Stereoselective Transformations of Chiral Amines

Sadri A. Said

January 2002

Norwegian University of Science and Technology
Department of Chemistry

A thesis submitted in partial fulfillment of the requirements for the Dr.ing. degree
Summary

Enantiomerically pure amines and alcohols are particularly important synthons for the preparation of pharmaceuticals and agrochemicals. Notwithstanding the advances that have been achieved in asymmetric synthesis, resolution of racemates is probably the most current approach for the preparation of pure enantiomers. On the other hand, resolution processes suffer from disadvantages of low yields caused by the loss of at least 50% of the undesired isomer. Among the attractive methods for avoiding the drawbacks of resolution processes is inversion of configuration of the unwanted isomer. Although there are several existing methodologies for inversion and stereoselective transformations of chiral alcohols, corresponding methods for inversion of chiral amines has received less attention. The main objective of the project “Stereoselective transformations of chiral amines” was therefore to develop effective methods for inversion and stereoselective transformations of chiral amines.

This thesis discuss the utility of three nucleophilic substitution methods in stereoselective transformations of chiral amines.

The first investigation towards this goal was carried out using cyclic aryldisulfonylimide leaving group. Substitution of a chiral amine via N,N-naphthalene-1,2-disulfonylimide intermediate gave azide and alcohol products with 60-73% inversion of configuration, which was 20-25% lower compared to the previously studied relative disulfonylimides. Displacement of this group using aroxide anions afforded chiral aryl ethers with 70-87% inversion of stereochemistry. Chiral analysis of the ether products required synthesis of authentic reference compounds. This was achieved via benzyne route and by nucleophilic substitution on the derivatives of chiral alcohols. The benzyne route gave chiral phenyl ether from enantiopure alcohols with complete retention of configuration while the trifluoroacetate derivatives of chiral alcohols produced chiral aryl ethers with complete inversion of stereochemistry.

The 2,4,6-triphenylpyridinium cations were the next intermediates investigated in this study. These derivatives were synthesized from 2,4,6-triphenylpyrylium tetrafluoroborate in 84-90% yields using procedures described by Katritzky. Nucleophilic substitution on pyridinium salts of aliphatic chiral amines using azide and hydroxide anions gave products with 96 to 100% inversion of configuration.

The utility of diazonium salts for inversion of chiral amines was also investigated in the present study. This method was only focused on
stereoselective transformations of \( \alpha \)-amino acids as diazotization-dediazoniation of other aliphatic amines is of little interest for organic synthesis. Diazotization of L-alanine and L-phenylalanine ethyl esters hydrochlorides using alkyl nitrites in aprotic solvents, in the presence of azide anion, yielded optically active chloro substituents as the only products, instead of the intended azide compounds. Attempts to avoid counterion substitution by using ammonium tosylate to replace the ammonium chlorides was not useful and a tosyl product was isolated instead. Proposals to rectify this problem have been suggested. These include the use of much more inert counterions such as tetrafluoroborate or replacing the hydrochlorides with hydroazides. An alternative which could deliver the nucleophile in an intramolecular fashion has also been postulated. Investigations of these hypotheses are currently conducted.

Parallel to diazotization reactions was an investigation on inversion of \( \alpha \)-amino acids via \( N,N \)-disulfonylimides and 2,4,6-triphenylpyridinium cation leaving groups. Studies with \( N,N \)-disulfonylimide derivatives showed that this leaving group is not useful for inversion of \( \alpha \)-amino acids. Nucleophilic substitution on the 2,4,6-triphenylpyridinium salts of amino acids afforded partial racemized substitution products. The drawback in the utility of the pyridinium salts has been identified and efforts are underway to remove this impediment.
# Table of Contents

Summary ................................................................. iii
Preface ................................................................. ix
Acknowledgements .................................................... xi
Abbreviations .......................................................... xiii
List of papers .......................................................... xv

## 1 Introduction ...................................................... 1

1.1 Background ....................................................... 1
1.2 Chiral amines ..................................................... 2
   1.2.1 Definition .................................................. 2
   1.2.2 Uses of chiral amines ..................................... 3
1.3 Chirality and its consequences .................................. 5
   1.3.1 Chirality and bioactivity ................................ 5
   1.3.2 Scientific implications ................................... 7
   1.3.3 Economic consequences ................................... 8
1.4 Sources of pure enantiomers ...................................... 8
   1.4.1 Chiral pool ............................................... 9
   1.4.2 Resolution methods ..................................... 10
      1.4.2.1 Kinetic resolution .................................. 10
      1.4.2.2 Preferential crystallization ......................... 12
      1.4.2.3 Resolution via diastereomer crystallization .... 12
   1.4.3 Asymmetric synthesis .................................... 13
   1.4.4 Resolution versus asymmetric synthesis ............... 14
   1.4.5 Deracemization techniques ................................ 15
      1.4.5.1 Repeated racemization and resolutions .......... 15
      1.4.5.2 Dynamic kinetic resolution ......................... 16
      1.4.5.3 Stereoinversion ..................................... 17
1.5 Stereoselective transformations ................................ 18
   1.5.1 Inversion of halides .................................... 18
   1.5.2 Transformations of alcohols ............................ 19
   1.5.3 Inversion of epoxides ................................... 19
   1.5.4 Stereoselective transformations of amines ............ 20
1.6 Nucleophilic substitution of amines .......................... 21
1.7 References ...................................................... 22
2 Preparation of inverted amines and alcohols via \(N,N\)-disulfonylimides .............................................. 27

2.1 Introduction .......................................................... 27
2.2 Previous investigations ............................................. 27
2.3 Preparation and nucleophilic substitution of cyclic aryl disulfonylimides ..29
  2.3.1 Previous work ......................................................... 29
2.4 Preparation and nucleophilic substitution of \(N,N\)-1,2-naphthalene-
  disulfonylimide derivative of (\(S\))-1-phenylethylamine .................30
  2.4.1 Results and discussion ............................................ 31
2.5 Chiral analysis of \(N,N\)-1,2-naphthalenedisulfonylimide derivative
  of (\(S\))-1-phenylethylamine ............................................. 36
2.6 Comparison between nucleophilic substitution of different
  \(N,N\)-disulfonylimides ...................................................... 38
2.7 Conclusion .............................................................. 39
2.8 References ............................................................... 39

3 Preparation of chiral aryl ethers via cyclic \(N,N\)-disulfonylimides 41

3.1 Introduction .......................................................... 41
3.2 Synthesis of (\(S\))-phenyl and (\(S\))-2-naphthyl 1-phenylethyl
  ethers from cyclic aryldisulfonylimides .................................. 42
  3.2.1 Results and discussion ............................................ 42
3.3 Chiral analysis and synthesis of reference compounds .................... 44
  3.3.1 Synthesis of (\(R\))-phenyl 1-phenylethyl ether via benzyne route .44
  3.3.2 Synthesis of (\(S\))-phenyl and (\(S\))-2-naphthyl 1-phenylethyl
  ethers from trifluoroacetate ester ....................................... 46
3.4 General discussion ..................................................... 48
3.5 Conclusion .............................................................. 49
3.6 References ............................................................... 49

4 Preparation of inverted amines and alcohols via 2,4,6-
  triphenylpyridinium salts ............................................. 51

4.1 Introduction .......................................................... 51
4.2 Nucleophilic substitution of amines using pyrylium cations ............. 52
4.3 Synthesis and nucleophilic substitution of chiral 1-cyclohexylethyl- and
  3-phenyl-1-methylpropyl-2,4,6-triphenylpyridinium tetrafluoroborates . 53
  4.3.1 Results and discussion ............................................ 54
4.4 Synthesis and nucleophilic substitution of 1-phenylethyl-
  2,4,6-triphenylpyridinium salt ........................................... 57
  4.4.1 Results and discussion ............................................ 57
5 Inversion of Amino Acids ................................. 61

5.1 Introduction..................................................61
5.2 Inversion of $\alpha$-amino acids via cyclic aryl disulfonylimides ........62
   5.2.1 Synthesis and nucleophilic substitution of $N,N$-1,2-benzene-
        disulfonimidimide derivative of L-phenylalanine ethyl ester ........63
   5.2.1.1 Results and discussion ................................ 63
5.3 Inversion of amino acids via 2,4,6-triphenylpyridinium salts ..........65
   5.3.1 Synthesis and nucleophilic substitution of 2,4,6-triphenylpyrid-
        inium tetrafluoroborate derivative of L-phenylalanine ethyl ester .65
   5.3.1.1 Results and discussion ................................ 65
5.4 Inversion of amino acids via diazonium salts..........................71
   5.4.1 Aprotic diazotization of aliphatic amines .....................73
   5.4.2 Diazotization of L-amino acid esters .......................74
   5.4.2.1 Results and discussion ................................ 74
   5.4.2.2 Alternative methods for diazotization of amino acids .......77
5.5 Conclusion ..................................................77
5.6 Experimental ................................................78
   5.6.1 General ............................................... 78
   5.6.2 $N,N$-Benzene-1,2-disulfonimidimide derivative of
        L-phenylalanine ethyl ester ............................ 78
   5.6.3 2,4,6-Triphenylpyridinium salt of phenylalanine ethyl ester .... 79
   5.6.4 2-Azido-3-phenylpropionic acid ethyl ester .................. 79
   5.6.5 2-Chloro-3-phenylpropionic acid ethyl ester .................. 80
   5.6.6 2-Chloropropionic acid ethyl ester ....................... 80
   5.6.7 3-Methyl-2-(toluene-4-sulfonyloxy)-butyric acid ethyl ester .... 81
5.7 References .................................................81
Appendices ..................................................... 83
Preface

This thesis discusses the utility of three nucleophilic substitution methods in stereoselective transformations of chiral amines.

The thesis is divided into five chapters. Chapters 2, 3, and 4 are based on the four appended published articles (Paper I-IV), which are the main sources of details for these three chapters especially the experimental ones.

Chapter 1 summarizes the role of chiral substances on the living system and the methods used to produce pure enantiomers, with emphasis on the procedures used to prepare chiral amines. The importance of chiral amines in organic preparations is briefly presented. A discussion on inversion and stereoselective transformations of various functional groups is provided. Finally, the general methods used in nucleophilic substitution of amines are mentioned.

Results for preparation and nucleophilic substitution of $N,N$-naphthalene-1,2-disulfonylimide derivative of a chiral amine are discussed in Chapter 2. Experimental details for this chapter are presented in Paper I.

Chapter 3 discusses the synthesis of chiral aryl ethers from the $N,N$-naphthalene- and benzene-1,2-disulfonylimide derivatives of chiral amines. Synthesis of authentic reference chiral aryl ethers which were required for chiral analysis of the aryl ethers is also presented in this chapter. Papers II and III are the primary sources of details for this chapter.

Stereochemical outcome of nucleophilic substitution on 2,4,6-triphenylpyridinium salts of chiral amines using azide and hydroxide anions is presented in Chapter 4. Paper IV is the source of details for this chapter.

The utility of the $N,N$-disulfonylimides and the 2,4,6-triphenylpyridinium cations in inversion of $\alpha$-amino acids is discussed in Chapter 5. Diazotization of $\alpha$-amino acids esters using alkyl nitrite in aprotic solvents is summarized. Since the information presented in this chapter has not been published experimental details are also included.
Acknowledgements

The work reported in this thesis was carried out at the Department of Chemistry, Norwegian University of Science and Technology (NTNU) from January 1998 to September 2001. Financial support from the Quota Program is gratefully acknowledged.

I am greatly indebted to my supervisor Assoc. Prof. Anne Fiksdahl for her never ending encouragement and enthusiasm.

I am also indebted to all colleagues at the Department of Organic Chemistry, NTNU. Special thanks to Prof. Per Carlsen for his extended assistance and supervision when my supervisor was on sabbatical leave in Australia.

I would like to thank Ph.D students Ingrid Sletvold and Molla Endeshaw for reading through this thesis, finding the small errors and giving helpful suggestions.

I owe special debt of gratitude to my family Talhiyah, Sumayyah, Ummulkhayr, Ahmad and the little Hanaan for my apparently endless neglect.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin converting enzyme</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2′-bis(diphenylphosphino)-1,1′-binaphthyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DABN</td>
<td>2,2′-diamino-1,1′-binaphthyl</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIPAMP</td>
<td>2,3-(bis(diphenylphosphino)-butane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-NN,N-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>L-Dopa</td>
<td>3-(3,4-dihydroxyphenyl)-L-alanine</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>M.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>mmol</td>
<td>millimoles</td>
</tr>
<tr>
<td>Ms</td>
<td>mesyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Ns</td>
<td>nosyl</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PPY</td>
<td>4-pyrroldinopyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>SSI</td>
<td>solvent separated ion pair</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIP</td>
<td>tight ion pair</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tol</td>
<td>toluene</td>
</tr>
<tr>
<td>TPP</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
</tr>
</tbody>
</table>
List of papers


1 Introduction

1.1 Background

Optically active compounds pervade many areas of our daily life. They are active ingredients of many pharmaceuticals, agrochemicals, flavours and fragrances. Indeed the essential components of life itself: proteins, carbohydrates, and other biomolecules are constructed from optically active building blocks. It is not surprising then that many synthetic chemists find the challenge of preparation of single enantiomers of chiral molecules both interesting and rewarding.

Since the pioneering work of Pasteur1 in the middle of the nineteenth century there has been continuing efforts in developing efficient methods for the synthesis of single enantiomers of chiral molecules. In recent times the increasing awareness of the importance of chirality in the context of biologically activity has stimulated an increasing demand for efficient methods for the industrial synthesis of homochiral compounds. This has led to a rapid development of asymmetric synthetic and biotechnological methods for the preparation of homochiral compounds in the last two decades. A number of elegant and impressive asymmetric procedures have been developed in this period2-6. However, for industrial production of homochiral compounds methods based on optical resolution are still among the most important and more profitable means7-10. On the other hand resolution methods suffer from the disadvantages of low yields caused by the loss of at least 50% of the undesired isomer when starting from racemic mixtures. Overall yield of resolution methods can be improved by repeated racemization and resolutions or more elegantly by dynamic resolution or in situ inversion of configuration of the unwanted enantiomer.

There are several existing methods for inversion and stereoselective transformations of chiral alcohols11-15, halides16-18, epoxides19-22, and other high value chiral synthons. However, corresponding methods for inversion and stereoselective transformations of chiral amines has not received the same attention as compounds with other functional groups. This has prompted endeavors to investigate suitable methods for inversion of chiral amines in Dr. Fiksdahl's laboratory at the Norwegian University of Science and Technology (NTNU) since the beginning of the last decade23-28. Most of these methods involve stereoselective nucleophilic displacement on activated derivatives of the
Chapter 1: Introduction

amines. The content of this thesis constitute a part of this project and describes some of the nucleophilic substitution methods which have recently been developed in this on going efforts on transformations of chiral amines.

Before proceeding to stereoselective transformations of amines in Chapters 2-5, the rest of this chapter will present a brief account of the impact of chiral substances on the living system and the necessity of preparing them. The existing methodologies used to produce pure enantiomers will be summarized, with emphasis on the methods used to prepare chiral amines. Furthermore, a brief discussion on inversion and stereoselective transformations of various functional groups will be provided. Finally, the general methods utilized in nucleophilic substitution of amines will be mentioned. Prior to this is the definition of chiral amines as used in this thesis and the importance of these compounds in organic preparations.

1.2 Chiral amines

Chiral amines is an important class of organic compounds because they are extensively used in asymmetric synthesis and are incorporated in a number of bioactive molecules. This section will cite some examples on the use of chiral amines in organic synthesis.

1.2.1 Definition

Chiral amines reported in this thesis refer to enantiomerically pure amines bearing a stereogenic carbon at the $\alpha$-position to the amino functionality (Figure 1.1).

$$\begin{align*}
\text{R}_1 & \quad \text{NH}_2 \\
\text{R}_2 & \\
* & \text{= stereogenic center (R or S)} \\
\text{R}_1, \text{R}_2 & \text{= alkyl or aryl}
\end{align*}$$

Figure 1.1 A chiral amine.
1.2.2 Uses of chiral amines

Enantiomerically pure amines play an important role in stereoselective organic synthesis. They are used as resolving agents, chiral auxiliaries and as building blocks in pharmaceuticals and other important bioactive molecules\textsuperscript{29-38}. Representative examples of chiral amines which are widely used in organic preparations are shown in Figure 1.2. Chiral 1-arylethylamines such as 1 and their analogues, example 2 are often used as chiral auxiliaries\textsuperscript{34} and as resolving agents\textsuperscript{9,29}. They are also used in the preparation of various bioactive molecules for instance compounds 7 and 8 (Figure 1.3)\textsuperscript{37,38}. \(\alpha\)-Amino acids such as L-proline (3) constitute a special class of chiral amines and are composing the main part of the chiral pool. The use of these compounds in enantioselective synthesis of pharmaceuticals, agrochemicals and several interesting natural products has been complied\textsuperscript{31}. Another important group of chiral amines are the quinuclidine family, for example the chiral 3- aminoquinclidine (4) is an important intermediate in the synthesis of the 5-HT\textsubscript{3} serotonin ligands\textsuperscript{39,40}, such as zacopride (10) (Figure 1.3). An additional category of chiral amines are the enantiomerically pure vicinal diamines such as 5 which are incorporated in various chemotherapeutic agents\textsuperscript{41,42}. Enantiomerically pure vicinal diamines and their derivatives are used increasingly in asymmetric synthesis as chiral auxiliaries or as metal ligands\textsuperscript{33}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chiralamines.png}
\caption{Kinds of enantiomerically pure amines.}
\end{figure}

Chiral amino functionality is found in several pharmaceutical important compounds with varying chemotherapeutic properties. Figure 1.3 depicts some of these compounds.
Chapter 1: Introduction

Figure 1.3 Pharmaceutical compounds containing chiral amino group.

6: Paclitaxel (Anticancer)

7: Labetalol (β-Blocker)

8: NPS R-568 (Calcium receptor agonist - Clinical trial phase II)

9: Enalapril (ACE inhibitor)

10: (S)-Zacopride (5-HT₃ agonist)

11: (S)-Dexfenfluramine (Antiobesity)

12: Ampicillin (Antibiotic)

13: Chloroamphenicol (Broad spectrum antibiotic)

14: Saquinavir (Protease inhibitor)
1.3 Chirality and its consequences

The interest in chirality and its consequences has raised increasing expectations in the last two decades due to ethical, scientific and economic reasons. This section discusses consequences of chirality on the living system and its scientific and economic implications.

1.3.1 Chirality and bioactivity

Chirality is a prominent feature of most biological systems. As a consequence, metabolic and regulatory processes mediated by biological systems are sensitive to stereochemistry. Different responses can often be observed when comparing the activities of a pair of enantiomers of a chiral bioactive compound which interact with the living system. There is a broad range of examples where the stereoisomers of drugs show differences in terms of their bioavailability, distribution, metabolic and excretion behaviour, and where stereochemical parameters have a fundamental significance in their action and disposition in biological systems\(^{43,44}\). This implies that when a given racemic mixture is administered as a drug both enantiomers should not have to be equally potent. In fact, very often one of them represents the more active isomer for a given action (the eutomer), while the other one (the distomer) might be even active in a different way, contributing to side effect, displaying toxicity, or acting as an antagonist\(^{43,45-47}\). Thus when a chiral drug interact with a biological system the following possibilities exist:

1. The distomer shows no serious side effect
2. The distomer exhibits an undesirable side effect
3. Both isomers have independent therapeutic value

It is common for the first situation to prevail. For example, in the case of the β-blockers such as 15-17 (Figure 1.4), the activity resides almost entirely to the (S)-enantiomers and the (R)-isomers, the distomers, are completely inactive and exhibit no side effect\(^{48}\).
Chapter 1: Introduction

Figure 1.4 The eutomers of some β-blockers.

Distomers which cause serious side effects that are not characteristics of the eutomers have also been reported in some cases. For example the (S)-enantiomer of ketamine (18) (Figure 1.5) is an effective anesthetic agent while its distomer, the (R)-enantiomer, is a hallucinogen. Another example is the antiarthritis agent, penicillamine (19) (Figure 1.5), whose distomer, the (R)-enantiomer, is mutagenic.

Figure 1.5 Chiral drugs whose distomer exhibit undesirable side effect.

Cases which represent the third situation are also known. Both enantiomers of propoxyphene (20) (Figure 1.6) have useful, but different biological activities. The D-isomer (Darvon) 20a is an analgesic, whereas the antipode, the L-isomer (Novrad) 20b exhibit antitussive effect but no analgesic properties.
Due to the potential problems related to the use of a racemate, chiral considerations should therefore be integral parts of drug research and development and the regulatory process. The phenomenon of enantioselectivity in biological action is not restricted to pharmaceuticals, but is a characteristic of all biologically active agents, including agrochemicals, flavours and fragrances. Therefore, stereochemistry has to be considered when studying all xenobiotics.

1.3.2 Scientific implications

Although pharmacokinetic and pharmacodynamic differences between the enantiomers of a chiral drug have been known or suspected for many years, racemate drugs have frequently been developed and approved without clinical and pharmacological consideration of their chiral components. In the middle of 1980s, the technology to isolate, prepare and detect pure enantiomers of racemate drugs became available. This advancement in chiral technology and the ability to produce enantiomerically pure compounds at industrial scale has created new demands on both pharmaceutical firms and regulatory agencies. The health and regulatory authorities have defined more strict requirements to patent new racemic drugs. They currently demand full documentation of the separate pharmacodynamic and pharmacokinetic profiles of the individual enantiomers as well as the racemates\textsuperscript{51-53}.

Apart from pharmaceutical industry, chirality has found various applications in the fields of agrochemicals and crop protection where the presence of a distomer just contributes to increase the levels of pollution without any benefit on the desired action. Furthermore, chirality has opened new avenue in food and clinical research. For example, the detection of D-amino acids in food is needed to assess the factor that influence their formation, biological function, safety and role, since they become part of our diet\textsuperscript{54}. In the clinic, a number of chiral
markers are used in diagnosis of diseases\textsuperscript{55}. Another interesting application of chirality is in the field of archeology where measurements of the degree of racemization of specific amino acids are used to date the age of human remains\textsuperscript{56}.

### 1.3.3 Economic consequences

Beside the ethical and environmental reasons for developing homochiral compounds, financial benefits single enantiomer type products might bring to a pharmaceutical or chemical firm is another convincing reason for development of homochiral ingredients. Single enantiomer drug sales show a continuous growth worldwide (21\% sales increment from 1997 over 1996) and many of the top-selling drugs are marketed as single enantiomers (54\% of the top 500 drugs)\textsuperscript{57,60}. Furthermore, development of single enantiomer drugs has opened a new market strategy, the so called chiral switches\textsuperscript{47,61}. These are chiral drugs that are already approved as racemates, but have been redeveloped and launched as single enantiomers. The increasing demand of homochiral compounds in pharmaceutical industry has also stimulated the development of new and more specialized companies in asymmetric synthesis providing enantiomerically pure substances, synthetic intermediates and catalysts\textsuperscript{62,63}. Simultaneously, biotechnology and biocatalysis are rapidly expanding fields to produce and to purify chiral intermediates\textsuperscript{64,65}.

### 1.4 Sources of pure enantiomers

Basically there are three major sources of enatiomerically pure compounds (Figure 1.7). These sources are:

- a. Chiral pool
- b. Resolution methods
- c. Asymmetric synthesis

The following sections will briefly discuss each of these sources citing examples focused on preparation of compounds containing chiral amino functionality.
1.4.1 Chiral pool

Chiral pool refers to the enantiomerically pure compounds available from natural sources. These include natural amino acids, terpenes, carbohydrates and alkaloids. Enantiomerically pure products that are readily available because they are chemically produced on a large scale, for example (R)-phenylglycine and (S)-malic acid, are also considered as part of the chiral pool. Compounds from a chiral pool can be transformed into a synthetic product either with retention or inversion of configuration. Several compounds containing the chiral amino functionality are obtained from the chiral pool. For example Cinchona alkaloids such as quinine (21) (Figure 1.8) which have various use in asymmetric synthesis\textsuperscript{66}, are isolated from the bark of the cinchona tree. These compounds are also potent antimalarial agents\textsuperscript{67}. Another example are the $\beta$-lactam antibiotics such as penicillin G (22) (Figure 1.8) which are obtained from microbial fermentation\textsuperscript{68}. Natural amino acids is another class of chiral amines harvested from the chiral pool\textsuperscript{69}.
Chapter 1: Introduction

1.4.2 Resolution methods

Racemates can be resolved into their enantiomers via three methods:

a. Kinetic resolution
b. Resolution by entrainment (preferential crystallization)
c. Crystallization of diastereomeric salts (classical resolution)

When resolution methods are used for drug manufacture maximum theoretical yield can never exceed a limit of 50%. Therefore, the use of the unwanted isomer, raises both economic and environmental concerns. This disadvantage may be overcome by dynamic resolution, stereoinversion or other deracemization techniques (see section 1.4.5).

1.4.2.1 Kinetic resolution

In this process the resolution is effected by converting one of the two enantiomers of the racemate into another compound. The success of this method relies on the difference in the rate of conversion of the racemate two isomers by a chiral entity. The chiral addend may be a chemical or a biocompound, and from an economic point of view it should be used in catalytic amount. Biocatalysts are particularly adept at this and have led to several important industrial processes. Among the six main groups of enzymes hydrolases and oxidoreductases are the most frequently used biomolecules in kinetic resolutions. For example, natural amino acids are produced in industrial scale using hydrolases. In this process the acylases hydrolyze racemic amides stereoselectively to give enantiomerically pure α-amino acids (Scheme 1.1).
Sources of pure enantiomers

Scheme 1.1  Kinetic resolution of α-amino acids.

Simple amines are also prepared using hydrolytic enzymes, Klibanov and his coworkers resolved a number of racemic amines, for example 1-(1-naphthyl)ethylamine (23) and α-methyltryptamine (24) (Figure 1.9), with high ee using a protease, subtilisin Carlsberg.

Figure 1.9  Examples of amines resolved by hydrolytic enzymes.

Kinetic resolution using chiral chemical catalysts is less well established in the synthesis of homochiral amines. However, some procedures have been reported, typical example is the recent reported non-enzymatic resolution of L-arylethylamines using a planar-chiral DMAP derivative, (-)-PPY (25) (Figure 1.10).

Figure 1.10  Catalyst for chemocatalytic kinetic resolution of L-arylethylamine.
1.4.2.2 Preferential crystallization

It is a method where a supersaturated racemic solution is seeded by one isomer which then crystallizes out preferentially\(^9\). It is technically feasible only with racemates which are conglomerates. These mixtures compose less than 10% of all racemates\(^9\). An application of preferential crystallization is found in manufacture of \(\alpha\)-methyl-L-dopa\(^75\) and chloroamphenicol\(^76\) intermediates, 26 and 27 respectively (Figure 1.11). The chance for a particular racemate to be a conglomerate is increased by salt formation with achiral acids or bases. The occurrence of conglomerates among salts is about 2-3 times higher than that of covalent compounds\(^9\). Nohira and his coworkers\(^77\) utilized this technique to resolve \(\alpha\)-methylbenzylamine (1) (Figure 1.2) and 1-phenyl-2-(\(p\)-tolyl)ethylamine (28) (Figure 1.11) via their cinnamic acid salts. \(\alpha\)-Amino acids are also resolved via these protocols\(^78,79\).

![Figure 1.11](image)

**Figure 1.11** Examples of amines resolved by preferential crystallization.

1.4.2.3 Resolution via diastereomer crystallization

Diastereomer crystallization is a method which utilizes an enantiomerically pure acid or base (the resolving agent) which forms diastereomeric salts with the racemate. Pure enantiomers are then obtained by selective crystallization of the diastereomeric salts. Although classical resolution is the oldest resolution process, it is still the most extensively used method for preparation of pure enantiomers. This method is widely used for the synthesis of pure enantiomers of amines\(^29,80\). For example, the Chiron Laboratories in Trondheim\(^23\) has developed a method for isolation of (\(R\))-29 from the racemic mixture of 1-methyl-3-phenylpropylamine (29) (Scheme 1.2).
1.4.3 Asymmetric synthesis

Asymmetric synthesis is referred as enantioselective conversion of a prochiral substrate to an optical active product using a chiral addend via asymmetric step. Asymmetric methods for the preparation of chiral amines have recently been reviewed\textsuperscript{34,35,81}. They are mainly involving 1,2-addition of nucleophiles to a C=N bond of imines. The asymmetric addition in these methods is achieved by incorporating the chirality information in the carbonyl part (R\textsubscript{1}) or the amine part (R\textsubscript{2}) of the imino substrate S. Alternatively, the chiral information is obtained from the nucleophilic reagent (R\textsubscript{3}) (Scheme 1.3)\textsuperscript{34}. Asymmetry could also be induced via external chiral ligand integrated in a chiral catalyst\textsuperscript{35}. 

\textit{Scheme 1.2 Optical resolution of racemic 1-methyl-3-phenylpropylamine (29).}
Another asymmetric method employed in the preparation of chiral amines is asymmetric hydrogenation of enamide intermediates using chiral catalysts. An example is the Monsanto asymmetric hydrogenation of compound 30 in the synthesis of L-Dopa intermediate 31 using rhodium diphosphine catalyst, DIPAMP (CHIRAPHOS) (Scheme 1.4)\textsuperscript{82}.

In theory the yield of asymmetric synthesis can be 100% because the unwanted isomer is not produced.

1.4.4 Resolution versus asymmetric synthesis

Since asymmetric synthesis has a theoretical yield of 100\%, it would seem to be a method of choice for synthesis of homochiral compounds over resolution processes which have a maximum theoretical yield of only 50\%. However, this is often counterbalanced by cheaper raw materials or simpler methods employed in resolution processes. Furthermore, resolution methods have an advantage that the enantiomeric excess of the remaining substrate can be turned to any required value simple by adjusting the degree of conversion\textsuperscript{10,70}. Therefore with regard to the method of choice there is no simple all including answer. As has been pointed out by Sheldon\textsuperscript{48}, the only golden rule is to plan your resolution early in order to avoid the 50\% isomeric ballast through the whole synthetic process.
1.4.5 Deracemization techniques

As described earlier, resolution methodologies are among the effective means for the production of enantiomerically pure compounds. However, these methods are obstructed by some disadvantages for practical applications. The most obvious limitation of resolution methodologies is that the theoretical yield cannot exceed the maximum of 50%. Therefore, any procedure that can directly convert a racemate to a single enantiomer is highly advantageous. These processes are generally known as ‘deracemization’ and are divided in three general categories:\(^3\): a) repeated racemizations and resolutions, b) dynamic kinetic resolution and c) enantioselective stereoinversion.

1.4.5.1 Repeated racemization and resolutions

The loss of half of the substrate in resolution processes could be avoided by racemization of the unwanted isomer after separation from the desired enantiomer and subjecting it again to resolution in the next cycle. This process can be repeated until all of the racemic material has virtually been converted to a single enantiomer. The overall yield of the desired isomer can reach a value of more than 95% after only few cycles when both racemization and resolution processes proceed without loss of the material\(^5\). Racemization can be achieved by several methods, but the most important industrial methods are acid- or base-catalyzed and thermal racemizations\(^4\) (Scheme 1.5).

The base catalyzed procedure is the most widely used process for racemization of secondary chiral amines and alcohols. It is applicable to all compounds bearing an acidic hydrogen at the stereogenic center and is achieved via achiral enolate type intermediates (Scheme 1.5). On the contrary, the acid catalyzed process is limited to only few substrates due to its restriction to compounds capable of keto-enol tautomerism. Heat labile chiral compounds such as those possessing axial chirality, for example DABN (32) (Scheme 1.5), can be racemized through rotation around a \(\sigma\)-bond and are viable substrates for thermal racemization.

Most of the racemization techniques suffer from the disadvantage that they require harsh reaction conditions leading to side reactions and loss of materials.
1.4.5.2 Dynamic kinetic resolution

Dynamic kinetic resolution is another important process for avoiding the disadvantages of kinetic resolution. Basically, this process is kinetic resolution which is combined with \textit{in situ} racemization of the unwanted isomer\textsuperscript{85-87}. In this process all of the racemic substrate ($R$+$S$) is eventually converted to the desired enantiomer, for instance ($R$)-P (Scheme 1.6) in 100\% theoretical yield. For dynamic kinetic resolution to be effective the rate of racemization $K_{\text{rac}}$ should be greater than the rate of resolution $K_{R}$\textsuperscript{86}. 

\begin{align*}
\text{Scheme 1.5} & \quad \text{Pathways for racemization.} \\
\text{Scheme 1.6} & \quad \text{Dynamic kinetic resolution.}
\end{align*}
The *in situ* racemization in dynamic kinetic resolution is usually achieved via acid or base catalyzed processes\textsuperscript{88-90}. However, these reagents cannot be used for *in situ* racemization when resolution is performed using a biocatalyst due to incompatibility of enzymes with these media. Under these circumstances the resolution process is combined with bio-compatible *in situ* racemization techniques. Typical examples include dynamic resolution of sec-alcohols\textsuperscript{91,92} and amines\textsuperscript{93} using enzymes combined with transition metals (Scheme 1.7 and 1.8).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme1_7.png}
\end{center}

\textit{Scheme 1.7} Dynamic resolution of sec-alcohols via lipase and Ru-catalysis.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme1_8.png}
\end{center}

\textit{Scheme 1.8} Dynamic resolution of 1-phenylethyamine (I) via lipase and Pd/C catalysis.

\subsection{1.4.5.3 Stereoinversion}

Substrates possessing configurationally stable stereogenic centers are difficult to racemize, hence are not amenable to dynamic kinetic resolution. In such cases the deracemization may be afforded by the so-called stereoinversion\textsuperscript{82}. In this scenario the unwanted enantiomer is inverted *in situ* to achieve the desired isomer in 100% theoretical yield. This strategy may be achieved via chemical or biocatalytic methods\textsuperscript{94-97}. In the former, the racemic substrate is subject to kinetic resolution followed by chemical inversion of the unwanted isomer without separation of the resolution products\textsuperscript{94,95} (Scheme 1.9). The latter involve *in situ* oxidation-reduction reactions using redox enzymes\textsuperscript{97} (Scheme 1.10). Once again,
most of the stereoinversion methods are dealing with \textit{in situ} inversion of alcohols and no attention has been focused on inversion of chiral amines.

\begin{center}
\textbf{Scheme 1.9} Stereoinversion using chemical compounds.
\end{center}

\begin{center}
\textbf{Scheme 1.10} Enzyme catalyzed stereoinversions.
\end{center}

\section*{1.5 Stereoselective transformations}

As noted earlier in section 1.1 and 1.4.5.3 there are several methods for inversion and stereoselective transformations of various functional groups. This section will give a brief discussion of the existing methodologies for inversion and stereoselective transformations of some of the important chiral synthons. These include alcohols, halides, epoxides and amines.

\subsection*{1.5.1 Inversion of halides}

Halides are frequently used as substrates in numerous stereochemical transformations. They are easily substituted by various nucleophiles via $S_{N2}$ processes giving products with inversion of configuration at the stereogenic center (Scheme 1.11)\textsuperscript{16,17,98}.


1.5.2 Transformations of alcohols

Alcohols can undergo stereospecific displacements with either inversion or retention of configuration at a stereogenic center depending on the conditions of the reaction. Chiral alcohols have been halogenated with complete retention of configuration using thionyl halides\(^9\). On the other hand nucleophilic substitution on sulfonate derivatives of alcohols is one of the straightforward methods for inversion of alcohols, often with high chemical and stereochemical yields\(^1,2,96\). The most famous method for inversion and stereoselective transformation of alcohols is the Mitsunobu reaction. In recent years this reaction has experienced a wide range of new and creative applications in asymmetric synthesis of several compounds\(^13\). In this process an alcohol is inverted to a compound with a different functional group using DEAD and TPP (Scheme 1.12).

![Scheme 1.12 The Mitsunobu reaction.](attachment:image.png)

1.5.3 Inversion of epoxides

Homochiral epoxides are extensively used in the synthesis of chiral compounds due to their ability to react with various nucleophiles (Scheme 1.13). The utility of these intermediates in asymmetric synthesis has triggered enormous efforts on development of catalytic methods for their production\(^100\). The nucleophilic epoxide ring-opening reactions are both regio- and stereoselective and have been achieved using both chemo- and biocatalysts\(^20\).
Chapter 1: Introduction

Scheme 1.13 Nucleophilic substitution of epoxides.

1.5.4 Stereoselective transformations of amines

Apart from conversion of amino acids to \( \alpha \)-halo and \( \alpha \)-hydroxycarboxylic acids with retention of configuration via diazotization reactions\(^{101}\), little has been done on stereoselective transformations of chiral compounds containing the amino group at a stereogenic center. However, in recent years Dr. Fiksdahl and her co-workers at the Norwegian University of Science and Technology (NTNU) have developed some methods for inversion and stereoselective transformations of chiral amines\(^{23-28}\). Most of these methods involve nucleophilic substitution of \( N,N \)-disulfonylimide derivatives of the amines (Scheme 1.14). Dr. Fiksdahl’s research has witnessed various expansions and modifications since its inception in early 1990’s and is still active in her laboratory. The content of this thesis constitutes a part of this project and describes some of the recent developments in this continuing investigations.

Scheme 1.14 Inversion of amines via \( N,N \)-disulfonylimides.
1.6 Nucleophilic substitution of amines

Although methods for the activation of hydroxyl groups for substitution are numerous and well documented, analogous functionalization of amines is considerably more difficult primarily because most nitrogen anions are relatively strong nucleophiles, and consequently, poor leaving groups. However, studies by Baumgarten and DeChristopher\textsuperscript{102,103} in 1960’s showed that this problem could be approached by using the anions of \(N,N\)-disulfonylimides (Scheme 1.15).

![Scheme 1.15 Nucleophilic substitution of amines via \(N,N\)-disulfonylimides.](image)

Two decades later Katritzky\textsuperscript{104} demonstrated the utility of triarylpyridinium salts in transformations of aliphatic amino groups to compounds with other functionalities via nucleophilic substitution reactions (Scheme 1.16).

![Scheme 1.16 Nucleophilic substitution of amines via triarylpyridinium salts.](image)

Information regarding successful use of the \(N,N\)-disulfonylimides and the triarylpyridinium salts in substitution of amines is generally fragmented in the literature\textsuperscript{105-111}. However, to the best of our knowledge, apart from investigations conducted in Dr. Fiksdahl’s Laboratory, these leaving groups have never been employed in studies towards inversion of chiral amines. Among the aims of the present study is therefore to investigate the utility of these leaving groups in stereoselective transformations of chiral amines including the natural L-\(\alpha\)-amino acids.

Amines could also be transformed via diazonium salts. The use of these intermediates is of little interest for organic synthesis, because they often lead to mixtures of substitution products as well as elimination and rearrangement.
products\textsuperscript{112}. However, there are few exceptions, such as the retentive hydroxy- and halo-deamination of \(\alpha\)-amino acids\textsuperscript{101} (Scheme 1.17).

![Scheme 1.17 Nucleophilic substitution of \(\alpha\)-amino acids via diazotization reactions.](image1)

Extension of this process by three more steps (Scheme 1.18) is an established procedure for preparation of D-\(\alpha\)-amino acids and their derivatives by inversion of the naturally occurring L-\(\alpha\)-amino acids\textsuperscript{11,113}. Although this sequence gives products with complete inversion of configuration, the overall yield is depleted due to a large number of steps involved in the whole process. Studies aimed to obtain D-\(\alpha\)-amino acids by direct inversion of L-\(\alpha\)-amino acid diazonium salts in a single step are therefore highly advantageous. Investigations towards this goal are reported in Chapter 5 of this thesis.

![Scheme 1.18 Inversion of amino acids via diazotization: a) \(\text{NaNO}_2/\text{H}^+\), b) \(\text{K}_2\text{CO}_3/\text{R}_1\text{I}\), c) \(\text{XCl}\).](image2)

References


22
References

69. Aida, K., Chibata, I., Nakayama, K., Takinami, K., Yamada, H. (Eds.) *Bio-


84. Ebbers, E. J., Ariaans, G. J. A., Houbiers, J. P. M., Bruggink, A., Zwanen-


Chapter 1: Introduction

2 Preparation of inverted amines and alcohols via \(N,N\)-disulfonylimides

2.1 Introduction

The resolution of racemates is probably the most current approach to the synthesis of homochiral compounds. Enantiomerically pure amines and alcohols are among the most important synthons for the preparation of chiral drugs and agrochemicals. Their resolution by enzymatic or non-enzymatic catalysts is abundantly documented. However, resolution methods suffers from disadvantages of low yields caused by the loss of at least 50% of the undesired isomer when starting from racemic mixtures. As a consequence, methods able to improve the overall yields of resolution processes, such as inversion of the unwanted isomer, are highly advantageous. As described in Chapter 1 there are several existing methodologies for inversion and other stereochemical manipulations of chiral alcohols and compounds with other functionalities, while little has been done on inversion of chiral amines. This has prompted us to embark on investigations aimed on stereoinversion of chiral amines.

2.2 Previous investigations

The project on stereoselective transformations of chiral amines was started in Dr. Fiksdahl’s laboratory at NTNU almost a decade ago. The main strategy adapted by then was to convert the amino functionality into a good leaving group, and develop a method which will replace it stereoselectively via a nucleophilic substitution reaction (Scheme 2.1).

\begin{align*}
\text{NH}_2 & \quad \rightarrow \quad \text{NX}_2 \\
\text{Nu} & \quad \rightarrow \quad \text{Nu}
\end{align*}

\textit{Scheme 2.1 Stereoselective transformation of amines.}
Chapter 2: Preparation of inverted amines and alcohols via N,N-disulfonylimides

Initial investigations were carried out using N,N-disulfonylimides. The utility of N,N-disulfonylimides (Scheme 2.2) in nucleophilic substitution of amines was first studied by Baumgarten and DeChristopher\textsuperscript{1,2} in 1960’s. In those preliminary studies and in succeeding investigations\textsuperscript{3-5} the N,N-disulfonylimide group could be substituted by a number of nucleophiles. However, these investigations were never focused on the stereochemical outcome of the substitution reaction.

Scheme 2.2 Substitution of amines via N,N-disulfonylimides.

Our group was thus interested in using the N,N-disulfonylimide derivatives of amines in an effort to transform chiral amines from one configuration to the other. Consequently, N,N-ditosyl-, N,N-dimesyl-, and N,N-dinosyl-imide derivatives of chiral amines 33-38 (Figure 2.1) were prepared, and stereoselectively substituted using azide and hydroxide anions giving products with inversion of configuration\textsuperscript{6-10}. The results obtained from these investigations were very satisfying. The substitution products prepared from compounds 33-38 showed a degree of inversions ranging between 82 and 100% (Table 2.2). Apparently, the use of N,N-disulfonylimides is one of the best methods for inversion and stereoselective transformations of amines. However, some disadvantages such as long reaction times and other unfavorable reaction conditions prompted endeavours to search for a more versatile procedure for inversion of amines as discussed in the rest of this chapter.

Figure 2.1 Previously studied N,N-disulfonylimides.
2.3 Preparation and nucleophilic substitution of cyclic aryl disulfonylimides

2.3.1 Previous work

Cyclic aryl disulfonylimides have long been recognized as attractive synthetic tools in substitution of amines\(^\text{11}\). The cyclic nature of these compounds is believed to substantially stabilize the negative charge on the imide anion, making it a poor nucleophile, and hence a good leaving group. Initial trials on this hypothesis by Henrickson and coworkers was disappointing. The cyclic intermediates were difficult to prepare and were found to be surprisingly inert in subsequent transformations\(^\text{11}\). Later modifications by Davis\(^\text{12}\) produced more interesting results, the derivatives were synthesized in high yields. Moreover, the nucleophilic displacement reactions were reported to be successful. Although Davis’s work was focused on preparation of fluorinating agents (Scheme 2.3) and not entirely related to alkylamines sulfonylimides, nonetheless, the cyclic \(N,N\)-disulfonylimides were shown to be more facile leaving group than the traditional non-cyclic \((\text{ArSO}_2)\_2\text{N}\)-group.

![Scheme 2.3 Preparation of fluorinating agents using arylsulfonamides.](image)

More recently, Carlsen\(^\text{13}\) from this university has re-investigated this procedure and found that cyclic aryl disulfonylimide is a facile and useful leaving group in nucleophilic substitution of amines. Carlsen’s modification was more appealing, as was directly connected to alkylamines and the cyclic disulfonylimide intermediates were synthesized in high yield. Furthermore, the displacement reactions were afforded at milder conditions compared to substitution of non-cyclic \((\text{ArSO}_2)\_2\text{N}\)-group. It was therefore decided to study the effectiveness of this method in inversion of chiral amines. Initial investigations were carried out using \(N,N\)-benzene-1,2-disulfonylimides as a leaving group. As predicted, the C-N bonds in \(o\)-benzenedisulfonylimides 43 and 44 (Scheme 2.4) were indeed weak, the \(N,N\)-disulfonylimide group was displaced at very mild conditions\(^\text{14}\). In addition, the substitution reaction proceeded stereoselectively giving products with inversion of configurations. However, stereoinversion of this reaction was a
little lower than that of the ditosylimides. Nevertheless, some improvement in
the reaction conditions, in both the synthesis and substitution of the \( N,N \)-
benzene-1,2-disulfonylimides prompted further investigations of the cyclic aryl
disulfonylimides.

2.4 Preparation and nucleophilic substitution of
\( N,N \)-1,2-naphthalenedisulfonylimide derivative
of (S)-1-phenylethylamine

Attempts to improve the degree of inversion in stereoselective transformation of
amines using cyclic aryldisulfonylimides resulted to the synthesis of \( N,N \)-1,2-
naphthalenedisulfonylimide derivatives of chiral amines. It was argued that this
group will diffuse the negative charge on the nitrogen anion more effectively
compared to its benzenedisulfonylimide analogue. This will in turn, decrease
further the nucleophilicity of the \( N,N \)-disulfonylimide anion and consequently,
increase its leaving group ability.

Initial test of this presumption was conducted on \( N,N \)-1,2-naphthalenedisulfonylimide derivative of the chiral amine, (S)-\( \alpha \)-
methylbenzylamine (50) which was prepared from naphthalene-1,2-disulfonyl
chloride (49) (Scheme 2.5). The leaving group ability of the \( N,N \)-disulfonylimide
moiety in this intermediate was studied by nucleophilic attack using potassium
nitrite and sodium azide, forming the corresponding alcohol 45 and azide 47
products (Scheme 2.10). The stereochemistry of the substitution reactions will be
discussed and compared with previous reported results for a series of \( N,N \)-
disulfonylimides6-10,14.

\[ \text{Scheme 2.4 Inversion of amines via } N,N\text{-benzene-1,2-disulfonylimides.} \]
Experimental details for the preparation and nucleophilic substitution of the \( N,N\)-1,2-naphthalenedisulfonylimide \( 50 \) are presented in Paper I.

### 2.4.1 Results and discussion

The cyclic \((S)-N,N\)-1,2-naphthalenedisulfonylimide intermediate \( 50 \) was obtained from \((S)-\alpha\)-methylbenzylamine \( 1 \) and naphthalene-1,2-disulfonyl chloride \( 49 \) in 42% yield (Scheme 2.5) by identical reaction conditions as previously reported for the preparation of \( N,N\)-1,2-benzenedisulfonylimide \( 43 \). The \( N,N\)'-bis-byproduct, the disulfonamide, \( R-NH-SO_2-Ar-SO_2-NH-R, \ 51 \) was also isolated and characterized.

\[
\begin{align*}
\text{NH}_2 \quad \text{SO}_2\text{Cl} & \quad \text{SO}_2\text{Cl} \\
\text{SOC} & \quad \text{S} & \quad \text{O} & \quad \text{O} & \quad \text{O}

\text{NH}_2 \quad \text{SO}_2\text{Cl} & \quad \text{SO}_2\text{Cl} \\
\text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2 & \quad \text{N} & \quad \text{H} & \quad \text{S} & \quad \text{N} & \quad \text{O} & \quad \text{O} & \quad \text{O}

\text{NH}_2 \quad \text{SO}_2\text{Cl} & \quad \text{SO}_2\text{Cl} \\
\text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2 & \quad \text{N} & \quad \text{H} & \quad \text{S} & \quad \text{N} & \quad \text{O} & \quad \text{O} & \quad \text{O}

\end{align*}
\]

**Scheme 2.5** Preparation of \((S)-N,N\)-naphthalene-1,2-disulfonylimide \( 50 \).

The reagent, naphthalene-1,2-disulfonyl chloride \( 49 \) was prepared from the readily available 2-aminonaphthalenesulfonic acid \( 52 \) via a modified Meerwein synthesis\(^{15,16}\) (Scheme 2.6 and 2.7).
Chapter 2: Preparation of inverted amines and alcohols via N,N-disulfonylimides

Scheme 2.6  Synthesis of naphthalene-1,2-sulfonic acid disodium salt (54).

Substitution of the diazonium group by sulfurdioxide in hydrochloric acid, in the second step of this sequence yielded less than 40% of the disulfonic acid sodium salt 54, together with the two expected17 unwanted products 2-hydroxynaphthalenesulfonic acid (55) and 2-chloronaphthalenesulfonic acid (56) (Scheme 2.6). The amount of the byproducts was reduced by replacing concentrated hydrochloric acid with glacial acetic acid.

Compound 54 was converted to naphthalene-1,2-disulfonyl chloride (49) using phosphorous pentachloride (Scheme 2.7).

Scheme 2.7  Preparation of naphthalene-1,2-disulfonyl chloride (49).

Surprisingly, compound 49 was formed in only 10% yield which is relatively low compared to our own experience14 and what has been reported elsewhere18-20. Attempts to optimize percentage yield of this reaction by using modified procedures for the preparation of sulfonyl chlorides from sulfonic acids were not successful. Both Fujita’s21 and Zollinger’s22 techniques (Scheme 2.8) gave high yields of anhydride product 57 with no traces of the disulfonyl chloride 49.
Preparation and nucleophilic substitution of N,N-1,2-naphthalenedisulfonylimide deriv-

Scheme 2.8 Catalytic methods for the synthesis of sulfonyl chlorides.

Tadia’s modification (Scheme 2.9) was also tested, but no reaction took place in this variant. Efforts to utilize the anhydride 57 as a starting material for the synthesis of the disulfonyl chloride 49 was also unproductive.

Scheme 2.9 Preparation of disulfonyl chlorides via sulfonic acid pyridinium salts.

Nucleophilic attack on the (S)-N,N-1,2-naphthalenedisulfonylimide intermediate 50 by potassium nitrite and sodium azide afforded the alcohol 45 and the azide 47 with 60-63% and 60-70% inversion of configuration respectively, (Scheme 2.10, Table 2.1).

Scheme 2.10 Nucleophilic substitution of (S)-N,N-naphthalene-1,2-disulfonylimide 50.
As can be seen from Table 2.1 the mildest reaction conditions for the substitution of the naphthalenedisulfonylimide substrate 50 with both nitrite and azide anions are comparable with the previously reported reaction conditions for the analogous benzenedisulfonylimide 43. Both 50 and 43 are more easily substituted than the corresponding ditosyl-, dimesyl- 36 and dinosyl-imides 38-10. This is particularly apparent at lower reaction temperatures. However, in
Preparation and nucleophilic substitution of \(N,N\)-1,2-naphthalenedisulfonylimide deriv-

contrast to what was observed for the \(N,N\)-1,2-benzenedisulfonylimides \(43\) and 
\(44\) (Scheme 2.4), the degree of inversion of the naphthalenedisulfonylimide \(50\) 
could not be optimized by varying the temperature, the reaction time or the 
solvent. Thus the stereoselectivity in the formation of \(45\) and \(47\) from \(50\) was not 
dependent on the reaction conditions (Table 2.1).

Other oxygen nucleophiles such as hydroxide, acetate and benzoate were used in 
addition to nitrite for the preparation of the alcohol \(45\) (Table 2.1, entry 5-7) 
giving no specific change in stereoselectivity.

The stereoselectivity in the formation of \(45\) and \(47\) from the \((S)\)-\(N,N\)-1,2-
naphthalenedisulfonylimide \(50\) is lower (60-70%) than for the analogous 
previously reported \(N,N\)-1,2-benzenedisulfonylimide \(43\) (Table 2.2, 84-94%). 
This may be explained by participation of the solvent used in the nucleophilic 
substitution reactions. It has previously been observed that DMF reacts as an O-

nucleophile with 1,2-benzenedisulfonylimide \(43\) (Scheme 2.11). Thus heating 
\(43\) in DMF produced the corresponding formate \(59\), presumably due to initial 
attack of DMF forming intermediate \(58\). Nucleophilic displacement of the 
formate \(59\) may produce a stable product, resulting in an overall retention of 
configuration, contrary to the product formed by direct nucleophilic reaction 
with \(43\). The higher stability of naphthalene over benzenedisulfonylimide 
leaving group might increase the possibility of the formation of racemized 
products via this phenomenon.

![Scheme 2.11 Reaction of (S)-\(N,N\),1,2-benzenedisulfonylimide 43 with DMF.](image)

Alternatively, the observed partial racemization may be explained by formation 
of ion-pairs during the substitution reaction. Thus, compound \(50\) may be in 
equilibrium with an initial tight ion-pair, TIP, which might equilibrate with the 
solvent separated ion-pairs, SSI, resulting in partial racemized products (Scheme
Chapter 2: Preparation of inverted amines and alcohols via N,N-disulfonylimides

2.12). For the time being it has not been fully established which of these two mechanisms actually take place. The reaction of 50 carried out in non-nucleophilic solvents, such as tetrahydrofuran and diethyl ether also resulted in partial racemized products. This indicates that the racemization observed in nucleophilic substitution reactions is mainly contributed by the ion-pair mechanism. However, this hypothesis needs to be justified and investigations of the real mechanism of this reaction is currently conducted.

Scheme 2.12 Proposed mechanism for racemization of (S)-N,N-naphthalenedisulfonylimide 50.

The low stereoselectivity in this process may also be caused by low enantiomeric purity of the disulfonylimide which might occur during preparation of this intermediate. The optical purity of this compound could not be obtained by employing several methods used to determine composition of enantiomers. Details of these studies are discussed in section 2.5 below.

2.5 Chiral analysis of N,N-1,2-naphthalenedisulfonylimide derivative of (S)-1-phenylethylamine

Among the methods employed to determine the enantiomeric excess of the (S)-N,N-naphthalenedisulfonylimide 50 was the NMR studies using β-cyclodextrins. 1H-NMR spectra of 1:3 mixture of racemic 50 and heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin at temperatures ranging between +10°C and -50°C showed no discrimination of any proton in compound 50. 13C-NMR studies of this mixture at the same temperature range was not useful either. Experiments using a lanthanide complex, tris(3-trifluoromethylhydroxymethylene-d-camphorato)europium(III), [Eu(tfc)3] (I) (Figure 2.2) was not successful. Other NMR chiral solvating agents such as camphor sulfonic acid (II) and 1,1,2-triphenyl-1,2-ethanediol (III) (Figure 2.2), which was prepared as described by Braun and his colleagues, were also tried, but once again no enantioseparation was observed in these media.
The failure of enantioseparation of compound 50 in these studies is probably due to the large size of this intermediate for inclusion mechanism or the lack of coordination sites at the chiral center in this molecule. The nitrogen lone pair which is supposed to play a major role in coordination with the chiral solvating agents is probably locked in resonance with S=O bond as depicted in Scheme 2.13.

Chiral GLC was not suitable as the disulfonylimide intermediate tends to decompose at high temperatures. The optical purity of 50 could therefore not be certainly established. However, stereoselectivity in nucleophilic substitution of this compound using aroside anions (Chapter 3) was comparable to that of its benzene analogue 43. This is a clue that the partial racemization observed in this study might not be exclusively contributed by the purity of substrate, and other factors should be considered. The mechanistic studies which are currently in progress will probably identify the real source of the partial racemized products.
Chapter 2: Preparation of inverted amines and alcohols via N,N-disulfonylimides

2.6 Comparison between nucleophilic substitution of different N,N-disulfonylimides

A comparison of the N,N-disulfonylimides 33-38, 43, 44 and 50 listed in Table 2.2 shows that only the ditosylimides (-NTs₂, 33, 34) give complete inversion of configuration by nucleophilic substitution independent of benzylic or aliphatic substrates. As expected, caused by the carbocation stabilizing effect, the benzylic substrates 34, 36, 38 and 43 in general give a lower degree of inversion than the corresponding aliphatic substrates 33, 35, 37 and 44. Furthermore, the ditosylimides 33 and 34 have yielded relatively higher yields than the rest of the N,N-disulfonylimides. However, it should be emphasized that these studies have been focused on stereoselectivity of the substitution reactions and no attempts to optimize the substitution yields were made.

Table 2.2: Comparison between nucleophilic substitution of different N,N-disulfonylimides

<table>
<thead>
<tr>
<th>Disulfonylimides (% yield)</th>
<th>Degree of inversion (Optimal reaction conditions) (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol products</td>
<td>Azide products</td>
</tr>
<tr>
<td>33 (50%)</td>
<td>100% (KNO₂, DMF, 120°C, 72 h) (67%)</td>
</tr>
<tr>
<td></td>
<td>100% (NaN₃, DMF, 135°C, 24 h) (98%)</td>
</tr>
<tr>
<td>34 (50%)</td>
<td>100% (as above) (95%)</td>
</tr>
<tr>
<td></td>
<td>100% (as above) (67%)</td>
</tr>
<tr>
<td>35 (32%)</td>
<td>93% (as above)</td>
</tr>
<tr>
<td>36 (41%)</td>
<td>82% (as above) (20-40%)</td>
</tr>
<tr>
<td>37 (17%)</td>
<td>95% (as above)</td>
</tr>
<tr>
<td>38 (23%)</td>
<td>82% (as above) (20-40%)</td>
</tr>
<tr>
<td>43 (47%)</td>
<td>84% (KNO₂, 30% DMF/DMSO, 0°C, 24 h) (50-83%)</td>
</tr>
<tr>
<td></td>
<td>94% (KNO₂, 30% DMF/DMSO, 0°C, 24 h) (35%)</td>
</tr>
<tr>
<td>44 (38%)</td>
<td>90% (KNO₂, DMF, 90°C, 72 h) (10-30%)</td>
</tr>
<tr>
<td></td>
<td>98% (KNO₂, DMF, 80°C, 4 d) (53%)</td>
</tr>
<tr>
<td>50 (42%)</td>
<td>60-63% (independent of reaction conditions) (analytical scale)</td>
</tr>
<tr>
<td></td>
<td>70% (independent of reaction conditions) (analytical scale)</td>
</tr>
</tbody>
</table>
2.7 Conclusion

To summarize, nucleophilic substitution of the $N,N$-1,2-naphthalenedisulfonylimide 50 by potassium nitrite and sodium azide afforded the alcohol 45 and the azide 47 with 60-63% and 60-70% inversion of configuration respectively. Stereoselectivity of these reactions are lower than what has been reported from the study of analogous intermediates, the $N,N$-1,2-benzenedisulfonylimides\textsuperscript{14}. Furthermore, the degree of inversion in the present study does not vary with reaction conditions which contradicts the results of previous investigations on the related intermediates\textsuperscript{14}. Among the so far investigated $N,N$-disulfonylimides, the $N,N$-ditosylimides (-NT$_2$, 33, 34) give the best and complete inversion of configuration independent of benzylic or aliphatic substrates.

References

Chapter 2: Preparation of inverted amines and alcohols via N,N-disulfonylimides

3 Preparation of chiral aryl ethers via cyclic N,N-disulfonylimides

3.1 Introduction

A variety of naturally occurring and medicinally important compounds contain a chiral aryl ether moiety\(^1\)-\(^7\). Among the most important methods for generation of aryl ethers are aromatic substitution and Cu-promoted radical coupling procedures. However, these methods often require harsh and restrictive conditions, and the desired compounds are produced in low yields\(^8\)-\(^10\). Furthermore, most of these techniques are not suitable for the synthesis of optically active products. Another important process for the preparation of alkyl aryl ethers are the Pd-catalyzed procedures developed by Buchwald and his coworkers\(^11\). These processes are believed to be superior alternatives for introduction of alkyl aryl ether moiety in organic compounds. However, these methods are only appropriate for intramolecular coupling of an alcohol and an aryl halide to form cyclic aryl ethers (Scheme 3.1).

\[ \text{Scheme 3.1} \quad \text{Synthesis of cyclic aryl ethers via Pd-catalyzed intramolecular C-O coupling.} \]

An alternative strategy for the preparation of chiral aryl ethers is nucleophilic substitution on aliphatic substrates. The most important method in this category is the Williamson ether synthesis\(^12,13\). This method has been widely applied in the synthesis of ethers, particularly the unsymmetrical ones. However, it suffers from disadvantages of low yields and the use of unfavorable reaction conditions. Moreover, it is not a suitable procedure for the preparation of chiral ethers, because it does not easily permits the use of hindered alcohols. A variant of the Williamson ether synthesis which has effected the synthesis of chiral ethers has
recently been reported by Smith and his coworkers\textsuperscript{14}. This procedure is among
the very few variants of the Williamson reaction since its inception 150 years
ago. Search for another method for preparation of chiral aryl ethers is therefore
of great importance. We have previously shown that \(N,N\)-disulfonylimides are
useful intermediates for the transformation of chiral amines into the
Corresponding alcohols and amines with inverted stereochemistry. We were
interested in using these intermediates in preparation of chiral aryl ethers. In this
chapter the synthesis and analysis of optically active aryl ethers using \(N,N\)-
aryldisulfonylimides derivatives of chiral amines will be described.

3.2 Synthesis of (S)-phenyl and (S)-2-naphthyl
1-phenylethyl ethers from cyclic aryldisulfo-
nylimides

Experimental details for the preparation of the phenyl and 2-naphthyl ethers \textsuperscript{60}
and \textsuperscript{61} (Scheme 3.3) from (S)-\(N,N\)-1,2-benzenedisulfonylimide \textsuperscript{43} and (S)-\(N,N\)-
1,2-naphthalenedisulfonylimide \textsuperscript{50} are presented in Papers II and III.

3.2.1 Results and discussion

The starting material, (S)-\(N,N\)-1,2-benzenedisulfonylimide \textsuperscript{43} and (S)-\(N,N\)-1,2-
naphthalenedisulfonylimide \textsuperscript{50} (Scheme 3.2) were synthesized from (S)-
phenylethylamine (1) and the corresponding benzene- and naphthalene-1,2-
disulfonyl chlorides \textsuperscript{39} and \textsuperscript{49} as described in Chapter 2.

![Scheme 3.2 Preparation of the \(N,N\)-disulfonylimides (S)-43 and (S)-50.](image-url)
Synthesis of (S)-phenyl and (S)-2-naphthyl 1-phenylethylamine ethers from cyclic aryld-

Nucleophilic substitution of the cyclic disulfonylimides (S)-43 and (S)-50 (Scheme 3.3) was accomplished using aroxide anions, prepared by sodium hydride deprotonation of phenol and 2-naphthol, respectively. The aryl ether products 60 and 61 were obtained in 39-68% yield (Table 3.1).

Scheme 3.3 Preparation of chiral aryl ethers from disulfonylimides (S)-43 and (S)-50.

(S)-N,N-1,2-Benzenedisulfonylimide 43 afforded 87 and 79% inversion of configuration for the preparation of ethers 60 and 61 respectively, while 83 and 70% inversion of configuration were observed for the synthesis of 60 and 61 from (S)-N,N-1,2-naphthalenedisulfonylimide 50 (Table 3.1).

Table 3.1: Results for preparation of ethers 60 and 61 from N,N-disulfonylimides (S)-43 and (S)-50

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Nucleophile</th>
<th>Product (yield%)</th>
<th>[α]D (CHCl₃)</th>
<th>Stereoselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-43</td>
<td>PhO⁻</td>
<td>(R)-60 (39)</td>
<td>+ 4.8 (c = 2)</td>
<td>87% inv.ᵃ</td>
</tr>
<tr>
<td>(S)-43</td>
<td>2-NaphthO⁻</td>
<td>(R)-61 (44)</td>
<td>+ 98 (c = 0.2)</td>
<td>79% inv.ᵇ</td>
</tr>
<tr>
<td>(S)-50</td>
<td>PhO⁻</td>
<td>(R)-60 (57)</td>
<td>+ 4.05 (c = 2)</td>
<td>83% inv.ᵃ</td>
</tr>
<tr>
<td>(S)-50</td>
<td>2-NaphthO⁻</td>
<td>(R)-61 (68)</td>
<td>+ 87 (c = 0.2)</td>
<td>70% inv.ᵇ</td>
</tr>
</tbody>
</table>

ᵃEnantiomeric purity of the phenyl ether products (R)-60 was based on chiral GLC.
ᵇEnantiomeric purity of the 2-naphthyl ether product (R)-61 is based on [α]D comparison with authentic enantiomerically pure synthetic standard of (S)-61 prepared via TFA ester (R)-66 (Scheme 3.7).
3.3 Chiral analysis and synthesis of reference compounds

The enantiomeric purity of the phenyl ether 60 was determined by chiral GLC. Its absolute configuration was assigned based on comparison of specific rotation data for the homochiral reference compound \((R)-\)phenyl 1-phenylethyl ether \([(R)-60]\), which was synthesized via a benzyne route as described in section 3.3.1. Optical purity of naphthyl ether 61 was established by comparison of optical rotation data with that of a homochiral reference compound \((S)-61\), synthesized by nucleophilic substitution of a trifluoroacetyl ester \((R)-66\) (see section 3.3.2). Experimental procedures for the synthesis of the reference compounds \((R)-60\) and \((S)-61\) are described in Papers II and III.

3.3.1 Synthesis of \((R)-\)phenyl 1-phenylethyl ether via benzyne route

Phenyl 1-phenylethyl ether 60 was analyzed directly by chiral GLC. However, in the beginning this compound could not be analyzed by our available analytical tools. It was thus, opted to determine its optical purity by comparing its specific rotation data with that of a homochiral reference compound \((R)-60\). The reference compound \((R)-60\) was not readily available, there was therefore, a need to prepare this molecule in its enantiopure form. Homochiral \((R)-\)\(\alpha\)-methylbenzyl alcohol (Scheme 3.5) was used in the synthesis of the reference compound \((R)-60\) in order to avoid construction of the alkyl C-O bond which could give partial racemized products. A number of nucleophilic displacement and aromatic substitution procedures were tested. However, as expected, all were either unreactive or not stereoselective.

To serve our purpose a method of choice should require only mild, basic, neutral or eventually slightly acidic conditions. Strong acidic conditions readily cleaved the benzylic ether bonds or resulted in racemization of the stereogenic carbon. Radical mechanisms were also avoided, ruling out copper promoted reactions\(^{10}\). Furthermore, to ensure that the chiral alcohol \((R)-45\) did not racemize during ether formation, the ideal reaction must occur away from the chiral center and not involve any alkyl C-O bond cleavage. These conditions could be fulfilled by nucleophilic aromatic substitution reactions. However, this is only possible if an activating group is present in the aromatic halide or exceedingly strenuous conditions are employed\(^8\). Otherwise, our requirements could be met by Buchwald Pd-catalyzed reactions\(^{11,15-16}\) which have been reported to be suitable methods for the synthesis of diaryl ethers or cyclic aryl alkyl ethers in an intramolecular fashion under mild conditions. Buchwald procedures were tested, but compound 60 was not formed in any of these variants.
Alternatively, our objective may be accomplished by the addition of alcohol (\(R\))-45 to unsubstituted benzyne\(^{17,18}\) (Scheme 3.6). The benzyne can be generated by diazotization of anthranilic acid (62). The use of this compound for generating benzyne has been described earlier\(^{19}\). In most of the described reactions the corresponding 2-diazoniumbenzoate (63) (Scheme 3.4) was isolated and thermolysed\(^{20-22}\).

\[
\text{Scheme 3.4} \quad \text{Generation of benzyne (64).}
\]

Examples where benzyne was generated directly from 62 by treatment with amyl nitrite in the presence of an acid catalyst and trapping agents have been reported\(^ {21,22}\). The addition of nucleophiles to benzyne has been studied\(^ {20,23-25}\). However, syntheses of aryl ethers by the addition of alcohols to benzyne were never really successful and have not found widespread use.

Classical experimental procedures for the generation of benzyne were not appropriate for our purpose, as they are conducted in alcohols which present a potential risk of alcoholysis of the diazonium salt that leads to depleted yields of the desired products. The procedures using the isolated diazonium salt also have the disadvantage that this compound is dangerously explosive when dry.

Despite these apparent disadvantages, the benzyne route appeared most appealing to our specific problem, making it worthwhile to reinvestigate. We decided to generate the benzyne in neutral solvent and trap it \textit{in situ} using the substrate (\(R\))-45. In this variant isoamyl nitrite was added to a solution containing anthranilic acid (62) together with (\(R\))-45 in refluxing monoglyme (Scheme 3.5). The benzyne was formed as the anthranilic acid disappeared. However, the major addition product isolated was the isoamyl phenyl ether (65) and the target compound 60 was formed only in minute amounts.
Chapter 3: Preparation of chiral aryl ethers via cyclic N,N-disulfonylimides

Scheme 3.5 Addition of alcohols to benzyne.

The observation that the isoamyl alcohol formed from the nitrite actually added to the benzyne was encouraging. Formation of the by-product 65 was eliminated by employing tert-butyl nitrite instead for generating the benzyne in order to reduce the reactivity of the alcohol formed from the nitrite. These changes afforded the desired product, (R)-60, in 42% isolated yield after flash chromatography (Scheme 3.6, Table 3.2). 9% of the unreacted starting material, (R)-45, was also isolated. Compound 60 prepared in this method was later shown to be enantiopure by chiral GLC, and it was used to determine absolute configuration of the phenyl ether 60 synthesized in the nucleophilic reaction between phenol and the disulfonylimides (S)-43 and (S)-50.

Scheme 3.6 Preparation of reference compound (R)-60 via benzyne.

3.3.2 Synthesis of (S)-phenyl and (S)-2-naphthyl 1-phenylethyl ethers from trifluoroacetate ester

The degree of inversion in the formation of 2-naphthyl 1-phenylethyl ether (61) from the disulfonylimides (S)-43 and (S)-50 could not be determined by chiral GLC or NMR shift reagents (Section 2.5) due to the lack of enantioseparation by both methods. Attempts to prepare the homochiral (R)-2-naphthyl 1-phenylethyl
ether, (61) using benzyne were also unsuccessful. However, the homochiral phenyl and 2-naphthyl ether reference compounds (S)-60 and (S)-61 could be prepared in 65-87% yield by nucleophilic substitution of the corresponding (R)-1-phenylethanol trifluoroacetyl ester (66) (Scheme 3.7, Table 3.2). The aroxide nucleophiles were prepared by treatment of phenol or 2-naphthol with sodium hydride. Complete inversion of stereochemistry was observed in this reaction, as shown by chiral GLC analysis of the phenyl ether product (S)-60. The optical purity of the 2-naphthyl ether products 61 from (S)-43 and (S)-50 was thus established based on comparison of its optical rotation data with that of homochiral reference compound (S)-61.

Scheme 3.7 Preparation of reference compounds (S)-60 and (S)-61 using trifluoroacetyl ester.
Chapter 3: Preparation of chiral aryl ethers via cyclic N,N-disulfonylimides

Table 3.2: Preparation of the homochiral ethers 60 and 61 via benzyne and TFA ester

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Nucleophile</th>
<th>Product (yield%)</th>
<th>[α]D (CHCl3)</th>
<th>Stereoselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>(R)-45</td>
<td>(R)-60 (42)</td>
<td>+ 5.55 (ε = 2)</td>
<td>100% ret.a</td>
</tr>
<tr>
<td>(R)-66</td>
<td>PhO</td>
<td>(S)-60 (65)</td>
<td>- 5.60 (ε = 2)</td>
<td>100% inv.a</td>
</tr>
<tr>
<td>(R)-66</td>
<td>2-NaphthO</td>
<td>(S)-61 (87)</td>
<td>- 124 (ε = 0.2)</td>
<td>100% inv.b</td>
</tr>
</tbody>
</table>

aEnantiomeric purity of the phenyl ether products (R)-60 and (S)-60 is based on chiral GLC.
bEnantiomeric purity of the 2-naphthyl ether products (S)-61 is based on the assumption that the stereoselectivity of this reaction is identical to that established by chiral GLC for the phenyl ether (S)-60.

3.4 General discussion

The results on nucleophilic substitution of the cyclic aryldisulfonylimides (S)-43 and (S)-50 using aroxide anions have revealed that in addition to other factors nucleophilic substitution of these compounds depends on the nucleophile. We have obtained higher stereoselectivity with aroxide anions compared to what we have previously observed during the formation of azides and alcohols using the same intermediates (Chapter 2, Paper II). Furthermore, in this study the leaving group, 1,2-naphthalenedisulfonylimide has afforded comparable enantioselectivity to the corresponding leaving group, 1,2-benzenedisulfonylimide. These observations are in contrast to our previous results for the synthesis of azide and alcohol products using the same procedures (Chapter 2), where the 1,2-naphthalene intermediate showed 20-25% lower stereoselectivity.

Assessment of the two nucleophilic substitution methods used in the synthesis of the aryl ethers 60 and 61 indicates that trifluoroacetates are superior intermediates over cyclic N,N-aryldisulfonylimides in stereoselective transformations. The trifluoro ester leaving group has been substituted stereoselectively with complete inversion of configuration, while the disulfonylimide derivatives of amines have afforded only 70-87% degree of inversion. Presumably, the O-TFA leaving group favours SN2 reaction due to its higher electron withdrawing character and lower nucleophilicity. This has been observed even when a less polar solvent (THF versus DMF) and mild reaction conditions (room temperature/100 °C) are used in the substitution of the disulfonylimides, which has occurred with partial racemization.
3.5 Conclusion

Nucleophilic substitution of (S)-N,N-1,2-benzenedisulfonylimide 43 and (S)-N,N-naphthalenedisulfonylimide 50 by aroside anions afforded phenyl 1-phenylethyl ether (60) and its 2-naphthyl analogue 61 in 39-68% yield with 83-87 and 70-79% inversion of configuration respectively. The enantiopure phenyl and 2-naphthyl ethers (S)-60 and (S)-61 were prepared alternatively from the corresponding chiral alcohol via the TFA ester (R)-66 with 100% inversion of configuration. Phenyl ether (R)-60 has also been synthesized from homochiral alcohol (R)-45 via a benzyne route with complete retention of configuration.

References

Chapter 3: Preparation of chiral aryl ethers via cyclic N,N-disulfonylimides

4 Preparation of inverted amines and alcohols via 2,4,6-triphenylpyridinium salts

4.1 Introduction

Apart from the \( N,N \)-disulfonylimide leaving group discussed in Chapter 2, amines could also be successfully substituted by various nucleophiles via triarylpyridinium salts (Scheme 4.1). The driving force for this reaction is the high stability of the neutral leaving group, 2,4,6-triphenylpyridine 67.

![Scheme 4.1 Nucleophilic substitution of amines via triarylpyridinium salts.](image)

The concept of utilizing triarylpyridinium cations in substitution of amines was first reported in 1926 by Ziegler and Fries\(^1\) who showed that 1-methyl-2,4,6-triphenylpyridinium chloride thermolysed to 2,4,6-triphenylpyridine and presumably, methyl chloride. Susan and Balaban\(^2\) reinvestigated the synthetic utility of this sequences in 1969 in an effort to transform alkyl- and benzyl-amines into their corresponding halides. Heating of 1-methyl-2,4,6-triphenylpyridinium chloride and iodide showed the expected loss in weights, but this procedure was not fully investigated by then. Detailed examination for synthetic application of this procedure was conducted by Katritzky and his co-workers\(^3-12\) in the early 1980’s. Katritzky has demonstrated that triarylpyridinium cations can be easily prepared by various routes and are smoothly replaced by numerous nucleophiles to give compounds of different functionalities. Following Katritzky discoveries in the past two decades this protocol has received several
applications in nucleophilic substitution of amines. However, to the best of our knowledge this method has not been utilized for substitution of chiral substrates, and the stereoselectivity of the displacement reaction has therefore never been studied. Hence, we decided to investigate the utility of this process in stereoselective transformation of chiral amines. This chapter discusses the preparation and nucleophilic substitution of chiral 2,4,6-triphenylpyridinium salts prepared from homochiral amines and 2,4,6-triphenylpyrylium cation.

Experimental details for this chapter are presented in Paper IV.

4.2 Nucleophilic substitution of amines using pyrylium cations

Activation of amines to pyridinium salts using pyrylium cations involves a complex reaction sequence. Katritzky, Brownlee and Musumarra have thoroughly investigated the mechanisms of this reaction and established that this sequence follows the pattern illustrated in Scheme 4.2. The first step in this sequence leads to the formation of 2-amino-2H-pyran via ammonium intermediate. The amino pyran is rapidly ring-open to the vinylogous amide. The ring-opening is followed by slow ring closure to the target pyridinium salt.
It has been demonstrated that for complete conversion of the amines to pyridinium salts, the amine:pyrylium ratio should be at least 2:1. It was later learnt that the role of the second molecule of amine is to deprotonate the ammonium intermediate 69 and hence transform it to pyran 70 and the amine ammonium salt. Therefore, one mole of the amine can be replaced by another base such as triethylamine. If the amine:pyrylium ratio is lower than 2:1, the diketone 72 is also formed via a reaction of water with the pyrylium salt cation 68. However, under these conditions the diketone 72 is eventually converted to the desired pyridinium salt 73 by reacting with the amine, but this happens at a much slower rate. The ring closure of the vinylogous intermediate 71 to the pyridinium salt 73 is the slowest and the rate-determining step. The rate of this reaction is greatly enhanced by carboxylic acids17. It is believed that the carboxylic acids catalyze this step in an electrocyclic fashion as depicted in Scheme 4.310.

For a successful nucleophilic substitution reaction the pyridinium salt counterion should be a weak nucleophile such as tetrafluoroborate. Counterions which are strong nucleophiles, such as halides, will interfere the displacement reaction and will result in insertion of the counterion in the substitution products.

Scheme 4.3 Acid catalysis of ring closure of vinylogous amides.

4.3 Synthesis and nucleophilic substitution of chiral 1-cyclohexylethyl- and 3-phenyl-1-methylpropyl-2,4,6-triphenylpyridinium tetrafluoroborates

1-Cyclohexylethyl- and 3-phenyl-1-methylpropyl-2,4,6-triphenylpyridinium tetrafluoroborates (R) or (S)-75 and (R)-76 were generated from (R) or (S)-1-cyclohexylethylamine (42) and (R)-3-phenyl-1-methylpropylamine (2) using the protocol described by Katritzky and his group9. The degree of inversion in the substitution reaction were studied for the formation of the alcohols 46 and 77,
Chapter 4: Preparation of inverted amines and alcohols via 2,4,6-triphenylpyridinium and the azides 48 and 78. The substrate \((R)-2\) was obtained by resolution of racemic 2 using \(N\)-acetylcysteine as depicted in Scheme 1.2.

4.3.1 Results and discussion

The primary amines \((R)-42\) or \((S)-42\) and \((R)-2\) reacted with 2,4,6-triphenylpyrylium tetrafluoroborate \(74\) via the discussed sequence of rapid ring opening to the vinylogous amide intermediate, which underwent slow ring closure to the 1-substituted 2,4,6-triphenylpyridinium salts \((R)-75\) and \((R)-76\) in 84-90% yield (Scheme 4.4, Table 4.1).

**Scheme 4.4** Preparation of 1-cyclohexyl- and 3-phenyl-1-methylpropyl- triphenyl pyridinium tetrafluoroborates \((R)-75\) and \((R)-76\).

All steps of this reaction could be followed by TLC and by characteristic changes of colours from yellow to dark-red/black and back to yellow. As discussed in section 4.2, the rate of conversion of the amines to pyridinium salts

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Triphenylpyridinium salt (yield)</th>
<th>([\alpha]_D) (c = 2, CHCl(_3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>((R)-42)</td>
<td>((R)-75) (84%)</td>
<td>-59.1</td>
</tr>
<tr>
<td>((S)-42)</td>
<td>((S)-75) (90%)</td>
<td>+61.7</td>
</tr>
<tr>
<td>((R)-2)</td>
<td>((R)-76) (89%)</td>
<td>-53.7</td>
</tr>
</tbody>
</table>
was enhanced by the presence of both bases and carboxylic acids. The ring opening reaction to the vinylogous amide intermediate was more rapid in the presence of triethylamine or using an excess of the substrate (2 equivalents). The cyclization step was strongly catalyzed by acetic acid. The rate-enhancing effect was manifested by a manifold increase in reaction rate, reducing the reaction time from 7 days to 5 h by the addition of one equivalent of acetic acid.

The mass spectra of the 2,4,6-triphenylpyridinium intermediates demonstrate the energetically highly favoured fragmentation of the triphenylpyridine from the molecular ions of 75 and 76. Due to the weak C-N-pyridinium bond, the molecular ions were always absent in the mass spectrum and the base peaks were the neutral triphenylpyridine fragment. ¹H NMR of the cyclohexyl intermediate 75 showed a characteristic phenyl ring current effect causing a high field resonance of two cyclohexyl protons as can be observed for (S)-75 δ 0.37 and 0.63. This specific shielding effect can be explained by the cyclohexyl ring conformations.

Nucleophilic substitution of the pyridinium intermediates (R)- or (S)-75 and (R)-76 using potassium nitrite and sodium azide afforded the alcohols 46 and 77 and the azides 48 and 78 respectively (Scheme 4.5). The stereoselectivity of this reaction was very high. The degree of inversion for the formation of the products 46, 77, 48 and 78 was 96-99% (Table 4.2).

Scheme 4.5  Nucleophilic substitution of 1-cyclohexyl- and 3-phenyl-1-methylpropyl-triphenyl pyridinium tetrafluoroborates (R)- or (S)-75 and (R)-76.
Chapter 4: Preparation of inverted amines and alcohols via 2,4,6-triphenylpyridinium

Table 4.2: Results for nucleophilic substitution of the homochiral pyridinium intermediates 75 and 76

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Alcohol products$^b$ Degree of inversion (Yield%)</th>
<th>Azide products$^c$ Degree of inversion (Yield%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-75</td>
<td>(S)-46 $&gt;$99% (21)</td>
<td>(S)-48 97% (37)</td>
</tr>
<tr>
<td>(S)-75</td>
<td>(R)-46 $&gt;$99% (17)</td>
<td>(R)-48 96% (43)</td>
</tr>
<tr>
<td>(R)-76$^a$</td>
<td>(S)-77$^a$ $&gt;$99% (41)</td>
<td>(S)-78$^a$ 98% (71)</td>
</tr>
</tbody>
</table>

$^a$Substrate (R)-2 had ee of 96%. The degree of inversion for products 77 and 78 has been corrected for this.

$^b$Enantiomeric purity of the alcohol products 46 and 77 is based on chiral GLC.

$^c$Enantiomeric purity of the azide products 48 and 78 is based on GLC analysis of the diastereomeric amides after reduction and derivatization with (S)-α-methoxyphenylacetyl chloride (79).

The chiral analysis of the alcohol products 46 and 77 was carried out directly by chiral GLC, while the azides 48 and 78 were reduced and analyzed via GLC separation of their corresponding amides 80 and 81 prepared from (S)-α-methoxyphenylacetyl chloride (79) (Scheme 4.6).

The substitution products 46, 48, 77 and 78 were formed in low to moderate yields (Table 4.2). However, these studies were only focused on stereochemical outcome of the substitution reaction and no attempts to optimize the yields of the substitution products were made.

Scheme 4.6 Reduction and derivatization of 1-cyclohexyl- and 3-phenyl-1-methylpropyl-azide (48 and 78).
The results obtained from the present investigations show the advantages of this method in stereoselective transformation of amines via nucleophilic displacement. The pyridinium intermediates 75 and 76 were synthesized in higher yields (84-90%) and at milder reaction conditions compared to the previously studied \(N,N\)-disulfonylimides\(^1\)\(^{\text{-}}\)\(^\text{24}. \) Furthermore, the triphenylpyridinium group has been shown to be a better leaving group than the \(N,N\)-disulfonylimides. Nucleophilic substitution of the triphenylpyridinium salts 75 and 76 were carried out at less vigorous reaction conditions (80-100°C, 5 h) than the \(N,N\)-disulfonylimides (120°C, 72 h). However, the pyridinium intermediates required more harsh reaction conditions than the cyclic aryldisulfonylimides, 1,2-benzene- and naphthalene-disulfonylimides (0°C, 24 h) (see Chapters 2 and 3).

The most interesting discovery in this study is the higher degree of inversion (96-99%) achieved in the nucleophilic substitution reaction of the pyridinium intermediates 75 and 76. Stereoselectivity of this reaction is comparable to that of ditosylimides\(^1\)\(^^{\text{-}}\)\(^\text{22} and is generally better than that of other previously reported \(N,N\)-disulfonylimides.

### 4.4 Synthesis and nucleophilic substitution of 1-phenylethyl-2,4,6-triphenylpyridinium salt

In addition to the chiral 1-cyclohexylethylamine and \((R\))-3-phenyl-1-methylpropylamine 2,4,6-triphenylpyridinium derivatives 75 and 76, we have also investigated the chemistry of the pyridinium salt of 1-phenylethylamine 82 (Scheme 4.7). The benzylic racemic 1-phenylethylamine (1) has previously been reported readily to form the triphenylpyridinium salt 82\(^2\). However, the intermediate pyridinium salt could not be isolated and the corresponding alcohol was always formed directly. Presumably, the benzylic pyridinium intermediate rapidly dissociates by an \(S_N1\) process to give the resonance stabilized secondary carbocation which is trapped by water to form the alcohol. Other products could not be prepared from this intermediate. We therefore wished to study the effect of adding nucleophiles during the preparation of 1-phenylethyl-2,4,6-pyridinium salt 82. Our intention was to achieve a combined preparation and nucleophilic substitution process in one-pot fashion.

#### 4.4.1 Results and discussion

1-Phenylethyl-2,4,6-triphenylpyridinium salt (82) was generated as described elsewhere\(^9\). The preparation of this intermediate was carried out in the presence of different nucleophiles so as to effectuate \textit{in situ} substitution of the salt once it has been synthesized from its individual constituents (Scheme 4.7).
Chapter 4: Preparation of inverted amines and alcohols via 2,4,6-triphenylpyridinium

Scheme 4.7  A combined preparation and nucleophilic substitution of 1-phenylethyl-2,4,6-triphenylpyridinium tetrafluoroborate (82).

The first reaction was conducted in the presence of potassium nitrite and afforded the anticipated alcohol 45 in 85% yield after hydrolysis of the reciprocating nitrite (Table 4.3). Addition of azide and arexes nucleophiles to the reaction vessel gave the corresponding azide 47 and ethers 60 and 61 in 70-73% yield. In general, the nucleophilic substitution of the pyridinium salt 82 furnished higher yields compared to pyridinium salts 75 and 76 (Table 4.2 and 4.3). However, as expected the substitution reaction of 1-phenylethyl-2,4,6-triphenylpyridinium salt 82 was not stereoselective and all products were almost racemic (Table 4.3). The alcohol 45 was always present as a by-product in all reactions even in predried solvent. This is primarily caused by the presence of water which is generated during the ring-closure reaction and ultimate formation of the pyridinium salt 82.

Table 4.3: Results for in situ nucleophilic substitution of 1-phenylethyl-2,4,6-triphenylpyridinium salt (82)

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>Stereoselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>85</td>
<td>12% ee</td>
</tr>
<tr>
<td>47</td>
<td>78</td>
<td>racemic</td>
</tr>
<tr>
<td>60</td>
<td>70</td>
<td>racemic</td>
</tr>
<tr>
<td>61</td>
<td>73</td>
<td>racemic</td>
</tr>
</tbody>
</table>
4.5 Conclusion

The synthesis and nucleophilic substitution of 2,4,6-triphenylpyridinium derivatives of chiral primary amines have demonstrated the utility of these intermediates in stereoselective transformation of chiral amines. The 2,4,6-triphenylpyridinium salts (R)- or (S)-75 and (R)-76 of the chiral primary aliphatic amines (R)- or (S)-42 and (R)-2 were prepared from 2,4,6-triphenylpyrylium tetrafluoroborate (74) in 84-90% yield. The alcohols 46 and 77 and azides 48 and 78 were obtained by nucleophilic substitution of the pyridinium intermediates with >99 and 96-98% inversion of stereochemistry, respectively. A benzylic substrate afforded racemic alcohol, azide and arylether products in 70-85% yield in a one-pot reaction.

References

Chapter 4: Preparation of inverted amines and alcohols via 2,4,6-triphenylpyridinium

5 Inversion of Amino Acids

5.1 Introduction

In recent years, the preparation of non-proteinogenic amino acids have received much attention because their inclusion in peptides often results in interesting bioactivity of the peptide. Among the important non-proteinogenic amino acids are the D-isomer of the natural L-α-amino acids. Asymmetric methods used to produce L-α-amino acids can be utilized for the production of their D-isomers by inverting the chirality of the asymmetric addend used in the process. These methods can be divided into three different categories (Scheme 5.1): a) Kinetic resolution of racemic mixtures of amino acids using enzymes, b) Catalytic asymmetric processes using transition metals and c) Asymmetric methods using stoichiometric amounts of chiral auxiliaries.

Scheme 5.1 Asymmetric methods for preparation of α-amino acids.

Scheme 5.1 Asymmetric methods for preparation of α-amino acids.
Chapter 5: Inversion of Amino Acids

An alternative approach for producing D-α-amino acids is by inversion of the readily available L-α-amino acids via stereosel ective nucleophilic substitution reactions. Activation and subsequent substitution of α-amino acids present a real challenge due to racemization problem caused by their α-proton propensity to deprotonating agents. As a consequence inversion of amino acids has attracted less attention. However, some investigations towards this goal have been reported. For example, Hoffman and Kim \(^{13}\) have prepared protected α-amino esters with complete inversion of configuration via a four step reaction sequence (Scheme 5.2). The diazotization reaction in this process is believed to proceed with retention of configuration due to anchimeric assistance by the amino acid carboxyl group\(^{14}\).

![Scheme 5.2](image-url)

Scheme 5.2  Inversion of amino acids via diazotization: a) NaNO\(_2\)/H\(^+\), b) K\(_2\)CO\(_3\)/CH\(_3\)I, c) NsCl/TEA/DMAP, d) RNH\(_2\).

Although this sequence gives complete inversion of configuration, it suffers from the disadvantages of low yields due to a large number of steps involved in the whole pathway. It is therefore worthwhile to investigate a more simple method for direct inversion of the L-α-amino acids to their D-antipodes. Our group has developed a number of general methods for inversion of chiral amines, it was thus decided to apply some of these methods on inversion of amino acids.

### 5.2 Inversion of α-amino acids via cyclic aryl disulfonylimides

The first attempt in the effort to invert the L-α-amino acids to their D-isomers was the use of cyclic aryl disulfonfylimide intermediates. These derivatives were selected as they can be prepared at less rigorous conditions and have been shown to be better leaving groups than their acyclic counterparts\(^{15,16}\). Both advantages are essential in avoiding the racemization of the amino acid derivative due to abstraction of the methine proton at the α-position during preparation of intermediates or in subsequent nucleophilic substitution steps.
5.2.1 Synthesis and nucleophilic substitution of \( N,N \)\(-1,2\)-benzenedisulfonylimide derivative of L-phenylalanine ethyl ester

The literature procedures for the preparation of \( N,N \)\(-1,2\)-benzenedisulfonylimides was followed\(^{16}\). The intermediate was then subjected to nucleophilic substitution reactions using azides and hydroxide anions in polar aprotic solvents.

5.2.1.1 Results and discussion

\((S)\)-\(N,N \)\(-1,2\)-benzenedisulfonylimide derivative \( \text{84} \) (Scheme 5.3) was obtained from L-phenylalanine ethyl ester hydrochloride \( \text{83} \) and benzene-1,2-disulfonyl chloride \( \text{39} \) in high yield (88\%) via a previously reported procedure\(^{16}\), basically using identical reaction conditions. However, for optimum reaction yields this process required much slower addition of deprotonated \( \text{83} \) to a solution of \( \text{39} \) in dichloromethane and high substrate dilutions. These variations demanded longer reaction times, which is a less favoured option for reactions involving amino acids due to their inherent problem of racemization. Nevertheless, compound \( \text{84} \) has indicated no sign of racemization as it possessed high optical rotation (Scheme 5.3). Efforts to verify the enantiopurity of \( \text{84} \) was not successful due to the lack of enantioseparation of this compound in various chiral solvating agents.

![Scheme 5.3 Synthesis of L-phenylalanine \( N,N \)\(-1,2\)-benzenedisulfonylimide (84).](image)

The nucleophilic substitution of \((S)\)-\( \text{84} \) (scheme 5.4) via described procedures\(^{15,16}\) was not successful. Surprisingly, this transformation could not be achieved by various reaction conditions (Table 5.1). These results are in contrary
to the previously observed facile displacement of the related cyclic
aryl-disulfonylimides\textsuperscript{15,16}. This problem is likely caused by the anionic character
of the $\alpha$-carbon. The presence of the disulfonylimide leaving group at $\alpha$-position
is expected to umpolung and reverse the nucleophilic property of this carbon.
However, it seems that is not the case for this molecule. Thus, the result of this
investigation do not support our original presumption that cyclic aryl
disulfonylimides would act as useful intermediates for inversion of chiral amino
acids.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme5.4.png}
\end{center}

\textit{Scheme 5.4}  \textit{Nucleophilic substitution of N,N-benzene-1,2-disulfonylimide derivative of (S)-phenylalanine ethyl ester 84.}

\begin{table}[h]
\centering
\caption{Reaction conditions for nucleophilic substitution of N,N-benzene-1,2-disulfonylimide derivative of (S)-phenylalanine ethyl ester 84}
\begin{tabular}{|c|c|c|}
\hline
Entry & Reaction conditions & Comments \\
\hline
1 & KNO\textsubscript{2}, THF, rt-reflux, 48 h & No reaction \\
2 & KNO\textsubscript{2}, DMF, rt- 80°C, 48 h & No reaction \\
3 & KNO\textsubscript{2}/crown ether, DMF, rt- 80°C, 48 h & No reaction \\
4 & KNO\textsubscript{2}, DMF, 130°C, 5 h & Complex mixtures \\
5 & NaN\textsubscript{3}, THF, rt-reflux, 48 h & No reaction \\
6 & NaN\textsubscript{3}, DMF, rt-80 °C, 48 h & No reaction \\
7 & NaN\textsubscript{3}, DMF, 110°C-reflux, 4 h & Complex mixtures \\
8 & TMSN\textsubscript{3}/TBAF, THF, reflux, 24 h & No reaction \\
\hline
\end{tabular}
\end{table}
5.3 Inversion of amino acids via 2,4,6-triphenylpyridinium salts

Our next investigations on the inversion of amino acids was focused on 2,4,6-triphenylpyridinium derivatives. These compounds are known to be valuable intermediates in nucleophilic substitution of primary and secondary amines\textsuperscript{17-25}. We have recently reported their use in inversion of chiral amines (Chapter 4 and Paper IV). The synthesis of these salts from amines is well documented\textsuperscript{19,23,24}. Furthermore, these compounds are thermally stable and are very reactive towards various nucleophiles. Apparently, this is a more promising leaving group than the cyclic aryldisulfonimidates. Investigations aimed on inversion of amino acids using these intermediates is therefore worthwhile.

5.3.1 Synthesis and nucleophilic substitution of 2,4,6-triphenylpyridinium terafluoroborate derivative of L-phenylalanine ethyl ester

The intermediate 2,4,6-triphenylpyridinium salt \textsuperscript{85} (Scheme 5.5) was prepared from 2,4,6-triphenylpyrylium tetrafluoroborate (\textsuperscript{74}) and (S)-phenylalanine ethyl ester hydrochloride (\textsuperscript{83}) by reported methods\textsuperscript{23}. Nucleophilic substitution was carried out using azide anion.

5.3.1.1 Results and discussion

The 2,4,6-triphenylpyridinium tetrafluoroborate derivative of (S)-phenylalanine ethyl ester \textsuperscript{85} (Scheme 5.5) was obtained in higher yields (96%) than the previously studied pyridinium salts \textsuperscript{75} and \textsuperscript{76} (Chapter 4, Table 4.1). The normal change of colours yellow-red-darkred/black-yellow was observed and the reaction was catalyzed by acetic acid (Chapter 4). One extra equivalent of triethylamine was required to deprotonate the substrate, (S)-phenylalanine ethyl ester hydrochloride (\textsuperscript{83}) before it could attack the 2,4,6-triphenylpyrylium cation \textsuperscript{74} (Scheme 5.5).
Chapter 5: Inversion of Amino Acids

Scheme 5.5 Preparation of 2,4,6-triphenylpyridinium salt of (S)-phenylalanine ethyl ester (85).

The nucleophilic displacement of compound (85) by sodium azide using same conditions as substitution of pyridinium salts 75 and 76 (Chapter 4) afforded moderate yields of the azide substitution product 86 (Scheme 5.6). However, the stereoselectivity of the substitution reaction was dissatisfying; the products showed only 54% inversion (Table 2, method A).

Scheme 5.6 Nucleophilic substitution of 2,4,6-triphenylpyridinium derivative of (S)-phenylalanine ethyl ester (85).
The poor stereoselectivity of this procedure might be caused by racemization of the pyridinium salt 85 during preparation or could be the consequence of the nucleophilic substitution reaction. The low optical rotation of the salt 85 compared to its analogues 75 and 76 (Chapter 4, Table 4.1) indicates the possibility of the former presumption. In this case the racemization of 85 might have happened via acid mediated tautomerization of the vinylogous intermediate 87 (Scheme 5.7). The presence of excess base may also cause racemization of the pyridinium salt itself once it has been formed from its individual constituents (Scheme 5.8).
In order to rectify this apparent problem we sought to avoid the use of both triethylamine and acetic acid. Since the presence of a base is necessary in this reaction, the amino acid (S)-83 was deprotonated and used in excess amount (2 equivalents). Compound 85 could not be formed under these conditions except at elevated temperatures or by adding small amounts of the acetic acid. Neither of these strategies improved the stereoselectivity of this process (Table 5.2 methods B and C).

Once again, the failure of these procedures is presumably due to racemization of 85 via tautomerization or the resonance stabilized iminium ion mechanism (Scheme 5.8). The methine proton in 85 can be easily abstracted even by a weak base especially at elevated temperatures to form a carbanion 88, which can racemize via a tautomer 89 or an iminium ion 90 (Scheme 5.8). The use of small amounts of acetic acid required long reaction times. Racemization of the vinylogous intermediate 87 or the pyridinium salt 85 could therefore not be ruled out under these conditions.
Evidence for tautomerization of the pyridinium salt 85 could be obtained via X-ray crystallography. The length of the C6-C32 bond in X-ray structure of the tautomer between compound 85 and 89 should lie between a single and a double bond. The X-ray data for 85 (Figure 5.1)\textsuperscript{26} (Appendix 5) was ambiguous due to the rolling of the BF\textsubscript{4} group throughout the crystal structure and the appearance of the two conformers of the ester moiety in the X-ray structure (Figure 5.2). Hence, the length of C6-C32 bond could not be exactly determined. However, the calculated value does not fit for the standard single or double bond lengths and could be positioned between these two values, which indicates the tautomerization phenomenon in the pyridinium salt 85. Detailed X-ray examination of 85 is in progress and the results will be published.
Chapter 5: Inversion of Amino Acids

Figure 5.1  X-ray structure of compound 85.
In summary, all attempted variations for the preparation of the pyridinium salt 85 have led to racemized products. The racemization problem is probably associated with the ester group in the used substrate. Replacement of this group with a less susceptible functionality such as the free acid or an alcohol should be considered in later developments of this strategy.

5.4 Inversion of amino acids via diazonium salts

As shown in Scheme 5.2 L-α-amino acids can be converted to their D-isomers in a four step process with complete inversion of configuration. However, the overall yield of the final inverted product is depleted due to a large number of steps involved in this sequence. The nucleophilic substitution of the diazonium salt in the first step of this procedure proceeds with retention of configuration,
which is the result of double inversion associated with anchimeric assistance by
the neighbouring amino acid carboxyl group\(^{14}\) (Scheme 5.9). The degree of
inversion reported in this method is therefore not achieved by direct
placement of the amino group. Indeed, it usually involves inversion of a
halide or an alcohol in subsequent steps. An investigation aimed to decrease the
number of steps by direct inversion of the amino group in the first step of this
process is therefore highly advantageous.

\[ \text{Scheme 5.9 Anchimeric assistance in diazotization of amino acids.} \]

Since the retention problem is related with anchimeric assistance by the
neighboring carboxyl group, a better strategy is to use a substrate which is
masked on the carboxyl end. Amino acid esters not only fit this requirement, but
are also readily available at affordable expenses.

Yamada and his group\(^{27}\) isolated small amounts of optically active diester (R)-93
together with other by products 94-96 in an effort to synthesize tropic acid (92)
by diazotization of L-phenylalanine ethyl ester (91) in acetic acid and NaNO\(_2\)
(Scheme 5.10). Apparently, compound (R)-93 has been formed via backside
attack on the diazonium salt by the solvent molecules. The results of this study
indicate the feasibility of inverting the amino functionality in the amino acids via
diazotization in a single step process. Yamada’s investigations produced
compound (R)-93 in very low yield. However, diazotization of compound 91 was
carried out in a polar protic solvent which is considered to be less favourable
conditions for diazotization-dediazoniation of aliphatic amines. Aprotic
diazotization is believed to be a superior alternative for transformation of these
substrates via diazonium salts\(^{28-30}\).

Diazotization of aliphatic amines in aprotic solvents is an effective method for
minimizing elimination, rearrangement, and oxidation processes normally
encountered in alternative diazotization procedures and facilitates product
recovery in high yields\(^{28}\).
**Inversion of amino acids via diazonium salts**

**5.4.1 Aprotic diazotization of aliphatic amines**

Diazotization of amines using alkyl nitrite in acidified aprotic solvents is referred to as aprotic diazotization. The mechanism of this reaction follow the usual diazotization sequence depicted in Scheme 5.11. The amine substitute the alkoxide group from alkyl nitrite to form a protonated nitrosoamine which loses a proton to give nitrosoamine and an alcohol. This is followed by rearrangement and the loss of water to give the alkyl diazonium salt.

![Scheme 5.10](#)

\[
\text{Scheme 5.10} \quad \text{Diazotization of (S)-phenylalanine ethyl ester 91 using nitrous acid.}
\]

**Scheme 5.11**  
Mechanisms for diazotization of amines using alkyl nitrites.

In 1957 Streitwieser and Schaeffer proposed the diazonium salt as the transient intermediate in the diazotization-dediazoniation of aliphatic amines. In the same report they postulated a series of potential reactions undergone by these intermediates (Scheme 5.12). As can be seen in this scheme (path a), it is feasible to substitute the diazonium salt stereoselectively with inversion of configuration. On the other hand, it should be pointed out that Streitwieser hypothesis has been a subject of great debate for decades, and it is believed that the branching point in diazotization of aliphatic amines are carbocations and the diazonium salts are not
involved in any of the subsequent reactions. However, Kirmse and Brosch reinvestigated Streitwieser proposition in 1991 using modern techniques and reiterated the concept of backside attack on diazonium salts in diazotization of aliphatic amines. Furthermore, it is an established fact that amino acids can be substituted with complete retention of stereochemistry via double inversion mechanisms (Scheme 5.9). In view of these observations it was decided to establish an investigation on inversion of amino acids via diazotization reactions.

5.4.2 Diazotization of L-amino acid esters

The diazotization reactions were carried out in aprotic solvents in the presence of nucleophiles to facilitate a coupled diazotization-dediazoniation process in a one-pot reaction. In a typical example L-phenylalanine ethyl ester hydrochloride (83) (Scheme 5.13) was diazotized in the presence of sodium azide using tertiary butyl nitrite in DME.

5.4.2.1 Results and discussion

The coupled diazotization-substitution reaction of L-phenylalanine ethyl ester hydrochloride (83) in DME (Scheme 5.13) gave only one product. Spectroscopic
Inversion of amino acids via diazonium salts

Analysis of this compound showed that the desired azide product 86 has not been formed and a chloro substituent 99 has been synthesized instead. Alanine ethyl ester hydrochloride (97) (Scheme 5.13) gave similar results, the chloro product 100 was isolated in high yields (Table 5.3) instead of the expected azide product 98.

Other aprotic solvents such as THF and diethyl ether were also tried, but the azide products 86 and 98 were once again not formed in these solvents. The failure of this reaction is presumably contributed by the low solubility of the sodium azide in the used solvents which allow the competing nucleophile, the chloride anion to attack the diazonium salt once it has been generated.

Techniques employed to increase the solubility of ionic nucleophiles in organic solvents, such as the use of crown ether, were attempted, but no improvement was achieved. The recent published elegant source of nucleophilic azide (Scheme 5.14) was also tried. However, no reaction was observed under these conditions, and the starting material was isolated as a free amino ester 91. The true cause of this problem could not be certainly justified. It is probably due to proton scavenging by the silicate TBAF complex 101 which could hamper the diazotization reaction.

Another alternative to circumvent the chloro substitution is to use a less nucleophilic counterion on the ammonium salt. L-Valine benzyl ester toluene-4-
sulfonate (102) was readily available, and it was used to replace phenylalanine ethyl ester hydrochloride (83) (Scheme 5.15). Once again, this reaction produced the tosylate 104 rather than the intended azide product 103. This implies that the sulfonate group was not neutral enough to avoid its attack on the diazonium salt in place of the less soluble nucleophile, the azide anion.

\[
\text{Scheme 5.15 Diazotization of L-Valine benzyl ester toluene-4-sulfonate (104).}
\]

To summarize, ammonium salts of amino acid esters can easily be diazotized in aprotic solvents using alkyl nitrites. We have obtained optical active substitution products in these reactions (Table 5.3). However, we have so far not been able to avoid the substitution of a diazonium salt by the competing ammonium salt counterions. Substitution products containing these ions were always the major reaction products in these transformations. Comparison of optical rotation data of compound 99 with that of enantiomerically pure reference compound (S)-99\(^{37}\) indicates that these reactions proceed with retention of configuration. Chiral identities of the chloro compound 100 and the tosylate 104 have not been fully established.

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Compound} & \text{Yield (\%)} & \text{Optical activity, } [\alpha]_D & \text{Stereo} \text{selectivity} \\
\hline
99 & 92 & + 4.7 (c = 2, EtOH) & 31\% \text{ retention}\(^a\) \\
100 & 90 & + 5.1 (c = 2, CHCl}_3 & \\
104 & 44 & + 3.6 (c = 2, CHCl}_3 & \\
\hline
\end{array}
\]

\(^a\)Chiral analysis of 99 is based on [\alpha]D comparison with an authentic compound (S)-99 reported in reference 37.
5.4.2.2 Alternative methods for diazotization of amino acids

The problem of substitution of diazonium salts by the ammonium salt counterions could be solved by using more inert counterions such as tetrafluoroborate or by diazotization of hydroazide salts instead of hydrochlorides. A more interesting strategy is to deliver the nucleophile intramolecularly as depicted in Scheme 5.16. These proposals are currently under investigations.

Scheme 5.16 IntraMolecular substitution of amino acid diazonium salts.

5.5 Conclusion

Three methods for preparation of D-amino acids by nucleophilic substitution have been attempted. The \(N,N\)-disulfonylimide intermediate of phenylalanine ethyl ester (84) (Scheme 5.3) was synthesized in high yield and optical purity, but the substitution reaction on this compound was not achieved.

The nucleophilic substitution on the alternative derivative, the triphenylpyridinium salt 85 (Scheme 5.5) was successful. However, the final azide product 86 in this variant was racemized. The disadvantage of this reaction is thought to be contributed by the nature of the used substrate and efforts are underway to remove this impediment.

Diazotization of amino acid ammonium salts 83, 97, and 102 (Schemes 5.13 and 5.15) in aprotic solvents gave optically active chloro and tosyl products 99, 100 and 104, respectively. However, the problem of the competing ammonium salt counterion remains to be solved. Alternative methods to circumvent this drawback have been suggested (Section 5.4.2.2) and are currently investigated.
5.6 Experimental

5.6.1 General

All chemicals and solvents used were of synthetic grade unless otherwise noted. 2,4,6-Triphenylpyrylium tetrafluoroborate, L-alanine ethyl ester hydrochloride, L-phenylalanine ethyl ester hydrochloride and L-valine benzyl ester toluene-4-sulfonate were obtained from Fluka, sodium azide from Merck and potassium nitrite, acetic acid and triethylamine were purchased from Acros. 1,2-Benzenedisulfonyl chloride was prepared as described elsewhere\textsuperscript{15}. DME and THF were distilled under nitrogen from sodium benzenophenone ketyl and used immediately. DMF and dichloromethane were distilled over CaH\textsubscript{2}. GLC: Carlo Erba Model 8130, split-injection, hydrogen, FID, column: Chrompack CP-Sil 5 CB (25 m). Chiral GLC analysis: Chrompack CP-CHIRALDEX-CB fused silica WCOT (25 m, 0.32 mm; 0.32 µm), carrier gas pressure 5–5.5 p.s.i. \textsuperscript{1}H/\textsuperscript{13}C NMR: Bruker Avance DPX 300/75.47 MHz and 400/100.61 MHz spectrometers, chemical shifts are reported in ppm downfield from TMS. MS: MAT 95 XL. IR: Nicolet 20SXC FT-IR spectrometer. [\textalpha\textsubscript{D}]: Perkin-Elmer 241 polarimeter (10 cm cell with a total volume of 1 mL). X-ray: Enraf-Nonius CAD-4 diffractometer.

5.6.2 \textit{N,N}-Benzene-1,2-disulfonylimide derivative of L-phenylalanine ethyl ester (\textit{84})

Benzene-1,2-disulfonyl chloride \textit{39} (4.5 g, 16.4 mmol) was dissolved in methylene chloride (400 ml) and brought to reflux. A solution of L-phenylalanine ethyl ester hydrochloride \textit{83} (2.5 g, 10.9 mmol) and triethylamine (4.8 ml, 34.6 mmol) in methylene chloride (150 ml) was added slowly over 50 hours at a rate of 3 ml/h. The reaction was refluxed for another 3 hours. The solvent was removed \textit{in vacuo} to yield 10.52 g of the off-white crystalline crude product. Triethylamine hydrochloride and excess benzene-1,2-disulfonyl chloride were separated from the product by flash chromatography (silica gel, dichloromethane) to yield 3.80 g (88\%) of compound \textit{84}. M.p. 130-132\degree C. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \textit{δ} 0.90 (t, \textit{J} = 7 Hz, 3H), 3.42 (dd, \textit{J} = 15 and 11 Hz, 1H), 3.72 (dd, \textit{J} = 5 and 15 Hz, 1H), 7.35 (m, 5 H), 7.84 (m, 2H), 7.92 (m, 2H); \textsuperscript{13}C NMR (75.47 MHz, CDCl\textsubscript{3}): \textit{δ} 13.60, 36.92, 62.42, 63.78, 121.75, 127.47, 128.96, 129.57, 134.42, 136.44, 138.30 168.04; MS [\textit{m/z} (rel. int.)]: 395 (M\textsuperscript{+}, 0.1\%), 322 (13\%), 304 (6\%), 232 (5\%), 220 (1.4), 176 (100\%), 148 (15\%), 131 (21\%), 104 (4\%), 91 (56\%); IR (KBr, cm\textsuperscript{-1}): 3094 (m), 3060 (w), 2976 (m), 1744 (s), 129.57, 134.42, 136.44, 138.30 168.04; MS [\textit{m/z} (rel. int.)]: 395 (M\textsuperscript{+}, 0.1\%), 322 (13\%), 304 (6\%), 232 (5\%), 220 (1.4), 176 (100\%), 148 (15\%), 131 (21\%), 104 (4\%), 91 (56\%); IR (KBr, cm\textsuperscript{-1}): 3094 (m), 3060 (w), 2976 (m), 1744 (s), 1447 (m), 1372 (s), 1200 (s), 1173 (s), 1074 (m), 949 (m), 901 (m), 819 (m), 762 (s) 744 (s), 697 (s), 627 (m), 591 (s), 557 (s), 505 (m); [\textalpha]\textsubscript{D} = -60.66 (c = 1, CHCl\textsubscript{3}).
5.6.3 2,4,6-Triphenylpyridinium salt of phenylalanine ethyl ester (85)

Method A: Procedure reported in Paper IV was followed: i.e. to a suspension of phenylalanine ethyl ester hydrochloride (83) (574 mg, 2.5 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (74) (1.0 g, 2.5 mmol) was added triethylamine (0.69 ml, 5.0 mmol) and the mixture was stirred at rt for 15 min. Acetic acid (0.29 ml, 5 mmol) was added, and the mixture was further stirred for 5 h at rt under nitrogen. The solvent was stripped off, and the crude product was purified by flash chromatography (gradient elution: dichloromethane, 5% methanol/dichloromethane) to yield the white crystalline pyridinium tetrafluoroborate 85 (1.35 g, 96%); mp 198-199 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.18 (t, J = 7 Hz, 3H), 2.85 (dd, J = 14 and 8 Hz, 1H), 3.46 (dd, J = 14 and 4 Hz, 1H), 5.63 (dd, J = 8 and 4 Hz, 1H), 6.77 (m, 2H), 7.08 (m, 3H), 7.53 (m, 11H), 7.83 (m, 4H), 7.94 (s, 2H); ¹³C NMR (100.61 MHz, CDCl₃): δ 16.80, 40.77, 66.62, 73.58, 130.30, 130.97, 131.68, 132.15, 132.23, 132.83, 134.63, 135.52, 136.87, 139.57, 160.08, 170.89; MS [m/z (rel. int.): 483 (M - BF₄, 15%), 410 (33%), 307 (PH₃Pyr, 100%), 230 (18%), 202 (12%), 176 (2%), 104 (11%), 91 (12%), 77 (6%); IR (KBr, cm⁻¹): 3064 (w), 2960 (w), 1755 (s), 1737 (s), 1598 (m), 1562 (m), 1553 (m), 1494 (m), 1447 (m), 1415 (w), 1381 (w), 1240 (m), 1216 (m), 1083 (s), 1058 (s), 1037 (s), 890 (w), 851 (w), 762 (s), 704 (s), 695 (s); [α]₀D = -1.75 (c = 2, CHCl₃).

Method B: A solution of phenylalanine ethyl ester (91) (1.00 g, 5.2 mmol) in THF (3 ml) was added to a yellow solution of 2,4,6-triphenylpyrylium tetrafluoroborate (74) (1.03 g, 2.6 mmol, 1/2 eq.). The mixture was stirred and heated to 50 °C for 48 h under nitrogen. Compound 85 was obtained in 67% yield using the usual work up and it was found to be optical inactive.

Method C: Method B was repeated, but acetic acid (0.1 eq) was added after addition of phenylalanine ethyl ester and 20 minutes of stirring. The reaction was complete after 7 days of stirring at room temperature. These conditions yielded only 48% of compound 85; [α]₀D = -2.25 (c = 2, CHCl₃).

5.6.4 2-Azido-3-phenylpropionic acid ethyl ester (86)

2,4,6-Triphenylpyridinium tetrafluoroborate 85 (2.5 g, 4.4 mmol) and NaN₃ (1.0 g, 15.4 mmol) in DMF were stirred and heated to 80°C for 8 h under nitrogen atmosphere. The mixture was cooled to room temperature, diluted with water, extracted with diethyl ether and washed with brine. The solution was dried over Na₂SO₄. Evaporation of solvent in vacuo gave an oily product which was purified by flash chromatography (silica gel, 1% acetone/heptane) to yield
compound 86 as a colorless oil (701 mg, 73%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.26 (t, $J = 7$ Hz, 3H), 3.03 (dd, $J = 14$ and 9 Hz, 1H), 3.17 (dd, $J = 14$ and 6 Hz, 1H), 4.03 (dd, $J = 9$ and 6 Hz, 1H), 4.21 (q, $J = 7$ Hz, 2H), 7.28 (m, 5H); $^{13}$C NMR (75.47 MHz, CDCl$_3$): $\delta$ 14.28, 37.82, 62.07, 63.41, 127.41, 128.83, 129.39, 136.16, 170.12; MS [m/z (rel. int.)]: 219 (M$^+$, 0.9%), 176 (63%) 148 (3%), 131 (3%), 118 (9%), 91 (100%); IR (neat, cm$^{-1}$): 3031 (w), 2983 (w), 2111 (s), 1741 (s), 1594 (w), 1549 (w), 1497 (m), 1455 (m), 1263 (s), 1197 (s), 1029 (m), 755 (m), 699 (s); $[\alpha]_D = -2.15$ (c = 2, CHCl$_3$).

5.6.5 2-Chloro-3-phenylpropionic acid ethyl ester (99)

Tertiary butyl nitrite [(90%), 0.86 ml, 7.2 mmol] was added to a stirred solution of phenylalanine ethyl ester hydrochloride (83) (1.0 g, 4.4 mmol) and NaN$_3$ (0.85 g, 13.1 mmol) in DME (10 ml). The mixture was stirred at rt under nitrogen atmosphere until the evolution of gas ceased (30 min). The solution was filtered, and the residue washed with diethyl ether. A yellowish oily product obtained after removal of solvent was purified by flash chromatography to give compound 99 (850 mg, 92%) as a colourless oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.25 (t, $J = 7$ Hz, 3H), 3.21 (dd, $J = 14$ and 7 Hz, 1H), 3.41 (dd, $J = 14$ and 7 Hz, 1H), 4.19 (q, $J = 7$ Hz, 2H), 4.46 (t, $J = 7$ Hz, 1H), 7.3 (m, 5H); $^{13}$C NMR (75.47 MHz, CDCl$_3$): $\delta$ 14.02, 41.20, 57.53, 62.09, 127.40, 128.66, 129.44, 136.03, 169.26; MS [m/z (rel. int.): 212 (2%), 177 (39%), 131 (100%), 135 (13%), 139 (10%), 101 (15%), 91 (100%), 93 (30%), 77 (33%), 29 (24%), 28 (45%); IR (neat, cm$^{-1}$): 3031 (w), 2983 (m), 1742 (s), 1498 (m), 1454 (m), 1391 (w), 1371 (m), 1294 (s), 1238 (m), 1178 (s), 1162 (s), 1030 (m), 747 (m), 698 (s); $[\alpha]_D = +2.1$ (c = 2, CHCl$_3$); HRMS: calculated for C$_{11}$H$_{13}$ClO$_2$: 212.0604; observed: 212.0603.

5.6.6 2-Chloropropionic acid ethyl ester (100)

Tertiary butyl nitrite [(90%), 0.32 ml, 2.4 mmol] was added to a stirred solution of alanine ethyl ester hydrochloride (97) (250 mg, 1.6 mmol) and NaN$_3$ (317 mg, 4.9 mmol) in DME (5 ml). The mixture was stirred at rt under nitrogen atmosphere until the evolution of gas ceased (30 min). The solution was filtered, and the residue washed with diethyl ether. A yellowish oily product obtained after removal of solvent was purified by flash chromatography to give compound 100 (200 mg, 90%) as a colourless oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.31 (t, $J = 7$ Hz, 3H), 1.68 (d, $J = 7$ Hz, 3H), 4.23 (q, $J = 7$ Hz, 2H), 4.40 ($J = 7$ Hz, 1H); $^{13}$C NMR (75.47 MHz, CDCl$_3$): $\delta$ 14.04, 41.52, 62.61, 126.06, 63.41, 127.41, 128.83, 129.39, 136.16, 170.12; MS [m/z (rel. int.)]: 137 (4%), 136 (2%), 135 (13%), 101 (15%), 93 (30%), 91 (100%), 73 (11%), 65 (23%), 63 (71%), 57 (56%), 55 (44%), 29 (77%); IR (neat, cm$^{-1}$): 2984
References

81

(104), 1743 (s), 1447 (m), 1302 (w), 1270 (s), 1184 (s), 1143 (s), 1074 (m), 1021 (m), 992 (w) 858 (w) 691 (w); [α]D = +5.1 (c = 2, CHCl3); HRMS: calculated for C5H9ClO2: 136.0291; observed: 136.0289.

5.6.7 3-Methyl-2-(toluene-4-sulfonyloxy)-butyric acid ethyl ester (104)

Tertiary butyl nitrite ([90%], 0.26 ml, 2.0 mmol) was added to a stirred solution of L-valine benzyl ester toluene-4-sulfonate (102) (500 mg, 1.3 mmol) and NaN3 (300 mg, 4.6 mmol) in DME (10 ml). The mixture was stirred at rt for 3 h under nitrogen atmosphere. The reaction mixture was then filtered and the residue washed with dichloromethane. A yellowish oily product obtained after removal of solvent was purified by flash chromatography (3% acetone/heptane) to give compound 104 (209 mg, 44%) as a colourless oil. 1H NMR (300 MHz, CDCl3): δ 0.87 (d, J = 4 Hz, 3H), 0.89 (d, J = 4 Hz, 3H), 2.20 (m, 1H), 2.42 (s, 3H), 4.68 (d, J = 5 Hz, 1H), 5.06 (s, 2H), 7.34 (m, 8H), 7.77 (d, J = 8 Hz, 2H); 13C NMR (75.47 MHz, CDCl3): δ 17.16, 18.48, 21.91, 31.34, 67.38, 82.27, 128.31, 128.58, 128.72, 128.79, 129.90, 133.39, 135.15, 145.14, 168.44; MS [m/z (rel. int.)]: 362 (M+, 0.11%), 279 (2.79%), 256 (7.71%), 227 (6.47%), 155 (96.76%), 107 (8.61%), 91 (100%); IR (neat, cm⁻¹): 3034 (w), 2989 (w), 1757 (s), 1455 (s), 1276 (m), 1177 (s), 997 (s), 839 (m), 697 (w); [α]D = +3.6 (c = 2, CHCl3).

References

26. X-ray diffraction experiment was conducted by Lars Kristian Hansen at the Department of Chemistry, University of Tromso.
Appendices
Appendix 1: Paper I

Preparation and nucleophilic substitution of the \( N,N \)-1,2-naphthalenedisulfonylimide derivative of a chiral amine

Sadri A. Said and Anne Fiksdahl

Organic Chemistry Laboratories, Norwegian University of Science and Technology, N-7034 Trondheim, Norway

Received 27 May 1999; accepted 22 June 1999

Abstract

In our series of nucleophilic substitution reactions on \( N,N \)-disulfonylimides we hereby report the preparation and the nucleophilic substitution of the \( N,N \)-1,2-naphthalenedisulfonylimide derivative 1a of the chiral amine 1. The disulfonimide was prepared by using the disulfonyl chloride reagent. Nucleophilic substitution of 1a by KNO\(_2\) and azide afforded the corresponding alcohol 2 and the azide product 3 with, respectively, 63 and 70\% inversion of configuration. The stereochemical results are compared with previously reported results for a series of \( N,N \)-disulfonylimides showing that the degree of inversion of 1a is lower than for the other \( N,N \)-disulfonylimides.

© 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

In our ongoing effort to develop stereoselective transformation reactions for chiral amines we have previously shown\(^1\)-\(^6\) that some \( N,N \)-disulfonyl derivatives of primary amines: \( N,N \)-ditosylimides, \( N,N \)-dimesylimides, \( N,N \)-dinosylimides and \( N,N \)-1,2-benzenedisulfonylimides, may be transformed by nucleophilic substitution reactions into the corresponding amines or alcohols with inversion of stereochemistry.

In the present study we report the preparation of the new cyclic \( N,N \)-1,2-naphthalenedisulfonylimide derivative 1a of the primary amine 1 using naphthalene-1,2-disulfonyl chloride. The leaving group ability of the \( N,N \)-1,2-disulfonylimide moiety in this intermediate was studied in the nucleophilic attack by KNO\(_2\) and azide. The corresponding alcohol 2 and azide 3 were formed. The stereochemistry of the substitution reactions are discussed and compared with our previously reported results for a series of \( N,N \)-disulfonylimides.\(^1\)-\(^6\)

* Corresponding author. Tel: +47 73 59 90 94; fax: +47 73 59 42 56; e-mail: anne.fiksdahl@chembio.ntnu.no

0957-4166/99 - see front matter © 1999 Elsevier Science Ltd. All rights reserved.

PII: S0957-4166(99)00258-X

URN:NBN:no-2330

tetasy 2904 Article
2. Results and discussion

The cyclic \(N,N\)-1,2-naphthalenedisulfonylimide derivative 1a was obtained from the primary amine 1 and naphthalene-1,2-disulfonyl chloride in comparable yields (42%) (Scheme 1) and by identical reaction conditions as previously reported for the \(N,N\)-1,2-benzenedisulfonylimides. The \(N,N\)′-bis-byproduct, the disulfonamide, \(R-NH-SO_2-Ph-SO_2-NH-R\), could be isolated as well and characterized. The reagent, naphthalene-1,2-disulfonyl chloride, was prepared in a three-step procedure via diazotization from 2-aminonaphthalenesulfonic acid essentially as previously described for benzene-1,2-disulfonyl chloride. In contrast to what was observed in the preparation of the benzene reagent, the 2-OH- and the 2-Cl-naphthalenesulfonic acids could be isolated and identified as byproducts. This can be rationalized by a displacement of the diazonium group in 2-position both by hydroxyl and chloro substituents and indicates a higher reactivity of the 2-position in 1-naphthalenesulfonic acid than the corresponding benzene compound.

\[ \text{Scheme 1.} \]

To reduce the amount of unwanted products, concentrated hydrochloric acid was replaced by glacial acetic acid in step two to dissolve the diazonium salt.

Nucleophilic attack on the \(N,N\)-1,2-naphthalenedisulfonylimide 1a by \(\text{KNO}_2\) and \(\text{NaN}_3\) afforded the alcohol 2 and azide 3 with, respectively, 60–63% and 60–70% inversion of configuration (see Table 1). The stereoselectivity in the formation of 2 and 3 from the \(N,N\)-1,2-naphthalenedisulfonylimide 1a is lower (60–70%) than for the analogous previously reported \(N,N\)-1,2-benzenedisulfonylimide (see Table 2, 8b, 84–94%). This might be explained by a higher contribution from an ionic or ion pair mechanism leading to partly racemized products because of the higher stability of the naphthalene relative to the benzenedisulfonylimide leaving group. The naphthalene leaving group is not expected to be a better nucleophile than the analogous benzene leaving group, and an explanation of the higher racemization for the former substrate would not be that the released disulfonylimide competes as a nucleophile on the starting material 1a. As can be seen from Tables 1 and 2 the mildest reaction conditions for the substitution of the naphthalenedisulphonylimide substrate 1a with both nitrite and azide are comparable with the previously reported reaction conditions for the analogous benzenedisulphonylimide 8b. Both 1a and 8b are more easily substituted than the corresponding ditosyl- 5b, dimesyl- 6b and dinosyl-imides 7b. This is particularly apparent at lower reaction temperatures. However, in contrast to what was observed for the \(N,N\)-1,2-benzenedisulfonylimides 8a,b, the degree of inversion of the naphthalenedisulphonylimide 1a could not be optimized by varying the temperature, the reaction time...
Table 1
Results for the nucleophilic substitution of 1a (>99% ee/S) shown in Scheme 1

<table>
<thead>
<tr>
<th>Substitution product, % ee/R (reaction conditions)</th>
<th>Degree of Inversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>entry 1 20 % ee/R (KNO₂/18-cr-6, DMF, 0°C, 3 hrs)</td>
<td>60 %</td>
</tr>
<tr>
<td>entry 2 20 % ee/R (as above, 30% DMF/DMSO, 0°C, 5 hrs)</td>
<td>60 %</td>
</tr>
<tr>
<td>entry 3 24 % ee/R (as above, DMF, 18°C, 24 hrs)</td>
<td>62 %</td>
</tr>
<tr>
<td>entry 4 20 % ee/R (as above, DMSO, 18°C, 24 hrs)</td>
<td>60 %</td>
</tr>
<tr>
<td>entry 5 24 % ee/R (KOH, DMF, 18°C, 24 hrs)</td>
<td>62 %</td>
</tr>
<tr>
<td>entry 6 26 % ee/R (NH₄OAc, DMF, 18°C, 24 hrs)</td>
<td>63 %</td>
</tr>
<tr>
<td>entry 7 26 % ee/R (NH₄OBz, DMF, 18°C, 24 hrs)</td>
<td>63 %</td>
</tr>
<tr>
<td>entry 8 20 % ee/R (KNO₂/18-cr-6, DMF, 80°C, 3 hrs)</td>
<td>60 %</td>
</tr>
<tr>
<td>entry 9 22 % ee/R (as above, DMSO, 80°C, 3 hrs)</td>
<td>61 %</td>
</tr>
<tr>
<td>Azide 3&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>entry 10 40 % ee/R (NaN₃, 30% DMF/DMSO, 0°C, 24 h)</td>
<td>70 %</td>
</tr>
<tr>
<td>entry 11 34 % ee/R (NaN₃, DMF, 18°C, 4 days)</td>
<td>67 %</td>
</tr>
<tr>
<td>entry 12 40 % ee/R (NaN₃, DMSO, 18°C, 24 h)</td>
<td>70 %</td>
</tr>
<tr>
<td>entry 13 20 % ee/R (NaN₃, DMF, 60°C, 24 h)</td>
<td>60 %</td>
</tr>
<tr>
<td>entry 14 36 % ee/R (NaN₃, DMSO, 60°C, 24 h)</td>
<td>68 %</td>
</tr>
</tbody>
</table>

<sup>a</sup> The % enantiomeric excess of the alcohol product 2 and the azide product 3 is based on the direct chiral GLC analysis.

or the solvent. Thus, the stereoselectivity in the formation of 2 and 3 from 1a was not dependent on the reaction conditions (see Table 1). Other oxygen nucleophiles such as hydroxide, acetate and benzoate<sup>3</sup> were used in addition to nitrite for the preparation of the alcohol 2 (see Table 1, entry 5–7) giving no specific change in stereoselectivity. A comparison of the N,N-disulfonylimides 1a, 5–8 listed in Table 2 shows that only the ditosylimides (-NTs₂, 5ₐ,ₐ) give complete inversion of configuration by nucleophilic substitution independent of benzylic or aliphatic substrates. As expected, caused by the carbocation stabilizing effect, the benzylic substrates 6b–8b in general give a lower degree of inversion than the corresponding aliphatic substrates 6a–8a. All these studies have focused on the degrees of inversion for the reactions and no attempts to optimize the yields were made.

3. Conclusion

In conclusion, nucleophilic attack on the N,N-1,2-naphthalenedisulfonylimides 1a by KNO₂ and NaN₃ afforded the alcohol 2 and azide 3 with, respectively, 60–63% and 60–70% inversion of configuration.
<table>
<thead>
<tr>
<th>Nucleophilic Substitution of N,N-disulfonylimides</th>
<th>Degree of inversion, (optimal reaction conditions)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alcohol product</td>
</tr>
<tr>
<td></td>
<td>O&lt;sub&gt;H&lt;/sub&gt;</td>
</tr>
<tr>
<td>5a</td>
<td>100 % (KNO&lt;sub&gt;2&lt;/sub&gt;, DMF, 120°C, 72h)</td>
</tr>
<tr>
<td>5b</td>
<td>100 % (as above)</td>
</tr>
<tr>
<td>6a</td>
<td>93 % (as above)</td>
</tr>
<tr>
<td>6b</td>
<td>82 % (as above)</td>
</tr>
<tr>
<td>7a</td>
<td>95 % (as above)</td>
</tr>
<tr>
<td>7b</td>
<td>82 % (as above)</td>
</tr>
<tr>
<td>8a</td>
<td>90 % (KNO&lt;sub&gt;2&lt;/sub&gt;, DMF, 90°C, 3d)</td>
</tr>
<tr>
<td>8b</td>
<td>84 % (KNO&lt;sub&gt;2&lt;/sub&gt;, 30%DMF/DMSO, 0°C, 24h)</td>
</tr>
<tr>
<td>1a</td>
<td>60-63 % (Independent of reaction conditions, see Table 1)</td>
</tr>
</tbody>
</table>
This is lower than for the previously reported analogous \(N,N\)-1,2-benzenedisulfonylimides\(^6\) (8a\textendash}b, 84\textendash}98\%). The degree of inversion by nucleophilic substitution of \(N,N\)-1,2-naphthalenedisulfonylimide 1a does not vary with reaction conditions in contrast to what has been observed for the previously reported \(N,N\)-1,2-benzenedisulfonylimides.\(^6\) Among the so far prepared \(N,N\)-disulfonylimides, the \(N,N\)-ditosylimides 5a,b, \(-\text{NTs}_2\), give the best and complete inversion of configuration independent of benzylic or aliphatic substrates.

4. Experimental

4.1. Chemicals

\((S)\)-1-Phenylethylamine 1, Hexel Chemical Products; NaH, Aldrich (>95%); phosphorus pentachloride, 18-crown-6, Fluka (\textit{purum}); 2-aminonaphthalenesulfonic acid, Fluka (\textit{pract}); sodium azide, Merck (\textit{reinst}); sodium nitrite, Merck (>99%); potassium nitrite, Acros (>97%). Solvents: \textit{pro analysi} quality. DMF and DMSO were dried over activated molecular sieve (4A). TLC: DC-Fertigplatten Kieselgel 60 F\textsubscript{254} (0.25 mm). Detection: UV light at 254 nm or preferentially by 5\% alcoholic molybdatophosphoric acid and heating. Flash chromatography: Kieselgel 60 (230\textendash}400 mesh) Merck. GLC: Carlo Erba Model 8130; injector: split (100 ml/min, T=300°C), hydrogen, detector: FID (T=270°C), column: Chrompack CP-SIL 5CB fused silica WCOT (25 m). Chiral GLC analysis: Chrompack CP-CHIRADEX-CB fused silica WCOT (25 m, 0.32 mm; 0.32 μm), carrier gas pressure 5\textendash}5.5 psi. Mps are uncorrected, and were measured on a Büchi apparatus. \(^1\)H NMR: Bruker Avance DPX 300 MHz and 400 MHz NMR spectrometer. MS: AEI MS-902. IR: Nicolet 20SXC FT-IR spectrometer.

4.2. Naphthalene-1,2-disulfonyl chloride from 2-aminonaphthalenesulfonic acid

Preparation of the title compound was carried out by a three step procedure from 2-aminonaphthalenesulfonic acid mainly as described elsewhere.\(^6\) 2-Aminonaphthalenesulfonic acid (12 g, 53.8 mmol) and sodium carbonate (3.36 g, 31.7 mmol) were dissolved in water (100 ml) by stirring and heating. The solution was cooled to 10°C and sodium nitrite (3.70 g, 53.8 mmol) in water (10 ml) was added dropwise. The resulting brown solution was poured onto a mixture of concentrated hydrochloric acid (10.5 ml) and crushed ice (60 g). After cooling for 1 hour the brown crystals were filtered off and immediately dissolved in concentrated acetic acid (50 ml). A suspension of cuprous(I) chloride (1 g, 10 mmol) in sulfur dioxide/acetic acid (75 ml, 30\% \(\text{SO}_2\) solution) was added with stirring and the temperature was slowly raised to 40°C. After 5 hours the solvent was stripped off. The resulting solid was stirred and heated with saturated sodium chloride (10 ml) to yield a green porridge which was cooled, filtered, washed with cold methanol and dried to give the disodium salt of 1,2-naphthalene disulfonic acid (14.87 g, 44.8 mmol, 83\%). \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}):\(\delta 7.65 \text{ (m, 2H)}, 7.93 \text{ (d, J=9.2 Hz, 1H)}, 8.06 \text{ (d, J=8.8 Hz, 1H)}, 8.19 \text{ (d, J=8.8 Hz, 1H)}, 8.92 \text{ (d, J=8.0 Hz, 1H)}.\) The disodium salt was heated overnight with phosphorus pentachloride (27.98 g, 134 mmol, 3 equiv.). Excess phosphorus pentachloride and the formed phosphorus oxychloride (POCl\textsubscript{3}) were distilled off under vacuum. The yellowish solid was added ice water (100 ml) and the mixture was extracted with chloroform (3\times 50 ml). The solvent was evaporated and naphthalene-1,2-disulfonyl chloride (1.71 g, 5.3 mmol, 10\% overall yield from 2-aminonaphthalenesulfonic acid) was obtained as a yellowish oil after flash chromatography.
(silica gel, 15% acetone/heptane). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.88 (m, 2H), 8.05 (d, J=9.0 Hz, 1H), 8.42 (s, 2H), 9.06 (d, J=8.8 Hz, 1H). $^{13}$C NMR (75.47 MHz, CDCl$_3$): $\delta$ 124.6, 126.6, 129.0, 129.1, 130.7, 131.0, 137.0, 137.1, 138.5, 142.5. The identity of the product was confirmed by HH/HC COSY and DEPT. MS [m/z (% rel. int.): 328/326/324 (M, 3.3/9.5/13.0%), 291 (36%), 289 (88%), 260 (30%), 226 (12%), 225 (12%), 198 (22%), 196 (30%), 177 (12%), 161 (87%), 127 (31%), 126 (100%). IR (KBr, cm$^{-1}$): 3100 (w), 3076 (w), 1372 (s), 1185 (s), 822 (m), 780 (m), 740 (m), 634 (s), 570 (s), 537 (m), 509 (s), 487 (m).

4.3. N,N'-1,2-Naphthalenedisulfonylimide formation

4.3.1. (S)-N,N'-1,2-Naphthalenedisulfonyl-1-phenylethylamine 1a

The preparation of the title compound from (S)-phenylethylamine 1 was carried out as described elsewhere.$^6$ Naphthalene 1,2-disulfonyl chloride (260 mg, 0.78 mmol) was dissolved in methylene chloride (30 ml) and brought to reflux. A solution of (S)-(+-)1-phenylethylamine (0.10 ml, 0.78 mmol) and triethylamine (0.239 ml, 1.72 mmol) in methylene chloride (10 ml) was added slowly over 12 hours. The reaction was allowed to reflux for another two hours. The solvent was evaporated in vacuo to yield 0.52 g of the crude product. The mixture was dissolved in hot acetone (10 ml), cooled to room temperature and triethylamine hydrochloride was filtered off. Compound 1a was isolated and separated from the N,N'-bis((S))-1-phenylethyl)-1,2-naphthalenedisulfonamide byproduct by flash chromatography (silica gel, 10% acetone/heptane) to yield 0.119 g (42%) of 1a. Mp 131–133°C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.12 (d, J=7.08 Hz, 3H), 5.50 (q, J=7.08 Hz, 1H), 7.38 (m, 3H), 7.65 (m, 2H), 7.80 (m, 3H), 8.02 (m, 1H), 8.25 (m, 1H), 8.41 (m, 1H). $^{13}$C NMR (75.47 MHz, CDCl$_3$): $\delta$ 19.9, 57.5, 115.8, 124.5, 125.2, 128.6, 129.0, 129.3, 129.6, 130.9, 131.2, 131.8, 134.0, 135.9, 136.5, 137.6. MS [m/z (% rel. int.): 373 (M, 0.4%), 358 (0.9%), 269 (30%), 244 (1.2%), 142 (11%), 126 (12%), 114 (24%), 105 (77%), 104 (100%). IR (KBr, cm$^{-1}$): 3075 (w), 1502 (w), 1454 (w), 1344 (s), 1326 (s), 1349 (s), 1201 (m), 1169 (s), 1143 (s), 1056 (s), 984 (m), 895 (m), 817 (m), 772 (s), 696 (s), 524 (s). [$\alpha$]$^D_{20}$ = −6.7 (c=1, CHCl$_3$). HRMS: calcd for C$_{18}$H$_{15}$NO$_4$S$_2$, 373.0443; observed, 373.0457.

4.3.2. N,N'-Bis((S))-1-phenylethyl)-1,2-naphthalenedisulfonamide

Yield 17%, colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.44 (d, J=6.7, 6H), 4.71 (m, 2H), 6.76 (NH, 2H), 6.87 (m, 6H), 7.04 (m, 4H), 7.52 (m, 2H), 7.63 (m, 2H), 7.72 (d, J=6.6, 1H), 9.19 (d, J=6.6, 1H).

4.4. 1-Phenylethanol 2 and 1-phenylethylazide 3 from (S)-N,N'-1,2-naphthalenedisulfonyl-1-phenylethylamine 1a

The nucleophilic substitution reactions for the preparation of the title compound were carried out using KNO$_2$/18-crown-6 and NaN$_3$ mainly as described elsewhere.$^1$–$^5$ Specific reaction conditions are listed in Table 1, including the degree of inversion. The alcohol 2 and the azide product 3 were characterized by $^1$H NMR and MS giving data in accordance with data for these substances published previously.$^3$–$^5$ The products 2 and 3 coeluted on GLC (both on an unpolar methylsilicone and a chiral cyclodextrin stationary phase) with the respective compounds prepared previously and characterized elsewhere.$^3$–$^5$ The percentage enantiomeric excess for 2 and 3 was based on chiral GLC analysis.
References

Appendix 2: Paper II

Stereoselective synthesis of optically active phenyl ethers
Sadri A. Said, Anne Fiksdahl and Per H. J. Carlsen*
Department of Chemistry, Norwegian University of Science and Technology, N-7491 Trondheim, Norway
Received 13 April 2000; accepted 23 May 2000

Abstract
Reacting the 1,2-naphthalenedisulfonimide of (S)-α-methylbenzylamine with phenol gave the corresponding α-methylbenzyl phenyl ether with 46% e.e. Synthesis of the authentic optically active phenyl ethers was accomplished under mild, neutral conditions by generating benzyne in the presence of optically active (R)-α-methylbenzyl alcohol. Benzyne was generated by reacting anthranilic acid with tert-butyl nitrite in refluxing monoglyme. © 2000 Elsevier Science Ltd. All rights reserved.

The stereochemistry of the nucleophilic reactions of 1,2-benzenedisulfonylimide derivatives of optically active amines has been studied.1 Similarly, the naphthalene-1,2-disulfonylimide-derivative of (S)-α-methylbenzylamine, (S)-1,2 was reacted with phenol under basic conditions in THF to yield the corresponding α-methylbenzyl phenyl ether, 2.3 However, we were not able to determine the optical purity of the product by chiral chromatography or by NMR, Scheme 1. The difficulty of determining the e.e. of phenyl ethers has been recognized by other groups.4 It was therefore decided to prepare an optically active reference compound of 2, starting from the readily available (R)-α-methylbenzyl alcohol, (R)-3. A number of nucleophilic displacement and aromatic

Scheme 1.

* Corresponding author. E-mail: per.carlsen@chembio.ntnu.no

0040-4039/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved. PII: S0040-4039(00)00872-8
substitution procedures were tested. However, as expected, all were either unreactive or not stereo-selective. The methods for the formation of the alkyl phenyl ether required mild, basic, neutral or eventually slightly acidic conditions. Strong acid conditions readily cleaved the benzylic ether bonds or resulted in racemization of the stereogenic carbon. Radical mechanisms were also avoided, ruling out Cu-promoted reactions.5

To ensure that the chiral alcohol \((R)-3\) did not racemize during ether formation, the ideal reaction must occur away from the chiral center and not involve any C–O bond cleavage. Nucleophilic aromatic substitution is only possible if an activating group is present in the aromatic halide or exceedingly strenuous conditions are employed.6 Formation of aryl ethers is generally difficult and yields are low.7 The Pd-catalyzed formation of phenyl ethers has also been reported.8 However, our objective may be accomplished by the addition of alcohol \((R)-3\) to unsubstituted benzyne,9 addressing the limitations mentioned above. The benzyne can be generated by diazotization of anthranilic acid, 4. The use of this compound for generating benzyne has been described earlier.10 In most of the described reactions the corresponding 2-diazoniumbenzoate, 5, was isolated and thermolyzed.11,12 However, examples where benzyne was generated directly from anthranilic acid by treatment with amyl nitrite in the presence of an acid catalyst and trapping agents have been reported.12 The addition of nucleophiles to benzyne has been studied.11,13 However, syntheses of aryl ethers by the addition of alcohols to benzyne were never really successful and have not found widespread use. Carrying out the reaction in an alcohol presented a potential risk of alcoholysis of the diazonium group. Thus, most of the described methods suffer from cumbersome experimental techniques and low yields of the desired products. The procedures using the isolated diazonium salt also have the disadvantage that this compound is dangerously explosive when dry.

Despite these apparent disadvantages, the benzyne route appeared most appealing to our specific problem, making it worthwhile to reinvestigate. As a result of this study we can report a modification of the anthranilic–benzyne procedure that proved successful for our system. Initially the reaction was carried out with isoamyl nitrite.14 Thus, when isoamyl nitrite was added to a solution containing anthranilic acid together with \((R)-3\), and refluxed overnight, the benzyne was formed as the anthranilic acid disappeared. However, the major addition product isolated was the isoamyl phenyl ether, 6, together with minute amounts of 2. This was encouraging, as the alcohol formed from the nitrite actually appeared to have added to the benzyne. Formation of the byproduct was eliminated by employing tert-butyl nitrite instead for generating the benzyne in order to reduce the reactivity of the alcohol formed from the nitrite. The only product observed was the desired product, which was assigned the structure \((R)-2\) (Scheme 2).

\[
\begin{align*}
\text{Scheme 2.}
\end{align*}
\]
The crude reaction mixture contained 2 together with 9% of unreacted (R)-3. The pure product was obtained in 42% isolated yield after flash chromatography. The spectroscopic properties were in agreement with the structure. The optical rotation was determined to \([\alpha]_{D}^{20} = 5.55\) (c 2.0, CHCl₃).

The starting material (R)-3 had e.e. > 99%. As it is reasonable to assume that isomerization of the stereogenic center does not take place during the transformations described here, the enantiomeric purity of ether 2 also corresponds to e.e. > 99%. From the measured optical rotation of the authentic product we can calculate the degree of racemization taking place in the reactions between (S)-1 and phenol. The data and the results including the degree of inversion in the nucleophilic displacement reactions with (S)-1 are shown in Table 1.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product (yield, %)</th>
<th>([\alpha]_{D}^{20}) (c=2.0, CHCl₃)</th>
<th>e.e %</th>
<th>Inversion %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-1 to 2</td>
<td>(R)-2, (57)</td>
<td>+ 4.05</td>
<td>46</td>
<td>73</td>
</tr>
<tr>
<td>(R)-3 + 4 to 2</td>
<td>(R)-2, (42)</td>
<td>+ 5.55</td>
<td>99</td>
<td>0</td>
</tr>
</tbody>
</table>

These data show that partial racemization takes place during the nucleophilic displacement reaction. The nature of this reactivity and its synthetic applications is currently being further investigated.

In conclusion, a new method is described for the synthesis of alkyl phenyl ethers under mild, neutral conditions by generating benzyne in the presence of the optically active (R)-α-methylbenzyl alcohol. Benzyne was formed from anthranilic acid by the reaction with tert-butyl nitrite in refluxing monoglyme.

Acknowledgements

The authors wish to thank The Norwegian Research Council, NFR, for financial support.

References

3. Methylbenzyl phenyl ether 3: To a stirred solution containing phenol (19.54 mg) and NaH (16.5 mg) in dry THF (15 ml) in a round bottom flask under nitrogen was added drop wise a solution of (S)-N,N-1,2-naphthalenedisulfonyl-1-phenylethylamine, 1, (70 mg) in THF (5 ml) and the resulting reaction mixture was stirred overnight at ambient temperature. Ether (20 ml) was added and the resulting solution was washed with water (25 ml), 0.1 M NaOH and finally with water. The ether phase was dried over anhydrous MgSO₄, filtered and the solvent evaporated under reduced pressure to yield a yellow oil, 54 mg, which was purified by flash chromatography to give 21 mg (57%) of product 2. The spectroscopic properties were all in agreement with those of an authentic sample. The optical rotation was measured to \([\alpha]_{D}^{20} = 4.05\) (c 2, CHCl₃).
14. Isoamyl phenyl ether 5; was prepared using the procedure described in Ref. 7 in 74% yield together with 2–3% of the target compound 2. Compound 6 exhibited the following spectroscopic properties: $^1$H NMR (300 MHz, CDCl₃): δ 1.0 (d, $J=6.6$ Hz, 6H), 1.74 (q, $J=6.7$ Hz, 2H), 1.91 (m, 1H), 4.05 (q, $J=6.7$ Hz, 2H), 6.97 (m, 3H), 7.33 (m, 2H) ppm. $^{13}$C NMR (75.47 MHz, CDCl₃): δ 22.8, 25.3, 38.2, 66.4, 114.7, 120.7, 129.6, 159.3 ppm.
15. (R)-Methylbenzyl phenyl ether (R)-3: To a refluxing solution of (R)-methylbenzyl alcohol 3 (1 ml, 1.01 g, 8.3 mmol) in 5 ml of monoglyme was added simultaneously solutions of anthranilic acid, 4, (3.4 g, 24.8 mmol) in 10 ml of glyme and tert-butyl nitrite (90 % pure, 3.3 ml, 2.9 g, ca. 25 mmol) in 10 ml of glyme, respectively, from two separate syringes over 10 min. The reaction mixture was then refluxed overnight. After cooling 50 ml of diethyl ether was added and the resulting mixture stirred with aqueous potassium hydroxide (3 M). The aqueous phase was extracted once with ether and the combined ether extracts were washed with water, dried (Na₂SO₄) and the solvent evaporated to give the crude product which was purified by flash column chromatography to yield 693 mg (42%) of pure ether 2. The optical rotation was measured to $[\alpha]_{D}^20 = 5.55$ (c 2.0, CHCl₃). The product exhibited the following spectroscopic properties: $^1$H NMR (300 MHz, CDCl₃): δ 7.36 (m, 4H), 7.19 (m, 3H), 6.86 (m, 3H), 5.30 (q, $J=6.4$ Hz, 1H), 1.63 (d, $J=6.4$ Hz, 3H) ppm. $^{13}$C NMR (75.47 MHz, CDCl₃): δ 24.7, 76.1, 116.1, 120.8, 125.8, 127.6, 128.8, 129.5, 143.5, 158.2 ppm. IR (NaCl): 3058, 3028, 2972, 2869, 1628, 1600, 1510, 1485, 1389, 1258, 1217, 1181, 1103, 837, 747, 700 cm⁻¹. MS [m/z, (% rel. int.)]: 198 (M⁺, 2), 106 (9), 105 (100), 104 (45), 103 (14), 94 (26), 79 (14), 78 (8), 77 (22).
Appendix 3: Paper III

Formation of chiral aryl ethers from enantiopure amine or alcohol substrates

Sadri A. Said and Anne Fiksdahl*

Organic Chemistry Laboratories, Norwegian University of Science and Technology, N-7491 Trondheim, Norway

Received 22 February 2001; accepted 15 March 2001

Abstract—Three methods for the preparation of chiral aryl ethers are demonstrated. N,N-Disulfonylimide derivatives are used in the stereoselective formation of aryl ethers from chiral amines. Nucleophilic attack of aryloxide anions on the cyclic N,N-disulfonylimide derivative of (S)-1-phenylethylamine afforded the (R)-1-phenylethyl phenyl and 2-naphthyl ethers with 83–87 and 70–79% inversion of configuration, respectively. The results are compared with results from alternative methods for the preparation of homochiral aryl ethers from chiral alcohols with complete retention and inversion of configuration, respectively.

© 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

We have previously shown1–7 that N,N-disulfonyl derivatives of primary amines (N,N-ditosylimides, N,N-dimesylimides, N,N-dinosylimides, N,N-1,2-benzenedisulfonylimides and N,N-1,2-naphthalenedisulfonylimides) are useful intermediates for the transformation of chiral amines into the corresponding alcohols or amines with inverted stereochemistry. We have also reported preliminary results for the preparation of chiral aryl ethers from disulfonylimides.8

Herein, we describe the preparation of chiral aryl ethers from amines via homochiral N,N-1,2-benzenedisulfonylimide or N,N-1,2-naphthalenedisulfonylimide derivatives. Application of two alternative methods for the preparation of homochiral (R)- or (S)-1-phenylethyl aryl ethers from (R)-1-phenylethanol, with either complete retention or inversion of configuration, are also presented.

2. Results and discussion

Cyclic (S)-N,N-1,2-benzenedisulfonylimide 2a and (S)-N,N-1,2-naphthalenedisulfonylimide 2b derivatives were prepared from (S)-phenylethylamine 1 and the respective benzene- and naphthalene-1,2-disulfonyl chlorides as previously described.5,7 Nucleophilic substitution of imides 2a and 2b with aryloxide nucleophiles, prepared by sodium hydride deprotonation of phenol and 2-naphthol, respectively, afforded the corresponding phenyl and 2-naphthyl ethers 3a and 3b in 39–68% yield (see Scheme 1). Stereoselectivity data indicated a degree of inversion of 87 and 83% for the preparation of 3a from 2a and 2b, respectively. In the preparation of 3b, 79 and 70% inversion was observed from 2a and 2b, respectively (see Table 1).

2.1. Chiral analysis and syntheses of reference compounds

The enantiomeric purity of aryl ether 3a was determined by chiral GLC. Confirmation of the absolute configuration of 3a was based on comparison of the specific rotation data for the homochiral reference compound (R)-phenyl-1-phenylethyl ether 3a, which was synthesised by a recently developed benzylene route8 from anthranilic acid 4 via diazotisation with tert-butylnitrite and thermal decomposition to benzylene followed by nucleophilic attack by (R)-1-phenylethanol. Complete retention of configuration is observed in this method (see Scheme 1 and Table 1). The present stereoselectivity results, based on chiral GLC, are higher than our previously reported results,8 which were based on the less accurate method of establishing enantiomeric purity of comparing the specific rotation of two samples.

The degree of inversion in the formation of 3b could not be determined by chiral GLC or NMR/shift reagents due to the lack of enantioseparation in both methods. Attempts to prepare the homochiral (R)-1-
phenylethyl 2-naphthyl ether $\textbf{3b}$ using the benzyne route were also unsuccessful. However, the homochiral phenyl and 2-naphthyl ether reference compounds $\textbf{3a}$ and $\textbf{3b}$ could be prepared in 65–87% yield by nucleophilic substitution of the corresponding $(R)$-1-phenylethanol TFA ester $\textbf{6}$ (see Scheme 1 and Table 1). The nucleophile was prepared by treatment of phenol with NaH. Complete inversion of stereochemistry was observed in this reaction, as shown by chiral GLC analysis of the phenyl ether product $\textbf{3a}$. The optical purity of the 2-naphthyl ether products ($\textbf{3b}$ from $\textbf{2a}$ and $\textbf{2b}$) was established based on comparison of optical rotation data with the homochiral reference compound $\textbf{3b}$. However, as mentioned above, this method is less

![Scheme 1.](image)

**Table 1. Results for reactions are shown in Scheme 1**

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Substrate</th>
<th>Nucleophile</th>
<th>Product (yield %)</th>
<th>$[\alpha]_D$ (CHCl$_3$)</th>
<th>Stereoselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\textbf{2a, 2b}$</td>
<td>(S)-2a</td>
<td>PhO$^-$</td>
<td>(R)-3a (39)</td>
<td>+4.8 ($c = 2$)</td>
<td>87% inv.$^a$</td>
</tr>
<tr>
<td></td>
<td>(S)-2a</td>
<td>2-NaphthO$^-$</td>
<td>(R)-3b (44)</td>
<td>+98 ($c = 0.2$)</td>
<td>79% inv.$^b$</td>
</tr>
<tr>
<td></td>
<td>(S)-2b</td>
<td>PhO$^-$</td>
<td>(R)-3a (57)</td>
<td>+4.05 ($c = 2$)</td>
<td>83% inv.$^c$</td>
</tr>
<tr>
<td></td>
<td>(S)-2b</td>
<td>2-NaphthO$^-$</td>
<td>(R)-3b (68)</td>
<td>+87 ($c = 0.2$)</td>
<td>70% inv.$^b$</td>
</tr>
<tr>
<td>$\textbf{4}$</td>
<td>4</td>
<td></td>
<td>(R)-3a (42)</td>
<td>+5.55 ($c = 2$)</td>
<td>100% ret.$^a$</td>
</tr>
<tr>
<td>$\textbf{6}$</td>
<td>(R)-6</td>
<td>PhO$^-$</td>
<td>(S)-3a (65)</td>
<td>-5.6 ($c = 2$)</td>
<td>100% inv.$^a$</td>
</tr>
<tr>
<td></td>
<td>(R)-6</td>
<td>2-NaphthO$^-$</td>
<td>(S)-3b (87)</td>
<td>-124 ($c = 0.2$)</td>
<td>100% inv.$^c$</td>
</tr>
</tbody>
</table>

$^a$ Enantiomeric purity of the phenyl ether products $(R)$- and $(S)$-3a is based on chiral GLC.

$^b$ Enantiomeric purity of the 2-naphthyl ether product $(R)$-3b is based on $[\alpha]_D$, comparison with authentic enantiomerically pure synthetic standard of $(S)$-3b prepared via the TFA ester $(R)$-6.

$^c$ Enantiomeric purity of the 2-naphthyl ether product $(S)$-3b is based on the assumption that the stereoselectivity of this reaction is identical to that established by chiral GLC for the phenyl ether $(S)$-(3a) formation above.

URN:NBN:no-2330
Based on previous experience, we have made the following observations regarding the effect of the leaving group, the substrate and the attacking nucleophile on the degree of inversion in nucleophilic substitution reactions of \( N,N \)-disulfonylimides:

1. Higher stereoselectivity was observed for the reported ether formation from the cyclic disulfonylimides relative to the corresponding azide and alcohol formation previously reported. This is demonstrated by the lower reaction temperatures required for the formation of ethers from 2a and 2b. The ethers were formed in 39–68% yield, which is higher than in our previous nucleophilic substitution reactions of \( N,N \)-disulfonylimides. All studies were focused on the degree of inversion for the reactions and no attempts were made to optimise the yields.

2. The reactions were carried out at ambient temperature overnight. As observed previously, both 2a and 2b were more easily substituted than the corresponding ditosyl-, dimesityl- and dinosylimides. This is caused by the carbocation stabilising effect of the latter. For aryl ether formation, higher stereoselectivity would, therefore, have been expected for non-benzylic substrates.

3. The reactions were carried out at ambient temperature overnight. As observed previously, both 2a and 2b were more easily substituted than the corresponding ditosyl-, dimesityl- and dinosylimides. This is caused by the carbocation stabilising effect of the latter. For aryl ether formation, higher stereoselectivity would, therefore, have been expected for non-benzylic substrates.

4. Two methods are presented for the formation of ethers 2a and 2b from amine and alcohol derivatives, respectively, by nucleophilic substitution with \( \text{ArO}^- \) to give inversion of configuration. Higher stereoselectivity is observed for the oxygen leaving group, \(-\text{O}\text{TFA} (100\% \text{ for substrate } 6)\), compared with the cyclic \( N,N \)-disulfonylimides (70–87\% for substrates 2a and 2b). The O-TFA leaving group, having higher electron withdrawing character and lower nucleophilic power, therefore seems to favour an \( S_N 2 \) reaction even when a less ionising solvent (THF versus DMF) and less vigorous reaction conditions (room temperature compared to 100°C) are used for the disulfonylimide reactions, which occur with partial racemisation.

### 4. Experimental

\((S)\)-\( N,N \)-1,2-Benzenedisulfonyl-1-phenylethylamine 2a and \((S)\)-\( N,N \)-1,2-naphthalenedisulfonyl-1-phenylethylamine 2b were prepared from \((S)\)-phenylethylamine 1 and benzene 1,2-disulfonfonyl chloride and naphthalene 1,2-disulfonfonyl chloride, respectively, as described elsewhere. Phenol ether 3a has also been synthesised via a benzyne route with complete retention of configuration.

#### 4.1. Preparation of \((R)\)-1-phenethyl phenyl ether 3a from \((S)\)-\( N,N \)-1,2-naphthalenedisulfonyl-1-phenylethylamine 2b

The preparation of \((R)\)-3a from \((S)\)-2b and the characterisation of \((R)\)-3a has been published elsewhere. HRMS calcd for C\(_{19}\)H\(_{17}\)O: 298.1045; obsvd: 298.1042. Chiral GLC indicated a degree of inversion of 83\% (\(R:S \) ratio 83:17).

#### 4.2. Preparation of \((R)\)-1-phenethyl 2-naphthyl ether 3b from \((S)\)-\( N,N \)-1,2-naphthalenedisulfonyl-1-phenylethylamine 2b

The reaction was carried out as described elsewhere for \((R)\)-3a using 2-naphthol (33 mg, 0.23 mmol), NaH (16.5 mg, 0.69 mmol, 3 equiv.) in dry THF (5 mL) and \((S)\)-\( N,N \)-1,2-naphthalenedisulfonyl-1-phenylethylamine (2b, 85 mg, 0.20 mmol) in dry THF (5 mL). The oily product (38.6 mg, 68\% yield) was obtained after flash chromatography. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 1.59 \) (d, \( J = 6.4 \) Hz, 3H), 2.79 (q, \( J = 7.3 \) Hz, 2H), 3.78 (d, \( J = 8.1 \) Hz, 1H), 7.18 (dd, \( J = 8.1 \) and 2 Hz, 1H), 7.30 (m, 5H), 7.42 (m, 2H), 7.58 (d, \( J = 8.1 \) Hz, 1H), 7.71 (dd, \( J = 8 \) and 1.8 Hz, 2H); \(^13\)C NMR (75.47 MHz, CDCl\(_3\)): \( \delta = 24.6, 76.2, 109.0, 119.7, 123.7, 125.8, 126.1, 126.4, 127.0, 127.6, 127.7, 128.9, 129.5, 134.6, 143.2, 156.5; MS \([m/z] (% \text{ rel. int.})\): 248 (M, 6\%), 145 (9\%), 144 (100\%), 127 (3\%), 105 (57\%), 104 (33\%), 77 (15\%); IR (neat film, cm\(^{-1}\))): 3058 (w), 3028 (w), 2972 (w), 2969 (w), 1528 (s), 1458 (s), 1386 (m), 1258 (s), 1217 (s), 1181 (m), 1103 (m), 837 (m), 747 (m), 700 (s). HRMS calcd for C\(_{19}\)H\(_{15}\)O: 248.1201; obsvd: 248.1203. \([\alpha]_D^{20} = 87 (c = 0.2, \text{CHCl}_3)\). Comparison of
specific rotation \([\alpha]D\) with an authentic homochiral standard of \((S)-3b\) (see below) indicated a degree of inversion of 70% \((R:S = 70:30)\).

### 4.3. Preparation of \((R)-1\)-phenylethyl phenyl ether 3a from \((S)-N,N-1,2\)-benzenedisulfonyl-1-phenylethylamine 2a

The preparation of \((R)-3a\) from \((S)-2a\) and phenol was carried out using a similar procedure to that described above and elsewhere.\(^8\) The oily product \((39\% \text { yield})\) was obtained after evaporation of the solvent, which was characterised giving data in accordance with \((R)-3a\) obtained from \((S)-2b\) above. \([\alpha]D = +4.8\ (c = 2, \text{CHCl}_3)\). Chiral GLC indicated a degree of inversion of 87% \((R:S = 87:13)\).

### 4.4. Preparation of \((R)-1\)-phenylethyl 2-naphthyl ether 3b from \((S)-N,N-1,2\)-benzenedisulfonyl-1-phenylethylamine 2a

The preparation of \((R)-3b\) from \((S)-2a\) and 2-naphthol was carried out using a similar procedure to that described above and elsewhere.\(^8\) The oily product \((44\% \text { yield})\) obtained after flash chromatography was characterised giving data in accordance with \((R)-3b\) obtained from \((S)-2b\) above. \([\alpha]D = +98\ (c = 0.2, \text{CHCl}_3)\). Comparison of the specific rotation \([\alpha]D\) with an authentic homochiral standard of \((S)-3b\) (see below) indicated a degree of inversion of 79% \((R:S = 79:21)\).

### 4.5. Preparation of \((R)-1\)-phenylethyl trifluoroacetate 6 from \((R)-1\)-phenylethanol 5

To a solution of \((R)-1\)-phenylethanol \((5, 0.5 \text { g, 4.1 mmol})\) and triethylamine \((0.68 \text { mL, 4.9 mmol, 1.2 equiv.})\) in dichloromethane \((10 \text { mL})\) was carefully added trifluoroacetic anhydride \((0.68 \text { mL, 4.9 mmol, 1.2 equiv.})\) at 0°C and the solution was stirred for 30 min. The yellowish oily crude product \((0.8 \text { g, 1.54 mmol, 1.5 equiv.})\) was obtained after evaporation of the solvent, which was purified by flash chromatography to give \((R)-6\) as an oil \((0.68 \text { g, 76% yield})\). \(^1\)H NMR \((300 \text { MHz, CDCl}_3)\): \(\delta = 1.67 (d, J = 6.6 \text { Hz, 3H}), 6.04 (q, J = 6.6 \text { Hz, 1H}), 7.36 (m, 5H), 13C \text{ NMR} \((75.47 \text { MHz, CDCl}_3)\): \(\delta = 22.0, 77.4, 114.7 (q, J = 286 \text{ Hz}), 126.3, 129.0, 129.1, 139.3, 157.3(q, J = 42 \text{ Hz}); MS [m/z (% rel. int.)]: 218 (M, 18%), 203 (3%), 122 (15%), 107 (44%), 105 (45%), 104 (100%), 91 (15%), 77 (53%). \([\alpha]D = +111.8\ (c = 2, \text{CHCl}_3)\).

### 4.6. \((S)-1\)-Phenylethyl phenyl ether 3a from \((R)-1\)-phenylethyl trifluoroacetate 6

A solution of phenol \((97 \text { mg, 1.03 mmol})\) and NaH \((37 \text { mg, 1.54 mmol, 1.5 equiv.})\) in DMF \((10 \text { mL})\) was stirred at rt until gas evolution ceased. \((R)-6\) \((150 \text { mg, 0.7 mmol})\) in DMF \((2 \text { mL})\) was added and the mixture was heated for 6 h at 100°C. Water \((25 \text { mL})\) was added after cooling, and \((S)-3a\) was obtained after extraction and flash chromatography \((89 \text { mg, 65% yield})\). The spectroscopic properties and GLC retention times were in agreement with those of \((R)-3a\) prepared from the \(N,N\)-disulfonylimides \(2a\) and \(2b\). \([\alpha]D = -5.6\ (c = 2, \text{CHCl}_3)\). Chiral GLC indicated a degree of inversion of 100% \((>99\% \text { ee} (S)-enantiomer)\).

### 4.7. Preparation of \((S)-1\)-phenylethyl 2-naphthyl ether 3b from \((R)-1\)-phenylethyl trifluoroacetate 6

The reaction was carried out as described above \((for the preparation of \((S)-3a\)) \(2317 \text { mg, 2.2 mmol), NaH (79 mg, 3.3 mmol, 1.5 equiv.) and \((R)-6\) \((320 \text { mg, 1.47 mmol})\) to give \((S)-3b\) \((317 \text { mg, 87% yield})\). The spectroscopic properties and GLC retention times were in agreement with those of \((R)-3b\) prepared from the \(N,N\)-disulfonylimides \(2a\) and \(2b\). \([\alpha]D = -124\ (c = 0.2, \text{CHCl}_3)\). Complete inversion for the 2-naphthyl ether \((S)-3b\) formation is based on the assumption that the stereoselectivity of this reaction is identical to that established by chiral GLC for the phenyl ether \((S)-3a\) formation above.

### 4.8. Preparation of \((R)-1\)-phenylethyl phenyl ether 3a from antranilic acid 4 and \((R)-1\)-phenylethanol 5

This method, via the benzyne intermediate, has been published elsewhere.\(^8\)

### References

Appendix 4: Paper IV

Stereoselective transformation of amines via chiral 2,4,6-triphenylpyridinium intermediates

Sadri A. Said and Anne Fiksdahl*

Organic Chemistry Laboratories, Norwegian University of Science and Technology, N-7491 Trondheim, Norway

Received 18 July 2001; accepted 30 July 2001

Abstract—We herein report the preparation and the nucleophilic substitution of the chiral 2,4,6-triphenylpyridinium tetrafluoroborates 2a and 2b. The triphenylpyridinium intermediates were generated from homochiral amines (1a, 1b) and 2,4,6-triphenylpyrylium tetrafluoroborate and used as substrates for stereoselective nucleophilic substitution. The degree of inversion in the substitution reactions has been studied. The alcohol (3a, 3b) and azide (4a, 4b) products were obtained with >99 and 96–98% inversion of configuration, respectively. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

When homochiral amino compounds are more easily accessible (e.g. from natural sources) than other alternative substrates like halides or alcohols there is a need for suitable methods for the stereoselective transformation of amines into other functionalities. In our ongoing effort to develop stereoselective transformation reactions for chiral amines we have previously shown that N,N-disulfonyl derivatives of chiral primary amines may be transformed by nucleophilic substitution reactions into the corresponding amines, alcohols and aryl ethers with inversion of stereochemistry.1–9

An alternative means of converting a primary amine into a suitable leaving group is to transform the amine RNH₂ into the 2,4,6-triphenylpyridinium compound III by treatment with 2,4,6-triphenylpyrylium salt I (see Fig. 1). It has been demonstrated that the bulky 2,4,6-triphenylpyridine ring acts as a good leaving group in synthetic transformations.10–18 The conversion of the pyrylium salt I involves a fast base-catalyzed ring opening reaction with primary amine RNH₂ and an acid-catalyzed rate-determining ring-closure step of the open-chain intermediate II to give the pyridinium salt III. When the counterion is non-nucleophilic, such as BF₄⁻, a nucleophile can add to afford the displacement product R-Nu IV and triphenylpyridine V. The driving force for this reaction is the good leaving group ability and high stability of 2,4,6-triphenylpyridine V.

To our knowledge this method has not been used for chiral substrates and the stereoselectivity of the displacement reaction has therefore never been studied. Our present work demonstrates the preparation and nucleophilic substitution of the chiral 2,4,6-triphenylpyridinium salts 2 formed from homochiral amines 1 and 2,4,6-triphenylpyrylium salt (see Scheme 1 and Table 1). The degree of inversion in the substitution reactions has been studied for the formation of the alcohol 3 and azide 4 products.
Scheme 1.

Table 1. Results for the reactions shown in Scheme 1

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Triphenylpyridinium intermediate 2 (yield %)</th>
<th>Alcohol 3&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Stereoselectivity (yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-1&lt;sup&gt;a&lt;/sup&gt;a</td>
<td>(R)-2&lt;sup&gt;a&lt;/sup&gt;a (84)</td>
<td>(S)-3&lt;sup&gt;a&lt;/sup&gt;a; &gt;99% inv. (21)</td>
<td>(S)-4&lt;sup&gt;a&lt;/sup&gt;a; 97% inv. (37)</td>
</tr>
<tr>
<td>(S)-1&lt;sup&gt;a&lt;/sup&gt;a</td>
<td>(S)-2&lt;sup&gt;a&lt;/sup&gt;a (90)</td>
<td>(R)-3&lt;sup&gt;a&lt;/sup&gt;a; &gt;99% inv. (17)</td>
<td>(R)-4&lt;sup&gt;a&lt;/sup&gt;a; 96% inv. (43)</td>
</tr>
<tr>
<td>(R)-1&lt;sup&gt;b&lt;/sup&gt;b</td>
<td>(R)-2&lt;sup&gt;b&lt;/sup&gt;b (89)</td>
<td>(S)-3&lt;sup&gt;b&lt;/sup&gt;b; &gt;99% inv. (41)</td>
<td>(S)-4&lt;sup&gt;b&lt;/sup&gt;b; 98% inv. (71)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Substrate 1<sup>b</sup>b had e.e. of 96%. The % degree of inversion for product 3<sup>b</sup>b and 4<sup>b</sup>b has been corrected for this.

<sup>b</sup> Enantiomeric purity of the alcohol products 3<sup>a</sup>a and 3<sup>b</sup>b is based on chiral GLC.

<sup>c</sup> Enantiomeric purity of the azide products 4<sup>a</sup>a and 4<sup>b</sup>b is based on GLC analysis of the diastereomeric amides after reduction and derivatization with (S)-α-methoxyphenylacetyl chloride.

2. Results and discussion

The primary amines 1<sup>a</sup>a and 1<sup>b</sup>b reacted with 2,4,6-triphenylpyridinium tetrafluoroborate by fast ring opening to the vinylogous amide (II), which underwent slow ring closure to the 1-substituted 2,4,6-triphenylpyridinium cations 2<sup>a</sup>a and 2<sup>b</sup>b in 84–90% yield (see Scheme 1 and Table 1). Both steps of the reactions could be followed by TLC and by characteristic changes of colour from yellow to dark red/black and back to yellow. The ring opening reaction was more rapid in the presence of Et<sub>3</sub>N or using an excess of the amine (2 equivalents). It is believed that the base is needed to remove the proton in one of the sub-steps in the formation of the vinylogous amide. The cyclization step is strongly catalyzed by acetic acid. The rate-enhancing effect was demonstrated by a manifold increase in reaction rate, reducing the reaction time from 7 days to 5 h by the addition of one equivalent of acetic acid.

The mass spectra of the 2,4,6-triphenylpyridinium intermediates demonstrate the energetically highly favoured fragmentation of triphenylpyridine from the molecular ions of 2<sup>a</sup>a, 2<sup>b</sup>b. Due to the weak C–N-pyridinium bond, the molecular ions were always absent in the mass spectrum and the base peak was the neutral triphenylpyridine fragment. <sup>1</sup>H NMR of the cyclohexyl intermediate 2<sup>a</sup>a showed a characteristic phenyl ring current effect<sup>19</sup> causing a high field resonance of two of the cyclohexyl protons as can be observed for (S)-2<sup>a</sup>a; δ 0.37 and 0.63. This specific shielding effect can be explained by the cyclohexyl ring conformation.

As can be seen from Table 1 the configuration of the aliphatic amine substrates 1<sup>a</sup>a and 1<sup>b</sup>b were nearly completely inverted by the nucleophilic substitution of the pyridinium intermediates 2<sup>a</sup>a, 2<sup>b</sup>b to give the alcohol 3<sup>a</sup>a, 3<sup>b</sup>b and azide 4<sup>a</sup>a, 4<sup>b</sup>b products. The azides 4<sup>a</sup>a, 4<sup>b</sup>b can be further reduced to the primary amines and thus afford the inverted amines. No attempts to optimize the yields of the substitution products 3<sup>a</sup>a, 3<sup>b</sup>b and 4<sup>a</sup>a, 4<sup>b</sup>b (17–71%) were made.

The following comments can be made on the advantages of the 2,4,6-triphenylpyridinium intermediates as
substrates for stereoselective conversion of chiral aliphatic primary amino groups into other functionalities by means of nucleophilic displacement. The formation of the intermediates 2a, 2b was carried out at room temperature. Less vigorous reaction conditions were needed and higher yields of intermediates 2a, 2b (84–90%) were obtained compared with previous  \( N,N \)-disulfonyl- \( \text{derivative} \) intermediates.\(^1\)–\(^9\) Triphenylpyridinium derivatives 2a, 2b showed comparable reactivity (80–100°C, 5 h) towards nucleophiles to ditosyl-, dimesyl- and dinosilyl-imides\(^1\)–\(^3\) (120°C, 72 h). They needed more vigorous reaction conditions than previous 1,2-benzene- and naphthalene-disulfonylimides (0°C, 24 h).\(^6\)–\(^9\) The stereoselectivity and degree of inversion (96–99%) for the substitution of intermediates 2a, 2b is comparable to that of disulfonylimides\(^1\)–\(^4\) and is generally better than other previously reported disulfonylimides.\(^5\)–\(^9\)

The benzylic racemic 1-phenylethylamine has previously been reported readily to form the triphenylpyridinium salt.\(^16\) However, the intermediate pyridinium salt could not be isolated and the corresponding alcohol product was formed directly. Presumably the benzylic pyridinium intermediate rapidly dissociates by an S_N1 process to give the resonance stabilized secondary carbocation which is trapped by water to give the alcohol. Other products could not be prepared.

Racemic products were therefore expected for the alcohol. Other products could not be prepared. Racemic products were therefore expected for the homochiral (\(R\))-1-phenylethylamine 1c (see Scheme 2). In addition to the alcohol 3c we were able to prepare the azide 4c and the aryl ether products 5c and 5d by one-pot procedures. However, all products had lost their optical activity being almost racemic. Water is generated in the ring-closure reaction for the formation of the intermediate 2c and the alcohol 3c was always present as a by-product for all reactions even in pre-dried solvents. The yields were in general higher for the nucleophilic substitution of 2c compared with 2a, 2b and the benzylic products 3c, 4c, 5c and 5d were obtained in 70–85% overall yields from the amine (\(R\))-1c.

3. Conclusion

The stereoselective conversion of chiral primary amines into alcohols and azides with inversion of configuration has been demonstrated. The 2,4,6-triphenylpyridinium derivatives 2a, 2b of the chiral primary aliphatic amines 1a and 1b were formed from 2,4,6-triphenylpyridinium tetrafluoroborate in 84–90% yield. The alcohol 3a, 3b and azide 4a, 4b products were prepared by nucleophilic substitution of the pyridium intermediates with >99 and 96–98% inversion of stereochemistry, respectively. A benzylic substrate afforded racemic alcohol, azide and aryl ether products in one-pot reactions in 70–85% yield. This process provides a method of achieving the stereoselective conversion of chiral aliphatic primary amino groups into alcohols and azides by means of nucleophilic displacement on the activated derivative.

4. Experimental

2,4,6-Triphenylpyrylium tetrafluoroborate, (\(R/S\))-1-cyclohexylethylamine and (\(S\))-\(\alpha\)-methoxyphenylacetic acid were obtained from Fluka, (\(R\))-1-phenylethylamine, potassium nitrite, triethylamine and acetic acid was prepared by optical resolution using diastereomeric crystallization with (\(S\))-N-acetylcysteine as described elsewhere.\(^1\) Phenol, 2-naphthol, sodium azide were obtained from Merck. DMF was dried over activated molecular sieves (4 Å). THF was distilled (\(N_2\)) from the sodium ketyl of benzophenone and used immediately. Solvents: pro analysis quality. GLC: Carlo Erba Model 8130, split-injection, hydrogen, FID, column: Chrompack CP-Sil 5 CB (25 m). Chiral GLC analysis: Chrompack CP-CHIRADEX-CB fused silica WCOT (25 m, 0.32 mm; 0.32 μm), carrier gas pressure 5–5.5 p.s.i. \(^1H/\,^{13}C\) NMR: Bruker Avance DPX 300/75.47 MHz and 400/100.5 MHz spectrometers, chemical shifts are reported in ppm downfield from TMS. MS: MAT 95 XL. IR: Nicolet 20SXC FT-IR spectrometer. [\(\alpha\)]_D; Perkin-Elmer 241 polarimeter (10 cm cell with a total volume of 1 mL).

4.1. Preparation of 1-(\(R \) or \(S\))-1-cyclohexylethyl)-2,4,6-triphenylpyridinium tetrafluoroborate 2a from (\(R\) or \(S\))-1-cyclohexylethylamine 1a

(S)-1-Cyclohexylethylamine (\(S\))-1a, 1.49 mL, 10.1 mmol) was added to a yellow solution of 2,4,6-triphenylpyrylium tetrafluoroborate (4.0 g, 10.1 mmol) in dichloromethane (20 mL) effecting a colour change of the mixture from yellow to red. Triethylamine (1.4 mL, 10 mmol, 1 equiv.) was added, and the deep red mixture was stirred at rt for 15 min. Acetic acid (0.58 mL, 10.1 mmol, 1 equiv.) was added turning the colour blackish. The reaction was further stirred for 8 h at rt under nitrogen. The reaction was followed by TLC and
was complete when the mixture was yellow. The crude product solidified at rt and was purified by flash chromatography (gradient elution: dichloromethane, 5% methanol/dichloromethane) to give the white crystalline pyridinium tetrafluoroborate (S)-2a (4.6 g, 90%; mp 151–153°C; 1H NMR (400 MHz, CDCl3); δ 0.37 (dq, J = 2 and 12 Hz, 1H), 0.63 (dq, J = 3 and 12 Hz, 1H), 0.85–1.70 (m, 9H), 1.58 (d, J = 7 Hz, 3H), 4.60 (dq, J = 7 and 11 Hz, 1H), 7.46–7.78 (m, 17H); 13C NMR (75.47 MHz, CDCl3); δ 21.1, 25.4, 25.59, 26.25, 30.2, 30.7, 42.4, 72.1, 128.5, 129.3, 129.8, 131.2, 132.3, 133.9, 155.3; MS [m/z (% rel. int.):] 307 (Ph3Pyr, 100%), 278 (2%), 230 (2%), 202 (6%), 110 (2%), 81 (4%); IR (KBr, cm−1): 3059 (w), 2929 (m), 2851 (m), 1617 (s), 1599 (m), 1562 (s), 1494 (m), 1411 (m), 1353 (s), 1082 (s), 1057 (s), 1034 (m), 892 (m), 763 (s), 702 (s), 532 (w), 521 (w). (S)-2a: [α]D +61.7 (c 2.0, CHCl3). (S)-2a was correspondingly prepared in 84% yield from (R)-1a and characterized: [α]D +59.1 (c 2.0, CHCl3).

4.2. Preparation of 1-((R)-1-methyl-3-phenylpropyl)-2,4,6-triphenylpyridinium tetrafluoroborate 2b from (R)-1-methyl-3-phenylpropylamine 1b

The preparation of (R)-2b from (R)-1b (96% e.e.) was carried out as described above for the preparation of (S)-2a. The crystalline product was obtained after flash chromatography (same solvent gradient as 4.1, 89% yield); mp 195–198°C; 1H NMR (300 MHz, CDCl3); δ 1.42 (d, J = 7 Hz, 3H), 1.73 (m, 1H), 2.15 (m, 2H), 2.34 (m, 1H), 4.86 (m, 1H), 6.84 (m, 2H), 7.13 (m, 3H), 7.46 (m, 10H), 7.65 (m, 7H). 13C NMR (75.47 MHz, CDCl3); δ 21.7, 32.5, 37.8, 66.1, 126.5, 128.1, 128.3, 128.8, 129.6, 130.9, 132.0, 133.8, 134.0, 139.0, 155.1, 157.3; MS [m/z (% rel. int.):] 307 (Ph3Pyr, 100%), 278 (3%), 230 (29%), 202 (15%), 152 (11%), 132 (14%), 102 (8%), 91 (27%); IR (KBr, cm−1): 3058 (w), 3026 (w), 2924 (w), 1617 (s), 1599 (w), 1583 (m), 1495 (m), 1410 (m), 1059 (s), 1036 (m), 890 (m), 764 (s), 701 (s), 520 (w). (R)-2b (96% e.e.): [α]D −53.7 (c 2.0, CHCl3).

4.3. Preparation of (S)- or (R)-1-cyclohexylethanol 3a from 1-((R)- or (S)-1-cyclohexylethyl)-2,4,6-triphenylpyridinium tetrafluoroborate 2a

((S)-1-Cyclohexylethyl)-2,4,6-triphenylpyridinium tetrafluoroborate ((S)-2a, 0.6 g, 1.19 mmol) and KNO3 (2 g, 23.5 mmol) in DMF (5 mL) was stirred and heated to 80°C for 5 h under a nitrogen atmosphere. The mixture was cooled to rt, diluted with water (40 mL), extracted with diethyl ether (2×25 mL) and washed with 0.5 M NaOH, water and brine. The solution was dried over Na2SO4. The yellowish crude oily product which was obtained after evaporation of the solvent, was purified by flash chromatography (5% acetone in heptane) to give (R)-3a as a colourless oil (26 mg, 17%). (S)-3a was correspondingly prepared in 21% yield from (R)-2a. The products were characterized giving data in accordance with (S)- and (R)-3a published elsewhere and coeluted on GLC with the respective compounds prepared previously.3 Chiral GLC indicated a degree of inversion of >99% for both reactions (R:S ratio: (R)-3a: >99:0.01 and (S)-3a: <0.01:99).

4.4. Preparation of (S)- or (R)-1-cyclohexylethyl azide 4a from 1-((R)- or (S)-1-cyclohexylethyl)-2,4,6-triphenylpyridinium tetrafluoroborate 2a

((S)-1-Cyclohexylethyl)-2,4,6-triphenylpyridinium tetrafluoroborate ((S)-2a, 3.7 g, 7.3 mmol) and NaN3 (1.6 g, 24.6 mmol, 3.3 equiv.) in DMF (10 mL) was stirred and heated to 100°C for 5 h under a nitrogen atmosphere. The mixture was cooled to rt, diluted with water (50 mL), extracted with diethyl ether (2×50 mL) and washed with brine. The crude oily product which was obtained after evaporation of the solvent, was purified by flash chromatography (heptane) to give (R)-4a as a colourless oil (433 mg, 39%). [α]D −35.8 (c 2.0, CHCl3). (S)-4a was correspondingly prepared in 37% yield from (R)-2a. The products were characterized giving data in accordance with (S)- and (R)-4a prepared previously.4 1H NMR (300 MHz, CDCl3); δ 0.90–1.80 (m, 11H), 1.25 (d, J = 6.6 Hz, 3H), 3.27 (quintet, J = 6.6 Hz, 1H); 13C NMR (75.47 MHz, CDCl3); δ 16.5, 26.2, 26.3, 26.5, 29.2, 29.4, 43.4, 63.2, 128.5, 129.3, 129.8, 131.2. The (R)- and (S)-azides 4a were reduced by catalytic hydrogenation to the corresponding amine and derivatized with (S)-α-methoxy-phenylacetyl chloride. Enantiomeric purity of the azide products (R)- and (S)-4a were based on GLC analysis of the diastereomeric amide derivatives, indicating a degree of inversion of 96–97% (R:S ratio: (R)-4a: 96:4 and (S)-4a: 3:97). The derivatized products coeluted on GLC with the respective compounds prepared previously.6

4.5. Preparation of (S)-1-methyl-3-phenylpropylazanol 3b from 1-((R)-1-methyl-3-phenylpropyl)-2,4,6-triphenylpyridinium tetrafluoroborate 2b

The nucleophilic substitution for the preparation of (S)-3b from (R)-2b (96% e.e.) and potassium nitrate was carried out as described for the preparation of (R)-3a from (S)-2a above. The oily product (41% yield) obtained after flash chromatography (5% acetone in heptane) was characterized giving data in accordance with (S)-3b published elsewhere.3 13C NMR (75.47 MHz, CDCl3); δ 23.9, 32.4, 41.1, 67.7, 126.0, 128.6, 142.3. The product coeluted on GLC with the respective compound prepared previously. The R:S ratio of 2:98 and a degree of inversion of >99%; (S)-3b (96% e.e.).

4.6. Preparation of (S)-1-methyl-3-phenylpropyl azide 4b from 1-((R)-1-methyl-3-phenylpropyl)-2,4,6-triphenylpyridinium tetrafluoroborate 2b

The nucleophilic substitution for the preparation of (S)-4b from (R)-2b (96% e.e.) and NaN3 was carried out as described for the preparation of (R)-4a from (S)-2a above. The oily product (71% yield) obtained after flash chromatography (2% acetone in heptane) was characterized giving data in accordance with (S)-4b published elsewhere.1 13C NMR (75.47 MHz, CDCl3); δ 19.7, 32.5, 38.1, 57.4, 126.2, 128.6, 128.7, 141.4. The azide (S)-4b
was reduced by catalytic hydrogenation to the corresponding amine and derivatized with (S)-3-\alpha-\text{methoxy-phenylethanol chloride. Enantiomeric purity of the azide product (S)-4b was based on GLC analysis of the diastereomeric amide derivatives, indicating an R:S ratio of 96:4 and a degree of inversion of 98%; (S)-4b (92% e.e.). The derivatized product coeluted on GLC with the respective compound prepared previously.}

4.7. Preparation of 1-((R)-1-phenylethyl)-2,4,6-triphenylpyrylium tetrafluoroborate 2c from (R)-1-phenylethylamine 1c

The preparation of (R)-2c from (R)-1c and 2,4,6-triphenylpyrylium tetrafluoroborate was carried out as described above for the preparation of (S)-2a but the nucleophile for the displacement reactions was added from the beginning. The intermediate was thus not isolated and the two-step reactions were carried out in one-pot as described below:

4.8. Preparation of 1-phenylethanol 3c from (R)-1-phenylethylamine 1c via 1-((R)-1-phenylethyl)-2,4,6-triphenylpyrylium tetrafluoroborate 2c

To a solution of 2,4,6-triphenylpyrylium tetrafluoroborate (1 g, 2.5 mmol) and KNO₂ (4.3 g, 50 mmol) in THF (10 mL) was added (R)-1-phenylethylamine ((R)-1c, 0.32 mL, 2.5 mmol) and triethylamine (0.34 mL, 2.5 mmol) using a syringe. The mixture was stirred for 20 min and acetic acid (0.14 mL, 2.5 mmol) was added. The reaction was completed after stirring for a further 10 h at rt. The product, isolated by standard procedure as a colourless oil (261 mg, 85%), was characterized giving data in accordance with 3c published elsewhere. The product coeluted on GLC with the respective compound prepared previously. Chiral GLC analysis indicated almost full racemization of the product (R:S ratio 44:56; 12% e.e. (S)-3c).

4.9. Preparation of 1-phenylethyl azide 4c from (R)-1-phenylethylamine 1c via 1-((R)-1-phenylethyl)-2,4,6-triphenylpyrylium tetrafluoroborate 2c

The nucleophilic substitution for the preparation of the azide 4c from (R)-1c was carried out as described above for the preparation of 3c from (R)-1c, replacing the nucleophile KNO₂ with NaN₃ (5 equiv.). The oily product (78% yield) obtained after flash chromatography was characterized giving data in accordance with 4c published elsewhere and the derivatized product coeluted on GLC with the respective compound prepared previously. The product showed no optical rotation and GLC of the diastereomeric amide derivatives indicated full racemization of the product (R:S ratio 1:1).

4.10. Preparation of 1-phenylethyl phenyl ether 5c and 1-phenylethyl 2-naphthyl ether 5d from (R)-1-phenylethylamine 1c via 1-((R)-1-phenylethyl)-2,4,6-triphenylpyrylium tetrafluoroborate 2c

The nucleophilic substitutions for the preparation of the products 5c and 5d from (R)-1c and phenol and 2-naphthol, respectively, were carried out as described above for the preparation of 3c from (R)-1c, replacing the nucleophile KNO₂ with phenol or 2-naphthol (3.3 equiv.). The oily products 5c (70%) and 5d (73% yield) obtained after flash chromatography (3% acetone in heptane) were characterized giving data in accordance with 5c and 5d reported elsewhere and they coeluted on GLC with the respective compounds prepared previously. The products showed no optical rotation and the enantioseparation of the phenyl ether 5c on chiral GLC indicated a racemic product (R:S ratio 1:1).

References

Appendix 5:

X-ray data for compound 85
Experimental

Crystal data

\( \text{C}_{24}\text{H}_{30}\text{BF}_{4}\text{NO}_{2} \)

\( M_r = 571.40 \)

Monoclinic

\( P2_1/c \)

\( a = 10.985 \) (6) \( \text{Å} \)

\( b = 15.501 \) (6) \( \text{Å} \)

\( c = 18.129 \) (6) \( \text{Å} \)

\( \beta = 106.41 \) (3) \( ^\circ \)

\( V = 2961 \) (2) \( \text{Å}^3 \)

\( Z = 4 \)

\( D_x = 1.282 \text{ Mg m}^{-3} \)

\( D_m \) not measured

Data collection

Enraf-Nonius CAD-4 diffractometer

\( \omega-2\theta \) scans

Absorption correction:

\( \psi \) scan (ABSCALC in OSCAIL; McArdle & Daly, 1999; North et al. 1986)

\( T_{\text{min}} = 0.9275, T_{\text{max}} = 0.9628 \)

5579 measured reflections

5204 independent reflections

Refinement

Refinement on \( F^2 \)

\( R[F^2 > 2\sigma(F^2)] = 0.0706 \)

\( wR(F^2) = 0.2713 \)

\( S = 1.097 \)

5204 reflections

383 parameters

H-atom parameters not refined

\( w = 1/[\sigma^2(F^2) + (0.1651P)^2 + 0.1363P] \)

where \( P = (F^2 + 2F^2)/3 \)

Mo \( K\alpha \) radiation

\( \lambda = 0.71069 \text{ Å} \)

Cell parameters from 25 reflections

\( \theta = 10-16^\circ \)

\( \mu = 0.095 \text{ mm}^{-1} \)

\( T = 298 \) (2) \text{ K} \)

Block

Colourless

0.60 \times 0.40 \times 0.20 \text{ mm}

Crystal source: ?

2672 reflections with

\( >2\sigma(\sigma) \)

\( R_{\text{int}} = 0.0151 \)

\( \theta_{\text{max}} = 25.00^\circ \)

\( h = 0 \rightarrow 13 \)

\( k = 0 \rightarrow 18 \)

\( l = -21 \rightarrow 20 \)

3 standard reflections

frequency: 120 \text{ min}

intensity decay: 2%

\( (\Delta/\sigma)_{\text{max}} = 0.147 \)

\( \Delta\rho_{\text{max}} = 0.587 \text{ e Å}^{-3} \)

\( \Delta\rho_{\text{min}} = -0.382 \text{ e Å}^{-3} \)

Extinction correction: \textit{SHELXL}

Extinction coefficient: 0.0030 (19)

Scattering factors from \textit{International Tables for Crystallography} (Vol. C)

\[ \text{URN:NBN:no-23} \]
Supplementary data

The tables of data shown below are not normally printed in Acta Cryst. Section C but the data will be available electronically via the online contents pages at http://journals.iucr.org/c/journalhomepage.html

Table S1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

<table>
<thead>
<tr>
<th>Occupancy</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U_EQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>1</td>
<td>0.6088 (2)</td>
<td>0.71869 (17)</td>
<td>0.18078 (15)</td>
</tr>
<tr>
<td>F1</td>
<td>1</td>
<td>0.5547 (2)</td>
<td>0.3731 (2)</td>
<td>0.30298 (17)</td>
</tr>
<tr>
<td>F2</td>
<td>1</td>
<td>0.6883 (3)</td>
<td>0.4129 (2)</td>
<td>0.33782 (16)</td>
</tr>
<tr>
<td>F3</td>
<td>1</td>
<td>0.7432 (3)</td>
<td>0.31117 (18)</td>
<td>0.42592 (19)</td>
</tr>
<tr>
<td>F4</td>
<td>1</td>
<td>0.7282 (3)</td>
<td>0.4472 (2)</td>
<td>0.46010 (16)</td>
</tr>
<tr>
<td>B1</td>
<td>1</td>
<td>0.6788 (4)</td>
<td>0.3869 (3)</td>
<td>0.4071 (2)</td>
</tr>
<tr>
<td>C1</td>
<td>1</td>
<td>0.5006 (3)</td>
<td>0.67638 (19)</td>
<td>0.18171 (18)</td>
</tr>
<tr>
<td>C2</td>
<td>1</td>
<td>0.4237 (3)</td>
<td>0.6440 (2)</td>
<td>0.11519 (17)</td>
</tr>
<tr>
<td>C3</td>
<td>1</td>
<td>0.4505 (3)</td>
<td>0.6517 (2)</td>
<td>0.04230 (19)</td>
</tr>
<tr>
<td>C4</td>
<td>1</td>
<td>0.5635 (3)</td>
<td>0.6927 (2)</td>
<td>0.0472 (2)</td>
</tr>
<tr>
<td>C5</td>
<td>1</td>
<td>0.6507 (3)</td>
<td>0.7201 (2)</td>
<td>0.1130 (2)</td>
</tr>
<tr>
<td>C6</td>
<td>1</td>
<td>0.6900 (3)</td>
<td>0.7625 (2)</td>
<td>0.25092 (19)</td>
</tr>
<tr>
<td>C7</td>
<td>1</td>
<td>0.6229 (3)</td>
<td>0.8317 (3)</td>
<td>0.2846 (2)</td>
</tr>
<tr>
<td>C8</td>
<td>1</td>
<td>0.7140 (3)</td>
<td>0.9009 (3)</td>
<td>0.3193 (2)</td>
</tr>
<tr>
<td>C9</td>
<td>1</td>
<td>0.7403 (4)</td>
<td>0.9656 (3)</td>
<td>0.2743 (3)</td>
</tr>
<tr>
<td>C10</td>
<td>1</td>
<td>0.8338 (5)</td>
<td>1.0284 (3)</td>
<td>0.3009 (3)</td>
</tr>
<tr>
<td>C11</td>
<td>1</td>
<td>0.8603 (4)</td>
<td>1.0389 (3)</td>
<td>0.2803 (3)</td>
</tr>
<tr>
<td>C12</td>
<td>1</td>
<td>0.8169 (4)</td>
<td>0.7978 (3)</td>
<td>0.4286 (3)</td>
</tr>
<tr>
<td>C13</td>
<td>1</td>
<td>0.7634 (3)</td>
<td>0.9117 (3)</td>
<td>0.3085 (2)</td>
</tr>
<tr>
<td>C14</td>
<td>1</td>
<td>0.4615 (3)</td>
<td>0.6669 (2)</td>
<td>0.25469 (18)</td>
</tr>
<tr>
<td>C15</td>
<td>1</td>
<td>0.3607 (3)</td>
<td>0.7172 (2)</td>
<td>0.2846 (2)</td>
</tr>
<tr>
<td>C16</td>
<td>1</td>
<td>0.3281 (4)</td>
<td>0.7076 (3)</td>
<td>0.3308 (2)</td>
</tr>
<tr>
<td>C17</td>
<td>1</td>
<td>0.3880 (5)</td>
<td>0.6481 (3)</td>
<td>0.3883 (2)</td>
</tr>
<tr>
<td>C18</td>
<td>1</td>
<td>0.4703 (4)</td>
<td>0.5966 (3)</td>
<td>0.3741 (2)</td>
</tr>
<tr>
<td>C19</td>
<td>1</td>
<td>0.5186 (4)</td>
<td>0.6049 (2)</td>
<td>0.3082 (2)</td>
</tr>
<tr>
<td>C20</td>
<td>1</td>
<td>0.7586 (3)</td>
<td>0.7732 (3)</td>
<td>0.1119 (2)</td>
</tr>
<tr>
<td>C21</td>
<td>1</td>
<td>0.6564 (4)</td>
<td>0.7312 (3)</td>
<td>0.1573 (3)</td>
</tr>
<tr>
<td>C22</td>
<td>1</td>
<td>0.6810 (4)</td>
<td>0.7709 (4)</td>
<td>0.1362 (4)</td>
</tr>
<tr>
<td>C23</td>
<td>1</td>
<td>0.9738 (5)</td>
<td>0.8624 (4)</td>
<td>0.1096 (3)</td>
</tr>
<tr>
<td>C24</td>
<td>1</td>
<td>0.8366 (5)</td>
<td>0.9001 (4)</td>
<td>0.0827 (3)</td>
</tr>
<tr>
<td>C25</td>
<td>1</td>
<td>0.7400 (4)</td>
<td>0.8549 (3)</td>
<td>0.0834 (2)</td>
</tr>
<tr>
<td>C26</td>
<td>1</td>
<td>0.3831 (4)</td>
<td>0.6196 (2)</td>
<td>-0.0277 (19)</td>
</tr>
<tr>
<td>C27</td>
<td>1</td>
<td>0.4804 (5)</td>
<td>0.5775 (3)</td>
<td>-0.0814 (2)</td>
</tr>
<tr>
<td>C28</td>
<td>1</td>
<td>0.3274 (6)</td>
<td>0.5491 (3)</td>
<td>-0.1400 (3)</td>
</tr>
<tr>
<td>C29</td>
<td>1</td>
<td>0.3015 (6)</td>
<td>0.5029 (3)</td>
<td>-0.1634 (3)</td>
</tr>
<tr>
<td>C30</td>
<td>1</td>
<td>0.1515 (5)</td>
<td>0.6048 (3)</td>
<td>-0.1115 (2)</td>
</tr>
<tr>
<td>C31</td>
<td>1</td>
<td>0.23255 (19)</td>
<td>0.63036 (15)</td>
<td>-0.04167 (13)</td>
</tr>
<tr>
<td>C32</td>
<td>0.50</td>
<td>0.80135 (19)</td>
<td>0.65252 (15)</td>
<td>0.25450 (13)</td>
</tr>
<tr>
<td>C33</td>
<td>0.50</td>
<td>0.81257 (19)</td>
<td>0.70728 (15)</td>
<td>0.36001 (13)</td>
</tr>
<tr>
<td>C34</td>
<td>0.50</td>
<td>0.77075 (19)</td>
<td>0.72398 (15)</td>
<td>0.38830 (13)</td>
</tr>
<tr>
<td>C35</td>
<td>0.50</td>
<td>0.65382 (15)</td>
<td>0.69682 (15)</td>
<td>0.40861 (13)</td>
</tr>
<tr>
<td>C36</td>
<td>0.50</td>
<td>0.70616 (19)</td>
<td>0.65000 (15)</td>
<td>0.38013 (13)</td>
</tr>
<tr>
<td>C37</td>
<td>0.50</td>
<td>0.74542 (19)</td>
<td>0.69475 (15)</td>
<td>0.30153 (13)</td>
</tr>
</tbody>
</table>

Table S2. Anisotropic displacement parameters (Å²)

<table>
<thead>
<tr>
<th></th>
<th>U₁₁</th>
<th>U₂₂</th>
<th>U₃₃</th>
<th>U₁₂</th>
<th>U₁₃</th>
<th>U₂₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>0.0411 (14)</td>
<td>0.0038 (16)</td>
<td>0.0043 (16)</td>
<td>0.0041 (12)</td>
<td>0.0152 (12)</td>
<td>0.0035 (13)</td>
</tr>
<tr>
<td>F1</td>
<td>0.0737 (16)</td>
<td>0.129 (2)</td>
<td>0.166 (3)</td>
<td>-0.0184 (15)</td>
<td>0.0094 (16)</td>
<td>-0.0018 (19)</td>
</tr>
<tr>
<td>F2</td>
<td>0.154 (3)</td>
<td>0.140 (2)</td>
<td>0.0961 (18)</td>
<td>0.000 (2)</td>
<td>0.0570 (17)</td>
<td>0.0225 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td>0.1023</td>
<td>0.0925</td>
<td>0.169</td>
<td>0.0057</td>
<td>0.0155</td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>0.149</td>
<td>0.116</td>
<td>0.108</td>
<td>-0.0300</td>
<td>-0.0040</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>0.068</td>
<td>0.069</td>
<td>0.065</td>
<td>-0.015</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>0.0149</td>
<td>0.0522</td>
<td>0.062</td>
<td>0.0040</td>
<td>0.0147</td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>0.0528</td>
<td>0.062</td>
<td>0.061</td>
<td>-0.0050</td>
<td>0.0210</td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>0.065</td>
<td>0.064</td>
<td>0.065</td>
<td>0.0068</td>
<td>0.0253</td>
<td></td>
</tr>
<tr>
<td>C4</td>
<td>0.064</td>
<td>0.072</td>
<td>0.065</td>
<td>0.0052</td>
<td>0.0298</td>
<td></td>
</tr>
<tr>
<td>C5</td>
<td>0.0500</td>
<td>0.066</td>
<td>0.075</td>
<td>0.0100</td>
<td>0.0257</td>
<td></td>
</tr>
<tr>
<td>C6</td>
<td>0.0157</td>
<td>0.077</td>
<td>0.069</td>
<td>-0.0017</td>
<td>0.0053</td>
<td></td>
</tr>
<tr>
<td>C7</td>
<td>0.056</td>
<td>0.130</td>
<td>0.081</td>
<td>-0.015</td>
<td>0.0156</td>
<td></td>
</tr>
<tr>
<td>C8</td>
<td>0.054</td>
<td>0.109</td>
<td>0.065</td>
<td>-0.001</td>
<td>0.0128</td>
<td></td>
</tr>
<tr>
<td>C9</td>
<td>0.091</td>
<td>0.106</td>
<td>0.081</td>
<td>0.015</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td>C10</td>
<td>0.106</td>
<td>0.085</td>
<td>0.122</td>
<td>0.015</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td>C11</td>
<td>0.073</td>
<td>0.086</td>
<td>0.132</td>
<td>0.004</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>C12</td>
<td>0.056</td>
<td>0.119</td>
<td>0.089</td>
<td>0.002</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>C13</td>
<td>0.060</td>
<td>0.118</td>
<td>0.080</td>
<td>-0.013</td>
<td>0.0274</td>
<td></td>
</tr>
<tr>
<td>C14</td>
<td>0.0523</td>
<td>0.069</td>
<td>0.0525</td>
<td>-0.0076</td>
<td>0.0128</td>
<td></td>
</tr>
<tr>
<td>C15</td>
<td>0.068</td>
<td>0.074</td>
<td>0.075</td>
<td>0.0037</td>
<td>0.0309</td>
<td></td>
</tr>
<tr>
<td>C16</td>
<td>0.096</td>
<td>0.093</td>
<td>0.087</td>
<td>0.000</td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td>C17</td>
<td>0.118</td>
<td>0.110</td>
<td>0.065</td>
<td>-0.018</td>
<td>0.043</td>
<td></td>
</tr>
<tr>
<td>C18</td>
<td>0.103</td>
<td>0.095</td>
<td>0.060</td>
<td>-0.011</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td>C19</td>
<td>0.069</td>
<td>0.066</td>
<td>0.066</td>
<td>-0.0045</td>
<td>0.0131</td>
<td></td>
</tr>
<tr>
<td>C20</td>
<td>0.0474</td>
<td>0.088</td>
<td>0.087</td>
<td>-0.0017</td>
<td>0.0283</td>
<td></td>
</tr>
<tr>
<td>C21</td>
<td>0.076</td>
<td>0.109</td>
<td>0.161</td>
<td>0.015</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>C22</td>
<td>0.053</td>
<td>0.165</td>
<td>0.180</td>
<td>0.017</td>
<td>0.049</td>
<td></td>
</tr>
<tr>
<td>C23</td>
<td>0.066</td>
<td>0.149</td>
<td>0.165</td>
<td>-0.019</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>C24</td>
<td>0.093</td>
<td>0.124</td>
<td>0.155</td>
<td>-0.007</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>C25</td>
<td>0.063</td>
<td>0.108</td>
<td>0.104</td>
<td>0.002</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>C26</td>
<td>0.083</td>
<td>0.064</td>
<td>0.060</td>
<td>-0.0082</td>
<td>0.0297</td>
<td></td>
</tr>
<tr>
<td>C27</td>
<td>0.123</td>
<td>0.085</td>
<td>0.069</td>
<td>0.013</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>C28</td>
<td>0.161</td>
<td>0.106</td>
<td>0.074</td>
<td>0.004</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>C29</td>
<td>0.163</td>
<td>0.096</td>
<td>0.066</td>
<td>-0.023</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>C30</td>
<td>0.104</td>
<td>0.102</td>
<td>0.066</td>
<td>-0.034</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>C31</td>
<td>0.076</td>
<td>0.081</td>
<td>0.067</td>
<td>-0.017</td>
<td>0.0235</td>
<td></td>
</tr>
<tr>
<td>C32</td>
<td>0.070</td>
<td>0.076</td>
<td>0.081</td>
<td>0.016</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>C33</td>
<td>0.264</td>
<td>0.103</td>
<td>0.101</td>
<td>-0.004</td>
<td>-0.008</td>
<td></td>
</tr>
<tr>
<td>C34</td>
<td>0.230</td>
<td>0.089</td>
<td>0.141</td>
<td>-0.053</td>
<td>-0.005</td>
<td></td>
</tr>
<tr>
<td>C35</td>
<td>0.096</td>
<td>0.217</td>
<td>0.344</td>
<td>0.015</td>
<td>-0.009</td>
<td></td>
</tr>
<tr>
<td>C36</td>
<td>0.095</td>
<td>0.090</td>
<td>0.117</td>
<td>0.013</td>
<td>-0.009</td>
<td></td>
</tr>
<tr>
<td>C37</td>
<td>0.30</td>
<td>0.098</td>
<td>0.061</td>
<td>0.007</td>
<td>-0.086</td>
<td></td>
</tr>
<tr>
<td>C38</td>
<td>0.116</td>
<td>0.057</td>
<td>0.118</td>
<td>0.031</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>C39</td>
<td>0.081</td>
<td>0.144</td>
<td>0.198</td>
<td>-0.045</td>
<td>-0.049</td>
<td>-0.080</td>
</tr>
</tbody>
</table>
Table S3. Geometric parameters (Å, °)

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1—C1</td>
<td>1.364 (4)</td>
<td>C18—H18</td>
</tr>
<tr>
<td>N1—C5</td>
<td>1.374 (4)</td>
<td>C19—H19</td>
</tr>
<tr>
<td>N1—C6</td>
<td>1.492 (4)</td>
<td>C20—C25</td>
</tr>
<tr>
<td>F1—B1</td>
<td>1.360 (5)</td>
<td>C20—C21</td>
</tr>
<tr>
<td>F2—B1</td>
<td>1.352 (5)</td>
<td>C21—C22</td>
</tr>
<tr>
<td>F3—B1</td>
<td>1.363 (5)</td>
<td>C22—C23</td>
</tr>
<tr>
<td>F4—B1</td>
<td>1.340 (5)</td>
<td>C23—C24</td>
</tr>
<tr>
<td>C1—C2</td>
<td>1.452 (4)</td>
<td>C24—H22</td>
</tr>
<tr>
<td>C2—C3</td>
<td>1.384 (4)</td>
<td>C25—H23</td>
</tr>
<tr>
<td>C2—H2</td>
<td>0.9300</td>
<td>C21—C25</td>
</tr>
<tr>
<td>C3—C4</td>
<td>1.385 (5)</td>
<td>C21—H24</td>
</tr>
<tr>
<td>C3—C26</td>
<td>1.485 (5)</td>
<td>C25—H25</td>
</tr>
<tr>
<td>C4—C5</td>
<td>1.355 (5)</td>
<td>C26—C27</td>
</tr>
<tr>
<td>C4—H4</td>
<td>0.9300</td>
<td>C26—C31</td>
</tr>
<tr>
<td>C5—C20</td>
<td>1.452 (5)</td>
<td>C27—C28</td>
</tr>
<tr>
<td>C6—C32</td>
<td>1.470 (4)</td>
<td>C27—H27</td>
</tr>
<tr>
<td>C6—C7</td>
<td>1.524 (5)</td>
<td>C28—C29</td>
</tr>
<tr>
<td>C6—H6</td>
<td>0.9800</td>
<td>C28—H28</td>
</tr>
<tr>
<td>C7—C8</td>
<td>1.514 (6)</td>
<td>C29—C30</td>
</tr>
<tr>
<td>C7—H7A</td>
<td>0.9700</td>
<td>C29—H29</td>
</tr>
<tr>
<td>C7—H7B</td>
<td>0.9700</td>
<td>C30—C31</td>
</tr>
<tr>
<td>C8—C9</td>
<td>1.361 (6)</td>
<td>C30—H30</td>
</tr>
<tr>
<td>C8—C13</td>
<td>1.300 (5)</td>
<td>C31—H31</td>
</tr>
<tr>
<td>C9—C10</td>
<td>1.377 (7)</td>
<td>O22—O11</td>
</tr>
<tr>
<td>C9—H9</td>
<td>0.9300</td>
<td>O22—O22</td>
</tr>
<tr>
<td>C10—C11</td>
<td>1.334 (6)</td>
<td>O22—O21</td>
</tr>
<tr>
<td>C10—H10</td>
<td>0.9300</td>
<td>O22—C32</td>
</tr>
<tr>
<td>C11—C12</td>
<td>1.356 (6)</td>
<td>O21—O12</td>
</tr>
<tr>
<td>C11—H11</td>
<td>0.9300</td>
<td>O21—C32</td>
</tr>
<tr>
<td>C12—C13</td>
<td>1.390 (6)</td>
<td>O21—C31</td>
</tr>
<tr>
<td>C12—H12</td>
<td>0.9300</td>
<td>O21—C32</td>
</tr>
<tr>
<td>C13—H13</td>
<td>0.9300</td>
<td>O12—C32</td>
</tr>
<tr>
<td>C14—C19</td>
<td>1.375 (5)</td>
<td>C31—C33</td>
</tr>
<tr>
<td>C14—C15</td>
<td>1.370 (5)</td>
<td>C31—C32</td>
</tr>
<tr>
<td>C15—C16</td>
<td>1.389 (5)</td>
<td>C31—H33A</td>
</tr>
<tr>
<td>C15—H15</td>
<td>0.9300</td>
<td>C31—H34B</td>
</tr>
<tr>
<td>C16—C17</td>
<td>1.370 (6)</td>
<td>C332—C331</td>
</tr>
<tr>
<td>C16—H16</td>
<td>0.9300</td>
<td>C332—H332</td>
</tr>
<tr>
<td>C17—C18</td>
<td>1.355 (6)</td>
<td>C331—H331</td>
</tr>
<tr>
<td>C17—H17</td>
<td>0.9300</td>
<td>O11—O12</td>
</tr>
<tr>
<td>C18—C19</td>
<td>1.387 (5)</td>
<td>C332—H332</td>
</tr>
<tr>
<td>C1—N1—C5</td>
<td>119.5 (3)</td>
<td>C5—C14—H4</td>
</tr>
<tr>
<td>C1—N1—C6</td>
<td>121.4 (3)</td>
<td>C3—C4—H4</td>
</tr>
<tr>
<td>C5—N1—C6</td>
<td>119.9 (3)</td>
<td>C4—C5—N1</td>
</tr>
<tr>
<td>F4—B1—F2</td>
<td>109.6 (4)</td>
<td>C4—C5—C20</td>
</tr>
<tr>
<td>F4—B1—F1</td>
<td>110.3 (4)</td>
<td>N1—C5—C20</td>
</tr>
<tr>
<td>F2—B1—F1</td>
<td>106.0 (3)</td>
<td>C2—O6—N1</td>
</tr>
<tr>
<td>F4—B1—F3</td>
<td>110.1 (3)</td>
<td>C2—O6—C7</td>
</tr>
<tr>
<td>F2—B1—F3</td>
<td>106.6 (4)</td>
<td>N1—O6—C7</td>
</tr>
<tr>
<td>F1—B1—F3</td>
<td>106.7 (3)</td>
<td>C2—O6—H6</td>
</tr>
<tr>
<td>C2—C1—N1</td>
<td>119.6 (3)</td>
<td>N1—C6—H6</td>
</tr>
<tr>
<td>C2—C1—C14</td>
<td>119.8 (3)</td>
<td>C7—C6—H6</td>
</tr>
<tr>
<td>N1—C1—C14</td>
<td>120.7 (3)</td>
<td>C8—C7—O6</td>
</tr>
<tr>
<td>C1—C2—C3</td>
<td>122.8 (3)</td>
<td>C8—C7—H7A</td>
</tr>
<tr>
<td>C1—C2—H2</td>
<td>118.6</td>
<td>C6—C7—H7A</td>
</tr>
<tr>
<td>C3—C2—H2</td>
<td>118.6</td>
<td>C8—C7—H7B</td>
</tr>
<tr>
<td>C4—C3—C25</td>
<td>115.3 (3)</td>
<td>C6—C7—H7B</td>
</tr>
<tr>
<td>C4—C3—C26</td>
<td>115.3 (3)</td>
<td>H7A—C7—H7B</td>
</tr>
<tr>
<td>C5—C4—C3</td>
<td>122.4 (3)</td>
<td>C9—C8—C13</td>
</tr>
<tr>
<td>C5—C4—C3</td>
<td>122.0 (3)</td>
<td>C9—C8—C7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>121.3 (4)</td>
</tr>
</tbody>
</table>

URN:NBN:no-2330
<p>| N1—C1—C2—C3 | 0.5 (5) | C27—C26—C31—C30 | -1.2 (5) |
| C14—C1—C2—C3 | 179.0 (3) | C3—C36—C31—C30 | 178.3 (3) |
| C1—C2—C3—C4 | 1.7 (5) | C32—O22—O21—O12 | 62.2 |
| C1—C2—C3—C26 | -177.2 (3) | C33—O22—O21—O12 | -111.2 |
| C2—C3—C4—C5 | -2.4 (5) | C34—O22—O21—C32 | 116 (6) |
| C26—C3—C4—C5 | 176.6 (3) | C35—O22—O21—C32 | -173.4 |
| C3—C4—C5—N1 | 0.8 (5) | C36—O22—O21—C33 | -57 (6) |
| C3—C4—C5—C20 | -177.2 (3) | C32—O22—O21—C33 | -173.2 |
| C1—N1—C5—C4 | 1.5 (5) | C332—O22—O21—C33 | 13.4 |
| O6—N1—C5—C4 | -175.1 (3) | C32—O22—O21—C33 | -70 (6) |
| C1—N1—C5—C20 | 179.6 (3) | C33—O21—O12—C32 | -145.7 |
| C6—N1—C5—C20 | 2.9 (4) | C33—O21—O12—C32 | -77.3 |
| C1—N1—C6—C32 | 77.5 (3) | C33—O21—O12—C32 | -71.9 |
| C5—N1—C6—C32 | -106.0 (3) | C33—O21—O12—C32 | 17.6 |
| C4—N1—C6—C7 | -58.6 (4) | C33—O21—O12—C32 | -5.4 |
| C82—O6—C7—C8 | 118.0 (4) | C33—O21—O12—C32 | -80.4 |
| N1—C7—C8—O6 | 83.4 (4) | C32—O21—O12—C32 | 158.9 |
| C6—C7—C8—O9 | -146.3 (3) | C32—O21—O12—C32 | 155.3 |
| C6—C7—O8—C13 | 75.9 (5) | C32—O21—O12—C32 | 119.4 |
| C13—C6—C7—C8 | 104.6 (4) | C32—O21—O12—C32 | 119.9 |
| C7—C8—O9—C10 | 1.6 (6) | C33—O21—O12—C32 | -99.1 |
| C6—C9—C10—C11 | -178.9 (4) | C33—O21—O12—C32 | 116.2 |
| C8—C9—C10—C11 | -1.7 (7) | C33—O21—O12—C32 | 124.3 |
| C9—C10—C11—C12 | 0.6 (7) | C33—O21—O12—C32 | 3.6 |
| C10—C11—C12—C13 | 0.4 (7) | C33—O21—O12—C32 | 155.3 |
| C11—C12—C13—C8 | -0.5 (6) | C33—O21—O12—C32 | 140.2 |
| C9—C8—C13—C12 | -0.6 (6) | C33—O21—O12—C32 | 158.9 |
| C7—C8—C13—C12 | 180.0 (4) | C33—O21—O12—C32 | 155.3 |
| C2—C1—C4—C9 | 101.3 (4) | C33—O21—O12—C32 | 119.4 |
| C1—C4—C9—C10 | -80.2 (4) | C33—O21—O12—C32 | 119.9 |
| N1—C4—C9—C15 | 105.3 (3) | C33—O21—O12—C32 | 116.2 |
| C19—C14—C15—C16 | 3.2 (5) | C33—O21—O12—C32 | 124.3 |
| C1—C14—C15—C16 | 177.8 (3) | C33—O21—O12—C32 | 3.6 |
| C14—C15—C16—C17 | -0.6 (6) | C33—O21—O12—C32 | 155.3 |
| C15—C16—C17—C18 | -1.6 (7) | C33—O21—O12—C32 | 102.7 |
| C16—C17—C18—C19 | 1.2 (7) | C33—O21—O12—C32 | 122.9 |
| C15—C14—C19—C18 | -3.7 (5) | C33—O21—O12—C32 | 122.9 |
| C1—C14—C19—C18 | -178.0 (3) | C33—O21—O12—C32 | 20.2 |
| C17—C18—C19—C14 | 1.4 (6) | C33—O21—O12—C32 | -99.2 |
| C4—C5—C20—C25 | 75.7 (5) | C33—O21—O12—C32 | 121.0 |
| N1—C5—C20—C25 | -102.3 (4) | C33—O21—O12—C32 | -99.2 |
| C4—C5—C20—C21 | -103.0 (5) | C33—O21—O12—C32 | 121.0 |
| C5—C20—C21—C22 | 1.7 (4) | C33—O21—O12—C32 | -99.2 |
| C5—C20—C21—C22 | -179.9 (5) | C33—O21—O12—C32 | 173.9 |
| C20—C21—C22—C23 | 0.3 (9) | C33—O21—O12—C32 | 7.3 |
| C21—C22—C23—C24 | -1.4 (10) | C33—O21—O12—C32 | -15.3 (2) |
| C22—C23—C24—C25 | 0.7 (9) | C33—O21—O12—C32 | 164.2 (2) |
| C21—C20—C25—C24 | -2.1 (7) | C33—O21—O12—C32 | 171.4 (2) |
| C5—C20—C25—C24 | 179.2 (4) | C33—O21—O12—C32 | 179.5 |
| C23—C24—C25—C20 | 1.1 (8) | C33—O21—O12—C32 | 162.3 |
| C4—C3—C26—C27 | 42.4 (5) | C33—O21—O12—C32 | 173.3 |
| C2—C3—C26—C27 | -188.7 (4) | C33—O21—O12—C32 | 179.5 |
| C4—C3—C26—C31 | -137.1 (3) | C33—O21—O12—C32 | -11.0 |
| C2—C3—C26—C31 | 41.8 (5) | C33—O21—O12—C32 | -137.8 |
| C31—C26—C27—C28 | 0.2 (6) | C33—O21—O12—C32 | 7.7 |
| C3—C26—C27—C28 | -179.3 (4) | C33—O21—O12—C32 | -5.3 |</p>
<table>
<thead>
<tr>
<th>Bond</th>
<th>Distance (Å)</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O12–O21–C32–C6</td>
<td>55.13 (18)</td>
<td></td>
</tr>
<tr>
<td>C331–O21–C32–C6</td>
<td>-159.38 (18)</td>
<td></td>
</tr>
<tr>
<td>O22–O21–C32–C6</td>
<td>-167.07 (18)</td>
<td></td>
</tr>
<tr>
<td>C332–O21–C32–C6</td>
<td>-172.37 (18)</td>
<td></td>
</tr>
<tr>
<td>O12–O21–C32–O11</td>
<td>-138.0</td>
<td></td>
</tr>
<tr>
<td>C331–O21–C32–O11</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>O22–O21–C32–O11</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>C332–O21–C32–O11</td>
<td>-5.5</td>
<td></td>
</tr>
<tr>
<td>C331–O21–C32–O12</td>
<td>145.5</td>
<td></td>
</tr>
<tr>
<td>O22–O21–C32–O12</td>
<td>137.8</td>
<td></td>
</tr>
<tr>
<td>C332–O21–C32–O12</td>
<td>132.5</td>
<td></td>
</tr>
<tr>
<td>N1–C6–C32–O22</td>
<td>36.1 (3)</td>
<td></td>
</tr>
<tr>
<td>C7–O6–C32–O22</td>
<td>169.6 (2)</td>
<td></td>
</tr>
</tbody>
</table>