A study of a chiral 4-substituted oxazolidin-2-one in asymmetric transformations via soluble polymer-supported synthesis and fluorous synthesis

By

Manjula Sudharshan

A Thesis
submitted to the Department of Graduate Studies
in partial fulfillment of the requirements
for the Degree of

Master of Science

Department of Chemistry
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THE UNIVERSITY OF MANITOBA

FACULTY OF GRADUATE STUDIES

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A Study of a Chiral 4-Substituted Oxazolidin-2-One in Asymmetric Transformations Via Soluble Polymer-Supported Synthesis and Fluorous Synthesis

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Abstract

Chiral auxiliaries remain one of the most reliable ways of generating new chiral molecules in a highly enantiomerically enriched form. We have synthesized a new chiral 4-substituted oxazolidin-2-one from *L*-tyrosine via a novel method. The potential of this methodology has been established. Supporting a chiral auxiliary on a polymer provides a convenient work-up and purification procedure and makes its recovery simple. Careful choice of polymer and auxiliary is essential for its success. The first synthesis of a soluble polymer-supported oxazolidinone from the tyrosine-derived oxazolidin-2-one and the soluble poly(ethylene glycol)-monomethyl ether (MeOPEG) has been described. The behavior of the MeOPEG-supported oxazolidin-2-one in the asymmetric alkylation and the Diels-Alder reaction has been disclosed. Fluorous synthesis introduces an alternative route to traditional and polymer-supported synthesis. The synthesis of a novel, highly fluorinated silyl fluorous tag has been described. The tyrosine-derived oxazolidin-2-one has been rendered fluorous upon attachment to the fluorous tag. Asymmetric aldol condensation of the fluorous-tagged oxazolidin-2-one has produced all four diastereoisomers and their stereochemical assignments have been confirmed. This is the first demonstration of the suitability of fluorous synthesis strategy for asymmetric synthesis of chiral oxazolidinones.

Acknowledgments

I am duty bound to express my deepest gratitude to my Supervisor Dr. P. G. Hultin, for his never ending patience, invaluable advice and encouragement in completing my research. I extend my special thanks to my colleagues for their friendship and suggestions throughout this ordeal. The technical assistance of Mr. T. Foniok, Mr. T. Woloweic and Dr. K. Marat of the NMR facility is greatly appreciated. Also thanks to Mr. C. Curtis of the chemical store and Mr. I. Ward of the glassblowing shop for their help. I would like to thank the University of Manitoba for the financial support during my work.

Finally, I would like to express my thanks to my parents and my husband for their love, support and encouragement during each and every endeavor I have undertaken.

Table of contents

Abbreviations

Ac_2O	acetic anhydride
acac	acetylacetonate
AcCl	acetyl chloride
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
BTF	benzotrifluoride
calcd	calculated
cbz	benzyloxycarbonyl
DCC	*N,N*-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIPEA	*N,N*-diisopropyl ethylamine
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EI	electron impact (in mass spectrometry)
EtOH	ethanol
FAB	fast atom bombardment (in mass spectrometry)
FC	fluoro carbon
LDA	lithium diisopropylamide
MeCN	acetonitrile
MEK	methylethylketone
MHz	megahertz
min	minute(s)
NBS	*N*-bromosuccinimide
NMO	*N*-methyl morpholine oxide

PFMC	perfluoromethylcyclohexane
RT	room temperature
NaHMDS	sodium hexamethyldisilazane
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilyl chloride
TBDMS-OTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TCE	1,1,2,2-tetrachloroethane
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TMGA/$TMGN_3$	tetramethylguanidium azide
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	trimethylsilyl chloride
p-TsOH	*p*-toluene sulfonic acid
4°	quaternary
C_{Ar}	aromatic carbon (in ^{13}C NMR)
Δ	heat

Introduction

General Introduction

This research is comprised of three major parts: (1) Chiral auxiliary, oxazolidin-2-one - synthesis of a new chiral 4-substituted oxazolidin-2-one via a novel method; (2) Soluble polymer-supported synthesis - preparation of a novel soluble polymer-supported oxazolidin-2-one and the study of its behavior in asymmetric synthesis; (3) Fluorous synthesis - synthesis of a novel fluorous-tagged oxazolidin-2-one and the investigation of its potential in asymmetric synthesis.

1. Chiral auxiliary, oxazolidin-2-one

Chiral auxiliary: General aspects

Asymmetric synthesis or stereoselective synthesis is one of the methods that provide routes for the preparation of a chiral compound in the form of a single enantiomer or diastereomer. In general, asymmetric induction is effected mainly by the use of an optically active substrate or by reacting with a chiral reagent, catalyst or solvent or with the help of a chiral auxiliary[1].

The use of chiral auxiliaries in asymmetric transformations is one of the most efficient and straightforward approaches in organic synthesis[2]. In many aspects, the application of a chiral auxiliary in organic synthesis resembles that of a protecting group. In this strategy, the prochiral substrate is attached to a chiral auxiliary, and after running an asymmetric reaction, the original auxiliary group is cleaved. During a chemical transformation, the chiral auxiliary can preferentially impose a high degree of asymmetric induction. Sometimes, it can be promoted by non-interactive means, such as by sterically blocking reaction at one face of the substrate.

It is important that the chiral auxiliary be stable under most reaction conditions. If further reactions are required the chiral moiety should not be destroyed or interfere with the subsequent reactions. It is also preferred that the diastereomeric derivative of the auxiliary is crystalline, as this allows the removal of impurities by crystallization.

The chiral auxiliaries are employed stoichiometrically because they are attached to the substrate compound. Thus, the attachment of an auxiliary to a substrate has to be feasible,

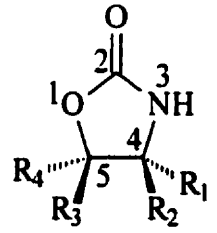
effective, and high yielding. Furthermore, the chiral auxiliary should have a very high optical purity. The auxiliary must be available at a reasonable cost or easily prepared.

After the stereospecific reaction, the chiral auxiliary needs to be removed from the product. The cleavage conditions should not damage or destroy any other delicate functionality elsewhere in the molecule as well as the chiral unit. Therefore, the chiral auxiliary should be removable under mild conditions. The cleavage must proceed in high yield as well. Once cleaved, the chiral auxiliary should be easily isolated from the other products. Since the auxiliary is recovered from the reaction, it would permit recycling of the chiral auxiliary. However, a considerable number of auxiliaries fail to fulfill this requirement.

Currently, an enormous number of chiral auxiliaries find successful applications in organic synthesis. Most of them are derivatives of naturally available chiral compounds such as chiral aminoacids[3], sugars[4], aminoalcohols[5], terpenoids[6,7], etc. Among them, the chiral oxazolidin-2-one is the most important chiral auxiliary available for the asymmetric synthesis of carboxylic acid derivatives.

Chiral oxazolidin-2-ones

The oxazolidin-2-one system has been first introduced as a chiral auxiliary by Evans[8,9]. The general structure of the oxazolidin-2-one is pictured in Figure 1.



R_1, R_2, R_3 and R_4 can be either H or/and other alkyl or aryl substituent/s

Figure 1

Usually, the attachment of the appropriate substrate occurs at position 3 (at the N atom) of the chiral moiety (Figure 2). Various prochiral substrates (most often derivatives of carboxylic

acids such as acid chlorides and anhydrides) are covalently attached to obtain a number of different sterically and stereochemically constrained *N*-derivatives of the auxiliary.

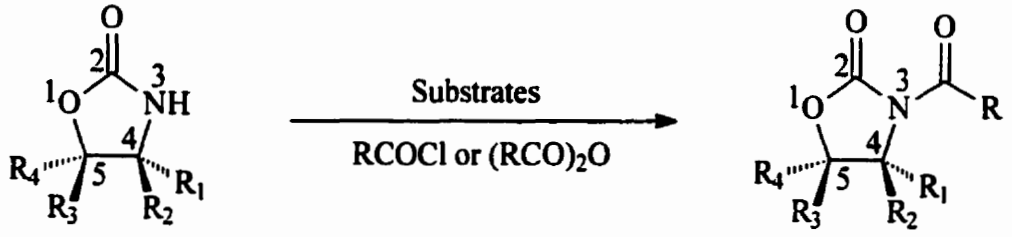


Figure 2

It is essential for a chiral auxiliary to control the relative and absolute chirality when new asymmetric centers are created in the attached substrate. Since the oxazolidinone auxiliary has a structurally organized diastereofacial bias established within the system, it can easily transfer the chirality to the attached substrates. The nature of the substituents (R_1-R_4) and the stereochemical arrangements at positions 4 and 5 of the oxazolidinone play an important role in the determination of the stereoselectivity in asymmetric transformations.

After the stereospecific conversion, the oxazolidinone can be removed without destroying the chiral centers of both the products and the auxiliary. The removal of the oxazolidinones is usually carried out under basic conditions[10]. The nucleophilic cleavage can undergo either exo- or endocyclic hydrolysis[10,11] as in Figure 3.

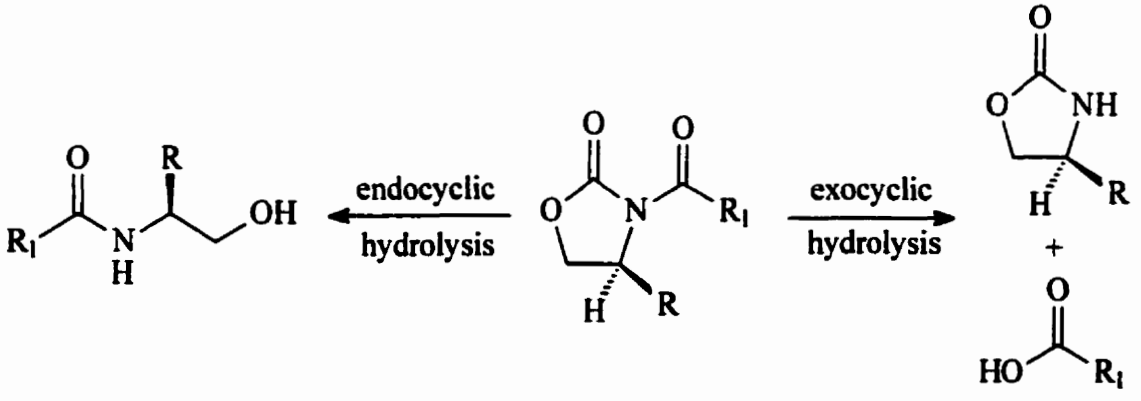


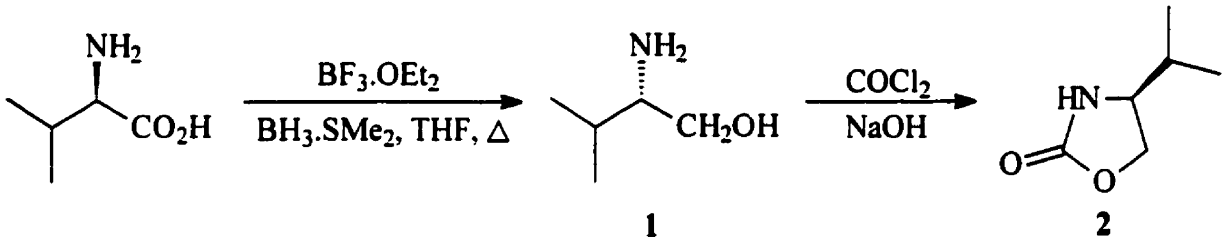
Figure 3

The recovery and recycling of the auxiliary are possible with most of the oxazolidin-2-ones by subjecting them to appropriate cleavage (exocyclic hydrolysis) conditions.

Synthesis of various oxazolidin-2-ones

These versatile auxiliaries are derived from various sources such as aminoacids, aminoalcohols, sugars, amino sugars, and terpenes. Besides, the synthesis also employs a variety of conditions to effect the production of the oxazolidinones.

Oxazolidin-2-ones are most commonly prepared from aminoacids. The procedure for the synthesis involves the reduction of the particular *R*-or *S*-aminoacid to an aminoalcohol followed by the formation of the oxazolidinone. This methodology has been first demonstrated by Evans and his co-workers[8] for the synthesis of (4*S*)-4-isopropyl-2-oxazolidinone **2** from (*S*)-valine as illustrated in Scheme 1.

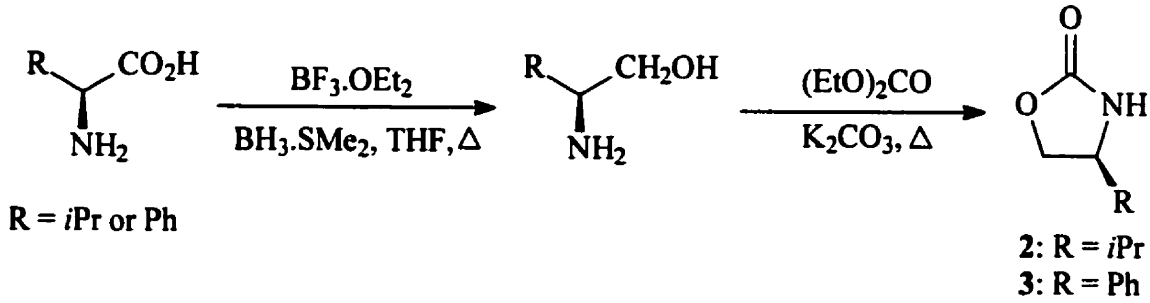


1 **2**

Scheme 1

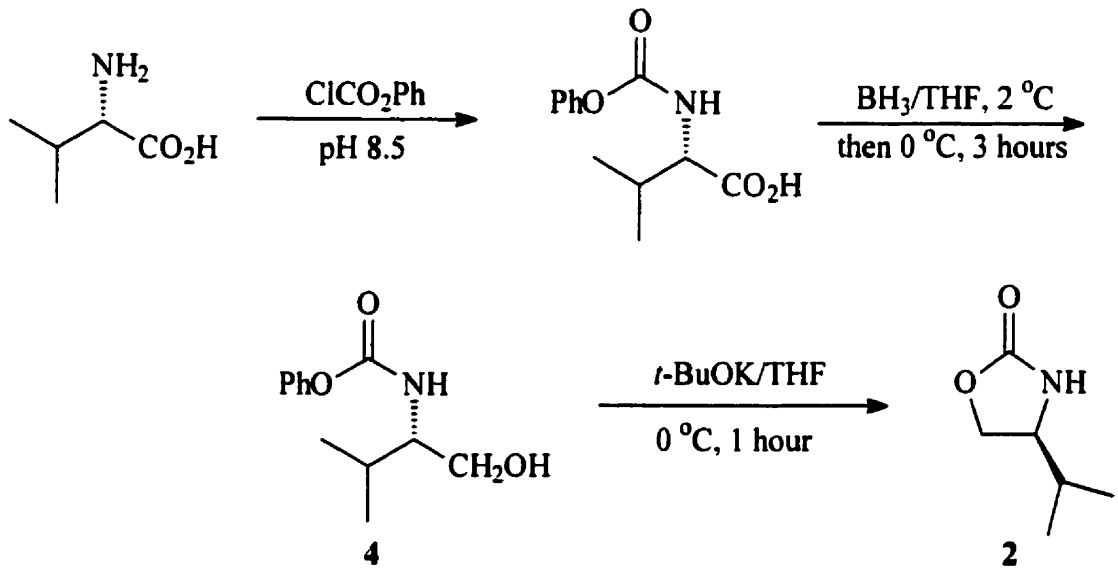
The reduction of (*S*)-valine by borane reducing agent ($BH_3.SMe_2$)[12] and the cyclization of the resulting (*S*)-valinol **1** by phosgene ($COCl_2$) provides the oxazolidinone **2**. While this method is successful, it requires the use of potentially hazardous and expensive borane and phosgene reagents. Furthermore, since the intermediate aminoalcohol is polar in nature it exhibits considerable solubility in water. Therefore, the isolation and purification of the alcohol may be difficult.

The above procedure has been modified to prepare (4*S*)-4-isopropyl-2-oxazolidinone[8] **2** and (4*S*)-4-phenyl-2-oxazolidinone[13] **3** as seen in Scheme 2. In this method, the cyclization of the aminoalcohol by diethyl carbonate ($(EtO)_2CO$) eliminates the use of phosgene for the synthesis, but it still incorporates the borane-mediated reduction step.



Scheme 2

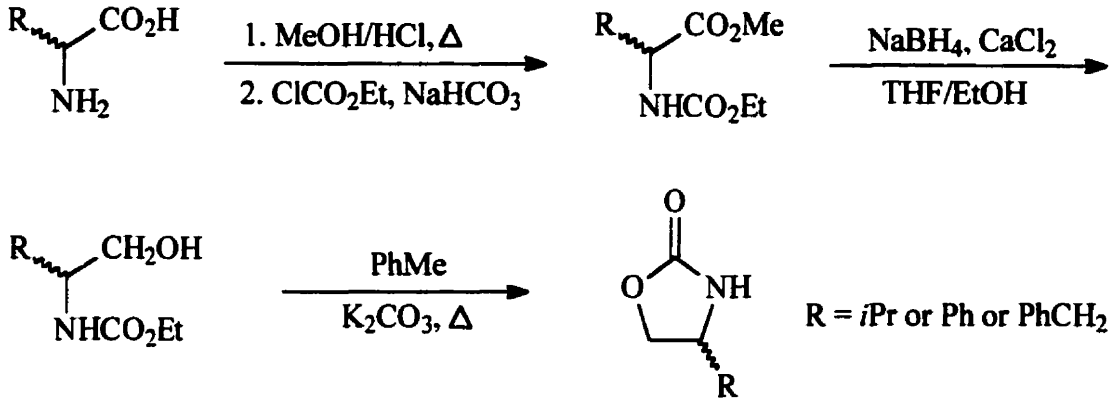
Another approach[14] for the derivation of (4*S*)-4-isopropyl-2-oxazolidinone begins with a Schotten-Baumann acylation of (*S*)-valine as shown in Scheme 3.



Scheme 3

The key to the success of this scheme lies in the use of phenyl carbonochloridate ($ClCO_2Ph$) for the protection of the amino group because it permits the formation of the oxazolidinone **2** by treating the resultant alcohol **4** with a catalytic amount of potassium *tert*-butoxide. The polarity of the alcohol **4** is reduced by this *N*-protection, thereby influencing the isolation. However, the reduction process still involves the borane reagent.

A recent report by Lewis and co-workers[15] advocates an alternative strategy for the preparation of oxazolidinones from aminoacids (Scheme 4). This method avoids the problems of borane reduction and the polar aminoalcohol intermediates.

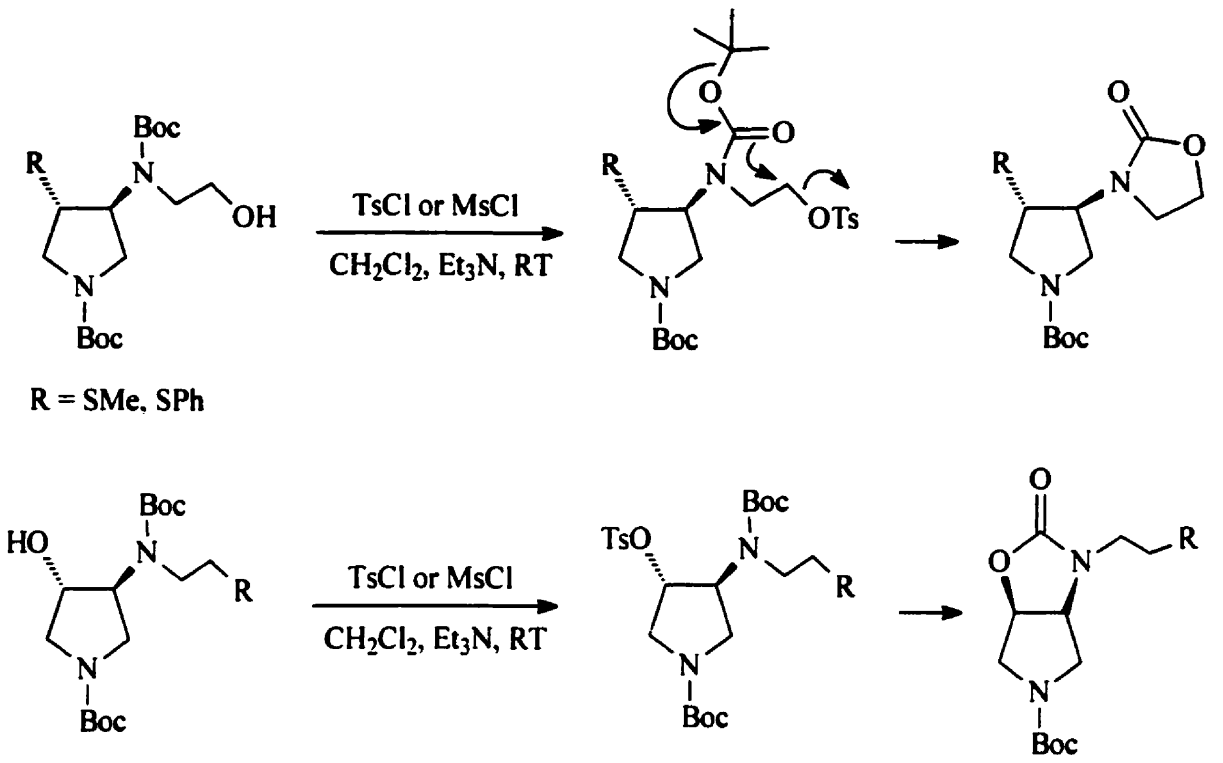


Scheme 4

In the initial step, the esterification and the *N*-carbamate protection of aminoacids provide the corresponding *N*-ethoxycarbonylamino methyl esters (Scheme 4). The reduction of these esters involves the inexpensive and non hazardous reagent, $Ca(BH_4)_2$. The cyclization simply proceeds in toluene and in the presence of mild base. The entire sequence requires neither inert atmosphere nor dry solvents. The advantage of this method is that it employs milder reduction and cyclization conditions, in comparison to previous cases.

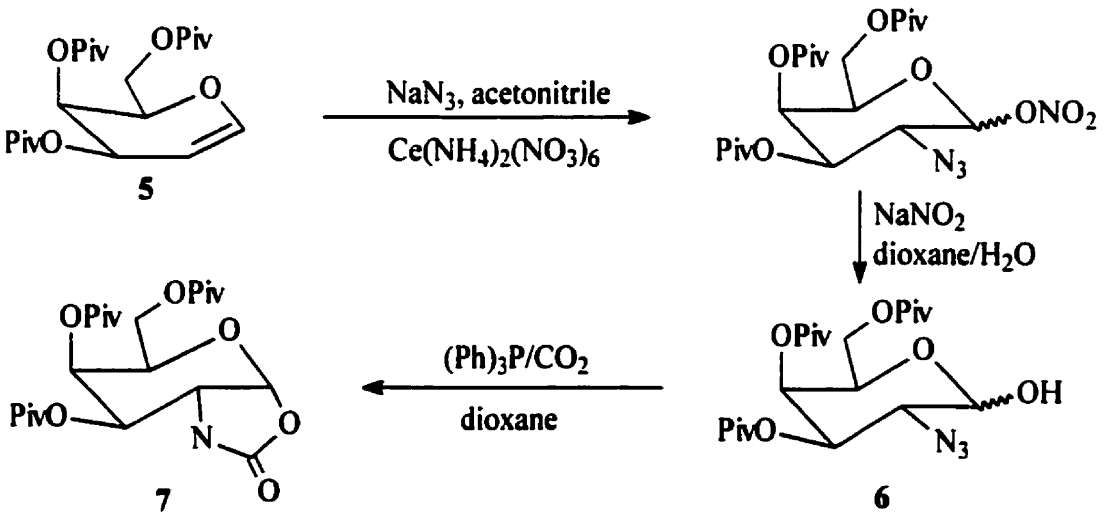
The methods described so far actually originate from an aminoacid source, though they include aminoalcohols as intermediates. There are approaches where the synthesis starts from the aminoalcohol itself. The example[16] illustrated in Scheme 5 explains the one pot synthesis of oxazolidinones by tosylation or mesylation of *N*-Boc derivatives of *β*-aminoalcohols.

The alcohol is initially converted to tosyl (OTs) or mesyl group (OMs). When the *N*-Boc-*O*-tosyl or *N*-Boc-*O*-mesyl aminoalcohol is reacted in the presence of triethylamine without heat, oxazolidinone results (Scheme 5). This method involves mild conditions and simple manipulation and is also amenable to multigram scales.



Scheme 5

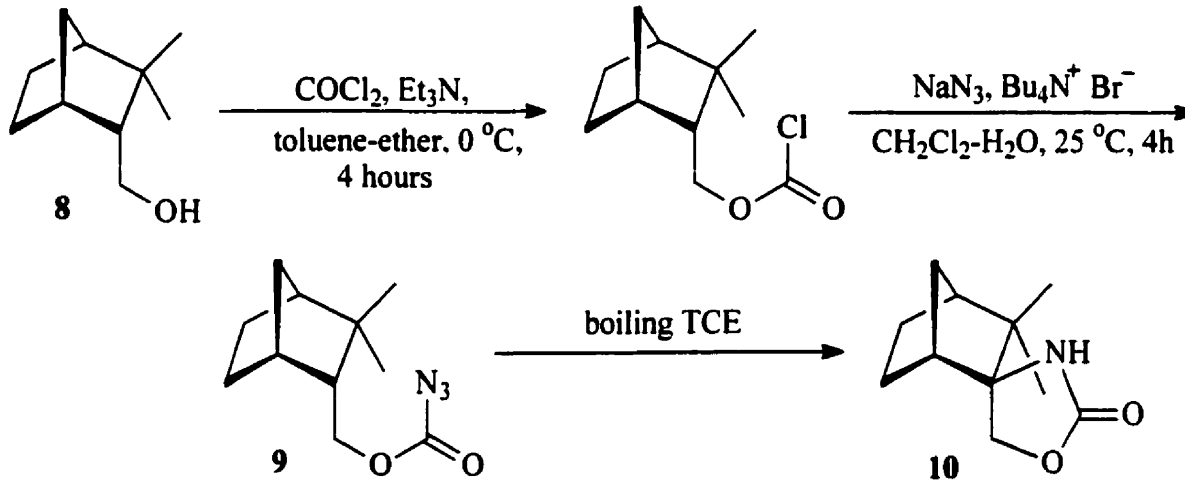
Bicyclic carbohydrate 2-oxazolidinones are unique compounds which illustrate that the oxazolidinones can also be derived from sugars[17,18] and amino sugars[19,20].



Scheme 6

Kunz et al.[21] have developed a methodology for the construction of bicyclic carbohydrate-derived oxazolidinones from the 2-aminodeoxy sugar derivatives as depicted in Scheme 6. The synthesis is easily accomplished from the *O*-pivaloyl protected D-galactal **5** via azidonitration and hydrolysis to give the 3,4,6-tri-*O*-pivaloyl-2-azido-2-deoxy-galactopyranose **6**, which is subsequently converted to oxazolidinone **7** by treatment with triphenylphosphine $((Ph)_3P)/CO_2$.

A synthetic methodology for terpenoid-based oxazolidinones is described in Scheme 7. It has been shown that these auxiliaries can be synthesized from a various terpene alcohols such as *iso*-menthol[22], (-)-3-pinanol[22], (-)-borneol[7] and endo-camphenol[6]. The preparative access to spirooxazolidinone **10** is achieved by a nitrene-mediated three step sequence from endo-camphenol **8**[22] (Scheme 7).



Scheme 7

The procedure incorporates the chloroformylation of the terpene alcohol **8** followed by conversion to the corresponding azidoformate **9**. The decomposition of this azidoformate in boiling TCE (thermolysis) yields the spiro-oxazolidin-2-one **10** in enantiomerically pure form.

As described, these synthetic methods provide routes to produce oxazolidin-2-ones with unique stereochemistry or substituents at position/s 4 or/and 5.

Uses of various oxazolidin-2-ones

Oxazolidin-2-ones are mainly used as chiral auxiliaries in organic synthesis. Besides functioning as chiral auxiliaries, some oxazolidinones are biologically active in their own right and are used for medicinal and biological purposes[23]. The parent oxazolidinone compound **11** and its 3-substituted (X) analogs are orally active synthetic anti bacterial agents, which are pictured in Figure 4.

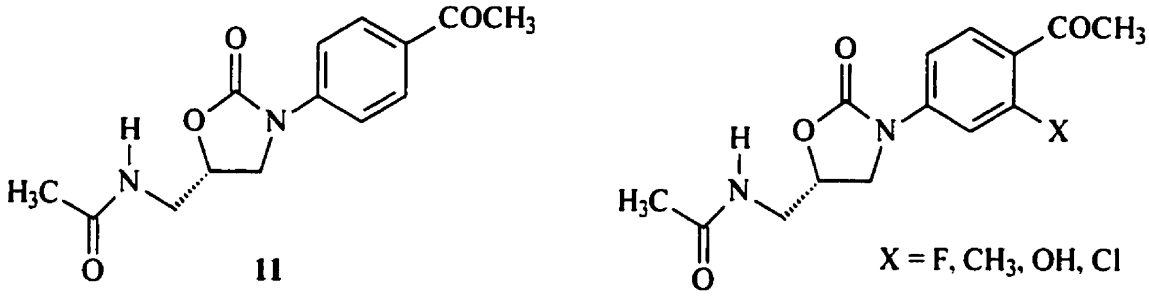
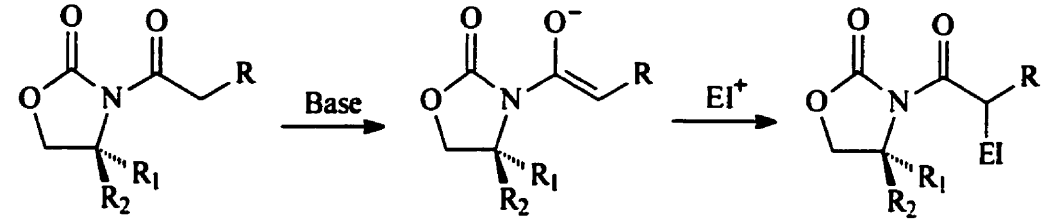


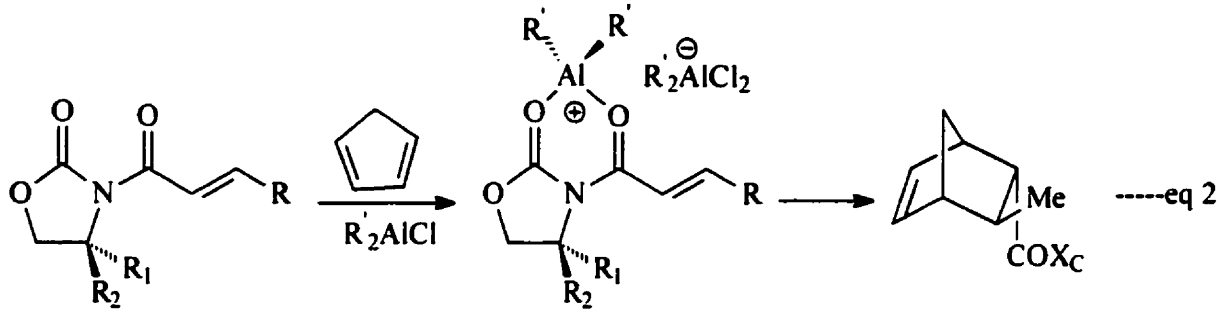
Figure 4

In a synthesis of a complex compound, chemists must deal with three distinct and interconnected problems: construction of the requisite molecular structure, disposition of the necessary functional groups at their proper sites, and control of relative chirality at the various points of asymmetry in the desired product.

Among them, the effective control of relative and absolute chirality is often troublesome. Here is where the use of chiral auxiliaries becomes very important. Substituted oxazolidin-2-one heterocycles have been established as versatile chiral auxiliaries for the synthesis of stereochemically pure substances and therefore, they can be utilized to regulate the selectivity in the required manner.

Enolates derived from *N*-acyl oxazolidinones have been documented to react with a variety of carbon and heteroatomic electrophiles with high diastereoselection (eq 1). This concept has proven to be useful in asymmetric enolate alkylation[24], aldol condensation[25], acylation[26], bromination[27], amination[28], hydroxylation[29], and azidation[30]. Similarly, α,β-unsaturated *N*-acyloxazolidinones have been used in Lewis-acid catalyzed Diels-Alder reactions[31] (eq 2).





It is well documented that such stereoselective transformations of oxazolidinones have been used in the synthesis of several natural products, macrolides and other antibiotics[2]. The utility of oxazolidinones can then be illustrated by choosing a few of their reactions that are employed in the preparation of complex molecules as examples. Only the main conversion, which incorporates the oxazolidinone, is considered.

Chiral enolates of various *N*-acyl oxazolidinone derivatives exhibit excellent levels of asymmetric induction in alkylation reactions. In general, the asymmetric induction is defined by the geometry of the enolate (cis- enolate (*Z*) or trans-enolate (*E*)) as well as by their mutual inclusion in the oxazolidinone ring[9]. Besides, chelation of metal enolates also plays an important organizational role in establishing a fixed stereochemical relationship between resident chirality and the enolate moiety. The metal-chelation control of *Z*-enolates and the resultant stereochemistry of the alkylation products are shown in Figure 5.

These chelated enolate structures (Figure 5) show that the C-4 substituent on the oxazolidinone ring imposes the requisite diastereofacial bias on the enolate system. As a consequence, the chelate-organized diastereoselective alkylations result high levels of stereoselectivities.

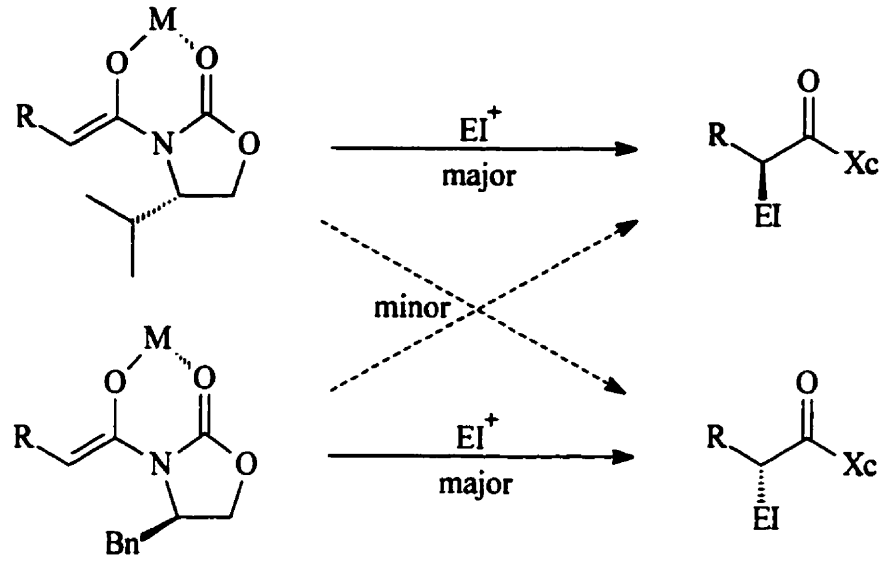
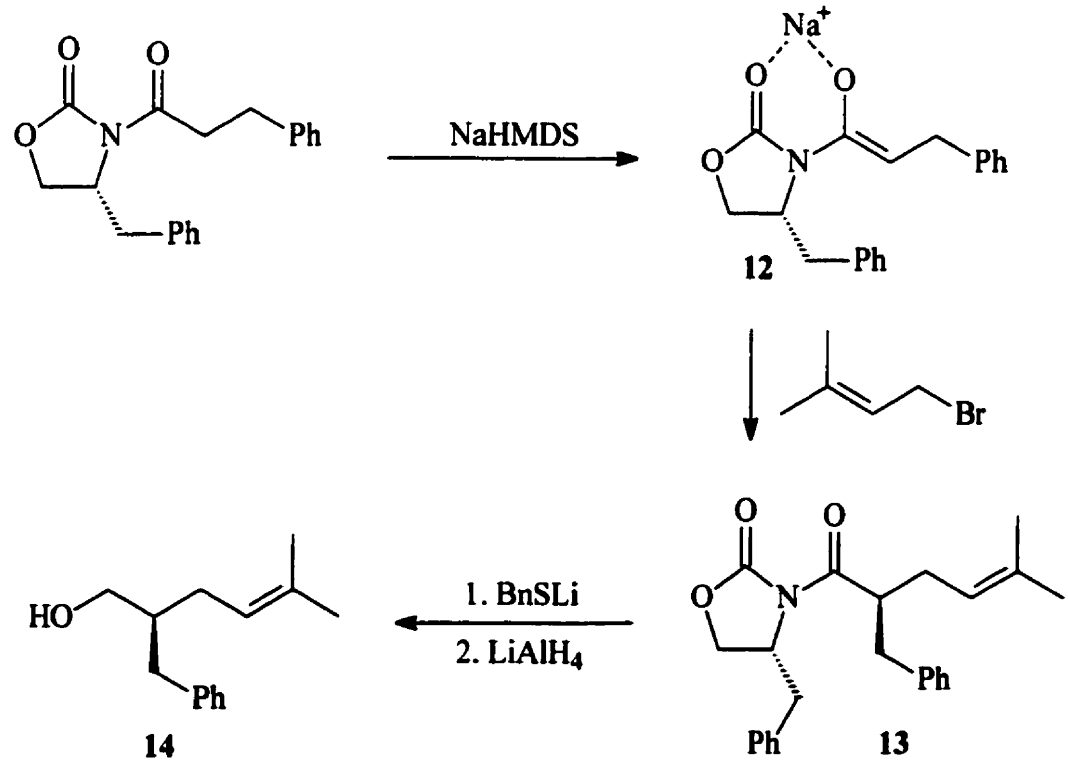


Figure 5

Several researchers have exploited these alkylation reactions of *N*-acyl oxazolidinones in the preparation of macromolecules[2]. Such an example is depicted in Scheme 8.

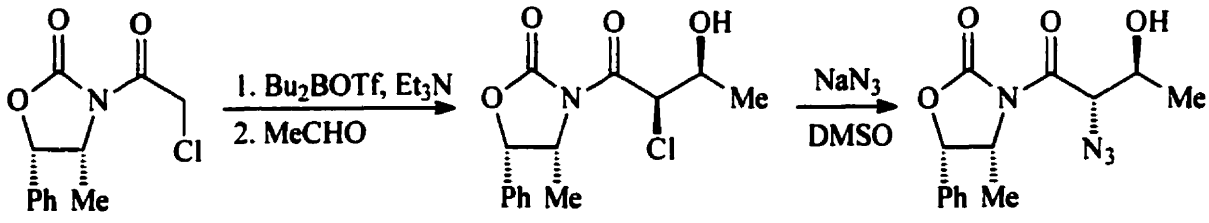


Scheme 8

The final product (compound **14**) of this sequence is an intermediate needed for the production of pyrrolinone-based HIV protease inhibitors[32]. It has already been shown that *N*-acyl-oxazolidinones exhibit exceptionally high levels of (*Z*)-enolization stereoselection with sodium amides (NaHMDS)[24]. The chelation of the sodium metal with the enolate oxygen and the carbonyl oxygen of the oxazolidinone ring provides a rigid structure for the *Z*-enolate **12**. The alkylation of this enolate **12** preferably and exclusively gives the desired, single diastereomer **13**. The steric interactions of the isopropyl group at position 4 promote this formation. Finally, the removal of the oxazolidinone from the diastereomer **13** yields the required intermediate **14**.

As mentioned before, *N*-acyl derivatives of 2-oxazolidinones are successfully used in asymmetric aldol condensations. It has been reported[33,34] that various metal (B, Ti, Sn, etc.) enolates of *N*-acyl conjugates undergo the aldol reaction with various aldehydes in a highly stereoregulated fashion, providing stereochemically pure aldol adducts in high yields. The nature of the substituents on the auxiliary as well as on the enolate system is considered one of the important variables that control the stereochemistry in aldol condensations. Sterically demanding metal centers and their ligands also play an important role in the enhancement of aldol stereoregulation[35].

The utility of these aldol reactions of oxazolidinones has achieved great success in the production of natural products, macrolides and other antibiotics as well. In the following example, the asymmetric aldol methodology[25] provides access to β-hydroxy-α-aminoacids and 3,4-disubstituted monolactam analogs (Scheme 9 and 10).



15 syn aldol **16** **17**

Scheme 9

β-Hydroxy-α-aminoacids are important because they are constituents of biologically active peptides and precursors to β-lactam antibiotics. As shown in Scheme 9, the enolization of **15** with dibutylboryl triflate and Et_3N followed by treatment with MeCHO affords the α-haloaldol adduct **16**.

It has been reported that enolization of *N*-acyl-oxazolidin-2-ones with boryl triflates in the presence of an amine base (such as DIPEA, Et_3N) shows a large preference for *Z*-enolate formation[35]. The preponderance of *Z*-enolate can be attributed to allylic strain considerations, which control the enolate stereochemistry in amide systems such as *N*-acyl oxazolidinones.

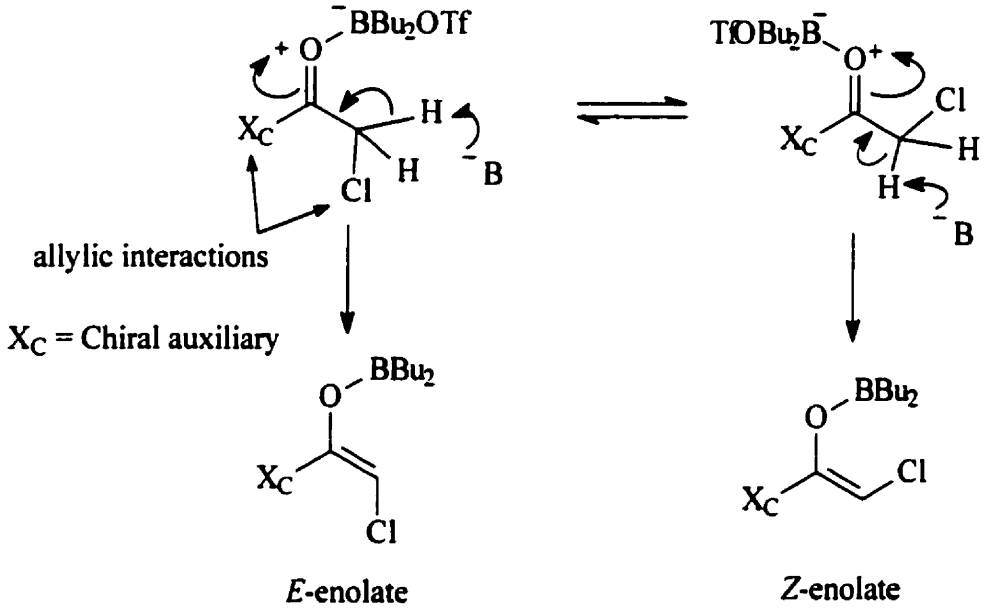
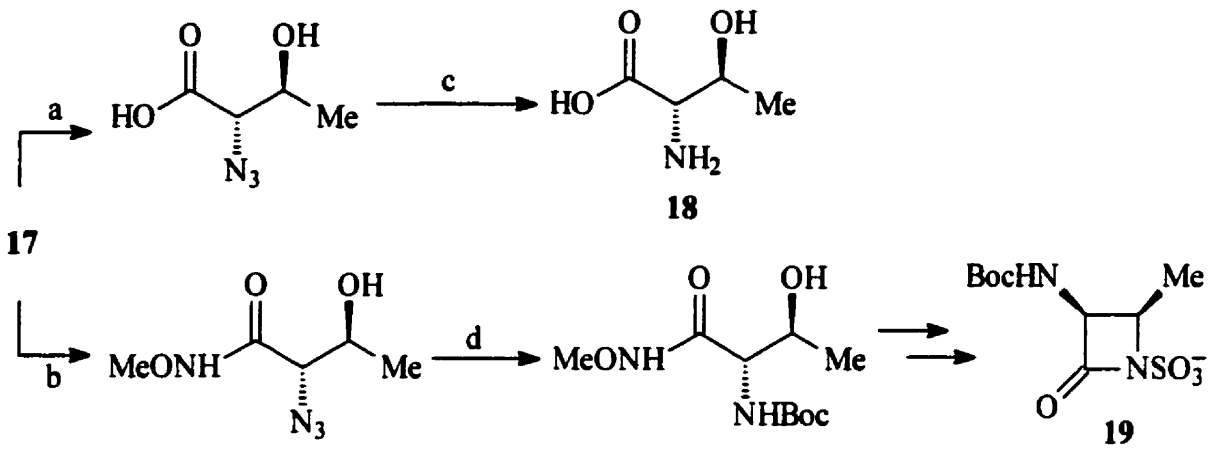


Figure 6

As indicated in Figure 6, due to strong allylic interactions in the transition state for the formation of the *E*-enolate, the *Z*-enolate is favorably produced. As the *Z*-enolate is usually formed for boron enolates, the syn adducts result. This is a general trend observed in the reactions of boron enolates with aldehydes and imines[35,36].

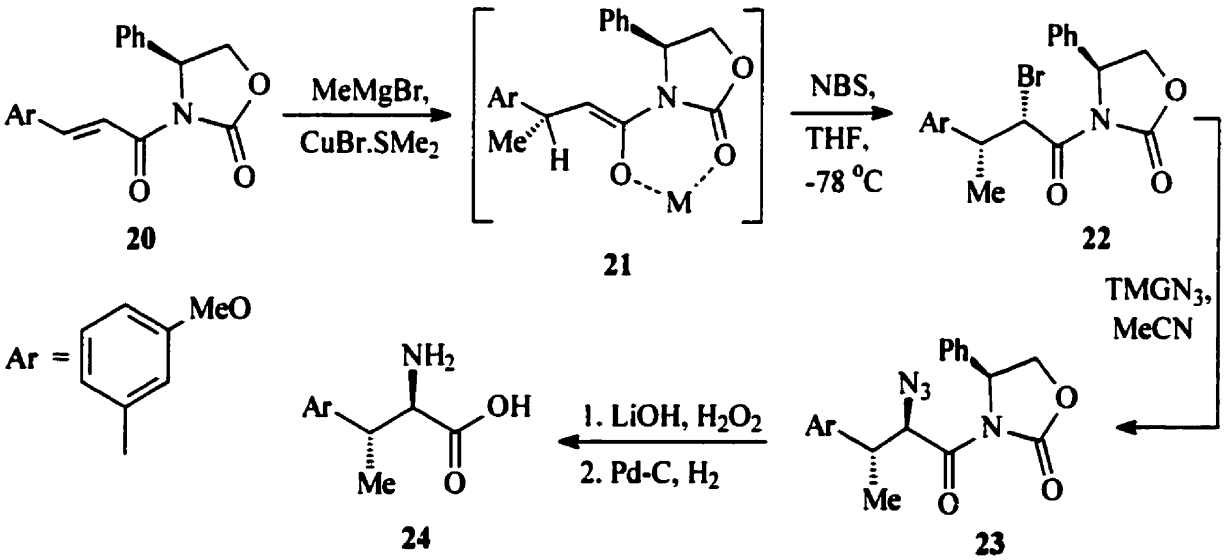
The reaction of the syn aldol **16** with NaN_3 gives the corresponding azide **17** as shown in Scheme 9. This azide can be converted to β-hydroxy-α-aminoacid **18** or β-lactam synthon **19** in the following manner[25] (Scheme 10).



a. LiOH, H_2O, Dioxane, 0 °C
b. $MeONH_2.HCl$, Me_2Al
c. H_2, Pd/C, TFA
d. i. H_2, Pd/C, ii. Boc_2O

Scheme 10

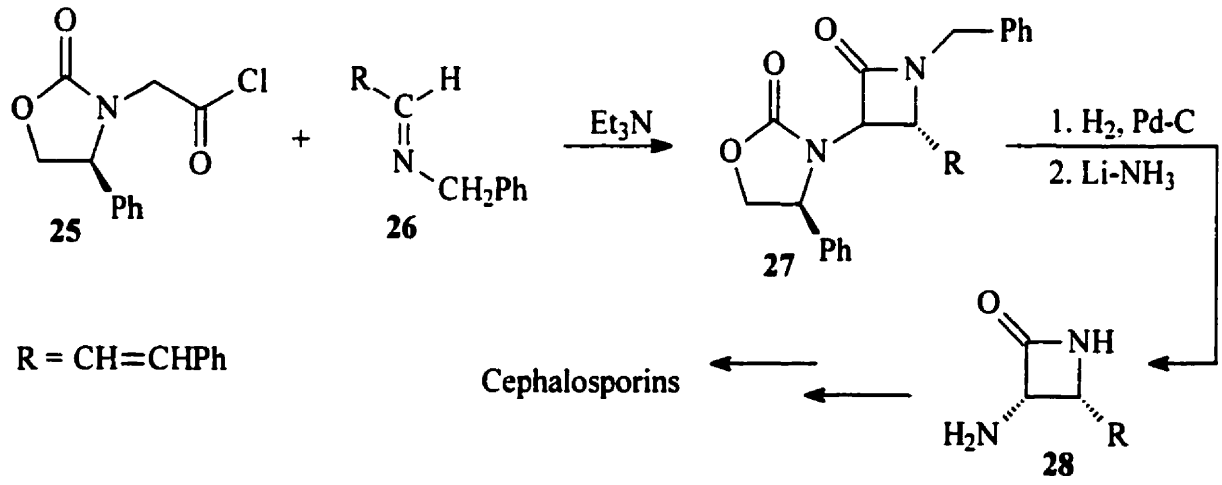
The next application involves the preparation of the nonproteinogenic and unusual α-aminoacids via α, β-unsaturated *N*-acyl oxazolidinones. The example described below is a synthetic scheme for an unusual tyrosine aminoacid (Scheme 11).



Scheme 11

Initially, the methylcopper reagent is generated by the reaction of MeMgBr and CuBr-Me_2S complex[37,38]. The addition of the methylcuprate to the enone-imide **20** leads to a metal enolate intermediate **21** that chelates the chiral auxiliary carbonyl oxygen thereby fixing the chiral auxiliary in a specific spatial conformation. Bromination of this enolate by NBS creates the second asymmetric center of the prospective aminoacid **24**. The bromide **22** is then subjected to SN2 azide displacement with TMGA or $TMGN_3$ to form **23**. The non-destructive removal of the auxiliary and the reduction of the azide result in the corresponding acid **24**.

The cycloaddition of imines with ketenes generated from acid chlorides and tertiary amines is recognized as one of the most convenient approaches to β-lactams. Evans has used this methodology[39] to produce carbacephem-related antibiotics, especially the carbacephalosporins. As pictured in Scheme 12, the cycloaddition of 4(*S*)-phenyloxazolidylacetyl chloride **25** and an imine **26** is the essential step in the preparation of β-lactams and cephalosporins.



Scheme 12

The acid chloride **25** is converted to the corresponding ketene by treating with triethylamine. When carried out with *E*-imines, the ketene-imine cycloaddition generally affords the cis disubstituted azetidinones with high stereoselectivity[39]. Thus, the [2+2] cycloaddition of this ketene with the imine **26** provides the adduct **27** which upon cleavage conditions produces the cis disubstituted azetidinone **28**. Both steric and electronic components participate in the

determination of stereoselectivity. Azetidinone **28** undergoes subsequent conversions to give cephalosporins.

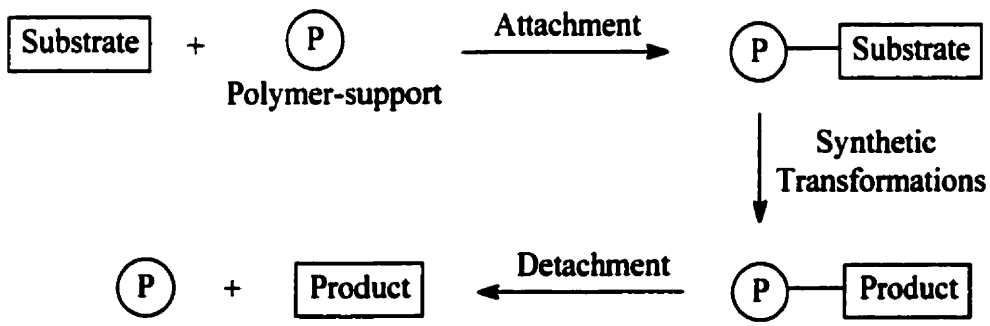
Applications of chiral oxazolidinones in the construction of complex molecules demonstrate their potential in asymmetric synthesis. The ability of *N*-acyl-oxazolidinones to form rigid chelates and their sterically and electronically demanding substituents make this chiral auxiliary system one of the most versatile available.

2. Soluble polymer-supported synthesis

Polymer-supported synthesis: General aspects

Over three decades after Merrifield's pioneering work on the solid-phase peptide synthesis[40], the area of organic synthesis on polymer supports has witnessed a great resurrection in recent years, particularly in the construction of small organic molecules. Since the discovery of Merrifield's resin, several insoluble (solid phase) and soluble (solution phase) polymer matrices have been recognized as organic species capable of functioning as polymer supports, and susceptible to chemical transformations under appropriate conditions. The polymer-supported methodology has found widespread applications in organic synthesis and related areas, such as combinatorial and pharmaceutical chemistry.

The general approach for polymer-supported organic synthesis is shown in Scheme 13. The initial step of the synthesis involves the attachment of a polymer support to an organic substrate.



Scheme 13

The resultant polymer-supported molecule can then undergo various synthetic transformations. Finally, detachment of the polymer linker will provide the desired product. Most frequently, the support can be recovered and recycled.

Owing to the intrinsic advantages of the polymer-supported approach an increasing number of polymeric supports and reagents have been designed. Some of the important benefits[41,42,43] generally expected from both the soluble and insoluble polymer-supported synthesis are listed below.

1. Simplification of product work-up, separation and isolation steps: This is usually considered the most important advantage. Time-consuming work-up process and purification steps are eliminated by binding to a polymer-support. This makes the recovery of the products easier.
2. Possibility of obtaining higher yields for the products. In insoluble polymer-supported synthesis, excess reagents may also be used to drive reactions to completion.
3. These polymers are nontoxic and odorless and hence lead to environmentally friendly chemistry. Toxic and malodorous materials can be rendered environmentally more acceptable.
4. Scarce and/or expensive materials can be efficiently retained when attached to a polymer. The reactivity of an unstable reagent or catalyst can be attenuated.
5. They display considerable versatility. In particular they have been successfully utilized in a variety of chiral chemical applications[41,42].
6. Asymmetric induction: The use of a chiral polymer can cause asymmetric induction. Sometimes, polymer chains may effect an increase in the stereoselectivities of the reagents[43,44,45].

Soluble and insoluble polymer supports have been employed in the synthesis of peptides[40,46], oligosaccharides[47,48], oligonucleotides[49,50], α-aminoacids[51], β-lactams[52] and various other organic compounds[41,53]. Several soluble and insoluble polymer-bound catalysts have been used in asymmetric dihydroxylation[54], epoxidation[55], reduction[56] and enantioselective C-C bond formation[57] reactions. Polymer-supported chiral auxiliaries and chiral reagents also

find increasing applications in asymmetric polymer-supported synthesis[42,53].

In organic syntheses, various substrates, reagents and conditions are generally employed. In some cases, extreme conditions are often required for satisfactory results. Therefore, the correct choice of the polymer support is the most decisive factor for the success of a polymer-supported synthesis. Since the introduction of Merrifield's polymer-supported peptide synthesis, insoluble (solid polymer) polymer supports have been extensively used in organic synthesis. Although highly successful, they also exhibit several drawbacks[58,59].

The most notable liability is the heterogeneous nature of the reaction conditions. This can also cause new difficulties such as unequal distribution and/or access to the chemical reaction, solvation problems, steric hindrance and nonlinear kinetic behavior[58,59,60]. Besides, the reactions involving the synthesis of polymer-bound substrates or cleavage of polymer supports can be incomplete because of the uneven distribution of reagents.

Excess reagents are often used to maintain equal distribution of reagents in the reaction, but it may be costly in the case of expensive reagents. These shortcomings may lead to slow reactions and poor yields[61]. Besides, the characterization of reaction on insoluble polymers can be difficult especially where the techniques require homogeneous solution such as ^{1}H NMR[58].

Supporting on soluble polymers

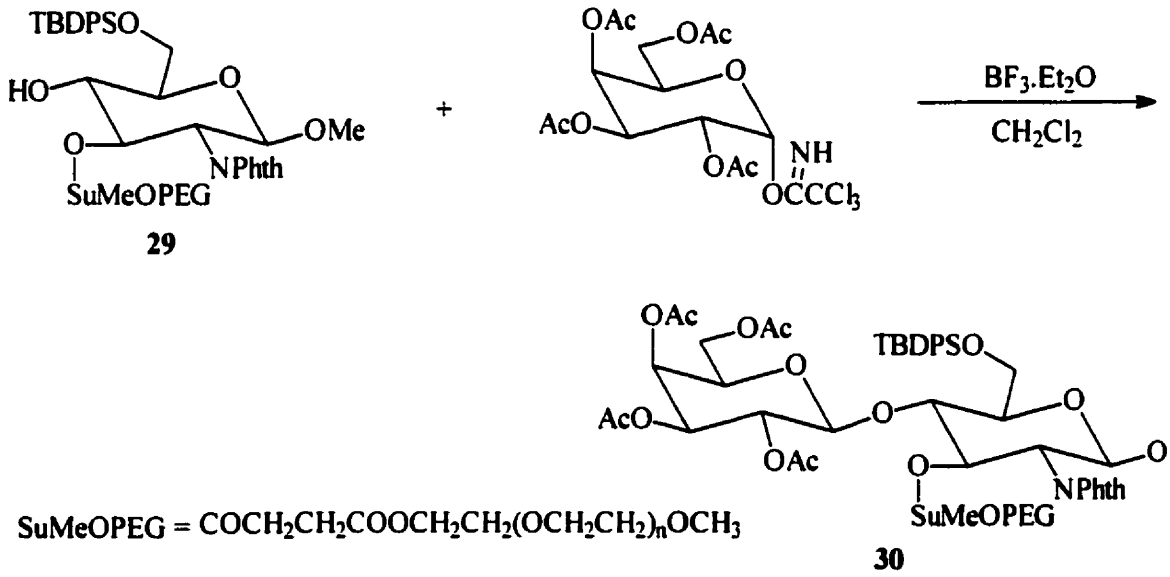
A potential solution to the problems encountered with the solid-phase synthesis would be to use soluble polymer supports instead[58]. The important advantage of this approach is its homogeneous reaction condition. This approach not only eliminates the problems associated with the solid phase by restoring homogeneous reaction conditions for the synthesis but also reinstates the reaction conditions of conventional organic chemistry.

Moreover, the product work-up and purification steps are still facilitated. Most often, the purification is effected by simple precipitation and filtration[58,61]. In this method, the homogeneous polymer solution is simply diluted with a solvent that induces the precipitation of the polymer support. The resulting heterogeneous mixture is filtered to isolate the polymer-supported product. The excess reagents and impurities are rinsed away during the filtration. Some polymers are amenable to recrystallization too. Several other methods[62] such as dialysis, ultrafiltration, centrifugation methods, gel permeation and absorption chromatography have also

been used for product separation.

Solution phase chemistry also has many other advantages over solid-phase synthesis. The characterization of the polymer-supported materials can be performed by solution spectroscopic techniques such as IR, UV-visible and NMR[62]. Unlike solid-phase synthesis, in this method, the cleavage of the products from the support for characterization is not necessary. Spectroscopic techniques particularly NMR can be used to monitor the reactions of soluble polymer-supported compounds[58,60]. Furthermore, the soluble polymer-supports provide better yields than insoluble supports.

There have been many examples[63,64] in the literature to demonstrate that the soluble polymer-supported strategy can be superior to the methods involving insoluble polymer-supports. One such example is the solution-phase synthesis of oligosaccharides introduced by Krepinsky et al.[65] (Scheme 14).



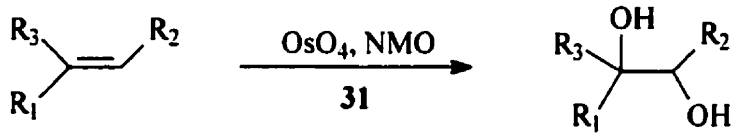
Scheme 14

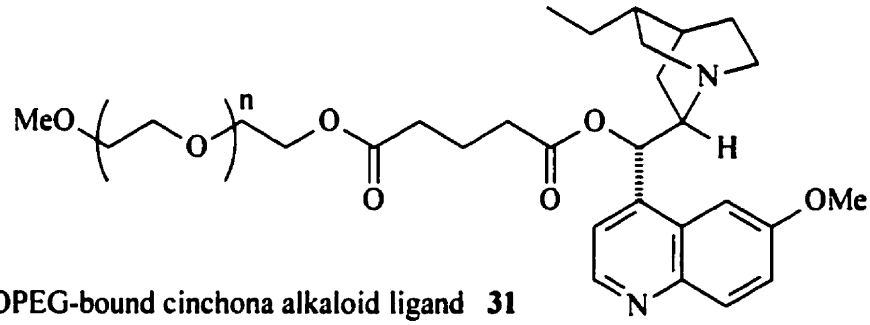
It was reported in the past that the solid-state approach for the synthesis of oligosaccharides was not successful[66]. It became clear that the heterogeneous nature of the reaction medium was the main reason for the unsuccessful glycosylation reaction. It posed problems such as decreased glycosylation rate compared to solution strategies, incomplete

coupling, and lack of complete stereoselectivity. No efforts to overcome these problems appeared until the work by Krepinsky in 1991.

Krepinsky et al. proved that these problems can be solved by soluble polymer-supported synthesis due to the advantages obtained by the homogeneous condition. As shown in Scheme 14, they carried out the glycosylation reaction using the MeOPEG-supported monosaccharide **29** in which the soluble polymer was attached to its hydroxyl group through a succinoyl diester linker. This methodology worked perfectly and provided the MeOPEG-bound oligosaccharide **30** in excellent yield.

Another example is the ligand-accelerated catalytic asymmetric dihydroxylation of olefins using soluble polymer-bound chiral cinchona alkaloid-ligand[67] depicted in Scheme 15.





MeOPEG-bound cinchona alkaloid ligand **31**

Scheme 15

Initially, researchers attempted asymmetric dihydroxylation employing insoluble polymer-bound cinchona alkaloid-ligands[68,69]. It was hoped that this approach would provide a convenient method for recovering the alkaloid ligand. However, it was considered to be less satisfactory than solution phase methodology because of increased reaction times, highly variable yields and lower enantioselectivity. The reason is that in the insoluble polymer-supported synthesis, the chiral alkaloid-ligand resides only in the insoluble phase while the rest of the reagents remain in solution. This heterogeneous nature prevents equivalent

access/distribution of the reagents. Hence, the most fundamental requirement for a successful ligand accelerated catalysis scenario can never be met.

K. D. Janda and his coworkers[67] showed clearly that the solution phase method would overcome these problems and provide a better pathway for the synthesis. They successfully performed the dihydroxylation on a variety of olefins by employing a MeOPEG-bound cinchona alkaloid ligand **31** (Scheme 15). The homogeneous reaction condition was the important factor for their success. They reported that the reaction time was rapid and the yield, reactivity and enantioselectivity were relatively high. Moreover, the product isolation and recovery seemed straightforward and they were able to optimize the recovery of the alkaloid-ligand to ≥ 98%.

General requirements of soluble polymer supports

The polymer support has to be cheap and readily available. It must withstand most of the reaction conditions used in solution chemistry. The polymer should provide appropriate functional groups for ready attachment of organic moieties. In principle, two types of functional supports can be considered[61] (Figure 7).

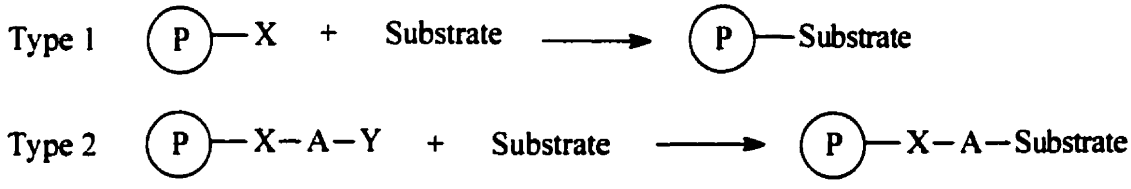


Figure 7

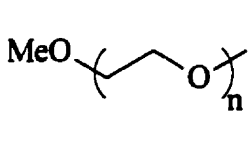
If the support itself has a suitable functional group which fulfills the requirements of attachment then the polymer support can be used without further modification. In type 1, the coupling can be achieved directly (Figure 7).

If the polymer support does not have an appropriate functional group for the direct attachment then the introduction of an anchor group or functionalization of the polymer is

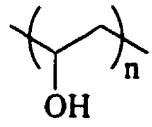
necessary. In type 2 (Figure 7) the polymer can be coupled to the substrate via an anchor group (A). This new linker group has to ensure its anchor stability during synthesis, improve accessibility to reagents, and facilitate cleavage for product recovery.

The essential feature of a soluble support is its solubility/insolubility properties. The polymer should exhibit high solubility in organic solvents, especially in useful aprotic solvents to permit homogeneous conditions. On the other hand, it must possess properties that give a satisfactory product separation. Most often, the isolation of polymeric product is achieved by precipitation and filtration. Thus, the polymer should be crystalline for ease of filtration.

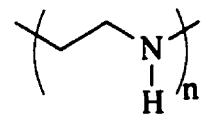
Soluble polymers in general must have molecular weights high enough to be solid or crystalline at room temperature, but not excessively high, so that they are soluble in variety of solvents. The selected polymeric matrix must provide a reasonable compromise between loading capacity and solubilizing power. The loading capacity of a polymer support is a measure of the number of anchoring sites per gram of polymer and it is expressed in units of millimoles per gram (mmol/g)[58]. Generally, solubilizing power decreases with increasing loading capacity. The reason is, as the polymer is further attached to organic units the solubility of the polymer support will be now determined by the properties of the polymer-supported organic moiety. Therefore, it is essential to obtain a compound-to-support ratio that prevents solubility changes noticeably.



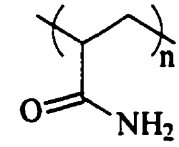
poly(ethylene glycol)-monomethyl ether (MeOPEG) **32**



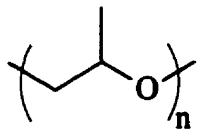
poly(vinyl alcohol)



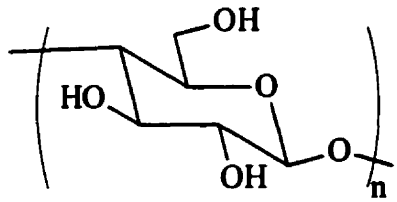
poly(ethylene imine)



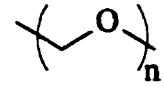
polyacrylamide



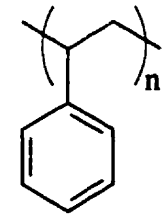
polypropylene oxide



cellulose



polymethylene oxide



polystyrene

Figure 8

Polymers which satisfy all the above basic requirements, can be successfully utilized in solution phase synthesis. A broad spectrum of soluble polymers are suitable for application as polymer supports. Some of them are pictured in Figure 8. Of the polymer supports listed, poly-(ethylene glycol)monomethyl ether **32** having an average molecular weight 5000 (a derivative of poly(ethylene glycol)) has proved to be the most appropriate polymer support for soluble polymer-supported synthesis[58,70]. Consequently, a brief discussion of this polymer is justified.

Poly(ethylene glycol)monomethyl ether (MeOPEG)

Poly(ethylene glycol)monomethyl ether **32** (average M_W 5000) is a polyether terminated by a methoxy group at one end and a free hydroxyl at the other. MeOPEG is a monofunctional polymer since it has one hydroxyl group to serve as an anchoring site.

The polymer has favorable properties for functioning as a support. The salient feature of MeOPEG is that it shows remarkable solubilities in a variety of organic and aqueous solvents such as CH_2Cl_2, acetone, benzene, acetonitrile and H_2O[58,62]. On the other hand MeOPEG is insoluble in Et_2O, *tert*-butylmethyl ether and hexane[58,62] and this feature makes the work-up and purification methods very simple. It can be readily precipitated and separated from the solution by adding one of these equals to the solvents.

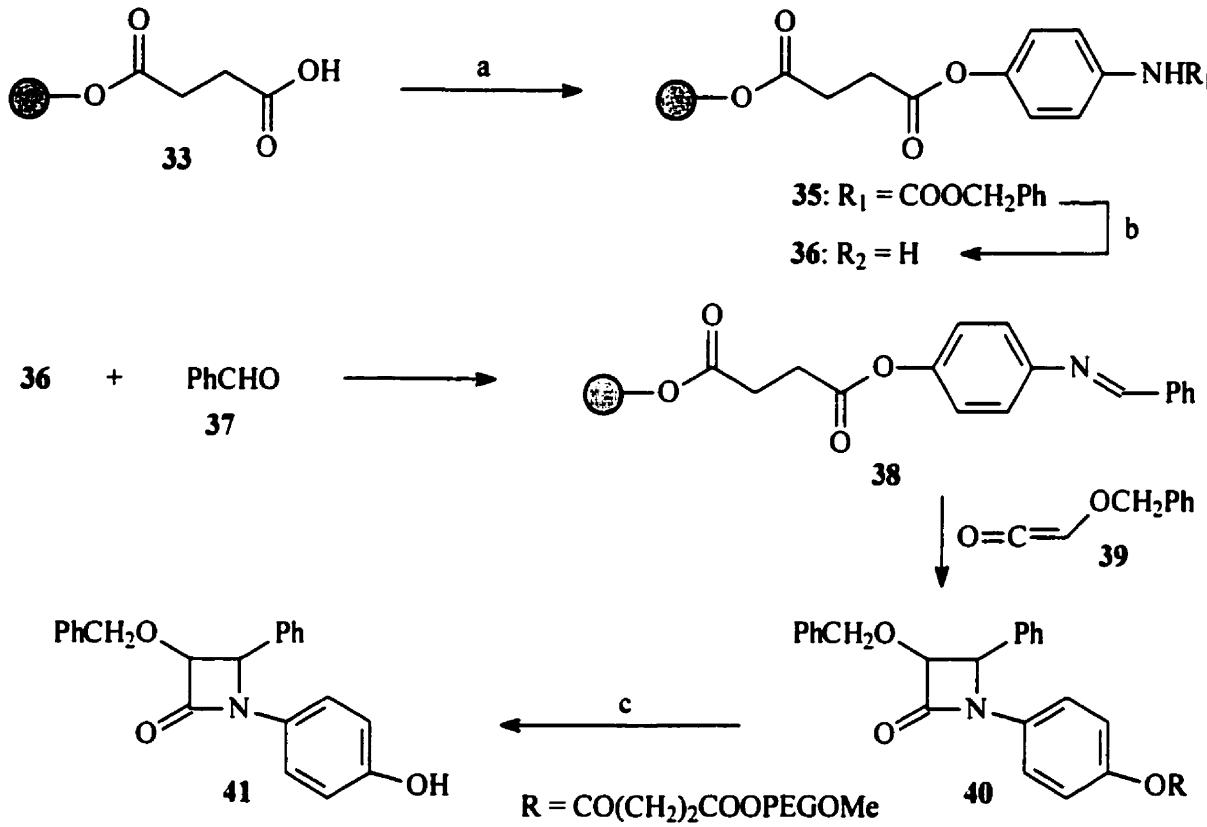
The solubilizing power of MeOPEG permits the characterization to be carried out without any cleavage of product from the polymer. In particular, ^1H NMR or sometimes ^{13}C NMR can be used to monitor the progress of a reaction[60,71]. The singlet signal obtained at δ 3.38 ppm for methoxy group of MeOPEG in the ^1H NMR can function as an internal reference[58,71]. It can also be used to calculate loading efficiency and reaction yield.

Furthermore, MeOPEG has a strong propensity to crystallize. Thus the polymer adducts can also be purified by recrystallization using solvents such as EtOH, MeOH or toluene[58,60]. Lastly, MeOPEG is an inexpensive, easy to use, harmless and commercially available in a wide range of molecular weights.

The MeOPEG polymer support exhibits successful applications in a variety of chemical and biological syntheses. It has been employed as supports[71,72], reagents[73], catalysts[74], and phase transfer catalysts[75]. The use of MeOPEG polymer as a support in oligosaccharides and as a catalyst in asymmetric dihydroxylation reactions have been described previously. A few more

examples are given here to demonstrate its potential in organic synthesis.

The first example is the MeOPEG polymer-supported synthesis of imines and β-lactams[52]. The support involved in this process is the mono MeOPEG succinate **33** (MeOPEG, average M_W 5000). The total synthesis is illustrated in Scheme 16.

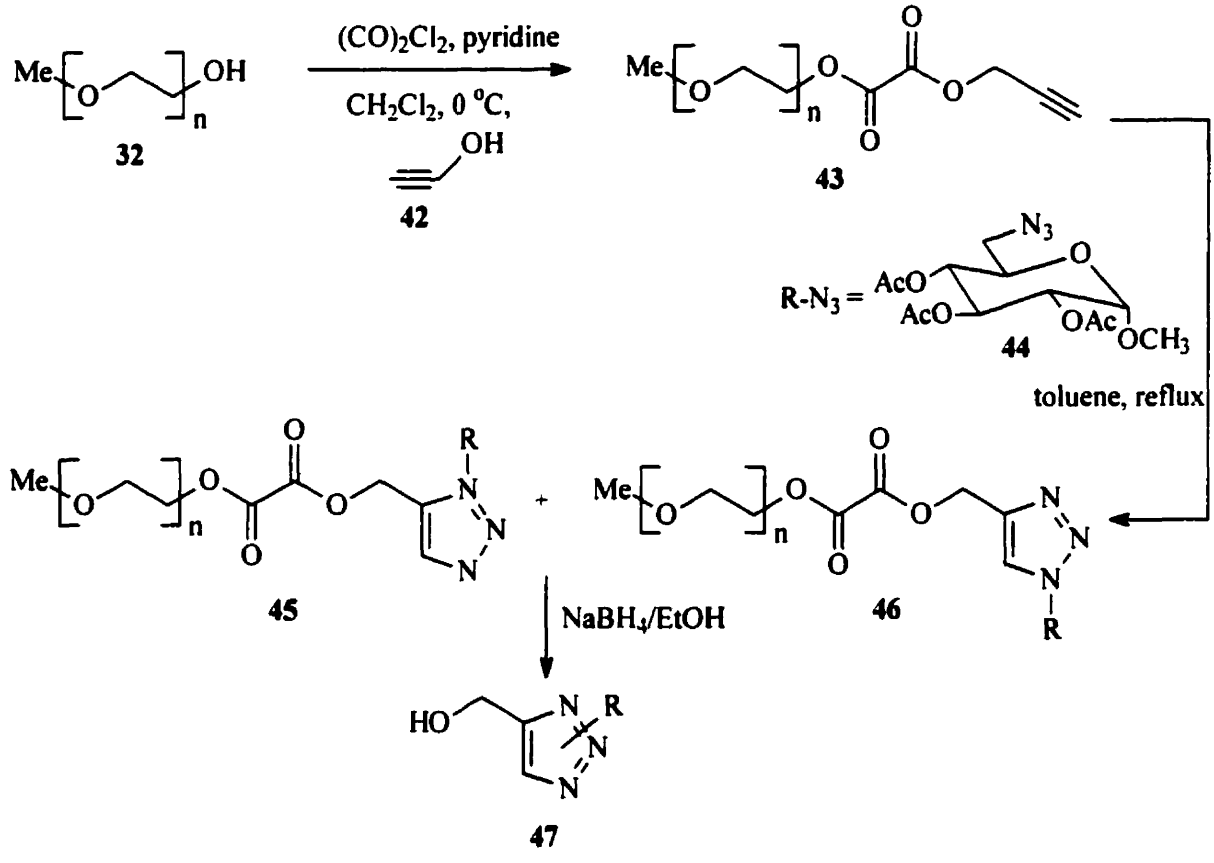


Reagents. a. 4-$PhCH_2OCONH-C_6H_4$-OH **34**, DCC, DMAP; b. H_2, 10% Pd/C;
c. MeOH, cat. conc. H_2SO_4, 60 °C, 4 hours

Scheme 16

The synthesis starts with the attachment of the polymer support **33** to *N*-(4-hydroxy-phenyl)-O-benzylcarbamate **34**. After deprotection, the reaction of amine **36** with aldehyde **37** leads to the formation of imine **38**. The cycloaddition of imine **38** with ketene **39** provides the polymer-bound β-lactam **40**. The cleavage of the polymer by the acid catalyzed methanolysis finally gives the β-lactam **41**.

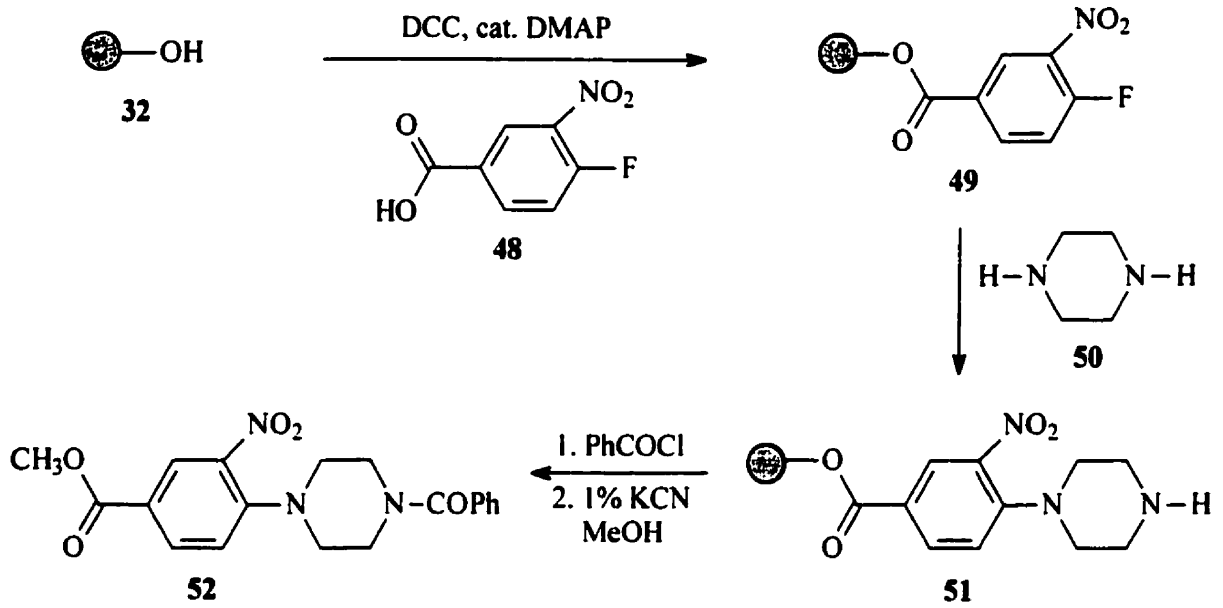
Another instance demonstrates the feasibility of generating triazoles by means of dipolar cycloaddition reactions on MeOPEG polymer-supported dipolarophiles[76] (Scheme 17). In this scheme, the treatment of MeOPEG **32** (average M_w 5000) with oxalyl chloride in CH_2Cl_2, followed by the addition of propargyl alcohol **42** affords the polymer-supported alkyne **43**. The reaction of this with azidodeoxy carbohydrate derivative **44** provides the regioisomeric mixtures of polymer-supported triazoles **45** and **46** via 1,3-dipolar cycloaddition. The liberation of the triazole **47** from the polymer is performed under mild conditions.



Scheme 17

The authors described that the polymer-supported synthetic approach influenced the ready isolation of the polymer-supported triazole using a general procedure of polymer precipitation followed by recrystallization. The major regioisomer **46** has the carbohydrate and polymer substituents in a head to tail orientation. It was suggested that the increased bulk of the polymer-supported dienophile likely accounts for this head to tail orientation.

The last example shows the MeOPEG-supported synthesis of an arylpiperazine[77]. As seen in Scheme 18, the polymer bound aryl fluoride **49** is prepared from MeOPEG **32** and 4-fluoro-3-nitrobenzoic acid **48** via ester linkage. The reaction of polymer-supported aryl fluoride **49** with piperazine **50** yields compound **51** and which is subsequently acylated with benzoyl chloride. The efficient removal of the polymer support by 1% KCN in MeOH results in the final product **52** in quantitative yield.



Scheme 18

As in previous cases, the polymer support was part of the reason for the efficient synthesis. All these examples prove that the MeOPEG can be successfully used as a polymer support in various organic syntheses.

Owing to the continued growth of asymmetric synthesis over recent years, the study of polymer-supported chiral auxiliaries and reagents has become an important and exciting field.

Polymer-supported chiral auxiliaries

The concept of using polymer supports (soluble or insoluble) in asymmetric synthesis is a particularly interesting one. In this strategy, an optically active compound or functional group is attached to a polymer support and then either an asymmetric synthesis is carried out on the

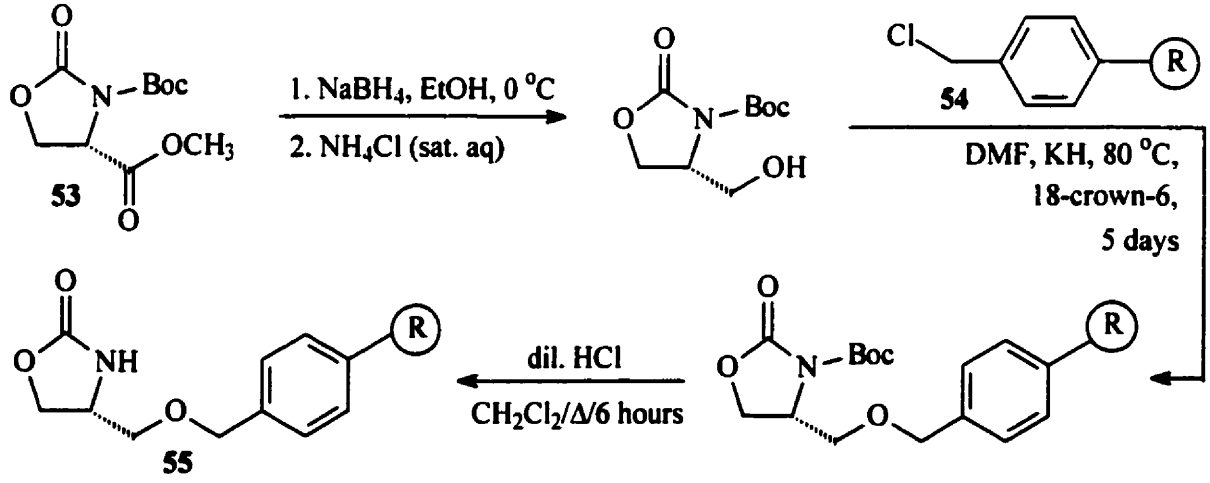
support or the optically active polymer is used as an asymmetric reagent or catalyst. Polymer-supported chiral reagents and auxiliaries have received a great amount of attention recently[53].

Performing asymmetric transformations on polymer supports seems to be very advantageous for the following reasons:

1. The isolation of the final chiral product is very much simplified.
2. Easy separation and recovery of expensive chiral species.
3. If properly designed, the chiral reagents or auxiliaries can be recycled.
4. While serving as a support, the polymer chain may sometimes impart asymmetric induction[43,71,76].

There have been several studies reported on the uses of polymer-supported chiral auxiliaries in asymmetric synthesis, however, this area of research still remains quite new. Recently, the synthesis and application of insoluble polymer-supported chiral oxazolidin-2-ones[45,78] have been of great interest and importance to several researchers. It is important to note that the investigations that have been carried out so far on this particular area have employed only insoluble polymers as supports[53]. Three examples of such systems and their applications are illustrated here.

Allin and Shuttleworth[45] have first introduced the polymer-supported Evans oxazolidin-2-one and showed its potential for carrying out asymmetric alkylation reaction (Scheme 19).

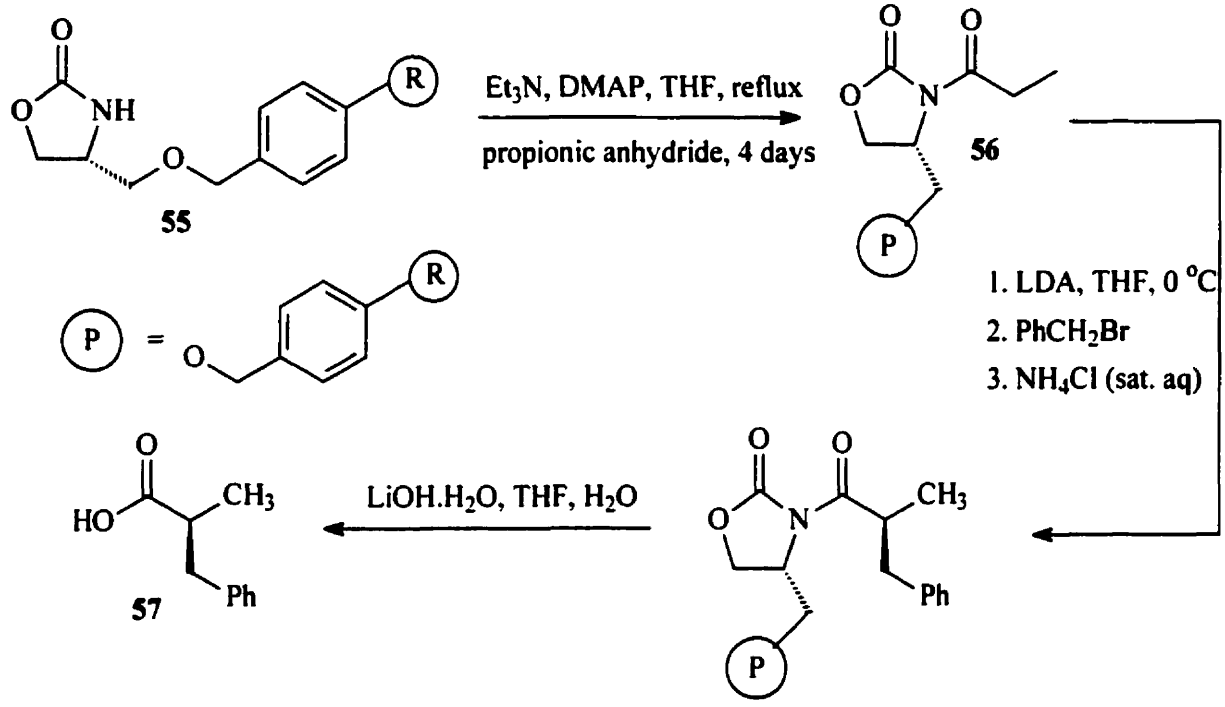


53 54 55

Scheme 19

They accomplished the preparation of the desired polymer-supported oxazolidinone **55** as shown in Scheme 19. The initial oxazolidinone **53** was derived from aminoacid *L*-serine[79]. They chose to employ Merrifield's resin **54** for their purpose reasoning that the bulky substituent would provide a high degree of steric bias in future asymmetric synthesis.

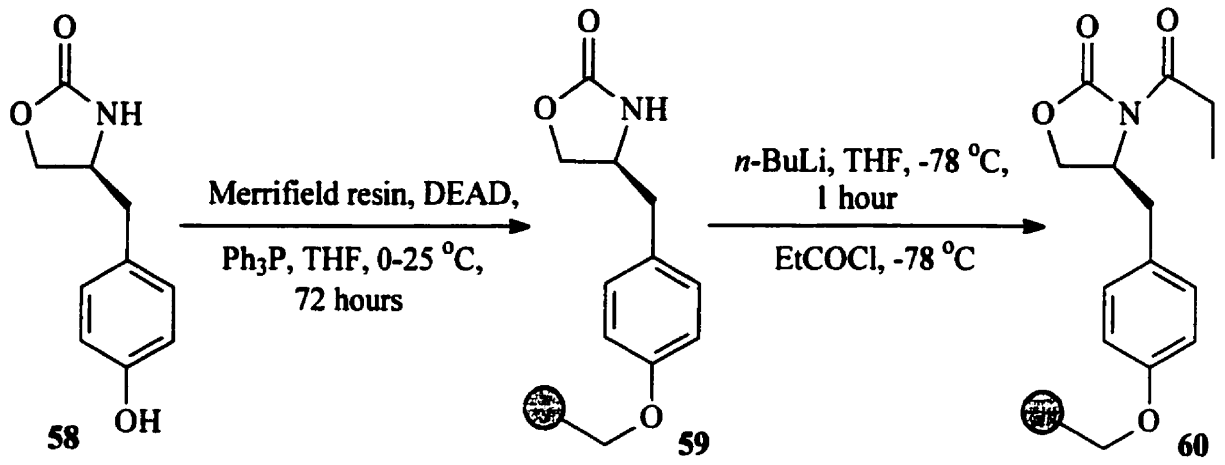
In order to examine the possibility of this new auxiliary system, they synthesized the *N*-acyl derivative **56** and performed the alkylation as depicted in Scheme 20.



Scheme 20

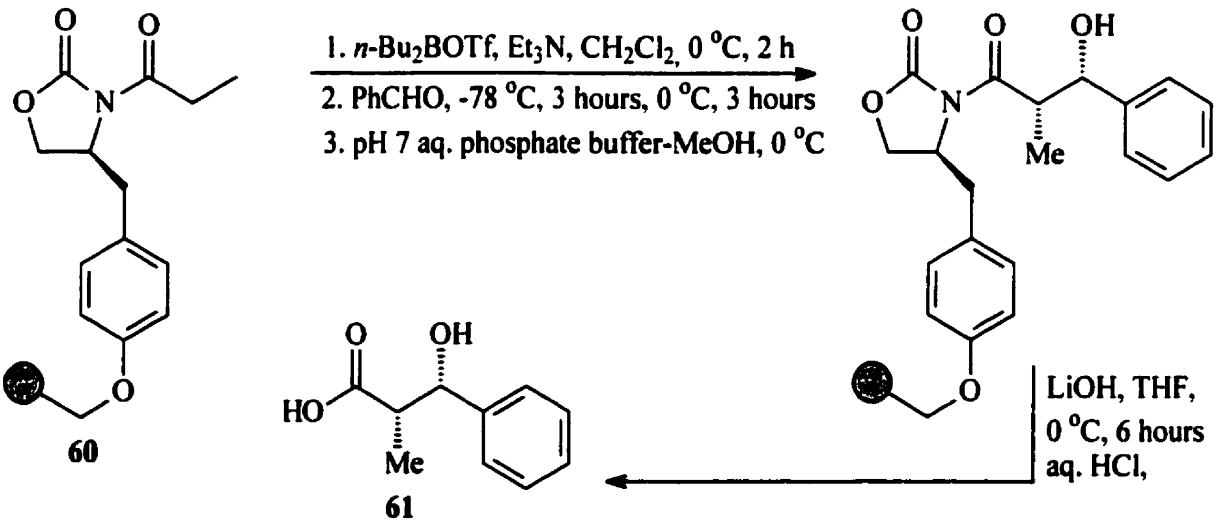
The removal of the final product from the polymer-bound auxiliary provided the desired α-alkylated carboxylic acid **57**. The NMR analysis revealed the presence of only one single enantiomer. The authors also found that the ^{1}H NMR and the optical rotation of **57** were identical to those values found in the literature. The use of the solid support provided the easy work-up and isolation steps. However, the yield was low (42%).

The next example[80] demonstrates the synthesis of solid polymer-supported chiral oxazolidinone **59** and its use in aldol reaction. The initial starting material **58** was prepared from aminoacid *L*-tyrosine using a protocol of Evans[8].



Scheme 21

As seen in Scheme 21, the attachment of the Merrifield resin to the oxazolidinone **58** under Mitsunobu conditions provided the desired polymer-bound oxazolidinone **59**. The *N*-acylated oxazolidinone **60** was then synthesized to test the potential of the system in asymmetric aldol reaction.

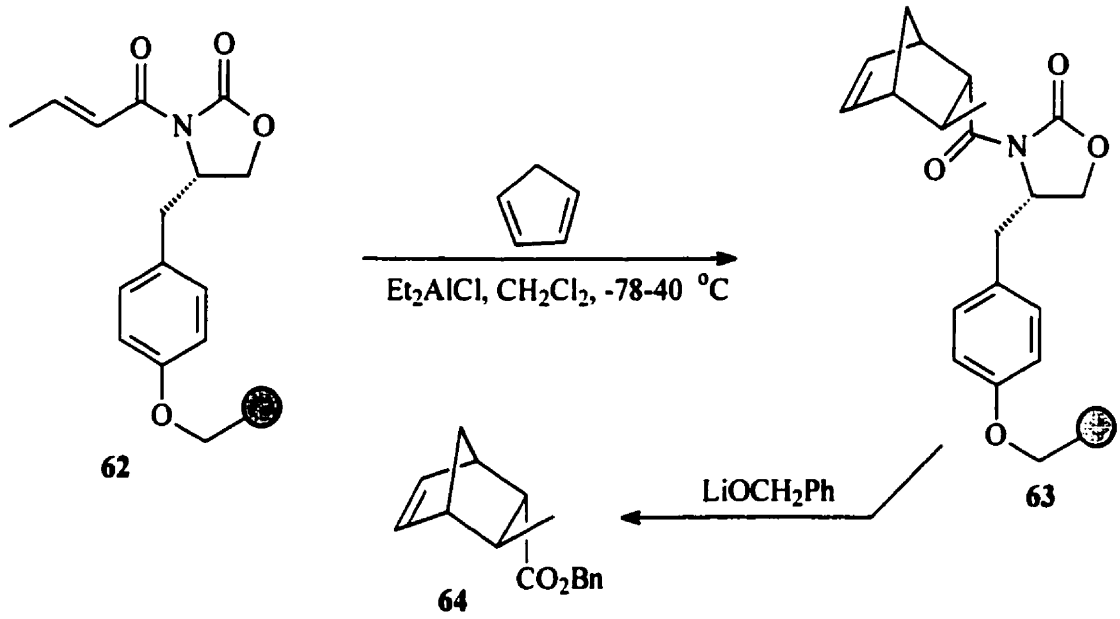


Scheme 22

According to Scheme 22, the aldol condensation of **60** was conducted by forming a boron enolate using *n*-dibutylboron triflate and triethylamine followed by the addition of

PhCHO. The cleavage of the aldol adduct from the auxiliary was attempted with LiOH in THF. The NMR analysis proved the presence of only the syn diastereoisomer **61** (de >98%). This result was identical to that reported by Evans for the normal boron-aldol reaction. They obtained a moderate yield for the aldol adduct **61** (63%). However, the yield was not quite satisfactory compared to that obtained for Evans aldol reaction[81].

The last example[82] is the synthesis of similar polymer-supported Evans oxazolidinone and the first application of this system to the Diels-Alder cycloaddition reaction. As illustrated in Scheme 23, the Merrifield resin-bound *N*-crotonylated oxazolidinone system **62** was used in the Lewis acid catalyzed cycloaddition with Et_2AlCl and cyclopentadiene at –78 °C.



Scheme 23

The exposure of the polymer-bound product **63** to lithium benzyloxide gave the endo adduct **64** in major amount. The stereoselectivities were comparable to those observed for the analogous reactions in solution. They obtained a very low yield (26%) for the overall synthesis.

These examples establish the successful applications of the solid polymer-supported oxazolidin-2- ones in asymmetric synthesis. Unlike solid polymer-supported oxazolidinone, the soluble polymer-supported oxazolidin-2-one system has never been synthesized or studied.

3. Fluorous synthesis

Fluorous phase concept: General aspects

Fluorous phase synthesis is a new synthetic methodology that emerged in the early part of this decade. The term fluorous represents the fact that the chemical transformation is primarily controlled by a substrate or a reagent or a catalyst designed to dissolve preferentially in the fluorous phase. The fluorous phase is defined as the fluorocarbon-rich or fluorohydrocarbon-rich phase.

In fluorocarbon-rich species, all H atoms are replaced with F atoms in the parent compound and these are called perfluorinated substances. Fluorohydrocarbons are partially fluorinated compounds in which at least one H is not replaced with F atoms in the parent structure. Fluorocarbons include perfluoalkanes, perfluoroalkylethers, and perfluoroalkylamines and are immiscible with many organic solvents[83,84].

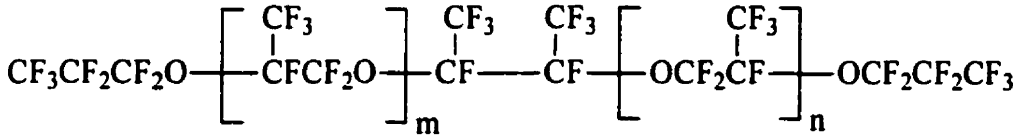
This fluorous phase strategy makes use of the restricted solubility and miscibility of partially or fully fluorinated compounds with nonfluorinated compounds[85]. The partially or fully fluorinated substances preferably dissolve in the perfluoro solvents and exhibit a large partition coefficient towards the fluorous phase in liquid-liquid extraction. Therefore, it is easy to conduct extractions between fluorous and organic or aqueous phases. This fluorous phase behavior of the reaction mixture at the purification step is the crucial feature for the fluorous phase approach.

The limited solubility or miscibility arises due to the sufficiently different intermolecular forces between the fluorinated and nonfluorinated species[83]. In the case of fluorocarbons (perfluorinated materials), the attractive forces between the fluorinated and nonfluorinated phases are highly restricted or negligible. However, the presence of a functional group or structural feature that shows intermolecular interactions could limit its solubility in the fluorous phase. This phenomenon is prominent in fluorohydrocarbon (partially fluorinated) compounds. In these cases, the possibilities for attractive forces increase between the nonfluorinated parts of the molecule with the other phase.

Thus, it is important to limit the attractive interactions by the use of more fluorocarbon moieties. In order to solubilize a nonfluorinated organic compound in saturated perfluorocarbons the presence of a sufficient number of perfluoroalkyl substituent groups is required.

The fluorinated or fluorous compounds (reagents, catalysts, etc.) can be prepared[86,87] by the addition of fluorocarbon groups to the compounds, fluorination or by total synthesis.

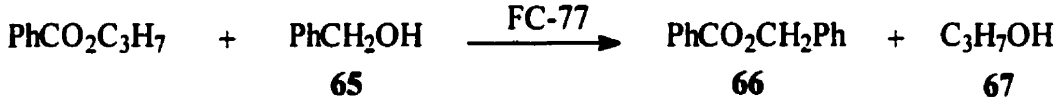
The use of the fluorous phase strategy has been recognized by researchers very recently. The fluorous phase concept was first described in the unpublished thesis of M. Vogt[85], who in 1991 attempted to utilize the solvophobic properties of perfluorinated ethers of the Hostinert 216 type (Figure 9) for phase separation in homogeneous catalysis reactions. Since the thesis has never been published, it is not well known.



Hostinert 216 type

Figure 9

The first application of fluorocarbon solvents in traditional organic synthesis appeared in 1993[88,89]. Dong-Wei Zhu performed a series of transesterification reactions in the perfluorinated FC-77 solvent (a fluorocarbon solvent containing isomers of C_8F_{18}). Fluorous transesterification is one of the few means to esterify an alcohol under neutral conditions. An example of such is shown in Scheme 24.



Scheme 24

In this approach, the low boiling alcohol **67** was replaced by a high boiling alcohol **65** during transesterification. The fluorous phase separation technique was carried out at two stages. First, the displaced, low boiling alcohol **67** in the reaction mixture was removed by phase separation using a distillation setup attached to an inverse Dean-Stark trap. Thereby the equilibrium was also driven forward. Second, the product ester **66** was separated from the FC-77 layer by phase

separation on cooling. The advantages obtained by this technique are ease of separation, faster reaction compared to esterification in nonfluorinated solvents and the use of nontoxic solvent.

Horvath and Rabai[83,89] first introduced the concept of fluorous biphasic catalysis for organic transformations. They synthesized a fluorous phosphine ligand **68** and used this to generate a rhodium catalyst for a standard hydroformylation reaction (Scheme 25). The authors reported that the ethylene (CH_2CH_2) spacer group (see phosphine ligand **68**) was important in order to decrease the strong electron-withdrawing effects of the fluorous segment.

Synthesis of fluorous phosphine ligand **68**

$$C_6F_{13}CH{=}CH_2 \;+\; PH_3 \xrightarrow[\text{2. azobis(isobutyronitrile), 80 °C, 8 hours}]{\text{1. azobis(isobutyronitrile), 100 °C, 1 hour}} (C_6F_{13}CH_2CH_2)_3P$$

68

Hydroformylation

$$H_3C{-}(CH_2)_7{-}CH{=}CH_2 \xrightarrow[C_6H_5CH_3/C_6F_{11}CF_3\ CO/H_2]{\textbf{68},\ Rh(CO)_2(acac)} CH_3(CH_2)_9CHO + CH_3(CH_2)_7\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CHO$$

Scheme 25

The hydroformylation was carried out in a biphasic mixture of perfluoromethylcyclohexane and toluene under a CO/H_2 atmosphere. The products were isolated from the catalyst by simple liquid-liquid extraction. The advantages of this approach are that it facilitates the ease of separation and the fluorous rhodium catalyst can be recovered and reused.

Curran and Hadida[90] recently succeeded in developing a new class of fluorous reagents.

$$C_6F_{13}CH_2CH_2Mg \xrightarrow{Cl_3SnPh} (Rf_6h_2)_3SnPh \xrightarrow{Br_2} (Rf_6h_2)_3SnBr \xrightarrow{LiAlH_4} (Rf_6h_2)_3SnH$$

69

$$C_6F_{13}CH_2CH_2 = Rf_6h_2$$

Scheme 26

Since they were interested in radical reactions, they targeted the important class of trialkyl tin reagents. The synthesis of such a fluorous tin reagent **69** is illustrated in Scheme 26.

The reduction of bromoadamantane **70** with the new fluorous tin reagent **69** in BTF afforded the adamantane **71** in high yields (Entry 1, Scheme 27). Initially, the reduction conducted in organic, fluorous or biphasic media worked poorly. The use of BTF solvent provided the homogeneous medium for the reaction since BTF has the ability to dissolve both organic as well as fluorous substances. The reactions were quenched by evaporating the BTF and partitioning the residue between PFMC and CH_2Cl_2. The CH_2Cl_2 contained only the adamantane **71** and the PFMC extract provided the tin bromide **72**.

70 **69** **71** **72**

Entry		equiv	solvent	additive	yields
1		1.2	BTF	none	90%
2	Catalytic reaction	0.1	BTF/*t*-BuOH(1/1)	$NaCNBH_3$	92%

Scheme 27

Similarly, a procedure using a catalytic amount (10%) of tin hydride **69** and $NaCNBH_3$ in BTF/*t*-BuOH (Entry 2, Scheme 27) provided the reduced adamantane **71** in higher yields too. The authors emphasized that the ethylene spacer group was necessary to prevent the electron-withdrawing effects of the fluorocarbons. The reaction also proved that the homogeneous reaction medium was important for the success.

It is apparent from the results that the perfluoroalkyl tin hydride **69** behaves like normal tin hydride reagent in radical reactions. Besides, it has significant practical advantages over normal tin hydrides. The tin reagent can be recovered and recycled. It is less toxic than normal tin hydrides. This fluorous method facilitates the easy work-up and purification by liquid-liquid phase separation and high purity can be obtained in the separation.

Similarly, the fluorous phase approach can be used to advantage in other traditional organic syntheses. In this regard, fluorous soluble reagents or substrates can be reacted with

nonfluorous soluble substrates or reagents. By dismissing phase separation problems in the reaction stage, a homogeneous condition can be maintained as in conventional methods. Finally, the purification can be effected by liquid-liquid extraction.

A new strategy by Curran – The Fluorous synthesis

Curran et al.[91,92] have introduced the concept of fluorous synthesis as a fundamental strategic alternative to traditional small molecule synthesis and solid phase synthesis. In this methodology, the initial organic substrate is rendered fluorous by attaching a fluorocarbon unit, the fluorous tag as shown in Figure 12. This fluorous tag must have sufficient structure size and fluorine content in order to make the attached organic molecule fluorous.

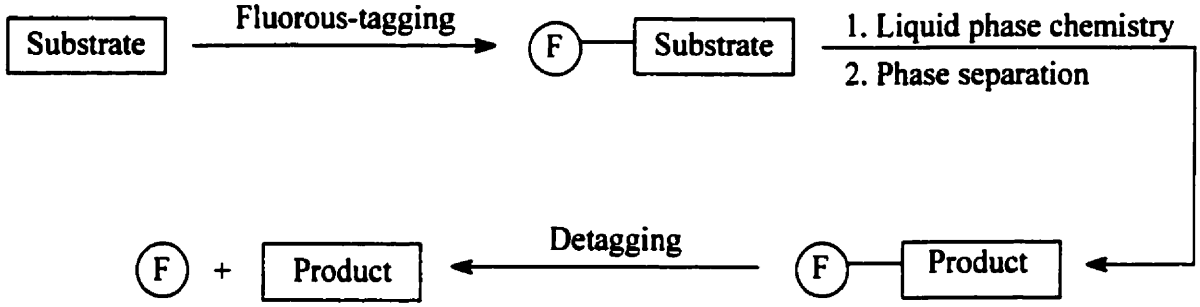
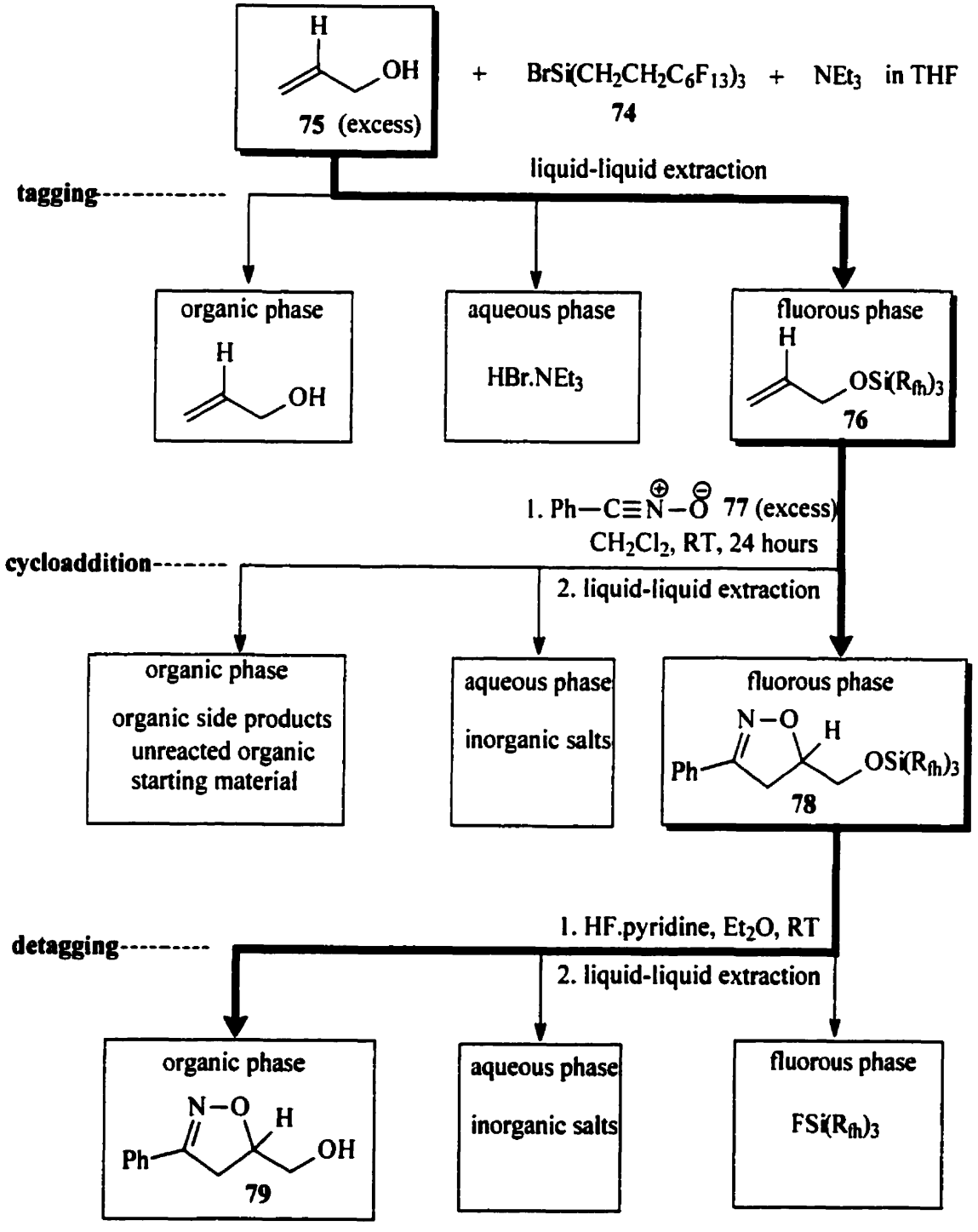


Figure 10

One or more organic reactions are then conducted. The fluorous-labeled products are subsequently separated from all non-fluorous components by liquid-liquid extraction. During the phase separation, the fluorous products partition into fluorous phase while the untagged organic molecules, excess reagents and insoluble additives partition into the organic or water phase. At the desired stage, the fluorous tag is cleaved and the organic product is released.

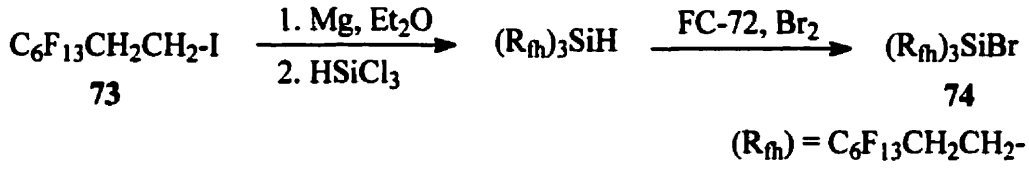
The concept of fluorous synthesis can be understood by considering a few examples. The first example describes the 1,3-dipolar cycloaddition of nitrile oxides to alkenes to form isoxazoline via fluorous synthesis introduced by Curran[92,93]. The general strategy for the preparation of isoxazoline is pictured in Scheme 28. As seen, the process occurs in three stages: fluorous tagging, cycloaddition, and detagging. At each stage, a reaction is performed and the

products are purified by a three-phase extraction with an organic solvent, fluorous solvent and water. Thick arrows show the phase of the target compound as it moves through the synthesis.



Scheme 28

The initial step involves the fluorous tagging. The tagging-reagent, a highly fluorinated bromo silane **74**, was synthesized from a perfluoro compound **73** according to Scheme 29[94].



Scheme 29

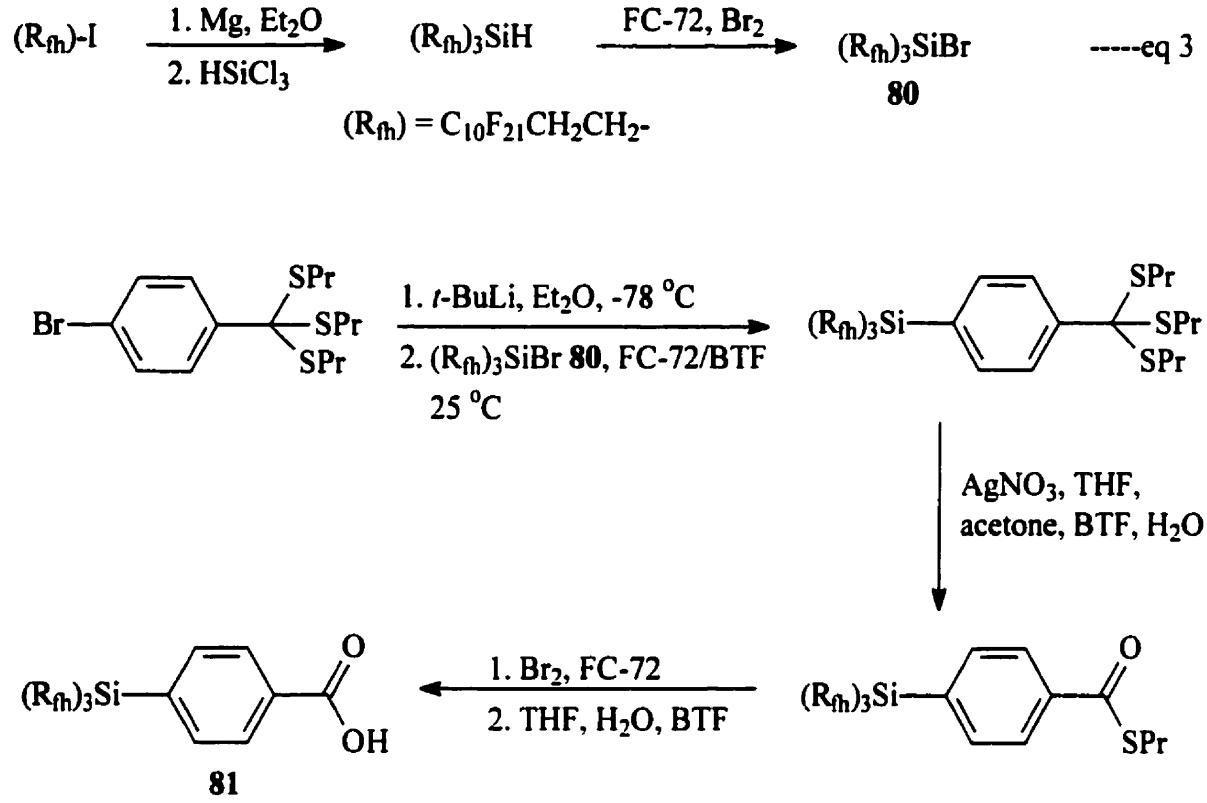
The attachment of the fluorous-tag **74** to the allyl alcohol **75** was carried out in THF with Et_3N (Scheme 28). After evaporation of the solvent, the crude mixture was purified by a three-phase extraction using FC-72 (perfluorinated solvent, bottom), CH_2Cl_2 (middle), and water (top). The analysis of these layers showed that the desired fluorous product **76** was only partitioned into the FC-72 layer and the phase separation was efficient. As shown in Scheme 28, the organic phase extracted the excess allyl alcohol and the inorganic salts formed during the reaction partitioned into the aqueous phase.

In the next step, the cycloaddition of fluorous silyl ether **76** with benzonitrile *N*-oxide **77** was performed in CH_2Cl_2 at room temperature for 24 hours. Excess nitrile oxides were added to force the reaction to completion. The products were purified by three-phase extraction using FC-72 (bottom), water (middle), and benzene (top). The fluorous FC-72 phase contained the fluorous-tagged cycloadduct **78**, an isoxazoline. The excess organic reagents and impurities were removed into the organic phase and the aqueous phase extracted the inorganic salts. The phase separation was proved to be highly efficient.

Finally, the desilylation of the fluorous isoxazoline **78** was carried out with HF.pyridine in Et_2O at room temperature. After evaporation of the solvents the liquid-liquid phase separation using FC-72, CH_2Cl_2, and aq. NH_4Cl was performed. The desired isoxazoline **79** was isolated from the organic phase in high yields. The remnant of the fluorous-tag was left in the fluorous phase. This whole scheme explains the fluorous synthesis strategy clearly.

Another example by Curran and coworkers[91,92] introduces a fluorous synthesis protocol for multicomponent condensation reactions. Multicomponent condensations are capable of forming highly variable side chains and core structures from simple starting materials in a single

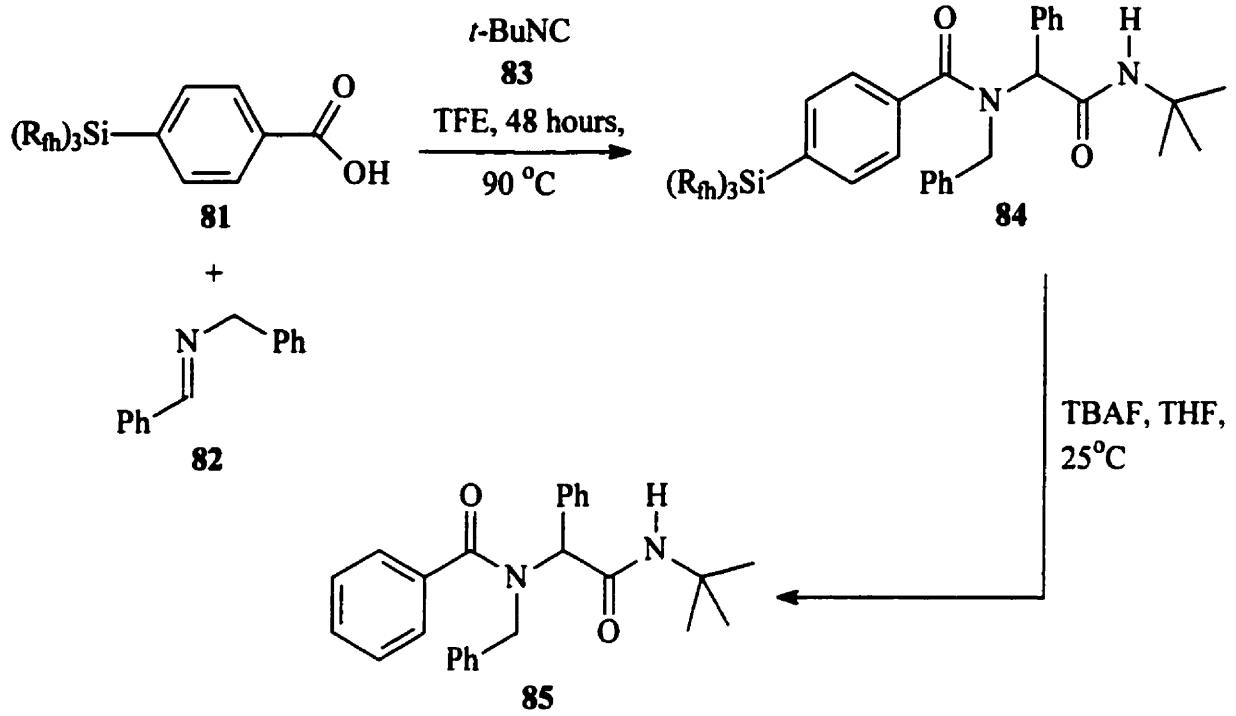
step. The Ugi and Biginelli are the two important classes of such condensations and an example of Ugi condensation via fluorous synthesis is described here.



Scheme 30

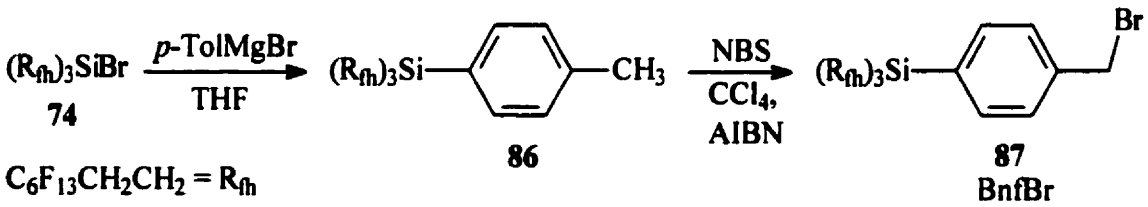
The synthesis of the required fluorous-labeled acid **81** for the Ugi condensation is illustrated in Scheme 30. The preparation of the fluorous-tag **80** is also depicted in the same scheme (eq 3). At the end of each conversion, a liquid-liquid three-phase separation (FC-72, benzene, and water) was performed to isolate the fluorous materials.

The Ugi three-component condensation (an acid, an imine and an isocyanide) of fluorous acid **81** with benzylbenzylideneamine **82** and *tert*-butyl isocyanide **83** was then conducted to form the aminoacid amide **84** as shown in Scheme 31. After removal of the solvents, the three-phase extraction yielded the fluorous Ugi product **84**. Cleavage of the product **84** with TBAF released the fluorous-free organic Ugi product **85** in good yields.



Scheme 31

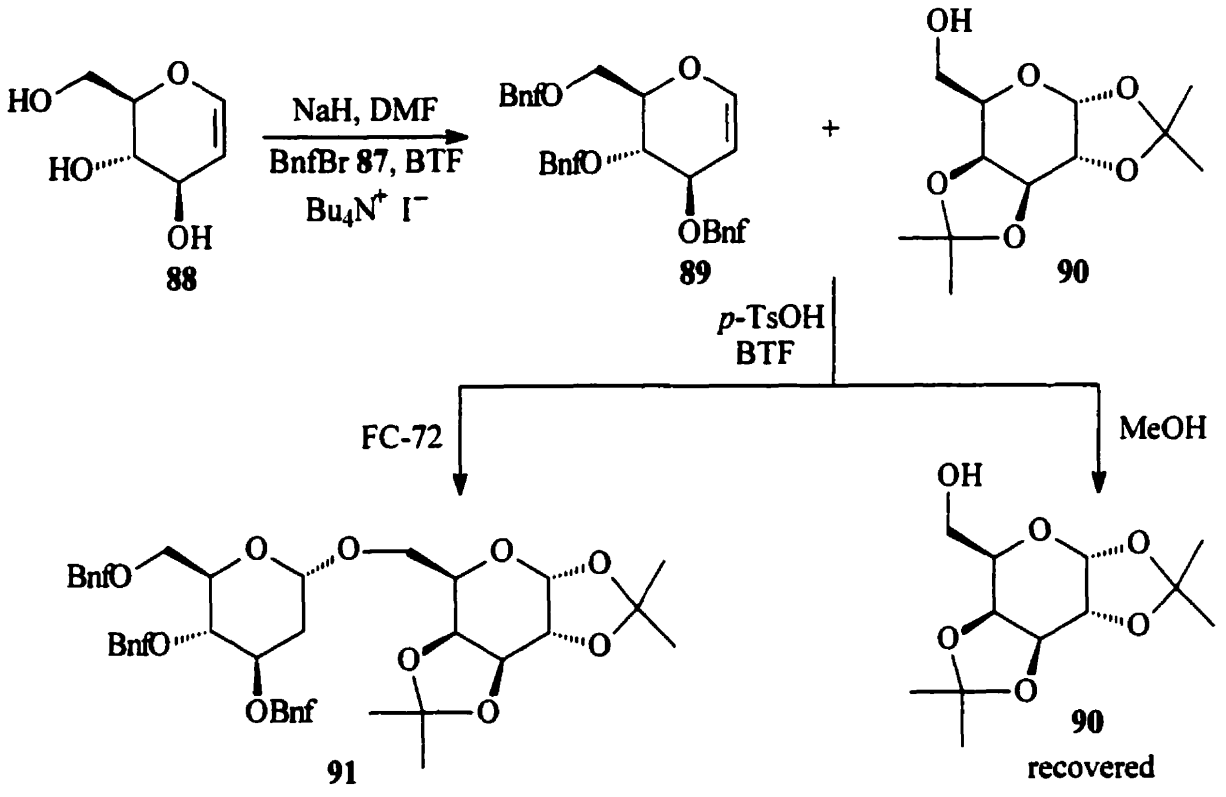
The last example[95] demonstrates the preparation of a fluorous benzyl protecting group and its use in a fluorous synthesis approach to a disaccharide. The synthesis of the novel fluorous benzyl protecting reagent **87** is outlined in Scheme 32. It is noteworthy that the flash chromatography was used to purify the fluorous benzyl bromide **87** from the unreacted fluorous material **86**.



Scheme 32

A glycal route is chosen to make the target disaccharide **91** as illustrated in Scheme 33. In the initial step, the fluorous benzyl protection of D-glucal **88** provided the fluorous glucal

derivative **89**. The three-phase (FC-72, CH_2Cl_2, water) extraction was performed to remove organic and inorganic materials. The fluorous glucal **89** was then coupled with diacetone galactose **90** using catalytic amount of *p*-TsOH. After the extraction, the evaporation of the fluorous phase afforded the pure fluorous disaccharide **91**. The unreacted diacetone galactose **90** was recovered from the organic phase.

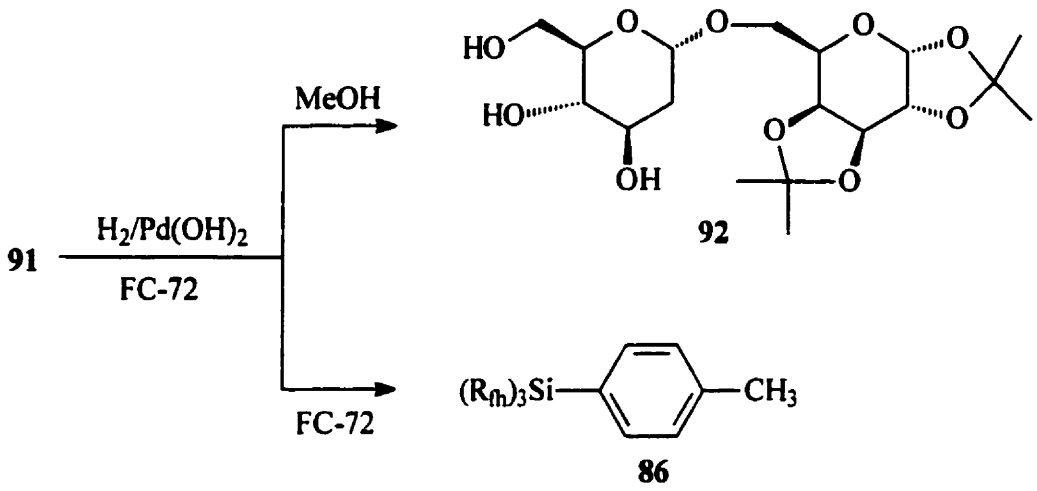


Scheme 33

The fluorous disaccharide **91** was then debenzylated by catalytic hydrogenation (Scheme 34). After three-phase extraction, the requested disaccharide **92** was obtained from the organic phase (MeOH). Evaporation of the fluorous phase gave the silane **86** and which was then brominated to regenerate the fluorous tagging reagent **87** (Scheme 32). The recovery and recycling of the fluorous benzyl group are one of the attractive features of this method.

In this methodology, large organic substrates are made fluorous by incorporating a highly fluorinated fluorocarbon chain. Chemical reactions are performed under homogeneous condition. The efficient phase separation technique eliminates the time consuming work-up and

isolation processes. All these synthetic applications prove that the fluorous synthesis approach can be used in traditional organic synthesis.



Scheme 34

In general, any fluorous materials preferentially partition into perfluorinated solvents. It is apparent that the peculiar characteristic features of the fluorous substances and solvents are responsible for this favorable phase behavior. Thus, it is appropriate to describe some of the essential properties of the fluorous solvents and substrates briefly.

Properties of perfluorinated solvents and fluorous substrates

Since the perfluorinated solvents have a large number of fluorine atoms in their structure, they exhibit unique physical properties[89]. The element fluorine has very high ionization potential and electronegativity and very low polarizability. Due to these reasons, perfluoro solvents have high densities, low polarity, extraordinarily lower boiling points than saturated hydrocarbons and the lowest dielectric constants[88].

Moreover, they show weak intermolecular forces such as Van der Waals interactions, because of low polarizabilities. As a consequence, perfluoro fluids are immiscible with many organic solvents at room temperature[84,85]. However, it is known that solvents like CCl_4, ether, and THF have the highest solubilities in fluorocarbon solvents at room temperature[89]. Perfluoro

fluids also show a low miscibility with toluene, acetone and alcohol[83]. Sometimes, they can be made miscible by warming[85,89].

The high purity, stability, and inert properties of perfluorinated solvents are suitable for reactions sensitive to polar environments, to moisture, and reactions carried at high temperatures for a prolonged period[88]. The fluorous solvents are chemically and thermally inert, stable materials because of their very strong carbon-fluorine bonds[88]. Their stability makes them nontoxic and nonflammable. Thus, they are environmentally friendly solvents[83,88]. These solvents also show several applications in other areas such as surface chemistry, biology and engineering[89].

Similarly, due to the presence of the perfluorinated chain, the fluorous substrates have low polarizabilities and are highly hydrophobic in nature[96]. Therefore, these substances only dissolve in limited organic solvents (such as acetone, THF, ether and CH_2Cl_2)[89]. They are soluble in perfluorinated solvents because of the similar attractive interactions between the perfluorinated solvents and the fluorous part of the substances.

If a fluorous molecule contains a solvophilic hydrocarbon portion in its structure then that molecule will at least exhibit some solubility in organic solvents[85]. Depending on the number of hydrocarbon units the solubility in organic solvents varies[97]. Like perfluorinated solvents, fluorous substrates are also chemically and thermally inert, stable materials and are environmentally safe materials.

Fluorous substrates should have an enough number of hydrocarbon (CH_2CH_2) spacer groups or intervening groups in between the fluoro part and the rest of the organic moiety (Figure 11). This spacer group prevents from transmitting the electron withdrawing effects of the fluorinated segment to the reaction center. This also ensures the electronic properties of the fluorous-tagged molecule will be close to those of the underivatized molecule.

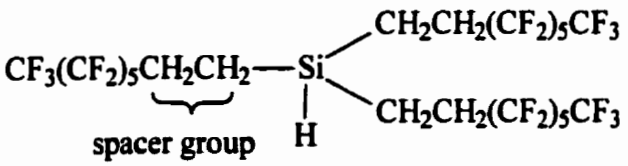


Figure 11

These properties of perfluorinated solvents and fluorous compounds strongly influence the synthesis based on fluorous phase concepts.

Advantages of fluorous synthesis

The fluorous synthesis combines the advantages of both solution and solid phase strategies. As described earlier, the reactions of fluorous substrates are performed in a homogeneous medium by standard solution phase methods. Thereupon, the reaction can be monitored by TLC and chromatographic techniques can be performed to separate the products[91]. The fluorous products are single molecules and can be characterized by spectroscopic methods (^{1}H, ^{19}F and ^{13}C NMR, IR and EI-MS)[93]. Purity of the products can be assessed at any stage and analytical techniques (HPLC) can be used for identification and analysis of the products.

Furthermore, in some cases[95], the fluorous-tagged compounds can be recovered and recycled. It is possible to use large excess of reagents and reactants to drive the reaction to completion as in solid phase synthesis since the excess materials can be simply removed by phase separation[91]. The fluorous labels can be easily cleaved off under appropriate conditions without affecting the other functional groups on the substrate. The fluorous labels are more robust than most polymers and linkers used in solid and solution phase synthesis. This method provides the products in acceptable purities and good yields.

The fluorous synthesis is particularly promising for traditional organic synthesis. There is much room for new synthetic contributions in this field. The future applications can be envisioned in the area of asymmetric synthesis. The fluorous synthesis approach has never been tested for stereoselective asymmetric reactions. Besides, there have not been any studies reported on fluorous-tagged chiral auxiliary system either.

Our work

includes

1. Synthesis of a new chiral 4-substituted oxazolidin-2-one via a novel method.
2. Synthesis of a novel soluble polymer-supported chiral 4-substituted oxazolidin-2-one and examination of its behavior in asymmetric synthesis.
3. Synthesis of a novel fluorous-labeled chiral 4-substituted oxazolidin-2-one and demonstration of its potential for asymmetric synthesis.

1. Synthesis of a new chiral 4-substituted oxazolidin-2-one via a novel method

Oxazolidin-2-ones are widely utilized in a broad spectrum of asymmetric transformations of carboxylic acid derivatives. A chiral 4-substituted oxazolidin-2-one forms a central skeleton system for our main projects.

Our idea for its synthesis from aminoacid *L*-tyrosine is outlined in Figure 12. We believe that the phenolic OH group should function as a point of attachment to link a polymer support or a fluorous tag.

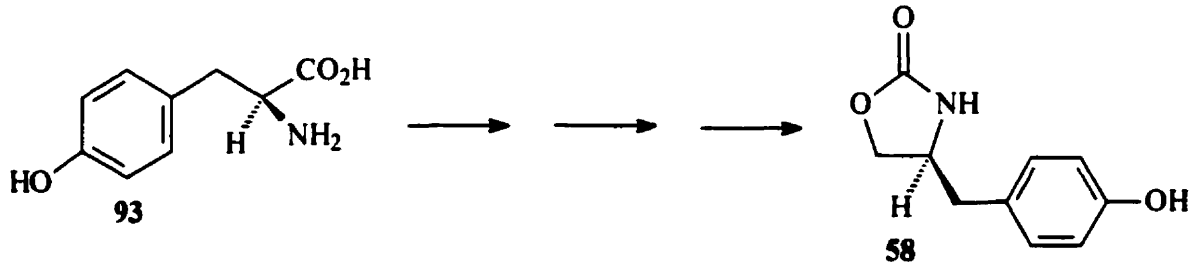


Figure 12

The synthesis should use less hazardous and inexpensive reagents and provide simpler and milder conditions than do most existing methods. It should not include too many steps in their preparation and should be amenable to larger scales.

2. Synthesis of a novel soluble polymer-supported chiral 4-substituted oxazolidin-2-one and examination of its behavior in asymmetric synthesis

Supporting a chiral auxiliary on a soluble polymer makes its recovery very simple. Soluble polymer-supported chiral oxazolidinones have never yet been prepared in organic synthesis.

Our plan for the synthesis of the novel soluble polymer-supported oxazolidinone and for performing asymmetric transformations is sketched in Figure 13.

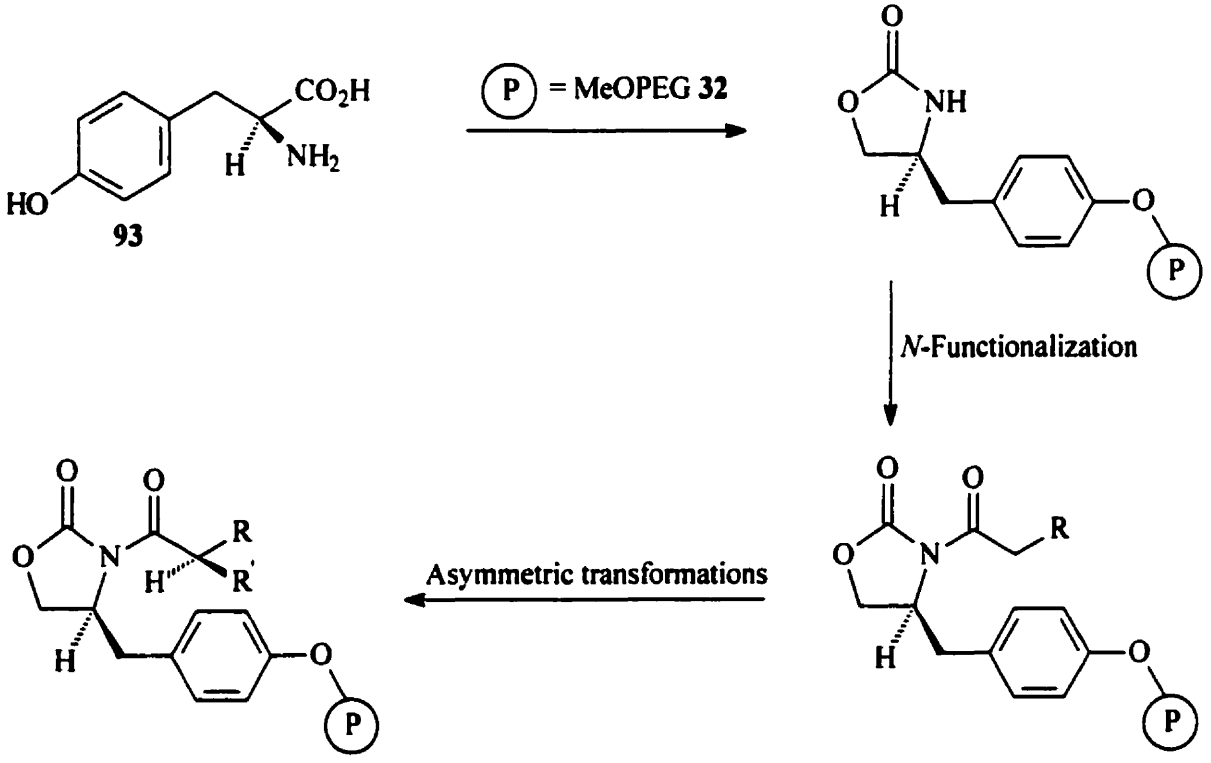


Figure 13

Our selection for the polymer is poly(ethylene glycol)monomethyl ether (MeOPEG) **32** (Figure 8, M_W 5000). We presume that MeOPEG will accomplish the demands of a polymer support. The new linkage between the polymer support and the substrate should be stable under most reaction conditions. We will study alkylation and the Diels-Alder reactions on the *N*-acyl derivatives of this MeOPEG-supported oxazolidinone.

3. Synthesis of a novel fluorous-labeled chiral 4-substituted oxazolidin-2-one and demonstration of its potential for asymmetric synthesis

The fluorous synthesis introduces an alternative route to polymer-supported synthesis and traditional organic synthesis. This strategy has never been applied in any area of asymmetric synthesis and no fluorous-labeled oxazolidinone has been prepared.

Our object for the novel synthesis of fluorous-labeled oxazolidinone and for conducting stereoselective conversion is pictured in Figure 14.

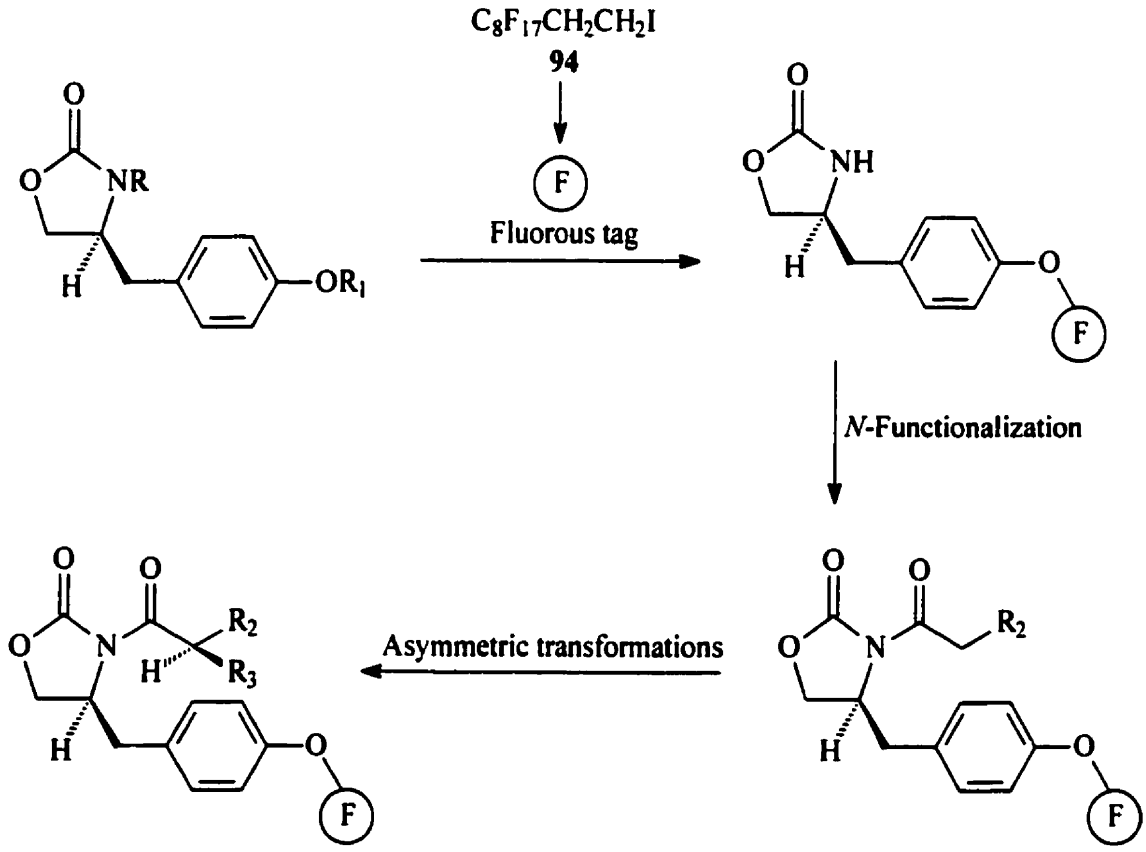


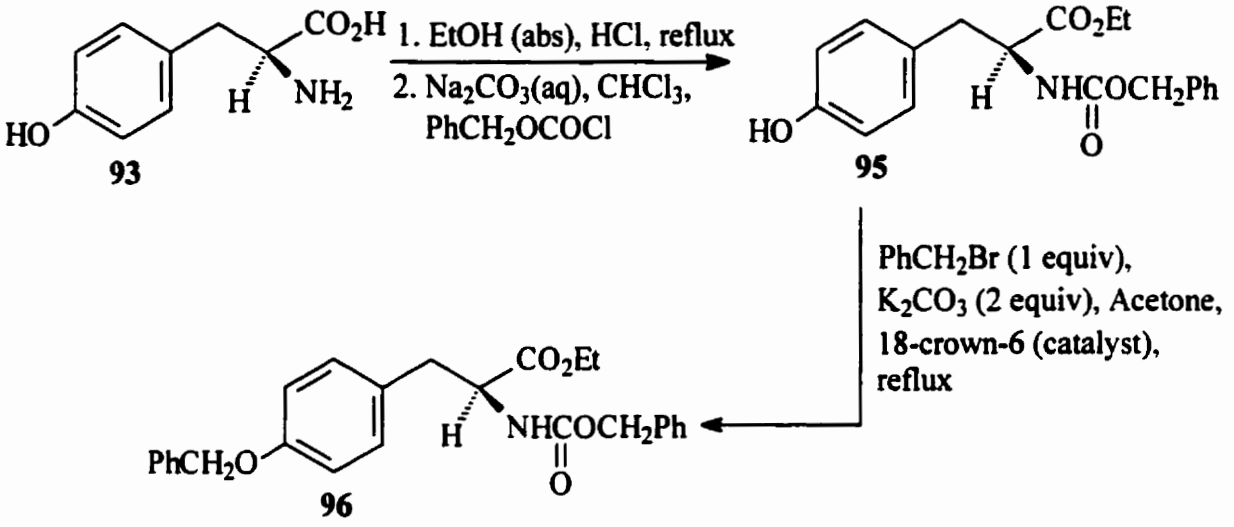
Figure 14

We will study an asymmetric aldol condensation reaction on this system. We believe that the fluorous synthesis can be an alternative methodology to the soluble polymer-supported oxazolidinone. It should be a viable approach for effecting various enolate chemistries and stereochemical transformations.

Results

1. Synthesis of chiral oxazolidin-2-ones

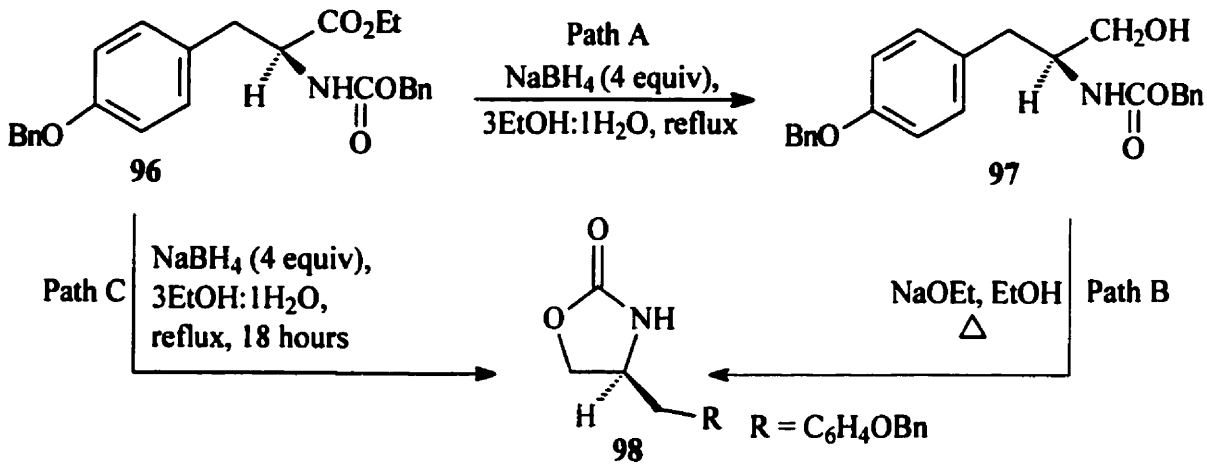
Our studies began with the synthesis of the required chiral auxiliary backbone, a 4-substituted oxazolidin-2-one. We prepared the well-protected precursor *O*-benzyl-*N*-(benzyl-oxycarbonyl)-*L*-tyrosine ethyl ester **96** from *L*-tyrosine **93** as shown in Scheme 35.



Scheme 35

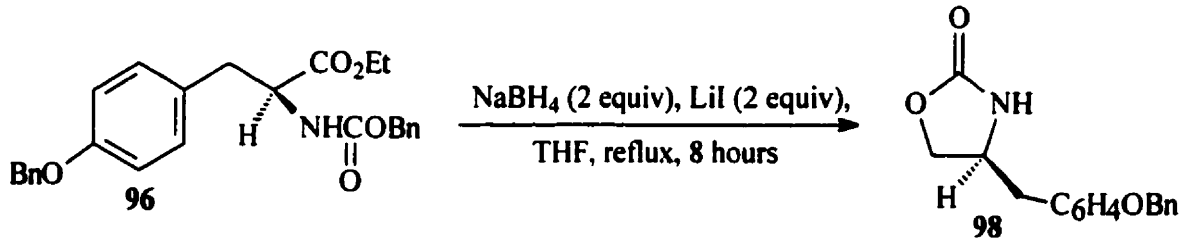
The esterification of the carboxylic acid moiety with ethanol and the protection of the amino group with carbobenzyloxy chloride (76%) were performed in the same pot[15,98] without isolating the intermediate ethyl ester. The free phenolic hydroxyl group of **95** was protected with benzyl bromide[99,100] to give **96** (79%).

According to our plan illustrated in Scheme 36, we decided to carry out the reduction of the ester **96** with $NaBH_4$ in 3:1 EtOH/H_2O[101,102] (Path A) and the cyclization of the resulting alcohol **97** with NaOEt/EtOH (Path B) in two separate steps. Surprisingly, when we tried the reduction reaction, the resultant alcohol **97** proceeded to form the cyclized material **98** under the same conditions (Path C). The NMR data proved that the obtained product was actually the desired oxazolidinone **98**. However, this method needed a longer time for the reduction and provided only a low yield of product **98** (~40%).



Scheme 36

In the process of improving the reaction conditions for reduction, we discovered a method for obtaining 4-substituted oxazolidin-2-ones in excellent yields.



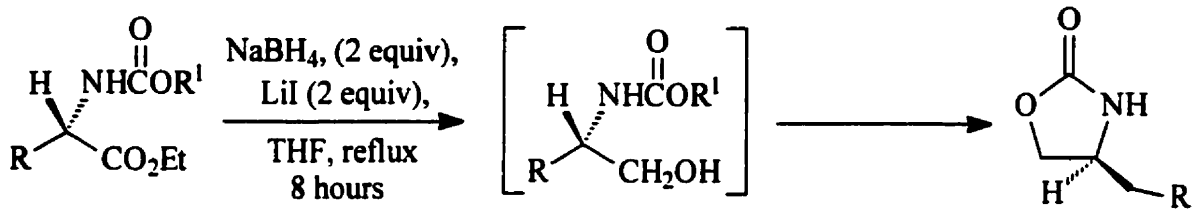
Scheme 37

As portrayed in Scheme 37, the reduction and the cyclization could be accomplished in one step, by reducing the ester **96** with $LiBH_4$ (formed in situ from $NaBH_4$ and LiI) in THF and heating the mixture under reflux for 8 hours (85%). The reaction proceeded equally well under dry conditions or with the system open to the atmosphere.

In order to demonstrate the utility of this methodology, we applied this protocol to the compounds summarized in Table 1. The popular 4(*S*)-isopropyl **2** and 4(*S*)-benzyl **3** oxazolidinones[15] were produced in excellent yields from Cbz-valine ethyl ester **2a** (Entry 1) and Cbz-phenylalanine ethyl ester **3a** (Entry 2) respectively. In contrast, *tert*-boc phenylalanine ethyl

ester[103] **99a** was only reduced to alcohol **99b** under same conditions (Entry 3). Similarly, the reduction of Cbz-tyrosine (OH) ethyl ester **95** by this approach produced only the alcohol **100** (Entry 4). We also observed that this reduced alcohol **100** precipitated out from THF. In entries 3 and 4, the cyclization did not occur even on extended heating.

Table 1. Application of our novel method



2a	**2b**	**2**
3a	**3b**	**3**
99a	**99b**	**99**
95	**100**	**58**

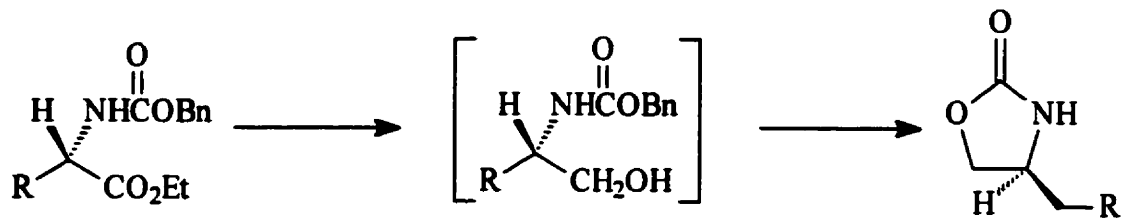
Entry	Ester	R	R^1	Product	Yield
1	**2a**	$(CH_3)_2CH$-	Bn-	**2**	96%
2	**3a**	$C_6H_5CH_2$-	Bn-	**3**	88%
3	**99a**	$C_6H_5CH_2$-	*t*-Bu-	**99b***	80%
4	**95**	$HOC_6H_4CH_2$-	Bn-	**100***	55%

* No cyclization occurred on extended heating.

Since we required the oxazolidin-2-one **58** (Table 1) for our main study, we wanted to find out conditions that could produce **58** in better yields by this type of reaction. We tested the synthesis by varying the solvent, lithium salt and metal borohydride. Table 2 presents the results obtained from the experiments.

We concluded that THF was the best solvent for the process. Reactions attempted with $NaBH_4$/LiCl were generally unsatisfactory (Entry 2). Entry 3 shows a reaction based on a literature procedure for ester reduction[15]; the two steps could be combined to produce a moderate yield of oxazolidin-2-one **58** (Entry 4).

Table 2. The effect of changing reaction conditions for reduction



95 **100** **58**
96 **97** **98**
3a **3b** **3**

Entry	Ester	R	Conditions	Product	Yield
1	**95**	$HOC_6H_4CH_2$-	A, diglyme, at 65 °C, 3 hours	**100**	100%
2	**3a**	$C_6H_5CH_2$-	B, THF, reflux ~48 hours	***3b**[a]	-
3	**3a**	$C_6H_5CH_2$-	(i). C, at RT, 18 hours		
			(ii). reflux 3-4 hours	**3**	75%
4	**95**	$HOC_6H_4CH_2$-	C, reflux 6-8 hours	**58**	50%
5	**95**	$HOC_6H_4CH_2$-	A, THF/EtOH (abs), reflux	***100**[b]	-
6	**95**	$HOC_6H_4CH_2$-	(i). A, THF, at RT, 3 hours		
			(ii). EtOH (abs), reflux, 7 hours	**58**	55%
7	**95**	$HOC_6H_4CH_2$-	(i). A, THF, reflux 1 hour		
			(ii). EtOH (abs), reflux, 7 hours	**58**	55%
8	**96**	$BnOC_6H_4CH_2$-	D, reflux 18-19 hours	**98**	83%
9	**96**	$BnOC_6H_4CH_2$-	(i). D, reflux 1 hour		
			(ii). H_2O (1 drop), reflux 9 hours[c]	**98**	88%

A. $NaBH_4$ (4 equiv.), LiI (4 equiv.).

B. $NaBH_4$ (4 equiv.), LiCl (4 equiv.).

C. $NaBH_4$ (4.3 equiv.), $CaCl_2$ (2.1 equiv.), THF/EtOH (abs).

D. Salt-free, commercial $LiBH_4$ reagent (4 equiv.), THF.

a. Traces of detected.

b. Traces of **58** and unreacted **95**.

c. Iodide salt instead of H_2O.

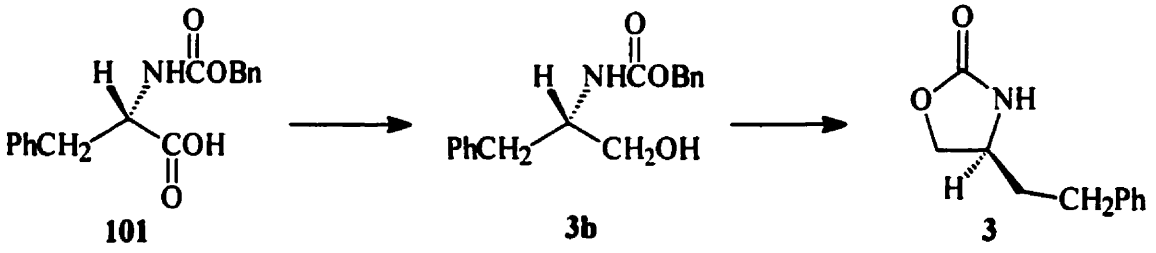
*Analyzed by TLC and NMR.

The reaction of **95** with $NaBH_4$/LiI in a mixture of THF/EtOH maintained the solubility of the materials, but provided only a trace of required material **58** (Entry 5). Besides, the resulting alcohol **100** precipitated from the solvent. Consequently, we conducted the reduction in THF first and after the completion of the reduction, we added the EtOH to the reaction mixture. The EtOH re-dissolved the resultant alcohol **100** and this promoted the reaction to form the oxazolidinone **58** (entries 6 & 7).

When the ester **96** was heated with halide-free commercial $LiBH_4$ in THF, it was reduced rapidly but the cyclization occurred very slowly requiring 18-19 hours to give the oxazolidin-2-one **98** (Entry 8). However, by adding iodide salt (LiI) or a drop of water after the completion of the reduction, the formation of the oxazolidin-2-one **98** was accelerated and finished within 9-10 hours (Entry 9). Nevertheless, this method was not suitable for larger-scale reactions.

We concluded that in most cases, $NaBH_4$/LiI in THF was the best satisfactory reagent and only the one method that involves the $NaBH_4$/LiI in THF/EtOH mixed solvent (entries 6 & 7) provided the **58** in moderate yields.

We next attempted to reduce the Cbz-phenylalanine **101** in THF by treating with $NaBH_4/I_2$ under reflux for 5 hours, adopting the protocol of Meyers et al.[104] (Scheme 38).



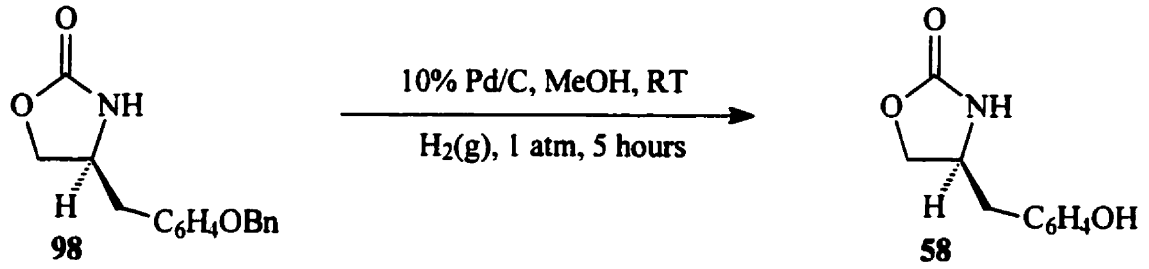
Scheme 38

We obtained a complex product, which contained neither the oxazolidin-2-one, nor the Cbz aminoalcohol. Analysis of this complex product by NMR suggested that reduction of the carbamate had actually taken place.

We also tried to reduce Cbz-phenylalanine **101** by stirring with borane methyl sulfide complex in THF at room temperature for 6 hours[105]. Slow reduction to aminoalcohol **3b** was

observed. When the mixture was heated for 18 hours, reduction occurred rapidly. Cyclization of **3b** did not occur even on extended heating, neither in the presence nor absence of iodide. NMR studies indicated the formation of polar products, similar to those observed in the previous case.

We also attempted an alternative method for the synthesis of **58** as shown in Scheme 39.

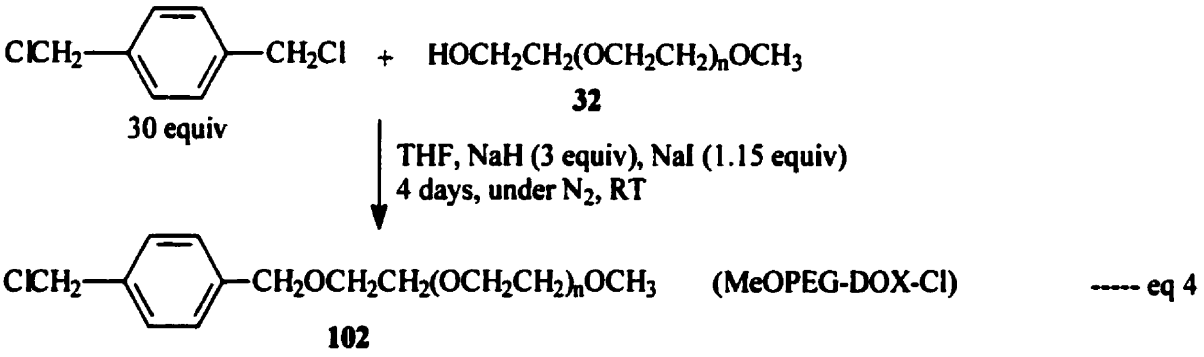


Scheme 39

Debenzylation[106] of oxazolidin-2-one **98** in methanol using 10 mol% of Pd/C and H_2 gas yielded the desired oxazolidin-2-one **58** (99%) within a few hours. This method worked perfectly even for larger amounts of substrates.

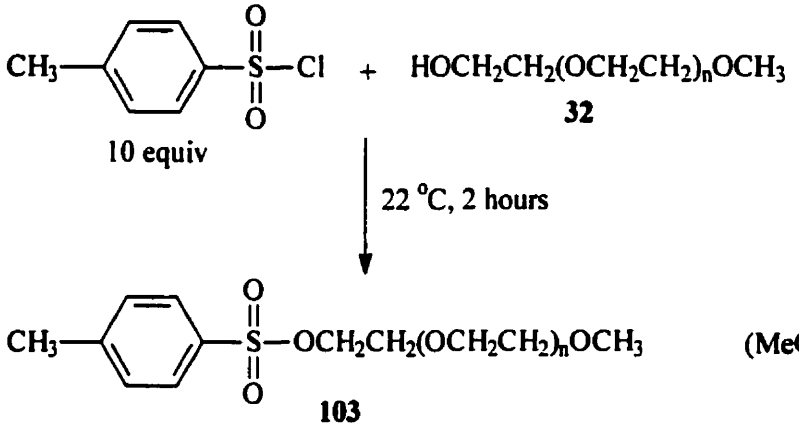
2. Synthesis of a soluble polymer-supported chiral oxazolidin-2-one

Having established the procedures for the synthesis of the required oxazolidinones **58** and **98**, we focused our attention on the next step, the synthesis of the soluble polymer-supported chiral oxazolidinone.



As mentioned earlier, we chose MeOPEG **32** as the supporting polymer. We used two MeOPEG linkers for this purpose. According to eq 4, MeOPEG-DOX-Cl linker **102** (95%) was prepared by treating the polymer **32** with α,α'-dichloro-*p*-xylene adopting a procedure of Krepinsky et al.[107].

Similarly, MeOPEG-OTs **103** (>90%) was produced by treating **32** with *p*-toluene-sulfonyl chloride using a published method[108,109] (eq 5).[1]



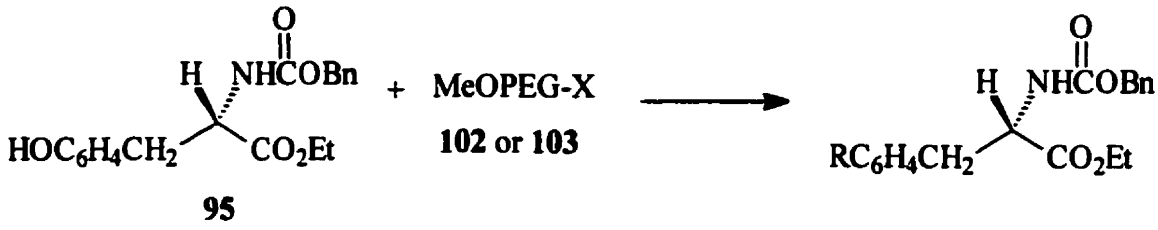
(MeOPEG-OTs) ----- eq 5

We considered the attachment of these polymer anchors (**102** and **103**) to the ester **95** first. We hoped that we could synthesize the requested polymer-supported oxazolidinone from this polymer-linked ester using our novel method. A series of attempts were made to anchor the MeOPEG-linkers with the ester **95**. The results are summarized in Table 3. In all cases, the polymer materials were isolated by precipitation with Et_2O and filtration. The crude materials were then analyzed by NMR[58]. Only traces of polymer-linked ester **104a** could be obtained (Entry 1 and 2).

Using oxazolidin-2one **58** instead of the ester **95** was promising as a new pathway to our target molecule. We used the MeOPEG-DOX-Cl linker **102** for this purpose. As outlined in Table 4, we achieved the coupling reaction of oxazolidin-2-one **58** with MeOPEG-DOX-Cl **102** in high yield (Entry 3). We monitored the reaction by NMR. The polymer products were isolated by precipitating with Et_2O.

[1] Linker **103** provided by Dr. P. G. Hultin.

Table 3. Coupling reaction of ester 95 with a polymer linker MeOPEG-X



104a: R = MeOPEGOCH$_2$C$_6$H$_4$CH$_2$O-
104b: R = MeOPEGO-

Entry	Conditions	Ester 95	MeOPEG-X	X	Product
1	A	1 equiv.	**102** (1.1 equiv.)	-OCH$_2$C$_6$H$_4$CH$_2$Cl	traces of **104a**
2	B	1 equiv.	**102** (0.5 equiv.)	-OCH$_2$C$_6$H$_4$CH$_2$Cl	traces of **104a**
3	B	1 equiv.	**103** (0.5 equiv.)	-OSO$_2$C$_6$H$_4$CH$_3$	-
4	C	1.75 equiv.	**102** (1 equiv.)	-OCH$_2$C$_6$H$_4$CH$_2$Cl	-
5	C	1.75 equiv.	**103** (1 equiv.)	-OSO$_2$C$_6$H$_4$CH$_3$	-
6	D	1.75 equiv.	**102** (1 equiv.)	-OCH$_2$C$_6$H$_4$CH$_2$Cl	-
7	D	1.75 equiv.	**103** (1 equiv.)	-OSO$_2$C$_6$H$_4$CH$_3$	-

A. K_2CO_3 (2 equiv.) and 18-crown-6 (catalyst) in acetone, under reflux, 18 hours[99,106].

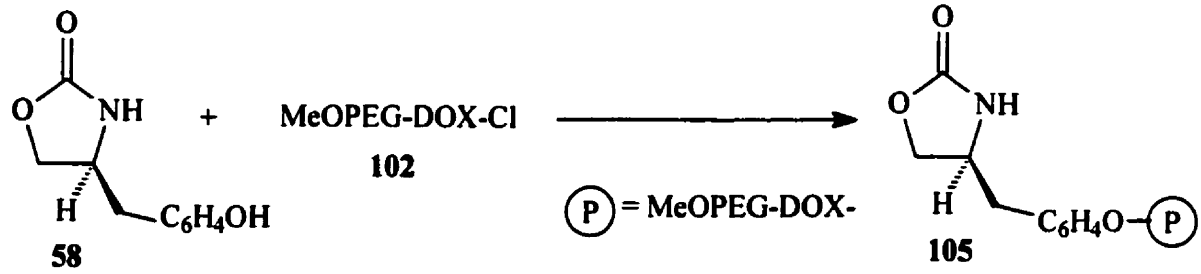
B. K_2CO_3 (2 equiv.), 18-crown-6 (catalyst) and NaI (0.5 equiv.) in acetone, reflux, 48 hrs.

C. NaH (4 equiv.) and NaI (1.5 equiv.) in THF, at 50 °C, 96 hrs[107].

D. NaH (4 equiv.) and NaI (1.5 equiv.) in DMF, at 80 °C, 48 hrs.

In order to examine the potential of our novel polymer-supported oxazolidin-2-one **105**, we were obliged to produce *N*-acyl derivatives. As shown in Table 5, we repeated the experimental protocol of Evans et al. for the propionylation and crotonylation[30,110] of the unsupported oxazolidin-2-one **98** first and obtained the products **106a,b** in good yields (Entry 1 and 2). We also tried the propionylation under milder conditions[111] (Entry 3). However, the NMR analysis showed that the propionylation was incomplete.

Table 4. Synthesis of MeOPEG-supported oxazolidin-2-one

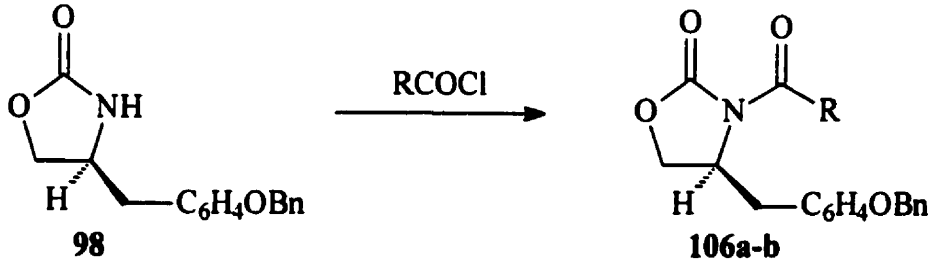


Entry	Conditions	58	102	Product 105
1	A, *n*-Bu_4N^+ I^- (0.5 equiv.)	2 equiv.	1 equiv.	50%*
2	A, NaI (0.5 equiv.)	1 equiv.	1 equiv.	50%*
3	A, KI (0.5 equiv.)	1.5 equiv.	1 equiv.	95%

A. K_2CO_3 (2 equiv.) and 18-crown-6 (catalyst) in acetone under reflux for 18 hours.

*Judged by NMR.

Table 5. *N*-acylation of unsupported oxazolidin-2-one 98



Entry	Conditions	R	RCOCl	Product	Yield
1	A	C_2H_5-	(1.2 equiv.)	**106a**	72%
2	A	CH_3CH=CH-	(1.2 equiv.)	**106b**	85%
3	B	C_2H_5-	(1.3 equiv.)	**106a**	~50%*

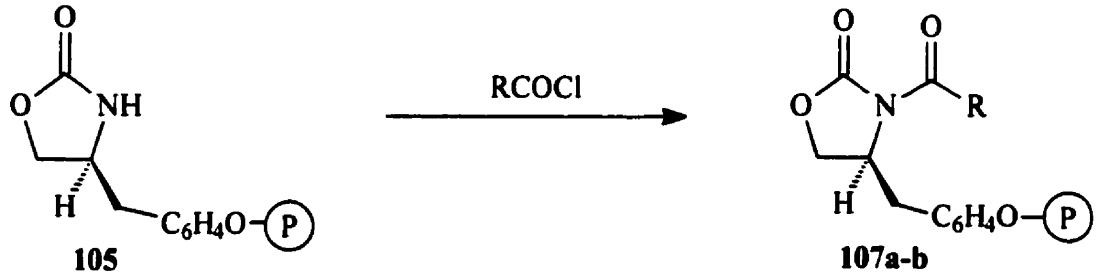
A. THF, $(Ph)_3CH$, –78 °C, *n*-BuLi (1.2 equiv.), 15 min[110].

B. CH_2Cl_2, Et_3N (1.2 equiv.), DMAP (0.2 equiv.), at RT, 18 hours[111].

* Judged by NMR; Unreacted starting material also present.

Table 6 gathers the experiments and the results of *N*-acylations of polymer bound oxazolidin-2-one **105**. We observed that the polymer compound precipitated from the solvent at temperatures less than 0 °C (Entry 1). We also learned that the reaction attempted with *n*-BuLi led to the cleavage of the polymer chain from the auxiliary (Entry 1). We concluded that the best results could be obtained using KH/18-crown-6 in THF (Entries 6 & 7).

Table 6. *N*-acylation of MeOPEG-supported oxazolidin2-one 105



105 **107a-b**

Entry	Conditions	R	Product	Yield
1	A	C_2H_5- (1.2 equiv.)	**P**	-
2	B, Et_3N (1.2 equiv.), at RT	C_2H_5- (1.3 equiv.)	-	-
3	B, DCC (1 equiv.), at 0 °C-RT	C_2H_5- (1.3 equiv.)	-	-
4	C, at RT, 18 hours	C_2H_5- (1.3 equiv.)	-	-
5	C, at 40 °C, ~48 hours	C_2H_5- (2 equiv.)	**107a**	<50%*
6	D	C_2H_5- (4 equiv.)	**107a**	70%
7	D	CH_3CH=CH- (4 equiv.)	**107b**	67%

A. THF, $(Ph)_3CH$, *n*-BuLi (1.2 equiv.), at –78 °C, 30 min[110].

B. CH_2Cl_2, DMAP (0.5 equiv.), 18 hours[111].

C. THF, NaH (3 equiv.), 18-crown-6 (catalyst)[112].

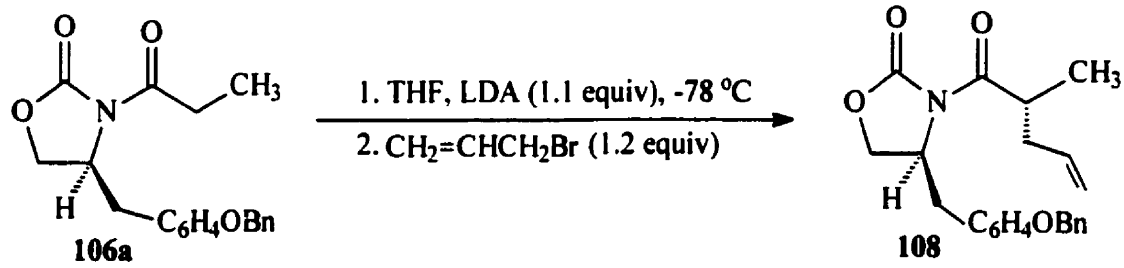
D. THF, KH (3 equiv.), 18-crown-6 (catalyst), at 40 °C, 18 hours.

P. Precipitation of the polymer compound and cleavage of the polymer linker.

* Judged by NMR.

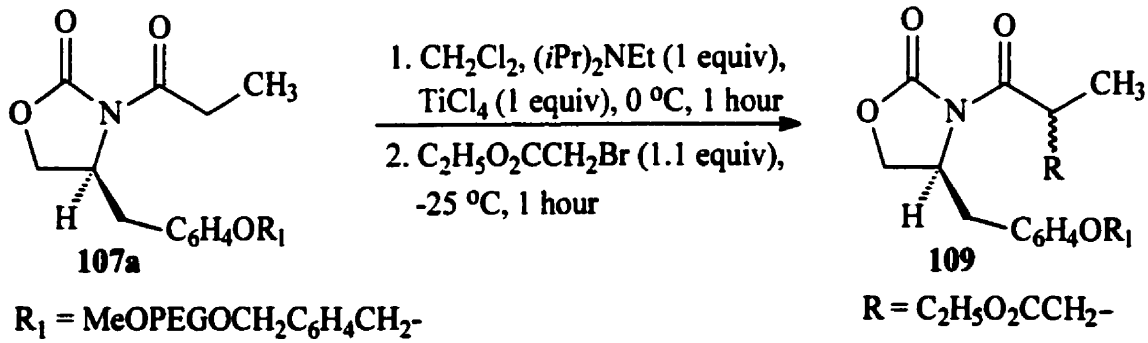
3. MeOPEG-supported chiral oxazolidin-2-one in asymmetric synthesis

We next studied the asymmetric alkylations of **106a** and **107a**, based on the method of Evans et al.[24]. Allylation of unsupported oxazolidin-2-one **106a** was performed at first (Scheme 40). NMR analysis indicated that a single diastereomer of **108** was formed selectively (kinetic diastereoselection ~100%) in ~50% yield. No further analysis was carried out on **108**.



Scheme 40

We already knew that the polymer-supported compound precipitated from the solvent at lower temperatures (<0 °C) and that the removal of the polymer linker from the auxiliary was promoted by strong base. Due to these reasons, alkylation of the polymer bound oxazolidin-2-one could not be performed under the conditions of Scheme 40. Thus, we attempted titanium-mediated alkylation[36,113] of **107a** as shown in Scheme 41.

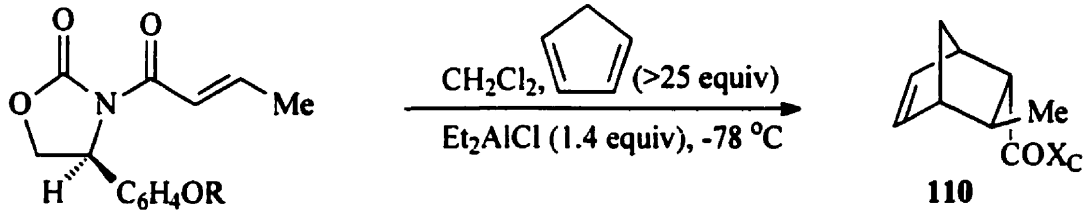


Scheme 41

When the polymer-supported oxazolidin-2one was dissolved in dichloromethane and cooled to –78 °C, there was no deposition of polymer material observed. However, the polymer did precipitate out from the solvent as soon as the $TiCl_4$ was added to the reaction mixture. Addition of ethylbromoacetate did not lead to any alkylated product.

We then turned our attention towards Diels-Alder cycloaddition reactions. We tested an aluminum-catalyzed low-temperature protocol[110] for this purpose. As indicated in Scheme 42, Lewis acid promoted-cycloaddition was carried out by treating the oxazolidin-2-one **106b** and cyclopentadiene in dichloromethane with diethylaluminum chloride at –78 °C.

Only one diastereoisomer **110** (72%) was obtained (judged by NMR). Comparison of the NMR data with the literature values[110] reported for a similar system showed that **110** was an endo product resulting from *si* face attack. We did not perform any further analysis on **110** to prove this result.



106b: R = $CH_2C_6H_5$
107b: R = $CH_2C_6H_4CH_2$OMeOPEG

110

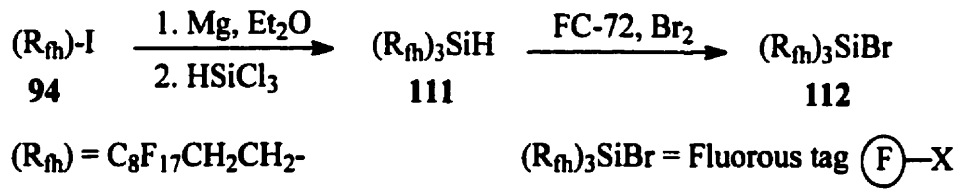
X_C = auxiliary part

Scheme 42

Likewise, we tried the cycloaddition of polymer-supported auxiliary **107b** (Scheme 42) using the same conditions, but the polymer material precipitated out immediately after the addition of diethylaluminum chloride. When the same reaction was performed at –30 to –40 °C, the precipitate formation was still observed. When diethylaluminum chloride was switched to TMS-OTf, no improvement was noticed.

4. Synthesis of a fluorous-tagged chiral oxazolidin-2-one

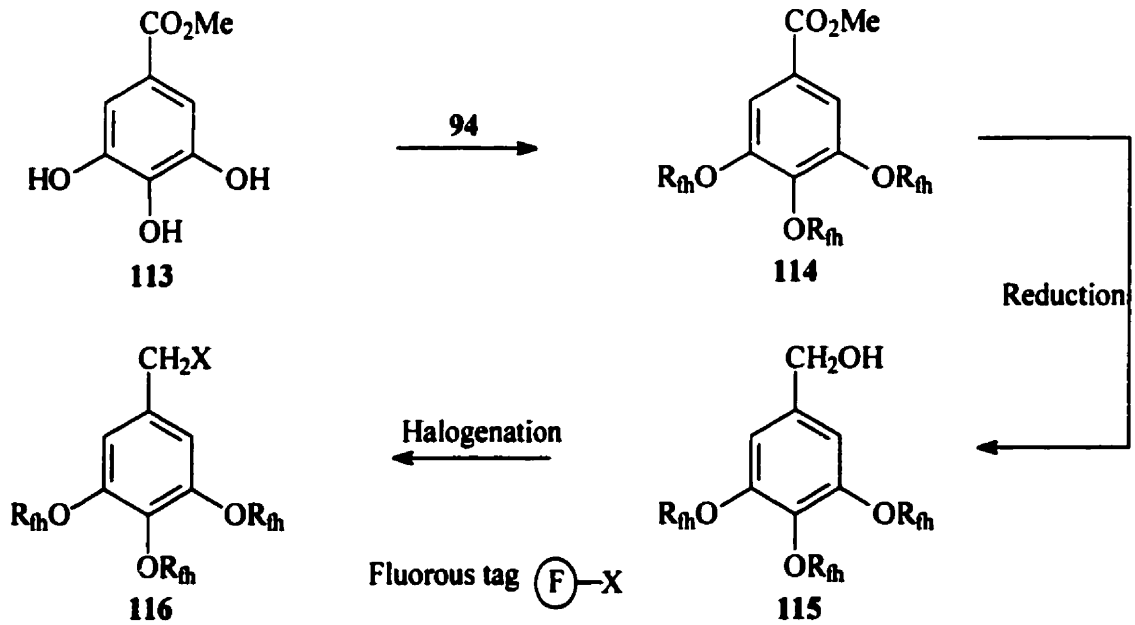
We next studied a fluorous synthesis approach[93] for our chiral auxiliary. As depicted in scheme 43, the synthesis of the fluorous tag was accomplished following a protocol of Curran et al.[91].



Scheme 43

Grignard formation of 1-iodo-1*H*,1*H*,2*H*,2*H*-perfluorodecane **94** in ether was immediately followed by perfluoroalkylation of trichlorosilane (60%). Bromination of silane **111** in FC-72 provided the desired perfluorous tag **112** (88%).

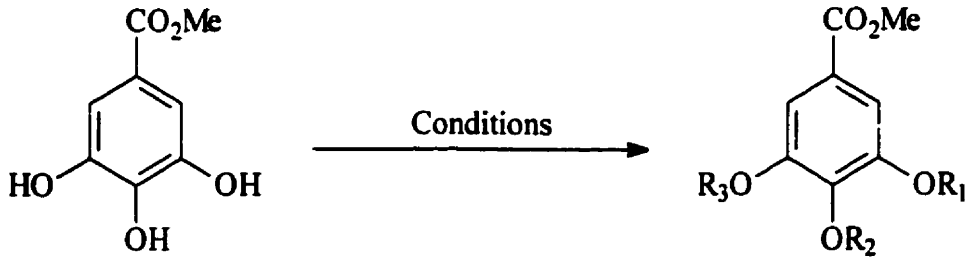
We also tried an alternative method using methyl gallate **113** as the substrate to produce a different fluorous tag **116** (Scheme 44).



Scheme 44

According to Scheme 44, we attempted the conversion of methyl gallate **113** to trisubstituted fluoro compound **114** first. The reaction conditions listed in Table 7 were employed to perform the conversion. NMR studies revealed that traces of mono, di and tri substituted products had been formed along with other unknown materials. However, none of them were successful.

Table 7. Reaction conditions used for the synthesis of 114



113 **114**

Conditions[a]	Solvent	Base	Catalyst	t °C
1	Acetone	K_2CO_3 (3.2 equiv.)	A	55
2[114]	DMF	K_2CO_3 (3.2 equiv.)	A	55
3	MEK[b]	K_2CO_3 (3.2 equiv.)	A	55
4	DMF	Cs_2CO3 (3 equiv.)	-	80
5	THF	NaH (3.2 equiv.)	-	RT
6[c]	CH_2Cl_2/H_2O	10% KOH	B	RT
7[c]	CH_2Cl_2/H_2O	10% NaOH	B	RT
8[c]	$MeOH/CHCl_3$	K_2CO_3 (4 equiv.)	B	RT

a. All reactions were carried out using 3.2 equiv. of **94** and under N_2.

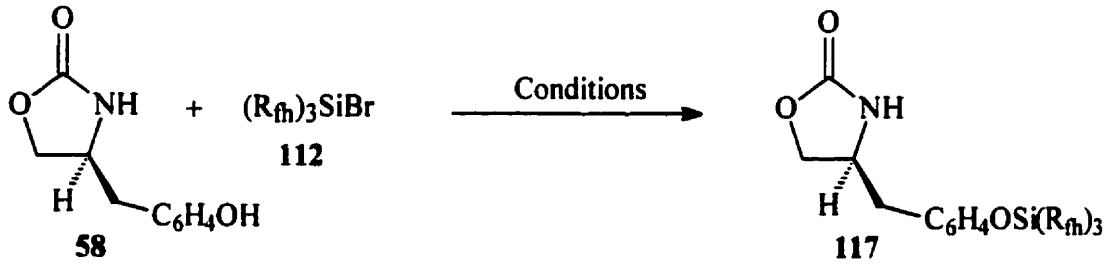
b. MEK- Methylethyl ketone.

c. Phase transfer catalyst reactions[115].

A.18-crown-6. B. $PhCH_2N^+(Et)_3Cl^-$ - Phase transfer catalyst.

Since all of our efforts to derive a fluorous phase tag from methyl gallate proved to be difficult, we decided to continue our study with the tris(perfluoroalkyl)silylbromide **112**. As outlined in Table 8, the next step involved the coupling of the fluorous tag **112** with oxazolidinone **58**. We attempted a series of reaction conditions to bring about the attachment of the fluorous tag **112** to the oxazolidin-2-one **58**.

Table 8. Reaction conditions used for the attachment of fluorous tag 112 to 58



Conditions[a]	58	58/Solvent	Base	Additive	112/solvent	t °C
1[106]	A	DMF	Imidazole (2.1 equiv.)	-	Et_2O	40
2	A	DMF	Imidazole (2.1 equiv.)	-	BTF	40
3[106]	A	Pyridine	Pyridine	-	Et_2O	40
4	A	Pyridine	Pyridine	DMAP	BTF	40
5	A	DMF	NaH (1.5 equiv.)	-	BTF	RT
6	A	Acetone	K_2CO_3 (2 equiv.)	KI/18-crown-6	BTF	55
7	B	THF	Et_3N (4 equiv.)	-	THF	RT
*8[116]	B	THF	Et_3N (4 equiv.)	AgOTf (catalyst)	BTF	RT
9	B	THF	Et_3N (4 equiv.)	AgOTf (1 equiv.)	BTF	RT
10[b]	B	THF	Et_3N (4 equiv.)	-	BTF	RT

A. 1.5 equiv. of **58**. B. 4 equiv. of **58**.

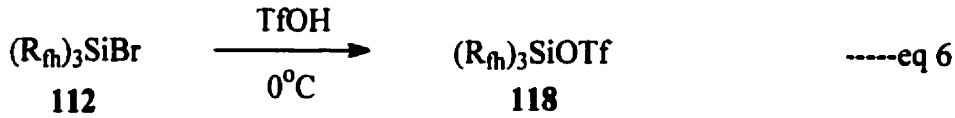
a. All attempts were performed using 1 equiv. of fluorous tag (**112** or **118**) and under N_2.

b. $(R_{fh})_3SiOTf$ **118** was used instead of **112**. $(R_{fh})_3SiOTf$ was synthesized by eq 6[117].

* Minor amount of product **117** formed.

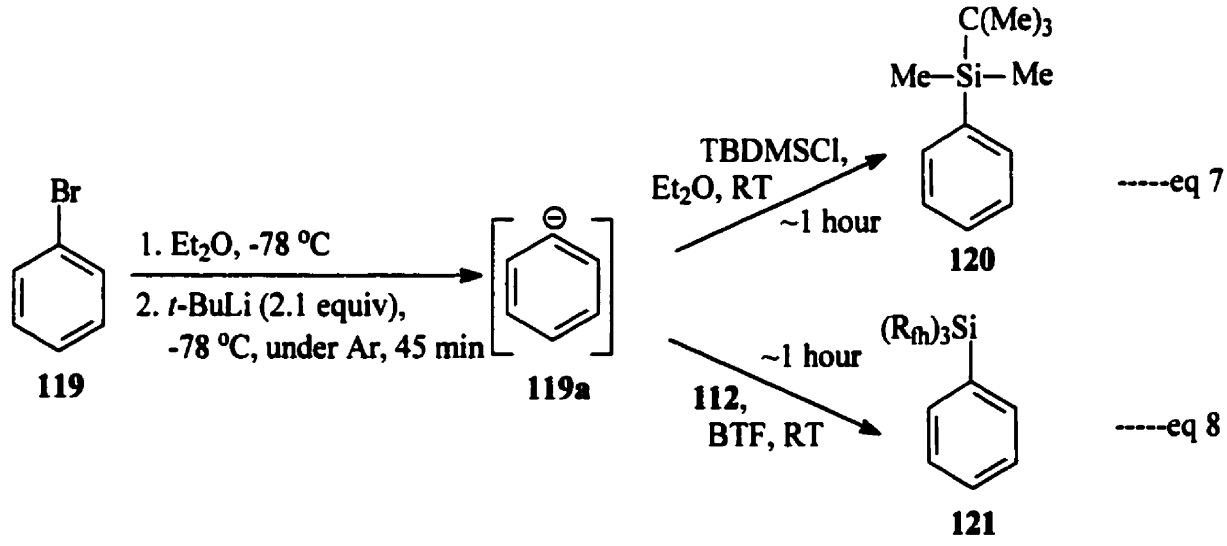
Based on the NMR analysis, we deduced that all reaction conditions, except the one involving a catalytic amount of AgOTf (Table 8; Condition 8), yielded the hydrolyzed products of silyl bromide **112** and the unreacted oxazolidin-2-one **58**. When we performed the reaction by dissolving the fluorous tag **112** in BTF and by adding AgOTf to catalyze the reaction (Condition 8), a minor amount of the coupled product was produced (analyzed by NMR). However, we could not reproduce this result. We tried adding 1 equiv.. of AgOTf, but it was not effective.

We also attempted to carry out the coupling process with the preformed tris(perfluoro-alkyl)silyltriflate **118** (Condition 10).



This silyltriflate **118** was prepared by treating the silylbromide **112** with TfOH in situ (eq 6), according to a literature method[117]. This method also formed only the hydrolyzed products of silylbromide **112**.

During the course of finding an alternative method for the coupling process, it occurred to us that metal-halogen exchange strategy of Curran et al. could work on our system too[91].

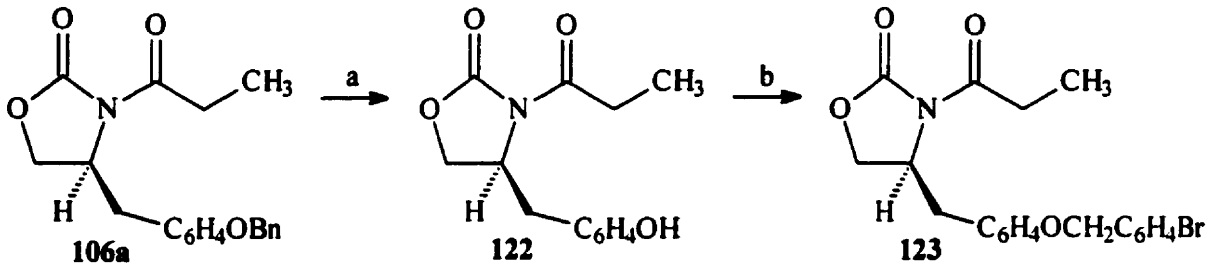


Scheme 45

Initially, we tried this protocol with bromobenzene **119**. As shown in Scheme 45, the coupling of TBDMSCl with **119** was done by a transmetallation reaction (96%; eq 7). We then tried this coupling process using our fluorous tag **112** and **119** (95%; eq 8). NMR analysis of both confirmed that the coupling had in fact been successful.

In order to apply this method to our system, we needed to modify our auxiliary as well. Attachment of an aryl halide system to our auxiliary was required to perform metal-halogen exchange reaction with silylbromide **112**.

According to our initial plan shown in Scheme 46, debenzylation[106] (Pd/C reduction) of compound **106a** provided the free hydroxyl group (**122**) for the new attachment (95%). Reaction of this hydroxyl group with 4-bromobenzylbromide under given conditions gave the required auxiliary **123** (76%).



106a **122** **123**

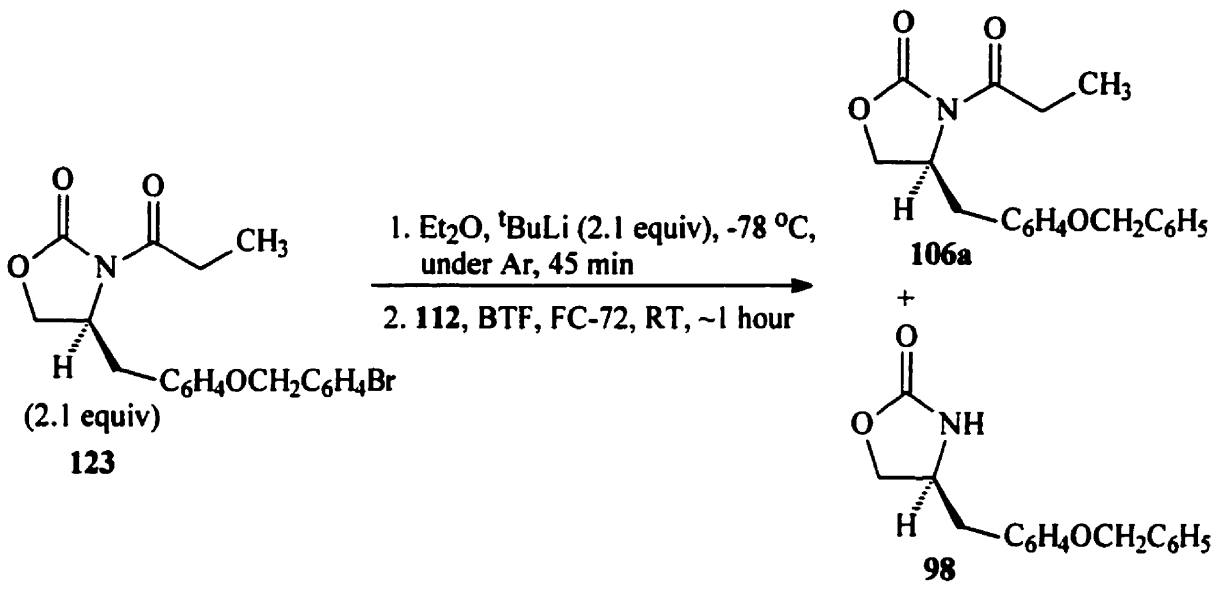
a. 10% Pd/C, MeOH, RT, H_2(g), 1 atm, 5 hours

b. $BrC_6H_4CH_2Br$ (1.5 equiv), K_2CO_3 (2 equiv), Acetone, 18-crown-6, reflux

Scheme 46

Bromine-lithium exchange reaction[91] of auxiliary **123** was then attempted as shown in Scheme 47. The auxiliary was not completely soluble in ether. Sonication of the mixture helped it dissolve slightly. We formed the aryl lithium by reacting **123** in ether with *tert*-butyllithium at –78 °C. After stirring for 45 min, this aryl lithium mixture was transferred in to the solution of fluorous tag **112** in BTF and FC-72 via a cannula at room temperature. After aqueous work up, the products were isolated by partitioning between CH_2Cl_2 and FC-72. NMR analysis of the crude product extracted with CH_2Cl_2 revealed that the formation of compounds **106a** and **98** (Scheme 47). This suggested that the reduction of the aryl anion and the removal of propionyl

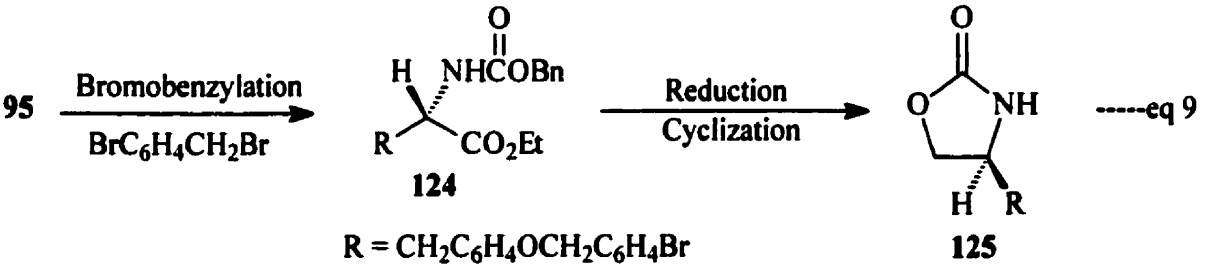
group had taken place. The NMR spectrum of the crude material obtained from the FC-72 layer showed that the hydrolysis of **112** had also occurred.



Scheme 47

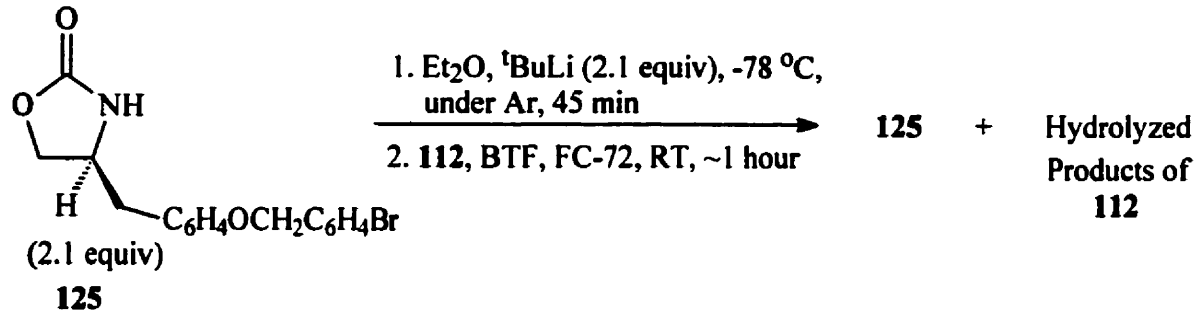
When we used THF instead of ether, the oxazolidin-2-one dissolved completely in THF, but the reaction gave the same results as in the above case. These observations implied that the *N*-propionyl group of the oxazolidin-2-one might interfere with the coupling process.

Since we required the auxiliary **125** for further studies, we synthesized it in larger amounts using our novel method as depicted below in eq 9.



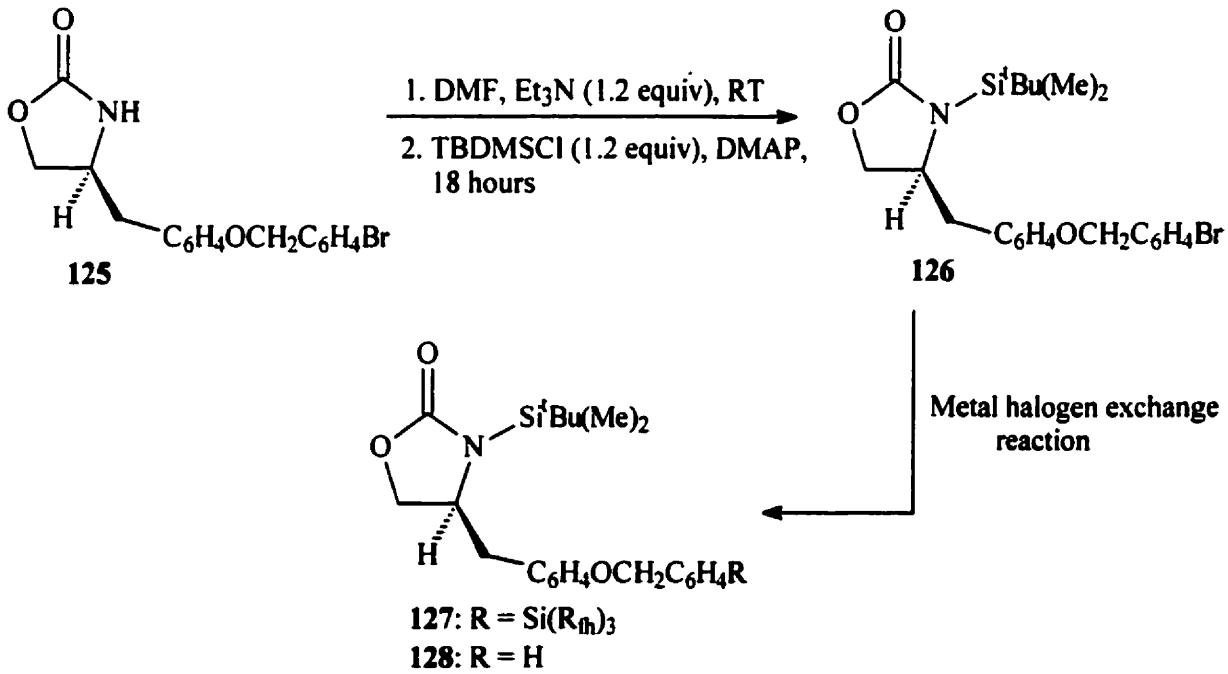
-----eq 9

In order to avoid the problem encountered in Scheme 47, we carried out the attachment of **112** to oxazolidin-2-one **125** via metal halogen exchange process as shown in Scheme 48.



Scheme 48

Hydrolysis of the fluorous tag **112** was only observed and the oxazolidin-2-one **125** was recovered without any change. From this attempt, it was then obvious that protection of the free amide NH group was necessary. Therefore, we developed a new strategy for the coupling of the fluorous tag **112** to the auxiliary **125** (Scheme 49).



Scheme 49

We accomplished the protection of the 2° amide by treating with triethyl amine and TBDMSCl in DMF in the presence of DMAP at room temperature[118] (85%) (Scheme 49). We

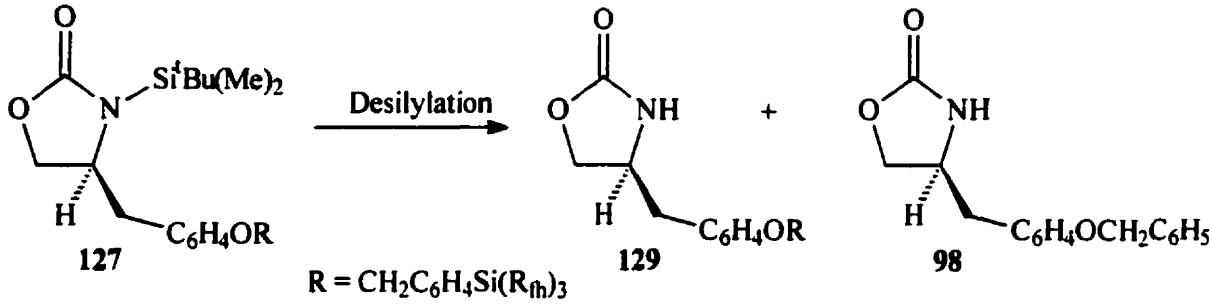
performed the transmetallation and the coupling according to the same protocol described in Scheme 47. The substrate **126** exhibited moderate solubility in Et_2O. However, we decided to use Et_2O since compound **126** does not dissolve in other less polar solvents (such as hexane, cyclohexane, petroleum ether). Examination of the NMR spectrum of the products proved that the reduction of the aryl anion (product **128**) and the hydrolysis of compound **112** had occurred. These results showed that the protection of the 2° amide by TBDMS group prevented the side reactions. However, further improvements were needed to make the coupling process successful.

In the next attempt, we modified the reaction conditions from earlier cases (Scheme 47). We used BTF/ether mixed solvent to dissolve the fluorous compound **112** and this solution was also kept at low temperature (-35 to -45 °C). *tert*-Butyllithium was added to the precooled solution of auxiliary **126** in ether. Immediately after the addition of *tert*-butyllithium, fluorous solution was added as quickly as possible. The reaction was quenched by adding H_2O. The isolation of the product was carried out by partitioning between H_2O, CH_2Cl_2, and FC-72.

NMR analysis proved that the coupling reaction had actually occurred this time. Analysis of the crude material obtained from evaporation of FC-72 layer showed the presence of the coupled product **127** (Scheme 49) and the hydrolyzed product of fluorous tag **112**. Analysis of CH_2Cl_2 layer indicated that it contained both the coupled product **127** and the reduced material **128**. We simply isolated the coupled product **127** from both crude materials by flash column chromatography. However, the total yield from both layers was found to be very low (~41%).

We also tried FC-72 and ether mixed solvent to dissolve the perfluoro compound and obtained the same results from the coupling reaction. We then thought that reduced solubility of the oxazolidin-2-one in ether might have caused the productivity. Since oxazolidin-2-one was completely soluble in THF, we decided to try this coupling reaction using THF/ether mixed solvent. A minimum amount of THF was added to dissolve the oxazolidin-2-one and this was then diluted with ether. Product (**127**) yield went up to 68% with this attempt. Finally, we were able to produce the coupled product in reasonable yields using this modified strategy. According to this strategy, THF/Et_2O mixed solvent was used to dissolve the oxazolidin-2-one **126**. Addition of precooled solution of **112** in BTF and *t*-BuLi were carried out almost at the same time.

Our next task was to demonstrate the use of the fluorous-tagged oxazolidin-2-one in organic synthesis. We decided to follow the same scheme designed to investigate the possibilities of MeOPEG-supported oxazolidin-2-one in asymmetric synthesis. Before we moved on to *N*-acylation reactions, we attempted the removal of the TBDMS group as illustrated in Scheme 50.



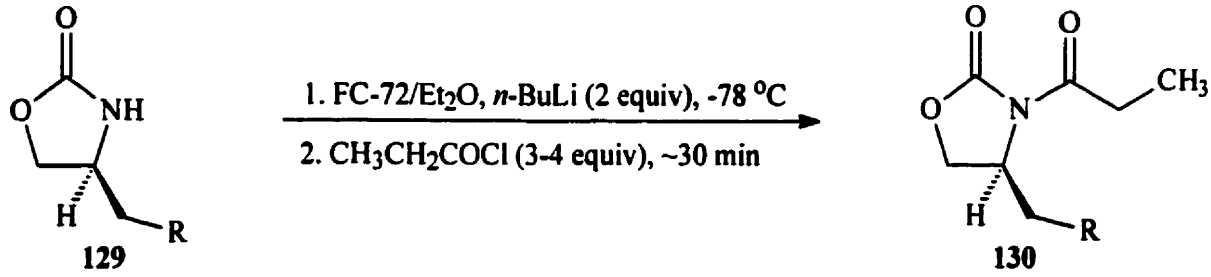
Scheme 50

In the first experiment, where we reacted the oxazolidin-2-one **127** in CH_2Cl_2 with 1 N HCl in MeOH at room temperature, desilylation was not observed[118]. When we treated the oxazolidinone **127** in CH_2Cl_2 with 9:1 TFA/H_2O at room temperature[119], the desilylated product **129** was formed. However, the reaction was sluggish and gave a very poor yield.

We the tried the desilylation by treating the oxazolidin-2-one **127** in CH_2Cl_2 with 1 equiv.. of 1 M TBAF in THF at room temperature for 30 min[120]. TLC showed appearance of two new spots. NMR studies on the crude product revealed that the cleavage of N-Si bond had yielded the desired compound **129** and the cleavage of both N-Si and C-Si bonds had led to the formation of **98**. Thus, we repeated the same procedure again and monitored the reaction carefully by TLC. We learned that the removal of the *N*-TBDMS group went to completion within 5-7 min.

From these results, it was clear that cleavage of the N-Si bond took place first, and leaving this molecule to react further under the same conditions led to the cleavage of the C-Si bond as well. NMR spectrum also confirmed that only compound **129** was produced in the reaction (60%). The yield was improved further (80%) by using BTF/CH_2Cl_2 mixed solvent instead of CH_2Cl_2.

We then considered performing the *N*-acylation reaction on the fluorous-tagged oxazolidin-2-one **129** as illustrated in Scheme 51.



129 **130**

$R = C_6H_4OCH_2C_6H_4Si(R_{fh})_3$

Scheme 51

Initially, we effected the propionylation of compound **129** using the previous method (*n*-BuLi, THF, RCOCl)[110] outlined in Table 5. We noticed that the compound **129** was not soluble in THF completely and no products were formed. Thus, we decided to use a combination of a perfluoro and an organic solvent. Since FC-72 and THF would not mix even at room temperature, we chose FC-72/ether mixed solvent for this purpose. In this solvent, the *N*-propionylation occurred smoothly affording **130** in excellent yield (87%; Scheme 51).

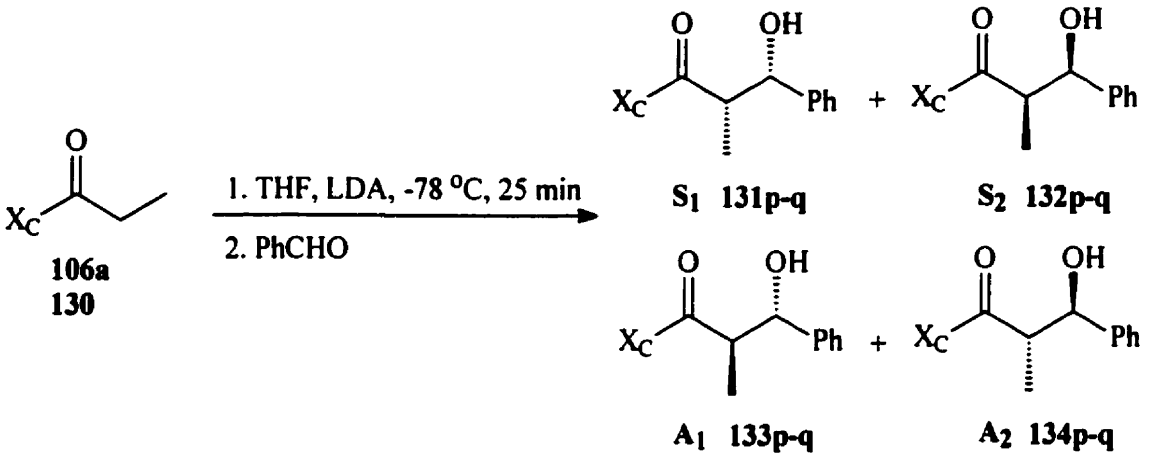
5. Asymmetric aldol reaction of a fluorous-tagged chiral oxazolidin-2-one

In order to show the efficacy of the fluorous phase conception, we decided to carry out the aldol reaction. The aldol reaction of oxazolidin-2-one **106a** with benzaldehyde was performed first as illustrated in Table 9. We used 1.1 equiv. of LDA and 1.2 equiv. of PhCHO for this purpose[121]. The reaction was quenched after 5 min. NMR analysis of the crude material proved the formation of aldol adducts (Table 9). HPLC analysis provided the ratio of all four stereoisomers (entry 1). The ratio of diastereomers was almost similar to that obtained by Evans et al. for the aldol reaction of Evans auxiliary using benzaldehyde[33].

We then tried the aldol reaction using fluorous-tagged oxazolidin-2-one **130** in FC-72 and ether mixed solvent. We noticed that when the temperature was brought down to –78 °C, cloudiness started to develop in the mixed solvent. The reaction was unsuccessful because of

this biphasic condition. In order to find a proper solvent for the reaction, we tested a series of solvents. Finally, we found out that THF was a perfect solvent to dissolve the material as well as a suitable solvent for the aldol reaction at low temperatures.

Table 9. Li-mediated aldol reactions of 106a and 130 with benzaldehyde



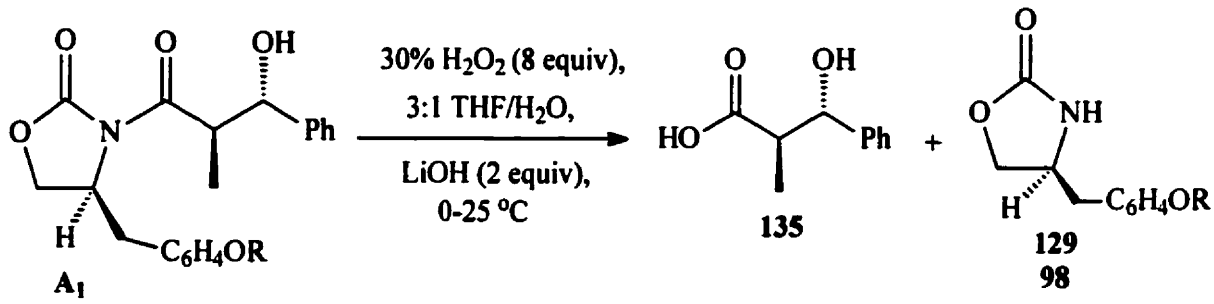
Entry	Compound	X_C (auxiliary)		Diastereomer present*				Yield[a]
				131 (S_1)	132 (S_2)	133 (A_1)	134 (A_2)	
1	**106a**	Unsupported	**p**	5.4	20.4	45.3	3.9	60%
2	**130**	Fluorous-tagged	**q**	20.3	27.6	34.4	1.6	54%

* Product ratios determined by HPLC. a. Yield% of total aldol products ($S_1 + S_2 + A_1 + A_2$).

We accomplished the Li-mediated aldol reaction of **130** using 5 equiv. of LDA and PhCHO following the similar procedure described above (Table 9). The NMR analysis proved that the aldol condensation had produced all four isomers (Table 9). HPLC analysis of the crude product provided the ratio of all four stereoisomers (Entry 2) and the ratio was comparable to that reported in the literature[33].

We also had to confirm the absolute stereochemistry of our aldol adducts. To prove that, the major anti A_1 isomer from both aldol reactions was isolated and subjected to hydrolysis using a published method[10] shown in Table 10.

Table 10. Hydrolysis of major anti product A_1



Entry	A_1	R	Acid 135	$[\alpha]_D^{25}$
1	**133p**	$-CH_2C_6H_5$	98%	–17.1° (c 0.45, $CHCl_3$)
2	**133q**	$-CH_2C_6H_4Si(R_{fh})_3$	50%	–20° (c 0.02, $CHCl_3$)

Table 10 gives the optical rotations obtained from both cases. Comparison of the NMR spectra and the optical rotation values with the published results[122] confirmed that Acid **135** had the 2*R*,3*S* configuration.

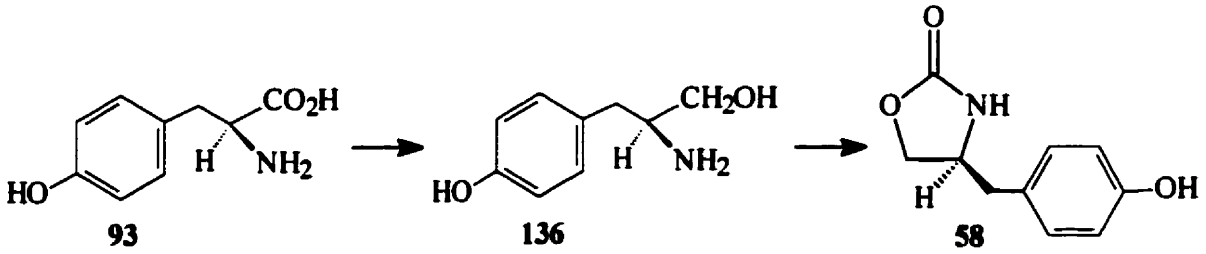
Discussion

1. Synthesis of chiral oxazolidin-2-ones

We required a 4-substituted oxazolidin-2-one for our main research. It has already been reported in the literature that these oxazolidin-2-ones can be derived directly from aminoacids[13,14]. We decided to use L-tyrosine **93** for our purpose because the phenolic hydroxyl group can be used to link to supports in the later studies. According to a commonly used method by Evans et al., chiral 4-substituted oxazolidin-2-ones are prepared by reduction of the appropriate aminoacid with $BH_3 \cdot SMe_2$ /$BF_3 \cdot OEt_2$, followed by treatment with phosgene or heating with diethyl carbonate[13]. This route has been successful and is still in use.

However, this method is time-consuming and requires the use of hazardous or expensive reagents. The reduction by borane complex is a vigorously exothermic reaction and evolves Me_2S and H_2. The process often involves difficult work-up procedures. The intermediate aminoalcohols possess considerable water solubility thereby making them hard to isolate and purify. On the other hand, most of the oxazolidinones are relatively expensive to purchase commercially. Therefore, it was necessary to find a cheaper, safer and simpler approach, especially for larger-scale work.

Initially, we planned the synthesis as pictured in Scheme 52. In this pathway, the reduction of L-tyrosine **93** using $NaBH_4/I_2$ was performed according to the protocol of Meyers et al.[104]. Meyers's method involves the reduction of various aminoacids to corresponding aminoalcohols by $NaBH_4/I_2$ in THF under reflux.



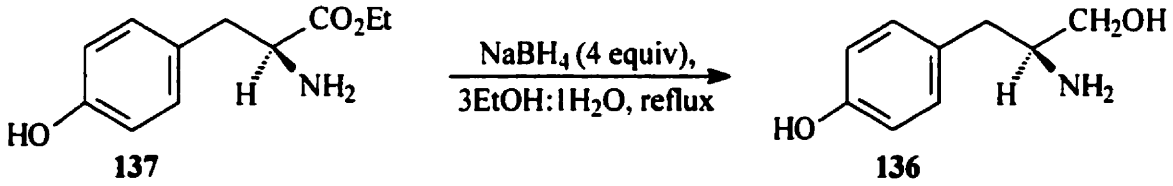
Scheme 52

However, our attempt to reduce **93** involved several long steps for work-up and purification and afforded a poor yield for the product, because of the higher solubility of the

resultant tyrosinol **136** in water. Since the direct reduction of L-tyrosine to tyrosinol **136** by published procedures[123] proved to be difficult, we then considered the reduction of amino esters using $NaBH_4$ in $EtOH/H_2O$ mixed solvent[101,102].

It is generally known that esters are essentially inert toward reduction by $NaBH_4$[124,125]. However, a few exceptions[126,127] are reported in the literature in which reduction of an ester to a primary alcohol has been achieved successfully. Esters having electron-withdrawing functional groups at α-position to the ester carbonyl group have been recognized to undergo abnormal reduction with $NaBH_4$. Examples of such activating functional groups are α-oxo[128,129], -halogeno[130], -hydroxyl[131], -amino[102], -cyano[132], -aromatic, and -heteroaromatic groups[133].

One such abnormal case is the reduction of amino esters derived from α-aminoacids published by Yamada et al.[101,102]. The authors have pointed out that an increase in the electro-positivity at the carbonyl carbon of an ester would facilitate its susceptibility to reduction by $NaBH_4$[130]. It was of interest to try this method for the reduction of a tyrosine ester **137**. Accordingly, we prepared the ethyl ester of L-tyrosine and treated it with $NaBH_4$ in a 3:1 $EtOH/H_2O$ mixed solvent (Scheme 53).



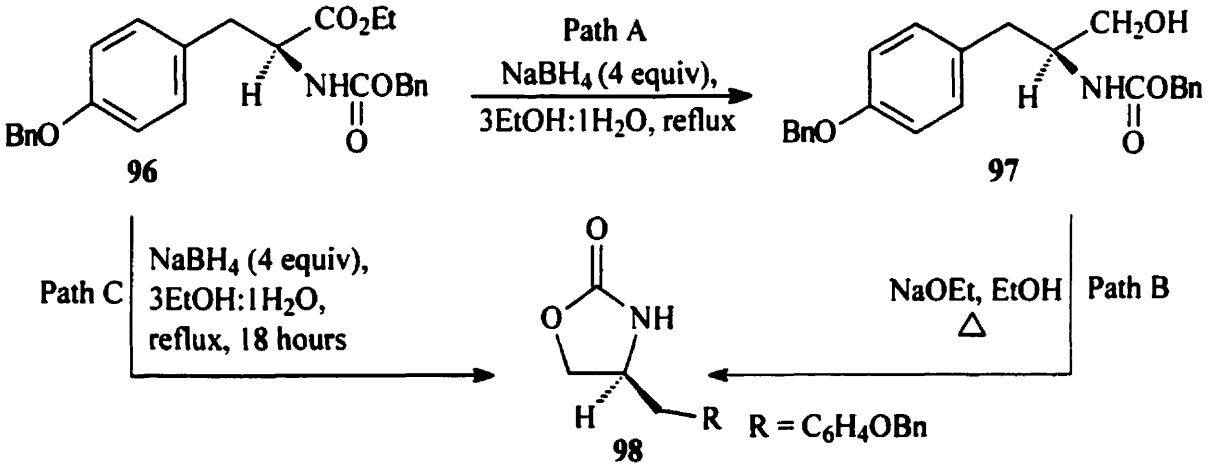
137 **136**

Scheme 53

We observed (on TLC) that the reduction of the ester had occurred to some extent. However, the extraction of the tyrosinol **136** after the work-up and the evaporation of the solvent (EtOH) was troublesome. As seen in Scheme 53, the tyrosinol **136** has a phenolic OH, an alcoholic OH and an amino group in its structure. Due to the presence of these polar groups, the solubility of **136** in organic solvents that are used for the extraction (such as CH_2Cl_2, $CHCl_3$, EtOAc, etc.) decreases drastically. More polar solvents might be used but the extraction from the aqueous layer would not be efficient. This eventually led us to the protection for the NH_2 and free phenolic OH group of the ethyl ester **137**.

The esterification and the carbamate protection of the L-tyrosine **93** could be performed in a single step[15,98] (Scheme 35 on page 51). Accordingly, the esterification of **93** was carried out with EtOH (abs) and HCl (produced in situ from AcCl)[15]. After completion of the reaction (judged by TLC using ninhydrin-spraying agent), the solvents were evaporated to yield the crude product, ethyl ester. This crude material was dissolved again in fresh EtOH and then the EtOH was evaporated. This was repeated several times to remove the excess HCl. The crude material was then taken into an aqueous medium and subjected to carbamate protection in the same pot. Finally, we performed the *O*-benzylation[99,100] on **95** to provide the well-protected precursor **96** (Scheme 35 on page 51).

Next, we started with the reduction of **96** (Path A), for the purpose of producing the oxazolidin-2-one **98**, which is illustrated in Scheme 36 (the same Scheme 36 on page 52).



Scheme 36

The reduction with $NaBH_4$ did indeed occur this time, but was much slower than expected. Interestingly, the analysis of the TLC revealed the appearance of a second spot as the reaction progressed. Quenching the reaction half way (with 10% aq HCl until pH ~ 3-4) and isolating the products by column chromatography left us with two products. The NMR and TLC studies on the products established that slow reduction of the ester to alcohol **97** occurs first and on prolonged heating, the alcohol cyclizes to form the oxazolidin-2-one **98** under the same conditions (via Path C). Besides, the ^1H NMR of the alcohol **97** showed the disappearance of the

signals for the ethyl (CH_3CH_2-) group of the ester **96** and the appearance of the new signals that are characteristic for the primary alcohol (a broad singlet at δ 2.17 and a pair of double doublets at δ 3.58 and 3.67 ppm).

Though this method was successful, the reduction of the ester **96** by $NaBH_4$ in 3:1 $EtOH/H_2O$ required longer reaction time for completion. It has been demonstrated[126] in the literature that the reduction of esters with $NaBH_4$ in H_2O would provide the resulting alcohols at faster rate and in high yields. In such cases, the water medium leads to an initial protonolysis of the borohydride anion[102,126] comparable to alcohol as solvent. Unlike in the alcohol medium, the loss of hydride in the water influences the formation of sodium hydroxyborohydrides as indicated in eq 10.

$$NaBH_4 + H_2O \longrightarrow NaBH_3(OH) + H_2 \quad \text{-----eq 10}$$

As a result, the solution becomes alkaline. Under alkaline medium, the $NaBH_4$ would be quite stable and its rapid decomposition would be avoided[126]. Besides, the mixture of $NaBH_4$ and sodium hydroxyborohydrides so formed could be a very efficient reducing agent for the reduction of esters[126]. Therefore, the reduction of the esters would occur at faster rate.

As seen in Scheme 36, we employed 3:1 $EtOH/H_2O$ medium for this purpose. Due to the presence of larger amount of EtOH the initial protonolysis would occur rapidly and generate the sodium ethoxyborohydride. The formation of sodium hydroxyborohydrides would be reduced and therefore, the medium would become less alkaline compared to pure water. The $NaBH_4$ would become unstable and decompose quickly. Thus, the reducing agent would have less amount of $NaBH_4$ along with sodium ethoxyborohydride. Consequently, the reduction would take place slowly. Moreover, it has been proven that when the aqueous alcohol solution is used as the medium the reduction of the ester occurs slowly and requires prolonged reaction time[102,126].

Besides slow reduction, the process required more $NaBH_4$. Yamada et al. have already reported[102] that the use of 4:1 $NaBH_4$/ester would afford the best results for the reduction. Accordingly, we also employed 4 equiv. of $NaBH_4$. In addition, the use of excess $NaBH_4$ is important because in alcohol medium, $NaBH_4$ reacts with the alcohol and decomposes rapidly at

elevated temperatures before it completes the reduction[125].

Furthermore, we also encountered problems in the work-up and extraction steps as we used more equiv.alents of $NaBH_4$. Due to the incomplete reduction and the inefficient work-up and extraction process, the yields of the resultant alcohol **97** and the oxazolidinone **98** were very low. Thus, this method is of little synthetic utility for our purpose because of the use of excess $NaBH_4$, the slow reduction and the low yield of the products.

The reducing potential of metal borohydrides can be increased by proper choice of reaction conditions[126], either by changing the cation, the solvent or both. Brown and his coworkers have investigated the effect of the metal borohydrides, $LiBH_4$, $Ca(BH_4)_2$, and $NaBH_4$ in aprotic solvents (THF, ether, diglyme etc.) on the reduction of esters[125]. It is apparent from their work that protic solvents are generally not useful for the reduction by $NaBH_4$ at higher temperatures. The use of aprotic solvents (ether solvents) would be the other alternative.

Moreover, their results indicate that in ether solvents $LiBH_4$ exhibits greater reactivity than $NaBH_4$[125]. Particularly, $LiBH_4$ in refluxing THF is more promising for the reduction of esters. This enhanced reactivity of $LiBH_4$ is due to the greater Lewis acid complexing power of Li^+ compared with Na^+[134]. Complexation of Li^+ activates the carbonyl oxygen of the ester thereby facilitating the reduction. The other advantage of $LiBH_4$ over $NaBH_4$ is its ready solubility in simple ether solvents[135]. $NaBH_4$ does not dissolve in most of the ether solvents even at elevated temperatures[125]. Therefore, $LiBH_4$ in refluxing THF was a more suitable reducing system for our purpose.

$LiBH_4$ is commercially available, but is relatively expensive and is air and moisture sensitive. Nevertheless, solutions of $LiBH_4$ can be easily prepared from $NaBH_4$ with the use of lithium halides in THF[136,137]. Initially, we tried $NaBH_4$/LiCl in refluxing THF for the reduction of **96**. This only resulted in a sluggish reduction to the aminoalcohol **97**.

Brown et al. have examined the rates of formation of $LiBH_4$ from $NaBH_4$ and the salts LiCl, LiBr and LiI in THF under reflux[137]. Their results prove that LiI reacts with $NaBH_4$ much faster than LiCl in refluxing THF under mechanical stirring. Besides, the studies by Kollonitsch et al.[136] also show that a smooth reduction takes place when a solution of ester in THF is stirred with $NaBH_4$ and LiI. Kollonitsch and Brown suggested the following explanations for the formation of $LiBH_4$ from $NaBH_4$ and LiI (eq 11).

$$NaBH_4 + LiI \longrightarrow LiBH_4 + NaI\downarrow \qquad \text{-----eq 11}$$

According to Kollonitsch et. al.[136], a small amount of $LiBH_4$ is formed initially and this in turn reduces the ester to alcohol. This process will push the equilibrium forward by removing the $LiBH_4$. In this manner, all the $NaBH_4$ will be transformed into $LiBH_4$ and eventually the ester will be reduced to alcohol completely.

Brown et. al.[137] explained that in the equilibrium shown in eq 11, the LiI is completely soluble in THF and it reacts with $NaBH_4$ to form the $LiBH_4$. The resultant salt NaI is not soluble in THF and consequently it precipitates in the solution. Since one of the products is removed from the equilibrium by precipitation, the reaction moves forward automatically. In this case, the equilibrium is driven forward by solubility. After the completion of the above transformation, the $LiBH_4$ is used for the reduction of esters.

We then tried the reduction using LiI instead of LiCl. We were pleased to discover that refluxing a THF solution of tyrosine ester **93** with $NaBH_4$ and LiI not only provided the alcohol **97** within 30 min but also yielded the oxazolidinone **98** in 85% yield within 8 hours (Scheme 37 on page 52). As expected, the reduction was very rapid compared to previous cases.

Exploration of the synthetic utility of this novel method shows that this method offers a simple mild condition for the synthesis of oxazolidinones in good yield from Cbz protected amino esters (Table 1 on page 53; Entry 1 and 2). It is known that *tert*- butoxycarbonyl (Boc) group is generally stable under basic conditions[16] and is resistant to reduction[104]. In order to test our novel method on a *tert*-Boc protected amino ester, we prepared the *tert*-Boc-phenylalanine ethyl ester **99a** from the Cbz-phenylalanine ethyl ester **3a** following a published method[103].

Accordingly, the Cbz-phenylalanine ethyl ester **3a** in EtOH was treated with 10% Pd/C, H_2 and *ditertbutyl*-dicarbonate for 48 hours. The appearance of the new singlet signal at δ 1.53 ppm (9 H) for the *tert*-butyl group on the NMR spectrum confirmed the successful transformation of Cbz-protecting group to *tert*-Boc group. Once again it was established that the *tert*-butoxycarbonyl group is not affected under these reduction conditions, since the reduction of **99a** provided only the alcohol **99b** (Entry 3). Moreover, it was not susceptible to nucleophilic attack by the resulting alcohol **99b** (ROH) or its alkoxide ion (RO^-).

The other exceptional case is the Cbz-tyrosine (OH) ethyl ester **95**. The reduction of **95** only yielded the alcohol **100** as a heavy white precipitate (Entry 4). One possible reason for this observation might simply be the insolubility of the resultant alkoxyborohydride **138** in hot THF (Figure 15). The actual mechanism for the reduction of esters by metal borohydrides has already been established in the literature[138].

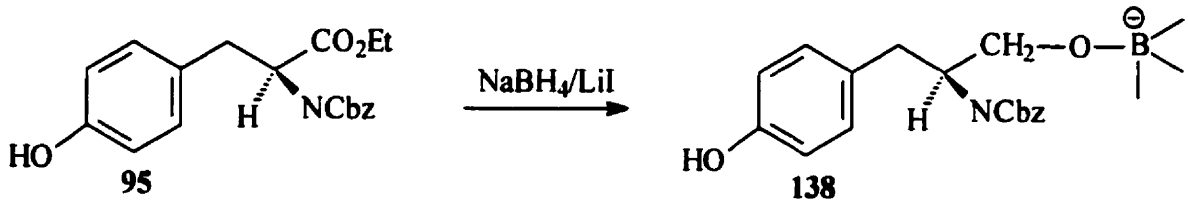


Figure 15

The other reason might be the participation of the free phenolic OH group of **138** in a stable borate/alkoxyborohydride complex **139** that is insoluble in hot THF. As pictured in Figure 16, the phenolic OH can react with excess BH_4^- anion and form an insoluble alkoxy borohydride complex **139**.

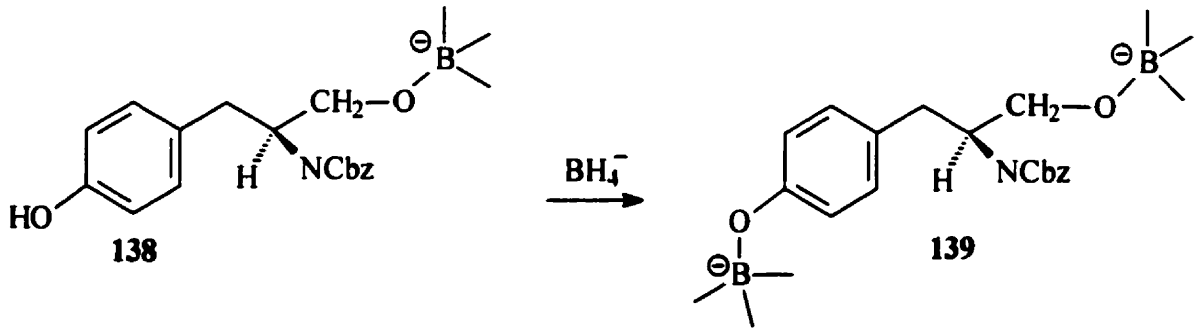


Figure 16

On the other hand, the phenolic OH of **138** can also react with its own species and form an insoluble complex **140** as shown in Figure 17.

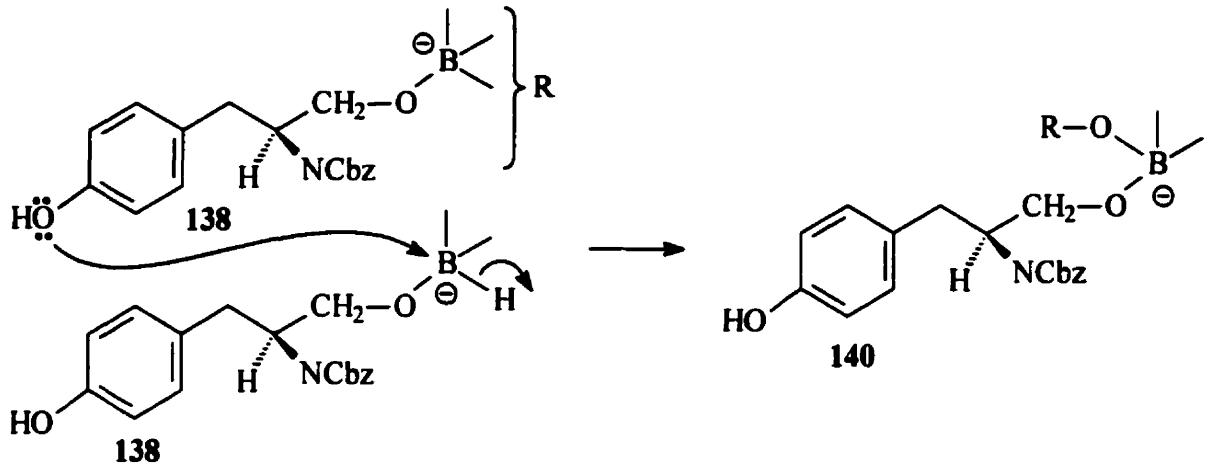


Figure 17

The production of one of these insoluble borate/alkoxyborohydride complexes during the reduction might cause the precipitate formation in hot THF. However, there is no direct evidence in the literature to support these explanations.

As mentioned earlier, the reduction of esters can be improved by varying the conditions. Changing the solvent from THF to diglyme hardly makes any improvement on the reduction of ester **95** (Table 2 on page 54; Entry 1). It is known that diglyme is slightly polar than THF and the metal borohydrides are soluble in diglyme[125]. One can possibly expect that this solvent would dissolve the precipitate (insoluble alkoxyborohydride complex of **100**). In contrast, we obtained the similar white precipitate when we tried the reduction in diglyme. This indicates that we need a more polar solvent than diglyme to dissolve the insoluble complex of **100**. Similarly, using LiCl instead of LiI leads to a slow reduction to the alcohol **3b** (Entry 2).

Lewis et al. have reported the reduction of carbamate protected ethyl esters by $NaBH_4/CaCl_2$ in a THF/EtOH mixed solvent[15]. This method employs $Ca(BH_4)_2$ as the reducing reagent. As anticipated, the reduction of **3a** by $Ca(BH_4)_2$ at room temperature resulted in forming only the alcohol **3b**. We learned that heating this alcohol mixture under reflux for a further 3-4 hours yielded the oxazolidinone **3** in good yield (Entry 3).

When we tried the reduction of **95** with $NaBH_4/CaCl_2$ in THF/EtOH under reflux, no precipitation was observed (Entry 4). Instead, oxazolidinone **58** was obtained in 50% yield.

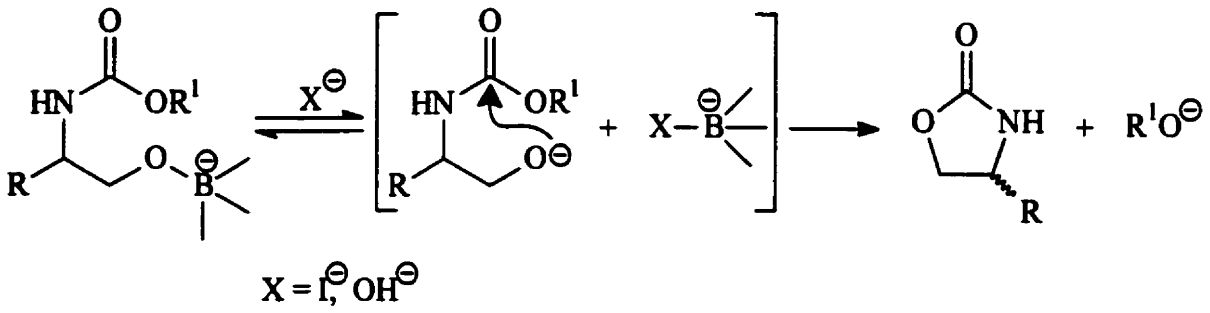
Brown et al. have indicated that $LiBH_4$ is more reactive than $Ca(BH_4)_2$ in refluxing THF[125]. Moreover, the same group have demonstrated that in alcoholic solvents the decomposition of $Ca(BH_4)_2$ is much faster than $LiBH_4$[125]. Thus, we carried out the reduction of **95** by $NaBH_4$/LiI in THF/EtOH under reflux (Entry 5). This system maintained the solubility of the materials, but destroyed the borohydride before ester reduction was complete[125]. Therefore, the reduction stopped half way, leaving some alcohol, traces of cyclized material and the unreacted ester **95** in the reaction mixture. We believe that $LiBH_4$ decomposes in EtOH much faster than expected.

In order to overcome the problem we performed the reduction of **95** in THF alone first. We observed the reduction to alcohol as well as the precipitate formation. We then added the EtOH to the reaction mixture and it dissolved the precipitate formed completely. Thereby the cyclization proceeded smoothly to give the oxazolidin-2-one **58** in moderate yield (Entry 6 and 7).

We also conducted the reduction of **96** using halide-free commercial $LiBH_4$ in THF (Entry 8). The reduction occurred rapidly, confirming that the $LiBH_4$ in refluxing THF is a powerful reagent for the reduction of ester, but the cyclization required a longer time to form the oxazolidinone **98**. However, it was observed that addition of iodide (LiI) or even a drop of water to the reaction mixture after the reduction was complete accelerated the cyclization to go to completion. This proves that the presence of iodide salt or a drop of water is necessary for cyclization process. In the next attempt, we demonstrated that the oxazolidinone **98** can be obtained within 9-10 hours and in good yields by adding a drop of water after the reduction by $LiBH_4$ (Entry 9).

However, for multi-gram scale reactions, we would require a large amount of $LiBH_4$ (4 equiv.) to effect the reduction. We already know that $LiBH_4$ is relatively expensive and highly air and moisture sensitive. In contrast, our novel system, $NaBH_4$/LiI in THF consists of inexpensive reagents and provides simpler and milder condition for the synthesis of oxazolidin-2-one. Thus, it would be wiser to use our novel method for larger-scale reactions.

Based on the results examined, we propose a plausible mechanism for the cyclization reaction as illustrated in Scheme 54. We believe that the exchange of X^- ion (iodide or hydroxide ion) with the alkoxy group in the intermediate alkoxyborohydride may initiate the cyclization process.



$X = I^{\ominus}, OH^{\ominus}$

Scheme 54

This mechanism is supported by a study reported by Brown et al.[139]. They describe that trialkoxyborohydrides undergo rapid disproportionation by exchanging alkoxy groups, on standing in THF[139,140]. In their work, they attempted to produce the sodium trimethoxyborohydride from NaH and methyl borate in THF as given in eq 12.

$$NaH + B(OCH_3)_3 \longrightarrow NaBH(OCH_3)_3 \qquad \text{-----eq 12}$$

$$NaBH(OCH_3)_3 \xrightarrow{THF} NaBH_4\downarrow + 3NaB(OCH_3)_4 \qquad \text{-----eq 13}$$

Unexpectedly, they observed some white precipitate formation during the reaction. Further studies on this particular conversion clearly indicated that initially trimethoxyborohydride was formed as expected and on standing in THF this material underwent rapid disproportionation to generate $NaBH_4$ and sodium tetramethoxy-borate (eq 13). Since $NaBH_4$ is insoluble in THF, it precipitated from the solution.

We thus presume that in our reactions, iodide or hydroxide enters this exchange process to release the nucleophilic alkoxy group in close proximity to the carbamate carbonyl, leading to the formation of oxazolidin-2-one (Scheme 54). The mechanism of the iodide or hydroxide mediated cyclization is supported by the experiment using the essentially salt-free commercial $LiBH_4$ as the reducing reagent. This experiment in fact proves that addition of iodide or even a drop of water accelerates the cyclization process to completeness within 9-10 hours. It is known that H_2O functions as a neutral nucleophile[141]. Besides, the tiny amount of water added to the

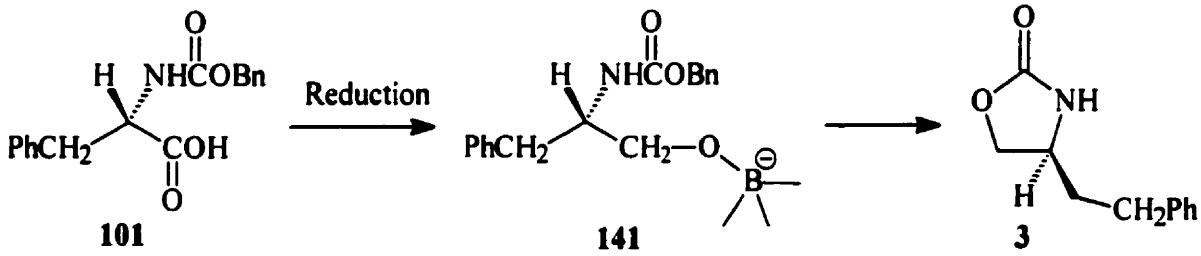
reaction medium would possibly react with the salt NaI, which is produced from $NaBH_4$ and LiI, and form the hydroxide anion (eq 14).

$$NaBH_4 + LiI \longrightarrow LiBH_4 + NaI$$

$$NaI + H_2O \longrightarrow Na^+ OH^- + HI \qquad \text{-----eq 14}$$

Either the hydroxide ion or the H_2O (neutral nucleophile) would participate in the exchange process as iodide ion. Similarly, other halide ions would be expected to promote the cyclization by this mechanism. This may also explain why we saw traces of oxazolidin-2-one in the reaction with LiCl and in other cases. The presence of chloride ion or even a trace of moisture may cause the cyclization to a limited extent.

We also wanted to know whether the direct reduction of Cbz-phenylalanine aminoacid **101** by Meyers's method would provide a direct route to oxazolidin-2-one **3** as portrayed in Scheme 55. According to Meyers's procedure[104], we treated the aminoacid **101** in THF with $NaBH_4/I_2$ under reflux for 5 hours.



101 **141** **3**

Scheme 55

Since the intermediate **141** formed in this reduction should be similar to that formed in our borohydride reduction, we though that it might cyclize to form the oxazolidin-2-one **3** in the presence of iodide ion. Disappointingly, we obtained a complex mixture of polar products (R_f lower than acid **101** on TLC) which contained neither the oxazolidinone nor the Cbz-aminoalcohol. The NMR looked complicated and suggested that the carbamate protection had been affected under this condition.

Meyers and coworkers have reported that the *t*-Boc group is inert to reduction and suggested that this might also be true for other carbamate protecting groups. However, a report by Giannis et al.[142] describes that a system of $LiBH_4$ or $NaBH_4/Me_3SiCl$ in THF reduces the carbobenzyloxy (Cbz) group and eventually removes the protection of the amino group. The authors suggest that $LiBH_4$ or $NaBH_4/Me_3SiCl$ in THF system forms a BH_3.THF complex as indicated in eq 15.

$$LiBH_4 + Me_3SiCl \longrightarrow LiCl + Me_3SiH + BH_3.THF \qquad \text{-----eq 15}$$

This BH_3.THF complex, with the assistance of excess Me_3SiCl, functions as the reducing agent. Since the Meyer's protocol also produces the similar BH_3.THF complex, it is highly unlikely not to attack the carbamate group of **101**.

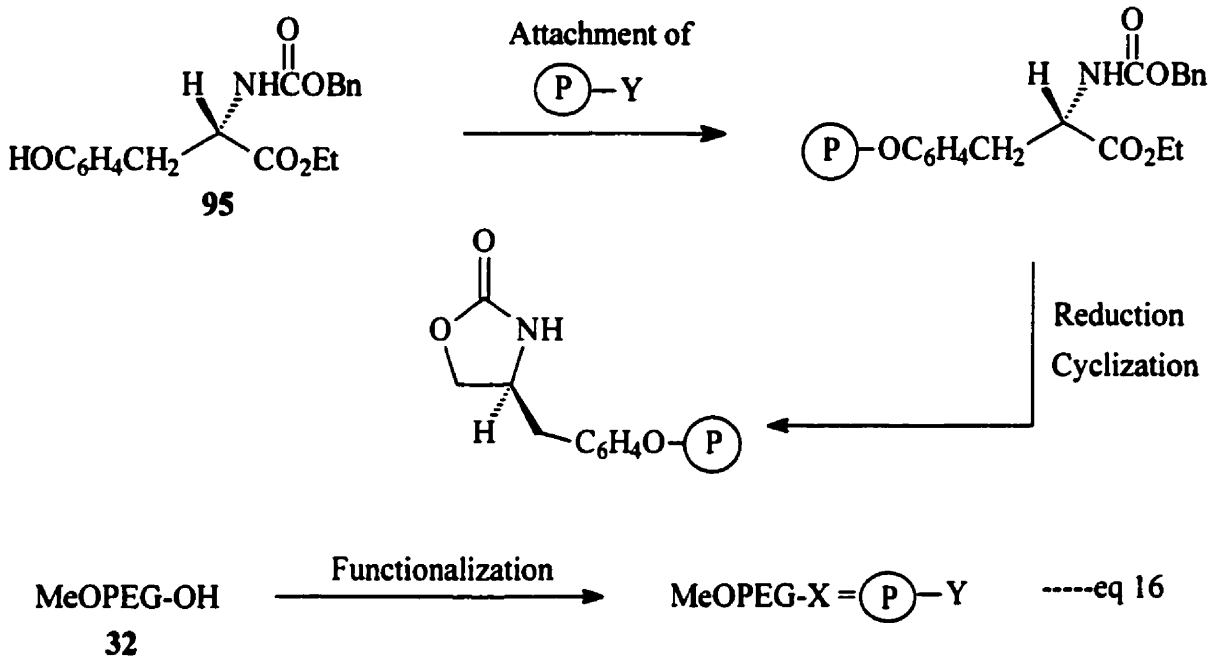
It was hoped that the reduction of **101** by $BH_3.SMe_2$ complex in THF would at least lead to the formation of **3** (Scheme 55). We observed a slow reduction at room temperature and upon heating, the reduction occurred rapidly. Nevertheless, cyclization of the resulting alcohol did not take place on prolonged heating, neither in the presence nor absence of iodide. The analysis of the crude products by NMR showed a mixture of polar products similar to those obtained from the reduction using Meyers's protocol.

The results discussed so far have been published by us recently[143]. It is also noteworthy that the synthesis of oxazolidin-2-one **58** can also be achieved using the alternative method shown in Scheme 39 (see on page 56). In this route, the oxazolidin-2-one **98** is subjected to debenzylation using 10 mol% Pd/C in MeOH and H_2[106]. This method can be used to produce **58** in multi-gram scale as well.

2. Synthesis of a soluble polymer-supported chiral oxazolidin-2-one

Intrigued by the potential of the solution phase methodology, we continued our research with the synthesis of a soluble polymer-supported chiral oxazolidin-2-one. As quoted earlier, we employed the MeOPEG (M_W 5000) as the polymer support. In the Introduction, we have already described its favorable characteristics for function as a support. This monofunctional polymer has one anchor site available for attachment of organic species as we wanted.

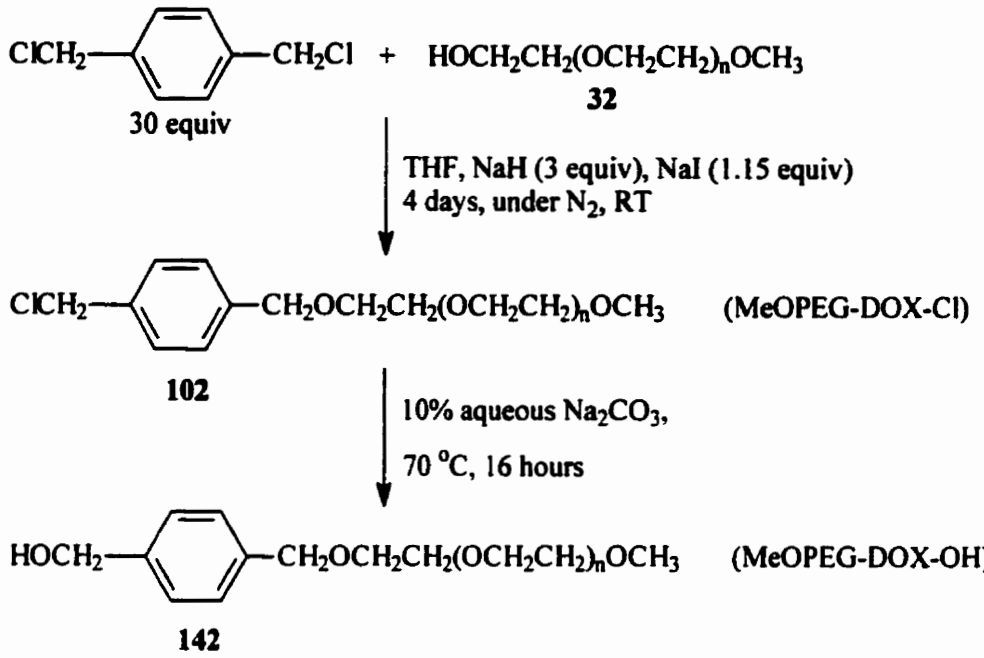
The first important step in the polymer-supported synthesis is the attachment of the synthetic unit to the polymer. The following scheme was our initial plan for the preparation of a MeOPEG-supported chiral oxazolidin-2-one.



Scheme 56

As we mentioned before, the OH group of the tyrosine ester **95** acts as a 'handle' for the attachment of the polymer (Scheme 56). However, the polymer **32** also contains a hydroxyl group at its active end. Under this circumstance, it is impossible to anchor the polymer **32** directly to the ester **95**. Therefore, the introduction of an anchor group or functionalization of the polymer **32** has to be achieved first (eq 16; Scheme 56).

In 1995 Krepinsky and his coworkers[107] introduced two novel versatile linkers derived from polymer **32** for their solution phase synthesis of oligosaccharides. Scheme 57 shows their method for the functionalization of the hydroxyl group on polymer **32** in order to form those anchors **102** and **142**. Despite the long reaction time, this approach only requires the commercially available, inexpensive materials, α,α'-dichloro-*p*-xylene and **32**.



Scheme 57

Since linker **102** has the benzyl chloride end in its structure, it can act as a benzyl-protecting group for the hydroxyl group of the ester **95**. We have already established that the hydroxyl group of this ester **95** can be protected with benzyl bromide via an ether bond under mild conditions. Thus, we hoped that the benzyl chloride associated with the long polymer chain would protect the hydroxyl group via an ether linkage.

It is important in a polymer-supported synthesis that the new linkage between the support and the substrate be stable under most reaction conditions. Besides, it has to be cleaved easily whenever it is necessary. Most of the ether linkages are known to be stable bonds but are easily removed by hydrogenolysis. Therefore, we selected this particular functionalization of MeOPEG to produce the new linker **102**. According to Scheme 57, the linker MeOPEG-DOX-Cl **102** is prepared from **32** and excess α,α'-dichloro-*p*-xylene by Williamson ether synthesis[107].

We also used a second linker monomethoxypoly(ethylene glycol) tosylate[108,109] **103** derived from **32** (eq 5 on page 57). The preparative method was comparably quick and inexpensive. In this functionalization, the OH group on MeOPEG **32** is esterified with *p*-toluenesulfonyl chloride at 22 °C for 2 hours to produce a reactive *p*-toluenesulfonate (-OTs)

ester. The sulfonic ester groups are excellent leaving groups and often used in organic synthesis[141]. Compounds having these groups are powerful alkylating agents as well. Thus, we believed that this anchor group would undergo alkylation reaction and would attach itself to the hydroxyl of ester **95** via an ether linkage.

Contrary to what we anticipated, the coupling of the ester **95** to polymer linkers **102** and **103** turned out to be unsuccessful (Table 3 on page 58). The conditions used for the synthesis are listed below.

Conditions

A. K_2CO_3 (2 equiv.) and 18-crown-6 (catalyst) in acetone, under reflux, 18 hrs.

B. K_2CO_3 (2 equiv.), 18-crown-6 (catalyst) and NaI (0.5 equiv.) in acetone, reflux, 48 hrs.

C. NaH (4 equiv.) and NaI (1.5 equiv.) in THF, at 50 °C, 96 hrs.

D. NaH (4 equiv.) and NaI (1.5 equiv.) in DMF, at 80 °C, 48 hrs.

We obtained only traces of coupled product with **102** under conditions A and B. Switching reaction conditions to C or D did not seem to work. We learned from this that allowing the reaction for longer periods or heating the reaction mixture did not induce any coupling.

The reasons for these unsuccessful results are not quite clear. The formation of aroxide ions would not have been a problem, since K_2CO_3 and NaH were successfully used in such deprotonation reactions[141]. We used 18-crown-ether to solubilize the K_2CO_3 in the organic solvents (condition A and B). We also tried adding the additive NaI in order to accelerate the process by replacing the leaving group chloride with iodide (condition B).

In aprotic solvents, the nucleophilic substitution reaction should proceed faster. The coupling reaction in acetone gave minor amount of products (condition A and B). Thus, we tested DMF and THF in order to eliminate any problems caused by the polarity of the solvents. The order of their polarities is given as DMF > acetone >THF[141]. In condition C, we employed NaH and NaI in THF at 50 °C. THF is a less polar aprotic solvent than acetone and a good solvent to dissolve NaH too. Similarly, in condition D, DMF was used instead of THF. DMF is more polar than acetone and dissolves the NaH completely. Both of these conditions (C and D) did not need any phase transfer catalysts, since NaH dissolves in DMF and THF. However, none

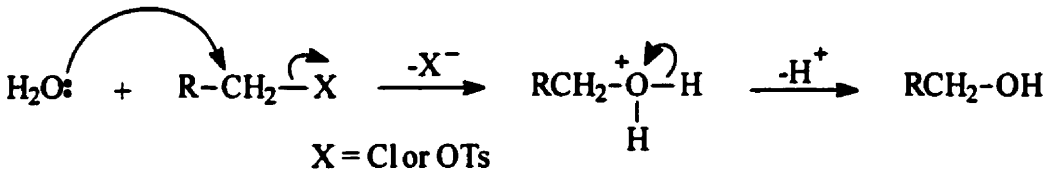
of the attempts provided any improvements or products. This suggests that the polarity of the solvents might not be a factor for these results.

We thought that perhaps the steric hindrance of the nucleophile or the long polymeric chain of the electrophile might have caused the problems. However, it has already been proved that the coupling of MeOPEG with α,α'-dichloro-*p*-xylene works perfectly under similar conditions (Scheme 57). This suggests that the polymer chain might not impose any steric effects and it might not be the reason for the unsuccessful results.

However, it is apparent that the nucleophile, ester **95** (Scheme 56) has bulky substituents (two phenyl rings and ethyl ester group). It is possible that the bulkiness of the nucleophile might have blocked its approach towards the electrophiles (linkers **102** and **103**).

For a reaction to take place, the nucleophile and the electrophile must be in proximity to each other. In this case, the electrophiles are linear polymeric chains (M_w 5000) and in solutions, these long chains would be folded and coiled randomly. We thought that it might be difficult for the bulky nucleophile to reach the electrophilic center on this network of the polymer chains. Diluting the reaction mixture might reduce this problem, but excess of reagents and/or vigorous stirring might be necessary to bring the the reactants into proximity.

Unless hydroxide ion or H_2O functions as a nucleophile, otherwise all nucleophilic substitution processes are carried under dry conditions. We already know that H_2O is a neutral nucleophile[141] and, like hydroxide ion, it will compete with the actual nucleophile to attack the electrophiles (linkers **102** and **103**).



Scheme 58

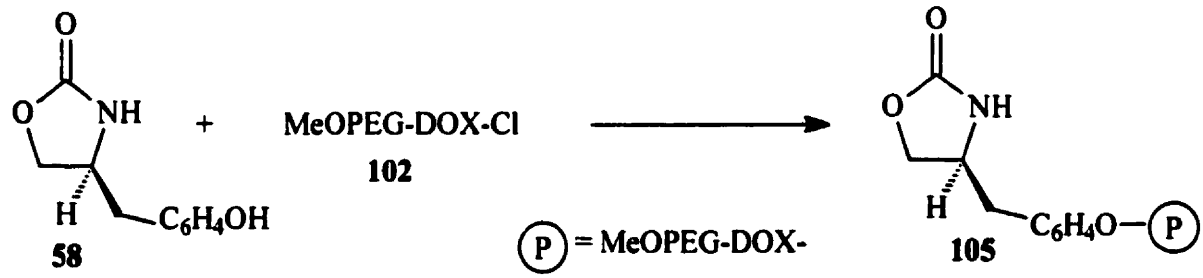
As shown in Scheme 58, the presence of H_2O hydrolyzes the alkyl halide/tosylate and forms the alcohol. Since the alkyl halide/tosylate gets destroyed during this process, the amount of alkyl halide/tosylate available for the actual reaction will be reduced considerably. Besides,

the resultant alcohol does not react with nucleophile either, because OH group is not a leaving group. Subsequently, the yield of the desired product is decreased. Depending on the amount of H_2O and the scale of the reaction, the degree of hydrolysis would vary. Especially in small (mmol) scales, even a tiny amount of moisture would be enough to destroy the entire alkyl halide/tosylate.

We dried all the reagents thoroughly before use and conducted the reactions under inert atmosphere. MeOPEG is hygroscopic in nature and hence keeping it away from atmospheric water is a particular problem. Nevertheless, there are methods[62] that help to dry these compounds very well. One method that we used in some cases is azeotropic distillation with benzene or toluene solution. It is reported that this method reduces the amount of water from 1.0% to less than 0.1% for lower molecular PEG compounds (approximately 1.0% water content for PEG with M_W 750).

The other method is more convenient one and we used it throughout the course of this study. Accordingly, the polymer materials are dried under vacuum over P_2O_5 drying agent for several hours[62,107]. These supports could be further dried by stirring with molecular sieves under vacuum prior to use. Though we dried them carefully, we did not perform any tests to see whether we removed the moisture completely. Therefore, more care must be taken in this regard in the future.

The repeated efforts to attain the attachment of the polymer finally succeeded in finding a good method for the preparation of polymer supported-organic species.



Scheme 59

Illustrated in Scheme 59 is the strategy for the synthesis. As it appears in the scheme, we decided to work with the oxazolin-2-one **58** instead of ester **95**. Similarly to ester **95**, this

possesses the same free hydroxyl arm as the point of attachment for chemical transformations. It also acts as the new nucleophile for the coupling reaction.

We have pointed out earlier that the bulky substituents on the nucleophile may effect the coupling reaction by their steric effects. It is apparent that the new substitute, chiral auxiliary **58** is also bulky, since it has a benzylic group and a five-membered ring in its structure. However, the lack of the extra phenyl ring (Cbz) as to ester **95** could make it less bulky. Furthermore, unlike the ester **95**, most of the free rotations/movements are restrained, due to its rigid cyclic structure. Hence, one could possibly expect that this defined molecular structure might eliminate the problems posed by steric effects on the nucleophilic substitution reactions.

We preferred employing the linker MeOPEG-DOX-Cl **102** for this purpose, because it had provided a trace amount of product in the previous attempts (Table 3 on page 58). Additionally, **102** can be bound to the oxazolidin-2-one **58** via an ether bond and when necessary it can be removed by hydrogenolysis[107]. The removal of the polymer chain can be achieved under either mild or vigorous conditions[107]. Under vigorous hydrogenolysis (10% Pd/C, 50% aq AcOH, 50 °C, H_2 at 3 atm pressure), the polymer support is completely detached from the organic moiety to give free OH. Under mild conditions (5% Pd black in EtOH at room temperature and H_2 at 1 atm pressure), MeOPEG is selectively removed to leave the hydroxyl protected with a *p*-tolylmethyl group ($CH_2C_6H_4CH_3$). These are the advantages of using **102** as polymer support for the synthesis.

The attachment of **102** to **58** was attempted only thrice, by treating them with K_2CO_3, 18-crown-6 and the additive salt in acetone under reflux for 18 hours. The only difference among all three attempts is the additive salt that was used to catalyze the process (Table 4 on page 59). We have already made the point that although chloride is a good leaving group, it can be replaced with a more powerful leaving group simply by adding the appropriate additive into the reaction mixture. We chose the iodide salt, since iodide is the best leaving group among halides[141].

In the first attempt, we used a quaternary ammonium salt, *n*-$Bu_4N^+ I^-$ as the additive (Entry 1). Quaternary ammonium halides ($R_4N^+ X^-$) are better sources for halogen nucleophiles (X^-) than metal halides in organic solvents[141]. Since R_4N^+ ions have sufficient alkyl groups, they are preferably soluble in organic solvents. The quaternary ammonium (R_4N^+) ions are highly solvated by organic solvents whereas metal cations are solvated by water[141]. Besides, R_4N^+ ions

are more diffuse cation than metal M^+ ions. As a result, the halide ions will move much freely with the R_4N^+ ions than with metal cations in organic solvents.

Particularly, when using *n*-Bu_4N^+ I^- as the iodide source, the diffusion of the iodide ions is further facilitated. The reason is in *n*-Bu_4N^+ I^-, the cation *n*-Bu_4N^+ is a hard acid and the anion I^- is a soft base. According to the principle of hard and soft acids and bases, hard acids prefer to bond to hard bases[144]. Therefore, the iodide ion is always bonded loosely to the ammonium ion and this lets the anion move more freely.

When we conducted the coupling reaction of **58** with **102** using *n*-Bu_4N^+ I^-, we obtained 50% (by NMR) of the coupled product **105** which was very promising (Scheme 59). The percentage yield (50%) was calculated regarding to **58** from the NMR data. We employed 2 equiv.alents of **58** and 1 equiv.alent of **102** for this purpose and the NMR of the final crude mixture revealed the presence excess **58** than required. We learned from this that we needed to optimize the amounts of the reagents.

We also had trouble removing the additive *n*-Bu_4N^+ I^- from the product. Unfortunately, similarly to the polymer bound materials, this ammonium salt is also not soluble in Et_2O. The addition of excess Et_2O to the mixture precipitated the polymer compounds as well as the ammonium salt. Instead of finding a solution for this problem, we wanted to try a different additive for this purpose.

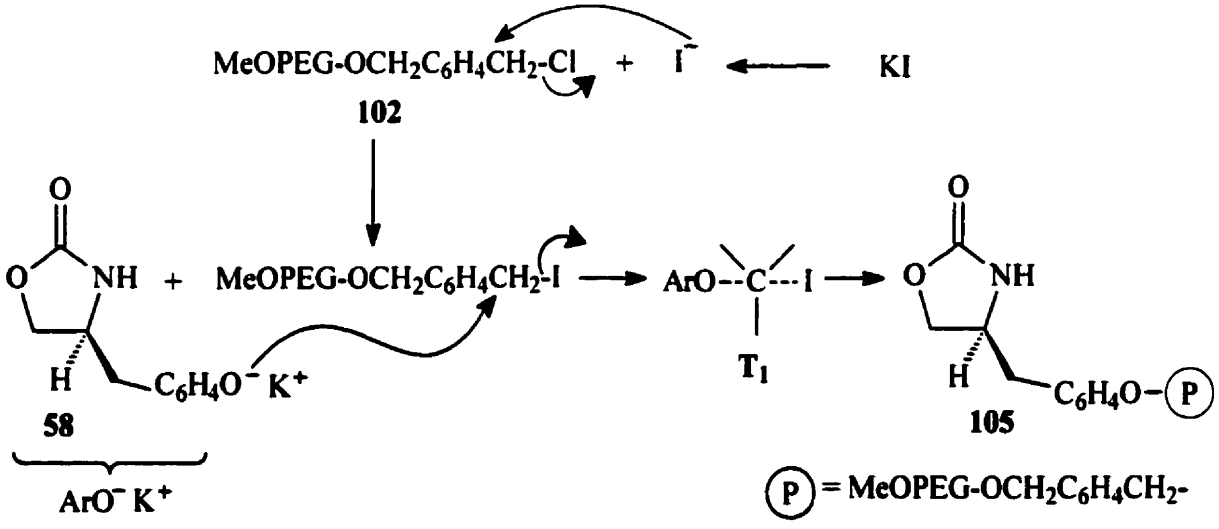
In the next experiment, we reduced the amount of **58** to 1 equiv.alent and kept the amount of **102** the same. In addition to that, we selected NaI, which is soluble in acetone as the additive (Entry 2). Again, the reaction proceeded up to 50% (by NMR) with respect to the linker **102**. The NMR data proved that there was still excess polymer linker **102** left in the mixture and the reaction needed more **58** to go to completion. The separation of the polymer bound product **105** from the unreacted polymer anchor **102** was impossible, since the both polymer compounds would precipitate with Et_2O. Thereupon we estimated the percentage of yield from the NMR data.

The observations from the earlier two attempts, suggested that the 1.5 equiv.alents of **58** and 1 equiv.alent of **102** might be the optimum values for the reaction. Since we had to add 18-crown-6 to solubilize K_2CO_3, we thought that we might as well use the KI salt as the additive (Entry 3). The crown ether would now form complexes with the K^+ ions from both salts. This

would actually increase the rate of formation of nucleophile as well as the displacement of the leaving group from chloride to iodide.

As we anticipated, the coupling reaction turned out to be total success under these modified conditions. Since we chose the optimum conditions, the reagents were converted to products completely and the isolation of the desired product was accomplished without any hassle. The final product simply precipitated out with the addition of extra Et_2O and recrystallization of the crude product from absolute ethanol provided the **105** in 95% yield. Further, these nucleophilic substitution reactions were monitored by NMR using the signal of the methoxy group of the polymer MeOPEG as the standard. The ^{1}H and ^{13}C NMR confirmed the formation of **105**.

The mechanism of the coupling process can be sketched as shown in Scheme 60. As we discussed before, the attachment of **102** to **58** is a nucleophilic substitution reaction proceeding through the SN2 mechanism. The nucleophile, aroxide anion, is produced from **58** with the help of K_2CO_3 and 18-crown-6. At the same time, the replacement of the chloride of **102** is accomplished using KI. It is significant to mention that the displacement process is accelerated by the presence of 18-crown-6. Since the K^+ ions complex with the crown ether, the iodide anions are set free in the reaction mixture. Thus, the freely moving iodide ions can easily come into contact with the **102**.



Scheme 60

Once this substitution of chloride by iodide is over, the actual coupling reaction starts to take place. The breaking of the C-I bond and the formation of the C-O ether bond occur at the same time. This leads to the transition state T_1 where the each lobe of the p orbital of carbon overlaps with the aroxide and the iodide ion. Finally, the polymer bound oxazolidinone **105** is successfully formed.

We believed that the change of starting material from ester **95** to oxazolidin-2-one **58** was responsible for this achievement. Presumably, the oxazolidin-2-one **58** reduces/eliminates the steric effects caused by the ester and allows the approach of the nucleophile towards the alkyl chloride **102**. Moreover, the addition of KI significantly promotes the process. This novel preparative strategy offers simple mild conditions for the attachment.

Furthermore, the polymer support provided a homogeneous medium as described at the beginning. This made the study of the reaction possible by NMR. As shown in Figure 18, the singlet signal obtained at d 3.38 ppm for the methoxy group of MeOPEG functions as an internal reference[58,71]. The reactions were deemed complete by comparing the ratios of the rest of the signals with the standard methoxy signal. We were able to calculate the approximate percentage yield of the products as well[76].

The work-up process was also remarkably simple and fast compared to other conventional methods. The final products were precipitated by adding excess Et_2O to the reaction medium. The heterogeneous nature of this resultant precipitate-solution mixture facilitated the separation of the products by filtration. Recrystallization from absolute EtOH purified the polymer-supported products further. The products were obtained in excellent yields.

As seen before, the applications of chiral oxazolidin-2-ones in the alkylation[24], aldol condensation[25], acylation[26], Diels-Alder reaction[31], etc. have been well established.

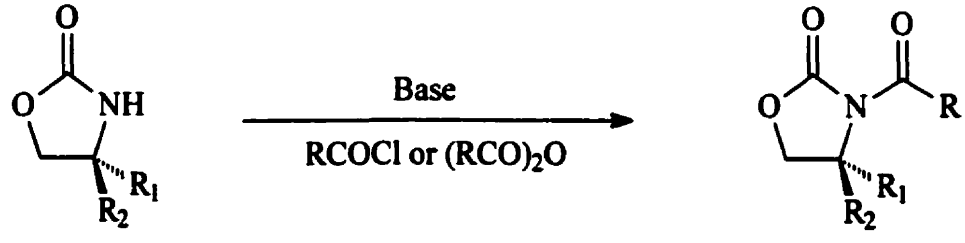


Figure 19

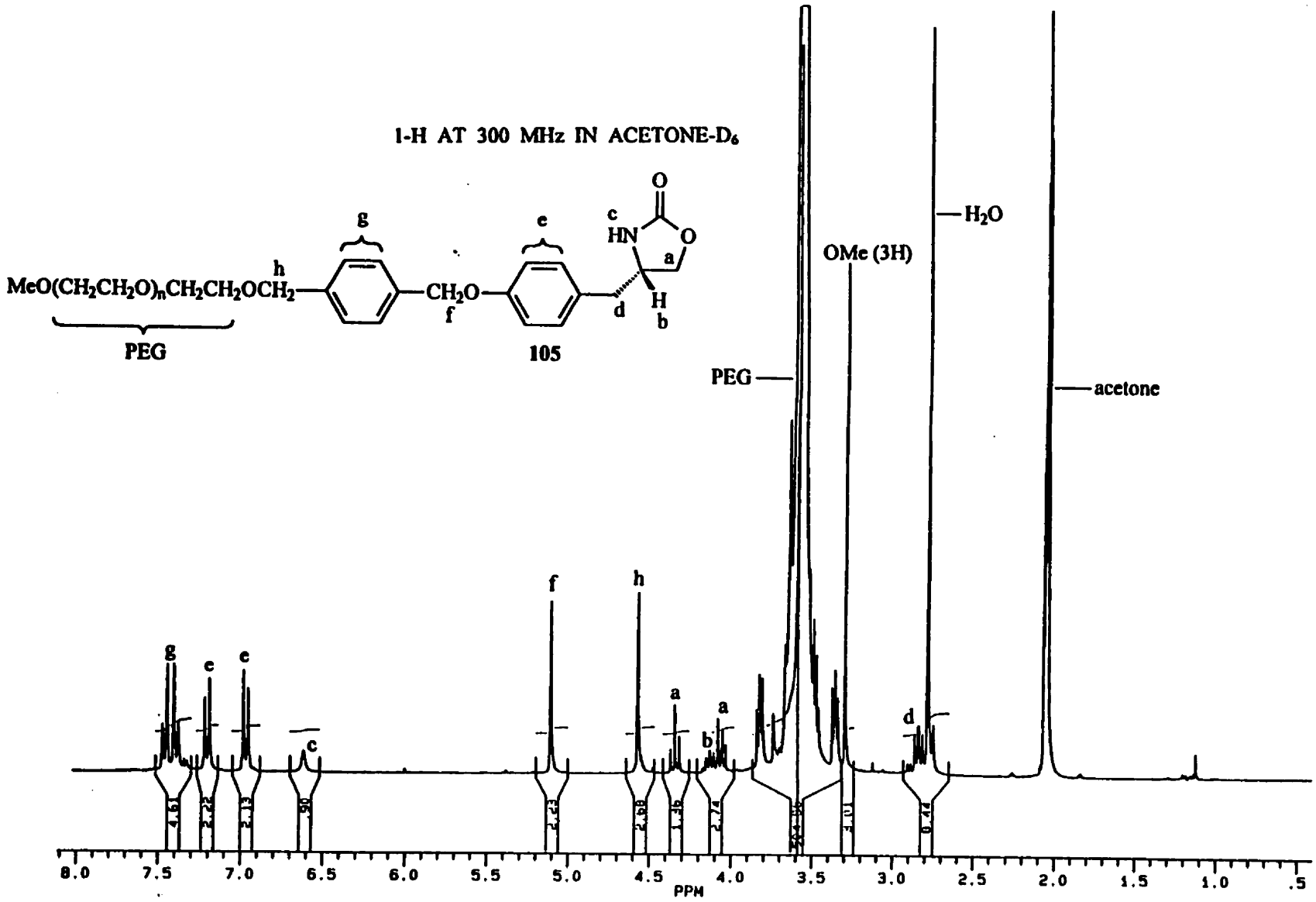
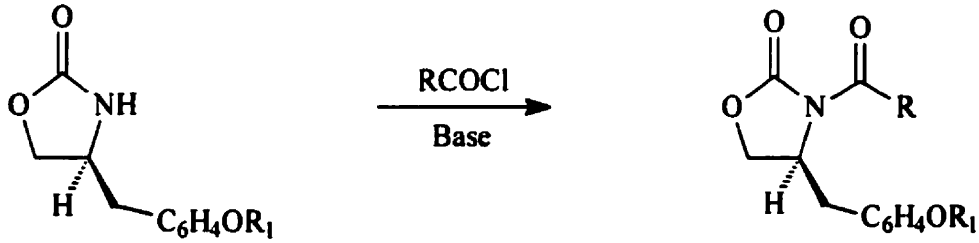


Figure 18. ^{1}H NMR of **105** shows that the singlet signal of the OMe group at δ 3.38 ppm acts as an internal reference.

The initial step in such asymmetric transformations involves the attachment of the appropriate substrate to the oxazolidin-2-one via *N*-acylation. This is generally executed with the help of a base and the acid chloride or anhydride of the substrate[8,81] (Figure 19).

In order to assess the scope of our new MeOPEG-supported oxazolidin-2-one **105**, we also needed the *N*-acyl precursors. We decided to carry out the *N*-acylation on the unsupported oxazolidin-2-one **98** first and also on the supported-auxiliary **105** (Scheme 61). In that way, we could produce a comparison between their similarities as well as differences in asymmetric syntheses.



98: R_1 = Bn
105: R_1 = (P)

106a-b: R_1 = Bn
107a-b: R_1 = (P)

Scheme 61

We prepared the *N*-propionyl[30] and *N*-crotonyl[110] derivatives of oxazolidin-2-one **98** according to the literature procedures (Table 5 on page 59; Condition A. THF, *n*-BuLi (1.2 equiv.), $(Ph)_3CH$, –78 °C, RCOCl, 15 min). The reactions were straightforward and the *N*-acylated oxazolidinones were obtained in good yields.

An alternate strategy by Ager et al.[111] provides a milder version for the synthesis of *N*-acylated oxazolidinones (Condition B. CH_2Cl_2, Et_3N (1.2 equiv.), DMAP (0.2 equiv.), RCOCl, at RT, 18 hours). This method eliminates the need for strong base (*n*-BuLi) since it can cause polymerization with certain conjugated acid chlorides such as crotonyl, and acrylolyl chlorides. A variety of acid chlorides and anhydrides (such as conjugated acid chlorides, symmetric and asymmetric acid anhydrides) can be used for *N*-acylation. The reaction does not require rigorously dried solvents. However, when we tried the propionylation reaction on **98** using this method, it took longer intervals to proceed and it was still incomplete at the end. We

concluded that though the first method needs a strong base and drier conditions, it produces the products much faster and in higher yields.

The next objective was to apply this *N*-acylation method on the polymer supported-oxazolidinone **105** (Scheme 61). We tried the propionylation reaction on **105** by employing the same conditions, *n*-BuLi and C_2H_5COCl in THF at –78 °C (Table 6 on page 60; Entry 1). In contrast to previous results, the reaction was discouraging in many ways. We found that the solubility of the polymer material was a major problem. Initially, the polymer compound **105** was soluble in THF at room temperature and it began to form a slurry/precipitate as the temperature went down to –78 °C.

In general, solubility decreases along with temperature. It has been reported in the literature that PEG polymers are insoluble in THF at low temperatures[58,76] and reactions of polymer-supported species may not be conducted in THF. A study by Kahn et al.[145] has also demonstrated that when the temperature goes to –78 °C or below, the MeOPEG-supported compounds precipitates from the solution.

Besides, we observed that the use of the strong base, *n*-BuLi, caused severe damage to the polymer supported-auxiliary. After the work-up by precipitating with Et_2O, we analyzed the isolated polymer material by NMR. The spectrum showed only the presence of the polymer material. It suggested us that the cleavage of the polymer chain from the oxazolidinone had occurred.

Further studies on the NMR data of the cleaved polymer indicated the appearance of three new signals along with the signals for the MeO and PEG groups. Those significant signals are three sets of double doublets at δ 3.93, 4.18 and 6.49 ppm. The analysis revealed that the removal of the PEG polymer had taken place in such a way that it excludes the cleavage of the linker dioxyxylyl (DOX) group as shown in Figure 20.

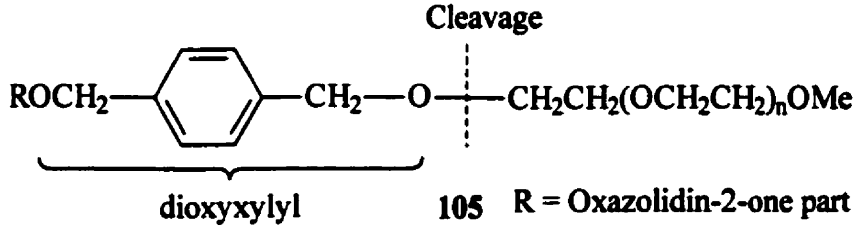


Figure 20

Furthermore, the chemical shifts and the splitting pattern of these new signals suggest that perhaps there is a terminal ethylene bond (-CH=CH_2) in the cleaved polymer chain.

It has already been demonstrated that the PEG derivatives have the property to complex metal cations[146,147] since they possess a large number of oxygen atoms in their polymer chain. A report by Whitfield et al.[148] mentions that a number of conventional metal based reagents cause the PEG derivatives to become unfilterable slurry by complexing with the polymer.

On the other hand, in PEG-supported compounds, the coordination of the oxygens on the PEG supports with the metal cations can assist their cleavage from the substrates. The following example of Krepinsky and coworkers[146] explains this concept well. In glycosylation reactions, the activation of the anomeric center of the glycosylating agent is important. This is usually performed with the help of promoters such as $BF_3.Et_2O$, AgOTf, etc[146]. Krepinsky and coworkers have proposed that the activation of the anomeric center of MeOPEG-glycoside **143** (in which the MeOPEG is linked at the anomeric position) can be achieved as portrayed in figure 21.

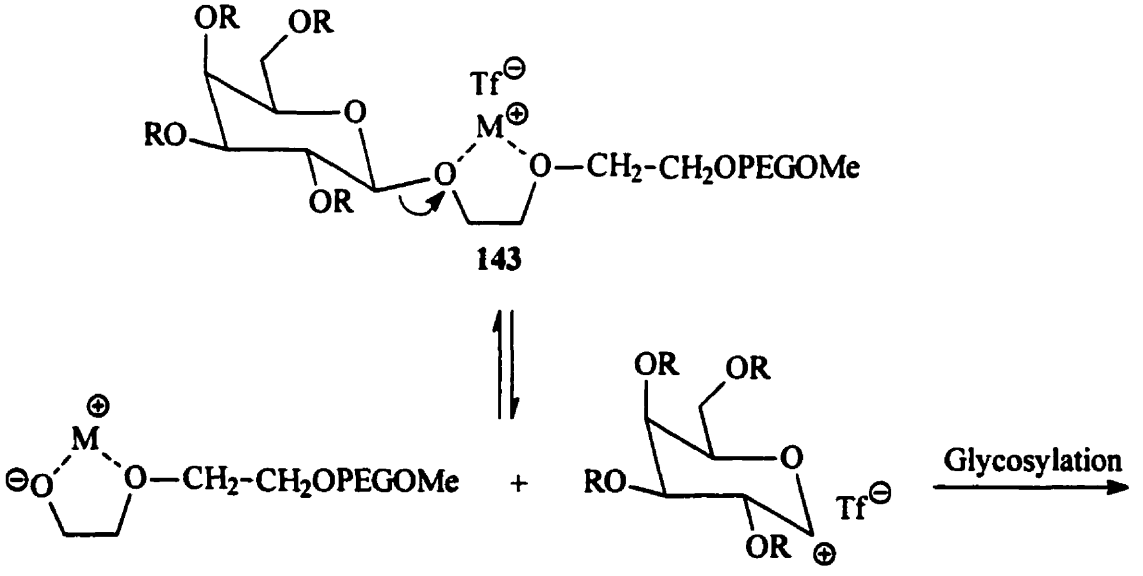
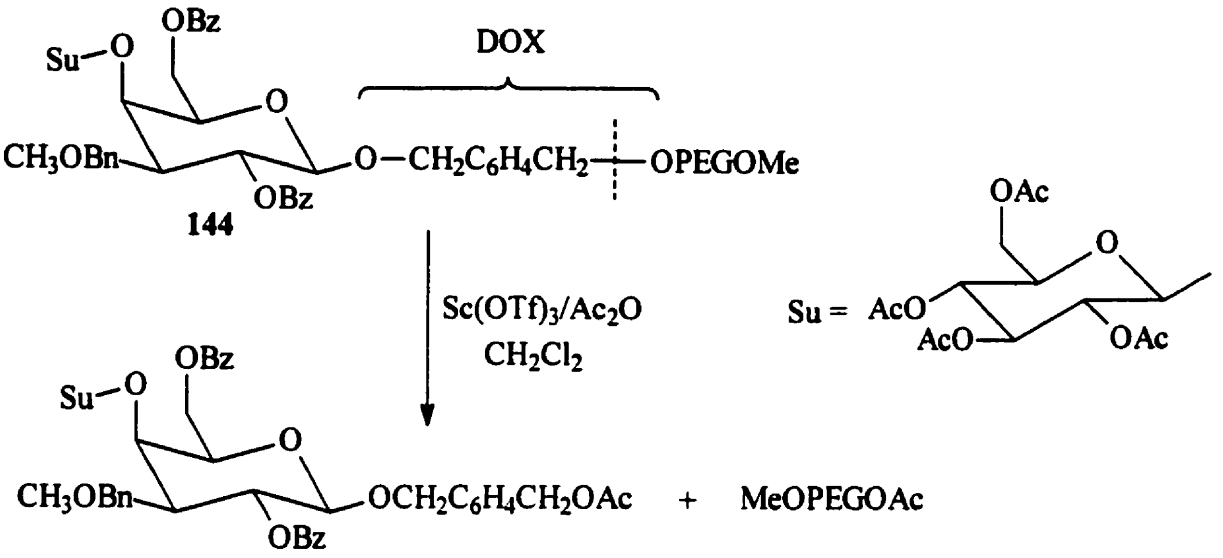


Figure 21

The coordination of the promoter ion M^+ to the oxygens of PEG and the sugar cleaves the C-O bond thereby activating the anomeric center.

In another example[148], Whitfield et al. describe the novel use of $Sc(OTf)_3/Ac_2O$ for the cleavage of the polymer chain from the MeOPEG-supported disaccharide **144**. Interestingly, their experiments reveal that the $Sc(OTf)_3/Ac_2O$ system causes the bond cleavage between the MeOPEG terminal oxygen and the benzylic carbon of the DOX (dioxyxylyl) linker, but not between the disaccharide and the DOX linker (Scheme 62).



Scheme 62

The authors propose a complexation mechanism to explain this phenomenon. The following two experiments support their idea that Sc(III) ion forms a complex with the MeOPEG polymer. In one experiment they demonstrated that though $Sc(OTf)_3$ is insoluble in CH_2Cl_2, it could be made soluble by adding PEG to the medium. They reason that the $Sc(OTf)_3$ forms a complex with PEG which dissolves in CH_2Cl_2 well.

In the other experiment, a sugar, 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranoside was subjected to cleavage conditions ($Sc(OTf)_3/Ac_2O$) for 90 hours, in the absence of MeOPEG. They observed a complete decomposition of the sugar. Conversely, in an analogous reaction conducted in the presence of 1 equiv.alent of MeOPEG, the sugar was recovered intact. This suggests that in the second case, the Sc metal ion forms a complex with the MeOPEG polymer and thus, the decomposition of the sugar is prevented. Subsequently, the complexation driven mechanism is asserted as depicted in Figure 22.

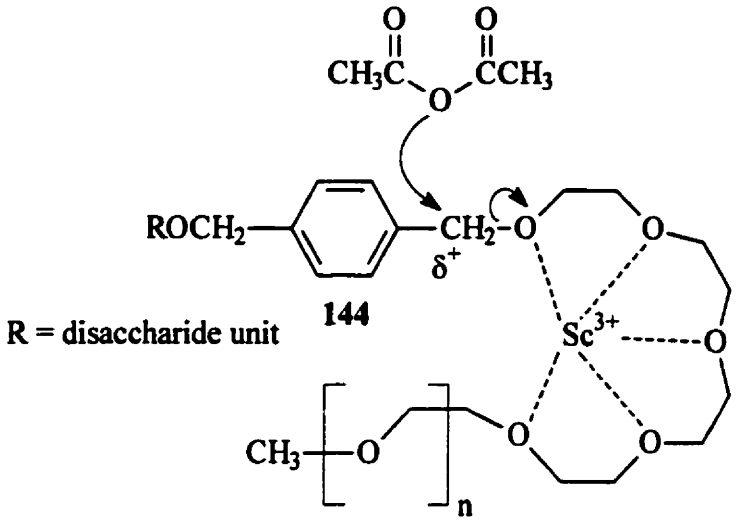


Figure 22

In analogy to above situation, we also suggest a similar pathway to explain the cleavage of the polymer MeOPEG by *n*-BuLi at the site of MeOPEG terminal carbon and the benzylic oxygen of the DOX linker (Figure 23). We think that first the Li^+ ion coordinates with the oxygen in the PEG chain as shown in Figure 23. It is well known that due to its smaller size, Li cations can undergo aggregation with substances carrying oxygen atoms[149].

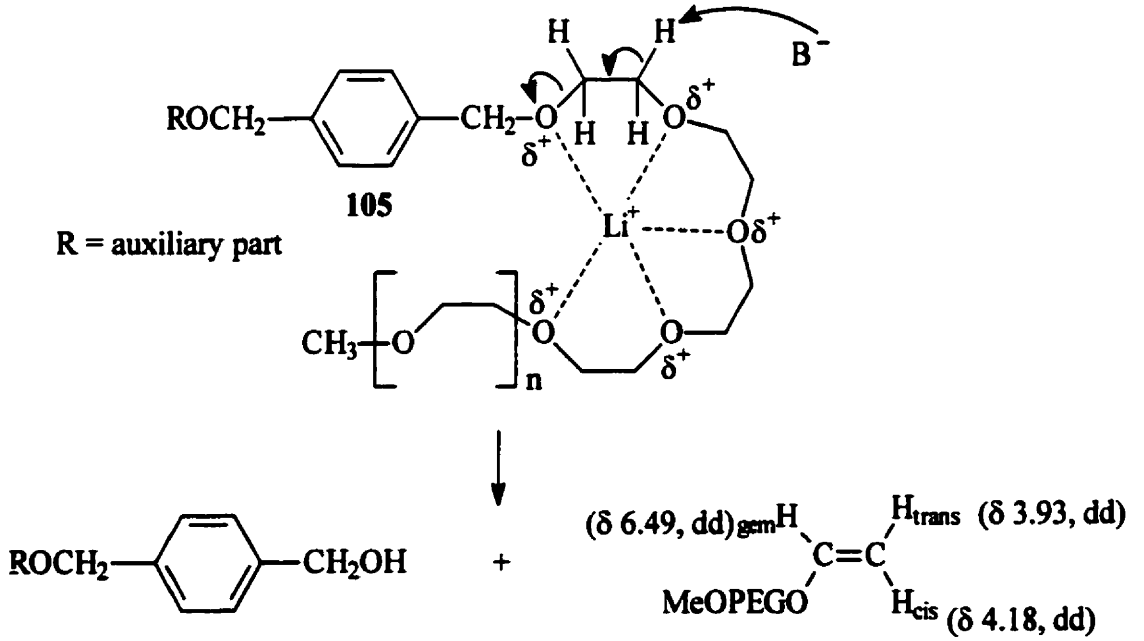


Figure 23

Next, the base comes to play its part. Since the ethyl hydrogen atoms are sitting next to the partially positive oxygen atoms, they are more acidic than amide NH of compound **105** and more likely to be attacked by the base. Pulling off a proton from the particular ethyl unit (Figure 23) leaves an anion on the carbon atom. The preferred backside attack of this anion eventually leads to the cleavage of the polymer by forming a double bond at the end of the polymer chain. The corresponding new signals on the spectrum (Figure 23) further confirm the sequence of our plausible mechanism. Nevertheless, we learned from this endeavor that conducting a reaction in THF at low temperature and use of strong bases are not suitable for polymer bound compounds.

Hoping to find new preparative methods for the *N*-acylation of polymer bound **105**, we attempted a set of reaction conditions (Table 6 on page 60). This time we repeated the propionylation of **105** with Et_3N and DMAP in CH_2Cl_2 at room temperature (Entry 2). These mild conditions eliminated several problems that had been troublesome in the previous case. This method employed CH_2Cl_2 and room temperature to prevent the deposition of PEG and the mild base to disable the splitting of the ether bond. However, no significant event was observed.

This method did not improve any further by using DMAP and DCC in CH_2Cl_2 instead of DMAP and Et_3N (Entry 3). This was not surprising because the similar conditions with unsupported auxiliary **98** the reaction was remarkably sluggish and we assumed perhaps this would be much slower or even not reactive.

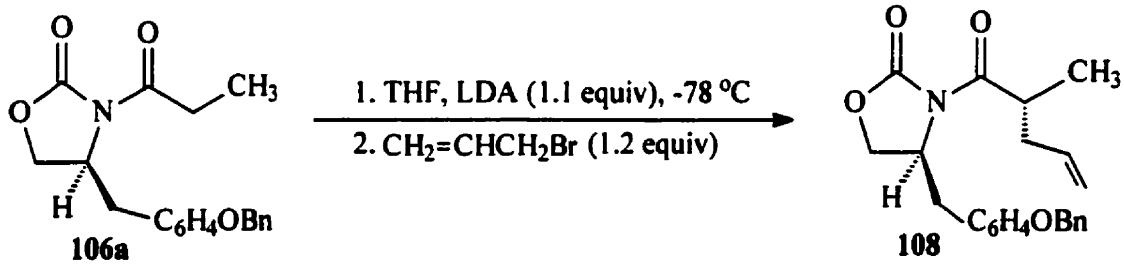
It is evident that the *N*-alkylation or *N*-allylation can be accomplished by the action of NaH and appropriate alkyl or allyl halides on a secondary amide[112]. The inorganic bases are non-nucleophilic and offer the advantage of the reaction being carried out in aprotic solvents at room temperature or higher[112]. Convinced by these facts, we carried out the propionylation using NaH and 18-crown-6 in THF at room temperature for 18 hours (Entry 4). No product was observed. In the next attempt we used the same condition but heated the reaction mixture at 40 °C for ~48 hrs (Entry 5). The reaction was promising, however, in the end, it only proceeded to <50% (by NMR).

It is accepted that the18-crown-6 is the best choice for K^+ ions[141]. It can be used with Na^+ ions since the difference between the sizes of these ions is very close. Nevertheless, it would not be as much effective as with K^+ ions. Besides, KH is in general much more reactive than NaH because the basicity of the metal hydrides increases when going down the periodic table. Thus,

we attempted the *N*-propionylation again with KH and 18-crown-6 in THF at 40 °C for 18 hours (Entry 6). The conversion was highly successful and provided the propionated product **107a** in good yield. Similarly, the crotonylation of **105** proceeded smoothly to give **107b** (Entry 7) and no other side reactions were observed in both cases. In all cases, the completeness of the reaction was confirmed by NMR.

3. MeOPEG-supported chiral oxazolidin-2-one in asymmetric synthesis

Our main purpose now was to explore the synthetic utility of the MeOPEG-supported auxiliary in asymmetric synthesis. The chemistry targeted for this study was asymmetric alkylation reactions. According to a procedure of Evans et al.[24], we performed the stereoselective allylation on the unsupported oxazolidin-2-one **106a** first (the same Scheme 40 on page 61).

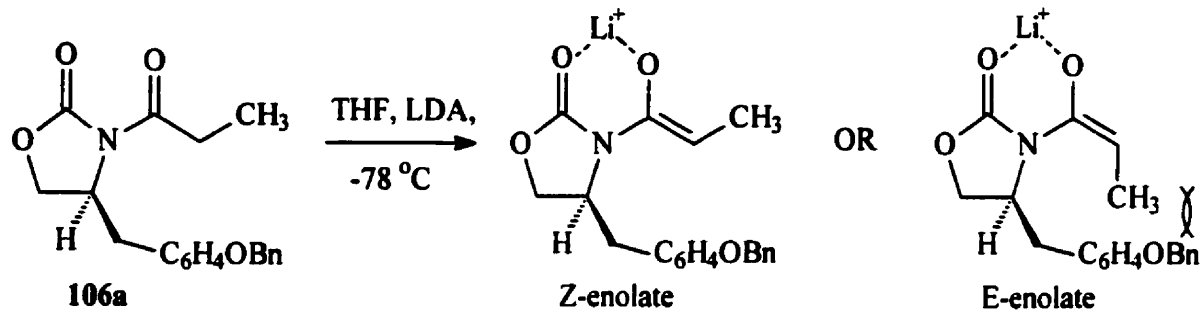


Scheme 40

The treatment of **106a** with LDA in THF at –78 °C formed an enolate which upon quenching with allyl bromide produced a single diastereomer, **108** with excellent diastereoselection (~100%)[113]. We determined the stereochemistry and the yield of **108** based on the NMR data. We performed this allylation on a small scale to observe the results first and we did not repeat the reaction again. Therefore, no experimental data were obtained on **108**.

It is obvious that the diastereofacial bias of enolates strongly influences the diastereoselectivity of the corresponding products. Evans et al. has reported that lithium amide bases selectively form *Z*-enolates with chiral imide such as oxazolidin-2-one **106a**[9,35]. Presumably, the same stereoselection is true for our case too. The reasons can be rationalized by

a consideration of the chelation of the Li^+ ion and the nonbonding interactions in the enolate transition state.



Scheme 63

As portrayed in Scheme 63, the Li^+ ion simultaneously coordinates with the enolate oxygen and the imide **106a** carbonyl oxygen and forms a six-membered ring transition state. The metal ion chelation controls the rotational degrees of freedom interconnecting chiral and prochiral centers thereby determining the geometry of the enolate. The nonbonding interactions such as steric effects and stereoelectronic effects also take part in the determination of the enolate forms. Consequently, *Z*-enolates are produced exclusively because the nonbonding interactions between methyl and benzyloxybenzyl groups in *E*-enolates disfavor their formation.

The attack of this *Z*-enolate with allyl bromide also takes place in a stereoselective manner. This asymmetric induction is dictated by steric effects imposed by the C_4-substituent on the oxazolidinone ring. Therefore, the allyl bromide attacks below the plane and only a single diastereomer (S,R) results from this allylation (Figure 24).

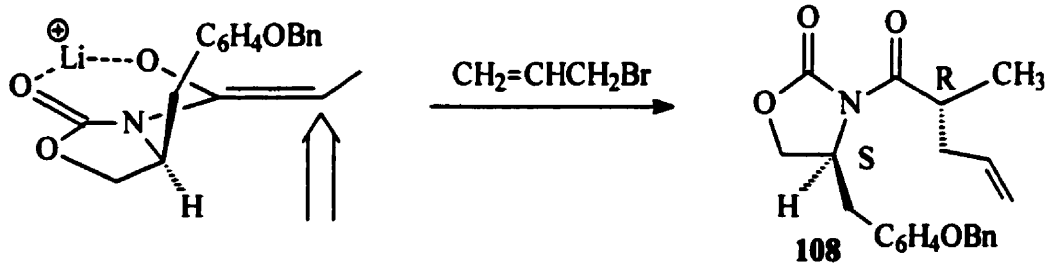
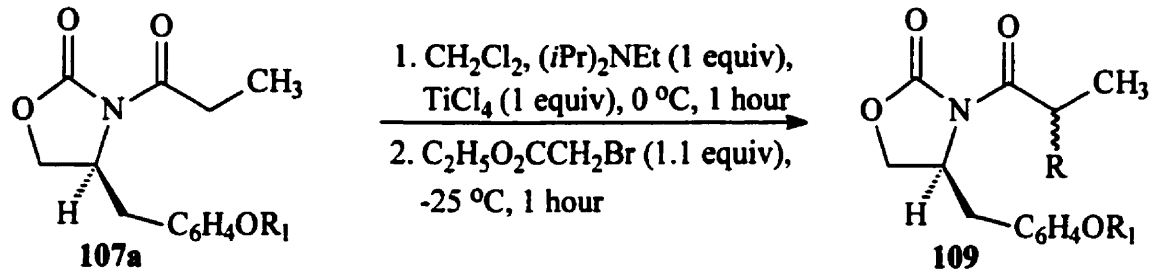


Figure 24

The lithium-mediated allylation requires the strong base, THF solvent and low temperature (–78 °C) for the allylation to take place. We knew already that these conditions are not appropriate for the polymer-supported auxiliary **107a**. Thus, we considered the titanium-mediated alkylation[36,113] for this purpose (the same Scheme 41 on page 61).



107a

$R_1 = MeOPEGOCH_2C_6H_4CH_2$-

109

$R = C_2H_5O_2CCH_2$–

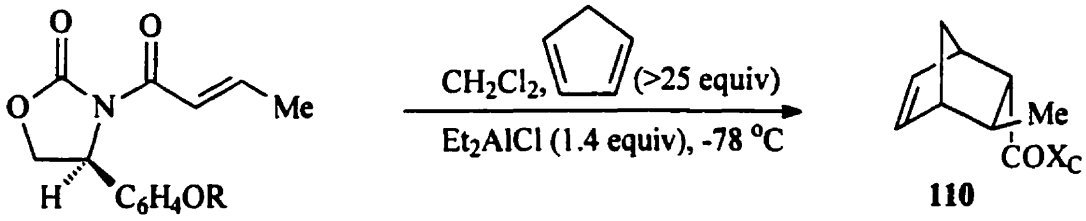
Scheme 41

Accordingly, the polymer compound **107a** dissolved in CH_2Cl_2 was reacted with $(iPr)_2NEt$ at 0 °C first. It is significant to note here that there was no precipitation observed at 0 °C or even at –78 °C. It appeared that the change of the solvent from THF to CH_2Cl_2 had removed the solubility problem. Disappointingly, the polymer started to precipitate with the addition of $TiCl_4$. There was no alkylated product **109** detected even when we continued the reaction by reacting with ethyl bromoacetate.

The reason for the deposition of the polymer is probably that the Ti atom forms an insoluble complex via coordination with the oxygens on the polymer. Titanium atom, especially Ti^{+4} has the ability to coordinate with oxygens[147]. It has a vacant d orbital for chelation and ligands to act as leaving groups (such as Cl). Therefore, we presume that the complex resulting from this would be the same as the one illustrated for the Li metal-MeOPEG complexation (Figure 23).

We next focused our attention on the Diels-Alder cycloaddition reaction. Initially, we subjected the unsupported **106b** to Lewis acid promoted-cycloaddition by treating with Et_2AlCl and cyclopentadiene (excess) in CH_2Cl_2 at –78 °C[110] (the same Scheme 42 on page 62). The NMR analysis of the final product indicated the presence of a single diastereomer **110**.

Comparison of the NMR data with the literature values obtained for a similar system confirmed that the diastereomer was resulted from the *si* face and endo attack[110]. Since our initial intention was to observe the results using this auxiliary, we performed the cycloaddition on a small scale first. However, we never repeated the reaction again and thus, no experimental data were obtained on **110**.



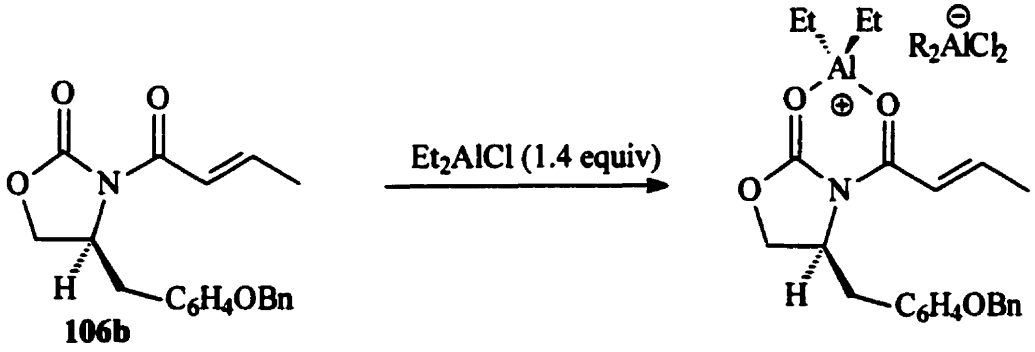
106b: R = $CH_2C_6H_5$
107b: R = $CH_2C_6H_4CH_2OMeOPEG$

110

X_C = auxiliary part

Scheme 42

It is assumed here that the uncomplexed α,β-unsaturated carbonyl moiety of **106b** would exclusively exist in the s-cis conformation[110] (Scheme 64). The s-trans conformation would never be a favored or stable form because the nonbonding interactions between the olefin and chiral auxiliary would be very strong. The use of the Et_2AlCl helps to achieve high degree of diastereofacial bias in the transition state. As depicted in Scheme 64, the bidentate Et_2AlCl coordinates with the carbonyl oxygens of **106b**. This chelation increases the bias by controlling the free rotations of the interconnecting N-C=O bond.



106b

Scheme 64

The following model explains the asymmetric induction leading to selective endo, *si* face cycloadduct **110** (Figure 25).

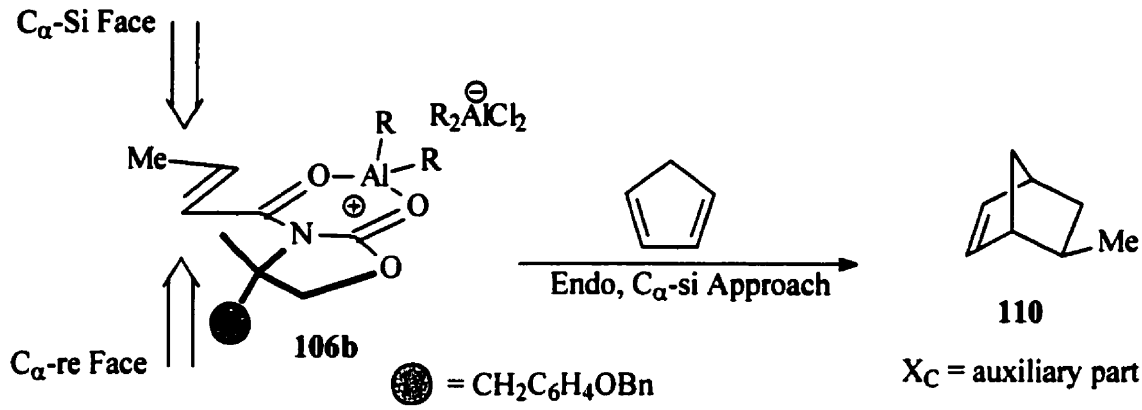


Figure 25

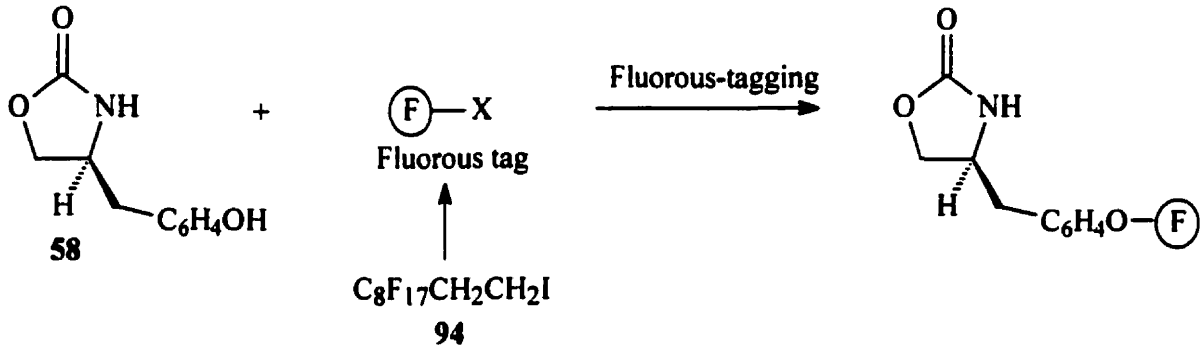
A study by Evans's group describes[110] that high levels of asymmetric induction are obtained for oxazolidinones bearing phenyl ring at C_4 position. The effects posed by this substituent are a combination of electronic interactions such as dipole-dipole and van der Waals attractions. Similarly, in our case, the imide contains a benzyloxy benzyl group at C_4 carbon and the electronic interaction between this group and the olefin would enhance the π-facial stereoselectivity (Figure 25).

Nevertheless, the cycloaddition of the polymer bound carboximide **107b** (Scheme 42) was unsuccessful under above conditions. Here again, the solubility of **107b** in CH_2Cl_2 at low temperature was not a problem. However, the addition of the Lewis acid Et_2AlCl induced the precipitation of the polymer. The same concept of metal (Aluminum) chelation with the polymer holds true for this observation too. When we conducted the cycloaddition at –30 °C, the deposition of the polymer persisted. The change of TMS-OTf instead of Et_2AlCl eliminated the precipitation with the polymer but the cycloaddition did not occur.

From these results and observations, it was clear that MeOPEG polymer might not be a good choice for organic reactions that are carried out in THF at low temperatures. Besides, the use of MeOPEG-supported compounds in organic transformations involving organometallic (alkali or transition metals) reagents might not be appropriate. Excess reagents and long reaction times might sometimes be required for the completion of reactions.

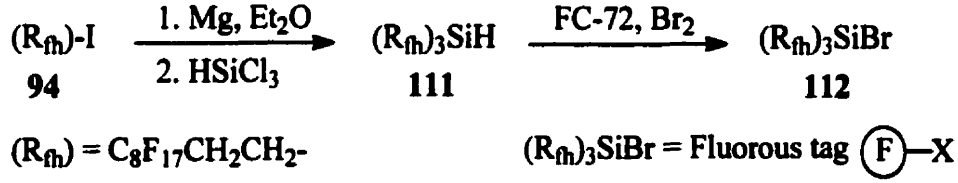
4. Synthesis of a fluorous-tagged chiral oxazolidin-2-one

Faced with the problems posed by the soluble polymer-supported methodology, we considered an alternative synthetic avenue, the fluorous synthesis approach by Curran, for our purpose. According to Curran's protocol[93], our initial task was to make our substrate sufficiently fluorous. We selected the oxazolidin-2-one **58** as the substrate to work on this project. The initial effort for the fluorous-tagging is outlined in Scheme 65.



Scheme 65

In order to carry out this scheme, we needed to synthesize the requisite fluorous-tag first. This was achieved with the help of the perfluoro compound, 1-iodo-1*H*,1*H*,2*H*,2*H*-perfluoro-decane **94**. The derivation of fluorous-tag was attempted in two different ways. The first and successful method was based on the procedure of Curran et al.[91], which is given in Scheme 43 (the same Scheme 43 on page 63).



Scheme 43

The generation of Grignard reagent from **94** and subsequent treatment with trichlorosilane provided the stable intermediate perfluoroalkyl silane **111**[91]. Bromination of **111** yielded the fluorous-tag **112**. Since halosilanes or alkylsilyl halides (TBDMSCl, TMSCl, etc.) are very useful protecting groups in organic synthesis, we thought that it would be advantageous to exploit bromosilane **112** as a fluorous labeling reagent.

The generation of the Grignard reagent was a bit challenging for us at the beginning. In almost all attempts, we obtained only the dimer **145** (Wurtz-coupling product)[150,151] as shown in eq 17, not the perfluoroalkylated silane. The structure of **145** was confirmed by NMR.

$$\underset{\mathbf{94}}{C_8F_{17}CH_2CH_2-I} \xrightarrow{Mg/Et_2O} C_8F_{17}CH_2CH_2MgI \xrightarrow{\mathbf{94}} \underset{\mathbf{145}}{C_8F_{17}(CH_2)_4F_{17}C_8} \quad \text{-----eq 17}$$

It is already proven that the perfluoroalkyl halides would form Grignard reagent[94,152] with magnesium metal efficiently. Pierce and co-workers[152] have suggested that the hydrocarbon spacer group between the perfluorinated alkyl part and the halide could be expected to completely mask the powerful electron attracting effect of the fluorinated portion and therefore, the perfluoroalkyl halides would form a normal Grignard reagent. Since the perfluoroalkyl iodide **94** has an ethylene spacer group, we presume that the presence of the perfluorinated carbon chain does not exert any effect on the process.

As claimed previously[91,153], the solubility of perfluoroalkyl or aryl halides could cause problems in conducting Grignard reactions in organic solvents. However, the perfluoroalkyl iodide **94** is completely soluble in ether at and above room temperature. Hence, in this respect, the solubility of **94** would not be troublesome. It is known in general that Grignard reagents from primary alkyl halides are easy to prepare and that the order of halide activity towards Grignard reaction is I > Br > Cl[150,153]. Therefore, the primary perfluoroalkyl iodide **94** would be expected to be as reactive as other normal primary alkyl iodides.

It is apparent that reactive halides can react with Mg metal and form Grignard reagents very rapidly. These reactive halides, however, sometimes produce Wurtz-type coupling product in the presence of excess halide by direct reaction between the halide and Grignard reagent[94,154]. The reason[154] is that in these particular cases, the resultant Grignard species does not diffuse

well in to the solution and accumulates on the magnesium surface. Consequently, the available surface area of active magnesium will be drastically reduced. In this situation, the resultant Grignard reagent (RMgX) is also in competition with Mg metal surface for the organic halide. The reaction of RMgX with excess halide leads to the formation of Wurtz-type coupling product (the dimer). Thus, the active magnesium surface is a critical factor here in order to produce RMgX species continuously. We think that this might be the reason for the dimer **145** formation in the first few efforts.

Nevertheless, we alleviated this problem by using special techniques. In order to make a clean active magnesium surface available during the process, we employed the entrainment method[153,155]. We used catalytic amounts of more reactive 1,2-dibromoethane as the entrainer to activate the metal at the beginning and during the process. This active halide cleans and activates the surface of the Mg, thus encouraging subsequent formation of Grignard reagent. Precisely, the following reaction occurs during the operation of the entrainer (eq 18).

$$Br\text{-}CH_2\text{-}CH_2\text{-}Br + Mg \longrightarrow BrMg\text{-}CH_2\text{-}CH_2\text{-}Br \longrightarrow CH_2{=}CH_2 + MgBr_2 \quad \text{----eq 18}$$

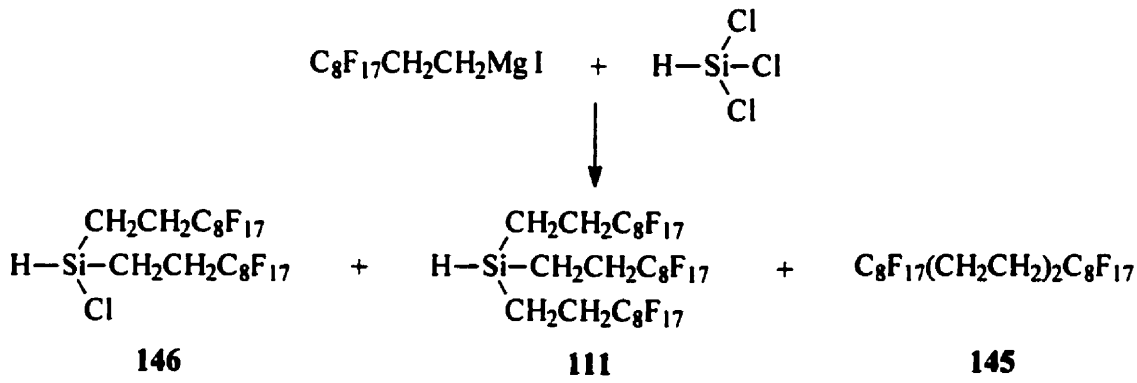
The 1,2-dibromoethane reacts with Mg and gives an unstable Grignard reagent, which rapidly eliminates the $MgBr_2$ to produce ethylene gas. Accordingly, the entrainer never interferes with the actual procedure and is the best option for our purpose.

Besides, we also purified the perfluoro alkyl iodide prior to conducting the reaction. We dissolved the halide in freshly distilled Et_2O and passed it through a column of alumina (neutral) to remove any impurities (such as HI)[156]. We slowly added the diluted halide solution in order to maintain the Et_2O under reflux constantly. In addition, we used freshly distilled trichlorosilane[157] each time. A combination of all these techniques eventually helped us in reducing the formation of the dimer **145**, but we still observed significant amount of dimer **145** product along with silane **111**.

In an experiment by Guida-Pietrasanta et al[94], the formation of the Grignard reagent from $C_6F_{13}C_2H_4I$ was followed by GC analysis on samples taken from the reaction mixture. Besides the expected product, they observed considerable amount of dimer, $C_6F_{13}C_2H_4\text{-}C_2H_4C_6F_{13}$ in the mixture. They further claimed that though the generation of the dimer depended on the conditions, they obtained at least 20% of the dimer even in very dilute solution.

Moreover, Fuchikami and his coworkers[158] reported that Grignard cross-coupling reactions are difficult with non-fluorinated alkyl halides and are possible with fluorinated ones. These observations support and strengthen our justification that the dimer formation is an inevitable side reaction and is not unusual in the preparation of Grignard reagents of reactive perfluorinated alkyl halides.

Immediately after the Grignard reaction, we performed the alkylation of the trichlorosilane with the Grignard reagent $R_{fh}MgI$ to afford the fluorous organosilane **111** (Scheme 43). This method is considered the most convenient approach to prepare fluorine-containing organosilanes[152]. Unfortunately, we obtained the disubstituted perfluoroalkyl silane **146** along with the desired product **111** and the dimer **145** as depicted in Scheme 66. The disubstituted product **146** was identified by NMR using its significant Si-H signals at 4.91 ppm.



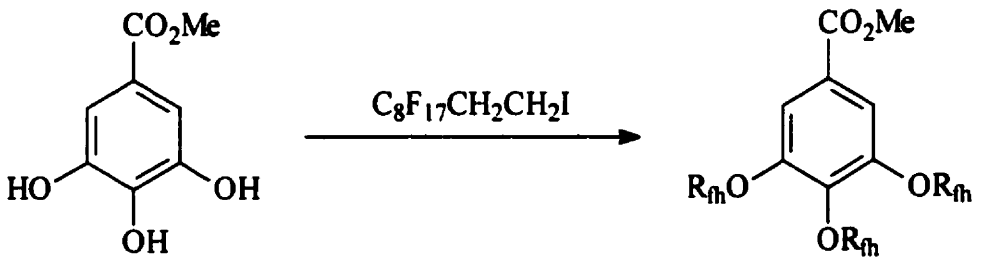
Scheme 66

This type of side reaction is possible when there is an excess amount of trichlorosilane present or/and not enough Grignard reagent formed in the medium. As a result, the mono- or/and the disubstituted species would be the dominating products. However, this problem could be diminished by reducing the amount of required trichlorosilane or by creating more Grignard reagent for the reaction. This was satisfactorily effected by reacting with less amount of trichlorosilane than calculated and by slow addition in order to provide time for tri substitution.

Finally, the bromination of silane **111** provided us with the fluorous bromosilane **112** as outlined in Scheme 43. We carried out the reaction in FC-72 using Br_2 according to a procedure

by Curran[91]. FC-72 is a perfluorinated solvent consisting mostly of isomers of perfluorohexanes (C_6F_{14}). Since the silane **111** is highly fluorinated it preferably and completely dissolves in such perfluoro liquids. The bromosilane **112** is highly sensitive to moisture and light. It will be hydrolyzed if it is exposed to air for a long period. Since it is an unstable compound, it has to be stored under vacuum or inert atmosphere and away from light. The best way is to prepare and use it immediately.

During the course of this project, we also attempted to prepare a second fluorous-tag **116** starting from 3,4,5-trihydroxymethyl benzoate (methyl gallate) **113** (Scheme 44 on page 63). Unfortunately, the very first step of the synthesis turned out to be a failure and is depicted in Scheme 67.



113 **114**

Scheme 67

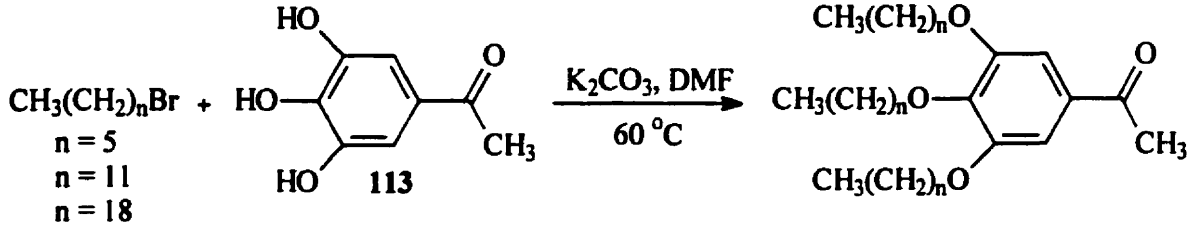
In analogy to previous *O*-benzylation/alkylation reactions, we tested a series of reaction conditions that could enhance the reactivity of this nucleophilic substitution reaction (Table 7 on page 64).

We employed different inorganic bases such as K_2CO_3, Cs_2CO_3, NaH, NaOH and KOH for the deprotonation of the three hydroxyl groups of **113**. The additive 18-crown-6 was added to promote the deprotonation. We conducted the conversion in less polar to more polar aprotic solvents (THF, acetone, MEK, DMF). It is noteworthy here that the perfluoroalkyl iodide **94** dissolved in these solvents without any trouble.

We also tried phase transfer catalyst methods[115]. The conditions attempted for this purpose involved the phase transfer catalyst benzyltriethylammonium chloride, the bases 10% KOH or NaOH and the solvent systems CH_2Cl_2/H_2O or $MeOH/CHCl_3$. However, neither of

these methods seemed to work. According to NMR analysis, only trace amounts of mono-, di- and tri- substituted products were obtained along with other unknown materials.

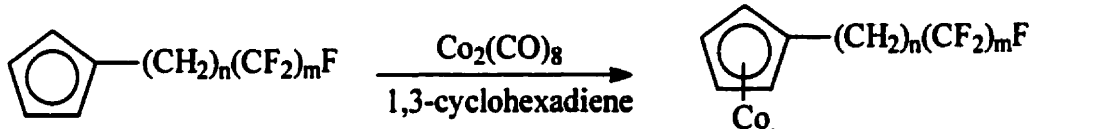
It has been demonstrated previously[114,159] that tri-alkylation of the three hydroxyl groups of methyl gallate **113** can be achieved successfully (Scheme 68).



Scheme 68

Interestingly, in all these examples, long chain alkyl halides (CH_3-$(CH_2)_n$-CH_2Br, where n = 5, 11, 18) have been exploited for *O*-alkylation. This was promising information for us because we also wanted to alkylate **113** using the ten-carbon chain, perfluoroalkyl iodide **94**.

Since the perfluoro compound **94** is a primary iodide, we thought that this would behave the same as the normal iodide does in nucleophilic substitutions. We also expected that the perfluorocarbon unit would be inert under these reaction conditions. An interesting experiment by Hughes and his coworkers[97] explains the necessity for the spacer group clearly. They investigated the differential effects of perfluorocarbon chain with and without ethylene spacer groups using the following cyclopentadienes and their corresponding cobalt carbonyl complexes illustrated in Scheme 69.



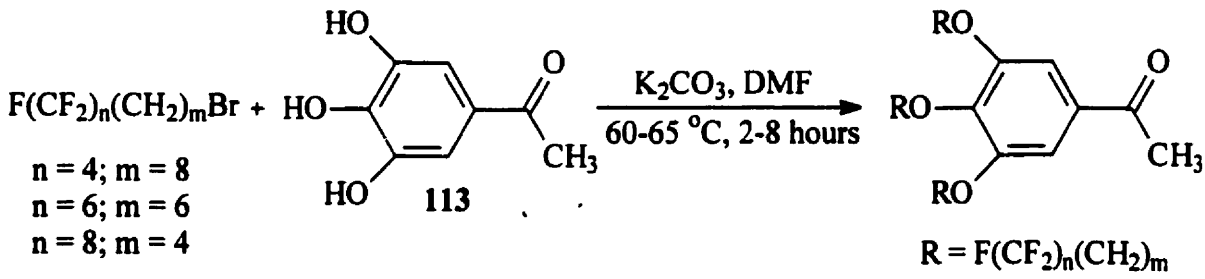
147a: n = 2; m = 10
147b: n = 0; m = 10

148a: n = 2; m = 10
148b: n = 0; m = 10

Scheme 69

They performed a direct complex formation reaction between the cyclopentadienes (**147a** and **147b**) and $Co_2(CO)_8$ in the presence of the hydrogen acceptor, 1,3-cyclohexadiene. The cyclopentadiene **147a** yielded the cobalt complex **148a** in 70% yield where as **147b** provided only 30% of complex **148b**. It was reasoned that the low yield was due to the lack of C_2H_4 spacer group. They further analyzed the carbonyl stretching frequencies of complex **148a** and **148b** and found that the carbonyl stretching of compound **148a** shifted to less energy than the unsubstituted cyclopentadiene cobalt complex. In contrast to that, the carbonyl stretching frequency of complex **148b** shifted to higher energy than that of unsubstituted compound. This again explained that the intervening ethylene groups serve as an insulating spacer group to isolate the strong electron withdrawing effect of perfluoroalkyl chain.

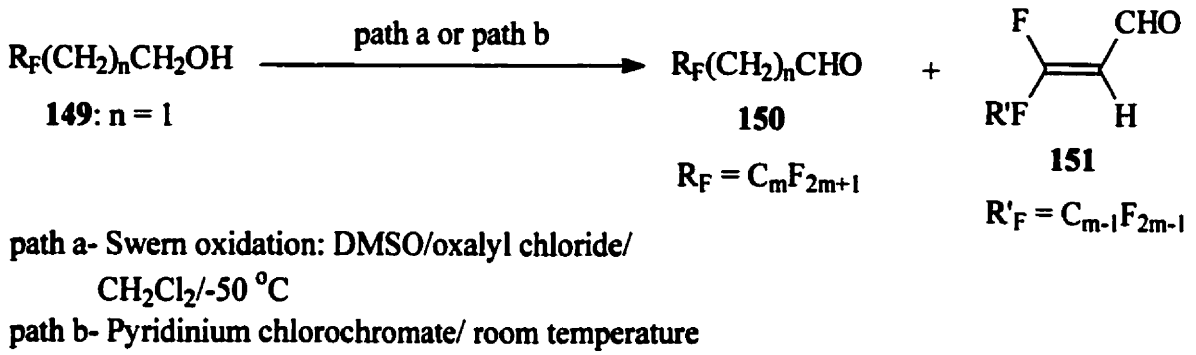
Though compound **94** has the C_2H_4 spacer unit, the substitution reaction did not work in our case. At this point, we found in the literature[160,161] that similar type of synthesis had been successfully done with methyl gallate **113** using perfluoroalkyl bromide having 4-8 CH_2 spacer units as given below in Scheme 70.



Scheme 70

From the above information, we could suggest that perhaps the perfluoroalkyl halide must have minimum four intervening CH_2 units for this particular reaction to occur smoothly.

Very recently, Le Blanc and coworkers[162] have attempted to find a method for synthesizing a series of perfluoroalkyl aldehydes from the corresponding perfluoro primary alcohols as illustrated in Scheme 71. They used a sequence of perfluoro alcohols of various lengths in the perfluorocarbon unit and in the polymethylene spacer group. Initially they tested the Swern oxidation and the pyridinium chlorochromate oxidation (Scheme 71). They found that the results depended on the length of the methylene spacer.



path a- Swern oxidation: DMSO/oxalyl chloride/
CH_2Cl_2/-50 °C
path b- Pyridinium chlorochromate/ room temperature

Scheme 71

When n = 4,3 and 2 both methods provided the aldehydes in high yields. However, when n = 1 (i.e. $R_FCH_2CH_2$-OH **149**), both methods gave a mixture of saturated **150** and unsaturated **151** aldehydes. Only the Z isomer of **151** was isolated and this was confirmed by the coupling constant values. The authors reasoned that the basic conditions used either during the work-up or in the reaction were responsible for the dehydrofluorination of the aldehydes. Accordingly, in the Swern oxidation, triethylamine which was used to quench the reaction would have caused the formation of the unsaturated aldehyde **151**. Similarly, in the pyridinium chlorochromate oxidation, the presence of excess pyridine in the medium would have triggered the dehydrofluorination.

Since the methylene hydrogens found in between the aldehyde and CF_2 unit are highly acidic in nature, the abstraction of the proton by the base results in the β-elimination of HF to form the unsaturated aldehyde as shown below in Figure 26.

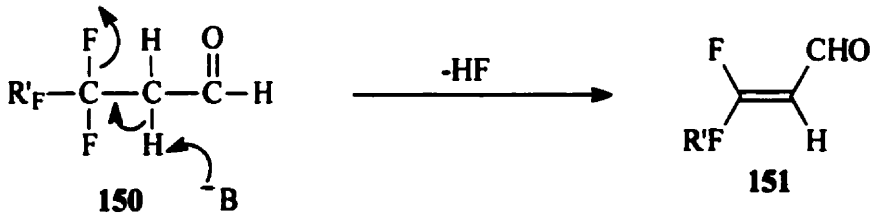


Figure 26

This evidence tells us that the number of intervening CH_2 unit is important to prevent the side reactions and it must be greater than two for this oxidation reaction to occur perfectly.

From these findings, we learned that the perfluoralkyl compounds having just a CH_2CH_2 spacer group between the fluorocarbon unit and the terminal functional group (-OH, -I, etc.), might be susceptible to bases. We thought then that in our case, the basic conditions employed for the *O*-alkylation process (K_2CO_3, NaH, NaOH, KOH, etc) might cause the perfluoroalkyl iodide **94** to undergo either of the elimination process suggested in Figure 27.

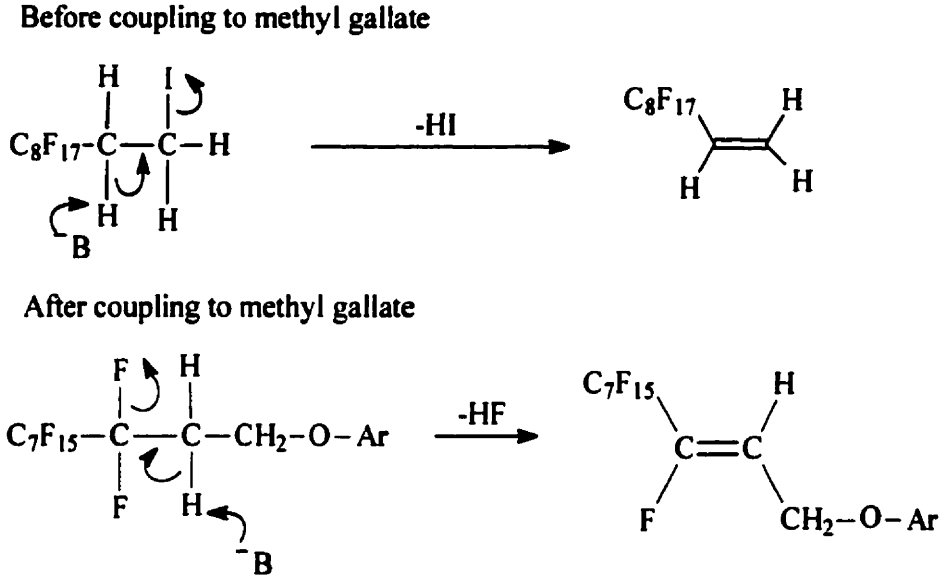
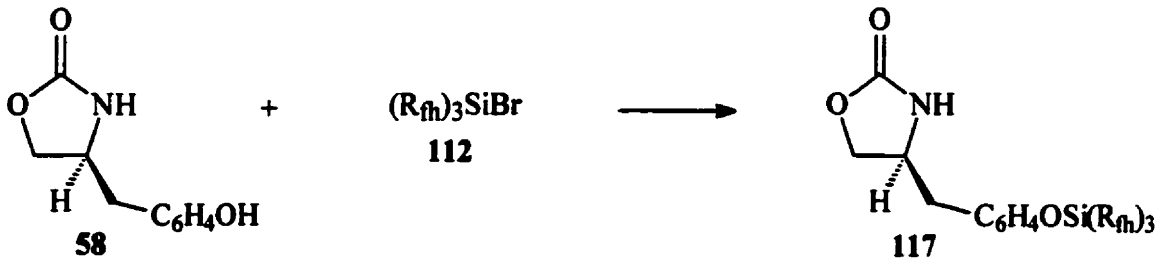


Figure 27

As we mentioned before, the unknown materials that we observed on the NMR might have resulted from these types of reactions. However, we do not have any strong evidence to prove that these elimination processes occur during the reaction. Finally, we abandoned this idea and continued our studies with bromosilane **112**.

We next focused on generating the fluorous labeled oxazolidin-2-one using the fluorous-tag bromosilane **112** and oxazolidinone **58**. According to Scheme 72, the phenolic OH group is converted to silyl ether by treating with **112**. In other words, the fluorous-tag **112** acts as a silyl protecting group. During this process a strong Si-O bond is formed. It is known that Si-O ether bond is stable under most reaction conditions and this type of protection is widely used in organic synthesis[106].



Scheme 72

We have tried a sequence of conditions for the synthesis. (Table 8 on page 65). These typical reaction conditions are widely applied for the protection of alcohol and phenols with silyl ethers[106]. In this scheme, the nucleophile is the aroxide ion and is produced with the help of variety bases from mild inorganic bases (K_2CO_3 and NaH) to organic bases (imidazole, pyridine and Et_3N). Besides, the bromosilane **112** acts as the electrophile. It is known that bromide is a good leaving group and the Si-Br bond can be easily cleaved under nucleophilic conditions[141].

It is worthy of note that we tried a combination of solvents in each trial to conduct the reaction. Since **112** does not dissolve in variety of organic solvents, we have to choose the solvents in which it dissolves completely. At the same time, we have to consider the miscibility of these solvents in the aprotic solvents used for the substitution reaction. Accordingly, we found that hybrid solvent benzotrifluoride (BTF) was the best solvent for this purpose. Benzotrifluoride has good dissolving power for organic molecules as well as fluorous materials and favorable physical properties like other organic solvents. It has been reported that BTF can be a potentially valuable alternative solvent to CH_2Cl_2[163].

We found that the benzotrifluoride was completely miscible with the aprotic solvents (THF, DMF, pyridine and acetone) that were used in the experiments and dissolved **112** completely at room temperature as well. Since **112** exhibited moderate to good solubility in Et_2O and THF, we also used these solvents (Table 8) instead of BTF for three attempts. Moreover, we examined the reaction by adding additives such as DMAP, KI/18-crown-6 and AgOTf.

Nevertheless, none of these conditions resulted in the formation of the fluorous-labeled product **117** except the one trial utilizing a catalytic amount of AgOTf (Condition 8; Table 8). The NMR of the crude product mixture suggested that the coupling of **112** had occurred to some

extent. In this attempt, the attachment of **112** in BTF to **58** in THF was carried out by treating with Et_3N and catalytic amount of AgOTf at room temperature[116]. This was a modified version of the procedure by Curran[93] in which a coupling of a fluorous-tag to an alcohol was carried using Et_3N in THF.

We believed that the addition of AgOTf promoted the coupling by displacing the leaving group bromide with triflate ion. It is known that triflates would act as better leaving groups than bromides for this purpose[141]. Since the AgBr precipitates out from the solution, the formation of the perfluoroalkyl silyl triflate **118** would be favored (eq 19).

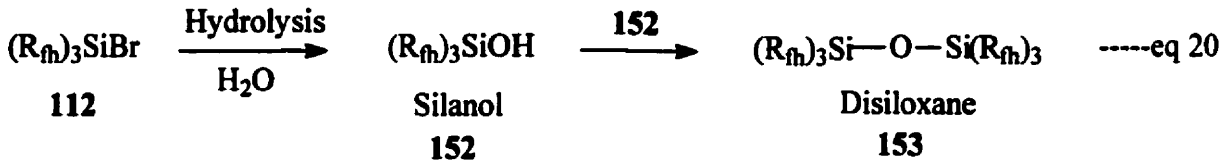
$$(R_{fh})_3SiBr + Ag^+ OTf^- \longrightarrow \underset{\mathbf{118}}{(R_{fh})_3SiOTf} + AgBr\downarrow \qquad \text{-----eq 19}$$

We thought that we had found the procedure to tag the fluorous compound with the auxiliary but could not reproduce the result under this condition. We next attempted the reaction with quantitative amount of AgOTf following a literature method[116], but it did not help either. Thus, we decided to prepare **118** first and try the reaction using the pre-formed triflate. Accordingly, we treated **112** with TfOH in situ[117] as shown in eq 6 (the same eq 6 on page 66).

$$\underset{\mathbf{112}}{(R_{fh})_3SiBr} \xrightarrow[0\,^{\circ}C]{TfOH} \underset{\mathbf{118}}{(R_{fh})_3SiOTf} \qquad \text{-----eq 6}$$

However, the fluorous-tagging method using **118** formed in situ did not seem to improve the process any further.

In almost all instances, we observed the hydrolysis of **112** and the recovery of the auxiliary **58**. The NMR analysis showed that the hydrolysis of **112** led to the formation of silanol **152** and the coupling of two **152** units formed the disiloxane **153** as in eq 20. It has been published that the hydrolysis of such halosilanes give silanol and upon treatment with acid, silanol produces disiloxanes[93,152]. The NMR data for the silanol **152** were in close agreement with those reported in the literature[93].



112 Silanol **152** Disiloxane **153**

Since **152** and **153** have very similar chemical shift values, it is difficult to differentiate them from each other. Hence, we assume that the hydrolyzed material may be the silanol or disiloxane or mixture of both.

During the course of searching for an alternative route to our goal, we were attracted by an approach of Curran et al.[91]. As depicted in Figure 28, they exploited the metal-halogen exchange (Lithium-bromine exchange) concept to link a fluorous-tag (R_3SiBr) to an organic compound.

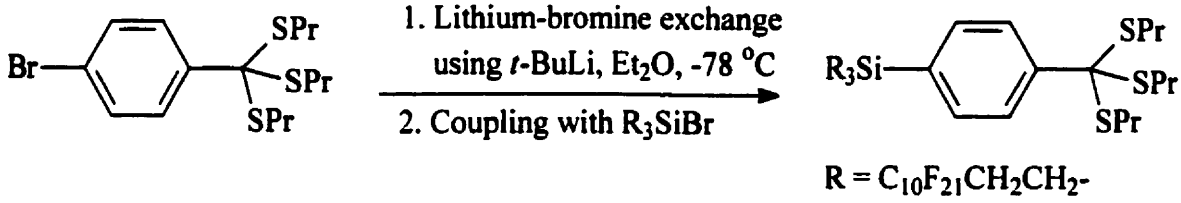
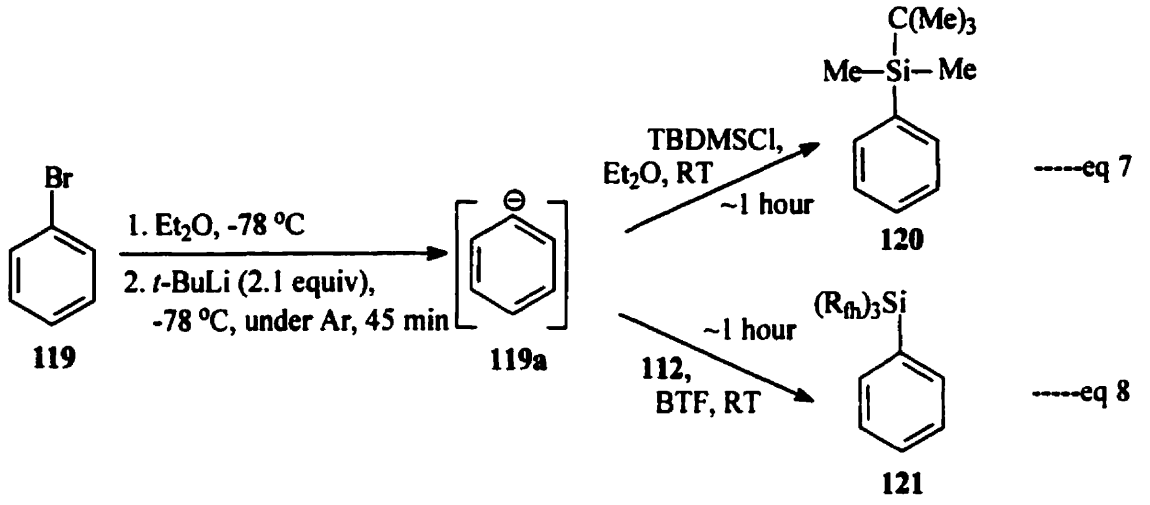


Figure 28

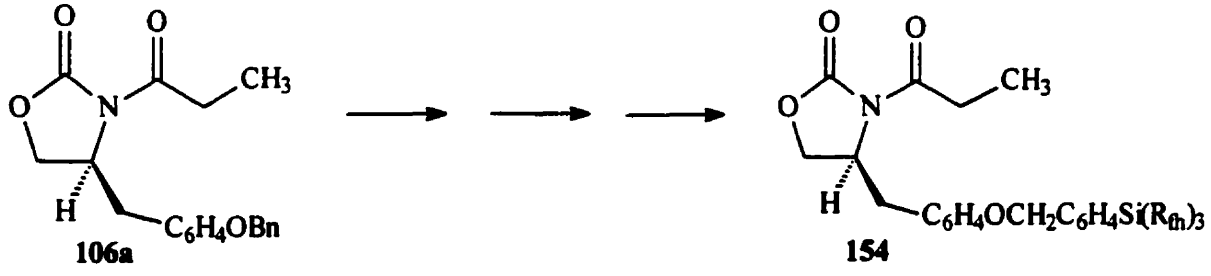
Convinced by their idea, we investigated the lithium-bromine exchange reaction using bromobenzene first (the same Scheme 45 on page 66). We treated the bromobenzene **119** with 2.1 equiv. of *t*-BuLi in Et_2O at –78 °C under Ar and after 45 min we transferred this aryl anion (**119a**) solution rapidly by a cannula into the solution of TBDMSCl in Et_2O at room temperature (eq 7). The NMR analysis of the product revealed the formation of the coupled adduct, *tert*-butyldimethylsilylbenzene **120**.

Similarly, we examined the same transformation with the fluorous-tag **112** in BTF under the above conditions (eq 8). As anticipated, the fluorous-labeled benzene adduct **121** was obtained in high yield. These results implied that the attachment of the fluorous compound to the auxiliary could possibly be achieved in a similar manner.



Scheme 45

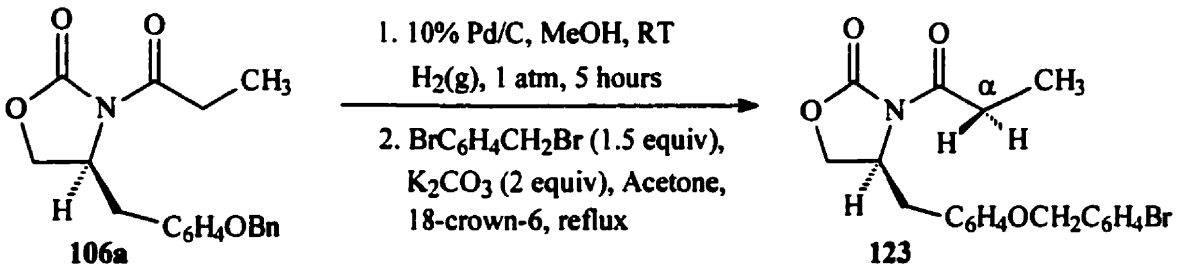
Encouraged by this finding we started to look into the possibilities of this approach on our chiral auxiliary system. We realized that attachment of an aryl halide (preferably aryl bromide) to our auxiliary was necessary in order to carry out the metal-halogen exchange process. Thus, we decided to modify the original structure of the oxazolidin-2-ones that we had had already in our hands. Accordingly, we planned the synthesis of **154** starting from **106a** first (Scheme 73).



Scheme 73

The initial step of the scheme involved the debenzylation[106] of oxazolidin-2-one **106a** by Pd/C (Scheme 74). The debenzylation yielded the free hydroxyl group for the attachment of the new group. Since the coupling reaction of Curran's and our test experiments worked well with aryl bromide system, we also wanted to attach an aryl bromide to our auxiliary. Subsequently,

we reacted the free hydroxyl group with the 4-bromobenzylbromide under given conditions and obtained the bromobenzylated compound **123** needed for the lithium-bromide exchange reaction and coupling process.



Scheme 74

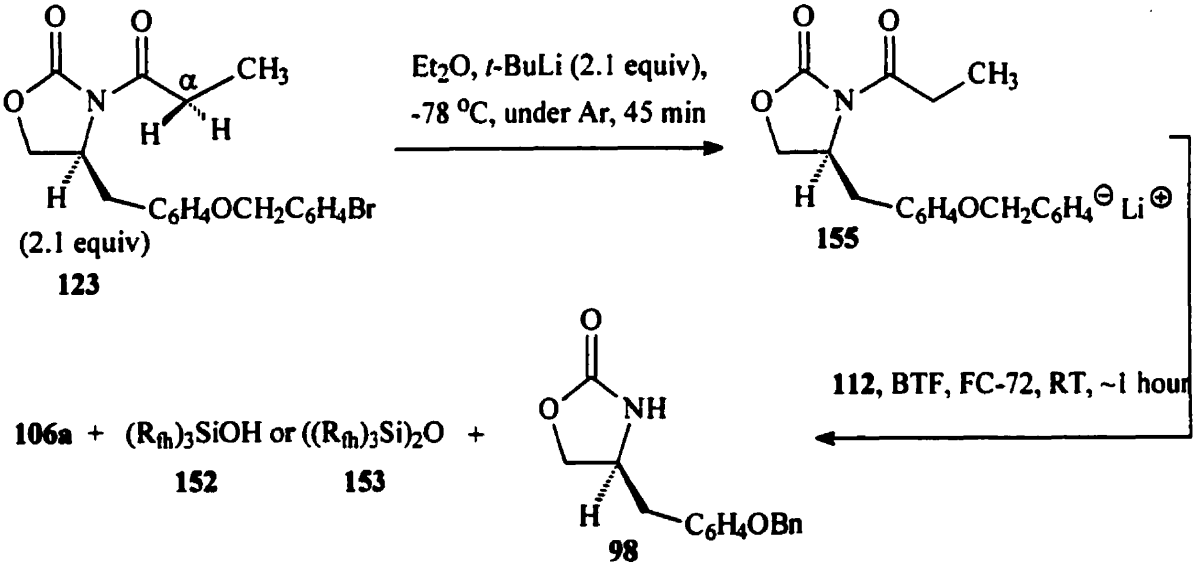
In fact, we knew that there was an active carbon center on the *N*-propionyl side chain (oxazolidinone **123** in Scheme 74). Usually, the transmetallation reaction uses a reactive organoalkyllithium such as *tert*-BuLi. Since *tert*-BuLi is a strong base, it might deprotonate the acidic hydrogen on the α-carbon of the acyl group. It is described in the literature that metal-halogen exchange reactions are rapid even at low temperatures[164,165]. However, we did not quite know at this point whether the lithium-bromide exchange or the deprotonation of the acidic α-hydrogen would occur first with **123**. We hoped that the transmetallation would be faster than deprotonation and decided to carry out the exchange reaction as illustrated in Scheme 75.

It must be noted that oxazolidinone **123** does not dissolve in Et_2O very well. Therefore, during the attempt, we sonicated the mixture until it dissolved almost completely. This was then treated with excess *tert*-BuLi (2.1 equiv.). It has been reported in the literature[164,166], the metal-halogen exchange between a primary alkyl bromide and *t*-BuLi most likely involves rapid, reversible attack of the *t*-BuLi on the bromine of the substrate. Many procedures recommend the use of excess organoalkyllithium to confirm the complete transformation of the aryl halide to aryl anion[91,164]. Thereupon, excess *t*-BuLi (2.1 equiv.) was used to ascertain the complete formation of the aryl lithium species.

The production of the aryl anion **155** was prominent because it formed a light yellow solution[91]. Cannulation of **155** into the solution of **112** in BTF/FC-72 was carried out at room

temperature. We used the BTF and FC-72 mixed solvent system in order to assure the solubility of **112** in the reaction medium. It is also significant to note that we were able to monitor the coupling process by thin layer chromatography.

After aqueous work-up and evaporation of the solvents (Et_2O, FC-72 and BTF) the crude products were extracted using three-phase separation technique. As described earlier, the phase separation at the purification step is the essential feature of this fluorous synthesis approach. Accordingly, the crude materials were partitioned into the organic (CH_2Cl_2), fluorous (FC-72) and aqueous layers. The NMR data of the crude product found in the CH_2Cl_2 layer revealed the presence of compound **106a** and **98** (Scheme 75). Similarly, the fluorous layer contained the silanol **152**/disiloxane **153** resulted from the hydrolysis of **112**. The aqueous layer extracted the inorganic lithium salts. None of the layers showed the expected fluorous-tagged product **154** (Scheme 73). The formation of **106a** and **98** will be explained after the next experiment.



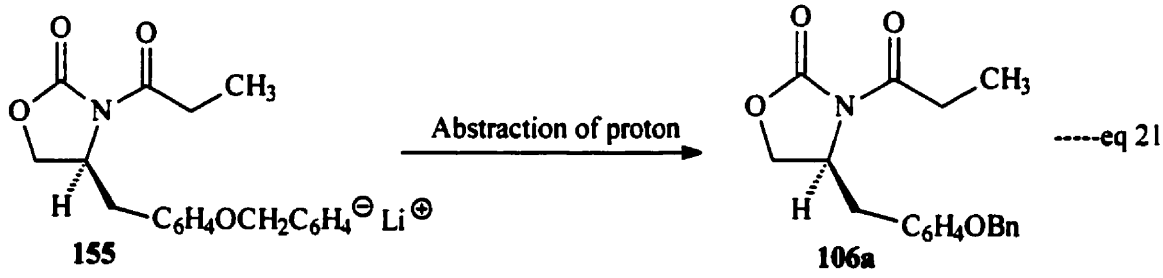
Scheme 75

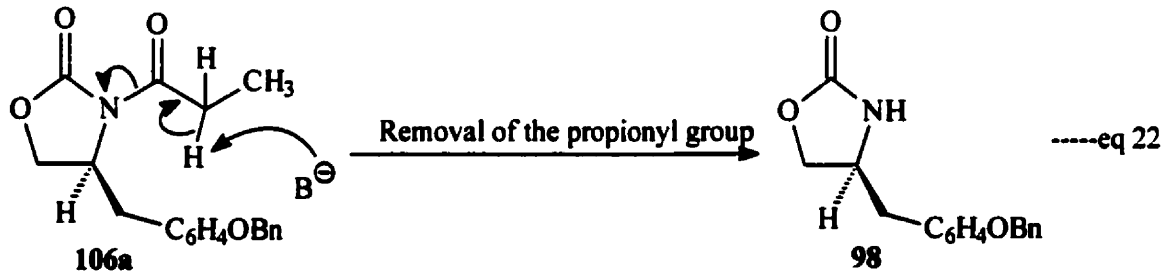
In order to eliminate the ambiguity regarding the solubility of **123** in Et_2O, we tested several other solvents (benzene, toluene, hexane, cyclohexane, and petroleum ether) that are suitable for this exchange process[164]. We found that **123** was not completely soluble in any of these solvents. However, it exhibited excellent solubility in THF and therefore, we decided to

conduct the metal-halogen exchange reaction in THF medium. Nonetheless, no significant change took place in the end and the reaction provided compounds **106a**, **98** and hydrolyzed products (**152** and **153**) as in the previous case.

It is important to note here that the use of THF solvent in these types of interchange reactions is not recommended in the literature[165,167]. A report by Negishi et al.[167] states that secondary and tertiary alkyllithiums do not give desired coupled products in THF. In another study[165] it is established that THF should not be used with *tert*-BuLi, since β-elimination and Wurtz-type coupling are the predominant modes of reaction of this base with primary halides in THF.

It became clear from the above two attempts that compound **123** would not be an appropriate substrate for transmetallation reactions because of it reactive propionyl side chain. The NMR studies showed that in both cases, the aryl anion **155** formation (eq 21) as well as the deprotonation of the α-hydrogen (eq 22) had occurred with *tert*-BuLi.

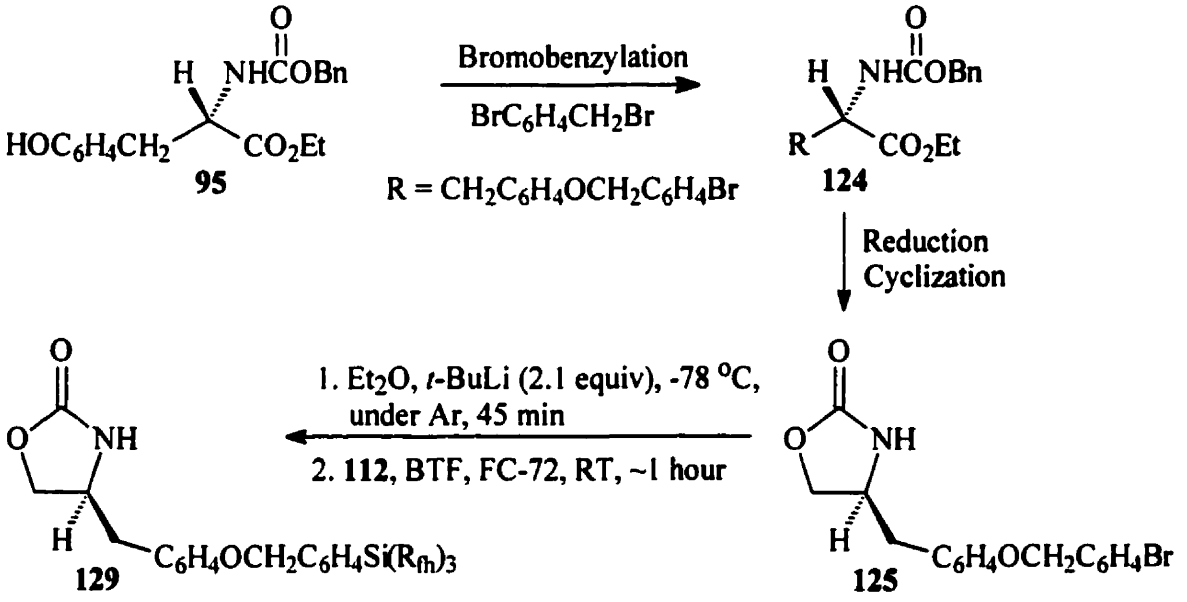




The formation of compound **106a** implies that actually the *tert*-BuLi reacts with the aryl bromide and produces the aryl anion **155**. The reduction of **155** gives **106a** as shown in eq 21. On the other hand, the presence of compound **98** indicates that the removal of the propionyl group occurs via a suggested mechanism indicated by eq 22. The abstraction of the acidic α-

hydrogen by *t*-BuLi leads to the ketene-type elimination of the propionyl group. We did not know which process occurred first. Nevertheless, we did not want to pursue this either, because we learned that compounds such as **123** are not good candidates for these types of conversions.

In another approach, we used oxazolidinone **125** for the metal-halogen exchange process. Compound **125** was prepared from ester **95** according to our novel method (Scheme 76). We noticed that the synthesis was fast and provided **125** in high yield. We then performed the exchange reaction with **125** under similar conditions used in Scheme 75.

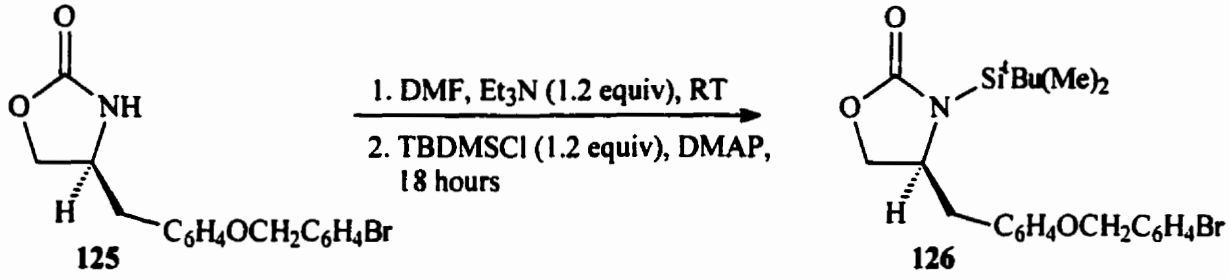


Scheme 76

The NMR studies on the isolated products confirmed only the presence of silanol or disiloxane and the starting material **125**. It proved that lithium-bromine exchange reaction had not occurred at all. The oxazolidin-2-one **125** was recovered unchanged. These results suggested that the *tert*-BuLi might be engaged in a side reaction probably in the deprotonation of the acidic proton on the free secondary amide (N-H) of **125**. In the *N*-acylation of oxazolidinones, *n*-BuLi is exploited to deprotonate the amide N-H proton and a similar logic may be true in this instance too.

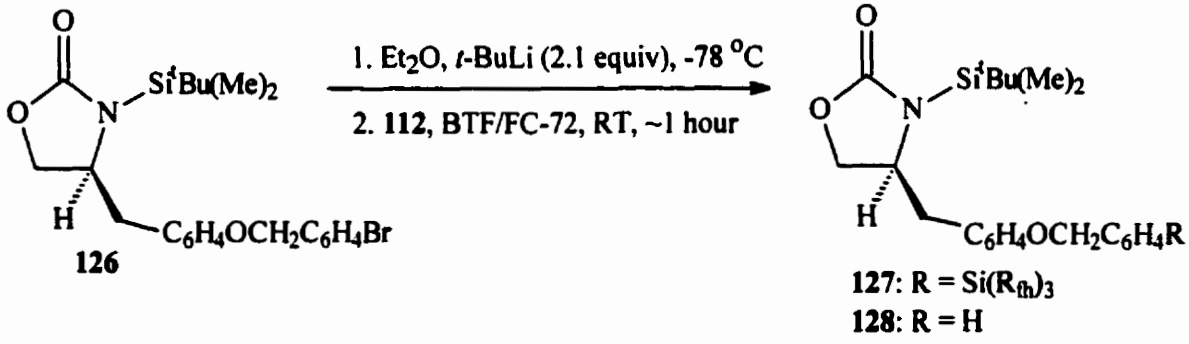
It became obvious then that the protection of the secondary amide on **125** is very important and the protecting group should be stable under most conditions and easily cleaved

whenever it is required. We accomplished the protection of **125** using *t*-butyldimethylsilyl chloride as given in Scheme 77[118]. Though it has been mainly used for protection of alcohols, there have been instances where it protects the amide N-H groups[118,168]. Reasons for selecting this group include ease of transformation, stability to most conditions and selective removal under mildly acidic or nonacidic conditions.



Scheme 77

We next performed the lithium-bromine interchange and the coupling reaction on **126** as portrayed in Scheme 78.



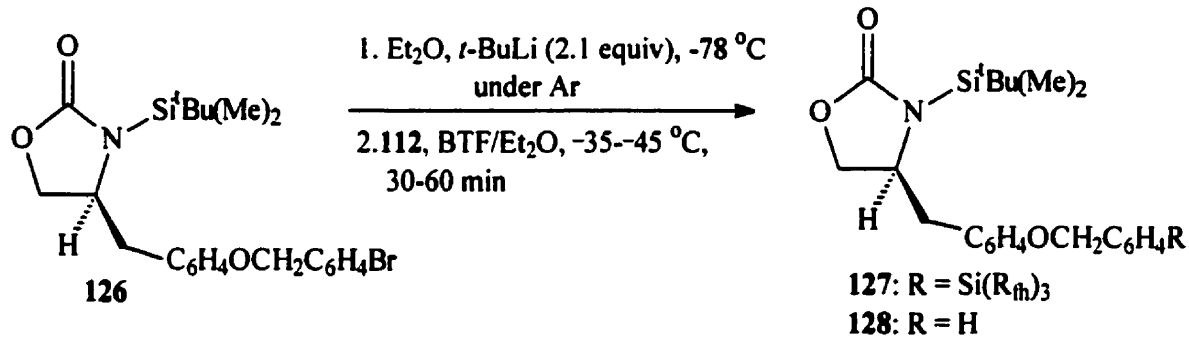
Scheme 78

Compound **126** dissolved in Et_2O moderately. Addition of more solvent and sonication helped to some extent. It was found that **126** dissolves completely in THF, however, THF is not suitable for this purpose. Besides, **126** is not soluble in other less polar solvents such as hexane, cyclohexane, petroleum ether and benzene. Nevertheless, we decided to perform the reaction in

Et_2O, because we did not have much choice of solvents.

The NMR identified the hydrolyzed materials of **112** and the reduced oxazolidinone **128**. No other by-products were detected. This implied that *t*-BuLi only participated in the interchange of bromine with lithium metal. Hence, the TBDMS-protection prevented the side reaction that had occurred at the nitrogen center in the previous case. Finally, we succeeded in generating the aryl anion by the metal-halogen exchange method. However, the coupling of the fluorous tag **112** was not yet successful.

We next attempted the metal-halogen interchange and coupling reaction under modified conditions (Scheme 79). This time we dissolved the bromosilane **112** in BTF/Et_2O mixed solvent and kept the solution at -35 to -45 °C. As we could not lower the temperature below that because the BTF solvent freezes at -29 °C, a mixture of BTF/Et_2O solvent was used, which maintains a liquid state at -35 to -45 °C.



Scheme 79

We treated the auxiliary **126** in Et_2O with 2.1 equiv. of *tert*-BuLi and added the precooled mixture of **112** immediately after the addition of *tert*-BuLi. We monitored the reaction by TLC and it showed a new high running spot. After stirring for 30-60 min, we quenched the reaction with H_2O. The final products were then extracted using three-phase (CH_2Cl_2, FC-72 and H_2O) separation technique.

As anticipated, the NMR of the crude materials showed that the coupling reaction had at last taken place. This validates the concept that the exchange process between the bromine and

the lithium is very fast and there is no need to stir the solution containing aryl lithium species for 45 min. Furthermore, the aryl anion has to be reacted with the fluorous material as soon as it is formed. This leads to the complete generation of the coupled product **127** (Scheme 79). This implies that conducting the metal-halogen exchange reaction at low temperature and for short periods of time avoids or at least minimizes interfering side reactions.

However, when we attempted the three-phase separation to isolate the fluorous-tagged product **127**, the phase separation was not as efficient as we expected. The NMR analysis indicated that the coupled product was present in the CH_2Cl_2 layer as well as in the FC-72 layer.

As we described at the beginning, a sufficient number of fluorine atoms are required in order to render an organic molecule completely fluorous and thereby making the extraction process efficient. Besides, the solubility of a fluorous compound in organic solvents increases with the number of solvophilic hydrocarbon portion. During the fluorous-tagging process, we are actually adding an organic molecule (molecular weight ~477) which shows high solubility in normal organic solvents to the perfluorous chain. Therefore, it is quite possible that this fluorous-labeled adduct **127** dissolves at least in limited organic solvents.

One example where the inefficient phase separation exists is the preparation of fluorous-labeled isoxazolines by cycloaddition of fluorous-tagged dipolarophiles to nitrile oxides[93] (Figure 29).

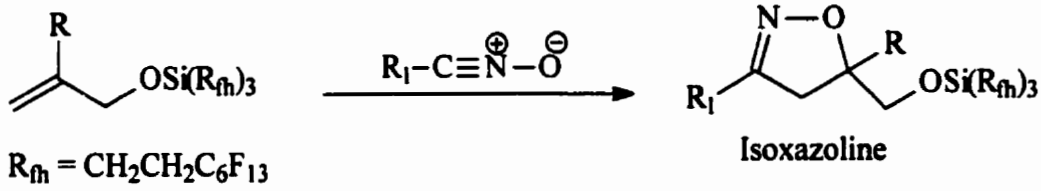
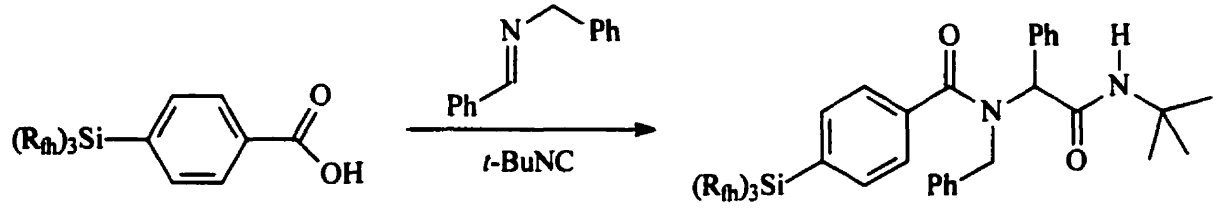


Figure 29

It was reported that in the extraction step, around 5% of the fluorous isoxazoline remained in the CH_2Cl_2 organic phase even after threefold extraction with FC-72.

Another example[91] is the multicomponent reaction (Ugi and Biginelli condensation) that uses highly fluorinated substances and is illustrated in Figure 30. This shows that the inefficient

phase extraction occurs due to the lower number of fluorine atoms in the fluorous chain of compound **157**-F_{39}. In the Ugi condensation using fluorous material **156** (contains 63 F atoms), it was found that more than 10% of the final fluorous product **157** remained in the CH_2Cl_2 layer even after multiple extractions with FC-72. However, the fluorous material **157** was not detected in other solvents (benzene and MeOH) that were used in the extraction step.



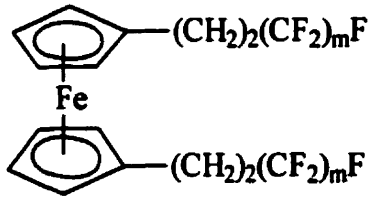
156: (R_{fh} = $C_{10}F_{21}CH_2CH_2$-)
156-F_{39}: (R_{fh} = $C_6F_{13}CH_2CH_2$-)

157
157-F_{39}

Figure 30

When using the **156**-F_{39} (lower homolog of **156**, only 39 F atoms), it was observed that 11%, 9% and 8% of the fluorous product **157**-F_{39} stayed in the benzene, MeOH and CH_2Cl_2 respectively. Here, **157**-F_{39} acted as an organic compound rather than a fluorous compound. The above experiments clearly explain that long perfluorinated chains or high number of F atoms are required to render an organic molecule completely fluorous. In other words, when there is enough hydrocarbon character present in a highly fluorinated molecule, it behaves like an organic as well as a fluorous molecule.

It has been emphasized that the number of the fluorine atoms is a crucial factor in a fluorous synthesis[95,97]. An interesting study by Hughes[97] explains that the solubilities of fluorous-tagged ferrocene organometallics in different solvents strongly depend on the length of the fluorous tail/the number of fluorine atoms.



158: m = 6
159: m = 8
160: m = 10

Figure 31

In this example, we shall consider the solubilities of **158**, **159** and **160** in various solvents at room temperature only (Figure 31). According to their experiment, ferrocene **158** dissolved readily in common nonpolar organic solvents. It was also slightly soluble in acetonitrile, MeOH and EtOH at room temperature. The complex **159** was less soluble than **158**, but it still dissolved in common organic solvents other than acetonitrile and alcohols. In contrast, the ferrocene **160** dissolved easily in Et_2O, moderately in hexanes, and sparingly in $CHCl_3$, acetone and toluene at room temperature. It was completely insoluble in alcohols and other polar solvents. However, all three complexes were readily soluble in perfluoroheptane and PFMC. It becomes clear that each additional C_2F_4 segment in the chain results in a significant decrease in the organic solubility.

Since we have attached the oxazolidinone **126** to the fluorous chain **112**, the fluorous nature of the tag would be weaker. However, we could overcome this issue by utilizing a longer fluorous chain instead. Nonetheless, there is also a disadvantage in employing a longer fluorous tail. In this regard, fluorous compounds bearing longer perfluoro chains cannot be purified by chromatography[97]. One reason is that low solubilities in common organic solvents limit the chromatography techniques. The other reason is that due to the low solubility and longer chain, it causes extensive tailing in chromatography purification[97]. For the chromatographic separation, shorter fluorous chains are convenient and preferred.

Chromatographic separation is necessary even in fluorous phase synthesis. In cases where the fluorous layer contains the desired fluorous-labeled products as well as fluorous impurities such as remnants of fluorous chains or unreacted fluorous materials, a good method to isolate the desired product is, by chromatography[95].

We also faced exactly the same situation in the present case. As indicated earlier, the FC-72 layer contained the coupled product **127** and the fluorous impurities (silanol/disiloxane). Similarly, the coupled product **127** and the reduced material **128** were found in the CH_2Cl_2 layer. In order to separate the desired coupled product from each of these layers, we used flash column chromatography. We were able to perform the chromatography separation easily and efficiently. We think that perhaps the less fluorous or slightly organic nature of **127** facilitates the purification by chromatography. This in turn can be connected to the fact that **127** has lower number of fluorine atoms or a shorter fluorous tail in its structure. Nevertheless, we needed to combine the phase-separation and the chromatography techniques to obtain the total fluorous-

labeled product. Since the total yield from this attempt was very low (41%), we also needed to improve the conditions further. In the next attempt, we tried the reaction again using FC-72 and Et_2O mixed solvent to dissolve **112**, but it also produced the same results.

At this point, it occurred to us that the reduced solubility of **126** in Et_2O could have been a reason for the poor yields. We knew that **126** dissolves completely only in THF. As discussed earlier, THF is not a suitable solvent for the metal-halogen exchange processes mediated by *t*-BuLi. However, THF is also known to promote Wurtz-type cross coupling reactions[165,167]. Since we also performed the Wurtz-type cross coupling between aryl lithium and bromosilane, we thought that the presence of THF might induce the cross coupling process.

Furthermore, we knew that Et_2O is compatible with *t*-BuLi and it is essential to conduct the bromine-lithium interchange process. Besides, Et_2O functions as a scavenger for the excess *t*-BuLi too[169]. Usually, the excess *t*-BuLi is destroyed by abstracting protons from Et_2O upon warming the organolithium mixture to room temperature. Consequently, we decided to use a combination of both THF and Et_2O solvents.

Accordingly, we dissolved the starting material **126** in a minimum amount of THF and added an excess amount of Et_2O to dilute the solution. We then carried out the coupling reaction using this substrate solution. We treated this solution with *t*-BuLi at –78 °C and immediately after the addition of *t*-BuLi, we introduced the precooled solution of **112** in BTF/Et_2O into the aryl anion mixture. After stirring for 10 min, we performed the aqueous work-up and extracted the final products using the three-phase separation technique.

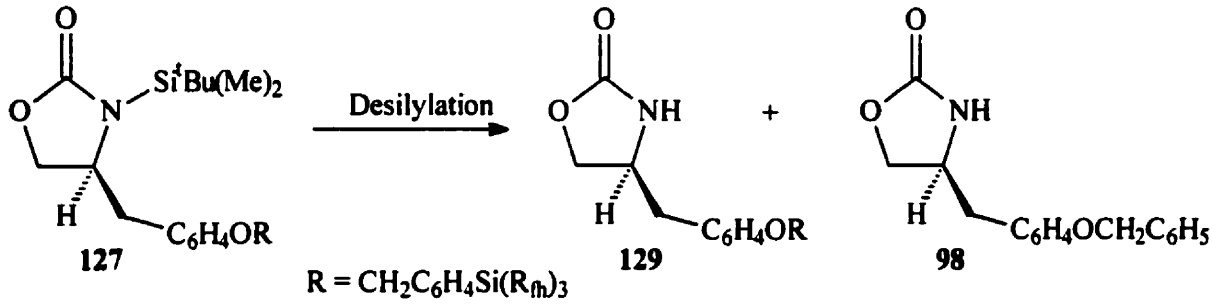
It must be noted here that more fluorous product **127** partitioned into the FC-72 layer during the extraction. However, we needed to use flash chromatography to isolate the desired product **127** from other impurities. In this attempt, the reaction proceeded smoothly and the product yield went up to 68%. We were pleased to note that the attachment of the fluorous tag **112** to oxazolidinone **126** had finally occurred using this modified strategy.

Having accomplished the synthesis of the fluorous-labeled oxazolidin-2-one, we decided to explore the synthetic utility of this new system. The next objective was then to prepare the *N*-acylated derivative of **127**. Since we had the nitrogen protected by a TBDMS group, we attempted the deprotection of the silyl group first (the same Scheme 50 on page 71).

Since the desilylation failed using 1N HCl in MeOH at room temperature[118], we tried it

with 9:1 TFA/H_2O at room temperature[119]. Though we observed the desilylated product **129**, we did not pursue this procedure because it was sluggish and gave a very poor yield. Presumably, this was due to the poor miscibility between the CH_2Cl_2 containing **127** and the aqueous desilylating reagents. In this respect, we found an alternative reagent, TBAF in THF[120], which is completely miscible in CH_2Cl_2.

We performed the deprotection using TBAF in THF at room temperature for 30 min according to a procedure of Curran[91].

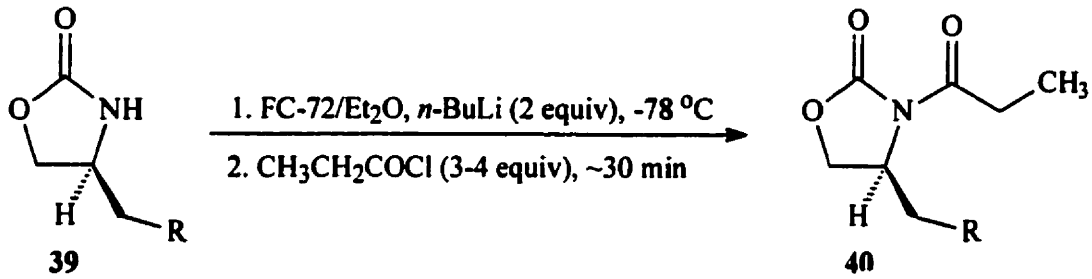


Scheme 50

The investigation of the reaction by TLC showed the appearance of two new spots in the end of the process. Analysis of the crude products by NMR clarified that the removal of the both N-Si and C-Si silyl groups from molecule **127** had led to the oxazolidin-2-one **98**. This proves that TBAF can cleave C-Si bonds as effectively as N-Si or O-Si bonds.

We repeated the procedure again, but this time we monitored the process carefully by TLC. The cleavage of N-Si bond was deemed complete within 5-7 min by TLC. The NMR of the corresponding product proved that only the TBDMS protecting group had been cleaved and the aryl carbon-silicon bond left untouched. These results suffice to conclude that TBAF cleaves the N-Si bond first and allowing it to react longer leads to the cleavage of the C-Si bond as well. Furthermore, we also succeeded in obtaining excellent yields by simply switching the solvents to BTF/CH_2Cl_2. Since the fluorous molecule dissolves in BTF very well and BTF and CH_2Cl_2 are highly miscible, a homogeneous condition is formed to promote the process. The phase-separation technique worked as before and the final desilylated material was purified from CH_2Cl_2 and FC-72 layers by chromatography.

The next step in the synthesis was the preparation of an *N*-propionated derivative and we chose to carry out the propionylation according to the original protocol of Evans[110]. Since the fluorous materials exhibited some solubility in organic solvents, we tried the propionylation in THF first. However, we immediately noticed that the solubility of **129** in THF was poor and the reaction conducted in THF produced no results.



39 **40**

R = $C_6H_4OCH_2C_6H_4Si(R_{fh})_3$

Scheme 51

The other option was now to dissolve the fluorous compound in a perfluorinated solvent, FC-72. However, in order to maintain a homogeneous reaction condition, we needed to use another organic solvent that was miscible in FC-72 at low temperatures. We preferred etherate solvents in light of the use of strong base in the reaction. Accordingly, we thought that FC-72 and THF would be perfect for this purpose. Unfortunately, these two solvents do not mix even at room temperature. In a recent publication[170], Curran and co-workers have demonstrated the use of biphasic nature of the THF and FC-72 in catalytic enatioselective protonation reactions at and below room temperature. Therefore, THF cannot be used with FC-72 for our purpose.

Finally, we were able to perform the *N*-propionylation of **129** using FC-72 and Et_2O mixed solvent (the same Scheme 51 on page 72). Though it appeared miscible at room temperature or even at low temperature, it formed some cloudiness at –78 °C. Therefore, it was necessary to stir the reaction mixture well to mix the reagents during the process. Moreover, the propionylation reaction required 2 equiv. of *n*-BuLi and 3-4 equiv. of propionyl chloride in order to go to completion.

Nevertheless, we obtained the *N*-propionated fluorous-labeled oxazolidinone **130** in excellent yield after the work-up and purification procedures. We employed the same three-phase separation (FC-72, CH_2Cl_2, and H_2O) to isolate the final products and remove the excess reagents. Although the separation of the fluorous products into FC-72 was not extremely efficient, we were able to extract a good amount of the fluorous products into fluorous layer. The rest of the products extracted into the CH_2Cl_2 layer were easily purified by chromatography. Thus, the *N*-propionated oxazolidinone **130** could be synthesized by following this methodology.

5. Asymmetric aldol reaction of a fluorous-tagged chiral oxazolidin-2-one

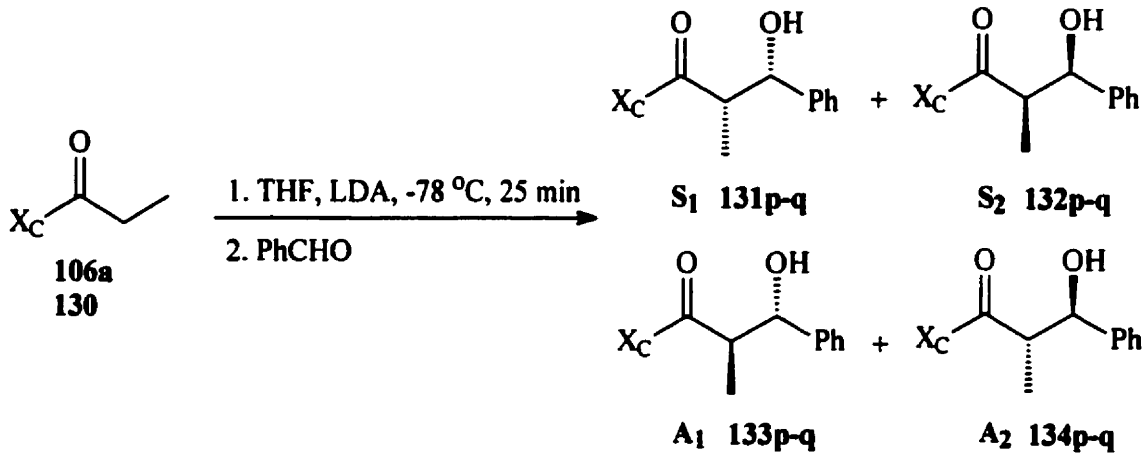
The main purpose of this study was to demonstrate the potential of the novel fluorous-labeled auxiliary in asymmetric synthesis. As described at the beginning, Evans type chiral oxazolidinones are successfully used in asymmetric aldol synthesis[25]. Hitherto, excellent stereoselectivities have been obtained with various metal enolates of such auxiliaries from these reactions. Consequently, we opted to carry out the aldol condensation on fluorous-tagged oxazolidin-2-one **130**. For comparison, we performed the aldol reaction on the unsupported oxazolidin-2-one **106a** as well.

Accordingly, Li-mediated aldol reaction of **106a** with LDA (1.2 equiv.) and benzaldehyde (PhCHO, 1.2 quiv) was conducted following a procedure of Heathcock[121]. The reaction produced a pair of syn stereoisomers (**131p** (S_1); **132p** (S_2)) and a pair of anti stereoisomers (**133p** (A_1); **134p** (A_2)) as reported in the literature[8,33] (Scheme 80). The total yield of those adducts ($S_1 + S_2 + A_1 + A_2$) was found to be 60%.

Similarly, the aldol condesation of **130** was attempted in FC-72/Et_2O mixed solvent that was used in the *N*-propionylation. However, as we observed in *N*-propionylation, the solution turned cloudy at –78 °C and thus, the aldol reaction could not be achieved. Though the FC-72 exhibits good solubility/miscibility in Et_2O at room temperature or even at slightly lower temperatures, it also has the tendency to form two layers upon cooling[85].

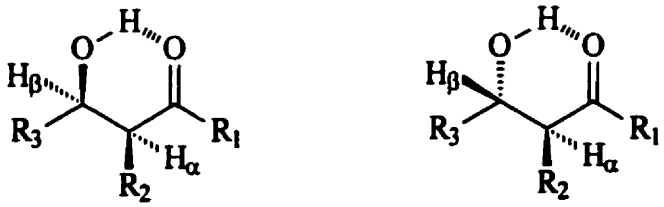
Therefore, we tested a series of solvents and found that THF dissolves the fluorous compound **130** completely. We were pleased to discover that the Li mediated aldol reaction of **130** in THF had actually taken place. Though we still observed some cloudiness at –78 °C, the

reaction proceeded with the addition of excess reagents (used 5 equiv. of LDA and PhCHO). The reaction provided a pair of syn stereoisomers (**131q** (S_1); **132q** (S_2)) and a pair of anti stereoisomers (**133q** (A_1); **134q** (A_2)) as obtained for compound **106a** (Scheme 80). The total yield of the four stereoisomers ($S_1 + S_2 + A_1 + A_2$) was 54%.



Scheme 80

The relative stereochemistries (syn or anti) of the four aldol adducts were assigned by the use of ^{1}H NMR spectroscopy and HPLC analysis. For convenience, we consider the assignment of the diastereoisomers **131p**, **132p**, **133p**, and **134p** (obtained from the unsupported auxiliary (**106a**)) first.



syn $J_{\alpha\beta}$ = 2-6 Hz anti $J_{\alpha\beta}$ = 7-10 Hz

Figure 32

In many instances, the stereostructural assignments may be made from the magnitude of the vicinal coupling constant $J_{\alpha\beta}$[171]. This is possible when there is a hydrogen at both the α and

β carbons relative to the carbonyl group and if both stereoisomeric aldols exist in an intramolecular hydrogen-bonded conformation as pictured in figure 32.

In such cases, the vicinal coupling constant $J_{\alpha\beta}$ is less for the syn isomer (2-6 Hz) than for the anti isomer (7-10 Hz)[171]. This trend can be well understood by considering the three-staggered rotamers of syn and anti β-hydroxy ketones, illustrated in Figure 33.

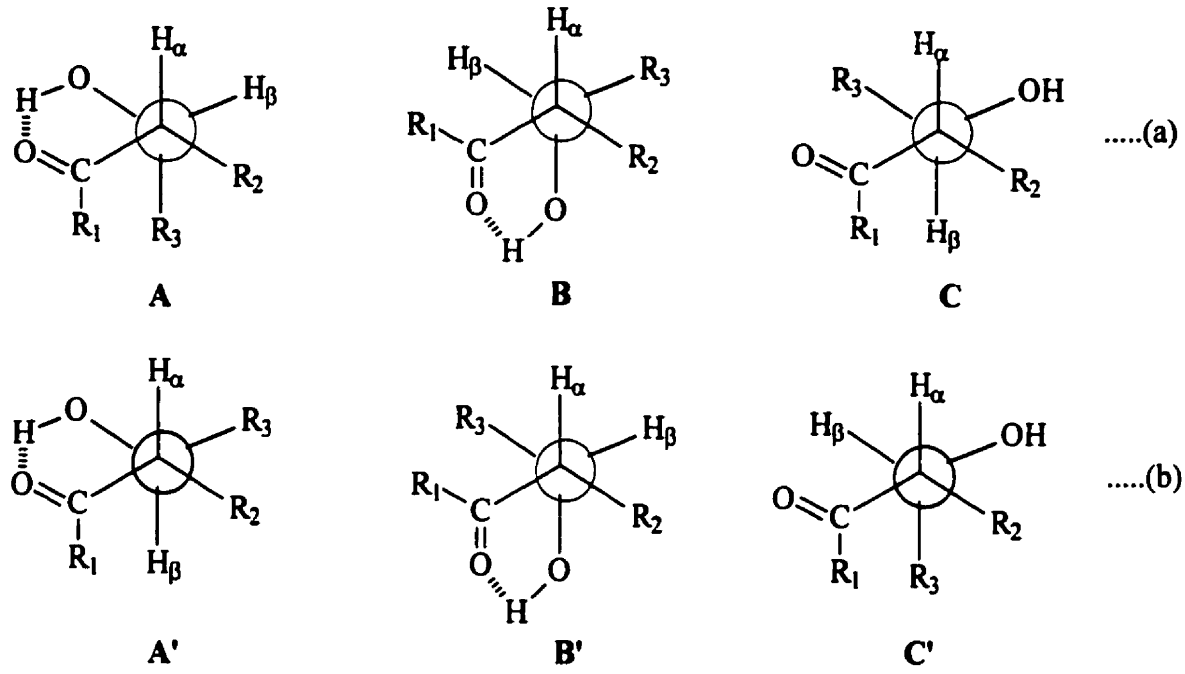


Figure 33 Conformations of (a) syn β-hydroxy ketone and (b) anti β-hydroxy ketone.

For the syn isomer (a), conformers **A** and **B** are hydrogen-bonded structures and they experience a gauche interaction between H_α and H_β hydrogens. Thus, their coupling constants $J_{\alpha\beta}$ are expected to be small. On the other hand, the anti isomer also has two hydrogen-bonded conformers. However, one of the comformers (**B'**) has H_α and H_β in a gauche relationship and the other isomer (**A'**) has them in an anti manner. Therefore, for the anti isomer, the coupling constant is a weighted average of a small (from conformer **B'**) and a large (from conformer **A'**) coupling constant.

Nevertheless, the actual conformer population depends strongly on the nature of R_1, R_2, and R_3. As the size of either R_2 or R_3 increases, the R_2-R_3 gauche interaction becomes important.

As a consequence, conformations **C** and **B'** become more important for syn and anti isomers respectively. However, in our case, we had a methyl group for R_2, a phenyl for R_3 and the chiral auxiliary for R_1 in the aldol structure, therefore, the determination of relative configuration (syn or anti) was possible.

Interestingly, the ^{1}H NMR of the crude mixture obtained from the aldol reaction of **106a** with PhCHO showed the major three isomers (Scheme 80) clearly. The fourth one was present in minor amount and we were able to see the doublet of its methyl group (d, C*H*$_3$CH-) on the spectrum. However, the signal for the vicinal hydrogens was not clear. We presumed that it would be the anti A_2 isomer, since previous results found in the literature proved that the A_2 isomer was the minor product in the Li-mediated aldol reactions of similar systems[8,33]. Nevertheless, later in the stereochemical studies, when we purified the crude mixture by flash chromatography, we were able to isolate this isomer and obtain the coupling constant for it.

Since all four quantities are significantly different, the assignment of stereochemistry is straightforward and conclusive. The chemical shifts and the coupling constants $J_{\alpha\beta}$ for the vicinal hydrogen (C*H*OH) of those four products are presented in Table 11.

Table 11. Stereochemical assignments for the aldol adducts of 106a

	131p	**132p**	**133p**	**134p**
Chemical Shift (C*H*OH) δ ppm	5.09	5.17	4.83	3.94
Coupling constant ($J_{\alpha\beta}$) Hz	6.7	4.2	7.5	11.5
Stereochemistry (syn/anti)	S_1	S_2	A_1	A_2
Retention time t_R (min)	32.8	24.9	27.6	31.7
Diastereomer ratio	5.4	20.4	45.3	3.9

According to above stereostructural assignments, an isomer, which has a coupling constant value between 2-6 Hz, is a syn isomer and which has a coupling constant between 7-10 Hz is an anti isomer. Therefore, we assigned that the aldol adducts having $J_{\alpha\beta}$ values 4.2 and 6.7 Hz were the syn isomers and the aldol adducts having $J_{\alpha\beta}$ values 7.5 and 11.5 Hz were the anti isomers.

We compared these coupling constant values with the literature values[33] obtained for Li-

mediated aldol reaction with benzaldehyde. According to reported results, the diastereomers assigned as S_1, S_2, and A_1 have the coupling constants $J_{\alpha\beta}$ 4.7, 3.9, 7.9 Hz respectively. The A_2 isomer was not listed, since it was not found in measurable amounts. By comparison, we determined the stereochemistries of our four isomers as given in Table 11.

We also carried out the HPLC analysis to further support our results. The analysis furnished us with the retention times and the diastereomer ratios for the four isomers. The values are listed in Table 11. It is significant that the HPLC analysis separated all four isomers distinctively. The diastereomer ratios corresponded with the literature values[33] which were shown to be S_1:S_2:A_1:A_2 = 7.6:31.7:58.8:1.8. HPLC also indicated that the major adduct was the A_1 and the second and third in the amount were S_2 and S_1 respectively. It is noteworthy that even the minor A_2 adduct was well separated and prominent on the HPLC chromatogram.

We further confirmed this by running authentic samples of the each isomer. As we mentioned earlier, we performed the flash column chromatography on the crude material using 2:1 hexane:ethyl acetate solvent system. Since we were able to see two major and one minor product spots along with other spots (baseline material and some unreacted starting material) on TLC, we thought to carry out the separation by chromatography.

We were able to isolate some of the major anti A_1 isomer and the minor anti A_2 isomer separately for the analysis. Unfortunately, we could not separate the syn materials S_1 and S_2 since they move in close proximity on the column. However, we ran these individual A_1, A_2 and the mixture of syn adducts again through HPLC and obtained the retention time for each of them. We were pleased to note that the retention times observed for these separated isomers matched with the previous values within experimental error. In addition, the NMR data obtained for the isolated A_1, A_2 and the mixture of S_1+S_2 also proved that the stereochemical assignments that we made so far were absolutely correct.

In direct analogy to above route, we examined the relative configuration of the stereoiosomers **131q**, **132q**, **133q**, and **134q** (obtained from auxiliary **130**) as well. The NMR of the crude material indicated the presence of three isomers. Unlike in the earlier case, the minor isomer (probably the anti A_2) was not visible on the spectrum. It is possible that it had been hidden within the peaks of other isomers. However, we observed the chemical shifts and coupling constants $J_{\alpha\beta}$ for the vicinal hydrogen (C*H*OH) that are tabulated in Table 12.

Table 12. Stereochemical assignments for the aldol adducts of 130

	131q	132q	133q	134q
Chemical Shift (C*H*OH) δ ppm	5.09	5.17	4.82	Not
Coupling constant ($J_{\alpha\beta}$) Hz	4.1	4.2	7.0	observed
Stereochemistry (syn/anti)	S_1	S_2	A_1	A_2
Retention time t_R (min)	22.9	20.5	11.9	11.1
Diastereomer ratio	20.3	27.6	34.4	1.6

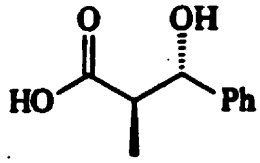
According to the syn/anti assignment, the two isomers having coupling constants 4.1 and 4.2 Hz were assigned as the syn isomers. The other isomer with the $J_{\alpha\beta}$ value 7.0 Hz was an anti adduct. The fourth adduct, presumably the anti isomer A_2 was not observed. Since we could not see the fourth adduct on the NMR, we decided to examine the crude material by HPLC. Interestingly, the HPLC analysis revealed all four isomers, especially the missing second anti isomer. We then compared these coupling constants with the reported values as well as with our assignments shown in Table 11 and finally, made the definite assignments for all the stereoisomers (Table 12).

The HPLC analysis also provided the retention times and the diastereomer ratios as listed in Table 12. It was apparent that the major adduct was the anti isomer A_1 and the second major isomer was the syn adduct S_2. It is significant to note that the amount of syn isomer S_1 increased noticeably compared to the previous case. In order to prove our assignments right, we decided to perform the HPLC analysis using authentic samples of the isomers.

Since the aldol products were separated well on TLC, we conducted the isolation of the isomers by chromatography. From this we obtained some of the major isomer A_1 and the two fractions for the mixture of the syn ($S_1 + S_2$) products separately for the analysis. By running the HPLC on these isolated samples, we obtained the same retention times (within the experimental error) listed in Table 12 for the isolated products which corroborated the assignment. Besides, the NMR data of the isolated product A_1 and $S_1 + S_2$ mixture also supported the syn/anti correlation.

Finally, in order to validate the absolute configuration of the major anti A_1 isomer, we

hydrolyzed the anti isomers 133p and 133q by reacting with H_2O_2/LiOH, in THF/H_2O at 0-25 °C according to a literature procedure[10]. The hydrolysis provided the carboxylic acid 135 and the optical rotation of the acid was determined. It is of note that we also recovered the corresponding chiral auxiliaries from the hydrolysis without any damage. The optical rotations of the acid listed below compared favorably with the literature value[122] at higher concentration $[\alpha]_D^{25}$ –17.5° (c 2.3, $CHCl_3$).



135

A_1		$[\alpha]_D^{25}$
133p	Acid 135	–17.1° (c 0.45, $CHCl_3$)
133q	Acid 135	–20° (c 0.02, $CHCl_3$)

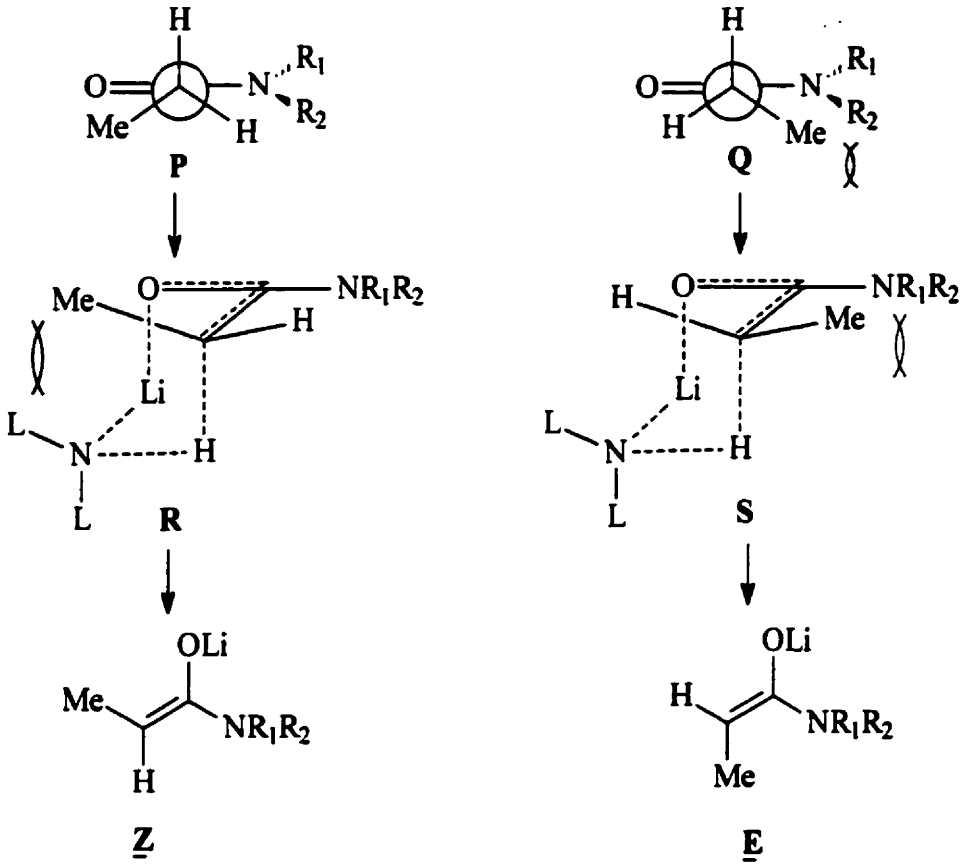
The correlation of the NMR spectra and the optical rotation with the published results[122] established that the acid 135 had the 2R,3S configuration.

Though we succeeded in utilizing fluorous-labeled oxazolidin-2-one for the asymmetric aldol synthesis, we noticed that the fluorous-tagged propionimide 130 and the four aldol adducts (131-134q) behaved more like the non-fluorous organic compounds. During the extraction, we used CH_2Cl_2 mostly. We were able to perform the column chromatography and HPLC analysis on those fluorous molecules without any difficulty because of their organic nature. Nevertheless, the results obtained for the fluorous-auxiliary were in accord with the results of the unsupported auxiliary. However, the syn vs anti selectivity was very poor in both cases as reported in the literature[33].

It is well accepted that Li-mediated aldol condensations exhibit low levels of stereoselection[35,171]. The stereochemical outcome of such reactions is governed mainly by three factors[122]: (1) the configuration of the enolate (*E* or *Z*); (2) which of the enolate diastereotopic faces reacts; (3) which of the aldehyde enantiotopic faces reacts. The configuration of the enolate can be established prior to addition of the aldehyde and is independent of the other two factors.

The factors 2 and 3 are usually dependent on each other and show coupled effects.

It is reported[35] that the amides and imides undergo highly stereoselective enolization with lithium amide bases (LDA, –78 °C, THF, kinetic enolization) to form the *Z*-enolates. Evans et al.[35] postulates that the high *Z*-stereoselection observed in these cases is a consequence of ground state allylic strain considerations (Scheme 81).

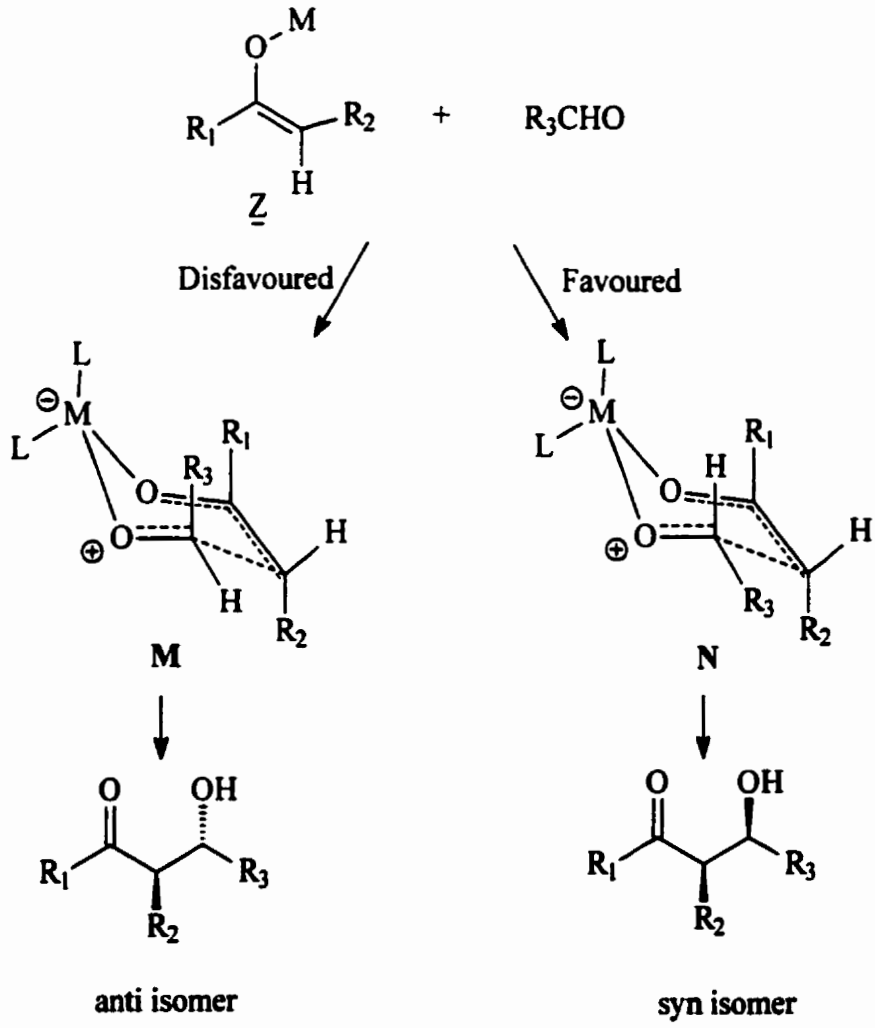


Scheme 81

As shown in the diagram, the allylic interactions between the methyl and the amide *N*-substitutions strongly disfavour amide conformation **Q**, and consequently the associated transition state **S** for deprotonation, to give *E*-enolates. In the conformer **P**, there is no such allylic strain observed and the corresponding transition state **R** leads to the *Z*-enolates. However, if the methyl substituent on the amide is replaced by a bulky group or the amide base has a bulky ligand, then there will be nonbonded interactions between the amide base ligand and the

substituent as indicated in the transition state **R**. This will disfavour the transition state **R** and prevent the formation of the *Z*-enolate. Nevertheless, with our system, the allylic interactions dominate and consequently, *Z*-enolate will be formed almost exclusively from the conformer **P** via transition state **R**.

It is generally expected that the *Z*-enolates would preferentially form syn aldol products[35,171]. However, this is not always true. In many instances, the opposite stereoselections have been noticed. We also observed the similar trend in our both aldol reactions. Though the lithium enolate aldol reaction gave the chelation controlled products A_1 and S_2, they showed poor control over syn vs anti stereochemistry. In both cases, the anti isomer A_1 was the major product. There have been several theories postulated to account for the lack of correlation between enolate geometry and product stereochemistry.

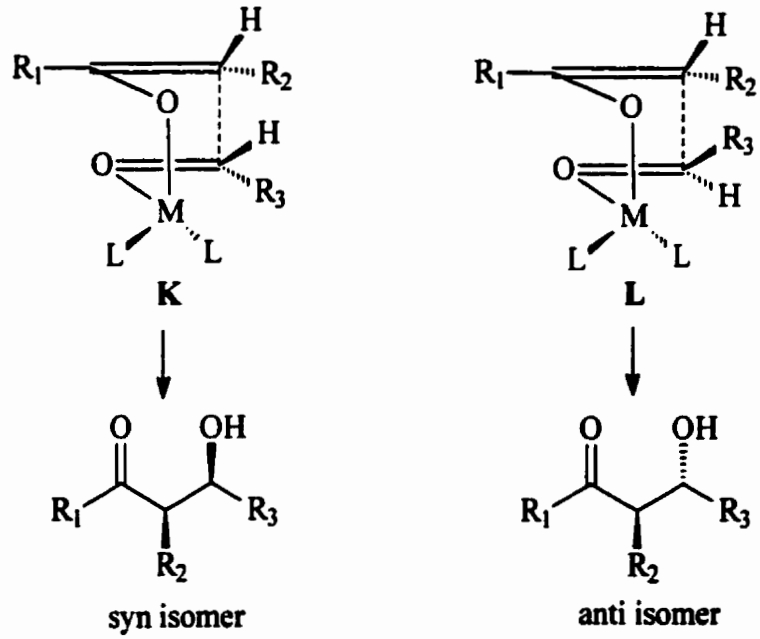


Scheme 82

Aldol reactions are thought to proceed through six-centered transition states in which the alkyl group of the aldehyde preferentially occupies an equatorial position in the chelated chairlike transition structure[122,171]. The correlation of metal enolate geometry and aldol product stereochemistry can be then understood via these diastereomeric chair-preferred transition states. The best model to illustrate this behavior is the Zimmerman and Traxler model[171].

Since the lithium bases preferentially form *Z* enolates with imides and amides, we only consider the two structures arisen from the *Z* enolates, which are shown in Scheme 82. As illustrated in Scheme 82, the transition state **M** is destabilized relative to **N**, because of the steric interactions (diaxial manner) between R_1 and R_3. Therefore, the respective transition state **N** would produce the expected syn products. This accounts for the formation of S_2 in substantial amounts in the reaction.

However, to explain the formation of anti A_1 isomers, chelated boatlike (or twist-boatlike) transition structures are postulated. The two possible chelated boatlike structures for the *Z*-enolates are illustrated in Scheme 83.



Scheme 83

In the boat transition state **L**, the substituents R_2 and R_3 are disposed in a staggered conformation as in the transition states **M** and **N**. In addition, the boat transition state **L** minimizes the eclipsing of R_1 and R_3 which is significant in chair transition state **M**. Therefore, the heat of formation of boat transition state **L** might be less than the heat of formation of the chair transition state **M**. Sometimes, it might even be less than the preferred chair transition state **N** for certain combinations of substituents R_1, R_2, and R_3. Consequently, the transformation of chairlike structures to boatlike structures will be favoured. Hence, more boat product, the anti isomer, is expected. Therefore, we believe that this might be the reason for getting more anti A_1 isomer in both of our aldol condensations.

Furthermore, in lithium enolates, as the lithium does not bear any ligand (except solvent), there will be no repulsive interaction between the quasi-axial enolate methyl (R_1 in scheme 83) and the metal ligand. It is known that the lithium enolates form a tetracoordinated aggregates in THF[171]. However, even with this lithium aggregates, the ligand-methyl repulsion would be expected to be little. Therefore, this will favor the anti A_1 adduct.

The above model theory explains the generation of the A_1 isomer in larger amount in the aldol condensations. As we discussed previously, the chelation control is high in lithium enolates. Due to this regulation, the free rotation of the propionyl carbonyl is restricted. Hence, the chelation control products S_2 and A_1 are formed in larger amounts than the other two isomers.

Finally, we have established that the fluorous-tagged chiral auxiliaries can be used in asymmetric synthesis. However, more improvements are needed to make the synthesis efficient. In order to obtain optimum fluorous-phase separation during extraction, the use of a fluorous material having a larger number of fluorines or a long fluorous-tail is required. However, the fluorous-phase methodology is expected to work better than the solid or solution phase strategy.

Conclusion

1. We developed a novel procedure for the synthesis of 2-oxazolidinones. Using this method we prepared the requisite novel chiral auxiliaries, (*S*)-4-((4-benzyloxyphenyl)methyl)-oxazolidin-2-one **98** and (*S*)-4-((4-hydroxyphenyl)methyl)oxazolidin-2-one **58**. In order to investigate the efficacy of this method, we also synthesized the popular 4(*S*)-isopropyl oxazolidin-2-one **2** and 4(*S*)-benzyl oxazolidin-2-one **3**.

Our method uses the combination of $NaBH_4$ and LiI and avoids the use of hazardous and expensive reagents for the reduction. The reduction and the cyclization steps are performed in a single operation and the process does not require the use of an inert atmosphere. The method is amenable to multi-gram scales. This novel method will facilitate the synthesis of important chiral oxazolidin-2-ones from chiral aminoacids.

2. We successfully constructed a novel soluble polymer-supported oxazolidin-2-one **105** by linking MeOPEG **32** to (*S*)-4-((4-hydroxyphenyl)methyl)oxazolidin-2-one **58** in high yields (95%). The procedure using K_2CO_3, KI and 18-crown-6 in acetone under reflux was the best of other methods attempted. We achieved the *N*-acyl functionalization of the polymer-supported oxazolidin-2-one **105** in good yields (70-85%). The method incorporating KH, THF, 18-crown-6 at 40 °C worked well for this purpose.

The readily available, inexpensive polymer MeOPEG **32** provided the easy attachment by functionalization of the hydroxyl group of the polymer. It maintained a homogeneous solution during reaction and facilitated the product isolation by filtration. NMR spectroscopic methods allowed the reaction to be studied.

The asymmetric alkylation and Diels-Alder reaction of the polymer-linked oxazolidinone **105** were unsuccessful. At lower temperatures (−78 °C) in THF the MeOPEG bound compound precipitated from the solution. Further, the metal ions (Li and Ti) used in the enolate chemistry formed insoluble complex with the oxygens on the MeOPEG chain. We concluded that the choice of MeOPEG polymer for this purpose might not be appropriate for reactions which are carried out at low temperatures and which involve organometallic

(alkali/transition metals) reagents.

3. We successfully prepared a novel fluorous-tagged chiral oxazolidin-2-one **129**. The attachment of the fluorous label **112** was carried out via metal-halogen exchange reaction. *N*-Propionylation of **129** was accomplished in high yields (87%). Li-mediated (LDA) asymmetric aldol condensation with PhCHO gave the all four diastereomers. The results were similar to those reported for Li-mediated aldol reactions of Evans oxazolidinones.

The fluorous synthesis maintained a homogeneous at the reaction stage and induced phase separation during extraction. However, the phase separation was not efficient enough to partition only into fluorous phase. For efficient synthesis, the use of a fluorous tag having a larger number of fluorines is recommended. We concluded that the fluorous synthesis for asymmetric reactions of oxazolidin-2-ones worked better than the soluble polymer-supported synthesis.

Suggestions for future work

1. The novel synthetic method for the chiral oxazoldin-2-one from chiral aminoacids is a milder and simpler method. It involves the reduction of the *N*-cbz protected aminoacid ethyl esters. The reduction of *N*-boc protected aminoacid ethyl ester has been tested. Similarly, the possibility of this method may be examined with various other *N*-carbamate protecting groups as well as ester groups of such aminoacids.

2. The soluble polymer-supported chiral oxazolidin-2-one may be tried for reactions that can be performed at warmer temperatures and do not include organometallic reagents.

3. The fluorous synthesis is a better methodology for asymmetric reactions of oxazolidinones. The ability to provide homogeneous conditions during reaction and feasible phase separation at purification step could expand its applications to various other areas in organic synthesis.

One important rule is that the fluorous substrates should be sufficiently fluorous to make this methodology a success. Though the synthesis and the application of our fluorous oxazolidin-2-one were highly successful, the phase separation during the extraction was unsatisfactory. The

process can be tried by incorporating a new fluorous tag containing a higher number of fluorocarbon units.

The aldol reaction of our fluorous oxazolidinone can be attempted with different metal enolates (B and Ti) and various aldehydes.

The chiral auxiliaries are increasingly used in asymmetric organic synthesis. The recovery and recycling of the chiral auxiliary are possible in the fluorous synthesis. Various other fluorous chiral auxiliaries (carbohydrates, oxazolines, oxazinones etc.) may be prepared and tested for enantioselective reaction.

The fluorous oxazolidinone may be used in other asymmetric transformations such as alkylation, acylation, cycloaddition, conjugate addition reactions, amination, etc.

In light of the easy work-up and phase separation technique of extraction, the application of fluorous synthesis may be extended to combinatorial synthesis.

Experimental

General methods

Perfluorinated solvent FC-72 (perfluorohexanes) and perfluoroheptanes were purchased from Fisher Scientific and PCR, Inc. respectively. Silica gel was obtained from Rose Scientific and Anachemia Science. All other solvents and chemical reagents were purchased from Aldrich.

When necessary, solvents and chemical reagents were further purified or dried prior to use, according to methods found in the literature[156]. Poly(ethylene glycol)monomethyl ether (MeOPEG, MW = 5000) was dried over P_2O_5 under vacuum before use[62]. 1-Iodo-1*H*,1*H*,2*H*,2*H*-perfluorodecane ($C_8F_{17}CH_2CH_2I$) was purified by passing through a column of alumina (neutral) and used immediately[156]. Trichlorosilane ($HSiCl_3$) was distilled from quinoline at atmospheric pressure[157].

Unless otherwise specified, all reactions were performed under a dry nitrogen atmosphere with oven-dried glassware. In all dry experiments involving highly reactive organometallic reagents, oven-dried glassware was flame-dried further and cooled under vacuum and a dry argon atmosphere was maintained throughout.

Proton NMR spectrometry was used to monitor the progress of all reactions involving MeOPEG supported compounds[71]. The singlet signal obtained at δ 3.36 ppm for the methoxy group of MeO-PEG in $CDCl_3$ was used as an internal reference for determining the completion of reactions[58]. All other reactions were studied by analytical thin layer chromatography (unless otherwise stated). Whatman Al SIL G/UV analytical thin layer chromatography plates with a thickness of 250 μm were utilized. Compounds were identified either by visualizing the plates under ultra violet light or by staining the plates with spraying reagents (ninhydrin for aminoacids and 5% H_2SO_4/ethanol for all other compounds).

Recrystallization and flash column chromatography were performed according to the standard procedures, to purify the final products[172].

Optical rotations were determined using an Autopol III polarimeter (cell length of 10 cm and concentrations measured in g/100 mL at 25 °C). Melting points were obtained using an Electrothermal melting point apparatus.

The ^1H NMR spectra were recorded on a Bruker AM-300 spectrometer at 300.133 MHz. The chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS)

on the δ scale. The signals obtained for the residual protons in the deuterated solvents were used as internal standards.

The ^{13}C NMR spectra were measured at 75.47 MHz on the AM-300 spectrometer and are reported in parts per million from tetramethylsilane on the δ scale. Chemical shifts in ppm downfield from TMS were measured by using the solvent signals as internal standards.

High-resolution mass spectra (HRMS) were obtained with a VG7070E-HF mass spectrometer using EI and FAB methods.

Elemental analysis was carried out by the Guelph Chemical Laboratories Ltd. (Guelph, Ontario).

N-(Benzyloxycarbonyl)-*L*-tyrosine ethyl ester (95)

L-Tyrosine (25.00 g, 138.0 mmol) was esterified with ethanol and carbamate protected using carbobenzyloxy chloride in the same pot, following a method found in the literature[15,98]. Recrystallization of the crude material from $CHCl_3$/hexane mixed solvent provided **95** (36.00 g, 76%) as white fluffy crystals.

mp 76.5-78 °C. (lit. mp 78 °C)[98].

$[\alpha]_D^{25}$ -4.0° (c 0.5, EtOH). (lit. $[\alpha]_D^{25}$ -4.7° (Alcohol))[98].

^{1}H nmr ($CDCl_3$) δ 1.24 (t, 3H, J = 7.1 Hz, C*H*$_3$), 2.96-3.10 (m, 2H, ArC*H*$_2$), 4.17 (q, 2H, J = 7.1 Hz, C*H*$_2$CH$_3$), 4.57-4.63 (m, 1H, C*H*N), 5.08 (dd, 1H, J = 12.4 Hz, PhC*H*HO), 5.11 (dd, 1H, J = 12.4 Hz, PhCH*H*O), 5.26 (brd, 1H, J = 8.1 Hz, N*H*), 5.49 (s, 1H, ArO*H*), 6.69 (d, 2H, J = 8.3 Hz, Ar-H), 6.95 (d, 2H, J = 8.3 Hz, Ar-H), 7.29-7.38 (m, 5H, Ar-H) ppm.

O-Benzyl-*N*-(benzyloxycarbonyl)-*L*-tyrosine ethyl ester (96)

A solution of **95** (4.00 g, 11.6 mmol) and K_2CO_3 (3.21 g, 23.2 mmol, 2 equiv.) in acetone (60 mL) was treated with benzyl bromide (1.4 mL, 11.6 mmol, 1 equiv.) and 18-crown-6 (catalytic amount)[99]. The resulting mixture was stirred and boiled under reflux for 16 hours. After cooling and filtration, the filtrate was evaporated to give a crude residue. This residue was dissolved in dichloromethane (~120 mL) and the organic solution was washed with 10% HCl (15 mL), H_2O (3 × 15 mL) and brine (20 mL), dried and evaporated to afford a yellow oil. This residue was recrystallized from hexane to yield **96** (3.98 g, 79%) as white needlelike fluffy crystals.

TLC (2:1 hexane:ethyl acetate) R_f 0.66.

mp 78-80 °C.

$[\alpha]_D^{25}$ +46.0° (c 0.25, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.24 (t, 3H, J = 7.1 Hz, C*H*$_3$), 3.06 (m, 2H, ArC*H*$_2$), 4.17 (q, 2H, J = 7.1 Hz, C*H*$_2$CH$_3$), 4.57-4.64 (m, 1H, C*H*N), 5.04 (s, 2H, PhC*H*$_2$O), 5.11 (s, 2H, PhC*H*$_2$OC=O), 5.23 (brd, 1H, J = 7.9 Hz, N*H*), 6.88 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.02 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.29-7.45 (m, 10H, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 14.21 (CH_3), 37.50 (ArCH_2), 54.99 (*C*HN), 61.51 (CH_2CH_3), 66.97 (PhCH_2OC=O), 70.06 (PhCH_2O), 114.97, 127.48, 127.99, 128.03, 128.11, 128.19, 128.54, 128.61 (C_{Ar}), 130.39 (4° C_{Cbz}), 136.33 (4° C_{Bn}), 137.01 (4° C_{Ar}), 155.63 (NC=O), 157.96 (4° C_{Ar}), 171.56 (CHC=O) ppm.

Anal. calcd for $C_{26}H_{27}NO_5$: C, 72.04; H, 6.28; N, 3.23. Found: C, 71.41; H, 5.92; N, 3.15.

(4*S*)-4-((4-Benzyloxyphenyl)methyl)oxazolidin-2-one (98)

A solution of **96** (4.00 g, 9.2 mmol) in THF (75 mL) was mixed with $NaBH_4$ (0.70 g, 18.4 mmol, 2 equiv.) and anhydrous LiI (2.50 g, 18.4 mmol, 2 equiv.). The resulting suspension was stirred and heated under reflux for 16 hours. The cooled mixture was adjusted to an apparent pH of 3-4 with 10% aqueous HCl, and the organic solvents were evaporated. The aqueous residue was diluted with H_2O (5-10 mL), and extracted with dichloromethane (~175 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 15 mL), aqueous $Na_2S_2O_3$ (2 × 15 mL), and brine (2 ×15 mL), before being dried and concentrated. The white solid residue was recrystallized from 1:1 hexane:ethyl acetate to afford white needlelike crystals of **98** (2.23 g, 85%).

TLC (1:1 hexane:ethyl acetate) R_f 0.21.

mp 136-138 °C.

$[\alpha]_D^{25}$ -84.8° (c 0.5, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 2.77 (dd, 1H, *J* = 7.7 and 13.7 Hz, ArC*H*H), 2.84 (dd, 1H, 6.1 and 13.7 Hz, ArCH*H*), 3.99-4.08 (m, 1H, C*H*N), 4.14 (dd, 1H, *J* = 5.5 and 8.6 Hz, C*H*HO), 4.46 (dd, 1H, *J* = 8.0 and 8.6 Hz, CH*H*O), 5.06 (s, 2H, PhCH_2O), 5.14 (brs, 1H, N*H*), 6.94 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.09 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.28-7.45 (m, 5H, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 40.47 (ArCH_2), 53.82 (*C*HN), 69.51 (CH_2O), 70.00 (PhCH_2O), 115.27, 127.37, 127.92, 128.11, 128.52 (C_{Ar}), 129.98 (4° C_{Bn}), 136.79, 157.89 (4° C_{Ar}), 159.38 (NC=O) ppm.

HRMS calcd for $C_{17}H_{17}NO_3$: 283.1208. Found: 283.1201.

Anal. calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.46; H, 5.71; N, 4.84.

(4*S*)-4-Isopropyloxazolidin-2-one (2)

L-Valine was converted to *N*-(benzyloxycarbonyl)-*L*-valine ethyl ester **2a** (84%) using the procedure described for **95**. Reduction and cyclization of **2a** adopting the method utilized for **98** provided **2** (96%).

mp 70-72 °C. (lit. mp 71.7-72.9 °C)[15].

$[\alpha]_D^{25}$ -14.6° (c 0.5, EtOH). (lit. $[\alpha]_D^{25}$ -18.4° (c 3.3, EtOH))[15].

^{1}H nmr ($CDCl_3$)[14] δ 0.91 (d, 3H, J = 6.7 Hz, C*H*$_3$CHCH$_3$), 0.96 (d, 3H, J = 6.7 Hz, CH$_3$CHC*H*$_3$), 1.68-1.79 (m, 1H, CH$_3$C*H*CH$_3$), 3.57-3.64 (m, 1H, C*H*N), 4.11 (dd, 1H, J = 6.3 and 8.7 Hz, C*H*HO), 4.45 (apparent t (AB system), J_{app} = 8.6 Hz, CH*H*O), 5.57 (brs, 1H, N*H*) ppm.

(4*S*)-4-Phenylmethyloxazolidin-2-one (3)

(4*S*)-4-Phenylmethyloxazolidin-2-one **3** (88%) was prepared in a similar manner to that given above for **2**.

mp 86-88 °C. (lit. mp 86-87.5 °C)[15].

$[\alpha]_D^{25}$ +5.9° (c 1.0, EtOH). (lit. $[\alpha]_D^{25}$ +5.9° (c 1.0, EtOH))[15].

^{1}H nmr ($CDCl_3$)[13] δ 2.87 (m, 2H, ArC*H*$_2$), 4.04-4.48 (m, 3H, NC*H*C*H*$_2$O), 5.73 (brs, 1H, N*H*), 7.16-7.33 (m, 5H, Ar-H) ppm.

(4*S*)-4-((4-Hydroxyphenyl)methyl)oxazolidin-2-one (58)

(*S*)-4-((4-Hydroxyphenyl)methyl)oxazolidin-2-one **58** was synthesized using either method A or method B.

Method A

A solution of **95** (1.00 g, 2.9 mmol) in THF (15 mL) was treated with $NaBH_4$ (0.44 g, 11.6 mmol, 4 equiv.) and LiI (1.55 g, 11.6 mmol, 4 equiv.). The resulting mixture was stirred and heated under reflux for ~1 hour. After cooling, absolute ethanol (30 mL) was added and the mixture was again heated under reflux for 8 hours. The rest of the process was carried out

following the same protocol detailed for compound **98**. Purification of the desired product by flash column chromatography (1:1 hexane:ethyl acetate) provided **58** (0.31 g, 55%) as a white powder.

TLC (1:1 hexane:ethyl acetate) R_f 0.16.

mp 175-178 °C.

$[\alpha]_D^{25}$ +8.6° (c 0.5, EtOH).

^{1}H nmr (acetone-d_6) δ 2.72-2.85 (m, 2H, ArC*H*$_2$), 4.03-4.14 (m, 2H, C*H*$_2$O), 4.28-4.38 (m, 1H, C*H*N), 6.60 (brs, 1H, N*H*), 6.77 (apparent d, 2H, J_{app} = 6.5 Hz, Ar-H), 7.08 (apparent d, 2H, J_{app} = 6.5 Hz, Ar-H), 8.25 (s, 1H, ArO*H*) ppm.

^{13}C nmr (acetone-d_6) δ 40.88 (ArCH$_2$), 54.37 (*C*HN), 69.50 (*C*H$_2$O), 116.19, 128.24 (C$_{Ar}$), 131.09, 157.04 (4° C$_{Ar}$), 159.48 (N*C*=O) ppm.

HRMS calcd for $C_{10}H_{11}NO_3$: 193.0739. Found: 193.0736.

Anal. cacld for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.44; H, 5.75; N, 6.95.

Method B

A solution of **98** (4.14 g, 14.6 mmol) in methanol (~150 mL) was degassed under vacuum. This degassed solution was reacted with 10% Pd/C (1.55 g, 1.46 mmol, 10 mol% of Pd) and H_2 (g) at atmospheric pressure and room temperature for 5-6 hours[106]. The reaction mixture was filtered through a Celite bed under vacuum and inert atmosphere. This was repeated on a fresh Celite bed to completely remove traces of fine Pd/C particles. Evaporation of the filtrate solution to dryness yielded **58** (2.80 g, 99%).

The physical data were identical to those obtained using method A.

4-(Chloromethyl)phenylmethyl monomethoxypoly(ethylene glycolyl) ether (MeOPEG-DOX-Cl) (102)

Compound **102** was synthesized by reacting poly(ethylene glycol)monomethyl ether **32** (5.00 g, 1.0 mmol, average m.w. 5,000) and α, α'-dichloro-*p*-xylene (5.25 g, 30.0 mmol, 30 equiv.) in THF with NaH (0.12 g, 3.0 mmol, 3 equiv.) and NaI (0.17 g, 1.15 mmol, 1.15 equiv.)

according to a literature procedure[107]. Recrystallization of the final product from absolute ethanol gave a white powder **102** (4.89 g, 95%).

mp 57.5-59 °C.

^{1}H nmr ($CDCl_3$) δ 3.34 (s, 3H, OCH_3), 4.52 (s, 2H, ArCH_2Cl), 4.54 (s, 2H, ArCH_2O), 7.29 (d, 2H, J = 9.0 Hz, Ar-H), 7.32 (d, 2H, J = 9.0, Ar-H) ppm.

(Note. The melting point of **102** was not reported in the literature. However, the NMR data were found to be identical with those published by Krepinsky et al.[107]).

(4*S*)-4-((4-(4-(4-monomethoxypoly(ethylene glycolyl)oxymethyl)benzyloxy)-phenyl)-methyl)oxazolidin-2-one (105)

A solution of **58** (0.23 g, 1.17 mmol, 1.5 equiv.) and K_2CO_3 (0.32 g, 2.34 mmol, 2 equiv.) in acetone (60 mL) was reacted with MeOPEG-DOX-Cl **102** (4.00 g, 0.78 mmol) and KI (~0.10 g, 0.58 mmol, 0.5 equiv.) in the presence of 18-crown-6 (catalytic amount). The mixture was heated under reflux for 16 hours. After cooling to room temperature, the reaction mixture was filtered through a Celite bed, which was subsequently washed with dichloromethane (5 mL). The combined filtrate and washings were concentrated and cooled on an ice-bath. Ether (~500 mL) was slowly added by a dropping funnel to precipitate the product and this mixture was further cooled to -4 °C for ~5 hours. The white precipitate was collected by vacuum filtration and washed with ether (20 mL) three times. Purification of this precipitate by recrystallizing from absolute ethanol yielded **105** (3.90 g, 95%) as a white powder.

mp 57-59 °C.

$[\alpha]_D^{25}$ -1.84° (c 0.76, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 2.79 (m, 2H, ArCH_2), 3.36 (s, 3H, OCH_3), 3.49-3.77 (m, ~ 4 × 110H, (OCH_2CH_2)$_n$), 3.99-4.07 (m, 1H, C*H*N), 4.11 (dd, 1H, J = 5.5 and 8.5 Hz, C*H*HO), 4.44 (apparent t (ABX system), 1H, J_{app} = 8.4 Hz, CH*H*O), 4.56 (s, 2H, MeOPEGOCH_2), 5.03 (s, 2H, ArCH_2O), 5.06 (brs, 1H, N*H*), 6.91 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.07 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.35 (d, 2H, J = 8.4 Hz, Ar-H), 7.38 (d, 2H, J = 8.4 Hz, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 40.72 (Ar*C*H$_2$), 53.89 (*C*HN), 59.06 (O*C*H$_3$), 69.58 (CH*C*H$_2$O), 69.64 (OCH$_2$*C*H$_2$O), 69.87 (MeOPEGO*C*H$_2$Ar), 70.60 (Ar*C*H$_2$O), 71.41, 71.97, 72.57, 72.95

(OCH_2CH_2O), 115.42, 127.48, 127.97, 128.26 (C_{Ar}), 129.99, 136.19, 138.21, 157.95 (4° C_{Ar}), 158.82 (*NC*=O) ppm.

(4*S*)-3-(1-Oxopropyl)-4-((4-benzyloxyphenyl)methyl)oxazolidin-2-one (106a)

A solution of **98** (1.00 g, 3.5 mmol) and triphenylmethane (~1 mg) in THF (15 mL) was cooled to -78 °C. To this solution was added *n*-butyllithium (2.5 M in hexane) dropwise until an orange colour persisted (1.7 mL, 1.2 equiv. required). Propionyl chloride (0.37 mL, 4.2 mmol, 1.2 equiv.) was added immediately and the resulting nearly colourless solution was stirred for 10-15 min at -78 °C and then warmed to 0 °C gradually[110]. The reaction mixture was then quenched with saturated $NaHCO_3$ (10 mL) and stirred at 20 °C for 30 min. The mixture was extracted with dichloromethane (3 × 30 mL) and the combined organic layers were washed successively with 5% aqueous Na_2CO_3 (10 mL) and saturated aqueous NaCl (10 mL), dried over $MgSO_4$ and evaporated to give a white crude solid. Recrystallization of the crude product from 1:1 hexane:ethyl acetate provided **106a** (0.87 g, 72%) as white fluffy crystals.

TLC (1:1 hexane:ethyl acetate) R_f 0.84.

mp 92-93.5 °C.

$[\alpha]_D^{25}$ +57.4° (c 0.5, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.21 (t, 3H, J = 7.3, CH_3), 2.73 (dd, 1H, J = 9.5 and 13.5 Hz, ArC*H*H), 2.86-3.07 (m, 2H, CH_2CH_3), 3.22 (dd, 1H, J = 3.3 and 13.5 Hz, ArCH*H*), 4.17 (dd, 1H, J = 2.7 and 9.0 Hz, C*H*HO), 4.20 (dd, 1H, J = 7.6 and 9.0 Hz, CH*H*O), 4.63 (dddd, 1H, 2.7, 3.3, 7.6 and 9.5 Hz, C*H*N), 5.05 (s, 2H, $PhCH_2O$), 6.94 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.13 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.30-7.45 (m, 5H, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 8.33 (CH_3), 29.19 (CH_2CH_3), 37.05 ($ArCH_2$), 55.23 (*C*HN), 66.21 (CH_2O), 70.04 ($PhCH_2O$), 115.28, 127.43, 127.47, 127.97, 128.56 (C_{Ar}), 130.42 (4° C_{Bn}), 136.82 (4° C_{Ar}), 153.49 (*NC*=O), 158.06 (4° C_{Ar}), 174.02 (CH_2C=O) ppm.

Anal. calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.42; H, 6.34; N, 4.03.

(4*S*)-3-((*E*)-2-Butenoyl)-4-((4-benzyloxyphenyl)methyl)oxazolidin-2-one (106b)

A solution of **98** (0.20 g, 0.7 mmol) in THF (3.0 mL) was acylated with (*E*)-crotonyl chloride (90 μL, 0.84mmol, 1.2 equiv.) according to the procedure described above for **106a**. Purification of the crude product by flash column chromatography (2:1 hexane:ethyl acetate) afforded **106b** (0.21 g, 85%) as white needles.

TLC (1:1 hexane:ethyl acetate) R_f 0.72.

mp 120-121 °C.

$[\alpha]_D^{25}$ +80.0° (c, 0.265, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.99 (d, 3H, J = 5.5 Hz, C*H*$_3$), 2.76 (dd, 1H, J = 9.3 and 13.5 Hz, ArC*H*H), 3.25 (dd, 1H, J = 3.3 and 13.5 Hz, ArCH*H*), 4.17 (dd, 1H, J = 2.9 and 9.1 Hz, C*H*HO), 4.21 (dd, 1H, J = 7.8 and 9.1 Hz, CH*H*O), 4.69 (dddd, 1H, J = 2.9, 3.3, 7.8 and 9.3 Hz, C*H*N), 5.05 (s, 2H, PhC*H*$_2$O), 6.94 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.13 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.17-7.26 (m, 2H, C*H*=C*H*), 7.31-7.45 (m, 5H, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 18.62 (*C*H$_3$), 37.06 (Ar*C*H$_2$), 55.40 (*C*HN), 66.16 (*C*H$_2$O), 70.10 (Ph*C*H$_2$O), 115.33 (C$_{Ar}$), 121.93 (CH=*C*HC=O), 127.49, 127.58, 128.03, 128.62 (C$_{Ar}$), 130.53 (4° C$_{Bn}$), 136.91 (4° C$_{Ar}$), 146.92 (CH3*C*H=CH), 153.50 (N*C*=O), 158.10 (4° C$_{Ar}$), 164.98 (CH=CH*C*=O) ppm.

Anal. calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.10; H, 5.70; N, 3.84.

(4*S*)-3-(1-Oxopropyl)-4-((4-(4-(4-monomethoxypoly(ethylene glycolyl)oxy-methyl)benzyloxy)phenyl)methyl)oxazolidin-2-one (107a)

To a solution of **105** (0.20 g, 40 μmol) in THF (10 mL) were added KH (24% in mineral oil; 20 mg, 120 μmol, 3 equiv.) and 18-crown-6 (catalytic amount). The resulting suspension was stirred for 10 min and was then treated with propionyl chloride (14 μL, 160 μmol, 4 equiv.). This reaction mixture was heated for 18 hours at 40 °C. After cooling to room temperature, the reaction mixture was filtered through a filter paper and the filtrate solution was diluted with *tert*-butylmethyl ether (~100 mL) and cooled at -4 °C for 3-5 hours. A white precipitate formed,

which was collected by filtration under vacuum and washed with *tert*-butylmethyl ether (3 × 10 mL). Recrystallization of the final product from absolute ethanol gave **107a** (0.14 g, 70%) as a white powder.

mp 58.5-60 °C.

$[\alpha]_D^{25}$ +2.7° (c 1.5, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.9 (t, 3H, J = 7.3 Hz, CH_3), 2.73 (dd, 1H, J = 9.0 and 13.5 Hz, ArCHH), 2.86-3.02 (m, 2H, CH_2CH$_3$), 3.21 (dd, 1H, J = 3.2 and 13.5 Hz, ArCHH), 3.37 (s, 3H, OCH_3), 3.49-3.78 (m, ~ 4 × 110H, (OCH_2CH_2)$_n$), 4.13-4.24 (m, 2H, CHCH_2O), 4.56 (s, 2H, MeOPEGOCH_2Ar), 4.58-4.65 (m, 1H, CHN), 5.02 (s, 2H, ArCH_2O), 6.92 (d, 2H, J = 8.6 Hz, Ar-H), 7.11 (d, 2H, J = 8.6 Hz, Ar-H), 7.35 (d, 2H, J = 8.3 Hz, Ar-H), 7.38 (d, 2H, J = 8.3 Hz, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 8.38 (*C*H$_3$), 29.24 (*C*H$_2$CH$_3$), 37.11 (Ar*C*H$_2$), 55.29 (*C*HN), 59.07 (O*C*H$_3$), 66.27 (CH*C*H$_2$O), 69.59 (O*C*H$_2$*C*H$_2$O), 69.88 (MeOPEGO*C*H$_2$O), 70.62 (Ar*C*H$_2$O), 71.99, 72.98 (O*C*H$_2$*C*H$_2$O), 115.34, 127.53, 127.97 (C$_{Ar}$), 130.46, 138.19, 158.07 (4° C$_{Ar}$), 174.07 (CH$_3$CH$_2$*C*=O) ppm.

(4*S*)-3-((*E*)-2-Butenoyl)-4-((4-(4-(4-monomethoxypoly(ethylene glycolyl)oxymethyl)benzyloxy)phenyl)methyl)oxazolidin-2-one (107b)

A solution of **105** (0.20 g, 40 μmol) in THF (15 mL) was acylated with (*E*)-crotonyl chloride according to the same protocol described above for **107a** to afford a white powder of **107b** (0.14 g, 67%).

mp 57.5-59 °C.

$[\alpha]_D^{25}$ +2.4° (c 1.0, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.98 (d, 3H, J = 5.5 Hz, CH=CHCH_3), 2.75 (dd, 1H, J = 9.3 and 13.5 Hz, ArCHH), 3.24 (dd, 1H, J = 3.0 and 13.6 Hz, ArCHH), 3.37 (s, 3H, OCH_3), 3.53-3.78 (m, ~ 4 × 110H, (OCH_2CH_2)$_n$), 4.13-4.24 (m, 2H, CHCH_2O), 4.56 (s, 2H, MeOPEGOCH_2Ar), 5.03 (s, 2H, ArCH_2O), 6.92 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.12 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.18-7.26 (m, 2H, CH=CH), 7.36 (d, 2H, J = 8.5 Hz, Ar-H), 7.39 (d, 2H, J = 8.5 Hz, Ar-H) ppm.

Tris(2-(perfluorooctyl)ethyl)silane (111)

To a suspension of Mg turnings (1.02 g, 41.76 mmol, 1.2 equiv.) in diethyl ether (5 mL) was added dibromoethane (5 drops) to activate the Mg turnings[91]. Once a vigorous reaction started, a solution of 1-iodo-1*H*,1*H*,2*H*,2*H*-perfluorodecane **94** (20.00 g, 34.80 mmol) in ether (~150 mL) was added slowly in order to maintain the ether at reflux. When the addition was complete, the mixture was heated under reflux for 2 hours. Trichlorosilane (0.63 mL, 6.26 mmol, ~0.18 equiv.) was added slowly and the mixture was heated under reflux for 16 hours when two phases were formed. After the mixture was cooled to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (~ 30 mL) and the resultant biphase was extracted with ether (2 × 150 mL). Evaporation of the combined ether layers and purification of the residue by bulb to bulb distillation (~1.0 mmHg, 160-170 °C) gave **111** as a white solid (5.20 g, 60%).

mp 33-34 °C.

^{1}H nmr (FC-72 with benzene-d_6 as internal lock) δ 1.16-1.23 (m, 6H, SiCH_2CH$_2$), 2.25-2.43 (m, 6H, SiCH$_2$CH_2), 4.15 (s, 1H, Si*H*) ppm.

Anal. calcd for $C_{30}H_{13}F_{51}Si$: C, 26.29; H, 0.96. Found: C, 26.40; H, 0.71.

Bromotris(2-(perfluorooctyl)ethyl)silane (112)

Bromination of **111** (1.00 g, 0.73 mmol) by a published procedure[91] afforded **112** (0.93 g, 88%).

mp 70-72 °C.

^{1}H nmr (FC-72 with benzene-d_6 as internal lock) δ 1.41-1.49 (m, 6H, BrSiCH_2CH$_2$), 2.34-2.51 (m, 6H, BrSiCH$_2$CH_2) ppm.

(4*S*)-3-(1-Oxopropyl)-4-((4-hydroxyphenyl)methyl)oxazolidin-2-one (122)

The procedure was similar to that of method B detailed above for **58**. Debenzylation of **106a** (0.40 g, 1.3 mmol) in methanol (25 mL) using 10% Pd/C (0.13 g, 0.13 mmol, 10 mol% of Pd) and H_2 (g) yielded **122** (0.30 g, 95%) as a white powder.

TLC (1:1 hexane:ethyl acetate) R_f 0.54.

mp 133-134 °C.

$[\alpha]_D^{25}$ +160.0° (c 0.02, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.21 (t, 3H, *J* = 7.3 Hz, C*H*$_3$), 1.69 (brs, 1H, ArO*H*), 2.74 (dd, 1H, *J* = 9.2 and 13.5 Hz, ArC*H*H), 2.85-3.04 (m, 2H, C*H*$_2$CH$_3$), 3.19 (dd, 1H, *J* = 3.3 and 13.5 Hz, ArCH*H*), 4.17 (dd, 1H, *J* = 2.8 and 9.0 Hz, C*H*HO), 4.21 (dd, 1H, *J* = 8.7 and 9.0 Hz, CH*H*O), 4.63 (dddd, 1H, *J* = 2.8, 3.3, 8.7 and 9.2 Hz, C*H*N), 5.34 (brs, 1H, N*H*), 6.79 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.06 (d, 2H, *J* = 8.3 Hz, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 8.39 (*C*H$_3$), 29.27 (*C*H$_2$CH$_3$), 37.07 (Ar*C*H$_2$), 55.29 (*C*HN), 66.33 (*C*H$_2$O), 115.87, 127.15 (C$_{Ar}$), 130.62 (4° C$_{Ar}$), 153.67 (N*C*=O), 155.06 (4° C$_{Ar}$), 174.24 (CH$_3$CH$_2$*C*=O) ppm.

Anal. calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 60.62; H, 5.72; N, 5.25.

(Note. Although the observed value for C did not match the calculated value, the ^{1}H and ^{13}C nmr spectra confirmed the structure of **122**).

(4*S*)-3-(1-Oxopropyl)-4-((4-(4-bromobenzyloxy)phenyl)methyl)oxazolidin-2-one (123)

Compound **123** was prepared by reacting a solution of **122** (0.30 g, 1.2 mmol) and K_2CO_3 (0.33 g, 2.4 mmol, 2 equiv.) in acetone (15 mL) with 4-bromobenzylbromide (0.36 g, 1.44 mmol, 1.2 equiv.) and 18-crown-6 using a similar protocol to that detailed above for **96**. Recrystallization of the final product from 1:1 hexane:ethyl acetate afforded **123** (0.38 g, 76%) as white needlelike crystals.

TLC (1:1 hexane:ethyl acetate) R_f 0.59.

mp 104-106 °C.

$[\alpha]_D^{25}$ +50.8° (c 0.5, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.20 (t, 3H, J = 7.3 Hz, CH_3), 2.74 (dd, 1H, J = 9.4 and 13.5 Hz, ArCHH), 2.85-3.06 (m, 2H, CH_2CH$_3$), 3.21 (dd, 1H, J = 3.1 and 13.5 Hz, ArCHH), 4.16 (dd, 1H, J = 2.6 and 9.1 Hz, CHHO), 4.21 (dd, 1H, J = 8.4 and 9.1 Hz, CHHO), 4.63 (dddd, 1H, J = 2.6, 3.1, 8.4 and 9.4 Hz, CHN), 4.99 (s, 2H, ArCH_2O), 6.91 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.12 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.29 (apparent d, 2H, J_{app} = 8.2 Hz, Ar-H), 7.51(apparent d, 2H, J_{app} = 8.4 Hz, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 8.38 (CH_3), 29.25 (CH_2CH$_3$), 37.10 (ArCH_2), 55.25 (CHN), 66.26 (CH_2O), 69.33 (ArCH_2O), 115.32 (C_{Ar}), 121.94 (4° C_{Ar}), 127.78, 129.07 (C_{Ar}), 130.53 (4° C_{Ar}), 131.75 (C_{Ar}), 135.92 (4° C_{Ar}), 153.53 (NC=O), 157.82 (4° C_{Ar}), 174.08 (CH$_3$CH$_2$C=O) ppm.

Anal. calcd for $C_{20}H_{20}BrNO_4$: C, 57.43; H, 4.82; N, 3.35. Found: 57.60; H, 4.30; N, 3.30.

O-(4-Bromobenzyl)-*N*-(benzyloxycarbonyl)-*L*-tyrosine ethyl ester (124)

O-(4-Bromobenzyl)-*N*-(benzyloxycarbonyl)-*L*-tyrosine ethyl ester **124** was prepared by reacting **95** (10.00 g, 29.1 mmol) with 4-bromobenzyl bromide (10.90 g, 43.7 mmol, 1.5 equiv.) according to the procedure detailed above for **96**. Recrystallization of the final product from hexane yielded **124** (13.00 g, 87%) as a white powder.

TLC (2:1 hexane:ethyl acetate) R_f 0.56.

mp 99.5-101 °C.

$[\alpha]_D^{25}$ +37.0° (c 0.5, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.23 (t, 3H, J = 7.1 Hz, CH_3), 2.99-3.12 (m, 2H, ArCH_2), 4.17 (q, 2H, J = 7.1 Hz, CH_2CH$_3$), 4.57-4.63 (m, 1H, CHN), 4.98 (s, 2H, ArCH_2O), 5.10 (s, 2H, PhCH_2OC=O), 5.22 (brd, 1H, J = 8.0 Hz, NH), 6.85 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.02 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.26-7.53 (m, 9H, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 14.21 (CH_3), 37.49 (ArCH_2), 54.97 (CHN), 61.52 (CH_2CH$_3$), 66.98 (PhCH_2OC=O), 69.29 (ArCH_2O), 114.95, 121.89, 128.11, 128.20, 128.31, 128.54, 129.06 (C_{Ar}), 130.45 (4° C_{Cbz}), 131.73 (C_{Ar}), 136.06 (4° C_{BrBn}), 136.32 (4° C_{Ar}), 155.61 (NC=O), 157.66 (4° C_{Ar}), 171.52 (CHC=O) ppm.

Anal. calcd for $C_{26}H_{26}BrNO_5$: C, 60.95; H, 5.11; N, 2.73. Found: C, 61.23; H, 5.22; N, 2.71.

(4*S*)-4-((4-(4-Bromobenzyloxy)phenyl)methyl)oxazolidin-2-one (125)

A solution of **124** (13.00 g, 25.4 mmol) in THF (~200 mL) was subjected to the same reduction and cyclization process described above for compound **98**. The final product was recrystallized from 1:1 hexane:ethyl acetate to give white needlelike crystals of **125** (6.52 g, 71%).

TLC (1:1 hexane:ethyl acetate) R_f 0.13.

mp 158.5-160 °C.

$[\alpha]_D^{25}$ -46.6° (c 0.5, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 2.81 (apparent d, 2H, J_{app} = 7.2 Hz, ArCH_2), 3.99-4.10 (m, 1H, C*H*N), 4.13 (dd, 1H, 6.2 and 8.9 Hz, C*H*HO), 4.44 (dd, 1H, J = 8.1 and 8.9 Hz, CH*H*O), 4.99 (s, 2H, ArCH_2O), 5.51 (brs, 1H, N*H*), 6.91 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.09 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.29 (apparent d, 2H, J_{app} = 8.4 Hz, Ar-H), 7.51 (apparent d, 2H, J_{app} = 8.4 Hz, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 40.64 (Ar*C*H$_2$), 53.91 (*C*HN), 69.35 (*C*H$_2$O), 69.65 (Ar*C*H$_2$O), 115.40, 121.95, 128.45, 129.06 (C_{Ar}), 130.12 (4° C_{Ar}), 131.77 (C_{Ar}), 135.91, 157.73 (4° C_{Ar}), 159.23 (N*C*=O) ppm.

Anal. calcd for $C_{17}H_{16}BrNO_3$: C, 56.37; H, 4.45; N, 3.87. Found: C, 56.14; H, 3.82; N, 3.75.

(4*S*)-3-(*tert*-Butyldimethylsilyl)-4-((4-(4-bromobenzyloxy)phenyl)methyl)-oxazolidin-2-one (126)

To a solution of **125** (2.00 g, 5.5 mmol) in DMF (40 mL) was added triethylamine (0.92 mL, 6.6 mmol, 1.2 equiv.) dropwise and the solution was stirred for ~15 min at room temperature. *tert*-Butyldimethylsilylchloride (2.50 g, 16.5 mmol, 3 equiv.) was slowly added, followed by the addition of DMAP (catalytic amount)[118]. After stirring for 16 hours at room temperature, the reaction mixture was quenched with H_2O (20 mL) and the resulting solution was then diluted with ether (100 mL). The phases were separated and the aqueous layer was further extracted with ether (5 × 50 mL). The combined ether layers were washed successively with H_2O (2 × 20 mL), saturated aqueous NaCl, dried over $MgSO_4$ and evaporated.

Recrystallization of the crude product from hexane provided **126** (2.25 g, 85%) as white needles.

TLC (1:1 hexane:ethyl acetate) R_f 0.77.

mp 113-115 °C.

$[\alpha]_D^{25}$ +41.0° (c 0.5, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 0.35 (s, 3H, C*H*$_3$SiCH$_3$), 0.43 (s, 3H, CH$_3$SiC*H*$_3$), 1.02 (s, 9H, C(C*H*$_3$)$_3$), 2.66 (dd, 1H, J = 10.8 and 13.6 Hz, ArC*H*H), 2.94 (dd, 1H, J = 3.4 and 13.6 Hz, ArCH*H*), 3.79-3.88 (m, 1H, C*H*N), 4.08 (apparent d (ABX system), 2H, J_{app} = 4.4 Hz, C*H*$_2$O), 4.99 (s, 2H, ArC*H*$_2$O), 6.90 (apparent d, 2H, J_{app} = 8.5 Hz, Ar-H), 7.07 (apparent d, 2H, J_{app} = 8.5 Hz, Ar-H), 7.29 (apparent d, 2H, J_{app} = 8.3 Hz, Ar-H), 7.51 (apparent d, 2H, J_{app} = 8.3 Hz, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ -4.78 (*C*H$_3$SiCH$_3$), -4.75 (CH$_3$Si*C*H$_3$), 19.24 (*C*(CH$_3$)$_3$), 26.97 (C(*C*H$_3$)$_3$), 41.10 (Ar*C*H$_2$), 58.13 (*C*HN), 67.88 (*C*H$_2$O), 69.34 (Ar*C*H$_2$O), 115.30 (C$_{Ar}$), 121.94 (4° C$_{Ar}$), 128.79, 129.05 (C$_{Ar}$), 130.25 (4° C$_{Ar}$), 131.76 (C$_{Ar}$), 135.93, 157.61 (4° C$_{Ar}$), 161.63 (N*C*=O) ppm.

Anal. calcd for $C_{23}H_{30}BrNO_3Si$: C, 57.97; H, 6.34; N, 2.90. Found: C, 58.09; H, 6.30; N, 2.91.

(4*S*)-3-(*tert*-Butyldimethylsilyl)-4-((4-(4-tris(2-(perfluorooctyl)ethyl)silyl-benzyloxy)phenyl)methyl)oxazolidin-2-one (127)

A solution of **126** (0.14 g, 0.29 mmol, 2.1 equiv.) in THF (0.5-1.0 mL) and diethyl ether (20 mL) was cooled to -78 °C. *tert*-Butyllithium (1.7 M in pentane; 0.36 mL, 0.61 mmol, 2.1 equiv.) was added and to the resulting yellow solution was added a precooled (¯30-¯40 °C) solution of bromosilane **112** (0.20 g, 0.14 mmol) in BTF (0.5 mL) and ether (7.0 mL) as rapidly as possible[91]. The resulting mixture was stirred for 10 min and was then quenched with H_2O (5 mL). This biphase was stirred for another 10 min at room temperature.

Three-phase extraction was carried out with FC-72, CH_2Cl_2 and H_2O and the organic layers were collected separately. These organic layers were successively washed with H_2O (2 × 10 ml), saturated aqueous NaCl, dried over $MgSO_4$ and evaporated to afford a crude oil. Purification of the crude oil using flash chromatography (4:1 hexane:ethyl acetate) provided **127** (0.15 g, 63%) as a colourless oil.

TLC (4:1 hexane:ethyl acetate) R_f 0.43.

$[\alpha]_D^{25}$ +1.1° (c 3.88, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 0.35 (s, 3H, CH_3SiCH_3), 0.43 (s, 3H, CH_3SiCH_3), 1.02 (s, 9H, $C(CH_3)_3$), 1.13-1.19 (m, 6H, $SiCH_2CH_2$), 1.93-2.12 (m, 6H, $SiCH_2CH_2$), 2.67 (dd, 1H, J = 10.7 and 13.6 Hz, ArCHH), 2.94 (dd, 1H, J = 3.4 and 13.6 Hz, ArCHH), 3.80-3.88 (m, 1H, CHN), 4.09 (apparent d (ABX system), 2H, J_{app} = 4.0 Hz, CH_2O), 5.07 (s, 2H, $ArCH_2O$), 6.94 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.09 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.48 (d, 2H, J = 8.0 Hz, Ar-H), 7.53 (d, 2H, J = 8.0 Hz, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ -4.81 (CH_3SiCH_3), -4.78 (CH_3SiCH_3), 1.58 ($SiCH_2CH_2$), 19.23 ($C(CH_3)_3$), 25.22, 25.54, 25.84 (t, J = 24.4 Hz, $SiCH_2CH_2CF_2$), 26.94 ($C(CH_3)_3$), 41.09 ($ArCH_2$), 58.11 (CHN), 67.84 ($CHCH_2O$), 69.66 ($ArCH_2O$), 115.22, 127.71, 128.87 (C_{Ar}), 130.28 (4° C_{Ar}), 130.99 (C_{Ar}), 133.99, 139.68, 157.76 (4° C_{Ar}), 161.62 (NC=O) ppm.

Anal. calcd for $C_{53}H_{42}F_{51}NO_3Si_2$: C, 36.05; H, 2.39; N, 0.79. Found: C, 36.04; H, 2.12; N, 0.73.

(4*S*)-4-((4-(4-tris(2-(perfluorooctyl)ethyl)silylbenzyloxy)phenyl)methyl)oxazolidin-2-one (129)

A solution of **127** (0.16 g, 90 μmol) in dichloromethane (10 mL) and BTF (10 mL) was stirred well with TBAF (1.0 M in THF; 90 μL, 90 μmol, 1 equiv.) for 5-7 min at room temperature[120]. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL). After evaporating the solvents, the crude product was extracted using three-phase extraction (CH_2Cl_2, FC-72 and H_2O). The organic layers were combined and washed successively with saturated NH_4Cl (2 × 10 mL), H_2O (3 × 15 mL), and brine, dried over $MgSO_4$, filtered and evaporated to give a crude oil. Flash chromatography (2:1 hexane:ethyl acetate) was carried out on the crude product to afford **129** (0.12 g, 80%) as a colourless oil.

TLC (2:1 hexanes:ethyl acetate) R_f 0.13.

$[\alpha]_D^{25}$ -6.0° (c 0.38, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.14-1.19 (m, 6H, $SiCH_2CH_2$), 1.96-2.14 (m, 6H, $SiCH_2CH_2$), 2.79 (dd, 1H, J = 8.5 and 13.7 Hz, ArCHHO), 2.85 (dd, 1H, J = 5.6 and 13.7 Hz, ArCHHO),

4.05 (dddd, 1H, J = 5.5, 5.6, 8.4 and 8.5 Hz, C*H*N), 4.15 (dd, 1H, J = 5.5 and 8.5 Hz, C*H*HO), 4.48 (dd, 1H, J = 8.4 and 8.5 Hz, CH*H*O), 4.92 (brs, 1H, N*H*), 5.08 (s, 2H, ArCH_2O), 6.96 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.11 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.48 (d, 2H, J = 8.0 Hz, Ar-H), 7.53 (d, 2H, J = 8.0 Hz, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 1.59 (Si*C*H_2CH$_2$), 25.22, 25.54, 25.86 (t, J = 24.0 Hz, SiCH$_2$*C*H$_2$CF$_2$), 40.72 (Ar*C*H$_2$), 53.89 (*C*HN), 69.69 (CH*C*H$_2$O), 75.74 (Ar*C*H$_2$O), 115.37, 127.69, 128.52 (C$_{Ar}$), 130.09 (4° C$_{Ar}$), 131.02 (C$_{Ar}$), 134.00, 139.64, 157.92 (4° C$_{Ar}$), 158.79 (N*C*=O) ppm.

Anal. calcd for $C_{47}H_{28}F_{51}NO_3Si$: C, 34.17; H, 1.71; N, 0.85. Found: C, 33.92; H, 1.36; N, 0.77.

(4*S*)-3-(1-Oxopropyl)-4-((4-(4-tris(2-(perfluorooctyl)ethyl)silylbenzyloxy)-phenyl)methyl)oxazolidin-2-one (130)

A solution of **129** (0.14 g, 80 μmol) in perfluorohexane (1.5 mL) and diethyl ether (2.0 mL) was subjcted to propionylation using *n*-BuLi (~2 equiv.) and propionyl chloride (3-4 equiv.) according to a similar procedure detailed above for compound **106a**. Purification of the crude product by flash chromatography (4:1 hexane:ethyl acetate) yielded **130** (0.12 g, 87%) as a colourless oil.

TLC (4:1 hexane:ethyl acetate) R_f 0.68.

$[\alpha]_D^{25}$ +13.9° (c 0.9, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.13-1.23 (m, 9H, SiCH_2CH$_2$, CH$_2$CH_3), 1.96-2.14 (m, 6H, SiCH$_2$CH_2), 2.77 (dd, 1H, J = 9.2 and 13.5 Hz, ArC*H*H), 2.88-3.04 (m, 2H, CH_2CH$_3$), 3.21 (dd, 1H, J = 3.1 and 13.5 Hz, ArCH*H*), 4.17 (dd, 1H, J = 2.5 and 9.0 Hz, C*H*HO), 4.21 (dd, 1H, J = 8.7 and 9.0 Hz, CH*H*O), 4.64 (dddd, 1H, J = 2.5, 3.1, 8.7 and 9.2 Hz, C*H*N), 5.07 (s, 2H, ArCH_2O), 6.95 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.14 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.48 (d, 2H, J = 8.0 Hz, Ar-H), 7.53 (d, 2H, J = 8.0 Hz, Ar-H) ppm.

^{13}C nmr ($CDCl_3$) δ 1.57 (Si*C*H$_2$CH$_2$), 8.35 (CH$_2$*C*H$_3$), 25.20, 25.53, 25.85 (t, J = 24.9 Hz, SiCH$_2$*C*H$_2$CF$_2$), 29.23 (*C*H$_2$CH$_3$), 37.09 (Ar*C*H$_2$), 55.23 (*C*HN), 66.23 (CH*C*H$_2$O), 69.64 (Ar*C*H$_2$O), 115.26, 127.73, 127.84 (C$_{Ar}$), 130.56 (4° C$_{Ar}$), 130.97 (C$_{Ar}$), 133.99, 139.67 (4° C$_{Ar}$), 153.52 (N*C*=O), 157.95 (4° C$_{Ar}$), 174.09 (CH$_3$CH$_2$*C*=O) ppm.

Anal. calcd for $C_{50}H_{32}F_{51}NO_4Si$: C, 35.16; H, 1.89; N, 0.82. Found: C, 35.42; H, 1.62; N, 0.79.

(4*S*)-3-((2*R*,3*S*)-3-Hydroxy-2-methyl-1-oxo-3-phenylpropyl)-4-((4-benzyloxy-phenyl)methyl)oxazolidin-2-one (133p (A_1))

A solution of diisopropylamine (0.10 mL, 0.7 mmol, 1.2eq) in THF (2.0 mL) was treated with *n*-butyllithium (2.5M solution in hexane; 0.23 mL, 0.58 mmol, 1.1 equiv.) at 0 °C. After stirring at 0 °C for 10 min, the mixture was cooled to -78 °C. A solution of **106a** (0.18 g, 0.53 mmol) in THF (2.0 mL) was then added dropwise over 3 min. The mixture was stirred for 25 min at -78 °C. To this enolate solution was added benzaldehyde (70 μL, 0.64 mmol, 1.2 equiv.) as quickly as possible[121]. The reaction was quenched after 5 min with saturated aqueous NH_4Cl (1.0 mL) and the reaction mixture was warmed to room temperature. The product was extracted with ether (5 × 30 mL) and the combined ether layers were washed with saturated aqueous NaCl (2 × 15 ml), dried over $MgSO_4$ and evaporated to give a crude product.

HPLC analysis (SYMMETRY C-18 reverse-phase cartridge column (3.9 × 150 mm) Waters Inc.) of the crude product (gradient elution with methanol/H_2O 6:4 to 7:3 over 40 min, λ = 254 nm) provided the following retention times for the isomers: **131p** (S_1) t_R 32.8 min, **132p** (S_2) t_R 24.9 min, **133p** (A_1) t_R 27.6 min, **134p** (A_2) t_R 31.7 min and it revealed a ratio of S_1:S_2:A_1:A_2 = 5.4:20.4:45.3:3.9[33].

The crude material was purified by flash column chromatography (2:1 hexane:ethyl acetate) and the aldol adducts were collected together. The total yield of the aldol adducts (**131p** (S_1) + **132p** (S_2) + **133p** (A_1) + **134p** (A_2)) was found to be 60%. The major anti product **133p** (A_1) (~50 mg) was separated for further analysis.

(Note. Since anti adduct **133p** (A_1) was mixed in other fractions, it was not possible to calculate the total percentage yield of A_1).

Anti adduct **133p** (A_1): 1H nmr ($CDCl_3$) δ 1.12 (d, 3H, J = 6.9 Hz, CHC*H*$_3$), 2.64 (dd, 1H, J = 9.0 and 13.7 Hz, ArC*H*H), 3.10 (dd, 3H, J = 3.3 and 13.7 Hz, ArCH*H*), 3.19 (appd, 1H, J_{app} = 6.0 Hz, CHO*H*), 4.09-4.22 (m, 2H, CHC*H*$_2$O), 4.30 (apparent quintet, 1H, J_{app} = 7.0 Hz, CH_3C*H*CH), 4.61-4.68 (m, 1H, C*H*N), 4.83 (apparent t, 1H, J_{app} = 7.5 Hz, PhC*H*OH), 5.04 (s,

2H, PhCH_2O), 6.91 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.06 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.26-7.45 (m, 10H, Ar-H) ppm.

In the ^{1}H NMR of the mixed fraction, the following signals (for vicinal hydrogen) were also diagnostic: δ 5.09 (J = 6.7 Hz, CHC*H*OH) for **131p** (S_1); δ 5.17 (J = 4.2 Hz, CHC*H*OH) for **132p** (S_2); δ 3.94 (J = 11.5 Hz, CHC*H*OH) for **134p** (A_2)[33].

(4*S*)-3-((2*R*,3*S*)-3-Hydroxy-2-methyl-1-oxo-3-phenylpropyl)-4-((4-(4-tris(2-(perfluorooctyl)ethyl)silylbenzyloxy)phenyl)methyl)oxazolidin-2-one (133q (A_1))

Lithium-mediated aldol reaction was performed by reacting a solution of **130** (60 mg, 40 μmol) in THF with LDA (5 eqiv) and PhCHO (5 equiv.) according to the similar procedure given above for **133p** (A_1).

HPLC analysis (μ- Porasil 3.9 × 300 mm silica column Waters Inc.) on the crude product, using a solvent system of 9:91 10% iPrOH in hexane/hexane (λ = 254 nm), furnished the following data.

Retention time for the four isomers: **131q** (S_1) t_R 22.96 min, **132q** (S_2) t_R 20.54 min, **133q** (A_1) t_R 11.9 min, **134q** (A_2) t_R 11.1 min. Ratio of the isomers: S_1:S_2:A_1:A_2 = 20.3:27.6:34.4:1.6[33].

The aldol adducts were separated together from the crude mixture by flash column chromatography (4:1 hexane:ethyl acetate). The total yield of the aldol adducts (**131q** (S_1) + **132q** (S_2) + **133q** (A_1) + **134q** (A_2)) was 54%. The major anti isomer **133q** (A_1) material (~15 mg) was obtained separately for further analysis.

(Note. Since anti adduct **133q** (A_1) was mixed in other fractions, it was not possible to calculate the total percentage yield of A_1).

Anti adduct **133q** (**A_1**): 1H nmr ($CDCl_3$) δ 1.09-1.19 (m, 6H, SiCH_2CH_2), 1.11 (d, 3H, J = 6.9 Hz, CHCH_3), 1.95-2.15 (m, 6H, SiCH_2CH_2), 2.69 (dd, 1H, J = 8.7 and 13.8 Hz, ArC*H*H), 3.09 (dd, 1H, J = 3.2 and 13.8 Hz, ArCH*H*), 3.12 (brs, 1H, CHO*H*), 4.11-4.24 (m, 2H, CH_2O), 4.34 (apparent quintet, 1H, J_{app} = 6.9 Hz, CH_3C*H*CH), 4.63- 4.69 (m, 1H, C*H*N), 4.82 (brd, 1H, J = 7.0 Hz, C*H*OH), 5.06 (s, 2H, ArCH_2O), 6.92 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.08 (apparent d, 2H, J_{app} = 8.6 Hz, Ar-H), 7.29-7.54 (m, 9H, Ar-H) ppm.

The following signals (for vicinal hydrogen) were identified on the spectrum of the mixed fraction: δ 5.09 (J = 4.1 Hz, CHC*H*OH) for **131q** (S_1), d 5.17 (J = 4.2 Hz, CHC*H*OH) for **132q** (S_2). (**134q** (A_2) was not observed by NMR)[33].

(−)-(2*R*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (135)

Hydrolysis of the anti aldol adduct 133p (A_1) to carboxylic acid 135

A solution of **133p** (30 mg, 50 μmol) in 3:1 THF/H_2O (1.5 mL) at 0 °C was reacted with 30% H_2O_2 (10 μL, 400 μmol, 8eq) and LiOH (2.4 mg, 100 μmol, 2 equiv.)[10]. The resulting solution was stirred at 25 °C for 18 hours. The reaction was quenched with 1.5 N aqueous Na_2SO_3 (1.1 equiv.). After evaporation of the organic solvent, the aqueous solution was extracted with dichloromethane (2 × 15 ml) to remove oxazolidin-2one 3. The remaining aqueous layer was acidified with 3N HCl (pH 1-2) and was then extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate layers were washed with saturated aqueous NaCl, dried over $MgSO_4$ and evaporated to give the acid **135** (~8.8 mg, 98%).

$[\alpha]_D^{25}$ -17.1° (c 0.45, $CHCl_3$). (lit. $[\alpha]_D^{25}$ -17.5° (c 2.3, $CHCl_3$))[122].

^{1}H nmr ($CDCl_3$)[122] δ 1.04 (d, 3H, J = 7.2 Hz, CHCH_3), 1.40-1.80 (brs, 1H, COO*H*), 2.86 (dq, 1H, J_{app} = 7.2 and 8.9 Hz, CH_3C*H*CH), 4.77 (d, 1H, J = 8.9 Hz, C*H*OH), 7.29-7.40 (m, 5H, Ar-H) ppm.

Hydrolysis of the anti aldol adduct 133q (A_1) to carboxylic acid 135

A solution of **133q** (9 mg, 5 μmol) was subjected to similar cleavage conditions described above to provide the acid **135** (~0.4 mg, 50%).

$[\alpha]_D^{25}$ -20° (c 0.02, $CHCl_3$). (lit. $[\alpha]_D^{25}$ -17.5° (c 2.3, $CHCl_3$))[122].

The NMR data were identical to those reported above for **135**.

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