, 6 H, *J* = 6.6 Hz), 0.87 (bs, 1 H), 1.71 (tsept, 1 H, *J* = 6.9, 6.6 Hz), 1.98 (d, 2 H, *J* = 7.5 Hz), 2.29 (s, 2 H), 2.35 (d, 2 H, *J* = 6.9 Hz), 4.99 (m, 2 H), 5.79 (ddt, 1 H, *J* = 9.2, 17.9, 7.5 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.6, 25.5, 27.9, 34.4, 44.7, 59.1, 60.3, 116.6, 135.7; IR (neat) 3359, 3077, 3005, 2957, 2872, 2811, 1640, 1466, 1385, 1364, 1121, 995, 912 cm^{-1}. Anal. Calcd for $C_{11}H_{23}N$: C, 78.04; H, 13.69; N, 8.27. Found: C, 77.64; H, 13.87; N, 7.68.

3-(*N*-(2-methylprop-1-yl)amino)-1-hexene (61). The appropriate trichloroacetamide (102 mmol)[33] was hydrolyzed in 200 mL of 6 *N* NaOH for 48 h. The organic portion was extracted using 3 x 100 mL of Et_2O, and the solution was carefully concentrated on a rotary evaporator below 0 °C. A flask containing the resulting amine and isobutyraldehyde (7.3 g, 101 mmol) in benzene (0.2 *M*) was equipped with a Dean-Stark trap that contained 4Å molecular sieves. The mixture was heated to reflux until imine formation was complete. Solid $LiAlH_4$ (3.86 g, 102 mmol) was added slowly over 20 min at 0 °C, the solution was stirred for 1 h, and then $AlMe_3$ (25.4 mL, 2.0 *M* in toluene, 50.8 mmol) was added dropwise *via* cannula over a period of 30 min at 0 °C. After 24 h, the solution was quenched at 0 °C by the sequential addition of 4.0 mL of H_2O, 4.0 mL of 15% w/v aq. NaOH, and 12.0 mL of H_2O, and then the mixture was stirred for 4 h. The aluminum salts were removed by filtration, and the combined filtrate and washings were concentrated and distilled (80 °C, 35 mmHg) to give **61** (3.2 g, 20.5 mmol) in 20% overall yield; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* =6.6 Hz, 6 H), 0.87 (t, *J* =6.9 Hz, 3 H), 1.2-1.5 (m, 4 H), 1.65 (nonet, *J* =6.6 Hz, 1 H), 2.26 (dd, *J* =11.5, 6.6 Hz, 1 H), 2.38 (dd, *J* =11.5, 7.1 Hz, 1 H), 2.90 (dt, *J*=5.5, 7.5 Hz, 1 H), 4.98-5.07 (m, 2 H), 5.53 (ddd, *J*=17.6, 9.5, 8.1 Hz, 1 H), N-H not observed; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 19.1, 20.7, 20.8, 28.4, 37.9, 55.4, 61.8, 115.3, 141.9; IR (neat) 3337, 3077, 2959, 2872, 1641, 1117 cm^{-1}; HRMS calcd for $C_{10}H_{21}N$ m/z (MH^+)156.1676, found 156.1762.

3-(*N*-(2-methylprop-1-yl)amino)-3-phenyl-1-propene (69). A flask containing the corresponding amine (7.0 g, 53 mmol)[33] and isobutylaldehyde (3.79 g, 53 mmol) in benzene (0.2 *M*) was equipped with a Dean-Stark trap that contained 4Å molecular sieves. The mixture was heated at reflux for 2 h until imine formation was complete by gas chromatographic analysis. Solid $LiAlH_4$ (2.0 g, 53 mmol) was added at 0

°C, and the mixture was warmed to room temperature and stirred for 10 h. The reaction was quenched at 0 °C by the sequential addition of 2.0 mL of H_2O, 2.0 mL of 15% w/v aq. NaOH, and 6.0 mL of H_2O. After stirring for 4 h, the aluminum salts were removed by filtration, and the combined filtrate and washings were concentrated and distilled to give **69** (8.1 g, 42.8 mmol) in 81% yield (65 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, *J* =6.6 Hz, 6 H), 1.34 (bs, 1 H), 1.65 (nonet, *J* = 6.6 Hz, 1 H), 2.19 (dd, *J* =6.9, 11.4 Hz, 1 H), 2.35 (dd, *J* =6.6, 11.4 Hz, 1 H), 4.14 (d, *J* =7.1 Hz, 1 H), 5.06 (ddd, *J* =0.9, 1.5, 10.1 Hz, 1 H), 5.19 (dt, *J* =17.1, 1.6 Hz, 1 H), 5.85 (ddd, *J*=7.1, 10.1, 17.1 Hz, 1 H), 7.22-7.39 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.67, 20.72, 28.4, 55.6, 66.2, 114.7, 127.0, 127.2, 128.2, 141.4, 143.2; IR (neat) 3310, 3027, 2955, 2870, 1620, 1116 cm^{-1} ; HRMS calcd for $C_{13}H_{19}N$ m/z 189.1513, found 189.1520.

(*E*)-1-(*N*-(2-methylprop-1-yl)amino)hex-2-ene (65). A small amount of 1,10-phenanthraline was added to a solution of 2-hexen-1-ol (4.01 g, 40 mmol) in 250 mL of THF.[22] The solution was cooled to -78 °C, and n-BuLi (28 mL, 1.6 *M* in hexanes) was added until the orange 1,10-phenanthraline endpoint was visible. Tosyl chloride (7.63 g, 40 mmol) was added in a single portion, and the mixture was stirred at -78 °C for 72 hr. The reaction was worked up by diluting with 500 mL cold petroleum ether, and washing with 2 x 100 mL of cold 50% sat. aq. $NaHCO_3$ followed by 1 x 100 mL of sat. aq. $NaHCO_3$. The aqueous layers were combined and extracted with 1 x 70 mL of petroleum ether, and the combined organic fractions were dried over K_2CO_3. After filtration and concentration of the mixture, the tosylate was taken up in 200 mL of Et_2O, dried, filtered, and concentrated in the same manner. The crude tosylate was then added to isobutyl amine (17.5 g, 240 mmol) at 0 °C, and stirred at room temperature for 24 h. Excess isobutyl amine was removed *in vacuo*, and the remaining oil was purified by Kugelrohr distillation (25 mmHg, 80-100 °C) to give **65** (5.47 g, 35.3 mmol) in 88% yield; ^{1}H NMR (300

MHz, $CDCl_3$) δ 0.84 (t, *J*=7.4 Hz, 3 H), 0.85 (d, *J*=6.8 Hz, 6 H), 1.33 (sext, *J*=7.4 Hz, 2 H), 1.68 (nonet, *J*=6.8 Hz, 1 H), 1.94 (m, 2 H), 2.35 (d, *J*=6.8 Hz, 2 H), 3.12 (d, *J*=5.0 Hz, 2 H), 5.40-5.58 (m, 2 H), N-H not observed; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 20.7, 22.4, 28.3, 34.4, 52.0, 57.5, 128.6, 132.3; IR (Neat) 3301, 2959, 2872, 2810, 1670, 1121, 970 cm^{-1}. HRMS calcd for $C_{10}H_{21}N$ m/z 155.1669, found 155.1683.

(*E*)-3-(*N*-(2-methylprop-1-yl)amino)phenylprop-1-ene (73). A mixture of cinnamaldehyde (15 g, 114 mmol) and isobutylamine (8.1 g, 111 mmol) in 380 mL of Et_2O was stirred over K_2CO_3 (≈15 g) for 12 h. The mixture was filtered and the solids were washed with 50 mL of Et_2O. Acetic acid (34 g, 570 mmol) was added to the combined organic fractions and the solution was stirred at room temperature for 30 min. $NaBH_4$ (1.12 g, 29 mmol) was added slowly over 20 min at 0 °C, and the mixture was warmed to room temperature and stirred for 8 h. The reaction was quenched at 0 °C with a mixture of sat. aq. NaOH/solid NaOH, and the organic layer was separated and dried (K_2CO_3). The solution was concentrated and then purified via column chromatography by eluting the column first with a petroleum ether:Et_2O (80:20) to remove nonpolar impurities, and then with Et_2O to give the crude **73**. Short path distillation gave **73** (3.2 g, 16.9 mmol) in 15% yield (bp 90-95 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, *J* =6.7 Hz, 6 H), 1.33 (bs, 1 H), 1.76 (nonet, *J* =6.7 Hz, 1 H), 2.42 (d, *J* =6.7 Hz, 2 H), 3.38 (dd, *J* =6.3, 1.2 Hz, 2 H), 6.31 (dt, *J* =15.9, 6.2 Hz, 1 H), 6.51 (bd, *J*=15.9 Hz, 1 H), 7.16-7.39 (m, 5 H); ^{13}C (75.5 MHz, $CDCl_3$) δ 20.7, 28.4, 52.1, 57.5, 126.2, 127.2, 128.4, 128.7, 131.0, 137.1; IR (neat) 3316, 3026, 2955, 2870, 2810, 1599, 1119, 966 cm^{-1}; HRMS calcd for $C_{13}H_{19}N$ m/z 189.1513, found m/z 189.1510.

Preparation of *N*-(2-methyl-1-propenyl)-*N*-((*E*)-hex-2-en-1-yl)-2-methylpropanamide. The trichloroacetamide (33.7 mmol, 8.20 g)[33] was added to 200 mL of 6 *N* NaOH, and heated at reflux for 15 h. Following hydrolysis, the amine was

separated, and the aqueous layer was washed with 2 x 15 mL portions of benzene. The organic layers were combined with 15 mL additional benzene, isobutyraldehyde (100 mmol, 7.21 g) was added, and the mixture was heated at reflux with azeotropic removal of water using a glass trap containing molecular sieves. After 20 h, Et_3N (36 mmol, 5.03 mL) was added, and the mixture was cooled to 0 °C. Isobutyryl chloride was added *via* syringe over a 10 min period. The reaction was then stirred for 36 h, filtered through a pad of silica, and washed with petroleum ether. The solvents were concentrated, and the crude enamide was purified by column chromatography (1:9 EtOAc:petroleum ether). Kugelrohr distillation (60-70 °C, <1 mmHg) gave 3.28 g of the enamide (44% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, *J*=7.2 Hz, 3 H), 1.01 (d, *J*=6.7 Hz, 6 H), 1.32 (sext, *J*=7.2 Hz, 2 H), 1.54 (s, 3 H), 1.70 (s, 3 H), 1.92 (q, *J*=6.9 Hz, 2 H), 2.68 (hept, *J*=6.7 Hz, 1 H), 3.91 (d, *J*=6.3 Hz, 2 H) 5.35 (dt, *J*=15.3, 6.3 Hz, 1 H), 5.47 (dt, *J*=15.3, 6.5 Hz, 1 H), 5.79 (bs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.5, 17.6, 19.1, 21.8, 22.2, 31.1, 34.2, 49.3, 123.3, 124.7, 133.8, 135.6, 177.2; IR (Neat) 2967, 2874, 1736, 1653, 1406, 1236, 970 cm^{-1}. HRMS calcd for $C_{14}H_{25}NO$ m/z 223.1936, found 223.1940.

Preparation of *N*-((*E*)-hex-2-en-1-yl)-*N*-(2-methyl-1-propyl)-(2-methyl)propenylamine (66). The enamide (4.0 mmol, 0.89 g) was taken up in 5 mL dry Et_2O, and LAH (5.0 mmol, 5 mL, 1.0 *M* in THF) was added dropwise over a 15 min period. After 1.5 h, the mixture was cooled to 0 °C and quenched as described for the workup of the $LiAlH_4$ reduction to make **61**. After 1.5 h, $MgSO_4$ was added, and the mixture was stirred for an additional 30 min. The solids were removed by filtration, and the mixture was concentrated. The enamine was purified by Kugelrohr distillation (60-65 °C, <1 mmHg) to give 0.83 g of **66** (99% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d *J*=6.7 Hz, 6 H), 0.89 (t, *J*=7.4 Hz, 3 H), 1.30-1.42 (m, 3 H), 1.58 (s, 3 H), 1.65 (s, 3 H), 1.96 (m, 2 H), 2.22 (d, *J*=7.3 Hz, 2 H), 3.08 (d, *J*=4.3 Hz, 2 H), 5.19 (bs, 1 H), 5.36-5.56 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 17.7, 20.7, 22.3, 22.5,

27.6, 34.5, 58.9, 62.9, 122.4, 128.1 132.4, 135.7 IR (Neat) 2965, 2803, 1673, 1468, 1377, 1188, 970 cm^{-1} (in heptane). HRMS calcd for $C_{14}H_{27}N$ m/z 209.2143, found 209.2126.

General Procedures for Isobutyraldehyde Condensation and 3-Aza-Cope Rearrangements with 61 and 65: A mixture of the secondary amine (1.0 equiv., 2-5 mmol, 0.2 *M* in solvent), isobutyraldehyde (3.0 equiv., 6-15 mmol), and pTsOH (0.0025 equiv.), was taken up in benzene (or toluene for **65**) and heated to reflux. The mixture was subject to azeotropic removal of water,[31] and reaction progress was monitored by GLC for disappearance of amine. Once the condensation was complete (12-24 h), he mixture was cooled to room temperature and the benzene was removed *in vacuo*. The crude enamine was taken up in toluene (0.2 *M*), and the appropriate reagent was added at room temperature (see Table I). After complete rearrangement in refluxing toluene, the imine was reduced at 0 °C by the addition of $LiAlH_4$ (1.1 equiv., 1.0 *M* in THF). After stirring for 6 h, the reaction was quenched by the sequential addition of H_2O (1 mL/1.0 g $LiAlH_4$), 15% w/v aq. NaOH (1 mL/1.0 g $LiAlH_4$), and then H_2O (3 mL/1.0 g $LiAlH_4$). The quenched mixture was stirred at room temperature overnight, filtered through K_2CO_3, concentrated, and purified by Kugelrohr distillation to give the corresponding product of condensation, rearrangement, and reduction (see Table I for yields).

(*E*)-1-(*N*-(2-methylprop-1-yl)amino)-2,2-dimethyl-4-octene (64): (bp 70-80 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 6 H), 0.86 (t, *J*=7.3 Hz, 3 H), 0.86 (d, *J*=6.6 Hz, 6 H), 1.35 (sextet, *J*=7.2 Hz, 2 H), 1.72 (nonet, *J*=6.6 Hz, 1 H), 1.87-1.99 (m, 4 H), 2.28 (s, 2 H,), 2.35 (d, *J*=6.9 Hz, 2 H), 5.35-5.41 (m, 2 H). N-H not observed; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 20.6, 22.8, 25.6, 28.0, 34.4, 34.8, 43.4, 59.1, 60.4, 126.9, 132.7; IR (Neat) 3352, 2959, 2872, 2810, 1670, 1120, 970 cm^{-1}. HRMS calcd for $C_{14}H_{29}N$ m/z 211.2293, found: 211.2281.

1-(*N*-(2-methylprop-1-yl)amino)-2,2-dimethyl-3-propyl-4-pentene (68): (bp 70-80 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (s, 6 H), 0.85 (d, *J*=6.1 Hz, 6 H), 0.86 (t, *J*=6.7 Hz, 3 H), 0.99-1.19 (m, 2 H), 1.30-1.42 (m, 2 H), 1.69 (nonet, *J*=6.6 Hz, 2 H), 4.90 (dd, *J*=10.3, 2.4 Hz, 1 H), 4.98 (dd, *J*=10.3, 2.4 Hz, 1 H), 5.55 (dt, *J*= 17.0, 10.3 Hz, 1 H), N-H not observed; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 20.6, 21.1, 23.3, 23.6, 27.9, 30.5, 36.2, 51.0, 59.1, 59.6, 115.7, 140.2; IR (Neat) 3310, 3075, 2959, 2872, 2811, 1638, 1119, cm^{-1}. HRMS calcd for $C_{14}H_{29}N$ m/z: 211.2293, found: 211.2264.

(*E*)-1-(*N*-(2-methylprop-1-yl)amino)-2,2-dimethyl-5-phenyl-4-pentene (72): (bp 70-80 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, *J*=6.7 Hz, 6 H), 0.93 (s, 6 H), 1.74 (nonet, *J*=6.7 Hz, 1 H), 2.15 (dd, *J*=7.3, 0.8 Hz, 2 H), 2.36 (s, 2 H), 2.39 (d, *J*=6.9 Hz, 2 H), 6.25 (dt, *J*=7.3, 15.9 Hz, 1 H), 6.38 (bd, *J*=15.9 Hz, 1 H), 7.15-7.37 (m, 5 H), N-H not observed; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.6, 25.7, 27.9, 35.1, 43.8, 59.0, 60.4, 125.9, 126.8, 127.7, 128.4, 131.9, 137.8; IR (Neat) 3325, 3083, 3061, 3027, 2955, 2870, 2811, 1599, 1117, 966 cm^{-1}. HRMS calcd for $C_{17}H_{27}N$ m/z 245.2143, found 245.2172.

1-(*N*-(2-methylprop-1-yl)amino)-2,2-dimethyl-3-phenyl-4-pentene (76): (bp 70-80°C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3 H), 0.87 (d, *J*=6.7 Hz, 3 H), 0.89 (d, *J*=6.7 Hz, 3 H), 0.90 (s, 3 H), 1.70 (nonet, *J*=6.7 Hz, 1 H), 2.20 (d, *J*=11.7 Hz, 1 H), 2.31 (d, *J*=7.0 Hz, 2 H), 2.34 (d, *J*=11.7 Hz, 1 H), 3.25 (bd, *J*=10.1 Hz, 1 H), 5.01-5.09 (m, 2 H), 6.28 (m, 1 H), 7.10-7.30 (m, 5 H), N-H not observed; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7, 23.6, 23.7, 28.1, 37.6, 57.3, 59.0, 59.3, 116.2, 126.0, 127.8, 129.3, 138.8, 142.5; IR (Neat) 3320, 3077, 3069, 3029,

2057, 2872, 2811, 1636, 1601, 1117 cm^{-1}; HRMS calcd for $C_{17}H_{27}N$ m/z 245.2143, found 245.2206.

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CHAPTER II

MECHANISTIC STUDIES OF INTRAMOLECULAR ZIEGLER-NATTA OLEFIN INSERTIONS: α- AND β-DEUTERIUM ISOTOPE EFFECTS AND CHAIN TRANSFER PROCESSES

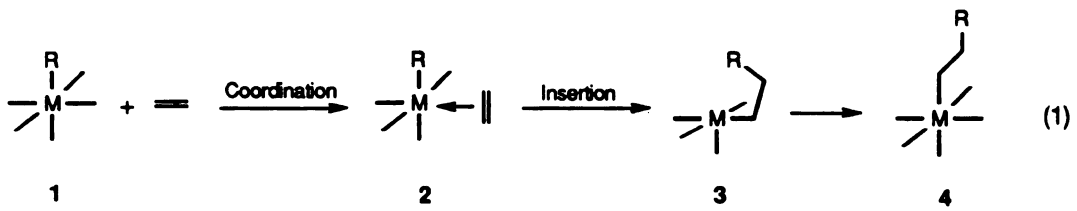
BACKGROUND AND SIGNIFICANCE

Historical Aspects of Ziegler-Natta Olefin Insertion Processes.

In 1963, the Nobel prize in chemistry was awarded to Karl Ziegler and Guilio Natta for their discovery of a remarkable class of catalysts.[1] These highly active catalysts facilitated selective polymerization of alkenes and dienes. As originally introduced, the Ziegler-Natta catalysts were defined as a transition metal compound with an organometallic compound of group I, II or III.[1]

Industrial use of Ziegler-Natta catalyst systems quickly replaced widely used preparations of polyethylene which employed radical catalysis at high pressures (1000-3000 atm) and high temperatures (150-230 °C).[1] Using Ziegler-Natta catalysts, propylene and other α-olefins can be polymerized into isotactic or syndiotactic structures preferentially over the statistical atactic structures.[1] The nature of these unexpected selectivities has prompted many questions regarding the specifics of olefin insertion under the influence of Ziegler-Natta catalysis. The widely accepted mechanism of olefin insertion resulting from Ziegler-Natta catalysis has two principal steps: 1) coordination of the alkene

to the active metal center, and 2) insertion of the activated monomer into a metal carbon bond (eq 1).[1]



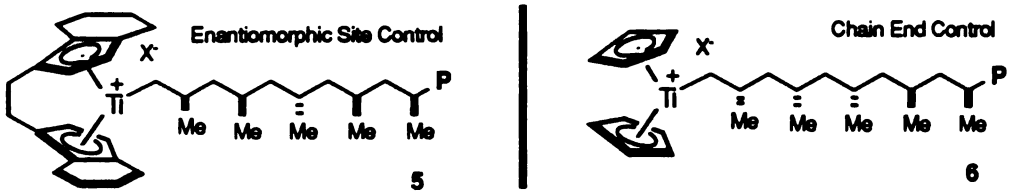
(1)

Most Ziegler-Natta catalyst systems are heterogeneous, but some homogeneous systems are known.[1a] The "Cp_2Ti" systems are homogeneous systems and have been studied in great detail for elucidation of the elementary steps of this polymerization process.[2] Despite the fact that these systems become heterogeneous as polyethylene forms, the "Cp_2Ti" system is one of the best understood Ziegler-Natta systems examined to date. Various opinions regarding the nature of the active center exist, but the formation of a complex between the titanium and the aluminum cocatalyst is generally accepted.[2,3]

The stereoregularity associated with olefin polymerization processes is important for defining the physical properties of the resultant polymer,[1] and a variety of stereoselectivities have been observed in the polymerization of propylene and styrene using assorted Ziegler-Natta catalysts and various cocatalyst.[3-6] Homogeneous α-olefin polymerization became a great deal more efficient through the introduction of methylaluminoxane (MAO) as a Ziegler-Natta cocatalyst.[3] MAO, which is formed through the slow addition of water to trimethyl aluminum (for details, see the Experimental Section), rapidly became one of the most used aluminum reagents as both isotactic and syndiotactic polymer formation could be affected through the use of this reagent.[3] For example, Cp_2TiR_2/MAO systems give isotactic polypropylene for both R=Me and R=Ph.[3] Both Cp_2ZrMe_2/MAO[4] and Cp_2ZrCl_2[5] catalyst systems provide atactic polypropylene, while reaction of propylene with Cp_2TiCl_2/MAO[5] produces syndiotactic polystyrene. In

addition, cationic catalyst systems with either titanium or zirconium polymerize propylene in an atactic fashion.[6]

Two process that have been identified that play a role in the stereoselection of polymerization: 1) enantiomorphic site control (**5**)[7] and 2) chain end control (**6**).[7] Catalytic systems subject to enantiomorphic site control have sterically demanding ligands which dominate the directing effect of the asymmetric polymer chain. The ligand directs approach of the incoming monomer, and this control prevents the propagation of unfavorable monomer insertions.[7] In instances of chain end control, stereoregulation is achieved through 1,3-asymmetric induction relative to the newly formed stereocenter at the position β-to the transition metal.[7] With this type of control, errors in olefin insertion are carried on in the polymerization process.



Variations in polymerization outcome raise the issue of defining the controlling factors at work in homogeneous Ziegler-Natta polymerization systems. While there has been a great deal of speculation as to the mechanism of olefin insertion, details of the process have not been proven unequivocally with respect to the role of the Lewis acid additive and participation of the growing polymer chain. Once the controlling features have been identified, new polymerization systems can be designed for increased efficiency of polymer formation.

Proposed Mechanisms for Ziegler-Natta Polymerization.

There are three fundamental mechanistic proposals for the Ziegler-Natta polymerization of α-olefins.[8-10]

1) the direct insertion mechanism[8] (Cossee and Arlman)

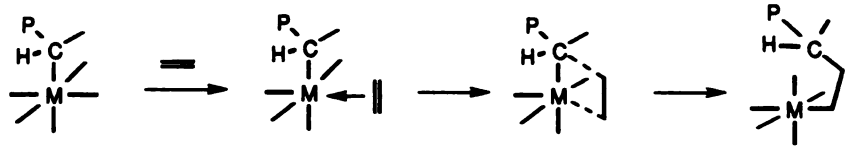
2) the metathesis mechanism[9] (Greene and Rooney)

3) the modified Greene and Rooney mechanism[10] (Brookhart and Green)

Through consideration of the interactive role of the growing polymer chain, each of these mechanisms provides partial explanations for the experimental observations associated with olefin insertion in Ziegler-Natta catalyst systems.

The direct insertion mechanism is characterized by a loosely coordinated four-centered transition state **9**.[8] According to Cossee, the active center for olefin insertion is an ion of a transition metal that is octahedrally coordinated and has one vacant site and one alkyl group in the coordination sphere. Another key aspect of this mechanistic proposal is coordination of the olefin to the $d_{x^2-y^2}$ orbital of the transition metal through a π-bond.[8] This type of M-alkene coordination has been shown in a number of cases, and plays an important role in the theoretical studies of olefin insertion.[11]

Scheme I. The Direct Insertion Mechanism.

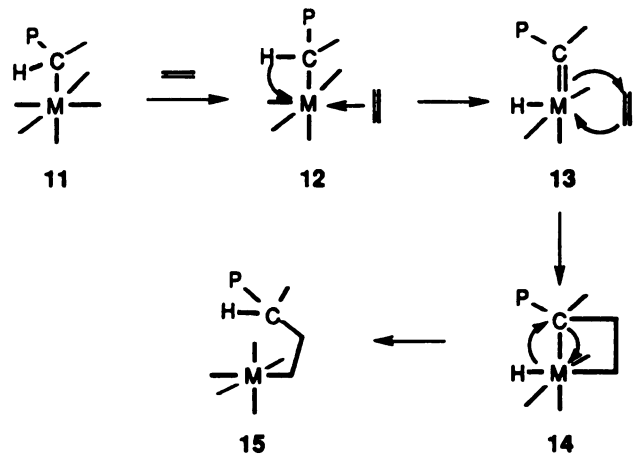


7 **8** **9** **10**

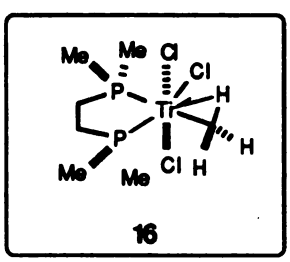
The metathesis mechanism was proposed by Green and Rooney in 1978.[9] This pathway is characterized by the formation of a metal carbene/alkylidene species (**13**) prior to formation of a metallocyclobutane intermediate (**14**). The alkylidene species forms

through transfer of an α-hydrogen from the polymer chain to the transition metal. Formation of the metallocyclobutane intermediate helps to explain the stereoregularity observed in the polymerization of propylene.[9]

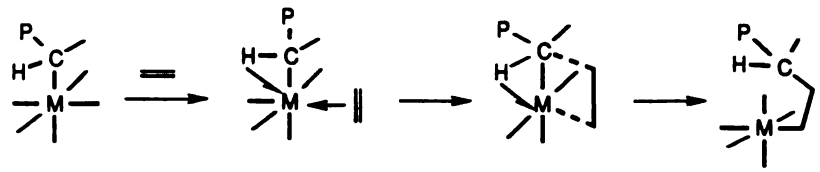
Scheme II. The Metathesis Mechanism.



Following the characterization of **16** in 1982,[12] Green and Brookhart presented a modified mechanism for olefin insertion that reflected an interaction between an α-hydrogen and the transition metal center of the Ziegler-Natta catalyst.[10] Steric restrictions in the insertions step could be decreased through such an interaction (referred to as an agostic interaction), and the bidentate nature of the M--H--C bonding could influence the stereoregularity of olefin insertion.[10]



Scheme III. The Modified Green-Rooney Mechanism.



17 18 19 20

The direct insertion mechanism[8] and the metathesis mechanism[9] represent two extremes on an olefin insertion mechanistic continuum. The first extreme does not involve the alkyl chain in any way, while the second extreme involves complete transfer of a hydrogen from the alkyl chain. The third mechanism is the medium which demonstrates the potential role of agostic interactions in olefin insertion with Ziegler-Natta catalysts.[10] The modified Greene-Rooney mechanism suggests that agostic interactions could contribute to defining the stereoregularity of polymer formation.[10] Experimental insights gained over the years have prompted this exploration of the role of α– and β-hydrogen interactions in the polymerization of α-olefins with Ziegler-Natta catalysts.

The Agostic Interaction.

Definition. The term "agostic", from the Greek word "αγοστω" means "to clasp or to hold oneself".[13] In 1983, this term was introduced by Brookhart in the context of organometallic chemistry. Accordingly,

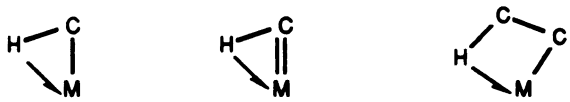
> "...the term agostic will be used to discuss the various manifestations of covalent interactions between carbon-hydrogen groups and transition metal centers in organometallic compounds. The word agostic will be used to refer specifically to situations in which a hydrogen atom is covalently bonded simultaneously to both a carbon atom and to a transition metal atom."[13]

There are various types of agostic interactions that have been observed and/or implicated in studies regarding the insertion of olefins into metal-carbon bonds (Figure 1).[14] The three most prominant types of agostic interactions are:[14]

1) α-agostic interactions in M-alkyl complexes (**21**)

2) α-hydrogen interactions in alkylidene complexes (**22**)

3) β-agostic interactions in M-alkyl complexes (**23**).



21 **22** **23**

Figure 1. Various Agostic Interactions.

For the purposes of this work, emphasis will be placed on interactions resembling **21** and **23**. A number of organometallic complexes have been examined for potential agostic interaction,[14] however, these ground state interactions only tell part of the olefin insertion story. Of equal or greater interest is the impact agostic interactions have on the formation of active intermediates and transition states. Such transition states were explored in detail in this study.

Theoretical Explorations. Numerous theoretical studies have been designed to probe agostic interactions in metal-alkyl species.[14-16] Several extended Huckel molecular orbital calculation studies for iron based systems have been reported, and these studies explored the effect of ligand variation on the nature of the proposed agostic interactions.[17] These reports also indicated that for electronic considerations, the agostic M-H-C interaction is a highly bent open system rather than a closed three membered ring.[18] Theoretical investigations of actinide systems revealed that for $Cp_2Th(C_2H_5)_2$, both α- and β- hydrogens can come close to the Th center without weakening the Th-C bond.[19]

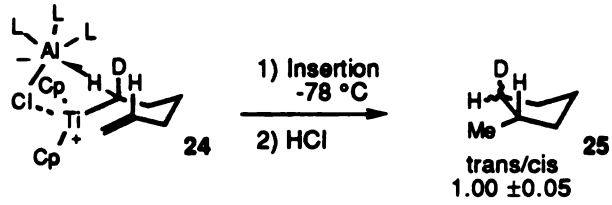
Systems modeling Ziegler-Natta olefin polymerization catalysts have also been the subject of many theoretical studies.[20-26] Deviations from the ideal octahedral metal field have been shown for d^0 hexacoordinated metal alkyl complexes, and the ideal field was not a minimum on the potential energy surface.[20] Transition states stabilized by agostic interactions of migrating alkyl groups have been demonstrated for zirconocene cations.[21] The existence of Zr-Hβ-C two electron interactions have been theoretically determined in compounds modeling proposed Ziegler-Natta polymerization intermediates.[22] Methyltitanium systems have been examined by *ab initio* molecular orbital calculations[23] as well as paired interacting orbital calculations.[24] Such calculations have shown that methyl distortions are due to direct interaction between the CH_α bond and the unoccupied Ti-d orbital.[23] Another study involving titanium as the metal center prompted Jolly and Marynick to report that the mechanistic pathway proposed by Cossee and Arlman was possible even without the involvement of agostic interactions.[25] The model system employed was $Cp_2Ti\text{-}CH_3^+ + C_2H_4 \text{ ---> } Cp_2TiC_3H_7^+$. However, when $Cl_2Ti\text{-}CH_3^+ + C_2H_4 \text{ ---> } Cp_2TiC_3H_7^+$ was used, strong agostic interactions were reported.[25] When zirconocene was examined as the transition metal for catalysis of olefin insertion, agostic interactions were again implicated as possible reaction intermediates.[26]

Experimental Evidence. In addition to the theoretical investigations of agostic participation, a great deal of physical evidence also supports the existence of such interactions.[27-31] In 1978, Williams *et al.* reported the results of a neutron diffraction study in which strong C-H-M interactions were shown for the first time (M=Fe).[27] In 1979, neutron diffraction evidence was also reported for similar interactions in an electron-deficient tantalum-neopentylidene complex.[28] Since that time, β-CH agostic interactions have also been shown for alkenyl zirconocene complexes,[29] and both alpha[30] and beta[31] agostic interactions have been shown for zirconium- and titanium-alkyl complexes as early as 1982. Now that agostic interactions in the catalyst resting state have been identified and

characterized, the potential role similar interactions play in the insertion of olefins in polymerization processes becomes an increasingly intriguing issue, and this is the direction that this study has taken.

Related Kinetic Isotope Effect Studies.

In 1985, Grubbs *et al.* examined the role of α-activation through an elegant study utilizing kinetic isotope effects in intramolecular olefin insertion reactions which introduced a direct probe for the analysis of C-H activation (eq. 2).[32] The intramolecular insertion system placed the olefin in the optimum position for insertion, and a high local concentration of olefin was created while maintaining the desired 1:1 stoichiometry of the olefin relative to the transition metal center. This system was designed to model the polymerization of ethylene, and involved both a transition metal catalyst and a Lewis acid cocatalyst.[32]



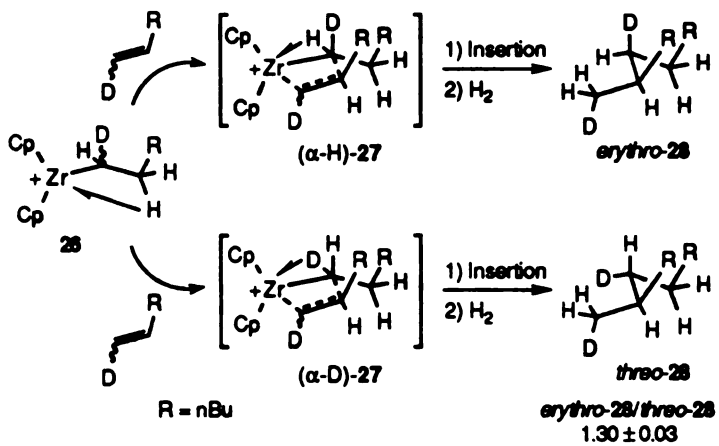
By selective deuteration of the α-carbon, and analysis of the stereochemical outcome of cyclization, a *cis/trans* ratio of 1.00 ±0.05 was observed.[32] From these results, Grubbs concluded that α-activation does not have a significant effect on the rate or stereochemistry of this olefin insertion reaction designed to model Ziegler-Natta polymerization conditions.[32]

Similarly, Brintzinger and coworkers reported a *cis/trans* ratio of 1.01 ±0.02 for the hydrocyclization of (*E,E*)-1,6-dideuterio-1,5-hexadiene when Cp_2ZrCl_2 activated by MAO was employed as the catalytic system.[33] However, utilization of a less

conformationally restricted intermolecular insertion reaction with the same catalytic activation gave markedly different results (Scheme IV).[33] The intermolecular insertion of appropriately labeled 1-hexene revealed a preference for formation of erythro 6-deuterio-5-deuteriomethylundecane (*erythro/threo* = 1.30 ±0.03).[33]

The formation of primarily erythro **28** indicates a preference for transition state (α-H)-**27** over (α-D)-**27**.[33] These findings provide the first experimental evidence for an α-agostic interaction in the transition state for olefin insertion promoted by a zirconocene/MAO catalytic system. Experimental evidence of this nature supports the modified Green-Rooney mechanism in which α-agostic activation is proposed.[10]

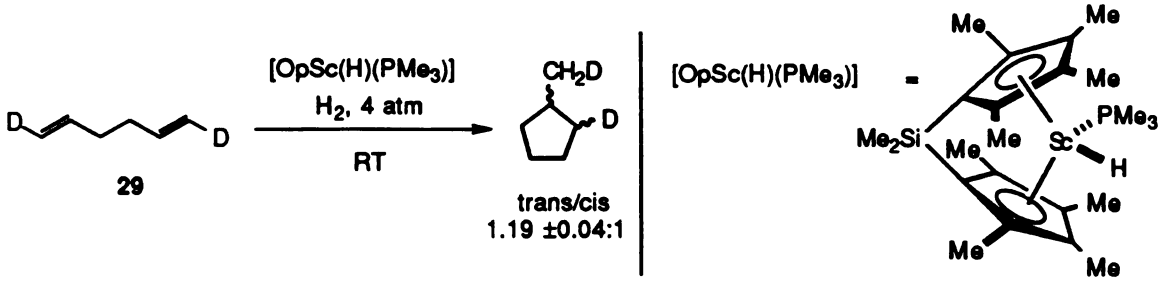
Scheme IV. Evidence For α-H Activation in a MAO/Zirconocene System.



Intramolecular hydrocyclizations of deuterium labeled dienes did reveal kinetic isotope effects in the formation of cyclopentane products when a scandium catalyst was employed in the absence of a Lewis acid cocatalyst (Scheme V).[34] Again, these results support the modified Green-Rooney mechanism because of the detectable role of the α-hydrogen in the rate determining step of olefin insertion.[10] The isotope effects observed are also suggested to rationalize the fact that active catalysts are 14-electron metal centers

with two vacant orbitals.[34] One vacant orbital is for coordination of the olefin, and the other is said to accommodate the agostic interaction.

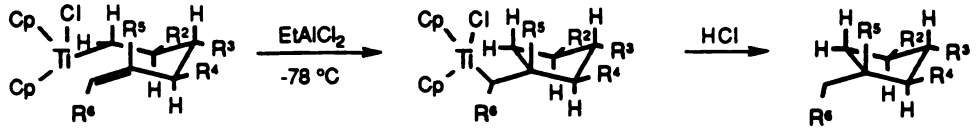
Scheme V. Isotope Effects in Scandocene Catalysis of Olefin Insertion.



Intramolecular Cyclizations.

The work described herein is part of a research program originally designed for the exploration of stereochemical and regiochemical control in the reaction of an activated carbon with an olefin for the formation of five- and six-membered carbocycles.[35] Based on some intriguing results obtained in the study of carbocycle formation, this portion of the investigation has been aimed at further clarification of the role of the cocatalyst and the growing polymer chain in the regulation of olefin insertion.[35] Results previously reported from these labs have shown outstanding selectivities in the formation of substituted and unsubstituted cyclopentanes under Ziegler-Natta olefin insertion conditions (Table I).[35a]

Table I. Selective Formation of Five-Membered Carbocycles.

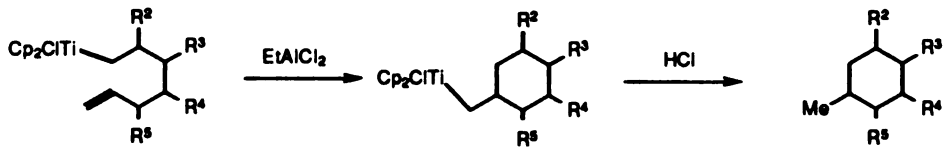


30 31 32

	R^2	R^3	R^4	R^5	R^6	trans:cis (32)	Yield (32)
a	H	H	H	H	H	——	85%
b	H	H	H	H	Me	——	79%
c	H	H	H	Me	H	——	93%
d	H	H	Me	H	H	94:6	93%
e	H	Me	H	H	H	0:100	93%
f	Me	H	H	H	H	100:0	94%

Further investigations revealed that six-membered ring formation serves as a better intramolecular model for the olefin insertions associated with Ziegler-Natta polymerization (Table II).[35c] The increased flexibility of the transition state for cyclohexane formation more accurately reflects the conformational freedom of the intermolecular insertions of Ziegler-Natta olefin polymerization processes.[35c]

Table II. Selective Formation of Six-Membered Carbocycles.



33 34 35

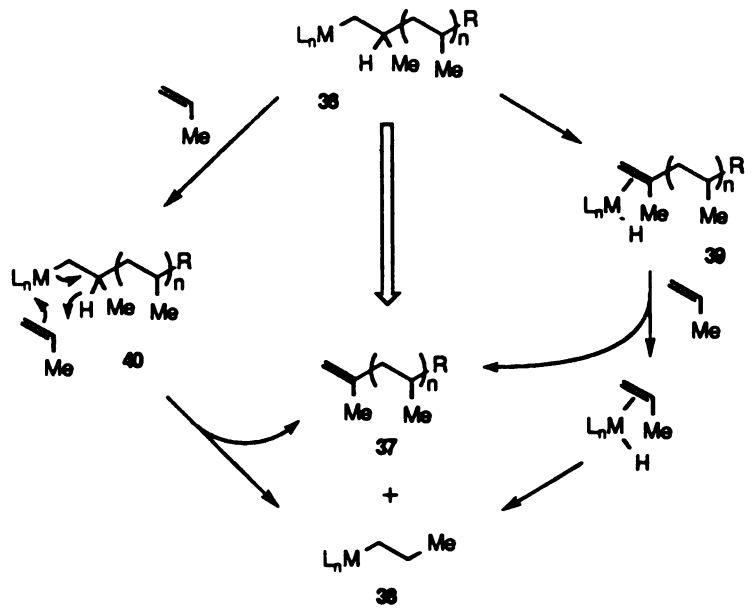
	R^2	R^3	R^4	R^5	trans:cis (35)	Yield (35)
a	H	H	H	Me	99:1	89%
b	H	H	Me	H	3:97	78%
c	H	Me	H	H	50:50	41%
d	H	iPr	H	H	23:77	47%
e	Me	H	H	H	81:19	71%
f	iPr	H	H	H	92:8	63%

Other interesting features identified through these studies include the acceleration of cyclization due to the presence of a substituent in the position beta to the transition metal.[35c] Also, product selectivity for the cyclization of **33e** varied with the variations of Lewis acid additive.[35] These selectivities include 80:20 trans:cis for $EtAlCl_2$ (-78 °C), 75:25 for MAO (-78 °C), and 33:67 for MgX_2 (25 °C).[36a] The currently accepted mechanisms for similar olefin insertion processes describe selectivity as arising from an α-hydrogen agostic interaction independent of cocatalyst.[1,8-10] The findings from these labs indicate that these homogeneous catalyst systems do not necessarily proceed through a common cationic intermediate with the Lewis acid additive simply serving as a non-participating anion.[35]

This study was designed to show the involvement of α- and β-hydrogens in the insertion of olefins in homogeneous catalytic systems in the presence of a cocatalyst. In addition to the role of the alkyl chain in activation of the Ti-C bond toward olefin insertion, chain transfer processes which were previously observed[36a] were investigated in greater detail.

For a number of years, researchers have known that β-H and β-Me migrations compete with olefin insertion in the termination of alkene oligomerization in Ziegler-Natta systems with d^0 early transition metal catalysts.[37] The understanding of these chain termination process is important in order to control chain length in polymerization reactions. To date, such process have not been identified in titanium systems, so the intramolecular olefin insertion was used as a probe to monitor chain transfer processes with respect to solvent dependence, monomer substituent or Lewis acid activation of olefin insertion.

Scheme VI. Chain Termination/Chain Transfer Pathways.



For Ziegler-Natta polymerization systems, chain termination through β-hydrogen transfer has been proposed.[37] There have been a number of investigations into these processes through end group analysis in polymerization reactions.[38-45] Scheme VI illustrates some of the possible chain termination processes.[38] Typically, termination of the growing polymer chain (**36**) results in the formation of the terminal olefin product (**37**), and the new polymer-metal complex **38**.[38] There are two possible pathways for the formation of the observed products. The first is through β-hydrogen elimination to give complex **39** which can undergo olefin exchange in the presence of an additional monomer unit. Insertion of the monomer into the metal-hydrogen bond forms **38**. An alternative mechanistic possibility is the simultaneous transfer of hydrogen to the monomer, coordination to the metal, and elimination of terminal olefin **37**.[38]

There have been a number of studies confirming the existence of chain transfer processes that have been reported.[39-45] Teuben has proposed that the β-Me transfer may be thermodynamically more favorable than β-hydrogen transfer based on *ab initio* calculations.[39] Similar preferences have been confirmed experimentally for cationic Hf and

Zr catalyst systems for cyclopolymerization,[40] ethene polymerization,[41] and propene polymerization.[41,42] Polymerization systems catalyzed by $Cp^*_2MCl_2$/MAO (M=Zr, Hf) have shown both β-Me and β-H transfer for the polymerization of propylene,[43] while polymerization of 1-butene was characterized by termination exclusively through β-H elimination to aluminum.[43a] The transfer of β-alkyl groups has also been reported in the related lanthanide model system for propene polymerization.[44] Bercaw and coworkers have provided a wealth of evidence for both β-hydrogen transfer and β-alkyl transfer in polymerization systems with scandocene catalysts.[45] Bercaw *et al.* have investigated the different effects of β-substituent variations on alkyl transfer process[45b] as well as the extent of competition between β-hydrogen transfer and β-alkyl transfer.[45c] Because titanium systems have been the subject of fewer studies, experiments were designed to show the existence of chain transfer processes in our intramolecular olefin insertion model of Ziegler-Natta polymerization.

EXPERIMANTAL GOALS

The goals of this work were to use intramolecular olefin insertion in the selective formation of six-membered rings to model interactions between the Ziegler-Natta catalyst/cocatalyst complexes and the growing chain of a poly-α-olefin. This system was to be utilized to explore both α- and β-deuterium isotope effects in Ziegler-Natta olefin polymerization model systems. The single olefin insertion process was also used to probe chain transfer/ligand transposition processes in the formation of both five- and six-membered carbocycles.

SYSTEM DESIGN

The system used in our studies was designed to model the polymerization of α-olefins in the presence of a Lewis acid cocatalyst. This was accomplished through examination of the intramolecular insertion of olefins tethered to titanium by an alkyl chain substituted β to the metal by a second alkyl chain (**41**, Figure 2).[36]

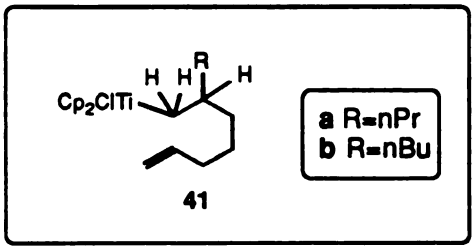


Figure 2. Ziegler-Natta α-Olefin Polymerization Model.

The intramolecular olefin insertion of **41** presented intriguing challenges for the study of competitive insertion rates. The α-hydrogens of these substrates are diastereotopic, and there is only one β-hydrogen present. Therefore, the effects of the β–alkyl substituent or β–hydrogen participation could not be determined through monitoring internal competition. For these reasons, a system was designed in which the competitive rates of cyclization were determined for the simultaneous reaction of **41a** and **41b** as well as the appropriately labeled analogs. This approach allowed for determination of the effects of the α- and /or β-interactions in the rate determining step of olefin insertion in a system modeling the polymerization of 1-pentene and 1-hexene for both homogeneous (MAO) and heterogeneous (MgX_2)[46] catalyst systems.

Intramolecular olefin insertions which result in the formation of 6-membered carbocycles have previously been identified as a sensitive probe for Ziegler-Natta olefin insertion, as well as an accurate model for polymerization.[35] The accuracy of this model is attributed to the presence of a high local concentration of olefin relative to the transition metal center, while an overall 1:1 stoichiometry is maintained. Due to the significance of

findings previously reported from these labs,[36] both MgX_2 and MAO were examined as Lewis acid additives in the competitive olefin insertion reactions of **41a** and **41b**. Because of the increased use in industrial polymerization processes, MAO was selected as the cocatalyst of choice for this study. Since previous investigations indicated that MgX_2 and MAO behave differently in the intramolecular olefin insertion process, MgX_2 was utilized for comparison in this investigation.

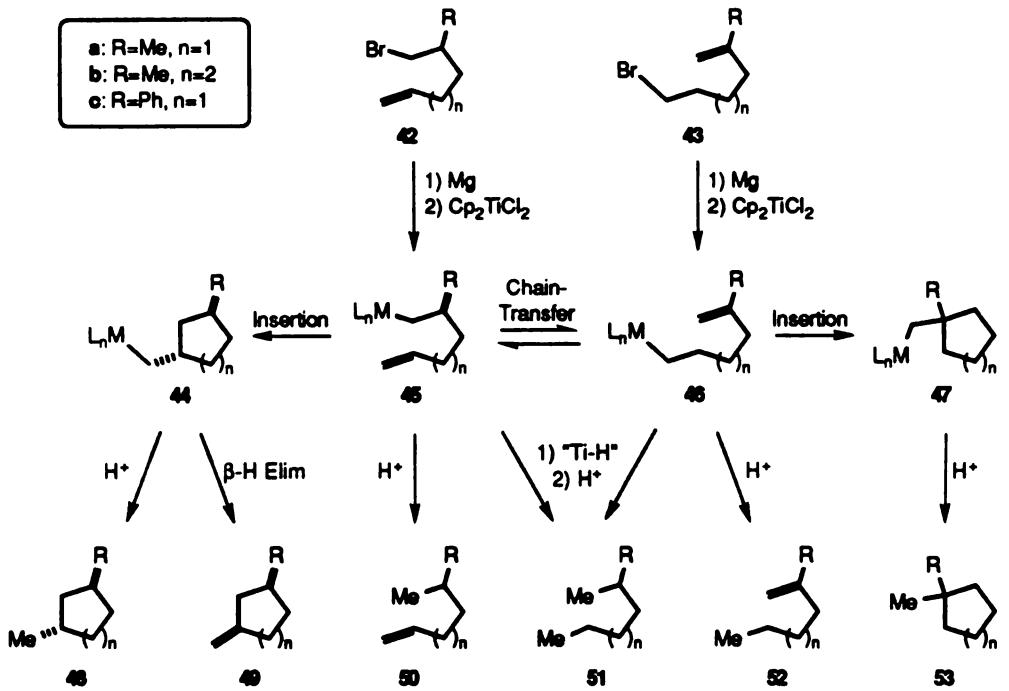
The nature of this competition study requires that the difference in cyclization rates attributable to the change in β–substituent be quantified. Through comparison of the relative rate of cyclization of **41a** and **41b** without deuterium labeling, a normalization factor can be obtained. Such a value allows for the calculation of k_H/k_D values from competitive cyclizations of α- and/or β-deuterium labeled substrates. An equally as informative value can be obtained *via* the cyclization of (α-D)-**41a** *vs.* (α-D)-**41b**.

Previous studies from this group revealed that intramolecular olefin insertions promoted by MgX_2 were solvent dependent.[36a] When CH_2Cl_2 was used as the solvent for cyclization, high conversion to a single cyclized product was efficiently achieved. However, the use of toluene as the cyclization solvent provided for the formation of several additional cyclic and acyclic products. Chain transfer was a likely explanation for the formation of several sideproducts.[36a] This ligand transposition was examined in greater detail throughout the cyclization of **42** and **43** (Scheme VII).

Reports have indicated that the presence of an olefin can trigger chain transfer as well as olefin insertion.[47] Because of these results, our intramolecular olefin insertion methodology was quite appropriate for study of the insertion of olefins into a titanium-alkyl bond. Bromide **42**, after treatment with magnesium, can be transmetallated to titanocene dichloride to generate alkyl titanocene **45**. Olefin insertion would give **41** which, upon hydrolysis, could give the expected cyclopentane product. Elimination of the β-hydrogen from the same intermediate gives **49**, and hydrolysis would yield **50**. Chain transfer/ligand transposition of **45** would give intermediate **46** which could undergo

insertion and hydrolysis to give **53**. In addition, intermediate **46** could be reduced and hydrolyzed to **51**, or simply hydrolyzed to **51**. Because **51** can arise with or without the chain transfer/ligand transposition process, the formation of **52** and **53** was used as the primary indicator of the chain transfer process.

Scheme VII. Chain Transfer Processes In Olefin Insertion Reactions.



RESULTS AND DISCUSSION

Substrate Preparation and Cyclization Methods. The preparation of cyclization substrates used in this study is illustrated in Scheme VIII.[36a] The appropriately substituted diethyl malonates were purchased from Aldrich Chemical Company, and were easily alkylated with 4-bromopentene after treatment with NaH. Deethoxycarboxylation provided **56**, which was a key intermediate for the preparation of all substrates used for the

cyclization reactions. The two step preparation of the alkylated ester could typically be accomplished in 80-90% yield.

Incorporation of deuterium alpha to the ester was most easily achieved by treatment with LDA followed by addition of nBuLi for deprotonation of the diisopropyl amine, and subsequent quenching with D_2O.[48] This procedure generally resulted in >97% deuterium incorporation in 89-92% overall isolated yield. Reduction of **56** or (β-D)-**56**with $LiAlH_4$ gave the corresponding alcohols in excellent yields. Formation of (α-D)-**57** and (α-D, β-D)-**57** was achieved in high yields by reduction of the ester with $LiAlD_4$.

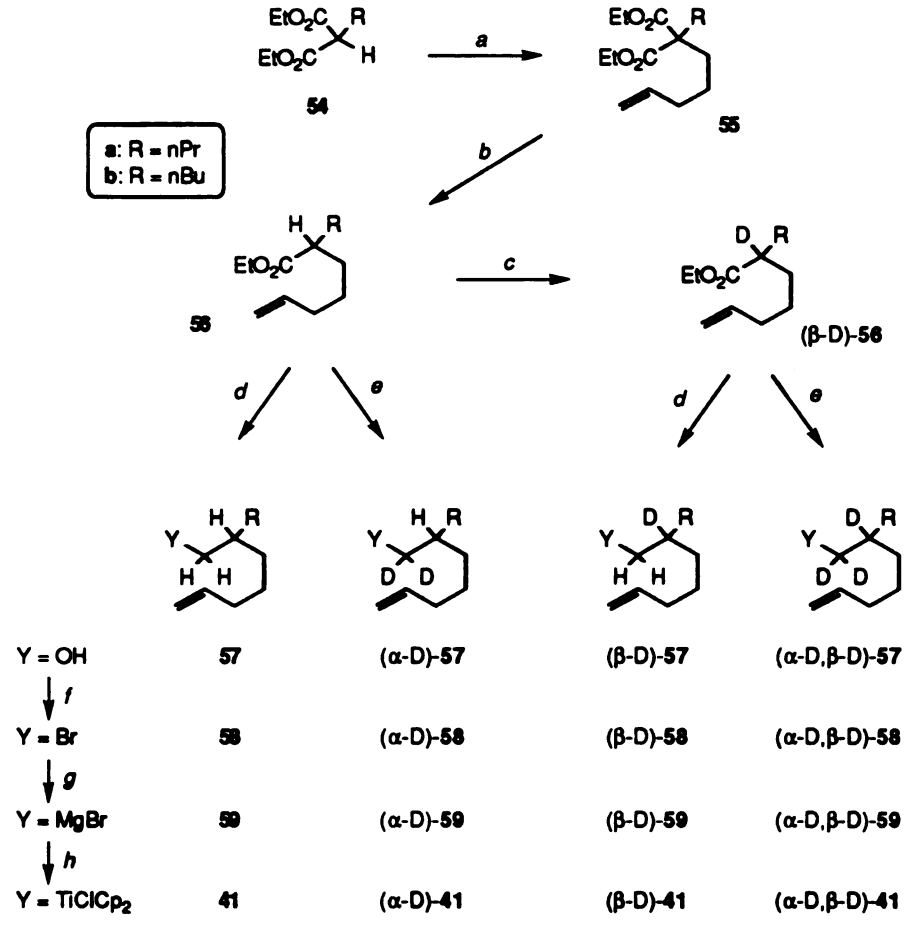
Treatment of the requisite alcohols with NBS and PPh_3 gave the desired bromides in 68-94% yield.[49] Once isolated, the bromides were stored in a -20 °C freezer, and passed down a short column of basic alumina prior to use. The organometallic species (**41**) was prepared by Grignard formation and transmetallation to Cp_2TiCl_2.

Cyclization results for both MAO and MgX_2 promoted reactions will be presented here for comparison and completeness.[50] The MAO promoted olefin insertions were performed by isolation of the alkyl titanocene complex which was subsequently taken up in toluene. The organometallic species was isolated since the byproduct of transmetallation, MgX_2, can promote intramolecular olefin insertion at room temperature. This olefin insertion was not surprising since isotactic polypropylene can be obtained through the use of the heterogeneous $Cp_2TiCl_2/MgCl_2/ TiCl_4/AlEt_3$ catalyst system.[51] However, Grignard formation and transmetallation in the presence of THF allowed for isolation of the alkyltitanium with less than 9% cyclization.

Aliquots of the organometallic solution were treated with MAO, and cyclization was shown to be very efficient, yet measurable at -45 °C, and the entire reaction was cooled to -78 °C and quenched with anhydrous HCl at the desired time intervals.[52] Parallels between this MAO promoted intramolecular cyclization system and Ziegler-Natta polymerization were clearly demonstrated by the formation of cyclohexane-capped oligomers (2-7

monomer units as shown by mass spectral analysis) when 1-hexene (10.0 equiv) was added to the organometallic solution in the presence of MAO.

Scheme VIII. Preparation of Cyclization Substrates.[a]

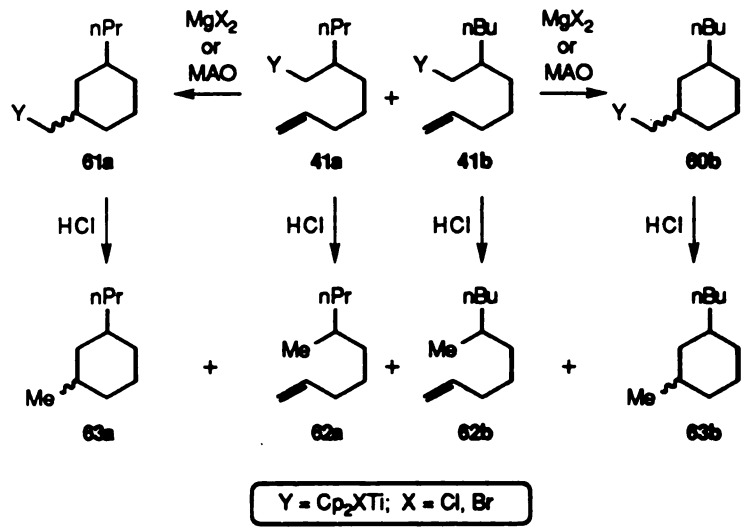


[a]Reaction conditions: (a) i. NaH, DMF, ii. 4-bromopentene (b: 99%); (b) H_2O, DMSO, LiCl, 180 °C (a: 90% from **54a**, b: 86%);(c) i. LDA, ii. *n*-BuLi, iii. D_2O (a: 89%, b: 92%); (d) i. $LiAlH_4$, ii. H_2O (90-98%); (e) i. $LiAlD_4$, ii. H_2O (92-95%); (f) NBS, PPh_3 (68-94%); (g) 4 equiv. of Mg, (h) Cp_2TiCl_2.

Reactions promoted by MgX_2 were performed by allowing the transmetallated solution to warm to room temperature. At the desired time intervals, aliquots were removed from the MgX_2 promoted reactions, cooled to -78 °C, and quenched with anhydrous HCl. The deuterium isotope effects reported in this study for both MAO and

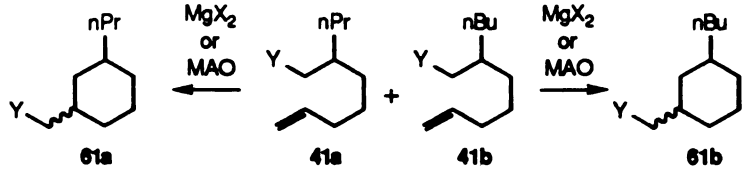
MgX_2 were obtained through the competitive cyclization of the appropriately labeled propyl (**41a**) and butyl (**41b**) substrates as illustrated in Scheme IX.

Scheme IX. Competitive Cyclizations of 41.



Normalization. As illustrated in Scheme IX, the relative rates of cyclization of the propyl and butyl substituted substrates was determined through examination of the product distribution resulting from cyclization of equimolar amounts of **41a** and **41b**. The cyclizations were quenched, and the hydrolysis products were quantified through capillary gas chromatographic analysis. The competitive cyclization of **41a** and **41b** allowed for determination of the combined steric and electronic contributions of the propyl β-substituent relative to that of the butyl β-substituent with respect to cyclization rate.[53] In addition, the competetive cyclization of (α–D)-**41a** and (α–D)-**41b** gave the same information which verified the internal consistency associated with this experimental design.

Table III. Relative Rates For Competitive Cyclization of 41a and 41b[a]



Y = Cp_2XTi; X = Cl, Br

		Relative Rates[b]	
Entry	41a:41b	MgX_2[c]	MAO[d]
1	α-H:α-H	1.14:1.00	1.33:1.00
2	α-D:α-D	1.19:1.00	1.43:1.00
3	α-H:α-D	1.43:1.00	1.26:1.00
4	α-D:α-H	1.00:1.09	1.51:1.00[e]
5	β-D:β-D	1.15:1.00	1.33:1.00
6	β-H:β-D	1.25:1.00	1.41:1.00
7	β-D:β-H	1.00:1.05	1.25:1.00
8	α-H,β-H:α-D,β-D	1.55:1.00	—
9	α-D,β-D:α-H,β-H	1.00:1.20	—

[a]Relative amounts determined by capillary GC (ref. 23). [b]Unless noted otherwise, errors in these values are ±0.02 or ±0.03. [c]Reaction conditions: i. 1.0 equiv. of **58a**, 1.0 equiv. of **58b**, Mg, Et_2O, 25 °C, ii. Cp_2TiCl_2, toluene, -30 °C to 25 °C. X = Cl, Br. [d]Reaction conditions: i. 1.0 equiv. of **58a**, 1.0 equiv. of **58b**, Mg, THF, 35 °C, ii. Cp_2TiCl_2, CH_2Cl_2, -30 ° to 25 °C, iii. Removal of inorganic salts, iv. **41**, toluene, MAO, -45 °C. [e]Values = ±0.04.

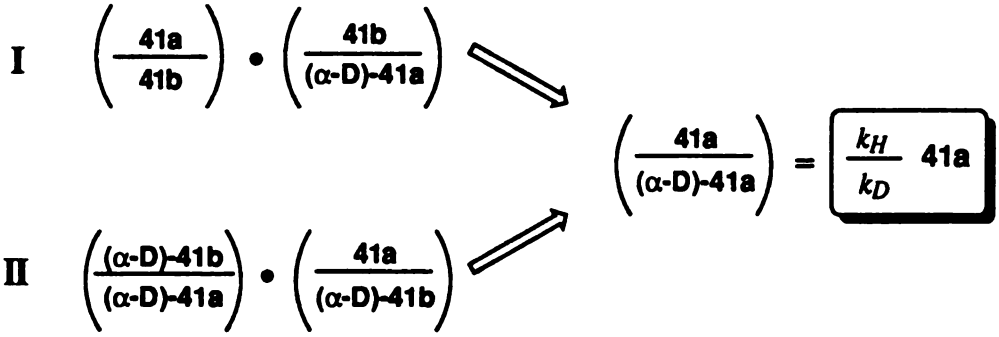
For MgX_2 promoted cyclizations, **61a** and **61b** were formed in a ratio of 1.14:1.00 (Table III, entry 1).[54] A greater difference in the rate of cyclization was observed for the MAO promoted cyclization (1.33:1.00).[55] When deuterated substrates were examined, cyclization promoted with MgX_2 resulted in a relative rate of formation of 1.19:1.00 for (α–D)-**61a** to (α–D)-**61b**, and MAO promoted cyclization gave a ratio of 1.43:1.00 (Table III, entry 2). The stereoselectivity of cyclization was shown to be

dependent upon reaction conditions. MgX_2 promoted cyclization (25 °C) reflected a preference for the formation of *cis* -**63** (40:60 trans/cis), while promotion with MAO resulted in a trans/cis ratio of 60:40. This variation in reaction selectivity paralleled that observed for the cyclization of **33e** (Table II). The greater selectivity for the cyclization of **33e** (90:10 for MAO) is a result of the greater steric requirements of the isopropyl substituent.[56]

The normalization values (Table III, entries 1-3), when incorporated in the evaluation of the remainder of the cyclization studies, allowed for the accurate determination of the actual deuterium isotope effects associated with the intramolecular olefin insertions.

α-Deuterium Isotope Effects. Table III, entries 3 and 4 shows the results for the competitive cyclization of **41a** and (α-D)-**41b** as well as for (α-D)-**41a** and **41b** respectively. The difference between the two Lewis acid additives is clearly illustrated in these two reactions. Deuteration decreases the cyclization rate for MgX_2 promoted cyclizations, whereas the insertion rate is increased for MAO accelerated reactions. While large deuterium isotope effects seem immediately obvious at this point, the relative rate differences based on β-alkyl substituent variation (propyl *vs.* butyl) must be taken into account in order to obtain the actual k_H/k_D values for the cyclization of **41**.

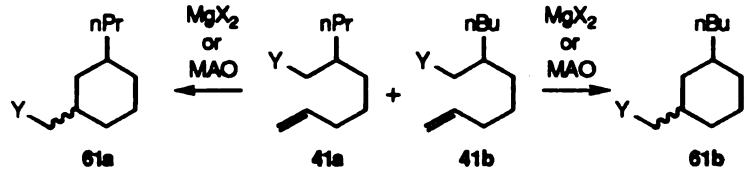
Scheme X. Calculation of the Alpha k_H/k_D for 41a.



Application of either normalization factor (Table III, entries 1 and 2) provides the actual k_H/k_D values for the cyclization of **41**, and comparison of these two k_H/k_D values illustrates the internal consistency inherent in the experimental design. Scheme X shows the way in which the normalized values are calculated, and the results are given in Table IV. Following equation **I** for the MgX_2 promoted cyclization gives k_H/k_D =1.14 • 1.09=1.24 ±0.03. Similarly, equation **II** gives k_H/k_D =1/1.19 • 1.43=1.20 ±0.03. The average of these two values results in a k_H/k_D propyl=1.22 ±0.03. Analysis of the cyclization of **41b** gives a k_H/k_D butyl value of 1.28 ±0.03.

Intramolecular olefin insertion promoted by MAO shows an opposite effect on the rate of insertion caused by α-deuteration. For **41a**, a k_H/k_D of 0.88 ±0.04 is obtained, and for **41b**, the value is 0.95 ±0.04. This unexpected inverse isotope effect is evidence that the rate of insertion is enhanced by the presence of an α-deuterium label. It is also interesting to note that the magnitude of the deuterium isotope effect increases for smaller β-substituents. Because of this, it is reasonable to anticipate and even greater isotope effect in the polymerization of propylene when catalyzed by MAO.

Table IV. Normalized α-Deuterium Isotope Effects for the Cyclization of 41a and 41b.[a]



Lewis Acid	Substrate	I[b]	II[c]	Average k_H/k_D
MgX_2	**41a**	1.24 ±0.03	1.20 ±0.03	1.22 ±0.03
MgX_2	**41b**	1.25 ±0.03	1.30 ±0.02	1.28 ±0.03
MAO	**41a**	0.88 ±0.04	0.88 ±0.04	0.88 ±0.04
MAO	**41b**	0.95 ±0.04	0.95 ±0.04	0.95 ±0.04

[a]Calculated from the values in Table III. [b]Calculated from equation **I**, Scheme X. [c]Calculated from equation **II**, Scheme X.

β-Deuterium Isotope Effects. The β-deuterium isotope effects were obtained in much the same way as described above. To monitor internal consistency, an additional normalization value was obtained through the relative rate of cyclization of (β-D)-**41a** with respect to (β-D)-**41b** (Table III, entry 5). MgX_2 promotion of olefin insertion for **41a** *vs.* (β-D)-**41b** and for (β-D)-**41a** *vs.* **41b** again reflected positive isotope effects (Table III, entries 6 and 7). Normalization of the raw data as shown in Scheme IX, gives the k_H/k_D values shown in Table V. These results indicate that the β-hydrogen is involved in the propagation step of the Ziegler-Natta polymerization of α-olefins.

In comparison to the MgX_2 promoted reactions, the MAO promoted reactions also show a positive isotope effect for deuteration in the β-position (Table III, entries 6 and 7, Table IV). Normalization of the rates of cyclization gives a β-deuterium isotope effect of 1.09 (propyl) and 1.10 (butyl) for MgX_2 promoted cyclizations, and 1.06 ±0.04 for both the propyl and butyl substrates for MAO activation. Again experimental evidence is provided through these studies for a deuterium isotope effect for this Ziegler-Natta olefin polymerization model.

Scheme XI. Calculation of the Beta k_H/k_D for 41a.

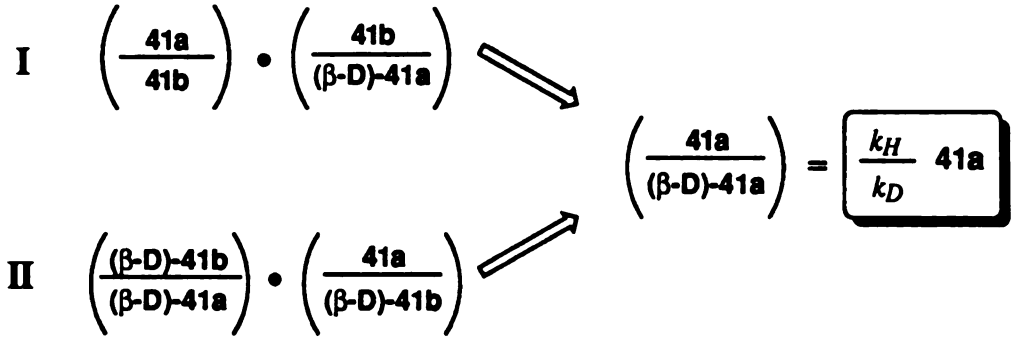
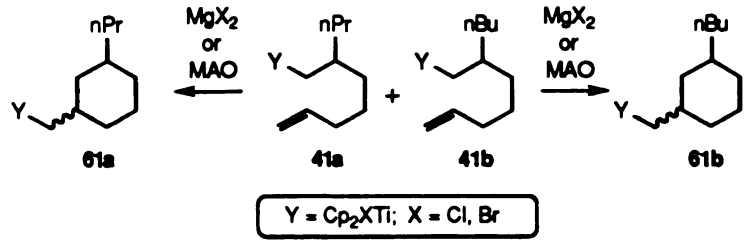


Table V. Normalized β-Deuterium Isotope Effects for the Cyclization of 41a and 41b.[a]



Lewis Acid	Substrate	I[b]	II[c]	Average k_H/k_D
MgX_2	**41a**	1.09 ±0.02	1.09 ±0.02	1.09 ±0.02
MgX_2	**41b**	1.10 ±0.02	1.10 ±0.02	1.10 ±0.02
MAO	**41a**	1.06 ±0.04	1.06 ±0.04	1.06 ±0.04
MAO	**41b**	1.06 ±0.04	1.06 ±0.04	1.06 ±0.04

[a]Calculated from the values in Table III. [b]Calculated from equation **I**, Scheme XI. [c]Calculated from equation **II**, Scheme XI.

Combined α- and β-Deuterium Isotope Effects. The observation of positive α- and β-isotope effects for MgX_2 promoted olefin insertion reactions prompted an investigation into the nature of the combined effect. This was examined through the competitive cyclization of **41a** *vs.* (α-D, β-D)-**41b** and of (α-D, β-D)-**41a** *vs.* **41b**. The relative rates of cyclization are shown in Table III, entries 8 and 9. The normalization process revealed cooperative isotope effects of 1.37 and 1.36 ±0.02 for **41a** and **41b**, respectively.

Mechanistic Implications. Figure 3 summarizes the observed kinetic isotope effects observed in this investigation. The variation of deuterium isotope effect resulting from the use of different Lewis acid additives shows that the same mechanistic pathway is not necessarily operative for both the heterogeneous (MgX_2) and the homogeneous (MAO) catalyst model systems as is often proposed for Ziegler-Natta polymerization systems.[1] This effect could be due to the difference in the nature of the Lewis acid additive, or due to

the difference in temperature required for olefin insertion under either set of conditions as has been reported for the changes in stereoregularity of polymer formation.[1-5]

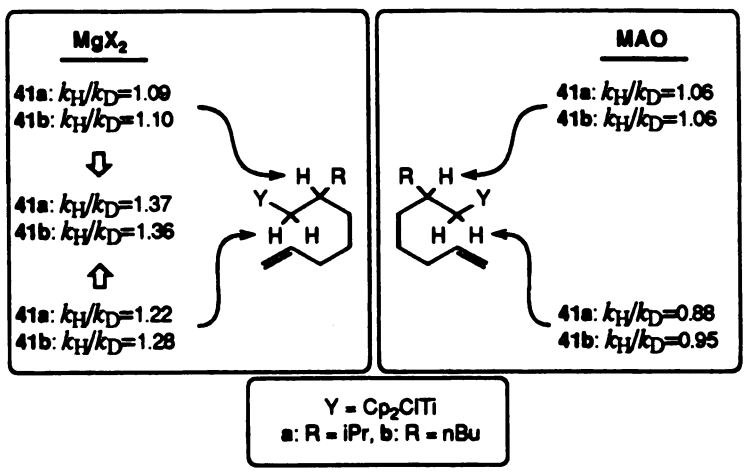


Figure 3. Summary of Kinetic Isotope Effects.

The deuterium isotope effects observed in this investigation contrast those reported by Grubbs from his studies of intramolecular olefin insertions in the formation of five-membered rings.[32] Whereas Grubbs did not observe an alpha isotope effect, this investigation revealed a positive interaction in the case of MgX_2 promoted cyclizations, and an inverse effect for MAO promotion. The isotope effects measured in this study of a titanium system with MgX_2 promotion are comprable to the reports of Brintzinger[33] and Bercaw[34] in which measureable isotope effects were observed. It is interesting to note that the isotope effects observed by Bercaw and coworkers did not involve a Lewis acid.[34]

The mere existence of the deuterium isotope effects shows that the alkyl chain is involved in the rate determining step of olefin insertion. Earlier studies have demonstrated that activation of the catalyst occurs by complexation of the transition metal with the Lewis acid additive which creates an electron deficient transition metal center.[57] Following activation, the main function of the cocatalyst is that of a bulky anion serving to stabilize the cationic transition metal complex. In light of the observed kinetic isotope effects,

ramifications of the involvement of the alkyl chain must be taken into account in mechanistic descriptions of olefin insertion reactions. Such ligand-catalyst/cocatalyst interactions provide insight into the potential causes of stereoselectivity in polymer formation.

When describing the interactions of the growing polymer chain model with the catalyst/cocatalyst system, there are several possibilities for ligand coordination that need to be considered. Scheme XII depicts several of these possibilities. Both MgX_2 and MAO are known to display an extended framework represented as -X-M-X-M-, where M=metal, and X=halogen or oxygen.[58] Following activation of the catalyst system, three of the major types of possible ligand interaction are:

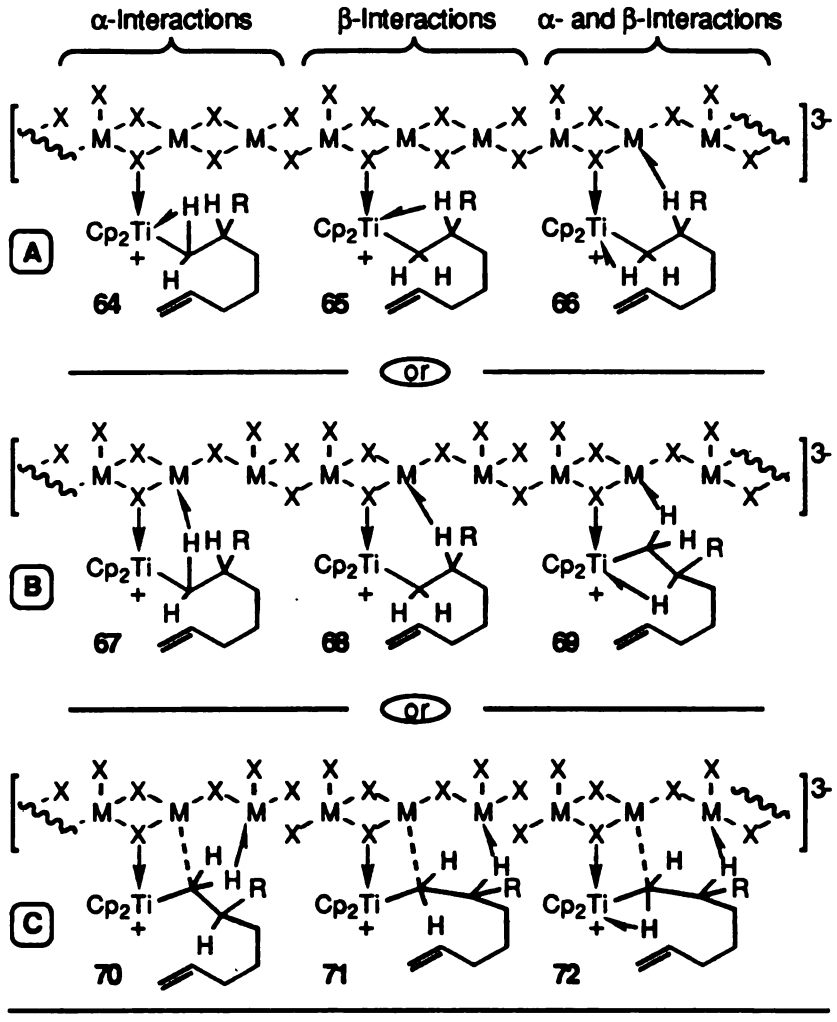
A) Agostic interaction with the transition metal.

B) Agostic interaction with the cocatalyst.

C) Combined bridging alkyl ligand and agostic interaction with the cocatalyst.[59]

As illustrated in Scheme XII, a positively chaged transition metal center is created through complexation with the cocatalyst framework. Involvement of the growing polymer chain model with the transition metal are shown for all three types of ligand interaction. Structures **64**, **65**, **67**, and **68** depict ligand-metal contact a single site on the alkyl chain, while **66** accounts for the combined α and β effects through α-hydrogen interaction with the transition metal and β-hydrogen coordination with the metal of the cocatalyst. The combined interactions shown for **69** demonstrate the possibility of the reverse interactions, specifically, α-hydrogen interaction with the cocatalyst metal and β-hydrogen coordination to the transition metal.

Scheme XII. Potential Ligand Catalyst/Cocatalyst Interactions.



Combined bridging alkyl ligand and agostic interaction with the cocatalyst is shown in line C in Scheme XII. Due to the polaraization of the carbon-titanium bond, the carbon can interact with the metal of the cocatalyst framework as in **70**, **71**, and **72**, thereby enhancing the activation of olefin insertion. Although the interactions are more complex, α- and β- agostic interactions are still possible under such ligand coordinating conditions.

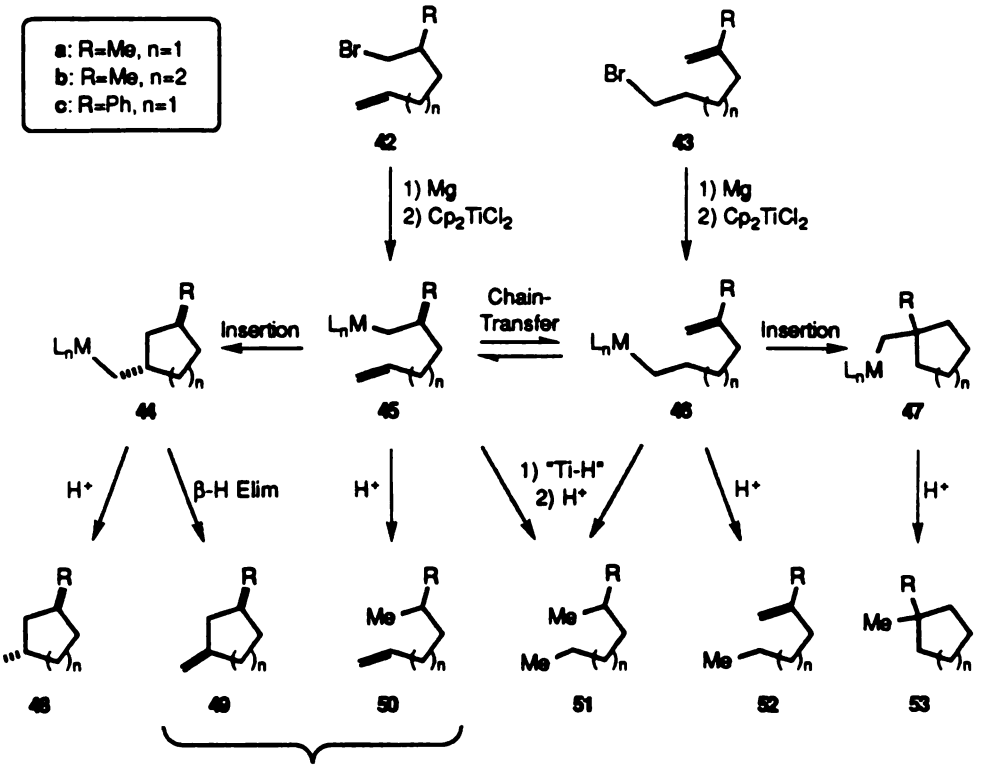
Any of these ligand interactions could be responsible for the weakening Ti-C bond and the corresponding increase in reactivity toward olefin insertion for the MgX_2 promoted

systems. The inverse α-deuterium isotope effect resulting from MAO accelerated cyclization suggests ground state stabilization through an agostic interaction, as the α-D-substrate would be expected to react more readily. Although the exact nature of the agostic interactions remains undetermined, involvement of the growing polymer chain model with the cocatalyst framework has been shown through the identification of these α- and β-deuterium isotope effects. Interaction between the growing polymer chain and the cocatalyst helps to explain the selectivities observed in the Ziegler-Natta polymerization of olefins.

Chain Transfer Reactions. The cyclization of **42a**, **42b**, and **43a** in toluene was performed under a variety of conditions which revealed evidence in support of the fact that chain transfer under these conditions is an intermolecular process (Scheme XIII).[60] For the cyclization of **42a**, a dependence of the formation of ligand transposition products on reaction concentration was observed. At 0.1*M* **52a** and **53a** were formed in 11% and 2% respectively. As the concentration was increased from 0.25*M* to 0.60*M*, the amount of formation of the products arising from chain transfer/ligand transposition increased. This dependence upon concentration suggests that the formation of the cyclization side products is an intermolecular process. Introduction of a β-deuterium, however, shut down the chain transfer processes.

The reverse reaction, namely the cyclization of **46a**, which results from Grignard formation and subsequent transmetallation of **43**, resulted in formation of 14% of the chain transfer product **48a**. The major product of this reaction was that of hydrolysis of **46a**. Other substrates examined include **42b** and **42c**. The effect of the formation of a six-membered ring was demonstrated by the cyclization of **42b**. The increased tether length had little effect on the formation of the chain transfer products, which also supports the proposal that the ligand transposition in an intermolecular process. Bromide **42c**, which was used to model the polymerization of styrene, revealed increased competition from the β-hydrogen elimination process.

Scheme XIII. Chain Transfer Processes In Olefin Insertion Reactions.



42a (0.10 *M*)	67%		*		21%	11%	2%
42a (0.25 *M*)	71%		5%		12%	12%	<2%
42a (0.44 *M*)	57%		*		18%	21%	4%
42a (0.60 *M*)	54%		*		17%	23%	7%
(β-D) **42a** (0.25 *M*)	60%		15%		14%	<2%	<2%
43a (0.25 *M*)	14%		<2%		5%	61%	<2%
42b (0.25 *M*)	61%		13%		12%	12%	2%
42c (0.25 *M*)	45%	24%		4%	10%	8%	<2%

*Accurate values could not be obtained due to interference from a solvent impurity.

CONCLUSIONS

For the first time, α-hydrogen interactions have been shown for a titanium based catalyst system, and, this is the first reported system modeling the polymerization of an α-olefin in either the heterogeneous (MgX_2) or the homogeneous (MAO) promoted system. In addition, a β-hydrogen interaction has been shown for the first time in a Ziegler-Natta catalyst/cocatalyst model system.

The kinetic isotope effects observed for the MgX_2 promoted olefin insertion, 1.22 and 1.28 are comparable to those previously reported for systems that modeled the polymerization of ethylene with zirconium[61] and scandium[62] catalysis. In contrast, the MAO promoted olefin insertion reactions resulted in an unexpected inverse α-isotope effect (0.88 and 0.95 for **41a** and **41b** respectively). The quantification of this effect supports the hypothesis that the role of the Lewis acid additive in olefin insertion reactions is not independent of the nature of the Lewis acid. The isotope effects measured in this study reflect the difference in stereoselectivities for the cyclization of **33e** and **41**, as well as the reported variations in the stereoregularity of polymer formation in titanium and zirconium systems.

Cyclization reactions of **42** and **43** provide evidence that chain transfer in titanium systems is an intramolecular process. These results are the first reported for titanium mediated olefin insertion systems.

EXPERIMENTAL SECTION

General Methods. All reactions were conducted under nitrogen or argon atmospheres. THF, Et_2O, toluene, and benzene were distilled from sodium/benzophenone prior to use. Hexane was stirred over sulfuric acid, and after 5 d, the hexane was washed sequentially with H_2O, saturated aqueous $NaHCO_3$, dried ($CaCl_2$), and distilled from sodium/benzophenone/tetraglyme. The Mg used for formation of the Grignard reagents was activated prior to use by washing with 10% HCl, H_2O, acetone, and finally with Et_2O. The turnings were then flame dried *in vacuo*, and stored in a desiccator. 4-Bromo-1-pentene[63] and MAO[64] were prepared according to literature procedure.

NMR spectra were obtained on a Varian Gemini 300 or a VXR-300 instrument with $CDCl_3$ as solvent. Signals are reported in units of ppm relative to $C(^1H)Cl_3$ or $^{13}CHCl_3$. Analytical gas chromatography (GC) was performed with a 50 m RSL200 column (5% methyl phenyl silicone equivalent to SE-54 or DB-5).

Activation of Magnesium. The Mg used for formation of the Grignard reagents was activated prior to use by washing with 10% HCl, H_2O, acetone, and finally with Et_2O. The turnings were then flame dried *in vacuo*, and stored in a desiccator. Immediately prior to use, the reaction vessel containing the Mg was heated under vacuum for 15 min, purged with argon, evacuated and purged again with argon.

Diethyl 2-(4-pentenyl)-2-(propyl)-propanedioate (55a). NaH (1.89 g, 79 mmol) was suspended in DMF (61 mL), and **54a** (14.78 g, 73 mmol) was added dropwise at room temperature over a 15 min period, and the resulting solution was stirred until all of the NaH was consumed (approx. 45 min). At this point, 4-bromo-1-pentene (10.0 g, 67 mmol) was added slowly, and the reaction was heated at 65 °C until the bromide was consumed (3-12 h). Upon completion of the alkylation, the mixture was cooled to 0 °C,

diluted with H_2O (120 mL), and the aqueous layer was extracted with Et_2O (3 x 60 mL). The organic extracts were washed with H_2O (3 x 30 mL) followed by saturated aqueous NaCl. The Et_2O layer was dried ($MgSO_4$), concentrated, and carried on without further purification.

Ethyl 2-propyl-6-heptenoate (56a). Crude diester **55a** (26.3 g, 97 mmol) and LiCl (7.9 g, 186 mmol) were taken up in DMSO (196 mL), and H_2O (1.8 mL, 100 mmol) was added. The mixture was heated in an oil bath at 180 °C until reaction was complete by NMR analysis (8-12 h). Dilution with H_2O (120 mL) was followed by extraction with Et_2O (3 x 60 mL). The organic layers were combined and washed with H_2O (2 x 30 mL), saturated aqueous $NaHCO_3$ (2 x 30 mL), and saturated aqueous NaCl (2 x 30 mL). The Et_2O layer was then dried ($MgSO_4$), concentrated, and distilled *via* Kugelrohr (oven temp 80-90 °C, <1 Torr) to give **56a** (17.68 g, 90 mmol) in 90% yield from **54a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 7.3 Hz, 3 H), 1.20-1.59 (m, 12 H), 2.00 (q, J = 7.3 Hz, 2 H), 2.30 (m, 1 H), 4.09 (q, J= 7.3 Hz, 2 H), 4.90 (m, 1 H), 4.95 (m, 1 H), 5.74 (ddt, J = 17.0, 10.1, 7.3, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.3, 20.6, 26.7, 31.9, 33.6, 34.7, 45.5, 60.0, 114.6, 138.5, 176.5; IR (Film) 3078, 2959, 2937, 2874, 1734, 1641, 1460, 1379, 1177, 911 cm^{-1}.

56b: (18.27 g, 86 mmol) in 86% yield from **54b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 7.1 Hz, 3 H), 1.14-1.50 (m, 12 H), 1.51-1.65 (m, 2 H), 2.00 (q, J = 7.1 Hz, 2 H), 2.31 (m, 1 H), 4.10 (q, J= 7.1 Hz, 2 H), 4.91 (m, 1 H), 4.98 (m, 1 H), 5.75 (ddt, J = 17.0, 10.1, 7.1, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.3, 22.6, 26.7, 29.6, 31.9, 32.2, 33.6, 45.6, 60.0, 114.6, 138.5, 176.5.

Ethyl 2-propyl-2-deuterio-6-heptenoate ((β-D)-56a). A solution of LDA was prepared by adding *n*-BuLi (2.5 M in hexanes, 17.0 mL, 43 mmol) to a 0 °C solution of *i*Pr_2NH (6.5 mL, 46 mmol) in THF (55 mL). Stirring was continued for 30 min, and

the mixture was cooled to -78 °C. Compound **56a** (7.64 g, 39 mmol) was added dropwise to the LDA solution and stirred for 50 min. *n*-BuLi (23.2 mL, 2.5 *M* in hexanes, 58 mmol) was added to the reaction mixture at -78 °C (to deprotonate iPr$_2$NH), and the mixture was stirred for 30 min. The reaction was then quenched with D_2O (25 mL), warmed to ambient temperature, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The Et_2O solution was washed with 1*M* HCl (2 x 30 mL), saturated aqueous $NaHCO_3$ (2 x 60 mL), saturated aqueous NaCl (60 mL), dried ($MgSO_4$), filtered, and concentrated to an oil. The crude oil was distilled under reduced pressure (oven temp 70-80 °C, <1 Torr) to give (β-D)-**56a** (6.8 g, 35 mmol, 89% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, *J*= 7.1 Hz, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 1.28-1.46 (m, 6 H), 1.50-1.63 (m, 2 H), 2.00 (q, *J* = 6.6 Hz, 2 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 4.90 (m, 1 H), 4.96 (m, 1 H), 5.73 (ddt, *J* = 17.1, 10.4, 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 13.9, 20.1, 26.2, 31.4, 33.2, 34.1, 59.5, 114.2, 138.1, 176.0; IR (Film) 3079, 2959, 2934, 2873, 2860, 2145, 1732, 1641, 1460, 1035, 911 cm^{-1}.

(β-D)-**56b:** (7.55 g, 35 mmol, 92% yield): Spectral data were similar to those obtained for **56b** with the following exceptions:^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 was absent; ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.6 was absent; IR (Film) 2130 cm^{-1} (C-D) was present.

General Procedure For $LiAlH_4$ Or $LiAlD_4$ Reduction Of Esters to 57. The reducing reagent (1.1 equiv. of $LiAlH_4$ or $LiAlD_4$) was suspended in Et_2O (0.5 *M*) at 0 °C, and a solution of **56** in Et_2O (1.0 equiv., 0.3 *M*) was added to the $LiAlH_4$ suspension over a period of 30 min. Once addition was complete, the ice bath was removed, and the mixture was stirred at room temperature until the reaction was complete as determined by NMR analysis. The reaction mixture was cooled to 0 °C and quenched by the slow sequential addition of H_2O (1.0 mL/g reducing reagent), 15% NaOH (1.0 mL/g reducing reagent), H_2O (3.0 mL/g reducing reagent) and stirred until all of the solids turned

white. At this time, $MgSO_4$ was added, and the mixture was stirred for an additional 30 min. The Et_2O was decanted from the solids, which were washed thoroughly with Et_2O, and the combined organic fractions were concentrated and distilled *via* Kugelrohr (oven temp 70-80 °C, <1 Torr) to provide the desired alcohol.

57a: (13.21 g, 85 mmol, 96% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J*= 6.8 Hz, 3 H), 1.13-1.50 (m, 10 H), 1.98-2.05 (m, 2 H), 3.49 (d, *J*= 5.4 Hz, 2 H), 4.92 (m, 1 H), 4.96 (m, 1 H), 5.77 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 20.0, 26.1, 30.4, 33.2, 34.1, 40.2, 65.6, 114.4, 138.9; IR (Film) 3337, 3079, 2958, 2930, 2872, 1641, 1460, 1040, 993, 911 cm^{-1}.

57b: (10.82 g, 64 mmol, 90% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J*= 7.0 Hz, 3 H), 1.20-1.50 (m, 13 H), 1.59 (s, 1 H), 2.02 (q, *J*=7.0 Hz, 2 H), 3.49 (d, *J*= 7.1 Hz, 2 H), 4.90 (m, 1 H), 4.95 (m, 1 H), 5.78 (ddt, *J* = 17.1, 10.7, 7.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 23.1, 26.1, 29.1, 30.4, 30.5, 34.1, 40.4, 65.5, 114.3, 138.9.

(α-D)-57a: (5.58 g, 35 mmol, 94% yield); Spectral data were similar to those obtained for **57a** with the following exceptions: ^1H NMR (300 MHz, $CDCl_3$) δ 3.49 was absent; ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.6 was absent; IR (Film) 2197 cm^{-1} (C-D) was present.

(α-D)-57b: (4.43 g, 28 mmol, 80% yield); Spectral data were similar to those obtained for **57b** with the following exceptions: ^1H NMR (300 MHz, $CDCl_3$) δ 3.49 was absent; ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.5 was absent; IR (Film) 2190 cm-1 (C-D) was present.

(β-D)-57a: (4.93 g, 34 mmol, 98% yield); Spectral data were similar to those obtained for **57a** with the following exceptions: ^1H NMR (300 MHz, $CDCl_3$) δ 1.16-1.42 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.2 was absent; IR (Film) 2130 cm^{-1} (C-D) was present.

(β-D)-57b: (5.07 g, 30 mmol, 84% yield); Spectral data were similar to those obtained for **57b** with the following exceptions: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-1.50 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.4 was absent; IR (Film) 2135 cm^{-1} (C-D) was present.

(α-D,β-D)-57a: (5.25 g, 33 mmol, 94% yield); Spectral data were similar to those obtained for **57a** with the following exceptions: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16-1.43 (m, 8 H), δ 3.49 was absent; ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.2 and 65.6 were absent; IR (Film) 2197 and 2097 cm^{-1} were present.

General Procedure For The Bromination Of Alcohols to 58. PPh_3 (3.15 g, 12.0 mmol) and alcohol **57** (1.15 g, 10.0 mmol) were combined in CH_2Cl_2 (20 mL), and cooled to 0 °C. NBS (2.14 g, 12.0 mmol) was added over 2 h by means of a solid addition funnel, stirred for 1 h at 0 °C, and an additional 3 h at ambient temperature. The reaction mixture was concentrated to a slurry, and the resulting solids were dissolved in a minimum of CH_2Cl_2. To this solution was added 50 mL of petroleum ether at ambient temperature, and the mixture was then cooled to 0 °C. The supernatant was filtered *via* cannula, with a piece of filter paper attached to the end of the cannula, using a positive pressure of argon. The solids were washed sequentially with petroleum ether (2 x 25 mL) at 0 °C as before. This filtration sequence was performed two additional times. The organic fractions were combined and concentrated to approximately 15 mL, and then filtered through a plug of basic alumina. Further concentration produced a residue, which was purified by distillation (oven temp 65-75 °C, <1 Torr) to give the corresponding bromide **58.**

58a: (3.97 g, 18 mmol, 94% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J= 6.3 Hz, 3 H), 1.21-1.46 (m, 8 H), 1.61 (m, 1 H), 1.97-2.10 (m, 2 H), 3.43 (d, J = 2.8 Hz, 2 H), 4.93 (ddt, J = 10.2, 2.0, 1.1 Hz, 1 H), 4.98 (dq, J = 17.0, 2.0 Hz, 1 H), 5.78 (ddt, J = 17.0, 10.0, 6.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 19.7, 25.8, 32.0,

33.8, 34.8, 39.1, 39.4, 114.5, 138.6; IR (Film) 3079, 2959, 2930, 2860, 1642, 1458, 1441, 992, 912 cm^{-1}. HRMS calcd for $C_{10}H_{19}Br$ *m/z* 218.0670, obsd *m/z* 218.0708.

58b: (2.27 g, 10 mmol, 65% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J*= 6.6 Hz, 3 H), 1.20-1.50 (m, 12 H), 1.62 (m, 1 H), 2.02-2.12 (m, 2 H), 3.45 (d, *J* = 4.8 Hz, 2 H), 4.93 (ddt, *J* = 10.1, 2.0, 0.86 Hz, 1 H), 5.05 (dq, *J* = 17.1, 2.0 Hz, 1 H), 5.81 (ddt, *J* = 17.1, 10.1, 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.8, 25.8, 28.7, 32.0, 32.2, 33.8, 39.3, 39.4, 114.5, 138.6; IR (Film) 3079, 2959, 2930, 2859, 1642, 1458, 1441, 1237, 992, 912 cm^{-1}.

(α-D)-58a: (3.58 g, 16 mmol, 88% yield); Spectral data were similar to those obtained for **58a** with the following exceptions: ^1H NMR (300 MHz, $CDCl_3$) δ 3.43 was absent; ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.4 was absent; IR (Film) 2250, 2190 cm^{-1} were present; HRMS calcd for $C_{10}H_{17}D_2Br$ *m/z* 220.0796, obsd *m/z* 220.0852.

(α-D)-58b: (4.05 g, 18 mmol, 66% yield); Spectral data were similar to those obtained for **58b** with the following exceptions: ^1H NMR (300 MHz, $CDCl_3$) δ 3.45 was absent; ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.4 was absent; IR (Film) 2197, 2097 cm^{-1} (C-D) were present.

(β-D)-58a: (4.60 g, 22 mmol, 65% yield); Spectral data were similar to those obtained for **58a** with the following exceptions: ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 was absent; ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.1 was absent; IR (Film) 2097 cm^{-1} (C-D) was present; HRMS calcd for $C_{10}H_{18}DBr$ *m/z* 219.0733, obsd *m/z* 219.0724.

(β-D)-58b: (4.60 g, 22 mmol, 65 % yield); Spectral data were similar to those obtained for **58a** with the following exceptions: ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 was absent; ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.4 was absent; IR (Film) 2097 cm^{-1} (C-D) was present.

(α-D,β-D)-58a: (4.54 g, 20 mmol, 81% yield); Spectral data were similar to those obtained for **58a** with the following exceptions: ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 and 3.43 were absent; ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.1 and 39.4 were absent; IR (Film)

2197, 2097, and 1995 cm^{-1} (C-D) were present; HRMS calcd for $C_{10}H_{16}D_3Br$ *m/z* 221.0859, obsd *m/z* 221.0830.

Preparation of Methylaluminoxane (MAO).[64] Using standard Schlenk techniques, $Al(SO_4)_2 \cdot 14H_2O$ (18.6 g, 28 mmol) was taken up in toluene (125 mL) and cooled to 0 °C. $AlMe_3$ (25 mL, Aldrich) was carefully transferred into the reaction vessel *via* cannula, the ice bath was removed, and the reaction was stirred at room temperature under argon for 24 h. At this time, the solution was filtered through a Schlenk frit, and the solvent was removed *in vacuo* to give a glass like solid. In an inert atmosphere box, the solids were scraped free from the sides of the flask, and powdered. The solids were placed under vacuum for an additional 3 to 6 h, and the resulting MAO (5.05 g, 33% yield) was stored at -40 °C in the dry box. A fresh 0.5 *M* solution was made for each series of cyclizations by taking 0.349 g MAO from the dry box in a stoppered Schlenk flask, and diluting with toluene (12 mL). Note: The MAO solution was stored in the freezer at -20 °C between cyclization runs, and was used within 48 h.

General Procedure For MgX_2 Promoted Cyclizations.[50] A mixture of the appropriately labeled bromides **58a** and **58b** (1 mmol each) was added *via* gas tight syringe over a 2 h period to activated Mg turnings (8.2 mmol, 0.20 g) suspended in Et_2O (2 mL) at room temperature. Analysis of the protonolysis products generated from an aliquot of the solution showed that 2-4 % cyclization had occurred during formation of the Grignard reagent. The solution containing the Grignard mixture was stirred for an additional 1-2 h at room temperature, and then was transferred *via* cannula to a -45 °C suspension of Cp_2TiCl_2 (2.4 mmol, 0.60 g) in CH_2Cl_2 (4 mL). The mixture was stirred at this temperature for 1 h, dodecane was added as an internal standard, and the mixture was warmed to room temperature. The reaction was monitored by capillary gas chromatographic analysis of samples obtained by cannula transfer of a small amount of the

crude reaction mixture into approximately 0.3 mL of a 1 *M* solution of HCl in Et_2O at -78 °C. This sample was then filtered through a small column of basic alumina prior to injection onto the GC.

General Procedure For MAO Promoted Cyclizations. Activated Mg (1.0 g, 41.0 mmol) was placed in a Schlenk flask with a stir bar and flamed dried under vacuum for 10-15 min. The flask was then allowed to cool under argon with vigorous stirring, at which time the Mg was suspended in 10 mL of THF, and warmed to 45 °C. A mixture of the appropriately labeled bromides **58a** and **58b** (5 mmol each) was added dropwise *via* syringe to the Mg over a 2 h period. After addition was complete, the reaction was allowed to stir at 45 °C for 3 h, and then cooled to ambient temperature. The Grignard solution was transferred *via* cannula to a -45 °C solution of Cp_2TiCl_2 (2.99 g, 12 mmol) in CH_2Cl_2 (35 mL), the Mg was washed with 5 mL THF, and the washings were transferred to the reaction mixture. After the transmetallation was stirred at room temperature for 1 h, the mixture was stored in the -20 °C freezer overnight. the solution was warmed to room temperature, pumped down to a burgundy oil, and then taken up in hexane (30 mL). Filtration of the hexane suspension was performed through a Schlenk frit, the solids were washed with hexane (2 x 15 mL) and toluene (2 x 5 mL), and the resulting solution was concentrated to an oil. The purified organometallic species was taken up in toluene (25 mL, to approximately 0.4*M*), and dodecane was added as an internal standard. This stock solution was stored in the freezer (-20 °C) until used. Dodecane was added as an internal standard, and the mixture was stored in the freezer (-20 °C) overnight. .

The organometallic solution was warmed to room temperature, and analysis of the protonolysis products showed that 3-9 % cyclization had occurred prior to the addition of MAO. Aliquots of the organometallic solution (2.0 mL), were placed in evacuated and argon purged flasks, and cooled to -78 °C. The MAO (0.70-0.72 mL) was added down the side of the flask slowly, the mixture then was brought immediately to -45 °C, and stirred

for the indicated amount of time (5-20 min). The reaction was quenched by cooling the mixture to -78 °C, and slowly adding anhydrous HCl in Et_2O, stirring for 5 min, and warming to room temperature. The quenched solution was passed down a pipette column of basic alumina prior to analysis by gas chromatography. Cis/trans assignments were made by comparison to an authentic sample prepared independently.

General Procedure For Polymerization of 1-Hexene. Activated Mg (0.29 g, 12.0 mmol) was placed in a Schlenk flask with a stir bar and flamed dried under vacuum for 10-15 min. The flask was then allowed to cool under argon with vigorous stirring, at which time the Mg was suspended in 5 mL of THF, and warmed to 45 °C. Bromide **58a** was added dropwise *via* syringe to the Mg over a 1.5 h period. After addition was complete, the reaction was allowed to stir at 45 °C for 3 h, and then cooled to ambient temperature. The Grignard solution was transferred *via* cannula to a -45 °C solution of Cp_2TiCl_2 (0.82 g, 3.3 mmol) in CH_2Cl_2 (6.0 mL), the Mg was washed with 1 mL THF, and the washings were transferred to the reaction mixture. After the transmetallation was stirred at room temperature for 1 h, the mixture was pumped down to a burgundy oil, and then taken up in hexane (10 mL). Filtration of the hexane suspension was performed through a Schlenk frit, the solids were washed with hexane (2 x 3 mL) and toluene (1 x 5 mL), and the resulting solution was concentrated to an oil. The purified organometallic species was taken up in toluene (5 mL), and 1-hexene (2.52g, 30 mmol) was added. The mixture was cooled to -78 °C, and MAO (3.0 mL, 1.0 *M* soln in toluene) was added. The mixture was stirred at -45 °C for 3 hours, cooled to -78 °C, quenched with anhydrous HCl in ether, and the resultant solids were filtered and dried *in vacuo*. The solids were then dissolved in CH_2Cl_2 and analyzed by mass spec.

Chain Transfer Cyclizations. Activated Mg turnings (4 mmol) were suspended in Et_2O (1.0 mL), and the bromide was added dropwise over a period of 2 h. The solution

was stirred at reflux for 3 h, and then transferred *via* cannula to a solution of Cp_2TiCl_2 (2.4 mmol) in toluene (4 mL) at ambient temperature. Methylcyclohexane was added as an internal standard for **42a** , **42b**, and **43a**, and dicyclohexyl was used for **42c**. After 12 h, aliquots were taken as described in *3.3.5.* and analyzed by capillary gas chromatography.

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(53) The values given in Table III are averages of multiple experiments. The complete data collected for the MAO promoted cyclization is given in Appendix I.

(54) Ratios for relative rate differences were examined in the range of 3% to 30% conversion to cyclic products for MgX_2, and values represent the average of at least five experimental runs. Beyond 30% conversion, mass balance of **62** and **63** dropped significantly, and accurate values for isotope effects could not be obtained. The combined mass balance for the conversion of **58** to (**62** + **63**) ranged from 70 to 80% yield, and the trans:cis ratio for the hydrolysis products (**62a** or **63b**)was the same (39:61 to 41:59) for each experimental run.

(55) Ratios for relative rate differences were examined in the range of 3% to 60% conversion to cyclic products for MAO (ratios did not fluctuate significantly up to 60% cyclization), and values represent the average of five to thirteen experimental runs. The trans:cis ratio for the hydrolysis products (**62a** or **63b**) was the same (59:41 to 61:39) for each experimental run, and the yields for the conversion of **58** to (**62** + **63**) were between 75 and 85%. Variation in the concentration of MAO and **41** in toluene, from 0.05 *M* to 0.3 *M*, did not affect the relative rates of cyclization for **41a** and **41b**.

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CHAPTER III

THE REACTION OF CHIRAL β-ENAMINO ESTERS WITH ACRYLATE DERIVATIVES: FORMATION OF QUATERNARY CENTERS THROUGH ASYMMETRIC AZA-ANNULATION.

BACKGROUND AND SIGNIFICANCE

Naturally occurring nitrogen heterocycles containing quaternary centers are quite common and display potent biological activity.[1] Several representative examples are shown in Figure 1. (+)-Aspidospermidine (**1**) has a pentacyclic skeleton with two nitrogen atoms and a quaternary center,[1] levorphanol (**2**) is a powerful analgesic,[2] and (-)-nitramine (**3**) is an example of a naturally occurring spirocyclic system.[1]

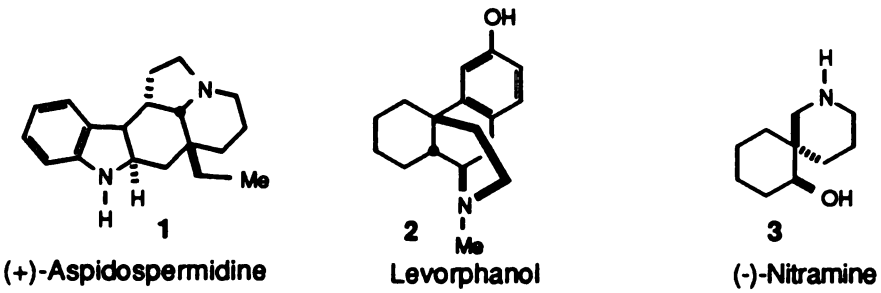
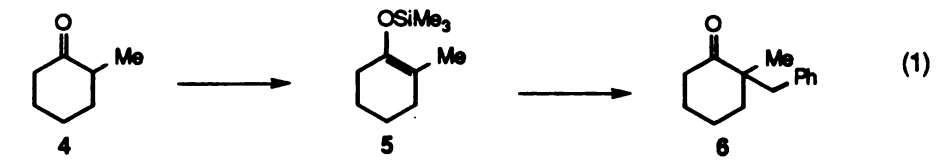


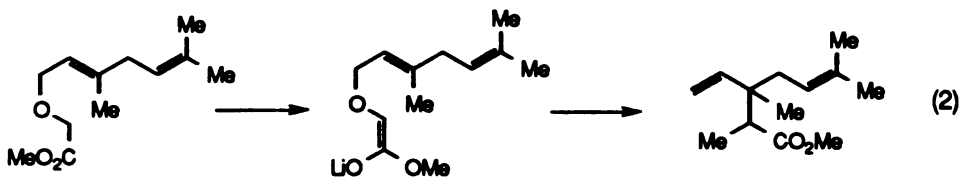
Figure 1. Nitrogen Heterocycles with Quaternary Carbon Centers.

Formation of Quaternary Centers. As a result of the biological significance of natural products containing quaternary centers, a number of methods have been developed for the formation of quaternary carbon centers.[3] Some of the more commonly used methods of formation include alkylation, rearrangement reactions, and cycloaddition

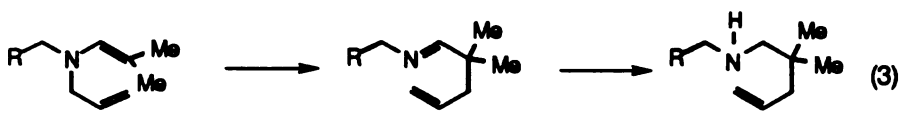
reactions.[3] One of the most prominent classes of ionic construction reactions is addition alpha to a carbonyl group (eq. 1).[4] Rearrangement reactions effective in the formation of quaternary carbon centers include the [2,3] sigmatropic shifts such as the [2,3]-Wittig rearrangement (eq. 2),[5] and [3,3] sigmatropic shifts such as the 3-aza-Cope rearrangement (eq. 3).[6] Cycloaddition reactions, such as the Simmons-Smith reaction, that involve geminally disubstituted alkenes also result in the efficient formation of quaternary carbon centers (eq. 4).[7] Among the most effective techniques for the stereoselective construction of quaternary centers is the Michael addition reaction,[8] which is an application of ionic construction.[3]



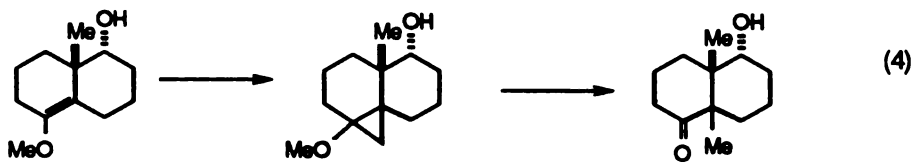
4 5 6 (1)



7 8 9 (2)

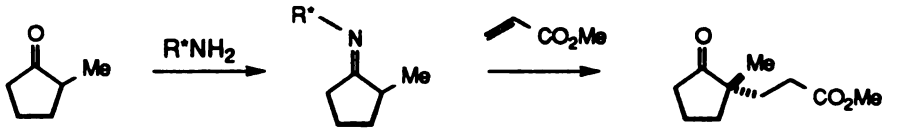


10 11 12 (3)



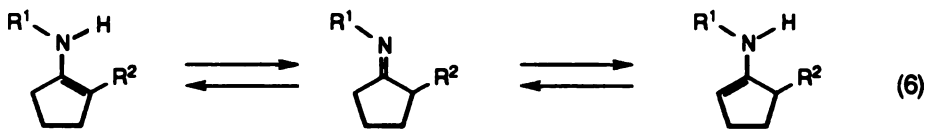
13 14 15 (4)

An important variation of the Michael addition reaction is the addition of imines to electron deficient olefins. This process has been utilized as a step in the formation of nitrogen containing heterocycles.[1] The conjugate addition of imines to electrophilic alkenes has been known since 1956, and several limitations accompanied the early synthetic applications of such reactions.[9] Two of the major drawbacks to the conjugate addition method were the incomplete control of regioselectivity, and incomplete control of the absolute configuration of the newly formed stereogenic center.[9] In 1985, d'Angelo and coworkers reported a new asymmetric conjugate addition reaction with chiral imines and electrophilic alkenes (eq. 5).[10] d'Angelo's reaction took place under neutral conditions to encourage participation of the enamine tautomer (**19** or **21**, eq. 6) for greater regioselectivity, and the asymmetry of the chiral imine was utilized to direct the orientation of the new stereogenic center.[10]



(5)

16 17 18



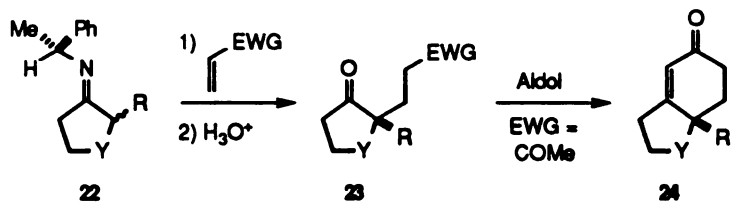
(6)

19 20 21

Conjugate addition of chiral imines to electrophilic alkenes is a deracemizing alkylation reaction that occurs through the more substituted enamine tautomer (**19**) and has been quite effective for the formation of quaternary centers (Scheme I).[1] Reactions of this nature typically result in 85-97% ee for substrates such as carbocyclic imines, (Y=CH_2[11] or $(CH_2)_2$[12] or Ar[13]) or heterocyclic imines (Y=O,[10] CH_2NMe,[15] or CH_2S[16]) with R=

Me, Et, OMe, or CH_2CO_2R'. In these cases, the electrophilic alkenes included methyl acrylate,[11,12b,15] vinyl ketones,[12,13,15,16] acrylonitrile,[10] and phenyl vinyl sulphone.[11,12]

Scheme I. Conjugate Addition to Chiral Imines.

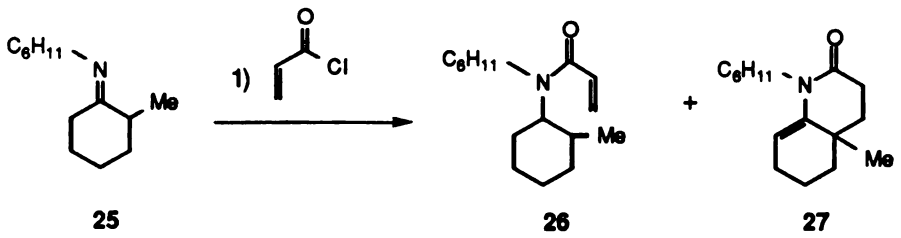


22 23 24

Stabilization of the chiral imine through conjugation with an electron withdrawing group (R=CO_2R' or COR'), caused a decrease in reaction efficiency.[17] To counter this rate retardation, the typical Michael receptor had to be used under high pressure or with Lewis acids for effective reaction.[17] Only alkylidene malonates have been reported to undergo effective conjugate addition without further assistance.[18] A general regio- and stereoselective method for formation of quaternary centers without the use of high pressure or Lewis acids is still needed in the repertoire of organic synthesis.

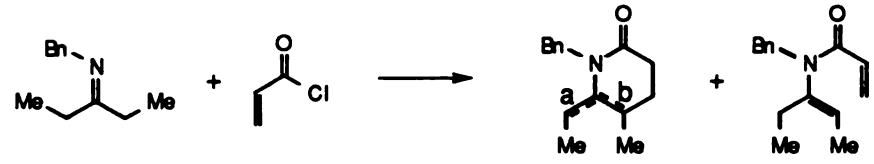
Aza-Annulation History. The addition of amines to electron deficient olefins has shown promise as a synthetic tool in the formation of nitrogen containing heterocycles. The reaction of α,β-unsaturated acids and acid chlorides with imines was reported in 1971 by Hickmott and coworkers (eq. 7).[19] The reaction was carried out both with and without TEA, and the results showed that in the presence of TEA, a 80:20 mixture of the *N*-acylated product (**26**) and the annulated product (**27**) was obtained. Without added TEA, the ratio increased to 80:20 in favor of the cyclic product.[19] In addition to these findings, Hickmott showed that acyclic imines would also undergo similar reactions (eq. 8).[19] With acyclic imine **28**, a 14% yield of the *N*-acylation product (**30**) was obtained, while the

annulated products (**29a** and **29b**) were obtained as an inseparable 75:25 mixture of olefin isomers in 38% combined yield.[19]



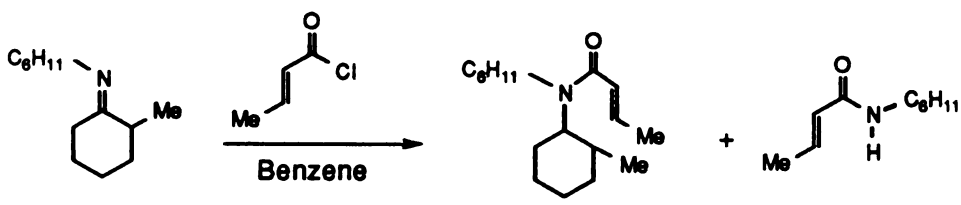
25 26 27 (7)

With TEA	50	:	50
Without TEA	20	:	80



28 29 30 (8)

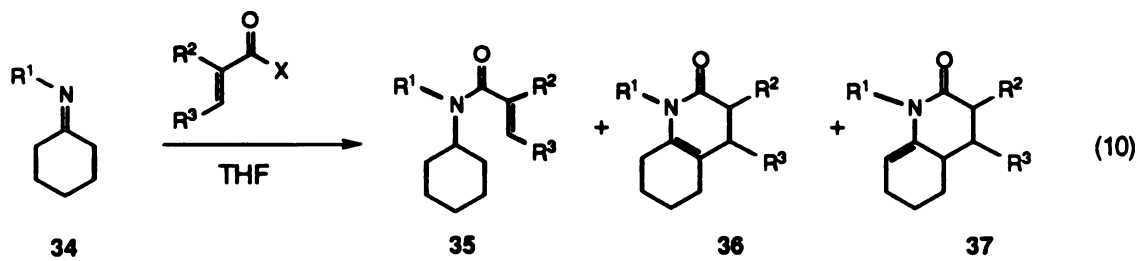
The use of substituted α,β-unsaturated acid chlorides in the reaction with imines has also been reported.[20] Hickmott showed that the reaction of crotonyl chloride with *N*-(2-methylcyclohexylidene)cyclohexyl amine resulted in 30% *N*-acylation (eq 9).[20] This reaction also gave amide **33** as a side product, and formation of the corresponding annulated product was not detected.[20] Ninomiya reported the formation of a 80:20 mixture of annulation to *N*-acylation products in a combined yield of 66% for the reaction of a tricyclic *N*-methyl imine with methacryloyl chloride.[21]



31 32 33 (9)

In addition to the reaction of imines and enamines with α,β-unsaturated acid chlorides, similar reactions have been carried out with α,β-unsaturated acids,[22] esters,[23] amides,[24] and anhydrides.[25] Hickmott has demonstrated that the reaction of acid chlorides with enamines stabilized by further conjugation can be utilized for the formation of tetrahydro-2-oxopyridines potentially through *N*-acylation followed by a [3,3] rearrangement and cyclization.[20] The potential for application of the annulation process prompted interest from these labs in the further development of this methodology.

Development of Aza-Annulation Methodology. A detailed study of the reaction of imines with activated acrylate derivatives was undertaken in these labs (eq. 5).[26] In this investigation, cyclic and acylic imines were subjected to numerous annulation conditions for the formation of nitrogen containing heterocycles. The goal of this methodological study was to find efficient annulation conditions for imine substrates that were not in conjugation with other functionality. These conditions were explored through variation of the methods used for the activation of the acrylate derivative. The influence of acrylate substituents was also investigated.[26]



34 35 36 37 (10)

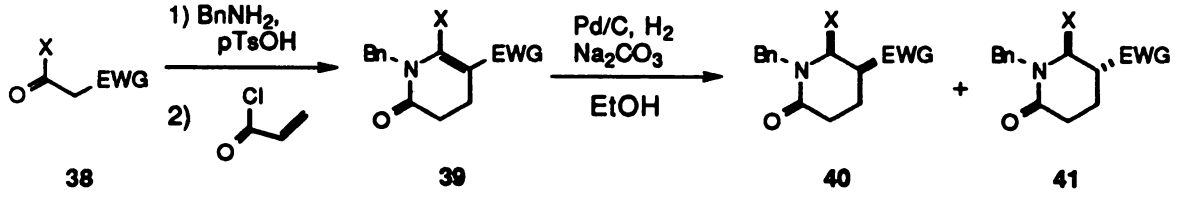
The results of this methodology study indicated that the optimum annulation conditions were achieved through the use of imines of cyclic ketones.[26] When the imine of *n*-butanal was subjected to annulation conditions, the major reaction product was that of *N*-acylation. Increasing the steric constraints of R^1 proved to increase the selectivity of δ-lactam formation (eq. 5). Substitution at the α-position of the acrylate derivative (R^2=Me;

R^3=H) did not affect the selectivity of product formation, however, β-substitution (R^2=H; R^3=Me) hindered annulation and favored formation of the *N*-acylated product (**35**).[26]

Finally, this study showed the effect of different methods of activation of the acrylate derivative.[26] While acrylic acid was effective for the annulation reaction, acrylic anhydride gave higher yields of the cyclic product. Although acrylic anhydride cleanly gave the desired product, the use of this reagent required two equivalents of the valuable acrylate unit. To avoid this waste, the sodium salt of acrylic acid was treated with ethyl chloroformate to provide a mixed anhydride-type reagent that was equally as effective in the annulation process.[26]

Applications of Aza-Annulation Methodology. Once the scope of the aza-annulation reaction had been investigated,[26] the optimum conditions were employed in a wide range of synthetic pathways. One such pathway was the construction of β-amino acid isosteres (Scheme II).[27] For these isosteres, δ-lactam systems were chosen because of the conformational constraints provided by the cyclic skeleton. The isosteres were obtained in good yields (56-91%) with cis to trans selectivities between 72:28 and >99:1.[27] Additional examples of the β-amino acid isosteres formed through the use of this methodology are given in Figure 2.[27]

Scheme II. Formation of β-Amino Acid Isosteres.



38 **39** **40** **41**

EWG= C(O)Me, C(O)Ph, CO_2Et, CO_2Me,C(O)NHPh, P(O)($OEt)_2$, SO_2Me, SO_2Ph
X=Me, CO_2Me;

Br

C

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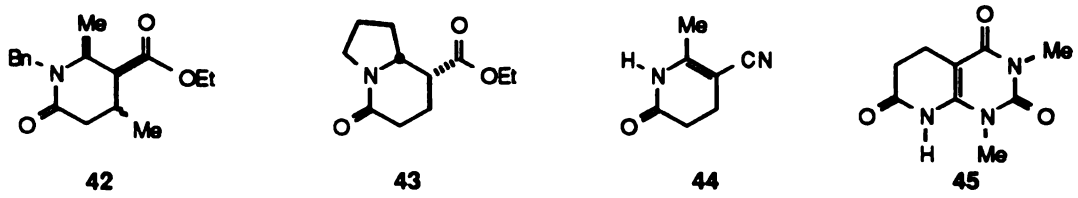
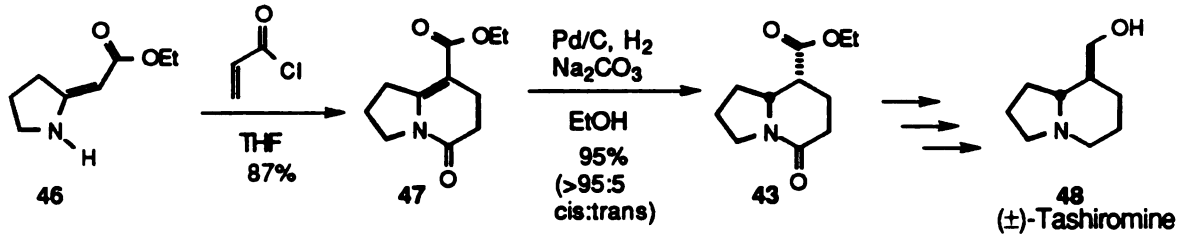


Figure 2. β-Amino Acid Isosteres.

The reaction of acryloyl chloride with *N*-alkyl enamines stabilized through conjugation with an electron withdrawing group demonstrated the suitability of the aza-annulation methodology for formation of the indolizidine ring system.[28] Application of the condensation/annulation/reduction process starting with **46** efficiently formed **43**, a precursor to (±)-tashiromine (Scheme III). Stabilization of the enamine through conjugation with an electron withdrawing substituent provided for complete alkene regioselectivity, thereby overcoming previous limitations of the reaction of imines with electron deficient olefins.[17]

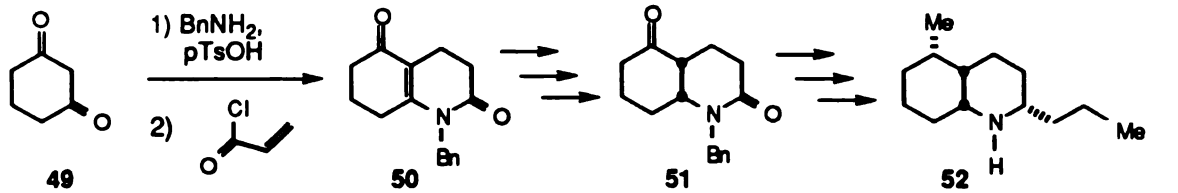
Scheme III. Preparation of (±)-Tashiromine.



Synthesis of (±)-5-epipumiliotoxin C (**52**) was used to showcase this aza-annulation process in the preparation of a decahydroquinoline alkaloid ring skeleton (Scheme IV).[29] The requisite cis ring fusion of epipumiliotoxin was efficiently obtained through selective hydrogenation of the key bicyclic lactam intermediate **50**, which was

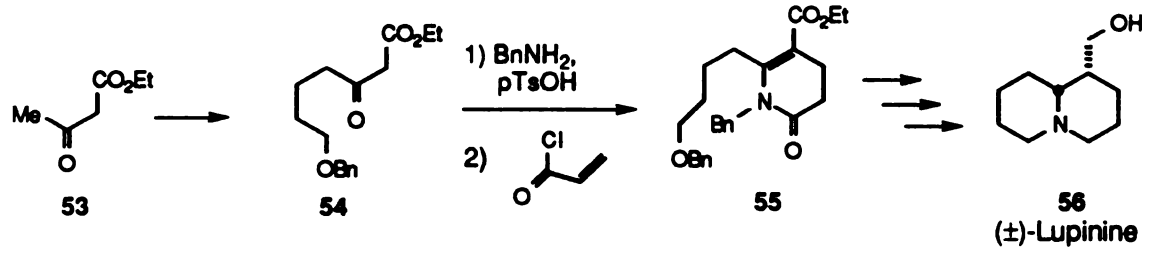
prepared from **49** in 76% yield through aza-annulation. Overall, (±)-5-epipumiliotoxin C was prepared in 6% yield from diketone **49**.[29]

Scheme IV. Synthesis of (±)-5-Epipumiliotoxin C.



Finally, the quinolizidine (±)-lupinine (**56**) was constructed through annulation of an acyclic enamine stabilized through conjugation with an ethyl ester (Scheme V).[30] Condensation of **54** with benzyl amine followed by annulation with acryloyl chloride gave intermediate enamide **55** in 80%yield.[30] Again, this synthesis illustrates the versatility of the newly developed aza-annulation methodology in the preparation of biologically important naturally occurring alkaloids.

Scheme V. Preparation of (±)-Lupinine.



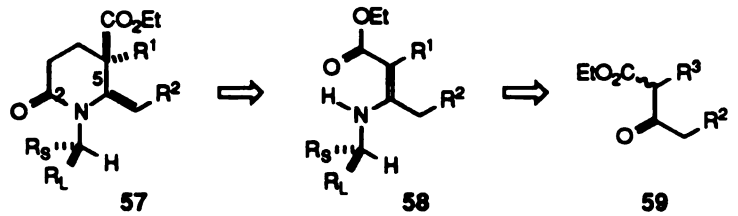
EXPERIMENTAL GOALS

The goal of this work was to extend the aza-annulation methodology[26] to include formation of asymmetric quaternary carbon centers in nitrogen heterocycles. The general applicability of this methodology was explored with respect to reaction temperature, solvent, and chiral auxiliary variation.

SYSTEM DESIGN

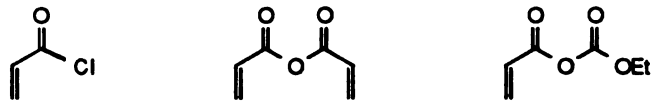
The system utilized in this investigation was designed to probe the efficiency of the aza-annulation methodology developed in these labs for the formation of asymmetric quaternary carbon centers at the C-5 position of the δ-lactam framework (Scheme VI). Lactam formation was accomplished *via* condensation of a β-ketoester with a chiral amine or amino acid ester to form a stabilized enamine, which underwent aza-annulation with electron deficient alkenes.

Scheme VI. General Formation of δ-Lactams.



Based on previous annulation studies,[26] a number of acrylate derivatives were employed as the electron deficient alkene fragment. These derivatives include acryloyl chloride (**60**), acrylic anhydride (**61**), and a mixed anhydride of acrylic acid and ethyl chloroformate (**62**) (Figure 3). In addition to variation the of acrylate derivative, the effects of temperature, solvent and chirality source on the outcome of the reaction were also

examined. The δ-lactams constructed through this aza-annulation process provide the framework for more complex biologically active such as peptide mimetics, the preparation of which is currently being investigated in these labs.[31]



60 61 62

Figure 3. Electron Deficient Olefins for Aza-Annulation.

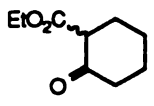
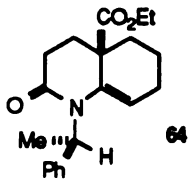
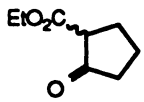
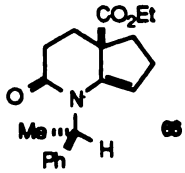
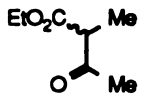
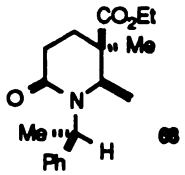
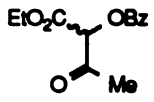
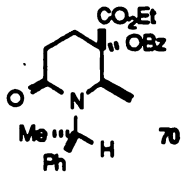
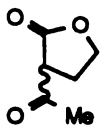
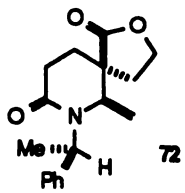
RESULTS AND DISCUSSION

Substrate Variation in the Aza-Annulation with Acryloyl Chloride.[32] Efficient formation of δ-lactams was achieved through the annulation of enamines derived from various β-keto esters and (*R*)-phenethylamine with acryloyl chloride. Undesired amide side products were avoided during the condensation reaction through the use of $Et_2O:BF_3$.[33] Prior to annulation, the catalyst was quenched by aqueous workup without harm to the enamine product. After workup, the solvent was changed to THF, and reaction with an electron deficient alkene resulted in formation of the desired δ-lactams.

Condensation of **63** with **73** followed by annulation gave bicyclic δ-lactam **64** in 85% isolated yield (Table I). The annulation process proved to be very selective in the formation of the quaternary center (>97:3) as can be seen from the proton NMR spectra (Figure 4). The spectra shows the signal for the methine proton of the chiral auxiliary, and the double bond proton, and only one signal for each type of proton could be detected. The stereochemical assignment which is addressed in the Mechanistic Implications section was made based upon comparison with related Michael addition reaction products,[17] and this assignment has been confirmed by X-ray crystal structure.[34] These reaction conditions offer two primary advantages over similar Michael addition processes. First, the reactions

proceed at atmospheric pressure in 4-6 hours, and second, Lewis acid catalysis is not required for complete reaction.

Table I. Asymmetric Induction with Respect to Substrate Variation.

Substrate	Product	Diastereomer Ratio[b]	Yield[c]
 63	 64	>97:3	85
 65	 66	97:3	76
 67	 68	97:3	92
 69	 70	92:8	58
 71	 72	94:6	80

[a]Reaction conditions: (i) (*R*)-PhCHMeNH$_2$ ((*R*)-73), Et$_2$O:BF$_3$, benzene, reflux; (ii) acryloyl chloride, THF, reflux. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Yield of the diastereomeric mixture after chromatography.

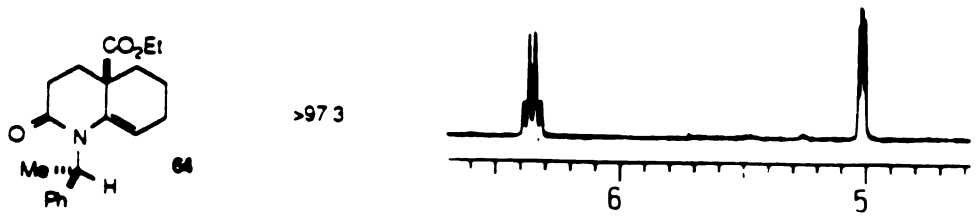


Figure 4. Partial ^{1}H NMR of 64.

Keto ester **65** could also be transformed efficiently to the corresponding δ-lactam (**66**) through the same procedure. The diastereoselectivity (97:3, Figure 5) was also comparable to that observed in the formation **64**. Unfortunately, the 6-5 ring system of **66** was a great deal more sensitive toward hydrolysis, and could be isolated in 76% yield at best after chromatography on a base washed silica gel column.

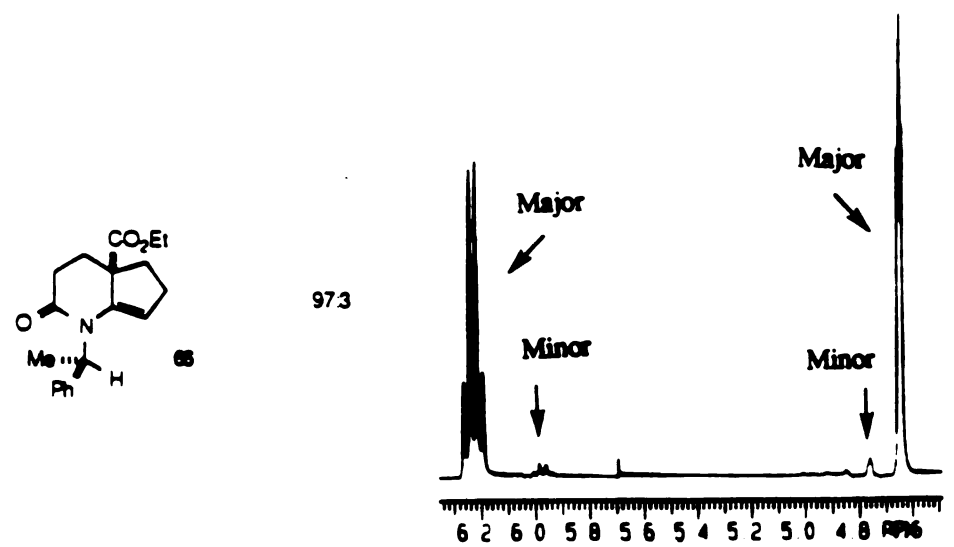


Figure 5. Partial ^{1}H NMR of 66.

Although the geometry of the enamine was restricted by the ring skeletons of **63** and **65**, the degree of diastereoselectivity was not compromised through the use of acyclic β-keto esters **67**, **69**, and **71**. Enamide **68** was obtained as a 97:3 mixture of diastereomers as determined from the NMR signal for the double bond protons (Figure 6). A 92:8 ratio of diastereomers was obtained for the formation of **70** (Figure 7), and a 94:6 ratio of **72** (Figure 8) was also obtained. The diastereomeric ratio of **72** was determined bfrom the ratio of the methine proton of the chiral auxiliary.

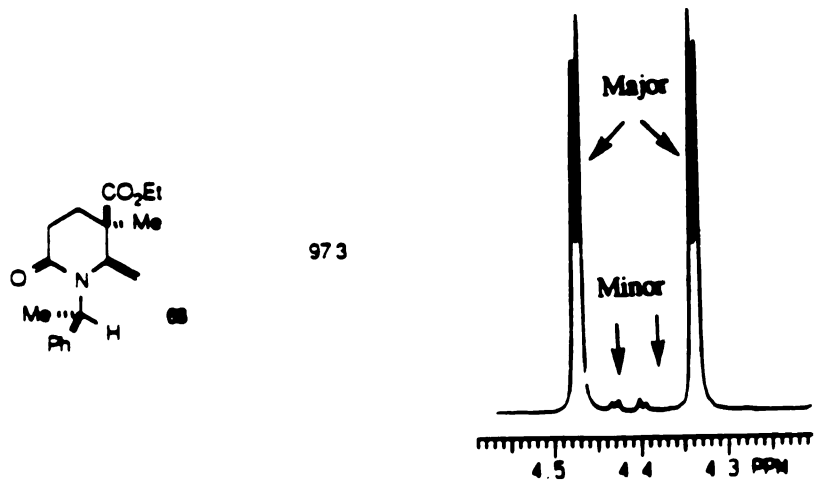


Figure 6 Partial ^{1}H NMR of 68.

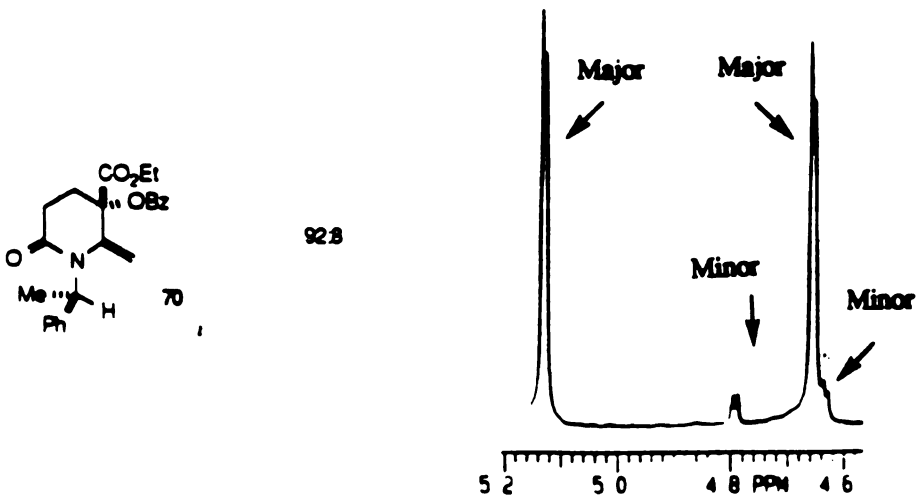


Figure 7. Partial ^{1}H NMR of 70.

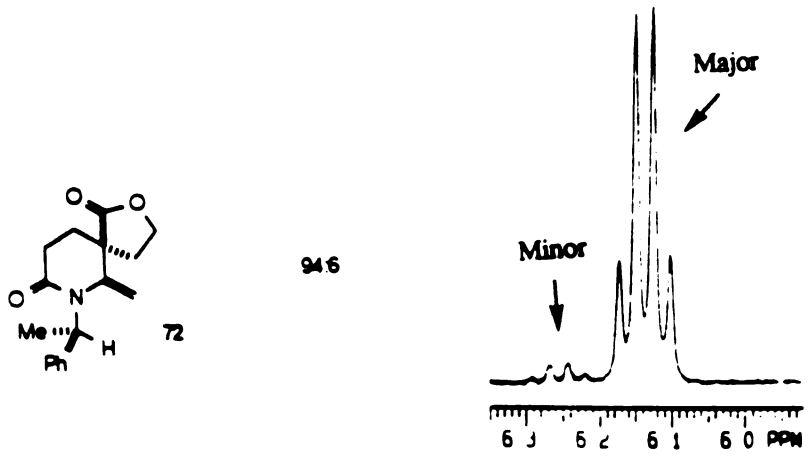
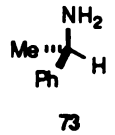
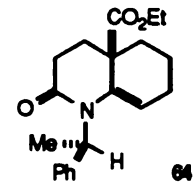
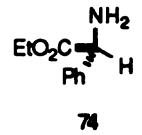
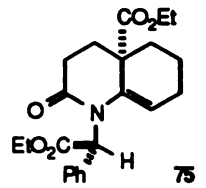
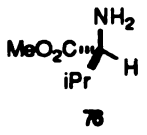
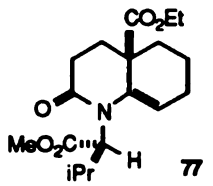


Figure 8. Partial ^{1}H NMR of 72.

Hydrogen bonding between the enamine hydrogen and the carbonyl of the ester functionality held the acyclic enamines in one conformation, thereby a highly selective annulation process (Figure 11).[17a] Little difference in selectivity was observed between **68** and **70**, however, **70** was much more sensitive to the isolation conditions due to the presence of a tertiary allylic ester, and could only be isolated in only 58% yield. Interestingly, the spiro lactam could be easily isolated in 80% yield.

Asymmetric Induction as a Function of Chiral Auxiliary. In addition to (*R*)-phenethyl amine, several other chiral amines were examined as auxiliaries for the stereoselective formation of quaternary centers through aza-annulation. Reaction of **63** with the ethyl ester of (*R*)-phenyl glycine (**74**) was achieved by isolation of the (*R*)-phenylglycine ethyl ester hydrochloride salt which was then washed with aqueous sodium bicarbonate into a benzene layer to which was added the β-keto ester and Et_2O:BF_3. The reaction with the methyl ester of L-valine (**76**) was accomplished in the same manner (Table II).

Table II. Asymmetric Induction and Chiral Auxiliary Variation.

Amine	Product	Diastereomer Ratio[b]	Yield[c]
 73	 64	>97:3	85
 74	 75	79:21	63
 76	 77	57:43	43

[a]Reaction conditions: (i) 1° amine, benzene, $Et_2O{:}BF_3$, reflux; (ii) acryloyl chloride, THF, reflux. [b]Determined by ^1H NMR of the crude reaction mixture. [c]Yield of the diastereomeric mixture after chromatography.

The ratio of diastereomers of **75** (79:21) was determined from the integration of the ^1H NMR signals arising from the double bond proton (Figure 9). Condensation of **63** with **76**, followed by aza-annulation gave **77** as a 57:43 ratio of diastereomers as determined from the chiral auxiliary methine proton signal (Figure 10).

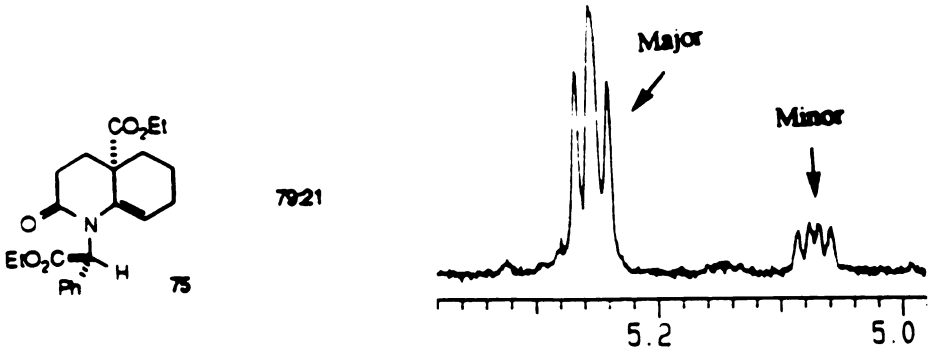


Figure 9. Partial ^{1}H NMR of 75.

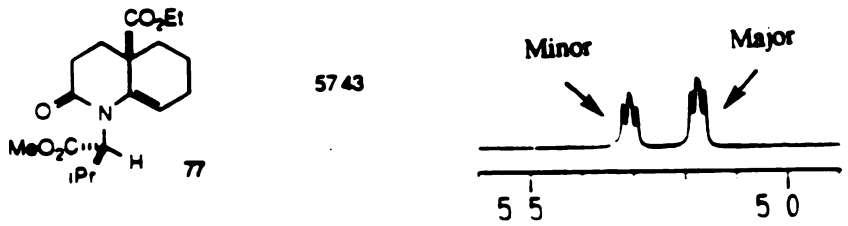


Figure 10 Partial ^{1}H NMR of 77.

In comparison to (*R*)-phenethyl amine, neither the phenyl glycine ethyl ester nor the valine methyl ester was as effective for the selective formation of δ-lactams. The results obtained for the variation of chiral auxiliary were interesting in that the phenyl-methyl combination seemed to be quite unique. The selectivities observed for the three different chiral auxiliaries can be rationalized through examination of the most stable enamine conformations. Conjugation with the ester functionality favors almost exclusively the enamine tautomer over the imine tautomer, and the orbital overlap in the enamino esters is great enough that the enamine is planar. In addition, the hydrogen bonding between the enamine proton and the carbonyl oxygen of the ester group limits the conformational freedom of these species. As a result, the selectivity of approach of the acrylate derivative is then determined by the amount of rotation around the bond between the nitrogen and the

chiral auxiliary. Figure 11 illustrates the rotational constraints of each chiral auxiliary based on the reported "A values".[35] The difference in selectivity between *R*)-phenethyl amine (**A**) and the phenyl glycine ethyl ester (**B**) arises from the difference in steric bias between the methyl group and the ethyl ester group. Since the methyl group is sterically more restricting, greater selectivities were obtained with (*R*)-phenethyl amine. Valine ethyl ester is sterically less demanding compared to both (*R*)-phenethyl amine and phenyl glycine ethyl ester, and as a result, the selectivities of annulation are lowest for the valine methyl ester.

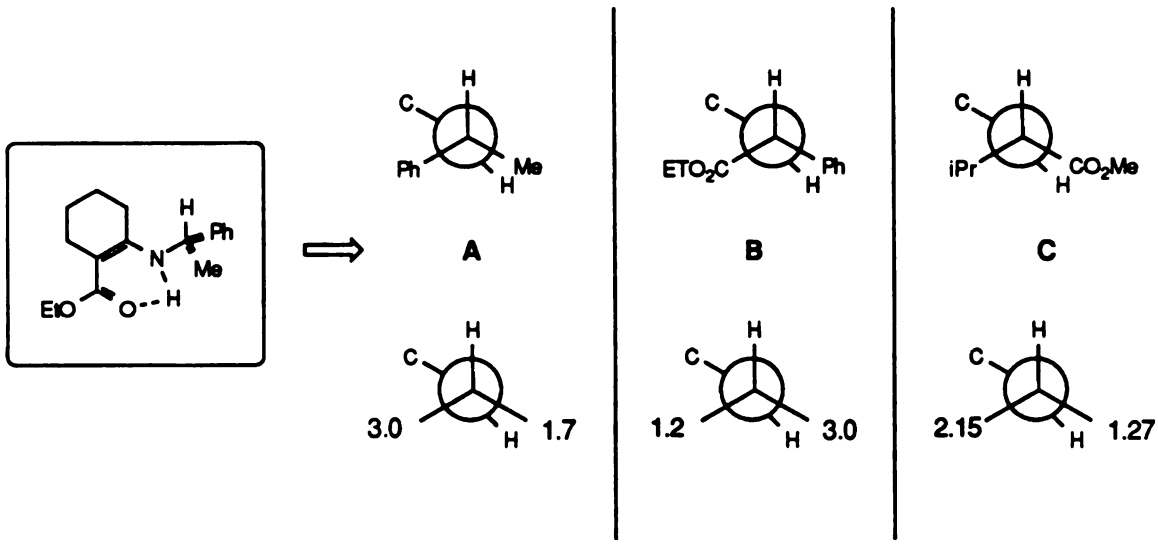
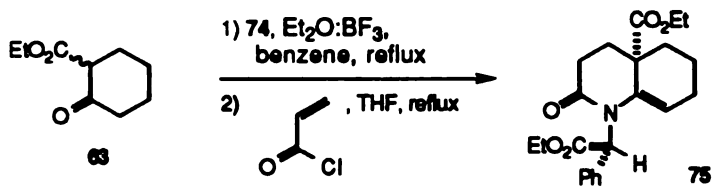


Figure 11. Comparison of Chiral Auxiliaries.

Temperature Dependence of Asymmetric Induction. As described above, the reaction of **63** with **74**, followed by aza-annulation with acryloyl chloride, did not lead to the highest selectivity for formation of the quaternary centers. However, this system was quite suitable for examination of the effects of reaction conditions (solvent and temperature) on product distribution. Reduction of the annulation temperature from 25 °C to -33 °C resulted in diastereoselectivities comparable to those obtained for the use of **73** (98:2) (Table III). Increasing the annulation temperature from -33 °C to 0 °C showed a small decrease in diastereoselectivity (93:7). The most notable reaction feature at this

temperature was the drastic difference between the isolated yields when dioxane was used as the solvent for annulation (92:8, 24% yield). As expected, the diastereoselectivity decreased as the reaction temperature increased. The yields also remained predictably low for the reactions in which dioxane was used as a solvent. Interestingly, the reaction in dioxane at reflux gave a very low yield with reversed product selectivity (36:64), perhaps due to a more rapid decomposition of one isomer over that of the other, or epimerization catalyzed by the HCl reaction byproduct.

Table III. Asymmetric Induction and Temperature Variation for the Conversion of 63 to 75.



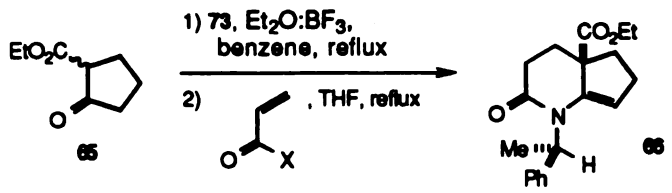
solvent	T °C	diastereomer ratio[b]	yield[c]
THF	-33	98:2	77
THF	0	93:7	68
dioxane	0	92:8	24
THF	66	79:21	63
dioxane	66	82:18	43
dioxane	101	36:64	28

[a]Reaction conditions: (i) (*R*)-74, 63, benzene, $Et_2O:BF_3$, reflux; (ii) acryloyl chloride. [b]Determined by ^1H NMR of the crude reaction mixture. [c]Yield of the diastereomeric mixture 75 after chromatography.

Asymmetric Induction and Acrylate Activation. The difference in reaction selectivity as a function of acrylate derivative was also explored, and the results are shown in Table IV. As previously described, the mixed anhydride species (62) was obtained

from the mixture of sodium acrylate and ethyl chloroformate (Table IV, X=OCO_2Et). Although the selectivity for the formation of **66** with the mixed anhydride was slightly lower (90:10) than that obtained for the use of acryloyl chloride (97:3), the increase in yield (87% and 64% respectively, Table IV) made this a synthetically favorable reaction .

Table IV. The Effect of Acrylate Reagent on the Formation of 66.

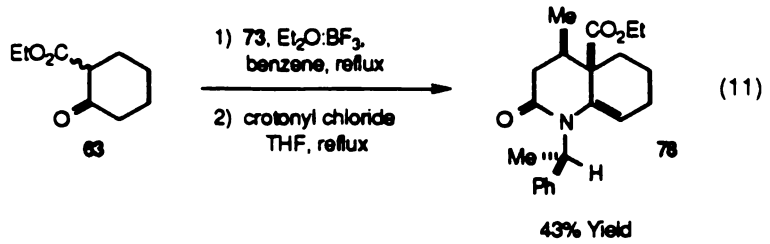


reagent -X	diastereomer ratio[a]	yield[b]
-Cl	97:3	64
$-O_2CCH{=}CH_2$	90:10	75
$-OCO_2Et$	90:10	87

[a]Determined by ^1H NMR of the crude reaction mixture.
[b]Yield of the diastereomeric mixture **66** after chromatography.

Acrylate Substitution Patterns and Asymmetric Induction. Variations in the substitution pattern of the acrylate derivatives were also examined for effectiveness in the simultaneous formation of two stereogenic centers. Annulation of the condensation product of **73** and **63** with crotonyl chloride was significantly slower that the corresponding reaction with acryloyl chloride (eq. 11). The reaction with crotonyl chloride required heating at reflux for 48 hours, and these rather vigorous conditions contributed to a low isolated yield of **78** (43%) after partial purification by column chromatography (≈90% pure). The prominent impurities from this reaction, were products of side reactions with the acrylate derivative, including MeHC=CHCONHCHMePh, and further purification

of the reaction mixture gave only a 30% yield of **78** as mixture of stereoisomers (94:4:2, Figure 12).



(11)

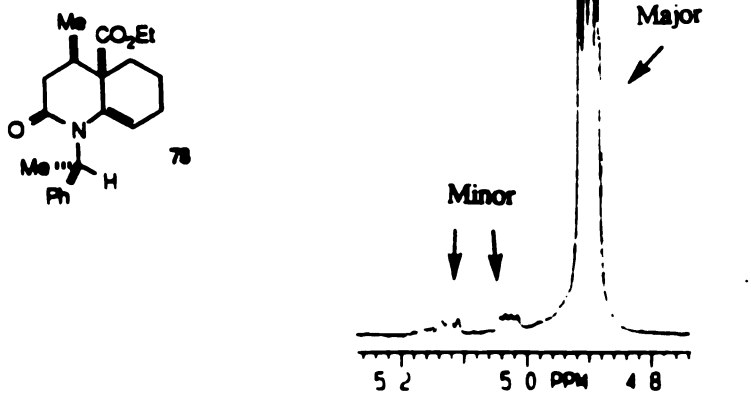
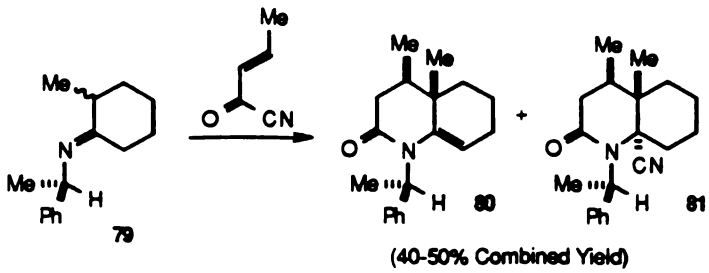


Figure 12. Partial ^{1}H NMR of 78.

The stereochemical assignment for **78** was made by comparison of the spectral data with that reported for **80** which was formed during the annulation of **79** (eq. 12).[36] The reported chemical shifts and coupling constants for the proton alpha to the lactam carbonyl in **80** are δ=2.28 ppm, dd, J = 18.5, 12.3 Hz, and δ=2.66 ppm, dd, J = 18.5, 6.4 Hz. The analogous protons in **78** are δ=2.25 ppm, dd, J = 18.1, 12.7 Hz, and δ=2.65 ppm, dd, J = 18.1, 5.7 Hz.



(12)

Treatment of the condensation product of **73** and **63** with methacryloyl chloride resulted in the formation of an inseparable mixture (52:48) of diastereomers of **82** (Figure 13). Although the selectivity was poor, treatment of the product mixture with NaH resulted in equilibration to an 83:17 ratio of diastereomers epimeric at the position alpha to the lactam carbonyl (eq. 13).

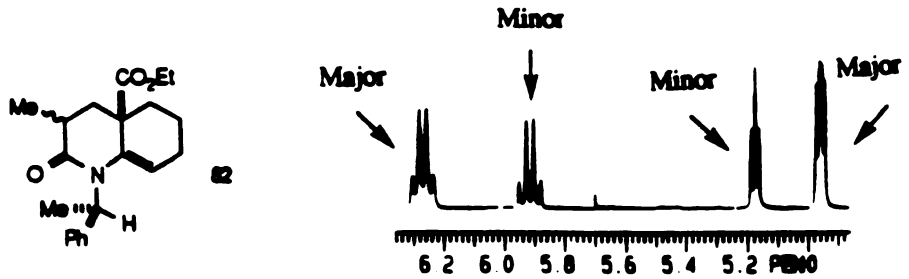
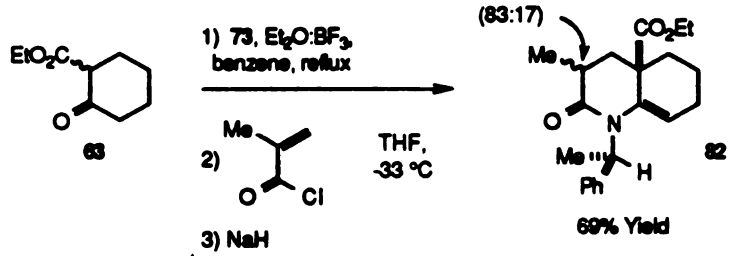


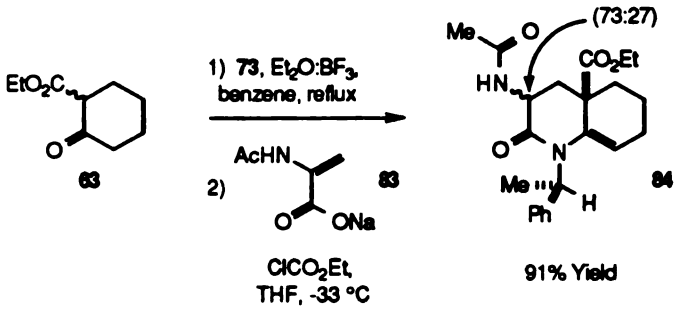
Figure 13. Partial ^{1}H NMR of 82.



(13)

Annulation with a mixture of **83** and ethyl chloroformate and the enamine derived from the condensation of **73** with **63** resulted in a mixture of four products in a ratio of

64:23:9:4 (**84**, eq. 14). Silica gel chromatography facilitated separation into two mixtures of two isomers each. The first mixture contained the original 64 and 9% isomers, and the second was composed of the isomers that constituted 23 and 4% of the original mixture. Treatment of the original reaction mixture or the separated mixtures with NaH, DBU or pTsOH in order to encourage equilibration, resulted in the slow disappearance of all four isomers.



(14)

The four isomers in the original mixture reflect the incomplete asymmetric induction in the formation of the quaternary center, as well as the existence of epimers at the carbon alpha to the lactam carbonyl (Figure 14). As observed for the formation of **82**, higher selectivity is obtained at the quaternary center than at the C-2 position in the concomitant formation of two stereogenic centers. Based on this observation, the ratio of C-2 epimers of **84** were assigned as [64+9]:[23+4], or 73:27, and the ratio of isomers at the quaternary center were 87:13 ([64+23]:[9+4]). The 87:13 ratio at the quaternary center parallels the 90:10 ratio observed in the formation of **66** through annulation with a mixed anhydride reagent (Table IV).

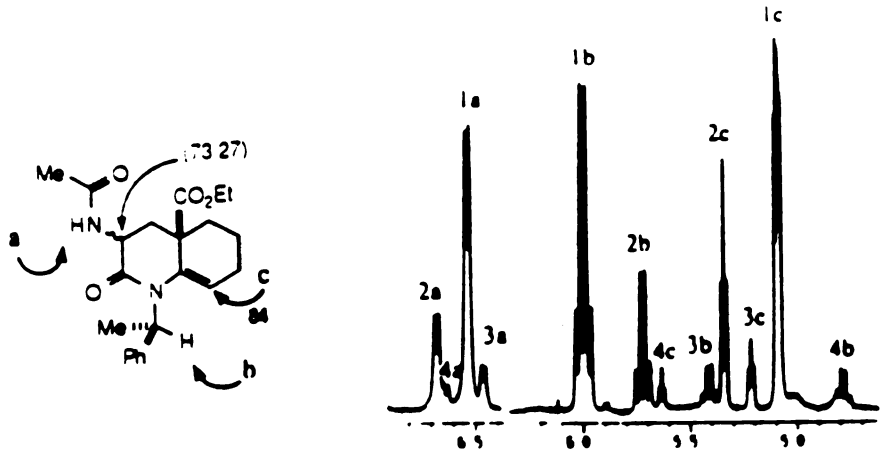


Figure 14 · Partial ^{1}H NMR of 84.

Mechanistic Implications. Several mechanistically interesting observations have been made through the course of this study. One such observation is the facial selectivity in the reaction of the enamine with the acrylate derivative (Figure 15). As discussed earlier, there is a hydrogen bonding interaction between the enamine hydrogen and the carbonyl oxygen of the ester group (**85**). This conformational restriction creates a facial bias for attack of the incoming acrylate derivative since one face of the enamino ester is more hindered due to the larger group R_L. The favored orientation of the stereogenic center has the hydrogen toward the CH_2 unit of the ketone substrate.[10,17,27] As illustrated, the favored approach of the acrylate derivative would be from the bottom face of the enamine, which would result in selective formation of the quaternary center.

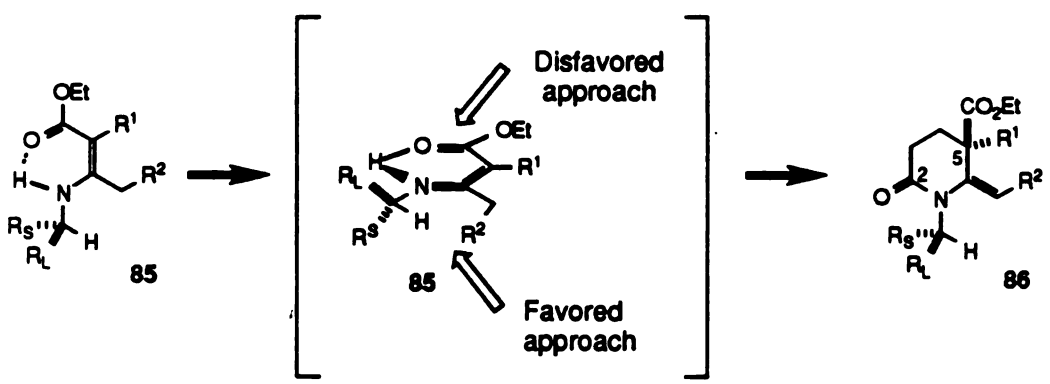
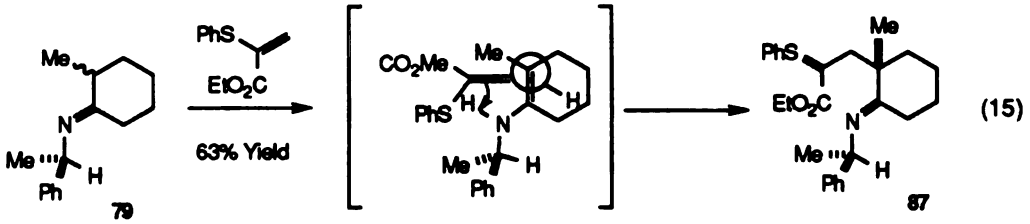


Figure 15. Enamine Facial Selectivity

Additional observations that give information regarding the mechanism involved in this process are the dependence of the selectivity upon temperature and acrylate derivative, and the lack of selectivity in formation of a stereogenic center alpha to the lactam carbonyl. The selectivity of Michael addition reactions has been reported to be independent of both temperature[3a] and acrylate derivative,[37] while the systems in this study have demonstrated contrasting behavior. Also, the Michael addition reaction of α-(phenylthio)acrylate with **79** to give **87** gives complete selectivity at the alpha center reportedly through an aza-ene type cyclic transition state. The cyclic transition state allows proton transfer to occur in a concerted fashion which results in high selectivity at the α-center (eq. 15).[1] However, the aza-annulation resulted in poor alpha selectivity, indicating a difference in the nature of the reactive intermediates.[36] The reactions of this study give good evidence that the same mechanistic pathway is not followed in the annulation process.



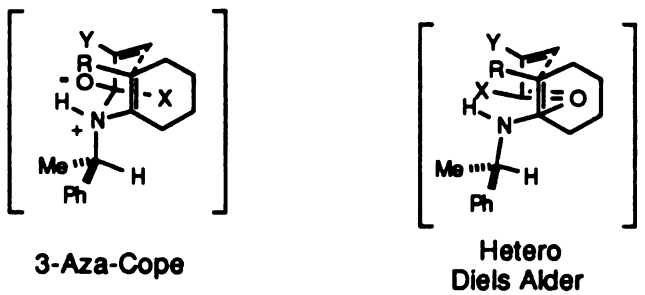


Figure 16. Mechanistic Alternatives for the Aza-Annulation.

In the aza-annulation reaction, selectivity at the β-position and the ring juncture, as well as the lack of selectivity at the α-center can be rationalized through alternative concerted transition states (Figure 16). The 3-aza-Cope transition state forms a chair through interaction of the carbonyl carbon with the enamine nitrogen. Since proton abstraction is not involved in a process that proceeds through such a transition state, avenues that allow for epimerization of the alpha center are not ruled out during bond formation. Both the 3-aza-Cope transition state and the hetero Diels Alder transition state are polarized to a greater extent than the aza-ene transition state which helps to explain the greater reactivity observed in the aza-annulation reaction. The differences observed in the aza-annulation reaction compared to the Michael reaction provide evidence that the two reactions occur through different pathways.

CONCLUSIONS

Aza-annulation has been shown to be effective for the efficient regio- and stereoselective formation of nitrogen heterocycles containing quaternary centers. Such heterocycles were obtained in yields from 43 to 87% with 84-96% de. The two step condensation/annulation procedure has become a valuable synthetic procedure for the preparation of potentially valuable heterocycles,[38] as well as intermediates in the preparation of naturally occurring alkaloids and nonnatural peptidomimetic molecules.[31]

EXPERIMENTAL SECTION.

General Methods. All reactions were carried out performing standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of nitrogen. Azeotropic removal of H_2O was assisted by the use of 4-Å molecular sieves.[39] Concentration of solutions after work up was performed by rotary evaporator. Keto esters **63**, **65**, **67**, and **71** were purchased from Aldrich Chemical Company, and **69** was prepared as previously reported.[40]Acryloyl chloride was purchased from Fluka and used without purification. The following reagents were purchased from Aldrich Chemical Company: (R)- and (S)-alphaphenethyl amine, (R)-phenyl glycine, L-valine, $Et_2O{:}BF_3$, crotonyl chloride, and methacryloyl chloride. 2-Acetamido acrylix acid was purchased from both Aldrich Chemical Company and Lancaster.

NMR Spectra were obtained on a Varian Gemini 300 instrument with $CDCl_3$ as the solvent. ^1H NMR spectral data are reported as follows: chemical shifts relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, b = broad), coupling, and integration. ^{13}C signals are reported in ppm relative to $CDCl_3$ (77.0 ppm).

General Procedure For $Et_2O{:}BF_3$ Catalyzed Enamine Formation ((*R*)-73):[33a] The β-keto ester (3.0 mmol) was combined with **73** (3.3 mmol) in benzene (23 mL), and $Et_2O{:}BF_3$ (0.15 mmol) was added at room temperature. The flask was fitted with a modified Dean-Stark trap filled with 4-Å molecular sieves, and the mixture was heated at reflux until the reaction was complete as determined by NMR analysis (6-18 h). The enamino ester was then washed with saturated aqueous $NaHCO_3$ (15 mL), the aqueous layer was extracted with Et_2O (15 mL), and the combined organic layers were washed with saturated aqueous NaCl. The organic fractions were then dried ($MgSO_4$), concentrated, taken up in THF[41] (20 mL), and carried on without further purification.

General Procedure For $Et_2O:BF_3$ Catalyzed Enamine Formation (Amino Acid Ester Salts):[33a] The amino acid ester salt (9.0 mmol) was suspended in benzene (13 mL) and washed with saturated aqueous $NaHCO_3$. After the aqueous layer was washed with benzene (10 mL), the benzene layers were combined, washed with saturated aqueous NaCl, and dried ($MgSO_4$). The benzene solution was then decanted into the flask containing the β-keto ester (3.0 mmol), and $Et_2O:BF_3$ (0.2 mL) was then added. Enamine formation was carried out as described above.

General Procedure For Aza-Annulation of Enamines (Acid Chloride Method): The acid chloride (3.9 mmol) was added to a solution of the corresponding enamine in THF (20 mL, *vide supra*). The reaction was stirred at the appropriate temperature until complete as indicated by NMR analysis of a sample quenched with saturated aqueous $NaHCO_3$ and dried with $MgSO_4$. When the reaction was complete, the mixture was stirred with 10 mL of 10% NaOH, and then extracted with Et_2O (3 x 10 mL). The organic extracts were combined and washed with saturated aqueous NaCl, dried ($MgSO_4$), concentrated, and purified by column chromatography.

General Procedure For Aza-Annulation of Enamines (Anhydride Method): Sodium acrylate (5.1 mmol) was suspended in THF (10 mL) and was treated with acryloyl chloride (0.31 mL, 3.9 mmol) or ethyl chloroformate (3.9 mmol) and the mixture was stirred at room temperature for 1h. The mixture containing the anhydride was then transferred *via* cannula to a solution of the β-enamino ester in THF (10 mL), and the mixture was stirred at the appropriate temperature until the reaction was complete. Work up conditions were as described for the acid chloride reactions.

64: (60:40/Et_2O:petroleum ether, 0.83 g, 2.55 mmol, 85% yield), $[\alpha]_D$ = -115.2, (c = 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ1.28 (t, *J* = 7.1 Hz, 3 H), 1.45-1.65 (m, 2 H), 1.70-1.82 (m, 2 H), 1.72 (d, *J* = 7.1 Hz, 3 H), 1.93 (m, 1 H), 2.11 (m, 1 H), 2.22 (m, 1 H), 2.34 (ddd, *J* = 13.1, 6.5, 2.1 Hz, 1 H), 2.53 (ddd, *J* = 18.4, 12.3, 6.4 Hz, 1 H), 2.68 (ddd, *J* = 18.4, 6.5, 2.1 Hz, 1 H), 4.13-4.28 (m, 2 H), 5.02 (dd, *J* = 5.4, 3.0 Hz, 1 H), 6.35 (q, *J* = 6.9 Hz, 1 H), 7.17-7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.7, 18.4, 24.4, 30.3, 30.9, 35.4, 46.5, 50.5, 61.2, 112.2, 125.5, 126.2, 128.4, 133.7, 142.3, 168.8, 174.3; IR (Film) 3056, 2986, 2920, 1725, 1669, 1636, 1285, 741 cm^{-1}; HRMS calcd for $C_{20}H_{25}NO_3$ *m/z* 327.1834, obsd *m/z* 327.1833.

66: (70:30/Et_2O:petroleum ether, 0.71 g, 2.28 mmol, 76% yield); $[\alpha]_D$ = -15.8, (c = 5.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.1 Hz, 3 H), 1.60-1.78 (m, 2 H), 1.62 (d, *J* = 7.1 Hz, 3 H), 2.12 (ddt, *J* = 15.3, 9.0, 3.2 Hz, 1 H), 2.24 (dd, *J* = 12.9, 7.6 Hz, 1 H), 2.34 (m, 1 H), 2.44 (m, 1 H), 2.51-2.69 (m, 3 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 4.63 (t, *J* = 2.8 Hz, 1 H), 6.22 (q, *J* = 7.1 Hz, 1 H), 7.12-7.30 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.2, 29.5, 30.3, 30.6, 35.7, 50.0, 55.2, 61.2, 110.4, 126.0, 126.6, 128.3, 137.9, 141.0, 169.0, 174.2; IR (Film) 3056, 2986, 2942, 2857, 1725, 1667, 1636, 1379, 1265, 741, 704 cm^{-1}; HRMS calcd for $C_{19}H_{23}NO_3$ *m/z* 313.1677, obsd *m/z* 313.1662.

68: (60:40/Et_2O:petroleum ether, 0.84 g, 2.76 mmol, 92% yield); $[\alpha]_D$ = -55.2, (c = 3.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3 H), 1.40 (s, 3 H), 1.43 (s, 3 H, minor isomer), 1.67 (d, *J* = 7.1 Hz, 3 H), 1.67-1.76 (m, 1 H), 2.34 (ddd, *J* = 13.4, 6.9, 4.4, Hz, 1 H), 2.60 (ddd, *J* = 18.3, 6.9, 4.1 Hz, 1 H), 2.73 (ddd, *J* = 18.3, 10.2, 6.9 Hz, 1 H), 4.09-4.20 (m, 2 H), 4.36 (d, *J* = 1.9 Hz, 1 H), 4.43 (d, *J* = 1.9 Hz, 1 H, minor isomer), 4.46 (d, *J* = 1.9 Hz, 1 H, minor isomer), 4.51 (d, *J* = 1.9 Hz, 1 H), 6.22 (q, *J* = 7.1 Hz, 1 H), 7.15-7.35 (m, 5 H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 13.6,

14.1, 23.6, 29.7, 29.8, 46.8, 50.8, 60.9, 98.1, 125.4, 126.0, 127.9, 141.4, 143.7, 169.2, 173.5; IR (Film) 3063, 3032, 2982, 2942, 1728, 1667, 1628, 1449, 1381, 1356, 911, 734, 700 cm^{-1}; HRMS calcd for $C_{18}H_{23}NO_3$ *m/z* 301.1678, obsd *m/z* 301.1686.

70: (90:10/Et_2O:petroleum ether, 0.71 g, 1.74 mmol, 58% yield); $[\alpha]_D$ = +74.6, (c = 6.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3 H), 1.60 (d, *J* = 7.1 Hz, 2 H), 2.45 (tdd, *J* = 13.9, 4.8, 1.1 Hz, 1 H), 2.58 (td, *J* = 10.5, 6.4 Hz, 1 H), 2.73 (tdd, *J* = 1.1, 5.9, 16.0 Hz, 1 H), 2.94 (ddd, *J* = 16.0, 10.2, 5.9 Hz, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 4.63 (m, 1 H, minor isomer), 4.65 (d, *J* = 1.9 Hz, 1 H), 4.81 (d, *J* = 1.9 Hz, 1 H, minor isomer), 5.13 (d, *J* = 1.9 Hz, 1 H), 6.11 (q, *J* = 7.1 Hz, 1 H), 7.21-7.62 (m, 8 H), 8.02 (dd, *J* = 8.4, 1.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 15.0, 27.2, 29.5, 51.7, 62.2, 80.5, 102.9, 126.3, 126.9, 128.5, 128.6, 129.3, 129.7, 133.6, 139.5, 141.2, 165.1, 168.6, 170.2; IR (Film) 3056, 2988, 1745, 1727, 1680, 1634, 1265, 738, 706 cm^{-1}; HRMS calcd for $C_{24}H_{25}NO_5$ *m/z* 407.1733, obsd *m/z* 407.1736.

72: (70:30/Et_2O:petroleum ether, 0.68 g, 2.40 mmol, 80% yield); $[\alpha]_D$ = +74.4, (c = 3.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6.9 Hz, 1 H, minor isomer), 1.74 (d, *J* = 7.2 Hz, 3 H), 1.80 (ddd, *J* = 13.3, 6.4, 4.4 Hz, 1 H), 2.17 (ddd, *J* = 12.9, 9.5, 8.2 Hz, 1 H), 2.35 (dtd, *J* = 12.9, 6.5, 2.5 Hz, 2 H), 2.59 (ddd, *J* = 17.5, 10.5, 6.6 Hz, 1 H), 2.83 (ddd, *J* = 17.5, 6.6, 4.5 Hz, 1 H), 3.98 (td, *J* = 9.5, 6.6 Hz, 1 H), 4.28 (d, *J* = 3.0 Hz, 1 H), 4.30 (td, *J* = 9.5, 2.8 Hz, 1 H), 4.51 (d, *J* = 3.0 Hz, 1 H), 5.08 (q, *J* = 7.0 Hz, 1 H, minor isomer), 6.17 (q, *J* = 7.4 Hz, 1 H), 7.20-7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 28.2, 29.5, 34.3, 48.5, 52.4, 65.2, 98.4, 126.5, 127.0, 128.4, 140.2, 140.6, 168.8, 176.6; IR (Film) 3056, 2988, 2800, 1717, 1690, 1422, 1265, 739, 706 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO_3$ *m/z* 285.1365, obsd *m/z* 285.1370.

75: (70:30/Et_2O:petroleum ether, 0.73 g, 1.89 mmol, 63% yield); $[\alpha]_D$ = +106.4, (c = 3.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, *J* = 7.1 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.16-1.32 (m, 1 H), 1.33-1.56 (m, 1 H), 1.57-1.70 (m, 1 H), 1.78 (td, *J* = 12.0, 6.3 Hz, 1 H), 2.05-2.18 (m, 2 H), 2.21-2.33 (m, 2 H), 2.45 (ddd, *J* = 18.1, 11.9, 5.9 Hz, 2 H), 2.56 (ddd, *J* = 18.1, 6.3, 2.7 Hz, 2 H), 3.89-4.11 (m, 2 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 5.05 (m, 1 H, minor isomer), 5.25 (dd, *J* = 4.4, 3.6 Hz, 1 H), 5.45 (s, 1 H, minor isomer), 5.79 (s, 1 H), 7.20-7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 18.3, 24.1, 30.2, 30.5, 34.8, 46.5, 61.1, 61.3, 109.0, 127.4, 127.7, 128.7, 134.5, 136.4, 168.5, 169.1, 173.7; IR (Film) 3058, 2982, 2938, 2872, 1727, 1673, 1645, 1453, 1401, 1267, 1202, 1028, 738, 704 cm^{-1}; HRMS calcd for $C_{22}H_{27}NO_5$ *m/z* 385.1889, obsd *m/z* 385.1916.

77: (70:30/Et_2O:petroleum ether, 0.44g, 1.29 mmol, 43% yield, 57:43 ratio of diastereomers); ^1H NMR (300 MHz, $CDCl_3$) characteristic peaks (both isomers) δ 0.78 (d, *J* = 7.0 Hz, 3 H, minor), 0.85 (d, *J* = 7.0 Hz, 3 H, major), 1.10 (d, *J* = 6.4 Hz, 3 H, minor), 1.61 (d, *J* = 6.4 Hz, 3 H, major), 3.63 (s, 3 H, major), 3.67 (s, 3 H, minor), 5.17 (dd, *J* = 3.1, 1.5 Hz, 1 H, major), 5.31 (dd, *J* = 3.1, 1.5 Hz, 1 H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) (both isomers) δ 14.0, 14.1, 18.2, 18.4, 18.6, 18.7, 21.9, 22.1, 24.1, 24.3, 26.8, 28.5, 29.9, 30.1, 30.3, 30.5, 35.2, 46.5, 46.6, 51.8, 51.9, 61.1, 61.3, 61.8, 61.9, 76.5, 77.0, 77.1, 77.4, 107.6, 107.8, 136.6, 168.4, 168.7, 171.2, 173.7; IR (Film) 3056, 2953, 2874, 2843, 1730, 1669, 1642, 1265, 1215, 1024, 745, 704 cm^{-1}; HRMS calcd for $C_{18}H_{27}NO_5$ *m/z* 337.1888 obsd *m/z* 337.1888.

78: (60:40/Et_2O:petroleum ether, 0.44 g, 1.29 mmol, 43% yield); $[\alpha]_D$ = -70.9, (c = 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.8 Hz, 3 H), 1.2 (d, *J* = 7.1 Hz, 3 H), 1.60 (d, *J* = 7.1 Hz, 3 H), 1.73-1.89 (m, 2 H), 1.92-2.54 (m, 2 H), 2.25 (dd, *J*

= 18.1, 12.7 Hz, 1 H), 2.51 (m, 1 H), 2.65 (dd, *J* = 18.1, 5.7 Hz, 1 H), 4.00-4.20 (m, 2 H), 4.90 (dd, *J* = 5.5, 2.8 Hz, 1 H), 6.44 (q, *J* = 6.8 Hz, 1 H), 7.10-7.30 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 15.3, 18.7, 24.4, 32.8, 36.1, 38.5, 49.2, 49.8, 60.7, 112.2, 125.3, 126.0, 128.0, 128.2, 133.9, 142.2, 168.7, 172.1; IR (Film) 3056, 2986, 2944, 1721, 1665, 1634, 1265, 911, 738, 708 cm^{-1}; HRMS calcd for $C_{21}H_{27}NO_3$ *m/z* 341.1991, obsd *m/z* 341.1989.

82: (60:40 Et_2O/petroleum ether, 0.65 g, 1.89 mmol, 63% yield); ^1H NMR (300 MHz, $CDCl_3$), (characteristic peaks both isomers) δ 1.61 (d, *J* = 7.3 Hz, 0.96 H), 1.67 (d, *J* = 7.1 Hz, 2.04 H), 4.95 (dd, *J* = 5.4, 2.9 Hz, 0.68 H), 5.17 (t, *J* = 3.9 Hz, 0.32 H), 5.90 (q, *J* = 7.2 Hz, 0.32 H), 6.26 (q, *J* = 7.3 Hz, 0.68 H); ^{13}C NMR (75 MHz, $CDCl_3$), (both isomers), δ 14.0, 14.1, 14.5, 15.4, 16.1, 18.3, 18.6, 23.9, 24.3, 34.5, 34.7, 34.9, 35.4, 38.2, 38.6, 40.0, 46.3, 47.4, 50.7, 52.5, 60.9, 61.1, 110.8, 117.5, 125.6, 125.8, 125.9, 126.1, 128.1, 134.4, 134.6, 142.3, 142.9, 171.9, 173.8, 174.4, 174.8; IR (Film) 3056, 2986, 2941, 1725, 1675, 1636, 1448, 1265, 748, 704 cm^{-1}; HRMS calcd for $C_{21}H_{27}NO_3$ *m/z* 341.1991, obsd *m/z* 341.1982.

84: (solvent gradient, 70:30/EtOAc:CH_2Cl_2-100% EtOAc, 1.01 g, 2.73 mmol, 91% yield); ^1H NMR (300 MHz, $CDCl_3$) (characteristic peaks for 4 isomers), δ 4.78 (q, *J* = 7.1 Hz, 0.04 H), 5.08 (dd, *J* = 2.8, 5.3 Hz, 0.64 H), 5.21 (t, *J* = 3.8 Hz, 0.09 H), 5.33 (t, *J* = 4.0 Hz, 0.23 H), 5.40 (q, *J* = 7.0 Hz, 0.09 H), 5.63 (t, *J* = 3.7 Hz, 0.04 H), 5.72 (q, *J* = 7.1 Hz, 0.23 H), 6.00 (q, *J* = 7.1 Hz, 0.64 H), 6.60 (d, *J* = 5.6 Hz, 0.09 H), 6.68 (d, *J* = 5.5 Hz, 0.68 H, two isomers), 6.72 (q, *J* = 5.8 Hz, 0.23 H); ^{13}C NMR (75 MHz, $CDCl_3$), (all isomers), δ 13.9, 14.0, 14.1, 15.1, 15.2, 16.6, 17.8, 18.0, 18.1, 18.3, 18.9, 19.8, 23.0, 23.1, 24.0, 24.1, 24.3, 33.8, 34.1, 34.8, 35.0, 36.6, 36.9, 37.0, 46.3, 46.6, 46.9, 48.6, 49.9, 52.7, 54.1, 57.5, 61.1, 61.3, 61.5, 110.4, 111.6, 121.1, 125.6, 125.8, 126.2, 126.3, 126.9, 128.2, 128.3, 128.4, 133.3, 133.7, 141.3, 141.6,

142.0, 166.5, 168.0, 169.9, 170.1, 170.3, 173.7, 174.2; IR (Film) 3056, 2986, 2944, 1725, 1669, 1644, 1265, 740, 704 cm^{-1}; HRMS calcd for $C_{22}H_{28}NO_4$ *m/z* 370.2019, obsd *m/z* 370.2082.

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(37) The stereoselectivity of the Michael addition with imine substrates **17** was independent of the type of electron deficient alkene used (vinyl sulfone, methyl acrylate and *tert*-butyl acrylate).[11a]

(38) The products of the aza-annulations reported in this study have been submitted for biological testing at Lilly Research Laboratories, Indianapolis, IN.

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(41) Dioxane was substituted here in the reactions indicated in Table III.

APPENDIX I

ZIEGLER-NATTA OLEFIN INSERTIONS WITH MAO

Legend For Data Tables

TIME: Given in minutes.

mL MAO: Amount of 0.5 *M* solution in toluene added to the reaction mixture.

%Prop t=0: Percentage of cyclization during formation and isolation of **43a**.

%But t=0: Percentage of cyclization during formation and isolation of **43b**.

%Prop - t=0: Amount of cyclization of **43a** obtained during the reaction minus the percentage of cyclization that had occurred during formation and isolation of **43a**.

%But- t=0: Amount of cyclization of **43b** obtained during the reaction minus the percentage of cyclization that had occurred during formation and isolation of **43b**.

c:t Prop: The ratio of cis to trans **46a** formed during cyclization.

c:t Prop: The ratio of cis to trans **46b** formed during cyclization.

K: The rate of cyclization of **43a** relative to **43b**.

COMMENTS: Indicates reaction runs that were not included in the average.

%cyc: Percentage of cyclization was not within the reaction parameters.

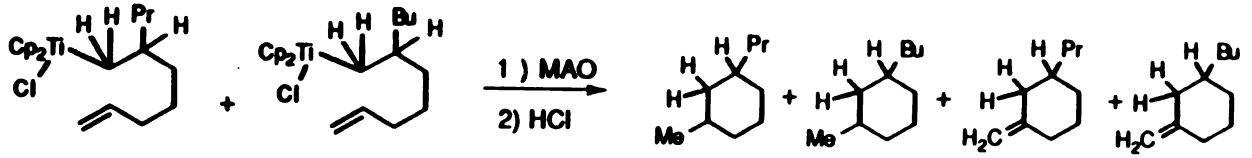
c/t: The cis:trans ratio fell outside the range typically observed.

b-H: Indicates that an excessive amount of b-hydrogen elimination had occurred.

bad MAO: Indicates that the MAO solution was not acceptable.

low/high: Indicates that when all values fell within the reaction parameters, the lowest and highest values were not included in the average.

ZIEGLER-NATTA OLEFIN INSERTIONS WITH MAO

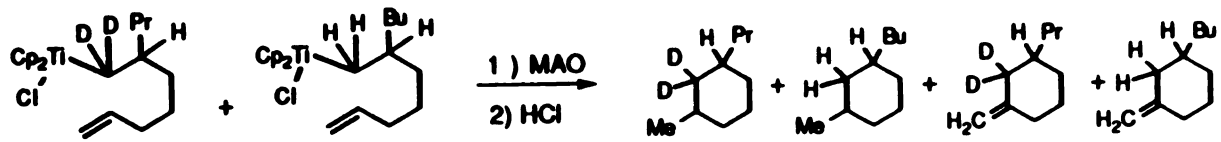


(α-H)41a (α-H)41b (α-H)63a (α-H)63b

SAMPLE	TIME	mL MAO	% Prop t=0	% But t=0	% Prop-t=0	% But-t=0	c:t Prop	c:t But	K	COMMENTS
B 2	30	0.75	6.33%	4.43%	73.07%	60.88%	32 : 68	39 : 61	1.20	% cyc
B 1	30	0.75	7.89%	5.34%	69.71%	56.71%	34 : 66	40 : 60	1.23	% cyc
B 1	15	0.75	3.77%	2.78%	27.50%	22.16%	40 : 60	44 : 56	1.24	% cyc
D 2	30	0.85	8.69%	6.49%	37.44%	29.58%	41 : 59	45 : 55	1.27	
D 1	30	0.8	7.50%	5.63%	35.43%	27.36%	40 : 60	44 : 56	1.29	
C 1	30	0.75	5.46%	3.77%	47.48%	35.82%	38 : 62	43 : 57	1.33	
B 2	15	0.75	2.73%	1.75%	30.66%	22.96%	39 : 61	44 : 56	1.34	
D 2	15	0.8	7.98%	5.30%	37.01%	27.66%	40 : 60	44 : 56	1.34	
C 2	15	0.75	3.26%	2.54%	36.74%	27.44%	39 : 61	43 : 57	1.34	
E 1	15	0.85	2.40%	1.81%	11.71%	8.67%	46 : 54	50 : 50	1.35	% cyc
D 1	15	0.8	9.34%	7.06%	37.33%	27.55%	39 : 61	45 : 55	1.36	
C 1	15	0.75	4.34%	3.00%	27.44%	20.06%	41 : 59	46 : 54	1.37	
C 2	30	0.75	5.56%	3.37%	58.28%	42.28%	35 : 65	41 : 59	1.38	c/t
A 1	30	0.7	5.89%	4.03%	42.52%	28.91%	34 : 66	39 : 61	1.47	c/t
A 2	30	0.8	3.56%	2.16%	49.68%	33.12%	33 : 67	39 : 61	1.50	c/t
E 2	30	0.85	0.00%	0.00%	17.48%	11.02%	43 : 57	49 : 51	1.59	% cyc

(α-H)41a:(α-H) 41b = 1.33 ±0.03

ZIEGLER-NATTA OLEFIN INSERTIONS WITH MAO

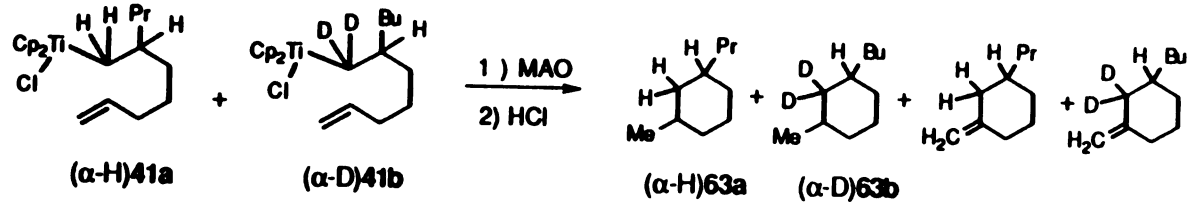


(α-D)41a (α-H)41b (α-D)63a (α-H)63b

SAMPLE	TIME	mL MAO	% Prop t=0	% But t=0	% Prop-t=0	% But-t=0	c:t Prop	c:t But	K	COMMENTS
D 1	15	0.7	1.73%	1.55%	11.52%	9.73%	44 : 56	48 : 52	1.18	% cyc
D 1	30	0.7	0.00%	0.00%	21.78%	16.33%	41 : 59	44 : 56	1.33	% cyc
B 2	30	0.7	11.05%	8.34%	44.69%	33.32%	40 : 60	45 : 55	1.34	b-H
B 1	30	0.7	13.83%	9.75%	46.10%	32.59%	41 : 59	46 : 54	1.41	c/t
A 1	20	0.7	4.23%	2.56%	60.85%	42.90%	35 : 65	39 : 61	1.42	% cyc
A 2	20	0.8	4.43%	2.71%	63.73%	43.91%	33 : 67	39 : 61	1.45	% cyc
C 1	15	0.7	0.00%	0.00%	29.77%	20.43%	37 : 63	42 : 58	1.46	
B 1	20	0.7	2.45%	1.81%	29.76%	20.05%	38 : 62	43 : 57	1.48	
B 2	15	0.7	2.41%	1.85%	40.08%	26.47%	36 : 64	41 : 59	1.51	
C 2	30	0.7	1.43%	1.07%	30.14%	19.72%	38 : 62	43 : 57	1.53	
C 2	15	0.7	1.99%	1.47%	44.04%	28.42%	36 : 64	41 : 59	1.55	
C 1	30	0.7	1.97%	1.54%	48.98%	31.53%	35 : 65	40 : 60	1.55	

(α-D) **41a**:(α-H) **41b** = 1.43 ±0.03

ZIEGLER-NATTA OLEFIN INSERTIONS WITH MAO

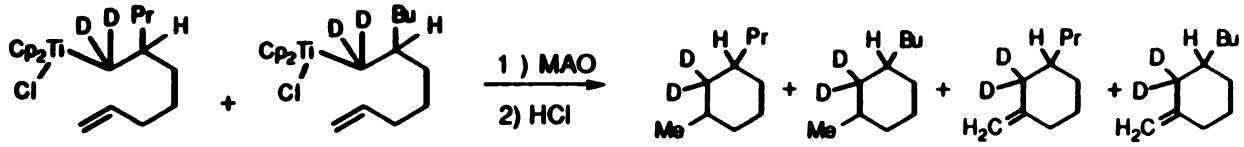


(α-H)41a (α-D)41b (α-H)63a (α-D)63b

SAMPLE	TIME	mL MAO	% Prop b-H	% But b-H	% Prop-t=0	% But-t=0	c:t Prop	c:t But	K	COMMENTS
A 1	15	0.7	4.27%	4.19%	29.10%	25.14%	40 : 60	44 : 56	1.16	low
B 2	15	0.7	4.07%	3.04%	21.94%	18.05%	41 : 59	44 : 56	1.22	
C 3	25	0.72	7.14%	4.16%	48.39%	38.99%	36 : 64	42 : 58	1.24	
B 3	25	0.7	5.62%	4.15%	52.46%	42.21%	37 : 63	41 : 59	1.24	
A 2	25	0.7	2.51%	1.92%	21.12%	16.82%	40 : 60	44 : 56	1.26	
B 2	25	0.7	4.45%	3.41%	51.36%	40.75%	36 : 64	41 : 59	1.26	
C 4	25	0.72	3.71%	2.93%	49.54%	38.84%	36 : 64	41 : 59	1.28	
B 1	15	0.7	4.84%	3.20%	24.41%	18.87%	40 : 60	44 : 56	1.29	
C 1	15	0.72	3.90%	2.79%	27.93%	21.50%	41 : 59	45 : 55	1.30	
C 2	15	0.72	3.40%	2.57%	33.23%	25.24%	40 : 60	44 : 56	1.32	high

(α-H) **41a**:(α-D) **41b** = 1.26 ±0.03

ZIEGLER-NATTA OLEFIN INSERTIONS WITH MAO

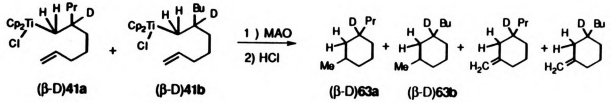


(α-D)41a (α-D)41b (α-D)63a (α-D)63b

SAMPLE	TIME	mL MAO	Prop B-H	But B-H	% Prop-t=0	% But-t=0	c:t Prop	c:t But	K	COMMENT
E 4	25	0.72	4.97%	3.50%	53.01%	39.50%	37 : 63	42 : 58	1.34	% cyc
E 3	25	0.72	6.45%	4.66%	53.43%	39.75%	36 : 64	42 : 58	1.34	% cyc/ b-H
D 3	25	0.72	6.74%	5.11%	42.64%	31.21%	38 : 62	43 : 57	1.37	b-H
F 1	15	0.72	3.14%	2.38%	42.89%	31.24%	37 : 63	42 : 58	1.37	
D 1	15	0.72	3.04%	2.50%	29.31%	21.13%	39 : 61	44 : 56	1.39	
D 4	25	0.72	9.12%	6.61%	47.03%	33.88%	38 : 62	43 : 57	1.39	b-H
C 2	25	0.72	4.74%	3.55%	28.98%	20.76%	42 : 58	47 : 53	1.40	
D 2	15	0.72	2.45%	1.95%	30.93%	21.94%	39 : 61	44 : 56	1.41	
E 2	15	0.72	3.03%	1.87%	40.05%	28.25%	40 : 60	42 : 58	1.42	
B 2	15	0.72	3.68%	2.77%	22.40%	15.73%	42 : 58	48 : 52	1.42	
B 4	25	0.72	4.05%	2.56%	31.91%	22.40%	40 : 60	45 : 55	1.42	
E 1	15	0.72	2.25%	1.68%	32.99%	23.05%	37 : 63	42 : 58	1.43	
B 3	25	0.72	5.33%	3.28%	40.70%	28.33%	38 : 62	43 : 57	1.44	
A 2	15	0.7	2.07%	1.72%	21.38%	14.83%	41 : 59	46 : 54	1.44	% cyc
C 1	15	0.72	2.75%	2.29%	31.75%	21.94%	38 : 62	43 : 57	1.45	
A 1	15	0.70	5.28%	2.31%	43.18%	29.48%	36 : 64	43 : 57	1.46	c/t
A 3	25	0.7	3.30%	2.19%	21.17%	14.17%	42 : 58	47 : 53	1.49	% cyc
A 4	25	0.7	3.39%	2.03%	30.49%	20.10%	39 : 61	44 : 56	1.52	
B 1	15	0.72	2.50%	1.53%	18.02%	11.72%	41 : 59	46 : 54	1.54	% cyc

(α-D) 41a:(α-D) 41b = 1.43 ±0.03

ZIEGLER-NATTA OLEFIN INSERTIONS WITH MAO

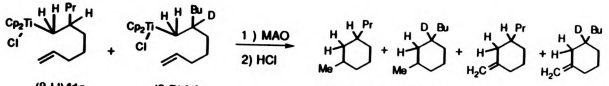


(β-D)41a (β-D)41b (β-D)63a (β-D)63b

SAMPLE	TIME	mL MAO	Prop B-H	But B-H	% Prop-t=0	% But-t=0	c:t Prop	c:t But	K	COMMENT
159-B 4	10	0.72	9.63%	7.56%	58.99%	46.28%	28 : 72	32 : 68	1.27	b-H
159-B 3	10	0.72	3.51%	2.66%	44.57%	34.93%	32 : 68	36 : 64	1.28	
159-A 2	12	0.70	5.57%	4.20%	41.75%	32.70%	34 : 66	36 : 64	1.28	bad MAO
159-C 3	12	0.73	20.91%	16.15%	77.92%	60.40%	28 : 72	35 : 65	1.29	b-H
159-C 4	12	0.73	5.86%	4.98%	65.68%	50.47%	30 : 70	36 : 64	1.30	b-H
159-D 2	10	0.73	0.00%	0.00%	20.49%	15.63%	38 : 62	41 : 59	1.31	
159-A 2R	12	0.70	3.85%	3.26%	33.72%	25.58%	36 : 64	38 : 62	1.32	
159-B 1	10	0.72	2.86%	2.58%	29.32%	22.00%	35 : 65	37 : 63	1.33	
159-C 1	10	0.73	3.36%	2.66%	32.05%	24.03%	34 : 66	38 : 62	1.33	
159-C 2	10	0.73	2.86%	2.33%	31.85%	23.52%	32 : 68	35 : 65	1.35	
159-A 1R	10	0.70	2.73%	2.28%	36.61%	26.95%	35 : 65	39 : 61	1.36	
159-B 2	10	0.72	1.88%	1.41%	28.37%	20.80%	34 : 66	38 : 62	1.36	
159-D 1	10	0.73	8.38%	5.69%	62.00%	45.14%	26 : 74	32 : 68	1.37	b-H
159-A 1	10	0.70	0.00%	0.00%	30.32%	21.31%	35 : 65	39 : 61	1.42	bad MAO

(β-D) **41a**:(β-D) **41b** = 1.33 ±0.03

ZIEGLER-NATTA OLEFIN INSERTIONS WITH MAO



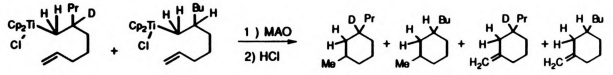
(β-H)**41a** (β-D)**41b** (β-H)**63a** (β-D)**63b**

SAMPLE	TIME	mL MAO	Prop B-H	But B-H	% Prop-t=0	% But-t=0	c:t Prop	c:t But	K	COMMENT
154-A 2	10	0.70	2.30%	2.12%	17.89%	14.16%	37 : 63	44 : 56	1.26	% cyc
154-C 1	6	0.75	3.65%	3.01%	30.66%	23.92%	33 : 67	38 : 62	1.28	% cyc
154-C 2	6	0.75	0.00%	0.00%	31.78%	23.39%	33 : 67	39 : 61	1.36	
154-C 3	10	0.75	5.00%	3.71%	48.04%	35.23%	31 : 69	36 : 64	1.36	
154-B 1	8	0.72	0.00%	0.00%	36.49%	26.55%	31 : 69	37 : 63	1.37	
145-A 1	10	0.75	3.54%	2.72%	38.90%	27.78%	33 : 67	38 : 62	1.40	
154-B 4	10	0.72	0.00%	0.00%	46.06%	32.86%	31 : 69	37 : 63	1.40	
145-B 1	10	0.75	4.04%	3.18%	34.64%	24.48%	34 : 66	41 : 59	1.42	
154-B 2	8	0.72	0.00%	0.00%	28.14%	19.78%	34 : 66	39 : 61	1.42	
154-A 1	10	0.70	0.00%	0.00%	21.65%	15.13%	35 : 65	40 : 60	1.43	
154-C 4	10	0.75	5.03%	3.31%	54.56%	37.90%	32 : 68	38 : 62	1.44	
154-B 3	10	0.72	0.00%	0.00%	27.39%	18.89%	32 : 68	37 : 63	1.45	

(β-H) **41a**:(β-D) **41b** = 1.41 ±0.03

ZIEGLER-NATTA OLEFIN INSERTIONS WITH MAO

ZIEGLER-NATTA OLEFIN INSERTIONS WITH MAO



(β-D)**41a** (β-H)**41b** (β-D)**63a** (β-H)**63b**

SAMPLE	TIME	mL MAO	Prop B-H	But B-H	% Prop-t=0	% But-t=0	c:t Prop	c:t But	K	COMMENT
B 2	10	0.60	1.59%	1.33%	7.68%	7.48%	43 : 57	47 : 53	**1.03**	% cyc
D 3	25	0.65	2.34%	1.92%	15.03%	13.30%	42 : 58	45 : 55	**1.13**	% cyc
B 1	10	0.70	13.52%	9.69%	73.18%	62.64%	29 : 71	37 : 63	**1.17**	% cyc
C 2	20	0.60	2.52%	1.99%	25.02%	20.87%	38 : 62	41 : 59	1.20	
F 2	20	0.66	2.89%	2.18%	28.28%	23.24%	36 : 64	40 : 60	1.22	
H 4	20	0.66	2.49%	1.87%	40.03%	32.81%	34 : 66	38 : 62	1.22	
H 2	10	0.66	2.00%	1.80%	35.29%	28.91%	34 : 66	37 : 63	1.22	
A 3	25	0.72	21.71%	15.53%	78.76%	64.35%	29 : 71	38 : 62	**1.22**	% cyc/ b-H
H 3	20	0.66	4.44%	3.24%	48.31%	39.23%	34 : 66	38 : 62	1.23	
E 2	20	0.70	3.65%	2.49%	61.26%	49.35%	31 : 69	36 : 64	**1.24**	cyc
D 2	15	0.65	3.19%	2.36%	25.53%	20.51%	38 : 62	42 : 58	1.24	
F 1	10	0.66	4.48%	2.59%	38.73%	30.94%	33 : 67	37 : 63	1.25	
H 1	10	0.66	2.35%	1.68%	28.29%	22.58%	35 : 65	39 : 61	1.25	
G 2	20	0.66	4.29%	3.01%	50.10%	39.68%	33 : 67	38 : 62	1.26	
D 1	15	0.65	0.00%	0.00%	21.39%	16.88%	37 : 63	41 : 59	1.27	
A 4	25	0.72	17.09%	12.60%	73.09%	57.67%	31 : 69	38 : 62	**1.27**	% cyc
G 1	10	0.66	1.92%	1.17%	24.45%	19.10%	36 : 64	40 : 60	1.28	
A 1	15	0.72	3.79%	2.99%	40.95%	31.74%	36 : 64	40 : 60	1.29	
E 1	10	0.70	2.73%	1.80%	48.76%	37.44%	32 : 68	37 : 63	1.30	
A 2	15	0.72	5.79%	3.83%	61.85%	47.26%	34 : 66	38 : 62	**1.31**	% cyc

(β-D) **41a**:(β-H) **41b** = 1.25 ±0.02

APPENDIX II

Related Publications

Chapter I

"Lewis Acid-Promoted 3-Aza-Cope Rearrangement of *N*-Alkyl-*N*-Allylenamines." Cook, G.R.; Barta, N.S.; Stille, J.R. *J. Org. Chem.* **1992**, *57*, 461-467.

"Studies of the Regiospecific 3-Aza-Cope Rearrangement Promoted by Electrophilic Reagents." Barta, N.S.; Cook, G.R.; Landis, M.S.; Stille, J.R. *J. Org. Chem.* **1992**, *57*, 7188-7194.

"An Efficient Apparatus for Removal of H_2O from Condensation Reactions." Barta, N.S.; Paulvannan, K.; Schwarz, J.B.; Stille, J.R. *Synth. Commun.* **1994**, *24*, 583-590.

Chapter II

"α- and β-Deuterium Isotope Effects in the MgX_2 and Methylaluminoxane Promoted Intramolecular Olefin Insertion of Cp_2TiClR Complexes. Insight Into Cocatalyst Dependence and Chain End Control in Ziegler-Natta Polymerization." Barta, N.S.; Kirk, B.A.; Stille, J.R. *J. Am. Chem. Soc.* **1994**, *116*, 0000. Accepted for Publication.

"Competitive Intramolecular Ti-C *versus* Al-C Alkene Insertions: Examining the Role of Lewis Acid Cocatalysts in Ziegler-Natta Alkene Insertion and Chain Transfer Reactions." Barta, N.S.; Kirk, B.A.; Stille, J.R. *J. Organomet. Chem.* **1994**. Accepted for publication.

Chapter III

"Asymmetric Formation of Quaternary Centers Through Aza-Annulation of Chiral β-Enamino Esters with Acrylate Derivatives." Barta, N.S.; Brode, A.; Stille, J.R. *J. Am. Chem. Soc.* **1994**, *116*, 6201-6206.