INFORMATION TO USERS

This manuscript has been reproduced from the microfiim master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

UMI®

UNIVERSITY OF ALBERTA

Investigation of Stereoselection by the Mitsunobu Reaction and Modification of the Hendrickson Reaction

BY

Jiasheng Fu 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

Spring 2000

UNIVERSITY OF ALBERTA

LIBRARY RELEASE FORM

NAME OF AUTHOR: Jiasheng Fu

TITLE OF THESIS: Investigation of Stereoselection by the Mitsunobu Reaction and Modification of the Hendrickson Reaction

DEGREE: Doctor of Philosophy

YEAR THIS DEGREE GRANTED: 2000

SIGNED: Jiasheng Fu

PERMANENT ADDRESS:

Biao Jian Chang

Jiajia, Jianyang

Sichuan, 641421, P. R. China

DATED: January 31, 2000

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled Investigation of Stereoselection by the Mitsunobu Reaction and Modification of the Hendrickson Reaction submitted by Jiasheng Fu in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Dr. John C. Vederas (Supervisor)

Dr. Derrick L. J. Clive

Dr. Neil Branda

Dr. George Kotovych

Dr. Edward E. Knaus

Dr. Frederick G. West (External)

DATED: January 24, 2000

To my wife, Li, and daughters, Jing and Kathy

ABSTRACT

Phosphonium salts produced during the Mitsunobu reaction or the Hendrickson reaction have been investigated in achiral, chiral and polymer-supported versions in order to activate carbon-oxygen bonds to form amides, anhydrides and esters. The reactivities and enantioselectivities of aminophosphines, phosphinites and a phosphonite have been studied in the Mitsunobu esterification. Aminophosphines such as 1,3-dimethyl-2-diazaphospholidine, phenylphosphonous acid *bis*(dimethyl)amide (**11**), 1,3-dimethyl-2-phenyl-1,3,2-diazaphosphinane (**12**) and (*S*)-*N*-methyl-*N*-(1-phenylethylamino)diphenylphosphine (**15**) direct the Mitsunobu reaction only for primary alcohols. The stereoselection of the Mitsunobu esterification for racemic secondary alcohols has also been investigated using chiral phosphorus compounds. Menthyldiphenylphosphinite (**27**) directs the Mitsunobu esterification for secondary alcohols with moderate e.e.'s for both esters and recovered alcohols. A variety of chiral phosphines have been synthesised and tested for reactivity and enantioselectivity in the Mitsunobu esterification. When (-)-menthyldiphenylphosphine (**36**) was used in the Mitsunobu reaction, moderate yields and enantioselectivities were obtained for most of the secondary alcohols tested. For example, 96% e.e. and 81% e.e. of the recovered alcohols were obtained for α-phenethyl alcohol and 2-decanol, respectively when the Mitsunobu reaction was repeated. The acidity of the carboxylic acid greatly influences the yield of the Mitsunobu esterification although it has no effect on the enantioselectivity.

1,2-*bis*(Diphenylphosphinyl)ethane (**86**), 1,3-*bis*(diphenylphosphinyl)propane (**87**) 1,4-*bis*(diphenylphosphinyl)butane (**88**) have been studied in the Hendrickson procedure. The formation of cyclised phosphonium anhydride and oxyphosphonium salt intermediates was observed by NMR spectroscopy when **87** was used. Polymer-supported 1,3-*bis*(diphenylphosphinyl)propane (**93**) was prepared and was found to direct the formation of anhydride and amide in moderate yields in the Hendrickson procedure. When an asymmetric version of the Hendrickson reaction was done using (-)-

menthyldiphenylphosphine oxide (**94**), 55% of the 4-toluic acid ester was obtained for α-phenethyl alcohol with no detectable enantioselectivity.

Three reagents, designed to mimic the key intermediate in the Mitsunobu reaction, *N*-(3-diphenylphosphinylpropionyl)-*N*'-methoxycarbonylhydrazine (**100**), *N*-(3-diphenylphosphinylpropionyl)-*N*'-methyl-*N*'-ethoxycarbonylhydrazine (**101**) and *N*-methyl-*N*-(3-diphenylphosphinylpropionyl)-*N*'-methoxycarbonylhydrazine (**102**), were prepared. Investigation by NMR spectroscopy showed that phosphonium salts, which might mimic the zwitterionic adduct of the Mitsunobu reaction, were observed following treatment with triflic anhydride. These phosphonium salts are very stable and could not be cleaved by alcohol or carboxylic acid.

3-Difluorophosphonoacetylpropionic acid (**106**) was synthesised and tested against succinyl CoA synthetase. It was found that compound **106** is not an inhibitor of succinyl CoA synthetase.

ACKNOWLEDGMENTS

I am most grateful to my supervisor, Professor John C. Vederas, for his excellent guidance, support, and encouragement throughout my studies. I thank all the members in our research group for their help at various points during this work, especially Dr. Joanna Harris for assistance in my research. I am indebted to Dr. Richard Hill and Dr. Andrew Sutherland for their help and proof-reading my thesis. In addition, the staff of spectral and analytical services in the Department of Chemistry are acknowledged for their assistance in characterizing compounds. Financial support from the University of Alberta is gratefully acknowledged. Finally, I would like to thank my wife Li for her love, understanding, and encouragement during this work.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

[α]	specific rotation
APT	attached proton test
Ar	aryl
bp	boiling point
br	broad
n-BuLi	*n*-butyllithium
calcd	calculated
Cbz	benzyloxycarbonyl
CI	chemical ionization
CoA	coenzyme A
concd	concentrated
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMSO	dimethyl sulfoxide
DVB	divinylbenzene
ee	enantiomeric excess
EI	electron impact
ES	electrospray
Et	ethyl
GDP	guanosine 5'-diphosphate
HRMS	high-resolution mass spectrum

IR	infrared
J	coupling constant
m	multiplet
m/z	mass to charge ratio
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile
Ph	phenyl
ppm	parts per million
pyr	pyridine
q	quartet
rt	room temperature
s	singlet
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t	triplet
TBP	tributylphosphine
Tf	trifluoromethanesulfonyl
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran

TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*,*N*-tetramethy-1,2-ethylenediamine
TMS	tetramethylsilane
TMSI	trimethylsilyl iodide
TPP	triphenylphosphine
UV	ultraviolet

INTRODUCTION

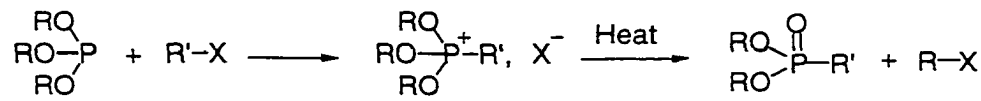
1.0 Objectives

The primary goals of this thesis are to explore modifications of the Mitsunobu and Hendrickson reactions, both of which involve phosphonium intermediates, in order to develop alternative esterification procedures. A key objective is to investigate possible kinetic resolution of racemic secondary alcohols by chiral Mitsunobu reagents. In addition, inhibition of thiolester formation by succinyl CoA synthetase using phosphonate derivatives is briefly examined.

1.1 Phosphonium from trivalent phosphorus

There is a considerable number of reagents for the activation of carbon-oxygen bonds in organic molecules to effect the removal of H_2O in an isohypsic manner.[1] The synthetic importance of such reagents lies in the occurrence of oxygen in common functional groups and the fact that many organic transformations involve the loss of H_2O. Among these reagents, phosphorus compounds play a very important role.

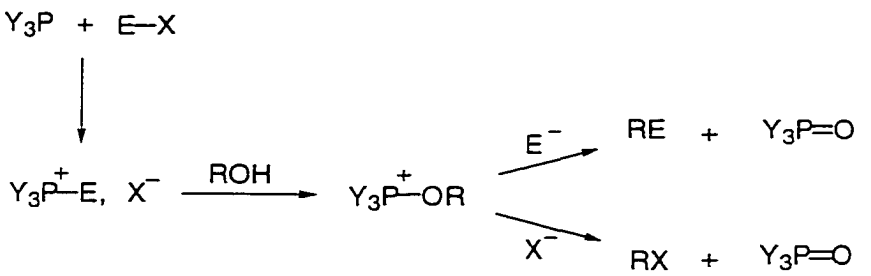
The Michaelis-Arbuzov reaction involves the formation of dialkyl alkylphosphonates by heating alkyl halides with trialkyl phosphites, *via* an intermediate phosphonium salt **1** (Scheme 1).



1

Scheme 1

Phosphonium salts analogous to **1** can be formed by reaction of a variety of trivalent phosphorus compounds with oxidizing electrophiles, and the resulting phosphonium intermediates can react with an alcohol or a carboxylic acid to form alkoxyphosphonium or carboxyphosphonium cations. These cations then undergo nucleophilic displacements, either with their own counterions or with added nucleophiles (Scheme 2).[1]

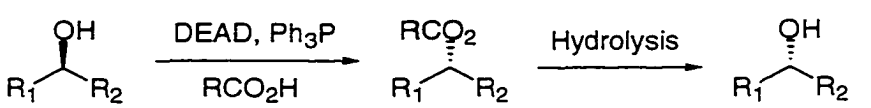


Scheme 2

The electrophilic phosphorus species ($Y_3P^+E\ X^-$ in Scheme 2) are equivalent to pentavalent phosphorus compounds (e.g. phosphorus pentachloride) and are also formed *in situ* from the reaction of trivalent phosphorus compounds with various oxidants. The most commonly used trivalent phosphorus compounds are triphenylphosphine, triphenylphosphite and tris(dimethylamino)phosphine. The most common oxidants are molecular halogens, alkyl halides, carbon tetrahalides, *N*-haloamides and diethyl azodicarboxylate (DEAD).[1] One of the most useful and studied combinations is triphenylphosphine and diethyl azodicarboxylate (DEAD) in the Mitsunobu reaction.[2]

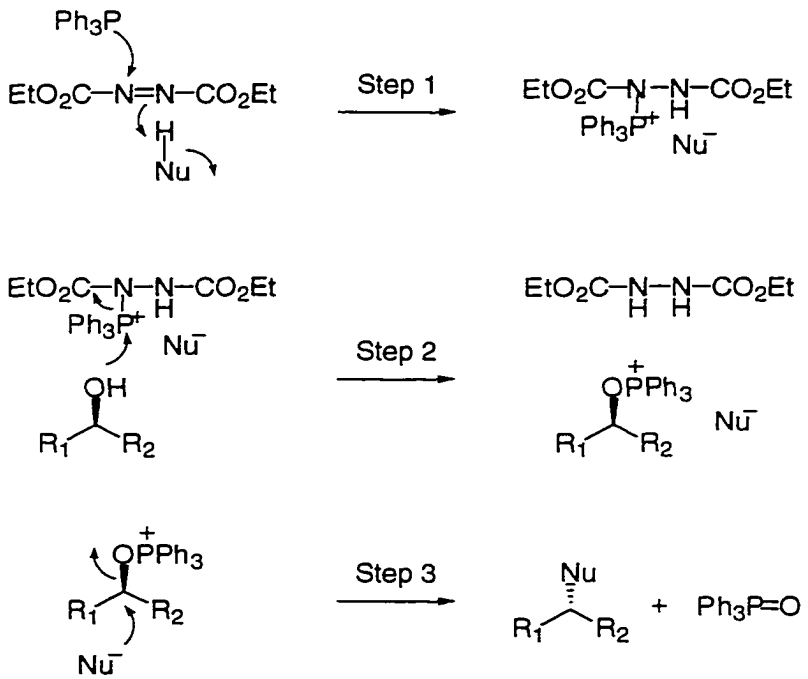
1.2 Mitsunobu reaction

In 1976 Mitsunobu and Yamada reported that carboxylic acids could be esterified with primary and secondary alcohols using a redox system of triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD).[2b] It was found that when optically pure secondary alcohols are used in this reaction, complete inversion of stereochemistry is obtained.[3] Hence this reaction is employed to achieve the desired configuration of alcohols *via* an esterification/hydrolysis procedure (Scheme 3).



Scheme 3

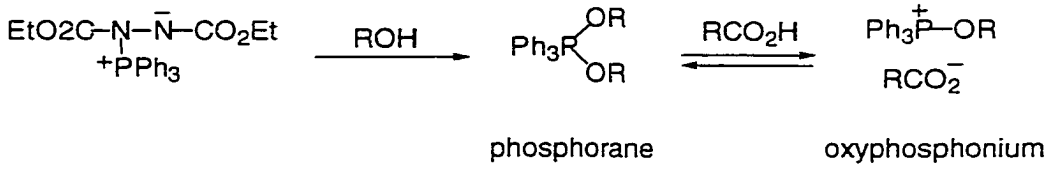
The widely accepted, but over-simplified, three-step mechanism of the Mitsunobu process is shown in Scheme 4. In the first step, triphenylphosphine rapidly reacts with diethyl azodicarboxylate (DEAD) to form the zwitterionic P-N adduct (also called betaine), which is protonated in the presence of NuH (the conjugate acid of the nucleophile, Nu) to form the phosphonium salt (also called protonated betaine). In the alcohol activation step (Step 2), the phosphorus is transferred to the alcohol to form the oxyphosphonium salt and the reduced hydrazide by-product. Finally, the deprotonated nucleophile reacts with the oxyphosphonium salt in an S_N2 reaction to provide the inverted product and triphenylphosphine oxide.[4,5]



Scheme 4

Modified mechanisms have been suggested by Camp *et al*,[6] Pautard-Cooper *et al* [7] and Varasi *et al.*[8] Their research showed that in addition to the key oxyphosphonium intermediate, pentavalent dialkoxyphosphorane may also be involved in the alcohol activation step. When one equivalent each of benzoic acid, triphenylphosphine, and DEAD, and two equivalents of alcohol are mixed at -78 °C in THF, peaks corresponding to both

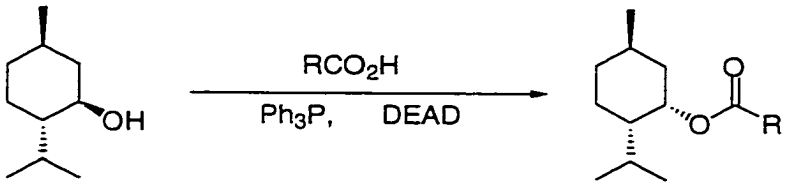
phosphorane and the oxyphosphonium salt are observed by ^{31}P NMR spectroscopy.[7] This data suggests that an equilibrium mixture of phosphorane and oxyphosphonium salt exists, with the nature of the alcohol, solvent and acid determining the equilibrium concentrations (Scheme 5).



Scheme 5

In addition to carboxylic acids, other acidic components (NuH) with a $pk_a \leq 11$[8] can be used, including certain protected amines,[9.10.11] phthalimides,[12.13.14] azides,[15] silanols,[16] thiolacetate[17] and some carbon-centered nucleophiles.[18.19.20.21] Thus, the Mitsunobu process permits transformation of alcohols to a large variety of other functional groups in a stereospecific fashion.

For many alcohol substrates in the Mitsunobu esterification, the carboxylic acid component is not critical and good yields can be obtained with acetic and benzoic acids. However, for sterically hindered alcohols, yields are often low with these acids. They can be improved through use of more acidic compounds such as 4-nitrobenzoic acid[22.23] or chloroacetic acid.[24] For example, Dodge and co-workers have shown that the Mitsunobu esterification of menthol proceeds in low yield with benzoic and acetic acid, but increases to 77% with 4-nitrobenzoic and to 60% with chloroacetic acid (Scheme 6). Similar results are obtained for the other sterically congested precursors, such as steroid alcohols.



RCO_2H	Yield (%)
R = 4-$NO_2C_6H_4$	77
R = $ClCH_2$	60
R = CH_3	0
R = Ph	20

Scheme 6

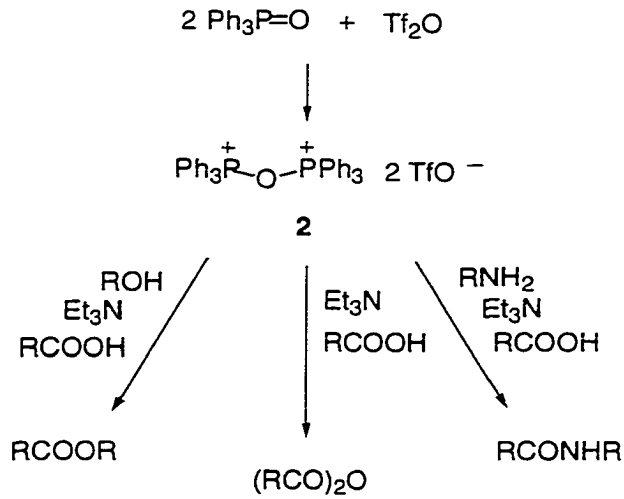
Camp and Jenkins[6] suggest that the oxyphosphonium ion (the reactive intermediate) is favoured over the phosphorane (unreactive intermediate) when the acid strength is increased.

Although triphenylphosphine and DEAD are the most common reagents in Mitsunobu esterifications, many modifications exist. Use of diphenyl(2-pyridyl)phosphine[25] and (4-dimethylaminophenyl)diphenylphosphine[26] can facilitate product isolation since the resulting phosphine oxide is removed by aqueous acid wash. Use of polystyrene-bound triphenylphosphine allows removal of phosphine oxide from the product by filtration.[27] Dimethyl azodicarboxylate is used less often, but has the advantage that the by-product, dimethyl hydrazodicarboxylate, can be removed by aqueous extraction.[28] Polymer-supported alkyl azodicarboxylates are also very effective, facilitate product purification and have the advantage of being readily recovered and reoxidized for repeated use.[29]

1.3 Phosphonium from pentavalent phosphorus: the Hendrickson reaction

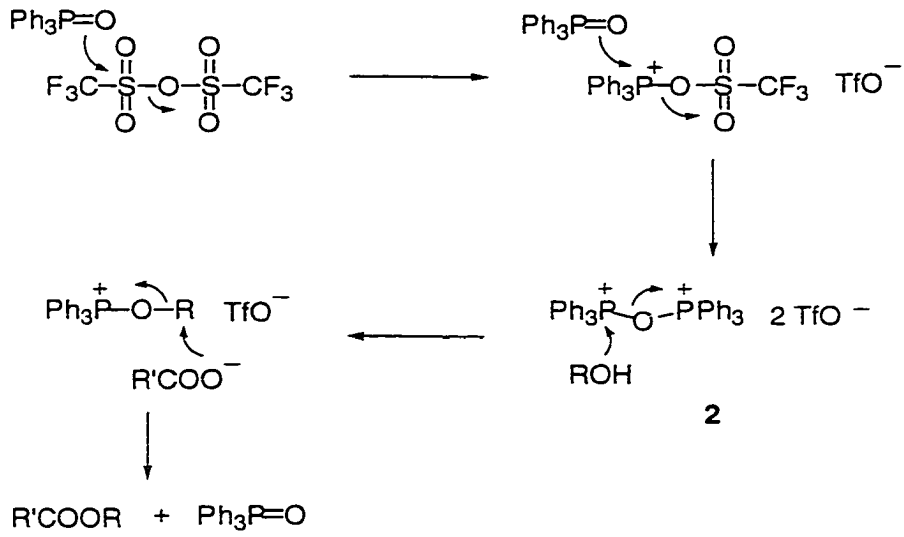
In 1987, Hendrickson reported the use of phosphonium triflate salt **2** as a reagent for the activation of the carbon-oxygen bond.[30,31] To generate this compound,

triphenylphosphine oxide is reacted with triflic anhydride. The phosphonium salt activates carboxylic acids to allow formation of esters, carboxylic anhydrides and amides (Scheme 7).



Scheme 7

The mechanism of this process (Scheme 8) probably involves reaction of triphenylphosphine oxide with triflic anhydride followed by displacement of triflate by a second molecule of triphenylphosphine oxide to give **2**. The activation of the carboxylic acid (or possibly an alcohol) proceeds by displacement on **2** to form a carboxyphosphonium salt (or an alkoxyphosphonium salt). This can then undergo attack with a molecule of alcohol, carboxylic acid or amine in the presence of triethylamine to form an ester, anhydride or amide, respectively.

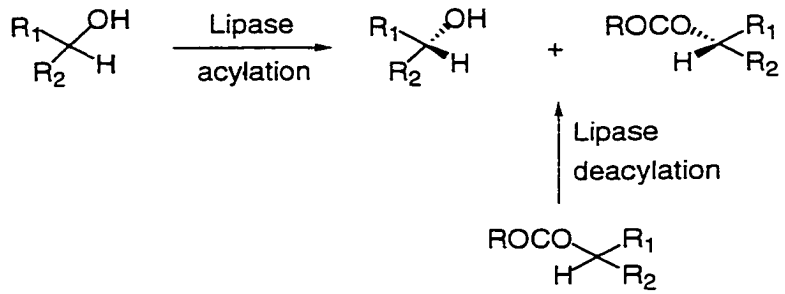


Scheme 8

In the formation of esters, if a mixture of an alcohol and a carboxylic acid is added to **2**, oxygen activation may potentially occur on either species. Both of the possible activation products would proceed to the formation of the ester; albeit with different stereochemical outcome at the alkoxy carbon. The advantage of this reagent is that triphenylphosphine oxide can be recycled after the reaction, the reaction conditions are mild, and the reported yields of the products are high (i.e. 70% to 95%).

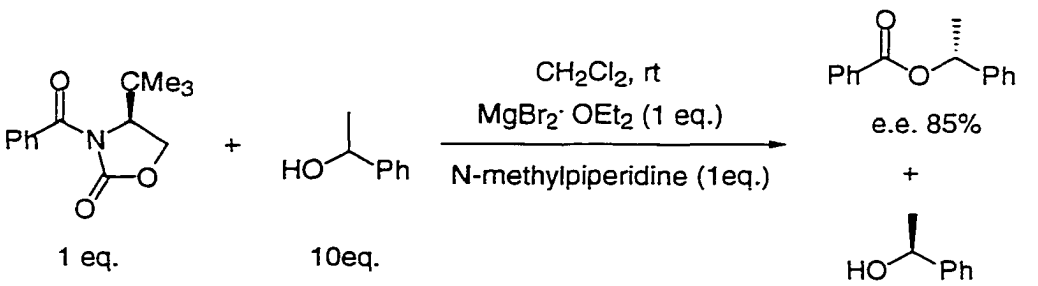
1.4 Kinetic resolution of alcohols

Kinetic resolution of racemic alcohols through lipase-catalyzed acylation or deacylation has been extensively studied,[32,33,34] and established as one of the most effective methods for the preparation of optically active alcohols (Scheme 9).[35]



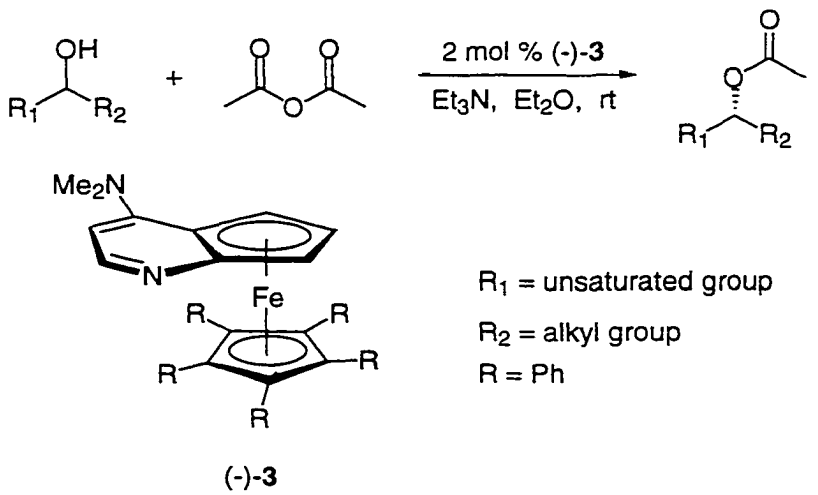
Scheme 9

Nonenzymatic alternatives involving stereoselective acylation have been developed recently. For example, a chiral imide was used by Evans and coworkers to selectively acylate one enantiomer of a racemic secondary alcohol (present in excess) in high e.e (Scheme 10).[36]



Scheme 10

In a catalytic process, Fu and co-workers recently reported an effective kinetic resolution of secondary alcohols using chiral catalyst **3**, which contains a DMAP moiety, with acetic anhydride as the acylating agent (Scheme 11). The e.e.'s of the recovered alcohols range from 92-99%.[37,38]



Scheme 11

A related example of the catalytic resolution of racemic alcohols has been reported by Fuji and co-workers.[39] They employed nucleophilic catalyst **4** which also contains a

DMAP moeity. This catalyst promotes the kinetic resolution of a racemic monoester of *cis*-cyclo-1,2-diol (Figure 1) through enantioselective acylation with isobutyric anhydride. Use of 5 mol% of the catalyst leads to the recovery of optically active alcohols in 92-99% ee at 68-77% conversion. Investigation of the catalyst using nuclear Overhauser effects suggests that it exists in an "open conformation" **4**. Reaction with isobutyric anhydride forms the reactive *N*-acyliminium intermediate **5**, which exists in a "closed conformation" with the *si* face of the carbonyl group blocked by the naphthalene ring and the *re* face open for the subsequent acylation with alcohols.

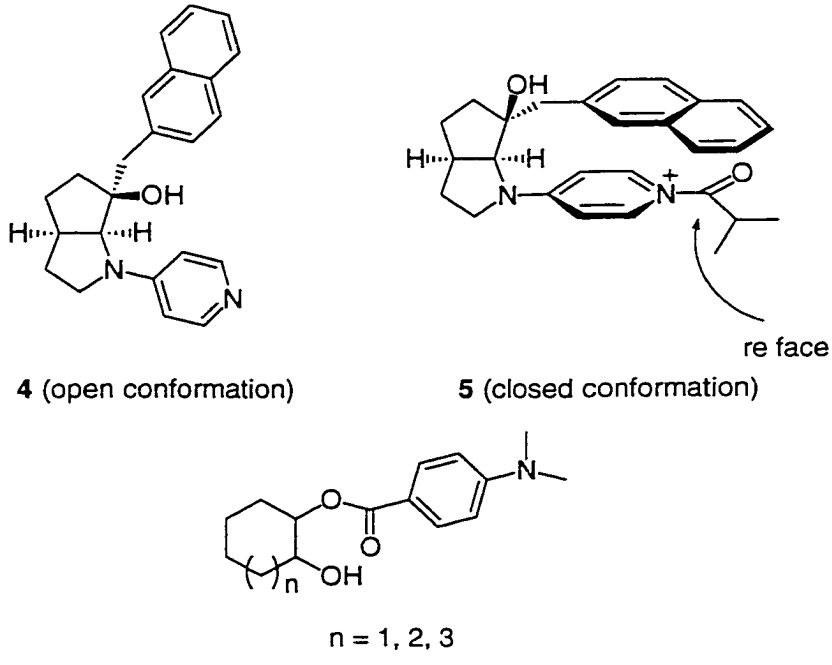
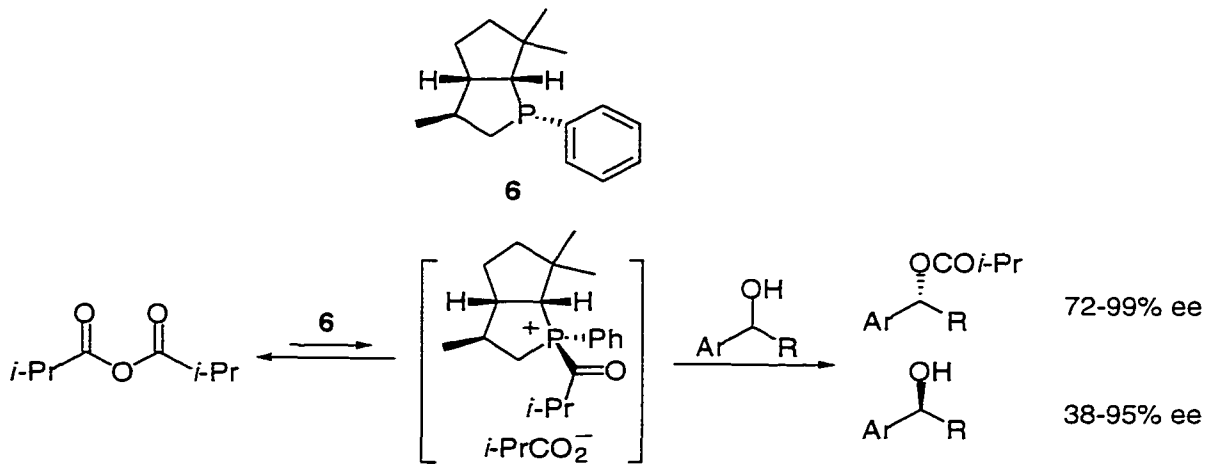


Figure 1: Structures of chiral DMAP analogues & racemic monoester of cis-cyclo-1,2-diol

A chiral phosphine **6** has also been reported to catalyze the kinetic resolution of racemic alcohols using $(i\text{-PrCO})_2O$ as the acylating agent.[40] This process may involve the reversible formation of a chiral acylating reagent by the reaction of **6** with the anhydride. Presumably, the chiral intermediate then reacts with only one enantiomer of the alcohol to form the ester (Scheme 12). This procedure produces esters with 72% to 99% e.e. and recovered alcohols with 38% to 95% e.e.



Scheme 12

The only report of a kinetic resolution of racemic alcohols using a selective Mitsunobu reaction is by Kellogg and co-workers in 1995.[41] In this work, chiral 1,3,2-dioxaphosphepane (Figure 2) were used to replace triphenylphosphine in the Mitsunobu esterification. Although the enantiomeric purities of product esters are low to moderate (0-39% e.e.), at the expense of high conversions (92-95%), the recovered alcohols have excellent e.e.'s (99%).

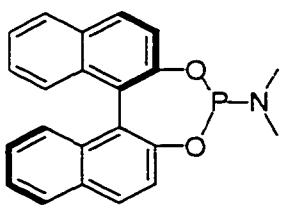
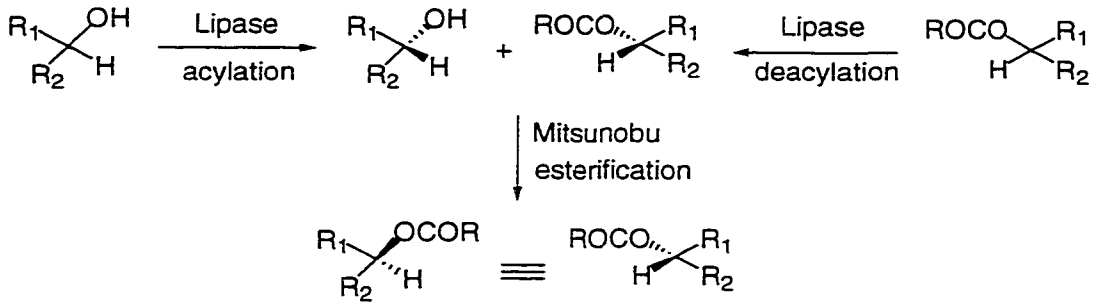


Figure 2: 1,3,2-dioxaphosphepane

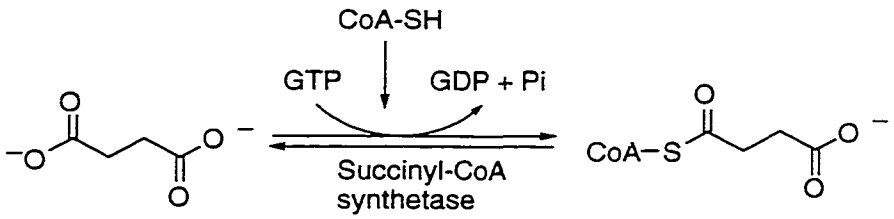
Interestingly, the combination of lipase-catalyzed resolution of alcohols with the Mitsunobu esterification has also been reported by Kanerva and co-workers in 1995.[42] This methodology involves a one-pot, two-step resolution-esterification procedure for the preparation of optically active esters of secondary alcohols and avoids typical problems of separation and low yields common in conventional resolutions (Scheme 13).



Scheme 13

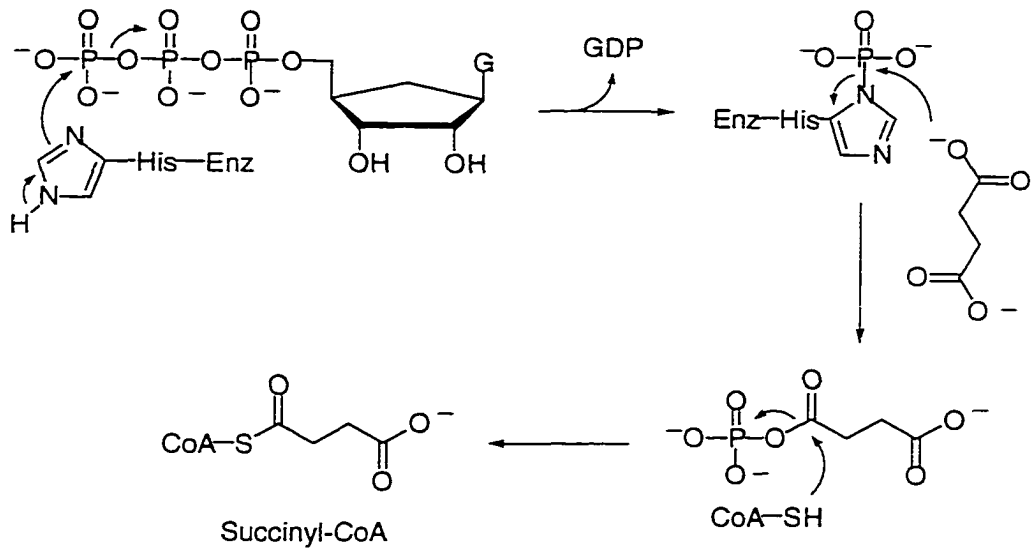
1.5 Succinyl CoA synthetase

A number of enzymatic thioester formations also take advantage of the "oxophilicity" of phosphorus and its electron-withdrawing capability, which can generate a good leaving group. Thus, activation of a host of carboxylic acids by nucleotide triphosphates (e.g. ATP, GTP) occurs by enzyme-catalyzed generation of mixed carboxylic-phosphate anhydrides that are the attacked by nucleophiles at the carbonyl. As a side project related to our interest in phosphonate chemistry, we examined synthesis of a potential inhibitor for succinyl CoA synthetase. This enzyme catalyzes the reversible conversion of succinnyl-CoA to succinate in the citric acid cycle (Scheme 14).[43]



Scheme 14

The mechanism of this enzyme reaction involves the formation of phosphoenzyme, and succinyl phosphate (Scheme 15).[43]

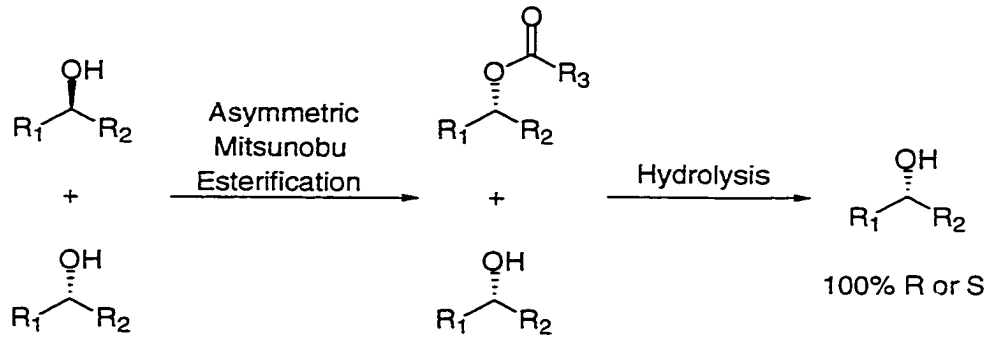


Scheme 15

Project objectives

Target 1: Asymmetric Mitsunobu esterification to resolve racemic secondary alcohols

In recent years, considerable work has been done on the mechanism of the Mitsunobu reaction.[6,7,8,44,45] However, there has been only one study of chiral selection in Mitsunobu reaction with racemic secondary alcohols.[41] An isomer-specific Mitsunobu esterification is particularly attractive for its potential use in the deracemization of secondary alcohols. In this approach, one enantiomer of a racemic mixture of alcohols is selectively esterified with inversion of stereochemistry, whereas the other enantiomer remains unreacted. Subsequent hydrolysis of the crude product mixture or of the separated ester gives a single enantiomer of the alcohol (Scheme 16). The advantage of this method is that ideally in just two reactions, 100% of the optically pure alcohols can be isolated without losing half as the unwanted enantiomer.

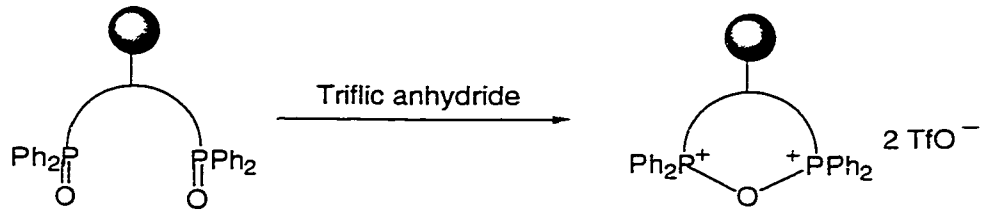


Scheme 16

In order to achieve this goal, potentially either a chiral azodicarboxylate or a chiral phosphine or a combination of both could be used. In this study, chiral azodicarboxylates and a variety of chiral or achiral phosphorus compounds such as aminophosphines (with N–P bond), phosphinites and phosphonites (with O–P bond) have been designed and synthesized. These compounds have been used to replace DEAD and triphenylphosphine in Mitsunobu esterifications to investigate reactivity and selectivity, and thereby to establish a methodology for the kinetic resolution of racemic secondary alcohols.

Target 2: Solid phase Hendrickson procedure

From the previous discussion of the Hendrickson procedure it is clear that the product triphenylphosphine oxide could be recycled after the reaction. Since polymer-supported reagents usually facilitate the isolation of the products, a solid phase version of the Hendrickson procedure could be expected not only to enhance purification but to allow recycling of the polymer-supported reagent without additional chemical transformation. In order to investigate this, a polymer-supported bis-triphenylphosphine oxide analogue (Scheme 17) was designed for the solid phase Hendrickson procedure. This analogue requires that the phosphorus oxygen double bonds are close enough for cyclization to occur.

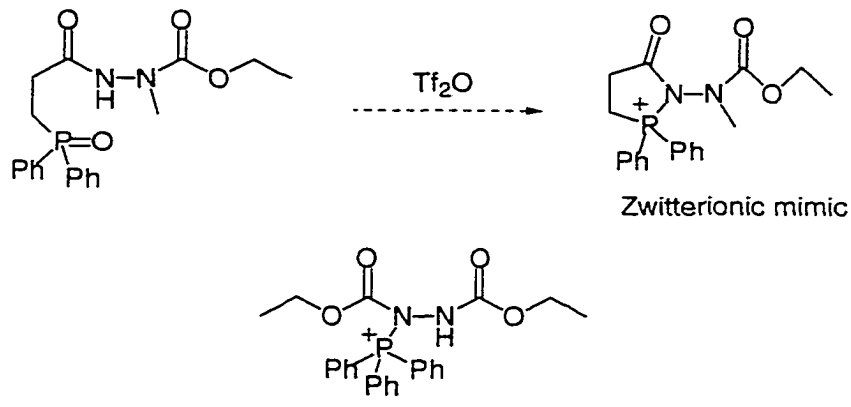


Scheme 17

Target 3: Mitsunobu mimics

Although the Mitsunobu reaction is a very useful process, there are drawbacks that limit its use. Azodicarboxylates are only moderately stable and some, such as dimethyl azodicarboxylate, can explode upon heating. Triphenylphosphine is a relatively cheap reagent, but the triphenylphosphine oxide formed during the Mitsunobu reaction is often difficult to remove from the product. Thus, purification problems can limit large scale use of Mitsunobu reactions.

In order to overcome these two drawbacks, we hoped to mimic this reaction without using azodicarboxylate esters and triphenylphosphine. From the mechanism of the Mitsunobu reaction, it is clear that the zwitterionic species formed from azodicarboxylate and triphenylphosphine is a key intermediate. This intermediate selectively activates the alcohol after protonation by an acid to form the oxyphosphonium intermediate. Thus a compound which has the phosphine and the reduced azo moiety linked could mimic the protonated zwitterion. This could potentially activate alcohols as in the traditional Mitsunobu reaction. The advantage of this modification is that the reagent could be recycled, and even a solid phase version of the Mitsunobu process could be established. A possible approach to generation of such a mimic is shown in Scheme 18.



Scheme 18

Target 4: Synthesis of a potential inhibitor of succinyl-CoA synthetase

Compound **7** (Figure 3) could mimic the succinyl phosphate intermediate in the succinyl CoA synthetase reaction and inhibit the enzyme. Halomethyl ketones **8** are known inhibitors of serine and cysteine proteinases, and can form stable tetrahedral intermediates, which in some cases subsequently alkylate active site residues.[46] Previously, compound **9** was made in this group and was found not to be an inhibitor.[47] It seemed that the electron-withdrawing ability of the two adjacent fluorine atoms would increase the electrophilicity of the carbonyl carbon to undergo nucleophilic attack, and could enhance the stability of the tetrahedral intermediate.

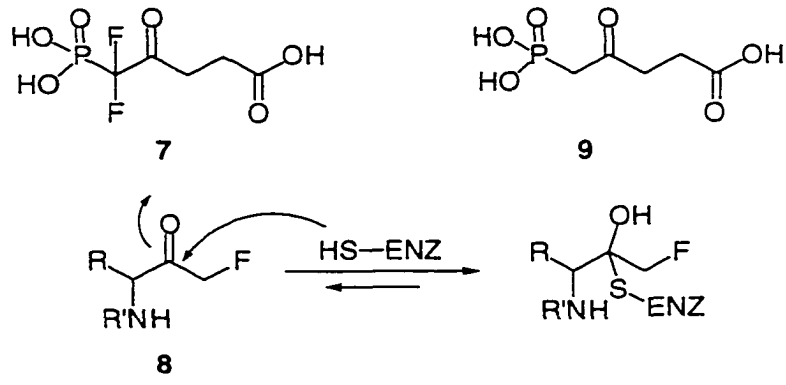


Figure 3: A potential inhibitor of succinyl CoA synthetase

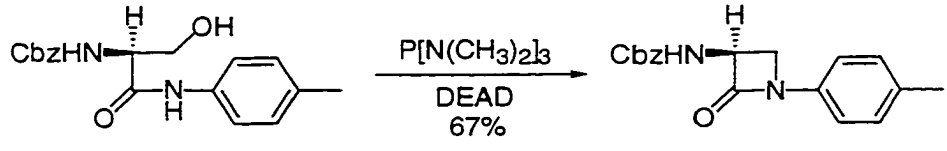
RESULTS AND DISCUSSION

Part 1. Stereoselection in the Mitsunobu esterification of racemic secondary alcohols

The only example of stereoselective Mitsunobu esterification of racemic secondary alcohols is the work of Kellogg and coworkers,[41] and this encouraged us to examine this area. As mentioned in the introduction, both chiral phosphine and chiral azodicarboxylates could potentially be used. Our studies began with an investigation of the Mitsunobu esterification using aminophosphines, phosphinites and phosphonites because a large number of commercially available chiral alcohols, amines, diamines and amino alcohols could be used to rapidly make chiral phosphorus compounds.

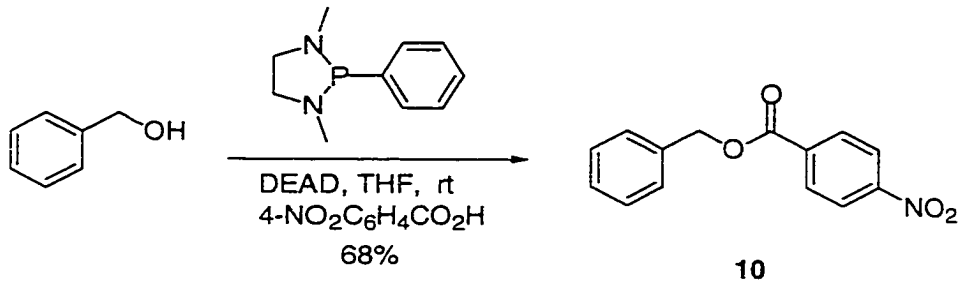
1.1 The synthesis of chiral and achiral aminophosphines and subsequent reactions in the Mitsunobu esterification

To the best of our knowledge, there has only been one report of an aminophosphine in the Mitsunobu reaction.[48] In this case tris(dimethylamino)phosphine was used in place of triphenylphosphine for the formation of a β-lactam (Scheme 19).



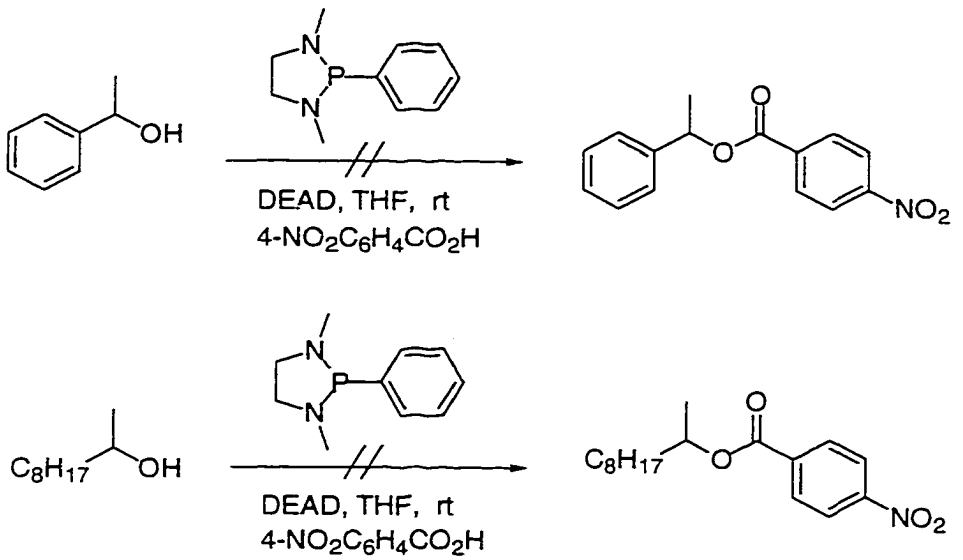
Scheme 19

Since the Mitsunobu reaction with aminophosphines had not been extensively studied, we decided to begin with an achiral aminophosphine. Commercially available 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine was used in the esterification of benzyl alcohol with 4-nitrobenzoic acid as the acidic component. In the presence of DEAD in THF at room temperature, the ester is obtained in 68% yield (Scheme 20).



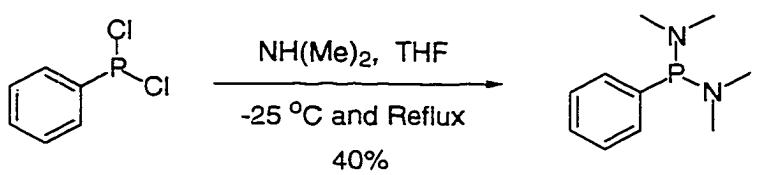
Scheme 20

For this reaction to be successful, the standard Mitsunobu conditions have to be altered. Normally, the azo compound is added to a pre-formed solution of the alcohol, acid and phosphine in a solvent such as THF. In the case of the 1,3-dimethyl-2-diazaphospholidine these conditions fail to give any desired product. Once the alcohol, acid and aminophosphine are mixed in THF a precipitate forms, possibly due to decomposition of the aminophosphine. However, the reaction is successful when the order of addition is changed. Pre-formation of the zwitterionic adduct by addition of DEAD to the aminophosphine followed by addition of alcohol and acid gives **10** as described above. This is the first report of the use of an aminophosphine in the Mitsunobu esterification. Encouraged by this result, secondary alcohols such as α-phenethyl alcohol and 2-decanol were reacted under similar conditions. Unfortunately, in both cases none of the desired ester was detected (Scheme 21).



Scheme 21

The failure of the Mitsunobu esterification of secondary alcohols using 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine could possibly be due to the rigidity of the diazaphospholidine ring. In order to investigate this, compound **11** lacking the five membered ring was synthesized according to the method of Maier[49] in 40% yield from dichlorophenyl phosphine (Scheme 22). Although sterically more crowded at phosphorus, the conformational mobility of the dimethylamino substituents could potentially increase the reactivity.

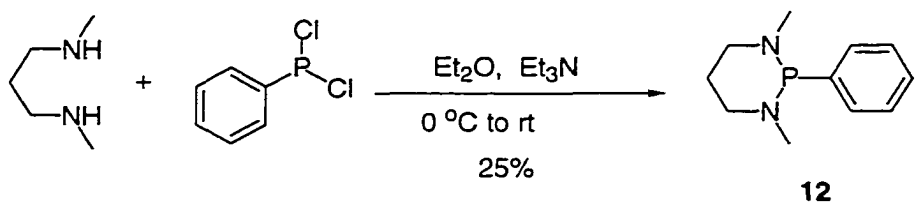


11

Scheme 22

However, this modification decreased the efficiency of the Mitsunobu esterification of benzyl alcohol with 4-nitrobenzoic acid. TLC showed no esterification at room temperature, and only 43% of ester **10** was isolated after reflux for 12 h. When compound **11** was mixed with DEAD, a precipitate formed indicating that the zwitterionic intermediate had

formed. Although solubility is a possible problem, the low reactivity exhibited by this intermediate is probably due to the increased steric hindrance at phosphorus, thereby limiting access of the alcohol to the reaction site. In order to better understand the influence of the ring on the reactivity of aminophosphines, compound **12** was prepared. Using the method of Hutchins,[50] **12** is obtained in 25% yield by the reaction of phenyldichlorophosphine and dimethyl-1,3-diaminopropane in the presence of Et_3N (Scheme 23).

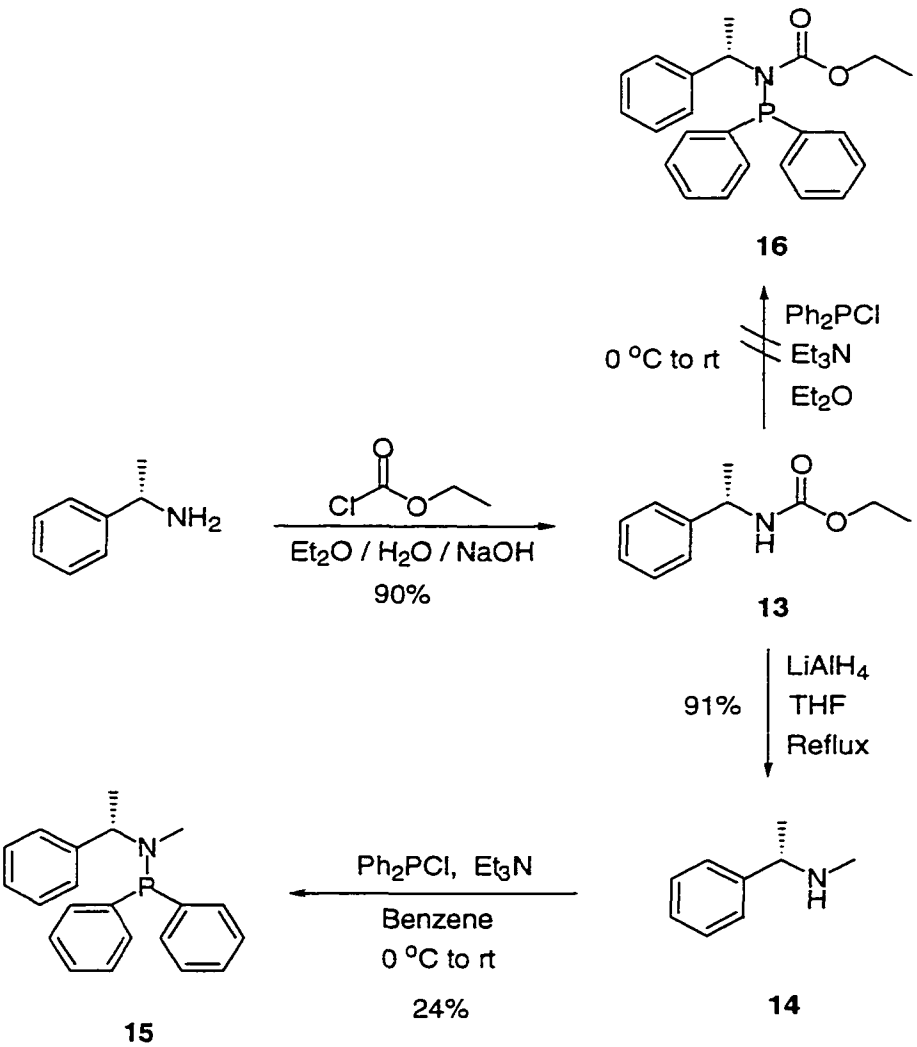


12

Scheme 23

When this compound is used, no Mitsunobu esterification of either benzyl alcohol or 2-decanol is observed. Although it is unclear as to why aminophosphine compounds are not good replacements for triphenylphosphine in the Mitsunobu esterification of secondary alcohols, it may be that steric factors combined with the lability of the two nitrogen phosphorus bonds prevents activation of the alcohol. In order to examine this hypothesis, we investigated phosphorus compounds with both 1 and 3 nitrogen ligands. When commercially available $P(NMe_2)_3$ was used in place of Ph_3P, neither primary nor secondary alcohols were esterified under Mitsunobu conditions even though $P(NMe_2)_3$ allowed cyclization of the β-lactam as shown in Scheme 19.[48] To test an aminophosphine containing only one nitrogen ligand, compound **15** was synthesised as outlined in Scheme 24. Optically pure material was prepared to test the enantioselectivity of the reaction. Following a literature procedure,[51] reaction of optically pure α-phenethylamine using ethyl chloroformate under basic conditions gives **13**. Reduction of **13** using $LiAH_4$ provides the chiral N-methylamine **14** in high yield. Reaction of compound **14** with Ph_2PCl in the presence of Et_3N affords the desired chiral aminophosphine **15** in modest yield. Attempts

to synthesize compound **16** using similar conditions to those described for the synthesis of **15** failed, probably due to the low nucleophilicity of the nitrogen caused by electron-withdrawing effect of the adjacent carbonyl.



Scheme 24

With compound **15** available, Mitsunobu esterification of both 2-decanol and benzyl alcohol with 4-nitrobenzoic acid was attempted. Only 13% of the ester was isolated for 2-decanol and 55% of the ester was obtained in the case of benzyl alcohol. Due to the low yield for the reaction with 2-decanol, no effort was made to examine the stereoselectivity with this alcohol.

The failures of the various aminophosphines in the Mitsunobu esterification for secondary alcohols could be explained from a mechanistic point of view. Since the aminophosphines are effective as triphenylphosphine replacements in the case of primary alcohols, it is obvious that the zwitterionic adduct forms in the first step. It is therefore likely that the alcohol activation step fails because of steric congestion or because of the decreased electrophilicity of the adjacent phosphorus atom caused by the nitrogen lone pairs (Figure 4). In principle, the downfall of the esterification could also be due to inability of the activated alcohol (phosphonium intermediate) to undergo S_N2 displacement, but this is less likely as such intermediates readily undergo elimination reactions if substitution is not possible.[52]

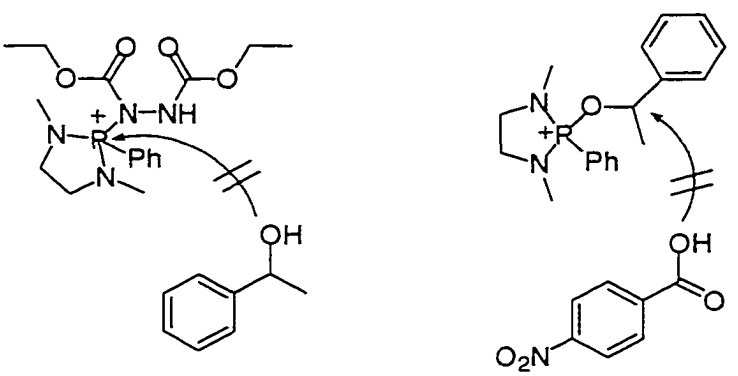
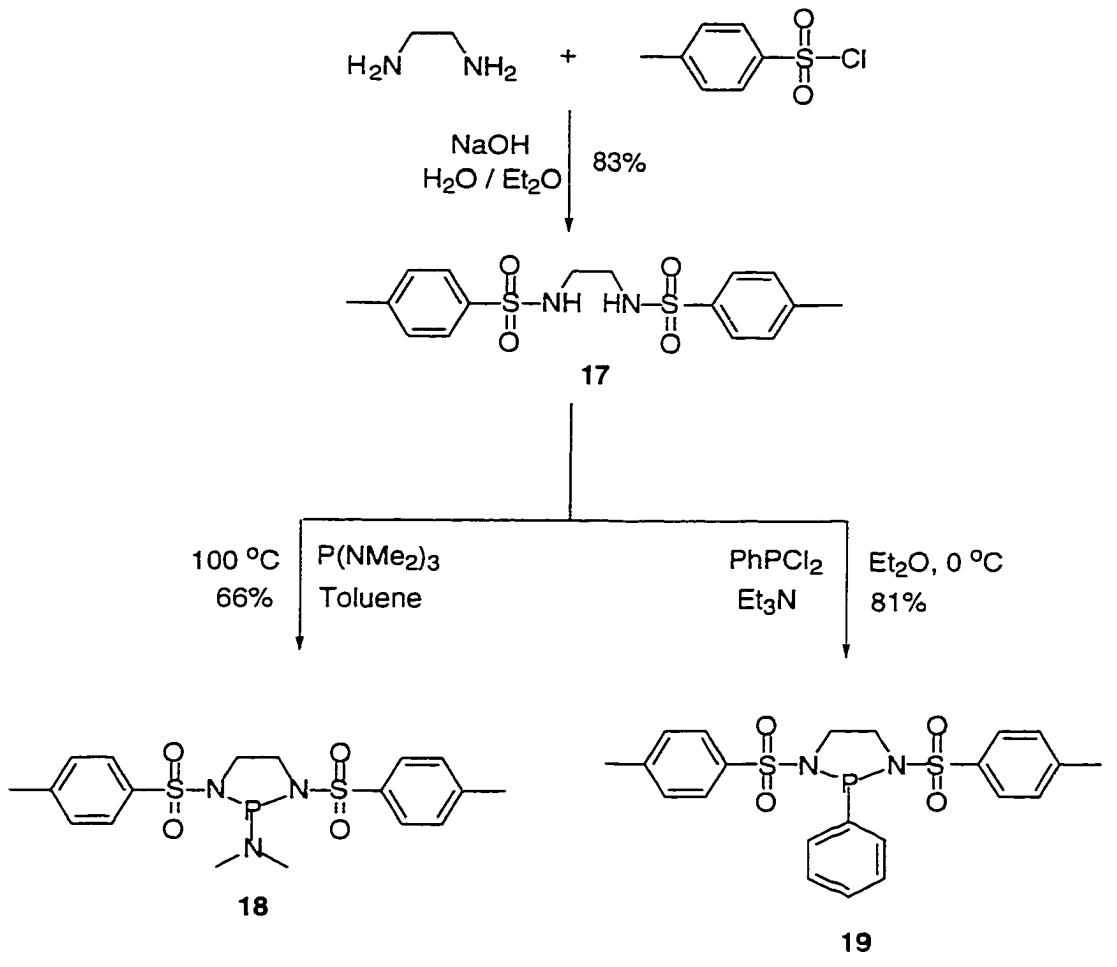


Figure 4: Two possibilities accounting for the failure of the Mitsunobu esterification.

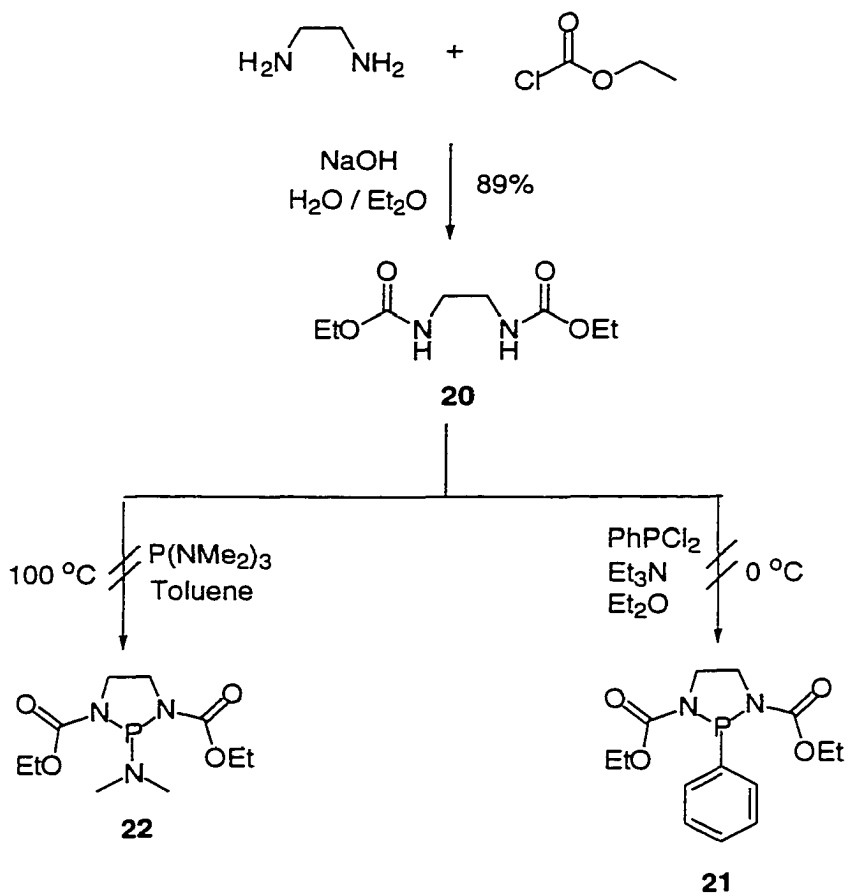
In order to examine influence of the nitrogen lone pairs, compounds **18** and **19** were synthesized (Scheme 25). The intention was to decrease electron donation to phosphorus by the adjacent nitrogen lone pairs through introduction of electron-withdrawing substituents such as tosyl.



Scheme 25

The synthesis of the compounds proceeds with bis-tosylation of 1,2-ethyldiamine in the presence of sodium hydroxide to give the known[51] bis-tosylated diamine **17** in good yield. Reaction of this compound with $P(NMe_2)_3$ or $PhPCl_2$ gives 2-dimethylaminodiazaphospholidine **18** and 2-phenyldiazaphospholidine **19**, respectively. Unfortunately neither compound could direct the Mitsunobu esterification for either primary alcohols or secondary alcohols. For compound **19**, the zwitterionic adduct did not form. This was confirmed by TLC and the continued appearance of the yellow colour of DEAD. Furthermore, TLC showed that both DEAD and compound **19** were still present even after 2 days at room temperature and 6 h at reflux. Similar results were obtained for compound **18**.

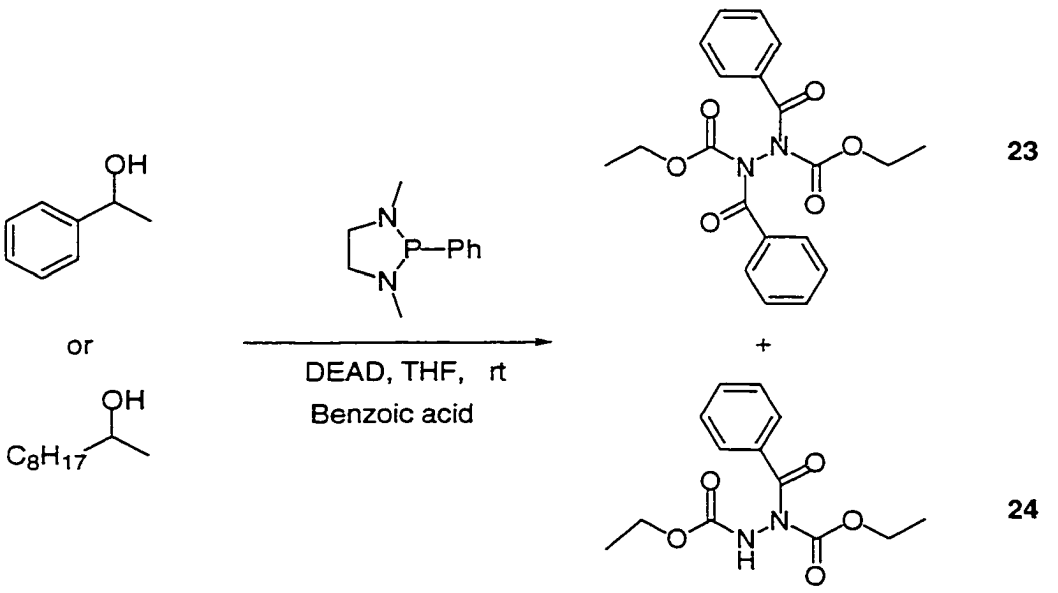
The failure of the formation of the zwitterionic adduct may be due to the decreased nucleophilicity of the phosphorus which is caused by the strong electron-withdrawing nature of the adjacent sulfonamides. In order to overcome this, we decided to utilise ethoxylcarbonyl substituents, which are less electron-withdrawing than tosyl. Although *N,N*-diethoxylcarbonylated diamine **20** is easily prepared, the cyclization of **20** with either $PhPCl_2$ or $P(NMe_2)_3$ did not result in the formation of either of the desired cyclic compounds **21** and **22** (Scheme 26).



Scheme 26

The effect of the acidity of the carboxylic acid in the Mitsunobu esterification has also been tested. The acid component used in the esterification attempts discussed in the above section is 4-nitrobenzoic acid (pKa = 3.41), which is more acidic than commonly-

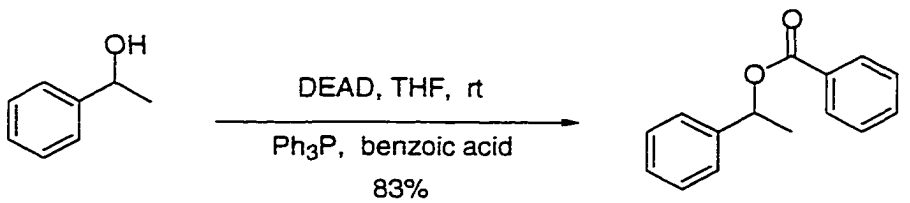
used benzoic acid (pKa = 4.19). In some cases the acidity of the carboxylic acid has a considerable influence on the reactivity.[22,23,24] The mechanistic study of the Mitsunobu esterification by Hughes *et al.*[44] suggests that the carboxylate (RCO_2^-) can function both as a nucleophile and as a base to deprotonate the alcohol. The authors proposed that 4-nitrobenzoate ($4\text{-}NO_2PhCO_2^-$) is not a strong enough base to deprotonate the secondary alcohol because of the strong electron-withdrawing effect of the nitro group. Interestingly, use of benzoic acid instead of 4-nitrobenzoic acid, 2-phenyldiazaphospholidine and DEAD did not give esterification of α-phenethyl alcohol or 2-decanol. Instead, compounds **23** and **24** were isolated, indicating activation of benzoic acid by the phosphine adduct with subsequent acylation of the nitrogen (Scheme 27).



	23	24
α-phenethyl alcohol	13%	38%
2-decanol	14%	36%

Scheme 27

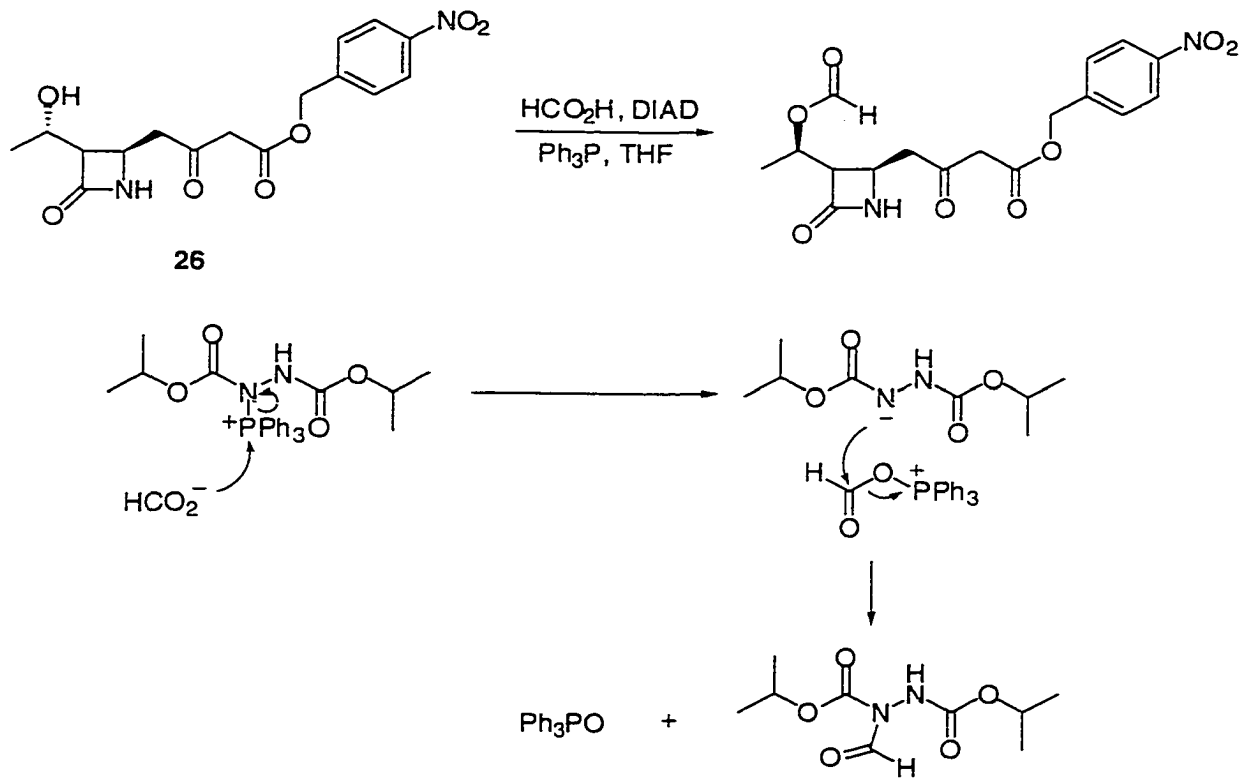
In both of the reactions, most of the secondary alcohol was recovered along with approximately 30% of the reduced DEAD ($DEADH_2$). Use of triphenylphosphine instead of the aminophosphine to esterify α-phenethyl alcohol under the same conditions described in Scheme 27 gives 83% of α-phenethyl benzoate **25** (Scheme 28). These results indicate that the properties (acidity, nucleophilicity) of the carboxylic acid component must be carefully balanced with those of the chosen phosphine, at present in an empirical fashion.



25

Scheme 28

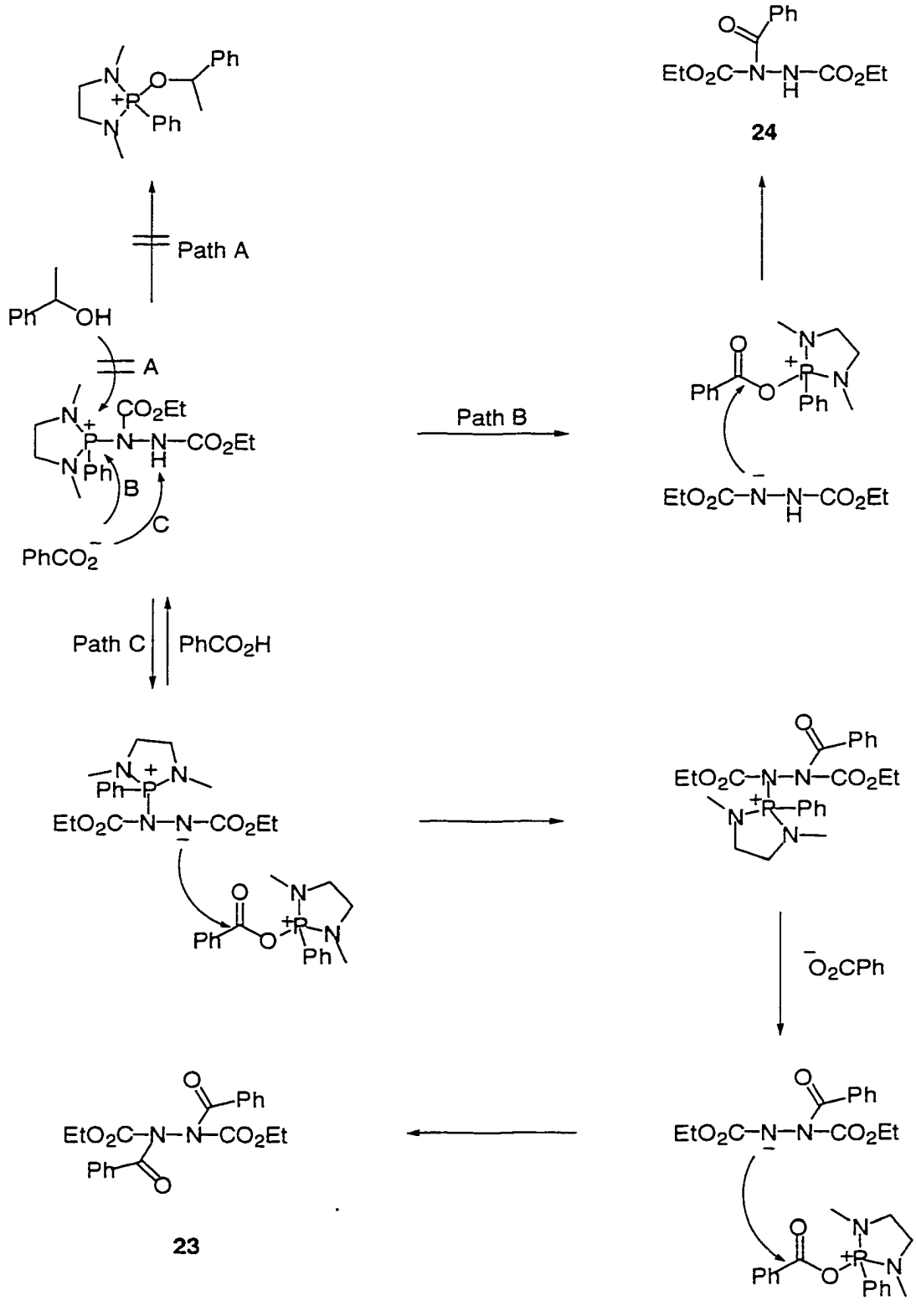
Some understanding of the mechanism is provided by studies of Hughes *et al.*[44] Esterification of azetidinone derivative **26** using one equivalent each of DIAD, Ph_3P and *two* equivalents of formic acid proceeds readily in good yield (Scheme 29). However, using the same conditions with only *one* equivalent of formic acid (or acetic acid) results in rapid N-formylation (or acetylation) to give the reduced hydrazodicarboxylate derivative . The authors propose that when one equivalent of formic acid is employed, protonation of the zwitterionic adduct of Ph_3P and DIAD results in quantitative formation of relatively nucleophilic formate anion which attacks phosphorus.



Scheme 29

The resulting activation of formate leads to N-acylation of the hydrazodicarboxylate anion. In contrast, they propose that use of two equivalents for formic acid may give a strongly hydrogen-bonded species, "bis-formate." An alternative possibility may be that the extra equivalent of formic acid protonates the hydrazodicarboxylate anion, thereby reducing its capacity for N-acylation. Equilibria between various phosphorus species bearing alcohol and/or carboxylate eventually leads to esterification.

Another study by Hughes and co-workers[53] showed that without an alcohol present, the zwitterionic adduct formed between Ph_3P and DIAD reacts with the carboxylic acid to form mono- and bis-acylated hydrazines, and an acid anhydride. Since no competitive alcohol activation step exists, the only pathway for the zwitterionic adduct is the activation of the carboxylic acid to form the observed mono and bis acylated hydrazines (Path B and Path C, Scheme 30).



Scheme 30

Clearly both steric and electronic factors will play key roles in multiple equilibria (which appear to include both pentavalent and tetravalent phosphorus species), and the Mitsunobu process is still not fully understood. A possible rationalization of our results is depicted in Scheme 30.

1.2 The synthesis of chiral phosphinites and phosphonites and their reactions in the Mitsunobu esterification

Since aminophosphines are not effective replacements for triphenylphosphine in our target reaction, phosphinites and phosphonites were investigated. These compounds are readily made by the reaction of chlorodiphenylphosphine with various alcohols. The alkoxyphosphonium species formed from either a phosphinite or a phosphonite will have two or three O–P bonds, respectively. Therefore displacement could occur at two positions: either at the carbon adjacent to the oxygen of the alcohol, which is the desired displacement; or at the carbon adjacent to original oxygen of the phosphinite or phosphonite, which is an undesired displacement. Although there are reports of trialkyl phosphite being employed in the Mitsunobu reaction to form β-lactams,[48,54,55,56] in order to block undesired displacements, phenoxydiphenylphosphine,[57] diphenoxyphenyl-phosphine[57] or triphenoxyphosphine[57] are usually used. Obviously, the sp^2 carbon hinders displacement of the original phosphorus ligand (Figure 5).

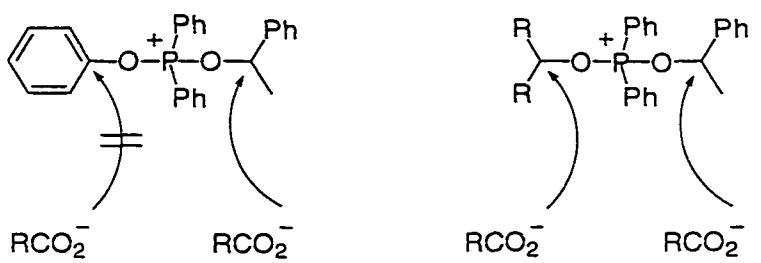
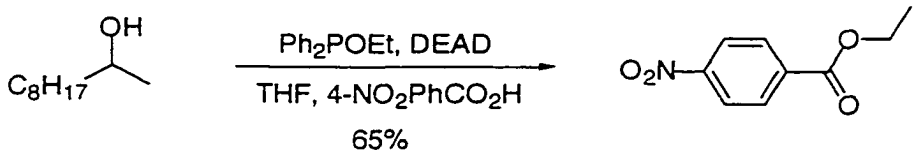


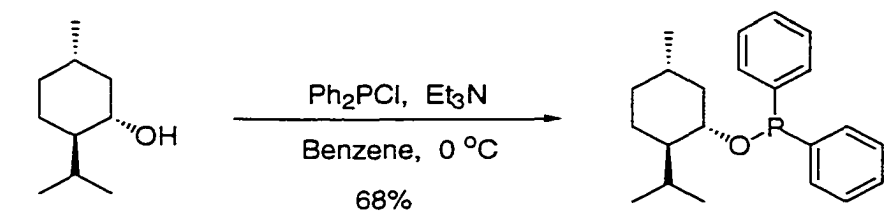
Figure 5: S_N2 displacement at one or two positions of the alkoxyphosphonium intermediate

In order to check whether esterification of secondary alcohols is feasible using such reagents, a model reaction was attempted. Use of ethyldiphenylphosphinite in place of triphenylphosphine in the Mitsunobu esterification of 2-decanol in the presence of DEAD and 4-nitrobenzoic acid gives 65% of ethyl 4-nitrobenzoate instead of the desired 2-decyl-4-nitrobenzoate (Scheme 31). This result is not surprising since the sterically less crowded ligand is attacked.



Scheme 31

Despite the possibility of displacement, it seemed that a sterically hindered chiral alkoxy ligand could avoid this undesired reaction. Since menthol is widely used as a chiral auxiliary in organic synthesis,[58] menthyldiphenylphosphinite (**27**) was synthesized using the modified procedure of Hidai *et al.*[59] Thus, treatment of (+)-menthol with diphenylphosphorus chloride in the presence of Et_3N gives the desired compound in 68% yield (Scheme 32).

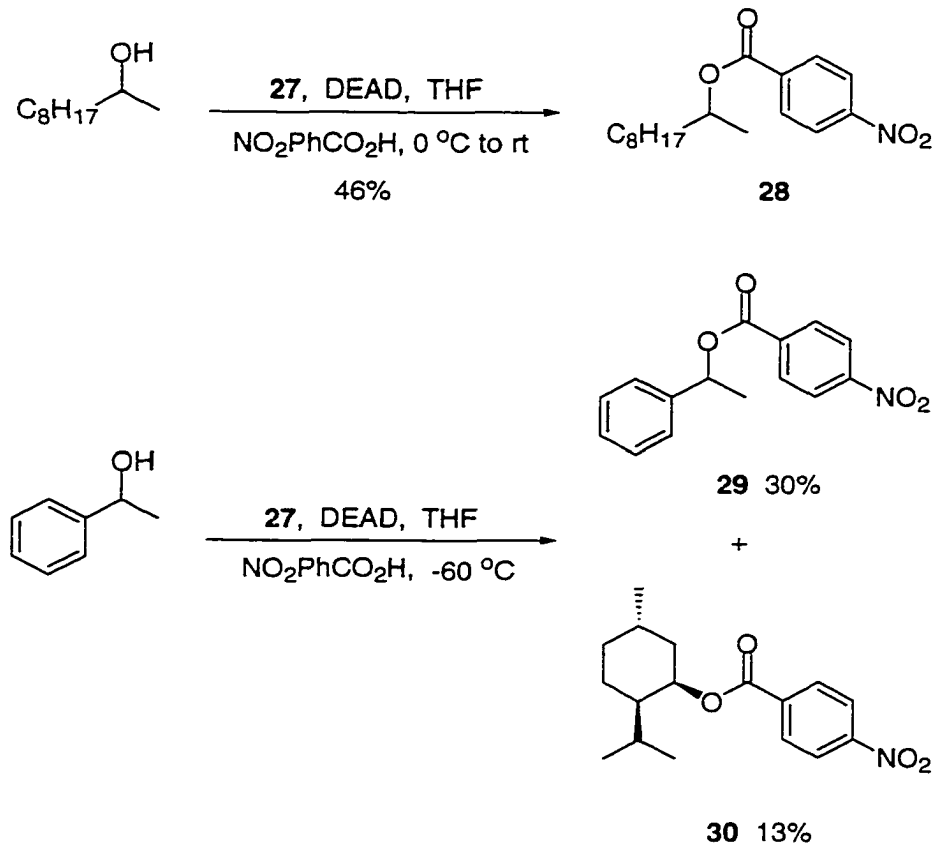


(+)-Menthol **27**

Scheme 32

The reactivity and the enantioselection of **27** were examined for the esterification of 2-decanol and α-phenethyl alcohol by 4-nitrobenzoic acid. For 2-decanol, the reaction was

done at room temperature to afford 46% of the 2-decyl ester **28**. For α-phenethyl alcohol the reaction was done at –60 °C, which allowed isolation of 30% of desired ester **29** and 13% of the undesired neomenthyl ester **30** (Scheme 33).

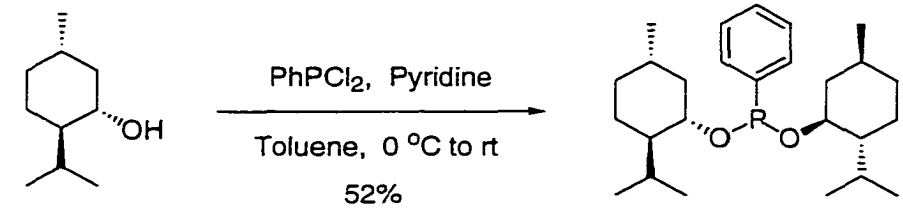


Scheme 33

The ratio of the two enantiomers of recovered alcohol could be determined by converting the alcohol to the corresponding Mosher's esters. It was found that there is no enantioselectivity for the esterification of 2-decanol, even when the reaction is done at -60 °C. However, NMR analysis of the Mosher ester of the recovered α-phenethyl alcohol shows that the e.e. is 40%. Hydrolysis of the 4-nitrobenzoic acid α-phenethyl ester (**29**) to

the alcohol followed by ^{1}H NMR analysis of the corresponding Mosher ester shows that its enantiomeric excess is 40%.

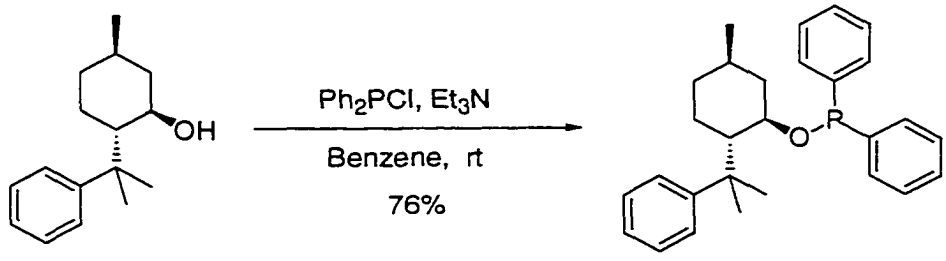
These results encouraged synthesis of dimenthylphenylphosphonite (**31**) using a similar procedure to that of Neuffer *et al.*[60] (Scheme 34). It seemed that the chiral environment generated by two menthol groups could show increased asymmetric selection. Unfortunately, the reaction with 2-decanol, under the same conditions as described above, gives neomenthyl 4-nitrobenzoate ester (**30**) in 91% yield, with almost quantitative recovery of unreacted 2-decanol.



(+)-Menthol **31**

Scheme 34

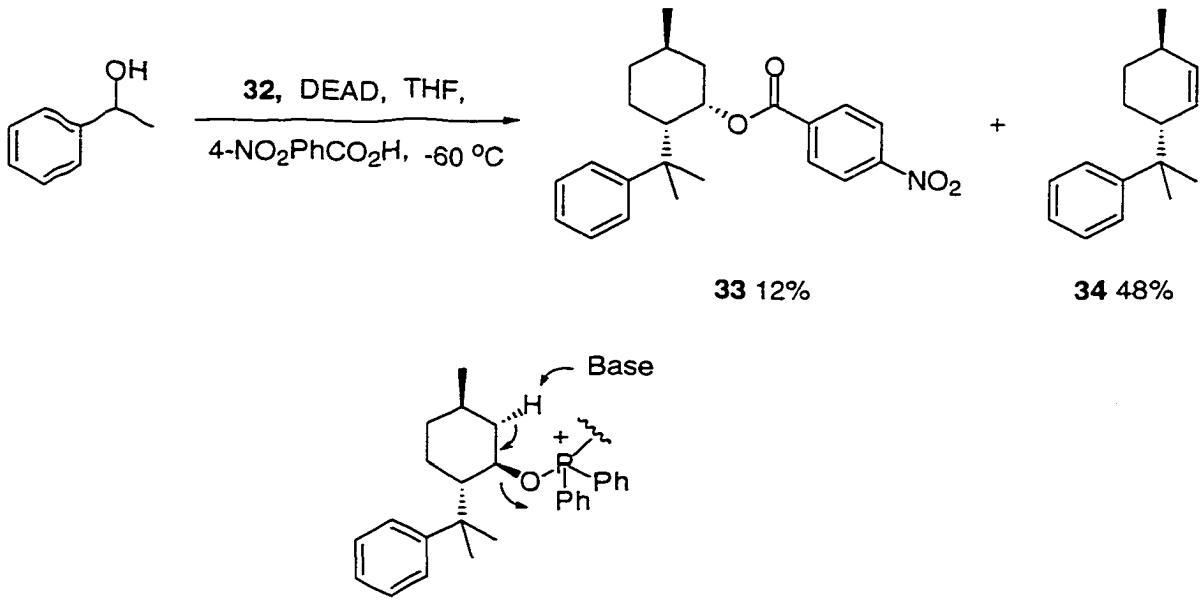
The chiral induction of menthol-based auxiliaries can be increased by modification of the substituents, and 8-phenylmenthol is widely used.[61,62,63,64] Optically pure 8-phenylmenthyldiphenylphosphinite **32** could be synthesized as shown in Scheme 35.[65]



(-)-8-Phenylmenthol **32**

Scheme 35

The additional phenyl group could potentially enhance the chiral selection and decrease the displacement of the chiral ligand due to the increased steric hinderance. However, when **32** was used in the Mitsunobu esterification for 2-decanol and α-phenethyl alcohol, no desired ester was isolated. In the latter case, 8-phenylneomenthyl ester **33** and the elimination product **34** were obtained (Scheme 36).

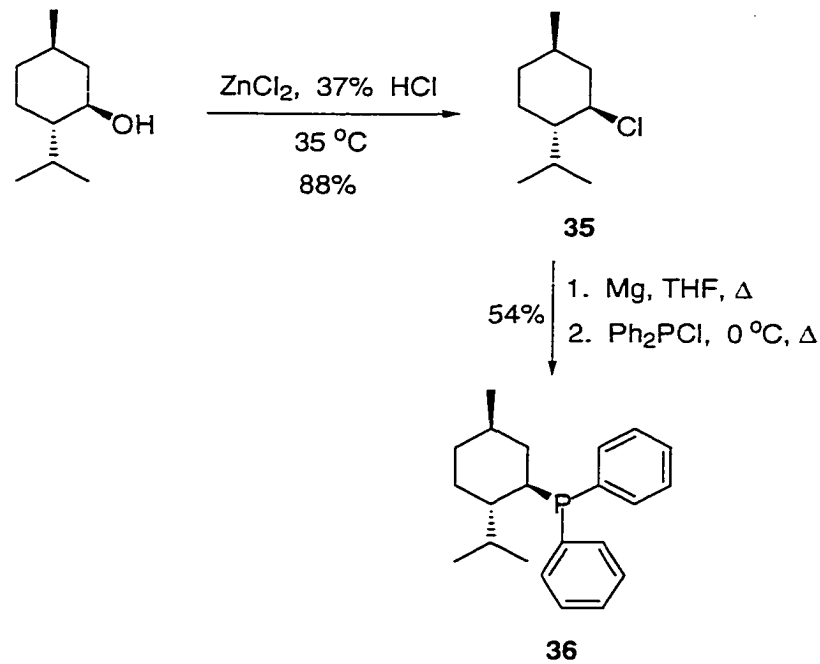


Scheme 36

1.3 The synthesis of (-)-menthyldiphenylphosphine and its reaction and the stereoselection in the Mitsunobu esterification

Many chiral phosphines are reported in the literature and their use as ligands in asymmetric catalysis is well documented.[66,67,68,69,70] (-)-Menthyldiphenylphosphine (**36**) was initially chosen for study of its reactivity and stereoselection in the Mitsunobu esterification. Since the phosphorus atom is closer to a stereogenic centre, greater selectivity could be possible. In addition, S_N2 displacement of the menthyl group is not likely. Menthyldiphenylphosphine (**36**) has the advantage of being relatively stable, although it does slowly oxidize in air to the corresponding phosphine oxide. It is crystalline and easily

synthesized by a literature procedure[71] in two steps from inexpensive menthol and chlorodiphenylphosphine (Scheme 37).

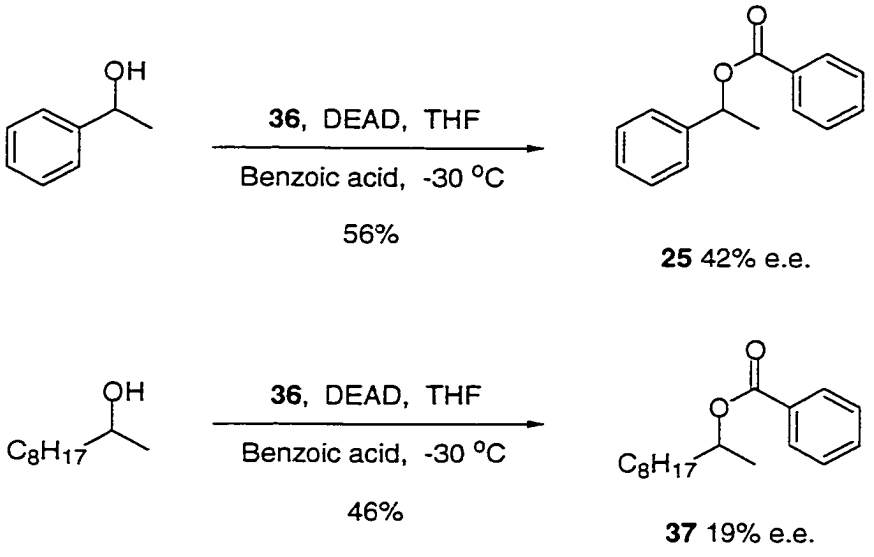


Scheme 37

Menthyl chloride (**35**) is easily obtained in 88% yield by chlorination of menthol using the Lucas reagent.[72] The stereochemistry of menthyl chloride was confirmed by ^{1}H NMR spectroscopy. The coupling constant of the proton on the carbon bearing chlorine with that on the adjacent methine is 11.1 Hz, which indicates that both protons are in the axial position. The phosphorus NMR spectrum shows a single peak at δ -5.4 ppm indicating that a single diastereoismer is present.

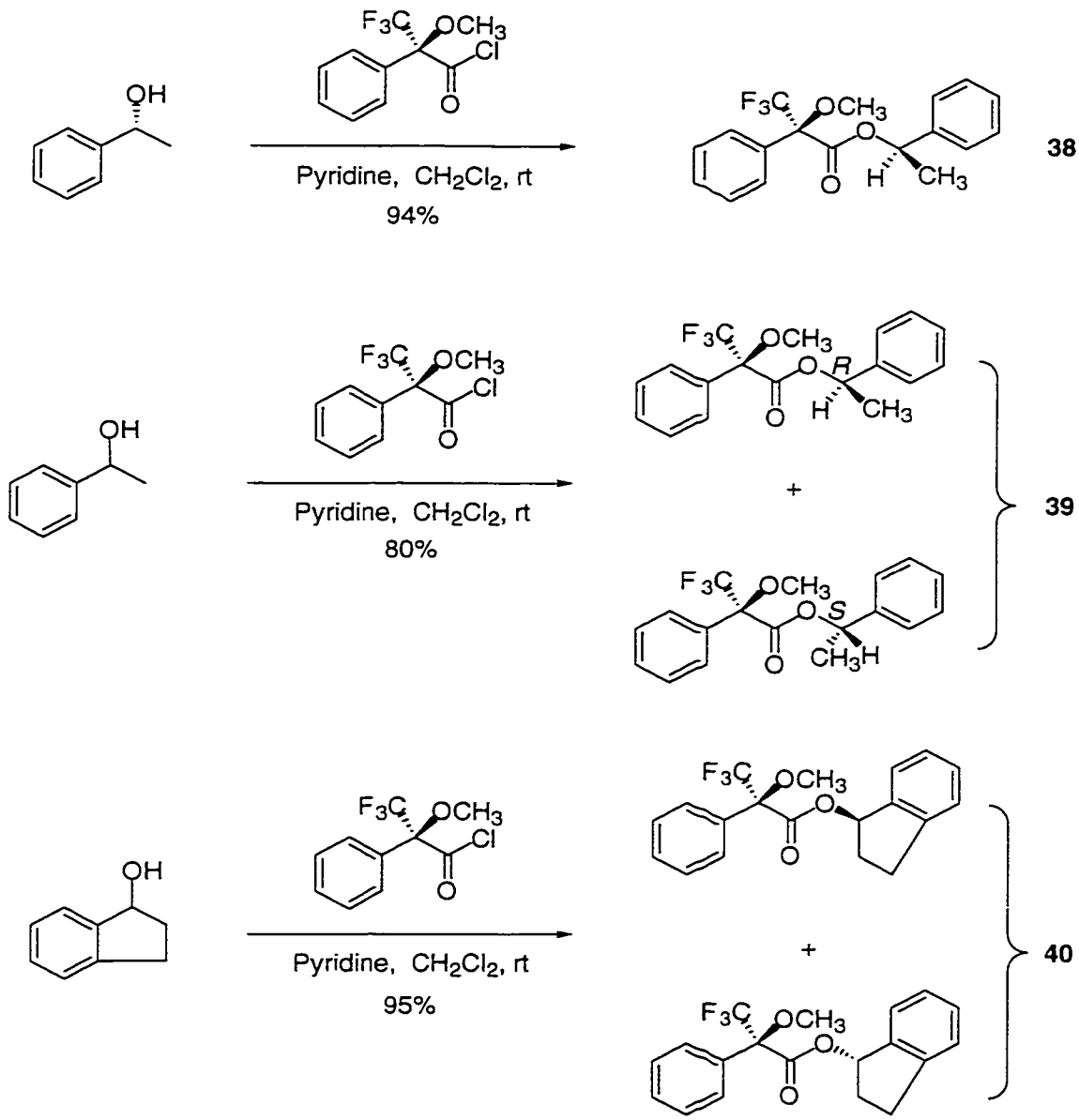
Initial studies of (-)-menthyldiphenylphosphine (**36**) in the Mitsunobu esterification of α-phenethyl alcohol with 4-nitrobenzoic acid resulted in a very low yield (12%) of the ester (even using a two-fold excess of alcohol and acid) with a low e.e. (13%) of the recovered alcohol. However, when benzoic acid is used in place of 4-nitrobenzoic acid, significant improvements in yield and e.e. are observed for both α-phenethyl alcohol and 2-

decanol (Scheme 38). In both reactions trace amounts of benzoic acid anhydride are also formed, which indicates that carboxylic acid activation also occurs.



Scheme 38

Determination of the e.e's. of the recovered alcohols is done by conversion to the corresponding Mosher's esters (Scheme 39) followed by NMR analysis. The results from this give 42% e.e. for α-phenethyl alcohol and 19% e.e. for 2-decanol. In order to determine which enantiomer of the the racemic α-phenethyl alcohol is converted faster with the chiral Mitsunobu reagent, optically pure Mosher's ester **38** of commercially available (*R*)-α-phenethyl alcohol was prepared with (*S*)-(+)- α-methoxyl-α-(trifluoromethyl)phenyl acetyl chloride (Scheme 39). Comparison of the ^{1}H NMR of **39** and **38** shows that the (*S*)-enantiomer of the racemic α-phenethyl alcohol reacts preferentially. Since optically pure 2-decanol is not commercially available, the configuration of the recovered alcohol was determined to be (*R*) by optical rotation.



Scheme 39

Determination of the enantiomeric excess of the ester formed during the Mitsunobu reaction is done by use of the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium(III) ([Eu(hfc)$_3$] (Figure 6), and ^{1}H NMR analysis of the methyl doublet. The e.e. of α-phenethyl benzoate is 42% and the e.e. of 2-decyl benzoate is 19%.

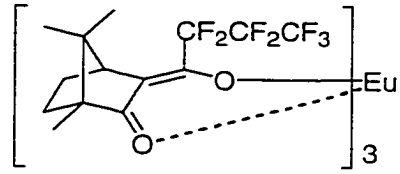
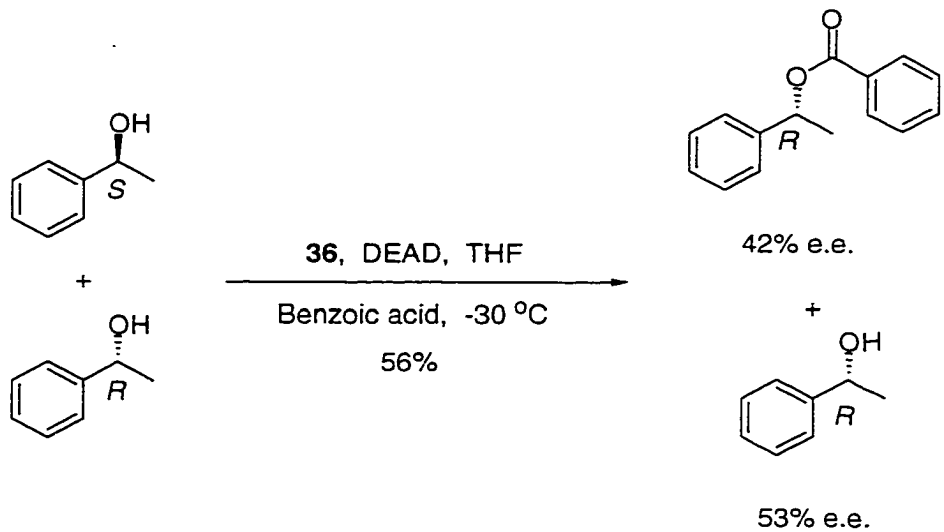


Figure 6: tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium (III)

Therefore after the Mitsunobu reaction of α-phenethyl alcohol using **36**, the unreacted alcohol is enriched in the (*R*)-enantiomer and the resulting benzoate ester is enriched in the (*R*)-enantiomer due to inversion of stereochemistry in the process (Scheme 40).



Scheme 40

The effects of varying the acid component, the azodicarboxylate, the temperature and the solvent on the reaction yields and e.e.'s of the esters and recovered alcohols were investigated using menthyldiphenylphosphine (**36**) (Table 1).

Table 1. Stereoselection with variation of Mitsunobu reaction conditions using chiral menthyldiphenylphosphine (36) and racemic α-phenethyl alcohol.

Entry	Carboxylic Acid[a]	Solvent, Temperature, Time	Ester Yield (%) e.e. (%)	Recovered Alcohol Yield (%) e.e. (%)
1	4-NO_2COOH[b]	THF, rt, 24 h	12 13	75 n.d.[c]
2	PhCOOH	THF, rt, 16 h	42 41	40 37
3	PhCOOH	THF, -30 °C, 24 h	56 42	36 53
4	PhCOOH	THF, -60 °C, 21 h	47 50	46 46
5	PhCOOH	Ether, -60 °C, 15 h	71 22	26 72
6	PhCOOH	Toluene, -30 °C, 70 h	54 32	18 44
7	PhCOOH	CH_3CN, -30 °C, 34 h	16 31	65 n.d.
8	4-MeOPhCOOH	THF, -30 °C, 7 h	72 28	16 n.d.
9	4-MeOPhCOOH[b]	THF, -78 °C, 12 h	82 44	55 n.d.
10	4-MeOPhCOOH[b]	Toluene, -30 °C, 3 h[d]	87 33	38 n.d.
11	1-$C_{10}H_6$COOH	THF, -60 °C, 18 h	42 40	35 34
12	2-$C_{10}H_6$COOH	THF, -60 °C, 48 h	39 43	32 32
13	PhCOOH	THF, -30 °C, 52 h[d]	34 53	45 20
14	PhCOOH	THF, -30 °C, 40 h[e]	30 42	38 15
15	PhCOOH	THF, 0 °C, 12 h[f]	36 50	n.d. n.d.

[a] Chloroacetic acid and formic acid were also used in the Mitsunobu reaction but no esterification was observed. [b] Two equivalents of acid and alcohol used. [c] n.d. = not determined. [d] (+)-Neomenthyldiphenylphosphine (Figure 7) was used instead of menthyldiphenylphosphine. [e] Di-*tert*-butyl azodicarboxylate was used instead of DEAD. [f] Dimenthyl azodicarboxylate was used instead of DEAD.

Equimolar amounts of the four reagents were used for all entries, with the exception of Entry 1 in which 2 equivalents of acid and alcohol were employed. The optimal conditions for ester formation and stereoselection are those shown in Entry 3 (DEAD and benzoic acid in THF at –30 °C). Interestingly, use of both a chiral phosphine and chiral dimenthyl azodicarboxylate (Entry 15) results in no significant increase in either conversion or selectivity. The reactivity of bulky dimenthyl azodicarboxylate is comparable to that of di-*tert*-butyl azodicarboxlate (Entry 14). In order to investigate the structural effects of the chiral phosphine reagent on the reactivity and asymmetric selection in the Mitsunobu reaction, commercially available (+)-neomenthyldiphenylphosphine (Figure 7) was also tested (Entry 13). Although the stereoselectivity of ester formation is slightly improved, the yield decreases and the e.e. of the recovered alcohol is lower. In terms of solvent effects, it seems that the conversion in diethyl ether (71% of the ester isolated) (Entry 5) is greater than that in any other solvent tested, resulting in higher e.e. (72%) of the recovered alcohol.

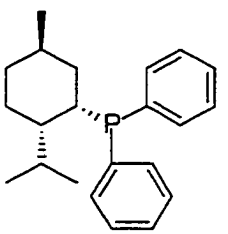


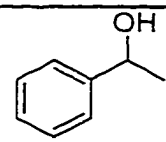
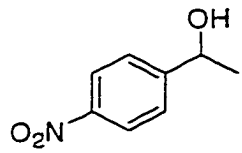
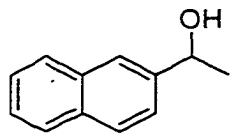
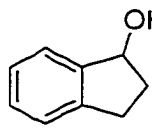
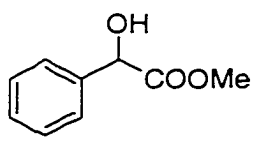
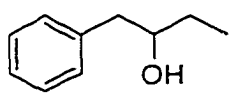
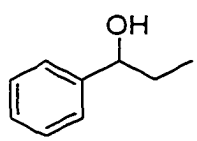
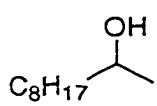
Figure 7: Neomenthyldiphenylphosphine

When less acidic 4-methoxybenzoic acid (pKa = 4.47) is used in the reaction a significant improvement of the yield of ester is observed (Entry 8) (72% of the ester) although there is no enhancement of selectivity (28% e.e. of ester). The higher reactivity of

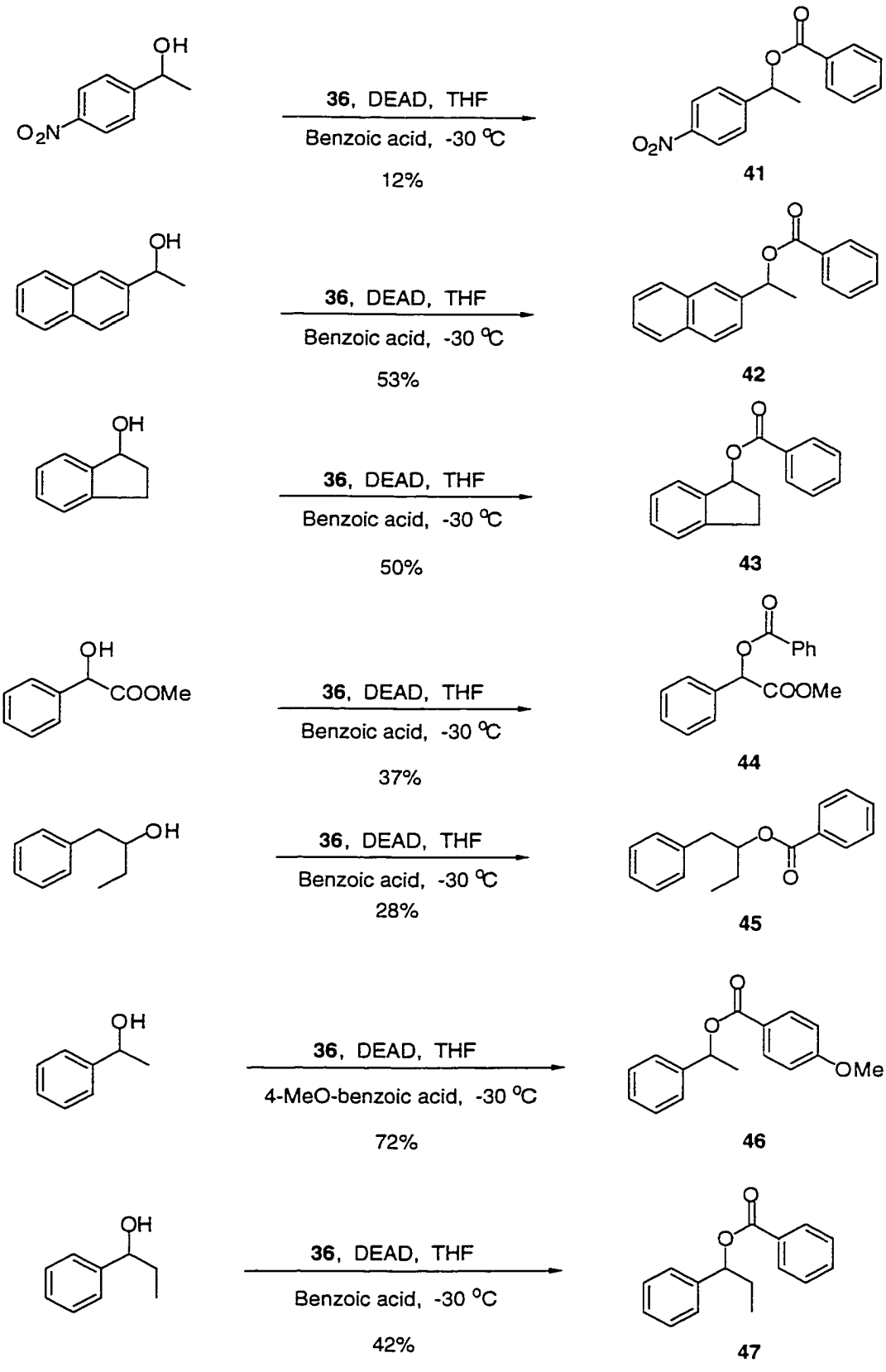
4-methoxybenzoic acid is also seen with the less effective neomenthyldiphenylphosphine (87% of the ester isolated). However, no improvement in selectivity is noted (Entry 10).

Using the optimized conditions of in Entry 3 in Table 1, different racemic secondary alcohols were investigated for stereoselective Mitsunobu esterification (Table 2 and Scheme 41). Most substrates display comparable conversions, but the benzylic alcohols generally show higher stereoselectivities. 1-(*para*-Nitrophenyl)ethyl alcohol has lower conversion, but higher selectivity with equimolar quantities of reagents. However, using two equivalents of acid and this alcohol, a 68% yield of ester with 58% e.e. is obtained. This observation of improved yields and comparable e.e.'s of the esters with excess reagents holds true for many of the alcohols tested. Methyl mandelate (Entry 5) in Table 2 shows low conversion and very poor selectivity, apparently due to the influence of the adjacent methyl ester group.

Table 2. Efficiency and e.e.'s of the Mitsunobu reaction using menthyldiphenylphosphine (36) under optimized conditions[a]

Entry	Substrate	Reaction Time	Ester Yield (%) e.e. (%)	Recovered Alcohol Yield (%) e.e. (%)
1		24 h	56 42	36 53
2		24 h	12 58	58 n.d.[b]
3		24 h	53 32	22 30
4		72 h	50 n.d.[b]	29 21
5		24 h	37 6	46 n.d.[b]
6		24 h	28 9	49 n.d.[b]
7		30 h	42 n.d.	46 35
8		15 h	46 19	34 20

[a] THF, -30 °C, 24 h, benzoic acid. [b] n.d., not determined due to poor resolution of NMR peaks in analysis with chiral shift reagent or corresponding Mosher's ester.

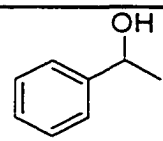
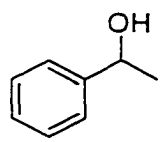
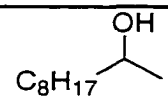
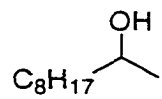
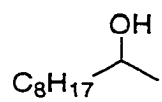


Scheme 41

1.4 Use of repeated Mitsunobu reaction to resolve secondary alcohols

Although the % e.e.'s for ester formation with menthyldiphenylphosphine (**36**) in the Mitsunobu reaction are only moderate, a repetition of the reaction using the recovered alcohol should further increase its e.e. (Table 3).

Table 3. Repeated Mitsunobu reaction to resolve secondary alcohols.

	Substrate	Ester Yield (%) e.e. (%)	Recovered Alcohol Yield (%) e.e.(%)
First reaction		56 42	36 53
Second reaction		51 16[a]	40 **96**
First reaction		46 19	34 20
Second reaction		48 7[a]	28 61
Third reaction		46 47[a]	39 **81**

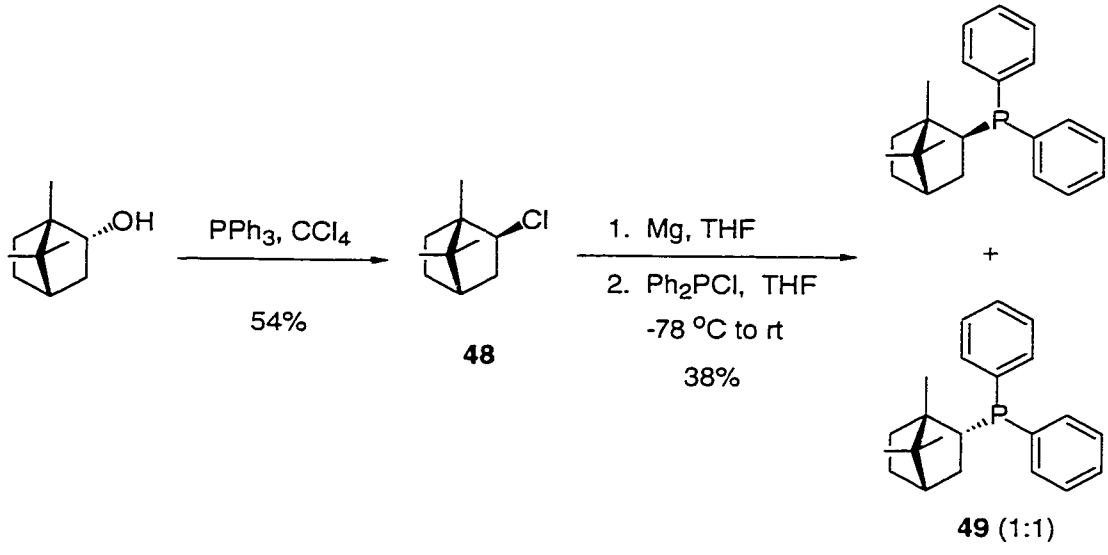
[a] The opposite ester enantiomer is formed in excess in the second and third subsequent reactions

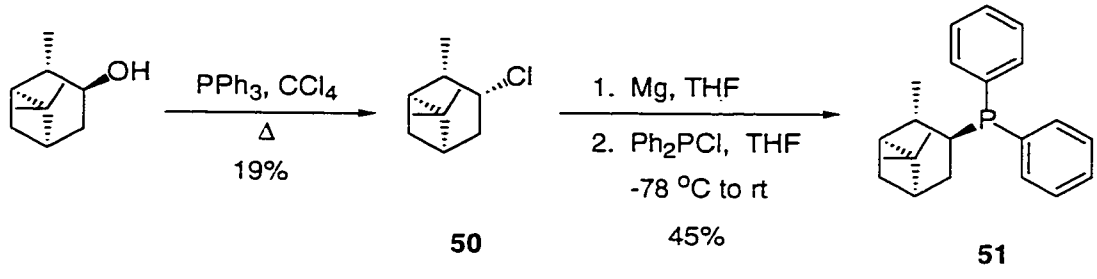
α-Phenethyl alcohol and 2-decanol were chosen as examples of benzylic and aliphatic alcohols, respectively, for this purpose. As shown in Table 3, after the recovered α-phenylethyl alcohol is subjected to a second Mitsunobu reaction, the e.e. of the recovered alcohol is 96%. For 2-decanol, the e.e. of the recovered alcohol after a second Mitsunobu reaction is 61%; a third Mitsunobu reaction with the recovered alcohol gives the alcohol

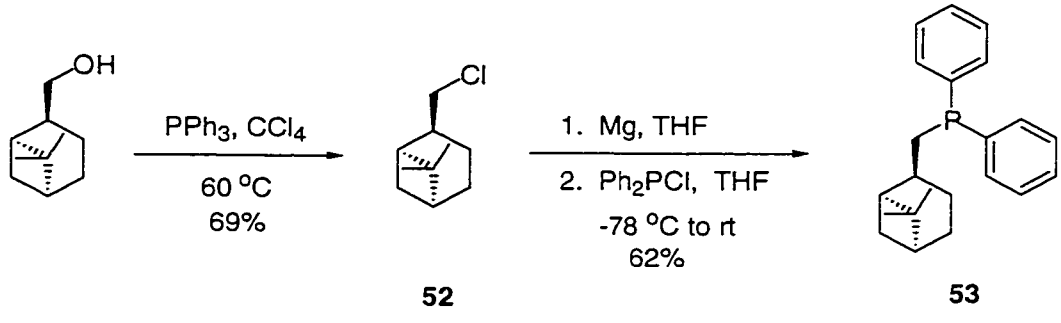
with an e.e. of 81%. In each case, the second and third Mitsunobu reactions produce esters with lower e.e.'s which are enriched in the opposite enantiomer. This is a result of the less reactive enantiomer being in excess in the recovered alcohol from the first reaction.

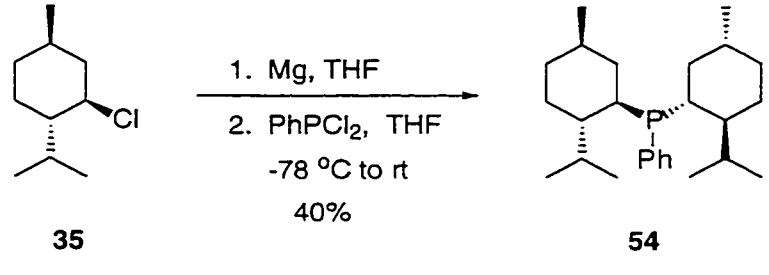
1.5 The synthesis of other chiral phosphines and their reaction and selectivity in the Mitsunobu esterification

The reactivity and selectivity of menthyldiphenylphosphine (**36**) in the Mitsunobu reaction is optimized by variation of solvent, temperature, carboxylic acid and the number of equivalents of reagent used. In order to improve this process, several other chiral phosphines were synthesized (Scheme 42). It seemed that a phosphine with a more rigid and bulky structure could result in greater asymmetric selection. The synthesis of the target compounds generally starts with inexpensive alcohols and requires only two steps. Typically, chlorination of the sterically hindered alcohols is done using Ph_3P and CCl_4 to give the corresponding chlorides **48**, **50** and **52** with inversion of stereochemistry in low to moderate yield (19-69%). These compounds are then converted to the corresponding phosphines **49**, **51** and **53** by formation of the Grignard reagent followed by reaction with Ph_2PCl. In the case of **49**, two diastereoisomers are obtained. The diastereoisomers were not separated due to the failure of this mixture to promote secondary alcohol esterification. The Mitsunobu reaction of secondary alcohols also fails with **51**. In contrast, esterification of α-phenethyl alcohol produces 69% of the desired ester using 2 equivalents of alcohol when compound **53** is used. However, no selection occurs, probably due to the remoteness of the stereogenic center from the phosphorus atom. Compound **54** was synthesized using a similar procedure as that described for menthyldiphenylphosphine (**36**) employing $PhPCl_2$ in place of Ph_2PCl.









Scheme 42

The X-ray crystal structure of compound **54** (**Figure 8**) shows that the stereochemistry is as indicated in Scheme 42. Unfortunately no esterification of secondary alcohols occurs when compound **54** was used in the Mitsunobu process. The failure of compounds **49**, **51** and **54** to mediate esterification is probably due to the increased steric hinderance at phosphorus.

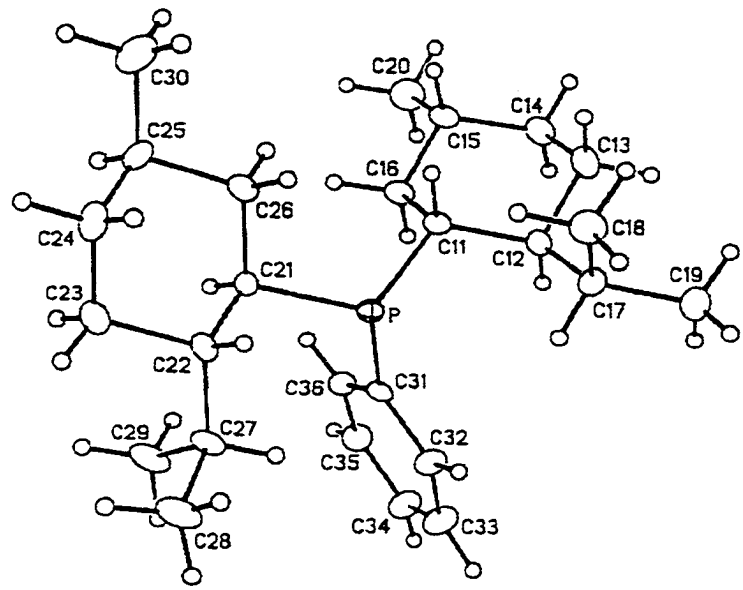
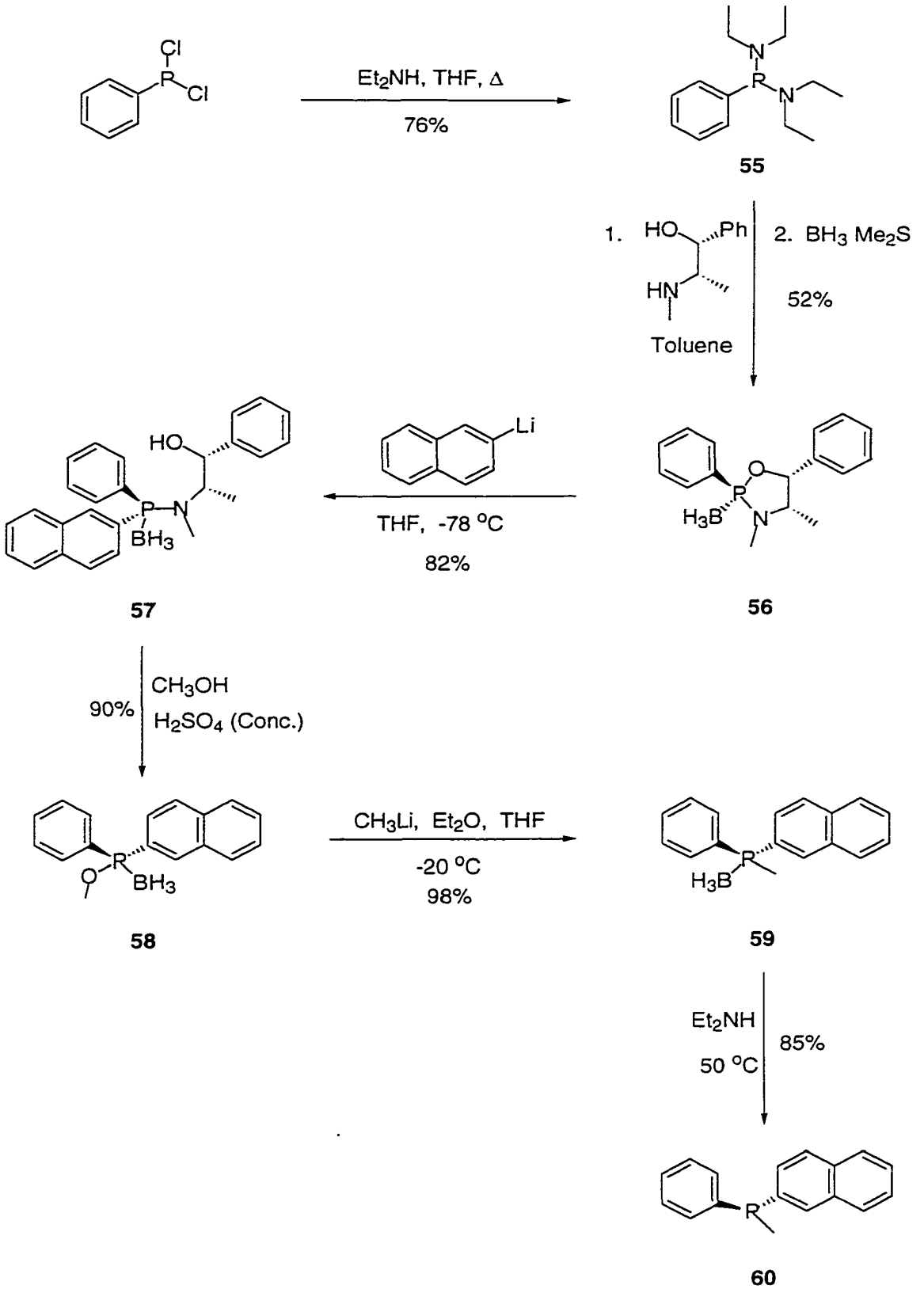


Figure 8: X-ray crystal structure of compound 54

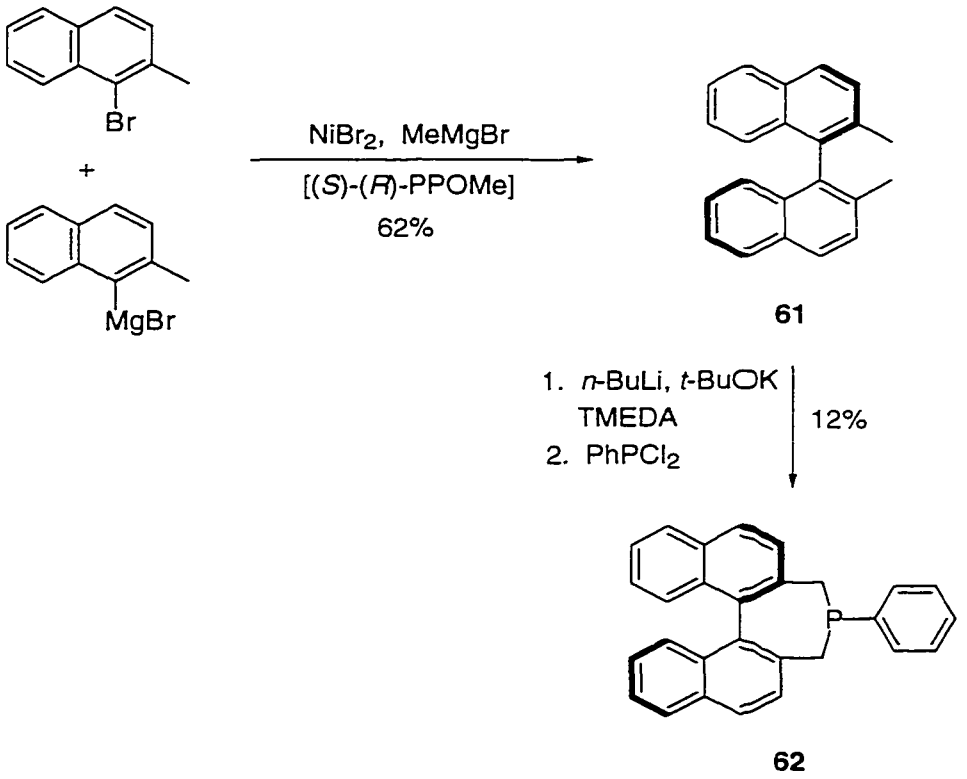
A chiral phosphine with phosphorus as the stereogenic center was also synthesized to test its effect on the Mitsunobu reaction. Naphthylmethylphenylphosphine (**60**) was chosen as it possesses three distinctly different sized groups. The compound can be synthesized using the method of Jugé *et al.*[73] (Scheme 43). Aminophosphine **55** is prepared in 76% yield following the procedure of Hayakawa *et al.*[74] using dichlorophenylphosphine and diethylamine . This is converted to the oxazaphospholidine **56** using (-)-ephedrine and $BH_3{\cdot}(Me)_2S$ in 52% yield. β-Napthyllithium reaction with **56** at low temperature in THF gives the corresponding diastereomerically pure aminophosphine borane **57** via P–O bond cleavage with the retention of configuration at the phosphorus atom. The X-ray study by Jugé *et al.*[75,76] shows the distorted oxazaphospholidine ring and

the methyl substituent on the nitrogen on the back side of the O-leaving group. Therefore the P–C bond formation is under kinetic control and the nucleophilic attack occurs on the less hindered face of the P–O bond which is opposite nitrogen. Acidic methanolysis of aminophosphine borane **57** gives the corresponding phosphinite **58** in 90% yield. The displacement reaction of **58** with methyllithium at -20 °C affords quantitatively the optically pure phosphine borane **59** with inversion of stereochemistry. Finally, transformation of phosphine borane **59** to the corresponding phosphine **60** proceeds without epimerisation in 85% yield by decomplexation of borane under mild conditions using diethylamine. Disappointingly, when **60** is used in the Mitsunobu reaction with α-phenethyl alcohol and DEAD, 69% of the ester is formed but with no stereoselectivity.



Scheme 43

Chiral compounds containing a binaphthyl skeleton have been widely used in asymmetric synthesis due to the excellent chiral induction afforded by this system.[77,78,79] Although Kellogg and coworkers have already shown that 1,3,2-dioxaphosphepane (Figure 2) exhibits only low selection in the Mitsunobu process,[81] it seemed that compound **62** which, unlike 1,3,2-dioxaphosphepane, has no oxygen phosphorus bonds, could have different selectivity. The two step synthesis[80] of **62** begins with the asymmetric cross-coupling of 1-bromo-2-methylnaphthalene with (2-methyl-1-naphthyl)magnesium bromide in the presence of a chiral [(alkoxyalkyl)ferrocenyl]monophosphine-nickel catalyst to give the (*R*)-enantiomer **61**. Metallation of **61** with *n*-BuLi, *t*-BuOK, TMEDA in hexane affords the dianion which is quenched with $PhPCl_2$ to give the known[81] compound **62** in 12% yield (Scheme 44).



Scheme 44

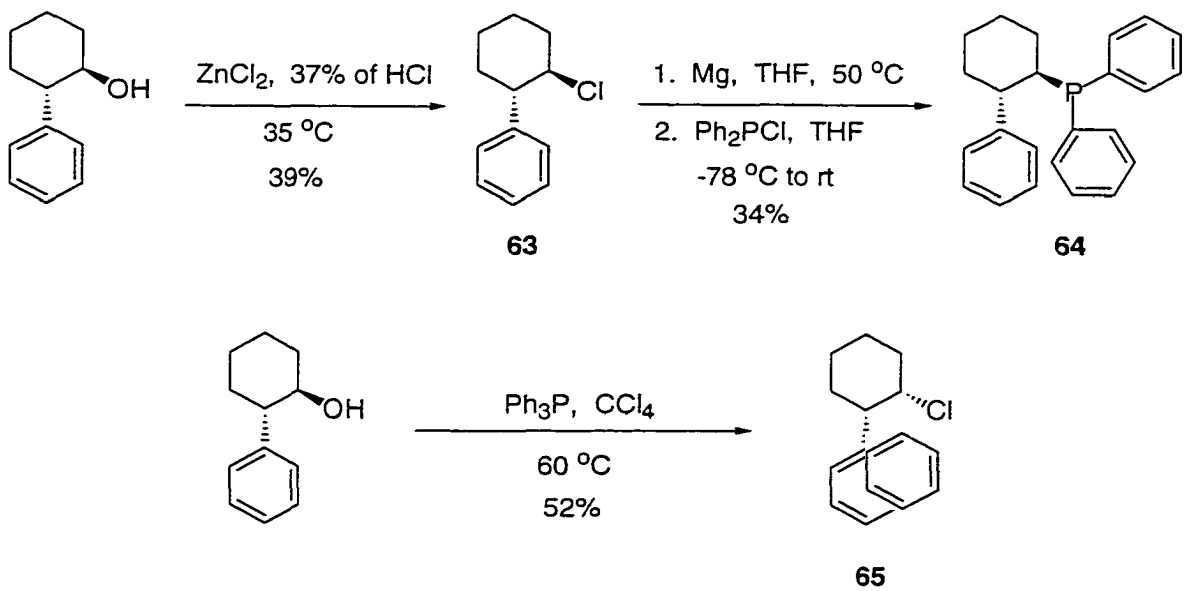
Unfortunately, no esterification of α-phenethyl alcohol occurs when **62** is used in the Mitsunobu reaction. Although the reason for this is not clear, it may be that the increased steric crowding in this binapthyl structure decreases its reactivity relative to that of 1,3,2-dioxaphosphepane.[41]

The reaction of different phosphorus ligands in the Mitsunobu esterification can be compared. From the studies in Section **1.1**, it is clear that aminophosphines can not effect the Mitsunobu esterification for *secondary* alcohols. Work by Kellogg *et al.*[41] demonstrates that compounds with one nitrogen phosphorus bond can be used in the Mitsunobu esterification of secondary alcohols (even with a sterically hindered binapthyl structure) provided an oxygen phosphorus bond is present. The results of the Mitsunobu esterification using different phosphorus reagents with nitrogen, oxygen and carbon containing ligands suggests the following reactivity order: O > C > N. Although the reactivity appears higher for phosphinites, the potential for displacement of a ligand on phosphorus by a carboxylic acid imposes limits on structures that can be used.

1.6 Modification of menthyldiphenylphosphine and subsequent reaction and the stereoselection in the Mitsunobu esterification

The Mitsunobu esterification of secondary alcohols fails for the phosphorus compounds **49**, **51**, **54** and **62**, probably due to the steric hindrance of the ligands. Although compounds **53** and **60** mediate the ester formation for the α-phenethyl alcohol in good yield, no selectivity is observed. It seemed that modification of menthyldiphenylphosphine (**36**) could increase selection. Since phenylcyclohexyl groups have been extensively used as chiral auxiliaries,[58,82] compound **64** was prepared. The synthesis of this compound starts with commercially available chiral *trans*-phenylcyclohexanol. Chlorination using the same procedure as that described for the

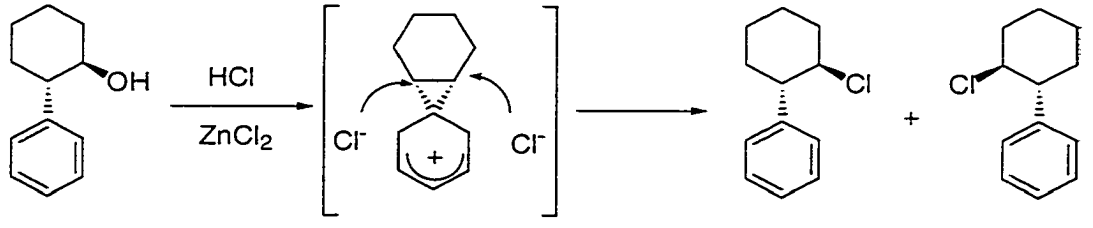
preparation of menthyl chloride (**35**) gives *trans*-phenylcyclohexanyl chloride (**63**) (Scheme 45).



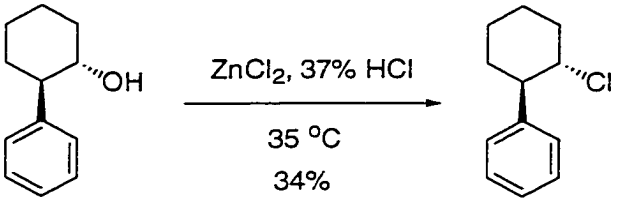
Scheme 45

Retention of the stereochemistry of the reacting centre is confirmed by the preparation of the diastereoisomer **65** using triphenylphosphine and CCl_4 (Scheme 45). The coupling constant between the proton adjacent to Cl and the proton α to the phenyl in compound **63** is 11.2 Hz, but the coupling constant for the same protons in compound **65** is only 2.6 Hz. Compound **63** is then converted to the corresponding chiral phosphine **64** by Grignard reaction in 34% yield. Although compound **64** could be used in the Mitsunobu esterification of α-phenethyl alcohol (53% yield), only 3% e.e. of the ester was found. Since the optical rotation of **63** is quite low (-3.8°) compared with that of the starting phenylcyclohexanol (-54.3°), there is a possibility that racemization may have occurred during chlorination. This could happen by formation of the intermediate **66**, which could be attacked by chloride on either side (Scheme 46). In order to examine this, compound

67, the enantiomer of **63**, was prepared using the same procedure (Scheme 46). ^{1}H NMR spectroscopy shows essentially identical spectra for **67** and **63**. The optical rotation of **67** is +3.8° which is exactly opposite the optical rotation of **63**. Since it is unlikely that partial racemization would occur to exactly the same extent in two separate reaction sequences, these results suggest that both **63** and **67** are optically pure and that no racemization occurs during chlorination.



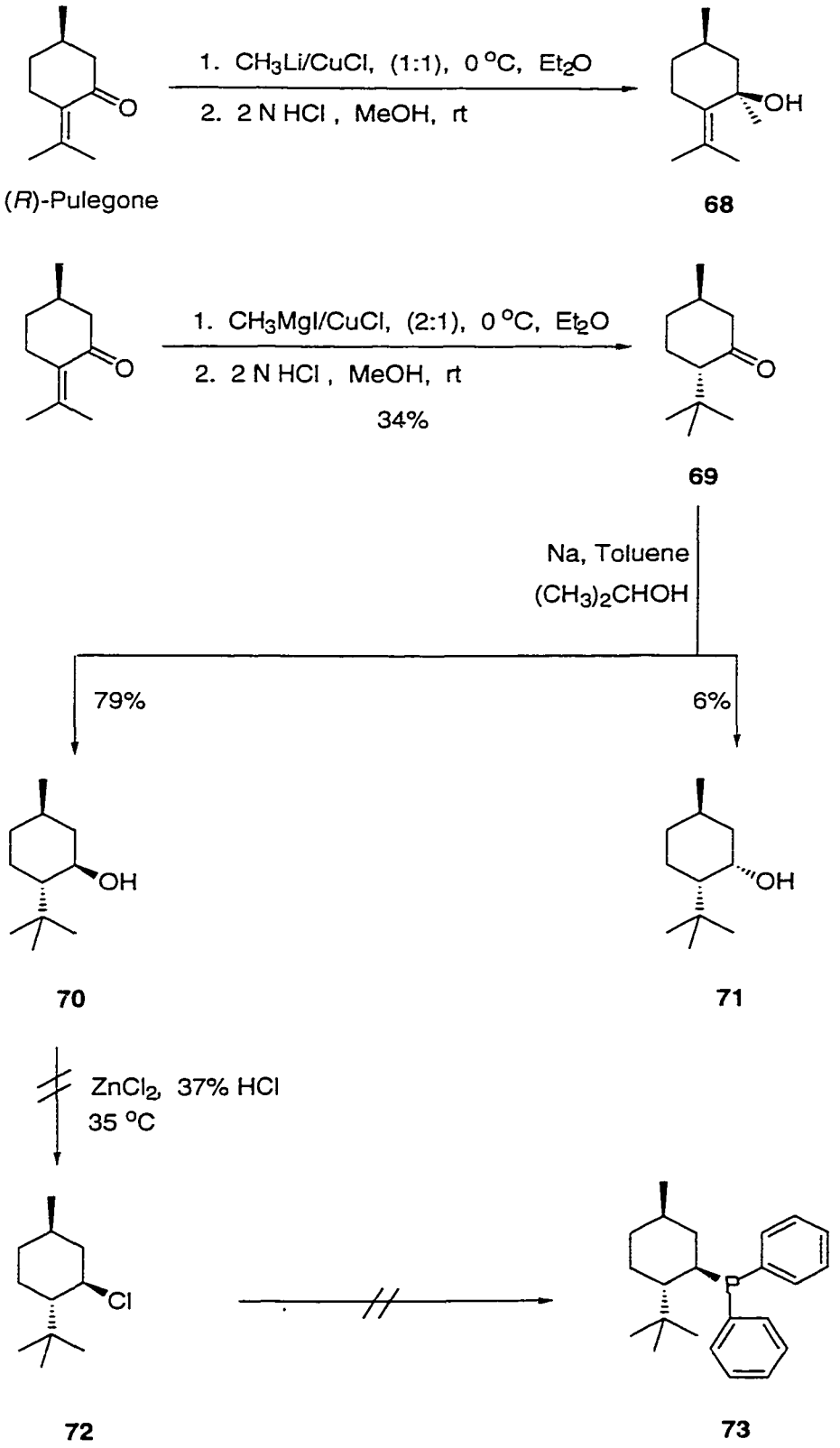
66



67

Scheme 46

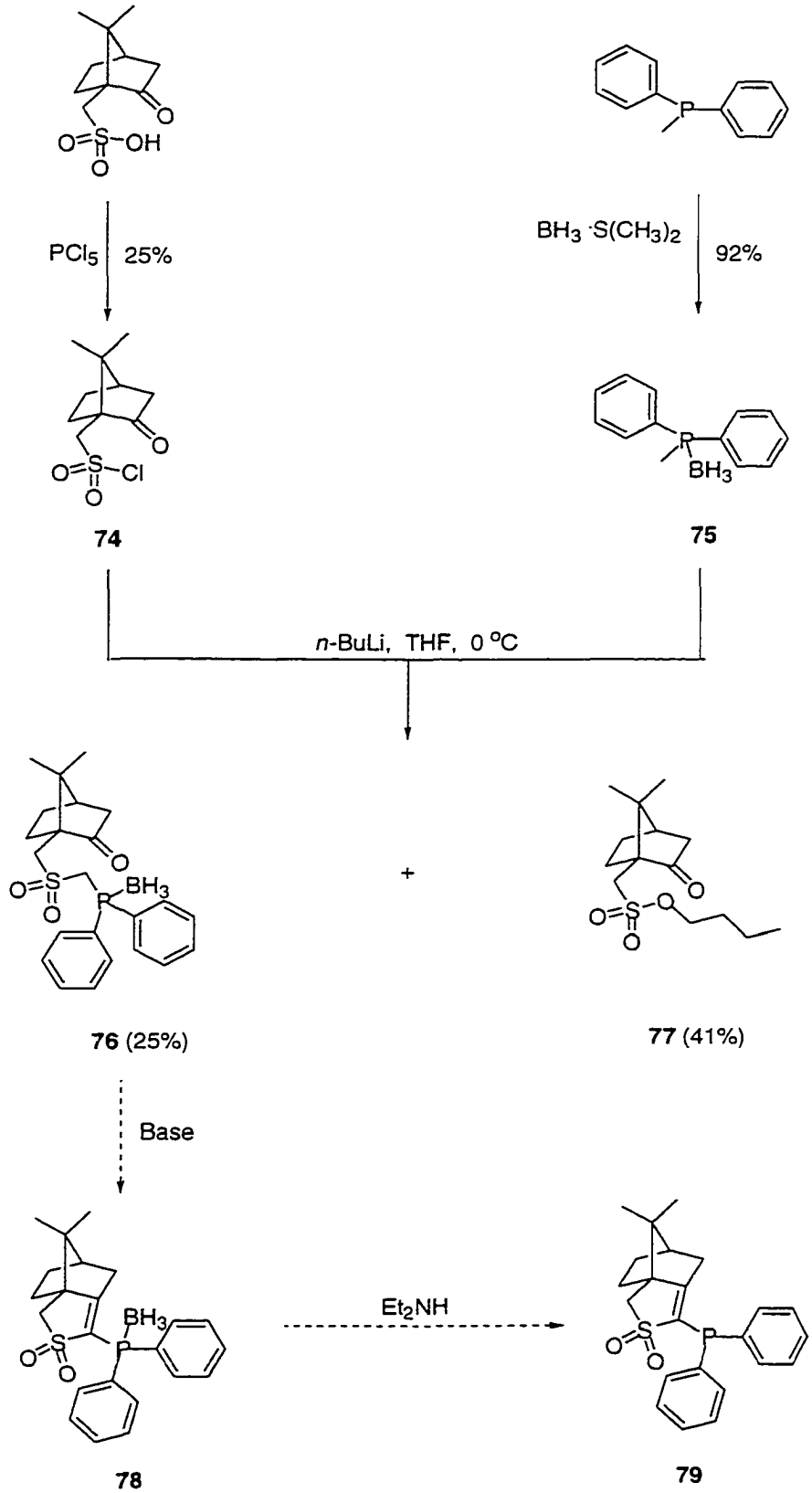
Since modification of the menthyl group by replacement of the isopropyl group with phenyl results in decreased selection in the Mitsunobu reaction, compound **73** was prepared to test the influence of the *t*-butyl group. The synthesis starts with (*R*)-pulegone using the modification of Whitesell and coworkers[63] for the preparation of **70** (Scheme 47). When a 1:1 mixture of methyllithium with anhydrous cuprous chloride is used in the methylation reaction, the undesired 1,2-addition product **68** is obtained. Using the Grignard reagent prepared from methyl iodide with half an equivalent of anhydrous cuprous chloride to form the methyl copper reagent, the desired 1,4-addition product **69** is isolated in 34% yield. Reduction of the ketone using sodium in toluene produces the corresponding alcohol as a mixture of diastereoisomers, **70** and **71**.



Scheme 47

Assignment of the structures depends largely on the coupling constants of the proton adjacent to OH and the proton adjacent to *t*-butyl group in the ^{1}H NMR spectra. The coupling constants for this system in compound **70** and **71** are 10.8 Hz and 8.3 Hz. respectively. This suggests that the former has the *trans*-configuration and the latter has the *cis*-configuration. Attempts to chlorinate **70** using the Lucas reagent generates a complex mixture of compounds, although mass spectrometry and ^{1}H NMR spectroscopy indicate the presence of the desired **72**. Purification of the mixture proved sufficiently difficult so as to make the route untenable for production of the target reagent.

The final chiral phosphine that we attempted to synthesize is compound **79** which contains a camphorsulfonyl moiety, a group which has been widely used in asymmetric synthesis.[83,84,85,86] The key step in the synthetic route is the coupling of camphorsulfonyl chloride **74** with diphenylmethylphosphine-borane **75**. These compounds are readily available from camphorsulfonic acid and diphenylmethylphosphine, respectively (Scheme 48). Reaction of camphorsulfonyl chloride **74** with the anion of diphenylmethylphosphine **75** formed by deprotonation using *n*-butyllithium gives the desired product **76** in 25% yield. Interestingly, compound **77** is also isolated in 41% yield, presumably due to the presence of n-butoxide in the *n*-butyllithium. Unfortunately, this reaction could not readily be repeated despite several attempts under a variety of conditions. The reasons are unclear, but may depend on impurities in the *n*-butyllithium. Due to the difficulty encountered during the preparation of **76**, this reaction route was abandoned.

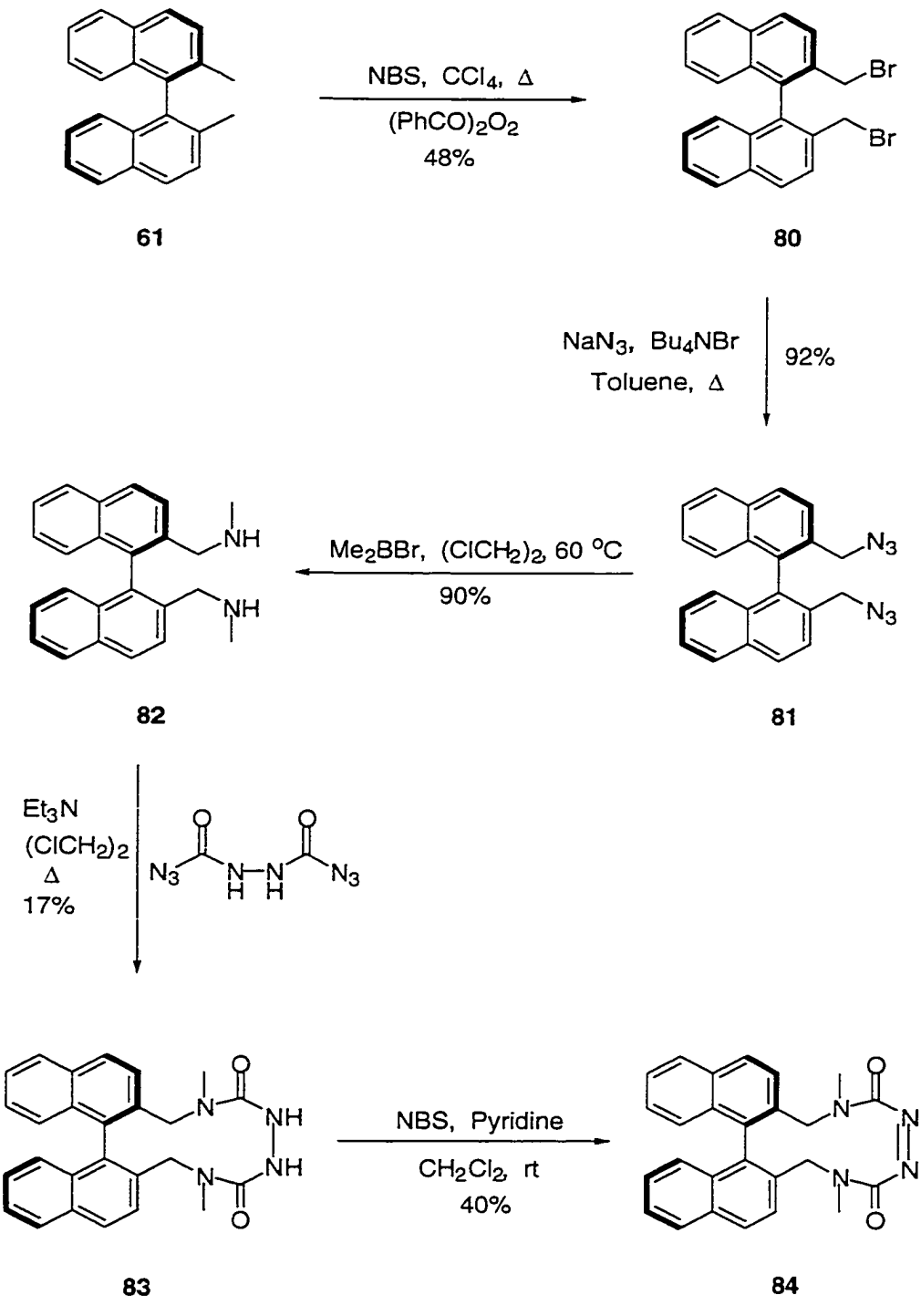


Scheme 48

1.7 The synthesis of a chiral azo compound and its reaction and stereoselection in the Mitsunobu esterification

The use of a chiral azo compound in the Mitsunobu esterification for secondary alcohols was also investigated. The chiral azo dicarboxamide **84** was previously synthesised in this laboratory by Dr. Joanna Harris.[80] Reaction of **84** with achiral oxazolidinone anions at -78 °C gives α-hydrazino acid derivatives with complete (>99%) stereoselectivity.[80] We repeated the preparation of **84** to examine whether the azo component could also effect stereoselection in the Mitsunobu esterification of secondary alcohols. The synthesis of **84** starts with *N*-bromosuccinmide (NBS) mediated bromination of 2,2'-dimethyl binaphthyl **61** to the corresponding dibromide **80** (Scheme 49). Dibromide **80** is converted to diazide **81** by NaN_3 in 92% yield. A high yield of bis(*N*-methylated) amine **82** is obtained on reaction of **81** with bromodimethylborane. Introduction of the dicarbonylhydrazine moiety of the hydrazodicarboxamide **83** proceeds by the attack of binapthyldiamine **82** on the reactive bis-azido hydrazodicarboxylate in the presence of triethylamine. Oxidation of **83** with NBS and pyridine gives the desired chiral binapthyl azodicarboxamide **84** in 40% yield.

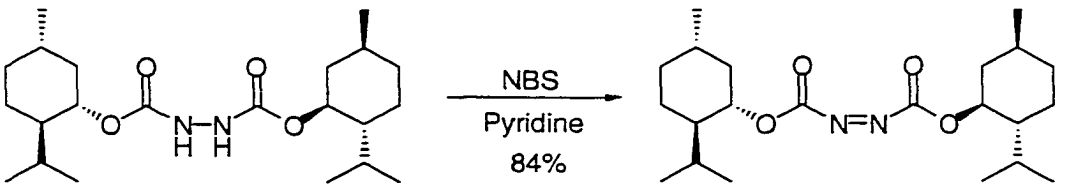
Azodicarboxamides have been used in the Mitsunobu reaction by Tsunoda et al.[87] who found that tributylphosphine (TBP) is more effective with azodicarboxamides than triphenylphosphine (TPP) in C–C and C–N bond-forming reactions in benzene. Following these procedures, use of TBP and benzene with azodicarboxamide **84** allows Mitsunobu esterification of benzoic acid with 2-decanol in 36% yield but with no stereoselectivity.



Scheme 49

The combination of a chiral phosphine and a chiral azodicarboxylate was also investigated with the hope that stereoselectivity could be enhanced. Hence,

enantiomerically pure dimenthyl azodicarboxylate **85** was prepared by oxidation of the corresponding hydrazine (Scheme 50), available from earlier work.[88] Stereochemically pure menthyldiphenylphosphine **36** and **85** allow the Mitsunobu esterification of α-phenethyl alcohol by benzoic acid in 36% yield with 50% e.e. On comparison with DEAD, there is no improvement on the stereoselection of the reaction. The failure to increase the selectivity may be due to the remoteness of the stereogenic centers of the azo compound from the reaction site. Alternatively, the key selection step occurs after the reduced azo moiety has been cleaved from the phosphorus. For example, a series of equilibria between various phosphonium and pentavalent phosphorus species may occur after the reduced hydrazo moiety has departed and the stereoselective step may be attack of benzoate on a phosponium intermediate bearing the secondary alcohol moiety.



85

Scheme 50

1.8 Summary

Detailed investigations have been done on the reaction and stereoselection in the Mitsunobu esterification for alcohols with examination of a variety of triphenylphosphine replacements, azo compounds and carboxylic acids. Several conclusions can be made based on the results of our investigations.

1. Aminophosphines are not suitable replacements for triphenylphosphine in the Mitsunobu esterification of secondary alcohols although they are effective for transformation of primary alcohols.

2. Although phosphinites and phosphonites are able to direct the Mitsunobu esterification of secondary alcohols, displacements of the oxygen substituent on the phosphinite ligands limit their use.

3. The conversions for the Mitsunobu esterification by a variety of phosphorus compounds differ greatly according to the nature of the phosphorus ligands. The reactivity order appears to be: O–P > C–P > N–P.

4. Stereochemically pure menthyldiphenylphosphine **36** and menthyldiphenylphosphinite **27** are able to selectively esterify one enantiomer of the racemic alcohols used with low to moderate e.e., but displacements by carboxylate on the phosphorus ligand of **27** limits its applicability.

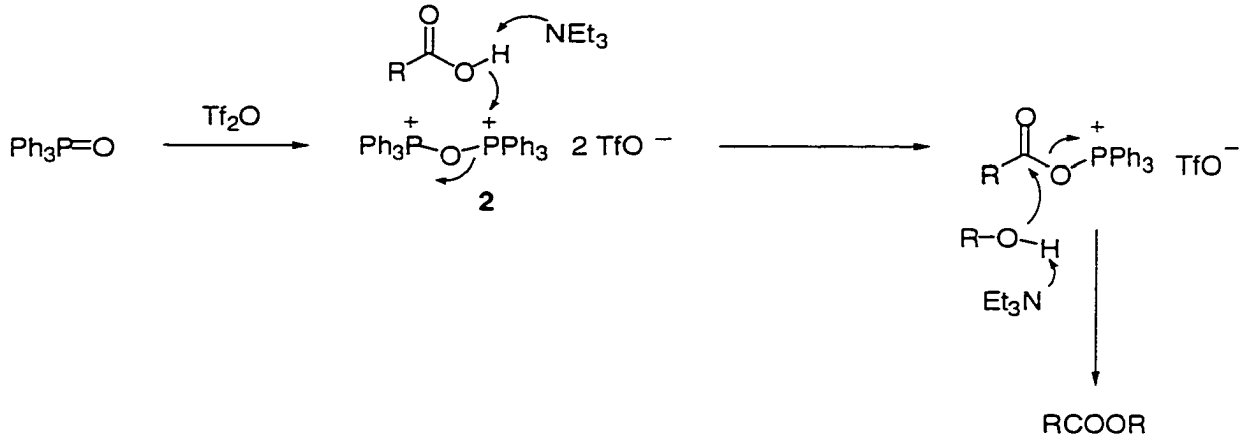
5. For menthyldiphenylphosphine **36**, the acidity of the carboxylic acid has a great influence on the esterification yields although the stereoselectivity of the reaction is not significantly affected.

6. The chirality of the azo compounds does not significantly influence stereoselection during the Mitsunobu reaction, possibly due to the remoteness of the stereogenic center to the reaction site.

Part 2 Polymer-supported version of the Hendrickson reaction

2.1 Solution version of the Hendrickson reaction

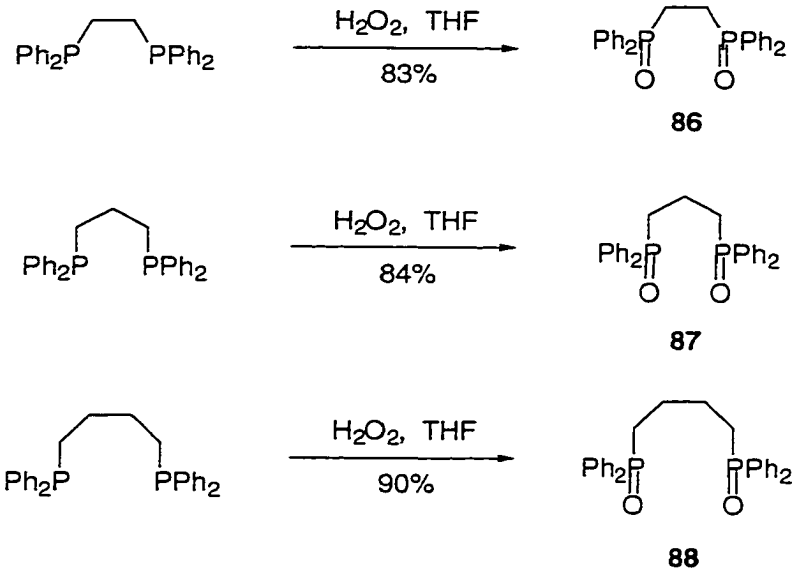
Phosphonium salt **2** is readily prepared by reaction of triflic anhydride with triphenylphosphine oxide (see Scheme 7) and has been sucessfully used as an activating agent for carboxylic acids[30,31,89] in the preparation of anhydrides, esters and amides (Scheme 51).



Scheme 51

The reported efficiency of the reaction and the ability to recycle triphenylphosphine oxide (or its analogue), led us to investigate a solid-supported version which would make purification and isolation easier.

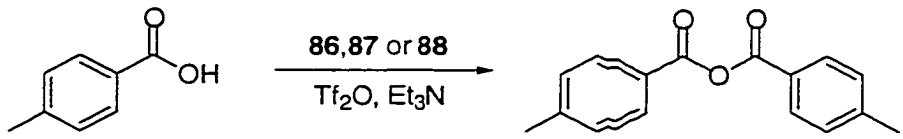
Since structures of solid-supported reagents can be difficult to analyze and verify, our investigations began by synthesis of several related bis-phosphine oxides for use in a solution phase Hendrickson procedure. For this purpose, commercially available *bis*(diphenylphosphinyl)-ethane, -propane and –butane were oxidized in high yield to the corresponding oxides **86**, **87**, **88** using hydrogen peroxide (Scheme 52).



Scheme 52

These three diphosphine oxides (**86-88**) were used as replacements for triphenylphosphine oxide in the Hendrickson procedure for the preparation of 4-toluic anhydride from the corresponding acid. It was found that 78% of the product was obtained using 1,3-bis(diphenylphosphinyl)-propane **87**, 55% of the product was obtained using 1,4-bis(diphenylphosphinyl)-butane **88** and only 5% of the product was obtained for 1,2-bis(diphenylphosphinyl)-ethane **86** (Scheme 53). When triphenylphosphine oxide is used in the Hendrickson procedure, the yield is 93%. The phosphonium anhydride formed from triphenylphosphine oxide is insoluble in dichloromethane and a clear solution forms when the carboxylic acid and triethylamine are added. In the case of **87**, no precipitation is observed. This is may be because the phosphonium anhydride that forms is soluble in dichloromethane. In the case of **88** and **86** the corresponding phosphonium anhydrides are also insoluble as in the case of triphenylphosphonium anhydride. Due to the low solubility of **88** in dichloromethane, the reaction was also done in chloroform in which **88**

has a higher solubility. In chloroform, the phosphonium anhydride is obtained in the form of an oil and allows generation of 4-toluic anhydride in ~4% yield.

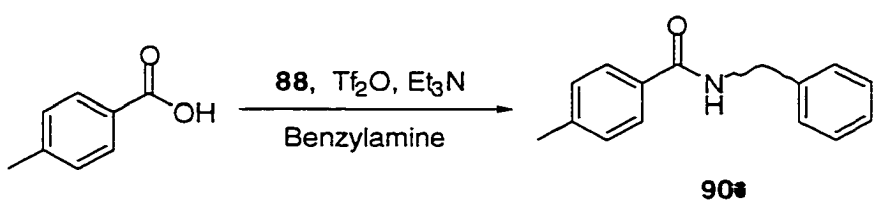


89

Compound	solvent	Yield
86	CH_2Cl_2	5%
87	CH_2Cl_2	78%
88	CH_2Cl_2	55%
88	$CHCl_3$	74%

Scheme 53

Amide formation was also examined using the phosphonium anhydride formed from **88** (Scheme 54). As observed for anhydride formation, the solvent influences the yields of the product. In dichloromethane, 30% of the amide is isolated, but in chloroform 43% of amide **90** is obtained.



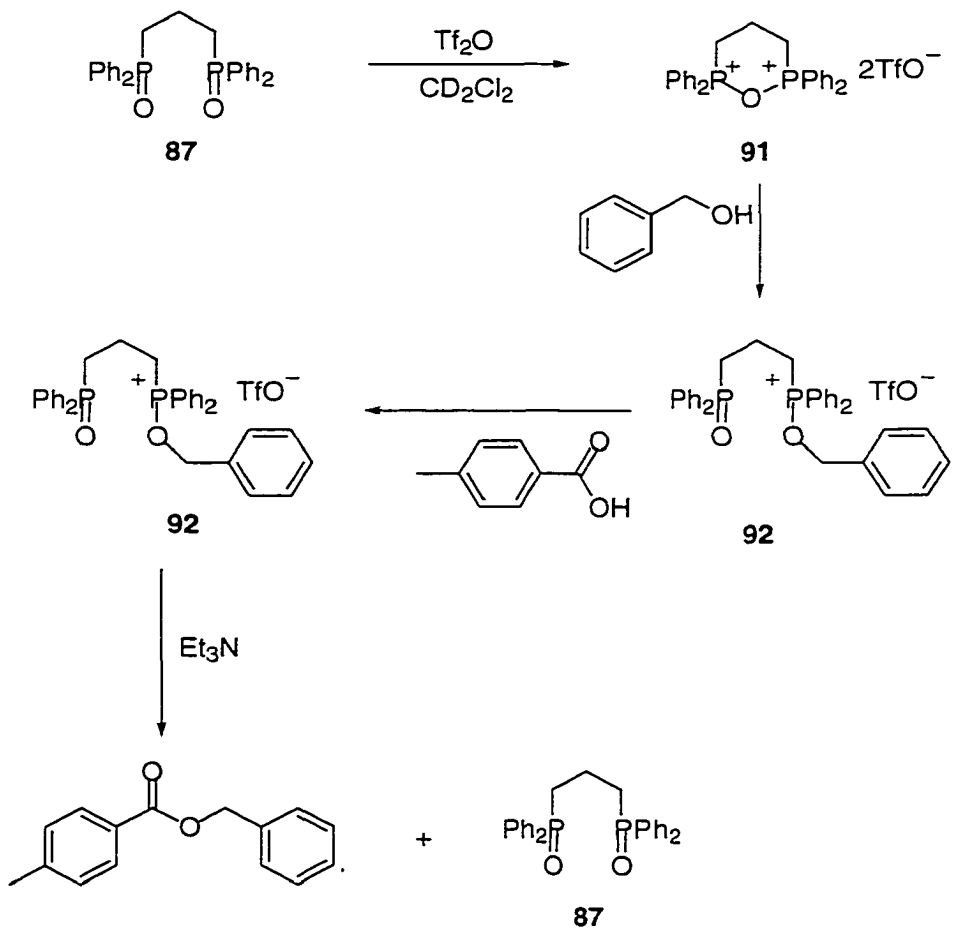
90

solvent	yield
CH_2Cl_2	30%
$CHCl_3$	43%

Scheme 54

Compared with triphenylphosphine oxide, the yields for both anhydride and amide formation using compounds **86**, **87** and **88** are considerably lower.

In order to confirm that the expected cyclized species forms from reaction of the corresponding phosphine oxide, ^{1}H NMR, ^{31}P NMR and ^{19}F NMR analyses were employed. Since insoluble precipitates form in dichloromethane and choroform from treatment of phosphine oxides **86** and **88** with triflic anhydride, the NMR studies were done on **87** which gives a product that is soluble in dichloromethane. The results indicate that both of the expected intermediates, the cyclized phosphonium salt **91** and the alcohol-activated phosphonium salt **92** generated from it, are formed, as described below (Scheme 55).

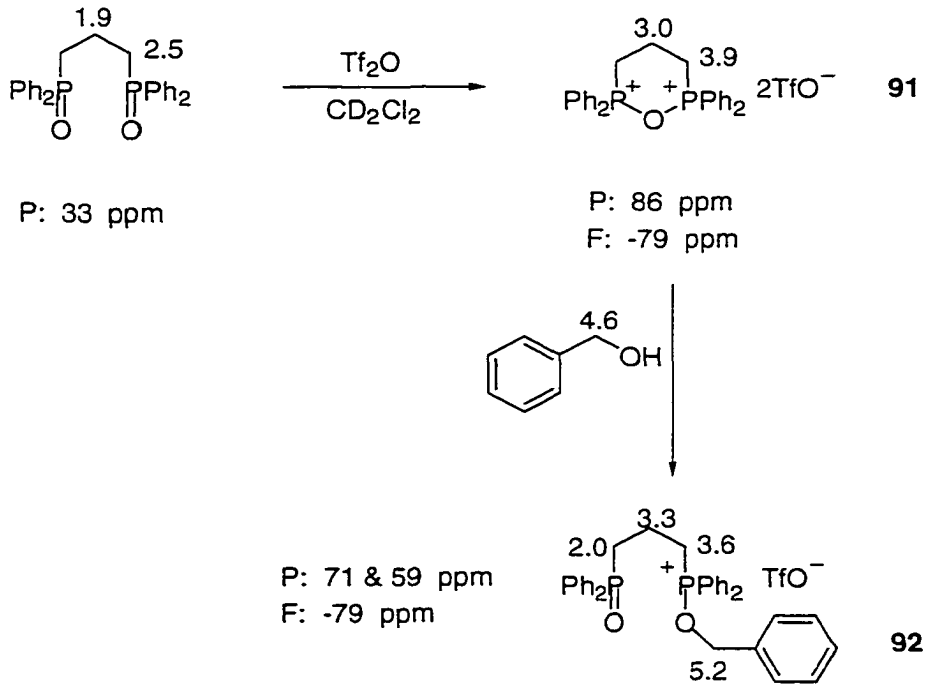


87 **91** **92** **92** **87**

Scheme 55

Interestingly, **92** appears to be stable to carboxylic acid in the absence of triethylamine. Only when triethylamine is added to the mixture can the formation of the ester occur with regeneration of phosphine oxide.

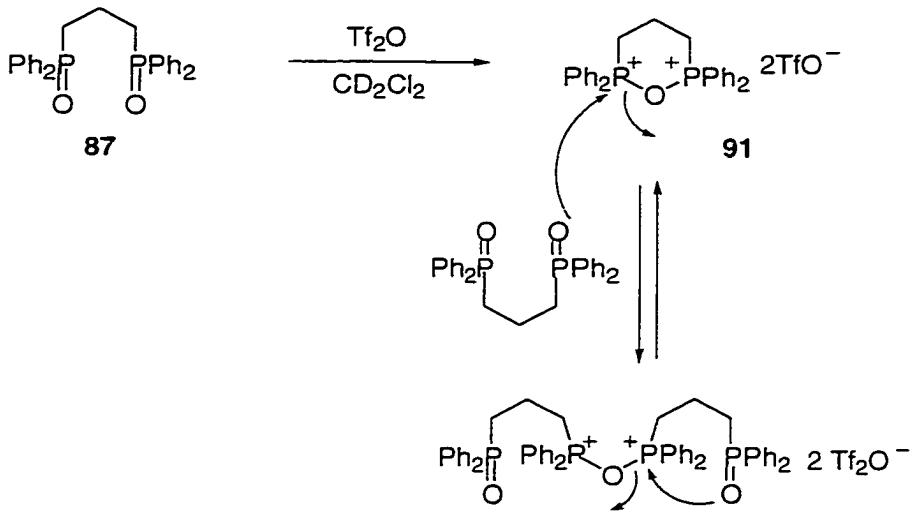
Comparisons of the chemical shifts of the protons, phosphorus, and fluorine in the starting materials with those of the species formed upon mixing of **87** and triflic anhydride in deuterated methylene chloride in an NMR tube indicate the formation of the cyclized phosphonium salt **91** (Scheme 56). The large shift of the phosphorus signal at δ 33 ppm for **87** to δ 86 ppm for **91** in the ^{31}P NMR spectrum supports the formation of this cyclized phosphonium salt. Addition of benzyl alcohol then appears to form the activated alcohol phosphonium salt **92.**



Scheme 56

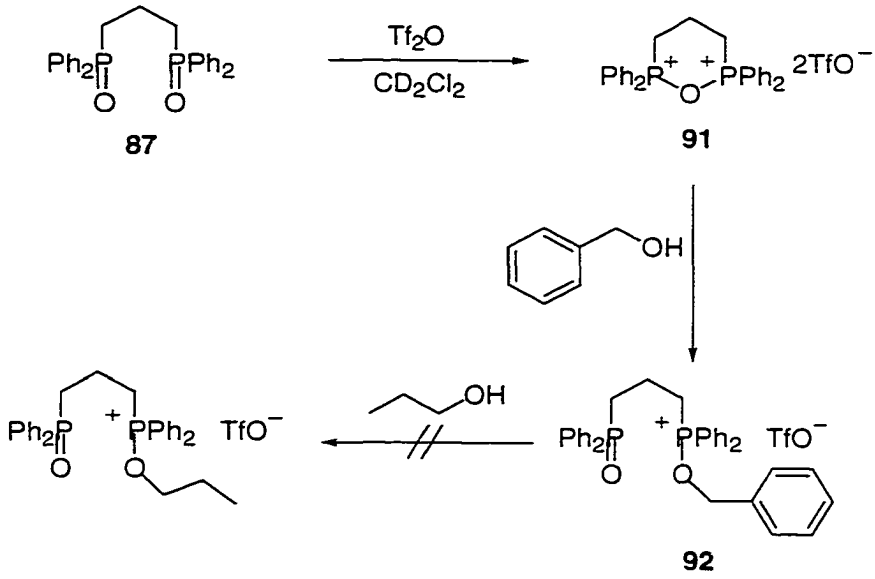
The formation of of **92** is evident from the appearence of a doublet at δ 5.2 ppm for the benzyl proton which in the starting material, benzyl alcohol, appears as a singlet at δ 4.6 ppm. The splitting of this signal from the adjacent phosphorus has a coupling constant of 7.8 Hz. The chemical shifts of this proton, the phosphorus and the coupling constant of the benzyl proton with phosphorus are comparable with the findings of a similar alcohol phosphonium salt studied by Walker and Hendrickson.[8,89]

Extensive dimerization or polymerization of **87** with triflic anhydride is ruled out by following the reaction by NMR spectroscopy. When half an equivalent of triflic anhydride is used in this reaction, ^{1}H NMR and ^{31}P NMR show broadening of the signals for both protons and the phosphorus. This suggests that half an equivalent of diphosphine oxide **87** reacts with triflic anhydride to form the cyclized phosphonium anhydride **91** which can then react with another half equivalent of **87** to form a dimeric (or possibly polymeric) species (Scheme 57). This intermediate can then dissociate to form **91** and **87**. This suggests that the dimer and monomer are in equilibrium, as indicated by the peak broadness in the ^{1}H and ^{31}P NMR spectra. When an equal amount of triflic anhydride and diphosphine oxide **87** are mixed together, no unreacted diphosphine oxide remains to react with monomer **91** to give rise to the dimer (or polymer) and sharp signals are observed as described above.



Scheme 57

Studies of the reactions represented in Scheme 55 suggest that there is no exchange between alcohol and carboxylic acid in the absence of base. This is further confirmed by an independent reaction studied by NMR spectroscopy using benzyl alcohol and *n*-propanol (Scheme 58). In this case, an equal amount of benzyl alcohol is added to the preformed cyclic phosphonium salt **91** to form the open benzyl alcohol adduct salt **92**. After one hour, *n*-propanol is added, but this does not react and none of the *n*-propanol activated phosphonium salt is observed. This shows that once the alcohol adduct phosphonium salt is formed, it is stable to either carboxylic acid or alcohol attack in the absence of triethylamine. The failure of the formation of the *n*-propanol activated phosphonium salt suggests that no equlibrium exists between the activated alcohol phosphonium salt **92** and the free alcohol or carboxylic acid.



Scheme 58

2.2 Polymer-supported version of the Hendrickson reaction

These studies on the solution phase Hendrickson reaction with bis-phosphine oxides encouraged investigation of a polymer-supported version. Commercially available chloromethyl polystyrene resin, known as Merrifield resin (1% DVB, 200-400 mesh, 1.0 mequiv/g), can be represented as a random repetition of two monomer units, 4-chloromethylstyrene and styrene with the ratio of M:N = 1:8 (based on elemental analysis) (Figure 9).

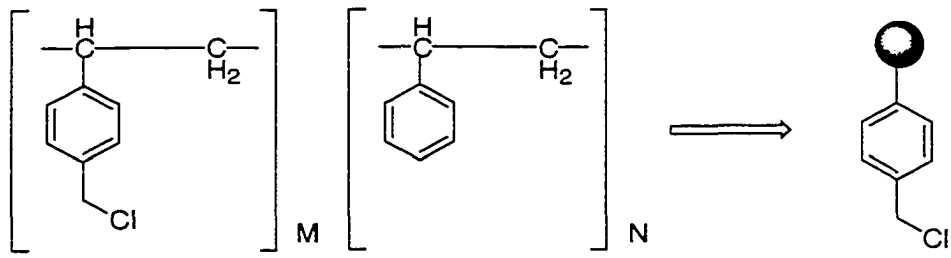
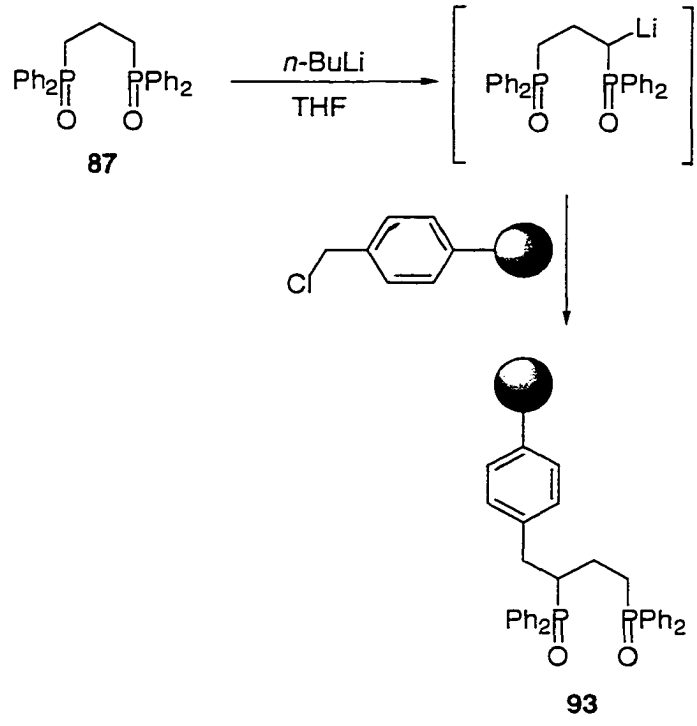


Figure 9: Chloromethyl polystyrene (M/N = 1/8)

Compound **87** was chosen for linking to this resin because its transformations were studied by NMR spectroscopy, and it gives good yields in the solution phase version of the Hendrickson reaction. The anion of **87** reacts with the Merrifield resin to form a polymer-supported reagent that may be represented by structure **93** (Scheme 59).

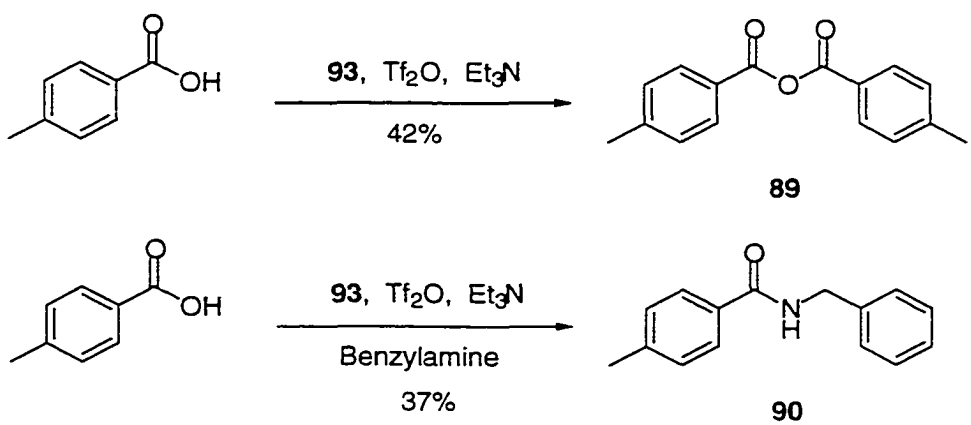


Scheme 59

The yield or the efficiency of the reaction (43%) is crudely estimated on the net weight increase of the carefully-washed (dichoromethane and THF) polymer after accounting for the loss of chlorine. Assuming that the weight increase is solely due to the reaction of **87** with Merrifield resin, 57% of the chlorine remains unreacted. Elemental analysis of the **93** is consistent with the theoretical calculation except for carbon (-0.5%). Standard ^{1}H and

^{13}C NMR spectra of **93** do not provide useful information due to the broadness of the signals. An IR spectrum of **93** shows a clear peak of P=O at 1200 cm^{-1} which is not present in the IR spectrum of the Merrifield resin. Two distinct phosphorus signals are present in the ^{31}P NMR spectrum at δ 32.5 and 27.9 ppm, which indicates two different phosphorus atoms in the reagent in accord with the proposed structure.

With the polymer supported phosphine oxide available, the Hendrickson reaction was attempted for the preparation of a carboxylic anhydride and an amide. It was found that, in comparison with the solution phase version using diphosphine oxides **87**, the yields are lower (Scheme 60). Since there was a significant difference in yield for the solution phase reaction (78%) compared with the solid phase version (42%) no efforts were made to test the recycled polymer in the same reactions.

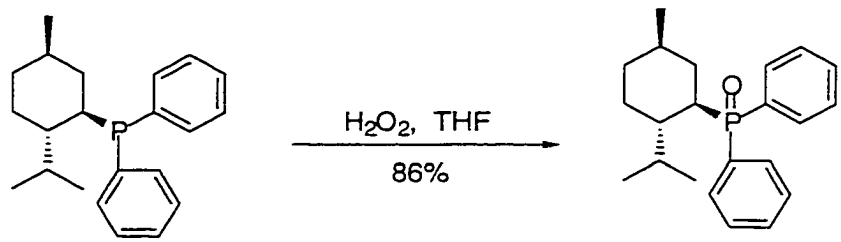


Scheme 60

2.3 Asymmetric version of the Hendrickson reaction

Chiral menthyldiphenylphosphine (**36**) was oxidized to phosphine oxide **94** in order to test if this compound could be used in a Hendrickson reaction to select one

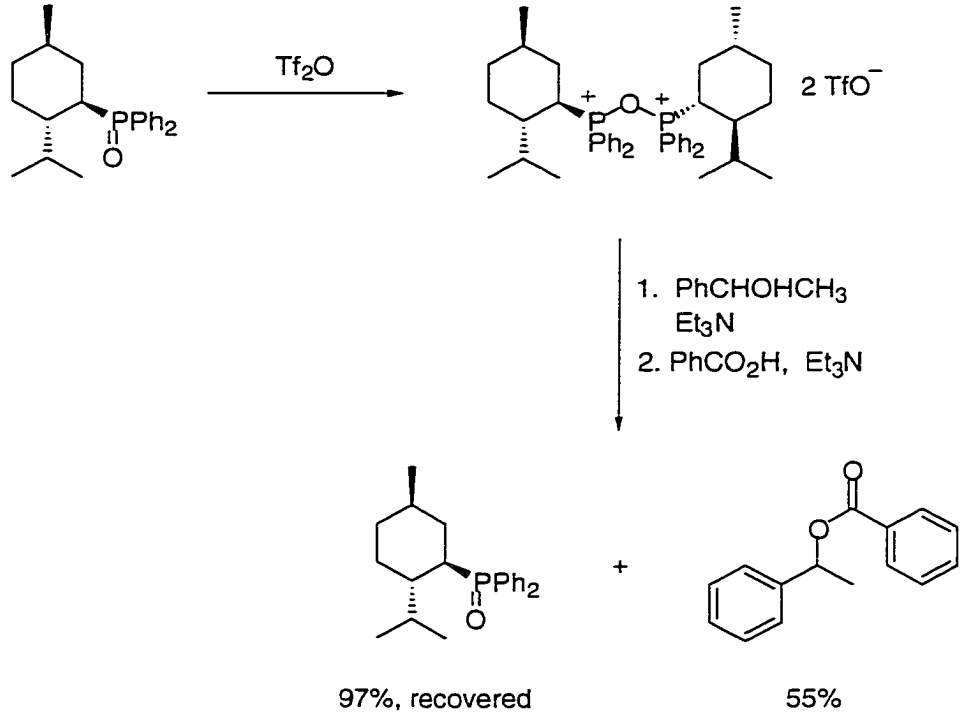
enantiomer of a racemic secondary alcohol. Oxidation proceeds readily in 86% yield using hydrogen peroxide (Scheme 61).



36 **94**

Scheme 61

Using a similar procedure to that described for the solution phase version of the Hendrickson reaction, compound **94** reacts with triflic anhydride to form the corresponding chiral phosphonium salt. In order to avoid competing reactions between the carboxylic acid and α-phenethyl alcohol, the alcohol is added first in order to form the alcohol activated phosphonium salt. Although 55% of the ester is isolated, chiral shift NMR spectroscopy shows that no selection occurs (Scheme 62). The chiral phosphine oxide **94** is recovered in almost quantitative yield. Since there is no selection in the initial study of this reaction, further investigations were not continued.

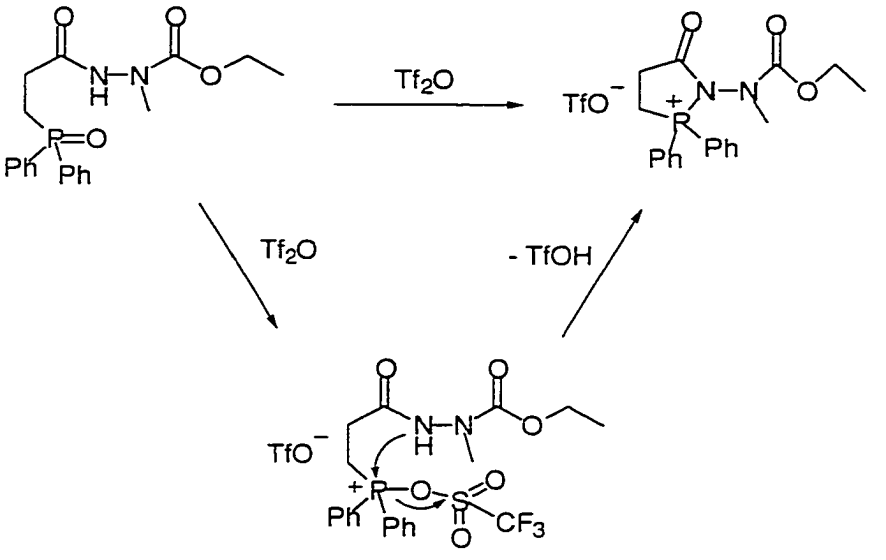


Scheme 62

Part 3. Reagents to Mimic Mitsunobu Reactions

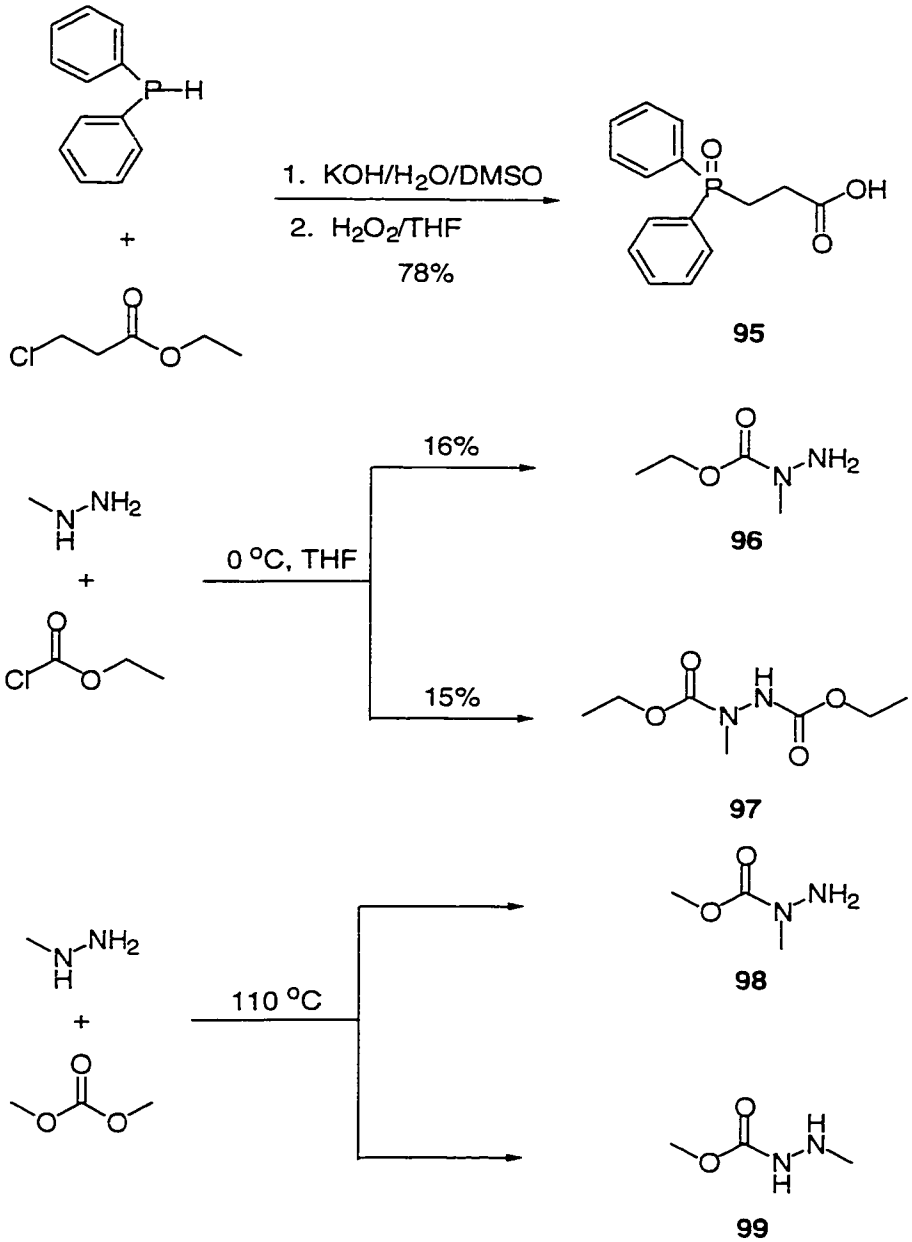
3.1 Synthesis of the Mitsunobu mimic regents

Three compounds **100**, **101** and **102**, were synthesized with each structure containing portions of triphenylphosphine and reduced DEAD motifs. It seemed that, upon treatment with triflic anhydride, cyclization could occur (Scheme 63) and that the resulting products could mimic the protonated zwitterionic intermediate in the Mitsunobu reaction.



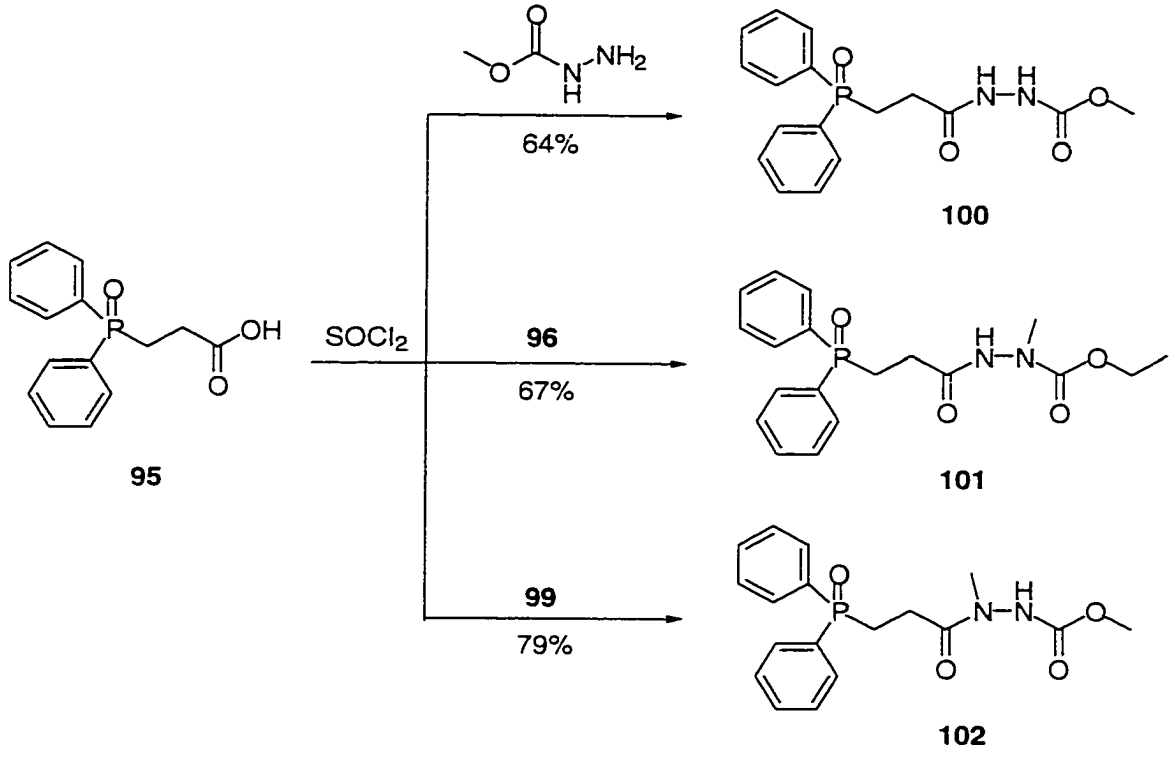
Scheme 63

The synthesis begins with the preparation of the phosphine containing moiety. 3-Diphenylphosphinyl carboxylic acid **95** is easily obtained in good yield by a one-pot reaction of diphenylphosphine and 3-chloropropionic acid ethyl ester, followed by the oxidation of phosphine to phosphine oxide[90] (Scheme 64). Reduced DEAD analogues **96** and **99** can be prepared with one of the nitrogens selectively methylated. This is done in order to control cyclization to either a 5 or 6 member ring upon treatment with triflic anhydride (Scheme 63). Reaction of methylhydrazine with ethyl chloroformate generates **96** and **97** in 16% and 15% yield, respectively. Using a procedure similar to that of Zinner *et al.*,[91] methylhydrazine reacts with methylcarbonate to give **98** and **99,** which are separated by flash chromatography (Scheme 64).



Scheme 64

Compounds **101** and **102** are available by the reaction of **96** and **99** with an acid chloride that is made *in situ* using thionyl chloride and carboxylic acid **95** (Scheme 65). Compound **100**, with neither nitrogen methylated, was also prepared in order to compare the cyclization reaction with **101** and **102.**

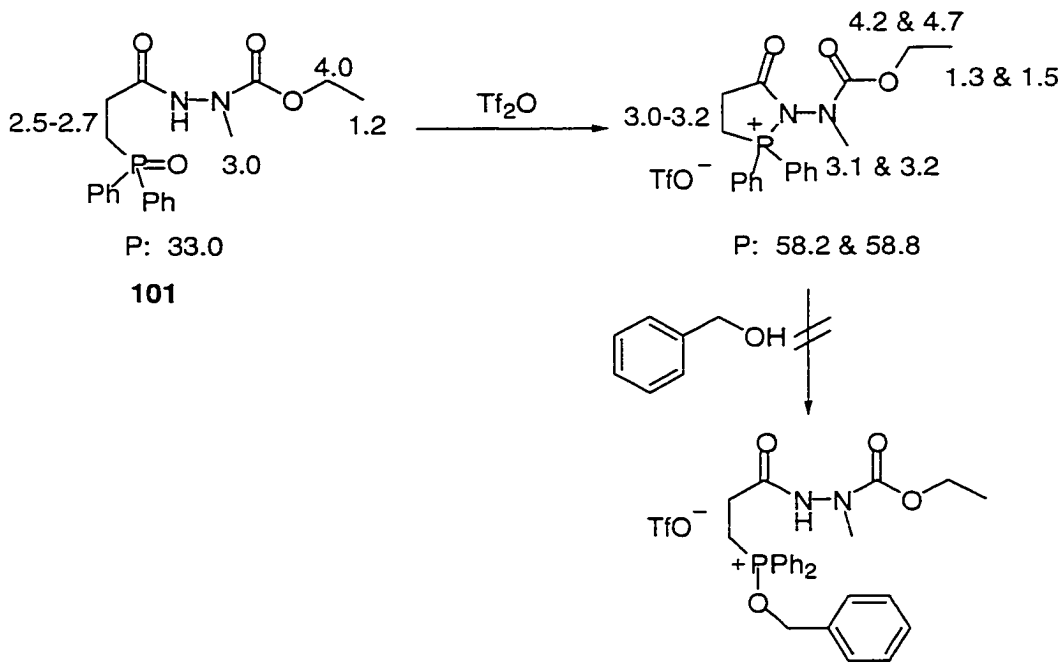


Scheme 65

3.2 NMR spectroscopic study of the Mitsunobu mimic reagents

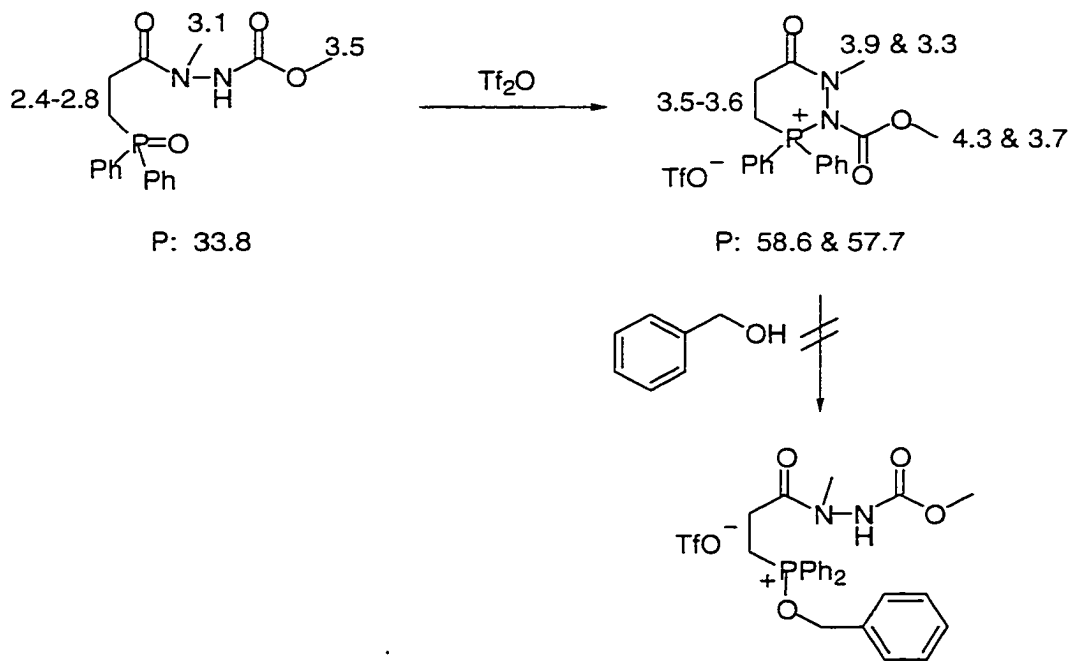
The cyclization of compound **101** and **102** by triflic anhydride and the subsequent reaction of the intermediate with either an alcohol or a carboxylic acid was investigated by NMR spectroscopy. Compound **101** was treated with one equivalent of triflic anhydride in CD_2Cl_2 at room temperature. After approximately 1h, ^1H and ^{31}P NMR spectra were recorded. Two phosphorus signals are observed at δ 58.2 and 58.8 ppm and in the ^1H spectrum, two sets of methyl and ethyl signals are found (Scheme 66). In both the ^{31}P and ^1H spectra, the two sets of signals are present in an approximate ratio of 1:2. The presence of two sets of the signals could possibly be due to two different conformations of the expected cyclized intermediate. However, the presence of an acyclic dimer cannot be excluded. The phosphorus chemical shifts at δ 58.2 and 58.8 are similar to those reported in the protonated zwitterionic adduct in the Mitsunobu reaction by

Jenkins *et al.* (δ 50 ppm)[6] and differ considerably from the starting material **101** whose phosphorus signal is at δ 33 ppm. To a solution of this "activated salt," a solution of one equivalent of benzyl alcohol in CD_2Cl_2 was added and both ^1H and ^{31}P NMR spectra were recorded. The phosphorus signals at δ 58.2 & 58.1 ppm shift slightly to 56.4 & 57.0 ppm and the benzyl protons of benzyl alcohol appear as a singlet at δ 4.6 ppm. No other changes of proton signals were detected (except for additional aromatic protons due to the benzyl alcohol). Even after 4-toluic acid is added the ratios and the chemical shifts for both the phosphorus and protons signals do not change detectably. These observations suggest that a cyclized phosphonium salt may form, but that it is too stable to be opened by either the alcohol or the carboxylic acid. The addition of triethylamine to the above mixture decomposes the putative cyclized phosphonium salt. The phosphorus signal representing the starting material **101** is again observed at δ 33.0 ppm.



Scheme 66

The same reaction as the one discussed above was done using compound **102**. Both of the phosphorus and proton signals move downfield in comparison with the starting material **101** after treatment with triflic anhydride. As with **101**, two sets of phosphorus and proton signals are observed (Scheme 67). The ratio of the two sets of signals is 1:4 for both the phosphorus and proton spectra. The putative cyclized phosphonium salt (or possibly acyclic dimer) is also stable to both the alcohol and the carboxylic acid. No chemical shift changes for either the phosphorus or the proton signals are detected upon exposure of the intermediate to either the alcohol or the carboxylic acid even after 12 h.



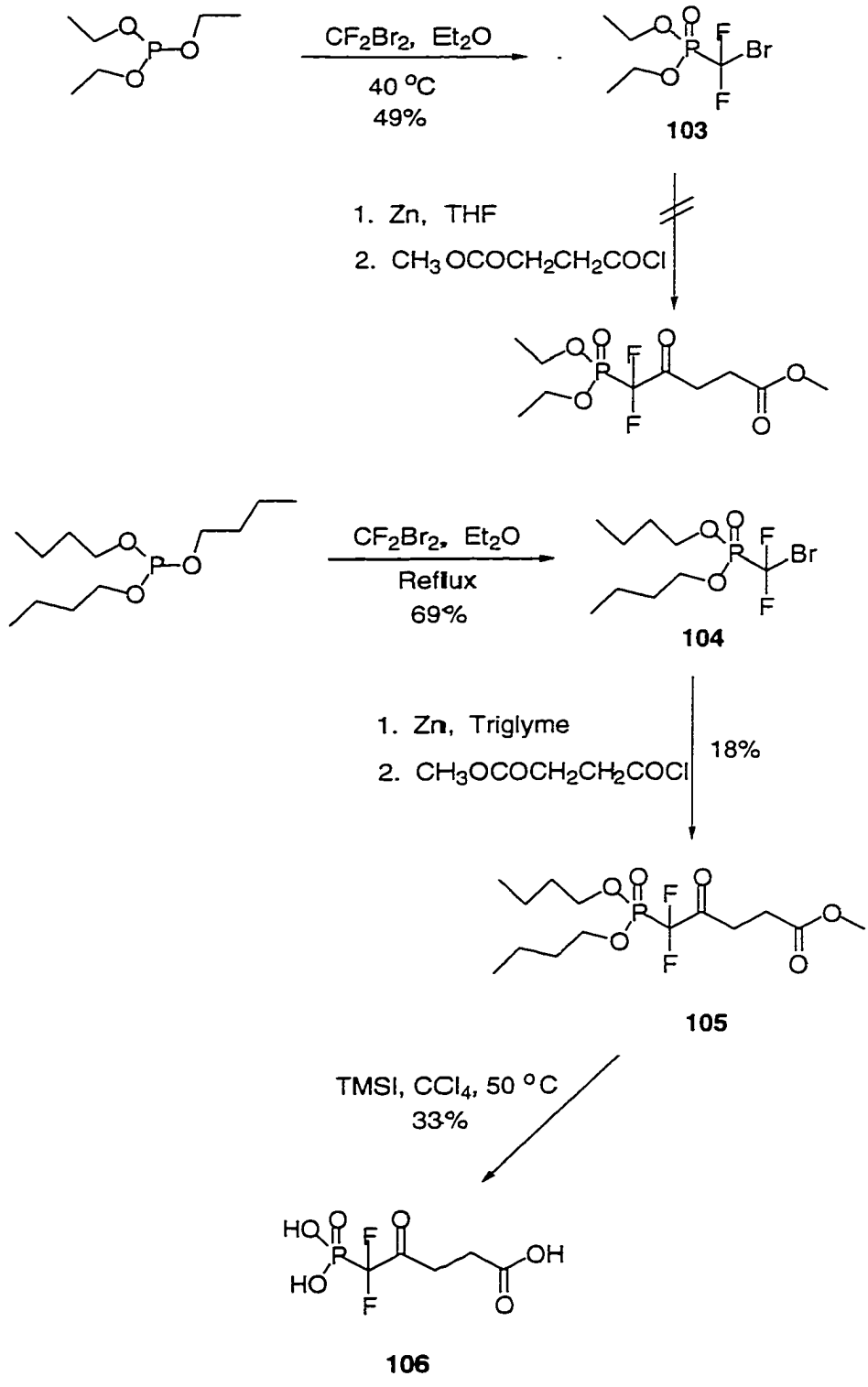
Scheme 67

This spectroscopic investigation of reactions of **101** and **102** suggests that the Mitsunobu reagent mimics may be formed by triflic anhydride, but that the resulting phosphonium salts are too stable to be cleaved by either alcohols or carboxylic acids. Therefore no further effort was made to investigate their possible use.

Part 4. The synthesis of a potential inhibitor of succinyl–CoA synthetase

As part of our interest in esterification and involvement of oxidized phosphorus intermediates, we briefly examined the synthesis of a potential inhibitor of succinyl CoA synthetase. As mentioned in the Introduction (section 1.5), activation of a host of carboxylic acids by nucleotide triphosphates (e.g. ATP, GTP) occurs by enzyme-catalyzed generation of mixed carboxylic-phosphate anhydrides that are the substrate attacked by nucleophiles at the carbonyl. Succinyl CoA synthetase catalyzes the reversible conversion of succinnyl-CoA to succinate in the citric acid cycle (Scheme 15). The mechanism of this enzyme reaction involves the formation of phosphoenzyme and succinyl phosphate. Based on this, it seemed that a stable tetrahedral adduct could be formed on the enzyme surface by reaction of the thiol of Coenzyme A with an α-haloketone such as **106**.

The synthesis of **106** begins with the preparation of dialkyl bromodifluoromethylphosphonate **103** and **104** (Scheme 68) by Michaelis-Arbuzov reaction using trialkylphosphite and dibromodifluoromethane as the starting materials.



Scheme 68

The treatment of diethyl bromodifluoromethylphosphonate **103** with activated zinc dust in THF gives the corresponding diethoxyphosphinyldifluoromethylzinc compound. Burton's paper states that the reaction of dialkoxyphosphinyldifluoromethylzinc compounds obtained in THF, dioxane and triglyme with acid halides gives the corresponding acyl phosphonate products.[92] Unfortunately, in our hands the zinc reagent obtained from **103** in THF and triglyme did not give the desired product. Using the same procedure, compound **104** did not yield the desired compound **105** in THF either. However, using triglyme as the reaction solvent, 18% of the desired product can be isolated. An excess of TMSI is used to convert **105** to the silyl ester which is easily hydrolyzed by H_2O at room temperature to afford the desired compound **106** in 33% yield.[93] Unfortunately compound **106** was found not to be an inhibitor of the succinyl–CoA synthetase by our collaborators, Dr. William Wolodko and Professor William Bridger (Biochemistry Department, University of Alberta).

Summary

A variety of phosphorus compounds have been synthesised and their reactivity examined in the Mitsunobu esterification. Aminophosphines mediate Mitsunobu esterification for primary alcohols, but not secondary alcohols. Phosphinites can be used in the Mitsunobu esterification for secondary alcohols, however a side reaction involving displacement at the carbon adjacent to the oxygen in the phosphinites was also observed. A variety of chiral phosphines have been prepared and tested for reactivity and stereoselection by Mitsunobu esterification using racemic secondary alcohols. Menthyldiphenylphosphine (**36**) deracemizes racemic secondary alcohols with low to

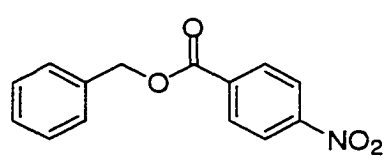
moderate stereoselection (6% to 58% e.e. of esters). Repetition of this reaction using recovered alcohol further increases the e.e. of the alcohol (96% e.e. for α-phenethyl alcohol, 81% e.e. for 2-decanol). Other chiral phosphines either fail in the Mitsunobu esterification, or do not show stereoselection. Solution version Hendrickson reactions have first been examined using bis-phosphine oxide **86**, **87** and **88**. Moderate to high yields of anhydride and amide are obtained. Polymer-supported Hendrickson reagent **93** was prepared. This reagent directs the formation of anhydride and amide, but the yields are low. Cyclized phosphonium salt and the subsequent alkoxyphosphonium salt were first formed and detected by NMR spectroscopy. Three protonated Mitsunobu intermediate mimics **100**, **101** and **102** were prepared. An NMR spectroscopy study suggests that the "cyclized activated species" may form upon treatment with triflic anhydride. It seems that the cyclized phosphonium salts are too stable to be opened by either carboxylic acid or alcohol. A potential succinyl-CoA synthetase inhibitor **106** was made; however, it was found that **106** is not an inhibitor.

EXPERIMENTAL SECTION

General methods and materials

All reactions involving air-sensitive reagents were performed under argon, using syringe-septum cap techniques. All glassware was oven-dried prior to use. All solvents were purified and distilled according to Perrin.[94] Solutions were evaporated under reduced pressure with a rotary evaporator. Melting points were determined on a Thomas-Hoover or Büchi oil immersion apparatus using open capillary tubes and are uncorrected. Mass spectra (MS) were recorded on a Kratos MS50 mass spectrometer for electron impact (EI) and on a Micromass ZabSpec Hybrid Sector-TOF for electrospray (ES). Infrared (IR) spectra were determined with a Nicolet Magna 750 FT-IR spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a micro cell (100 mm, 0.9 mL). $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were completed at the University of Alberta Microanalytical Laboratory. The determination of the enantiomeric excess of ester formed during Mitsunobu reactions was achieved by titration of the ester with the chiral shift reagent $Eu(hfc)_3$ in $CDCl_3$ and measurement of the ^1H NMR integrals. Good separation was obtained by zero-filling the FID (32 K) to 64 K and applying Gaussian multiplication (GB = 0.5, LB = 0.5 to 1.2 Hz) for resolution enhancement before Fourier transformation. The ratio of the two enantiomers of recovered alcohol was determined by converting the alcohols to the corresponding Mosher's esters with (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. ^1H, ^{13}C, ^{31}P, and ^{19}F NMR spectra were recorded on Bruker WH200, AM300, WM360 or AM400 instruments. ^1H NMR chemical shifts are reported in parts per million (ppm) downfield relative to

tetramethylsilane (TMS) using the solvent resonance as the reference: $CDCl_3$ δ 7.26, CD_2Cl_2 δ 5.32, and CD_3OD δ 3.30. ^{13}C chemical shifts are reported relative to $CDCl_3$ δ 77.0, CD_2Cl_2 δ 53.8, and CD_3OD δ 49.0. ^{31}P NMR chemical shifts are relative to external 85% H_3PO_4 set at 0.0 ppm. ^{19}F NMR chemical shifts are relative to $CFCl_3$ set at 0.0 ppm. Selective homonuclear decoupling, NOE and attached proton test (APT) were occasionally used for signal assignments. ^1H NMR data are recorded in the following order: Multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant(s) in Hertz (Hz), number of protons, and assignment. Where appropriate, the multiplicity is preceeded by br, indicating that the signal was broad. Reactions and fractions from column chromatography were monitored and analyzed by thin-layer chromatography (TLC) using glass plates with UV fluorescent indicator (normal silica, Merck 60 F_{254}; reverse phase, Merck RP-8 and RP-18 F_{254}). One or more of the following methods were used for visualization: UV absorption by fluorescence quenching; iodine staining; phosphomolybdic/ceric sulfate/sulfuric acid (10 g : 1.25 g : 8% 250 mL) spray; and 0.1% $KMNO_4$ spray. Flash column chromatography was performed using 230-400 mesh silica (Merck, silica gel).

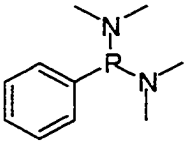


10

Benzyl 4-nitrobenzoate 10

This compound was prepared using the modified procedure of Dodge *et al.*[22] To a solution of 1,3-dimethyl-2-phenyl-1,3,2-diazophosphinolidine (0.49 g, 2.52 mmol) in

THF (5 mL) was slowly added DEAD (0.44 g, 2.52 mmol) in THF (5 mL) *via* an addition funnel under argon at 0 °C. The reaction was stirred for 15 min to form a pink solution. To this solution a mixture of benzyl alcohol (0.27 g, 2.52 mmol) and 4-nitrobenzoic acid (0.42 g, 2.52 mmol) in THF (10 mL) was slowly added *via* an addition funnel during which the solution turned brown. The reaction mixture was stirred under argon at room temperature for 18 h and then concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/hexane 1/5) to give benzoic acid benzyl ester (0.44 g, 68%) as a white solid. mp 78–80 °C (Lit.[95] 82-83 °C); IR ($CHCl_3$, cast) 1725 (C=O), 1658, 1527, 1347, 1272, 1115, 1101, 718 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.22-8.31 (m, 4H, Ar), 7.38-7.48 (m, 5H, Ar), 5.40 (s, 2H, OCH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.5, 150.6, 135.5, 135.2, 130.8, 128.7, 128.6, 128.4, 123.5, 67.6; HRMS (EI) Calcd. for $C_{14}H_{11}NO_4$ (M^+) 257.0688, Found 257.0682.

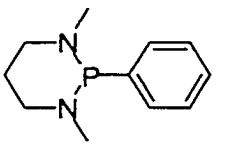


11

Phenylphosphonous acid *bis*(dimethyl)amide 11

This compound was prepared using a similar procedure to that of Maier.[49] To a solution of dimethylamine (4.51 g, 100 mmol) in THF (50 mL) was added dichlorophenylphosphine (2.87 g, 16.0 mmol) in THF (20 mL) under argon at -25 °C dropwise *via* an addition funnel over 15 min during which the temperature rose to -10 °C with the formation of solid. In order to ease stirring, THF (20 mL) was added to dilute the reaction mixture. The reaction was warmed to room temperature and stirred for 1 h and then heated under reflux

for 45 min. After cooling to room temperature the reaction was stirred for 3 h, filtered and the filtrate was purified by distillation to give phenylphosphonous acid *bis*(dimethyl)amide (1.27 g, 40%) as a colourless liquid; bp 102–104 °C/1mm Hg; IR ($CHCl_3$, cast) 2968, 1445, 1261, 956, 970, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.35-7.40 (m, 5H, Ar), 2.75 (d, J = 9.2 Hz, 12H, CH_3) ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.2, 130.9, 128.2 (d, J = 3.1 Hz), 127.4, 41.8 (d, J = 15.5 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 100.0 (s); HRMS (EI) Calcd. For $C_{10}H_{17}N_2P$ (M^+) 196.1129. Found 196.1138.

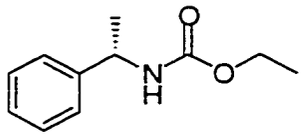


12

1,3-Dimethyl-2-phenyl-1,3,2-diazaphosphinane 12

This compound was prepared using a similar procedure to that of Hutchins *et al.*[50] To a solution of *N,N*-dimethyl-1,3-propylenediamine (4.67 g, 45.7 mmol) and triethylamine (18.2 g, 183 mmol) in dry Et_2O (100 mL) was added dichlorophenylphosphine (8.17 g, 45.7 mmol) in Et_2O (20 mL) under argon at 0 °C dropwise over 30 min during which time a heavy precipitate had formed. The reaction was stirred at room temperature for 12 h and the solid removed by filtration. The filtrate was concentrated *in vacuo* and purified by distillation to give 1,3-dimethyl-2-phenyl-1,3,2-diazaphosphinane (2.10 g, 24.5%) as a colourless liquid; bp. 112-114 °C /0.1mm Hg (Lit.[50] 119-123 °C/0.3mm Hg); IR ($CHCl_3$, cast) 2927, 1477, 1433, 1417, 1162, 1091, 899, 688, 642 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.44-7.48 (m, 2H, Ar), 7.33-7.38 (m, 2H, Ar), 7.23-7.28 (m, 1H, Ar), 3.24 (dt, J = 13.1, 2.5 Hz, 2H, 2 x CH_2CH_aHN), 3.00 (d, J = 15.6 Hz, 6H, 2 x CH_3N), 2.63-2.70 (m,

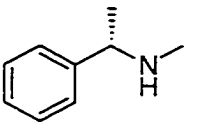
2H, 2 x CH_2CH_bHN), 2.15-2.24 (m, 1H, CH_aCH_2N), 0.98 (m, 1H, CH_bCH_2N); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.6 (d, J = 11.5 Hz), 130.3 (d, J = 14.6 Hz), 128.3 (d, J = 3.4 Hz), 127.3, 46.9 (d, J = 6.0 Hz), 43.0 (d, J = 33.1 Hz), 20.8 (d, J = 1.9 Hz); ^{31}P NMR ($CDCl_3$, 81 MHz) δ 92.1 (s); HRMS (EI) Calcd. For $C_{11}H_{17}N_2P$ (M^+) 208.1129, Found 208.1120.



13

(*S*)-1-Phenylethyl carbamic acid ethyl ester 13

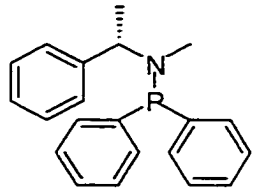
This compound was prepared using a similar procedure to that of Searle *et al.*[51] To a solution of (S)-1-phenylethylamine (2.50 g, 20.7 mmol) and NaOH (0.83 g, 20.7 mmol) in water (40 mL) was added a solution of ethyl chloroformate (2.24 g, 20.7 mmol) in Et_2O (70 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 48 h, the layers were separated and the organic layer dried over Na_2SO_4 and concentrated *in vacuo* to give a colourless residue. The residue was purified by a short silica gel column (EtOAc/Hexane 1/4) to give (*S*)-1-phenylethyl carbamic acid ethyl ester (3.59 g, 90%) as a pure colourless liquid; IR ($CHCl_3$, cast) 3322 (NH), 2977, 1694 (CO), 1533, 1248, 1095, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.24-7.36 (m, 5H, Ar), 4.94 (br s, 1H, N*H*), 4.84 (br s, 1H, PhC*H*CH_3NH), 4.09 (qd, J = 7.1, 2.5 Hz, 2H, OCH_2CH_3), 1.49 (d, J = 6.8 Hz, 3H, CH_3CH), 1.22 (t, J = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.9, 143.8, 128.6, 127.2, 125.9, 60.8, 50.6, 22.5, 14.6; HRMS (EI) Calcd. for $C_{11}H_{15}NO_2$ (M^+) 193.1103, Found 193.1109.



14

(*S*)-Methyl-(1-phenethyl) amine 14

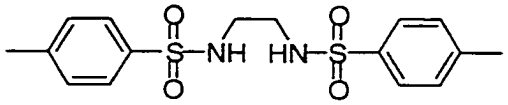
This compound was prepared using a similar procedure to that of Bennani *et al.*[96] To a suspension of lithium aluminium hydride (2.35 g, 62.1 mmol) in THF (80 mL) was slowly added a solution of (*S*)-1-phenylethyl carbamic acid ethyl ester (2.40 g, 12.4 mmol) in THF (20 mL) under argon at 0 °C. The reaction was heated under reflux for 18 h, then cooled to 0 °C, and quenched with H_2O (addition of H_2O until no more H_2 evolution). The reaction mixture was basified to pH 11 with 15% aq. NaOH during which a thick precipitate formed. The solid was removed by filtration and washed with THF. The filtrate was concentrated *in vacuo* to give a residue which was redissolved in CH_2Cl_2 (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give (*S*)–methyl–(1–phenylethyl) amine (1.52 g, 91%) as a pale yellow liquid which was used for spectroscopic analysis without further purification; IR ($CHCl_3$, cast) 3288 (NH), 2968, 2787, 1492, 1475, 1136, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23-7.36 (m, 5H, Ar), 3.64 (q, J = 6.6 Hz, 1H, PhC*H*CH_3N), 2.31 (s, 3H, C*H*$_3$N), 1.83 (br s, 1H, N*H*), 1.38 (d, J = 6.6 Hz, 3H, C*H*$_3$CHN); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.0, 128.4, 126.9, 126.6, 60.2, 34.3, 23.7; HRMS (EI) Calcd. for $C_9H_{13}N$ (M^+) 135.1048, Found 135.1053.



15

(*S*)-*N*-Methyl-*N*-(1-phenylethylamino)diphenylphosphine 15

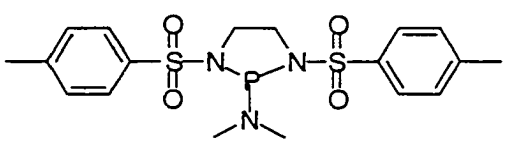
This compound was prepared by a similar procedure to that of Fiorini *et al.*[97] To a solution of (*S*)-methyl-(1-phenylethyl) amine (1.14 g, 8.43 mmol) and triethylamine (1.01 g, 10.0 mmol) in benzene (20 mL) under argon at 0 °C was added a solution of chlorodiphenylphosphine (1.84 g, 8.43 mmol) in benzene (5 mL) over 30 min during which time a heavy precipitate had formed. The reaction mixture was stirred at room temperature for 12 h and the solid was removed by filtration. The filtrate was concentrated *in vacuo* to give a residue which was purified by dissolving in CH_2Cl_2 (30 mL), and passage through a short silica column. The column was washed with CH_2Cl_2 (100 mL); and the combined eluent was concentrated *in vacuo* to give (*S*)-*N*-methyl-*N*-(1-phenylethylamino)diphenyl-phosphine (0.65 g, 24%) as a colourless oil; $[\alpha]_D$ +69.4° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cast) 2969, 1449, 782, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.26-7.58 (m, 15H, Ar), 4.64 (dq, *J* = 10.6, 7.0,Hz, 1H, PhC*H*CH_3), 2.23 (d, *J* = 3.0 Hz, 3H, C*H*$_3$N), 1.58 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CHN); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8 (d, *J* = 5.6 Hz), 139.6 (d, *J* = 2.3 Hz), 132.6 (d, *J* = 20.7 Hz), 131.8 (d, *J* = 19.7 Hz), 128.3, 128.0 (d, *J* = 6.0 Hz), 127.4, 126.8, 63.8 (d, *J* = 38.8 Hz), 31.7 (d, *J* = 9.7 Hz), 18.1 (d, *J* = 9.6 Hz); ^{31}P NMR ($CDCl_3$, 81 MHz) δ 60.4 (s); HRMS (EI) Calcd. For $C_{21}H_{22}NP$ (M^+) 319.1490, Found 319.1480.



17

1,2-*Bis*-(toluene-4-sulfonylamino)ethane 17

This compound was prepared by a modified procedure of Searle *et al.*[51] To a solution of 1,2-ethylenediamine (6.0 g, 0.10 mol) and NaOH (8.0 g, 0.20 mol) in water (80 mL) was added TsCl (40 g, 0.20 mol) in Et_2O (200 mL) *via* an addition funnel at 0 °C. The reaction mixture was stirred for 3 h at room temperature during which time heavy crystals had formed. The solid was collected by filtration and purified by recrystallization from hot methanol to give 1,2-*bis*-(toluene-4-sulfonylamino)ethane (30.6 g, 83%) as white needle prisms; mp. 159-162 °C (Lit.[51] 162-164 °C); IR ($CHCl_3$, cast) 3284 (NH), 1678, 1407, 1185, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.70 (d, J = 8.3 Hz, 4H, Ar), 7.30 (d, J = 8.3 Hz, 4H, Ar) 4.85 (br s, 2H, 2 x N*H*), 3.07 (d, J = 3.2 Hz, 2H, 2 x CH_aH_bN), 3.05 (d, J = 3.2 Hz, 2H, 2 x CH_aH_bN), 2.43 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8, 136.4, 129.9, 127.1, 43.0, 21.5; HRMS (EI) Calcd. for $C_{16}H_{21}N_2O_4S_2$ (M^+) 369.0943, Found 369.0932.

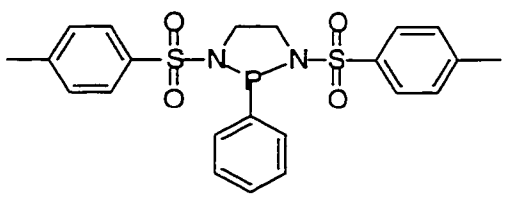


18

1,3-Di-4-tolysulfonyl-2-dimethylamino-1,3,2-diazaphospholidine 18

This compound was prepared following a similar procedure to that of Tye *et al.*[98] A solution of 1,2-*bis*-(toluene-4-sulfonylamino)ethane (1.97 g, 5.34 mmol) and hexamethylphosphorous triamide (0.87 g, 5.34 mmol) in toluene (100 mL) was heated

under reflux for 30 h with argon passing through the reaction system during which the reaction was monitored by pH indicator until no more dimethylamine was produced. After the reaction mixture was concentrated, the residue was purified by redissolving in CH_2Cl_2 (50 mL), passing through a short column of silica gel to give 1,3-di-4-tolysulfonyl-2-dimethylamino-1,3,2-diazaphospolidine (1.56 g, 66%) as a white solid; mp. 132-134 °C; IR ($CHCl_3$, cast) 2893, 1597, 1185, 1159, 1131, 1089, 816, 682, 589. 562 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.69 (d, J = 8.4 Hz, 4H, Ar), 7.26 (d, J = 8.5 Hz, 4H, Ar), 3.65 (m, 2H, $CH_aH_bCH_aH_b$), 3.17 (m, 2H, $CH_aH_bCH_aH_b$), 2.60 (d, J = 9.8 Hz, 6H, 2 x CH_3N), 2.42 (s, 6H, 2 x $ArCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8, 136.0, 129.6, 127.3, 46.8 (d, J = 6.7 Hz), 37.4 (d, J = 19.7 Hz); ^{31}P NMR ($CDCl_3$, 81 MHz) δ 99.3 (s); HRMS (EI) Calcd. for $C_{18}H_{24}N_3O_4S_2P$ (M^+) 441.0946, Found 441.0946.

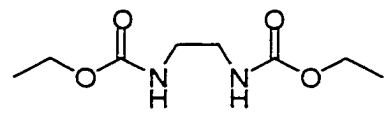


19

1,3-Di-(4-tolysulfonyl)-2-phenyl-1,3,2-diazaphospholidine 19

This compound was prepared by a similar procedure to that of Hersh *et al.*[99] To a suspension of 1,2-*bis*-(toluene-4-sulfonylamino)ethane (3.18 g, 8.64 mmol) and triethylamine (2.18 g, 21.5 mmol) in Et_2O (220 mL) was slowly added dichlorophenylphosphine (1.54 g, 8.64 mmol) in Et_2O (40 mL) *via* an addition funnel during which time a heavy precipitate had formed. The reaction mixture was stirred at room temperature for 3.5 h and then concentrated *in vacuo*. The crude material was purified by dissolving in dry CH_2Cl_2 (20 mL), filtering through a pad of silica gel, and

washed with CH_2Cl_2 (300 mL). After solvent removal *in vacuo* 1,3-di-4-tolysulfonyl-2-phenyl-1,3,2-diazaphospholidine was obtained (3.32 g, 81.%) as white crystals; mp 160-168 °C; IR (CH_2Cl_2, cast) 1596, 1343, 1160, 1089, 988, 749, 548 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.68-7.73 (m, 2H, Ar), 7.64 (d, J = 8.0 Hz, 4H, Ar), 7.45 (m, 3H, Ar), 7.16 (d, J = 8.0 Hz, 4H, Ar), 3.52 (m, 2H, $CH_aH_bCH_aH_b$), 3.22 (m, 2H, $CH_aH_bCH_aH_b$), 2.45 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.9, 135.9, 130.5, 129.7, 129.6, 129.3, 128.8 (d, J = 5.1 Hz), 127.3 (d, J = 2.0 Hz); ^{31}P NMR ($CDCl_3$, 81 MHz), δ 90.7 (s); HRMS (EI) Calcd. for $C_{22}H_{23}N_2O_4PS_2$ (M^+) 474.0837, Found 474.0833.

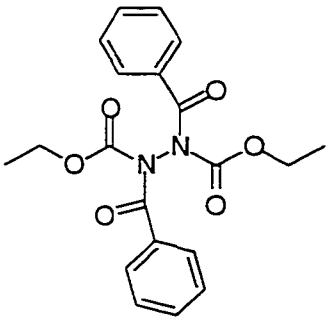


20

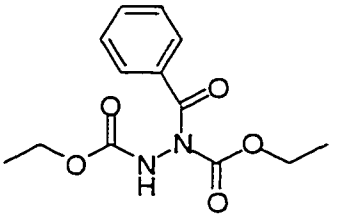
***N,N'*-Ethanediyl-*bis*-carbamic acid diethyl ester 20**

This compound was prepared by a similar procedure to that of Searle *et al.*[51] To a solution of 1,2-ethylenediamine (6.0 g, 0.10 mol) and NaOH (8.0 g, 0.20 mol) in H_2O (80 mL) was added a solution of ethyl chloroformate (40 g, 0.2 mol) in Et_2O (200 mL) using an addition funnel at 0 °C. The reaction was then stirred at room temperature for 3 h during which time a heavy precipitate had formed. The precipitate was collected by filtration and recrystallized from boiling methanol to give *N,N'*-ethanediyl-*bis*-carbamic acid diethyl ester (30.6 g, 83%) as a white solid; mp 109-110 °C (Lit.[100] 110-111 °C); IR ($CHCl_3$, cast) 3315 (NH), 3067, 2975, 2930, 2868, 1686 (C=O), 1547, 1479, 1449, 1365, 1319, 1275, 1240, 1168, 1115, 1030, 988, 886, 783 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 5.15 (br s, 2H, 2 x N*H*), 4.08 (q, J = 7.0 Hz, 4H, 2 x CH_2O), 3.29 (br s, 4H, 2 x CH_2N), 1.22 (t, J =

7.1 Hz, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.0, 60.6, 40.9, 14.4; HRMS (EI) Calcd, for $C_8H_{17}N_2O_4$ (MH^+), 205.1188, Found, 205.1197.



23

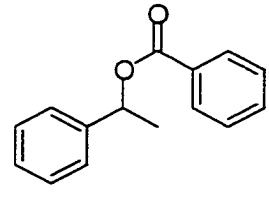


24

N,N'-Diethoxycarbonyl N,N'-dibenzoylhydrazine 23 & N,N'-diethoxycarbonyl N-benzoylhydrazine 24

To a solution of 1,3-dimethyl-2-phenyl-1,3,2-diazophosphinolidine (100 mg, 0.51 mmol) in THF (2 mL) was added DEAD (89.6 mg, 0.51 mmol) *via* syringe under argon at room temperature and the reaction was stirred for 20 min. To this solution a mixture of benzoic acid (62.8 mg, 0.51 mmol) and α-phenylethyl alcohol (62.9 mg, 0.51 mmol) in THF (2 mL) was added. The reaction was stirred at room temperature for 12 h and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/hexane 1/3) to give *N,N'*-diethoxycarbonyl *N,N'*-dibenzoylhydrazine (25 mg, 13%) as a white solid and *N,N'*-diethoxycarbonyl *N*-benzoylhydrazine (56.7 mg, 39%) as a colourless oil. Data for *N,N'*-diethoxycarbonyl *N,N'*-dibenzoylhydrazine **23**: mp 75-78 °C; IR ($CHCl_3$, cast) 1760 (C=O), 1707 (C=O), 1449, 1394, 1294, 1252, 1177, 1059, 1009, 647 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.70-7.72 (m, 4H, Ar), 7.52-7.56 (m, 2H, Ar), 7.41-7.46 (m, 4H, Ar), 4.18 (q, J = 7.1 Hz, 4H, 2 x OCH_2), 1.08 (t, J = 7.1 Hz, 6H, 2 x CH_3CH_2O); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 169.2, 152.4, 134.5, 132.1, 128.2, 64.2, 13.7; LRMS (ES) 385.1 (MH^+, 6%), 407.1 (MNa^+, 100%), HRMS (EI) Calcd. for $C_{20}H_{20}N_2O_6$ (M^+) 384.1321, Found 384.1323. Data for *N,N'*-diethoxycarbonyl *N*-benzoylhydrazine **24**: IR ($CHCl_3$, cast) 3311(NH), 2984, 1743 (C=O), 1710 (C=O), 1504, 1493, 1478, 1448, 1255, 1059, 724 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.69 (br d, *J* = 7.1 Hz, 2H, Ar), 7.50-7.55 (m, 1H, Ar), 7.40-7.44 (m, 2H, Ar), 6.95 (br s, 1H, N*H*), 4.26 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 4.15 (q, *J* = 7.2 Hz, 2H, CH_3CH_2O), 1.30 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O), 1.07 (t, *J* = 7.0 Hz, 3H, CH_3CH_2O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6, 153.4, 134.8, 132.0, 128.1, 62.4, 62.7, 14.4, 13.7; HRMS (EI) Calcd. for $C_{10}H_{12}N_2O_3$ (MH^+-C_2H_5OCO) 208.0848 found 208.0867.

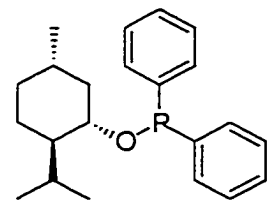


25

α-Phenethyl benzoate 25

To a solution of triphenylphosphine (0.135 g, 0.515 mmol) in THF (2 mL) was added DEAD (89.6 mg, 0.515 mmol) at room temperature under argon followed by addition of a solution of α-phenethyl alcohol (62.8 mg, 0.515 mmol) and benzoic acid (62.8 mg, 0.515 mmol) in THF (2 mL). The reaction was stirred at room temperature for 24 h and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/hexane: 1/2) to give α-phenethyl benzoate (97.1 mg, 83%) as a colourless oil; IR ($CHCl_3$, thin film) 3064, 3034, 2981, 1718, 1601, 1585, 1495, 1375, 1314, 1271, 1209,

1109, 1069, 1027, 712, 699, 549 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.09 (m, 2H, Ar), 7.58 (m, 1H, Ar), 7.45 (m, 4H, Ar), 7.39 (m, 2H, Ar), 7.31 (m, 1H, Ar), 6.15 (q, J = 6.6 Hz, 1H, C*H*OCH_3), 1.68 (d, J = 6.6 Hz, 3H, CHOC*H*$_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.8, 141.8, 132.9, 130.5, 129.6, 128.5, 128.3, 127.9, 126.0, 72.9, 22.4; HRMS (EI) Calcd. for $C_{15}H_{14}O_2$ (M^+) 226.0994, Found, 226.0997.

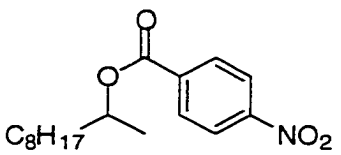


27

Menthyl diphenylphosphinite 27

This compound was prepared by a modified procedure of Mikolajczyk *et al.*[65] To a solution of (+)-menthol (3.54 g, 22.7 mmol) and triethylamine (2.53 g, 25.0 mmol) in benzene (100 mL) was added chlorodiphenylphosphine (5.00 g, 22.7 mmol) in benzene (40 mL) dropwise under argon at 0 °C. The reaction mixture was stirred for 24 h allowing the temperature to rise to room temperature during which heavy crystals had formed. The solid was removed by filtration and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography (short column) (EtOAc/Hexane 1/10) to give menthyl diphenylphosphinite (5.20 g, 68%) as a viscous liquid which solidified on freezing; $[\alpha]_D$ +53.1° (*c* 15, $CHCl_3$) [Lit.[59] -50.5° (*c* 15, CH_2Cl_2)], for the other enantiomer); IR ($CHCl_3$, cast) 3070, 2919, 2869, 1586, 1479, 1434, 1096, 1077, 990, 790, 793, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.49 (m, 4H, Ar), 7.33 (m, 6H, Ar), 3.67–3.76 (m, 1H, C*H*O), 2.11 (m, 2H), 1.65 (m, 2H), 1.09-1.15 (m, 2H), 0.90-1.02 (m, 1H), 0.85 (d, J = 6.5 Hz, 3H,

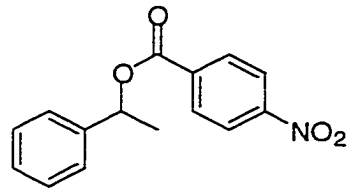
CH_3), 0.81 (d, J = 6.6 Hz, 3H, CH_3), 0.63 (d, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 81.2 (d, J = 18.7 Hz), 49.4 (d, J = 6.3 Hz), 45.1, 34.4, 31.7, 25.6, 23.2, 21.9, 21.0, 15.3; ^{31}P NMR ($CDCl_3$, 81 MHz) δ 106.9 (s); HRMS (EI) Calcd. for $C_{22}H_{29}OP$ (M^+), 340.1956, Found 340.1961.



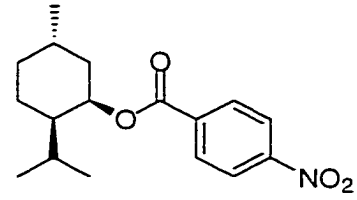
28

2-Decyl 4-nitrobenzoate 28

To a solution of menthyldiphenylphosphinite (0.11 g, 0.32 mmol) and DEAD (55.1 mg, 0.32 mmol) in THF (2 mL) was added a solution of 2-decanol (50.1 mg, 0.32 mmol) in THF (1 mL) at 0 °C under argon, followed after 25 min by addition of a solution of 4-nitrobenzoic acid (52.8 mg, 0.32 mmol) in THF (2 mL). The reaction was warmed to room temperature and stirred for 48 h. After concentration *in vacuo*, the residue was purified by flash chromatography (EtOAc/hexane: 1/4) to give 2-decyl 4-nitrobenzoate (44.0 mg, 46%) as a yellow oil; IR ($CHCl_3$, cast) 3118, 2927, 2856, 1722 (C=O), 1607, 1529, 1466, 1409, 1348, 1277, 1114, 1102, 719 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.26-8.29 (dd, J = 8.8, 2.1 Hz, 2H, Ar), 8.17-8.20 (dd, J = 8.8, 2.1 Hz, 2H, Ar), 5.13-5.22 (sextet, J = 6.2 Hz, 1H, C*H*O), 1.71-1.77 (m, 1H), 1.59-1.66 (m, 1H), 1.35 (d, J = 6.3 Hz, 3H, CH_3CH), 1.24-1.31 (m, 12H), 0.84-0.88 (t, J = 6.6 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.2, 150.1, 136.3, 130.6, 123.4, 73.1, 35.9, 31.7, 29.4, 29.1, 25.3, 22.6, 19.9, 14.0; HRMS (EI) Calcd. for $C_{17}H_{25}NO_4$ (M^+) 307.1783, Found 307.1781.



29

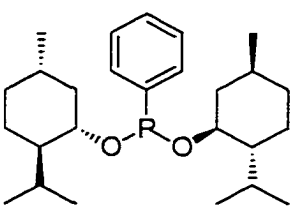


30

α-Phenethyl 4-nitrobenzoate 29 & neomenthyl 4-nitrobenzoate 30

To a solution of menthyl diphenylphosphinite (0.14 g, 0.4 mmol) in THF (4 mL) was added DEAD (69.7 mg, 0.400 mmol) *via* syringe and the reaction was stirred under argon at -60 °C for 30 mins. To the reaction mixture was added a solution of α-phenethyl alcohol (48.7 mg, 0.39 mmol) in THF (1.5 mL), followed after 30 min by the addition of 4-nitrobenzoic acid (55.7 mg, 0.33 mmol) in THF (1.5 mL). The reaction was then stirred at –60 °C for 48 h. After concentration *in vacuo* the residue was purified by flash chromatography (EtOAc/hexane 1/10) to give α-phenethyl 4-nitrobenzoate (27.1 mg, 30%) as a pale yellow solid and neomenthyl 4-nitrobenzoate (13.5 mg, 13%) as a white solid. Data for α-phenethyl 4-nitrobenzoate **29**; mp 41-42 °C (Lit.[101] 42-44 °C); IR ($CHCl_3$, cast) 2982, 1723, 1607, 1527, 1495, 1453, 1351, 1320, 1272, 1209, 1115, 1102, 1061, 1014, 994, 873, 841, 719, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.22-8.30 (m, 3H, Ar), 7.26-7.46 (m, 6H, Ar), 6.15 (q, J = 6.6 Hz, 1H, C*H*CH_3), 1.72 (d, J = 6.6 Hz, 3H, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.9, 150.6, 141.0, 135.9, 130.7, 128.7, 128.3, 126.2, 123.5, 74.6, 22.2; HRMS (EI) Calcd. for $C_{15}H_{13}NO_4$ (M^+), 271.0845, Found, 271.0840. Data for neomenthyl 4–nitrobenzoate **30**; mp 90-92 °C; $[\alpha]_D$ –15.1° (*c* 1.4, $CHCl_3$); IR ($CDCl_3$, cast) 2963, 2942, 2919, 2866, 1712, 1674, 1527, 1368, 1347, 1321, 1278, 1122, 1102, 1012, 873, 838, 719 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.28–8.30 (dd, J = 7.0, 1.8 Hz, 2H, Ar), 8.19–8.22 (dd, J = 7.2, 1.8 Hz, 2H, Ar), 5.49 (br d, J = 1.7

Hz, 1H, C*H*O), 2.06-2.12 (ddd, J = 14.3, 5.8, 3.3 Hz, 1H), 1.82–1.89 (m, 2H), 1.64-1.72 (m, 1H), 1.45-1.57 (m, 2H), 1.10-1.25 (m, 2H), 0.95-1.07 (m, 1H), 0.94 (d, J = 6.7 Hz, 3H, CH_3), 0.91 (d, J = 6.7 Hz, 3H, CH_3), 0.89 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.0, 150.5, 136.5, 130.7, 123.6, 73.3, 47.0, 39.2, 34.8, 29.5, 26.9, 25.4, 22.2, 21.0, 20.8; HRMS (EI) Calcd. for $C_{17}H_{23}NO_4$ (M^+) 305.1627, Found 305.1611.

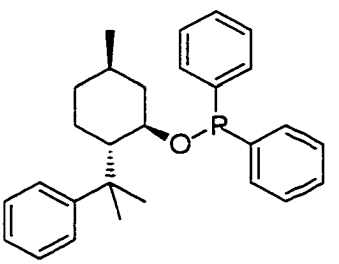


31

Dimenthyl phenylphosphonite 31

This compound was prepared by a similar procedure to that of Neuffer *et al.*[60] To a solution of dichlorophenylphosphine (13.2 g, 73.7 mmol) in toluene (100 mL) was added a solution of menthol (23.0 g, 147.4 mmol) in pyridine (11.7 g, 147.4 mmol) over *ca.* 30 min under argon at room temperature during which a heavy solid had formed. The reaction was stirred for 24 h at room temperature and the solid was removed by filtration. The filtrate was concentrated *in vacuo* and the crude product was purified by recrystallization from dry acetone to give dimenthyl phenylphosphonite (16.0 g, 52.1%) as white crystals; mp. 53-54 °C (Lit.[60] 54 °C); $[\alpha]_D$ +74.9° (*c*, 33.4, $CHCl_3$); IR ($CHCl_3$, cast) 2955, 2923, 2871, 1456, 1436, 1023, 978, 814 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.62-7.70 (m, 2H, Ar), 7.36-7.44 (m, 3H, Ar), 3.76-3.87 (m, 1H, CHO), 3.68-3.74 (m, 1 H, C*H*O), 2.26-2.36 (m, 1 H), 2.04-2.18 (m, 3H), 1.60-1.73 (m, 5H), 1.30-1.50 (m, 5H), 1.05-1.24 (m, 5H), 0.95 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 7.1 Hz, 3H), 0.89 (d, J = 6.6 Hz,

3H), 0.86 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H), 0.70 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.2 (d, J = 13.5 Hz), 130.1, 129.7 (d, J = 2.7 Hz), 128.1 (d, J = 6.4 Hz), δ 79.7 (d, J = 17.9 Hz), 77.8 (d, J = 11.2 Hz), 49.2 (d, J = 6.3 Hz), 49.1 (d, J = 4.6 Hz), 44.7 (d, J = 5.1 Hz), 44.4 (d, J = 2.6 Hz), 34.3, 34.2, 31.9, 31.7, 25.2, 24.9, 22.9, 22.8, 22.2, 21.3, 21.1, 16.1, 15.7, 15.2; ^{31}P NMR ($CDCl_3$, 81 MHz) δ 75.3 (s); HRMS (EI) Calcd. For $C_{26}H_{43}O_2P$ (M^+) 418.3008, Found, 418.3012.

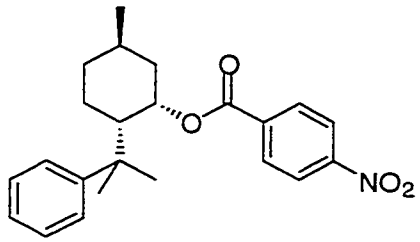


32

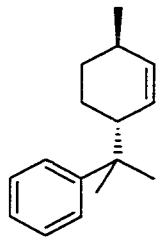
(-)-8-Phenylmenthyl diphenyl phosphinite 32

This compound was prepared by a similar procedure to that of Mikolajczyk *et al.*[65] To a solution of (-)-8-phenylmenthol (0.47 g, 1.88 mmol) and triethylamine (0.20 g, 2.00 mmol) in benzene (18 mL) was added a solution of chlorodiphenylphosphine (0.415 g, 1.88 mmol) in benzene (2 mL) under argon at 0 °C during which time a precipitate had formed. The reaction was stirred at 0 °C for 48 h and then the solid was removed by filtration. The filtrate was concentrated *in vacuo* and purified by flash chromatography (EtOAc/Hexane, 1/15) to give (-)-8-phenylmenthyl diphenyl phosphinite (0.19 g, 26%) as a colourless viscous oil; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.43-7.51 (m, 4H, Ar), 7.33-7.37 (m, 6H, Ar), 7.17-7.26 (m, 4H, Ar), 7.02-7.09 (m, 1H, Ar), 3.88 (m, 1H, C*H*O), 2.19 (m, 1H, 2-C*H*), 1.96 (dt, J = 9.3, 5.0 Hz, 1H, 6-C*H*), 1.51 (m, 1H), 1.29 (m, 2H), 1.22 (s, 3H,

CH_3), 1.14 (s, 3H, CH_3), 1.04 (m, 1H), 0.93 (m, 2H), 0.78 (d, J = 6.5 Hz, 3H, CH_3); ^{31}P NMR ($CDCl_3$, 81 MHz) δ 97.6 (s); HRMS (EI) Calcd. For $C_{28}H_{33}OP$ (M^+), 416.2269, Found 416.2267.



33

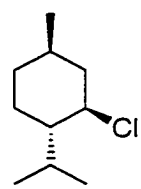


34

(-)-8-Phenylneomenthyl 4-nitrobenzoate 33 & (3*R*,6*R*)-3-methyl-6-(1-methyl-1-phenylethyl)cyclohexene 34

To a solution of 8-phenylmenthyldiphenylphosphinite (0.188 g, 0.45 mmol) in THF (4 mL) was added DEAD (86.2 mg, 0.50 mmol) under argon, at -60 °C and the reaction was stirred for 0.5 h. To this solution a mixture of α-phenethyl alcohol (60.4 mg, 0.50 mmol) and 4–nitrobenzoic acid (82.6 mg, 0.50 mmol) in THF (2 mL) was added and the reaction was stirred at –60 °C for 24 h and then at -15 °C for 24 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (EtOAc/hexane from 1/10 to 1/5) to give (-)-neophenylmenthyl 4-nitrobenzoate (20.0 mg, 11%) as a pale white solid and (3*R*,6*R*)-3-methyl-6-(1-methyl-1-phenylethyl)cyclohexene (46.5 mg, 48%) as a colourless oil; Data for (-)-8-phenylneomenthyl 4-nitrobenzoate **33**; mp 117–120 °C; $[\alpha]_D$ +39.2° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$, cast) 2949, 2869, 1720, 1607, 1527, 1496, 1346, 1274, 1102, 1014, 719, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.27 (dd, J = 9.1, 2.2 Hz, 2H, Ar), 8.08 (dd, J = 9.1, 2.1 Hz, 2H, Ar), 5.28 (br d, J = 1.4 Hz, 1H, C*H*O), 1.98 (ddd, J = 14.3, 5.9, 3.6 Hz, 1H), 1.80–1.90 (m, 2H), 1.71–1.78 (m, 2H),

1.36 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.13 (ddd, J = 14.4, 12.4, 2.4 Hz, 1H), 0.89–1.01 (m, 2H), 0.83 (d, J = 6.6 Hz, 3H, CH_3); ^{1}H NMR ($CDCl_3$, 75 MHz) δ 148.7, 130.8, 130.5, 128.8, 128.0, 126.0, 125.7, 123.4, 73.0, 51.6, 39.9, 35.3, 27.1, 27.0, 26.5, 22.7, 21.9; HRMS (EI) calcd for $C_{23}H_{27}NO_4$ (M^+) 381.1940, Found 381.1951. Data for (3*R*,6*R*)-3-methyl-6-(1-methyl-1-phenylethyl)cyclohexene **34**; $[\alpha]_D$ +17.5° (*c* 2.5, $CHCl_3$); IR ($CHCl_3$, cast) 3086, 3057, 3022, 2871, 1709, 1656, 1599, 1495, 1444, 1385, 1366, 1233, 1146, 1030, 766, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.26-7.37 (m, 4H, Ar), 7.17-7.20 (m, 1H, Ar), 5.52 (ddd, J = 10.3, 3.8, 1.6 Hz, 1H, C*H*=CH), 5.44 (ddd, J = 10.3, 3.7, 1.7 Hz, 1H, CH=C*H*), 2.41-2.46 (m, 1H, C*H*CH_3), 2.08 (m, 1H, C*H*CCH_3CH_3), 1.78 (m, 1H), 1.53 (m, 1H), 1.39 (d, J = 11.8 Hz, 2H), 1.30 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.12 (m, 1H), 0.92 (d, J = 7.1 Hz, 3H, CHCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.8, 135.0, 128.2, 126.2, 125.4, 119.3, 46.7, 40.2, 32.4, 30.9, 25.2, 24.9, 24.8, 21.9; HRMS (EI) Calcd. for $C_{16}H_{22}$ (M^+) 214.1722, Found, 214.1719.

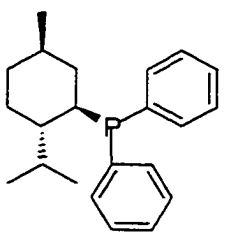


35

(-)-Menthyl chloride 35

This compound was prepared by a modified procedure of Smith *et al.*[72] To a solution of $ZnCl_2$ (226 g, 1.66 mol) in 36% HCl (154 mL, 1.84 mol) was added (-)-menthol (78.2 g, 0.5 mol) in one portion. The heterogeneous mixture was stirred vigorously at 35 °C for 7 h and then poured into a separatory funnel. The top layer was collected and diluted with

petroleum ether (100 mL), washed with H_2O (3 x 50 mL), saturated aqueous NaCl (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude liquid was purified by vacuum distillation to give (-)–menthyl chloride (77.0 g, 88%) as a colourless liquid; bp, 115-118 °C/25mmHg (Lit. 101-105 °C/21mmHg); $[\alpha]_D$ -41.1° (neat) [Lit.[72] $[\alpha]_D$ -45.0°, (neat)]; IR ($CHCl_3$, cast) 2956, 2870, 1455, 1387, 1369, 975, 874, 775, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 3.78 (td, J = 11.1, 4.2 Hz, 1H, C*H*Cl), 2.35 (m, 1H, 2-C*H*), 2.22 (m, 1H), 1.70-1.75 (m, 2H), 1.33-1.46 (m, 3H), 0.97-1.09 (m, 2H), 0.91 (d, J = 7.1 Hz, 6H, 2 x CH_3), 0.78 (d, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 63.8, 50.5, 46.8, 34.3, 33.4, 27.2, 24.3, 21.9, 21.0, 15.2; HRMS (EI) Calcd. for $C_{10}H_{18}$ (M^+–HCl), 138.1409, Found 138.1412.



36

(-)-Menthyldiphenylphosphine 36

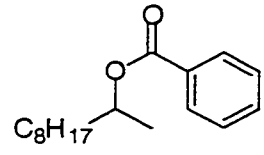
This compound was prepared by a similar procedure to that of Tanaka *et al.*[71] A mixture of magnesium turnings (10.2 g, 0.41 mol) and THF (100 mL) in a 500 mL round bottomed flask was treated with ethyl bromide (1.5 mL). The reaction was heated to 52 °C and a solution of (-)-menthyl chloride (56.2 g, 0.321 mol) in THF (120 mL) was slowly added over *ca.* 4 h. The reaction was then stirred at 50 °C for another 2 h followed by heating under reflux for 30 min during which a deep brown solution formed. The solution was transferred to a 1000 mL round bottomed flask *via* cannula and to this

solution, chlorodiphenylphosphine (60.0 g, 0.273 mol) was added dropwise at 0 °C, during which the colour faded. Stirring at 0 °C was continued for 30 min, followed by heating under reflux for 20 min. After the mixture was cooled to 0 °C, argon saturated H_2O (150 mL) was added to quench the reaction. The mixture was extracted with hexane (100 mL) and Et_2O (100 mL) under an argon atamosphere. The organic layer was washed with H_2O (50 mL) and dried over $CaSO_4$. The solution was concentrated *in vacuo* and purified by vacuum distillation to give menthyldiphenylphosphine (47.9 g, 54%) as a colourless liquid which was crystallized from methanol to give white crystals; mp 50–52 °C (Lit.[71] 53–54 °C); $[\alpha]_D$ –95.4° (*c* 1.2, CH_2Cl_2) [Lit.[71] $[\alpha]_D$ -93.5°(*c* 1.6, CH_2Cl_2)]; IR (CH_2Cl_2, cast) 2924, 2867, 1455, 739, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.41–7.48 (m, 4H, Ar), 7.25–7.37 (m, 6H, Ar), 2.80 (dddd, *J* = 27.2, 13.2, 5.7, 2.0 Hz, 1H, C*H*P), 2.15 (m, 1H), 1.71 (m, 3H), 1.36 (m, 1H), 1.13 (m, 2H), 0.94 (d, *J* = 7.0 Hz, 3H, CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, CH_3), 0.75 (d, *J* = 6.3 Hz, 3H, CH_3), 0.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.0 (d, *J* = 13.1 Hz), 135.6 (d, *J* = 18.6 Hz), 135.2 (d, *J* = 19.8 Hz), 132.1 (d, *J* = 15.9 Hz), 128.7, 128.2 (d, *J* = 4.1 Hz), 127.9 (d, *J* = 7.3 Hz), 127.2, 45.2 (d, *J* = 12.5 Hz), 37.8 (d, *J* = 16.7 Hz), 37.2, 35.0, 33.7, 28.3 (d, *J* = 20.2 Hz), 25.5 (d, *J* = 8.6 Hz), 22.5, 21.5; ^{31}P NMR ($CDCl_3$, 81 MHz) δ -5.4 (s); HRMS (EI) Calcd. for $C_{22}H_{29}P$ (M^+) 324.2007, Found 324.2005.

General procedure for the asymmetric Mitsunobu esterification using (-)-menthyldiphenylphosphine in deracemization of secondary alcohols.

To a solution of the phosphine (1.10 mmol) in THF (5 mL) at -30 °C, under argon, was added the neat azodicarboxylate (1.10 mmol). After stirring for 30 min, a solution of

alcohol (1.10 mmol) and acid (1.10 mmol) in THF (2 mL) was added to the pre-formed betaine adduct. The reaction was stirred at -30 °C under argon for 24 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (EtOAc/Hexane. 1/10) to give ester and recovered alcohol.



37

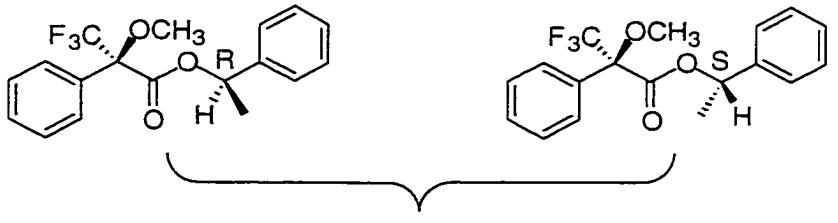
2-Decanyl benzoate 37[102]

The reaction was carried out according to the general procedure above using 2-decanol (62.0 mg, 0.39 mmol), benzoic acid (47.9 mg, 0.39 mmol), diethyl azodicarboxylate (68.3 mg, 0.39 mmol) and (-)-menthyldiphenylphosphine (0.13 g, 0.39 mmol). Yield, 47.6 mg, 46%; IR ($CHCl_3$, thin film) 2927, 1718, 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03 (m, 2H, Ar), 7.52 (m, 1H, Ar), 7.41 (m, 2H, Ar), 5.14 (m, 1H, C*H*O), 1.71-1.74 (m, 1H), 1.59-1.64 (m, 1H), 1.26-1.42 (m, 15H), 0.87 (d, J = 6.5 Hz, 3H, CH_3CHO); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.2, 132.6, 130.9, 129.5, 128.3, 71.7, 36.0, 31.8, 29.5, 29.2, 25.4, 22.6, 20.0, 14.1; HRMS (EI) Calcd. for $C_{17}H_{26}O_2$ 262.1933, Found, 262.1926.

General procedure for the preparation of a Mosher's ester[103]

The recovered secondary alcohol (0.16 mmol) was dissolved in CH_2Cl_2 (2 mL). Pyridine (15.8 mg, 0.20 mmol) and (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (49.6 mg, 0.20 mmol) were added to this solution. The reaction mixture was stirred at room temperature under argon for 12 hours, and concentrated *in vacuo*. Column

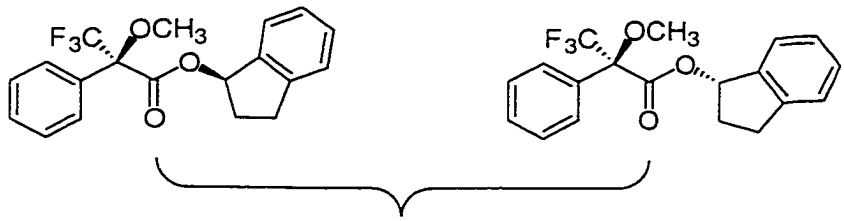
chromatography (EtOAc/hexane, 1/10) gave the Mosher's ester (80-95% yield) as a colourless oil.



39

(*S*)-α-Methoxy-α-(trifluoromethyl)phenyl acetic acid (*R*,*S*) α-phenethyl ester 39

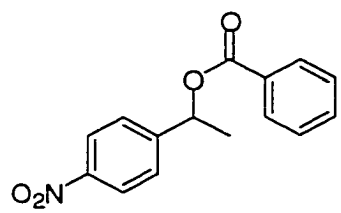
The reaction was carried out according to the general procedure above using α-phenethyl alcohol (20.0 mg, 0.16 mmol). Ratio (*R*/*S*. 2/1); Yield. 43.0 mg, 80%; IR ($CHCl_3$, cast) 2984, 2950, 1747 (C=O), 1496, 1451, 1270, 1169, 1122, 1059, 1017, 994, 762, 716, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.26–7.44 (m, 20H, Ar), 6.11–6.17 (q, *J* = 6.6 Hz, 1H, OC*H*Ph–*R*), 6.07–6.12 (q, *J* = 6.7 Hz, 1H, OC*H*Ph–*S*), 3.56 (q, *J* = 1.3 Hz, 3H, OCH_3–*S*), 3.48 (q, *J* = 1.3 Hz, 3H, OCH_3–*R*), 1.64 (d, *J* = 6.6 Hz, 3H, CH_3–*S*), 1.59 (d, *J* = 6.7 Hz, 3H, CH_3–*R*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 165.7, 140.2, 140.2, 132.4, 132.3, 129.6, 129.5, 128.7, 128.5, 128.4, 128.3, 128.28, 127.4, 126.4, 126.2, 124.8, 121.9, 75.0, 74.9, 55.5, 55.4, 22.2, 21.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -71.6 (s, CF_3–*R*), -71.8 (s, CF_3–*S*); HRMS (EI) Calcd. for $C_{18}H_{17}O_3F_3$ (M^+) 338.1130, Found 338.1129.



40

(*S*)-α-Methoxy-α-(trifluoromethyl)phenyl acetic acid (*R,S*) 1-indanyl ester 40

The reaction was carried out according to the general procedure above using 1-indanol Ratio (10/6); Yield. 95%; IR ($CHCl_3$, cast) 3073, 3030, 2949, 2850, 1743, 1496, 1480, 1451, 1313, 1255, 1169, 1122, 1018, 760, 713 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.25–7.55 (m, 6H, Ar), 7.21–7.52 (m, 12H, Ar), 6.41–6.49 (dd, *J* = 7.0, 3.2 Hz, 2H, OC*H*), 3.52 (d, *J* = 0.9 Hz, 3H, OCH_3), 3.48 (d, *J* = 1.0 Hz, 3H, OCH_3), 3.05–3.14 (m, 2H), 2.84–2.96 (m, 2 H), 2.45–2.62 (m, 2H), 2.10–2.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.56, 144.77, 144.43, 139.86, 139.81, 132.52, 132.32, 129.55, 129.52, 129.49, 129.37, 128.36, 127.47, 127.31, 126.88, 126.83, 125.78, 125.67, 125.30, 125.00, 124.90, 121.47, 80.94, 80.90, 55.42, 32.18, 31.91, 30.23; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -71.7, -71.9; HRMS (EI) calcd for $C_{19}H_{17}O_3F_3$ (M^+) 350.1130, found 350.1132.

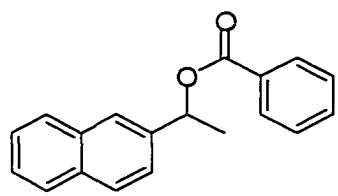


41

***sec*-4-Nitro-phenethyl benzoate 41**[104]

The reaction was carried out according to the general procedure above using *sec*-4-nitro-phenethyl alcohol (0.18 g, 1.10 mmol), benzoic acid (0.13 g, 1.10 mmol), diethyl

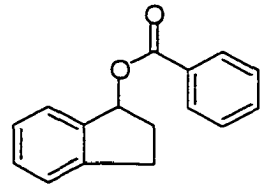
azodicarboxylate (0.19 g, 1.10 mmol) and (-)-menthyldiphenylphosphine (0.36 g, 1.10 mmol). Yield, 35.0 mg, 12%; IR ($CHCl_3$, thin film) 3072, 2985, 2935, 1787, 1721, 1600, 1585, 1523, 1348, 1270, 1213, 1173, 1110, 1070, 1039, 1016, 997, 855, 777, 706 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.22 (m, 1H, Ar), 8.15 (m, 2H, Ar), 8.07 (m, 1H, Ar), 7.66 (m, 2H, Ar), 7.45-7.61 (m, 3H, Ar), 6.17 (q, J = 6.7 Hz, 1H, C*H*CH_3), 1.69 (d, J = 6.7 Hz, 3H, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.6, 134.5, 133.3, 130.6, 129.6, 128.9, 128.5, 126.7, 123.9, 71.8, 22.4; HRMS (EI) Calcd. for $C_{15}H_{13}NO_4$ (M^+) 271.0845, Found, 271.0845.



42

α-Methyl-2-naphthalenemethyl benzoate 42[105]

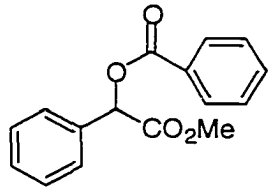
The reaction was carried out according to the general procedure above using α-methyl-2-naphthalenemethyl alcohol (0.19 g, 1.10 mmol), benzoic acid (0.13 g, 1.10 mmol), diethyl azodicarboxylate (0.19 g, 1.10 mmol) and (-)-menthyldiphenylphosphine (0.36 g, 1.10 mmol). Yield, 0.16 g, 53%; IR ($CHCl_3$, thin film) 3058, 2979, 1716, 1651, 1601, 1583, 1505, 1451, 1333, 1313, 1271, 1175, 1112, 1067, 1025, 710, 689, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10-8.12 (m, 2H), 7.82-7.89 (m, 4H), 7.43-7.59 (m, 6H), 6.30 (q, J = 6.6 Hz, 1H, C*H*CH_3), 1.76 (d, J = 6.5 Hz, 3H, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 165.9, 139.2, 133.3, 133.1, 133.0, 130.6, 129.7, 128.5, 128.4, 128.1, 127.7, 126.3, 126.1, 125.0, 124.1, 73.1, 22.4; HRMS (EI) Calcd. for $C_{19}H_{16}O_2$ 276.1150, Found, 276.1151.



43

1-Indanyl benzoate 43[106]

The reaction was carried out according to the general procedure above using 1-indanol (0.15 g, 1.10 mmol), benzoic acid (0.13 g, 1.10 mmol), diethyl azodicarboxylate (0.19 g, 1.10 mmol) and (-)-menthyldiphenylphosphine (0.36 g, 1.10 mmol). Yield, 0.13 g, 50%; IR ($CHCl_3$, thin film) 3071, 3029, 2943, 1715, 1602, 1584, 1461, 1450, 1314, 1270, 1176, 1111, 1026, 934, 755, 711, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.00-8.07 (m, 2H, Ar), 7.50-7.57 (m, 2H, Ar), 7.40-7.44 (m, 2H, Ar), 7.28-7.33 (m, 2H, Ar), 7.23-7.28 (m, 1H, Ar), 6.47 (dd, J = 7.1, 4.1 Hz, 1H, C*H*O), 3.20 (ddd, J = 15.8, 8.6, 5.9 Hz, 1H, ArCH_a), 2.96 (ddd, J = 15.8, 8.6, 5.2 Hz, 1H, ArCH_b), 2.62-2.68 (m, 1H, ArCHOCH_a), 2.22-2.30 (m, 1H, ArCHOCH_b); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 144.4, 141.2, 132.9, 130.5, 129.7, 129.0, 128.3, 126.8, 125.7, 124.9, 79.0, 32.5, 30.3; HRMS (EI) Calcd. for $C_{16}H_{14}O_2$ 238.0994, Found, 238.0986.

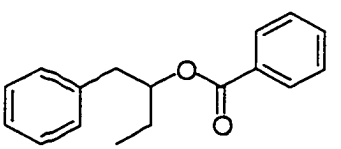


44

α-Methoxycarbonyl benzyl benzoate 44[107]

The reaction was carried out according to the general procedure above using mandelic acid methyl ester (0.13 g, 0.77 mmol), benzoic acid (94.2 mg, 0.77 mmol), diethyl azodicarboxylate (0.13 g, 0.77 mmol) and (-)-menthyldiphenylphosphine (0.25 g, 0.77

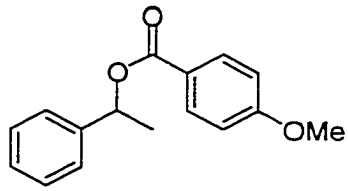
mmol). Yield, 77.5 mg, 37%; IR ($CHCl_3$, thin film) 3064, 2954, 1788, 1758, 1725, 1600, 1585, 1452, 1436, 1351, 1315, 1281, 1258, 1214, 1173, 1109, 1070, 1038, 1016, 733, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.12-8.18 (m, 3H, Ar), 7.68 (m, 1H, Ar), 7.53-7.60 (m, 3H, Ar), 7.42-7.48 (m, 3H, Ar), 6.17 (s, 1H, C*H*), 3.76 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 162.4, 134.5, 134.0, 130.6, 130.0, 129.3, 129.2, 128.4, 127.6, 74.9, 52.6; HRMS (EI) Calcd. for $C_{16}H_{14}O_4$ 270.0892, Found, 270.0892.



45

α-Ethylphenethyl benzoate 45[108]

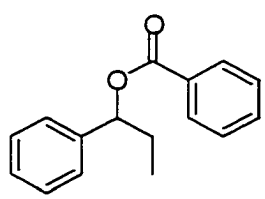
The reaction was carried out according to the general procedure above using α-ethylphenethyl alcohol (0.16 g, 1.10 mmol), benzoic acid (0.13 g, 1.10 mmol), diethyl azodicarboxylate (0.19 g, 1.10 mmol) and (-)-menthyldiphenylphosphine (0.36 g, 1.10 mmol). Yield, 78.9 mg, 28%; IR ($CHCl_3$, thin film) 1716, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.01-8.43 (m, 2H, Ar), 7.53-7.55 (m, 1H, Ar), 7.41-7.46 (m, 2H, Ar), 7.20-7.28 (m, 5H, Ar), 5.27 (m, 1H, C*H*O), 3.05 (dd, J =13.8, 6.4 Hz, 1H, PhCH_a), 2.94 (dd, J =13.8, 6.4 Hz, 1H, PhCH_b), 1.72 (m, 2H, CH_3CH_2), 0.98 (t, J = 7.6 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.2, 132.8, 130.7, 129.6, 128.4, 128.3, 126.5, 76.6, 40.2, 26.4, 9.8; HRMS (EI) Calcd. for $C_{17}H_{18}O_2$ 255.1385, Found, 255.1367.



46

α-Phenethyl 4-methoxybenzoate 46[109]

The reaction was carried out according to the general procedure above using α-phenethyl alcohol (0.182 g, 1.49 mmol), 4-methoxybenzoic acid (0.114 g, 0.75 mmol), diethyl azodicarboxylate (0.130 g, 0.75 mmol) and (-)-menthyldiphenylphosphine (0.242 g, 0.75 mmol). Yield, 0.16 g, 82%; IR ($CHCl_3$, cast) 2977, 2933, 2839, 1709 (C=O), 1606, 1582, 1510, 1494, 1453, 1420, 1316, 1257, 1209, 1167, 1100, 1063, 1029, 1008, 995, 847, 768, 698, 635 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.04 (dd, J = 8.9 Hz, 2.0 Hz, 2H, Ar), 7.30-7.46 (m, 5H, Ar), 6.93 (dd, J = 8.9 Hz, 2.1 Hz, 2H, Ar), 6.12 (q, J = 6.6 Hz, 1H, C*H*), 3.86 (s, 3H, CH_3O), 1.67 (d, J = 6.6 Hz, 3H, CH_3CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 163.4, 142.1, 131.7, 128.5, 127.8, 126.1, 123.0, 113.6, 72.5, 55.4, 22.5; HRMS (EI) Calcd. for $C_{16}H_{16}O_3$ (M^+), 256.1100, Found, 256.1101.

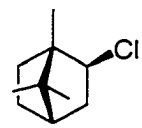


47

α-Phenpropylbenzoate 47[110]

The reaction was carried out according to the general procedure above using α-phenpropyl alcohol (0.149 g, 1.10 mmol), benzoic acid (0.134 g, 1.10 mmol), diethyl azodicarboxylate (0.191 g, 1.10 mmol) and (-)-menthyldiphenylphosphine (0.355 g, 1.10

mmol). Yield, 0.112 g, 42%; IR ($CHCl_3$, cast) 3063, 3032, 2969, 2935, 2877, 1718, 1601, 1585, 1493, 1451, 1381, 1347, 1314, 1271, 1207, 1176, 1110, 1069, 1025, 942, 908, 711, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (m, 2H, Ar), 7.55 (m, 1H, Ar), 7.22-7.50 (m, 7H, Ar), 5.92 (t, J = 1H, C*H*O), 1.90-2.16 (m, 2H, CH_2CH_3), 0.93 (t, J = 3H, CH_3), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.9, 140.6, 132.9, 130.6, 129.6, 128.5, 128.4, 127.9, 126.5, 77.9, 29.6, 10.0; HRMS (EI), Calcd for $C_{16}H_{16}O_2$ (M^+), 240.1154, Found, 240.1150.

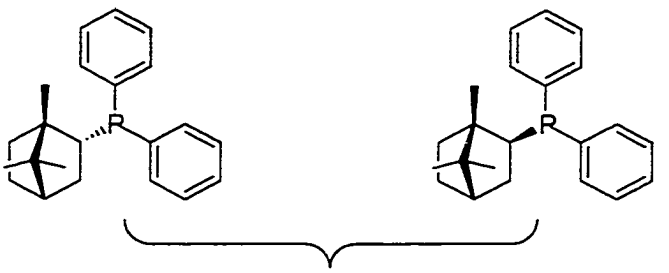


48

(1*S*)–*exo*–Isobornyl chloride 48

This compound was prepared by a similar procedure to that of Marinetti *et al.*[111] A solution of (1*S*)-(-)-borneol (24.0 g, 0.16 mol) and triphenylphosphine (81.6 g, 0.31 mol) in CCl_4 (330 mL) was heated under reflux for 22 h and then cooled to room temperature. To the reaction hexane (200 mL) was added to precipitate triphenylphosphine oxide. The solid was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was further extracted with hexane (200 mL) in order to remove any remaining triphenylphosphine oxide. The hexane extract was concentrated *in vacuo* to give (1*S*)-*exo*-isobornyl chloride (14.5 g, 54%) as a white solid which was used in the next reaction without further purification; $[\alpha]_D$ +41.3° (*c*, 5.1, $CHCl_3$) [Lit.[111] +52° (*c*, 1.0, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 360 MHz) δ 3.94 (dd, J = 8.5, 4.6 Hz, 1H, C*H*Cl), 2.21 (m, 1H, 3-CH_a), 2.01 (dd, J = 13.8, J = 8.5 Hz, 1H, 3-CH_b), 1.79 (m, 1H), 1.68–1.73 (m, 4H), 0.85 (s, 3H,

CH_3), 1.02 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 68.4 (CHCl), 49.8, 47.4, 46.1, 42.4, 36.3, 27.0, 20.5, 20.1, 13.4; HRMS (EI), Calcd. for $C_{10}H_{17}{}^{37}Cl$ (M^+), 174.0989, found, 174.0993 (0.6%), Calcd. for $C_{10}H_{17}{}^{35}Cl$ (M^+), 172.1019, found, 172.1015 (1.96%).

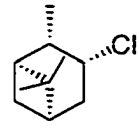


49

Isobornyldiphenylphosphine & bornyldiphenylphosphine 49[71]

Ratio (1/1). A suspension of magnessium (1.04 g, 43.4 mmol) in THF (15 mL) was treated with ethylbromide (0.20 g, 1.80 mmol). To this mixture was added a solution of isobornyl chloride (5.00 g, 28.9 mmol) in THF (10 mL) *via* addition funnel over *ca.* 1 h. The reaction was stirred at 55 °C for 6 h during which time a deep brown solution formed. The solution was then transferred *via* cannula to a solution of chlorodiphenylphosphine (5.51 g, 25.0 mmol) in THF (5 mL) under argon at –78 °C and stirring continued for 17 h whilst allowing the temperature to rise to room temperature. The reaction was quenched by the addition of argon saturated H_2O (15 mL), extracted with hexane (15 mL) and Et_2O (15 mL) and the extract was dried over Na_2SO_4. The extract was concentrated *in vacuo* to give a residue which was purified by vacuum distillation to give a colourless oil. The crude product was further purified by flash chromatography (EtOAc/Hexane 1/10) to give a *ca.* 1/1 ratio of mixture of isobornyldiphenylphosphine & bornyldiphenylphosphine (3.46 g, 38%) as an oil which

solidified on cooling; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.63–2.74 (m, 2 H), 2.30–2.38 (m, 1H), 2.02–2.12 (m, 1H), 1.69–1.81 (m, 3H), 1.60–1.67 (m, 3H), 1.35–1.50 (m, 4H), 1.15–1.25 (m, 3H), 1.20 (s, 3H, CH_3), 0.95–1.05 (m, 1H), 0.90 (s, 3H, CH_3), 0.85 (s, 6H, 2 x CH_3), 0.81 (s, 3H, CH_3), 0.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 49.7 (d, J = 3.6 Hz), 49.2 (d, J = 10.1 Hz), 48.5 (d, J = 8.7 Hz), 45.5 (d, J = 3.2 Hz), 44.8, 43.4 (d, J = 17.4 Hz), 41.6 (d, J = 9.4 Hz), 40.7 (d, J = 3.5 Hz), 35.9 (d, J = 16.3 Hz), 34.8 (d, J = 7.1 Hz), 32.1, 31.7, 28.3, 27.4, 20.9 (d, J = 18.4 Hz), 20.5, 19.2, 18.6, 15.7, 14.6 (d, J = 12.0 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ -10.2, (s), -12.9 (s); HRMS (EI) calcd. for $C_{22}H_{27}P$ (M^+) 322.1850, Found 322.1848.

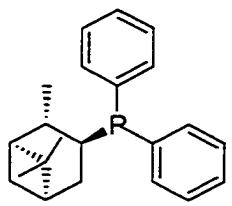


50

(1*S*)–Neo-*iso*pinocampheylchloride 50[111]

The same procedure as that described for the preparation of the (1*S*)-*exo*-isobornyl chloride was used to obtain (1*S*)–neo-isopinocampheylchloride (5.01 g, 19%) as a colourless liquid; bp 66–68 °C/1mmHg (Lit.[111] 30 °C/0.1mmHg); $[\alpha]_D$ –24.6° (*c*, 7.1, $CHCl_3$) [Lit.[111] +25°, (neat) for its enantiomer); IR ($CHCl_3$, cast) 2993, 2912, 2872, 1651, 1457, 1385, 869, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.70–4.72 (td, J = 10.0, 7.3 Hz, 1H, C*H*Cl), 2.57–2.70 (m, 2H), 2.18–2.26 (m, 2H), 1.88–1.99 (m, 2H), 1.24 (d, J = 10.4 Hz, 1H), 1.22 (d, J = 7.8 Hz, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.8, 48.5, 41.5, 39.6, 39.5, 38.8, 28.5, 27.3, 23.2, 18.4; HRMS (EI)

calcd. for $C_{10}H_{17}{}^{37}Cl$ (M^+) 174.0989, Found 174.0988, calcd. for $C_{10}H_{17}{}^{35}Cl$ (M^+) 172.1019, Found 172.1020.



51

(1*S*)-Neo-*iso*pinocampheyldiphenylphosphine 51

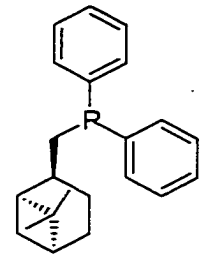
This compound was prepared by a similar procedure to that of Tanaka *et al.*[71] A suspension of magnesium (1.04 g, 43.4 mmol) in THF (20 mL) was treated with ethylbromide (0.20 g, 1.80 mmol). To the reaction a solution of (1*S*)-neoisopinocampheylchloride (5.01 g, 28.9 mmol) in THF (10 mL) was added at 50 °C over about 1 h and stirring was continued at 50 °C for *ca.* 5 h. The solution was cooled to room temperature and transferred *via* cannula to a solution of chlorodiphenylphosphine (4.25 g, 19.3 mmol) in THF (10 mL) under argon at –78 °C. The reaction was stirred for 20 h allowing the temperature to rise to room temperature followed by heating under reflux for 30 min. The reaction was quenched by the addition of H_2O (20 mL) and extracted with hexane (10 mL) and Et_2O (10 mL). The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and the residue purified by flash chromatography (hexane/CH_2Cl_2 10/1) to give (1*S*)–neo-*iso*pinocampheyldiphenylphosphine (2.80 g, 45%) as colourless oil; IR ($CHCl_3$, cast) 3055, 2903, 2868, 1437, 1182, 1118, 1104, 752, 719, 697, 662, 538, 527 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.57–7.62 (m, 3H), 7.46–7.56 (m, 2H), 7.34–7.42 (m, 2H), 7.22–7.30 (m, 3H), 2.40–2.46 (m, 2H), 2.15–2.25 (m, 3H),

1.67–1.74 (m, 2H), 1.20–1.31 (m, 1H), 1.18 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 0.48 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 47.3 (d, $J_{C\text{-}P}$ = 5.8 Hz), 40.3 (d, $J_{C\text{-}P}$ = 4.4 Hz), 38.6, 34.6, 33.9, 30.8, 27.7 (d, $J_{C\text{-}P}$ = 2.5 Hz), 27.5, 22.9, 22.6; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 5.28 (s); HRMS (EI) calcd for $C_{22}H_{27}P$ (M^+) 322.1850 found 322.1847.

52

(1*S*,2*S*,5*S*)-Myrtanylchloride 52

This compound was prepared using a similar procedure to that of Marinetti *et al.*[111] A solution of (1*S*,2*S*,5*S*)–(-)–myrtanol (10.0 g, 64.8 mmol) and triphenylphosphine (34.0 g, 129 mmol) in CCl_4 (200 mL) was stirred at 70 °C for 18 h during which a heavy precipitate had formed. The reaction was cooled to room temperature and hexane (200 mL) was added to precipitate triphenylphosphine oxide. After filtration the clear solution was concentrated *in vacuo* and purified by vacuum distillation to give (1*S*,2*S*,3*S*)-myrtanylchloride (7.68 g, 69%) as colourless liquid; $[\alpha]_D$ -25.5° (neat); bp 88–89 °C/2mmHg; IR (neat, film) 2981, 2920, 2868, 1474, 1386, 1274, 1233, 1188, 724 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 3.40 (dd, J= 10.6, 7.2, Hz, 1H, CH_aHCl), 3.35 (dd, J= 10.6, 7.2, Hz, 1H, CHH_bCl), 2.25 (quintet, J = 7.7 Hz, 1H, $CHCH_2Cl$), 2.07 (m, 1H), 1.89–1.95 (m, 2H), 1.73–1.86 (m, 3H), 1.28–1.33 (m, 2H), 1.22 (s, 3H, CH_3), 0.84 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 49.6, 43.4, 40.9, 39.5, 38.0, 26.6, 24.0, 23.4, 20.3, 20.1; HRMS (EI) calcd. for $C_{10}H_{17}{}^{35}Cl$ (M^+) 172.1019, Found 172.1014.

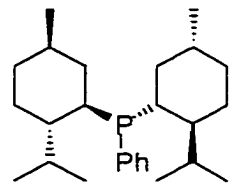


53

(1*S*,2*S*,5*S*)-Myrtanyldiphenylphosphine 53

This compound was prepared by a similar procedure to that of Tanaka *et al.*[71] A suspension of magnesium (1.04 g, 43.4 mmol) in THF (20 mL) was treated with ethylbromide (0.196 g, 1.80 mmol), followed by addition of a solution of (1*R*)-myrtanylchloride (5.01 g, 28.9 mmol) in THF (10 mL) in portions over *ca.* 1 h at 50 °C. Stirring at 50 °C was continued for 6 h to give a deep brown solution. The Grignard reagent was transferred to a solution of chlorodiphenylphosphine (4.25 g, 19.3 mmol) in THF (10 mL) under argon at –78 °C and stirring continued for 22 h whilst the reaction warmed to room temperature. The reaction was heated under reflux for 30 min and then quenched with argon saturated H_2O (20 mL) and extracted with hexane (10 mL) and Et_2O (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* followed by purification by vacuum distillation to give (1*S*,2*S*,3*S*)–myrtanyldiphenylphosphine (3.85 g, 62%) as a colourless oil; bp 200–210 °C/0.5mm Hg; $[\alpha]_D$ -2.6° (*c*, 1.0, $CHCl_3$); IR ($CHCl_3$, cast) 3069, 3052, 2979, 2910, 2865, 1479, 1459, 738, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.39–7.44 (m, 4H, Ar), 7.30–7.34 (m, 6H, Ar), 2.00-2.09 (m, 4H), 1.95 (t, *J* = 5.4 Hz, 1H), 1.85–1.69 (m, 1H), 1.72–1.76 (m, 3H), 1.37–1.51 (m, 2H), 1.19 (s, 3H, CH_3), 0.73 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.9 (d, $J_{C\text{-}P}$ = 3.2 Hz), 132.6 (d, $J_{C\text{-}P}$ = 3.0 Hz), 128.4, 128.3 (d, $J_{C\text{-}P}$ = 6.8 Hz), 47.0 (d, $J_{C\text{-}P}$ = 9.7 Hz), 40.8, 39.5, 36.0 (d,

$J_{C\text{-}P}$ = 10.9 Hz), 32.4 (d, $J_{C\text{-}P}$ = 12.5 Hz), 26.7, 24.5, 24.2 (d, $J_{C\text{-}P}$ = 10.5 Hz), 23.3, 20.0; ^{31}P NMR ($CDCl_3$, 162 MHz) δ -20.8 (s); HRMS (EI) calcd for $C_{22}H_{27}P$ (M^+) 322.1850, Found 322.1848.

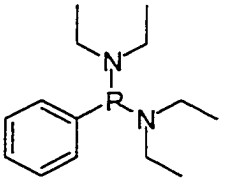


54

Dimenthylphenylphosphine 54

This compound was prepared by a similar procedure to that of Tanaka *et al.*[71] A mixture of magnesium (2.54 g, 104.4 mmol) and ethylbromide (0.514 g, 4.72 mmol) in THF (20 mL) was heated to 50 °C. To this was added a solution of menthyl chloride (14.0 g, 80.3 mmol) in THF (10 mL) slowly over 4 h. The deep brown solution formed was heated under reflux for *ca.* 30 min and then transferred to another flask *via* cannula. To the Grignard solution, dichlorophenylphosphine (7.19 g, 40.4 mmol) in THF (20 mL) was slowly added under argon at 0 °C and stirring continued for 12 h whilst allowing the temperature to rise to room temperature. After heating under reflux for 30 min, the reaction was cooled to 0 °C and quenched by slow addition of argon saturated H_2O (50 mL). The mixture was extracted with hexane (50 mL) and Et_2O (50 mL) and the organic extracts washed with H_2O (20 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by vacuum distillation to give dimenthylphenylphosphine (12.4 g, 40%) as colourless viscous liquid which was crystallized from $CHCl_3$ to give white cubic crystals; mp 80-85 °C; $[\alpha]_D$ -39.9° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$, cast) 2951, 2926, 2867, 1454, 1435, 1384, 1250, 750, 523 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.75 (t, J = 8.7 Hz,

2H, Ar), 7.47 (m, 3H, Ar), 3.00 (br s, 1H), 2.03–2.16 (m, 2H), 1.84 (m, 2H), 1.46–1.75 (m, 8H), 1.36 (m, 1H), 1.04–1.08 (m, 3H), 0.98 (d, J = 6.4 Hz, 3H, CH_3), 0.89 (d, J = 4.4 Hz, 3H, CH_3), 0.88 (d, J = 6.4 Hz, 3H, CH_3), 0.72 (d, J = 7.1 Hz, 3H, CH_3), 0.70 (d, J = 6.9 Hz, 3H, CH_3), 0.27 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.1 (d, J = 79.1 Hz), 130.9 (d, J = 7.9 Hz), 130.7 (d, J = 2.6 Hz), 127.8 (d, J = 10.4 Hz), 43.5 (d, J = 3.2 Hz), 42.9 (d, J = 3.6 Hz), 39.4, 38.5, 37.2, 36.3, 36.2, 34.8, 34.5, 34.0 (d, J = 3.3 Hz), 33.4, 33.3, 33.2, 32.9, 27.8 (d, J = 1.4 Hz), 27.3 (d, J = 3.5 Hz), 25.0, 24.8, 22.9, 21.5; ^{31}P NMR ($CDCl_3$, 81 MHz) δ 44.4 (s); HRMS (EI) Calcd. for $C_{26}H_{43}P$ (M^+) 386.3102, Found 386.3101.

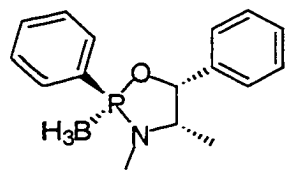


55

Phenylphosphonous acid *bis*(diethyl)amide 55

This compound was prepared by a similar procedure to that of Hayakawa *et al.*[74] To a solution of dichlorophenylphosphine (33.0 g, 184 mmol) in THF (300 mL) was added diethylamine (56.6 g, 774 mmol) dropwise under argon at 0 °C during which a heavy solid had formed. The reaction was heated under reflux for 24 h. The reaction mixture was transferred to another flask *via* a filter cannula in which one end was sealed by gauze to remove the solid. The solution was concentrated *in vacuo* and the resulting residue was purified by vacuum distillation to give phenylphosphonous acid *bis*(diethyl)amide (35.0 g, 76%) as a colourless liquid; bp 140–145 °C /0.1mmHg (Lit.[74] 137-142 °C /0.1mmHg); IR ($CHCl_3$, cast) 3069, 3054, 2965, 2929, 2854, 1477, 1460, 1433, 1373, 1343, 1291,

1185, 1092, 1071, 1023, 917, 701, 665, 632, 541, 503; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.46 (m, 2H, Ar), 7.32–7.36 (m, 2H, Ar), 7.22–7.25 (m, 1H, Ar), 3.05–3.13 (m, 8H, 4 x NCH_2), 1.10–1.13 (t, J = 7.0 Hz, 12H, 4 x CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.0 (d, $J_{C\text{-}P}$ = 3.3 Hz), 131.0, 128.1 (d, $J_{C\text{-}P}$ = 3.4 Hz), 127.2, 42.8 (d, $J_{C\text{-}P}$ = 3.3 Hz), 14.6; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 97.2 (s); HRMS (EI) calcd for $C_{14}H_{25}N_2P$ (M^+) 252.1755, found 252.1750; Anal. Calcd. for $C_{14}H_{25}N_2P$, C, 66.66; H, 9.92; N, 11.11, Found C, 66.32; H, 10.01; N, 10.92.

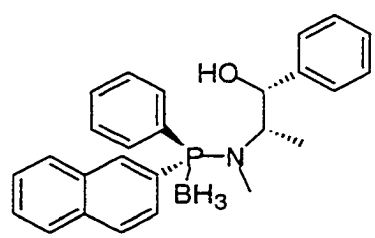


56

(2*R*,4*S*,5*R*)-3, 4-Dimethyl-2, 5-diphenyl-1,3,2-oxazaphospholidine-borane 56

This compound was prepared by a similar procedure to that of Jugé and co-workers.[75] A solution of L-(-)-ephedrine (12.9 g, 78.2 mmol) and phenylphosphonous acid *bis*(diethyl)amide (19.7 g, 78.2 mmol) in toluene (350 mL) was stirred at 95 °C for 20 h under argon atmosphere. The resulting colourless solution was cooled to 0 °C and to this mixture was added a solution of borane-methyl sulfide complex (BH_3 concentration 10.0-10.2 M) (8.0 mL, 78.2 mmol) in toluene (50 mL) dropwise. The solution was stirred at room temperature for 12 h and concentrated *in vacuo*. The residue was purified by flash chromatography (toluene) to give (2*R*,4*S*,5*R*)-3,4-dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine-borane (11.5 g, 52%) as white solid; mp 100-105 °C (Lit.[75] 107 °C); $[\alpha]_D$ +1.2° (*c* 4.1, $CHCl_3$); IR ($CHCl_3$, cast) 3060, 2976, 2933, 2379, 1496, 1453, 1380, 1368, 1327, 1310, 1207, 1177, 1082, 1057, 965, 917, 748, 737, 699, 667 cm^{-1}; ^{1}H NMR

($CDCl_3$, 400 MHz) δ 7.85 (m, 2H, Ar), 7.48–7.58 (m, 3H, Ar), 7.30–7.41 (m, 5H, Ar), 5.60 (dd, $J_{H\text{-}P}$ = 6.1, $J_{H\text{-}H}$ = 3.1 Hz, 1H, OC*H*Ph), 3.68 (m, 1H, NC*H* CH_3), 2.78 (d, $J_{H\text{-}P}$ = 11.1 Hz, 3H, NCH_3), 0.83 (d, $J_{H\text{-}H}$ = 6.8 Hz, 3H, CHCH_3), 0.80–1.25 (br q, $J_{H\text{-}B}$ = 86 Hz, 3H, BH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.1 (d, $J_{C\text{-}P}$ = 5.4 Hz), 134.0, 133.2 (d, $J_{C\text{-}P}$ = 1.9 Hz), 131.8 (d, $J_{C\text{-}P}$ = 12.0 Hz), 129.4 (d, $J_{C\text{-}P}$ = 9.8 Hz), 129.2, 129.1, 127.4, 84.2 (d, $J_{C\text{-}P}$ = 7.8 Hz), 59.0 (d, $J_{C\text{-}P}$ = 1.5 Hz), 29.7 (d, $J_{C\text{-}P}$ = 7.6 Hz), 13.6 (d, $J_{C\text{-}P}$ = 3.4 Hz); ^{31}P NMR ($CDCl_3$, 163 MHz) δ +133.0 (q, $J_{P\text{-}B}$ = 72 Hz); ^{11}B NMR ($CDCl_3$, 128 MHz, ^1H–decoupled) δ -40.5 (d, $J_{B\text{-}P}$ = 77 Hz); HRMS (EI) Calcd. for $C_{16}H_{20}NO^{11}BP$ (M^+) 284.1376, Found 284.1385; Anal. Calcd. for $C_{16}H_{20}NOBP$ C, 67.42; H, 7.37; N, 4.95. Found C, 67.39; H, 7.52; N, 5.00.

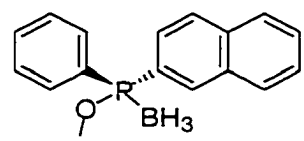


57

(*S*)-(2*R*,1*S*)-*N*-Methyl-*N*-(2-phenyl-2-hydroxy-1-methyethyl)amino phenyl-β-naphthylphosphine-borane 57

This compound was prepared by a similar procedure to that of Jugé and co-workers.[75] To a solution of β-naphthylbromide (2.06 g, 9.97 mmol) in THF (30 mL) was added *n*-BuLi (3.98 mL, 9.97 mmol) under argon at –78 °C and the reaction was stirred for 30 mins to give a cloudy mixture. The reaction mixture was transferred to a solution of (2*R*,4*S*,5*R*)-3,4-dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine-borane (2.84 g, 9.97 mmol) in THF (20 mL) at -78 °C to give a clear solution and the reaction was stirred for 30 min. The

reaction was quenched by the addition of H_2O and the resulting mixture was concentrated *in vacuo*. The residue was extracted with CH_2Cl_2 and the CH_2Cl_2 extracts were dried over Na_2SO_4. The crude product was purified by flash chromatography (EtOAc/hexane 1/5) to give (*S*)-(2*R*,1*S*)-*N*-methyl-*N*-(2-phenyl-2–hydroxy-1-methyethyl)amino phenyl-β-naphthylphosphine-borane (3.39 g, 82%) as a colourless oil; $[\alpha]_D$ +57.0° (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2, cast) 3510 (OH), 2972, 2919, 2382 (BH), 1494, 1454, 1436, 1081, 1062, 1021, 740, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.10 (d, *J* = 12.3 Hz, 1H, Ar), 7.84–7.89 (m, 3H, Ar), 7.51–7.62 (m, 3H, Ar), 7.40–7.48 (m, 3H, Ar), 7.28–7.38 (m, 5H, Ar), 7.19–7.27 (m, 2H, Ar), 4.86 (d, *J* = 6.0 Hz, 1H, OC*H*Ph), 4.36 (m, 1H, NC*H*CH_3), 2.54 (d, $J_{H\text{-}P}$ = 7.7 Hz, 3H, NCH_3), 1.28 (d, *J* = 6.7 Hz, 3H, CH_3C), 0.95–1.85 (br q, 3H, BH_3); ^{13}C NMR ($CDCl_3$, 52 MHz) δ 142.5, 134.4, 134.0, 132.8, 132.6, 132.2, 131.3, 130.8, 130.0, 128.8, 128.6, 128.5, 128.3, 128.0, 127.9, 127.8, 127.6, 126.8, 78.8 (d, $J_{C\text{-}P}$ = 5.4 Hz), 58.3 (d, $J_{C\text{-}P}$ = 10.0 Hz), 30.6 (d, $J_{C\text{-}P}$ = 3.1 Hz), 13.5; ^{31}P NMR ($CDCl_3$, 81 MHz) δ +71.3 (d, $J_{P\text{-}B}$ = 73.5 Hz); ^{11}B NMR ($CDCl_3$, 64 MHz) δ -36.7 (d, $J_{B\text{-}P}$ = 43.4 Hz); HRMS (EI) calcd for $C_{26}H_{28}NOBP$ (M^+) 412.2006, Found 412.1998.

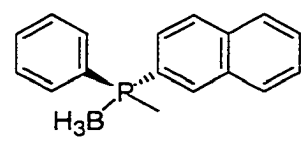


58

(*R*)-Methylphenyl-β-naphthylphosphinite-borane 58

This compound was prepared by a similar procedure to that of Jugé and co-workers.[75] A solution of (*S*)–(2*R*,1*S*)-*N*–methyl–*N*–(2–phenyl-2–hydroxy-1-methylethylamino) phenyl-β-naphthylphosphine–borane (3.31 g, 8.02 mmol) and conc. H_2SO_4 (0.79 g, 8.02 mmol)

in CH_3OH (65 mL) was stirred at 25 °C for 20 h and the solution was concentrated *in vacuo*. The residue was then purified by flash chromatography (EtOAc/hexane 1/5) to give (*R*)-methylphenyl-β-naphthylphosphinite-borane (2.01 g, 90%) as a colourless oil: $[\alpha]_D$ +38.1° (*c* 1.3, CH_2Cl_2); IR (CH_2Cl_2, cast) 3056, 2943, 2384 (BH), 1437, 1089, 1062, 750, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.36 (d, J = 12.6 Hz, 1H, Ar), 7.85–7.94 (m, 3H, Ar), 7.74–7.79 (m, 2H, Ar), 7.66-7.69 (td, J = 8.7, 1.5 Hz, 1H, Ar), 7.51–7.61 (m, 2H, Ar), 7.43–7.52 (m, 3H, Ar), 3.80 (d, $J_{H\text{-}P}$ = 12.0 Hz, 3H, OCH_3), 0.66–1.56 (br q, J = 97.2 Hz, 3H, BH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 134.7, 133.6, 133.3, 132.6, 131.9, 131.4, 128.9, 128.7, 128.5, 128.2, 127.8, 126.9, 126.0, 125.8, 54.1 (s, OCH_3); ^{31}P NMR ($CDCl_3$, 81 MHz) δ +107.5 (q, $J_{P\text{-}B}$ = 53 Hz); ^{11}B NMR ($CDCl_3$, 128 MHz) -41.2 (d, $J_{B\text{-}P}$ = 64 Hz); HRMS (EI) Calcd. for $C_{17}H_{18}O^{11}BP$ (M^+) 280.1184, Found 280.1179; Anal. Calcd. for $C_{17}H_{18}OBP$, C, 72.91; H, 6.43, Found C, 72.73; H, 6.55.

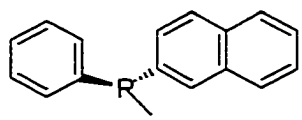


59

(*S*)-Methylphenyl-β-naphthylphosphine-borane 59

This compound was prepared by a similar procedure to that of Jugé and co-workers.[75] To a solution of (*R*)-methylphenyl-β-naphthylphosphinite-borane (0.60 g, 2.14 mmol) in THF (20 mL) was added methyl lithium (4.29 mL of a 1.4 M solution in Et_2O, 6.00 mmol) under argon at –20 °C and the reaction was stirred for 30 min. The reaction was quenched by the addition of H_2O, warmed to room temperature and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, dried over Na_2SO_4 and concentrated *in*

vacuo to give (*S*)-methylphenyl-β-naphthylphosphine-borane (0.55 g, 98%) as a colourless oil which was used in next reaction without further purification; $[\alpha]_D$ -16.4° (*c* 1.4, $CHCl_3$) [Lit.[75] $[\alpha]_D$ +19° (*c* 1.3, $CHCl_3$) for the other enantiomer]; IR (CH_2Cl_2, cast) 3055, 2378 (BH), 1436, 1062, 1027, 999, 965, 777, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.28 (d, J = 12.8 Hz, 1H, Ar), 7.85–7.92 (m, 3H, Ar), 7.67–7.72 (m, 2H, Ar), 7.55–7.61 (m, 3H, Ar), 7.44–7.48 (m, 3H, Ar), 1.96 (d, $J_{H\text{-}P}$ = 10.1 Hz, 3 H, PCH_3), 0.80–1.45 (br q, 3H, BH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.2 (d, $J_{C\text{-}P}$ = 3.52 Hz), 133.4 (d, $J_{C\text{-}P}$ = 11.7 Hz), 132.6 (d, $J_{C\text{-}P}$ = 10.9 Hz), 131.7 (d, $J_{C\text{-}P}$ = 9.16 Hz), 131.0 (d, $J_{C\text{-}P}$ = 2.40 Hz), 130.8, 130.2, 128.8 (d, $J_{C\text{-}P}$ = 9.10 Hz), 128.6, 128.5, 127.9, 127.7, 126.9, 126.7, 12.0 (d, $J_{C\text{-}P}$ = 39.6 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ +10.4 (q, $J_{P\text{-}B}$ = 43.8 Hz); ^{11}B NMR ($CDCl_3$, 128 MHz) δ -38.0 (d, $J_{B\text{-}P}$ = 58.5 Hz); HRMS (EI) Calcd. for $C_{17}H_{18}{}^{11}BP$ (M^+) 264.12393, Found 264.12362; Anal. Calcd. for $C_{17}H_{18}BP$ C, 77.31; H, 6.81, Found C, 77.31; H, 6.87.

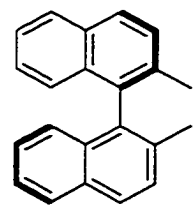


60

(*S*)-Methylphenyl-β-naphthylphosphine 60

This compound was prepared by a similar procedure to that of Jugé and co-workers.[75] A mixture of (*S*)-methylphenyl-β-naphthylphosphine-borane (0.47 g, 1.78 mmol) and dry diethyl amine (5 mL) was stirred under argon at 50 °C for 3 h. The reaction mixture was then concentrated *in vacuo* and the residue was purified by flash chromatography (EtOAc/hexane 1/10) to give (*S*)-methylphenyl-β-naphthylphosphine (0.38 g, 85%) as a

white solid; mp 48–50 °C (Lit.[75] 50 °C); $[\alpha]_D$ +12.8° (*c* 0.88, $CHCl_3$); IR ($CHCl_3$, cast) 3050, 2966, 2903, 1586, 1499, 1482, 1420, 1334, 881, 855, 741, 695, 635 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.0 (dd, J = 8.5, 0.6 Hz, 1H, Ar), 7.80–7.87 (m, 3H, Ar), 7.44–7.54 (m, 5H, Ar), 7.33–7.39 (m, 3H, Ar), 1.75 (d, $J_{H\text{-}P}$ = 3.4 Hz, 3H, PCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ, 140.2 (d, $J_{C\text{-}P}$ = 11.2 Hz), 137.5 (d, $J_{C\text{-}P}$ = 12.6 Hz), 133.2 (d, $J_{C\text{-}P}$ = 8.95 Hz), 132.3, 132.1, 132.0, 128.7, 128.6, 128.4, 127.9, 127.8, 127.6, 126.4, 126.2, 12.6 (d, $J_{C\text{-}P}$ = 13.7 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ -26.0 (s); HRMS (EI) Calcd. for $C_{17}H_{15}P$ (M^+) 250.0911, Found 250.0912.

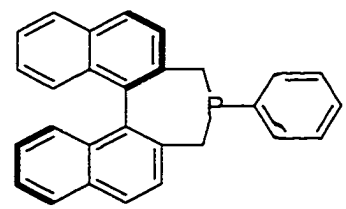


61

(*R*)-2,2'-Dimethyl-1,1'-binaphthyl 61

This compound was prepared by a similar procedure to that of Vederas and co-workers.[80] To a suspension of magnesium turnings (1.23 g, 50.6 mmol) in Et_2O (10 ml) was added a solution of 2-methyl-1-naphthyl bromide (6.63 g, 30.0 mmol) in dry toluene (50 ml) over *ca.* 1 h with ultrasonication and the reaction mixture was sonicated for another 2 h, then diluted with toluene (70 ml) to give a yellow slurry of Grignard reagent. To a mixture of (*S*)–1–[(*R*)–2–(diphenylphosphino)–ferrocenyl]ethyl methyl ether (0.29 g, 0.68 mmol), anhydrous $NiBr_2$ (78.0 mg, 0.36 mmol) and 2-methyl-1-naphthyl bromide (8.84 g, 40.0 mmol) in Et_2O (10 mL) was added CH_3MgBr (0.107 g, 0.90 mmol) (0.30 mL of 3.0 M solution in Et_2O) and the brown solution which was obtained was heated under reflux for

10 min, then cooled to -10 °C. To this solution the Grignard reagent was added *via* cannula and the reaction was stirred at -5 °C for 96 h and then at 0 °C for 24 h. The reaction was quenched with dilute HCl, extracted with Et_2O and the ether extracts were concentrated *in vacuo*. The residue was purified by chromatography (hexane) to give (*R*)-2,2'-dimethyl-1,1'-binaphthyl (5.26 g 62%) as a colourless oil; IR ($CHCl_3$, cast) 3048, 3007, 2916, 2855, 1442, 810, 743 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 7.92 (d, *J* = 8.2 Hz, 2H, Ar), 7.91 (d, *J* = 8.2 Hz, 2H, Ar), 7.55 (d, *J* = 8.4 Hz, 2H, Ar), 7.42 (dd, *J* = 8.1, 7.0 Hz, 2H, Ar), 7.23 (dd, *J* = 8.1, 7.0 Hz, 2H, Ar), 7.01 (d, *J* = 8.5 Hz, 2H, Ar), 2.03 (s, 6H, 2 x CH_3); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 135.4, 134.8, 133.1, 132.7, 129.1, 128.3, 127.8, 126.4, 125.8, 125.3, 20.0; HRMS (EI) Calcd. for $C_{22}H_{18}$ (M^+) 282.1408, Found, 282.1408.

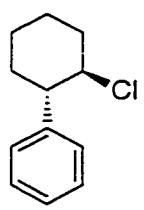


62

(*R*)-(+)-4-Phenyl-4,5-dihydro-3H-dinaphtho (2,1-c; 1',2'-e) phosphepine 62

This compound was prepared by a similar procedure of Gladiali and co-workers.[81] To a solution of (*R*)-2,2'-dimethyl-1,1'-binaphthyl (87.9 mg, 0.31 mmol) in hexane (4 mL) was added 2.5 M *n*-BuLi in hexane (1.25 mmol, 0.5 mL) followed by *t*-BuOK (105 mg, 0.94 mmol) and TMEDA (109 mg, 0.935 mmol) under argon at about –25 ° C during which a dark brown solution was obtained. The coloured solution was stirred at –78 °C for 24 h and then concentrated *in vacuo* at 0 °C. The residue was re-dissolved in THF (4

mL) and to this solution was added dichlorophenylphosphine (390 mg, 2.18 mmol). The reaction was stirred under argon at –20 °C for 24 h and then quenched with argon saturated H_2O and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give a residue which was purified by flash chromatography (CH_2Cl_2/hexane 1/3) to give (*R*)-(+)-4-phenyl-4,5-dihydro-3H-dinaphtho (2,1-c; 1',2'-e) phosphepine (15 mg, 12 %) as a pale yellow solid; mp. 180-184 °C (Lit.[81] 189-190 °C); $[\alpha]_D$ +43.5° (*c* 0.69, $CHCl_3$) [Lit.[81] $[\alpha]_D$ -90.2° (*c* 0.79, $CHCl_3$), for *S*-enantiomer]; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.92-7.96 (dd, *J* = 8.4, 2.0 Hz, 2H, Ar), 7.87 (d, *J* = 8.2 Hz, 1H, Ar), 7.71 (d, *J* = 8.4 Hz, 1H, Ar), 7.67 (dd, *J* = 8.4, 1.0 Hz, 1H, Ar), 7.41 (m, 2H, Ar), 7.22–7.30 (m, 9H, Ar), 6.89 (d, *J* = 8.3 Hz, 1H, Ar), 2.72–3.00 (m, 4H, 2 x C*CH*$_2$P); ^{13}NMR ($CDCl_3$, 75 MHz) δ 32.3 (d, $J_{C\text{-}P}$ = 21.1 Hz), 30.4 (d, $J_{C\text{-}P}$ = 15.3 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 6.6 (s); HRMS (EI) calcd. for $C_{28}H_{21}P$ (M^+) 388.1381, found 388.1375.

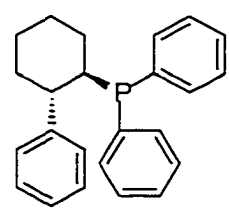


63

(1*R*,2*S*)-(-)-*trans*–2-Phenyl-cyclohexanyl chloride 63

This compound was prepared by a similar procedure to that of Smith and co-workers.[72] To a solution of zinc chloride (4.86 g, 35.7 mmol) in 36 % HCl (3.4 mL, 40.8 mmol) was added (1*R*, 2*S*)-(-)–*trans*–2–phenyl–cyclohexanol (1.80 g, 10.2 mmol) in one portion. The reaction was stirred for 24 h at 35 °C to give a brown mixture to which H_2O (5 mL) was

added. The mixture was extracted with $CHCl_3$ (10 mL) and the extract was washed with H_2O (5 mL), dried over Na_2SO_4 and purified using flash chromatography (hexane) to give recovered cyclohexanol (0.5 g, 28%) and (1*R*,2*S*)-(-)-*trans*–2-phenyl-cyclohexanyl chloride (0.78 g, 39%) as a colourless liquid; $[\alpha]_D$ -3.8° (*c* 1.31, CH_3OH); IR ($CHCl_3$, cast) 3062, 3028, 2934, 2856, 1499, 1447, 780, 754, 697, 530 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.31–7.36 (m, 2H, Ar), 7.21-7.27 (m, 3H, Ar), 4.04 (td, J = 11.2, 4.3 Hz, 1H, C*H*Cl,), 2.70 (td, J = 11.4, 3.6 Hz, C*H*Ph, 1H), 2.36-2.42 (m, 1H, 6-CH_a), 1.94–2.01 (m, 1H, 6-CH_b), 1.86–1.92 (m, 1H, 3-CH_a), 1.77-1.85 (m, 2H, 3-CH_b, 5-CH_a), 1.51–1.59 (m, 1H, 5-CH_b), 1.42–1.49 (m, 2H, 4-CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.9, 128.4, 127.4, 126.7, 64.3, 53.7, 37.9, 35.7, 26.6, 25.9; HRMS (EI) calcd. for $C_{12}H_{15}{}^{37}Cl$ (M^+) 196.0833, found 196.0833, calcd. for $C_{12}H_{15}{}^{35}Cl$ (M^+) 194.0862, found 194.0864; Anal. Calcd. C, 74.03; H, 7.77, Found, C, 74.13; H, 7.82.

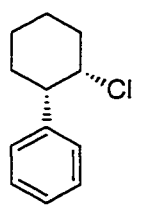


64

(1*R*,2*S*)-(-)-*trans*–2-Phenyl-cyclohexanyldiphenylphosphine 64

This compound was prepared by a similar procedure to that of Tanaka *et al.*[71] A mixture of (1*R*,2*S*)-(-)-*trans*–2-phenyl-cyclohexanylchloride (0.34 g, 1.73 mmol), magnesium (0.12 g, 5.19 mmol) and 5 drops of ethyl bromide in THF (3 mL) was stirred at 50 °C for 6 h. The Grignard reagent was then transferred to a solution of chlorodiphenylphosphine (0.44 g, 2.00 mmol) in THF (2 mL) at –78 °C. The reaction was then stirred for 24 h

allowing the temperature to rise to room temperature. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (EtOAc/hexane 1/10, Rf = 0.48) to give (1*R*,2*S*)-(-)-*trans*–2phenyl-cyclohexanyldiphenylphosphine (0.20 g, 34%) as white solid; mp 60-64 °C; $[\alpha]_D$ –3.4° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$, cast) 3051, 3025, 2928, 2849, 1584, 1491, 1479, 1446, 1430, 750, 740, 696 cm^{-1}; ^1H NMR ($CHCl_3$, 360 MHz) δ 7.70-7.78 (m, 2H, Ar), 7.51-7.61 (m, 4H, Ar), 7.25-7.38 (m, 6H, Ar), 7.01-7.12 (m, 3H, Ar), 3.01-3.16 (m, 2H, C*H*Ph & C*H*P), δ 1.76-1.98 (m, 4H), 1.54-1.72 (m, 2H), 1.42-1.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) aliphatic only δ 46.7, 43.8, 42.5, 41.5, 36.0, 26.2; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 1.32 (s); HRMS (EI) calcd. for $C_{24}H_{25}P$ (M^+) 344.1694 found 344.1688.

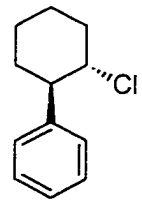


65

(1*S*,2*S*)-(-)-*cis*–2-Phenyl-cyclohexanyl chloride 65

This compound was prepared by a similar procedure to that of Marinetti *et al.*[111] A solution of (1*R*,2*S*)-(-)-*trans*–2-phenyl-cyclohexanol (0.22 g, 1.25 mmol) and triphenylphosphine (0.655 g, 2.50 mmol) in CCl_4 (10 mL) was stirred at 70 °C for 12 h and was then concentrated *in vacuo*. The residue was purified by flash chromatography (hexane) to give (1*S*,2*S*)-(-)-*cis*–2-phenyl-cyclohexanyl chloride (0.127 g, 52 %) as a colourless liquid; $[\alpha]_D$ +81.1° (*c* 2.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.30–7.35 (m, 2H, Ar), 7.22–7.26 (m, 3H, Ar), 4.52 (br d, *J* = 2.6 Hz, 1H, C*H*Cl), 2.96–3.01 (dt, *J* = 12.4, 2.9 Hz, 1H, C*H*Ph), 2.15–2.19 (m, 2H, 6-CH_2), 1.84–2.03 (m, 3H, 3-CH_2, 5-CH_2),

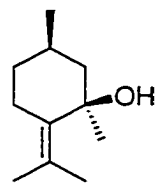
1.71–1.78 (m, 1H, 5-CH_b), 1.59–1.64 (m, 1H, 4-CH_a), 1.37–1.50 (m, 1H, 4-CH_b); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 132.3, 128.1, 127.8, 126.6, 66.0, 48.0, 35.1, 26.0, 24.5, 19.5; HRMS (EI) calcd. for $C_{12}H_{15}{}^{37}Cl$ (M^+) 196.0833, found 196.0833, calcd. for $C_{12}H_{15}{}^{35}Cl$ (M^+) 194.0862, found 194.0862.



67

(1*R*,2*R*)-(-)-*trans*–2-Phenyl-cyclohexanyl chloride 67

The same procedure as that described for the preparation of (1*S*,2*R*)-(-)-trans-2-phenyl-cyclohexanyl chloride was used to provide the title compound as a oil (34%); $[\alpha]_D$ +3.8° (*c* 1.33, CH_3OH); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.31–7.36 (m, 2H, Ar), 7.21–7.27 (m, 3H, Ar), 4.00–4.08 (td, *J* = 11.2, 4.3 Hz, 1H, C*H*Cl,), 2.67–2.74 (td, *J* = 11.4, 3.6 Hz, C*H*Ph, 1H), 2.36–2.42 (m, 1H, 6-CH_a), 1.94–2.01 (m, 1H, 6-CH_b), 1.86–1.92 (m, 1H, 3-CH_a), 1.77–1.85 (m, 2H, 3-CH_b, 5-CH_a), 1.51–1.59 (m, 1H, 5-CH_b), 1.42–1.49 (m, 2H, 4-CH_2).

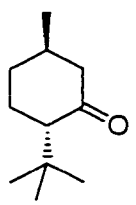


68

(1*R*,5*R*)-1,5-Dimethyl-2-(1-methylethylidene) cyclohexanol 68

This compound was prepared using a modified procedure of Whitesell and co-workers.[63] To a solution of methyl lithium (8.85 g, 0.30 mol) in Et_2O (215 mL) was added anhydrous copper(I) chloride (28.5 g, 0.29 mol) at 0 °C in one portion and the resulting mixture was

stirred for 10 min to give a dark brown suspension. To this suspension a solution of (*R*)–(+)–pulegone (15.1 g, 98.5 mmol) in Et_2O (50 mL) was added at 0 °C over *ca.* 10 min. The reaction was stirred at 0 °C for 2 h then at 25 °C for 12 h and the mixture was poured into ice cold 2M HCl (250 mL). The Et_2O layer was separated and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with H_2O (100 mL), pre-dried with sat. NaCl (2 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo* at room temperature to give a pale yellow liquid. The liquid was redissolved in MeOH (100 mL) and to the solution, 2N NaOH (2 mL) was added. The mixture was then stirred at room temperature for 3 days. The solvent was removed *in vacuo* to give a residue which was purified by flash chromatography (EtOAc/hexane 1/5) to give (1*R*,5*R*)-1,5-dimethyl-2-(1-methylethylidene) cyclohexanol as a colourless liquid; IR ($CHCl_3$ cast) 3263 (OH, br), 2948, 2911, 2871, 2822, 1455, 1374, 1360, 1223, 1148, 883, 862 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.99–2.05 (m, 2H, 6-C*H*$_2$), 1.85 (s, 3H, CC*H*$_3$OH), 1.61–1.69 (m, 2H, 3-C*H*$_2$), 1.50–1.58 (m, 1H, 5-C*H*), 1.47 (s, O*H*), 1.35 (s, 3H, C*H*$_3$C=C), 1.33 (s, 3H, C*H*$_3$C=C), 1.19–1.26 (m, 1H, 4-C*H*$_a$), 0.99–1.13 (m, 1H, 4-C*H*$_b$), 0.90 (d, J = 6.3 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.3, 128.2, 74.4, 43.0, 31.8, 30.0, 29.3, 28.7, 27.6, 21.6, 21.4; HRMS (EI) calcd. for $C_{11}H_{20}O$ (M^+) 168.1514, found, 168.1510.

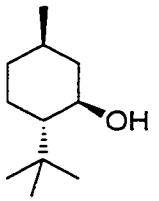


69

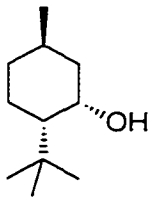
(2*S*,5*R*)-2-*t*-Butyl-5-methyl cyclohexanone 69

This compound was prepared by a similar procedure to that of Whitesell and co-workers.[63] To a suspension of magnesium turnings (7.20 g, 300 mmol) in Et_2O (100 mL) was added several drops of a solution of CH_3I (40 g, 282 mmol) in Et_2O (50 mL) and the reaction was slightly heated with a heat gun to start the reaction. Once the reaction had begun the remaining Et_2O solution of CH_3I was added dropwise to keep the reaction boiling. When addition was complete the exothermic reaction continued for *ca* 30 min until boiling had stopped. The Grignard reagent was then transferred to a flask containing Et_2O (100 mL), to the solution anhydrous copper(I) chloride (14.0 g, 142 mmol) was added at 0 °C with vigorous stirring to give a dark brown suspension. To the mixture a solution of (*R*)–pulegone (21.5 g, 142 mmol) in Et_2O (50 mL) was added dropwise at 0 °C and then the reaction was stirred at 0 °C for 12 h. After gravity filtration the solution was poured into 2 N HCl (200 mL) at 0 °C. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a deep brown residue which was decolourized by passing through a short silica gel column. The residue was redissolved in CH_3OH (150 mL) and to this solution 2 N NaOH (2 mL) was added. The mixture was stirred at room temperature for 3 days and concentrated *in vacuo*. To the residue Et_2O (300 mL) was added, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*. The residue was purified with flash chromatography (EtOAc/hexane 1/50) to give (2*S*,5*R*)-2-*t*-butyl-5-methyl cyclohexanone (8.10 g, 34%) as a pale yellow liquid; $[\alpha]_D$ -14.4° (*c* 1.44, $CHCl_3$); IR ($CHCl_3$, cast) 2953, 2926, 2869, 1711 (C=O), 1482, 1362, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.25 (dd, *J* = 3.9, 2.3 Hz, 1H, 6-CH_a), 2.02–2.15 (m, 2H, 2-C*H*, 6-CH_b), 1.97 (dd, *J* = 10.8, 1.5 Hz, 1H), 1.80–1.91 (m, 2H), 1.25–1.48 (m, 2H,

4-CH_2), 0.98 (d, J = 6.4 Hz, 3H, CH_3), 0.97 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.1 (C=O), 59.4, 52.5, 36.4, 34.8, 31.7, 28.6, 27.7, 22.4; HRMS (EI) calcd for $C_{11}H_{20}O$ (M^+) 168.1514, found 168.1513.



70

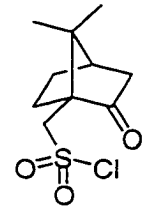


71

(1*R*,2*S*,5*R*)-2-*t*-Butyl-5-methyl-cyclohexanol 70 & (1*S*,2*S*,5*R*)-2-*t*-butyl-5-methyl-cyclohexanol 71

These compounds were prepared by a similar procedure to that of Whitesell and co-workers.[63] Sodium sand was prepared by vigorous stirring of a refluxing mixture of sodium (3.32 g, 144 mmol) in toluene (60 mL) for *ca.* 10 mins followed by cooling down without any movement. To the sodium sand was added a solution of (2*S*,5*R*)-2-*t*-butyl-5-methyl cyclohexanone (8.10 g, 48.1 mmol) in isopropylalcohol (14.4 g, 240 mmol) over *ca.* 10 min with stirring. The reaction was stirred at room temperature for 12 h. Excess sodium sand was removed by vacuum filtration and the filtrate was concentrated *in vacuo* to give a residue, which was diluted with H_2O (100 mL) and then extracted with Et_2O (2 x 150 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a residue which was purified by flash chromatography (EtOAc/hexane 1/10) to give (1*R*,2*S*,5*R*)-2-*t*-butyl-5-methyl-cyclohexanol (6.5 g, 79%) and (1*S*,2*S*,5*R*)-2-*t*-butyl-5-methyl-cyclohexanol (0.5 g, 6%) both as colourless liquids. Data for (1*R*,2*S*,5*R*)-2-*t*-butyl-5-methyl-cyclohexanol; $[\alpha]_D$ −30.9° (*c* 0.55, $CHCl_3$); IR

($CHCl_3$, cast) 3357 (br, OH), 2951, 2916, 2868, 1481, 1456, 1392, 1268, 1093, 1019, 989 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.50 (ddd, *J* = 10.8, 9.4, 4.2 Hz, 1H, C*H*OH), 1.90 (ddd, *J* = 12.1, 6.1, 3.8 Hz, 1H, 2-C*H*), 1.77 (ddd, *J* = 11.4, 5.1, 2.1 Hz, 1H, 6-CH_a), 1.60–1.67 (m, 2H, 6-CH_b, 3-CH_a), 1.37–1.47 (m, 2H), 1.10 (d, *J* = 5.8 Hz, O*H*), 1.01–1.05 (m, 1H), 0.98 (s, 9H, 3 x CH_3), 0.91–0.94 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 73.1, 53.2, 46.7, 34.9, 32.8, 31.6, 29.3, 26.4, 22.0; HRMS (EI) calcd for $C_{11}H_{22}O$ (M^+) 170.1671, found 170.1671. Data for (1*S*,2*S*,5*R*)-2-*t*-butyl-5-methyl-cyclohexanol; $[\alpha]_D$ +37.8° (*c* 1.1, $CHCl_3$),; IR ($CHCl_3$, cast) 3358 (br, OH), 2954, 2868, 1457, 1392, 1378, 1363, 1113, 1068, 1013, 982, 644 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 3.80 (td, *J* = 8.3, 4.2 Hz, 1H, C*H*OH), 2.01 (m, 1H), 1.56–1.68 (m, 2H), 1.42–1.52 (m, 2H), 1.33 (d, *J* = 4.2 Hz, 1H, O*H*), 1.20–1.30 (m, 1H), 0.98 (s, 9H, 3 x CH_3), 0.92–0.94 (d, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75) δ 68.7, 53.4, 42.4, 31.7, 31.3, 29.2, 27.2, 21.1, 19.2; HRMS (EI) calcd for $C_{11}H_{22}O$ (M^+) 170.1671, found 170.1678.

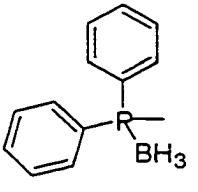


74

(1*S*)-(+)-10-Camphorsulfonyl chloride 74

This compound was prepared using a similar procedure to that of Bartlett and co-workers.[112] To a three neck round flask (500 mL) containing phosphorus pentechloride (15.7 g, 75.0 mmol), was added in portions (1*S*)-(+)-10-camphorsulfonic acid (15.0 g,

64.6 mmol) under an argon atmosphere at 0 °C. The solid mixture was vigorously stirred at room temperature for 5 h during which time the solid mixture liquified. The reaction was quenched by the addition of ice (40 mL) and stirring continued until a solid had formed. The solid was collected by vacuum filtration, dried under vacuum for 12 h and purified by recrystallization from hexane to give (1*S*)-(+)-10-camphorsulfonyl chloride (4.1 g, 25%) as white crystals; mp 59-64 °C (Lit.[112] 65–67 °C); $[\alpha]_D$ +29.3° (*c* 3.2, $CHCl_3$); IR ($CHCl_3$, cast) 2966, 1747 (C=O), 1378, 1162, 524, 505 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 4.29 (d, *J* = 14.6 Hz, 1H, CH_aSO_2Cl), 3.72 (d, *J* = 14.6 Hz, 1H, CH_bSO_2Cl), 2.39–2.49 (m, 2H, CH_2CO), 2.15 (t, *J* = 4.5 Hz, 1H), 2.03–2.13 (m, 1H), 1.97 (d, *J* = 18.8 Hz, 1H), 1.77 (ddd, *J* = 14.0, 9.3, 4.7 Hz, 1H), 1.47 (ddd, *J* = 12.7, 9.3, 3.8 Hz, 1H), 1.13 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.7, 64.3, 59.7, 48.2, 42.8, 42.3, 26.8, 25.2, 19.7, 19.6; HRMS (EI) calcd for $C_{10}H_{15}O_3S^{37}Cl$ (M^+) 252.0401, found 252.0402, calcd for $C_{10}H_{15}O_3S^{35}Cl$ (M^+) 250.0431 found 250.0432.

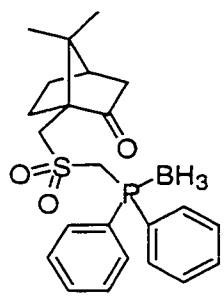


75

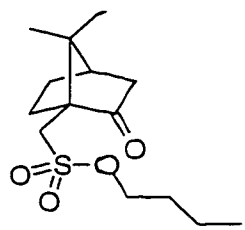
Diphenylmethylphosphine-borane 75[75]

To a solution of diphenylmethylphosphine (5.54 g, 27.6 mmol) in toluene (50 mL) was added borane-methylsulfide complex in toluene (10 mL) dropwise under argon at 0 °C. The reaction was stirred for 10 h at 25 °C and then concentrated *in vacuo* to give a residue which was purified by short column flash chromatography (EtOAc/hexane 1/5, $R_f = 0.33$) to give diphenylmethylphosphine–borane (5.40 g, 92%) as a colourless liquid; IR ($CHCl_3$,

cast) 3077, 3056, 2917, 2379 (B–H), 1436, 1109, 1062, 904, 891, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.63–7.69 (m, 4H, Ar), 7.43–7.47 (m, 6H, Ar), 1.87 (d, J_{H-P} = 10.2 Hz, 3H, CH_3), 0.61–1.40 (br q, J_{H-B} = 91.8 Hz, 3H, BH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.8 (d, J_{C-P} = 9.6 Hz), 131.2 (d, J_{C-P} = 1.8 Hz), 130.9 (d, J_{C-P} = 45.5 Hz), 128.9 (d, J_{C-P} = 9.9 Hz), 12.2 (d, J_{C-P} = 40.4 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz, ^1H–decoupled) δ 9.68–10.72 (q, J_{P-B} = 54.7 Hz); ^{11}B NMR ($CDCl_3$, 128 MHz, ^1H–decoupled) δ -38.2 (d, J_{B-P} = 56.2 Hz); HRMS (EI) calcd for $C_{13}H_{15}P^{11}B$ [(M–1)$^+$] 213.1005 found 213.1004, calcd for $C_{13}H_{14}P^{11}B$ [(M–2)$^+$] 212.0926, found 212.0941, calcd for $C_{13}H_{13}P^{11}B$ [(M–3)$^+$] 211.0848, found 211.0847.



76

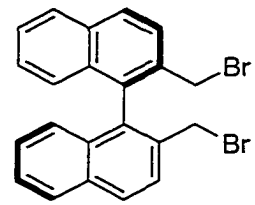


77

Camphorsulfonylmethyldiphenylphosphine-borane 76 & camphorsulfonic acid *n*–butyl ester 77

To a solution of diphenylmethylphosphine–borane (0.11 g, 0.52 mmol) in THF (1 mL) was added *n*-BuLi (0.21 mL of 2.5 M solution in hexane, 0.52 mmol) under argon at 0 °C to give a slightly yellow solution. The reaction was stirred for 0.5 h at this temperature and then cooled down to –78 °C. To this mixture a solution of camphorsulfonylchloride (0.13 g, 0.52 mmol) in THF (1.5 mL) was added dropwise. The reaction was stirred for 22 h allowing the temperature to rise to room temperature. After concentration *in vacuo*,

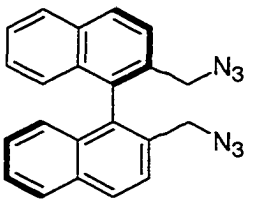
the residue was purified by flash chromatography (EtOAc/hexane 1/5) to give camphorsulfonylmethyldiphenylphosphine–borane (0.06 g, 25%) and camphorsulfonic acid *n*–butyl ester (62.0 mg, 41%) both as a colourless oils. Data for camphorsulfonylmethyldiphenylphosphine-borane: IR ($CHCl_3$, cast) 2960, 2389 (B–H), 1745 (C=O), 1454, 1368, 1168, 1057, 991, 741cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.71–7.77 (m, 4H, Ar), 7.48–7.55 (m, 6H, Ar), 5.07 (dd, $J_{H\text{-}H}$ = 12.8, $J_{H\text{-}P}$ = 1.9, 1H, SCH_aP), 4.95 (dd, $J_{H\text{-}H}$ = 12.7, $J_{H\text{-}P}$ = 2.3 Hz, 1H, SCH_bP), 3.47 (d, J = 15.1 Hz, 1H, CCH_aS), 2.87 (d, J = 15.1 Hz, 1H, CCH_bS), 2.33 (dt, J = 18.5, 4.0 Hz, 1H, CH_aCO), 2.24 (td, J = 13.2, 3.7 Hz, 1H, CH_bCO), 2.06 (t, J = 4.4 Hz, 1H), 1.19 (m, 1H), 1.84 (d, J = 18.5 Hz, 1H), 1.25-1.44 (m, 3H), 1.00 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.60-1.10 (br q, 3H, BH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.8 (C=O), 133.1, 132.0, 129.1, 125.6 (d, $J_{C\text{-}P}$ = 57.2 Hz), 64.8 (d, $J_{C\text{-}P}$ = 37.6 Hz), 57.8, 48.0, 47.2, 42.6, 42.3, 26.8, 26.6, 24.6, 19.5; ^{31}P NMR (^{1}H–decoupled) ($CDCl_3$, 162 MHz) δ 18.5 (br); ^{11}B NMR (^{1}H–decoupled) ($CDCl_3$, 128 MHz) δ -40.5 (br); LRMS (ES) 467.1 (MK^+, 100%). Data for camphorsulfonic acid *n*–butyl ester: IR ($CHCl_3$, cast) 2961, 2875, 1747 (C=O), 1358, 1171, 939, 572 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.22–4.32 (m, 2H, OCH_2), 3.58 (d, J = 15.1 Hz, 1H, CH_aS), 2.97 (d, J = 15.1 Hz, 1H, CH_bS), 2.49 (ddd, J = 14.7, 11.8, 4.4 Hz, 1H, CH_aCO), 2.38 (dt, J = 18.4, 4.2 Hz, 1H, CH_bCO), 2.11 (t, J = 4.4 Hz, 1H), 1.99–2.08 (m, 1H), 1.94 (d, J = 18.5 Hz, 1H), 1.60–1.75 (m, 3H, $OCH_2CH_2CH_2$), 1.37–1.47 (m, 3H, CH_2CH_3), 1.11 (s, 3H, CH_3), 0.94 (t, J = 7.4 Hz, 3H, CH_2CH_3), 0.87 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.4, 57.9, 47.9, 46.6, 42.8, 42.5, 31.2, 26.7, 24.9, 19.8, 19.7, 18.7, 13.5; HRMS (EI) calcd for $C_{14}H_{24}O_4S$ (M^+) 288.1395 found 288.1389, Calcd for $C_{10}H_{15}O_3S$ [$(M–C_4H_9O)^+$] 215.0742, Found 215.0736.



80

(*R*)-2,2'-*bis*(Bromomethyl)-1,1'-binaphthyl 80

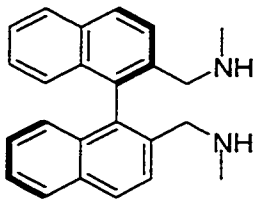
This compound was prepared using a similar procedure to that of Harris *et al.*[80] A mixture of (*R*)-2,2'-dimethyl-1,1'-binaphthyl (3.29 g, 11.6 mmol), NBS (4.27 g, 24.0 mmol) and benzoyl peroxide (58.1 mg, 0.24 mmol) in CCl_4 (60 ml) was heated under reflux under argon for 24 h to give a slightly yellow suspension. The reaction was cooled to room temperature, filtered under vacuum through a silica pad and concentrated *in vacuo*. The crude solid was purified by recrystallization from toluene/hexane to give (*R*)-2,2'-*bis*(bromomethyl)-1,1'-binaphthyl (2.45 g, 48%) as a white solid; mp 170-172 °C (Lit.[80] 171-174 °); $[\alpha]_D$ +158.3° (*c* 1.2, benzene) [Lit.[80] +148° (*c* 1.7, benzene)]; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.07 (d, *J* = 8.4 Hz, 2H, Ar), 7.98 (d, *J* = 8.1 Hz, 2H, Ar), 7.79 (d, *J* = 8.4 Hz, 2H, Ar), 7.53 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 2H, Ar), 7.30 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 2H, Ar), 7.07 (d, *J* = 8.4 Hz, 2H, Ar), 4.28 (s, 4H, 2 x CH_2Br); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 134.7, 134.4, 133.7, 132.9, 129.7, 128.4, 128.1, 127.2, 127.1, 116.6, 33.0; HRMS (EI) Calcd. for $C_{22}H_{16}{}^{81}Br_2$ (M^+) 441.9578, Found, 441.9582, Calcd. for $C_{22}H_{16}{}^{79}Br^{81}Br$ (M^+) 439.9598, Found 439.9615, Calcd. for $C_{22}H_{16}{}^{79}Br_2$ (M^+) 437.9619, Found, 437.9623.



81

(*R*)-2,2'-*bis*(Azidomethyl)-1,1'-binaphthyl 81[80]

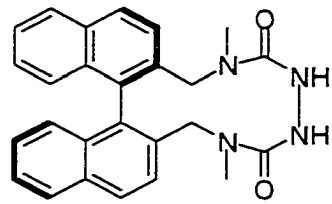
A solution of (*R*)-2,2'-*bis*(bromomethyl)-1,1'-binaphthyl (1.04 g, 2.38 mmol) in toluene (30 ml) was treated with NaN_3 (0.62 g, 9.50 mmol) followed by *tetra*butyl ammonium bromide (38.2 mg, 0.12 mmol). The reaction was heated under reflux for 24 h and then concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/hexane 1/10) to give (*R*)-2,2'-*bis*(azidomethyl)-1,1'-binaphthyl (0.80 g, 92%) as a white oil; IR ($CHCl_3$, cast) 3369, 3056, 2096 (N_3), 1278, 1258, 817, 754, 582, 533 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.07 (d, J = 8.5 Hz, 2H, Ar), 7.98 (d, J = 8.2 Hz, 2H, Ar), 7.73 (d, J = 8.5 Hz, 2H, Ar), 7.48–7.52 (ddd, J = 8.2, 6.9, 1.2 Hz, 2H, Ar), 7.27–7.31 (ddd, J = 8.5, 6.9, 1.3 Hz, 2H, Ar), 7.08 (d, J = 8.5 Hz, 2H, Ar), 4.08 (s, 4H, 2 x CH_2N_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.0, 133.3, 132.74, 132.71, 129.2, 128.2, 127.0, 126.6, 126.15, 126.11, 53.0 HRMS (EI) calcd for $C_{22}H_{16}N_6$ (M^+) 364.1437, Found 364.1428.



82

(*R*)-2,2'-*bis*(Methylaminomethyl) -1,1'-binaphthyl 82[80]

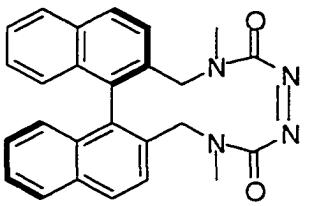
A solution of (*R*)-2,2'-*bis*(azidomethyl)-1,1'-binaphthyl (0.80 g, 2.18 mmol) in 1,2–dichloroethane (40 mL) was treated with bromodimethylborane (0.58 g, 4.80 mmol) under argon at room temperature. Release of nitrogen gas and the change of colour from pale to dark yellow was observed. The reaction was stirred at 60 °C for 1 h and cooled to room temperature. Ethanol (0.30 mL, 4.34 mmol) was added to quench the reaction and the mixture was then stirred at room temperature for 20 mins. After concentration *in vacuo*, CH_2Cl_2 (25 mL) and sat. aq. Na_2CO_3 (25 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL) and the combined extracts were washed with H_2O and dried over Na_2SO_4. Concentration *in vacuo* gave (*R*)-2,2'-*bis*(methylaminomethyl)-1,1'-binaphthyl (0.67 g, 90%) as a yellow solid which was used in the next step reaction without further purification; IR (CH_2Cl_2, cast) 3265 (NH) cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 8.05 (d, J = 8.6 Hz, 2H, Ar), 7.92 (d, J = 8.1 Hz, 2H, Ar), 7.75 (d, J = 8.4 Hz, 2H, Ar), 7.50 (ddd, J = 8.0, 6.9, 1.1 Hz, 2H, Ar), 7.25 (ddd, J = 8.5, 6.9, 1.3 Hz, 2H, Ar), 7.10 (d, J = 8.5 Hz, 2H, Ar), 3.45 (d, J = 13.0 Hz, 2H, 2 x CCH_aN), 3.35 (d, J = 13.0 Hz, 2H, 2 x CCH_bN), 2.25 (s, 6H, 2 x NCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.9, 134.3, 133.2, 132.9, 128.8, 128.2, 127.6, 126.8, 126.3, 125.9, 52.7, 35.4; HRMS (EI) Calcd. for $C_{24}H_{24}N_2$ (M^+) 340.1939, Found 340.1948.



83

(*R*)-4,9-Dimethyl-3,4,5,6,7,8,9,10-octahydrodinaphtho [2,1-*f*:1',2'-*h*] [1,2,4,11] tetraazacyclododecine-5,8-dione 83[80]

A solution of (*R*)-2,2'-*bis*(methylaminomethyl)-1,1'-binaphthyl (0.20 g, 0.59 mmol) in 1,2–dichloroethane (25 mL) was treated with triethylamine (0.178 mL, 1.29 mmol) and stirred at room temperature for 15 min. To the reaction was added *N*,*N*'-*bis*(azidocarbonyl)hydrazine (0.10 g, 0.59 mmol). The reaction was stirred for another 15 min at room temperature and then heated under reflux for 24 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash chromatography ($CH_3OH/CHCl_3$ 1/30) to give (*R*)-4,9-dimethyl-3,4,5,6,7,8,9,10-octahydrodinaphtho [2, 1–*f*: 1', 2'–*h*] [1, 2, 4, 11] tetraazacyclododecine-5,8-dione (0.043 g, 17%) as an oil; IR ($CHCl_3$, cast) 3278 (br, NH), 1651 (C=O), 1561, 1507, 1424, 1400, 1380, 1315, 814, 750, 527 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, J = 8.6 Hz, 2H, Ar), 7.95 (d, J = 8.2 Hz, 2H, Ar), 7.68 (d, J = 8.6 Hz, 2H, Ar), 7.50 (ddd, J = 8.1, 7.0, 1.1 Hz, 2H, Ar), 7.32 (ddd, J = 8.3, 7.0, 1.1 Hz, 2H, Ar), 7.04 (d, J = 8.6 Hz, 2H, Ar), 5.97 (s, 2H, 2 x N*H*), 4.28 (d, J = 17.0 Hz, 2H, 2 x CCH_aN), 3.95 (d, J = 17.0 Hz, 2H, 2 x CCH_bN), 2.96 (s, 6H, 2 x NCH_3);^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 135.5, 132.9, 132.8, 132.4, 129.1, 128.4, 127.2, 126.2, 125.4, 124.9, 52.7, 39.1; LRMS (ES), 425.2 (NH^+, 23%), 447.1 (MNa^+, 100%).

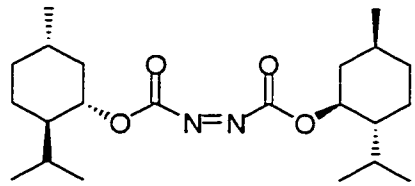


84

(*R*)-4,9-Dimethyl-4,5,9,10-tetrahydro-3H,8H-naphtho [2, 1-*f*: 1', 2'-*h*] [1, 2, 4, 11] tetraazacyclododecine-5,8-dione 84[80]

A solution of (*R*)-4,9-dimethyl-3,4,5,6,7,8,9,10-octahydrodinaphtho [2, 1-*f*: 1', 2'-*h*] [1, 2, 4, 11] tetraazacyclododecine-5,8-dione (0.16 g, 0.39 mmol) and pyridine (30.6 mg, 0.39 mmol) in CH_2Cl_2 (2.5 mL) was stirred under argon at room temperature for 5 min. To this solution was added *N*-bromosuccinimide (70.3 mg, 0.40 mmol) and the colourless solution turned orange. The reaction was stirred under argon at room temperature for 24 h. The reaction mixture was washed with H_2O (10 mL) and brine (10 mL) and dried over Na_2SO_4. Chromatographic purification (EtOAc/hexane 1/1) gave (*R*)-4,9-dimethyl-4,5,9,10-tetrahydro-3H,8H-naphtho [2, 1-*f*: 1', 2'-*h*] [1, 2, 4, 11]tetraazacyclododecine-5,8-dione (65.1 mg, 40%) as a yellow solid; mp 221-223 °C (Lit.[80] 214-218 °C); $[\alpha]_D$ +207° (*c* 0.4, $CHCl_3$) [Lit.[80] $[\alpha]_D$ +217° (*c* 0.28, $CHCl_3$)]; IR (CH_2Cl_2, cast) 3055, 2932, 1714 (C=O), 1691, 1450, 1424, 1394, 1199, 815, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, *J* = 8.7 Hz, 2H, Ar), 7.96 (d, *J* = 8.1 Hz, 2H, Ar), 7.65 (d, *J* = 8.7 Hz, 2H, Ar), 7.50 (ddd, *J* = 8.1, 6.7, 1.1 Hz, 2H, Ar), 7.33 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 2H, Ar), 7.06 (d, *J* = 8.4 Hz, 2H, Ar), 4.16 (d, *J* = 17.4 Hz, 2H, 2 x CH_aN), 3.87 (d, *J* = 17.4 Hz, 2H, 2 x CH_bN), 3.52 (s, 6H, 2 x NCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.1, 133.7, 132.8, 132.2, 129.5, 128.5, 127.4, 126.6, 125.8, 123.8, 50.4, 39.6;; LRMS (ES) 423.3 $(M + 1)^+$,

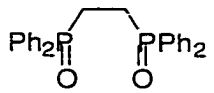
424.3 $(M + 2)^+$; Anal. Calcd. C, 73.92 ;H, 5.25; N, 13.26, Found C, 73.52; H, 5.26; N, 13.12.



85

Dimenthyl azodicarboxylate 85[80]

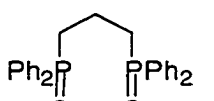
To a solution of *N,N'*-dimenthoxycarbonylhydrazine (1.41 g, 3.56 mmol) and pyridine (0.36 g, 5.00 mmol) in THF (60 ml) was added *N*-bromosuccinimide (0.75 g, 4.20 mmol) in one portion at 0 °C and the reaction was warmed to room temperature and stirred for 18 h. The reaction was concentrated *in vacuo* and the residue was purified by flash chromatography (EtOAc/hexane 1/10) to give dimenthyl azodicarboxylate (1.18 g, 84%) as a yellow solid; mp 67-69 °C; $[\alpha]_D$ +63° (*c*, 1.0, $CHCl_3$); IR ($CHCl_3$, cast) 2957, 2928, 2871, 1771, 1456, 1389, 1371, 1235, 1181, 1037, 962, 844 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 4.87–4.94 (td, *J* = 11.0, 4.5 Hz, 2H, 2 x C*H*O), 2.15–2.20 (m, 2H), 1.93–2.01 (m, 2H), 1.70–1.77 (m, 4H), 1.50–1.59 (m, 4H), 1.05–1.20 (m, 4H), 0.95 (d, *J* = 6.6 Hz, 6H, 2 x CH_3), 0.93 (d, *J* = 7.0 Hz, 6H, 2 x CH_3), 0.81 (d, *J* = 6.9 Hz, 6H, 2 x CH_3), 0.80–0.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2, 80.4, 46.9, 40.3, 33.9, 31.4, 25.9, 23.2, 21.8, 20.6, 16.0; LRMS (Cl/NH_3) *m/z* 412.4627 (MNH_4^+).



86

1,2-*Bis*(diphenylphosphinyl)ethane 86

This was prepared by a similar procedure to that of Kauffman and co-workers.[113] To a solution of 1,2-*bis*(diphenylphosphine) ethane (10.0 g, 25 mmol) in THF (300 mL) was added 30% H_2O_2 (12 mL) dropwise at 0 °C. The reaction mixture was stirred for 4 h. A slightly yellow residue was obtained by concentration *in vacuo*. The residue was purified by recrystallization from ethanol to give 1,2-*bis*(diphenylphosphinyl) ethane (8.9 g, 83%) as a white solid; mp 263–265 °C; (Lit.[114] 263-264 °C); IR ($CHCl_3$, cast) 1190 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.65-7.71 (m, 8H, Ar), 7.39-7.50 (m, 12H Ar), 2.50 (d, $J_{H\text{-}P}$ = 2.7 Hz, 4H, 2 x CH_2PO); ^{13}C ($CDCl_3$, 75 MHz) δ 132.7 (d, $J_{C\text{-}P}$ = 100.1 Hz), 132.0, 130.8 (t, $J_{C\text{-}P}$ = 4.7 Hz), 128.8 (d, $J_{C\text{-}P}$ = 5.8 Hz), 21.6 (d, $J_{C\text{-}P}$ = 67.2 Hz); HRMS (EI) calcd for $C_{26}H_{23}O_2P_2$ [$(M - H)^+$] 429.1173, found 429.1168.

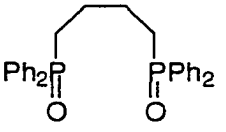


87

1,3-*Bis*(diphenylphosphinyl)propane 87

This was prepared by a similar procedure to that of Kauffman *et al.*[113] A solution of 1,3-*bis* (diphenylphosphine) propane (1.0 g, 2.4 mmol) in THF (25 mL) was treated with 30% H_2O_2 (1.0 mL) at 0 °C for 30 min. After solvent removal *in vacuo*, the residue was purified by flash chromatography ($CHCl_3$/ethyl acetate: 5/1) to give 1,3-*bis*(diphenylphosphinyl)

propane (0.90 g, 84%) as a white solid; mp 260-262 °C; IR ($CHCl_3$, cast) 3053, 3022, 2987, 2922, 1590, 1483, 1437, 1194, 1120, 781, 740, 727, 565 cm^{-1}, ^1H NMR ($CDCl_3$, 360 MHz) δ 7.41-7.75 (m, 20H, Ar), 2.51 (dt, J = 15.3, 7.5 Hz, 4H, 2 x CH_2PO), 1.97 (m, 2H, CH_2CH_2PO); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.2 (d, $J_{C\text{-}P}$ = 98 Hz), 132.4 (d, $J_{C\text{-}P}$ = 3.8 Hz), 131.8 (d, $J_{C\text{-}P}$ = 9.4 Hz), 127.5 (d, $J_{C\text{-}P}$ = 12.3 Hz), 29.5 (d, $J_{C\text{-}P}$ = 9.2 Hz), 15.8; ^{31}P NMR (CD_2Cl_2, 81 MHz) 30.8; HRMS (EI) Calcd. for $C_{27}H_{26}O_2P_2$ (M^+) 444.1408. Found: 444.1395.

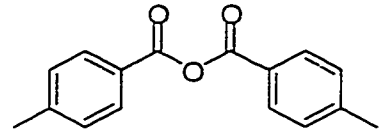


88

1,4-*Bis*(diphenylphosphinyl)butane 88

This was prepared by a similar procedure to that of Kauffman *et al.*[113] To a solution of 1,4-*bis*(diphenylphosphine) butane (10.1 g, 24.5 mmol) in THF (80 mL) and CH_2Cl_2 (120 mL), was added 30% H_2O_2 (10 mL) dropwise at 0 °C. The reaction mixture was stirred for 12 h at room temperature during which time a heavy precipitate formed. After concentraction *in vacuo*, the crude material was purified by recrystallization from methanol to give 1,4-*bis*(diphenylphosphinyl) butane (9.08 g, 90%) as a white solid; mp 255-257 °C (Lit.[115] 257-260 °C); IR (KBr, film) 3051, 2942, 2936, 2924, 2898, 2870, 1437, 1183, 1160, 1120, 844, 766, 747, 718, 695, 554, 551 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.64-7.69 (m, 8H, Ar), 7.40–7.48 (m, 12H, Ar), 2.19–2.26 (dt, $J_{H\text{-}P}$ = 15.2 Hz, J = 5.5 Hz, 4H, 2 x CH_2PO), 1.70 (dt, $J_{H\text{-}P}$ = 11.3 Hz, J = 5.4 Hz, 4H, 2 x CH_2CH_2PO); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.4 (d, $J_{C\text{-}P}$ = 98.0 Hz), 131.6 (d, $J_{C\text{-}P}$ = 2.3 Hz), 130.7 (d, $J_{C\text{-}P}$ =

9.4 Hz), 128.7 (d, $J_{C\text{-}P}$ = 11.8 Hz), 29.8 (d, $J_{C\text{-}P}$ = 71.3 Hz), 22.9 (dd, $J_{C\text{-}P}$ = 15.6, $J_{C\text{-}P}$ = 3.3 Hz); ^{31}P NMR ($CDCl_3$, 81 MHz) δ 31.9 (s); HRMS (EI) Calcd. for $C_{28}H_{28}O_2P_2$ (M^+) 458.1565. Found: 458.1561.



89

Method A: Solution version

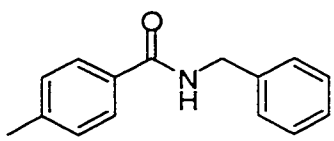
4-Toluic anhydride 89

To a solution of 1,3-*bis*(diphenylphosphinyl) propane (0.40 g, 1.13 mmol) in CH_2Cl_2 (20 mL) was added triflic anhydride (0.32 g, 1.13 mmol) in CH_2Cl_2 (5 mL) dropwise, under argon at 0 °C. The reaction was continued for 3 h. 4-Toluic acid (0.31 g, 2.26 mmol) in CH_2Cl_2 (15 mL) was added slowly, followed by triethylamine (0.23 g, 2.26 mmol). The reaction was warmed to room temperature and stirring was continued at room temperature for 12 h. A slightly yellow residue was obtained after concentration *in vacuo*. Flash chromatography (hexane/ethyl acetate: 3/1) gave 4-toluic anhydride (0.23 g, 78%) as a white solid; mp 92-94 °C (Lit.[31] 92-93 °C); IR ($CHCl_3$, cast)1776, 1712, 1609, 1226, 1209, 1173, 1050, 1015, 1004, 973, 838, 750, 683, 573 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.01 (dt, J = 8.4, 1.9 Hz, 4H, Ar), 7.30 (dt, J = 8.4, 1.9 Hz, 4H, Ar), 2.44 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.6, 145.6, 130.6, 129.5, 126.2, 21.8; HRMS (EI) Calcd. for $C_{16}H_{15}O_3$ [$(M+1)^+$] 255.1021, Found 255.0976.

Method B: Polymer-supported version

4-Toluic anhydride 89

Polymer-supported 1,3-*bis*(diphenylphosphinyl) propane (0.94 g, 0.68 mmol) was swollen in dry CH_2Cl_2 (25 mL). To this mixture, triflic anhydride (0.19 g, 0.68 mmol) was added under argon at 0 °C. The reaction was stirred for 8 h during which the colour changed from pink to brown. The reaction mixture was filtered and the polymer washed with ice-cold CH_2Cl_2 (3 x 30 mL) and CH_2Cl_2 (30 mL) was added to the washed polymer. 4-Toluic acid (0.18 g, 1.35 mmol) in CH_2Cl_2 (2 mL) was added followed by triethylamine (0.14 g, 1.35 mmol) and stirring was continued for 12 h at room temperature. The solution was collected by filtration and concentrated *in vacuo*. Purification by flash chromatography(EtOAc/Hexane 1/4) gave 4-toluic anhydride (36.1 mg, 40%). Spectroscopic data as above.



90

Method A: Solution version

4–Toluic acid benzylamide 90

To a solution of 1,4-*bis*(diphenylphosphinyl) butane (0.50 g, 1.09 mmol) in $CHCl_3$ (20 mL) was added a solution of triflic anhydride (0.31 g, 1.09 mmol) in $CHCl_3$ (5 mL) under argon at 0 °C. A cloudy solution was instantly obtained and the solution was stirred for 3.5 h. A solution of benzylamine (0.12 g, 1.09 mmol) in $CHCl_3$ (2.5 mL) was added dropwise, followed by addition of 4-toluic acid (0.15 g, 1.09 mmol) in $CHCl_3$ (5 mL) and

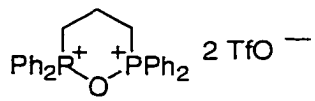
triethylamine (0.221 g, 2.18 mmol). The clear solution which was obtained was concentrated *in vacuo* and the residue purified by flash chromatography (hexane/ethyl acetate: 5/1) to give 4-toluic acid benzylamide (0.11 g, 43 %) as a white solid; mp136-138 °C (Lit.[31] 138-139 °C); IR ($CHCl_3$, cast) 3307 (NH), 3033, 2920, 1638, 1547, 1506, 1495, 1451, 1421, 1357, 1322, 1309, 1258, 1078, 1058, 1029, 992, 841, 752, 738, 721, 697, 675, 637 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, J = 8.0 Hz, 2H, Ar), 7.23-7.35 (m, 5H, Ar), 7.20 (d, J = 8.1 Hz, 2H, Ar), 6.45 (br s, 1H, N*H*), 4.62 (d, J = 5.7 Hz, 2H, CH_2NH), 2.36 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.3, 141.9, 138.3, 131.5, 129.3, 128.8, 127.9, 127.6, 127.0, 44.1, 21.5; HRMS (EI), Calcd for $C_{15}H_{15}NO$ (M^+), 225.1154, Found, 225.1154.

Method B: Polymer-supported version

4–Toluic acid benzylamide 90

Polymer-supported 1,3-*bis*(diphenylphosphinyl) propane (1.68 g, 1.38 mmol) was swollen with CH_2Cl_2 (25 mL). To this polymer, triflic anhydride (0.35 g, 1.24 mmol) was added under argon at 0 °C. A pink solution was obtained instantly and the mixture was stirred for 1 h. The reaction mixture was filtered and the polymer washed with CH_2Cl_2 (3 x 30 mL) and swollen with CH_2Cl_2 (20 mL). To the mixture, a solution of 4-toluic acid (0.17 g, 1.24 mmol) in CH_2Cl_2 (15 mL) was added. After stirring for 1 h excess 4-toluic acid was removed by filtration. The polymer was washed with CH_2Cl_2 (2 x 30 mL) and swollen with CH_2Cl_2 (20 mL). A solution of benzylamine (0.13 g, 1.24 mmol) in CH_2Cl_2 (2.5 mL) was added at 25 °C and the reaction was stirred for 5 h. A colourless solution was obtained

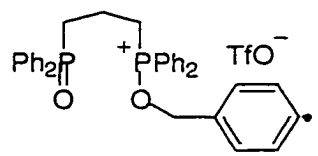
after filtering. Concentration and flash chromatography (EtOAc / Hexane: 1 / 2) gave 4-toluic benzyamide (62.4 mg, 37%) as a white product. Spectroscopic data as above.



91

2,2,6,6,-Tetraphenyl-2$^{\lambda5}$,6$^{\lambda5}$-(1,2,6)oxadiphosphinane ditriflate 91

To a solution of 1,3-*bis*(diphenylphosphinyl) propane (62 mg, 0.14 mmol) in CD_2Cl_2 (0.5 mL) at 0 °C, was added neat triflic anhydride (40 mg, 0.14 mmol)*via* syringe. The reaction mixture was occasionally manually shaken. After 2 h, ^1H, ^{31}P, and ^{19}F NMR at 0 °C showed that all of the starting materials had reacted and the desired cyclized phosphonium triflate salt had formed, as seen by the appearance of distinct new peaks and the chemical shift changes compared with the starting materials. ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.53-8.05 (m, 20H, Ar), 3.92 (br s, 4H), 2.95 (br s, 2 H); ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 86.1 (s); ^{19}F NMR (CD_2Cl_2, 188 MHz) δ -79.5 (s).



92

Benzyl monophosphonium triflate 92

To a solution of cyclized diphosphonium triflate in CD_2Cl_2 (prepared as above) was added neat benzyl alcohol (15 mg, 0.14 mmol) at 0 °C. The reaction mixture was occasionally manually shaken for 3 h. At 0 °C ^1H, ^{31}P, ^{19}F NMR showed that all of the cyclized diphosphonium triflate had reacted and benzyl monophosphonium triflate had formed. To

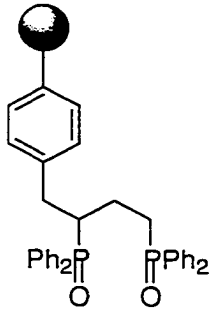
this mixture a solution of 4-toluic acid (19 mg, 0.14 mmol) in CD_2Cl_2 (0.5 mL) was added. The mixture was occasionally manually shaken for 0.5 h and then ^1H, ^{31}P, ^{19}F NMR spectra were recorded at 0 °C. Finally, triethylamine (28 mg, 0.28 mmol) was added. The spectra were recorded at 0 °C 0.5 h later. Data for benzyl monophosphonium triflate. ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.20-8.13 (m, 25H, Ar), 5.15 (d, J = 7.8 Hz, 2H, OCH_2Ph), 3.58 (dd, J = 10.8, 7.2 Hz, 2H, $CH_2P^+Ph_2$), 3.30 (dd, J = 12.0, 7.3 Hz, 2H, CH_2PPh_2), 1.94 (br, 2H, $PCH_2CH_2CH_2P^+$); ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 71.3 (d, J = 7.08 Hz), 58.9 (d, J = 3.94 Hz); ^{19}F NMR (CD_2Cl_2, 188 MHz) δ -79.4 (s).

Procedure of NMR tube reaction: Test of dimerization or polymerization.

To a solution of 1,3-*bis*(diphenylphosphinyl) propane (**87**) (41 mg, 0.09 mmol) in CD_2Cl_2 (1.0 mL) was added neat triflic anhydride (13 mg, 0.07 mmol) *via* syringe. The reaction mixture was occasionally shaken at 0 °C for 3 h. Then ^1H, ^{31}P NMR spectra were recorded.

Procedure of NMR tube reaction: Examination of the exchange between benzyl alcohol and *n*-propyl alcohol.

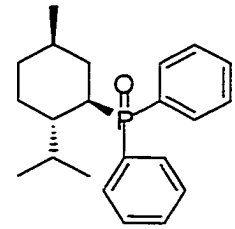
To a solution of 1,3-*bis*(diphenylphosphinyl) propane (**87**) (35 mg, 0.08 mmol) in CD_2Cl_2 (0.5 mL) was added neat triflic anhydride (22 mg, 0.08 mmol) at 0 °C. After 0.5 h benzyl alcohol (8.5 mg, 0.08 mmol) was added. ^1H, ^{31}P, NMR spectra were recorded after 1 h reaction at 0 °C. To this mixture *n*-propyl alcohol (5.7 mg, 0.08 mmol) was then added and the reaction was occasionally shaken for 1 h before ^1H, ^{31}P NMR spectra were recorded.



93

Polymer-supported 1,3-*bis*(diphenylphosphinyl)propane 93

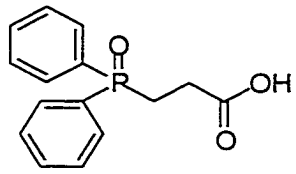
Before use, Merrifield resin, (1% DVB, 200-400 mesh, 1.0 mmol/g) was washed with CH_2Cl_2, THF, CH_2Cl_2 and dried *in vacuo* at 70 °C for 36 h. To a solution of 1,3-*bis*(diphenylphosphinyl) propane (0.61 g, 1.38 mmol) in THF (40 mL) was added *n*-BuLi (2.5 M in THF) (0.56 mL, 1.40 mmol) *via* syringe at approximately -25 °C under argon. A deep-red solution was instantly obtained, and stirring was continued at approximately –45 °C for 1 h. The deep-red solution was transferred *via* cannula to a flask containing Merrifield resin (1.31 g, 1.31mmol) swollen in THF (25 mL). The reaction mixture was warmed to room temperature over 20 h, during which time the colour subsided. The reaction was cooled to 0 °C, quenched with H_2O (5 mL) and filtered. The polymer was washed with THF and CH_2Cl_2 repeatedly until a white solid (1.54 g, 41%) was obtained which was dried *in vacuo* for 12 h. IR (KBr, film)3081, 3058, 3025, 3001, 2922, 2850, 1601, 1493, 1437, 1196 (P=O), 1156, 1145, 1117, 1028, 756, 719, 698 cm^{-1}; ^{31}P NMR (THF-d_8, 161 MHz) δ 32.5 (br s), 28.0 (br s); Anal. Calcd. C, 87.85; H, 7.77; Cl, 1.57. Found: C, 87.35; H, 7.35; Cl, 1.16.



94

Menthyldiphenylphosphine oxide 94

To a solution of menthyldiphenylphosphine (5.18 g, 12.2 mmol) in THF (50 mL) was added 30% H_2O_2 (2 mL) slowly at 0 °C. The reaction was stirred at room temperature for 30 min. After concentration *in vacuo*, the residue was purified by flash chromatography (Hexane/EtOAc: 2/1) to give menthyldiphenylphosphine oxide (4.63 g, 86%) as a white solid; mp 179-180 °C; $[\alpha]_D$ -67.4° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cast) 3053, 2955, 2869, 1454, 1437, 1386, 1368, 1179, 1113, 1071, 995, 742, 716, 695, 556, 542 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.82-7.88 (m, 2H, Ar), 7.74-7.79 (m, 2H, Ar), 7.43 (m, 6H, Ar), 2.34 (m, 1H, C*H*PO), 1.96-2.03 (m, 1H), 1.67-1.76 (m, 3H), 1.48-1.58 (m, 1H), 1.25-1.40 (m, 1H), 1.04-1.15 (m, 2H), 0.82-0.96 (m, 1H), 0.78 (d, J = 6.8 Hz, 3H, CH_3), 0.76 (d, J = 6.4 Hz, 3H, CH_3), 0.47 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.9 (d, J = 122.1 Hz), 131.0 (d, J = 8.2 Hz), 130.6 (d, J = 8.9 Hz), 128.5 (d, J = 11.2 Hz), 43.4 (d, J = 2.7 Hz), 40.0 (d, J = 70.0 Hz), 36.1, 34.4, 33.5 (d, J = 13.3 Hz), 28.2 (d, J = 2.8 Hz), 25.0 (d, J = 12.3 Hz), 22.5, 21.6, 15.7; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 33.9 (s); HRMS (EI) Calcd. for $C_{22}H_{29}OP$ (M^+) 340.1956, Found, 340.1957; Anal. Calcd. for $C_{22}H_{29}OP$; C, 77.65; H, 8.53, Found, C, 77.58; H, 8.70.

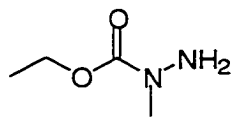


95

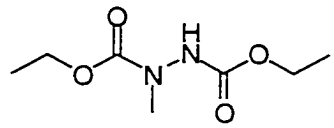
3-Diphenylphosphinylpropionic acid 95

This compound was prepared using a similar procedure to that of Tsvetkov and co-workers.[90] To a solution of diphenylphosphine (10.8 g, 56.2 mmol) in DMSO (60 mL) was added dropwise 27% aqueous KOH solution (8.16 g, 145 mmol in 30 mL). A yellow solution was instantly obtained to which a solution of γ-chloropropionic ethyl ester (8.20 g, 60.0 mmol) in DMSO (20 mL) was added at room temperature. The resulting colourless solution was stirred for 2 h at room temperature and then diluted with water (120 mL) and washed with benzene. The aqueous layer was acidified with aq. HCl to pH 2 during which a heavy precipitate formed. The mixture was extracted with benzene (3 x 80 mL) and dried over Na_2SO_4. After removal of solvent, the crude compound was dissolved in THF (50 mL). To this solution 30% of H_2O_2 (8 mL) was added in several portions at 0 °C. After stirring for 30 mins at 25 °C, the reaction mixture was diluted with water (120 mL) and extrated with $CHCl_3$ (3 x 80 mL). The $CHCl_3$ extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a colourless oil which was purified by flash chromatography ($CHCl_3/CH_3OH$ 10/1) to give 3-diphenylphosphinylpropionic acid (12.5 g, 78%) as a white solid; mp 100–102 °C (Lit.[90] 102-103 °C); IR (CH_2Cl_2, cast) 2400–3400 (OH), 1720 (CO), 1437, 1240, 1156, 1121, 1098, 795, 741, 721, 694, 534, 516 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 12.2 (br s, 1H, COO*H*), 7.72–7.80 (m, 4H, Ar), 7.48–7.58 (m, 6H, Ar), 2.60–2.75 (m, 4H, PCH_2CH_2CO); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 174 (d, $J_{C\text{-}P}$ = 16.1 Hz), 132.6, 132.3 (d, $J_{C\text{-}P}$ = 101.0 Hz), 131.2 (d, $J_{C\text{-}P}$ = 9.67 Hz), 129.3

(d, $J_{C\text{-}P}$ = 11.9 Hz), 26.7, 25.4 (d, $J_{C\text{-}P}$ = 73.3 Hz); ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 35.6 (s); HRMS (EI) Calcd. for $C_{15}H_{15}O_3P$ (M^+) 274.0759, Found 274.0758; Anal. Calcd. for $C_{15}H_{15}O_3P$: C 65.69, H 5.47, Found C 65.24, H 5.55.



96

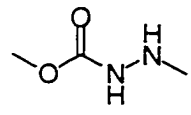


97

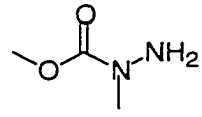
_N_–Ethoxycarbonyl _N_-methyl hydrazine 96 & _N,N_-diethoxycarbonyl _N_-methyl hydrazine 97

To a solution of methylhydrazine (13.0 g, 282 mmol) in THF (150 mL) was added ethyl chloroformate (16.4 g, 141 mmol) in THF (20 mL) dropwise *via* an additional funnel at 0 °C. During addition a heavy precipitate appeared and the reaction mixture was stirred at room temperature for 12 h. To the reaction mixture, H_2O (200 mL) was added to dissolve the solid. The solution was extracted with $CHCl_3$ (2 x 100 mL) and the combined organic layers were dried over Na_2SO_4. A colourless residue (16.8 g) was obtained after solvent removal *in vacuo*. The residue was purified by distillation to give *N*-ethoxycarbonyl *N*-methyl hydrazine (5.22 g, 16%) and *N,N*-diethoxycarbonyl *N'*-methyl hydrazine (4.95 g, 15%) as colourless liquids. Date for *N*-ethoxycarbonyl *N-methyl* hydrazine; bp 90-93 °C/18 mmHg (Lit.[91] 77-78 °C/12mmHg); IR ($CHCl_3$, cast) 3335 (NH_2), 1699 (CO), 1480, 1439, 1396, 1379, 1177, 961 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 4.13 (br s, 2H, N*H*), 4.04 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 3.00 (s, 3H, NCH_3), 1.20 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 61.9, 38.3, 14.8; HRMS (EI) calcd. for $C_4H_{10}N_2O_2$ (M^+) 118.0742, Found 118.0740. Data for *N,N*-diethoxycarbonyl *N'*-methyl hydrazine; IR ($CHCl_3$, cast) 3299 (br, NH), 2983, 2937, 2914, 1716 (CO), 1512, 1481,

1445, 1428, 1397, 1379, 1348, 1325, 1250, 1181, 1095, 1049, 764 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 7.12 (br s, 1H, N*H*CO), 4.13 (m, 4H, CH_3CH_2O), 3.11 (s, 3H, NCH_3), 1.24 (m, 6H, CH_3CH_2O); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 63.4, 62.2, 38.1, 14.7, 14.6; HRMS (EI) Calcd. for $C_7H_{14}N_2O_4$ (M^+) 190.0954, Found 190.0950.



98

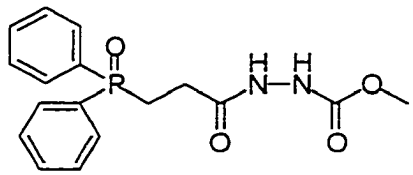


99

_N_-Methoxycarbonyl _N'_-methyl hydrazine 98 & _N_-methoxycarbonyl _N_-methyl hydrazine 99

These compounds were prepared using a similar procedure to that of Zinner and co-workers.[91] To a round bottomed flask was added methylhydrazine (20.7 g, 449 mmol) and dimethylcarbonate (40.5 g, 449 mmol). This flask was filled with a fractional distillation column and the reaction mixture was heated at *ca.* 100 °C for 4 h during which methanol distilled off. The colourless solution was concentrated *in vacuo* and purified by distillation to give a viscous liquid (19.2 g, 25–52 °C/1mmHg). The reaction mixture was purified by repeated flash chromatography ($CHCl_3/CH_3OH$, 20/1) to give *N*-methoxycarbonyl *N'*-methyl hydrazine (1.10 g) and *N*-methoxycarbonyl *N*-methyl hydrazine (105 mg). Data for *N*–methoxycarbonyl*N'*–methyl hydrazine: IR ($CHCl_3$, cast) 3303 (br, NH), 1717 (CO), 1544, 1478, 1446, 1364, 1276, 1209, 1146, 1051, 851, 776 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 6.85 (br, 1H, N*H*CO), 3.66 (s, 3H, CH_3O), 3.48 (br, 1H, N*H*CH_3), 2.57 (s, 3H, NHC*H*$_3$); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 158.3, 53.1, 39.2; HRMS (EI) Calcd. for $C_3H_8N_2O_2$ (M^+) 104.0586. Found 104.0587. Data for *N*–methoxycarbonyl *N*–methyl hydrazine, IR ($CHCl_3$, cast) 3335 (NH_2), 1700 (CO), 1635,

1456, 1374, 1320, 1253, 1196, 1170, 768 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 4.10 (br s, 2H, NH_2), 3.66 (s, 3H, CH_3O), 3.04 (s, 3H, NCH_3); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 158.4, 53.0, 38.4; HRMS (EI) Calcd. for $C_3H_8N_2O_2$ (M^+) 104.0664, Found 104.0624.

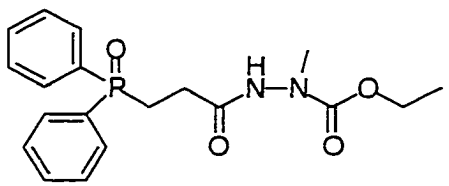


100

***N*-(3-Diphenylphosphinylpropionyl) *N'*-methoxycarbonylhydrazine 100**[116]

To a solution of 3-diphenylphosphinylpropionic acid (4.23 g, 15.5 mmol) in THF (50 mL) was added thionyl chloride (2.76 g, 23.2 mmol) in THF (3 mL) dropwise under argon at room temperature and the reaction was stirred for 6 h. The reaction was concentrated *in vacuo* to give a yellow oil which was dried under vacuum for 12 h. The yellow oil was re-dissolved in THF (50 mL) and to this mixture a solution of methoxycarbonylhydrazine (4.18 g, 46.4 mmol) in THF (80 mL) was added slowly under argon at room temperature during which time a heavy precipitate had formed. Stirring was continued for 12 h, the reaction mixture was dissolved in water (100 mL) and extracted with $CHCl_3$ (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product which was purified by flash chromatography (EtOAc/CH_3OH 10/1) to give *N*-(3-diphenylphosphinylpropionyl) *N'*-methoxycarbonylhydrazine (3.40 g, 64%) as a white solid; mp 110–115 °C; IR ($CHCl_3$, cast) 3207 (br, NH), 1744 (CO), 1685 (CO), 1526, 1437, 1239, 1173, 1121, 741, 694, 535 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.99 (br, 2H, 2 x N*H*), 7.66–7.73 (m, 4H, Ar), 7.38–7.52 (m, 6H, Ar), 3.61 (s, 3H, OCH_3), 2.55–2.66 (m, 4H, PCH_2CH_2CO); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.7 (d, $J_{C\text{-}P}$ = 15.1 Hz),

156.9, 132.3 (d, $J_{C\text{-}P}$ = 100.4 Hz), 132.0 (d, $J_{C\text{-}P}$ = 2.62 Hz), 130.8 (d, $J_{C\text{-}P}$ = 9.58 Hz), 128.9 (d, $J_{C\text{-}P}$ = 11.8 Hz), 52.7, 25.8, 25.2 (d, $J_{C\text{-}P}$ = 72.8 Hz); ^{31}P NMR ($CDCl_3$, 81 MHz) δ 34.4 (s); HRMS (EI) Calcd. for $C_{17}H_{19}N_2O_4P$ (M^+) 346.1083, Found 346.1078;

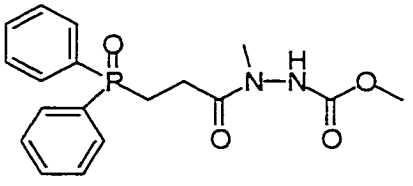


101

***N*-(3-Diphenylphosphinylpropionyl) *N'*-methyl *N'*-ethoxycarbonylhydrazine 101**[116]

To a solution of 3-diphenylphosphinylpropionic acid (0.37 g, 1.35 mmol) in THF (6 mL) was added thionyl chloride (0.22 g, 1.82 mmol) *via* syringe under argon at 0 °C. The reaction was stirred for 6 h and then concentrated *in vacuo* to give a colourless oil which was dried under high vacuum for 1 h. The oil was re-dissolved in THF (5 mL) and to this mixture a solution of *N*-methyl-*N*-ethoxycarbonylhydrazine (0.32 g, 2.70 mmol) in THF (3 mL) was added slowly at room temperature. Stirring was continued for 30 h and then the reaction mixture was diluted with water (20 mL) and extracted with $CHCl_3$ (2 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a colourless oil which was purified using flash chromatography (EtOAc/CH_3OH 15/1) to give *N*-(3-diphenylphosphinylpropionyl) *N'*-methyl *N'*-methoxycarbonylhydrazine (0.34 g, 67%) as a colourless foam; IR ($CHCl_3$, cast) 3187 (br, NH), 1715 (CO), 1692 (CO), 1437, 1177, 1120, 742, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 10.0 (br s, 1H, N*H*), 7.68–7.73 (m, 4H, Ar), 7.44–7.55 (m, 6H, Ar), 4.08 (br, 2H, CH_2CH_3), 3.09 (s, 3H, NCH_3), 2.57–2.69 (m, 4H, $POCH_2CH_2CO$), 1.15 (br, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0, 156.2, 132.3 (d, $J_{C\text{-}P}$ = 100.4 Hz), 132.1 (d,

$J_{C\text{-}P}$ = 3.03 Hz), 130.7 (d, $J_{C\text{-}P}$ = 9.58 Hz), 128.9 (d, $J_{C\text{-}P}$ = 11.7 Hz), 62.1, 37.1, 25.9, 25.2 (d, $J_{C\text{-}P}$ = 73.0 Hz), 14.4; ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 33.2 (s); HRMS (EI), Calcd. for $C_{19}H_{23}N_2O_4P$ (M^+) 374.1396, Found 374.1398; Anal. Calcd. for $C_{19}H_{23}N_2O_4P$; C, 60.90; H, 6.19; N, 7.48. Found, C, 60.66; H, 6.27; N, 7.34.



102

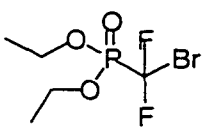
***N*-Methyl *N*-(3-diphenylphosphinylpropionyl) *N'*-methoxycarbonylhydrazine 102**[116]

To a solution of 3-diphenylphosphinylpropionic acid (0.80 g, 2.93 mmol) in THF (12 mL) was added thionyl chloride (0.35 g, 2.93 mmol) under argon at room temperature. The reaction mixture was stirred for 4 h and concentrated *in vacuo* to give a colourless oil which was dried under high vacuum for 1.5 h, and re-dissolved in THF (10 mL). To this mixture a solution of *N*-methoxycarbonyl *N'*-methyl hydrazine (0.61 g, 5.86 mmol) in THF (5 mL) was added slowly and the reaction was stirred for 12 h at room temperature, during which time a heavy precipitate appeared. The mixture was dissolved in water (25 mL) and extracted with $CHCl_3$ (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a colourless residue which was purified with flash chromatography (EtOAc/CH_3OH, 10/1) to produce *N*-Methyl *N*-(3-diphenylphosphinylpropionyl) *N'*-methoxycarbonylhydrazine (0.83 g, 79%) as a white solid; mp 140-142 °C; IR ($CHCl_3$, cast) 3157 (NH), 1741 (CO), 1641 (CO), 1437, 1421, 1256, 1172, 1119, 1069, 749, 720, 696, 536 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 9.96 (br s, 1H, NH), 7.66–7.71 (m, 4H, Ar), 7.45 – 7.53 (m, 6H, Ar), 3.55 (s, 3H, OCH_3), 3.07 (s,

3H, NCH_3), 2.54 (br s, 4H, POCH_2CH_2CO); ^{13}C NMR (CD_2Cl_2, 100 MHz), δ 174.0 (d, J_{C-P} = 15.3 Hz), 156.5, 132.3, 131.0 (d, J_{C-P} = 8.95 Hz), 129.3 (d, J_{C-P} = 11.4 Hz), 52.7, 35.7, 25.3, 24.8 (d, J_{C-P} = 17.4 Hz); ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 33.8 (s); HRMS (EI) Calcd. for $C_{18}H_{22}N_2O_4P$ (M^+), 361.1317, Found 361.1303.

General procedure of NMR tube reaction: To test the possibility of cyclization of Mitsunobu mimic reagents upon treatment with triflic anhydride and the subsequent reaction.

To a solution of compound **101** (40 mg, 0.10 mmol) in CD_2Cl_2 (0.5 mL) was added triflic anhydride (27 mg, 0.10 mmol) at room temperature. The reaction was occasionally shaken for 1 h and then ^{1}H, ^{31}P NMR spectra were recorded. To the reaction mixture was added neat benzyl alcohol (10 mg, 0.10 mmol). ^{1}H and ^{31}P NMR spectra were recorded after 1 h. A solution of 4-toluic acid (13 mg, 0.10 mmol) in CD_2Cl_2 (0.5 mL) was added and the ^{1}H and ^{31}P NMR spectra were recorded 0.5 h after. Finally triethylamine (19 mg, 0.12 mmol) was added and ^{1}H, ^{31}P NMR spectra were recorded after a further 0.5 h.

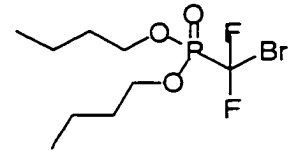


103

Difluorobromomethyldiethylphosphonate 103 [92]

To a solution of freshly distilled triethylphosphite (10.6 g, 64 mmol) in dry Et_2O (30 mL) was slowly added dibromodifluoromethane (13.4 g, 64 mmol) under argon at 0 °C with stirring. After addition, the reaction was heated under reflux for 24 h. The solvent and low

boiling impurities were removed *in vacuo* and the residue was subjected to vacuum distillation to give a colourless liquid. Redistillation of the liquid gave difluorobromomethyldiethylphosphonate (8.4 g, 49%) as a colourless liquid; bp 65-70 °C/1mmHg (Lit.[117] 99-102 °C/16mmHg); IR ($CHCl_3$, cast) 2987, 2936, 2916, 1479, 1445, 1285, 1164, 1144, 1092, 983, 796, 626 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.35 (m, 4H, 2 x CH_2O), 1.38 (t, J = 6.0 Hz, 6 H, 2 x CH_3); ^{31}P NMR (Ether-d_{10}, 162 MHz) δ -0.20 (t, J_{P-F} = 94.1 Hz); ^{19}F NMR (Ether-d_{10}, 376 MHz) δ -63.2 (d, J_{F-P} = 93.9 Hz); HRMS (EI) calcd for $C_{10}H_{10}O_3F_2P$ [(M–Br)$^+$] 187.0336, found 187.0329.

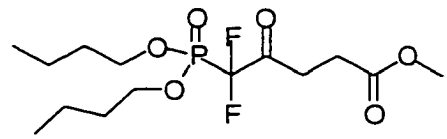


104

Difluorobromomethyldibutylphosphonate 104[92]

To a solution of tributylphosphite (20.0 g, 80 mmol) in dry THF (40 mL) was added difluorodibromomethane (18.9 g, 90 mmol) under argon at 0 °C. The reaction mixture was heated under reflux for 24 hours. After removal of the solvent and low boiling impurities *in vacuo*, the colourless residue was purified by vacuum distillation to give difluorobromomethyldibutylphosphonate (17.9 g, 69%) as a colourless liquid; bp 97-99 °C/0.5mmHg; IR (neat, KBr) 2963, 2936, 2912, 2876, 1466, 1383, 1289, 1234, 1147, 1093, 1058, 1023, 958, 875, 626, 553 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 4.29 (m, 4H, CH_2O), 1.71 (quintet, J = 6.6 Hz, 4H, 2 x CH_2CH_2O), 1.43 (sextet, J = 7.4 Hz, 4H, 2 x CH_3CH_2), 0.95 (t, J = 7.3 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 106.8-126.2 (td, J_{C-F} = 569 Hz, J_{C-P} = 235 Hz), 69.8 (d, J_{C-P} = 6.8 Hz), 32.3 (d, J_{C-P} = 5.3 Hz), 18.4 (s), 13.4

(s); ^{31}P NMR ($CDCl_3$, 162 MHz) δ -0.51 (t, J_{P-F} = 93.3 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -61.2 (d, J_{F-P} = 93.3 Hz); HRMS (EI) Calcd. for $C_9H_{19}O_3F_2P^{81}Br$ (M^+), 325.0203, Found, 325.0183, Calcd. for $C_9H_{19}O_3F_2P^{79}Br$ (M^+), 323.0223, Found, 323.0207.

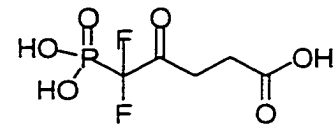


105

3-Carbomethoxylpropionyldifluoromethyldibutylphosphonate 105

To a solution of difluorobromomethyldibutylphosphonate (2.72 g, 8.42 mmol) in triglyme (5 mL) was added zinc dust, which had previously been activated using the method of Perrin[91] and the mixture was stirred at 60 °C for 1 h during which time most of the zinc dust reacted. The colourless solution was transferred to an addition funnel and then added dropwise to a solution of carbomethoxypropionyl chloride (1.28 g, 8.5 mmol) in triglyme (1 mL) under argon at 0 °C. The brown solution which was obtained was warmed up to room temperature and stirred for 20 h. The reaction mixture was poured onto ice water and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography ($CHCl_3$/ether 10/1) to give 3–carbomethoxylpropionyldifluoromethyldibutylphosphonate (0.54 g, 18%) as a colourless oil; IR ($CHCl_3$, cast) 2963, 2937, 2876, 1742 (C=O), 1466, 1438, 1412, 1396, 1381, 1284, 1234, 1215, 1097, 1060, 1022, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 4.20 (m, 4H, CH_2O), 3.68 (s, 3H, CH_3O), 3.11 (t, J = 6.4 Hz, 2H, CF_2COCH_2), 2.64 (t, J = 6.6 Hz, 2H, CH_2COOCH_3), 1.69 (quintet, J = 6.6 Hz, 4H, 2 x CH_2CH_2O), 1.41 (sextet, J = 7.6

Hz, 4H, 2 x CH_3CH_2), 0.93 (t, J = 6.1 Hz, 6H, 2 x CH_2CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 69.0, 67.3, 32.9, 32.3, 26.8, 18.5, 13.4; ^{31}P NMR ($CDCl_3$, 81 MHz) δ 2.91 (t, J_{P-F} = 92.5 Hz): ^{19}F NMR ($CDCl_3$, 376 MHz) δ -119.9 (d, J_{F-P} = 96.3 Hz); LRMS (CI, NH_3 / Cl), 359.0 (MH^+, 85%), 376.1 (MNH_4^+, 100%).



106

3–Difluorophosphonoacetylpropionic acid 106

This compound was prepared using a similar procedure to that of Blackburn *et al.*[93] To a solution of 3-carbomethoxypropionyldifluoromethyldibutylphosphonate (0.24 g, 0.67 mmol) in CCl_4 (8 mL) was added iodotrimethylsilane (0.54 g, 2.68 mmol) under argon at 0 °C. The reaction mixture was warmed to 50 °C and stirred for 20 hours during which time a brown solution was obtained. The reaction mixture was concentrated *in vacuo* and water (5 mL) and CH_3CN (2 mL) were added. The reaction mixture was stirred for 24 hours at 25 °C and the solvents removed *in vacuo*. The colourless residue was purified by HPLC to give 3-difluorophosphonoacetylpropionic acid (50.9 mg, 33%) as a colorless oil; IR ($CHCl_3$, cast) 2350–3600 (OH, br), 1737 (CO), 1461, 1383, 1217, 1089, 1021, 744, 611, 527 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz) δ 3.10 (t, J = 6.7 Hz, 2H, CF_2COCH_2), 2.62 (t, J = 6.0 Hz, 2H, CH_2COOH); ^{13}C NMR (CD_3OD, 75 MHz) δ 199.9, 175.8, 111.2–121.3 (sextet, J_{C-F} = 270 Hz, J_{C-P} = 190 Hz) 33.6, 27.8; ^{31}P NMR (CD_3OD, 81.0 MHz) δ 0.84 (t, J_{P-F} = 97.2 Hz); ^{19}F NMR (CD_3OD, 188.3 MHz) δ -121.5 (d, J_{F-P} = 92.8 Hz); LRMS (ES), 255.0 (MNa^+, 100%).

References

1. Castro, B. R. *Organic Reactions* **1983**, *29*, 1-157
2. (a) Mitsunobu, O. *Synthesis* **1981**, 1-28. (b) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc., Jpn.* **1967**, *40*, 2380-2382.
3. Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc., Jpn.* **1971**, *44*, 3427-3430.
4. Hughes, D. V. *Org. Prep. Proced. Int.* **1996**, *28*, 127-164.
5. Hughes, D. V. *Organic Reactions* **1992**, *42*, 337-656.
6. Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045-3049.
7. Pautard-Cooper, A.; Evans, S. A. *J. Org. Chem.* **1989**, *54*, 2485-2488.
8. Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235-4238.
9. Nikam, S. S.; Kornberg, B. E.; Rafferty, M. F. *J. Org. Chem.* **1997**, *62*, 3754-3757.
10. Fukuyama, T.; Cheung, M.; Jow, C. K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831-5834.
11. Berrée, F.; Michelot, G.; Le Corre, M. *Tetrahedron Lett.* **1998**, *39*, 8275-8276.
12. Mulzer, J.; Funk, G. *Synthesis* **1995**, *1*, 101-112.
13. Aronov, A. M.; Gelb, M. H. *Tetrahedron Lett.* **1998**, *39*, 4947-4950.
14. Jia, Z. Z. J.; Kelberlau, S.; Olsson, L.; Anikumar, G.; Fraser-Reid, B. *SynLett* **1999**, 565-566.
15. Bravo, P.; Cavicchio, G.; Crucianelli, M.; Poggiali, A.; Volonterio, A.; Zanda, M. *J. Chem. Res. (S)* **1998**, 666-667.
16. Clive, D. L. J.; Kellner, D. *Tetrahedron Lett.* **1991**, *32*, 7159-7160.

17. Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119-3122.

18. Yu, J.; Cho, H. S.; Flack, J. R. *J. Org. Chem.* **1993**, *58*, 5892-5894.

19. Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Ito, S. *Tetrahedron Lett.* **1995**, *36*, 2531-2534.

20. Cravotto, G.; Giovenzana, G. B.; Sisti, M.; Palmisano, G. *Tetrahedron* **1996**, *52*, 13007-13016.

21. Shing, T. K. M.; Li, L. H.; Narkunan, K. *J. Org. Chem.* **1997**, *62*, 1617-1622.

22. Dodge, J. A.; Trujillo, J. I.; Presnell M. *J. Org. Chem.* **1994**, *59*, 234–236.

23. Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017-3020

24. Saïah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317-4320.

25. Camp, D.; Jenkins, I. D. *Aust. J. Chem.* **1988**, *41*, 1835-1839.

26. Kay, P. B.; Trippett, S. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1813-1815.

27. Amos, R. A.; Emblidge, R. W.; Havens, N., *J. Org. Chem.* **1983**, *48*, 3598-3600.

28. Spry, D. O.; Bhala, A. R. *Heterocycles* **1986**, *24*, 1653-1661.

29. Arnold, L. D.; Assil, H. I.; Vederas, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 3973-3976.

30. Hendrickson, J. B.; Hussion, M. S. *J. Org. Chem.* **1987**, *52*, 4137-4139.

31. Hendrickson, J. B.; Hussion, M. S. *J. Org. Chem.* **1989**, *54*, 1144–1149.

32. Chen, C. S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695-707.

33. Klibanov, A. M.; Turner, N. J.; Willetls, A. J. *Acc. Chem. Res.* **1990**, *23*, 114-120.

34. Roberts, S. M. *Chimia* **1993**, *47*, 85-92.

35. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons: New York, 1994.

36. Evans, D. A.; Anderson, J. C.; Taylor, M. K. *Tetrahedron Lett.* **1993**, *34*, 5563-5566.

37. Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492-1493.

38. Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794-2795.

39. Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169-3170.

40. Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813-5814.

41. Hulst, R.; Basten, A. V.; Fitzpatrick, K.; Kellogg, R. M. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2961-2963.

42. Vänttinen, E.; Kanerva, L. *Tetrahedron: Asymmetry* **1995**, *6*, 1779-1786.

43. Lehninger, A. L.; Nelson, D. L.; Cox, M. M. *Principles of Biochemistry*; Worth Publishers: New York, 1993.

44. Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487-6491.

45. Camp, D.; Hanson, G. R.; Jenkins, I. D. *J. Org. Chem.* **1995**, *60*, 2977-2980.

46. Kreutler, K.; Steinmetz, A. C. U.; Liang, T. C.; Prorok, M.; Abeles, R. H.; Ringe, D. *Biochemistry* **1994**, *33*, 13792-13800.

47. Innocentin, D.; Vederas, J. C. Unpublished results, University of Alberta.

48. Bose, A. K.; Manhas, M. S.; Sahu, D. P.; Hegde, V. R. *Can. J. Chem.* **1984**, *62*, 2498-2505.

49. Maier, V. L. *Helv. Chim. Acta.* **1963**, *300*, 2667-2676.

50. Hutchins, R. O.; Maryanoff, B. E.; Albrand, J. P.; Cogne, A.; Gagnaire, D.; Robert, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 9151-9157.

51. Searle, G. H.; Geue, R. J. *Aust. J. Chem.* **1984**, *37*, 959–970.

52. Ramer, S.E.; Moore, R.N. and Vederas, J.C. *Can. J. Chem.* **1986**, *64*, 706-713.

53. Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967–2971.

54. Townsend, C. A.; Nguyen, L. T. *Tetrahedron Lett.* **1982**, *23*, 4859-4862.

55. Bhagwat, S. S.; Hamann, P. R.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 6372-6376.

56. Townsend, C. A.; Nguyen, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 4582-4585.

57. Morrison, M. A.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 4421-4423.

58. Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953-964.

59. Hidai, M.; Mizuta, H.; Yagi, H.; Nagai, Y.; Hata, K.; Uchida, Y. *J. Organomet. Chem.* **1982**, *232*, 89-98.

60. Neuffer, J.; Richter, W. J. *J. Organomet. Chem.* **1986**, *301*, 289–297.

61. Comins, D. L.; Weltzien, L. G. *Tetrahedron Lett.* **1996**, *37*, 3807-3810.

62. Takagi, R.; Kimura, J.; Shinohara, Y.; Ohba, Y.; Takezono, K.; Hiraga, Y.; Kojima, S.; Ohkata, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 689-698.

63. Whitesell, J. K.; Lawrence, R. M.; Chen, H. H. *J. Org. Chem.* **1986**, *51*, 4779-4784.

64. Meyer, L.; Poirier, J. M.; Duhamel, P.; Duhamel, L. *J. Org. Chem.* **1998**, *63*, 8094-8095.

65. Mikolajczyk, M.; Perlikowska, W.; Omelañczuk, J. *Synthesis* **1987**, *11*, 1009–1012.

66. Graf, C. D.; Malan, C.; Harms, K.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 5581-5588.

67. Saitoh, A.; Misawa, M.; Morimoto, T. *Synlett* **1999**, 483-485.

68. Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988-2989.

69. Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569-592.

70. Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195-2202.

71. Tanaka, M.; Ogata, I. *Bull. Chem. Soc. Jp.* **1975**, *48*, 1094-1094.

72. Smith, J. G.; Wright, G. E. *J. Org. Chem.* **1952**, *17*, 1116–1121.

73. Jugé, S.; Stephan, M.; Merdés, R.; Genet, J. P.; Desportes, S. H. *J. Chem. Soc. Chem. Commun.* **1993**, 531-533.

74. Hayakawa, Y.; Hirose, M.; Hayakawa, M.; Noyori, R. *J. Org. Chem.* **1995**, *60*, 925–930.

75. Jugé, S.; Stephan, M.; Laffitte, J. A.; Genet, J. P. *Tetrahedron Lett.* **1990**, *51*, 6357–6360.

76. Jugé, S.; Stephan, M.; Genet, J. P.; Desportes, S. H.; Jeannin, S. *Acta. Crystallogr. Sect. C: Cryst. Struct. Commun.* **1990**, *46*, 1869-1872.

77. Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629-635.

78. Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187-208.

79. Rossini, C.; Franzini, L.; Rafaelli, A.; Salvadori, P. *Synthesis* **1992**, 503-517.

80. Harris, J. M.; McDonald, R.; Vederas, J. C. *J. Chem. Soc. Perkin Trans. 1* **1996**, 2669–2674.

81. Gladiali, S.; Dore, A.; Fabbri, D.; Lucchi, O. D.; Manassero, M. *Tetrahedron: Asymmetry* **1994**, *5*, 511–514.

82. Whitesell, J. K.; Wong, M. S. *J. Org. Chem.* **1991**, *56*, 4552-4554.

83. Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241-1250.

84. Kim, K. S.; Kim, B. H.; Park, W. M.; Cho, S. J.; Mhin, B. J. *J. Am. Chem. Soc.* **1993**, *115*, 7472-7477.

85. Kapron, J. T.; Santarsiero, B. D.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1993**, 1074-1076.

86. Kim, B. H.; Lee, J. Y.; Kim, K.; Whang, D. *Tetrahedron: Asymmetry* **1991**, *2*, 27-30.

87. Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Ito, S. *Chem. Lett.* **1994**, 539-542.

88. Mendonca, A. J. *Development of a Chiral Aminating Reagent and Amination Studies on Chiral and Achiral Molecules* **1989**, M Sc thesis, University of Alberta.

89. Hendrickson, J.B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, *4*, 277-280.

90. Tsvetkov, E. N.; Bondarenko, N. A.; Malakhova, I. G.; Kabachnik, M. I. *Synthesis* **1986**, *3*, 198–208.

91. Zinner, G.; Gebhardt, U. *Arch. Pharm. (Weinheim)* **1971**, *304*, 706-713.

92. Burton. D. J.; Ishihara, T.; Maruta, M. *Chem. Lett.* **1982**, 755-758.

93. Blackburn, G. M.; Ingleson, D. *J. Chem. Soc. Perkin Trans. 1* **1980**, 1150-1153.

94. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, Pergamon Press, New York, 2nd Edn., **1980**.

95. Volwiler, V.; Vliet, E. B. *J. Am. Chem. Soc.* **1921**, *43*, 1672-1676.

96. Bennani, Y. L.; Hanessian, S. *Tetrahedron* **1996**, *52*, 13837-13866

97. Fiorini, M.; Marcati, F.; Ginogo, G. M. *J. Mol. Catal.* **1978**, *4*, 125–134.

98. Tye, H.; Smyth, D.; Eldred, C.; Wills, M. *J. Chem. Soc. Chem. Commun.* **1997**, 1053–1054.

99. Hersh, W. H.; Xu, P.; Wang, B.; Yom, J. W.; Simpson C. K. *Inorganic Chemistry* **1996**, *35*, 5453–5459.

100. Curry, H. M.; Mason, J. P. *J. Am. Chem. Soc.* **1951**, *73*, 5043-5046.

101. Goering, H. L.; Briody, R. G.; Sandrock, G. *J. Am. Chem. Soc.* **1970**, *92*, 7401-7407.

102. Maillard, B.; Cazaux, M.; Lalande, R. *Bull. Soc. Chim. Fr.* **1971**, 467–475.

103. Schuler, H. R.; Slessor, K. N. *Can. J. Chem.* **1977**, *55*, 3280-3287.

104. Smith, G. G.; Lum, K. K.; Kirby, J. A.; Posposil, J. *J. Org. Chem.* **1969**, *34*, 2090–2095.

105. Collyer, T. A.; Kenyon, J. *J. Chem. Soc.* **1940**, 676–679.

106. Whitmore, W. F.; Gebhart, A. *J. Am. Chem. Soc.* **1942**, *64*, 912–917.

107. Nuñez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928–1932.

108. Lagerev, S. P. *Chem. Abstr.* **1941**, 2119–2120.

109. Strazzolini, P.; Giumanini, A. G.; Verardo, G. *Tetrahedron* **1994**, *50*, 217-254.

110. Evans, D. A.; Anderson, J. C.; Marta, K. *Tetrahedron Lett.* **1993**, *34*, 5563-5566.

111. Marinetti, A.; Buzin, F. X.; Ricard, L. *J. Org. Chem.* **1997**, *62*, 297–301.

112. Bartlett, P.D.; Knox, L. H. *Organic Synthesis* **1973**, Coll. Vol. V. 196.

113. Kauffman, T.; Antflang, E.; Olbrich, J. *Chem. Ber.* **1985**, *118*, 1022–1030.

114. Rabinowitz, R.; Pellon, J. *J. Org. Chem.* **1961**, *26*, 4623-4626.

115. Baizer, M. M.; Anderson, J. D. *J. Org. Chem.* **1965**, *30*, 3138-3141.

116. Vangveravong, S.; Nichols, D. E. *J. Org. Chem.* **1995**, *60*, 3409–341.

117. Burton, D. J.; Flynn, R. M. *J. Fluorine Chem.* **1977**, *10*, 329-332.