Development of Sequential Olefin Cross Metathesis–Organocatalysis Methodology

Thesis by

Brian Joseph Kwan

Submitted in Partial Fulfillment of the Requirements

for the Degree of

Master of Science

Division of Chemistry and Chemical Engineering

California Institute of Technology

Pasadena, CA

(Submitted June 4, 2004)

For Mom, Dad, and Jen, who taught me that the manner in which a task is completed–with patience, hard work, and most importantly, honor and integrity– is just as important as completing the task itself

Acknowledgments

The Chinese have a saying that reads, "May you live in interesting times." My experience over the past three years at Caltech would certainly fall into the category cited by the Chinese. I think it is fair to say that the circumstances under which I leave Caltech are different from those that I had originally envisioned in that hot, smoggy, yet nevertheless exciting autumn of 2000. Whatever the conditions of my departure from Caltech, there are a great many people without whose assistance and encouragement I could not have reached this point.

First and foremost, I would like to thank my research advisor, Professor Dr. David W. C. MacMillan. There was quite a large class of entering graduate students in 2000, and Dave took me into his group over many other students, the overwhelming majority of whom had a great deal more experience in synthetic organic chemistry than myself. Dave worked tirelessly to create an environment that would be conducive to cutting edge research, and to ensure that we as graduate students lacked for nothing. Many visitors to the group from industrial labs were known to comment that the facilities in our labs were siginificantly superior to their own labs. Dave was also incredibly patient with my (numerous!) shortcomings as I tried to surmount the steep curve of learning the ins and outs of being a synthetic organic chemistry.

I would be remiss in not acknowledging the assistance of Professor Dr. Robert H. Grubbs, the chair of my candidacy committee and an always friendly and helpful person. Bob was instrumental in convincing me to come to Caltech and upon my arrival, went to great lengths to make me feel welcome. I would also like to thank Bob's wife, Helen, for

being such a kind soul and making me feel welcome at the Grubbs group events held at Bob's house.

I'm afraid I didn't have a chance to interact a great deal with Professor Dr. Nate Lewis, but I very much appreciated the time he put into being on my candidacy committee. His comments during my candidacy exam were both extremely informative and very helpful.

I have had the privilege of working with a great many talented chemists during my time in the MacMillan group. Nick Paras, now at Amgen, would be at the top of that list. For all intents and purposes, Nick trained me and put up with my incessant questions and idiosyncrasies as I worked next to him for my first year in the group. He is a brilliant chemist whose insights have greatly contributed to the understanding of the fundamental aspects of organocatalysis.

Jake Wiener was one of the first graduate students I met in Dave's group, and certainly the funniest. I had the distinct privilege of working next to Jake for my last three months in the group, and only regret that it could not have been longer. Not only did I thoroughly enjoy Jake's sense of humor (of which I found myself a frequent target), but also Jake helped me get adjusted to the rigors of graduate research and taught me a great deal about chemistry. When we worked together in room 3, I had frequent enjoyable conversations with Jake about all sorts of things, including chemistry. I will never forget Jake's willingness to be patient with me and to provide never-ending encouragement. I will miss not being able to work next to Jake in the future, but I know that he has a bright career in chemistry ahead of him.

Vy Dong (now a postdoc in Robert Bergmann's group at Berkeley) was an amazingly patient and helpful "go to" person during my time in the group. She always made the time to help me and answer any questions I might have had, no matter how busy she was. One of the most amazing things about Vy was her willingness to admit that she didn't know something (although those circumstances were admittedly quite rare).

Tristan Lambert had the rather dubious distinction of working next to me for most of my remaining time in the group, during which time Tristan corrupted me with endless playings of the Jerky Boys, and we became good friends. I will always admire his patience and dedication to chemistry, even when things weren't going as planned. I wish him the best with his postdoc in the Danishefsky group and know that he will be successful as his career progresses.

Tehshik Yoon was a great help to me when I joined the group, and I frequently stood in awe of his mastery of the most arcane details of chemistry. He is a model of hard work, perseverance, and a true intellectual. I look forward to reading the (surely many) publications to emerge from his future research pursuits in the academic realm.

I'm sorry I didn't get a chance to know Jim Falsey better prior to his untimely departure from the group. We had a great time in the conference room as we both struggled to prepare for our respective candidacy exams. Ben Edelson of the Dervan group was a wonderful roommate for my first year, and I'm glad we had a chance to become friends. I hope he decides to continue on in chemistry and pursue an academic career. The field of chemistry would be greatly enhanced by his decision to do so. Drs. Christopher Sinz and Claudia Roberson joined the group as postdocs in August 2001, and

I profited immeasurably from their wisdom, chemistry–related and otherwise, and their invaluable perspective on the graduate experience. One of these days, I'll be able to return Chris' kick serve with some consistency.

Finally, Joel Austin...well, I'm not quite sure what to say about Joel. Certainly, he is a great chemist whose brilliance is underappreciated by many, and he is able to think in unconventional ways like few people I have ever met in my life. He's been a friend in both good times and bad, and was always the first person to ask me how I was doing whenever he passed by. I'll just say that I'm lucky I had a chance to be associated with him.

I would be remiss in not mentioning Wendy Jen and Ian Mangion for their frequent assistance and good chemistry conversation. I still owe Ian a martini at the bar at the Standard, or some similar place on the Westside, and I'm sure he won't let me forget about it.

I was also privileged to work with and learn from the many outstanding people who come to Caltech to be a part of Bob's group, including (now Professors) Dr. Dean Toste and Dr. Justin Gallivan, and also Drs. Stuart Cantrill and Jon Efskind. Many graduate students also contributed to making my experience a wonderful one, including (now Professor Dr.) Melanie Sanford, Jacob Berlin, J.P. Morgan, Dan Sanders, Erin Guidry, and Arnab Chatterjee.

I would like to thank several people from Bob's group who truly helped me through the graduate experience. Dr. Steven Goldberg taught me a great deal about chemistry, and more generally (and more importantly) about what it means to be a true scientist. His guidance was invaluable, in matters both scientific and political. From the

first time I asked Steve to tell me about his Ph.D. research, to the innumerable times I trudged upstairs to 130 Church to ask for his help, he always put down whatever he was doing to help me.

Dr. (and now Professor) Jennifer Love has also been a great friend and also a wonderful teacher. From her, I learned a great deal about how to think about chemistry, as well as the importance of conducting oneself as a professional scientist with integrity, lessons that many others would do well to heed. Jen and her husband, Pierre, are at the very beginning of what is sure to be a brilliant career at the University of British Columbia in Vancouver, and I thank them for their support and wish them the best.

It would be hard to imagine life in grad school without Andrew Waltman. I think some of the greatest conversations I had at Caltech were with Drew late at night when he would come downstairs to chat and to dance to the Honky Tonk Hiccup. I will always also have fond memories of talking trash over the foozball table in the Rathskeller, and talking with him, Dean, Arnab, Steve, Jacob, and Justin in 130 Church (a.k.a. the Den of Sin). I was always impressed by Drew's willingness to show leadership in many areas in which other people refused to, most of the time out of sheer laziness. I hope he will find what he is looking for at the end of his graduate studies.

The administrative staff of the Division has assisted me in ways too innumerable to count. Although rarely acknowledged for their hard work, without them the machinery that enables research to go forward on a daily basis would grind to a screeching halt. Among those persons deserving thanks are Joe Drew and Moses Renteria of the Chemistry Stockroom, Steve Gould and Lillian Kremar in the Purchasing Office, Larry Martinez and Tom Winiecki in Environmental Health and Safety, and Ron Anderson in

the Custodial Services Department. In particular, Dian Buchness was always extraordinarily helpful and kind. Chris Smith was never too busy to lend an ear and a helping hand, especially as I struggled through the final months of my time at Caltech.

Finally with regard to Caltech people, I'd like to thank Jessica Gamboa and Deanna Thomas, of the Davidson Group in the Division of Biology, for always being ready with an open mind and friendly smiles. I will greatly miss their company as I move on.

There are several people from outside Caltech who helped me weather the slings and arrows of graduate school. Professor Dr. Shirley Lin, now at the United States Naval Academy, has proved to be an invaluable source of guidance and advice both during my time at Caltech, and as an undergraduate in Bob Waymouth's lab, when Shirley was there as a graduate student. From Shirley, I learned the value of doing things properly and in a meticulous fashion, as well as the importance of propriety and integrity in research. It is unfortunate that the vast majority of the scientific community does not hold itself to the same standards of excellence that Shirley maintains. I will never forget the many conversations we had during my time at Caltech, and thank her for her time and attention.

Mike Chilk was one of the first people I met after moving to southern California, and I still cannot quite bring myself to call him Jonah, despite the fact that it is his "real" name. Mike provided many entertaining and worthwhile sets of Sunday tennis, and he and Patrick Horn have been good friends. I also met Dr. Carolyn Lyons shortly after my arrival, and she has been truly a good friend and, perhaps more importantly, an amazingly patient listener. I hope that if I return to Los Angeles at some point in the future, we will be able to continue to converse.

Vik Gupta continued my string of wonderful roommates, and I feel quite lucky to have lived with him, even if only for three short months. I wish him and his fiancée, Joni, the best. Vik also introduced me to Marlo Miura and Mikhail Pyogortovskiy, who have helped introduce me to the finer (and usually undiscovered) culinary establishments in Los Angeles. I will miss their company. Crosby Grant was also a great roommate; unfortunately, external circumstances prevented him from staying in Pasadena longer than intended. I apologize for not warning about the complete dearth of attractive women in Pasadena, and wish him the best in the future.

Dr. Stanley Rossman and Mrs. Beryl Rossman have always been great supporters and friends, and I feel truly honored and privileged to have made their acquaintance. From providing an extra seat at High Holiday services, to Passover seders and Thanksgiving dinners, they have always made me feel at home and provided a wonderful chance to relax and feel like part of the family. Without their support my experience in graduate school would have been incalculably more difficult.

I didn't meet Jared Gold until the middle of my third year, and I regret every day previous to that when I didn't have the chance to know him. I think it does Jared a disservice even to call him a truly gifted artist, since any attempt to characterize his brilliance with the written word would be utterly futile. Despite his brilliance, he is one of the most unassuming and self–effacing people I have ever met, and as a result, is often surrounded by people who are vastly superior at (undeservedly) emphasizing their own importance, and yet who are vastly inferior in every other respect. In addition to his professional genius, Jared is also an amazingly sensitive and caring person. Finally, on a

rather selfish note, I can't begin to imagine how much more dull and empty my life would be without his company and friendship.

I would also like to briefly thank those who helped instill an interest and passion for organic chemistry during my wonderful time at Stanford. Thanks are certainly due to Professor Drs. Robert Waymouth and Tom Wandless, and especially Justin DuBois. Messrs. Clint Brown and Larry Formulak are acknowledged for doing their best to educate this reluctant chemist in high school, and in a sense, getting me into this whole mess.

Finally, and most importantly, I would like to thank my parents, Alex and Jacki, and my sister, Jen. They have been my supporters and cheering section in times both good and bad, and have never hesitated to tell me how much they cared for me and loved me. Mom and Dad, I have tried my best to absorb the many lessons you taught me about how to live my life and hope that I have at least partially lived up to your expectations. Jen, I always will stand in awe of your courage and grace in dealing with the heaps of (often steaming) garbage you have had to navigate up to this point. I will never forget how you would always put down what you were doing to talk to me, and nothing makes me happier than knowing that we have been able to renew our relationship after years of being separated by several thousand miles.

Mom, Dad, and Jen, I want you to know that I love you more than life itself.

Table of Contents

List of Figures

List of Tables

List of Schemes

Chapter One

Introduction to Enantioselective Amine Catalysis

1.1 Introduction

The awarding of the 2001 Nobel Prize in Chemistry to Sharpless, Knowles, and Noyori provided an incontrovertible, if overdue, confirmation of the importance of the field of asymmetric catalysis in the pantheon of scientific pursuits. The advancement of this field over the past forty years has proved to be extraordinarily useful not only in practical, but also conceptual research fields. The use of chiral Lewis acids and organometallic catalysts has provided some of the most spectactular accomplishments. However, the use of purely organic molecules as asymmetric catalysts has been frequently overlooked, despite the fact that enantioselective methodologies using amine catalysis appeared in the literature in some cases before the many of the landmark organometallic papers. Additionally, many amine catalyst systems provide conceptually interesting mechanistic insights into catalysis and are often simpler and therefore better understood than their organometallic counterparts.

What follows is a summary of the pertient reports of enantioselective amine catalysis, in some cases going back over sixty years, categorized by the role of the amine catalyst. Although every effort was made to be inclusive and comprehensive, any omissions of content that may have occurred are the sole responsibility of the author, and as such are not intended as an intentional dimunition of the contributions of any particular research group.

1.2 Iminium Catalysis

1.2.1 Catalyst Activation

1.2.1.1 The Strecker Reaction

The importance of amino acids to many areas of chemistry and biology is without question, and, consequently, synthetic chemists have invested a great deal of effort into developing methodologies for the preparation of amino acids, both natural and unnatural, in enantiomerically pure form. Perhaps the oldest method of amino acid synthesis is the Strecker reaction, first introduced in 1850 (Figure 1).[1] Several attempts have been made to develop enantioselective versions of this venerable reaction.

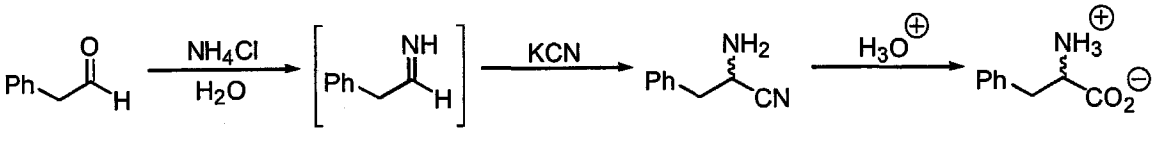
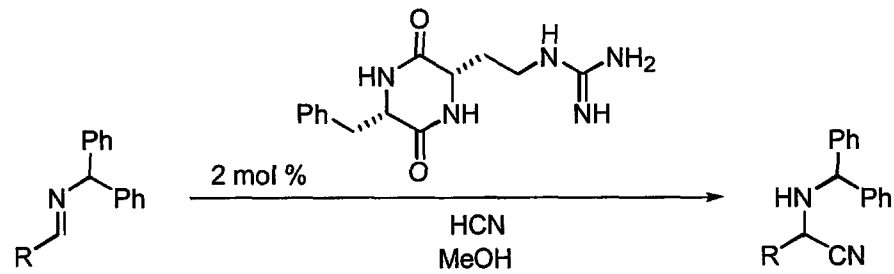


Figure 1. Hypothetical sequence for preparation of DL-phenylalanine *via* a Strecker reaction.

Lipton and coworkers introduced the first broadly applicable stereoselective Strecker methodology.[2] Catalyst **1**, prepared in several steps from glutamic acid and phenylalanine, was found to catalyze the cyanation of various *N*-benzhydryl imines to afford α-amino nitriles (Table 1). The benzhydryl substitution proved to be crucial to the successful hydrolysis of the nitrile products to the corresponding amino acids. When the aldehyde used to prepare the aldimine contained an aryl group, the yields and enantioselectivities were quite high; however, when benzaldehydes with strongly electron withdrawing substituents or aliphatic aldehydes were used, significant erosion in stereoselectivity was observed. The mechanistic basis for these results was not clearly understood at the time, although it was determined that a guanidine unit on the catalyst

and the benzhydryl substitution on the aldimine were necessary for good conversions and stereoselectivities.

Table 1. Scope of Lipton and coworkers' organocatalytic asymmetric Strecker reaction.

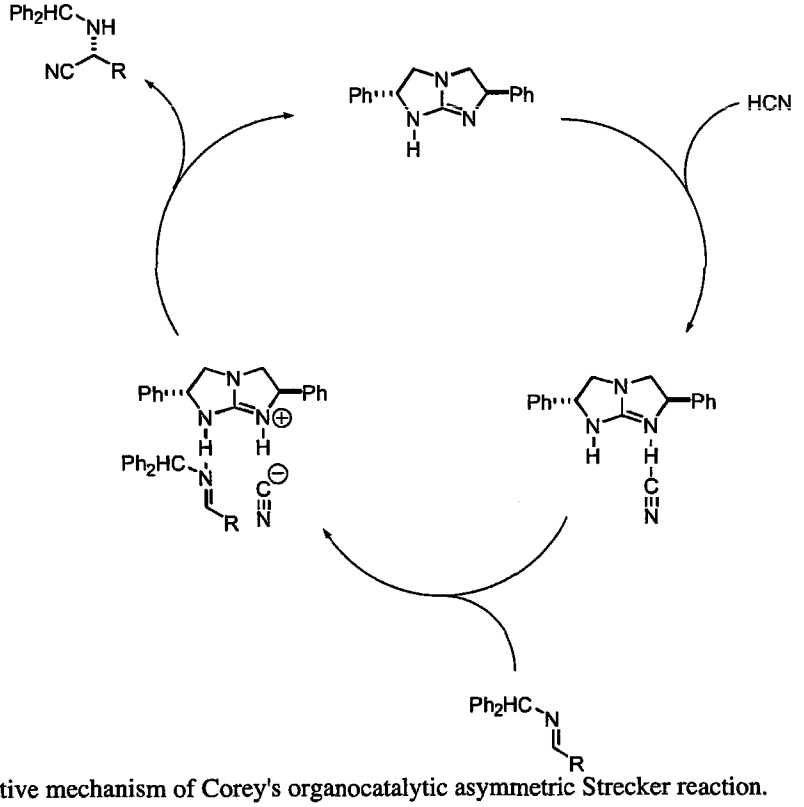


Entry	R	Temp / °C	NMR yield / %	ee / %
1	Ph	– 25	97	> 99
2	4-ClPh	– 75	94	> 99
3	4-OMePh	– 75	90	96
4	3-ClPh	– 75	80	> 99
5	3-OMePh	– 75	82	80
6	3-NO2	– 75	71	< 10
7	3-pyridyl	– 75	86	< 10
8	2-furyl	– 75	94	32
9	*i*-Pr	– 75	81	< 10
10	*t*-Bu	– 75	80	17

A logical rationale for these observations, as well as a reasonable mechanism for the cyanation (Scheme 1) was advanced several years later by Corey. In this work, the C_2 symmetric guanidine **2** was found to catalyze the cyanation of benzhydryl substituted aldimines similar to those used by Lipton.[3] With excess hydrogen cyanide at –40 °C in toluene, Corey observed slightly lower enantioselectivities, but catalyst **2** was found to be be more general than Lipton's diketopiperazine catalyst (Table 2).

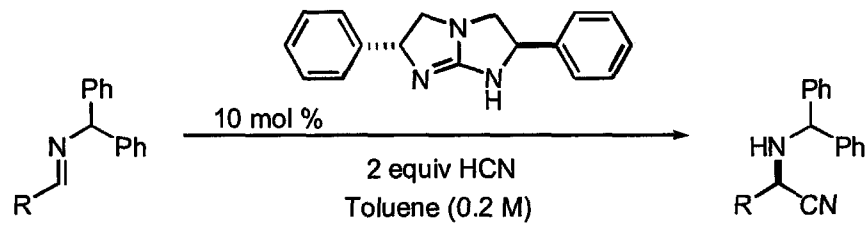
Based on crystallographic evidence, **2** was assumed to have a conformation somewhat similar to that illustrated in Figure 2. In order to explain the observed

stereoselectivities, the following organizational elements were postulated as being vital to preorganization of the substrate and catalyst: (1) hydrogen bonding between the aldimine nitrogen and proton on the secondary amine **2**; (2) cation-π interactions between the phenyl substituent of **2** and one of the phenyl groups on the aldimine benzhydryl group; (3) ion-pair association of the free cyanide anion with the positively charged guanidinium framework of **2**; and (4) accommodation of the benzaldehyde-derived aryl group in a vacant quadrant adjacent to **2**. This last factor also takes into account potential edge-on attractions between the aldimine phenyl group and the distal phenyl group on the catalyst. With these preorganizational elements in place, the *re* face of the aldimine is predisposed to attack by the cyanide ion, an outcome confirmed by numerous experiments. The *si* face of the aldimine is blocked by the phenyl group of the benzhydryl group not engaged in a cation-π interaction with the catalyst.



Scheme 1. Putative mechanism of Corey's organocatalytic asymmetric Strecker reaction.

Table 2. Scope of Corey's C_2-symmetric guanidine-catalyzed asymmetric Strecker reaction.



Entry	R	Temp / °C	t / h	yield / %	ee / %
1	Ph	– 40	20	96	86
2	*p*-tolyl	– 40	20	96	80
3	*o*-tolyl	– 20	12	88	50
4	3,5-xylyl	– 40	16	96	79
5	4-*t*-Bu-Ph	– 40	72	80	85
6	4-OTBS-Ph	– 40	38	98	88
7	4-OMe-Ph	– 40	28	99	84
8	4-F-Ph	– 40	23	97	86
9	4-Cl-Ph	– 20	20	88	81
10	1-Naphthyl	–20	12	90	76

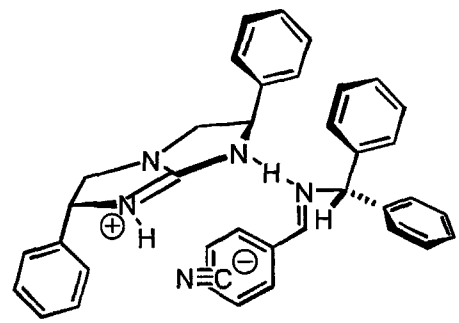


Figure 2. Rationale for stereoselectivity observed in catalytic Strecker reactions with **2**.

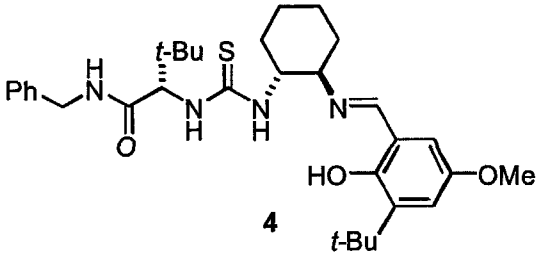
Several experiments provided additional evidence supporting the stereochemical rationale advanced by Corey. Benzaldehyde was condensed separately with both enantiomers of *sec*-phenethylamine. The aldimine derived from (*S*)-*sec*-phenethylamine

was observed to give the Strecker product in high diastereoselectivity, whereas the aldimine of the opposite enantiomeric series afforded the analogous product with virtually no diastereoselectivity. When both enantiomers are placed into the same preorganizational framework detailed above, the aldimine containing the (*S*)-*sec*-phenethylamine moiety gives the expected product; however, if its enantiomer is submitted to the same model, the methyl group α to the phenyl blocks the *re* face of the aldimine, resulting in erosion in stereoselectivity. Moreover, the aldimines prepared from condensation of benzaldehyde with benzylamine and fluorenylamine afforded products with markedly lower stereoselectivity, reiterating the importance of having two phenyl groups. The presence of phenyl groups on **2** was found to be crucial; replacement of the phenyl groups with cyclohexyl rings afforded in a 30% drop in enantiomeric excess with the benzaldehyde-derived aldimine.

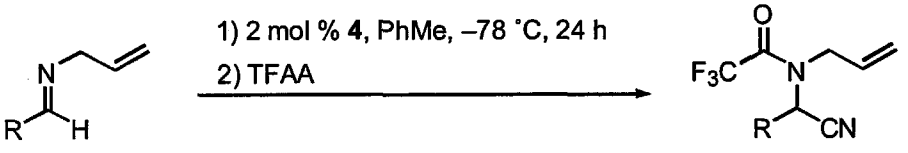
Jacobsen and coworkers took a radically different approach to the design of catalysts for the asymmetric Strecker reaction. The mechanism of this Strecker reaction has not been clarified, but it is a direct complement to the Strecker methods detailed above. A strategy rooted in combinatorial methods was utilized to ascertain the ideal catalyst structure.[4] After several rounds of structure-based variation, amino-acid derived catalyst **4** was identified as the optimal catalyst for the cyanation with a variety of alkyl and aryl aldimines (Table 3). Replacement of the methoxy group of **4** with a *tert*-butyl ester resulted in a catalyst that successfully catalyzed the asymmetric cyanation of a very broad range of *N*-substituted aldimines, with over twenty substrates converted to the corresponding aminonitriles in 77 – 97% ee.[5] Moreover, when ketoimines were used as

substrates in conjunction with a slightly modified catalyst, a variety of quaternary amino acids were accessed on gram scale in enantiomerically pure form, after recrystallization.[6]

Table 3. Combinatorially-optimized organocatalyst used for asymmetric Strecker reactions.



4



Entry	R	Yield / %	ee / %
1	C_6H_5	78	91
2	C_6H_4OMe-4	92	70
3	C_6H_4Br-4	65	86
4	2-Napthyl	88	88
5	*t*-Bu	70	85
6	*c*-C_6H_{11}	77	83

In an elegant and concise series of experiments, Jacobsen and coworkers provided a coherent mechanistic explanation for the cyanation reaction.[7] It was demonstrated that only those imines having a *Z* configuration were catalytically active, presumably since the *E* analogs do not meet the steric requirements for binding to the catalyst. Computational studies as well as solution NMR experiments demonstrated that the imine nitrogen is doubly bound by the thiourea protons, with the substrate oriented perpendicular to the plane of the thiourea. The amino acid portion of the catalyst then

blocks one enantioface of the bound imine, leaving the opposite face proximal to the salicylaldimine moiety open to attack by cyanide anion.

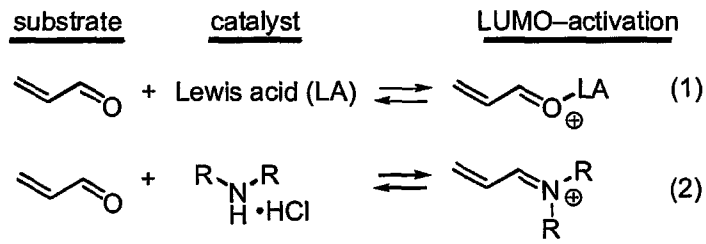
1.2.2 Substrate Activation

1.2.2.1 Cycloadditions

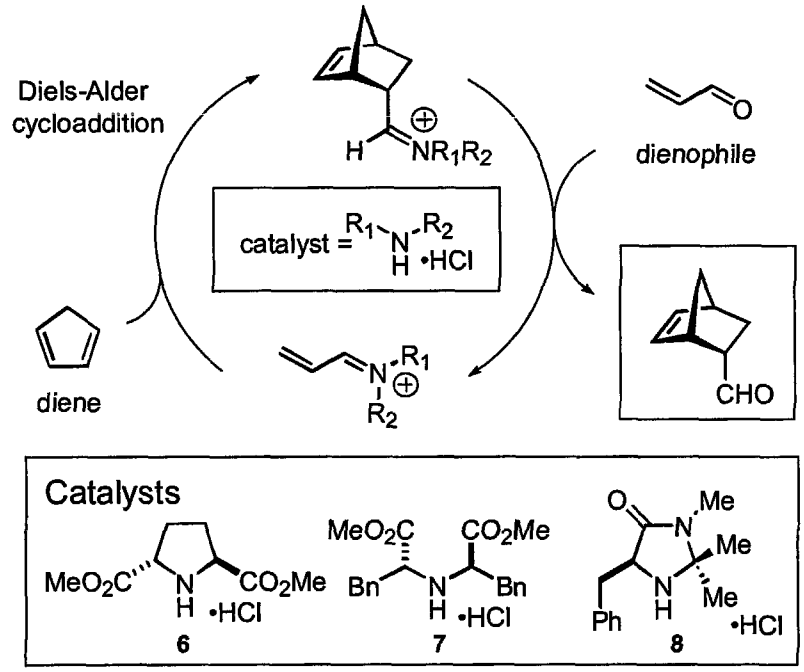
A conceptually distinct approach from that taken with the Strecker reaction is to use formation of an iminium to activate the substrate for a reaction. This is essentially the principle that has guided the development of chiral Lewis acid catalysts, in which the electrophilicity of a transition metal or main group atom is used to effect reaction acceleration by lowering the energy of the lowest unoccupied molecular orbital (LUMO) of a substrate. A thorough discussion of the theory behind this effect is beyond the scope of this article; however, an excellent monograph by Fleming provides an exhaustive treatment of the theoretical aspects of LUMO-lowering catalysis.[8]

The Diels–Alder reaction is one of the most well studied reactions in organic chemistry, and provides one of the most easily accessible means to rapidly assemble complex molecules. Chiral Lewis acids have been used extensively to effect enantioselective cycloadditions, and therefore the Diels–Alder reaction was one of the first to be targeted for potential enantioselective organocatalytic activation.[9] MacMillan and coworkers approached the problem by seeking to duplicate the aspects of Lewis acid catalysis used previously with great success. A variety of chiral Lewis acids functioned by formation of a dative bond with the carbonyl of an α,β-unsaturated carbonyl compound, thereby activating the olefin of the substrate by lowering the energy of its LUMO. This reactivity could theoretically be mimicked by the formation of an α,β-

unsaturated iminium ion, produced by condensation of an α,β-unsaturated ketone or aldehyde and a secondary amine (Scheme 2). Subsequent to condensation, a catalytic cycle was envisioned where the now activated iminium-dienophile could undergo reaction with a suitable diene to afford cycloadduct. Iminium ion **5** would then be subject to hydrolytic cleavage to release the desired product and regenerate the catalyst to undergo further reaction (Scheme 3).



Scheme 2. General paradigm for unsaturated carbonyl activation by Lewis acids (eq. 1) or condensation with a secondary amine (eq. 2).



Scheme 3. Hypothetical reaction sequence for asymmetric organocatalytic Diels–Alder cycloaddition

Amino acid derivatives were chosen for initial screens due to their wide availability, low cost, structural variability, and ease of handling and manipulation. Several catalysts were examined, as shown in Table 1.[10] The hydrochloride salts of (*S*)-proline and (*S*)-abrine methyl esters were screened, as well as pseudo-C_2-symmetric catalyst **6** and (*S*)-phenylalanine derived catalysts **7** and **8**, in the Diels-Alder reaction between cyclopentadiene and cinnemaldehyde (Table 4). Benzylimidizolidinone **8**, readily prepared by condensation of (*S*)-phenylalanine methyl amide and acetone, afforded the best yields and enantioselectivities. The stereoselectivity was rationalized by simple molecular modeling calculations, as shown for the iminium prepared from **8** and acrolein in Figure 3. The benzyl moiety of the catalyst served to shield the *re* face of the incipient unsaturated iminium ion from cycloaddition; additionally, the phenyl ring on the catalyst seemed to be well situated for a stabilizing cation-π interaction with the iminium. The control of iminium geometry was also a crucial factor, since *cis* -and *trans*-iminium ions each lead to enantiomerically divergent products. The *gem*-dimethyl substituent of the catalyst was theorized to control the iminium geometry; unfavorable nonbonded interactions would serve to direct the formation of iminium toward the vacant quadrant of space adjacent to the benzyl functionality. A wide variety of α,β-unsaturated aldehydes and cyclic and acyclic dienes were shown to undergo this organocatalyzed Diels-Alder reaction with good yields and excellent enantioselectivities, although, with few exceptions, the diastereoselectivities were low to moderate. Wipf later demonstrated that this methodology could be applied to the preparation of cyclic β-amino acids by using a diene with a protected amine on the terminus.[11]

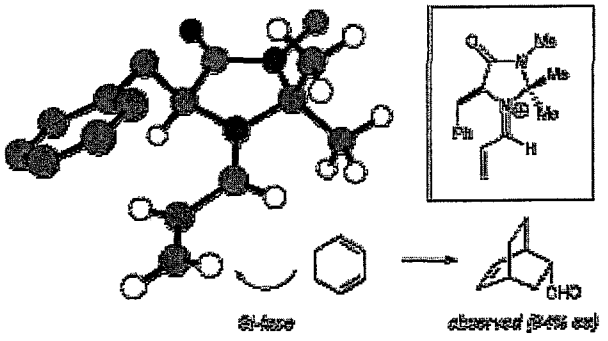
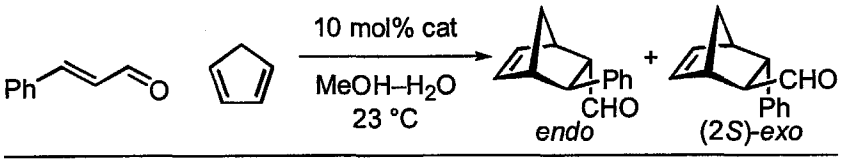


Figure 3. Calculated mimized geometry at the MM3 level of **8** condensed with acrolein.

Table 4. Results of initial catalyst screens for cycloaddition of cinnemaldehyde and cyclopentadiene.



Entry	Catalyst	Time / h	yield / %	*exo*:*endo*	*exo* ee / %
1	(*S*)-Pro-OMe•HCl	27	81	2.7:1	48 (2*R*)
2	(*S*)-Abr-OMe•HCl	10	80	2.3:1	59 (2*S*)
3	**6**	23	92	2.6:1	57 (2*R*)
4	**7**	84	82	3.6:1	74 (2*R*)
5	**8**	8	99	1.3:1	93 (2*S*)

Diels – Alder reactions with simple unsaturated ketones proved to be a formidable challenge. The lack of any inherent structural or electronic elements controlling the location of electon density around the carbonyl oxygen of such ketones mantifested itself in poor stereoselectivity of enone-derived cycloadducts. Prior efforts directed towards the development of an asymmetric Diels-Alder reaction in the regime of Lewis-acid catalysis had found success only with unsaturated carbonyl substrates that provide some sort of inherent selectivity for the location of the metal catalyst. In the case of aldehydes, steric considerations dictate binding of the metal *cis* to the hydrogen (Figure 4). With

unsaturated esters, stereoelectronic effects that minimize opposing dipoles direct the metal atom to be opposite the oxygen of the alkoxy component. Bidentate substrates, such as Evans-type imides, provide a satisfactory degree of preorganization due to two-point association of the catalyst with the two carbonyls. With a high-symmetry arrangement of lone pairs on the associated ketones, quinones have been used in several enantioselective Diels – Alder processes; unfortunately, structurally they comprise a very limited subset of available dienophiles, thereby limiting the utility of this method. [12] An iminium-based organocatalytic strategy seemed to be a promising avenue to asymmetric Diels-Alder reactions with enones, since a condensation product between an enone and amine catalyst would have severely restricted rotation about the carbon-nitrogen double bond. This conformational restriction would hopefully provide the stable steric and electronic environments necessary for good enantioinduction (Scheme 4).

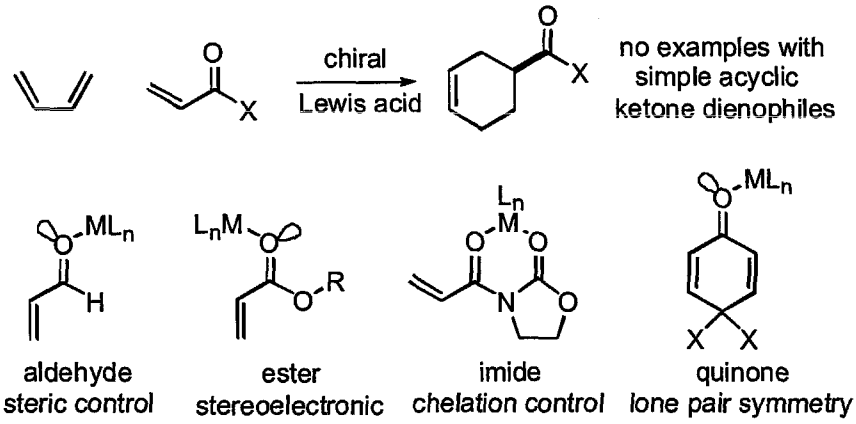
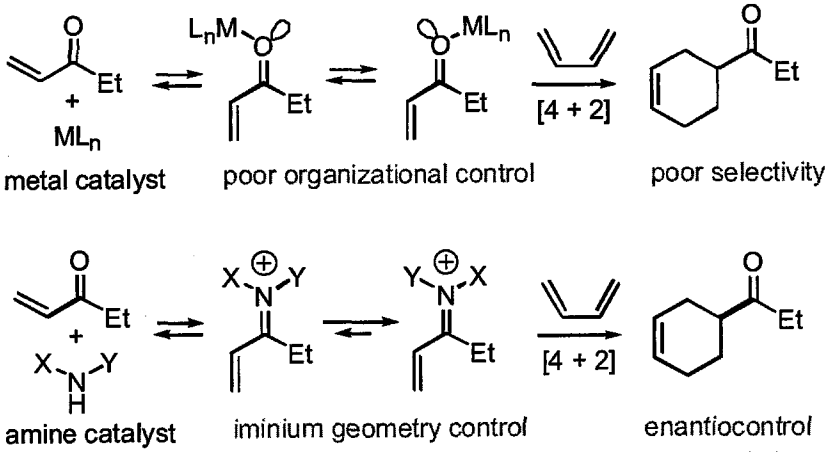


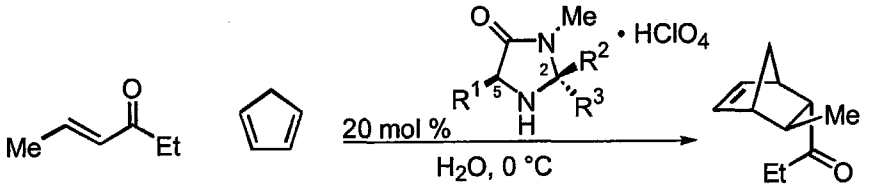
Figure 4. Schematic representation of structural stereocontrolling elements for binding of Lewis acidic metal complexes present in some unsaturated carbonyl derivatives.



Scheme 4. Conceptual rationale for the implementation of iminium catalysis in a catalytic asymmetric Diels–Alder reaction.

Initially, an organocatalytic asymmetric Diels – Alder reaction of 4-hexen-3-one and cyclopentadiene was attempted with several catalysts that all contained the imidazolidinone framework detailed above (see Scheme 3).[13] . Disappointingly, catalyst **9**, which has proven useful in conjugate addition chemistry (*vide infra*) gave racemic product. Substitution of a phenyl group for the *tert*-butyl group in **9** resulted in a dramatic rise in enantioselectivity (to 82% ee), while substitution of a 5-methyl-furyl for the *tert*-butyl group afforded the highest enantioselectivity (90% ee, Table 5). This series of optimizations not only allowed the preparation of a new and better catalyst, but also emphasized the highly advantageous structural flexibility of the imidizolidinone framework of the organocatalyst **9**. It is noteworthy that the "green" aspect of these reactions does not merely consist of the solely organic nature of the catalyst, but also of the solvent, as the reactions were carried out in pure water; few examples of asymmetric metal-catalyzed methodologies exist that are compatible with experimental conditions featuring water as the only solvent.

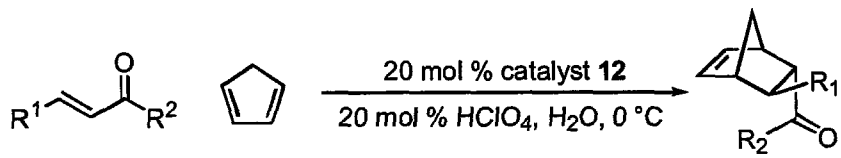
Table 5. Effect of the amine architecture on the Diels – Alder reaction between 4-hexen-3-one and *cyclopentadiene*.



Entry	Catalyst	R^1	R^2 (R^3)	Time / h	Yield / %	*endo*:*exo*	ee / %
1	**8**	Bn	Me (Me)	48	20[c]	7:1	0
2	**9**	Bn	*t*-Bu (H)	48	27[c]	9:1	0
3	**10**	Ph	Ph (H)	22	88	21:1	47
4	**11**	Bn	Ph (H)	42	83	23:1	82
5	**12**	Bn	5-Me-furyl (H)	22	89	25:1	90

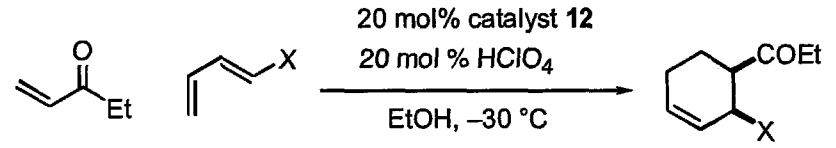
Variation of the substituents on the enone proved to have a dramatic effect on reaction efficiency and selectivity, as shown in Table 6. Alteration of the alkyl groups distal to the carbonyl had little effect on selectivity (Entries 2, 6, and 7), whereas changing the alkyl group proximal to the carbonyl afforded both products with good yields and enantioselectivities, or uniformly poor yields and selectivities, in the case where R_2 was an isopropyl group. This mitigative effect is presumably due to the steric bulk associated with the isopropyl group, which retards iminium formation to the point where background thermal cycloaddition is the dominant reaction manifold. The diene component displayed no such variable selectivity; a range of synthetically useful acyclic dienes were shown to undergo organocatalytic Diels–Alder reactions with ethyl vinyl ketone in good yields and enantioselectivities (85 – 98% ee, Table 7).

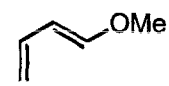
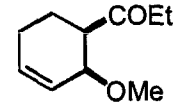
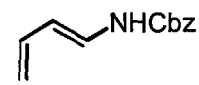
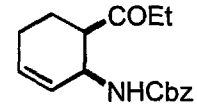
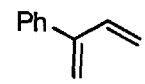
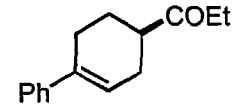
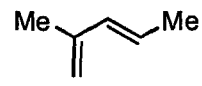
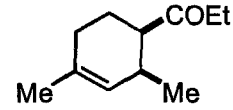
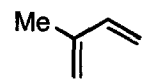
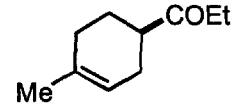
Table 6. Organocatalyzed Diels–Alder cycloadditions between cyclopentadiene and representatives acyclic enones.



Entry	R^1	R^2	Yield / %	*endo*:*exo*	ee / %
1	Me	Me	85	14:1	61
2	Me	Et	89	25:1	90
3	Me	*n*-Bu	83	22:1	92
4	Me	*i*-Am	86	20:1	92
5	Me	*i*-Pr	24	8:1	0
6	*n*-Pr	Et	84	15:1	92
7	*i*-Pr	Et	78	6:1	90

Table 7. Organocatalyzed Diels–Alder cycloadditions between ethyl vinyl ketone and representative dienes.



Entry	Diene	Product	*endo*:*exo*	Yield / %	ee / %
1			>200:1	88	96
2			>100:1	91	98
3			>200:1	92	90
4			>200:1	90	90
5			>200:1	79	85

A rationale for the stereochemical outcome of these reactions depends mostly on torsional strain arguments. A computational model of iminium formation with ethyl vinyl ketone clearly shows the *trans* iminium isomer to be the favored over the *cis* isomer, due to unfavorable nonbonded interactions between the catalyst and the methylene group of the ethyl substituent on the dienophile-derived portion of the intermediate iminium ion. The *trans* isomer bears no such destabilizing interaction due to the sp^2 hybridization of the vinyl substituent on the enone substrate. This model also explains the lower enantioselectivity observed with the cycloaddition of cyclopentadiene and methyl vinyl ketone. Despite the fact that the *trans* iminium isomer is still favored computationally, the decreased steric impedance of the methyl group results in accessibility of both enantiotopic faces of the enone to cycloaddition.

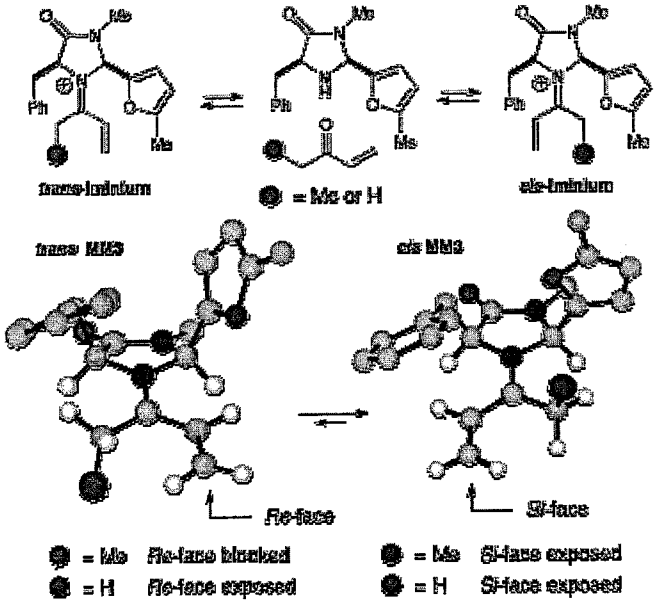
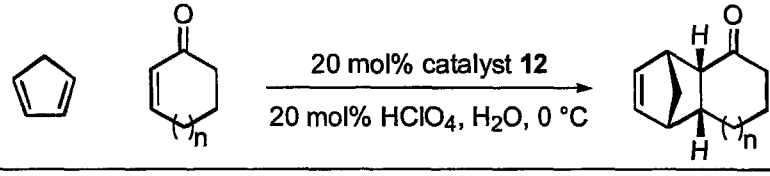


Figure 5. Minimized geometry of **12** condensed with two enones as calculated by MM3 methods.

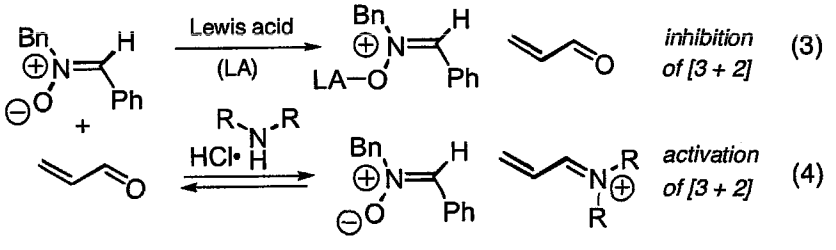
These rationalizations also support the results of an investigation of the organocatalyzed cycloaddition of cyclopentadiene with several cyclic enones. In accord with the reasoning above, increased torsional freedom of the methylene adjacent to the ketone should enhance unfavorable nonbonded interactions present in the *cis* iminium isomer, resulting in more highly stereocontrolled additions. Since smaller ring sizes would conceivably afford lower degrees of torsional freedom due to geometric constraints, it would be expected that enantioselectivity in the cycloaddition should be directly proportional to ring size. Lending support to this theory was the discovery that low enantioselectivities were observed with cyclopentenone and cyclohexenone (Table 8, entries 1 and 2); , whereas cycloaddition with (*E*)-cyclopentadecen-2-one afforded the corresponding Diels – Alder product in 93% ee. The work described above constituted the first example of highly enantioselective catalytic Diels–Alder methodology with simple unsaturated ketones.[14]

Table 8. Organocatalyzed Diels–Alder cycloadditions between cyclopentadiene and representative cyclic enones.



Entry	n	Time / h	Yield / %	*endo*:*exo*	ee / %
1	0	12	81	15:1	48
2	1	17	81	12:1	63
3	2	28	85	18:1	90
4	3	72	83	6:1	91
5	10	72	88	5:1	93

The validation of the conceptual aspects of iminium catalysis in the context of the Diels-Alder reaction prompted the investigation of other reactions also susceptible to LUMO-lowering catalysis. In this regard, the [3 + 2] cycloaddition reaction of nitrones with α,β-unsaturated carbonyls proved to be an attractive target for methodological development, due to the rapid, efficient assembly of structural and stereochemical complexity associated with this reaction. Chiral Lewis acid catalysis had been successfully applied to this reaction;[15] however, due to the undesired, but irreversible binding of Lewis acids to the oxygen on the nitrone substrates, these methodologies suffered from the adamantine constraint that only bidentate dipolarophiles could be utilized. The benzylimidizolidinone **8** does not suffer from this liability, due to the much lower electophilicity of nitrogen and the inability of the protonated amine nitrogen to accommodate additional ligating species (Scheme 5).

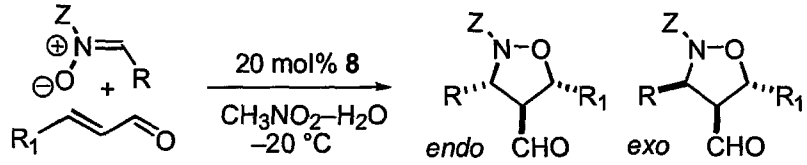


Scheme 5. Illustration of conceptual inhibition of nitrone cycloaddition by Lewis acids (eq 3) contrasted with successful reaction catalyzed by a secondary amine (eq 4).

Catalyst **8** was shown to afford nitrone cycloaddition products in good yields and excellent diastereo- and enantio- selectivities (90 – 99% ee), as shown in Table 9.[16] A wide range of nitrones were used in the [3 + 2] cycloaddition reaction with acrolein and crotonaldehyde. It was also demonstrated that the nitrogen-oxygen bond in the nitrone products could be readily cleaved under reducing conditions to afford enantiomerically

enriched β-amino alcohols, a useful synthon in natural product chemistry and the assembly of ligands for asymmetric catalysis.

Table 9. Scope of the organocatalytic asymmetric [3 + 2] nitrone cycloaddition.



Entry	Z	R	R_1	*endo*:*exo*	Yield / %	ee / % (*endo*)
1	Bn	Ph	Me	94:6	98	94
2	Allyl	Ph	Me	93:7	73	98
3	Me	Ph	Me	95:5	66	99
4	Bn	C_6H_4Cl-4	Me	92:8	78	95
5	Me	C_6H_4Cl-4	Me	93:7	76	94
6	Bn	C_6H_4OMe-4	Me	98:2	93	91
7	Me	C_6H_4Me-4	Me	93:7	82	97
8	Bn	2-naph	Me	95:5	98	93
9	Bn	*c*-hex	Me	99:1	70	99
10	Bn	Ph	H	86:14	80	92[a]
11	Bn	C_6H_4Me-4	H	85:15	80	90[a]
12	Bn	C_6H_4Cl-4	H	80:20	80	91[a]
13	Bn	2-naph	H	86:14	80	90[a]
14	Bn	C_6H_4OMe-4	H	91:9	83	90[a]

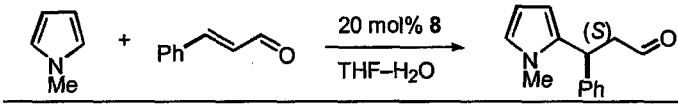
[a] Reaction conducted with triflate salt of catalyst **8**.

1.2.2.2 Conjugate Additions

Conjugate addition of nucleophiles also represented an attractive target for methodology development, particularly since, in theory, LUMO lowering activation should also predispose an enal towards 1,4-addition. These reactions presented additional challenges not present in cycloaddition chemistry, as they were not as well studied mechanistically and did not necessarily proceed through highly ordered, closed transition states.

Pyrroles had been observed to add to unsaturated carbonyls conjugately in a thermally activated process; however, attempts to effect Lewis acid catalysis in this reaction have resulted solely in addition to the carbonyl carbon.[17] In fact, subsequent dehydration of the 1,2-adduct and further additions resulted in the formation of porphyrin-like molecules. In this context, achieving enantioselective conjugate addition of pyrroles to enals represented an attractive target for the development of new methodology. Initial attempts to foster conjugate additions demonstrated that the reaction was highly sensitive to the nature of the acid cocatalyst, as shown in Table 10.[18] Cocatalysts with lower pK_as afforded significant enhancements both in conversion and enantioselectivity. Ultimately, the trifluoroacetate salt of **8** proved to be the optimal catalyst. A wide range of alkyl and aryl substituents were observed to undergo conjugate addition of *N*-methylpyrrole in a highly enantioselective fashion. Several differentially alkylated pyrroles (at the nitrogen and 2- and 3-positions) also added to cinnamaldehyde under organocatalytic conditions with good yields and enantioselectivities, as illustrated in Table 12.

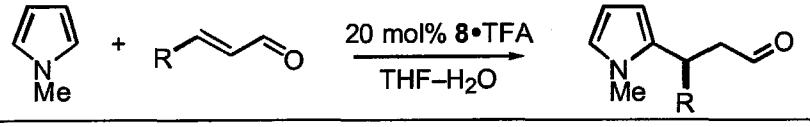
Table 10. Investigation of acid cocatalyst effect on asymmetric addition of *N*-methyl pyrrole to cinnemaldehyde.



Entry	H–X cocatalyst	Temp / °C	Time / h	Yield / %[a]	ee / %
1	$NCCH_2CO_2H$	23	32	10	80
2	Cl_2CHCO_2H	23	32	62	80
3	Cl_3CCO_2H	23	3	64	81
4	TFA	23	3	78	81
5	TFA	–30	42	87	93

[a]Yields based on isolation of the corresponding alcohol after $NaBH_4$ reduction.

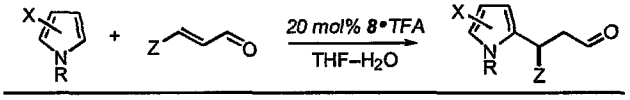
Table 11. Investigation of scope of organocatalytic asymmetric conjugate addition of *N*-methyl pyrrole to various unsaturated aldehydes.

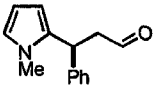
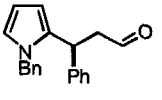
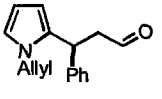
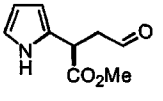
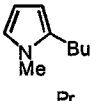
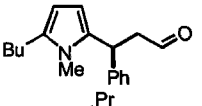
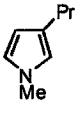
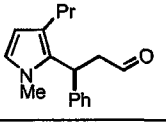


Entry	R	Temp / °C	Time / h	yield / %[a]	ee / %
1	Me	–60	72	83	91[b]
2	Pr	–50	72	81	90
3	*i*-Pr	–50	72	80	91
4	C_6H_5	–30	42	87	93
5	C_6H_4OMe-4	–30	104	79	91
6	CH_2OBn	–60	72	90	87[b]
7	CO_2Me	–50	104	72	90[c]

[a]Yields based on isolation of the corresponding alcohol after $NaBH_4$ reduction. [b]Using 10 mol % 8•TFA. [c]Using cyanoacetate salt of **8**.

Table 12. Effect of differential substitution of pyrroles on organocatalytic addition to unsaturated aldehydes.



entry	pyrrole	Z	product	yield / %[a]	ee / %
1		Ph		87	93
2		Ph		80	89[b]
3		Ph		83	91[b]
4		CO_2Me		74	90[c]
5		Ph		87	90
6		Ph		68	97

[a]Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction. [b]Using trichloroacetate salt of **8**. [c]Using cyanoacetic acid salt of **8**.

With the success of the pyrrole conjugate addition, the organocatalytic conjugate addition technology was expanded to encompass other heterocyclic aromatic nucleophiles. The indole moiety proved to be an attractive nucleophile, due to the ubiquity of indolic stereocenters in molecules with desirable biological activities.[19] Initial attempts to effect conjugate addition of *N*-methylindole to crotonaldehyde proved disappointing; after extensive optimization, the conjugate adduct was obtained in 83% yield and 56% ee after two days. These results were not altogether unexpected, since the nucleophilicity of pyrrole had been observed experimentally to be superior to many other heteroaromatic nucleophiles.[20] Attempts to add furans conjugately to crotonaldehyde met with similarly discouraging results. It was therefore decided to search for a second-generation organocatalyst. Ultimately, the modified benzyl imidizolidinone **9** was identified as an optimal agent for organocatalytic conjugate additions. This catalyst was accessed in a manner analogous to that used to prepare **8**, except that the (*S*)-phenylalanine methyl amide was condensed with pivaldehyde, followed by separation of the resulting diastereomers by chromatography or recrystallization.

Several structural features of **9** explain its superior performance (Figure 6). Initial kinetic studies indicated that the overall rate of the iminium-catalyzed processes was directly related to the rate of iminium formation. The amine lone pair in **9** no longer possesses the unfavorable eclipsing interaction with the *gem*-dimethyl substituent present in **8**, making the lone pair more accessible to engage in iminium formation. Moreover, iminium ion geometry was controlled by avoidance of steric impedance between the *tert*-butyl group and the alkyl portion of the iminium ion. Finally, enantiofacial coverage of the incipient unsaturated iminium ion was enhanced by the addition of the *tert*-butyl

group. The improved catalyst **9** exhibited dramatic enhancements in rate and selectivity in the organocatalytic conjugate addition of *N*-methylindole to crotonaldehyde. The overall reaction time was reduced by more than half, yet this reduction in time was accompanied by concomitant increases in yield (56% to 82%) and enantiomeric excess of the product (56% to 92%). As with the pyrrole conjugate additions, the indole additions proved to be highly sensitive to the acid cocatalyst; again, the trifluoroacetate salt of the catalyst demonstrated superior activity in all respects (see Table 13). A variety of alkyl- and aryl-substituted enals underwent conjugate addition with good yields and stereoselectivities (Table 14); variation of substitution on the indole was also accommodated with similarly excellent levels of enantioselectivity (Table 15).

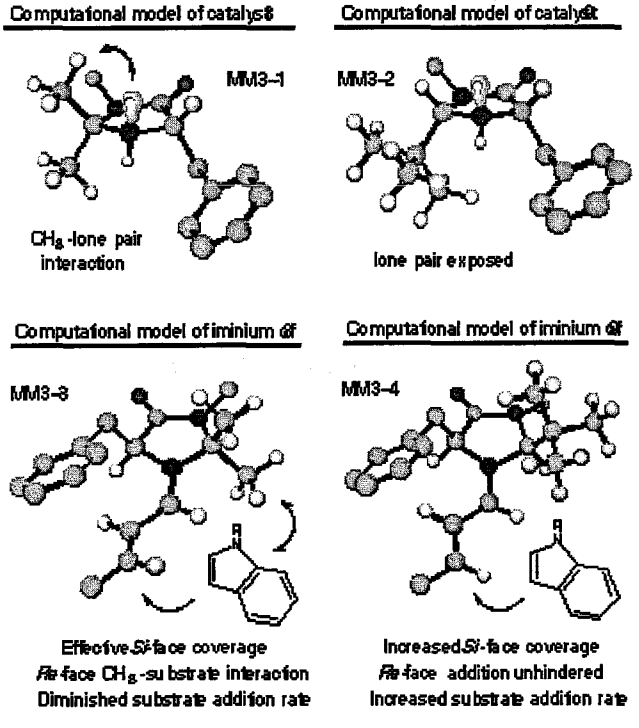
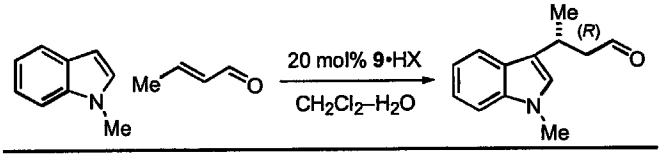


Figure 6. Explanation for increased reaction rates and superior selectivities using organocatalyst **9**.

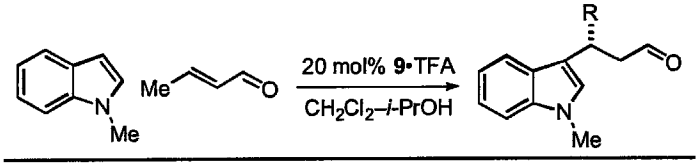
Table 13. Effect of catalyst architecture and acid cocatalyst on asymmetric organocatalytic conjugate addition of *N*-methylindole to crotonaldehyde.



entry	cocatalyst	Temp / °C	Time / h	yield / %	ee / %
1	TFA	–40	1.5	70	85
2	*p*–TSA	–40	4	98	88
3	2–NO_2PhCO_2H	–40	22	88	88
4	*p*–TSA	–83	48	15	80
5	TFA	–83	31	84	92
6	TFA	–83	19	82	92[a]

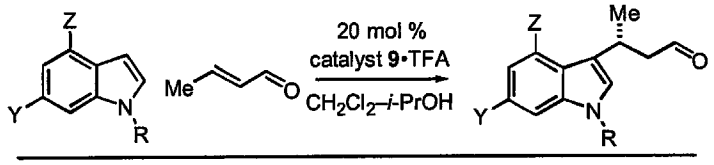
[a]Reaction conducted with CH_2Cl_2 – *i*-PrOH (85 : 15 *v/v*) as solvent.

Table 14. Organocatalyzed alkylation of *N*-methylindole with representative unsaturated aldehydes.



entry	R	Temp / °C	Time / h	Yield / %	ee / %
1	Me	–83	19	82	92
2	*n*–Pr	–60	6	80	93
3	*i*–Pr	–50	32	74	93
4	CH_2OBz	–83	18	84	96
5	Ph	–55	45	84	90
6	CO_2Me	–83	21	89	91

Table 15. Enantioselective organocatalytic alkylation of representative indoles with (*E*)-crotonaldehyde.



Entry	indole substituents			Temp / °C	Time / h	Yield / %	ee / %
	R	Y	Z				
1	Me	H	H	–87	19	82	92
2	H	H	H	–60	22	72	91
3	allyl	H	H	–72	20	70	92
4	CH_2Ph	H	H	–60	120	80	89
5	H	H	Me	–60	3	94	94[a]
6	Me	H	OMe	–87	19	90	94[a]
7	H	Cl	H	–60	13	73	97[a]

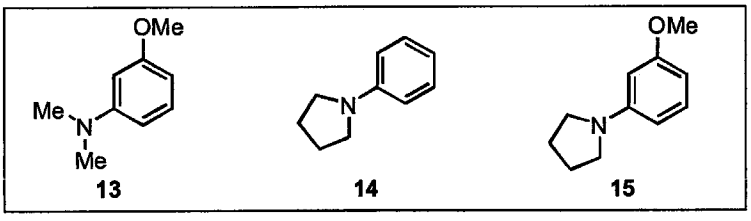
[a]Reaction conducted with (*E*)–$BzOCH_2CH{=}CHCHO$.

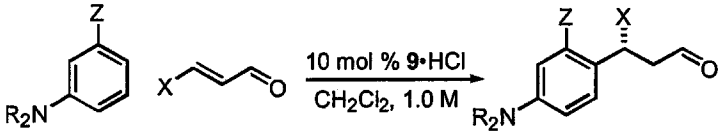
Conjugate addition of furans proved to be the most challenging problem, corresponding to the lower susceptibility of furans towards electrophilic substitution relative to pyrroles and indoles.[20b] As with pyrroles, prior attempts to effect chiral Lewis acid catalysis of conjugate addition of silyloxy furans to unsaturated carbonyls resulted solely in isolation of the 1,2–addition product.[21] Initial studies of the reaction between silyloxy furans and crotonaldehyde gave the corresponding quaternary butenolide with good stereocontrol (6 : 1 dr, 82% ee) but poor conversion (5%). Various alcohols were added to scavenge the silyl cation generated by conjugate addition, with addition of water affording the best results; a dramatic increase in yields was observed (5% to 84%) as well as increases in the diastereoselectivity (22 : 1 / *syn* : *anti*) and enantioselectivity (92% ee). Using these optimized conditions, it was demonstrated that this methodology was amenable to conjugate addition to a wide variety of conjugated aldehydes (81 – 87% yield, up to 31: 1 dr, 84 – 99% ee); additionally, a range of substitution on the silyloxy furan was tolerated, with diastereoselectivities ranging from 7 : 1 to 24 : 1 and enantiomeric excesses greater than 90%. The synthetic utility of this procedure was demonstrated by the rapid and efficient total synthesis of the commercial biosurfactant spiculisporic acid. Both the title compound and its C2 epimer were accessible in excellent levels of stereocontrol using the organocatalytic conjugate silyloxyfuran addition.

In accord with its status as the least activated aromatic nucleophile, the ultimate challenge in asymmetric Friedel-Crafts alkylation methodology would be to develop a means of alkylating benzene. In earlier preliminary screens of pyrrole conjugate additions, toluene had been used on many occasions as solvent, without the observation

or isolation of any toluene alkylation products. However, an alternate strategy presented itself in the addition of activated benzene rings to electrophiles, following by cleavage of the activating group. Substituted anilines proved to be an attractive lead in satisfying these requirements. Preliminary reaction studies with the use of aniline **14** and anisidines **13** and **15** showed that several differentially substituted enals underwent conjugate addition with good levels of enantioselectivity (87 – 92% ee, Table 16).[22] The addition of these anilines to methyl 4-oxobutenoate proceeded with even greater selectivities. Remarkably, the product corresponding to addition of **13** to methyl-4-oxobutenoate was obtained in 73% yield and 91% ee at room temperature after five minutes (Entry 12, Table 18).

Table 16. Organocatalyzed alkylation of anilines **13**, **14**, and **15** with represntative α,β-unsaturated aldehydes.

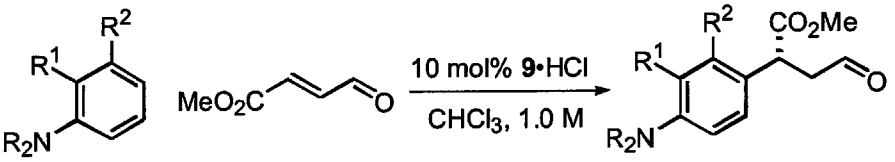




entry	aniline	X	temp / °C	time / h	yield / %	ee / %[a]
1	**13**	Me	–40	36	86	89
2	**14**	Me	–20	48	70[b]	87
3	**13**	Et	–50	48	68	88
4	**13**	CH_2OBz[c]	–20	24	89	92
5	**14**	CH_2OBz[c]	+20	24	73	90
6	**13**	CO_2Me[c]	–20	8	90	92
7	**15**	Ph	–50	36	82[b]	84
8	**15**	*p*-Cl-Ph	–50	30	80[b]	92
9	**14**	*p*-NO_2-Ph	–10	48	87	92
10	**13**	*p*-NO_2-Ph	+20	48	82	90

[a]Ratios determined by chiral HPLC analysis of corresponding alcohol after $NaBH_4$ reduction. [b]Using 20 mol % catalyst. [c]Reaction conducted at 1.0 M in $CHCl_3$.

Table 17. Organocatalyzed alkylation of methyl-4-oxobutenoate with representative anilines.

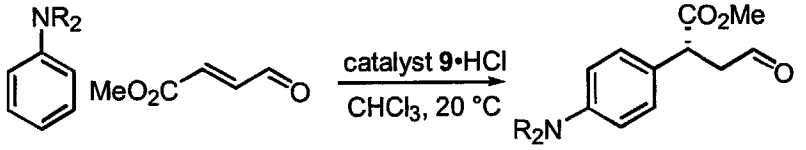


Entry	NR_2	R^1	R^2	Temp / °C	Time / h	Yield / %	ee / %[a]
1	NMe_2	H	H	–10	48	86	96[b]
2	NMe_2	H	H	+20	5	77	94[b]
3	NBn_2	H	H	+20	24	65	96
4	1-pyrrolidino	H	H	–20	8	97	97
5	1-pyrrolidino	H	H	+20	0.3	96	95
6	1-pyrrolidino	Ph	H	+20	12	94	99
7	$-N(Me)CH_2CH_2^-$		H	–20	8	94	98
8	$-N(Me)CH_2CH_2^-$		H	+20	0.3	93	93
9	NMe_2	$-CH=CH-CH=CH^-$		+20	36	89	93
10	NMe_2	H	Me	–10	10	89	84
11	NMe_2	H	OMe	–20	8	90	92
12	NMe_2	H	OMe	+20	0.1	73	91
13	NMe_2	H	SMe	–20	8	92	91
14	NMe_2	H	Cl	–20	80	73	93[b]
15	NMe_2	H	Cl	+20	12	66	86

[a]Ratios determined by chiral HPLC analysis of corresponding alcohol after $NaBH_4$ reduction. [b]Using catalyst **9** (20 mol % amine, 15 mol % HCl).

The low cost and trivial preparation of catalyst **9** made the need for elevated catalyst loadingssignificantly less costly. However, in the case of the aniline conjugate addition, at catalyst loadings similar to or lower than that of standard organometallic catalysts (2 mol %), **11** was shown to add to methyl 4-oxobutenonate in 92% yield and 92% ee after 12 hours (Table 18).

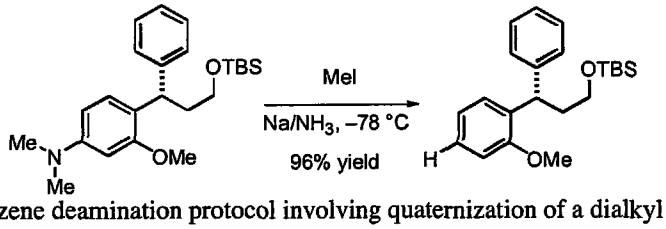
Table 18. Effect of catalyst loading on organocatalytic asymmetric addition of 1-phenylpyrrolidine to methyl-4-oxobutenoate.



Entry	9•HCl / mol %	Time	Yield / %[a]	ee / %
1	10	20 min	96	95
2	5	2 h	92	94
3	2	12 h	92	92
4	1	40 h	87	88

[a]NR_2 = 1-pyrrolidino.

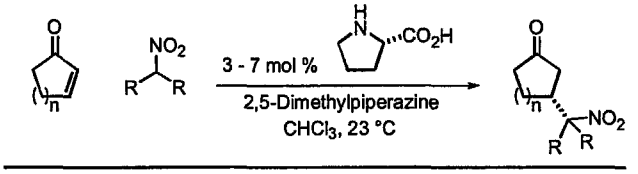
Unfortunately, deamination of the aniline adducts under the standard conditions (diazotization followed by treatment with hypophosphoric acid) yielded the corresponding benzene adducts in poor conversions. A novel deamination procedure was therefore developed to address this problem. As shown in Scheme 6, the aniline adducts were subjected to quaternization by methyl iodide (or, alternatively, methyl triflate or dimethyl sulfate) followed by reduction under standard Birch conditions. Yields are uniformly excellent (> 90% in most cases) and no erosion in enantioselectivity was observed as a result of exposure of the substrate to the relatively harsh conditions of the Birch reduction. The implementation of this new deamination procedure allows anilines to function as benzene surrogates in asymmetric Friedel-Crafts alkylations.[23]



Scheme 6. Novel benzene deamination protocol involving quaternization of a dialkyl aniline, followed by reductive cleavage of the carbon-nitrogen bond.

A recent report by Hanessian expanded the scope of organocatalyzed conjugate addition to cyclic enones.[24] Previously, Yamaguchi and coworkers had reported the rubidium prolinate-catalyzed asymmetric conjugate addition of malonates to cyclic and acyclic enones, albeit in moderate enantioselectivities.[25] Hanessian found that the amino acid itself was capable of catalyzing the addition of various alkyl nitro compounds to cyclic enones with moderate to good enantioselectivities (62–93% ee). The highest enantioselectivities were obtained with the addition of symmetrically substituted secondary nitro compounds, such as 2-nitropropane, nitrocyclopentane, and nitrocyclohexane (all 75 – 93% ee), to cyclic enones, as shown in Table 19. When primary or secondary nitro compounds such as nitroethane or nitromethane were added, the enantioselectivities dropped off slightly (62 – 87% ee, Table 20). In all cases, the use of L-proline afforded selectivities that were superior to the use of rubidium prolinate as catalyst. Variation of the catalyst structure to encompass larger and smaller ring sizes as well as differential substitution on the catalyst resulted in the selection of proline as the optimal catalyst.

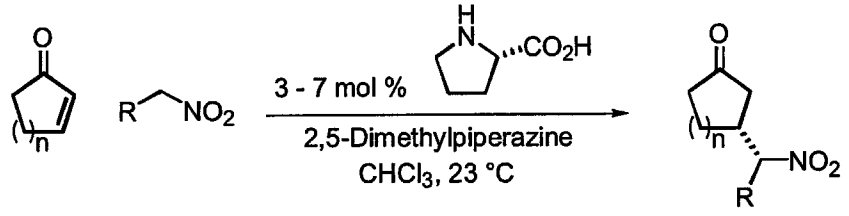
Table 19. L-Proline-catalyzed asymmetric conjugate addition of symmetrical nitroalkanes to cyclic enones.



Entry	n	R	Yield / %	ee / %[a]
1	1	Me	66	75
2	1	$(CH_2)_4$	66	76
3	1	$(CH_2)_5$	62	76
4	2	Me	88	93
5	2	$(CH_2)_4$	68	93
6	2	$(CH_2)_5$	73	93
7	3	Me	61	86
8	3	$(CH_2)_4$	71	87
9	3	$(CH_2)_5$	49	89

[a] Enantiomeric excesses determined by ^{13}C NMR of corresponding ketal derived from (*2R,3R*)-2,3-butanediol.

Table 20. L-Proline-catalyzed asymmetric conjugate addition of primary nitroalkanes to cyclic enones.



Entry	n	R	Yield / %	dr	ee / %[a,b]
1	1	Me	71	1 : 1	65 / 64
2	1	3-butenyl	81	1 : 1	76 / 63
3	1	H	30	na	62
4	2	Me	86	1 : 2	72 / 74
5	2	3-butenyl	71	1 : 2	87 / 77
6	2	H	61	na	71

[a] Ratio of more polar to less polar isomer. [b] Multiple enantiomeric excesses are given for the isomers in order of decreasing polarity, if applicable. [c] Enantiomeric excesses determined by ^{13}C NMR of corresponding ketal derived from (*2R,3R*)-2,3-butanediol.

Interestingly, it was determined that in order to obtain optimal results, it was also necessary to add an exogenous base, with *trans*-2,5-dimethylpiperazine furnishing the highest overall levels of both yield and ee. The added base affected the overall reaction time, but not the yield or enantioselectivity of the resulting conjugate adduct. Meticulous exclusion of water from the reaction medium resulted in a complete inhibition of reactivity, providing some support for the intermediacy of an iminium ion. A small amount of water may be necessary not only to increase the stability of the incipient iminium, but for hydrolysis of the iminium formed after the addition event. Finally, a distinct nonlinear effect was observed with the use of several exogenous bases. This suggests a somewhat different reactive structure, from the one present with the rubidium prolinate work of Yamaguchi, possibly some form of oligomeric complex of catalyst and base or a dimeric catalyst resting state. In Yamaguchi's study, there were no deviations from linearity observed between the enantiopurity of the catalyst and that of the product.

A thorough accounting of the mechanism of this reaction and improvement in both its scope and its selectivity have yet to be accomplished.

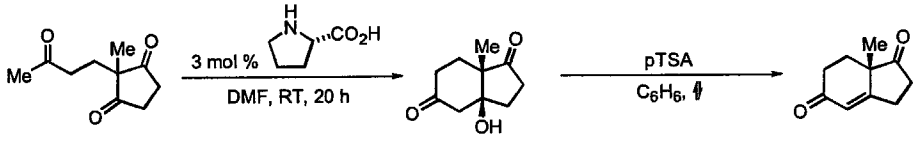
1.3 Enamine Catalysis

1.3.1 Substrate Activation

1.3.1.1 The Aldol Reaction

It is difficult to understate the importance and primacy of the aldol reaction as a rapid and efficient means of assembly of both simple and complex polyol architectures. Accordingly, a great deal of effort has been invested in the development of stereoselective versions of this reaction, with outstanding methodologies emerging from the laboratories of Evans,[26] Heathcock,[27] Masamune,[28] and Mukaiyama.[29] In contrast to other technologies, a highly efficient asymmetric version of this reaction catalyzed by a chiral amine preceded the development of metal– or Lewis acid–catalyzed aldol methodologies.

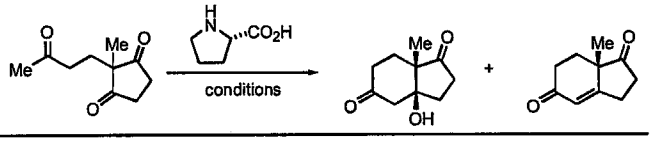
Two research groups independently made the discovery in the early 1970s that L-proline catalyzed the asymmetric Robinson annulation of the symmetrical molecule 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione to afford the corresponding ketol (or enone, upon dehydration). This reaction, referred to as the Hajos-Parrish-Eder-Sauer-Wiechert reaction, proceeded in essentially quantitative conversion and outstanding enantioselectivity (93% ee, Scheme 7).[30] This discovery constituted the first example of an asymmetric catalytic aldol-type reaction.



Scheme 7. Highly enantioselective, L-proline-catalyed cyclization of a triketone as discovered independently by Hajos and Parrish[30a] and Eder, Sauer, and Wiechert.[30b]

The mechanism of the reaction was a matter of great controversy for some time. Hajos and Parrish conducted several experiments that helped elucidate some of the mechanistic aspects of the reaction. Initially, alcohols were used as solvent, with a distinct trend observed that as the steric bulk of the alkyl groups increased, the enantioselectivity increased (Table 21). Based on an assumption that hydrogen bonding might serve as a crucial organizational element in the transition state, Hajos and Parrish selected polar, aprotic solvents, in the hope that the lack of hydrogen bonding capability on the part of the solvent would avoid solvent-induced disruptions of any hydrogen bonding networks present in the transition state. On switching to dimethylformamide (DMF) as solvent, the enantiomeric excess of the product increased to 93%. The relative stereochemistry at the ring junctions was determined to be *cis* by means of circular dichroism spectroscopy.

Table 21. Results of screens conducted by Hajos and Parrish to determine optimal solvent system for proline-catalyzed cyclization.



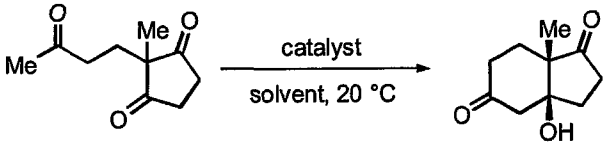
Entry	equiv. (*S*)-Pro	Solvent	Temp / °C	Ketol Optical Yield / %[a]	Enone Optical Yield / %[a]
1	1.00	EtOH	20	0	28
2	1.00	*n*-BuOH	20	0	32
3	1.00	*i*-PrOH	20	0	61
4	0.10	*i*-PrOH	20	28 (61% ee)	57
5	1.00	*t*-BuOH	20	0	84
6	1.00	CH_3CN	20	97	n.d.
7	0.03	DMF	20	93 (93% ee)	0

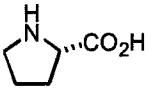
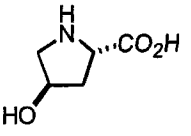
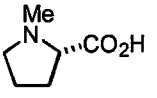
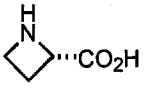
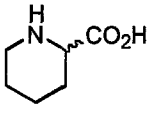
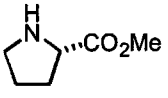
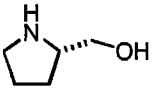
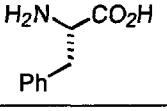
[a]Optical yield = enantiomeric excess / chemical yield.

Alteration of the morphology of the catalyst also provided some mechanistic insights, as shown in Table 22. Use of (2*S*)-(–)-*trans*-4-hydroxyproline as catalyst in acetonitrile afforded no conversion due to the marginal solubility of the catalyst (Entry 2); isopropyl alcohol as solvent afforded poor conversion (12%, Entry 3) and only moderate enantioselectivity (73%). Blocking the nitrogen of proline as its *N*-methyl derivative [(*S*)-(–)-hygrinic acid, Entry 4] suppressed all catalytic activity; only trace amounts of product were observed, attributable to the racemic background reaction. This result provided some evidence that the reaction did indeed proceed through an iminium or enamine intermediate, or quite possibly a combination of both. The size of the carbocyclic portion of the catalyst also had a profound effect on reactivity; utilization of (*S*)-(–)-azetidine-2-carboxylic acid (Entry 5) afforded the desired product in 51% yield and 64% ee; use of the racemic analog of proline (±)-2-piperidinecarboxylic acid, (Entry 6) resulted only in the recovery of starting material.

The substitution pattern of the amine also proved to be vital to obtaining high yields and enantioselectivities. When (*S*)-phenylalanine was used as catalyst (Entry 9) , the ketol was isolated after seven days in only 37% yield and 19% ee. Interestingly, use of the secondary β-amino alcohol (–)-ephedrine resulted in the formation of two diastereomeric products, which Hajos and Parrish assumed to be the carbinolamines, derived from the condensation of ephedrine with the ketone distal to the 6-5-ring junction.

Table 22. Effects of modification of catalyst architecture on proline-catalyzed cyclization.



Entry	Equiv. cat.	Catalyst	Solvent	Yield / %	ee / %
1	0.03		DMF	> 99	93
2	1.00		CH_3CN	0	0
3	1.00		*i*-PrOH	12	73
4	1.00		*i*-PrOH	trace	n.d.
5	0.03		CH_3CN	51	64
6	1.00		*i*-PrOH	0	0
7	1.00		CH_3CN	47	~ 0
8	1.00		CH_3CN	59	17
9	1.00		*i*-PrOH	37	19

Esterification to the ethyl ester resulted in a dramatic diminution in enantioselectivity (93% ee to 6% ee); reduction of the acid to a hydroxymethyl group afforded the product in only 14% ee. Taken together, these results provide compelling evidence for the existence of a hydrogen-bonding network in the transition state of the cyclization, as well as its importance to generating products of high stereochemical purity.

Hajos and Parrish proposed two distinct mechanistic possibilities for the cyclization reaction, both of which are shown in Figure 7. The first (structure **A**) involved attack of the proline carboxylate on the eniminium carbon, with concomitant attack of the proximal olefin on the cyclopentyl ketone as the key carbon-carbon bond-forming event. Hydrolysis of the carbinolamine would then afford the desired product. Hajos and Parrish discounted the likelihood of this reaction manifold due to the observation that when the transformation was carried out in ^{18}O-labelled water, no incorporation of ^{18}O into the product was detected. Transition state **B** was advanced as an alternative; in this scheme, proline was theorized to attack the pentacyclic ketone first. A hydrogen bond between the protonated proline hydrogen and the enol preorganized the substrate for attack of the enol olefin on the proline-derived carbinolamine. In this case, due to the steric impedance associated with its carboxylic acid moiety, proline would approach from the α face of the cyclopentadione molecule to give the β hydroxyl. A major discrepancy in this hypothesis, pointed out quite correctly by Jung, is that this carbon-carbon bond formation would have to occur with retention of configuration to give the product with the observed *cis* stereochemistry. This is clearly a highly unlikely eventuality when the unyielding stereoelectronic requirements of the S_N2 reaction are taken into consideration.[31] In order for this type of reaction to occur, proline would have to approach from the same side of the cyclopentadione moiety as the methyl group. Such an intermediate might be stabilized by hydrogen bonding between the proline carboxylate and the hydroxyl adjacent to the quaternary stereocenter. Carbon-carbon bond formation might then occur from the less sterically encumbered α face of the ring to afford the desired *cis*-fused [4.3.0] bicycle.

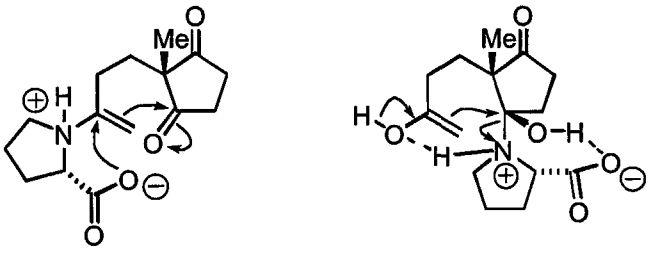


Figure 7. Mechanistic hypotheses advanced by Hajos and Parrish to account for highly enantioselective cyclization.

Until very recently, a concise and satisfying mechanistic proposal explaining the stereochemical outcome of the Hajos-Parrish reaction remained elusive. However, in 2001, Houk proposed a transition state structure based on computational studies performed at the B3LYP/6-31G* level that was devoid of the mechanistic uncertainties that plagued the previously described proposals. Two chair-like transition states were identified, each leading to the different enantiomers of the bicyclic ketol product (Figure 8). The first transition state (**TS-1**) was computed to be approximately 3.4 kcal mol^{-1} lower than the transition state leading to the minor enantiomer (**TS-2**). Two structural elements were determined to be the dominant stereocontrolling elements; the first was the fact that the iminium ion derived from carbon-carbon bond formation in **TS-1** was significantly less distorted from planarity than that resulting from **TS-2**. Hydrogen bonding was found to play a crucial role; however, it was not the carboxylic acid-ketone hydrogen bond interaction that was found to be the most important, but rather the hydrogen bonding occurring between the ketone and protons on the proline ring adjacent to the nitrogen, which were determined computationally to have a significant partial positive charge. This bond distance was calculated to be 2.4 Å in length in **TS-1**, as

compared with 3.4 Å in **TS-2**. The hydrogen bond distances between the carboxylic acid proton and the ketone were computed to be approximately 1.4 Å for both **TS-1** and **TS-2**.

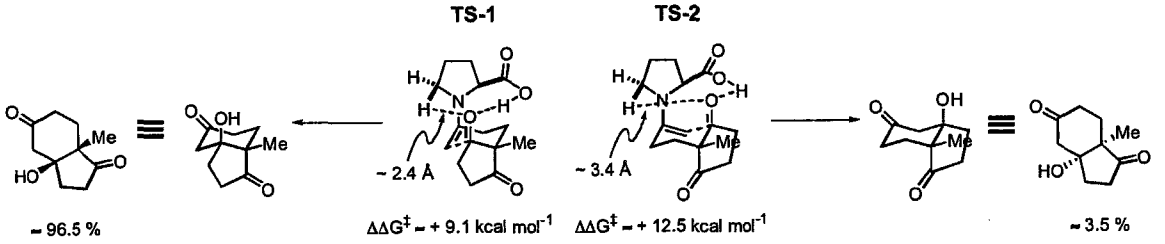
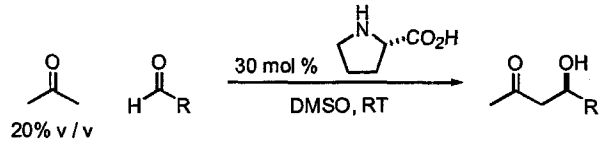


Figure 8. Illustration of calculated minimized chair transition states for the Hajos-Parrish reaction, according to Houk et al.

While the proline-catalyzed intramolecular aldol reaction has been thoroughly studied, until recently, the intermolecular variant remained an unknown reaction. In the course of conducting a research program designed to elucidate the mode of action of several enzymes that catalyzed the intermolecular aldol reaction, List, Lerner, and Barbas reported the first proline-catalyzed enantioselective intermolecular aldol reaction.[32] In an initial experiment, acetone and *p*-nitrobenzaldehyde were mixed with 30 mol % proline in DMSO to afford the corresponding aldol product in 68% yield and 76% ee (Table 23). This work was subsequently expanded to encompass a wider range of aldehydes. In general, aldol acceptors with α-substituents were found to afford products with much higher degrees of enantioselectivity (60 – greater than 99% ee) than those with only methylenes adjacent to the carbonyl (36 – 73% ee). The side products isolated from these reactions consisted solely of the aldol condensation products resulting from dehydration of the aldol adducts, and the acetone self-condesnation product.[33] One drawback to this aldol methodology is that a large excess of the aldol donor (ketone) is required in order to obtain good reaction efficiencies.

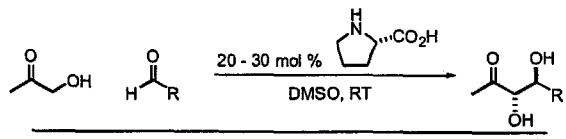
Table 23. Initial results of proline-catalyzed intermolecular asymmetric aldol reaction between acetone and various aldehydes.

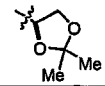


Entry	R	Yield / %	ee / %
1	$C_6H_4NO_2$-4	68	76
2	C_6H_5	62	60
3	C_6H_4Br-4	74	65
4	C_6H_4Cl-2	94	69
5	2-Naphthyl	54	77
6	*i*-Pr	97	96

Ketones with α-subsitution as donors gave products of moderate to good enantioselectivities; in addition, hydroxyacetone was found to be an excellent donor, providing, in the majority of cases, aldol products with excellent enantioselection, in some cases greater than 99% (Entries 1 and 2, Table 24). The aldol products obtained with hydroxyacetone as donor displayed mostly the *anti* diol, making these molecules potentially valuable synthons in the preparation of natural products and ligands for metal-based catalytic asymmetric systems.[34]

Table 24. Demonstration of use of hydroxyacetone as donor in proline-catalyzed aldol reaction to give *anti*-1,2-diols.



Entry	R	Yield / %	*anti* : *syn*	ee / %[a]
1	*c*-C_6H_{11}	60	> 20 : 1	> 99
2	*i*-Pr	61	> 20 : 1	> 99
3	CH(Me)Ph[b]	51[c]	> 20 : 1[d]	> 95[d]
4	C_6H_4Cl-2	95[c]	1.5 : 1[e]	67
5	neopentyl	38[c]	1.7 : 1	> 97
6		40[c]	2 : 1	> 97[f]

[a]ee of the *anti* diastereomer. [b]Used as a 2 : 1 mixture of isomeric aldehydes. [c]Combined yield of separated diasteromers. [d]Identical ee and dr values for both diastereomers. [e]Diastereomers were inseparable. [f]As determined by optical rotation.

A reasonable mechanism for these reactions involves attack of proline on the aldol donor to form a carbinolamine, which is subsequently dehydrated to give an iminium (Figure 9). Proton transfer results in enamine formation, followed by formation of the iminium-aldol product subject to the stereoelectronic constraints of the proposed transition state. Hydrolysis of the iminium results in regeneration of the proline catalyst and release of the aldol byproduct. Initially, a transition state for the carbon-carbon bond forming event was proposed by analogy to the well-studied Zimmermann–Traxler model for lithium enolate aldol reactions advanced in the 1950s.[35] For ketones other than acetone, however, an open transition state, more akin to that proposed by Heathcock in Lewis-acid mediated *anti*-aldol reactions,[36] has been suggested as a refinement; this contention has been supported by computational studies.

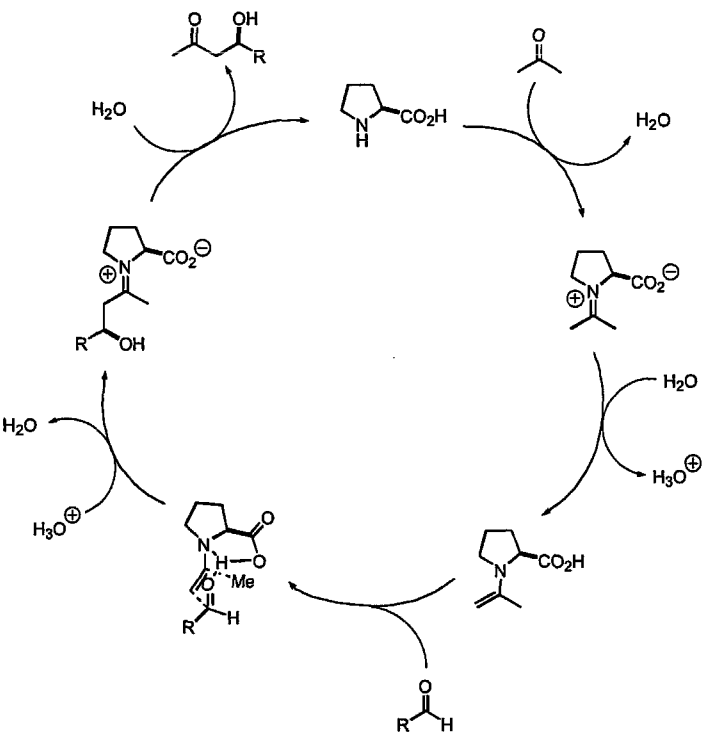
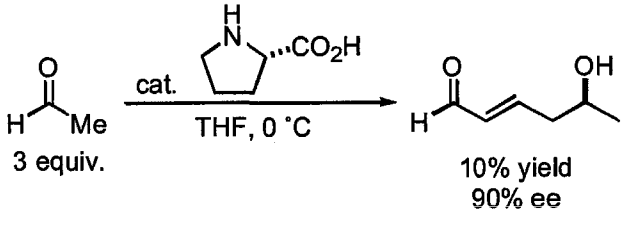


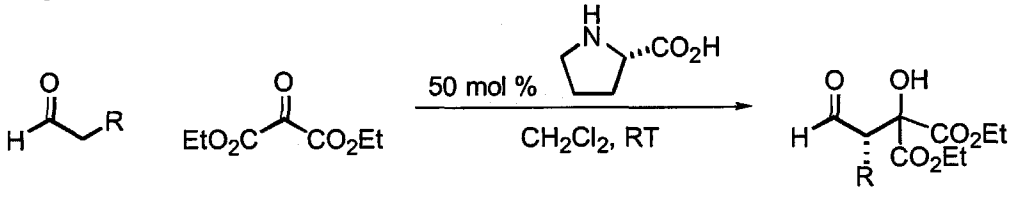
Figure 9. Putative mechanism of organocatalytic asymmetric intermolecular aldol reaction.

Development of a direct organocatalytic asymmetric cross-aldol reaction between two aldehydes proved to be a much more formidable task. Barbas and coworkers had demonstrated the use of proline in the asymmetric trimerization of acetaldehyde; the product was obtained with good enantioselectivity, but unfortunately, a poor yield (Figure 10, top).[37] Jørgensen reported a proline-catalyzed aldol reaction between various aldehydes and highly activated oxoesters, as shown in the bottom portion of Figure 10. While some of these reactions yielded products with useful enantioselectivities, the rather restricted structural requirements of the aldol acceptor rendered the resulting aldol products of diminished general synthetic value.[38]

Barbas and coworkers:



Jørgensen and coworkers:

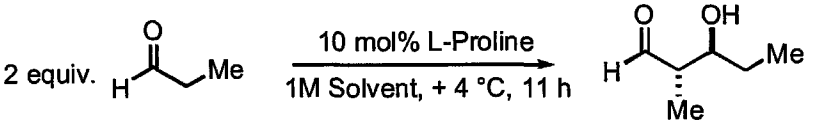


Entry	R	Time / h	Yield / %	ee / %
1	Me	3.00	90	90
2	Et	1.25	91	85
3	*i*-Pr	2.00	88	85
4	2-propenyl	3.00	94	88
5	*n*-hexyl	1.50	91	84
6	C_6H_5	1.00	97	0

Figure 10. Initial attempts to develop a proline-catalyzed asymmetric organocatalytic intermolecular aldol reaction with aldehyde donors.

Shortly after the work of Jørgensen and coworkers appeared in the literature, MacMillan reported the first direct enantioselective cross-aldol reaction between two aldehydes.[39] The enantioselective dimerization of propionaldehyde was shown to proceed in a variety of solvents with a wide range of polarities. The enantioselectivities were uniformly excellent (96 – greater than 99% ee); dimethylformamide was the only solvent that gave useful conversions (Table 25). In the cross aldol reaction, a range of aldehyde donors and acceptors furnished *anti*-aldol products in good yields and synthetically useful enantioselectivities (see Table 26). Homodimerization of the donor aldehyde was suppressed by a simple syringe pump addition of the donor aldehyde to the acceptor aldehyde. Interestingly, propionaldehyde was shown to add to isovaleradehyde to afford only one regioisomer (Entry 2, Table 26) despite the fact that both donor and acceptor aldehydes have two enolizable protons.

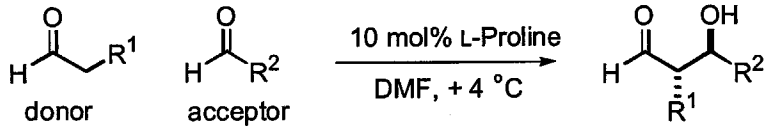
Table 25. Effect of solvent on proline-catalyzed asymmetric propionaldehyde dimerzation.



Entry	Solvent	Conversion / %[a]	*anti*:*syn*	ee / %[b] (*anti*)
1	Ph-H	32	5:1	>99
2	$CHCl_3$	29	4:1	98
3	EtOAc	41	5:1	99
4	THF	36	4:1	98
5	Dioxane	41	4:1	98
6	CH_3CN	42	3:1	96
7	DMSO	38	3:1	>99
8	NMP	62	3:1	98
9	DMF	91	3:1	99

[a]Relative conversion at an arbitrary 11 h time point. [b]Obtained from GLC analysis of the 2,2-dimethylpropane-1,3-diol-derived acetal.

Table 26. Scope of proline-catalyzed intermolecular aldol condensation with aldehyde donors.

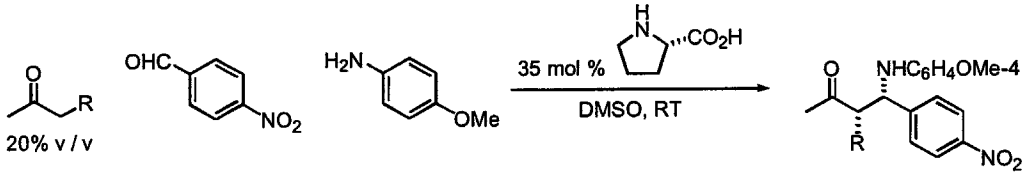


Entry	R^1	R^2	Yield / %[a]	*anti* : *syn*	ee / %
1	Me	Et	80	4 : 1	99
2	Me	*i*-Bu	88	3 : 1	97
3	Me	*c*-C_6H_{11}	87	14 : 1	99
4	Me	Ph	81	3 : 1	99
5	Me	*i*-Pr	82	24 : 1	> 99
6[b]	*n*-Bu	*i*-Pr	80	24 : 1	98
7[b]	Bn	*i*-Pr	75	19 : 1	91

[a]Yield represents the combined yield of diastereomers. [b]Conducted at 23 °C.

Further advances in the development of the asymmetric organocatalytic aldol reaction involved the use of electrophiles other than aldehydes and ketones. The Mannich reaction, the products of which are the nitrogen-bearing analogues of the aldol reaction, was found to be amenable to organocatalysis. In 2000, List reported the first highly enantioselective direct three-component Mannich reaction (Table 27).[40] In this regard, the organocatalytic version of the Mannich reaction is superior to the existing metal-based asymmetric Mannich reaction methodologies, which require the use of a pre-formed enolate equivalent.[41]

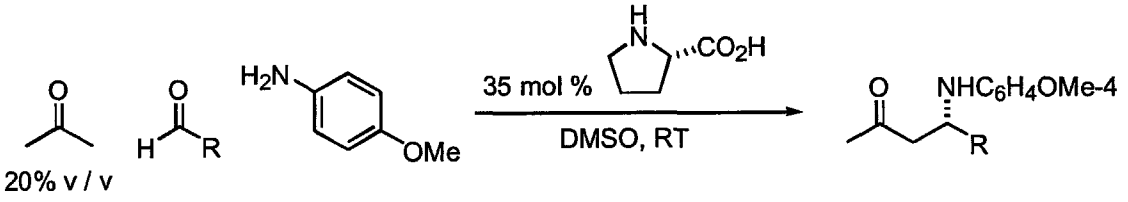
Table 27. L-Proline-catalyzed asymmetric three-component Mannich reaction reported by List and coworkers.



Entry	R	Yield / %	dr	ee / %
1	H	50	—	94
2	Me	96	> 39 : 1	99
3	OMe	93	> 39 : 1	98
4	OH	92	> 39 : 1	> 99

In these reactions, excess acetone was mixed with the desired aldehyde, *para*-anisidine, and proline in DMSO as solvent. This operationally trivial procedure was found to give good to excellent selectivities with a wide range of ketone donors and aldehyde acceptors, as shown in Table 28. (*S*)-Proline outpaced all other structurally similar catalysts in both conversion and selectivity. An important caveat was that the only amine source that afforded excellent yields and enantioselectivities was *para*-anisidine.

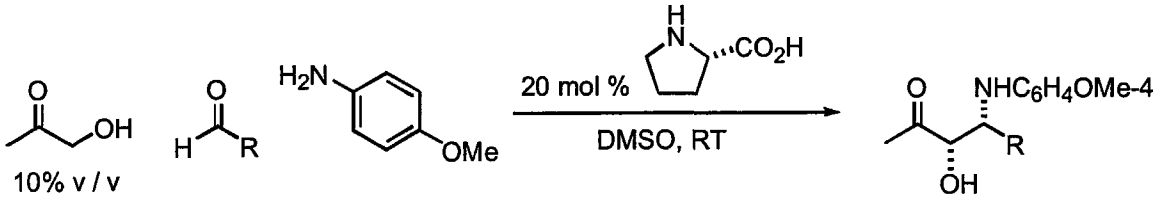
Table 28. Scope of acceptor aldehydes in List's L-proline-catalyzed asymmetric three-component Mannich reaction.



Entry	R	Yield / %	ee / %
1	*n*-Am	74	73
2	*i*-Bu	90	93
3	CH_2OBn	82	75
4	4-pentenyl	60	80
5	$CH_2CH_2C_6H_5$	80	93
6	2-napthyl	35	96
7	*i*-Pr	56	70

When hydroxyacetone was used as the ketone donor, this technology afforded *syn*-1,2-amino alcohols, molecules that are intrinsically valuable synthetically (Table 29). In general, this reaction was most efficient when aromatic aldehydes were utilized. The Boc-protected amino alcohol could be obtained by a four-step sequence involving oxazolidinone formation, followed by protecting group manipulation, Baeyer-Villiger oxidation, and borohydride reduction. The resulting amino alcohols were obtained with essentially complete stereochemical fidelity, as determined by optical rotation and HPLC analysis.

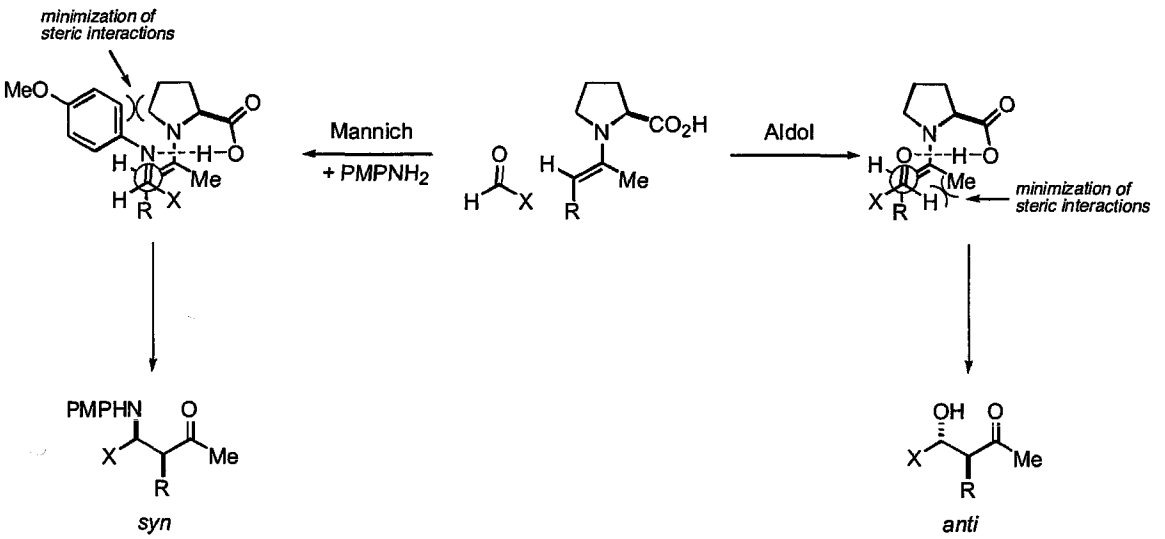
Table 29. Preparation of derivatized, enantiomerically enriched *syn*-1,2-amino alcohols via organocatalytic Michael reaction.



Entry	R	Yield / %	dr	ee / %
1	$C_6H_5NO_2$-4	92	20 : 1	> 99
2	C_6H_5CN-4	88	15 : 1	99
3	C_6H_4Br-4	90	15 : 1	98
4	C_6H_4Ph-4	79	8 : 1	94
5	C_6H_5	83	9 : 1	93
6	$C_6H_4CH_3$-4	85	5 : 1	86
7	$C_6H_4OCH_3$-4	88	3 : 1	61
8	$CH(CH_3)_2$	57	17 : 1	65

The mechanism of this process was hypothesized to be analogous to that of the proline-catalyzed aldol reaction (see Figure 9).[42] A ρ value of +1.36 was computed for this reaction. The magnitude and sign of the reaction constant are consistent with the buildup of negative charge in the transition structure and a large degree of charge separation, both of which are required by the proposed mechanism.[43] The carbon-carbon bond forming step was similarly proposed to be proline-enamine addition to the imine that is simultaneously and reversibly formed during the course of reaction. Consequently, a mechanistically peculiar point is the relative stereochemistry of the adduct; in the three-component Mannich reaction, the products bear the *syn* stereochemistry, whereas in the analogous aldol reaction, the products are *anti*. This stereochemical divergence was rationalized with the key assumption that the imine formed in the Mannich reaction is only of the (*E*) topology, due to steric considerations. In this eventuality, the enamine would conceivably attack the *si* face of the imine as

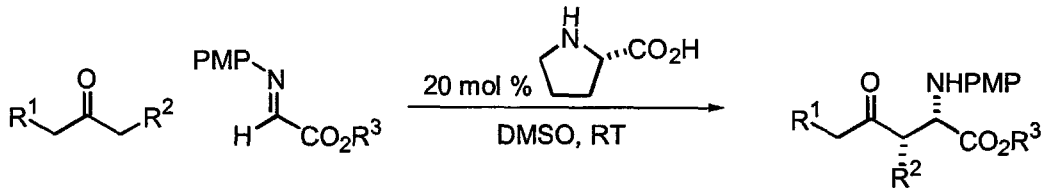
illustrated in Scheme 8. Attack on the *re* face of the imine would result in highly energetically unfavorable nonbonded interactions between the phenyl group of the imine and the pyrrolidine ring portion of the proline-derived enamine. The *anti* stereochemistry of the aldol adducts was rationalized by the absence of the steric impedance of the imine phenyl group; in this case, the dominant stereocontrol element is avoidance of steric repulsion between the proline enamine and aldol acceptor, biasing the acceptor towards *re* face attack by the enamine.



Scheme 8. Rationalization of stereochemical divergence between products of L-proline-catalyzed Mannich and aldol reactions.

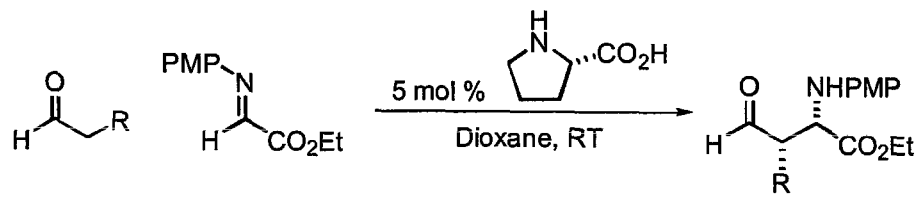
Somewhat later, Barbas and coworkers demonstrated that imines preformed *via* condensation of alkyl glyoxylates and *para*-anisidine could also be used as electrophiles.[44] These reactions proceed with good yields and enantioselectivities with both ketones (Table 30) and aldehydes (Table 31) as Mannich donors.

Table 30. Results of L-proline-catalyzed Mannich reaction between ketone donors and pre-formed imine acceptors.



Entry	R^1	R^2	R^3	Yield / %	*syn* : *anti*	ee / %
1[c]	H	H	Et	86	–	99
2	H	H	*i*-Pr	85	–	97
3	H	Me	Et	72	> 19 : 1	> 99
4	Me	Me	Et	47	> 19 : 1	> 99
5	$-CH_2CH_2CH_2-$		Et	81	> 19 : 1	> 99
6	H	Allyl	Et	79	> 19 : 1	> 99
7	F	H	Et	77	–	61
8	H	OH	Et	62	> 19 : 1	99

Table 31. Results of L-proline-catalzyed Mannich reaction between aldehyde donors and pre-formed imine acceptors.

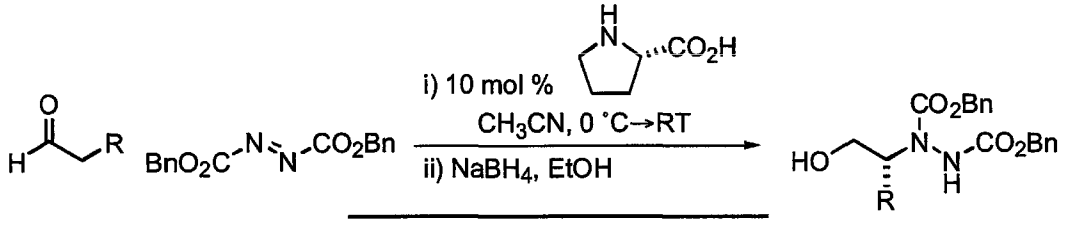


Entry	R	Yield / %	*syn* : *anti*	ee / %
1	*i*-Pr	81	> 10 : 1	93
2	Me	72	1.1 : 1	99
3	Et	57	1.5 : 1	99
4	*n*-Bu	81	3 : 1	99
5	*n*-Am	81	> 19 : 1	> 99
6	2-octenyl	89	> 19 : 1	99
7	3-butenyl	71	> 19 : 1	> 99

In 2002, List reported an intriguing expansion of proline-enamine catalysis to encompass dialkyl diazodicarboxylates as electrophiles (Table 32).[45] In an initial

reaction, isobutyraldehyde and di-*tert*-butyl azodicarboxylate were dissolved in acetonitrile with proline at ambient temperature; subsequent *in situ* borohydride reduction of the adduct afforded the corresponding 2-hydrazino alcohol in 97% yield and 92% ee (Entry 1). A variety of azodicarboxylates, including the diethyl and diisopropyl variants, also gave alkylation products; however, the dibenzyl congener was selected for further study. This choice was made in order to take advantage of the facile cleavage the resulting benzyl carbamate, as well as the useful handle for ultraviolet detection. Various alkyl substituted aldehydes were shown to participate successfully in this reaction, yielding uniformly excellent yields (93 – 99%) and outstanding enantioselectivities (95 – 97% ee). The computational model advanced by Houk (*vide supra*) also served to explain the observed selectivities in this reaction (Figure 11, structure **A**).

Table 32. L-Proline-catalyzed asymmetric addition of aldehyde enamines to dialkyl azodicarboxylates.



Entry	R	Yield / %	ee / %
1	*i*-Pr	99	96
2	*n*-Pr	93	> 95
3	*n*-Bu	94	97
4	Me	97	> 95
5	Bn	95	> 95

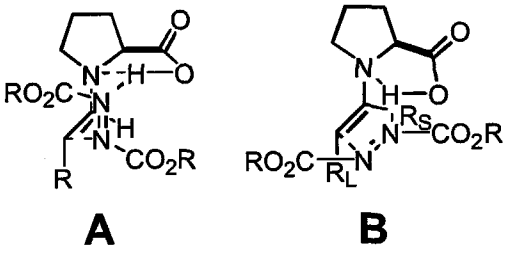
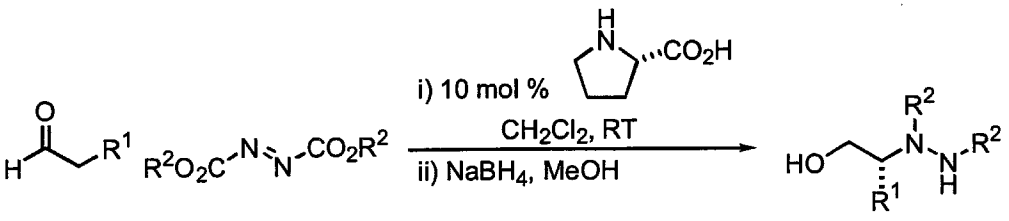


Figure 11.. Models advanced by List (**A**) and Jørgensen (**B**) to account for stereoselectivity in L-proline-catalyzed asymmetric addition of aldehyde enamines to dialkyl azodicarboxylates.

Coeval with List's work, Jørgensen also reported the proline-catalyzed asymmetric amination of aldehydes.[46] Using an analogous protocol, similar products were prepared, albeit with several cosmetic differences: diethyl azodicarboxylate was used as the primary amination agent and less polar solvents (methylene chloride, toluene, dichloroethane) were utilized at room temperature (Table 33). The enantioselectivities were, in general, lower than those reported by List; however, all of the reactions performed by Jørgensen were done at ambient temperature, whereas List in some cases carried out reactions at 0 °C. In contrast to the model advanced by List emphasizing a chair topography, Jørgensen proposed a boat-like transition state to explain the observed stereochemical outcomes, as shown in structure **B** in Figure 11, but provided no evidence to support this contention.

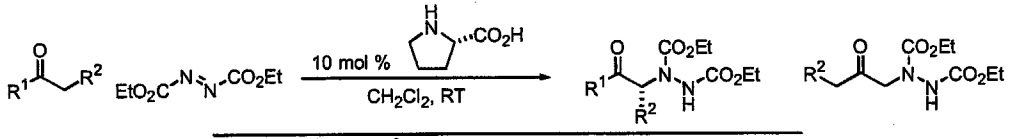
Table 33. L-Proline-catalyzed asymmetric addition of aldehyde enamines to dialkyl azodicarboxylates, as reported by Jørgensen and coworkers.



Entry	R^1	R^2	Yield / %	ee / %
1	Me	Et	67	93
2	Et	Et	77	95
3	*i*-Pr	Et	83	93
4	*t*-Bu	Et	57	91
5	Allyl	Et	92	93
6	Bn	Et	68	89
7	*i*-Pr	Bn	70	91

Shortly thereafter, Jørgensen published the expansion of this methodology to include ketones as donor molecules.[47] Enantioselectivities were good to excellent with several ketones; regioisomeric control proved to be a more difficult issue, with amination generally occurring on the α-carbon with the greater degree of steric encumbrance. The limited range of substrates reported afforded products with variable regioselectivities (approximately 3:1 to 10:1, Table 34).

Table 34. Scope of organocatalytic asymmetric addition of ketones to diethyl azodicarboxylate.

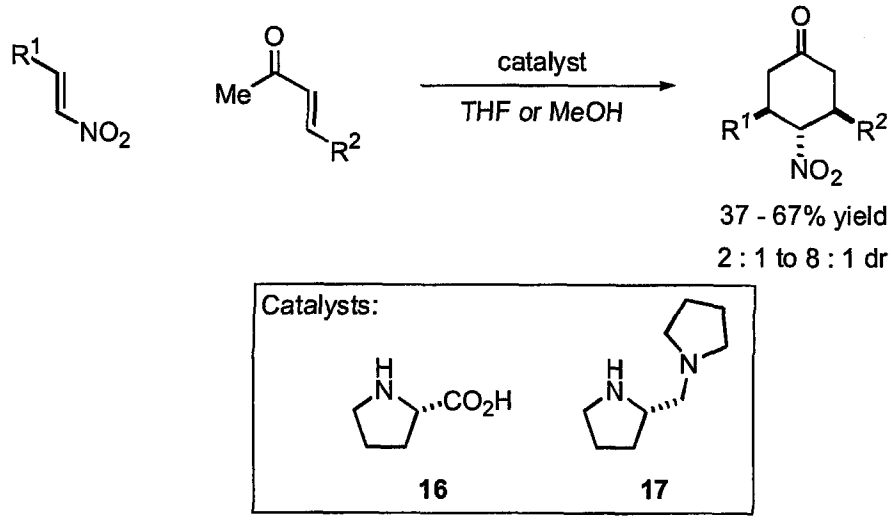


Entry	R^1	R^2	Time / h	rr[a]	Yield / %	ee / %
1	$-(CH_2)_4-$		23	–	67	79
2	Me	Me	10	10 : 1	80	93
3	Me	Et	20	4 : 1	77	96
4	Me	Bn	24	5 : 1	92	94
5	Me	*i*-Pr	96	3 : 1	69	99
6	Et	Me	60	–	79	93

[a]rr = Regioisomeric ratio.

1.3.1.2 The Diels–Alder Reaction

Very little work has been done in the catalysis of Diels – Alder reactions *via* enamines. Conceptually, enamine catalysis would rely on raising the energy of the highest occupied molecular orbital of the diene component, rather than a lowering in energy of the lowest unoccupied molecular orbital of the dienophile,as is the case with other catalytic Diels–Alder reactions.. L-Proline as well as its derivative shown below were utilized to induce cycloaddition between various nitro olefins and alkyl vinyl ketones. *Diastereomeric ratios (2 : 1 to 8 : 1) and yields (37 – 67%) were moderate.*[48] The authors declined to report the enantioselectivity of the reaction, with the exception of one product ($R^1 = C_6H_4OMe$-4, R^2 = Ph) which was isolated in in 38% ee.



Scheme 9. Diastereoselective Diels–Alder reactions catalyzed by L-proline and its derivative **17**.

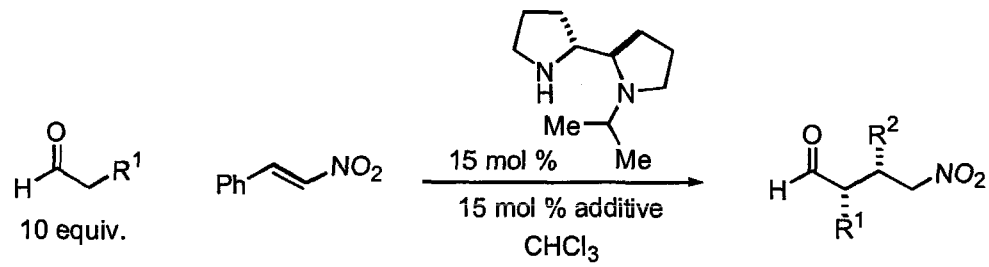
A similar strategy was used for the self-condensation of various vinyl alkyl ketones. A bifunctional catalytic scheme was envisioned in which the dienophile would be activated by iminium formation, and the diene activated as above by enamine

formation. The cyclohexanone products were formed in moderate yield (54 – 75%) and with diastereoselectivities in the range of 1 : 1 to 4.5 : 1. Again, enantioselectivities were not reported with the exception of one substrate , which was isolated in 23% ee.[49]

1.3.1.3 The Michael Reaction

Enamine catalysis has only recently been applied to asymmetric conjugate additions. Alexakis et al. reported the use of the bis-pyrrolidinyl catalyst X for conjugate addition of aldehydes and ketones to nitrostyrene. With aldehydes as surrogate Michael donors, the conjugate adducts were isolated in 70 – 99% yield, a 3 : 1 to 24 : 1 ratio of *syn* to *anti* diastereomers, and variable ee (61 – 85%).

Table 35. Organocatalytic conjugate additions of aldehydes to β-nitrostyrene.

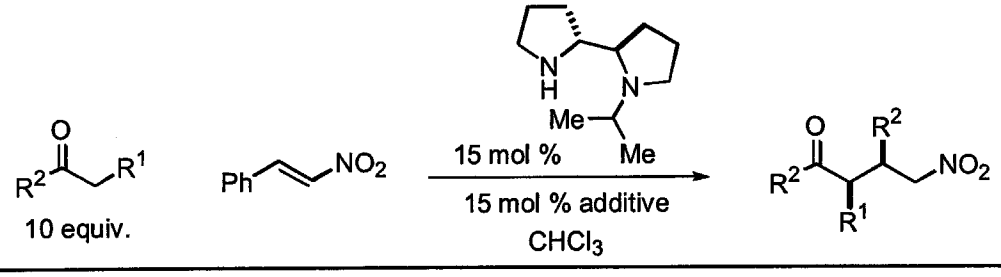


Entry	R^1	Additive	Temp / °C	Time / d	Yield / %	*syn* : *anti*	ee / %
1	Me	none	–25	2	71	95 : 5	83
2	Me	HCl	0	2	83	94 : 6	85
3	Et	none	–25	4	70	90 : 10	70
4	Et	HCl	0	2	82	88 : 12	68
5	*n*-Pr	none	–25	4	98	96 : 4	73
6	*n*-Pr	HCl	0	2	82	96 : 4	72
7	*i*-Pr	none	RT	2	99	87 : 13	61
8	*i*-Pr	HCl	RT	5	95	95 : 5	68

The use of ketones as Michael donors proved to be much less selective. Although diastereoselectivities were reasonable, (2.1 : 1 to 19 : 1), regioisomeric ratios were poor

(1.3 : 1 to 2.8 : 1) and the enantioselectivities of the *syn* products did not reach synthetically useful levels (23 – 76% ee).[50]

Table 36. Organocatalytic conjugate additions of ketones to β-nitrostyrene.



Entry	R^1	R^2	Additive	Temp / °C	Time / d	Yield / %	rr[a]	*syn* : *anti*	*ee* / % (syn)
1	H	Me	none	23	0.63	29	–	–	29
2	Me	Me	HCl	23	6	55	74 : 26	4 : 1	51
3	Et	Me	*p*TSA	60	7	82	40 : 60	7 : 3	36
4	Me	Et	HCl	60	7	65	–	5 : 1	67

[a] rr = regioisomeric ratio.

1.4 Phase Transfer Catalysis

1.4.1 Introduction

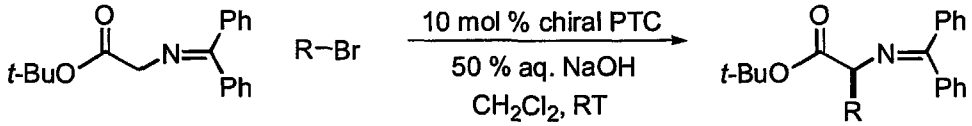
Since its inception, the field of phase transfer catalysis (PTC) has experienced phenomenal growth, due to increasing attention from both academic and industrial chemists.[51] PTC offers many potential operational advantages, such as vastly simplified reaction work up and product isolation procedures, increased reaction rates, and the lack of requirements for rigorously dried solvents. In the academic realm, efforts to apply PTC to asymmetric catalysis have naturally resulted from interest in the field, as demonstrated in this section.

1.4.2 Enolate Alkylations

As with many other catalytic asymmetric methodologies, research on phase transfer catalysis (PTC) with amines applied to enolate alkylation evolved from a desire for new methods to make amino acids, especially those with unnatural architectures, in enantiopure form. O'Donnell and coworkers conducted the pioneering research in this field.[52] Prior work had demonstrated the value of PTC in the asymmetric alkylation of substituted indanones.[53] In this work, a quaternized cinchona alkaloid was utilized as the catalyst.

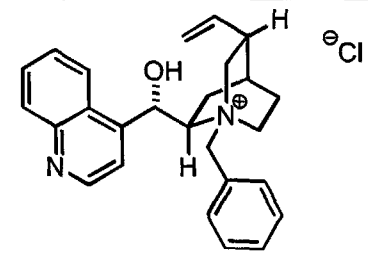
With 10 mole percent of the catalyst, 20 equivalents of sodium hydroxide, and allyl bromide as the electrophile, the corresponding enantioenriched alkylated product was isolatedin good yield. Increasing the concentration of the starting material in the organic phase to 0.64 M decreased the reaction time by greater than a factor of 20. Ultimately, these experimental modifications allowed the protected glycine starting material to be alkylated with a variety of alkyl bromides, but the enantioselectivities did not exceed 66% ee in any case (Table 37). In order to circumvent this limitation, a recrystallization procedure was developed which enabled the isolation of enantiopure material. However, the overall yield for this process was approximately 50%, leaving significant room for improvement.

Table 37. *Asymmetric enolate alkylation under phase transfer conditions as reported by O'Donnell et al.*

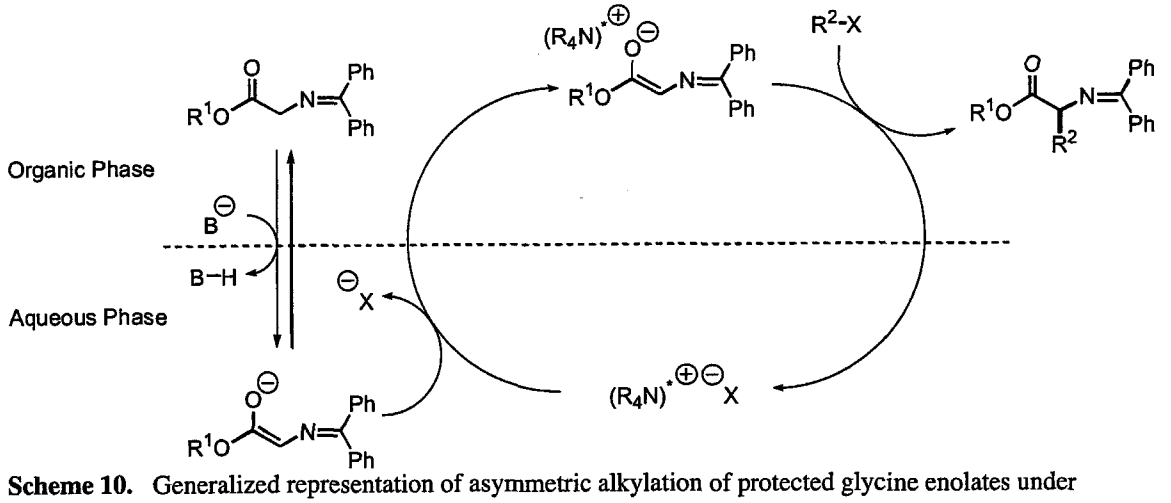


Entry	R	Equiv R–Br	Time / h	Yield / %	ee / %
1	Allyl	5.0	5	75	66
2	Bn	1.2	9	75	66
3	Me	5.0	24	60	42
4	*n*-Bu	5.0	14	61	52
5	C_6H_4Cl-4	1.2	12	81	66
6	CH_2-2-naph	1.2	18	82	54

Chiral PTC:



A putative mechanistic scheme for this reaction can be conceived as in Scheme 10. The substrate is deprotonated by a base, and the resulting enolate is transported into the aqueous phase. Anion metathesis with the catalyst results in association of the substrate enolate with the chiral quaternary ammonium salt, which is then transposed into the organic phase, due to the decreased aqueous solubility of the ion-paired complex. Once in the nonaqeous layer, alkylation occurs to afford the desired product with regeneration of the ammonium catalyst, which can then re-enter the aqueous phase and alkylate another substrate.



Scheme 10. Generalized representation of asymmetric alkylation of protected glycine enolates under phase-transfer conditions.

Eight years later, Corey developed an improved procedure for asymmetric PTC alkylation using similar cinchona alkaloids. Based on a great deal of work designed to clarify the origins of enantioselectivity in the cinchona-alkaloid / osmium tetroxide-catalyzed-olefin dihydroxylation developed by Sharpless,[54] a more rational approach was tested in an attempt to optimize the enantioselectivities of the alkylations to synthetically useful levels (Figure 12). The nitrogen in the bridgehead was regarded as the center of a tetrahedron whose "back" face was blocked entirely by the remainder of the [2.2.2] bicycle. A second facial area was blocked by the substituent used to alkylate the cinchona derivative; in the case of alkylation with 9-(chloromethyl)anthracene, steric considerations resulted in the restricted motion of the anthracenyl group, preventing rotation that might serve to mitigate the blockage of that particular quadrant of the putative tetrahedron. Alkylation of the hydroxyl group β to the quaternized ammonium (a point of variation not pursued by O'Donnell) would hypothetically block a third tetrahedral face, leaving only one region of space where the presumptive enolate would be able to associate with the catalyst. These concepts were validated, at least in the

crystal, by means of X-ray diffraction analyses of the catalysts. In the case of small anions such as bromide, as well as much more sterically imposing ones, such as 4-nitrophenoxide, the counterion associated with the ammonium was found to be associated with the catalyst in the one "open" tetrahedral face, the area distal to the vinyl group on the [2.2.2] bicycle.

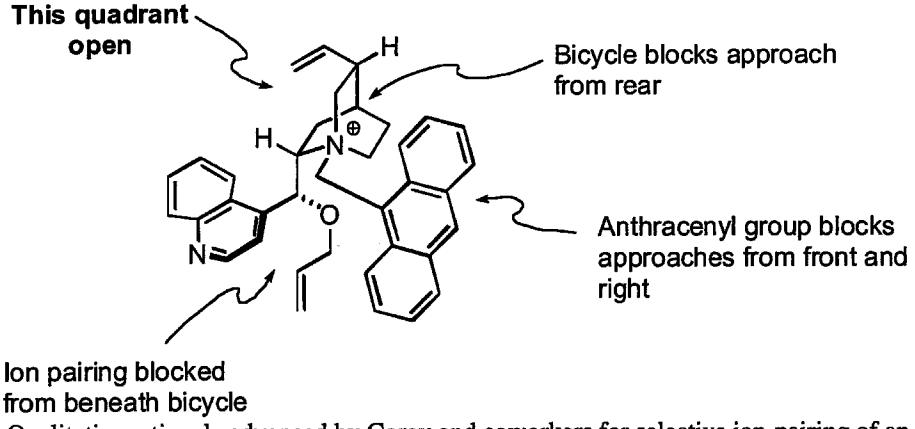
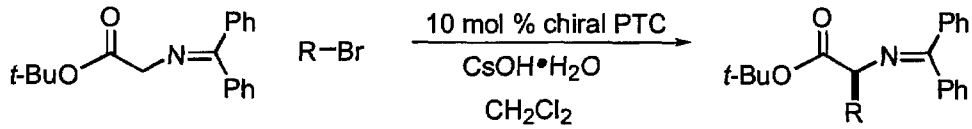
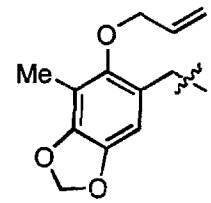
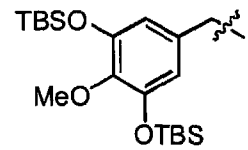


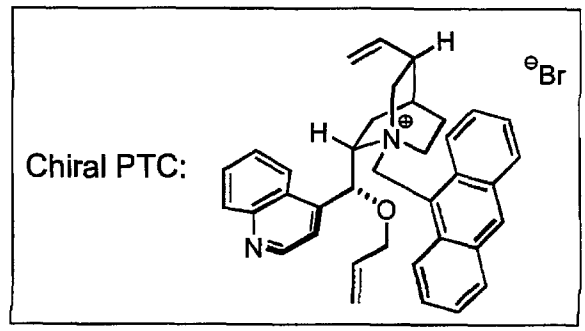
Figure 12. Qualitative rationale advanced by Corey and coworkers for selective ion-pairing of an enolate and a derivatized quaternized cinchona alkaloid.

The conjectural rationale for selective enolate association was supported by the experimental results shown in Table 38. The *N*-diphenylmethyelene-protected *tert*-butyl glycinate used by O'Donnell et al. was successfully alkylated with a wide variety of alkyl bromides in a highly enantioselective fashion (92 – greater than 99 % ee), obviating the need for the previously reported inefficient and laborious recrystallization procedure. Several changes were effected in the reaction conditions; the reaction was conducted in methylene chloride and the "aqueous phase" was not water itself, but rather solid cesium hydroxide monohydrate. This modification also allowed the use of cryogenic temperatures, otherwise precluded by the existence of a discrete aqueous layer.

Table 38. Results of asymmetric alkylation methdology reported by Corey et al. featuring a modified *cinchona* alkaloid as phase-transfer catalyst.

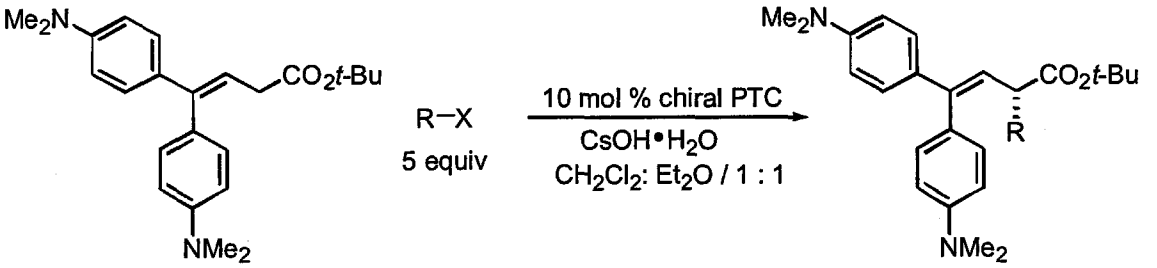


Entry	R	Equiv RX	Temp / °C	Time / h	Yield / %	ee / %
1	Me	5.0	–60	28	71	97
2	Et	5.0	–60	30	82	98
3	*n*-Hexyl	5.0	–60	32	79	> 99
4	CH_2c-C_3H_5	5.0	–60	36	75	99
5	Allyl	5.0	–78	22	89	97
6	Methallyl	5.0	–78	20	91	92
7	$CH_2C{\equiv}CTBS$	5.0	–78	18	68	95
8	Bn	5.0	–78	22	73	> 99
9		1.5	–78	24	81	96
10		1.5	–78	24	67	97



In a later series of experiments, Corey and coworkers demonstrated the applicability of the general PTC strategy for alkylation of different substrate types (Table 39). The β-diphenylene *tert*-butyl ester shown was successfully alkylated by a variety of alkyl iodides and bromides with good yields (62 – 81%) and enantioselectivities (94 – 98% ee). The resulting products could be converted to chiral 1,3-propanediol derivatives by a somewhat cumbersome sequence of reductions, oxidations, and protections. However, significant evidence was provided in support of the contact-ion pair mechanism advanced previously. Alteration of the substituents *para* to the alkylidene subunit on the starting material substrate by using functional groups with increasing resonance electron-donating ability resulted in higher enantioselectivities in the alkylation of the ester derivative with allyl bromide (Table 40). A clear and convincing trend emerged that suggested that more electron-rich substituents afforded products of higher ee; this was rationalized by the hypothesis that increasing the electron density on the putative enolate intermediate would result in a stronger and more proximate ionic attraction between the enolate and quaternary ammonium catalyst. To date, this remains the only mechanistic hypothesis for this class of phase transfer reactions for which reasonable supporting evidence has been supplied.

Table 39. Enantioselective alkylation of β-diphenylalkylidene ester enolates under phase transfer conditions.



Entry	R	Temp / °C	Time / h	Yield / %	ee / %
1	Me	–50	12	68	98
2	*n*-Hexyl	–45	12	73	95
3	$Cl(CH_2)_3$	–45	12	71	95
4	$Cl(CH_2)_4$	–45	12	62	94
5	Allyl	–65	36	76	96
6	Bn	–65	36	83	94
7	(2-Ph)Bn	–65	12	81	98

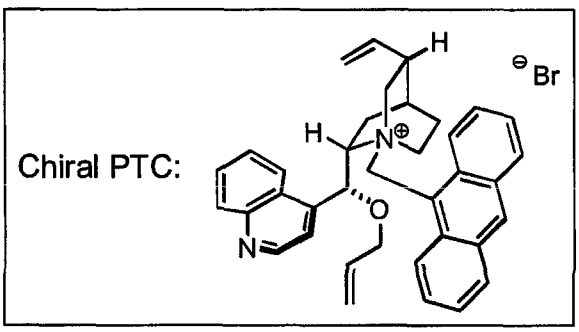
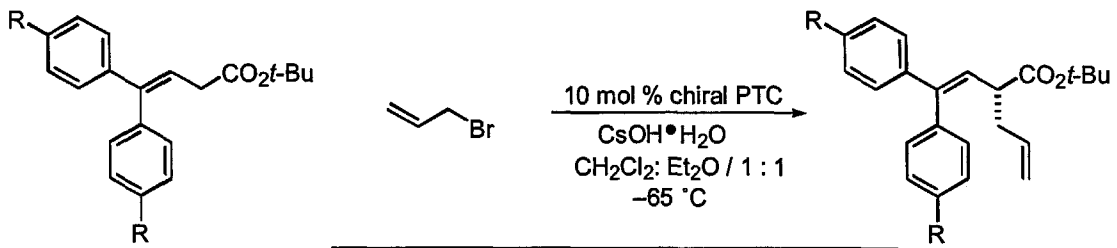


Table 40. Experimentally demonstrated correlation between Hammett substituent coefficient and enantioselectivity in asymmetric enolate alkylation under phase transfer conditions.



Entry	R	σ_p	ee / %
1	C_6H_5	0.00	67
2	*t*-Bu	– 0.15	81
3	OMe	– 0.28	91
4	NMe_2	– 0.63	96

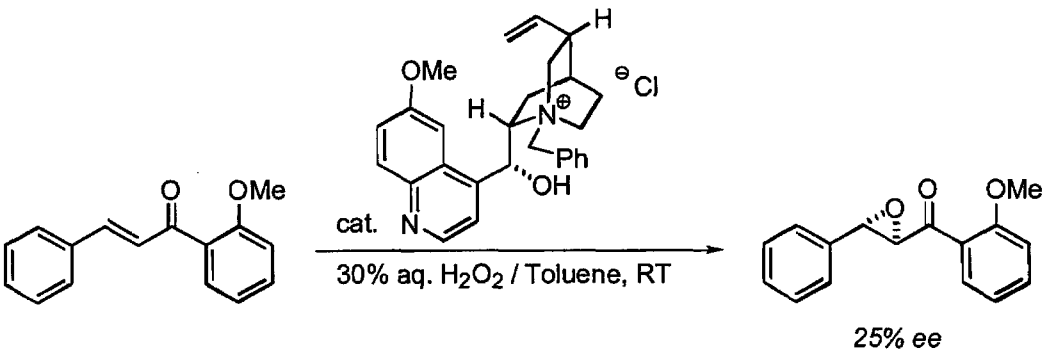
1.4.3 Olefin Epoxidations

Epoxides have proven to be key functionalities in several areas, including natural product synthesis and bioorganic and medicinal chemistry,; furthermore, they are also valuable as versatile chiral synthons. Consequently, a great deal of effort has been devoted to the development of catalytic asymmetric olefin epoxidation technologies, in many cases based on the pioneering work of Sharpless[55] and Jacobsen.[56] Non-metal-based catalytic asymmetric epoxidations have also been investigated. In most cases where phase transfer catalysis has been applied, the epoxidations are nucleophilic and performed on electron deficient olefins, usually those that are conjugated to a carbonyl.

Wynberg was the first to report the asymmetric nucleophilic epoxidation of various unsaturated carbonyl compounds. Initially, quinine itself was used directly in a mixture of 30% aqueous hydrogen peroxide and ethanol for the epoxidation of several quinones. The yields of epoxide were goodthough the products were of uniformly low enantioselectivity and reproducibility in the reaction was found to be lacking. Utilizing phase transfer conditions in which the reaction was performed in a mixture of toluene, sodium hydroxide, and 30% aqueous ethanol resulted in one case in isolation of a product of approximately 8% ee, as measured by optical rotation.

Acyclic substrates, in particular derivatives of chalcone, yielded much more promising results. When the modified chalcone was exposed to the quinine-derived catalyst partitioned between toluene and sodium hydroxide in 30% aqueous hydrogen peroxide, the corresponding α,β-epoxy ketone was isolated in 25% ee, as determined by ^{1}H NMR with the chiral shift reagent Eu(hfc)$_3$ (Scheme 11).[57] Various unsaturated olefins were also observed to undergo epoxidation, although the enantiopurity of these products

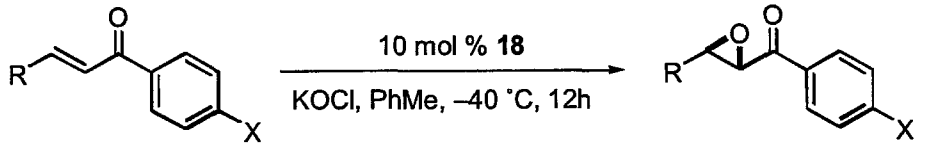
was not determined conclusively. In a later report, 2,3-epoxycyclohexanone was also prepared in an ee of approximately 20%.[58] Other attempts to prepare epoxides enantioselectively *via* alternate reactions, such as Darzens condensations, kinetic resolution of halohydrin ring closure products, and cyanide addition to α-haloketones, afforded products with modest enantioselectivities (< 10% ee).[59]



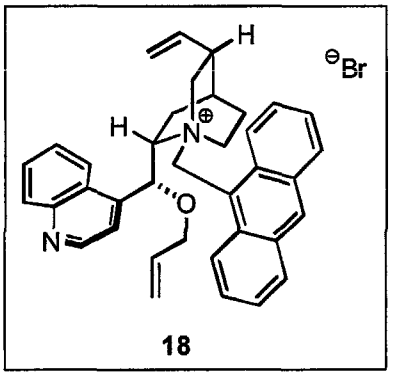
Scheme 11. Initial report of asymmetric epoxidation of chalcone *via* phase-transfer catalysis.

Optimization of this reaction to afford highly enantiomerically enriched α,β-ketoepoxides, as well as the development of a coherent mechanistic hypothesis, remained formidable challenges and were not accomplished for over twenty years after Wynberg's initial report. As a result of insights gained during a research program designed to elucidate the origin of stereoselectivity in the Sharpless dihydroxylation reaction, Corey and coworkers reported in 1999 the first highly enantioselective catalytic asymmetric nucleophilic epoxidation reaction. Using the catalyst shown in Table 41, a wide range of chalcone derivatives was epoxidized in good yields and excellent enantioselectivity (91 – 98.5% ee).[60]

Table 41. First highly enantioselective epoxidation of chalcone and derivatives *via* chiral phase-transfer catalysis.



Entry	R	X	Yield / %	ee / %
1	C_6H_5	H	96	93
2	C_6H_5	F	93	98
3	C_6H_5	Br	92	93
4	$C_6H_4NO_2$-4	H	90	94
5	$C_6H_4NO_2$-4	F	97	95
6	*n*-C_5H_{11}	F	90	91
7	*c*-C_6H_{11}	H	85	94
8	*c*-C_6H_{11}	F	87	95
9	$C_6H_4CH_3$-4	H	70	94
10	C_6H_4Cl-4	H	94	92
11	C_6H_4Cl-4	F	94	98.5
12	$C_6H_4OCH_3$-4	H	70	95
13	C_6H_5	OC_6H_5	89	93
14	C_6H_5	$OC_6H_3Br_2$-2,4	90	98
15	2-naphthyl	H	97	93



18

Interestingly, when exocyclic enones were submitted to the optimized epoxidation conditions, dramatic erosions in enantioselectivity were observed. Based on this result and mechanistic proposals developed for the asymmetric alkylation technology previously reported (*vide supra*), the rationale for the observed stereoselectivity was

advanced as shown in Figure 13. The "front" and "rear" views of the catalyst are depicted relative to the substituent protruding from the nitrogen in the [2.2.2]bicyclooctane ring. The hypochlorite anion was envisaged to be located in the "open" quadrant of space around the catalyst (*cf.* Figure 12), forming an ion-contact pair with the quaternized nitrogen of the catalyst. The chalcone-derived substrate was theorized to be oriented so that the ketone oxygen, with its partial negative charge, was in van der Waals contact with the catalyst nitrogen. This alignment of catalyst, hypochlorite ion, and enone not only resulted in positioning of the oxygen proximate to the β-carbon of the enone, but also allowed for electrostatic mitigation of the negative charge developing in the transition state of the epoxidation. The catalyst and reagent configurations shown in Figure 13 also correctly predict the observed sense of stereoinduction. There is one discrepancy in this model: results indicated that the ability of the enone to distort out of π-conjugation was important for high levels of stereoinduction. This contention does not seem to be consistent with a conjugate addition of hypochlorite to the enone olefin, in which conjugation between the carbonyl and olefin would seem to be necessary to stabilize the presumptive anionic intermediate. However, a mechanistic postulate involving a highly concerted reaction with a relatively early transition state would seem to ameliorate these contradictions.[61]

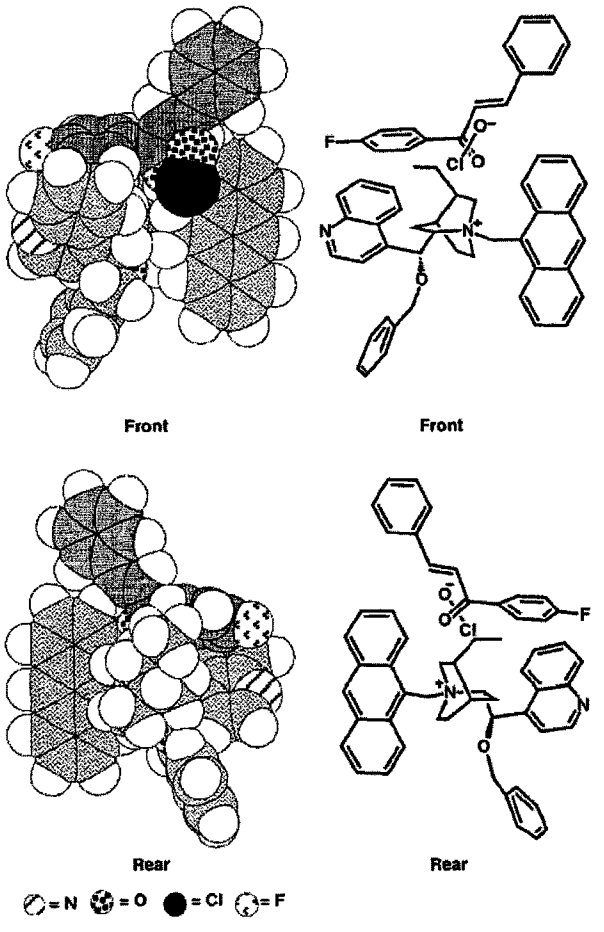
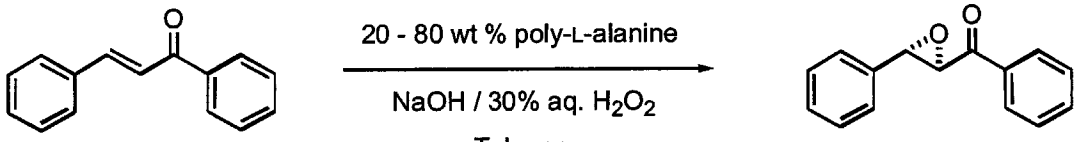


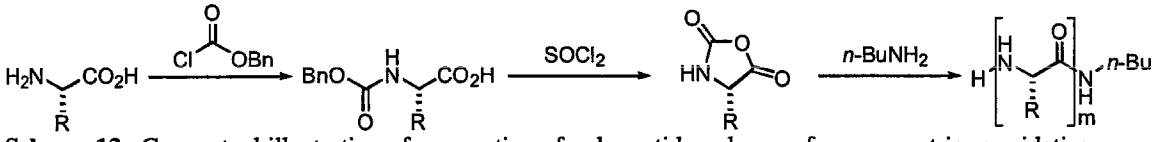
Figure 13. Three-dimensional illustration of presumptive transition state proposed by Corey et al. for asymmetric nucleophilic epoxidation with chiral PTC.

A completely different, but similarly creative, approach to the olefin epoxidation problem involves the use of polymeric peptide catalysts in the so-called Juliá-Colonna epoxidation. First reported in 1980, this reaction involves the subjection of an enone to a triphasic mixture. The three phases of this system are an organic solvent (toluene), an aqueous layer (a basic hydrogen peroxide solution), and the catalyst, a solid polypeptide (Scheme 12). The optimal catalyst in the initial investigations was determined to be a 10-mer derived from the amino acid L-alanine; Juliá and Colonna described the catalyst somewhat simplistically and optimistically as a "synthetic enzyme."



Scheme 12. Asymmetric nucleophilic epoxidation by a polypeptide under PTC conditions, as reported by Juliá, Colonna, and coworkers.

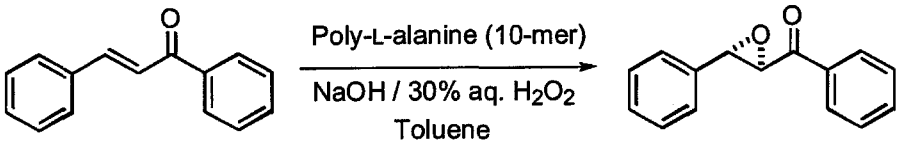
The preparation of the catalyst was carried out as illustrated in Scheme 13. L-Alanine was converted to the *N*-carboxyanhydride derivative by exposure to benzyl chloroformate, followed by thionyl chloride. The polymerization of the carboxyanhydride was then initiated by the addition of *n*-butylamine as an exogenous nucleophile. The polymeric catalyst was assumed to contain approximately ten alanine units; this figure was determined by ^{1}H NMR analysis of the products and titration of the acidic or basic end groups of the catalyst.



Scheme 13. Conceptual illustration of preparation of polypeptide polymers for asymmetric epoxidation reactions.

When chalcone was subjected to the prescribed oxidative conditions the product was isolated in variable yields and enantioselectivities; however, use of 80 weight percent catalyst resulted in the formation of chalcone epoxide in 85% yield and 93% ee (Table 42, Entry 5). Attempts to recycle the catalyst afforded products of lower yields and enantioselectivities, presumably due to degradation of the amide bonds in the catalyst on exposure to the strongly basic conditions of the aqueous layer.

Table 42. Results of asymmetric nucleophilic epoxidation with poly-L-alanine catalyst under PTC conditions.



Entry	Polymer loading / wt. %	Time / h	Yield / %	ee / %
1	0	48	0	0
2	20	48	76	86
3	40	48	70	86
4	80	48	26	97
5	80	24	85	93
6	80	48	80	93
7	80	48	36	72

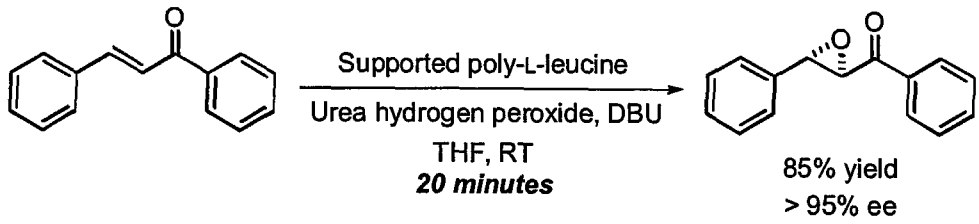
Significant efforts were devoted to explain the origin of stereoselectivity in this reaction.[62] The physical properties of the triphasic system were rather illdefined; phase separation was observed between the organic and aqueous layers, with the solid catalyst being localized in the interface between the two layers. The presence of both an organic solvent and water were determined to be vital to reactivity, possibly highlighting the importance of the conformation of the catalyst to the reaction. A series of additional experiments provided more convincing evidence of this point. Different amino acids were used to prepare a series of polymers, and poly-L-alanine was found to be the best overall catalyst for the epoxidation of chalcone and its congeners. Interestingly, those polymer catalysts that displayed superior tendencies to form extended α-helical secondary structures gave product with the best conversions and enantioselectivities. Polypeptides that adopted a β-pleated sheet secondary structure afforded products with

little or no enantioselectivity, with the exception of the catalyst poly-L-isoleucine, which gave the chalcone epoxide in 95% ee, despite having a β-pleated sheet morphology.

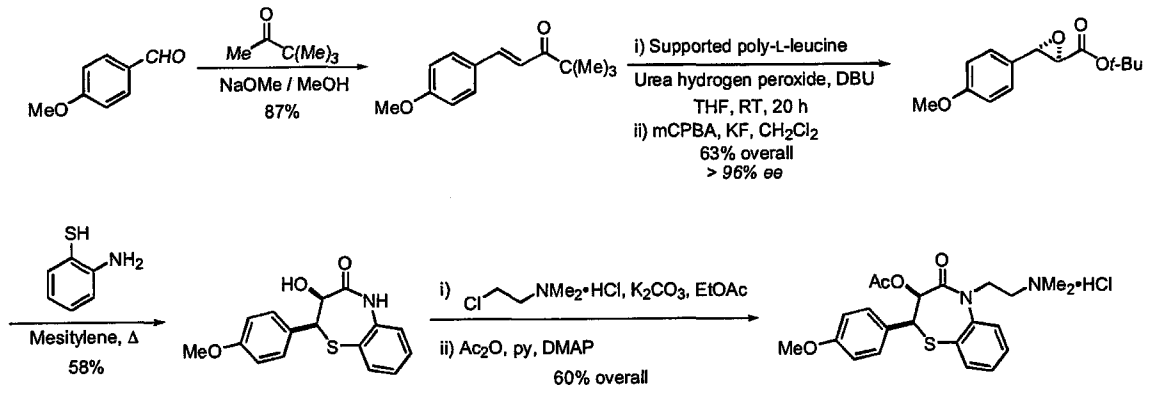
The length of the polypeptide was observed to have a pronounced effect on both enantioselectivity and conversion; in general, these two parameters were directly related. Catalysts with a degree of polymerization (DP) less than ten units afforded minimal conversions and enantioselectivities. When the DP was increased to 30, significant increases in the yield and enantiopurity of the epoxide product were observed in all cases; the highest ee recorded (96%) was obtained with a 30-mer catalyst derived from L-alanine. Finally, carrying the reaction out in organic solvents of high polarity (i.e., methanol) resulted in the formation of completely racemic product. This last experiment provided the most direct evidence that hydrogen bonding, and consequently, the conformation of the catalyst in solution, is crucial to the production of epoxides of high enantiopurity.

Several disadvantages to the original Juliá–Colonna protocol clearly exist, including poor reproducibility in the products on recycling of the catalyst, extended reaction times (24 – 72 hours), the use of a high-boiling organic solvent, and the inability to use substrates that are sensitive to the basic conditions of the aqueous phase. Alteration of the reaction conditions, as reported by Roberts and coworkers, provided a means to circumvent all of these impediments.[63] The overall number of phases in the reaction is reduced to two by removal of the aqueous layer. The oxidant is the inexpensive and commercially available urea hydrogen peroxide, and the reactions are carried out in tetrahydrofuran or *tert*-butyl methyl ether, with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) used as an external base. The catalyst used was

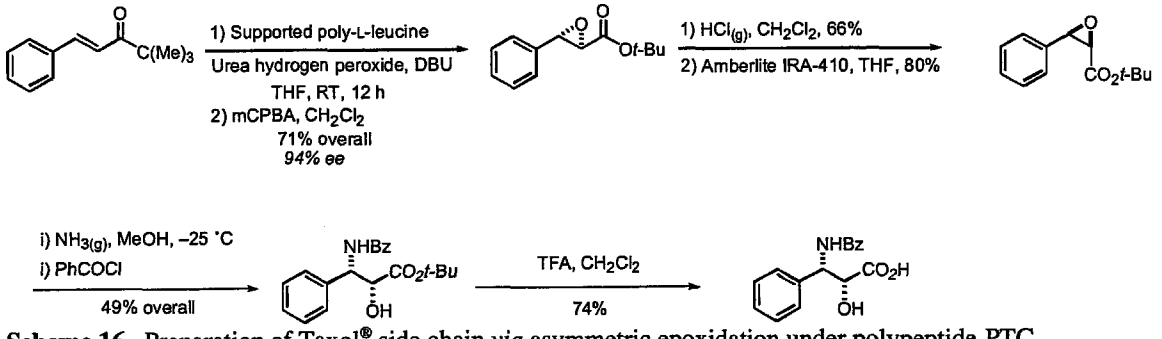
poly-L-leucine, supported on a poly(styrene-co-divinylbenzene) support.[64] When chalcone was subjected to these conditions, the product was obtained in 85% yield and > 95% ee after only twenty minutes (Scheme 14). These outstanding results may be compared favorably with the outcome using the original Juliá-Colonna conditions [80% yield, 97% ee (as measured by ^{1}H NMR with Eu(hfc)$_3$ as a chiral shift reagent, and a reaction time of 29 hours)]. In a dramatic demonstration of the synthetic utility of these conditions, the anti-hypertensive agent diltiazem (Scheme 15) and the side chain of Taxol (Scheme 16) were prepared using these improved epoxidation conditions, with enantioselectivities in the epoxidation step of > 96% and 94%, respectively. Some degradation in ee was observed when the catalyst was recycled; however, upon reactivation of the catalyst (washing with 4 M aqueous NaOH, drying, and addition of 10 weight percent fresh catalyst to account for transfer losses), enantioselectivities were restored to their previous levels.



Scheme 14. Improved conditions, developed by Roberts and coworkers, for the Juliá-Colonna epoxidation.

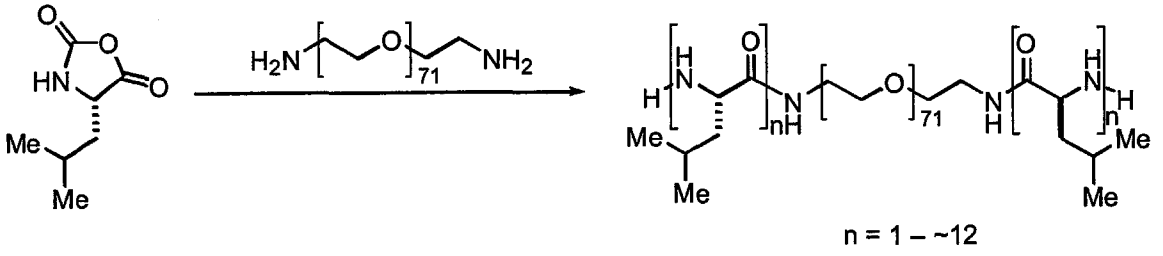


Scheme 15. *Asymmetric synthesis of the anti-hypertensive diltiazem featuring polypeptide-catalyzed* enantioselective epoxidation.



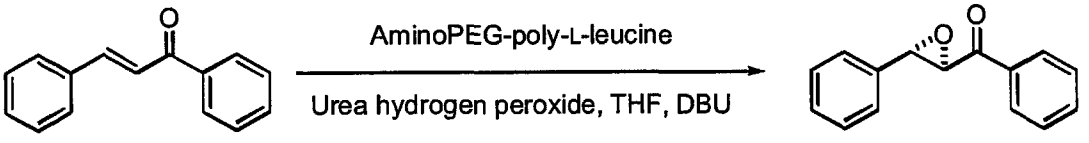
Scheme 16. Preparation of Taxol® side chain *via* asymmetric epoxidation under polypeptide-PTC conditions.

The most recent results in this area, also published by Roberts and coworkers, involve the use of polyethylene glycol diamine as both polymerization initiator and solid support (Scheme 17).[65] Once the polymer was prepared, it was found to be fully soluble in THF, unlike the previous versions. Yields and enantioselectivities in the epoxidation of chalcone were uniformly excellent. The high solubility of the catalyst also allowed shortening of the chain length while the high levels of enantioinduction were fully preserved. As displayed in Table 43, catalysts containing as few as eight L-leucine units still afforded chalcone epoxide in 80% conversion and 98% ee. Shortening of the catalyst to four L-leucine units resulted in a precipitous drop in the enantioselectivity, giving epoxide of only 5% ee.



Scheme 17. Method for preparation of aminoPEG supported poly-L-leucine catalyst.

Table 43. Results of asymmetric nucleophilic epoxidation of chalcone using improved poly-L-leucine-derived phase transfer catalysis.

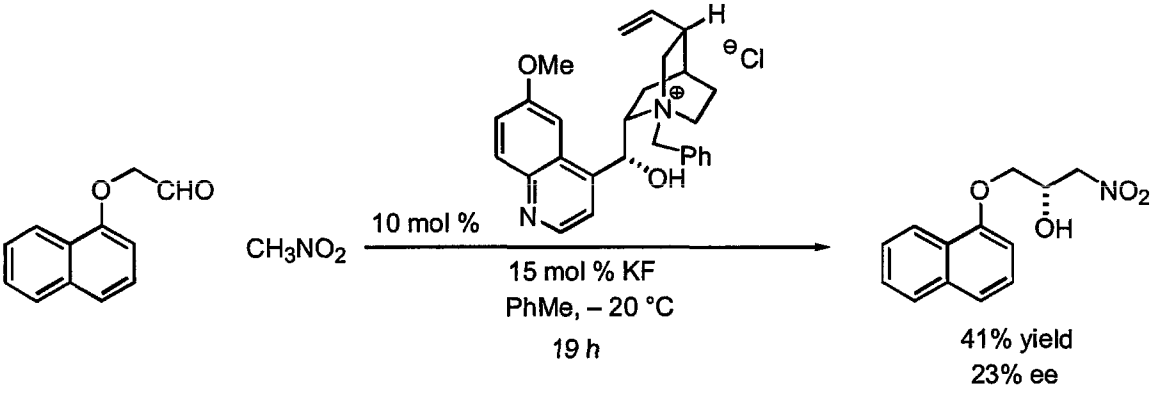


Entry	Leucine units (n)	Time / h	Conversion / %	ee / %
1	~ 8	1	39	97
2	~ 8	24	80	98
3	~ 15	1	39	97
4	~ 15	24	80	97
5	~ 23	1	36	98
6	~ 23	24	63	95
7	~ 24	1	34	97
8	~ 24	24	58	96

Infrared experiments on the catalyst were conducted in order to determine the secondary structure, which was found to be α-helical. The amide I band of the infrared spectrum had previously been determined to be indicative of the secondary structure of polypeptides.[66] Control catalysts prepared with exactly two or four leucine units displayed IR absorbance bands in the region corresponding to essentially unordered structures, whereas the longer chain catalysts gave rise to IR bands characteristic of polypeptides bearing α-helix secondary structures.

1.4.4 The Aldol Reaction

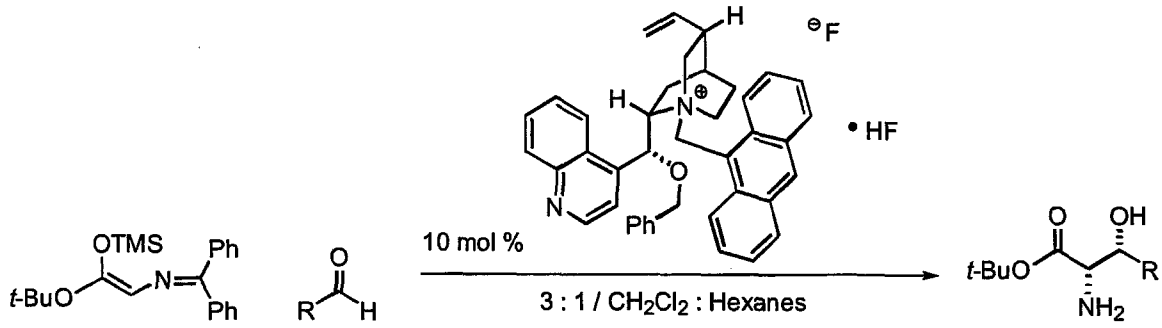
The first report of an organocatalytic phase transfer aldol reaction came from Shibasaki's laboratories in 1993. During a research program directed towards the development of a catalytic asymmetric Henry (nitroaldol) reaction involving lanthanum binaphthol complexes, Shibasaki and coworkers attempted to use cinchona alkaloids, with potassium fluoride as base, to accomplish the same result (Scheme 18).[67] Several cinchona-derived salts were used as catalysts, and although some selectivity was observed in the reaction of the hydroxyformylmethyl naphthol derivative with nitromethane, enantioselectivities were modest and the catalysts were outperformed by the lanthanum BINOL catalysts described in the report.



Scheme 18. Catalytic asymmetric aldol reaction under PTC conditions as reported by Shibasaki.

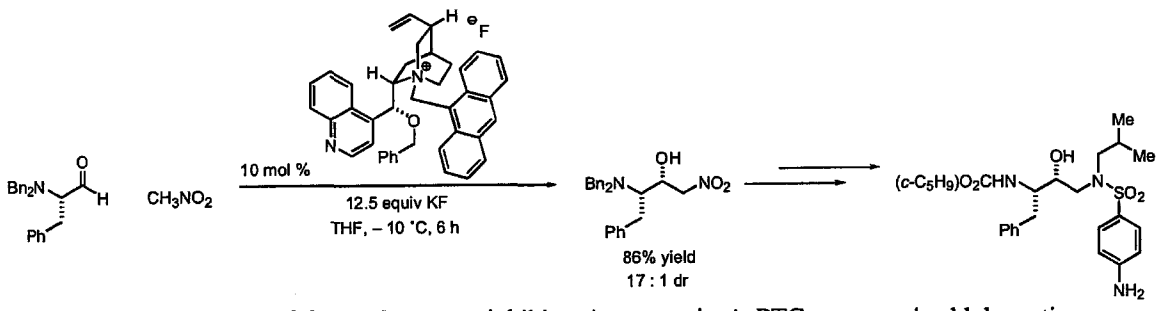
Corey and coworkers achieved slightly better selectivities when preformed ester enolate equivalents were added into saturated aldehydes in the presence of the cinchonidine-derived catalyst shown in Table 44.[68] The yields of the resulting amino alcohols were moderate to good, with in some cases excellent diastereo- and enantioselectivities, although the substrate scope was somewhat limited.

Table 44. Corey's phase-transfer catalyzed asymmetric aldol reaction.



Entry	*R*	Temp / °C	Time / h	Yield / %	*syn* : *anti*	*syn* ee / %	*anti* ee / %
1	*i*-Pr	– 78	7	70	6 : 1	83	95
2	*c*-C_6H_{11}	– 50	1	81	13 : 1	46	88
3	*n*-C_6H_{13}	– 78	2	79	3 : 1	91	89
4	$(CH_2)_3Cl$	– 78	2	48	1 : 1	86	82
5	$(CH_2)_2Ph$	– 78	6	64	1 : 1	86	72
6	*i*-Bu	– 45	2	61	3 : 1	70	76

Following this study, Corey extended similar methodology to diastereoselective Henry reactions with chiral aldehydes in an effort to develop a novel, efficient method of accessing stereochemistry present in the compound Amprenavir, an HIV protease inhibitor.[69] The key step was performed in 17 : 1 diastereoselectivity (Scheme 19). A diastereomer of Amprenavir was also prepared, with slightly lower diastereoselectivity (9 : 1). In both cases the selectivity in addition could be rationalized by similar arguments used to justify enantioselectivity in the PTC-enolate alkylation (see section IV. B.). In these cases, π-stacking of the many aromatic systems played a much greater role in shielding one diastereoface of the aldehyde from nucleophilic attack and thus dictating the stereochemical outcome of the reaction.



Scheme 19. Preparation of the HIV protease inhibitor Amprenavir *via* PTC asymmetric aldol reaction.

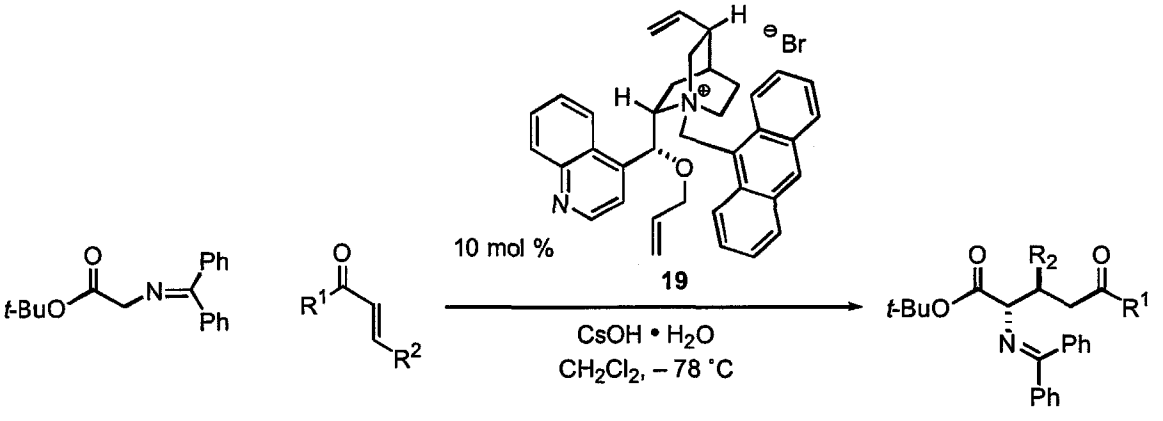
1.4.5 The Michael Reaction

Attempts have also been made to conduct Michael reactions in an enantioselective fashion by phase transfer catalysis, again featuring the use of quaternized cinchona alkaloid derivatives. There exists a separate collection of methodologies involving the alkaloids themselves as chiral basic catalysts in the Michael reaction; these will not be discussed here, but in the next section on catalysis with amines as chiral nucleophiles (*vide infra*).

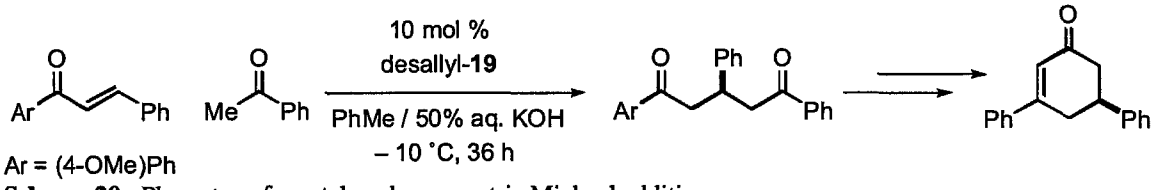
The application of PTC technology to the Michael reaction is a relatively recent development, with the first reports based on the work of Corey appearing in 1998. The *N*-diphenylmethylidene *tert*-butyl glycinate used in the enolate alkylation methodology (*vide supra*) was used again; in this case, it was added to methyl acrylate, cyclohexenone, ethyl vinyl ketone, and acrylonitrile in excellent yields (85 – 88%) and enantioselectivities (91 – 99% ee, Table 45).[70] Of particular note is the outstanding diastereoselection (dr 25 : 1) in the addition of the glycinate to cyclohexenone. The products thus obtained from the addition could then be derivatized in various ways, most notably to molecules bearing amino acid-type functionality. Simple acyclic enolates could also be added to conjugated ketones; acetophenone was added to the chalcone

shown in Scheme 20 in 72% yield and 80% ee. Following Baeyer-Villiger oxidation and saponification of the resulting ester, the acid thus obtained was purified to 99% ee following one mixed-solvent recrystallization. After several simple operations, the acid could be converted into a chiral 2-cyclohexenone.[71] These results present a completely novel method of accessing enantiomerically enriched substrates of that structure. Interestingly, the phase transfer catalyst used had the free, rather than the allylated, hydroxyl group.

Table 45. Asymmetric PTC Michael reaction with *N*-protected glycinate esters.



Entry	R^1	R^2	Yield / %	dr	ee / %
1	OMe	H	85	–	85
2	Et	H	85	–	91
3	$-CH_2CH_2CH_2-$		88	25 : 1	99

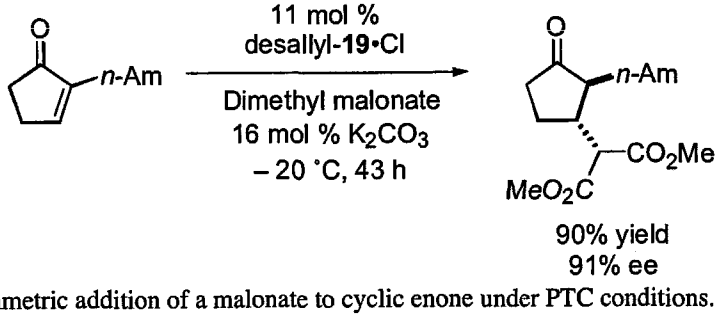


Ar = (4-OMe)Ph

Scheme 20. Phase-transfer catalyzed asymmetric Michael addition.

This requirement was also verified by later work in which methyl dihydrojasmonate was prepared in enantiomerically enriched form by means of cinchona alkaloid PTC. As shown in Scheme 21, dimethylmalonate was added conjugately to 2-

amylcyclopentenone in 90% ee and 91% yield.[72] Use of the *O*-allylated catalyst resulted in complete inhibition of the Michael reaction. An alternate transition state for the addition was proposed in which the nucleophile, rather than the electrophile, is associated with the quaternary nitrogen of the catalyst. The free hydroxyl is required for hydrogen bonding with the enone and thus ensures close association of the nucleophile and the electrophile. The methoxy group on the quinoline portion of the catalyst was demonstrated to have a beneficial effect on the asymmetric induction; this was rationalized by invoking an associative electrostatic interaction between the methoxy oxygen and the β-carbon of the substrate. The anthracenyl group was postulated to provide additional rigidity in the transition state by severely restricting the degrees of rotational freedom of the enone. Malonate addition then takes place from the open *si* face of the enone to afford the observed product.

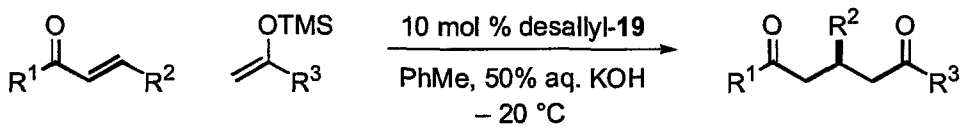


Scheme 21. Asymmetric addition of a malonate to cyclic enone under PTC conditions.

Finally, the phase transfer approach to enantioselective Michael addition was also validated with the use of enolate equivalents as nucleophiles. Silyl enol ethers, both unsubstituted (Table 46) and those bearing an alkyl group on the α-carbon (Table 47), were observed to add to a range of chalcones in a highly enantioselective fashion. The diastereoselectivity in the addition of α-methyl silyl enol ethers was shown to be

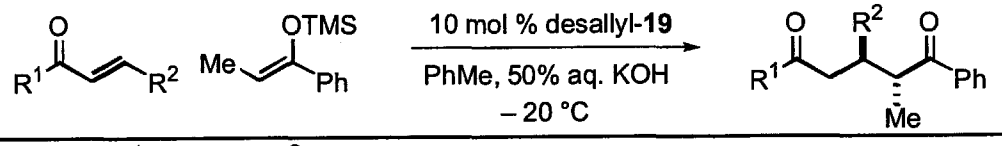
moderate to excellent (3 : 1 – 20 : 1). Again, the catalyst with the free hydroxyl group was shown to afford optimal levels of stereoselection. However, the stereochemical rationale proposed for the malonate addition shown in Scheme 21 does not satisfactorily explain the selectivity, since the nucleophile does not possess two carbonyl groups to engage in a favorable electrostatic interaction with the quaternary nitrogen on the catalyst.

Table 46. Asymmetric addition of silyl enol ethers to enones *via* PTC.



Entry	R^1	R^2	R^3	Time / h	Yield / %	ee / %
1	C_6H_4F-4	Ph	Ph	8	85	95
2	C_6H_4Cl-4	Ph	Ph	4	91	94
3	C_6H_4OMe-4	Ph	Ph	24	80	92
4	C_6H_4Me-4	Ph	Ph	16	94	91
5	C_6H_4F-4	C_6H_4Cl-4	Ph	4	87	91
6	C_6H_4F-4	C_6H_4OMe-4	Ph	16	92	94
7	2-NaphOMe-6	Ph	Ph	24	82	94
8	1-Naph	Ph	Ph	10	81	95
9	C_6H_4F-4	Ph	C_6H_4Me-4	15	79	92
10	C_6H_4F-4	Ph	C_6H_4Ph-4	16	92	93
11	C_6H_4F-4	Ph	2-Naph	10	81	95

Table 47. Highly diastereo- and enantioselective addition of substituted enolate equivalents to enones under PTC.



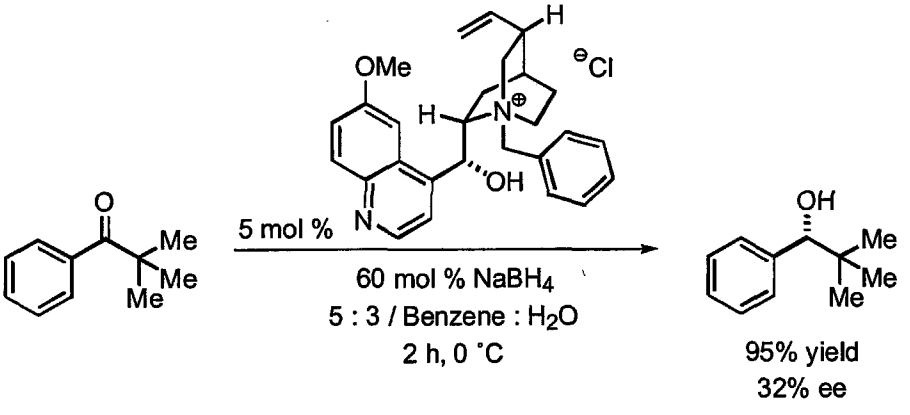
Entry	R^1	R^2	Time / h	Yield / %	*anti* : *syn*	*anti* ee / %	*syn* ee / %
1	Ph	Ph	10	90	9 : 1	99	90
2	C_6H_4F-4	Ph	10	95	10 : 1	99	94
3	C_6H_4Br-4	Ph	10	88	10 : 1	99	84
4	C_6H_4OMe-4	Ph	40	93	4 : 1	98	90
5	Ph	C_6H_4Me-4	15	85	10 : 1	99	81
6	Ph	$C_6H_4NO_2$-4	40	87	3 : 1	97	95
7	Ph	C_6H_4Br-4	10	94	7 : 1	92	95
8	Ph	1-Naph	15	82	20 : 1	92	n.d.

1.4.6 1,2 – Carbonyl Additions

1.4.6.1 Hydride Reductions

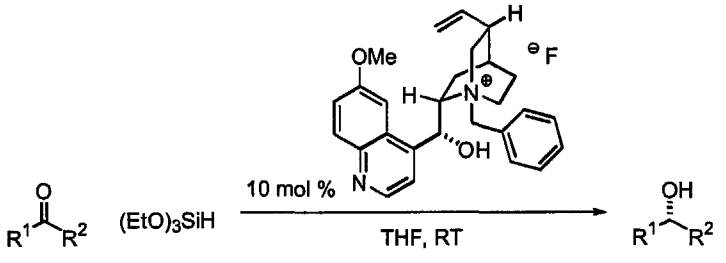
Chiral phase-transfer catalysts have also been used to effect reduction at the carbonyl carbon. Colonna and coworkers first reported this reaction in 1976. Several differentially quaternized ephedrinium salts were used as phase transfer catalysts; sodium borohydride served as the hydride source, and the two-phase system used was composed of benzene and water.[73] Most of the ketones subjected to the protocol gave essentially racemic product, however *tert*-butyl methyl ketone was reduced in 14% ee. An improvement on this work appeared in the literature several years later; the ubiquitous cinchona alkaloids were used as chiral phase-transfer catalysts, resulting in superior enantioselectivities.[74] Water / benzene was again used as the two-phase system, and sodium borohydride employed as the reductant. Several different ketones were subjected to the reductive conditions; however, as before, only *tert*-butyl phenyl ketone showed

appreciable levels of selectivity. The cinchona alkaloid catalyst depicted in Scheme 22 gave the highest enantioselectivity (32% ee). Marginal improvement in this methodology was achieved with the use of triethoxysilane as the reducing agent. Presumably, the fluoride counterion of the catalyst would attack silicon, resulting in the formation of a hypervalent silicate, with the nucleophilicity of the hydride increased accordingly. Several ketones were subjected to this protocol, and the corresponding alcohols were isolated in 11 – 65% ee (Table 48).[75]



Scheme 22. Asymmetric reduction of *tert*-butyl methyl ketone with quaternary cinchona PTC.

Table 48. Asymmetric reduction of ketones with triethoxysilane / quaternary PTC system..



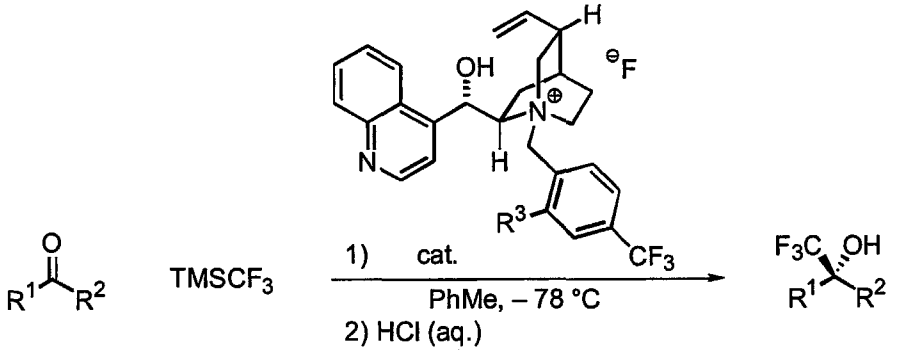
Entry	R^1	R^2	Yield / %	ee / %
1	Ph	Me	94	51
2	C_6H_4Cl-4	Me	68	35
3	Ph	Et	83	65
4	Ph	*i*-Pr	86	65
5	*c*-C_6H_{11}	Me	68	11
6	CH_2Bn	Me	97	11

When tris(trimethoxy)silane was used as the reducing agent, modest increases in enantioselectivity were observed, most likely due to the dramatically increased steric bulk of the hydride source. Interestingly, when polymethylhydrosiloxane (PMHS) was used as reductant, the enantioselectivity of the reduction dropped, but a dramatic rate enhancement was measured. The authors attributed this phenomenon to intramolecular hydride transfer along the polymeric silicon chain, an effect that they termed "zipper catalysis." No further optimization of these reaction conditions have appeared in the literature, although the oxazaborolidine catalyst discovered by Itsuno[76] and optimized by Corey[77] has proved quite adept at reducing an impressive array of ketones with a high overall degree of enantioinduction.

1.4.6.2 Addition of Trifluoromethyl Groups

Iseki and Kobayashi described a system with a quaternized cinchona alkaloid as catalyst that catalyzed the asymmetric addition of trifluoromethyl groups to aldehydes and ketones. Triflouromethyltrimethylsilane was used as the source of trifluoromethyl anions, with initial activation of the silane due to attack by the fluoride associated with the catalyst. Several different aldehydes and ketones were submitted to the reaction conditions; the addition proved to be fairly efficient (87 – greater than 99% yield), but lacking in stereospecificity (15 – 51% ee, Table 49).[78]

Table 49. Catalytic asymmetric trifluoromethylation of ketones under PTC conditions.

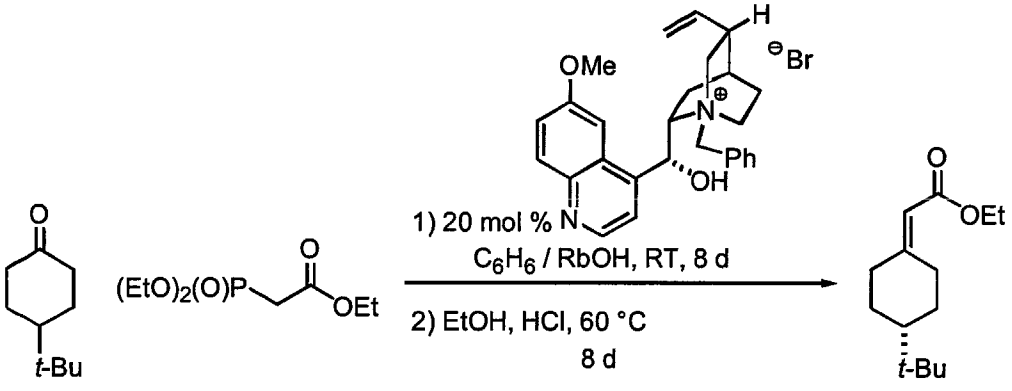


Entry	R^1	R^2	R^3	Cat. Loading / mol %	Time / h	Yield / %	ee / %
1	Ph	H	CF_3	20	2	> 99	46
2	n-C_7H_{15}	H	H	20	2	> 99	15
3	9-Anth	H	H	10	2	98	45
4	Ph	Me	H	20	2	91	48
5	Ph	*i*-Pr	H	20	8	97	51

1.4.6.3 The Horner-Wadsworth-Emmons Reaction

The olefination of carbonyls with nucleophilic phosphorus ylides, as exemplified by the Wittig reaction[79] and the related Horner-Wadsworth-Emmons reaction,[80] has found many applications in natural product synthesis. Attempts to effect this reaction in an enantioselective fashion have been published, although the first reports in this area required the use of stoichiometric amounts of chiral reagents.[81] Arai and Shiori reported the first catalytic asymmetric version of this reaction, which made use of cinchona alkaloids as phase transfer catalysts in a solid-liquid phase transfer process analogous to that used by Corey for enolate alkylations (see section IV. B.). The only substrate examined in this report was 4-*tert*-butylcyclohexanone, a meso compound, making the methodology, in effect, a desymmetrization. The reaction proved to be highly sensitive to the alkyl substituents on the phosphonate as well as the counterion of the phase

transfer catalyst. The bromide salt combined with trimethylphosphonoacetate afforded alkylidene products in 43% ee, but also with a low yield (15%)[82]. Acidification of the reaction medium at the end of the reaction and isolation with an acid-base extractive workup proved to be beneficial to the yields of alkylidenes. Using rubidium hydroxide monohydrate as base instead of potassium hydroxide also boosted both the yields and enantioselectivities. Ultimately, the best results obtained were 69% yield and 57% ee (Scheme 23). Although this reaction would represent a valuable addition to the repertoire of asymmetric phase-transfer catalysis, clearly a great deal of optimization needs to be carried out to give products of synthetically useful levels of conversion and enantioselectivity.



Scheme 23. Desymmetrization of 4-*tert*-butylcyclohexanone under phase transfer conditions.

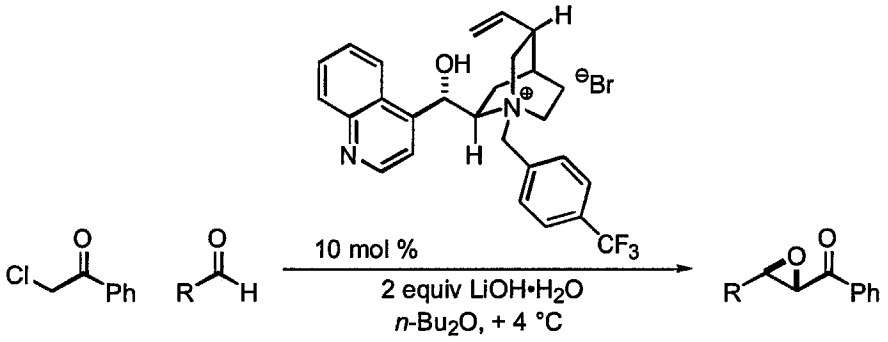
1.4.7 The Darzens Reaction

The Darzens reaction has proved to be one of the most versatile means of forming α,β-epoxy carbonyl compounds, with concomitant creation of two new stereocenters.[83] In this reaction, an electron-withdrawing group (capable of stabilizing an adjacent

carbanion) bearing an α-halide is enolized and added to a carbonyl compound. The resulting alkoxide then attacks the carbon α to the electron withdrawing group, displacing the halide in an S_N2 fashion and resulting in formation of an epoxide. The Darzens reaction had resisted the development of a catalytic asymmetric variant due to the fact that addition of a catalytic amount of base would result in the formation of a metal halide, a species insufficiently basic to enolize most carbonyl compounds.

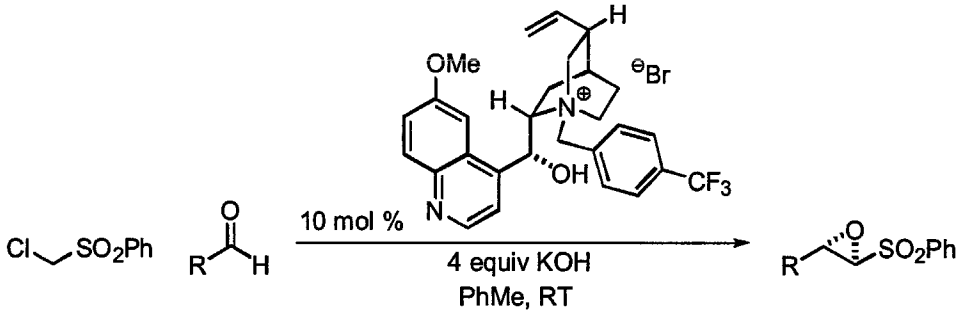
Phase transfer catalysis provided a conceptual solution to this problem in that a large excess of base could be utilized, with the catalyst transporting the minimal quantities of base into the organic layer necessary to induce complete enolization of the substrate. In an initial study, 2-chloroacetophenone was subjected phase-transfer catalysed Darzens condensation, as depicted in Table 50.[84] The best result from these reactions was with propionaldehyde as the electrophile, giving the corresponding α,β-epoxy ketone in 79% ee (but with 32% yield). Attempts were also made to extend this general concept to the use of α-chlorophenyl phenyl sulfone and a variety of aryl aldehydes.[85] Initial screening led to the identification of toluene as the optimal organic solvent and the alkaloid shown in Table 51 as the catalyst of choice. When different aryl aldehydes were subjected to these conditions, enantioenriched epoxysulfones were isolated; 4-*tert*-butyl benzaldehyde afforded the corresponding Darzens adduct in 70% yield and a respectable 81% ee.

Table 50. Preparation of enantioenriched epoxyketones *via* PTC.



Entry	R	Time / h	Yield / %	ee / %
1	*i*-Pr	60	80	53
2	Et	117	32	79
3	*n*-Pr	60	82	57
4	*i*-Bu	134	73	69
5	CH_2t-Bu	91	50	62
6	CH_2CHEt_2	117	76	58
7	CH_2Bn	114	83	44
8	*c*-C_6H_{11}	61	47	63
9	Ph	69	43	42

Table 51. Scope of Arai's PTC-asymmetric Darzens reaction with chlorophenylsulfones.



Entry	R	Time / h	Yield / %	ee / %
1	C_6H_4Br-4	1.0	80	64
2	C_6H_4Br-3	1.5	69	71
3	C_6H_4Me-4	2.0	84	78
4	C_6H_4t-Bu-4	2.0	70	81
5	C_6H_4Ph-4	1.5	71	72
6	C_6H_4OPh-4	1.5	83	65
7	C_6H_4Me-3	1.0	82	74
8	2-Naphthyl	1.0	94	68

1.5 Amines as Chiral Nucleophilic Catalysts

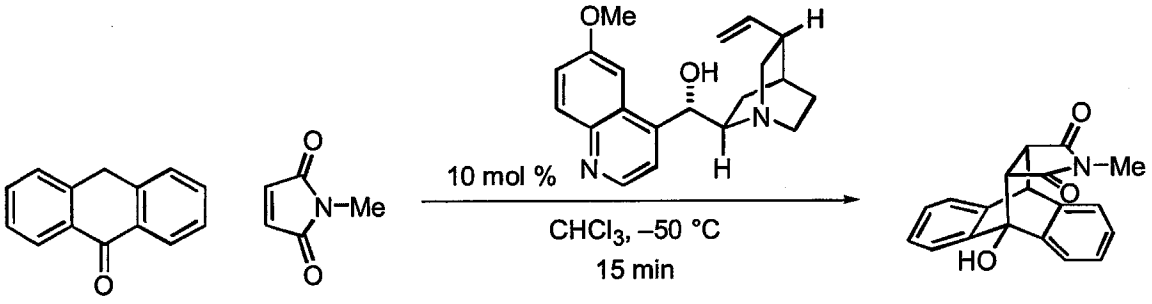
1.5.1 Introduction

The use of chiral Lewis acids as catalytic species has provided an important foundation for the explosive growth in development and application of new catalytic asymmetric methdolologies; however, the analogous use of chiral Lewis bases has remained a conceptually underexploited field. The development of Lewis bases as chiral catalysts has in many cases allowed the preparation of a diverse array of organic architectures in a highly enantioenriched fashion, in many cases in a manner perhaps unsuited to the use of chiral Lewis acids.

1.5.2 The Diels–Alder Reaction

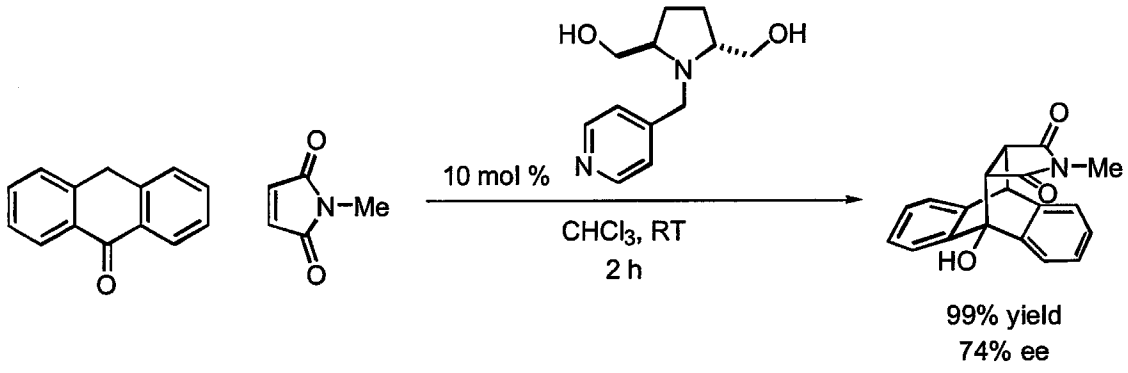
Many methodologies have emerged involving phase-transfer catalysis of the Diels–Alder reaction; however, much less prevalent are examples of cycloadditions catalyzed by chiral amines acting as bases. Kagan first observed this phenomenon in 1989. He reported the catalytic asymmetric cycloaddition of anthrone with *N*-methylmaleimide, as shown in Scheme 24. Various chiral bases were added to catalyze this reaction, with the optimal results found with 10 mole percent of quinidine at –50 °C in chloroform. The cycloadduct was isolated in 97% yield and 61% ee.[86] The mechanism of the observed transformation was not investigated thoroughly; however, Kagan ruled out an asynchronous "cycloaddition" consisting of enolization of anthrone, conjugate addition to the dienophile, and subsequent attack of the enolate thus generated on the anthrone carbonyl. The evidence for the exclusion of this manifold was obtained from isolation of the conjugate adduct and subjection to the reaction conditions in a

separate step, whereupon no cycloaddition product was observed. Rather, an alternate explanation was advanced that involved deprotonation of anthrone, followed by association of the protonated catalyst to the dienophile and subsequent cycloaddition.



Scheme 24. Initial report by Kagan of asymmetric base–catalyzed Diels–Alder reaction.

Even after some time had passed since Kagan's initial report, there remained some lingering interest in optimizing the cycloaddition between anthrone and *N*-methylmaleimide. Consequently, different catalyst architectures were employed in an attempt to boost the stereoselectivity of the reaction. The C_2 symmetric pyrrolidine derivative shown in Scheme 25 (with R = H) was utilized to catalyze the cycloaddition at ambient temperature to give the corresponding bicyclic product in 88% yield. The *endo* diastereomer was found to have an ee of 61%.[87] This result was improved to 99% yield and 74% ee by using the pyridinylmethyl substituted catalyst. A transition state was proposed as shown in Figure 14, in which hydrogen bonding between the catalyst and both the deprotonated anthrone and the maleimide serve to assemble the reactants into a specific conformation for cycloaddition.[88] Other catalyst modifications, including alteration of cinchona alkaloids with perfluorinated alkyl chains, afforded only marginal stereoselectivities.[89]



Scheme 25. Use of C_2–symmetric pyrrolidine derivative in base-catalyzed Diels–Alder reaction.

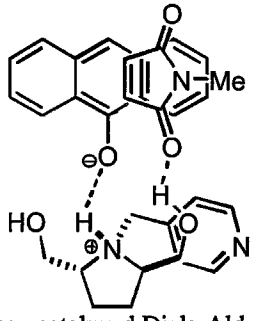
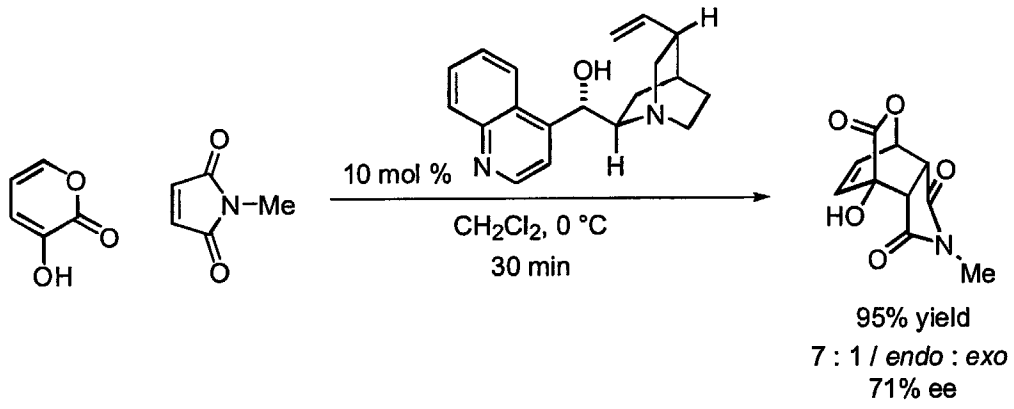


Figure 14. Proposed transition state for base-catalyzed Diels-Alder reaction in Scheme 25.

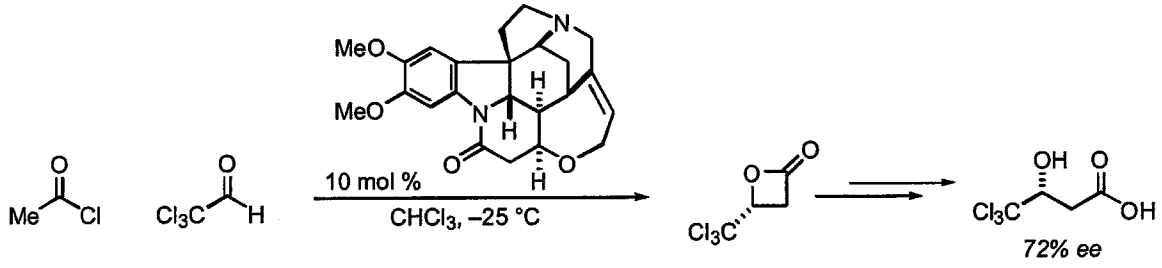
An analogous process was observed with hydroxypyrones acting as the diene component. Exposure of 3-hydroxy-2-pyrone and *N*-methylmaleimide to 10 mole percent of cinchonine in methylene chloride at 0 °C gave the corresponding cycloadduct in 95% yield, with an *endo* : *exo* ratio of 7 : 1 (Scheme 26). The endo isomer was isolated in 71% ee.[90] Attempts to increase the stereoselectivity of the reaction by screening a variety of solvents were unsuccessful. The enantioselectivity of the reaction displayed an inverse temperature profile, although the ratio of diastereomers did increase to 12 : 1 on cooling to –78 °C. Conducting the reaction in methanol resulted in quantitative formation of racemic product, potentially suggesting the importance of hydrogen bonding to enantioselectivity.



Scheme 26. Extension of Kagan's Diels–Alder reaction to pyrones.

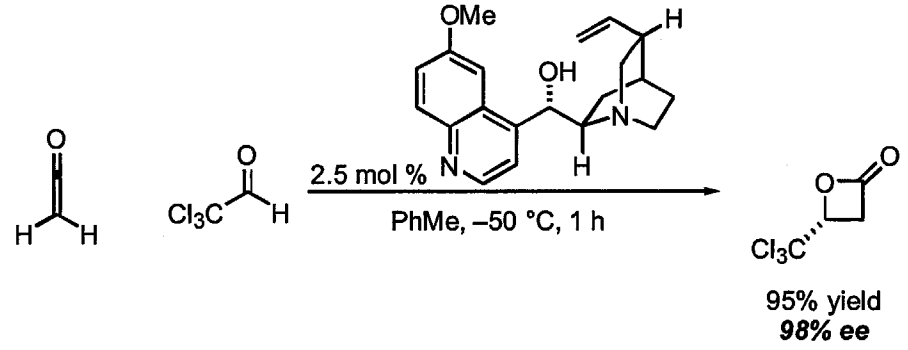
1.5.3 Catalytic Asymmetric Synthesis of β-Lactones

The preparation of the β-lactone functionality in enantiomerically enriched form using chiral basic catalysts has been known for well over thirty years. In 1966, Borrmann and Wegler published the formation of racemic β-lactones from the reaction of an acid chloride, an aldehyde, and a tertiary amine base.[91] Shortly thereafter, the reaction was made both catalytic and enantioselective by the use of cinchona alkaloids as nucleophilic catalysts. Several different ketene surrogates and aldehydes were processed according to their reaction conditions. On cooling the reaction to –25 °C and conducting the reaction in chloroform, with brucine as catalyst, the ee of the acid increased to 72% (Scheme 27).[92] This result was quite remarkable given the rather primitive state of the field of asymmetric catalysis at the time.



Scheme 27. First report by Borrmann and Wegler of asymmetric β–lactone synthesis with chiral base catalyst.

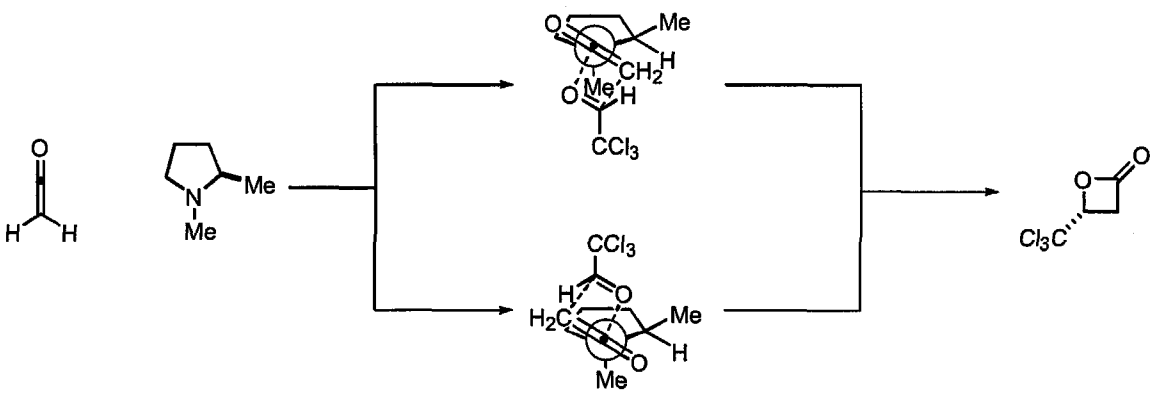
In 1982, Wynberg published the preparation of an enantiomerically enriched β-lactone with a cinchona alkaloid acting as a chiral nucleophilic catalyst. When chloral was dissolved in toluene with 2.5 mole percent of quinidine and ketene vapor was bubbled through the solution, the corresponding β-lactone adduct was isolated in 95% yield and 98% ee (Scheme 28).[93] A variety of other cinchona alkaloids were also examined for activity, but none furnished lactones with enantioselectivities approaching the products formed by quinidine catalysis. This result, along with the Hajos–Parrish reaction (section III.B.1.), stands as one of the first truly outstanding asymmetric catalytic reactions ever reported, organocatalytic or otherwise.



Scheme 28. Highly enantioselective lactone preparation under cinchona alkaloid catalysis.

A somewhat primitive model was advanced to account for the high degree stereoselectivity transferred during the course of the reaction. Reflecting what was

presumed at the time to be the dominant stereocontrol element, 1,2-dimethylpyrrolidine was advanced as a simplified model for the alkaloid catalyst (Scheme 29). Wynberg described the association of ketene and imine in a poorly defined "complex" with the central ketene carbon atom positioned over the pyrrolidine nitrogen. Such a complex was theorized to have two low-energy rotameric forms, one in which the ketene oxygen pointed towards the methylene adjacent to the pyrrolidine nitrogen, and another in which the terminal ketene carbon was directed towards the same methylene. In the form in which the ketene oxygen was facing the methylene, chloral was theorized to approach the ketene-amine complex with the trichloromethyl group directed away from the steric impedance of the methyl group on the catalyst. In the other form, the methylene of the ring would serve as the dominant stereocontrolling element and thus the trichloromethyl would orient itself away from these protons before cyclization occurred. It was not stated which rotamer was thought to be favored, but both would, in theory, afford products with the same stereochemical orientation.

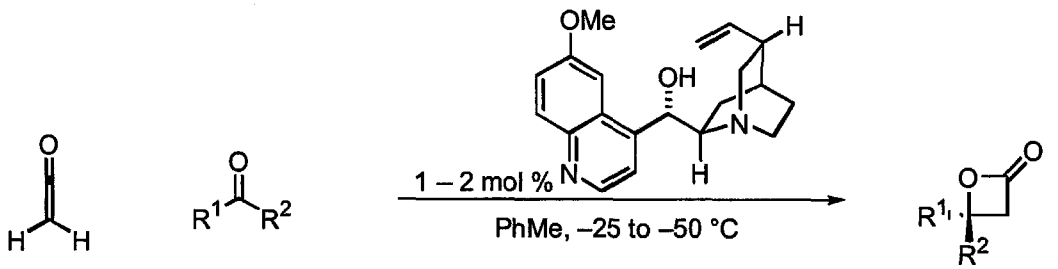


Scheme 29. Preliminary rationale for stereochemical outcome of reaction shown in Scheme 28.

This revolutionary work was followed by an attempt to expand the scope of the reaction beyond chloral. Various chloral derivatives were observed to react with good

yields and enantioselectivities (67 – 95% yield, 89 – 94% ee, Table 52).[94] There were several exceptions; α,α-dichloroacetaldehyde was generated with a moderate ee (Entry 2, 45%), perhaps suggesting the importance of the steric bulk associated with the trichloromethyl group to obtaining good enantioinduction. When the aldehyde was replaced with a phenyl or ethyl group (Entries 7, 8), the reactivity dropped off abruptly. Nevertheless, ketones with aryl groups bearing electron withdrawing groups did successfully participate in the reaction.

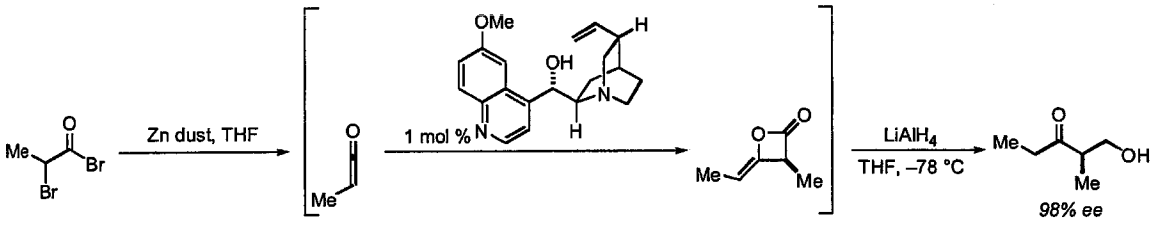
Table 52. Extension of scope of catalytic asymmetric lactone synthesis with cinchona alkaloid catalysts.



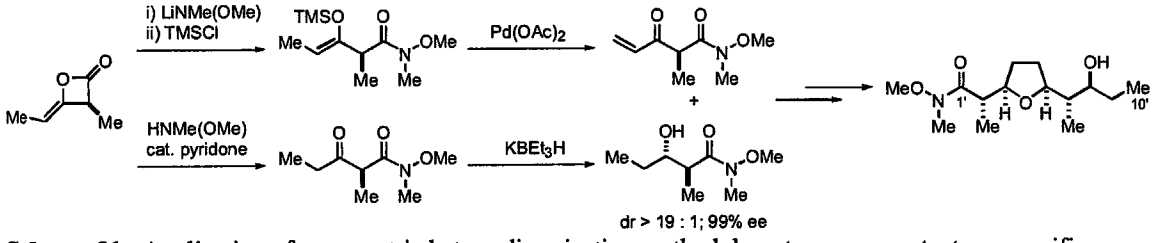
Entry	R^1	R^2	Yield / %	ee / %
1	CCl_3	H	89	98
2	$CHCl_2$	H	67	45
3	CCl_2CH_3	H	95	91
4	$CCl_2CH_2CH_3$	H	87	89
5	$CCl_2C_6H_5$	H	89	90
6	CCl_3	CH_3	72	94
7	CCl_3	CH_2CH_3	1	n.d.
8	CCl_3	C_6H_5	0	n.d.
9	CCl_3	C_6H_4Cl-4	68	90
10	CCl_3	$C_6H_4NO_2$-4	95	89

One unfortunate operational detail of the methodology reported by Wynberg was that ketene was used in gaseous form, which required the use of specialized equipment

and glassware; moreover, only certain highly electron deficient aldehydes successfully underwent reaction. In order to circumvent the first shortcoming, Calter and coworkers reported the use of *in situ* ketene generation according to the method of Ward.[95] This procedure, itself a modification of the protocol published by Staudinger,[96] involved treating α-bromo acid bromides with activated zinc dust. Reformatsky-type insertion of zinc into the carbon-bromine bond was followed by extrusion of zinc bromide and concomitant formation of ketene, as shown in Scheme 30. The ketene was then used a solution in THF. Calter found that methylketene could be dimerized in a highly enantioselective fashion (up to 98% ee) by exposing a solution of methyl ketene to 1 mole percent of a cinchona alkaloid at –78 °C.[97] The resulting lactone was reductively opened to afford the aldol-type product shown. The synthetic utility of this process was demonstrated in the preparation of the $C_{1'}$–$C_{10'}$ segment of the antibacterial macrocycle Pamamycin 621A (Scheme 31).[98]



Scheme 30. Catalytic asymmetric ketene dimerization as reported by Calter and coworkers.



Scheme 31. Application of asymmetric ketene dimerization methodology to convergent, stereospecific total synthesis of a portion of Pamamycin 621A.

Romo and coworkers used an analogous approach to *in situ* ketene generation, *via* dehydrohalogenation of acid chlorides with an exogenous, readily available amine base.[99] This procedure was not only much less operationally intensive, but would allow the preparation of a much wider array of structurally distinct ketenes, limited only by the number of commercially available acid chlorides. A probable mechanism for this reaction is presented in Figure 15. The exogenous base would abstract a proton from the acid chloride, resulting in generation of ketene. The ketene would be activated by addition of the catalyst to give the acylammonium enolate intermediate, which would then add to the substrate aldehyde. The resulting alkoxide might then participate in an addition-elimination reaction at the acyl carbon, releasing the chiral catalyst and generating the β-lactone product.

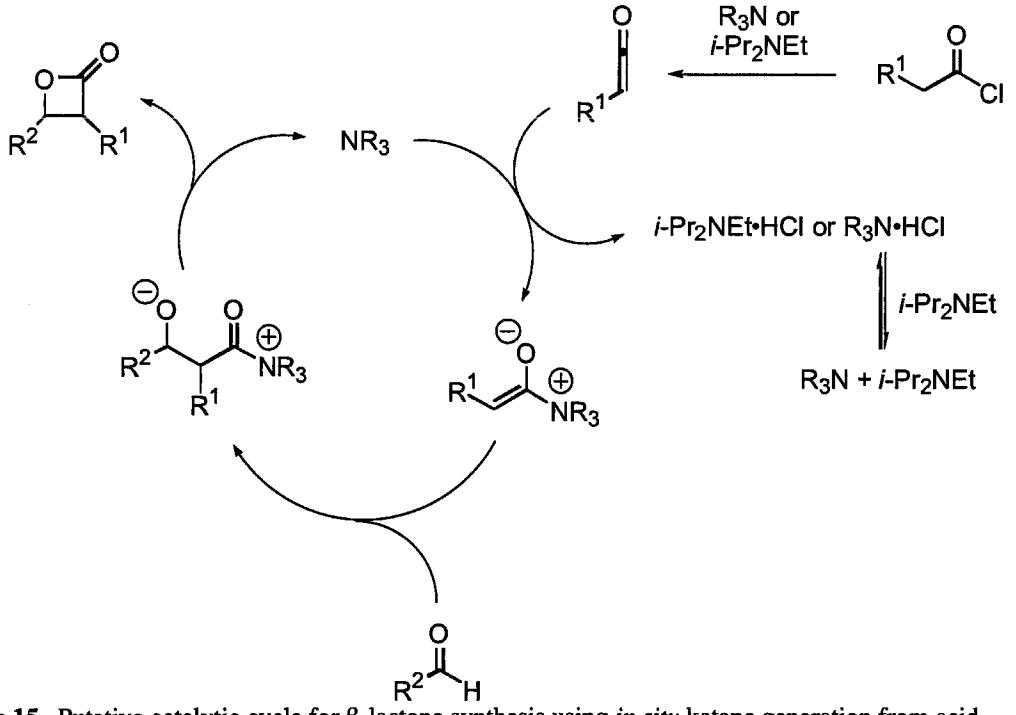
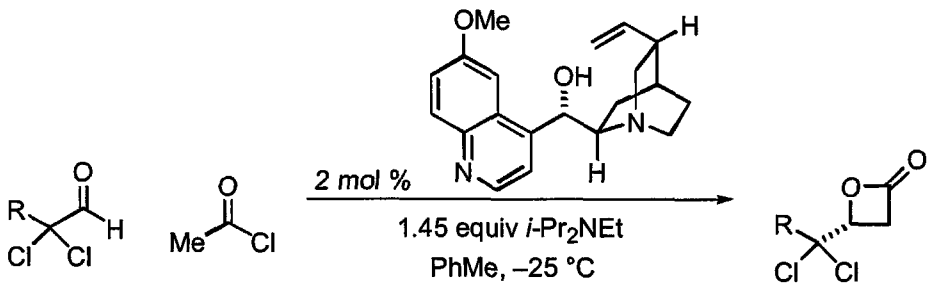


Figure 15. Putative catalytic cycle for β-lactone synthesis using *in situ* ketene generation from acid chlorides.

One potential problem with this approach was that of nucleophilic competition between the base and the chiral nucleophilic catalyst. If the catalyst were the agent that generated ketene rather than the base, it would preclude the source of asymmetry from participating in the catalytic cycle. Conversely, if the exogenous base were to act as the nucleophilic catalyst, clearly a possibility since it would be present in vast excess relative to the catalyst, then the product of the cyclization would be devoid of any optical activity. However, Romo et al. observed in a series of control experiments that when a sterically hindered base, such as Hünig's base, was used without alkaloid present, no lactone formation was detected. By adding the acid chloride to a solution of Hünig's base, substrate aldehyde, and catalytic quantities of quinidine in toluene at subambient temperature, several lactone adducts were isolated in low to good yields and excellent enantioselectivities (Table 53). These adducts were shown to be readily convertible to other, more useful organic molecules, including aldol-type products, as well as α-azido ketones and molecules bearing propargylic and allylic stereocenters.[100]

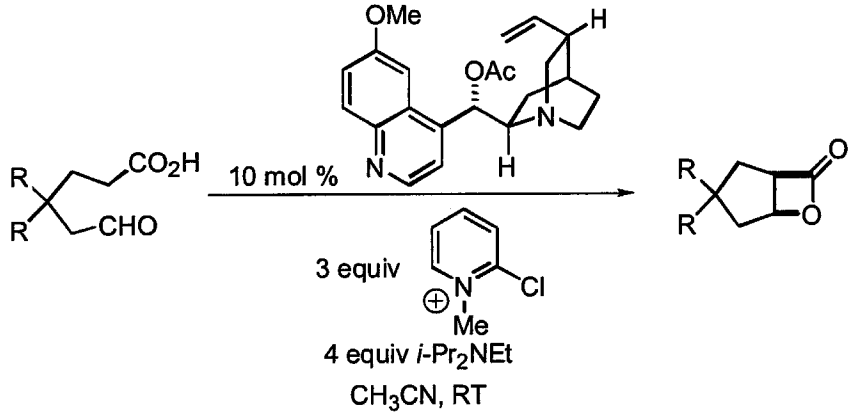
Table 53. Catalytic asymmetric lactone synthesis with chloral derivatives.



Entry	R	Yield / %	ee / %
1	CH_2Ph	85	94
2	*n*-C_6H_{13}	73	93
3	$(CH_2)_2OPiv$	80	94
4	*i*-Pr	40	98

This reactivity was further extended to intramolecular cyclizations with ω-formyl acids to form bicyclic β-lactones. The acids were activated by reaction with 2-chloro-*N*-methylpyridinium iodide (Mukaiyama's reagent) followed by *in situ* ketene generation and cyclization. A variety of formyl acids were observed to undergo racemic reaction, and several demonstrated a propensity to cyclize in a highly enantioselective fashion (86 – 92% ee, Table 54).[101] One stereochemical rationale for this reaction was based on a determination of the functional groups required on the catalyst as well as conformational analysis of the cinchona alkaloid. Blocking the hydroxyl group on the alkaloid with various carbonyl derivatives did not affect the enantioselectivity to a great degree, although the yields of the reaction were affected noticeably. Attaching a carbamate to the catalyst affected stereoselectivity only when the reaction was carried out in a nonpolar solvent. A second, more satisfying stereochemical rationale involves a description of the conformation of the catalyst itself. Upon generation of the acylammonium enolate, the aldehyde was thought to approach the enolate from the *si* face, away from the methoxyquinoline moiety, resulting in a product with the observed stereogenicity (Figure 16).[101, 102]

Table 54. Asymmetric preparation of bicyclic lactones *via* intramolecular activation of ketene equivalents.



Entry	R	Yield / %	ee / %
1	H	54	92
2	OCH_2CH_2O	37	92
3	Me	45	90

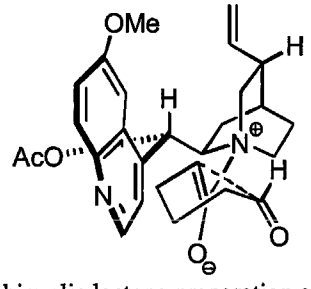
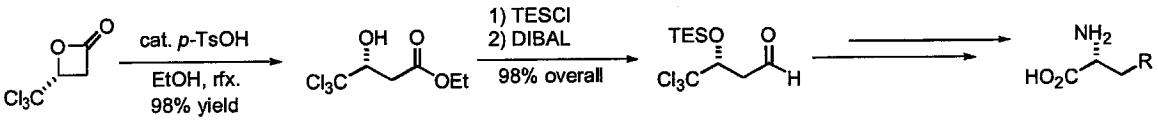


Figure 16. Proposed transition state of bicyclic lactone preparation as in Table 54.

This methodology could also be used to prepare amino acids with γ-substitution, taking advantage of Corey's previously reported method of converting *gem*-trichloromethyl alcohols to amino acids (Scheme 32).[103] The requisite precursor could be accessed from enantiomerically enriched β-lactones by enantioselective cyclization, followed by acid-catalyzed transesterification-ring opening and protecting group manipulation.[104]

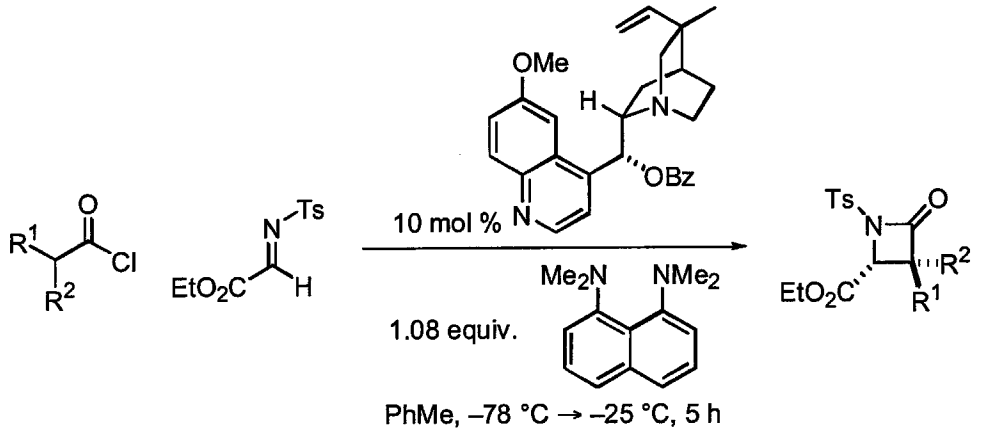


Scheme 32. Extension of Romo's ketene cyclization reaction to preparation of enantioenriched amino acids.

1.5.4 Catalytic Asymmetric Synthesis of β-Lactams

The β-lactam functionality, the nitrogen analog of the β-lactone, has found myriad uses in both academic and industrial settings, particularly as the key functional group component of several important antibacterial compounds. In 1989, Alper reported a rhodium(I)-catalyzed carbonylative resolution of racemic aziridines to give enantioenriched β-lactams; however, the substrate scope of this reaction was extremely limited.[105] Eleven years later, Lectka divulged the first truly catalytic asymmetric β-lactam methodology.[106] In this report, ketene equivalents were generated *in situ* by dehydrochlorination of the appropriate acid chloride, followed by activation of the ketene by attack from a cinchona alkaloid catalyst. The resulting acylammonium enolate was then condensed with a glyoxylate-derived *N*-toluenesulfonyl imine to afford the lactam. The catalyst was regenerated in a process analogous to that of the β-lactone methodology described above (section V.C.). Although yields were at best moderate (36 – 65%), enantioselectivities and diastereoselectivities were excellent (95 – 99% ee, dr 99 : 1 or greater, Table 55). Lectka later adapted this methodology to what he termed "column asymmetric catalysis," in which a column with the phosphoramide resin and one with the alkaloid on solid support were connected sequentially. The column was then "loaded" with the appropriate acid chloride and eluted, with the imine injected between the two columns. The lactam was collected at the end of the alkaloid-containing column in excellent yields and enantioselectivities.[107]

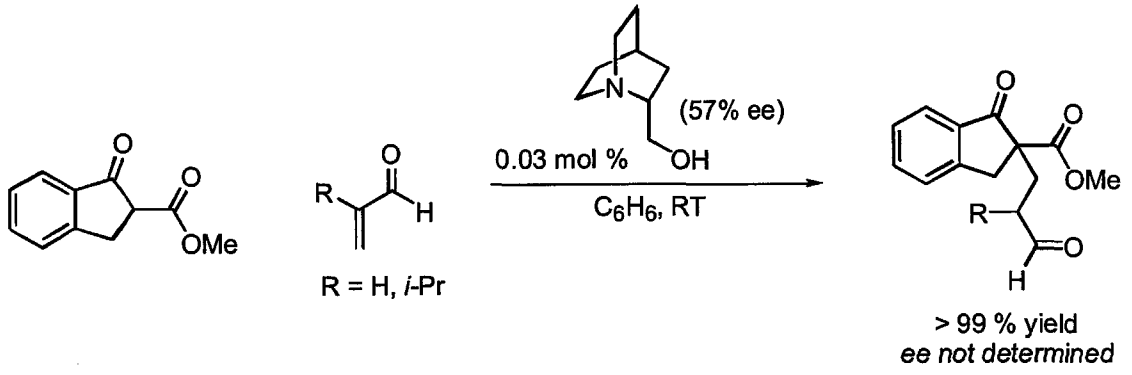
Table 55. Scope of Lectka's catalytic asymmetric β-lactam methodology.



Entry	R^1	R^2	Yield / %	dr	ee / %
1	Ph	Ph	36	–	99
2	H	Ph	65	99 : 1	96
3	H	Et	57	99 : 1	99
4	H	OPh	45	99 : 1	99
5	H	OAc	61	> 99 : 1	98
6	H	OBn	56	99 : 1	95

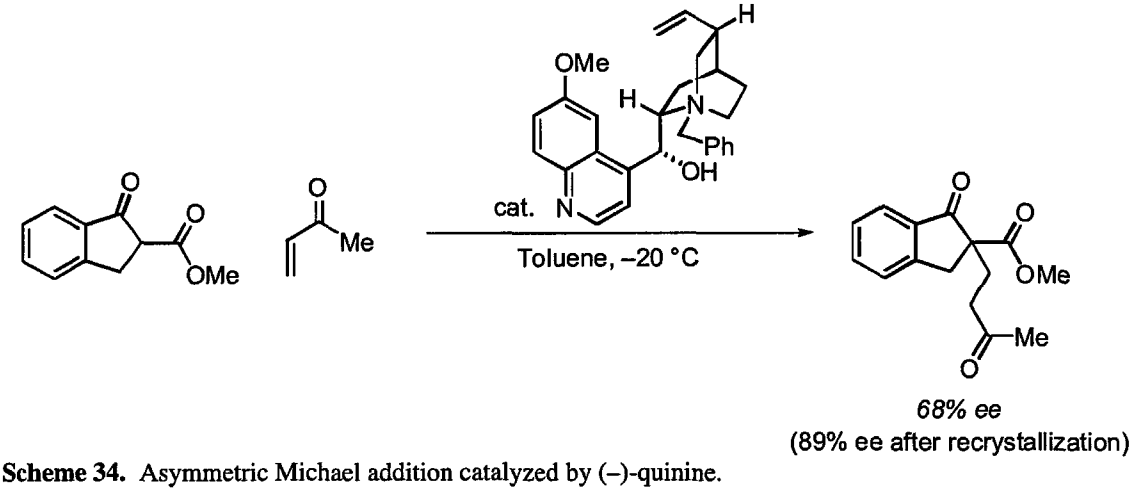
1.5.5 The Michael Reaction

Commensurate with its status as arguably one of the most important and efficient means of stereocontrolled carbon-carbon bond formation, chiral nucleophile-based catalysis has also been applied to the catalytic asymmetric Michael reaction. Methodology development in this area was spurred by the first base-catalyzed asymmetric Michael reaction,[108] reported by Långström and Bergson in 1973.[109] In this work, 2-(hydroxymethyl)-quinuclidine of 57% ee was used to catalyze the addition of the carboxyindanone to acrolein and 2-(1-methylethyl)-acrolein, in the process generating an quaternary carbon stereocenter (Scheme 33). In both cases, the products were formed quantitatively, and, after isolation and purification, were observed to have an optical rotation, although the enantiomeric purity of the products was not determined.



Scheme 33. First reported catalytic asymmetric Michael reaction.

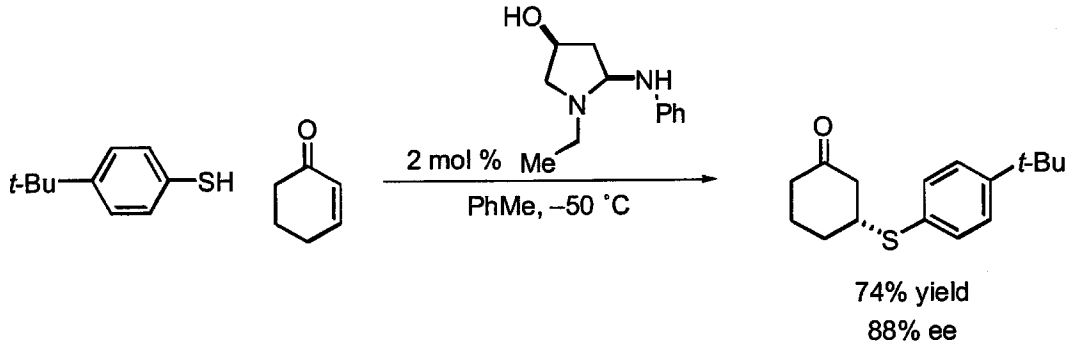
Wynberg was the first to adapt this result with the use of enantiomerically pure cinchona alkaloids. The carboxyindanone was added to methyl vinyl ketone in toluene in the presence of catalytic amounts of quinine to afford the corresponding adduct in 68% ee (89% ee after two recrystallizations, Scheme 34). A variety of nitroalkanes and β-diketones were also used as Michael donors; however, the enantioselectivities of these reactions were not determined.[110] This reaction was potentially quite useful, as it represented the first example of enantioselective organocatalytic quaternary stereocenter construction.



Scheme 34. Asymmetric Michael addition catalyzed by (–)-quinine.

Polymer-derived alkaloids were also tested as catalysts in order to facilitate isolation and purification of the products. In particular, the vinyl group of the catalyst was used to polymerize the alkaloid with copoly(styrene – 2% divinylbenzene); however, testing of a variety of catalysts afforded the Michael adducts in a maximum of 11% ee.[111] Copolymerization with acrylonitrile instead, initiated by AIBN, resulted in the formation of a quinidine-acrylonitrile polymer that catalyzed the addition of the carboxyindanone to methyl vinyl ketone in 92% yield and 42% ee.[112]

Several groups have attempted to effect conjugate thiol additions using amino-acid derived catalytic systems. In particular, Inoue reported the catalytic asymmetric conjugate addition using a poly-(S)-alanine derived catalyst.[113] Initially, monomeric amino-acid-derived molecules, such as (S)-alanine-N-propylamide, did not catalyze the reaction with any appreciable degree of asymmetric induction. However, a proline-derived catalyst prepared by Mukaiyama proved to be more adept at catalyzing conjugate addition. 4-tert-Butylthiophenol was added to cyclohexenone in a conjugate fashion in 74% yield and 88% ee (Scheme 35).[114] The enantioselectivity was rationalized with the simple model shown in Figure 17. A hydrogen bonding interaction between cyclohexenone and the hydroxyl group on the catalyst pyrrolidine ring provided the basis for preorganization in the transition state. The arylthiolate was associated with the catalyst by an ionic interaction as well as a π-stacking arrangement with the pendant aniline. Addition then occurred from the re face of the enone to afford the product with the observed enantioselectivity. Addition to the si face was disfavored by nonbonded interactions between the enone and the aniline of the catalyst.[115]



Scheme 35. Organocatalytic asymmetric thiol conjugate addition reported by Mukaiyama.

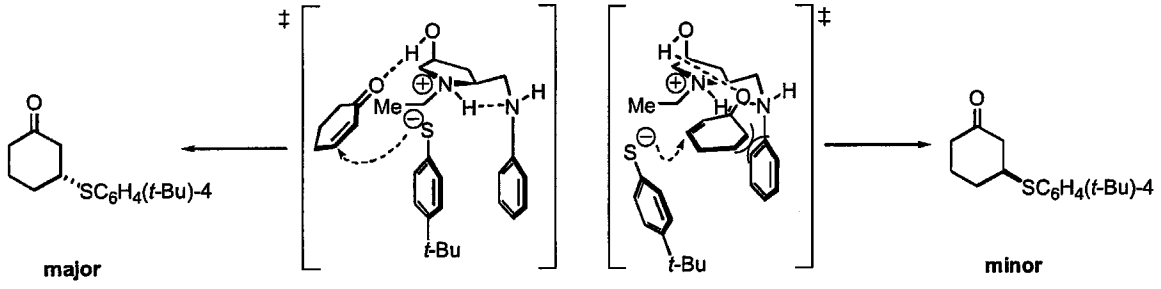
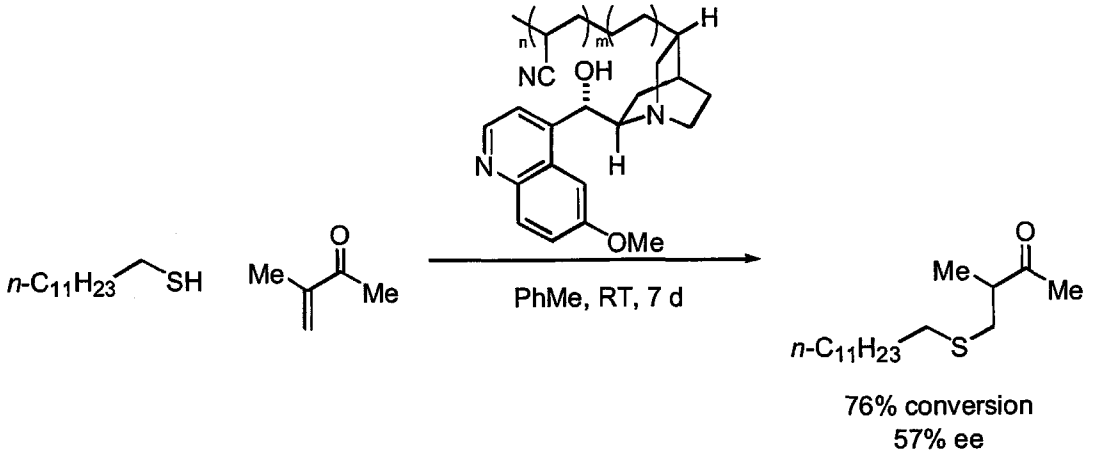


Figure 17. Stereochemical rationale for generation of the major enantiomer in Scheme 35.

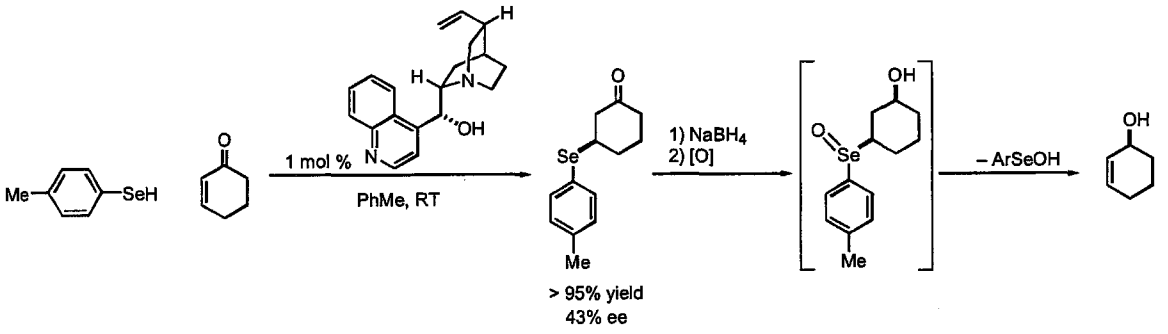
Kobayashi et al. reported the asymmetric addition of dodecylthiol to methyl isopropenyl ketone in 76% conversion and 57% ee using a poly(quinine-acetonitrile) catalyst (Scheme 36), This reaction proceeded in greater enantioselectivity than was observed with the monomeric alkaloid (51% ee).[112] A Japanese group attempted to increase the rate of these reactions by highlighting the often-overlooked fact that reactions have not only an activation energy, but also an activation volume well. Increasing the pressure under which the reaction was conducted (400 – 1500 MPa) caused a reduction in reaction times; unfortunately, decreases in enantioselectivity were observed in the addition of phenylthiols to cyclohexenone, as well as the addition of nitromethane to chalcone and the addition of Wynberg's carboxyindanone to methyl

vinyl ketone. The enantioselectivities, even in the best cases, were unremarkable, with the best results for each reaction at 900 MPa being 52% ee, 60% ee, and 44% ee, respectively.[116]



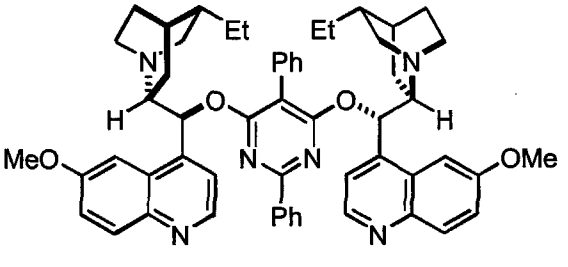
Scheme 36. Asymmetric conjugate addition of a thiol to an enone with polymeric cinchona alkaloid catalyst.

Wynberg extended this general concept to asymmetric phenylselenol additions to cyclohexanone. Several different selenols and cyclohexenones were subjected to nucleophilic catalysis; the best result obtained was that of p-methylphenylselenol to cyclohexenone. The corresponding selenoether was isolated in greater than 95% yield and 43% ee (Scheme 37). In a clever extension of the conjugate addition methodology, Wynberg noted that the selenium-containing products could be converted to the chiral allylic alcohols by diastereoselective borohydride reduction, followed by oxidation to the selenoxide and subsequent syn thermal elimination of the arylseleninic acid.[117]



Scheme 37. Preparation of enantioenriched allylic alcohols via arylselenol addition to enones.

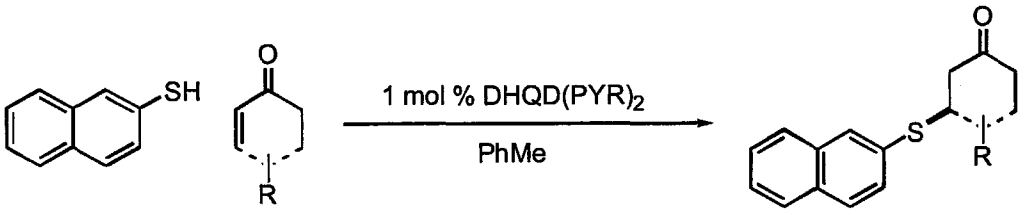
Deng and coworkers were able to optimize the catalytic thiol conjugate additions pioneered by Wynberg by making use of cinchona alkaloids utilized in the Sharpless asymmetric dihydroxylation reaction.[54] An ee of 53% was obtained in the addition of thiophenol to cyclohexanone with the ligand $(DHQD)_2PYR$ (Figure 18). Variation of the thiol structure revealed that 2-thionaphthol was obtained with the highest level of enantioinduction (77% ee at room temperature with 1 mole percent catalyst). Addition of 2-thionaphthol to a variety of cyclic enones proceeded in excellent levels of enantiocontrol (92 to 99% ee, Table 56). The one anomalous result was with cyclopentenone, in which case the corresponding conjugate adduct was isolated in a disappointing 41% ee.[118] Despite this particular outcome, these results represent to date the most enantioselective conjugate addition of thiols to cyclic enones.

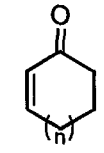
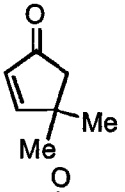
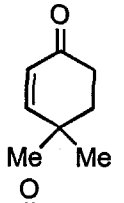
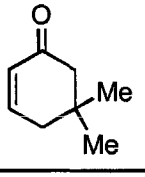


$DHQD(PYR)_2$

Figure 18. Organocatalyst employed by Deng and coworkers in asymmetric conjugate addition reactions.

Table 56. Catalytic asymmetric additions of 2-thionaphthol to enones under basic organocatalytic conditions.

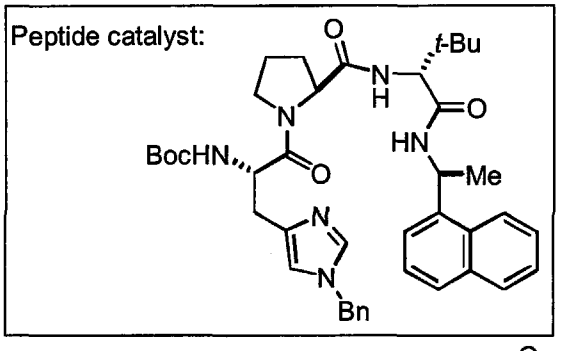


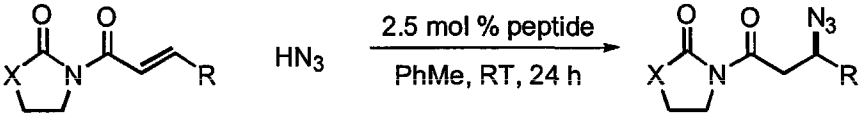
Entry	Substrate	n	Temp / °C	Time / h	Yield / %	ee / %
1		0	–60	23	55	41
2		1	–60	17	77	94
3		2	–60	20	86	97
4		3	–60	30	82	> 99
5		4	–60	48	91	97
6		–	–55	69	71	92
7[a]		–	–50	120	88	95
8		–	–60	64	88	93

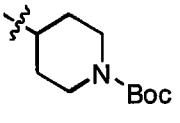
Miller and coworkers developed the peptide-based catalyst shown in Table 57 for organocatalytic asymmetric azide additions.[119] The conjugate addition of azides to several structurally distinct unsaturated imides proceeded in 79 – 91% yield and 45 – 85% ee.[120] In these reactions, hydrazoic acid was generated in low equilibrium concentrations by the reaction of trimethylsilyl azide with acetic acid; catalyst loadings were low (2.5 mole percent). Several different catalyst architectures were also examined, and even minute changes in the conformation of the β-turn of the catalyst had dramatic effects on the enantioselectivity, resulting in the extreme in the isolation of racemic

product, and even complete turnover in the stereoselectivity. Slight improvements in selectivity were observed upon utilizing the second-generation catalyst containing a β-substituted histidine residue, prepared through standard oxazolidinone chemistry. Adding a methyl group to the histidine residue gave the best enantioselectivity in the addition of azide to similar imides; improvements were observed in all cases, although additional cooling of the reaction was required to obtain optimal increases.[121]

Table 57. Scope of Miller's peptide-catalyzed asymmetric azidation reaction.

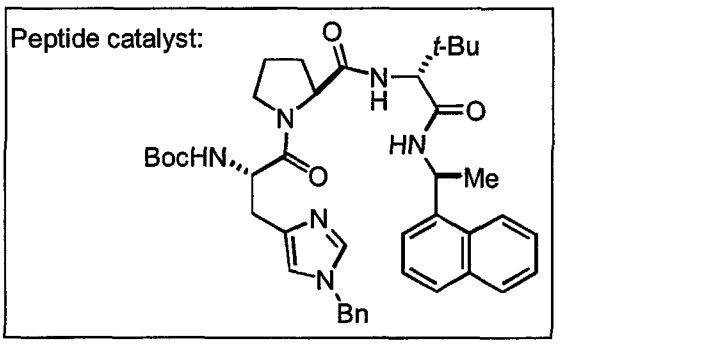


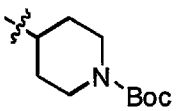


Entry	R	X	Yield / %	ee / %
1	Me	CH_2	97	63
2	*c*-C_6H_{11}	CH_2	79	85
3	*i*-Pr	CH_2	84	82
4		CH_2	85	71
5	Et	CH_2	91	71
6	Me	O	85	45

Miller also demonstrated that the conjugate adduct of the propionate imide could be converted to the corresponding benzyl carbamate in 80% yield, by catalytic hydrogenation of the azide followed by acylation; the imide was then cleaved in refluxing methanol followed by addition of lithium hydroxide to afford the protected β-amino acid in 52% yield for two steps. Alternatively, the azide could be induced to undergo a [2 + 3] cycloaddition with endogenous or exogenous alkynes to afford enantiomerically enriched triazoles. Yields and enantioselectivities for a range of substrates were shown to be good to excellent (Table 58).[122]

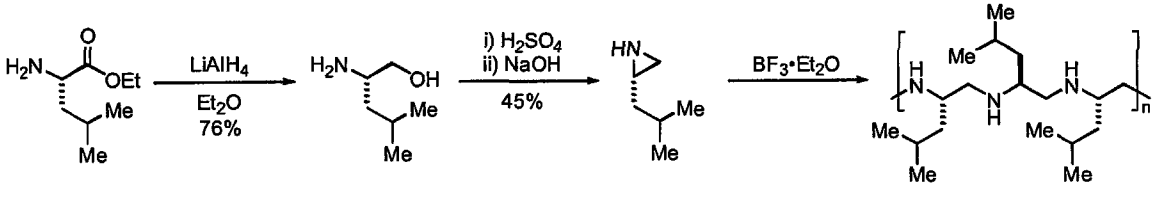
Table 58. Preparation of enantioenriched triazoles *via* asymmetric azidation reactions.



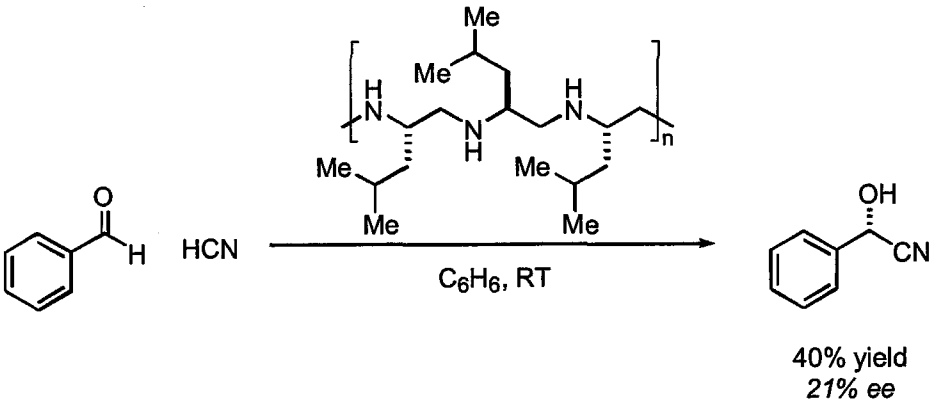
Entry	R	X	Yield / %	ee / %
1	Me	CH_2	97	63
2	*c*-C_6H_{11}	CH_2	79	85
3	*i*-Pr	CH_2	84	82
4		CH_2	85	71
5	Et	CH_2	91	71
6	Me	O	85	45

1.5.6 Asymmetric Carbonyl Hydrocyanations

The addition of a cyanide anion to a carbonyl compound to afford a cyanohydrin is one of the first organic reactions for which quantitative evidence for a reasonable mechanism was amassed. The pioneering studies of Lapworth at the turn of twentieth century demonstrated that this reaction is catalyzed by base and that the nucleophilic addition is reversible.[123] Given the reversibility of cyanide addition, and the dimerization of benzaldehyde under similar conditions in a benzoin condensation, development of an asymmetric carbonyl cyanation reaction has presented a formidable challenge to synthetic chemists. The first attempts at application of asymmetric catalysis to a cyanohydrin formation reaction were published in the early 1960s. Tsuboyama described the preparation of a poly-(*S*)-isobutylethylenimine from L-leucine as depicted in Scheme 38).[124] When 100 milligrams of the catalyst (molecular weight 4 – 6 kDa) were added to a solution of benzaldehyde and HCN in benzene and the mixture stirred for twenty hours at room temperature, benzaldehyde cyanohydrin was isolated in 40% yield and in 21% ee (Scheme 39). This result was unsurpassed by the use of other catalysts, such as those derived from sugars (14 – 84% yield, 1 – 7% ee), amino alcohols (leucinol, 7% yield, racemic), or cinchona alkaloids (quinine, 74% yield, 2% ee). Presumably, a significant portion of the starting material would be consumed in a benzoin condensation, although no evidence supporting this contention was provided.



Scheme 38. Preparation of Tsuboyama's polymeric catalyst for aldehyde hydrocyanation.



Scheme 39. Asymmetric hydrocyanation of benzaldehyde catalyzed by polymeric amine catalyst.

Neither cross-linking of the polymer chains with different isocyanates[125] nor substitution of the nitrogen on the catalyst chain yielded significant improvements in reaction efficiency or enantioselectivity.[126] A primitive model was advanced to explain the stereoselectivity in which the polymeric catalyst was postulated to have a more micelle-like quaternary structure, due to the nonpolar nature of the solvent (Figure 19). The amine moiety of the catalyst was envisioned to abstract a proton from HCN, inducing the benzaldehyde carbonyl to experience an electrostatic attraction with the ammonium salt thus generated. Blockage of one enantioface of the aldehyde was caused by a protruding isobutyl chain on the surface of the catalytic "micelle."[126]

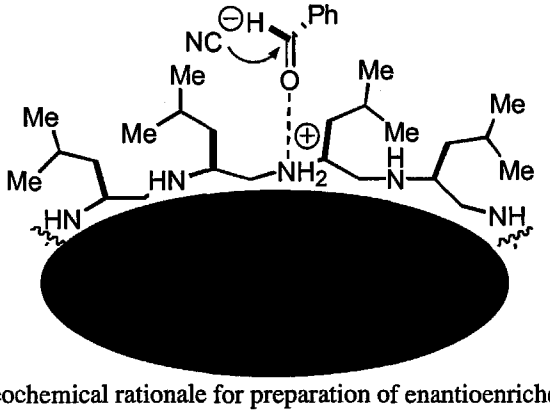
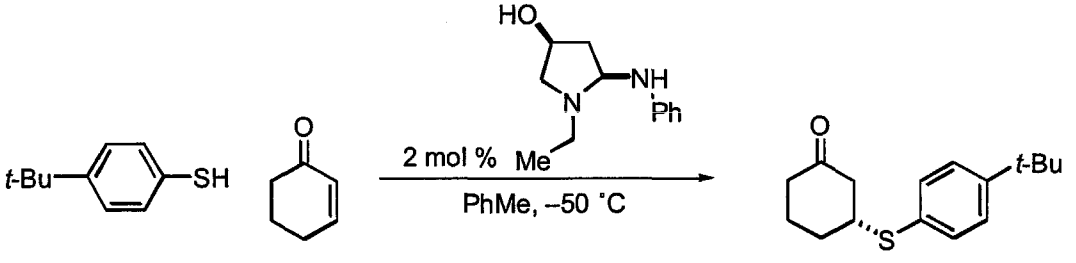


Figure 19. Preliminary stereochemical rationale for preparation of enantioenriched mandelonitrile as in Scheme 39. The shaded area represents the interior of the catalyst micelle.

In 1981, Inoue and coworkers reported the asymmetric hydrocyanation of benzaldehyde with a cyclic dipeptide catalyst. Exposure of equimolar amounts of benzaldehyde and hydrogen cyanide to two mole percent of *cyclo*–(L–phenylalanyl–L–histidine) in benzene at 35 °C afforded, after thirty minutes, mandelonitrile in 40% conversion and 90% ee (Scheme 40).[127] A dramatic erosion in the ee of the product was observed at extended reaction times (after 72 hours, the ee had dropped to 12%), implying that racemization was occurring as the reaction proceeded. Jackson reported several years later that the product could be isolated in enantiomerically pure form and in 83% yield by cooling the reaction to 4 °C. A study of different catalyst architectures confirmed that the phenylalanyl histidine catalyst afforded the optimal results.[128]



Scheme 40. Initial report by Inoue and coworkers of asymmetric hydrocyanation with dipeptide catalyst.

Several groups became engaged in an effort to describe the mechanistic origins of enantioselectivity in the hydrocyanation reaction. Inoue made the first reasonable proposal involving the following interactions in the transition state: (i) an attractive electrostatic interaction between the cyanide anion and protonated imidazole of the catalyst; (ii) a hydrogen bond between benzaldehyde and a proton on one of the amides

of the diketopiperazine scaffold; and (iii) steric shielding of the *re* face of benzaldehyde by the side chain of the catalyst phenylalanine residue (Figure 20).[129] Kinetic and spectroscopic evidence to support this proposal was lacking, however, providing an impetus for continued mechanistic investigations.

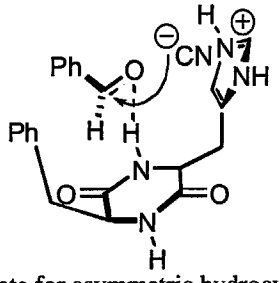


Figure 20. Inoue's proposed transition state for asymmetric hydrocyanation of benzaldehyde.

The observation was made that a high degree of crystallinity in the catalyst microstructure (obtained by rapid precipitation of the catalyst) was necessary to obtain the optimal enantioselectivities.[130] Preliminary computational studies provided evidence that the interaction between HCN and the catalyst imidazole was not ionic, but had more hydrogen bond character. The interaction between benzaldehyde and the pendant catalyst phenyl group was also stated to be an edge-face aromatic interaction rather than a face-face interaction.[131] North and coworkers proposed a radically different mechanism, involving formation of an aminol, followed by S_N2–type displacement of the aminol by cyanide anion to afford the mandelonitrile product (Figure 21). Clearly, the enantiospecificity would have to arise from either (i) completely diastereoselective aminol formation or (ii) nonselective thermodynamic aminol formation, followed by displacement of one diastereomeric aminol at a rate far exceeding that of the other diastereomer. While no direct evidence in support of this manifold was advanced, the

proposal was made by analogy to the oxidation of benzaldehyde to benzoic acid by the Inoue catalyst, as directly observed by North.[132] Solid state NMR experiments indicated that the catalyst existed in a folded conformation; however, this evidence was not sufficient to conclusively eliminate any mechanistic alternatives.[133]

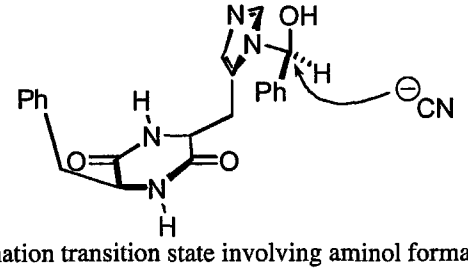


Figure 21. Alternate hydrocyanation transition state involving aminol formation, as proposed by North.

Other peculiarities were observed in regard to the reaction, dramatically complicating the mechanistic picture. These included the effect of stirring on the enantioselectivity,[130] as well as a pronounced nonlinear effect. The reaction displayed the characteristics of asymmetric autocatalysis, a subset of the phenomenon of nonlinear effects.[134] When catalyst of 2% ee was used in conjunction with 0.09 equivalents of mandelonitrile of high enantiomeric purity (92% ee), the product was isolated in 82% ee.[135] This observation, as well as the fact that in the crystal, the catalyst of 2% ee was observed to have a different structure than that of enantiomerically pure catalyst, provided the first evidence that the active catalytic species was more dimeric in nature.

In 1996, Shvo et al. confirmed this suspicion by kinetic experiments that resulted in determination of second-order dependence of catalyst on the reaction rate.[136] In theory, the origin of the second-order dependence might be from cooperative catalyst activation in a "push-pull" type interaction. One imidazole might hydrogen bond to benzaldehyde, activating it towards nucleophilic attack, while an imidazole on another catalyst molecule

could deprotonate HCN, resulting in formation of the nucleophilic cyanide anion. Presumably, the asymmetric environment would be created by the interaction of the two catalyst molecules, by some form of hydrogen bonding. Ultimately, it is clear that the ill-defined nature of the solid state of the catalyst has hampered the determination of a convincing mechanistic description of this intriguing reaction.

Very recently, Deng and coworkers have described the catalytic asymmetric cyanation of ketones with cinchona alkaloid catalysts.[137] The catalytic cycle proposed for this reaction is somewhat unusual and deserving of comment (Figure 22). The cyanide necessary in this reaction was not generated by deprotonation of HCN, but rather from the acylation of the cinchona alkaloid by ethyl cyanoacetate. This chiral ion pair was then believed to interact with the substrate ketone, with formation of the cyanoalkoxide followed by transacylation to regenerate the amine catalyst and release of the carbonate derivative of the cyanohydrin. This process is notable in that it is not necessary to directly handle dangerous and toxic forms of hydrogen cyanide.

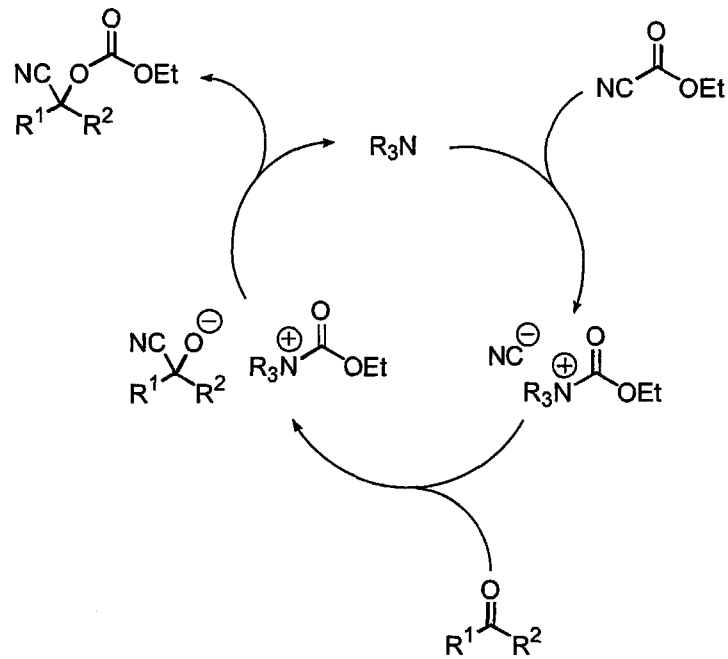


Figure 22. Catalytic cycle for ketone hydrocyanation as described by Deng.

Using the dimeric cinchona alkaloid catalysts shown in Figure 23, a range of cyclic and acyclic aliphatic ketones were converted to the corresponding cyanohydrins in moderate to excellent yields (52 – 99% ee), and, with few exceptions (two examples with ee < 60%), the enantioselectivities were high to excellent (81 – 97% ee, Table 59). With certain substrates, erosion in the enantioselectivity was observed as the reaction progressed; this phenomenon was ascribed to the possibility of the reaction actually being a dynamic kinetic resolution. This explanation would require (i) reversible cyanide addition to ketone, a reasonable mechanistic hypothesis, along with (ii) the rate of E_{1cb}-like explusion of cyanide (racemization) being faster than esterification of the cyanoalkoxy anion (conversion to product).

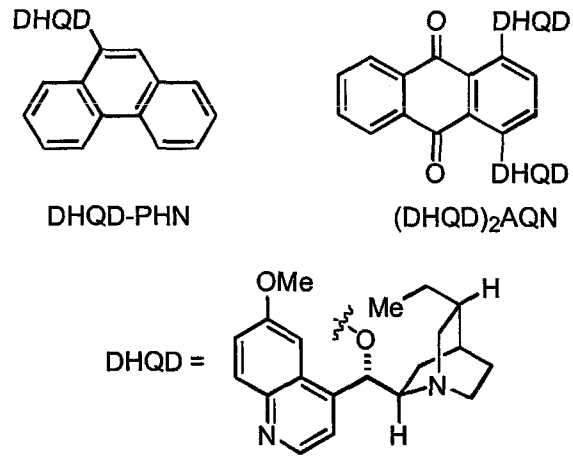
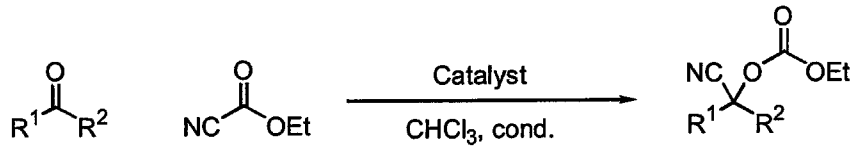
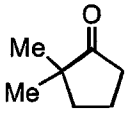
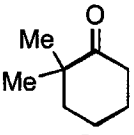
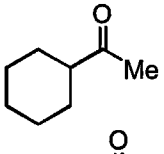
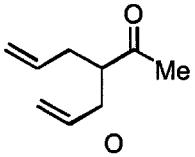
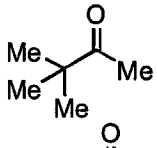
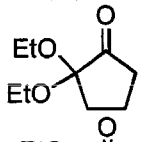
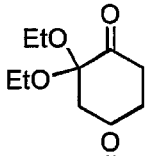
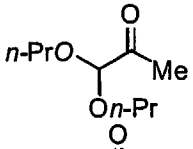
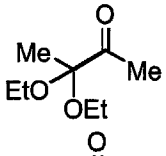
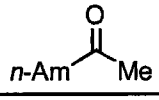


Figure 23. Ligands employed by Deng in his ketone hydrocyanation methodology.

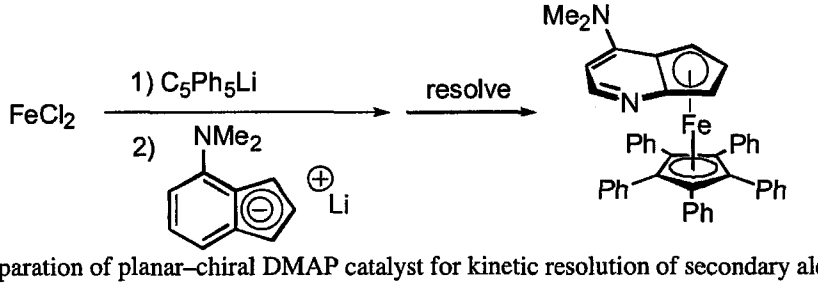
Table 59. Scope of catalytic asymmetric cyanocarbonate reaction with ketones and ethyl cyanoformate.



Entry	Substrate	Catalyst	Loading / mol %	Temp / °C	Time / d	Yield / %	ee / %
1		$(DHQD)_2AQN$	15	–24	2	66	97
2		$(DHQD)_2AQN$	20	–24	4	91	62
3		$(DHQ)_2AQN$	20	–24	2	52	87
4		$(DHQ)_2AQN$	20	–24	2	54	81
5		$(DHQD)_2AQN$	30	–24	5	55	88
6		DHQD-PHN	10	–24	7	99	94
7		DHQD-PHN	35	–12	5	78	96
8		DHQD-PHN	30	–24	4	86	96
9		DHQD-PHN	35	–12	4	65	90
10		$(DHQD)_2AQN$	20	–24	0.5	54	59

1.5.7 Kinetic Resolution of Secondary Alcohols

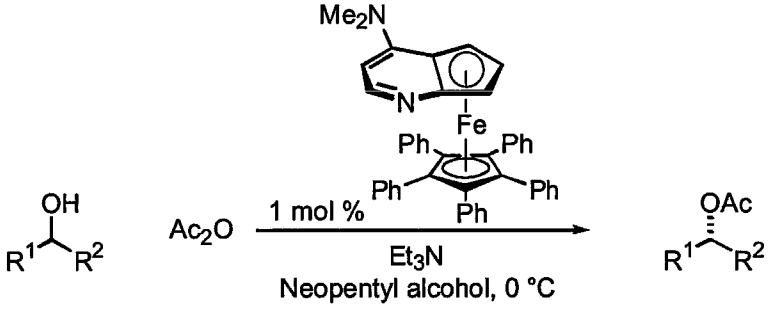
The hydroxyl group is ubiquitous in natural products and simple organic feedstocks, and as such there has been a great deal of interest in developing methods to obtain enantiomerically enriched alcohols. Recently, methodology has emerged from the laboratories of Stoltz[138] and Sigman,[139] involving a palladium(II) sparteine-catalyzed kinetic resolution. However, resolutions using purely organic amines also have been adapted for this purpose. Fu and coworkers carried out the initial work in this field as part of their research program devoted to the development of planar-chiral DMAP analogs for nucleophilic catalysis.[140] The paradigm followed by Fu in the design of his planar-chiral DMAP was to effect structural changes to the presumptive catalyst in order to be able to distinguish spatially the area "above" the endocyclic nitrogen from "below," while simultaneously doing the same between the areas to the "left" and "right." The optimal catalyst system was determined to be the ferrocenyl DMAP molecule shown in Scheme 41, the enantiomers of which were separated *via* chiral HPLC. Although these structures contain an iron atom as part of the ferrocenyl scaffold, the chemistry is done entirely by the nitrogen of the DMAP ring, and thus the active portion of the catalyst is purely organic in nature.[141]



Scheme 41. Preparation of planar–chiral DMAP catalyst for kinetic resolution of secondary alcohols.

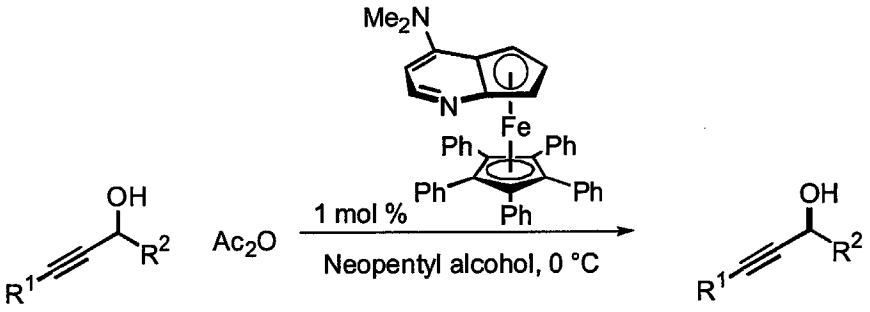
A wide variety of secondary aryl-alkyl alcohols was separated with 1 mole percent of the catalyst at 0 °C in neopentyl alcohol. Important building blocks, such as *sec*-phenethylalcohol, were obtained in outstanding enantioselectivities (95 – 99% ee) and essentially quantitative conversions (~ 50% in all cases, Table 60). This methodology was also extended to the resolution of secondary propargylic alcohols; again, excellent conversions and enantioselectivities were observed (Table 61).[142] The outstanding work of Fu in this field is noteworthy not only for the excellent results obtained in resolution reactions, but also as one of the few examples to date in asymmetric catalytic methodology in which truly *de novo* rational catalyst design was accomplished.

Table 60. Scope of Fu's alcohol kinetic resolution protocol using planar–chiral DMAP derivatives. In the table, s = selectivity factor.



Entry	R^1	R^2	Conv. / %	ee / %	s
1	Ph	Me	55	99	43
2	Ph	Et	54	99	59
3	Ph	*i*-Pr	52	97	87
4	Ph	*t*-Bu	52	96	95
5	Ph	CH_2Cl	56	98	32
6	C_6H_4Me-2	Me	53	99	71
7	1-Naph	Me	52	95	65
8	$C_6H_3Me_2$-2,6	*t*-Bu	51	99	> 200

Table 61. Extension of Fu's resolution methodology to encompass propargylic alcohols.

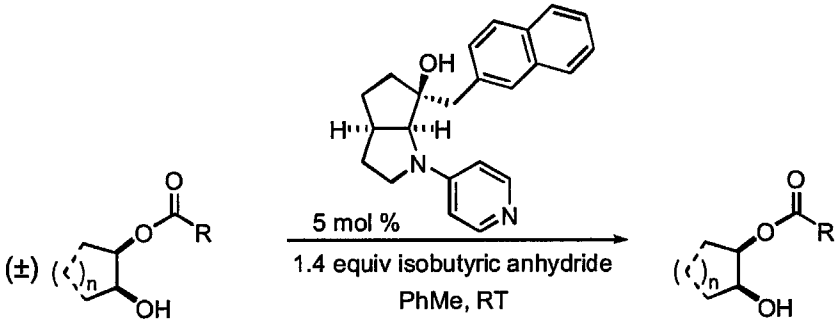


Entry	R^1	R^2	Conv. / %	ee / %	*s*
1	Ph	Me	58	96	20
2	Ph	Et	58	94	18
3	Ph	*i*-Pr	63	93	11
4	Ph	*t*-Bu	86	95	3.8
5	C_6H_4OMe-4	Me	60	94	14
6	$C_6H_4CF_3$-4	Me	71	99	10
7	C_6H_4F-4	Me	65	97	13
8	C(O)Me	Me	64	95	12
9	C≡C*n*-Bu	Me	66	95	10
10	isopropenyl	Et	69	94	7.9

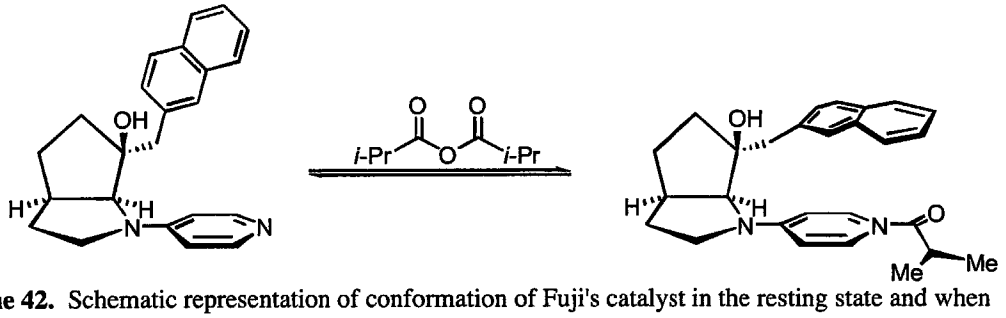
A range of other approaches to the alcohol resolution problem followed shortly thereafter. Fuji and coworkers developed a nucleophilic catalyst with the structure shown in Table 62, featuring a 4-pyrrolidinopyridine moiety. The primary observations that were taken into account during the design of the catalyst were that (i) previous investigations had shown that the 4-pyrrolidinopyridine molecule was one of the most active acylating agents known,[143] and (ii) the results of Vedejs in a stoichiometric alcohol resolution had indicated that placing the chirality too close to the acylation site precluded catalytic activity.[140] Several kinds of *syn* cyclohexanolamines were resolved with 54 – >99% ee and recovered in 19 – 27% yield. The proposed mode of action of the catalyst

is quite interesting; in the resting (non-acylated) state, the catalyst was thought to have the conformation **A** shown in Scheme 42. When acylated, the catalyst was theorized to exist in the conformation **B**. The napthyl ring "snaps shut" to block the *si* face of the acyl ammonium ion from nucleophilic attack. This conformational change was thought to be induced by a stabilizing cation-π interaction between the naphthyl and acylated pyridyl ring. This proposal was supported by a series of NOE experiments.

Table 62. Scope of protected diol desymmetrization as reported by Fuji.

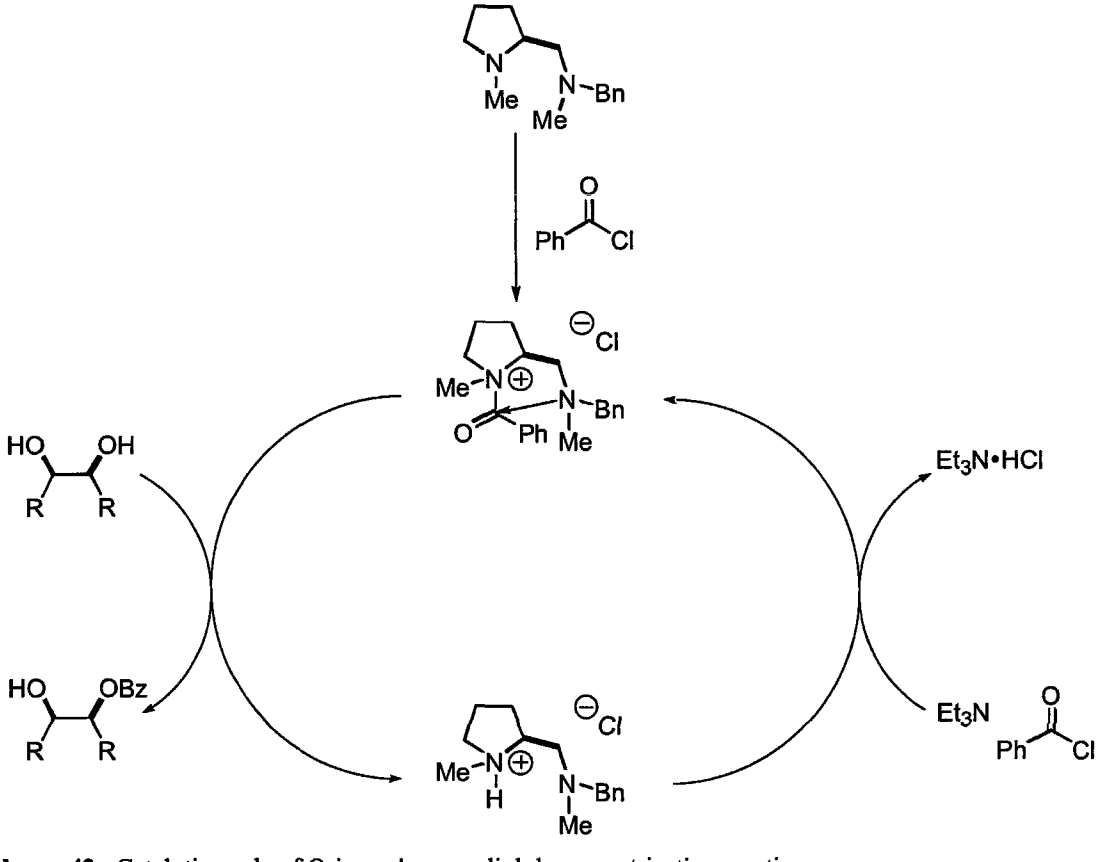


Entry	R	n	Time / h	Conv / %	ee / %	*s*
1	*i*-Pr	2	5	69	76	4.3
2	*t*-Bu	2	4	68	94	8.3
3	$C_6H_4NO_2$-4	2	5	73	54	2.4
4	Ph	2	5	71	81	4.5
5	C_6H_4OMe-4	2	2	70	85	5.3
6	$C_6H_4NMe_2$-4	2	3	72	> 99	> 10.1
7	$C_6H_4NMe_2$-4	1	4	71	94	8.3
8	$C_6H_4NMe_2$-4	3	4	70	92	6.5
9	$C_6H_4NMe_2$-4	4	5	73	92	5.8
10	$C_6H_4NMe_2$-4	0	4	77	92	4.7



Scheme 42. Schematic representation of conformation of Fuji's catalyst in the resting state and when acylated.

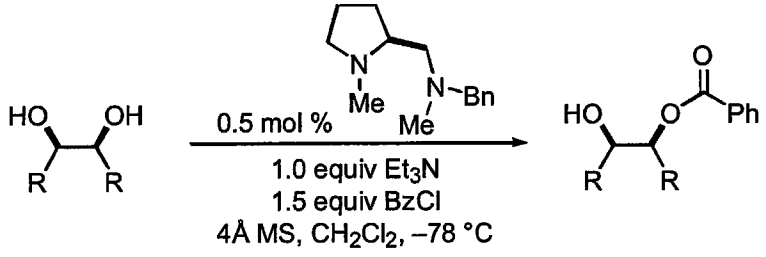
Oriyama and coworkers highlighted the use of the proline-derived catalyst shown in Scheme 43 for the desymmetrization of *meso*-diols. The authors propose the acylation of the catalyst by the endocyclic nitrogen with concomitant stabilization by the pendant tertiary amine, followed by acyl transfer and subsequent desymmetrization of the appropriate diol. An exogenous base was necessary to scavenge the HCl generated during the course of catalyst addition.[144] A first-generation proline-derived compound was reported where the exocyclic amine was part of an isoindoline functionality; however, this molecule was only able to effect efficient resolution in stoichiometric quantities.[145]



Scheme 43. Catalytic cycle of Oriyama's *meso* diol desymmetrization reaction.

A range of *meso*-diols were desymmetrized in good yields (73 – 89%) and moderate to good enantioselectivities (66 – 97% ee, Table 63). Diacylation was, for the most part, minimzed (1 – 3% in a few cases). Later reports demonstrated the capacity of the first generation isoindoline catalyst to effect resolution of chiral secondary alcohols. Conversions were good and enantioselectivities were moderate to good; however, it is notable that the catalyst failed to efficiently resolve acyclic secondary alcohols.[146]

Table 63. Scope of alcohol desymmetrization reaction developed by Oriyama and coworkers.



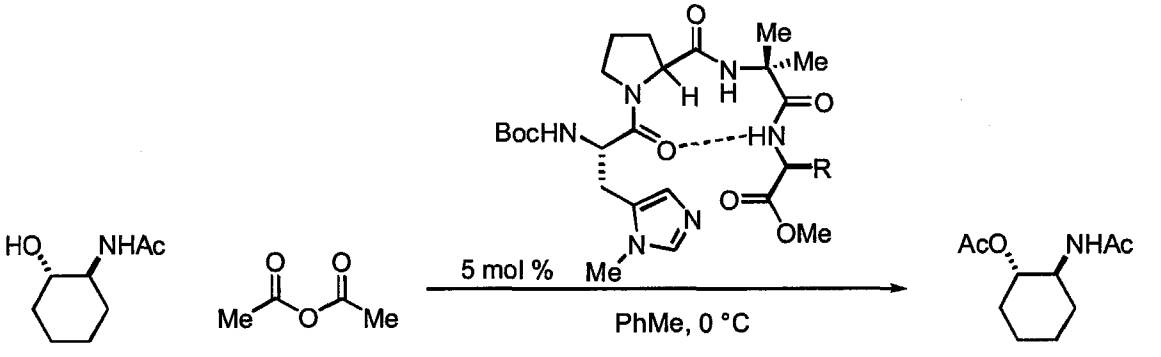
Entry	R	Time / h	Yield / %	ee / %
1	$(CH_2)_4$	3	83	96
2	$CH_2CH{=}CHCH_2$	24	81	90
3	Tetralinyl	3	89	66
4	Ph	24	80	60
5	Me	3	85	94
6	CH_2OBn	24	73	82

At roughly the same time, Miller reported the preparation and use of polypeptides for kinetic resolution of cyclic amino alcohols. The first generation catalyst was a tetrapeptide composed of a protected histidine, proline, dimethylglycine, and α-methylbenzylamine. Presumably, on exposure to acetic anhydride, the *N*-methylimidazole portion of the catalyst is acylated and then resolution occurs *via* selective transfer of the acyl group.[147] Competition experiments confirmed that the *N*-methylimidazole moiety was necessary for acylation to take place, and that the catalyst,

unlike *N*-methylimidazole itself, was capable of distinguishing between structurally different alcohols. Racemic *trans*-*N*-acetyl-1,2-hydroxycyclohexylamine was resolved with good enantioselectivity (up to 84% ee).

Second generation catalysts were developed with a phenylalanine residue replacing the α-methylbenzylamine fragment (Scheme 44). Not only was it established that this catalyst was a much more efficient resolving agent (nonacylated alcohol recovered in up to 99% ee), but intriguingly, the stereochemistry of the β-turn of the peptide proved to be the dominant stereocontrolling functionality (Figure 24).[148] The peptide containing the L-proline residue gave slightly lower selectivities, and opposite enantioselectivities, than the catalyst containing the D-proline residue. This effect was explained by examination of the conformation of the respective catalysts, as theorized based on NOE experiments. The catalyst containing the L-proline residue was thought to assume the conformation shown, with the hydrogen bond between the histidine and phenylalanine residue causing the peptide to adopt a cyclic form in solution. Moreover, the *N*-methylimidazole fragment was thought to exist "above" the proline ring, due to minimization of allylic strain about the proline-histidine amide bond that causes the α-proton of the histidine residue to be coplanar with the proximal C – N bond of the proline pyrrolidine ring. The catalyst containing the unnatural proline residue had an additional hydrogen bond interaction between the phenylalanine methyl ester carbonyl and the hydrogen adjacent to the Boc group on the protected histidine residue. This additional stabilization was observed to have a dramatic effect on the conformation of the catalyst; the molecule containing only one hydrogen bond was believed to exist as a 4 : 1 mixture of conformers, whereas the other catalyst existed as one conformer. The orientation of

the histidine side chain in the more rigid catalyst was also controlled by allylic strain; in the catalyst incorporating D-proline, the *N*-methylimidazole was located much closer to the scaffold of the peptide, perhaps explaining the higher and more general selectivities observed in alcohol resolutions with this catalyst. Other catalysts were also developed with more peptide units;[149] ultimately, an octapeptide structure that proved to be somewhat general for alcohol resolutions was identified by combinatorial methods.[150]



Scheme 44. Kinetic resolution of cyclic 1,2–acetamido alcohols under polypeptide catalysis.

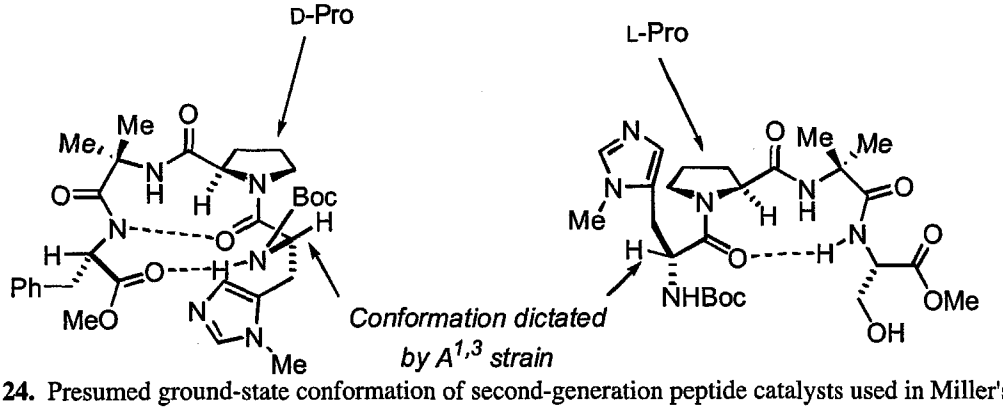
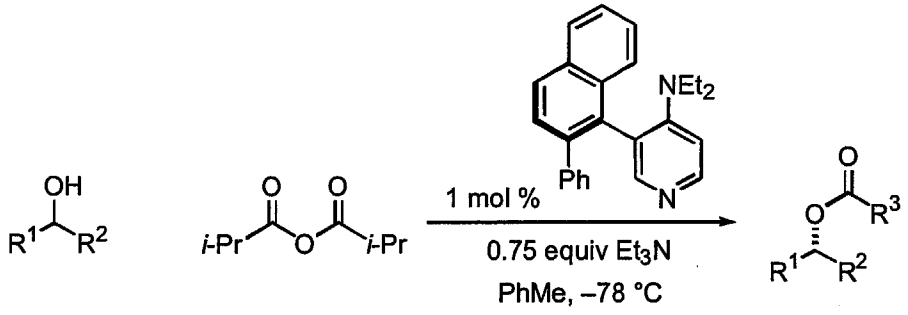


Figure 24. Presumed ground-state conformation of second-generation peptide catalysts used in Miller's acetamido alcohol resolution.

Finally, attempts were made to take advantage of potential axial chirality with DMAP analogs. Spivey and coworkers demonstrated that the catalysts of the type shown in Table 64, prepared by palladium-catalyzed aryl-aryl bond formation, followed by

classical resolution, would effect kinetic resolution of several aryl-alkyl secondardy alcohols.[151] The carbonates derived from the *R* alcohol were isolated in moderate conversions and enantioselectivities (64 – 91% ee).

Table 64. Scope of Spivey's secondary alcohol resolution reaction using axially chiral DMAP–based catalysts.

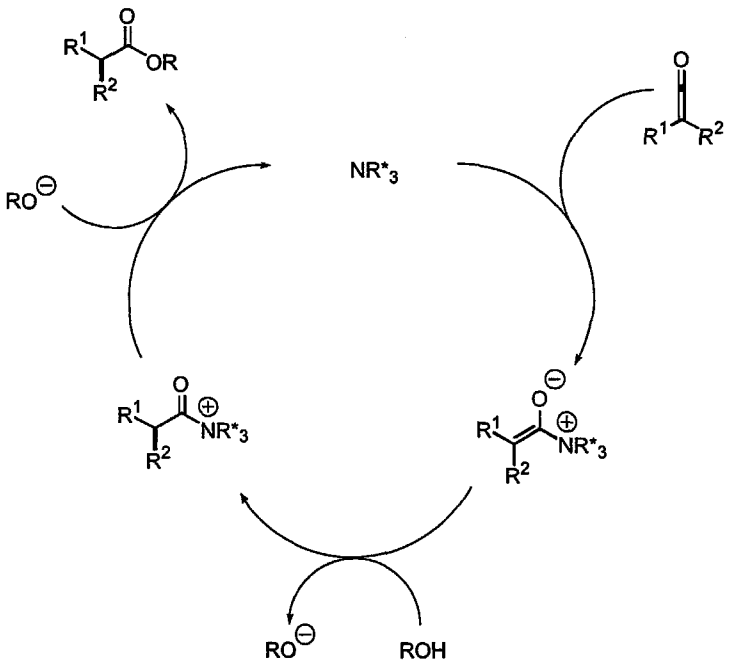


Entry	R^1	R^2	Time / h	Conv / %	ee / %	*s*
1	1-Naph	Me	9.0	45	84	24.0
2	Ph	Me	7.6	39	78	13.0
3	Ph	Et	9.7	35	79	13.0
4	Ph	*i*-Pr	10.1	29	73	8.4
5	Ph	*t*-Bu	10.5	18	89	20.0
6	C_6H_4Me-2	Me	9.5	41	86	25.0
7	C_6H_4OMe-2	Me	12.1	33	82	15.0
8	$C_6H_4Me_2$-2,6	Me	8.0	19	91	25.0

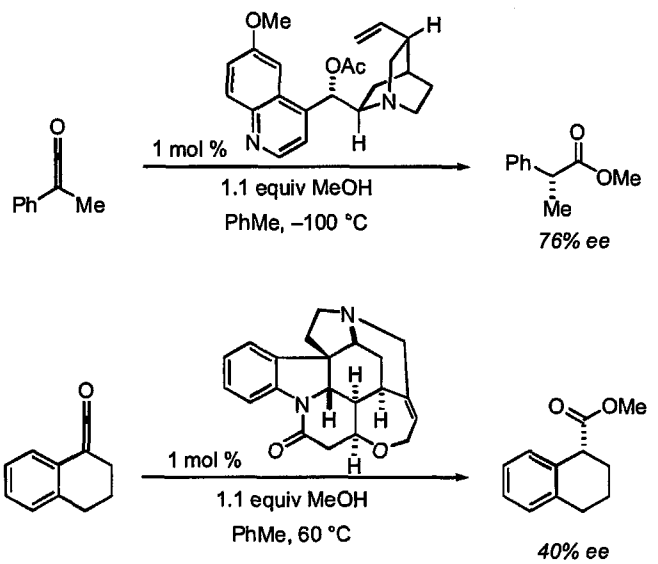
1.5.8 Ketene Alcoholysis

Among the first asymmetric organocatalytic reactions reported was the methanolytic cleavage of ketenes, first reported by Pracejus in 1960. A putative mechanism for this reaction is detailed in Scheme 45; the stereodetermining step in this reaction amounts to an asymmetric enolate protonation.[152] Under these conditions, phenylmethyl ketene and phenyl-α-*o*-trimethyleneketene underwent methanolysis in 76%

ee and 40% ee, respectively (Scheme 46).[153] An analog of the planar-chiral DMAP later used by Fu for alcohol resolution (section V. G.) also catalyzed this reaction; a much wider range of substrates were observed to undergo alcoholytic cleavage in excellent yields (80 – 97%) and good enantioselectivities (74 – 80% ee, Table 65).[141]

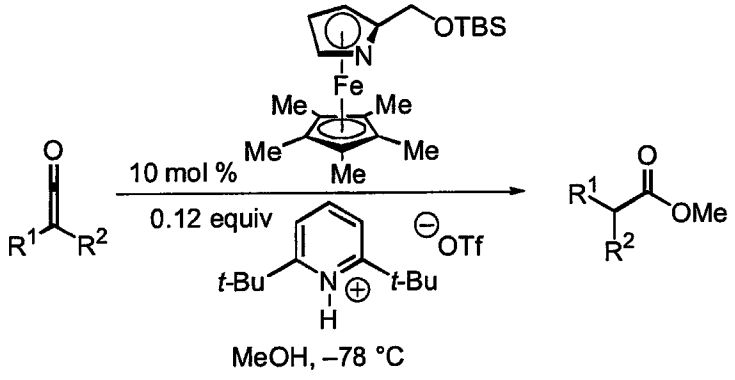


Scheme 45. Catalytic cycle for asymmetric alcoholytic cleavage of ketenes catalyzed by chiral tertiary amines.



Scheme 46. Initial reports of ketene methanolysis under nucleophilic catalysis according to Pracejus.

Table 65. Scope of Fu's ketene methanolysis methodology featuring a planar–chiral nucleophilic catalyst.



Entry	R^1	R^2	Yield / %	ee / %
1	C_6H_5	Me	77	87
2	C_6H_4*t*-Bu-4	Me	77	88
3	C_8H_6OMe-4	Me	75	80
4	C_6H_4OPh-2	Me	74	96
5	C_6H_5	Et	68	92
6	PTMK[a]		80	97

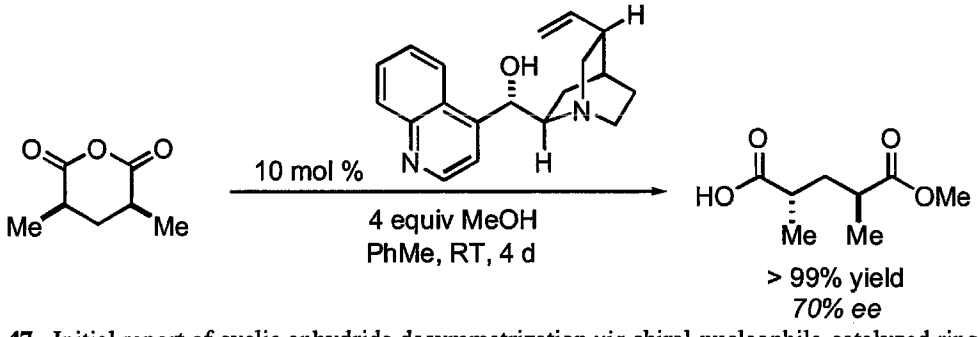
[a]PTMK = phenyl-α-*o*-trimethyleneketene.

1.5.9 Kinetic Resolutions of Carboxylic Acid Derivatives

The desymmetrization of cyclic anhydrides by ring opening represented one of the earliest targets for development of organocatalytic resolution technology, due to the well-known propensity of enzymes to catalyze ring opening of *meso*-anhydrides in an enantioselective fashion. Enzymatic resolutions suffer from the disadvantages of high cost of the enzymes and the fact that for a given enzyme, only certain molecules with very specific functionalities undergo efficient resolution. Alternative means of anhydride resolution therefore have received increased attention.

Oda carried out the pioneering work in this field. It was demonstrated that cinchona alkaloids in 10 mole percent loading, with methanol in either toluene or ether,

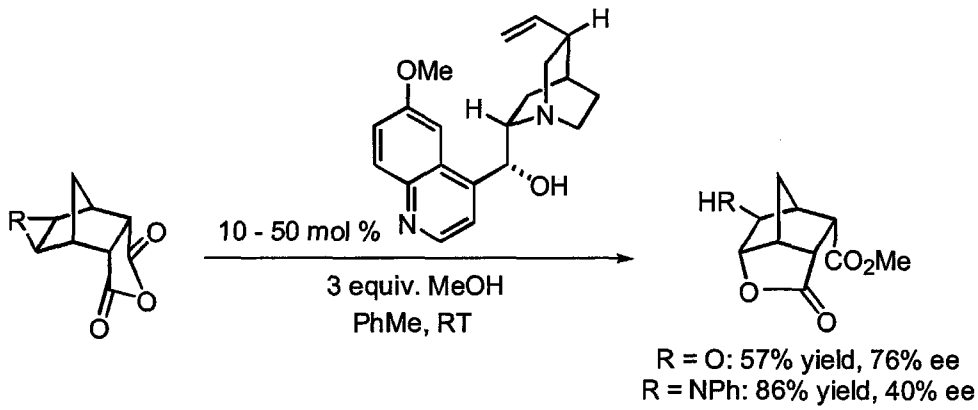
catalyzed the ring opening of *meso* anhydrides with moderate enantioselectivity (24 – 70% ee, Scheme 47).[154] In some preliminiary mechanistic experiments, a primary kinetic deuterium isotope effect of magnitude 2.3 was measured. This number is on the order of that measured for hydrolysis of acetic anhydride at elevated pH, providing evidence that this reaction procedes *via* general base catalysis. In another experiment, quinuclidine and quinoline were separately subjected to the reaction conditions and only quinuclidine catalyzed the ring-opening reaction efficiently. This result suggested that it was the bridgehead nitrogen atom of the alkaloid, and not the quinoline nitrogen, that was the site of deprotonation. Several other symmetric substrates were also ring opened under similar conditions. The optimal catalyst was highly substrate dependent, with some catalysts giving moderate enantioselectivities for one substrate, but not for any others.[155]



Scheme 47. Initial report of cyclic anhydride desymmetrization *via* chiral-nucleophile-catalyzed ring opening reaction.

Aitken examined the ring opening of epoxyanhydrides under conditions analogous to those used by Oda. Quinine proved to be the optimal catalyst for most substrates, giving selectivities from 33 – 76% ee, although the products could be recrystallized to virtual enantiopurity (Scheme 48). The product that was isolated was not the free dicarbonyl, but rather the product resulting from attack of the carboxylate on

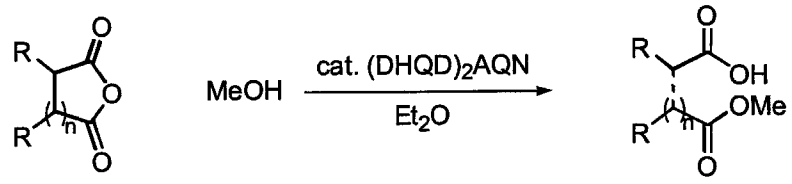
the distal epoxide or aziridine ring. The enantioselectivities proved to be highly dependent on the alcohol used for hydrolysis, with methanol giving the best overall results.[156] The norbornene (i.e. not epoxidized) analogs of these substrates were also observed to undergo ring opening in moderate enantioselectivities (35 – 67% ee).[157]

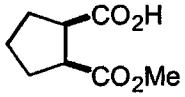
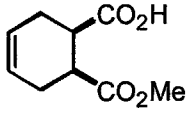
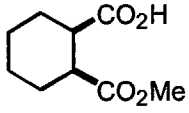
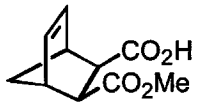
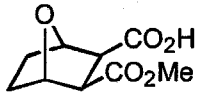
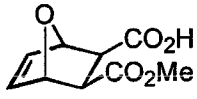
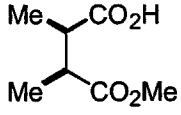
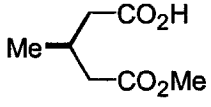
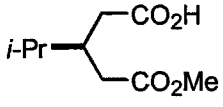


Scheme 48. *Aitken's ring opening of norbornene-derived polytcyclic anhydrides under nucleophilic* catalysis.

The optimization of this reaction to afford products in high ee was carried out by Deng, who took advantage of the new cinchona alkaloid-derived ligands first used in the Sharpless asymmetric dihydroxylation reaction. The ligand $(DHQD)_2AQN$ was found to be the most general catalyst. When present in 5 – 30 mole percent loading with excess methanol in ether at subambient temperatures, the corresponding monoacids were isolated in 70 – 99% yield and 90 – 98% ee (Table 66).[158]

Table 66. Deng's cyclic anhydride ring opening/desymmetrization methodology.

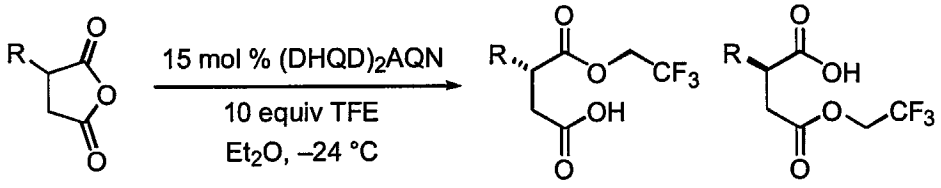


Entry	Product	Cat. Loading / mol %	Temp / °C	Yield / %	ee / %
1		8	–30	99	95
2		7	–20	95	98
3		5	–20	97	97
4		10	–30	82	95
5		15	–20	88	96
6		20	–20	74	92
7		5	–20	93	98
8		30	–40	70	91
9		30	–40	72	90

Deng and coworkers extended their initial work on anhydride hydrolysis to encompass a variety of other reactions. The same cinchona-derived alkaloid catalyst was employed with great efficiency in a parallel kinetic resolution of racemic monosubstituted anhydrides. Using ether as solvent with trifluoroethanol as the

hydrolytic agent and 15 – 20 mole percent $(DHQD)_2AQN$, several alkyl-substituted substrates were converted to the corresponding monoesters in excellent enantioselectivities, although the degree of enantioselection varied (91 – 98% ee for the *S* enantiomer, Table 67).[159] Aryl substrates were also resolved in a highly stereoselective fashion (Entries 5 – 7).

Table 67. Kinetic resolution of monosubstituted cyclic anhydrides catalyzed by a chiral nucleophile.



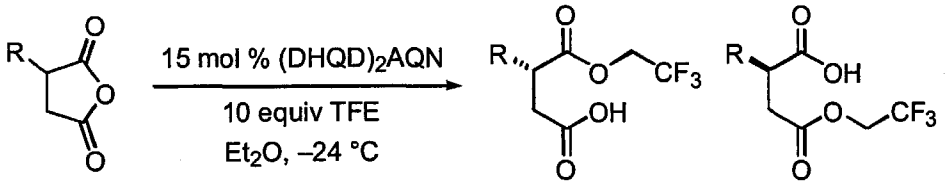
A **B**

Entry	R	**A** Yield / %	**A** ee / %	**B** Yield / %	**B** ee / %
1	Me	36	93	41	80
2	Et	38	91	50	70
3	*n*-C_8H_{17}	38	98	41	66
4	Allyl	40	96	49	82
5	Ph	44	95	32	87
6	C_6H_4OMe-3	45	96	30	83
7	C_6H_4Cl-4	44	96	29	76

This parallel kinetic resolution/ring opening strategy was also applied to the preparation of α-hydroxy carboxylic acids, molecules of great synthetic import. The racemic substrate was protected as the corresponding 1,3-dioxolane-2,4-dione by exposure of the hydroxy acid to diphosgene and activated charcoal in THF. In this case, the ligand also served as base; a racemization step was thought to occur, due to the relatively high acidity of the proton adjacent to the lactone functionality. Aryl-substituted acids with both electron donating and electron withdrawing substituents were isolated in moderate to good yields (61 – 85%, Table 68) and mostly excellent

enantioselectivities (91 – 96% ee, except for Entries 9 and 10).[160] The examples of low enantioselectivity resulted from the low acidity of the α-proton of these substrates and concomitant resistance to epimerization, caused by unfavorable nonbonded interactions derived from allylic strain in the enolate. The decreased acidity of the α-protons of alkyl-subsituted racemates rendered the resolution of these molecules non-dynamic; however, the enantioselectivity of the isomers thus isolated was still excellent.

Table 68. Preparation of α-hydroxy acids *via* chiral-nucleophile-catalyzed parallel kinetic resolution.



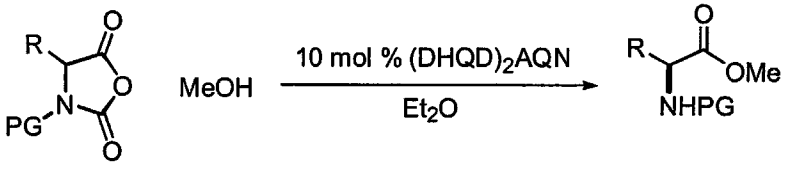
A **B**

Entry	R	**A** Yield / %	**A** ee / %	**B** Yield / %	**B** ee / %
1	Me	36	93	41	80
2	Et	38	91	50	70
3	*n*-C_8H_{17}	38	98	41	66
4	Allyl	40	96	49	82
5	Ph	44	95	32	87
6	C_6H_4OMe-3	45	96	30	83
7	C_6H_4Cl-4	44	96	29	76

Finally, Deng and coworkers further demonstrated the utility of the cinchona-alkaloid catalyzed resolution process by showing the ability to resolve α-amino acids *via* their urethane derivatives. Under virtually identical conditions, both alkyl- and aryl-substituted urethanes were obtained in excellent yields and enantioselectivities (Table 69). Unlike in previous uses of this methodology, both enantiomers were isolated in approximately the same level of enantiopurity in most cases.[161] Kinetic experiments

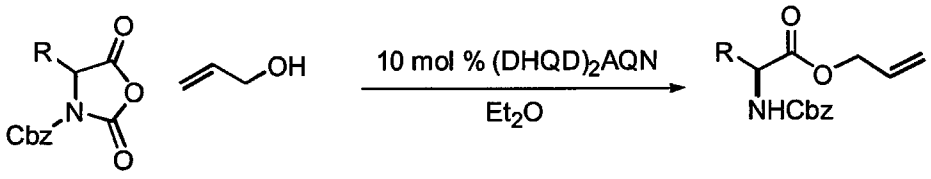
determined the reaction to be first-order in methanol, urethane, and catalyst, and a primary kinetic deuterium isotope effect of 1.3 was measured. Taken together, these observations strongly suggest that general basic catalysis is operative. By increasing the reaction temperature from subambient levels, the classical resolution was made dynamic. In the dynamic resolution, allyl alcohol was utilized as the hydrolytic agent instead, necessitating an additional step to cleave the allyl group (Table 70). Enantioselectivties remained excellent and little or no racemization was observed as a result of the basic conditions required for deallylation.[162]

Table 69. Deng's route to α-amino acid derivatives *via* kinetic resolution of urethane-protected amino acid *N*-carboxyanhydrides.



Entry	R	PG	Temp / °C	Time / h	**S** Yield / %	**S** ee / %	**R** Yield / %	**R** ee / %	*s*
1	Bn	Cbz	–60	17	48	98	48	93	114
2	$CH_2(C_6H_4F\text{-}4)$	Cbz	–78	31	42	93	48	92	79
3	$CH_2(C_6H_4Cl\text{-}4)$	Cbz	–60	18	43	97	52	88	59
4	$CH_2(C_6H_4Br\text{-}4)$	Cbz	–78	45	39	92	51	87	45
5	2-thienylmethyl	Cbz	–78	25	47	95	49	94	115
6	$(CH_2)_5CH_3$	Cbz	–60	37	47	95	49	94	78
7	CH_2OBn	Cbz	–78	72	44	96	49	89	69
8	*i*-Pr	Cbz	0	22	40	96	58	67	19
9	Ph	Cbz	–78	16	46	84	45	97	170
10	$C_6H_4OMe\text{-}4$	Cbz	–78	85	43	95	56	74	23
11	Bn	Fmoc	–78	46	47	96	50	92	93
12	CH_2CH_2Ph	Alloc	–60	36	41	96	53	81	35

Table 70. Dynamic kinetic resolution of UNCA compounds to afford protected amino acids.

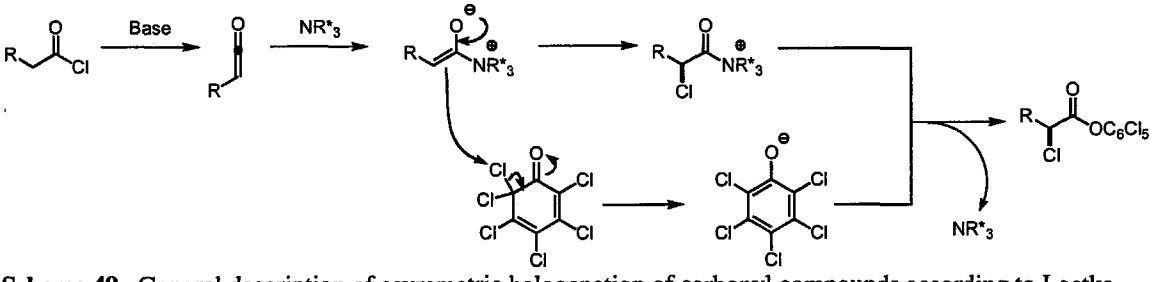


Entry	R	Temp / °C	Time / h	Yield / %	ee / %
1	Ph	23	1	97	91
2	C_6H_4F-4	23	1	96	90
3	C_6H_4Cl-4	23	1	97	92
4	$C_6H_4CF_3$-4	23	1	95	90
5	2-thiophenyl	–30	2	93	92
6	3-thiophenyl	23	1	95	91
7	2-furyl	23	0.5	98	91
8	2-(5-Me-furyl)	23	0.5	97	93
9	3-(1-Tosylindolyl)	0	1.5	95	90

1.5.10 Asymmetric Halogenation of Carbonyl Compounds

There exist very few methods for the enantioselective installation of halogen groups α to carbonyls. Moreover, the oxidizing powers and instability of most halogenation agents, as well as the increased acidity of the resulting α-halo carbonyl, present a formidable challenge to the development of an asymmetric catalytic version of this reaction. Lectka and coworkers recently published a successful application of the same general methodology used in their asymmetric organocatalytic β-lactam methodology (section V. D.). Conceptually, as with the lactam synthesis, an exogenous base would effect dehydrohalogenation to afford ketene *in situ*, which would then be activated by addition of a chiral nucleophile. Quenching of the enolate-like intermediate followed by hydrolytic cleavage of the carbon-nucleophile would afford the halogenated carbonyl compound, with concomitant regeneration of catalyst (Scheme 49).[163] Initial

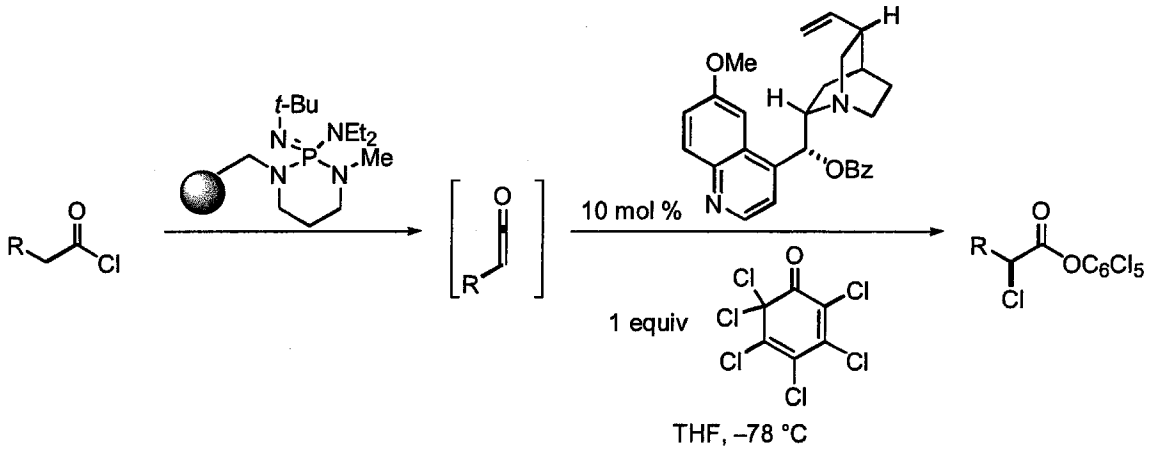
attempts to use *N*-halosuccinimides or alkyl hypochlorites as halogen sources failed. The molecule shown in Scheme 49 became a promising candidate for use as a chlorination agent, as it is both stable and commercially available. Attack of a nucleophile on one of the two *gem* chlorides afforded a highly stabilized enolate, which could then go on to cleave the acylammonium ion resulting from the halogenation event.



Scheme 49. General description of asymmetric halogenation of carbonyl compounds according to Lectka and coworkers.

In the same publication, a clever method was reported to circumvent the problem of exogenous bases in solution interacting unfavorably with the chlorination agent. The resin shown in Table 71 was previously reported to be capable of *in situ* ketene generation. The ketene was thus prepared by exposure of a THF solution of the desired acid chloride to the resin in an addition funnel, and then careful addition of the resulting solution to a pre-cooled (– 78 °C) solution of the catalyst and chlorination agent. This strategy proved to be highly successful; the chlorinated product derived from phenylacetyl chloride was obtained after quenching and column chromatography in 80% yield and 99% ee. A wide range of acid chlorides underwent chlorination with this protocol in moderate yield (51 – 80%) and good to excellent enantioselectivities (80 – 99% ee).

Table 71. Scope of asymmetric carbonyl halogenation reaction with *in situ* ketene generation.



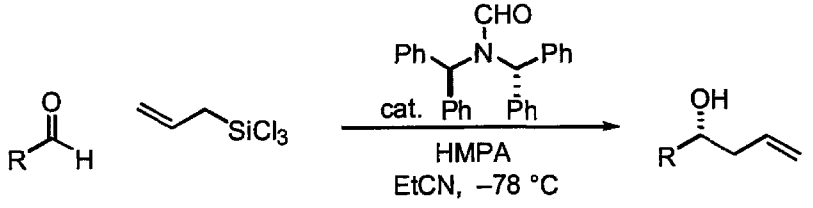
Entry	R	Yield / %	ee / %
1	Ph	80	99
2	CH_2OPh	57	97
3	1-Naphthyl	57	95
4	2-Naphthyl	63	94
5[a]	2-Thiophenyl	66	80
6	Br	51	97

1.5.11 Asymmetric Allylations

Catalytic asymmetric allylation reactions provide convenient access to enantiomerically enriched homoallylic alcohols. The work of Yamamoto[164] and Keck,[165] featuring chiral Lewis-acid-catalyzed allylations, and Denmark,[166] involving chiral phosphoramides, established the viability of catalytic asymmetric versions of this reaction. Several attempts have been made to induce catalysis in this reaction with chiral amines as catalytic nucleophiles. The first report of an asymmetric organocatalytic allylation reaction came from Iseki using the chiral formamide shown in Table 72. Derived from formylation of the corresponding commercially available dibenzylamine, the catalyst was found to allylate a range of alkyl and aryl aldehydes at 20 to 40 mole percent loading in propionitrile at -78 °C.[167] Yields were in most cases moderate (51 –

84% yield) and enantioselectivities moderate to excellent (68 – 98% ee). One notable exception was the allylation of benzaldehyde (Entry 9); the corresponding homoallylic alcohol was isolated in 94% yield and a disappointing 8% ee.

Table 72. Asymmetric allylation with chiral formamide catalyst.

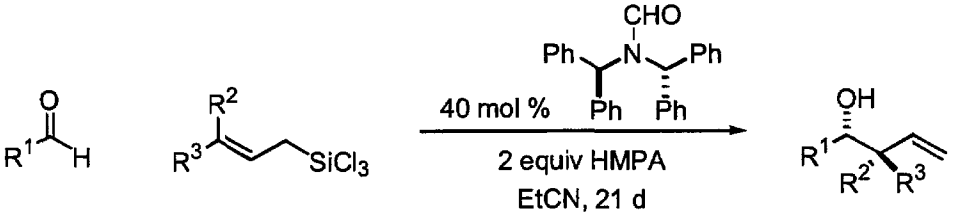


Entry	R	Cat. loading / mol %	HMPA / equiv.	Time / d	Yield / %	ee / %
1	*c*-C_5H_9	20	1.0	14	72	91
2	CH_2CH_2Ph	20	1.0	21	84	95
3	$CH(CH_2CH_3)_2$	20	1.0	21	74	93
4	*t*-Bu	40	2.0	28	61	98
5	$(CH_2)_5CH_3$	40	2.0	28	53	68
6	3-Butenyl	20	1.0	21	56	86
7	3-Butynyl	40	2.0	21	51	88
8	(*E*)-1-heptenyl	40	2.0	7	91	22
9	Ph	20	1.0	7	94	8

Several disadvantages to this methodology include the use of stoichiometric or superstoichiometric quantities of the highly toxic additive HMPA, as well as the extended reaction times required (no less than seven days, and as long as four weeks). Certain aldehydes could also be crotylated with variable yields (19 – 97%, Table 73) and in 94 – 98% ee (of the dominant diastereomer). The use of the (*E*)-crotylsilane afforded excellent levels of diastereocontrol (> 99 : 1 / *anti* : *syn*), with the (*Z*)-crotylsilane giving rise to products of significantly lower dr (3 : 2 / *anti* : *syn*). These Sakurai-type reactions are thought to proceed through the transition state shown, featuring a hypervalent silicon

in a closed, chair-like transition state. The conformation of the catalyst is as shown in Figure 25. The low diastereoselectivity obtained in the reaction of the *cis*-crotylsilane can be rationalized by unfavorable nonbonded interactions between the terminal methyl group of the silane (R^2 in Figure 25) and the HMPA coordinated to the silicon.[168]

Table 73. Asymmetric crotylation of aldehydes with Iseki's chiral formamide.



Entry	R^1	R^2	R^3	Temp / °C	Yield / %	*anti* : *syn*	*ee* / %
1	c-C_6H_{11}	H	Me	–20	34	1 : 19	3 (*syn*)
2	c-C_6H_{11}	H	Me	–78	92	> 99 : 1	98 (*anti*)
3	c-C_6H_{11}	Me	H	–78	19	3 : 2	98 (*anti*)
4	CH_2CH_2Ph	H	Me	–78	97	> 99 : 1	94 (*anti*)

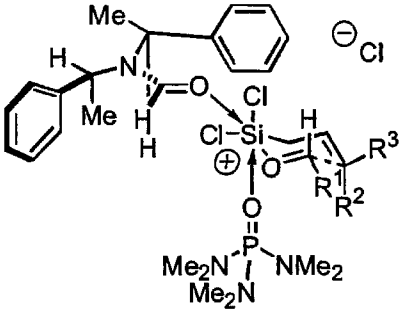


Figure 25. Transition state proposed by Iseki et al. to account for observed stereoselectivity in organocatalytic asymmetric allylation reactions.

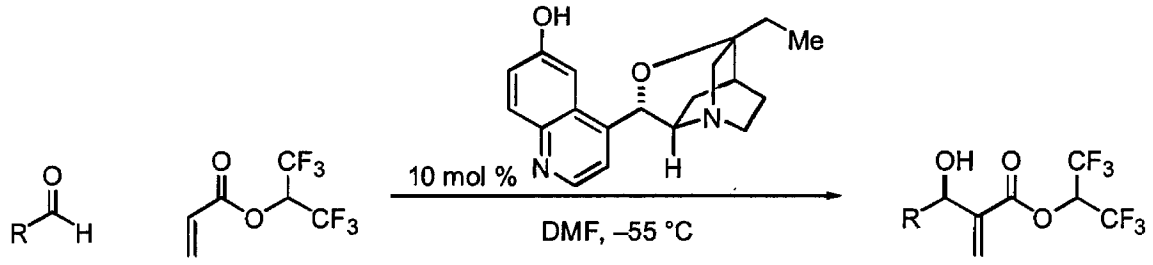
Based on the presumptive intimate association of HMPA with the silicon atom in the transition state, Gennari and coworkers attempted to use chiral urea derivatives to induce asymmetry. This approach was not successful, as enantioselectivities were quite low (8 – 16% ee).[169]

1.5.12 The Baylis–Hillman Reaction

The Baylis–Hillman reaction, involving the tertiary-amine catalyzed aldol reaction between unsaturated carbonyl compounds and aldehydes, constitutes an important synthetic avenue to α-substituted methylidene carbonyl compounds. The Baylis-Hillman reaction is well known for slow rates and particular reaction conditions for optimal conversion; moreover, a catalytic asymmetric version of the reaction had proved frustratingly elusive. Leahy and coworkers reported the first highly diastereoselective version of the reaction, using the acryloyl derivative of Oppolser's camphorsultam. The products were isolated in essentially enantiopure form; however, the asymmetric reagent was required in stoichiometric amounts, and aryl aldehydes displayed no activity whatsoever.[170]

The widespread use of DABCO as the catalytic base in the Baylis-Hillman naturally led to the notion to use chiral derivatives of DABCO in an effort to induce asymmetry in the resulting aldol products. Since they are essentially asymmetric versions of DABCO, the cinchona alkaloids made ideal choices for screening as asymmetric catalysts for the Baylis-Hillman reaction. Hatakeyama reported the successful use of a quinidine derivative in an asymmetric Baylis-Hillman reaction in the late 1990s. The catalyst shown in Table 74 afforded optimal reactivity and selectivity; the "tying back" of the side chain was thought to increase reaction rates by diminishing the steric impedance in proximity to the bridgehead nitrogen arising from free rotation of the quinoline side chain. Enantioselectivities were excellent (91-99% ee) for a range of alkyl and aryl aldehydes, although yields proved to be problematic in some cases.

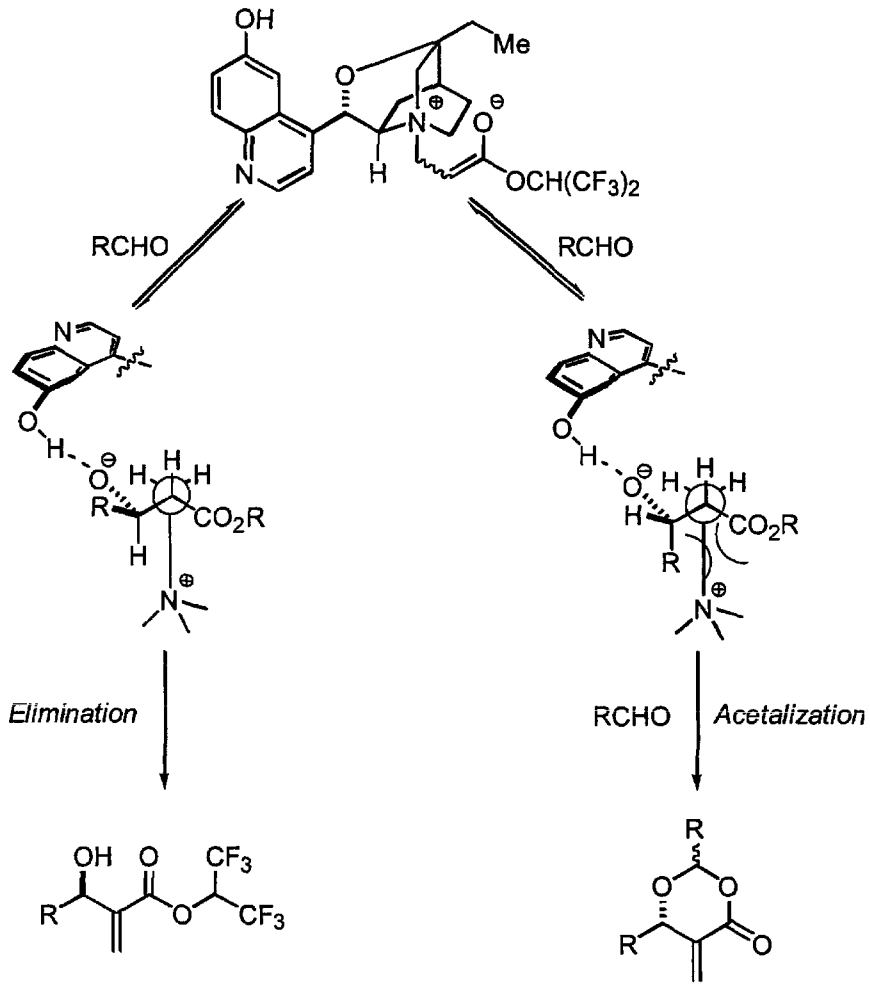
Table 74. Scope of organocatalytic asymmetric Baylis–Hillman reaction.



Entry	R	Time / h	Yield / %	ee / %
1	$C_6H_4NO_2$-4	1	58	91
2	C_6H_5	48	57	95
3[a]	(*E*)-CH=CHC_6H_5	72	50	92
4	CH_2CH_3	4	40	97
5[b]	$CH_2CH(CH_3)_2$	4	51	99
6	*i*-Pr	16	36	99
7	*c*-C_6H_{11}	72	31	99
8	*t*-Bu	72	0	0

The major side product was the dioxanone derived from acetalization of the Baylis-Hillman product by additional aldehyde in the reaction vessel. Interestingly, the stereochemical configuration in the dioxanone was determined to be opposite to that of the aldol product. This peculiarity was rationalized based on stereoelectronic grounds; the two diastereomeric intermediates of the enolate addition to the aldehyde shown in Figure 26 were thought to be stabilized by hydrogen bonding interactions with the quinoline hydroxyl group. Unfavorable nonbonded interactions in the intermediate **B** between the ester of the acrylate starting material and the substituent of the aldehyde were thought to disfavor the rotameric conformation shown, which also has the requisite *anti*-periplanar geometry favored for E2 (or E1cb) elimination to give the Baylis-Hillman product. The alternate rotamer does not possess this steric interaction, leaving it free to undergo elimination of the catalyst and generation of the aldol product. The alternate

rotamer **A** (with the opposite stereochemical configuration at the aldehyde carbon) was then theorized to undergo acetalization, explaining the stereodivergence between the aldol and dioxanone products experimentally observed.



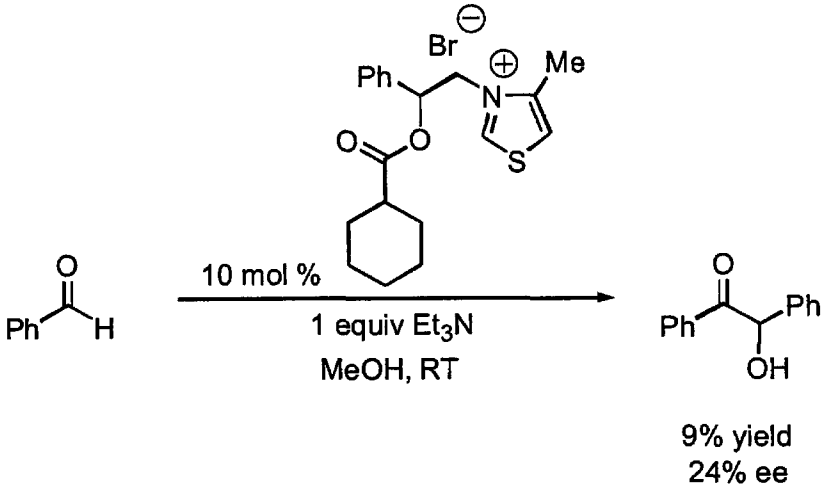
Scheme 50. Rationale for opposite stereogenicity between Baylis–Hillman and acetalization products.

1.5.13 The Benzoin Condensation

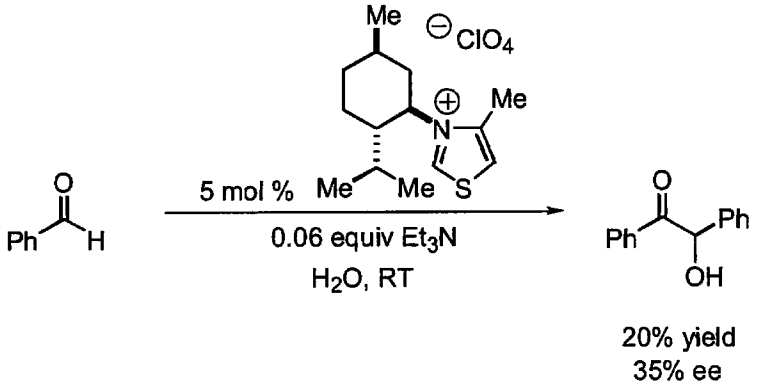
The benzoin condensation between two molecules of benzaldehyde is one of the first organic reactions to be discovered[171] and one of the earliest reactions to have been shown to be amenable to organocatalysis. The first report of catalysis of this reaction by a thiazolium ylide appeared in 1943.[172] Numerous attempts have been made since that

time to generate chiral products in the benzoin condensation using enantiomerically enriched thiazolium salts.

The first such report appeared in the 1960s. In a brief communication, Sheehan described the use of the thiazolium catalyst described in Scheme 51 in the benzoin condensation, with benzoin obtained in 24% ee as determined by optical rotation.[173] In a later report, variation of the substituent at the stereogenic carbon, specifically substituted by a naphthyl group, afforded a product in 52% ee, but with a disappointing 6% yield. Substitution with a phenyl group instead afforded products of superior yield (68 – 78%), but greatly diminished enantiopurity (7 – 8% ee).[174] Tagaki and coworkers reported the use of the menthol-derived catalyst shown in Scheme 52, which afforded benzoin in 35% ee and 20% yield when the reaction was carried out under "micellar" conditions in water.[175] Later reports using the Tagaki's catalyst with much more nonpolar groups, along with a lipophilic additive to create better-defined micelles afforded no improvement in enantioselectivity.[176] Catalysts with acyclic chiral substituents were also used, although, again, results were disappointing, with the maxiumum ee observed being 12%.[177]



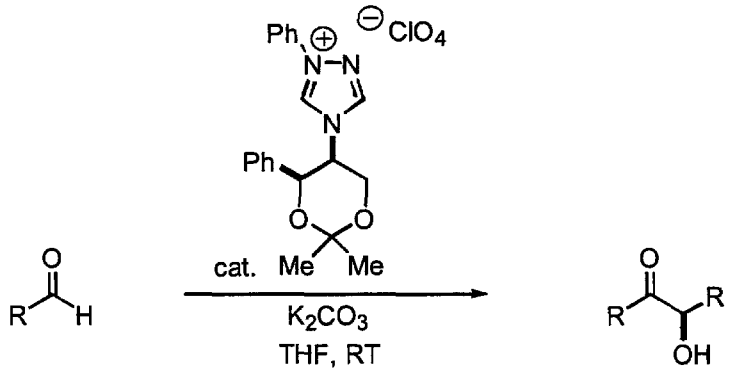
Scheme 51. Initial report by Sheehan of catalytic asymmetric benzoin condensation.



Scheme 52. Tagaki's asymmetric benzoin condensation with menthol–derived thiazolium salt catalyst.

A change in catalyst morphology proved to be vital for the development of organocatalytic benzoin condensations with enantioselectivities approaching synthetically useful levels. Enders and coworkers reported the use of triazolium salts with the asymmetry located in a dioxolane ring appended to one of the catalyst nitrogens (Table 75). A range of aryl aldehydes were processed to afford the corresponding benzoins in variable yields (22 – 72%) and enantioselectivities (20 – 86% ee). A transition state like that shown in Figure 26, based on work previously reported by Breslow,[178] was invoked by Enders to account for the observed stereoselectivity. The phenyl group associated with the dioxolane moiety was thought to shield the *re* face of the putative enol intermediate, leaving only one face open for the condensation. In all likelihood, however, this model is a dramatic simplification of the actual carbon-carbon bond forming event, since the enantioselectivity displayed a nonlinear dependence on the reaction temperature.

Table 75. Enders' first generation triazolium salt catalyst for asymmetric benzoin/acyloin condensations.



Entry	R	Cat. loading / mol %	Yield / %	ee / %
1	C_6H_5	1.25	66	75
2	C_6H_4OMe-3	1.25	41	66
3	C_6H_4OMe-4	5.00	22	86
4	C_6H_4Me-3	1.25	54	76
5	C_6H_4Me-4	5.00	46	82
6	C_6H_4F-4	1.25	48	44
7	C_6H_4Cl-4	1.25	51	29
8	C_6H_4Br-4	1.25	76	20

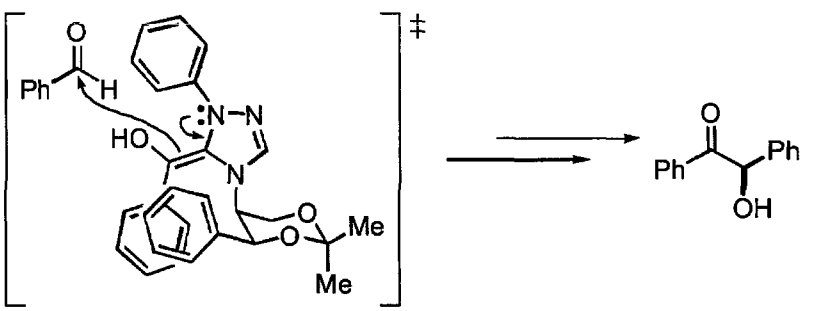
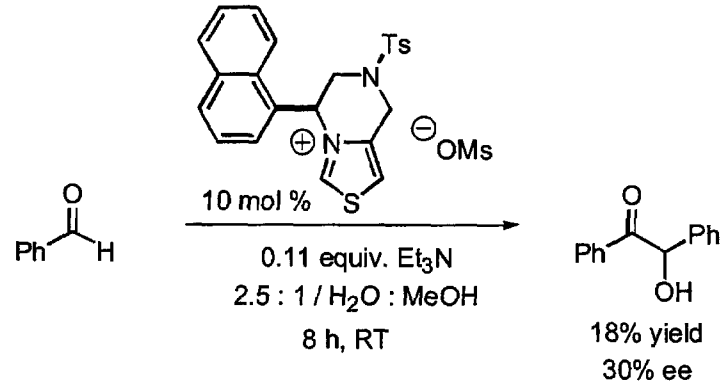


Figure 26. Rationale for observed stereochemistry in benzoin products obtained *via* chiral triazolium salt catalysis.

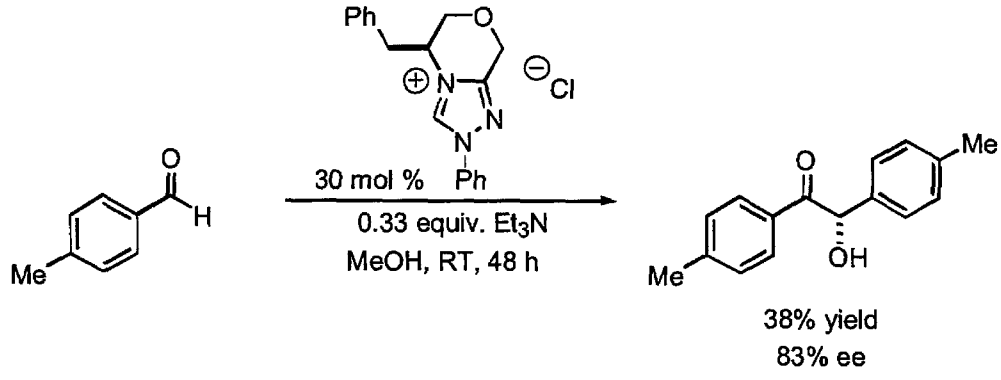
Thiazolium salts seemed to be inferior to triazolium salts in terms of both efficiency and selectivity. The most recent work on the benzoin condensation involving a thiazolium salt catalyst appeared in 1998 from the laboratories of Rawal. The phenyl and

napthyl derivatives of the thiazolium salt shown gave benzoin in a maximum of 30% ee (and 18% yield, Scheme 53).[179]



Scheme 53. Rawal's thiazolium catalyst for asymmetric benzoin condensations.

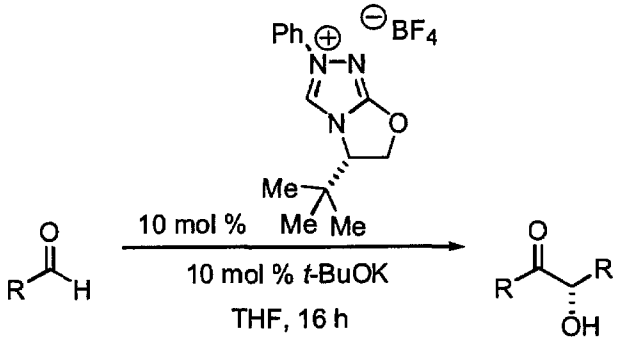
Knight and Leeper prepared triazolium salts with the asymmetry appended to a cycle attached to the triazole ring, which catalyzed the benzoin condensation of a range of aromatic aldehydes. The enantioselectivities in the reaction with *p*-methylbenzaldehyde reached 83%, although the yields were, in general, substandard (11 – 50%, Scheme 54).[180]



Scheme 54. Asymmetric acyloin condensation with bicyclic trizaolium salt catalyst.

Enders et al. synthesized a second generation analog of their previously reported triazolium catalyst, starting from the desired imidizolidinone. A procedure analogous to that of Leeper was followed to afford the bicyclic triazolium salt shown. This catalyst provided benzoins with the highest enantioselectivity yet reported for this reaction (90% for benzoin itself; 91 – 95% ee for other differentially substituted analogs, Table 76).[181] In addition, yields were generally superior to those previously reported.

Table 76. Scope of first general highly enantioselective organocatalytic benzoin condensation, as reported by Enders.



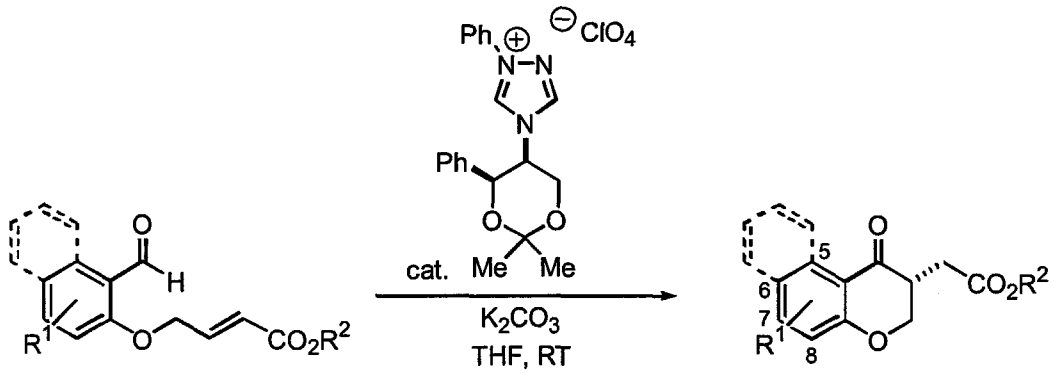
Entry	R	Temp / °C	Yield / %	ee / %
1	C_6H_5	18	83	90
2	C_6H_4F-4	0	61	91
3	C_6H_4Cl-4	0	44	89
4	C_6H_4Br-4	0	59	91
5	C_6H_4Cl-3	0	85	86
6	C_6H_4Me-4	18	16	93
7	C_6H_4Me-3	0	36	91
8	C_6H_4OMe-4	18	8	95
9	2-Furyl	–78	41	88
10	*2-Naphthyl*	*18*	*69*	*80*

1.5.14 The Intramolecular Stetter Reaction

The Stetter reaction, first reported in the 1970s, is a closely related analog of the benzoin condensation, in which the electrophile is an α,β-unsaturated carbonyl compound, rather than another molecule of substrate aldehyde.[182] As with the benzoin condensation, the Stetter reaction represents an elegant route to the generation of acyl anion equivalents; efforts to develop a catalytic asymmetric version of this reaction were spurred on by the observation that thiazolium salts also catalyze the Stetter reaction. Unfortunately, the Stetter reaction has proved to be a much more formidable challenge, and the only asymmetric versions of this reaction reported in the literature are of the intramolecular variant.

The first example that appeared in the literature was from Enders' group. The first-generation catalyst (see Table 75) for the benzoin condensation was also found to catalyse the cyclization of the substituted phenyl allyl ether shown in Table 77.[183] Yields of up to 73% and enantiomeric excesses of 60% were reported for the substrates lacking substitution on the phenyl ring; with a methoxy group in the 7 position, the corresponding Stetter adduct was isolated in 22% yield and 71% ee.

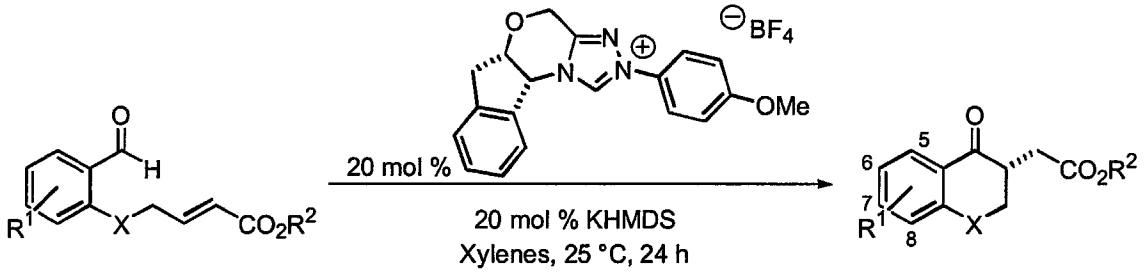
Table 77. Scope of asymmetric intramolecular Stetter reaction with triazolium salt catalysts.



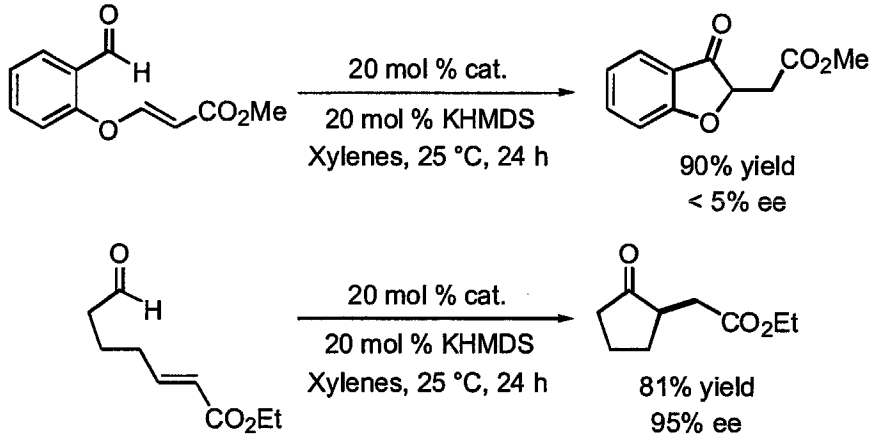
Entry	R^1	R^2	Cat. Loading / mol %	Yield / %	ee / %
1	–	Me	20	73	60
2	–	Et	20	69	56
3	8-OMe	Me	20	44	68
4	8-OMe	Et	20	69	42
5	7-OMe	Me	50	22	71
6	6-OMe	Me	20	56	61
7	6-Cl	Me	10	50	41
8	5,6-fused Ph	Me	20	51	65

A very recent communication from the laboratories of Rovis demonstrated that enantioselectivities could be increased to synthetically useful levels. Using the aminoindanol modified triazole shown in Table 78, a wide range of phenyl ethers were converted to the appropriate bicycles in 82 – 97% ee with variable yields. Unfortunately, due to the high basicity of the catalyst, substrates with a very acidic α-proton in the product were subject to racemization (Scheme 55). The benzofuran shown was isolated in less than 5% ee; however, removal of the offending phenoxy moiety led to formation of nearly enantiopure product.

Table 78. Scope of highly enantioselective intramolecular Stetter reaction.



Entry	R^1	R^2	X	Yield / %	ee / %
1	–	Et	O	94	94
2[a]	6-Me	Et	O	80	97
3	8-Me	Et	O	90	84
4[a]	8-OMe	Et	O	95	87
5	–	Me	S	63	96
6	–	Me	NMe	64	82
7	–	Me	$NCH_2CH{=}CHCO_2Me$	72	84
8[b]	–	Et	CH_2	35	94



Scheme 55. Demonstration of detrimental effect on enantioselectivity of nucleophilicity of triazolium salt catalyst.

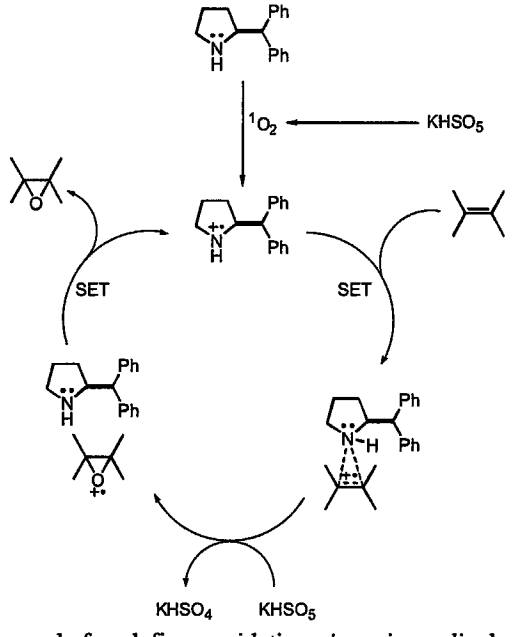
1.6 Miscellaneous Reactions

1.6.1 Olefin Epoxidation *via* Amine Radical Cations

In 2000, Aggarwal reported the use of amine radical cations as asymmetric epoxidation catalysts, a methodology resists classification in one of the three major

categories described above. Given the major advances that have been made in catalytic asymmetric epoxidation technology over the last thirty years, this report seems to be more of a curiosity than a synthetically valuable protocol. However, it is unique in the use of a presumably nucleophilic organic molecule for non-nucleophilic epoxidations.

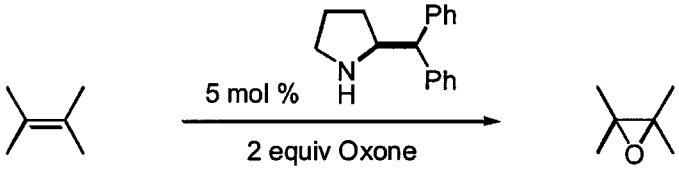
The chiral amine shown in Scheme 56 was implicated as the pre-catalyst. Singlet oxygen generated by decomposition of Oxone® caused abstraction of an electron from the amine to generate the radical cation **A**, which then associates with the substrate olefin in an as yet undetermined fashion (structure **B**). Oxidation of this catalyst-olefin complex to the epoxide by Oxone® would in principle afford the amine catalyst and the radical cation of the epoxide product. Single electron transfer to the catalyst completes the cycle with formation of the epoxide and regeneration of the amine radical cation. The intermediacy of a radical cation was implicated by several experiments in which certain epoxide products previously shown to be selectively formed by radical cation oxidation were obtained exclusively.[184]



Scheme 56. Proposed catalytic cycle for olefin epoxidation *via* amine radical cation catalysis. SET = single electron transfer.

A range of olefins was successfully expoxidized, although only a few were isolated in non–racemic form (Table 79). Certain olefins, such as stilbenes and long-chain internal alkenes, did not react at all. This work displays many of the advantages of organocatalytic technologies, most notably greatly reduced cost relative to the corresponding organometallic-based protocols; however, clearly, the efficacy of the catalyst system must be improved dramatically in order to successfully compete with more established epoxidation procedures.

Table 79. Initial attempts at asymmetric olefin epoxidation *via* chiral single electron transfer agents.



Entry	Olefin	NMR Yield / %	ee / %
1	Methylenecyclohexane	29	0
2	1-Methylcyclohexene	90	15
3	Indene	20	25
4	1-Phenylcyclohexene	96	57
5	α-Methylstyrene	65	15
6	β-Methylstyrene	21	13
7	Styrene	93	9
8	*trans*-Stilbene	6	0
9	*cis*-Stilbene	9	0

1.7 Conclusion

As the field of asymmetric catalysis continues to expand and mature, no doubt further uses will be found for the employment of enantiomerically enriched amines as catalysts. The basic physical and chemical properties of amines that have been known for hundreds of years continue to provide inspiration for new organic methodologies. Given the prevalence of amine–containing molecules in nature, continued research in the area of amine catalysis will hopefully shed light on some of the more mysterious questions surrounding the origin of life.

1.8 References

(1) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.
(2) Iyer, S. M.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910.
(3) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.
(4) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.
(5) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279.
(6) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867.
(7) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.
(8) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, 1976; p 5.
(9) For recent reviews of enantioselective Diels—Alder reactions mediated by chiral Lewis acids, see: (a) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 5. (b) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (c) Oh, T.; Reilly, M. *Org. Prep. Proc. Int.* **1994**, *26*, 129. (d) Dias, L. C.; *J. Braz. Chem. Soc.* **1997**, *8*, 289.
(10) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
(11) Wipf, P.; Wang, X. *Tetrahedron Lett.* **2000**, *41*, 8747.
(12) For examples of successful catalytic asymmetric Diels – Alder reactions with quinones or chelating ketone substrates, see: Quinones: (a) Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 643. (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812. (c) White, J. D.; Choi, Y. *Org. Lett.* **2000**, *2*, 2373. (d) Engler, T. A.; Letavic, M. A.; Lynch Jr., K. O.; Takusagawa, F. *J. Org. Chem.* **1994**, *59*, 1179. (e) Engler, T. A.; Letavic, M. A.; Takusagawa, F. *Tetrahedron Lett.* **1992**, *33*, 6731. (f) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*,

1559. Chelating ketone dienophiles: (g) Honda, Y.; Date, T.; Hiramatsu, H.; Yamauchi, M. *Chem. Commun.* **1997**, 1411. (h) Otto, S.; Boccaletti, G.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238. (i) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 6798. (j) Schuster, T.; Bauch, M.; Durner, G.; Gobel, M. W. *Org. Lett.* **2000**, *2*, 179.

(13) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

(14) Several months after the publication of ref. 15, Corey and coworkers reported the use of chiral oxazaborolidines in highly enantioselective Diels–Alder using simple acyclic enones: Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992.

(15) (a) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687. (b) Gothelf, K. D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710. (c) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *Tetrahedron Lett.* **1996**, *37*, 5947. (d) Ukaji, Y.; Taniguchi, K.; Sada, K.; Inomata, K. *Chem. Lett.* **1997**, 547. (e) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471. (f) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (g) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355.

(16) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

(17) (a) Gupta, R. R.; Kumar, M; Gupta, V. *Heterocyclic Chemistry*; Springer-Verlag: Heidelberg, 1999; Vol. 3. (b) Strell, A.; Kalojanoff, R. *Chem. Ber.* **1954**, *87*, 1954.

(18) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

(19) A survey of the Beilstein chemical database revealed that over 3,000 natural products possess such stereogenic substitution. Additionally, 40 medicinally active agents also bear indolic stereogenicity. See Kleeman, A.; Engel, J.; Kutscher, B.; Reichert. D. *Pharmaceutical Substances*, 4th ed.; Thieme: New York, 2001.

(20) (a) Cipciani, A.; Clementi, S.; Linda, P.; Marino, G.; Savelli, G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1284. (b) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500.

(21) (a) von der Ohe, F.; Brucker, R. *Tetrahedron Lett.* **1998**, *39*, 1909. (b) von der Ohe, F.; Bruckner, R. *New J. Chem.* **2000**, *24*, 659.

(22) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

(23) The scope of this procedure has been thoroughly investigated and will be published shortly: Paras, N. A.; MacMillan, D. W. C. *Org. Lett.* **2003**, submitted for publication.

(24) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975.

(25) (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*(8), 1177. (b) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*(44), 8233. (c) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*(32), 11223.

(26) (a) Evans, D. A.; Nelson, J. V.; Taber, T. In *Topics in Stereochemistry*; John Wiley & Sons: New York, 1982; Vol. 13, p. 1. (b) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (d) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(27) (a) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, part B, p. 111. (b) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. (c) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076. (d) Heathcock, C. H. *Science* **1981**, *214*, 395. (e) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173.
(28) (a) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford: 1991; Vol. 2 (Heathcock, C. H., Ed.), Chapter 1.7, p. 239. (b) Masamune, S.; Ali, S.; Snitman, D. L.; Garvey, D. S. *Angew. Chem.* **1980**, *92*, 573. (c) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (d) Masamune, S.; Sato, T.; Kim, B.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279.
(29) (a) Mukaiyama, T. In *Organic Reactions*; John Wiley & Sons: New York, 1982: Vol. 28, p. 203. (b) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, *9*, 1011. (c) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (d) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761.
(30) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496.
(31) Jung, M. E. *Tetrahedron* **1976**, *32*, 3.
(32) List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
(33) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573.
(34) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.
(35) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(36) (a) Heathcock, C. H.; Hug, K. T.; Flippin, L. A. *Tetrahedron Lett.* **1984**, *25*, 5973. (b) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747.
(37) Córdova, A.; Notz, W.; Barbas III, C. F. *J. Org. Chem.* **2002**, *67*, 301.
(38) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620.
(39) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.
(40) (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827.
(41) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044..
(42) List, B. *Tetrahedron* **2002**, *58*, 5573.
(43) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; HarperCollins: New York, 1987; p. 143.
(44) (a) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas III, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (b) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas III, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1866.
(45) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5657.
(46) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790.
(47) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254.
(48) Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas III, C. F. *Tetrahedron Letters* **2002**, *43*, 3817.
(49) Ramachary, D. B.; Chowdari, N. S.; Barbas III, C. F. *Tetrahedron Lett.* **2002**, *43*, 6743.

(50) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.
(51) For some recent reviews on PTC, see: (a) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*; VCH Publishers: New York, 1993. (b) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman & Hall: New York, 1994. (c) *Phase Transfer Catalysis: Mechanisms and Syntheses*; Halpern, M. E., Ed.; American Chemical Society: Washington, D. C., 1997.
(52) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353.
(53) (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (b) Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Schönewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745, and references cited therein.
(54) Mechanistic investigations of the asymmetric olefin dihydroxylation reaction: (a) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038. (b) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579. (c) Corey, E. J.; Noe, M. C.; Sarshar, S. Tetrahedron *Lett.* **1994**, *35*, 2861. (d) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319. (e) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828. (f) Corey, E. J.; Noe, M. C.; Ting, A. *Tetrahedron Lett.* **1996**, *37*, 1735. For excellent reviews of the Sharpless asymmetric dihydroxylation reaction, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483; (b) Markó, I. E.; Svendsen, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: New York: 1999; Vol. 2, Chapter 20. (c) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 6D.
(55) For reviews of the Sharpless asymmetric epoxidation reaction, see: (a) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: New York: 1999; Vol. 2, Chapter 18.1. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 6E.
(56) For an excellent review of the Jacobsen epoxidation reaction, see Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: New York: 1999; Vol. 2, Chapter 18.2
(57) Helder, R.; Hummelen, J. C.; Laane, R W. P. M.; Wiering, J. S.; Wynberg, H. *Tetrahedron Lett.* **1976**, *19*, 1831. For a later reference concerning proof of absolute stereochemistry of the product, see Marsman, B.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2312.
(58) Wynberg, H.; Marsman, B. *J. Org. Chem.* **1980**, *45*, 158.
(59) Hummelen, J. C.; Wynberg, H. *Tetrahedron Lett.*, **1978**, *21*, 1089.
(60) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287.
(61) A comprehensive mechanistic study of these reactions has not yet been carried out; however, studies by Lygo et al. have demonstrated the importance of certain reaction conditions in promoting highly enantioselective epoxidations. See Lygo, B.; To, D. C. M. *Tetrahedron Lett.* **2001**, *42*, 1343.
(62) (a) Juliá, S.; Guixer, J.; Masana, J.; Rocas, J; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc. Perkin Trans. 1* **1982**, 1317. (b) Colonna, S.; Molinari, H.; Banfi, S.;

Juliá, S.; Masana, J.; Alvarez, A. *Tetrahedron* **1983**, *39*, 1635. (c) Banfi, S.; Colonna, S.; Molinari, H.; Juliá, S.; Guixer, J. *Tetrahedron* **1984**, *40*, 5207.
(63) (a) Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackon, M. P.; McCague, R.; Nugent, T. C.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3501. (b) Allen, J. V.; Bergeron, S.; Griffiths, M. J.; Mukerjee, S.; Roberts, S. M.; Williamson, N . M.; Wu, L. E. *J. Chem. Soc. Perkin Trans. 1* **1998**, 3171.
(64) For preparation of this catalyst, see Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.* **1990**, *55*, 6047.
(65) Flood, R. W.; Geller, T. P.; Petty, S. A.; Roberts, S. M.; Skidmore, J.; Volk, M. *Org. Lett.* **2001**, *3*, 683.
(66) (a) Krimm, S.; Bandekar, J. *Adv. Protein Chem.* **1986**, *38*, 181. (b) Arrondo, J. L. R.; Muga, A.; Castresana, J.; Goñi, F. M. *Prog. Biophys. Mol. Biol.* **1993**, *59*, 23. (c) Surewicz, W. K.; Mantsch, H. H.; Chapman, D. *Biochemistry* **1993**, *32*, 389.
(67) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 855.
(68) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843.
(69) Corey, E. J.; Zhang, F.-Y. *Angew. Chem. Int. Ed.* **1999**, *38*, 1931.
(70) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347.
(71) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.
(72) Perrard, T.; Plaquevent, J.-C.; Desmurs, J.-R.; Hébrault, D. *Org. Lett.* **2000**, *2*, 2959.
(73) Balcells, J.; Colonna, S.; Fornasier, R. *Synthesis* **1976**, 266.
(74) Colonna, S.; Fornasier, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 371.
(75) Drew, M. D.; Lawrence, N. J.; Watson, W.; Bowles, S. A. *Tetrahedron Lett.* **1997**, *38*, 5857.
(76) (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc. Chem. Comm.* **1983**, 469. (b) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem.* **1984**, *49*, 555. (c) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *J. Chem. Soc. Perkin Trans. I* **1985**, 2615.
(77) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. For an excellent review of the scope and selectivity of the chiral oxazaborolidine catalyst, see (c) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.
(78) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137.
(79) (a) Wittig, G.; Rieber, M. *Ann.* **1949**, *562*, 187. (b) Wittig, G.; Geissler, G. *Ann.* **1953**, *580*, 44. (c) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318. (d) Gensler, W. J. *Chem. Rev.* **1957**, *57*, 191.
(80) (a) Horner, L.; Hoffman, H.; Wippel, J. H. G.; Klahre, G. *Ber.* **1959**, *92*, 2499. (b) Wadsworth Jr., W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.
(81) (a) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699. (b) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7655. (c) Hanessian, S.; Beaudoin, S.; *Tetrahedron Lett.* **1992**, *33*, 7659. (d) Tanaka, K.; Ohta, S.; Fuji, K. *Tetrahedron Lett.* **1993**, *34*, 4071. (e) Kumamoto, T.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 753. (f) Musierowicz, S.; Wroblewasi, A.; Krawczyk, H. *Tetrahedron Lett.* **1975**, *16*, 437. (g) Kann, N.; Rein, T. *J. Org. Chem.* **1993**, *58*, 3802. (h) Denmark, S. E.;

753. (f) Musierowicz, S.; Wroblewasi, A.; Krawczyk, H. *Tetrahedron Lett.* **1975**, *16*, 437. (g) Kann, N.; Rein, T. *J. Org. Chem.* **1993**, *58*, 3802. (h) Denmark, S. E.; Chen, C. T. *J. Am. Chem. Soc.* **1992**, *114*, 10674. I) Legros, J. Y.; Fiaud, J. C. *Tetrahedron*, **1994**, *50*, 465. (j) Denmark, S. E.; Rivera, I. *J. Org. Chem.* **1994**, *59*, 6887, and references cited therein.
(82) Arai, S.; Hamaguchi, S.; Shiori, T. *Tetrahedron Lett.* **1998**, *39*, 2997.
(83) (a) Darzens, G. *Compt. Rend.* **1904**, *139*, 1214. (b) Darzens, G. *Compt. Rend.* **1906**, *142*, 214. (c) Ballester, M. *Chem. Rev.* **1953**, *53*, 283.
(84) Arai, S.; Shiori, T. *Tetrahedron Lett.* **1998**, *39*, 2145.
(85) Arai, S.; Ishida, T.; Shiori, T. *Tetrahedron Lett.* **1998**, *39*, 8299.
(86) Kagan, H. B.; Riant, O. *Tetrahedron Lett.* **1989**, *52*, 7403.
(87) Tokioka, K.; Masuda, S.; Fujii, T.; Hata, Y.; Yamamoto, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 101.
(88) Uemae, K.; Masuda, S.; Yamamoto, Y. *J. Chem. Soc. Perkin Trans. I* **2001**, 1002.
(89) Fache, F.; Piva, O. *Tetrahedron Lett.* **2001**, *42*, 5655.
(90) Okamura, H.; Nakamura, Y.; Iwagawa, T.; Nakatani, M. *Chem. Lett.* **1996**, 193.
(91) Borrmann, D.; Wegler, R. *Chem. Ber.* **1966**, *99*, 1245.
(92) Borrmann, D.; Wegler, R. *Chem. Ber.* **1967**, *100*, 1575.
(93) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166.
(94) Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977.
(95) McCarney, C. C.; Ward, R. S. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1600.
(96) Staudinger, H. *Ber.* **1905**, *38*, 1735.
(97) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006.
(98) Calter, M. A.; Bi, F. C. *Org. Lett.* **2000**, *2*, 1529.
(99) *In situ* ketene generation had already been validated in the context of other reactions; see (a) Boivin, J.; Kaim, L E.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2573. (b) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726. (c) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742.
(100) Tennyson, R.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248.
(101) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945.
(102) Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731.
(103) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906.
(104) Tennyson, R. L.; Cortez, G. S.; Galicia, H. J.; Kreiman, C. R.; Thompson, C. M.; Romo, D. *Org. Lett.* **2002**, *4*, 533.
(105) (a) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931. (b) Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518.
(106) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury III, W. J.; Lectka, T. *J. Am. Chem. Soc.* **1999**, *122*, 7831.
(107) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury III, W. J.; Lectka, T. *Org. Lett.* **2000**, *2*, 3963.
(108) Some prior publications had appeared regarding the use of chiral polymers to catalyze the asymmetric conjugate addition of long-chain thiols to enones; however, the reaction conditions were poorly defined and optical rotations of the products were so small as to be barely measurable. See (a) Ohashi, S.; Inoue, S. *Makromol. Chem.*

(109) Långström, B.; Bergson, G. *Acta Chem. Scand.* **1973**, *27*, 3118.
(110) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *16*, 4057.
(111) Hermann, K.; Wynberg, S. *Helv. Chim. Acta* **1977**, *60*, 2208.
(112) Kobayashi, N.; Iwai, K. *J. Am. Chem. Soc.* **1978**, *100*, 7071.
(113) Ohashi, S.; Inoue, S. *Makromol. Chem.* **1972**, *160*, 69.
(114) Suzuki, K.; Ikegawa, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277.
(115) For additional applications of the proline-derived catalyst and its congeners, see Mukaiyama, T. *Tetrahedron* **1981**, *37*, 4111.
(116) Sera, A.; Takagi, K.; Katayama, H.; Yamada, H.; Matsumoto, K. *J. Org. Chem.* **1988**, *53*, 1157.
(117) Pluim, H.; Wynberg, H. *Tetrahedron Lett.* **1979**, *20*, 1251.
(118) McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem. Int. Ed.* **2002**, *41*, 338.
(119) For initial development of the racemic azide addition, see Guerin, D. J.; Horstmann, T. E.; Miller, S. J. *Org. Lett.* **1999**, *1*, 1107.
(120) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 3635.
(121) Jacobsen also reported an aluminum salen catalyst for asymmetric azidation of unsaturated amides: Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959.
(122) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134.
(123) (a) Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995. (b) Lapworth, A. *J. Chem. Soc.* **1904**, *85*, 1206. (c) As cited in March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*; John Wiley & Sons: New York, 1992 (4th ed.); p 965. (d) As cited in McMurry, J. *Organic Chemistry*; Brooks–Cole: Pacific Grove, CA, 1996; p 730.
(124) Tsuboyama, S. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1004.
(125) Tsuboyama, S. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 354.
(126) Tsuboyama, S. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 698.
(127) Oku, J.-I.; Inoue, S. *J. Chem. Soc. Chem. Comm.* **1981**, 229.
(128) Jackson, W. R.; Jayatilake, G. S.; Matthews, B. R.; Wilshire, C. *Aust. J. Chem.* **1988**, *41*, 203.
(129) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181.
(130) Danda, H. *Synlett* **1991**, 263.
(131) Callant, D.; Coussens, B.; Maten, T. v. d.; de Vries, J. G.; de Vries, N. K. d. *Tetrahedron: Asymmetry* **1992**, *3*, 401.
(132) Hogg, D. J. P.; North, M.; Stokoe, R. B.; Teasdale, W. G. *Tetrahedron: Asymmetry* **1993**, *4*, 1993.
(133) Apperley, D.; North, M.; Stokoe, R. B. *Tetrahedron: Asymmetry* **1995**, *6*, 1869.
(134) For excellent reviews of nonlinear effects, as well as intriguing aspects of asymmetric autocatalysis, see: (a) Girard, C.; Kagan, H. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 2923. (b) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382. (c) Blackmond, D. *Acc. Chem. Res.* **2000**, *33*, 402. (d) Blackmond, D. *Adv. Synth. Catal.* **2002**, *344*, 156.
(135) Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740.
(136) Shvo, Y.; Gal, M.; Becker, Y.; Elgavi, A. *Tetrahedron: Asymmetry* **1996**, *7*, 911.

(135) Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740.
(136) Shvo, Y.; Gal, M.; Becker, Y.; Elgavi, A. *Tetrahedron: Asymmetry* **1996**, *7*, 911.
(137) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195.
(138) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725.
(139) (a) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475. (b) Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202.
(140) Evans was the first to recognize the value inherent in alcohol resolution protocols; for a stoichiometric kinetic resolution, see Evans, D. A.; Anderson, J. C.; Taylor, M. K. *Tetrahedron Lett.* **1993**, *34*, 5563. Vedejs reported the use of a chiral DMAP analog for alcohol resolution before Fu's work appeared; however, the selectivities were moderate and the resolving agent was employed stoichiometrically. See Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809.
(141) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412, and references cited therein.
(142) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091, and related correction (Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 10452).
(143) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.
(144) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529.
(145) Oriyama, T.; Imai, K.; Hosoya, T.; Sano, T. *Tetrahedron Lett.* **1998**, *39*, 397.
(146) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, 265.
(147) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629.
(148) Copeland, G. T.; Jarvo, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784.
(149) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, Jr., P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638.
(150) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496.
(151) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154.
(152) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9.
(153) (a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 23. (b) Pracejus, H.; Tille, A. *Chem. Ber.* **1963**, *96*, 854. (c) Pracejus, H.; Mätje, H. *J. Prakt. Chem.* **1964**, *24*, 195. (d) Pracejus, H.; Kohl, G. *Justus Liebigs Ann. Chem.* **1969**, *722*, 1.
(154) Hiratake, J.; Yamamoto, Y.; Oda, J. *J. Chem. Soc. Chem. Commun.* **1985**, 1717.
(155) Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc. Perkin Trans. I* **1987**, 1053.
(156) Aitken, R. A.; Gopal, J.; Hirst, J. A. *J. Chem. Soc. Chem. Commun.* **1988**, 632.
(157) Aitken, R. A.; Gopal, J. *Tetrahedron: Asymmetry* **1990**, *1*, 517.
(158) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542.
(159) Chen, Y.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 11302.
(160) Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870.
(161) Hang, J.; Tian, S.-K.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 12696.
(162) Hang, J.; Li, H.; Deng, L. *Org. Lett.* **2002**, *4*, 3321.
(163) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury III, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531.

(164) (a) Furuta, K.; Môri, M.; Yamamoto, H. *Synlett* **1992**, 561. (b) Ishihara, K.; Môri,, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490. (c) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: New York: 1999; Vol. 2, Chapter 27.
(165) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (b) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827. (c) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543. (d) Keck, G. E.; Krishnamurthy, D.; Chen, X. *Tetrahedron Lett.* **1994**, *35*, 8323.
(166) (a) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (b) Denmark, S. E.; Stavenger, R. A.; Su, X. P.; Wong, K. T.; Nishigaichi, Y. *Pure Appl. Chem.* **1998**, *70*, 1469. (c) Denmark, S. E.; Su, Y. P.; Nishigaichi, Y.; Coe, D. M.; Wong, K. T.; Winter, S. B. D.; Choi, J. Y. *J. Org. Chem.* **1999**, *64*, 1958. (d) Denmark, S. E.; Fu, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 12021. (e) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199. (f) Denmark, S. E.; Fu, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 9488.
(167) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 2767.
(168) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977.
(169) Chataigner, I.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, *40*, 3633.
(170) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317.
(171) Wöhler, F.; Liebig, J. *Ann. Pharm.* **1832**, *3*, 249.
(172) Ukai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296.
(173) Sheehan, J. C.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666.
(174) Sheehan, J. C.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196.
(175) Tagaki, W.; Tamura, Y.; Yano, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478.
(176) Yamashita, K.; Sasaki, S.; Osaki, T.; Nango, M.; Tsuda, K. *Tetrahedron Lett.* **1995**, *36*, 4817.
(177) Martí, J.; Castells, J.; López-Calahorra, F. *Tetrahedron Lett.* **1993**, *34*, 521.
(178) (a) Breslow, R. *J. Org. Chem.* **1958**, *80*, 3719. (b) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699.
(179) Dvorak, C. A.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 2925.
(180) (a) Knight, R. L.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3611. (b) Gerhard, A. U.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3615. (c) Knight, R. L.; Leeper, F. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1891.
(181) Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743.
(182) (a) Stetter, H. *Angew. Chem. Int. Ed.* **1976**, *15*, 639. (b) Stetter, H.; Kuhlmann, H. *Chem. Ber.* **1976**, *109*, 2890. (c) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407.
(183) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899.
(184) Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317.

Chapter Two

Development of Sequential Olefin Cross Metathesis–Organocatalysis Methodology

2.1 Introduction

The development of new methods for the formation of carbon-carbon bonds lies at the heart of the pursuit of synthetic organic chemistry. Additionally, the recent awarding of the 2001 Nobel Prize in Chemistry has highlighted the importance of stereoselective bond formation in synthesis.

Many catalytic asymmetric methods used to form carbon-carbon bonds employ chiral Lewis acids. Several of these methods have been thoroughly investigated and found to be widely applicable to the catalysis of a variety of transformations. The reliability and versatility of these Lewis acid catalysts are often balanced by the fact that the catalysts usually have one or more drawbacks. Among these are oxygen and moisture sensitivity, the expense of the metal used, and costly and time-consuming preparation of enantiopure ligand sets.

The use of organic molecules as catalysts presents a potential alternative to traditional metal-based Lewis acid catalysis that addresses many of the shortcomings cited above. One reaction of organic molecules that closely mimics the activation of unsaturated carbonyl compounds by Lewis acids is the formation of an iminium ion via reaction of a secondary amine with an enal (Figure 1, Equation 2). Condensation can occur between the amine and carbonyl, affording an α,β-unsaturated iminium ion. Formally, a positive charge is now located adjacent to the olefin, lowering the energy of

the associated LUMO. This is analogous to the effect of Lewis acid coordination to the carbonyl oxygen (Figure 27, Equation 1).[1]

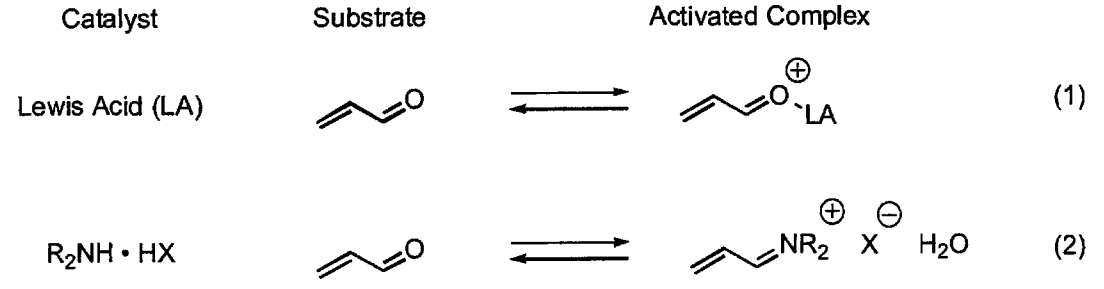


Figure 27. Reprentative equilibria comparing Lewis acid and iminium activation of a,b-unsaturated aldehydes.

Research in the MacMillan group has focused on the development and application of chiral secondary amine catalysts for enantioselective transformations. In particular, the catalyst **1** was found to successfully catalyze various stereoselective transformations susceptible to LUMO-lowering activation, such as conjugate nucleophilic addition and the Diels-Alder reaction (Figure 28, Equations 3-4).[2a-e]

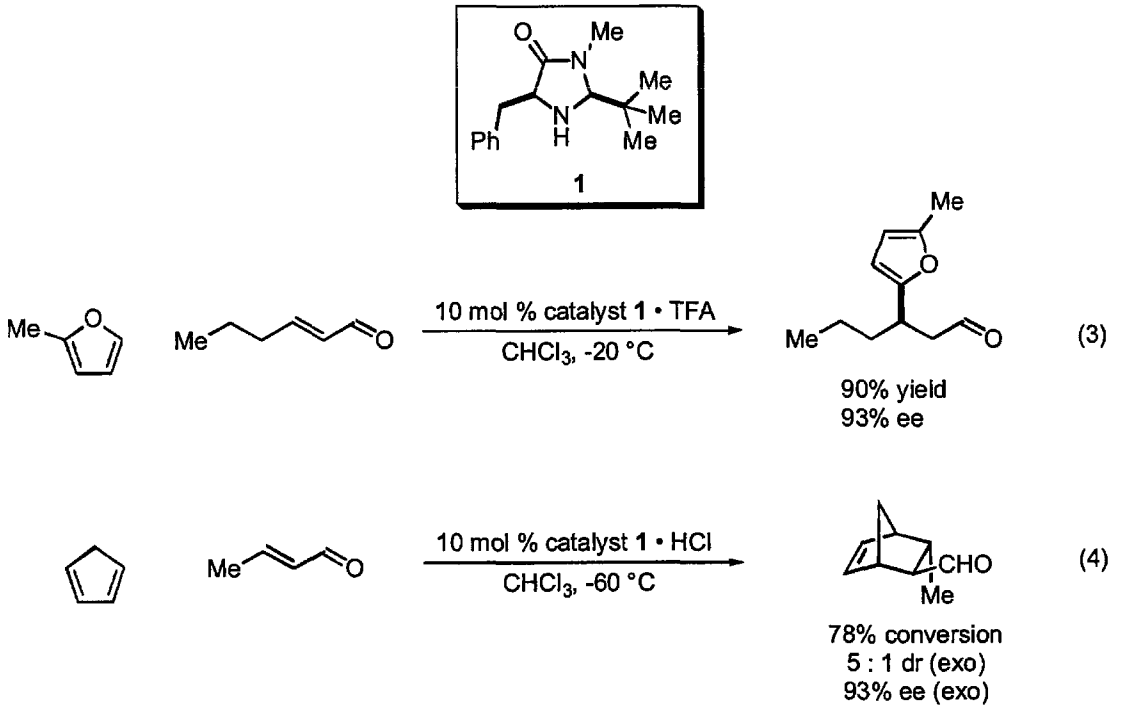


Figure 28. Examples of enantioselective organocatalytic conjugate addition and Diels-Alder cycloaddition.

One limiting factor in the applicability of organocatalysis to synthetic problems is the restricted availability of a wide variety of α,β-unsaturated aldehydes. We envisioned that olefin cross metathesis would be a highly effective method of expanding the structural diversity of aldehydes. The recent development of olefin metathesis by Grubbs,[3] Schrock,[4] and others as a powerful means of carbon-carbon bond formation has been extensively documented in the literature.

Conceptually, an enal could be prepared by means of a cross metathesis reaction between an olefin and an readily available unsaturated aldehyde surrogate, such as acrolein or crotonaldehyde. Given the demonstrated functional group tolerance of the metathesis catalyst **2** and organocatalyst **1**, we also sought to develop a procedure for the rapid assembly of enantioenriched organic molecules by means of sequential olefin metathesis and organocatalytic reactions (Figure 29).

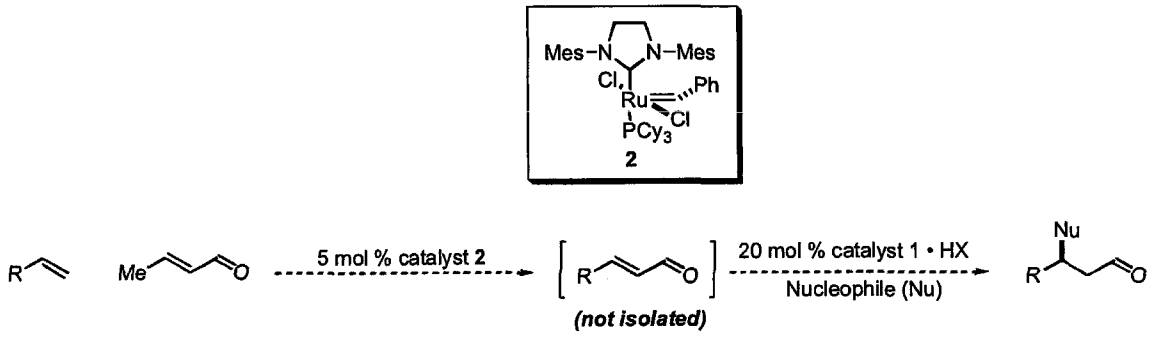
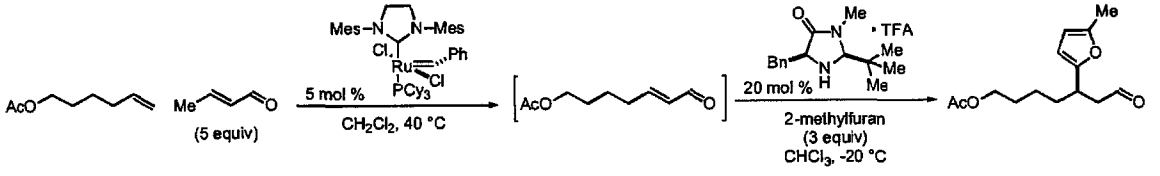


Figure 29. Proposed scheme of sequential olefin metathesis-organocatalysis reactions.

2.2 Examination of Substrate Scope

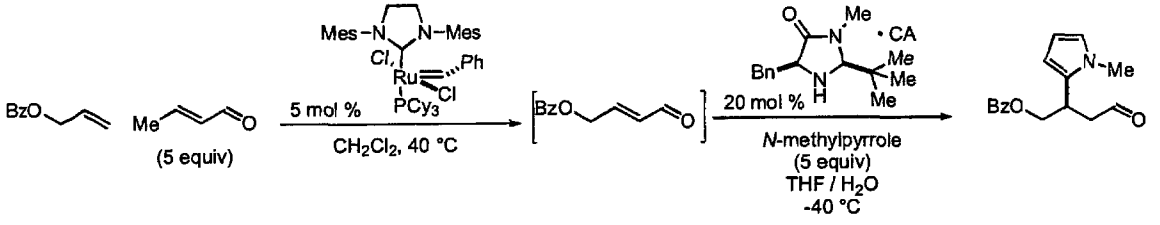
The alkylation of 2-methylfuran was selected as a platform from which we could study the viability of this tandem catalysis strategy. In conjunction with catalyst **1**, this simple heterocycle had been found to display both excellent reactivity and enantioselectivity with a wide range of electrophiles.[2a] The cross metathesis reaction was

carried out between crotonaldehyde and 5-hexenyl acetate to afford the cross product 7-oxo-5-heptenyl acetate. Initially, the aldehyde was purified before attempting the organocatalysis reaction. We found that both the yield of the reaction (71% overall) and enantiomeric excess (92%) were excellent. We next tried subjecting the crude metathesis product to the organocatalytic reaction without intervening purification. Gratifyingly, we found that the use of the crude aldehyde cross product had little effect on the reaction efficiency. The yield increased slightly (72%) and the ee was virtually unchanged (91%, Scheme 57).



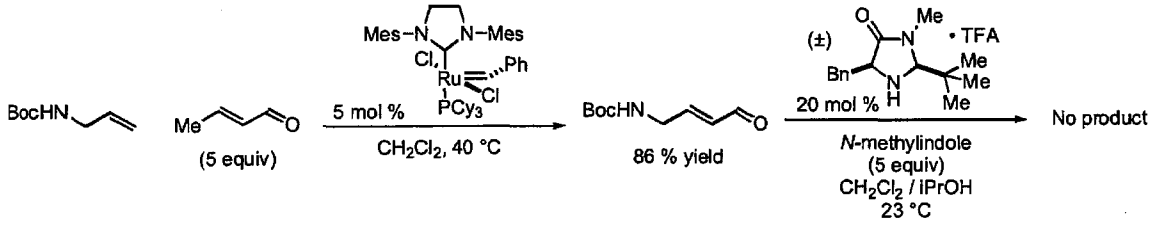
Scheme 57. *Reaction of 2-methylfuran with crude aldehyde cross metathesis product.*

We next turned our attention to the use of pyrrole as nucleophile.[5] Starting from allyl benzoate, the crude aldehyde 4-oxo-2-butenyl benzoate was prepared via cross metathesis. The organocatalytic conjugate addition proceeded to yield the desired aldehyde, which was immediately reduced with sodium borohydride to the corresponding alcohol.[6] Overall, a 67% yield was obtained for the cross metathesis, conjugate addition, and reduction. HPLC analysis showed the product to be of 90% ee (Scheme 58). The product of this reaction was used in the first enantioselective total synthesis of (*S*)-Ketorolac, a pharmaceutical currently marketed as a racemate.[7]



Scheme 58. Reaction of N-methylpyrrole with crude aldehyde cross metathesis product.

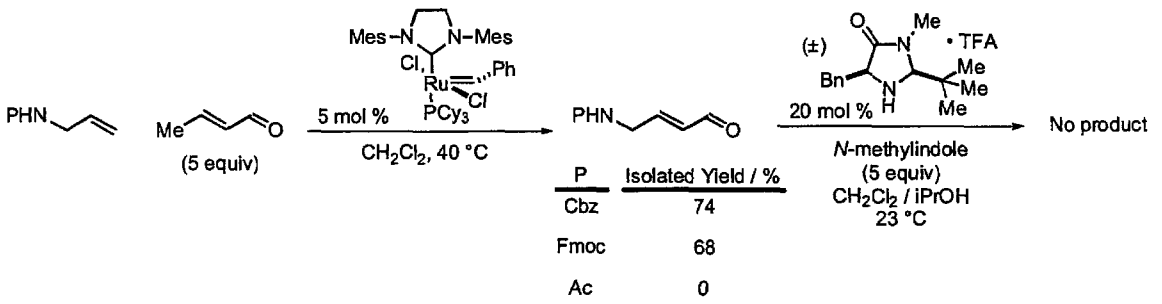
In our attempts to further expand the scope of organocatalytic Friedel-Crafts reactions with our tandem strategy, we gained some insight into the limitations of the organocatalysis platform. We examined the conjugate addition of indoles to crude unsaturated aldehydes. In an attempt to introduce heteroatomic functionality to conjugate adducts of indoles,[2c] we used a protected allylamine as a cross partner. Initially, the *tert*-butoxycarbonyl (Boc) group was chosen as protecting group due to its low cost and ease of introduction and removal.[8] Boc-protected allylamine underwent cross metathesis efficiently to afford the corresponding cross product in 86% yield. After purification, however, this aldehyde did not engage in organocatalytic conjugate addition. A range of decomposition products was observed, with ^{1}H NMR of the crude reaction mixture showing no evidence of the desired product. (Scheme 59).



Scheme 59. Attempted organocatalytic indole reaction with a protected amine.

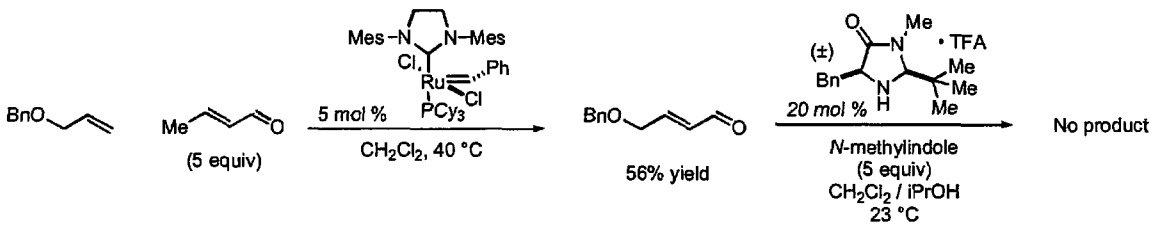
In order to solve this problem, we tried using several different protecting groups on allylamine to ensure that the protecting groups were not hindering the organocatalytic reaction. Thus, the acetyl, 9-fluorenylmethylcarbonyl (Fmoc), and benzyloxycarbonyl

(Cbz) protected allylamine compounds were prepared and crossed with crotonaldehyde. The *N*-allylacetamide failed to undergo cross metathesis, but the Cbz and Fmoc analogues afforded the corresponding cross products in 74% and 68% yields, respectively.[9] Unfortunately, neither the Cbz nor the Fmoc compound was observed to afford the corresponding indole conjugate adduct at both room temperature and lower temperatures. Analysis of the reaction mixtures showed no presence of any compound resembling the product (Scheme 60).



Scheme 60. Attempted organocatalytic reactions of differentially protected amine cross products.

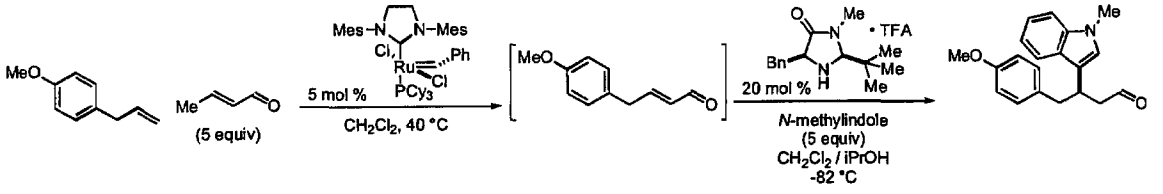
With these results in hand, we decided to opt for a cross partner containing a different heteroatom. Cross metathesis between benzyl allyl ether and crotonaldehyde proceeded in moderate yield (56%). Disappointingly, when this product was reacted with indole, no conjugate adduct was observed (Scheme 61).



Scheme 61. Organocatalytic reaction of benzyl allyl ether with *N*-methylindole.

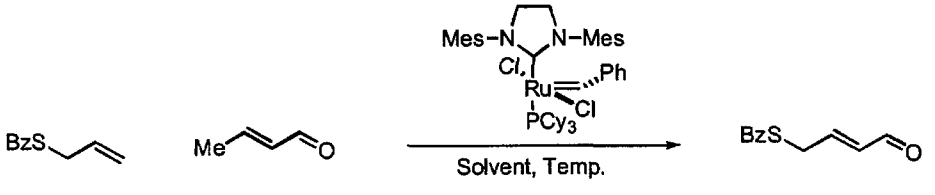
The cross metathesis reaction of 4-allylanisole proceeded efficiently to afford 4-(4-methoxyphenyl)-2-butenal in 94% yield. When the crude unsaturated aldehyde was

subjected to conditions for organocatalysis, the product was isolated in 76% yield for two steps and 92% ee (Scheme 62).



Scheme 62. Successful organocatalytic indole addition to 4-allylanisole-derived cross product.

Shortly before this indole reaction was completed, work done in our laboratory had demonstrated that electron-rich benzenes could also be used successfully as nucleophiles for organocatalytic conjugate addition.[10] We therefore decided to extend the olefin-metathesis / organocatalysis methodology to encompass this new methodology. In accord with our prior attempts to introduce new heteroatomic functionality, a sulfur-containing substrate was examined as a prospective electrophile. In the cross metathesis reaction between *S*-allylthiobenzoate and crotonaldehyde a disappointing yield of 39% was obtained. Variation of the catalyst loading, reaction temperature, and equivalents of crotonaldehyde provided little improvement in reaction efficiency (Table 80).

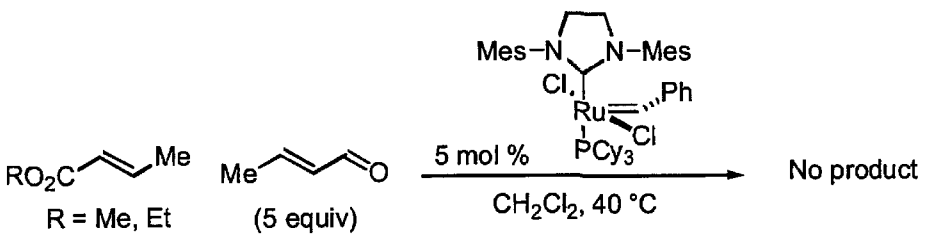


Entry	Cat. Loading / mol %	Solvent	Temp / °C	Equiv. Crotonaldehyde	Isolated Yield / %
1	5	CH_2Cl_2	40	5	39
2	10	CH_2Cl_2	40	5	42
3	10	CH_2Cl_2	40	15	29
4	10	$ClCH_2CH_2Cl$	82	5	37
5	10	$ClCH_2CH_2Cl$	82	15	50

Table 80. Attempts to optimize the yield of the cross reaction between crotonaldehyde and *S*-allylthiobenzoate.

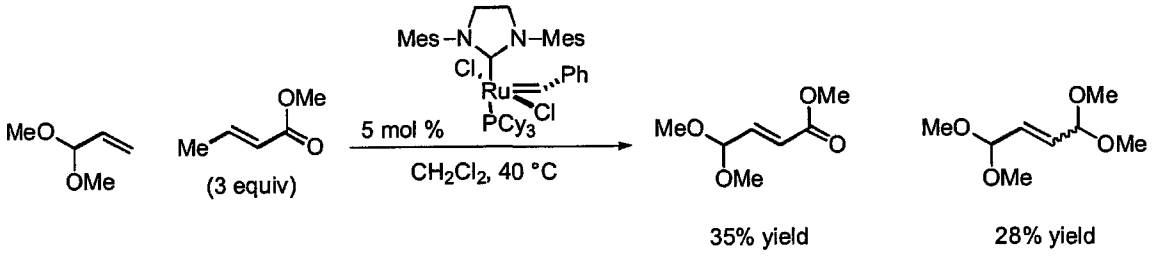
Presumably, the reaction is retarded by coordination of sulfur to ruthenium.[11] No cross metathesis dimer was observed to form in this reaction, providing some evidence for sulfur coordination.

Work in our laboratories had demonstrated that the molecule methyl-4-oxo-2-butenoate was an extremely reactive electrophile for conjugate addition, presumably due to the highly electron-withdrawing effect of the ester group appended to the unsaturated olefin. Thus, we attempted to prepare the molecule via olefin cross metathesis for use in organocatalysis. Initial experiments with crotonaldehyde and either methyl or ethyl crotonate proved fruitless. The only products isolated from the reaction mixture were starting material and cinnemaldehyde (Scheme 63).



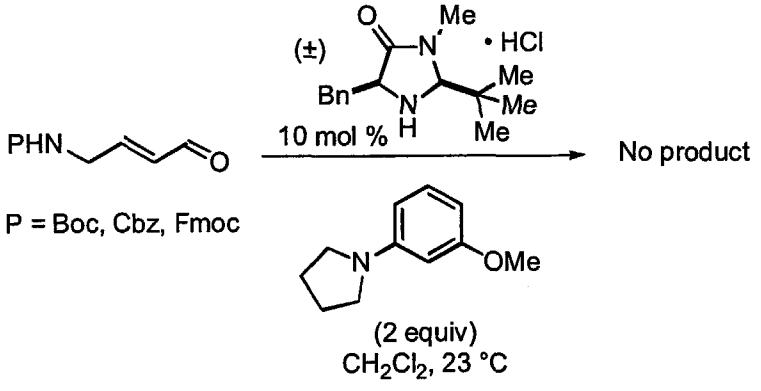
Scheme 63. Attempted cross metathesis reactions between crotonaldehyde and ethyl and methyl crotonate.

As an alternate route to the desired compound, we next tried the cross reaction of methyl acrylate with acrolein dimethyl acetal. The acetal functioned as a surrogate for the desired unsaturated compound and we surmised that under the acidic conditions of organocatalysis, acetal hydrolysis might occur to unmask the unsaturated enal moiety. Disappointingly, the cross product was isolated in only 35% yield, with significant amount of product being the dimer of acrolein dimethyl acetal (Scheme 64).



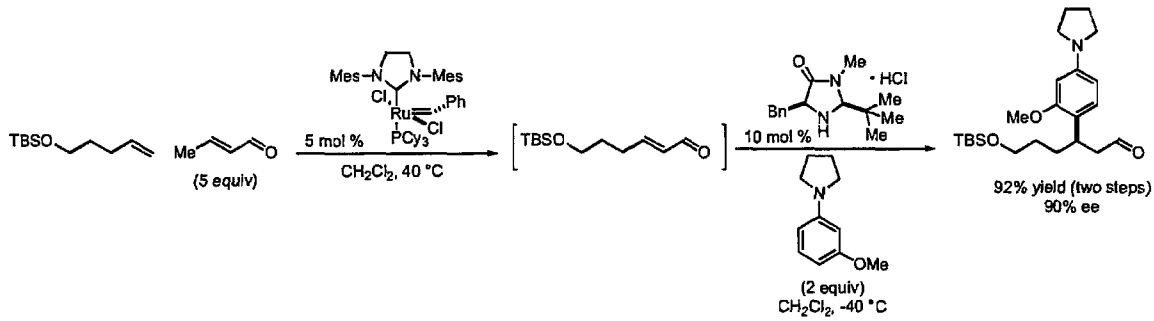
Scheme 64. Results of cross metathesis reaction between acrolein dimethyl acetal and methyl crotonate.

The protected allylamine compounds initially prepared for conjugate addition of indoles were also submitted to organocatalysis with an aniline. Monitoring of the reaction via LC/MS showed no indication of the formation of any of the desired product (Scheme 65).



Scheme 65. Reaction of protected allylamine cross products with electron-rich benzene.

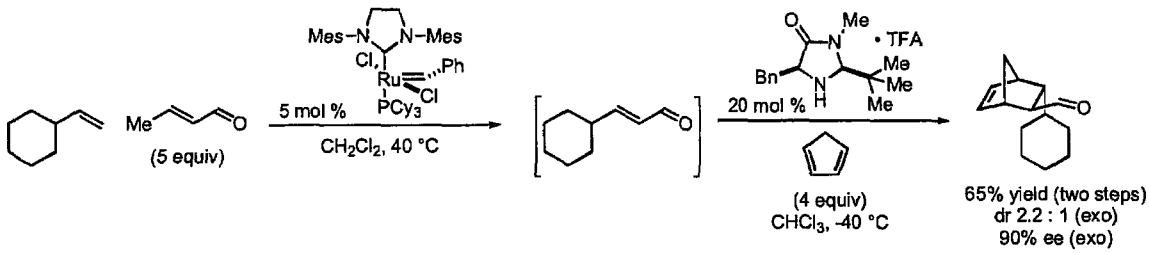
The silyl ether compound shown below displayed excellent compatibility with the aniline reaction. Cross metathesis of the olefin with crotonaldehyde followed by use of the crude product in organocatalysis furnished the aniline conjugate adduct in 92% yield for two steps and 90% ee (Scheme 66).



Scheme 66. Successful organocatalytic conjugate addition of an aniline to crude cross metathesis product.

With an example completed from each of the optimized organocatalytic conjugate additions, we next looked at attempting cycloadditions. Both Diels-Alder and [3 + 2] nitrone cycloadditions had proven successful and highly enantioselective with organic catalysis using the benzyl imidizolidinone framework.[2e, 12a-d]

Cross metathesis of vinylcyclohexane with crotonaldehyde, followed by reaction with cyclopentadiene afforded the chiral norbornene shown in Scheme 67. The product was obtained 65% yield for two steps with a diastereomeric ratio of 2.15 : 1. The major diastereomer was determined to be the *exo* isomer, which had an ee of 90%.



Scheme 67. Application of sequential cross metathesis/organocatalysis to the Diels-Alder reaction.

The final reaction that we examined was the organocatalytic [3 + 2] nitrone cycloaddition. Initially, we pursued olefins containing protected phosphorus, since these molecules have received little attention as cross metathesis partners in the literature. Additionally, after cycloaddition, deprotection, and cleavage of the N-O bond of the

product isoxazolidine, this was considered to be a potential route to enantiomerically enriched tridentate ligands for organometallic catalysts (Figure 30).

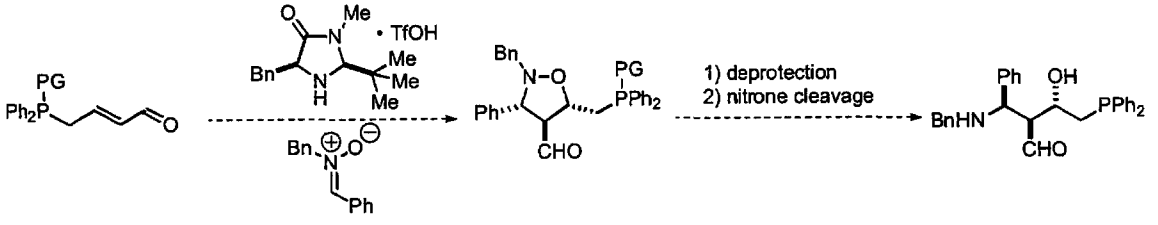
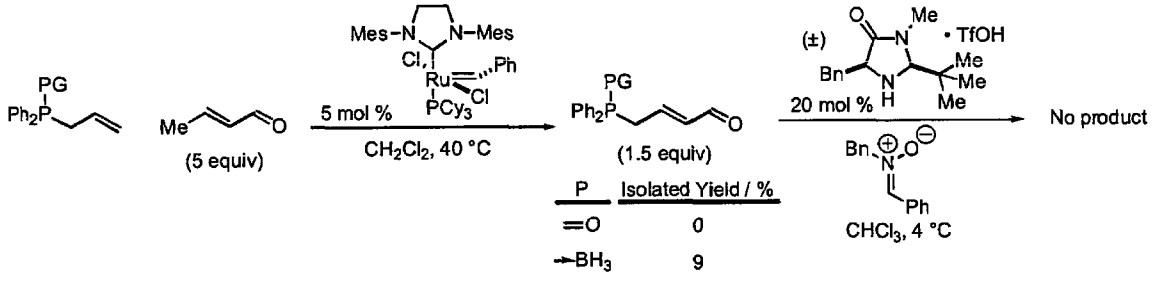


Figure 30. Hypothetical sequence for preparation of enantioenriched tridentate ligands *via* organocatalytic nitrone cycloaddition.

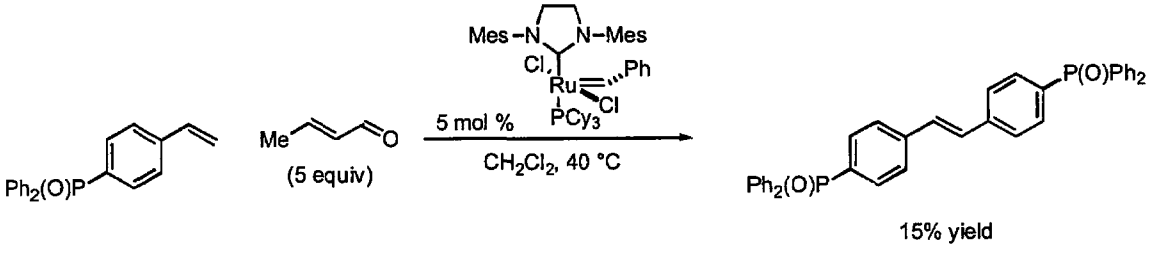
Initially, we used the commercially available allyldiphenylphosphine oxide as a cross partner. Under standard cross metathesis reaction conditions, no cross product was formed. The material that was isolated from the reaction was determined to be the exclusively the dimer of the cross reaction. Use of the borane-protected phosphine gave the cross product in 9% yield. Unfortunately, no product was isolated on reaction of this aldehyde with the nitrone and organic catalyst (Scheme 68).



Scheme 68. Attempted use of phosphorus-containing cross products in nitrone cycloaddition.

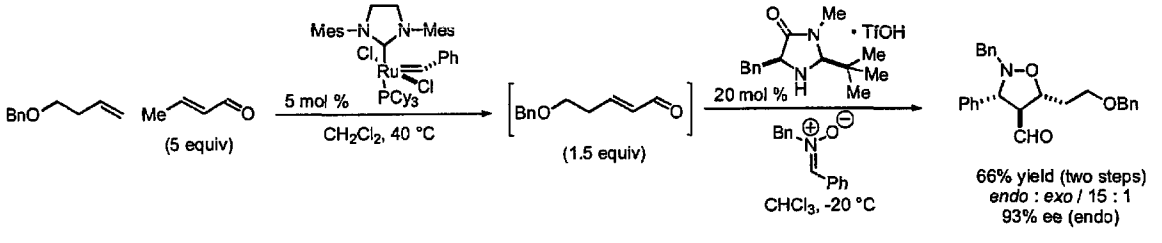
One possible explanation for the substandard reactivity of the phosphine oxide is that it is capable of forming a cyclic chelate with the ruthenium catalyst. To eliminate this possibility, 4-vinylphenyldiphenylphosphine oxide was used as cross partner instead. Although it is geometrically impossible for a chelate to form, the oxide underwent cross

metathesis inefficiently, furnishing the cross partner in 15% yield. These types of phosphine-containing substrates were therefore not pursued any further (Scheme 69).



Scheme 69. Preparation of phosphorus-containing unsaturated aldehyde by cross metathesis.

As seen in prior cases, use of more conventional olefins as cross partners resulted in increases in yield. The metathesis reaction between 4-benzyloxybutene and crotonaldehyde proceeded smoothly to afford the unsaturated aldehyde in 84% yield. When the crude cross product was subjected to organocatalysis, the reaction proceeded in good yield (66% for two steps) and high stereoselectivity [*endo* : *exo* / 15 : 1, 93% ee (*endo*)] (Scheme 70).



Scheme 70. Successful application of sequential olefin metathesis/organocatalysis methodology to nitrone cycloadditions.

2.3 Conclusions and Directions for Future Research

In summary, we have demonstrated the successful application of olefin metathesis and organocatalysis to the rapid construction of enantioenriched organic molecules. Our system features two operationally simple methodologies and does not require isolation

and purification of reaction intermediates. We expect the sequential method developed herein to be a convenient expansion of the utitlity of cross metathesis and organocatalysis.

There are several issues which remain to be addressed, including further extension of cross metathesis to allow the incorporation of heteroatoms in cross partners, and a more thorough investigation of the use of these molecules in organocatalytic conjugate additions.

2.4 References

(1) For an excellent monograph on LUMO-lowering activation, see Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*. New York: John Wiley & Sons, 1976.

(2) Conjugate additions: (a) Brown, S. P. ; MacMillan, D. W. C. Unpublished results; (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, accepted for publication; (c) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. Cycloadditions: (e) Wiener, J. J. M..; MacMillan, D. W. C. unpublished results..

(3) See Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res* . **2001**, *34*, 18, and references cited therein.

(4) See Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868, and references cited therein.

(5) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

(6) In prior experiments, this was deemed necessary in order to suppress product decomposition. Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *123*, 4370.

(7) Paras, N. A.; Countryman, C. C.; Brown, S. P.; MacMillan, D. W. C., unpublished results.

(8) Kocienski, P. J. *Protecting Groups*. New York: Georg Thieme Verlag, 2000.

(9) The lack of reactivity of the *N*-allyl acetamide is in accord with recent results published by Grubbs and coworkers. In the attempted preparation of a,b-unsaturated amides *via* cross metathesis, amides with insufficiently bulky substituents showed poor reactivity due to formation of a chelate. Choi, T. L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1277.

(10) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, submitted for publication.

(11) (a) Shon, Y .-S.; Lee, T. R. *Tetrahedron Lett.* **1997**, *38*, 1283; (b) Toste, F. D.; Chatterjee, A. K.; Grubbs, R. H. *Pure Appl. Chem.* **2002**, *74*, 7.

(12) Diels—Alder: (a) Ahrendt, K. A . ; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243; (b) Wiener, J. J. M.; MacMillan, D. W. C., unpublished results; Nitrone cycloaddition: (c) Jen, W. S.; Wiener, J. J. M., MacMillan, D. W. C. *J. Am.*

Chem. Soc. **2000**, *122*, 9874; (d) Wiener, J. J. M.; MacMillan, D. W. C., unpublished results.

Chapter Three

Experimental

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method described by Still.[2] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching and/or potassium permanganate, anisaldehyde, vanillin, phosphomolybdic acid, or 2,4-dinitrophenyl hydrazine stain.

^{1}H and ^{13}C NMR spectra were recorded on Varian I-500 (500 MHz and 125 MHz, respectively) or Varian Mercury-300 (300 MHz and 75 MHz, respectively), as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported with chemical shift (d ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sxt = sextet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C NMR are reported with chemical shift. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were recorded on a JASCO P-1010 polarimeter (WI lamp, 589 nm, ambient temperature). High-resolution mass spectra were obtained from the UC Irvine Mass Spectral Facility. Gas chromatography was performed

(1) D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford, 1988.
(2) W. C. Still, M. Khan, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

on Hewlett-Packard 5890A and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex G-TA (30 m x 0.25 mm) or b-DM (30 m x 0.25 mm) column. HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm), OJ (25 cm) and OJ guard (5 cm), and AS (25 cm) and AS guard (5 cm).

(5*R*)-5-(5-methyl-2-furyl)-7-oxoheptyl acetate (Scheme 57). An oven-dried two-necked 25 mL round bottom flask was charged with catalyst **2** (91.2 mg, 0.11 mmol). The flask was connected to a reflux condenser and the setup purged with argon. After approximately 10 minutes the catalyst was dissolved in 10.50 mL of CH_2Cl_2. Crotonaldehyde (0.635 mL, 537.2 mg, 7.66 mmol) and 5-hexenyl acetate (216.7 mg as a solution in 1.00 mL of CH_2Cl_2) were added simultaneously *via* syringe, and the reaction was placed in an oil bath preheated to 40 °C. The reaction was allowed to stir for 15 hours, at which time the reaction contents were concentrated on the rotary evaporator, followed by high-vacuum for 45 minutes to remove excess crotonaldehyde. A 2 dram vial equipped with a magnetic stirbar was charged with catalyst **1** (75.1 mg, 0.31 mmol) followed by $CHCl_3$ (2.50 mL), TFA (0.024 mL, 34.8 mg, 0.31 mmol), and the crude 7-oxo-5-heptenyl acetate as a solution in $CHCl_3$ (0.50 mL). The resulting mixture was cooled to –20 °C and stirred for ~ 5 minutes. 2-Methylfuran (0.41 mL, 374.9 mg, 4.567 mmol, precooled to –20 °C) was added and the reaction mixture stirred until the starting material was judged to be consumed *via* TLC (approximately 18 hours). The reaction mixture was concentrated and purified *via* direct flash chromatography (6 : 1 / hexanes : ethyl acetate) to afford the title compound as a dark yellow oil (274.9 mg, 71.50% yield

for two steps); R_f = 0.47 (3 : 1 / hexanes : ethyl acetate); $[a]_D^{23}$ +11.7 (*c* = 1.10, $CHCl_3$); IR (thin film): n_{max} = 2940, 1739, 1565, 1383, 1366, 1242, 1036, 961, 786 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): d = 9.64 (t, $^3J(H,H)$ = 2.4 Hz, 1H, **CHO**), 5.83 (d, $^3J(H,H)$ = 3.3 Hz, 1H, furyl 3**H**), 5.77 (m, 1H, furyl 4**H**), 3.96 (t, $^3J(H,H)$ = 6.6 Hz, 2H, AcO**CH**$_2$), 3.17 (p, $^3J(H,H)$ = 7.1 Hz, 1H, **CH**CH_2CHO), 2.61 (qdd, $^3J(H,H)$ = 17.6, 6.6, 1.5 Hz, 2H, **CH**$_2$CHO), 1.97 (s, 3H, OCO**CH**$_3$), 2.18 (s, 3H, furyl **CH**$_3$), 1.57 (m, 4H, AcO**CH**$_2$**CH**$_2$**CH**$_2$), 1.27 (sxt, $^3J(H,H)$ = 7.8 Hz, 2H, AcOCH$_2$**CH**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): d = 201.3, 170.9, 154.5, 150.7, 106.2, 105.8, 64.2, 47.8, 33.6, 33.4, 28.4, 23.5, 21.0, 13.6; 91% ee. Ratio of product enantiomers was determined by HPLC analysis of the alcohol obtained from sodium borohydride reduction of the title compound [Chiraldex AS column and AS guard (2% ethanol in hexanes, 1 mL min^{-1}), detector wavelength = 220 nm; *S* isomer t_r = 51.306 min and *R* isomer t_r = 57.683 min].

4-Hydroxy-(2*R*)-(1*H*-pyrrol-2-yl)-butyl benzoate (Scheme 58). An oven-dried two-necked 25 mL round bottom flask was charged with catalyst **2** (63.6 mg, 0.075 mmol). The flask was connected to a reflux condenser and the setup purged with argon. After approximately 5 minutes the catalyst was dissolved in CH_2Cl_2 (7.00 mL). Crotonaldehyde (0.625 mL, 528.8 mg, 7.54 mmol) and allyl benzoate (261.9 mg, 1.49 mmol, as a solution in 0.5 mL CH_2Cl_2) were added simultaneously *via* syringe and the reaction was placed in an oil bath preheated to 40 °C. The reaction was allowed to stir for 13 hours, at which time the reaction contents were concentrated on the rotary evaporator, followed by high-vacuum for 45 minutes to remove excess crotonaldehyde. A 2 dram vial equipped with a magnetic stirbar was charged with catalyst **1** (73.4 mg, 0.298 mmol) followed by ether (0.170 mL) water (0.030 mL), and chloroaceetic acid

(28.2 mg, 0.298 mmol). The vial was cooled to –30 °C and stirred for 5 minutes before pyrrole was added (0.52 mL, 7.50 mmol). After an additional 5 minutes of stirring, the crude 7-oxo-5-heptenyl acetate was added dropwise as a solution in ether (0.100 mL). After 14 hours, the reaction was was judged to be complete by TLC. The reaction mixture was transferred cold into a 20 mL vial containing ethanol (5.00 mL) and excess sodium borohydride (110 mg, 2.95 mmol). After 15 minutes, the reaction was quenched by addition of a saturated aqueous solution of sodium bicarbonate. This mixture was extracted into CH_2Cl_2 (3 x 10 mL) and the collected organic layers were washed with brine, dried over anhydrous sodium sulfate, concentrated, and purified *via* flash chromatography (3 : 2 / hexanes : ethyl acetate) to afford the product as a clear oil that crystallized on standing (258.9 mg, 67% yield for three steps); $R_f = 0.11$ (3 : 1 / hexanes : ethyl acetate); $[a]_D^{22}$ –20.2 (*c* = 1.0, $CHCl_3$); IR (thin film): n_{max} = 3485, 2957, 1699, 1651, 1454, 1277, 1177, 1120, 1070, 1027, 712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): d = 8.46 (br s, 1H, pyrrole N**H**), 7.98-8.06 (m, 2H, Ar**H**), 7.54-7.62 (tt, $^3J(H,H)$ = 7.8, 1.2 Hz, 1H, Ar**H**), 6.70-6.74 (m, $^3J(H,H)$ = 2.7, 1.8 Hz, 1H, Ar**H**), 6.14-6.20 (dd, $^3J(H,H)$ = 6, 2.7 Hz, 1H, Ar**H**), 6.06 (t, $^3J(H,H)$ = 3.6 Hz, 1H, Ar**H**), 4.50-4.58 (m, 1H, C**H**HOBz), 4.42-4.50 (m, 1H, CH**H**OBz), 3.72-3.84 (m, 1H, C**H**HOH), 3.62-3.72 (m, 1H, CH**H**OH), 3.32-3.44 (m, 1H, C**H**CH_2OBz), 2.02-2.16 (m, 1H, C**H**HCH_2OH), 1.86-2.02 (m, 1H, CH**H**CH_2OH), 1.48 (br s, 1H, O**H**); ^{13}C NMR (125 MHz, $CDCl_3$): d = 133.3, 131.6, 130.2, 129.7, 128.6, 117.2, 108.5, 105.4, 68.4, 60.8, 35.3, 34.5; 90% ee. Ratio of product enantiomers was determined by HPLC analysis [Chiraldex AD column and AD guard (10% isopropanol in hexanes, 1 mL min^{-1}), detector wavelength = 254 nm; *S* isomer t_r = 18.791 min and *R* isomer t_r = 20.395 min].

(3*R*)-4-(4-methoxyphenyl)-3-(1-methyl-1*H*-indol-3-yl)butanal (Scheme 62). An oven-dried two-necked 25 mL round bottom flask was charged with catalyst **2** (42.7 mg, 0.05 mmol). The flask was connected to a reflux condenser and the setup purged with argon. After approximately 10 minutes the catalyst was dissolved in 5.00 mL of CH_2Cl_2. Crotonaldehyde (0.42 mL, 355.3 mg, 5.07 mmol) and 4-allyl anisole (0.155 mL, 149.6 mg, 1.01 mmol) were added simultaneously *via* syringe, and the reaction was placed in an oil bath preheated to 40 °C. The reaction was allowed to stir for 12 hours, at which time the reaction contents were concentrated on the rotary evaporator, followed by high-vacuum for 45 minutes to remove excess crotonaldehyde. A 2 dram vial equipped with a magnetic stirbar was charged with catalyst **1** (49.8 mg, 0.20 mmol) followed by CH_2Cl_2 (1.30 mL), isopropyl alcohol (0.20 mL), and TFA (0.016 mL, 23.7 mg, 0.20 mmol). The reaction was cooled to –82 °C and after five minutes of stirring, *N*-methyl indole was added (0.39 mL, 400.1 mg, 3.05 mmol). After an additional 5 minutes, the crude cross metathesis product as a solution in CH_2Cl_2 (0.50 mL) was added dropwise with stirring. The reaction mixture was stirred until the starting material was judged to be consumed *via* TLC (approximately 96 hours). The reaction mixture was concentrated and purified *via* direct flash chromatography (2 : 1 / hexanes : ethyl acetate) to afford the title compound as a yellow oil (234.7 mg, 75.64% yield for two steps); R_f = 0.19 (2 : 1 / hexanes : ethyl acetate). The product was characterized as the alcohol obtained from borohydride reduction of the title compound; $[a]_D^{23}$ +28.8 (*c* = 2.10, $CHCl_3$); IR (thin film): n_{max} = 3385, 3054, 2932, 2834, 1611, 1582, 1511, 1465, 1374, 1326, 1300, 1245, 1177, 1035, 819, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): d = 7.70 (d, $^3J(H,H)$ = 8 Hz, 1H, indole 7**H**), 7.32 (d, $^3J(H,H)$ = 8 Hz, 1H, indole 4**H**), 7.25 (dd, $^3J(H,H)$ = 8, 6.5 Hz, 1H,

indole 5**H**), 7.20 (d, ^{3}J(H,H) = 8.5 Hz, 2H, phenyl 3**H**), 7.13, (dd, ^{3}J(H,H) = 8, 6.5 Hz, 1H, indole 6**H**), 6.789 (s, 1H, indole 2**H**), 6.79 (d, ^{3}J(H,H) = 8.5 Hz, 2H, phenyl 2**H**), 3.82 (s, 3H, phenyl O**CH$_3$**), 3.78 (s, 3H, indole **CH$_3$**), 3.61 (m, 1H, **CH**HOH), 3.54 (m, 1H, CH**H**OH), 3.10 (dd, ^{3}J(H,H) = 13.5, 7 Hz, 1H, ArC**H**H), 3.00 (m, 1H, ArCH$_2$C**H**), 2.92 (dd, ^{3}J(H,H) = 13, 9 Hz, 1H, ArCH**H**), 2.00 (m, 2H, C**H$_2$**CH$_2$OH), 1.20 (br s, 1H, O**H**); ^{13}C NMR (125 MHz, $CDCl_3$): d = 157.9, 137.5, 133.2, 130.4, 127.3, 126.4, 121.5, 119.7, 119.6, 119.0, 117.6, 113.6, 110.0, 61.9, 42.3, 37.7, 37.6, 36.0, 36.0, 32.7; 92% ee. Ratio of product enantiomers was determined by HPLC analysis of the alcohol obtained from sodium borohydride reduction of the title compound [Chiraldex AD column and AD guard (2% ethanol in hexanes, 1 mL min^{-1}), detector wavelength = 254 nm; *S* isomer t_r = 73.359 min and *R* isomer t_r = 77.529 min].

6-(*tert*-Butyl-dimethylsilanyloxy)-(3*R*)-(2-methoxy-4-pyrrolidin-1-yl-phenyl)hexanal (Scheme 66). An oven-dried two-necked 25 mL round bottom flask was charged with catalyst **2** (43.8 mg, 0.05 mmol). The flask was connected to a reflux condenser and the setup purged with argon. After approximately 10 minutes the catalyst was dissolved in 5.00 mL of CH_2Cl_2. Crotonaldehyde (0.44 mL, 372.2 mg, 5.31 mmol) and *tert*-butyldimethyl-4-pentenyloxysilane (210.3 mg in 0.5 mL CH_2Cl_2, 1.05 mmol) were added simultaneously *via* syringe, and the reaction was placed in an oil bath preheated to 40 °C. The reaction was allowed to stir for 16 hours, at which time the reaction contents were concentrated on the rotary evaporator, followed by high-vacuum for 45 minutes to remove excess crotonaldehyde. A 2 dram vial equipped with a magnetic stirbar was charged with catalyst **1** (25.9 mg, 0.11 mmol) followed by CH_2Cl_2 (0.95 mL), and HCl (0.027 mL as a 4N solution in dioxane, 0.11 mmol). The reaction

was cooled to –40 °C and after five minutes of stirring, 1-(3-methoxyphenyl)pyrrolidine was added (0.35 mL, 372.1 mg, 2.10 mmol). After an additional five minutes, the crude aldehyde was added as a solution in CH_2Cl_2 (0.50 mL). The reaction mixture was stirred until the starting material was judged to be consumed *via* TLC (approximately 4.5 days). The reaction mixture was concentrated and purified *via* direct flash chromatography (19 : 1 / hexanes : ethyl acetate) to afford the title compound as a yellow oil (392.9 mg, 92.34% yield for two steps); R_f = 0.48 (6 : 1 / hexanes : ethyl acetate). The product was characterized as the alcohol obtained from borohydride reduction of the title compound; $[a]_D^{23}$ –6.8 (*c* = 1.23, $CHCl_3$); IR (thin film): n_{max} = 3440, 2934, 2844, 1616, 1566, 1515, 1456, 1372, 1247, 1223, 1096, 1038, 835, 772, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): d = 6.96 (d, $^3J(H,H)$ = 8.4 Hz, 1H, phenyl 2**H**), 6.19 (dd, $^3J(H,H)$ = 8.1, 2.1 Hz, 1H, phenyl 5**H**), 6.09 (d, $^3J(H,H)$ = 2.1 Hz, 1H, phenyl 4**H**), 3.82 (s, 3H, phenyl OC**H**$_3$), 3.55 (t, $^3J(H,H)$ = 6.6 Hz, C**H**$_2$OTBS), 3.46 (m, 1H, C**H**HOH), 3.30 (m, 1H, CH**H**OH), 3.28 (dd, $^3J(H,H)$ = 6.6, 4 Hz, 4H, pyrrolidinyl 2**H**), 3.10 (m, 1H, ArC**H**), 2.08 (br s, 1H, O**H**), 2.00 (m, 4H, pyrrolidinyl 3**H**), 1.90 (m, 2H, C**H**$_2$CH$_2$OH), 1.64 (m, 2H, C**H**$_2$CH$_2$CH$_2$OTBS), 1.40 (m, 2H, C**H**$_2$CH$_2$OTBS), 0.88 (s, 9H, Si((*t*-**Bu**)(CH$_3$)$_2$), 0.02 (s, 6H, Si((*t*-Bu)(C**H**$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): d = 158.3, 147.4, 127.8, 119.1, 104.8, 95.1, 63.5, 61.3, 55.7, 47.9, 40.2, 32.4, 32.1, 31.9, 31.2, 26.3, 25.7, 23.0, 18.7, 14.5, -5.0; 90% ee. Ratio of product enantiomers was determined by HPLC analysis of the alcohol obtained from sodium borohydride reduction of the title compound [Chiraldex OD-H column and OD guard (2% isopropanol in hexanes, 1 mL min^{-1}), detector wavelength = 254 nm; *S* isomer t_r = 51.773 min and *R* isomer t_r = 69.005 min].

(1*R*,2*S*,3*S*,4*R*)-3-cyclohexylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde

(Scheme 67). An oven-dried two-necked 25 mL round bottom flask was charged with catalyst **2** (65.1 mg, 0.08 mmol). The flask was connected to a reflux condenser and the setup purged with argon. After approximately 10 minutes the catalyst was dissolved in 6.7 mL of CH_2Cl_2. Crotonaldehyde (0.85 mL, 716.6 mg, 10.22 mmol) and vinylcyclohexane (0.28 mL, 225.4 mg, 2.05 mmol) were added simultaneously *via* syringe and the reaction was placed in an oil bath preheated to 40 °C. The reaction was allowed to stir for 16 hours, at which time the reaction contents were concentrated on the rotary evaporator, followed by high-vacuum for 45 minutes to remove excess crotonaldehyde. The crude concentrate was then dissolved in $CHCl_3$ (2.05 mL) and catalyst **1** was added (100.8 mg, 0.41 mmol) 0.31 mmol) followed by $CHCl_3$ (2.50 mL), and TFA (0.032 mL, 47.4 mg, 0.41 mmol). The resulting mixture was cooled to –40 °C and stirred for 5 minutes. Freshly distilled cyclopentadiene (0.68 mL, 545.4 mg, 8.25 mmol, precooled to –40 °C) was added and the reaction mixture stirred until the starting material was judged to be consumed *via* TLC. The reaction mixture was concentrated and purified *via* direct flash chromatography (49 : 1 / pentane ether) to afford the title compound as a clear, colorless oil (271.6 mg, 65.01% yield for two steps); R_f = 0.56 (9 : 1 / hexanes : ethyl acetate); IR (thin film): n_{max} = 2924, 2851, 1720, 1699, 1448, 756, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): d = 9.78 (d, $^3J(H,H)$ = 2.7 Hz, 1H, exo **CHO**), 9.35 (d, $^3J(H,H)$ = 3.3 Hz, 1H, endo **CHO**), 6.13 (m, 2H, **CH=CH**), 2.97 (dd, $^3J(H,H)$ = 35.7, 26 Hz, 2H, CH=CHCH**CH$_2$**), 1.5-1.95 (m, 4H, **CH**CH$_2$**CH**, **CH**CHO, **CH**Cy), 0.60-1.50 (m, 11H, cyclohexyl **H**s); ^{13}C NMR (75 MHz, $CDCl_3$): d = 205.3, 204.1, 138.9, 136.1, 135.8, 133.0, 58.4, 57.7, 48.8, 48.7, 46.8, 45.2, 44.9, 44.3, 44.3, 42.4, 42.0, 32.8, 32.6, 32.5,

32.2, 26.7, 26.7, 26.6, 26.5, 26.3; 90% ee (*exo* isomer). Ratio of product enantiomers was determined by GC analysis of the product [b-DM column, 10 degree min^{-1} ramp from 70 °C, 1 mL min^{-1}), *exo* isomer t_r = 12.958 and 13.075 min; *endo* isomer t_r = 13.278 and 13.380 min].

(3*R*,4*S*,5*R*)-2-benzyl-5-(2-benzyloxyethyl)-3-phenylisoxazolidine-4-carbaldehyde (Scheme 70). An oven-dried two-necked 25 mL round bottom flask was charged with catalyst **2** (88.2 mg, 0.10 mmol). The flask was connected to a reflux condenser and the setup purged with argon. After approximately 10 minutes the catalyst was dissolved in 10.30 mL of CH_2Cl_2. Crotonaldehyde (0.85 mL, 721.6 mg, 10.30 mmol) and 4-benzyloxybutene (0.35 mL, 333.9 mg, 2.06 mmol) were added simultaneously *via* syringe, and the reaction was placed in an oil bath preheated to 40 °C. The reaction was allowed to stir for 16 hours, at which time the reaction contents were concentrated on the rotary evaporator, followed by high-vacuum for 45 minutes to remove excess crotonaldehyde. A 2 dram vial equipped with a magnetic stirbar was charged with catalyst **1** (101.4 mg, 0.41 mmol), (*Z*)-*N*-benzylidenebenzylamine *N*-oxide (289.8 mg, 1.37 mmol), $CHCl_3$ (12.70 mL), and trifluoromethanesulfonic acid (0.0365 mL, 61.9 mg, 0.41 mmol). The reaction was immediately cooled to –20 °C. After 15 minutes, the crude aldehyde was added dropwise as a solution in $CHCl_3$ (1.00 mL). The reaction mixture was stirred until the starting material was judged to be consumed *via* TLC (approximately 2 days). The reaction mixture was concentrated and purified *via* direct flash chromatography (5 : 1 / hexanes : ethyl acetate) to afford the title compound as a brown oil (365.9 mg, 66.42% yield for two steps); R_f = 0.23 (5 : 1 / hexanes : ethyl acetate); IR (thin film): n_{max} = 3030, 2864, 1722, 1644, 1495, 1454, 1099, 736, 598 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): d = 9.80 (d, ^{3}J(H,H) = N.D. 1H, *exo* **CH**O), 9.76 (d, ^{3}J(H,H) = 2.4 Hz, 1H, *endo* **CH**O), 7.20-7.50 (m, 15H, Ar**H**), 4.59 (dt, ^{3}J(H,H) = 7.8, 5.4 Hz, 1H, OC**H**CHCHO), 4.16 (d, ^{3}J(H,H) = 7.8 Hz, 1H, PhC**H**CHCHO), 4.01 (d, ^{3}J(H,H) = 14.4 Hz, 2H, OC**H**$_2$Ph), 3.82 (d, ^{3}J(H,H) = 14.4 Hz, 2H, NC**H**$_2$Ph), 3.59 (t, ^{3}J(H,H) = 6 Hz, 2H, C**H**$_2$OBn), 3.29 (m, 1H, C**H**CHO), 2.31 (m, 1H, C**H**HCH$_2$OBn), 2.03 (m, 1H, CH**H**CH$_2$OBn); ^{13}C NMR (75 MHz, $CDCl_3$): d = 198.7, 138.3, 138.2, 137.5, 129.0, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 127.7, 127.2, 127.0, 75.1, 73.3, 71.2, 70.2, 67.0, 59.6, 35.7; 15 : 1 / *endo* : *exo* (diastereomeric ratios determined by ^{1}H NMR analysis); 90% ee. Ratio of product enantiomers was determined by HPLC analysis of the alcohol obtained from sodium borohydride reduction of the title compound [Chiraldex AD column and AD guard (6% isopropanol in hexanes, 1 mL min^{-1}), detector wavelength = 254 nm; 3*S*,4*R*,5*S* isomer t_r = 23.140 min and 3*R*,4*S*,5*R* isomer t_r = 27.569 min].