Stereoselective Transformations of Chiral Amines

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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 α-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 α-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 α-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

URN:NBN:no-2330

Preface

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

The thesis is divided in 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 summarize 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 discuss 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 α-amino acids is discussed in Chapter 5. Diazotization of α-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.

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

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Abbreviations

Ac	acetyl
ACE	angeotensin converting enzyme
Ar	aryl
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Bn	benzyl
Bu	butyl
δ	chemical shift
d	doublet
DABN	2,2’-diamino-1,1’-binaphthyl
DEAD	diethyl azodicarboxylate
DIPAMP	2,3-(bis(diphenylphosphino)-butane
DMAP	4-*N,N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
Et	ethyl
h	hour
Hz	hertz
IR	infrared
J	coupling constant
L-Dopa	3-(3,4-dihydroxyphenyl)-L-alanine
m	multiplet
M.p.	melting point
Me	methyl
mmol	millimoles
Ms	mesyl
MS	mass spectroscopy
NMR	nuclear magnetic resonance
Ns	nosyl
o	ortho
p	para
Ph	phenyl
PPY	4-pyrrolidinopyridine
q	quartet
rt	room temperature
s	singlet
SSI	solvent separated ion pair
TBAF	tetrabutylammonium fluoride

TEA	triethylamine
TFA	trifluoroacetyl
THF	tetrahydrofuran
TIP	tight ion pair
TMS	trimethylsilyl
Tol	toluene
TPP	triphenylphosphine
Ts	tosyl

List of papers

1. Said, S. A., Fiksdahl, A. “Preparation and nucleophilic substitution of the *N,N*-1,2-naphthalenedisulfonylimide derivative of a chiral amine”, *Tetrahedron: Asymmetry* **1999**, *10*, 2627-2633.

II Said, S. A., Fiksdahl, A., Carlsen, P. H. J. “Stereoselective synthesis of optically active phenyl ether”, *Tetrahedron Lett.* **2000**, *41*, 5593-5596.

III Said, S. A., Fiksdahl, A. “Formation of chiral aryl ethers from enantiopure amine or alcohol substrates”, *Tetrahedron: Asymmetry* **2001**, *12*, 893-896.

IV Said, S. A., Fiksdahl, A. “Stereoselective transformation of amines via chiral 2,4,6-triphenylpyridinium intermediates”, *Tetrahedron: Asymmetry* **2001**, *12*, 1947-1951.

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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 Pasteur[1] 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 period[2-6]. However, for industrial production of homochiral compounds methods based on optical resolution are still among the most important and more profitable means[7-10]. 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 alcohols[11-15], halides[16-18], epoxides[19-22], 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 decade[23-28]. Most of these methods involve stereoselective nucleophilic displacement on activated derivatives of the

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.

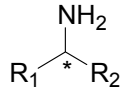
Before proceeding to stereoselective transformations of amines in Chapters 2-5, the rest of this chapter will present a brief account of the impact of chiral substances on the living system and the necessity of preparing them. The existing methodologies used to produce pure enantiomers will be summarized, with emphasis on the methods used to prepare chiral amines. Furthermore, a brief discussion on inversion and stereselective 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 α-position to the amino functionality (Figure 1.1).



* = stereogenic center (*R* or *S)*

R_1, R_2 = alkyl or aryl

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[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[34] and as resolving agents[9,29]. They are also used in the preparation of various bioactive molecules for instance compounds **7** and **8** (Figure 1.3)[37,38]. α-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[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_3 serotonin ligands[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[41,42]. Enantiomerically pure vicinal diamines and their derivatives are used increasingly in asymmetric synthesis as chiral auxiliaries or as metal ligands[33].

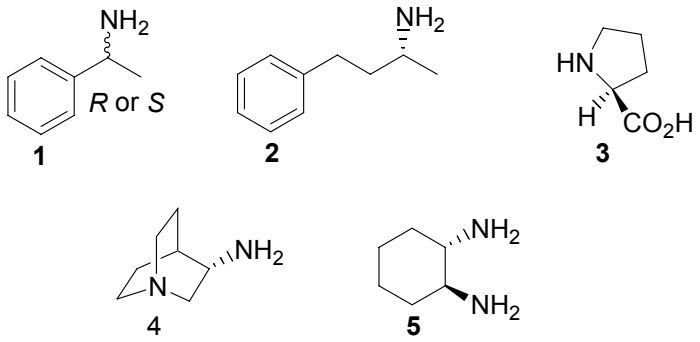


Figure 1.2 Kinds of enantiomerically pure amines.

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

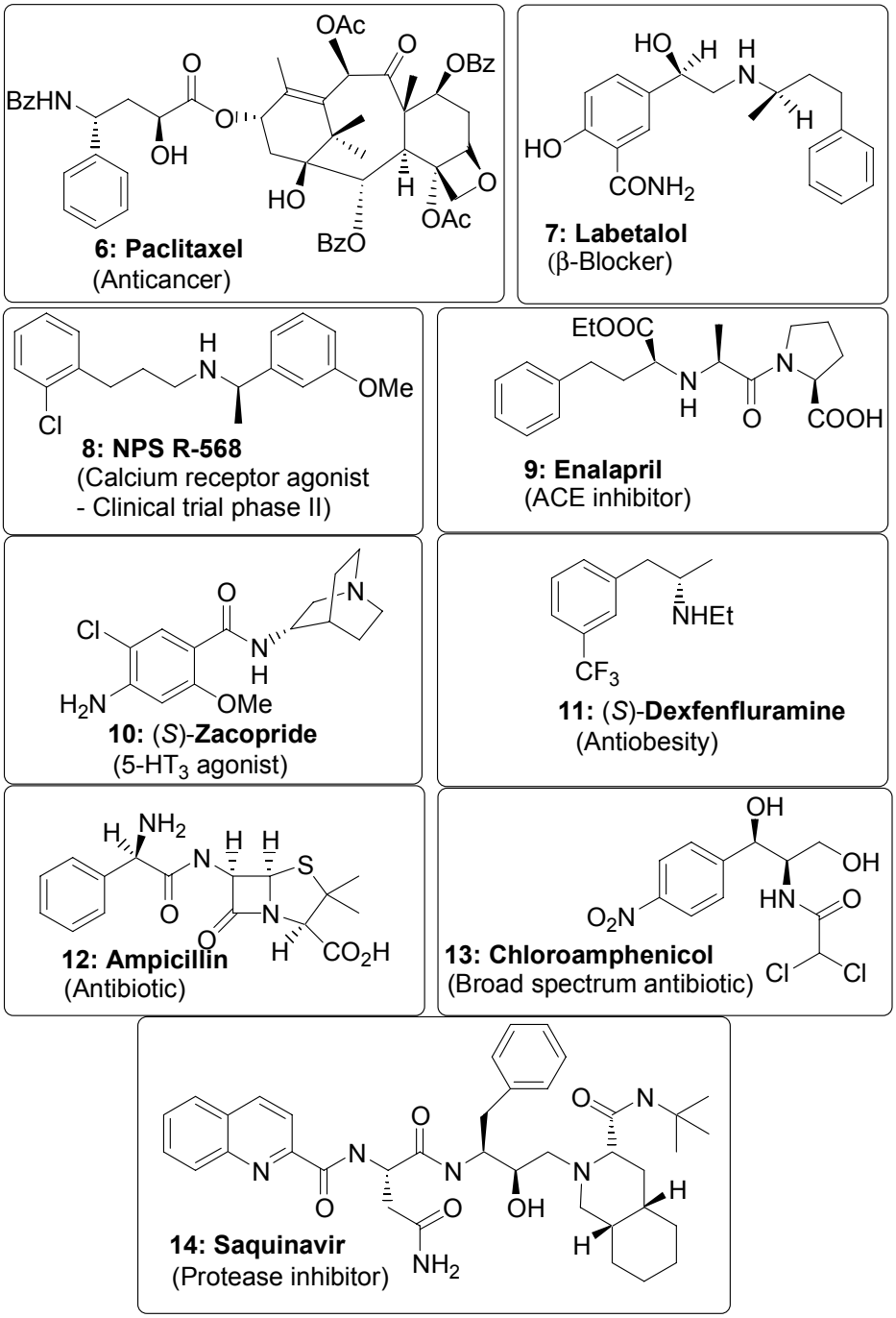


Figure 1.3 Pharmaceutical compounds containing chiral amino group.

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 discuss 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 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 reside almost entirely to the (*S*)-enantiomers and the (*R)*-isomers, the distomers, are completely inactive and exhibit no side effect[48].

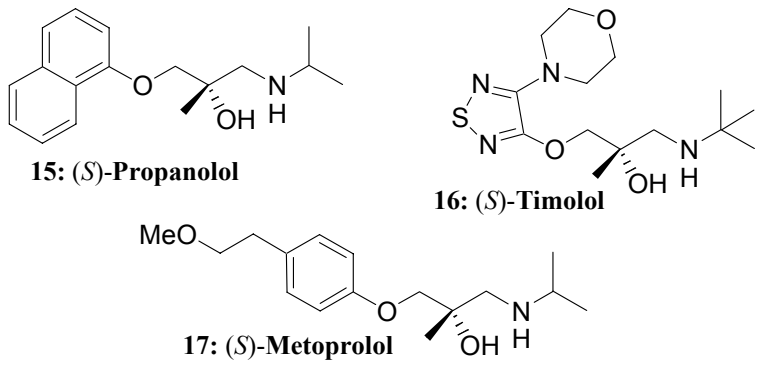


Figure 1.4 The eutomers of some β-blockers.

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[43]. Another example is the antiarthritic agent, penicillamine (**19**) (Figure 1.5), whose distomer, the (*R*)-enantiomer, is mutagenic[49].

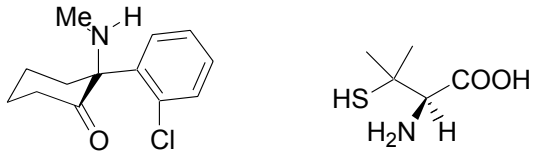
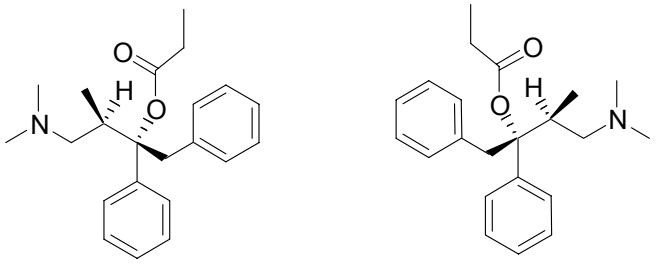


Figure 1.5 Chiral drugs whose distomer exhibit undesirable side effect.

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[50].



20a: Darvon **20b: Novrad**

Figure 1.6 Enantiomers exhibiting useful but different biological activities.

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[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[54]. In the clinic, a number of chiral

markers are used in diagnosis of diseases[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[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)[57-60]. Furthermore, development of single enantiomer drugs has opened a new market strategy, the so called chiral switches[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[62,63]. Simultaneously, biotechnology and biocatalysis are rapidly expanding fields to produce and to purify chiral intermediates[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.

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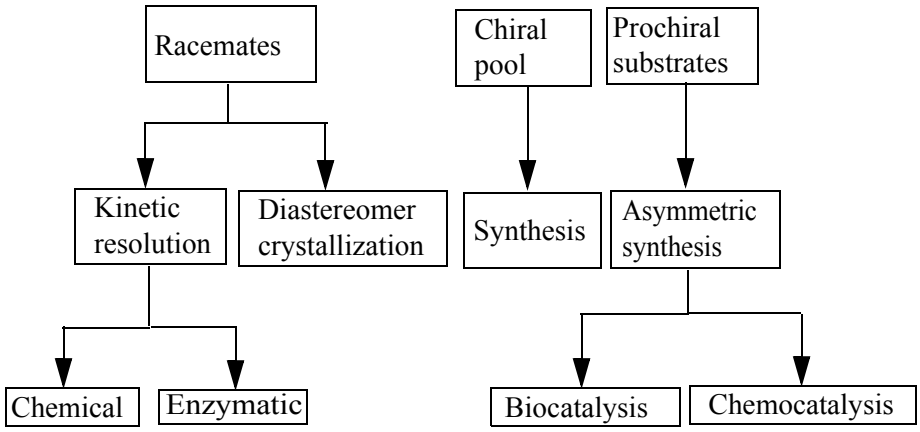


Figure 1.7 Methods for preparation of enantiomerically pure compounds[48].

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[66], are isolated from the bark of the cinchona tree. These compounds are also potent antimalarial agents[67]. Another example are the β-lactam antibiotics such as penicillin G (**22**) (Figure 1.8) which are obtained from microbial fermentation[68]. Natural amino acids is another class of chiral amines harvested from the chiral pool[69].

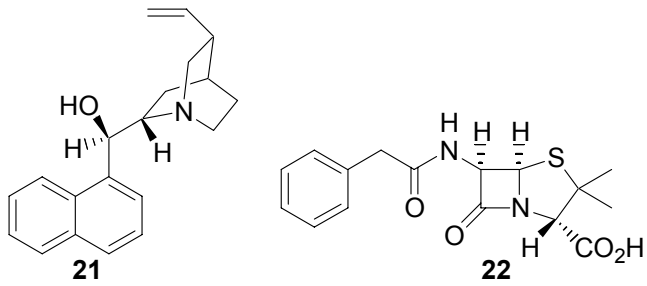


Figure 1.8 Examples of chiral amines obtained from the chiral pool.

1.4.2 Resolution methods

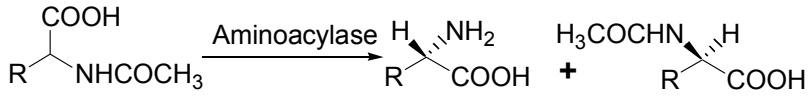
Racemates can be resolved into their enantiomers via three methods:

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[70]. 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[48,64,71]. Among the six main groups of enzymes hydrolases and oxidoreductases are the most frequently used biomolecules in kinetic resolutions[70]. For example, natural amino acids are produced in industrial scale using hydrolases[72]. In this process the acylases hydrolyze racemic amides stereoselectively to give enantiomerically pure α-amino acids (Scheme 1.1).



Scheme 1.1 Kinetic resolution of α-amino acids.

Simple amines are also prepared using hydrolytic enzymes, Klibanov and his coworkers[73] 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.

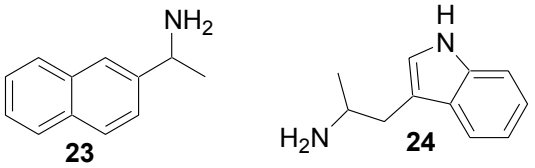


Figure 1.9 Examples of amines resolved by hydrolytic enzymes.

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 1-arylethylamines using a planar-chiral DMAP derivative, (-)-PPY (**25**) (Figure 1.10)[74].

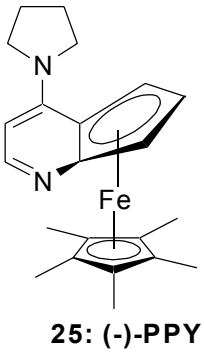


Figure 1.10 Catalyst for chemocatalytic kinetic resolution of 1-arylethylamine.

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 α-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 α-methylbenzylamine (**1**) (Figure 1.2) and 1-phenyl-2-(*p*-tolyl)-ethylamine (**28**) (Figure 1.11) via their cinnamic acid salts. α-Amino acids are also resolved via these protocols[78,79].

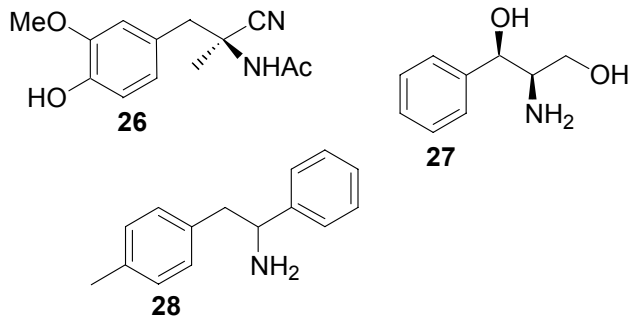
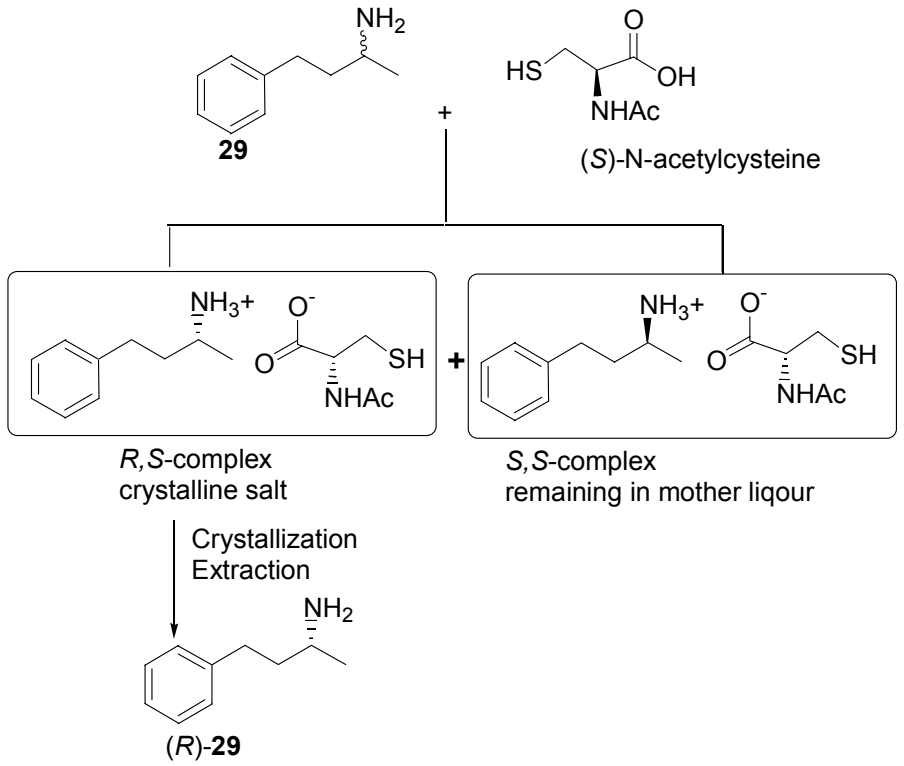


Figure 1.11 Examples of amines resolved by preferential crystallization.

1.4.2.3 Resolution via diastereomer crystallization

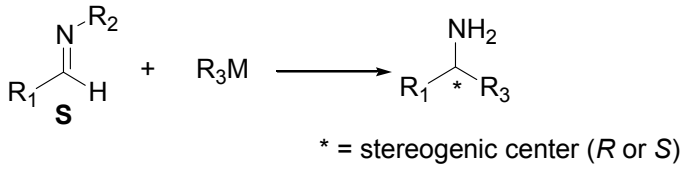
Diastereomer crystallization is a method which utilizes an enantiomerically pure acid or base (the resolving agent) which forms diastereomeric salts with the racemate. Pure enantiomers are then obtained by selective crystallization of the diastereomeric salts. Although classical resolution is the oldest 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).



*Scheme 1.2 Optical resolution of racemic 1-methyl-3-phenylpropylamine (**29**).*

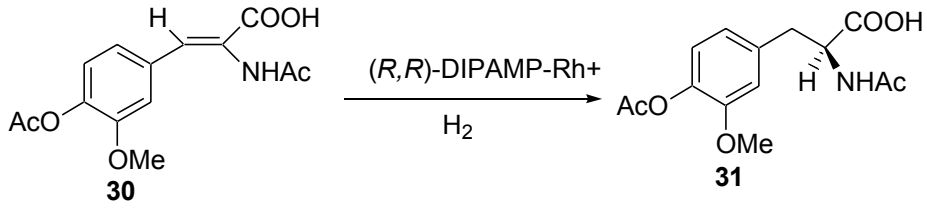
1.4.3 Asymmetric synthesis

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[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_1) or the amine part (R_2) of the imino substrate **S**. Alternatively, the chiral information is obtained from the nucleophilic reagent (R_3) (Scheme 1.3)[34]. Asymmetry could also be induced via external chiral ligand intergrated in a chiral catalyst[35].



Scheme 1.3 Asymmetric synthesis of chiral amines.

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)[82].



Scheme 1.4 Preparation of chiral amines by catalytic asymmetric hydrogenation.

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[10,70]. Therefore with regard to the method of choice there is no simple all including answer. As has been pointed out by Sheldon[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

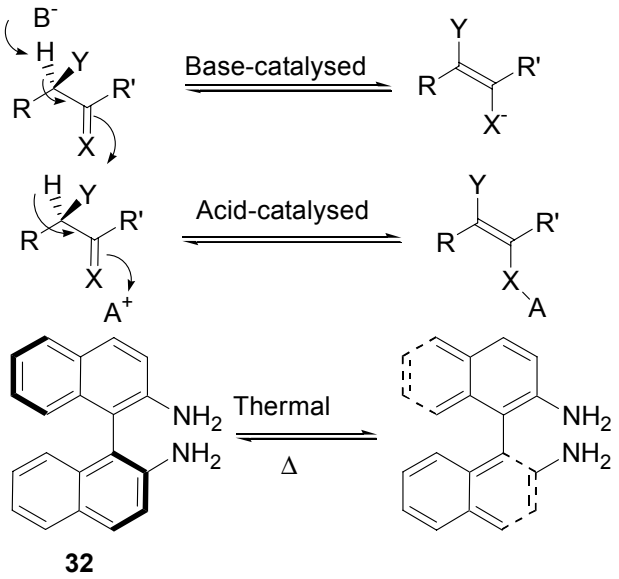
As described earlier, resolution methodologies are among the effective means for the production of enantiomerically pure compounds. However, these methods are obstructed by some disadvantages for practical applications. The most obvious limitation of resolution methodologies is that the theoretical yield can not 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[83]: 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[83]. Racemization can be achieved by several methods, but the most important industrial methods are acid- or base-catalyzed and thermal racemizations[84] (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 σ-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.

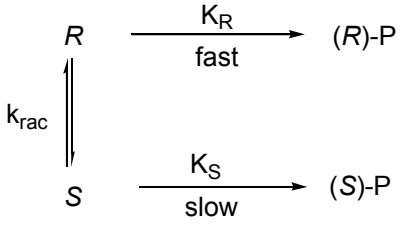


32

Scheme 1.5 Pathways for racemization.

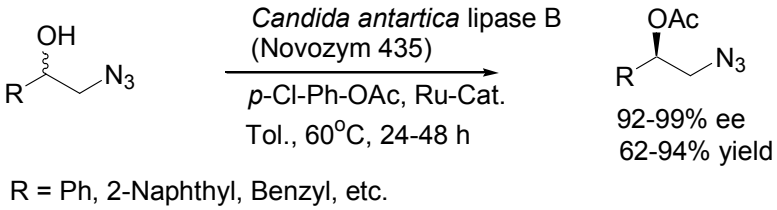
1.4.5.2 Dynamic kinetic resolution

Dynamic kinetic resolution is another important process for avoiding the disadvantages of kinetic resolution. Basically, this process is kinetic resolution which is combined with *in situ* racemization of the unwanted isomer[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_{rac} should be greater than the rate of resolution K_R[86].

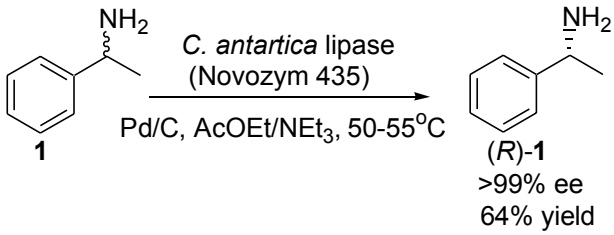


Scheme 1.6 Dynamic kinetic resolution.

The *in situ* racemization in dynamic kinetic resolution is usually achieved via acid or base catalyzed processes[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[91,92] and amines[93] using enzymes combined with transition metals (Scheme 1.7 and 1.8).



Scheme 1.7 Dynamic resolution of sec-alcohols via lipase and Ru-catalysis.

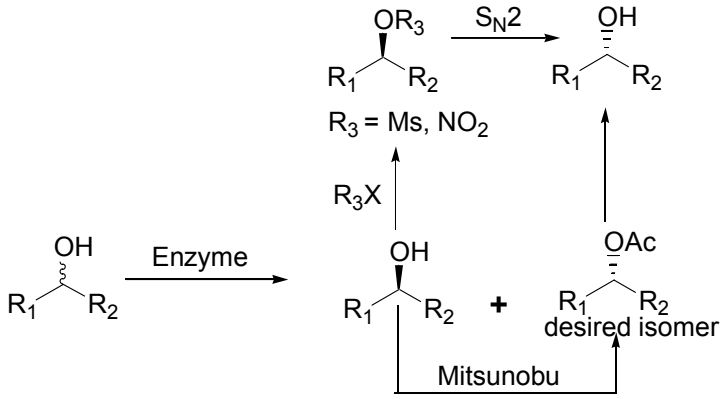


*Scheme 1.8 Dynamic resolution of 1-phenylethyamine (**1**) via lipase and Pd/C catalysis.*

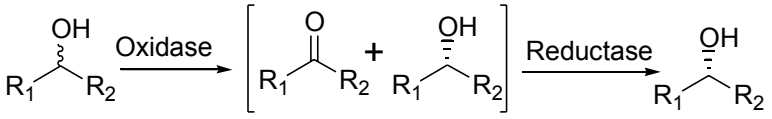
1.4.5.3 Stereoinversion

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[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[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[94,95] (Scheme 1.9). The latter involve *in situ* oxidation-reduction reactions using redox enzymes[97] (Scheme 1.10). Once again,

most of the stereoinversion methods are dealing with *in situ* inversion of alcohols and no attention has been focused on inversion of chiral amines.



Scheme 1.9 Stereoinversion using chemical compounds.



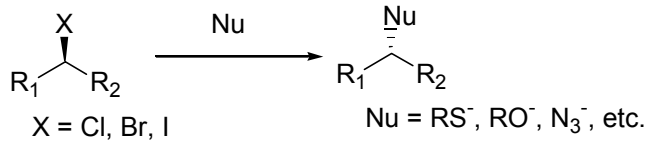
Scheme 1.10 Enzyme catalyzed stereoinversions.

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.

1.5.1 Inversion of halides

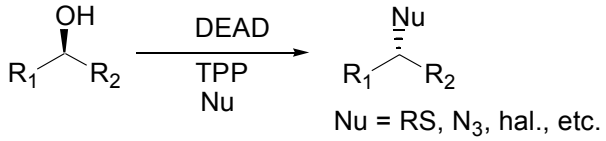
Halides are frequently used as substrates in numerous stereochemical transformations. They are easily substituted by various nucleophiles via S_N2 processes giving products with inversion of configuration at the stereogenic center (Scheme 1.11)[16,17,98].



Scheme 1.11 Inversion of alkylhalides.

1.5.2 Transformations of alcohols

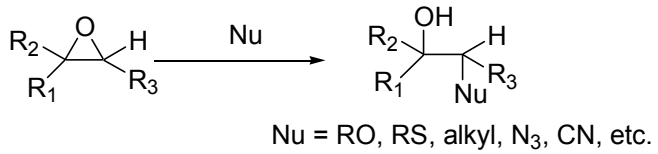
Alcohols can undergo stereospecific displacements with either inversion or retention of configuration at a stereogenic center depending on the conditions of the reaction. Chiral alcohols have been halogenated with complete retention of configuration using thionyl halides[99]. On the other hand nucleophilic substitution on sulfonate derivatives of alcohols is one of the straightforward methods for inversion of alcohols, often with high chemical and stereochemical yields[11,12,96]. 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.

1.5.3 Inversion of epoxides

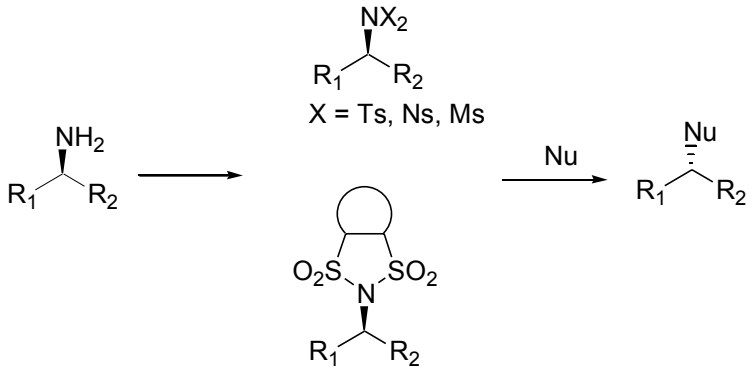
Homochiral epoxides are extensively used in the synthesis of chiral compounds due to their ability to react with various nucleophiles (Scheme 1.13). The utility of these intermediates in asymmetric synthesis has triggered enormous efforts on development of catalytic methods for their production[100]. The nucleophilic epoxide ring-opening reactions are both regio- and stereoselective and have been achieved using both chemo- and biocatalysts[20-22].



Scheme 1.13 Nucleophilic substitution of epoxides.

1.5.4 Stereoselective transformations of amines

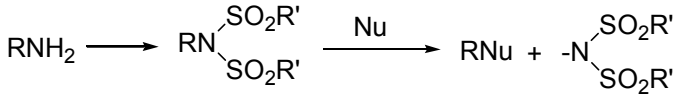
Apart from conversion of amino acids to α-halo and α-hydroxycarboxylic acids with retention of configuration via diazotization reactions[101], little has been done on stereoselective transformations of chiral compounds containing the amino group at a stereogenic center. However, in recent years Dr. Fiksdahl 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.

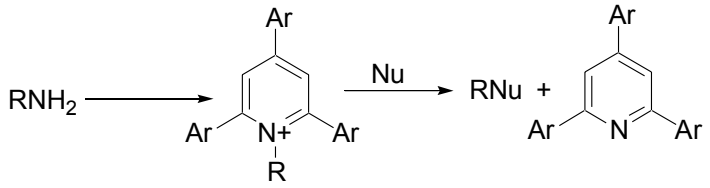
1.6 Nucleophilic substitution of amines

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[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.

Two decades later Katritzky[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).

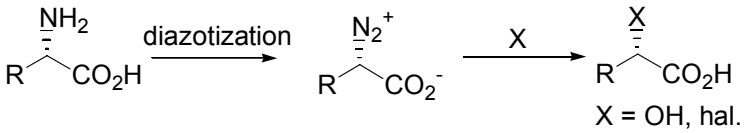


Scheme 1.16 Nucleophilic substitution of amines via triarylpyridinium salts.

Information regarding successful use of the *N,N*-disulfonylimides and the triarylpyridinium salts in substitution of amines is generally fragmented in the literature[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-α-amino acids.

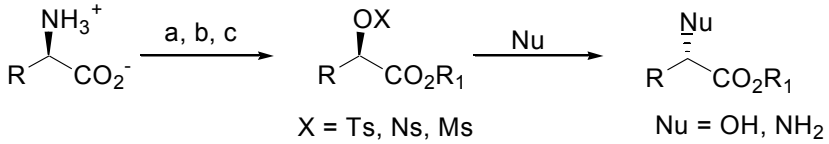
Amines could also be transformed via diazonium salts. The use of these intermediates is of little interest for organic synthesis, because they often lead to mixtures of substitution products as well as elimination and rearrangement

products[112]. However, there are few exception, such as the retentive hydroxy- and halo-deamination of α-amino acids[101] (Scheme 1.17).



Scheme 1.17 Nucleophilic substitution of α-amino acids via diazotization reactions.

Extension of this process by three more steps (Scheme 1.18) is an established procedure for preparation of D-α-amino acids and their derivatives by inversion of the naturally occurring L-α-amino acids[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-α-amino acids by direct inversion of L-α-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) $NaNO_2/H^+$, b) K_2CO_3/R_1I, c) XCl.

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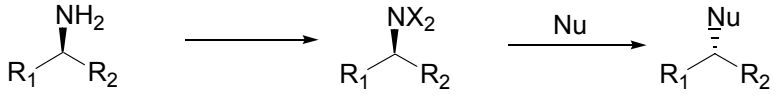
2 Preparation of inverted amines and alcohols via *N,N*-disulfonylimides

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.

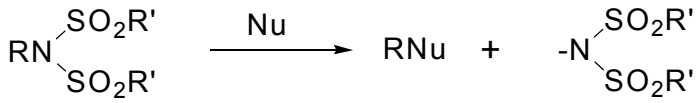
2.2 Previous investigations

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).



Scheme 2.1 Stereoselective transformation of amines.

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[1,2] in 1960's. In those preliminary studies and in succeeding investigations[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[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). Apparantly, 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.

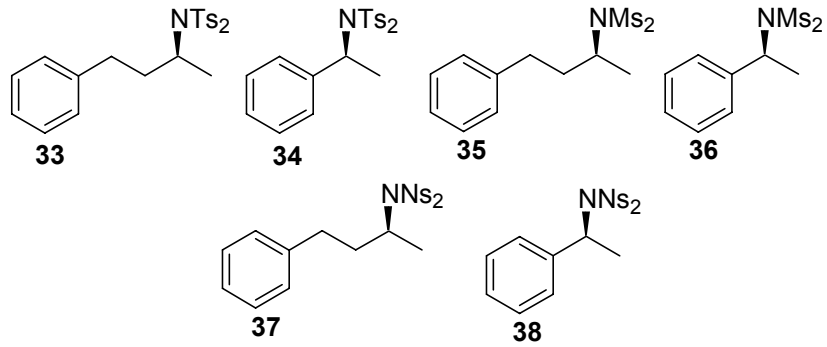
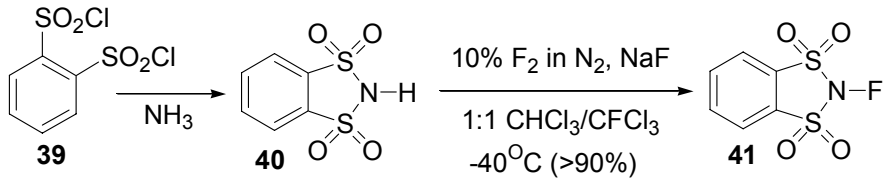


Figure 2.1 Previously studied N,N-disulfonylimides.

2.3 Preparation and nucleophilic substitution of cyclic aryl disulfonylimides

2.3.1 Previous work

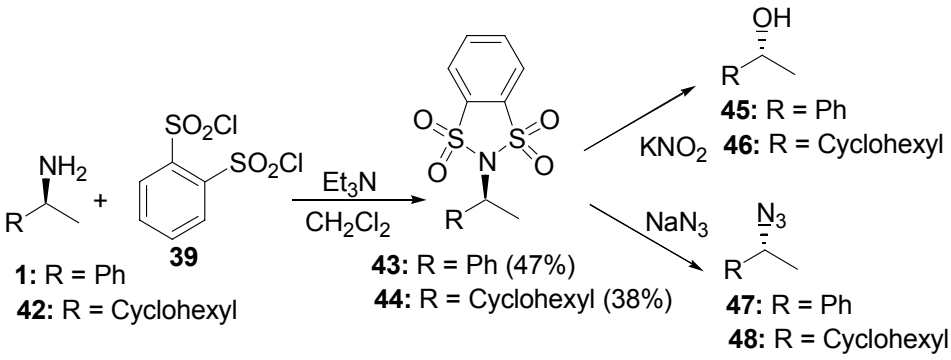
Cyclic aryldisulfonylimides have long been recognized as attractive synthetic tools in substitution of amines[11]. The cyclic nature of these compounds is believed to substantially stabilize the negative charge on the imide anion, making it a poor nucleophile, and hence a good leaving group. Initial 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[11]. Later modifications by Davis[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 $(ArSO_2)_2N$-group.



Scheme 2.3 Preparation of fluorinating agents using arylsulfonamides.

More recently, Carlsen[13] from this university has reinvestigated 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 $(ArSO_2)_2N$-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[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.



Scheme 2.4 Inversion of amines via N,N-benzene-1,2-disulfonylimides.

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

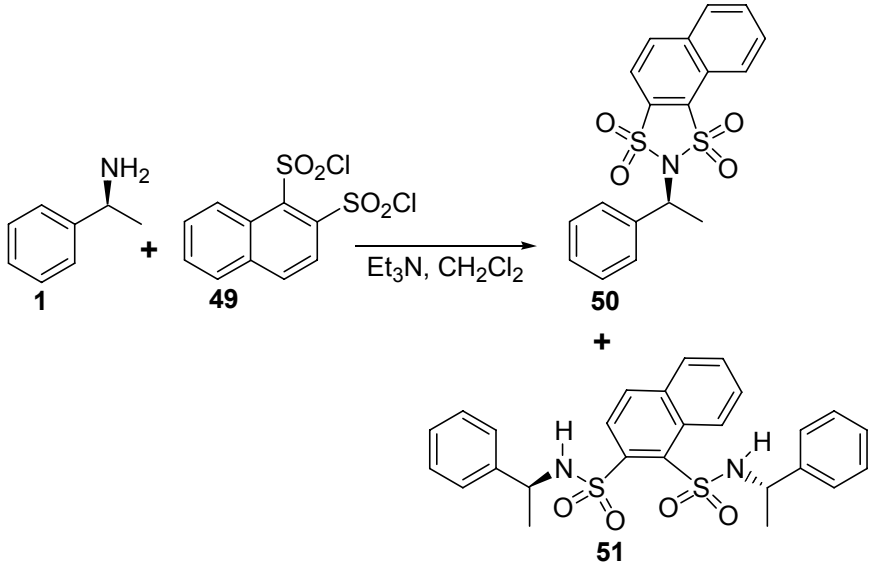
Attempts to improve the degree of inversion in stereoselective transformation of amines using cyclic aryldisulfonylimides resulted to the synthesis of *N,N*-1,2-naphthalenedisulfonylimide derivatives of chiral amines. It was argued that this group will diffuse the negative charge on the nitrogen anion 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*)-α-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*-disulfonylimides[6-10,14].

Experimental details for the preparation and nucleophilic substitution of the *N,N*-1,2-naphthalenedisulfonylimide **50** are presented in Paper I.

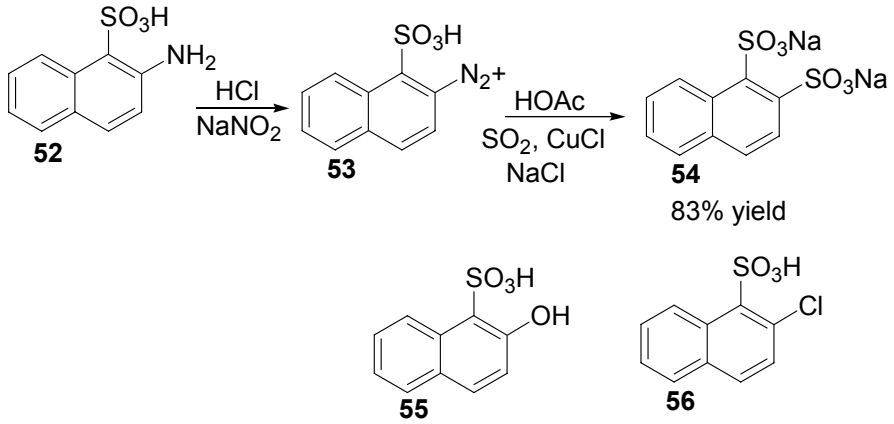
2.4.1 Results and discussion

The cyclic (*S*)-*N,N*-1,2-naphthalenedisulfonylimide intermediate **50** was obtained from (*S*)-α-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**[14]. The *N,N*'-bis-byproduct, the disulfonamide, R-NH-SO_2-Ar-SO_2-NH-R, **51** was also isolated and characterized.



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

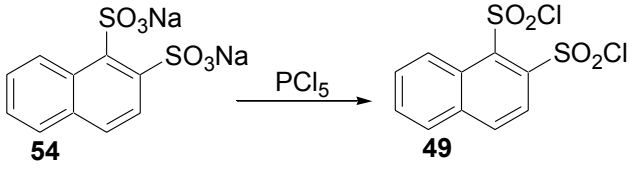
The reagent, naphthalene-1,2-disulfonyl chloride (**49**) was prepared from the readily available 2-aminonaphthalenesulfonic acid (**52**) via a modified Meerwein synthesis[15,16] (Scheme 2.6 and 2.7).



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

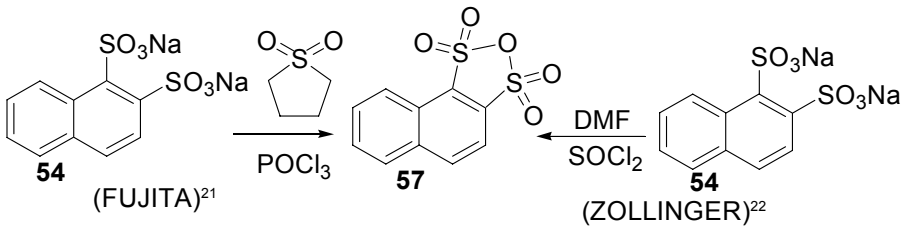
Substitution of the diazonium group by sulfurdioxide in hydrochloric acid, in the second step of this sequence yielded less than 40% of the disulfonic acid sodium salt **54**, together with the two expected[17] unwanted products 2-hydroxynaphthalenesulfonic acid (**55**) and 2-chloronaphthalenesulfonic 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).



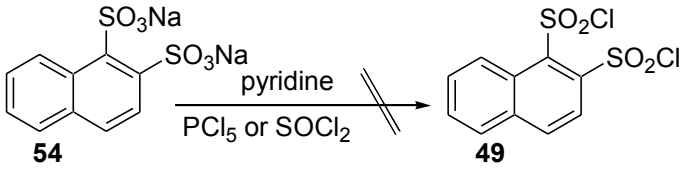
*Scheme 2.7 Preparation of naphthalene-1,2-disulfonylchloride (**49**).*

Surprisingly, compound **49** was formed in only 10% yield which is relatively low compared to our own experience[14] and what has been reported elsewhere[18-20]. 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's[21] and Zollinger's[22] techniques (Scheme 2.8) gave high yields of anhydride product **57** with no traces of the disulfonyl chloride **49**.



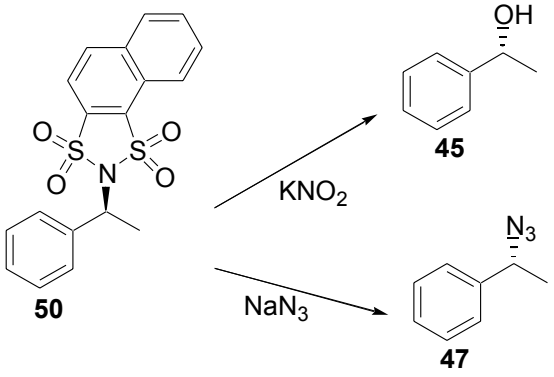
Scheme 2.8 Catalytic methods for the synthesis of sulfonyl chlorides.

Tadia's[23] 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**.*

*Table 2.1: Results for nucleophilic substitution of (S)-N,N-naphthalene-1,2-disulfonylimide **50***

Entry	**Substitution product, % *ee/R* (reaction conditions)**	**Degree of inversion**
	Alcohol 45[a]	
1	20% *ee/R* (KNO_2/18-cr-6, DMF, 0°C, 3 h)	60%
2	20% *ee/R* (as above, 30% DMF/DMSO, 0°C, 5 h)	60%
3	24% *ee/R* (as above, DMF, 18°C, 24 h)	62%
4	20% *ee/R* (as above, DMSO, 18°C, 24 h)	60%
5	24% *ee/R* (KOH, DMF, 18°C, 24 h)	62%
6	26% *ee/R* (NH_4OAc, DMF, 18°C, 24 h)	63%
7	26% *ee/R* (NH_4OBz, DMF, 18°C, 24 h)	63%
8	20% *ee/R* (KNO_2/18-cr-6, DMF, 80°C, 3 h)	60%
9	22% *ee/R* (as above, DMSO, 80°C, 3 h)	61%
	Azide 47[a]	
10	40% *ee/R* (NaN_3, 30% DMF/DMSO, 0°C, 24 h)	70%
11	34% *ee/R* (NaN_3, DMF, 18°C, 4 days)	67%
12	40% *ee/R* (NaN_3, DMSO, 18°C, 24 h)	70%
13	20% *ee/R* (NaN_3, DMF, 60°C, 24 h)	60%
14	36% *ee/R* (NaN_3, DMSO, 60°C, 24 h)	68%

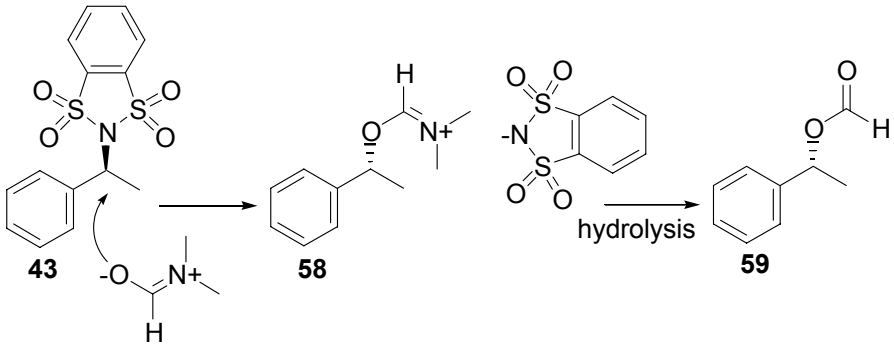
[a]The % *ee* of the alcohol product **45** and azide product **47** is based on the direct chiral GLC analysis.

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- **34**, dimesyl- **36** and dinosyl-imides **38**[6-10]. This is particularly apparent at lower reaction temperatures. However, in

contrast to what was observed for the *N,N*-1,2-benzenedisulfonylimides **43** and **44**[14] (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.

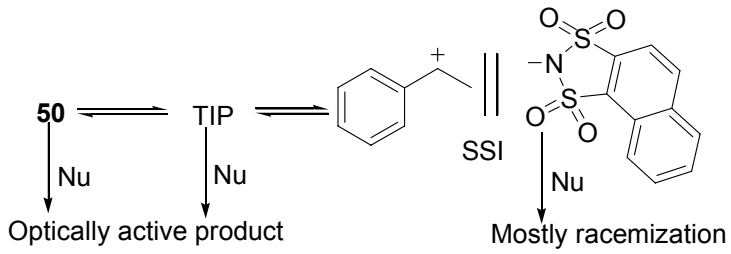
The stereoselectivity in the formation of **45** and **47** from the (*S*)-*N,N*-1,2-naphthalenedisulfonylimide **50** is lower (60-70%) than for the analogous previously reported *N,N*-1,2-benzenedisulfonylimide **43**[14] (Table 2.2, 84-94%). This may be explained by participation of the solvent used 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)[14]. 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.*

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

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[24-26]. ^{1}H-NMR spectra of 1:3 mixture of racemic **50** and heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin at temperatures ranging between +10^{o}C and -50^{o}C showed no discrimination of any proton in compound **50**. ^{13}C-NMR studies of this mixture at the same temperature range was not useful either. Experiments using a lanthanide complex[27], 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[28] (**III**) (Figure2.2), which was prepared as described by Braun and his colleagues[29], were also tried, but once again no enantioseparation was observed in these media.

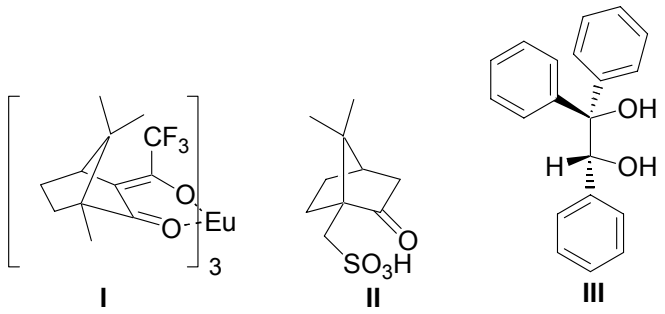
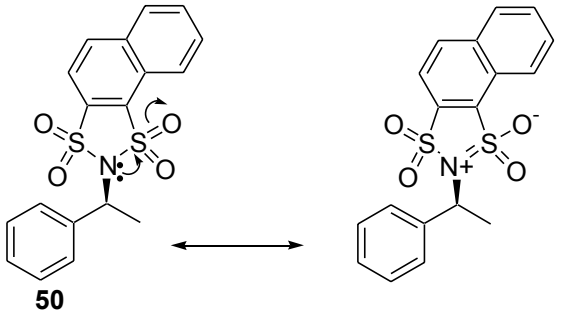


Figure 2.2 Chiral solvating agents.

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.



*Scheme 2.13 Proposed resonance structures of **50**.*

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 aroxide 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.

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 (-NTs_2, **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

Disulfonylimides (% yield)	**Degree of inversion (Optimal reaction conditions) (% yield)**	
	Alcohol products	**Azide products**
33 (50%)	100% (KNO_2, DMF, 120^{o}C, 72 h) (67%)	100% (NaN_3, DMF, 135^{o}C, 24 h) (98%)
34 (50%)	100% (as above) (95%)	100% (as above) (67%)
35 (32%)	93% (as above)	-
36 (41%)	82% (as above) (20-40%)	-
37 (17%)	95% (as above)	-
38 (23%)	82% (as above) (20-40%)	-
43 (47%)	84% (KNO_2, 30% DMF/DMSO, 0^{o}C, 24 h) (50-83%)	94% (KNO_2, 30% DMF/DMSO, 0^{o}C, 24 h) (35%)
44 (38%)	90% (KNO_2, DMF, 90^{o}C, 72 h) (10-30%)	98% (KNO_2, DMF, 80^{o}C, 4 d) (53%)
50 (42%)	60-63% (independent of reaction conditions) (analytical scale)	70% (independent of reaction conditions) (analytical scale)

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[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[14]. Among the so far investigated *N,N*-disulfonylimides, the *N,N*-ditosylimides (-NTs_2, **33**, **34**) give the best and complete inversion of configuration independent of benzylic or aliphatic substrates.

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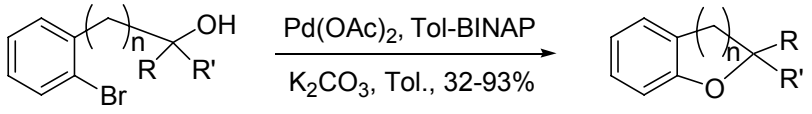
3 Preparation of chiral aryl ethers via cyclic N,N-disulfonylimides

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).



Scheme 3.1 *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

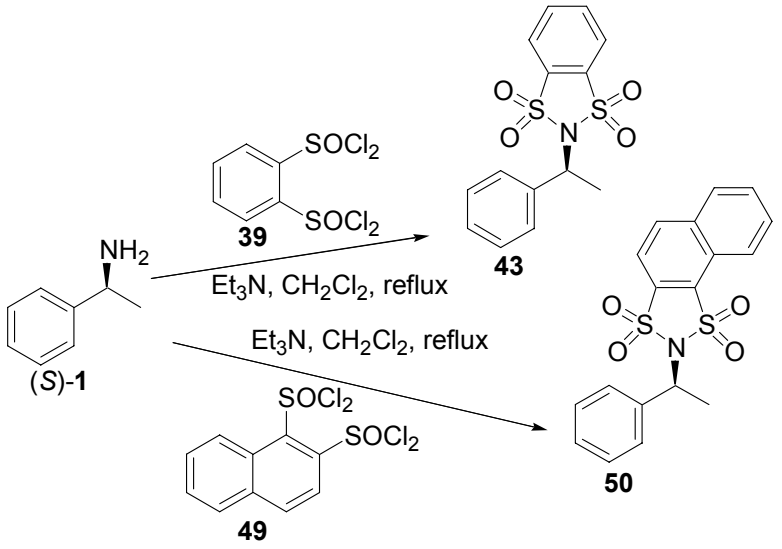
recently been reported by Smith and his coworkers[14]. This procedure is among the very few variants of the Williamson reaction since its inception 150 years ago. Search for another method for preparation of chiral aryl ethers is therefore of great importance. We have previously shown that *N,N*-disulfonylimides 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 aryldisulfonylimides

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

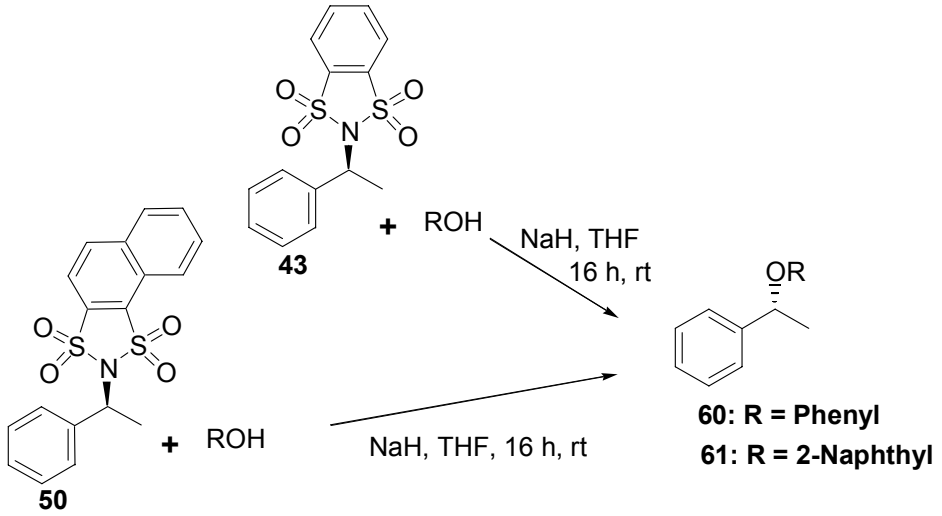
3.2.1 Results and discussion

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



*Scheme 3.2 Preparation of the N,N-disulfonylimides (S)-**43** and (S)-**50**.*

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***

Substrate	**Nucleophile**	**Product (yield%)**	**$[\alpha]_D$ ($CHCl_3$)**	**Stereoselectivity**
(*S*)-**43**	PhO^-	(*R*)-**60** (39)	+ 4.8 (*c* = 2)	87% inv.[a]
(*S*)-**43**	2-NaphthO^-	(*R*)-**61** (44)	+ 98 (*c* = 0.2)	79% inv.[b]
(*S*)-**50**	PhO^-	(*R*)-**60** (57)	+ 4.05 (*c* = 2)	83% inv.[a]
(*S*)-**50**	2-NaphthO^-	(*R*)-**61** (68)	+ 87 (*c* = 0.2)	70% inv.[b]

[a]Enantiomeric purity of the phenyl ether products (*R*)-**60** was based on chiral GLC.

[b]Enantiomeric purity of the 2-naphthyl ether product (*R*)-**61** is based on $[\alpha]_D$ 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

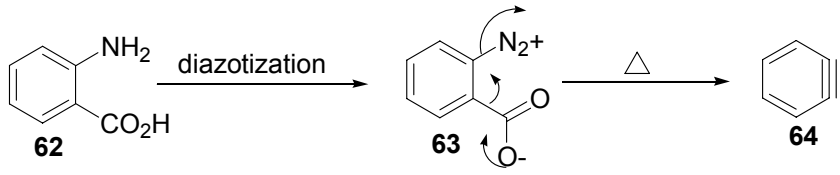
The enantiomeric purity of the phenyl ether **60** was determined by chiral GLC. Its absolute configuration was assigned based on comparison of specific rotation data for the homochiral reference compound (*R*)-phenyl 1-phenylethyl ether [(*R*)-**60**], which was synthesized via a benzyne route as describe 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*)-α-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].

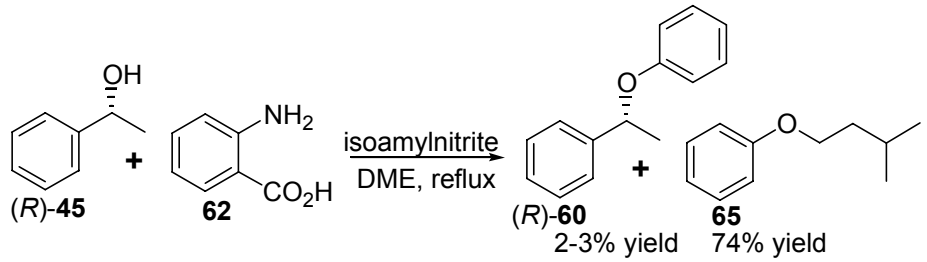


*Scheme 3.4 Generation of benzyne (**64**).*

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.

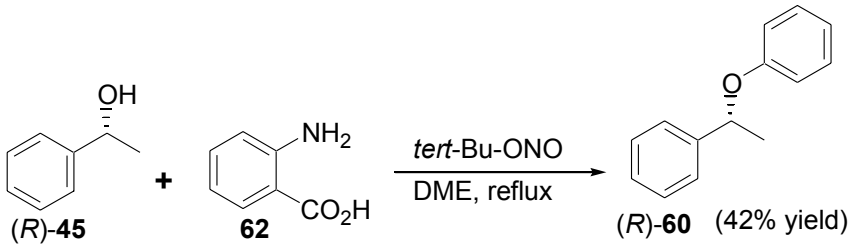
Classical experimental procedures for the generation of benzyne were not appropriate for our purpose, as they are conducted in alcohols which present a potential risk of alcoholysis of the diazonium salt that leads to depleted yields of the desired products. The procedures using the isolated diazonium 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 *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.



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**.

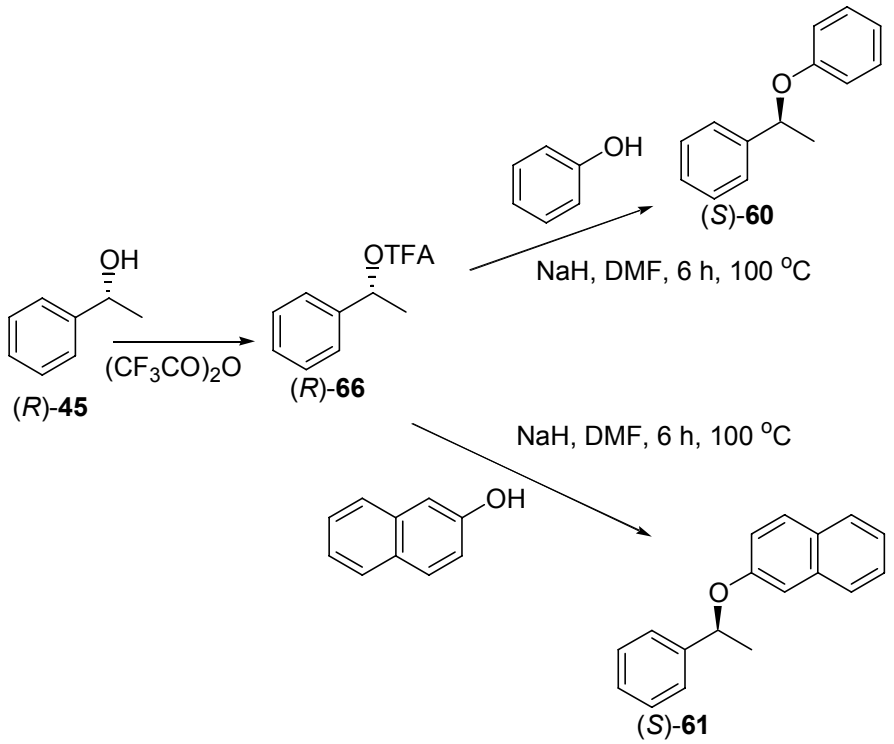


*Scheme 3.6 Preparation of reference compound (R)-**60** via benzyne.*

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[26] (**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.*

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

Substrate	Nucleophile	Product (yield%)	$[\alpha]_D$ ($CHCl_3$)	Stereoselectivity
62	(*R*)-**45**	(*R*)-**60** (42)	+ 5.55 (*c* = 2)	100% ret.[a]
(*R*)-**66**	PhO^-	(*S*)-**60** (65)	- 5.60 (*c* = 2)	100% inv.[a]
(*R*)-**66**	2-$NaphthO^-$	(*S*)-**61** (87)	- 124 (*c* = 0.2)	100% inv.[b]

[a]Enantiomeric purity of the phenyl ether products (*R*)-**60** and (*S*)-**60** is based on chiral GLC.

[b]Enantiomeric 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 S_N2 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 ^oC) 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 aroxide 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.

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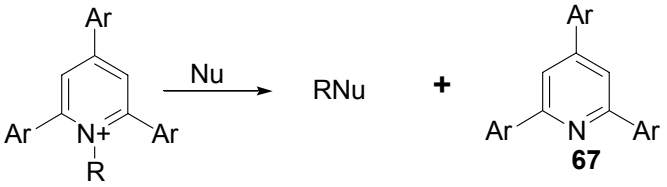
4 Preparation of inverted amines and alcohols via 2,4,6-triphenylpyridinium salts

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-triarylpyridine **67**.



Scheme 4.1 Nucleophilic substitution of amines via triarylpyridinium salts.

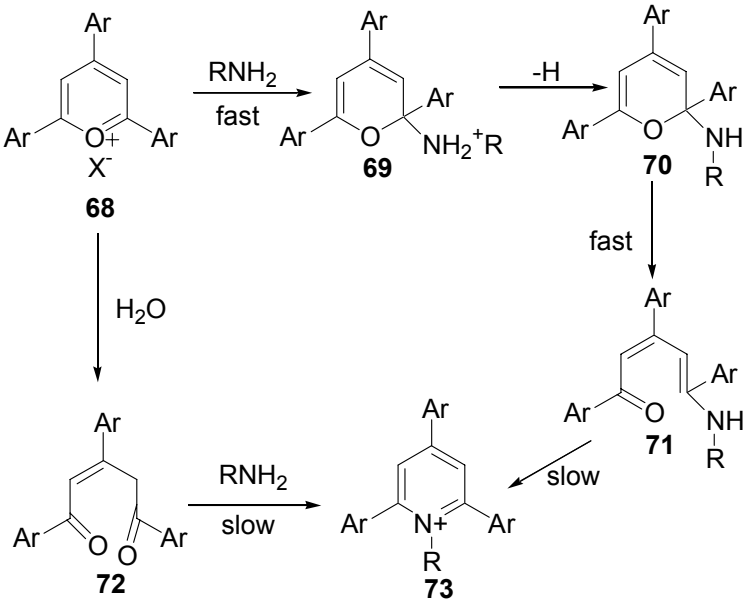
The concept of utilizing triarylpyridinium cations in substitution of amines was first reported in 1926 by Ziegler and Fries[1] who showed that 1-methyl-2,4,6-triphenylpyridinium chloride thermolysed to 2,4,6-triphenylpyridine and presumably, methyl chloride. Susan and Balaban[2] reinvestigated the synthetic 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 nucleophlic substitution of amines[13-16]. 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 discuss 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

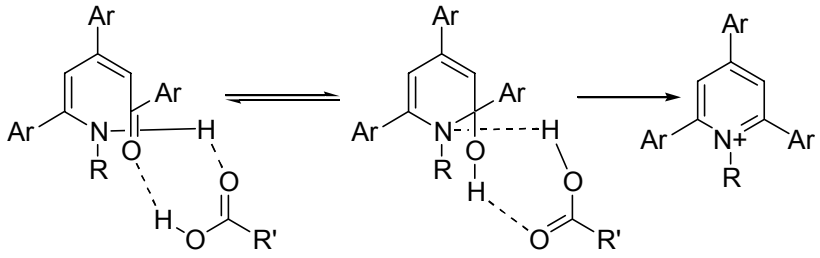
Activation of amines to pyridinium salts using pyrylium cations involves a complex reaction sequence. Katritzky, Brownlee and Musumarra have thoroughly investigated the mechanisms of this reaction and established that this sequence follow the pattern illustrated in Scheme 4.2[7]. The first step in this sequence lead to the formation of 2-amino-2H-pyran **70** from pyrylium salt **68** via ammonium intermediate **69**. The amino pyran **70** is rapidly ring-open to the vinylogous amide **71**. The ring-opening is followed by slow ring closure to the target pyridinium salt **73**.



Scheme 4.2 Mechanism for preparation of pyridinium salts from pyrylium cations.

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 acids[17]. It is believed that the carboxylic acids catalyze this step in an electrocyclic fashion as depicted in Scheme 4.3[10].

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.

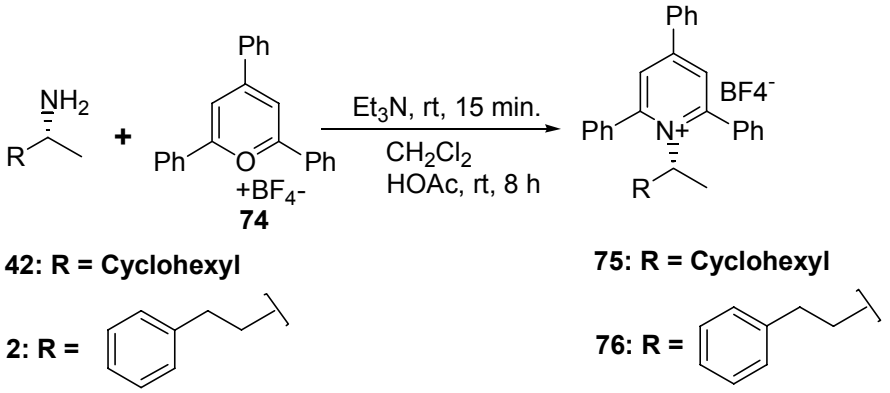
4.3 Synthesis and nucleophilic substitution of chiral 1-cyclohexylethyl- and 3-phenyl-1-methylpropyl-2,4,6-triphenylpyridinium tetrafluoroborates

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 group[9]. The degree of inversion in the substitution reaction were studied for the formation of the alcohols **46** and **77**,

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*)- 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*)- or (*S*)-**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**.*

*Table 4.1: Percentage yields and optical rotation data for the triphenylpyridinium salts (R)- or (S)-**75** and (R)-**76***

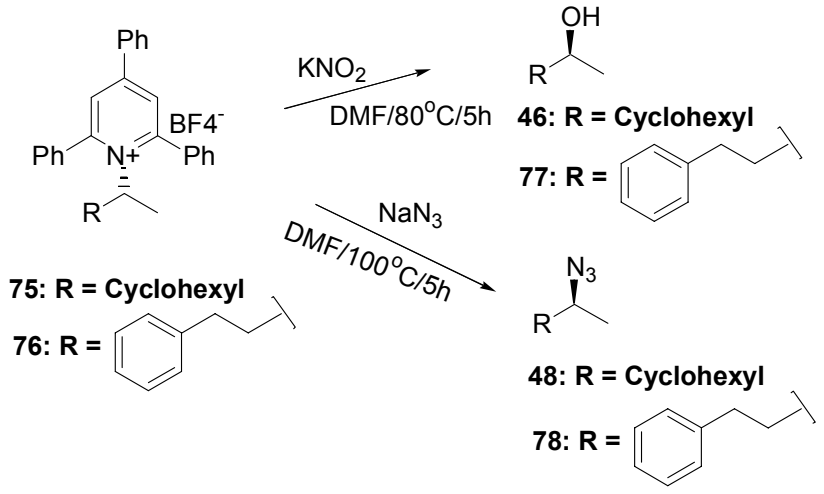
Substrate	**Triphenylpyridinium salt (yield)**	**$[\alpha]_D$ (c = 2, $CHCl_3$)**
(*R*)-**42**	(*R*)-**75** (84%)	-59.1
(*S*)-**42**	(*S*)-**75** (90%)	+61.7
(*R*)-**2**	(*R*)-**76** (89%)	-53.7

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

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. ^{1}H NMR of the cyclohexyl intermediate **75** showed a characteristic phenyl ring current effect[18] 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**.*

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

Substrate	Alcohol products[b] Degree of inversion (Yield%)	Azide products[c] Degree of inversion (Yield%)
(*R*)-**75**	(*S*)-**46** >99% (21)	(*S*)-**48** 97% (37)
(*S*)-**75**	(*R*)-**46** >99% (17)	(*R*)-**48** 96% (43)
(*R*)-**76**[a]	(*S*)-**77**[a] >99% (41)	(*S*)-**78**[a] 98% (71)

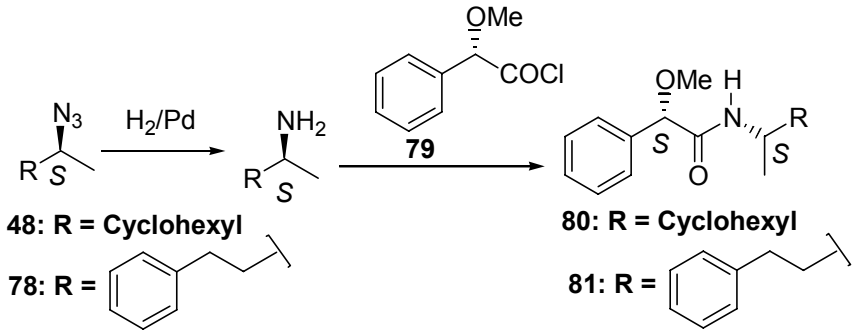
[a]Substrate (*R*)-**2** had *ee* of 96%. The degree of inversion for products **77** and **78** has been corrected for this.

[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[19-24]. 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^{o}C, 5 h) than the *N,N*-disulfonylimides (120^{o}C, 72 h). However, the pyridinium intermediates required more harsh reaction conditions than the cyclic aryldisulfonylimides, 1,2-benzene- and naphthalene-disulfonylimides (0^{o}C, 24 h) (see Chapters 2 and 3).

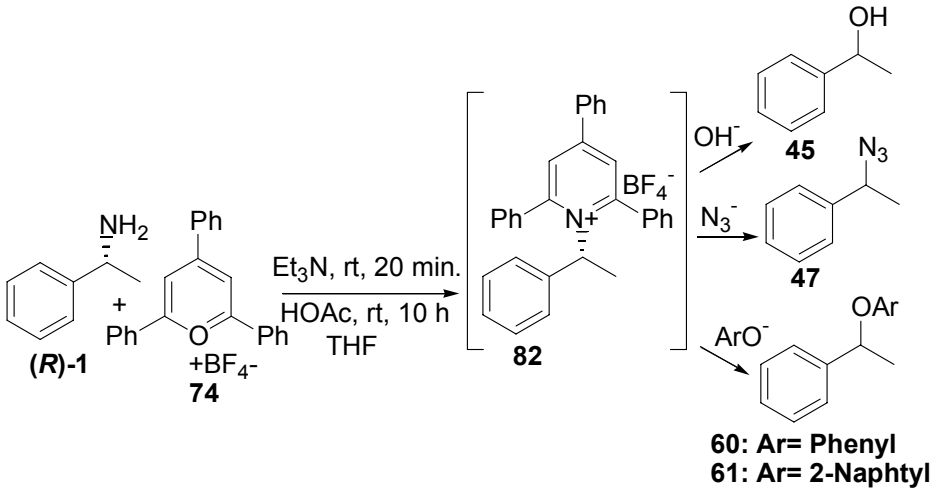
The most interesting discovery in this study is the higher degree of inversion (96-99%) achieved in the nucleophilic substitution reaction of the pyridinium intermediates **75** and **76**. Stereoselectivity of this reaction is comparable to that of ditosylimides[19-22] and is generally better than that 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**[9]. 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 *in situ* substitution of the salt once it has been synthesized from its individual constituents (Scheme 4.7).



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 aroxides 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**)*

Product	Yield (%)	Stereoselectivity
45	85	12% *ee*
47	78	racemic
60	70	racemic
61	73	racemic

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.

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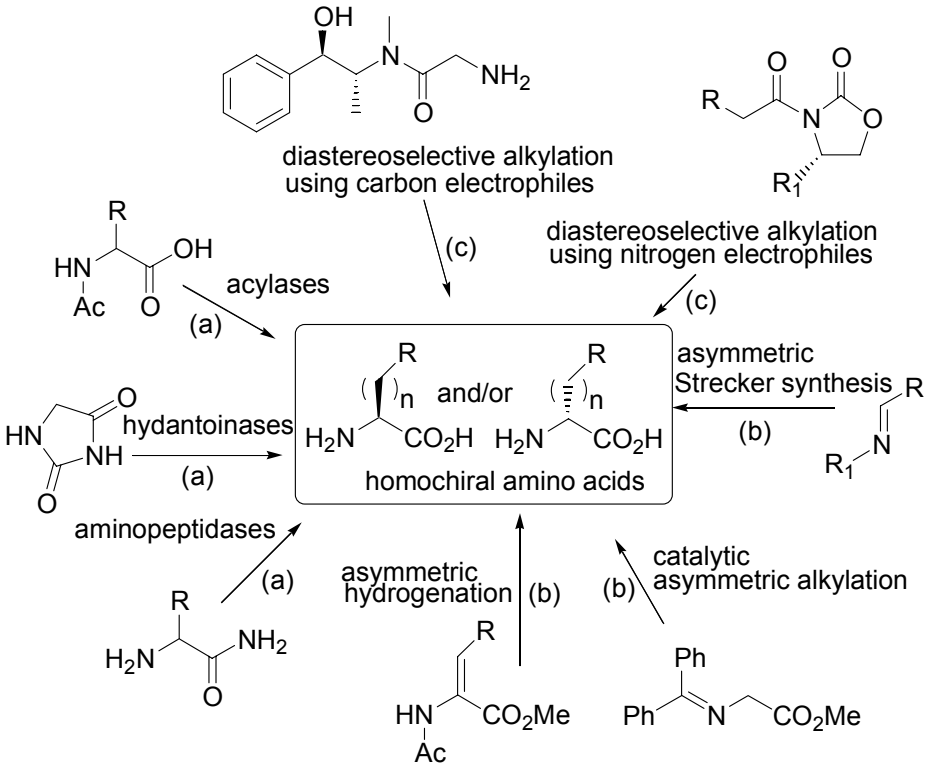
5 Inversion of Amino Acids

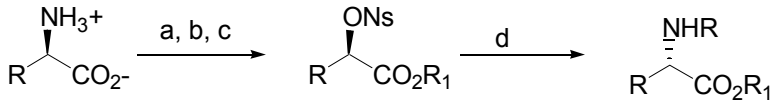
5.1 Introduction

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[1-9]. Among the important non-proteinogenic amino acids are the D-isomer of the natural L-α-amino acids[9]. 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 in three different categories (Scheme 5.1)[10-12]: a) Kinetic resolution of racemic mixtures of amino acids using enzymes, b) Catalytic asymmetric processes using transition metals and c) Asymmetric methods using stoichometric amounts of chiral auxiliaries.



Scheme 5.1 Asymmetric methods for preparation of α-amino acids[12].

An alternative approach for producing D-α-amino acids is by inversion of the readily available L-α-amino acids via stereoselective 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 *Inversion of amino acids via diazotization: a) $NaNO_2/H^+$, b) K_2CO_3/ CH_3I, 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

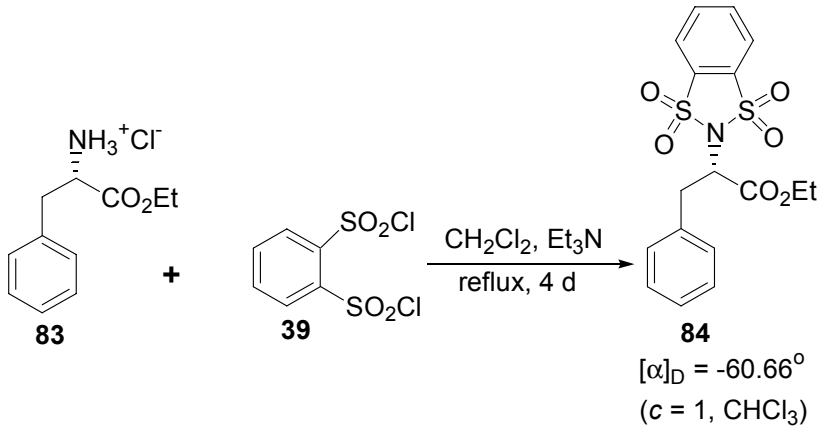
The first attempt in the effort to invert the L-α-amino acids to their D-isomers was the use of cyclic aryldisulfonylimide intermediates. These derivatives were selected as they can be prepared at less vigorous conditions and have been shown to be better leaving groups than their acyclic counterparts[15,16]. 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

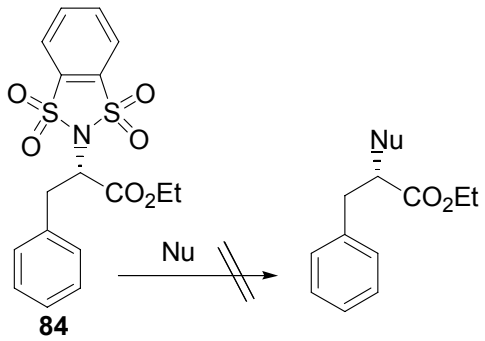
(*S*)-*N,N*-1,2-benzenedisulfonylimide derivative **84** (Scheme 5.3) was obtained from L-phenylalanine ethyl ester hydrochloride **83** and benzene-1,2-disulfonyl chloride **39** in high yield (88%) via a previously reported procedure[16], basically using identical reaction conditions. However, for optimum reaction yields this process required much slower addition of deprotonated **83** to a solution of **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 **84** has indicated no sign of racemization as it possessed high optical rotation (Scheme 5.3). Efforts to verify the enantiopurity of **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**).*

The nucleophilic substitution of (*S*)-**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 aryldisulfonylimides[15,16]. This problem is likely caused by the anionic character of the α-carbon. The presence of the disulfonylimide leaving group at α-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.



84

Scheme 5.4 *Nucleophilic substitution of N,N-benzene-1,2-disulfonylimide derivative of (S)-phenylalanine ethyl etser **84**.*

*Table 5.1: Reaction conditions for nucleophilic substitution of N,N-benzene-1,2-disulfonylimide derivative of (S)-phenylalanine ethyl ester **84***

Entry	Reaction conditions	Comments
1	KNO_2, THF, rt- reflux, 48 h	No reaction
2	KNO_2, DMF, rt- 80^oC, 48 h	No reaction
3	KNO_2/crown ether, DMF, rt- 80^oC, 48 h	No reaction
4	KNO_2, DMF, 130^oC, 5 h	Complex mixtures
5	NaN_3, THF, rt-reflux, 48 h	No reaction
6	NaN_3, DMF, rt-80 ^oC, 48 h	No reaction
7	NaN_3, DMF, 110^oC-reflux, 4 h	Complex mixtures
8	$TMSN_3$/TBAF, THF, reflux, 24 h	No reaction

5.3 Inversion of amino acids via 2,4,6-triphenylpyridinium salts

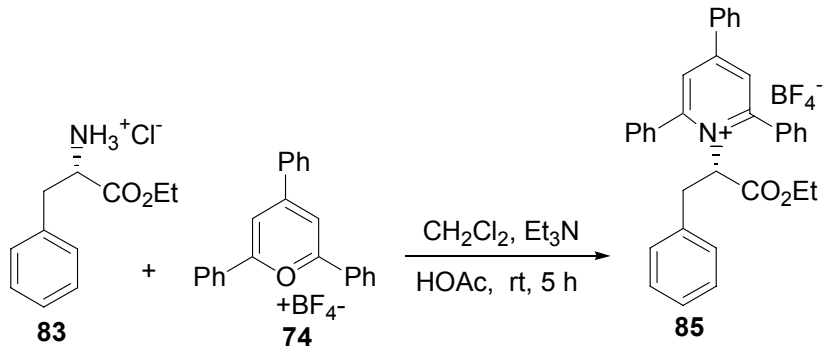
Our next investigations on the inversion of amino acids was focused on 2,4,6-triphenylpyridinium derivatives. These compounds are known to be valuable intermediates in nucleophilic substitution of primary and secondary amines[17-25]. We have recently reported their use in inversion of chiral amines (Chapter 4 and Paper IV). The synthesis of these salts from amines is well documented[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 aryldisulfonylimides. 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 **85** (Scheme 5.5) was prepared from 2,4,6-triphenylpyrylium tetrafluoroborate (**74**) and (*S*)-phenylalanine ethyl ester hydrochloride (**83**) by reported methods[23]. Nucleophilic substitution was carried out using azide anion.

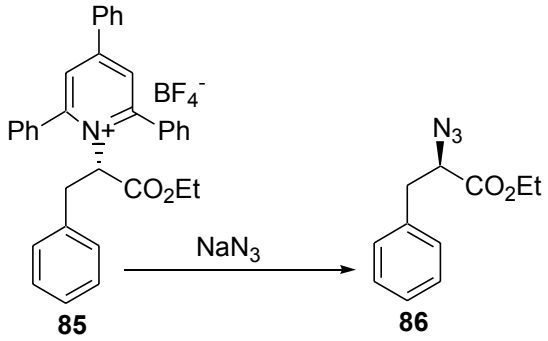
5.3.1.1 Results and discussion

The 2,4,6-triphenylpyridinium tetrafluoroborate derivative of (*S*)-phenylalanine ethyl ester **85** (Scheme 5.5) was obtained in higher yields (96%) than the previously studied pyridinium salts **75** and **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 (**83**) before it could attack the 2,4,6-triphenylpyrylium cation **74** (Scheme 5.5).



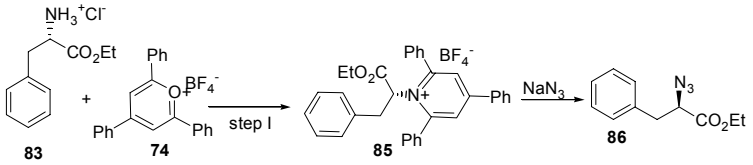
Scheme 5.5 *Preparation of 2,4,6-triphenylpyridinium salt of (S)-phenylalanine ethyl ester(**85**).*

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**).*

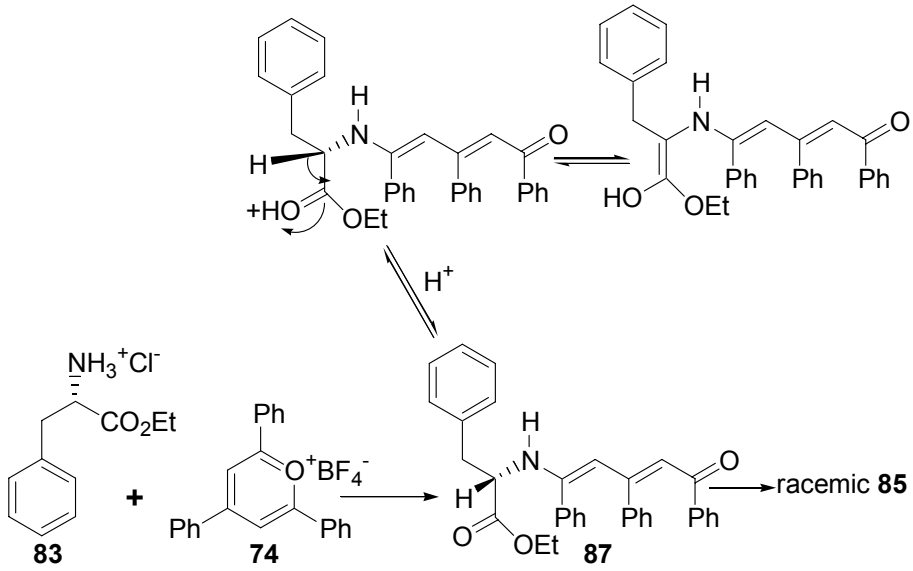
Table 5.2: Preparation and nucleophilic substitution of 2,4,6-triphenylpyridinium salt of (S)-phenylalanine ethyl ester ***85***



83 **74** **85** **86**

Method	**Reaction condition Step I (yield %)**	**Optical activity for 85 $[\alpha]_D$ (*c* = 2,$CHCl_3$)**	**86 yield (%)**	**Degree of inversion for 86**
A	Et_3N (2 eq.), HOAc, CH_2Cl_2, rt, 5 h (96)	- 1.75	73	54%
B	**83** (2 eq.), THF, reflux, 48 h (67)	0	-	-
C	**83** (2 eq.), HOAc (0.1 eq.), CH_2Cl_2, rt, 7 days (48)	- 2.25	64	56%

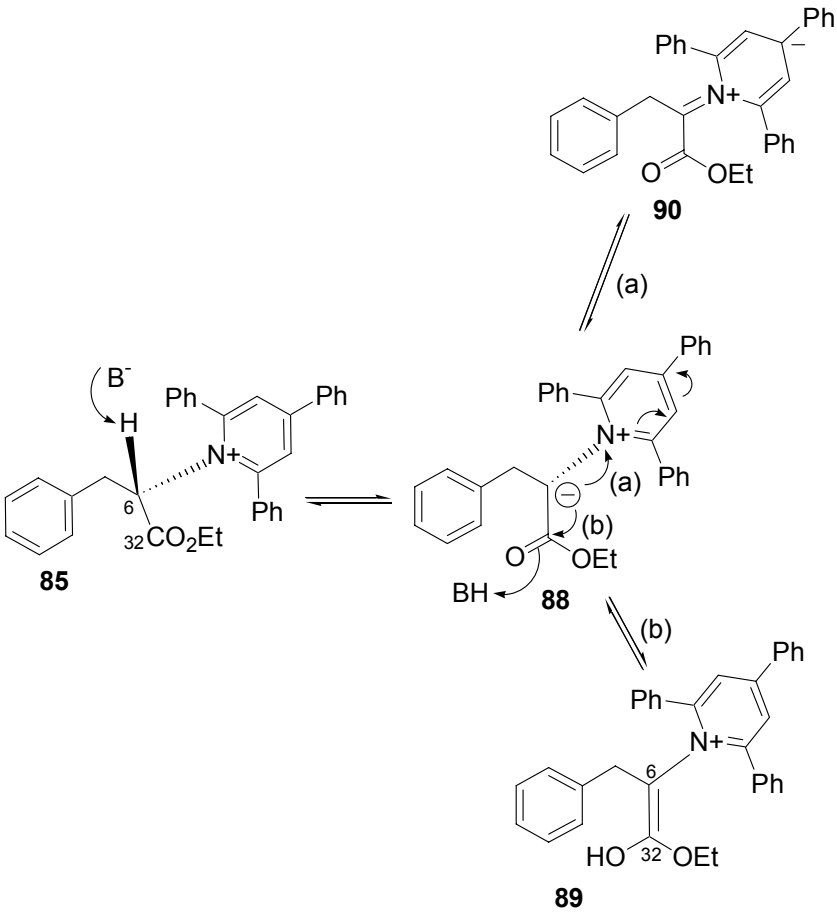
The poor stereoselectivity of this procedure might be caused by racemization of the pyridinium salt **85** during preparation or could be the consequence of the nucleophilic substitution reaction. The low optical rotation of the salt **85** compared to its analogues **75** and **76** (Chapter 4, Table 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).



Scheme 5.7 *Proposed mechanism for racemization of (S)-phenylalanine ethyl ester vinylogous intermediate **87**.*

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.



Scheme 5.8 *Proposed mechanism for base catalyzed racemization of the pyridinium salt of (S)-phenylalanine ethyl ester **85**.*

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)[26] (Appendix 5) was ambiguous due to the rolling of the BF_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.

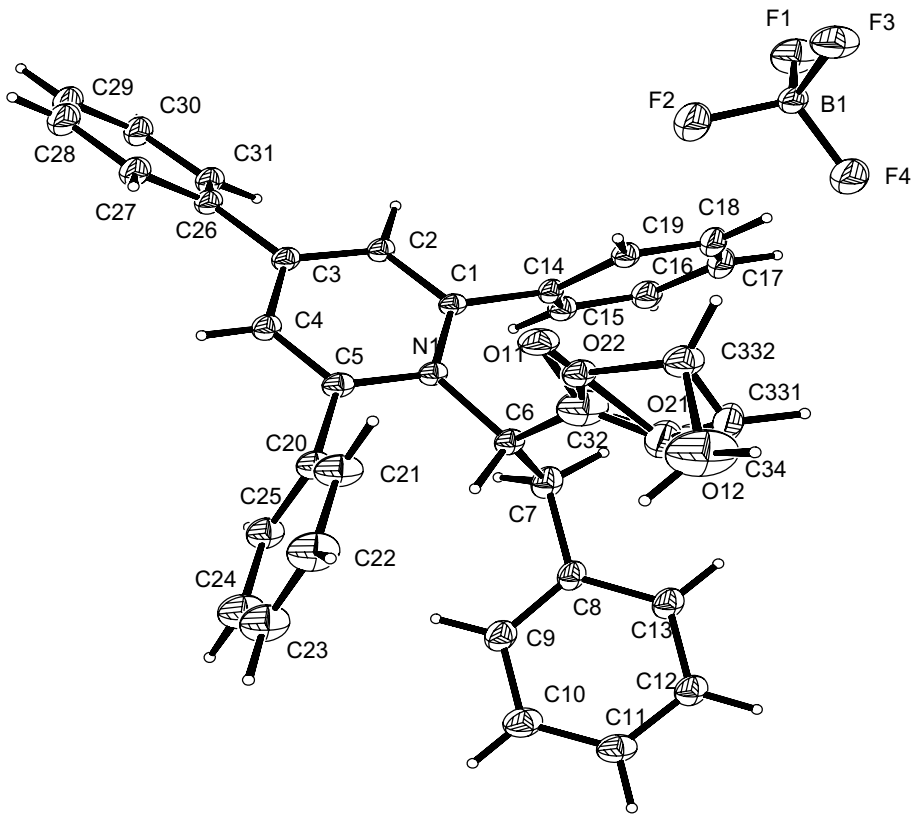


*Figure 5.1 X-ray structure of compound **85**.*

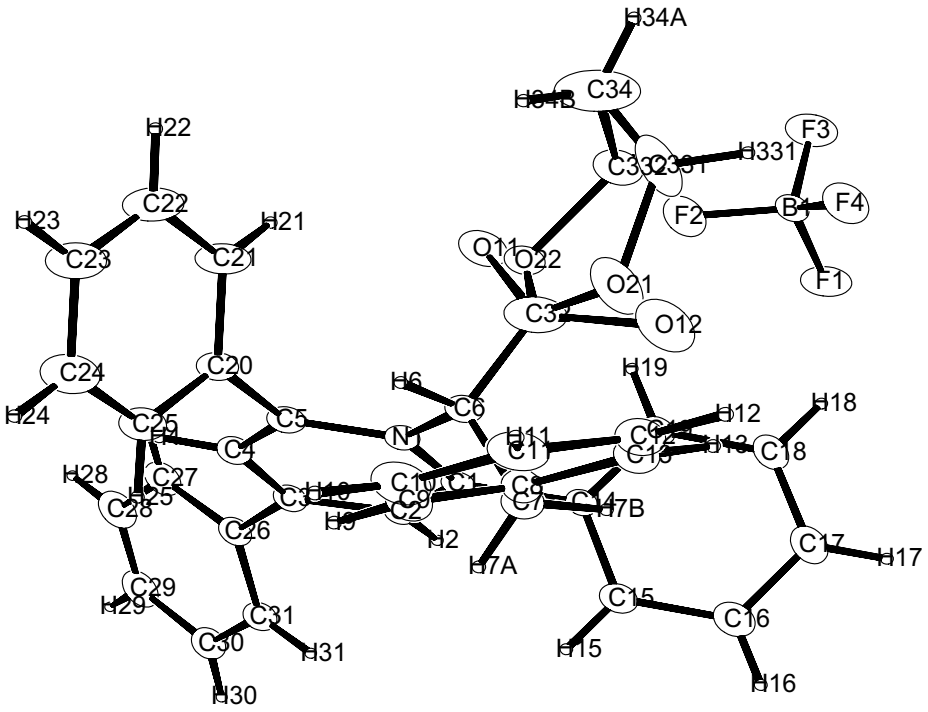


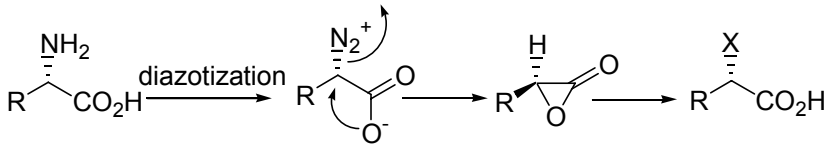
*Figure 5.2 X-ray structure showing the two conformers of the ester moiety in **85**.*

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 displacement 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.

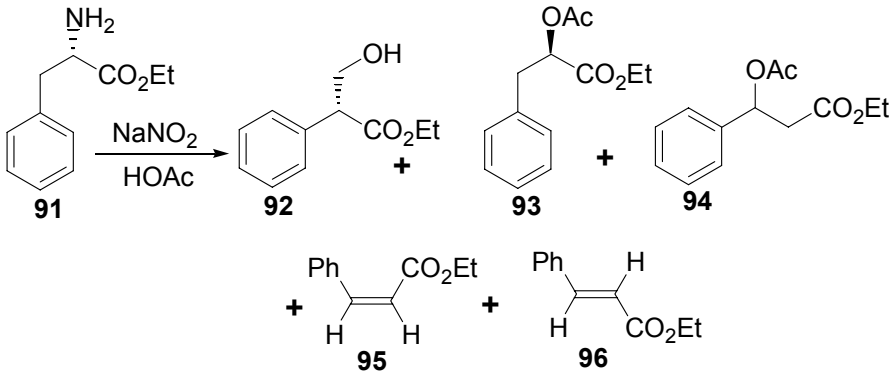


Scheme 5.9 Anchimeric assistance in diazotization of amino acids.

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].

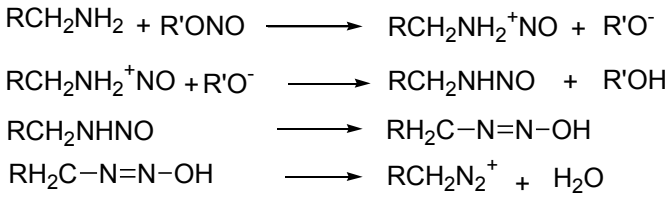


91 **92** **93** **94** **95** **96**

*Scheme 5.10 Diazotization of (S)-phenylalanine ethyl ester **91** using nitrous acid.*

5.4.1 Aprotic diazotization of aliphatic amines

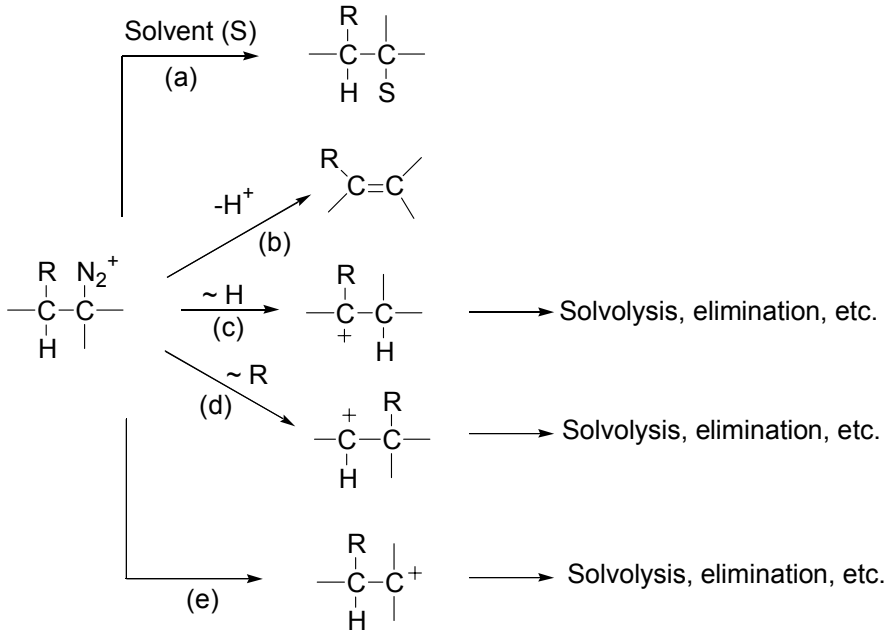
Diazotization of amines using alkyl nitrite in acidified aprotic solvents is referred to as aprotic diazotization[29]. The mechanism of this reaction follow the usual diazotization sequence depicted in Scheme 5.11[31]. The amine substitute the alkoxide group from alkyl nitrite to form a protonated nitrosoamine 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 5.11 Mechanisms for diazotization of amines using alkyl nitrites.

In 1957 Streitwieser and Schaeffer[32] 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[33]. However, Kirmse and Brosch[34] 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)[35]. In view of these observations it was decided to establish an investigation on inversion of amino acids via diazotization reactions.



Scheme 5.12 Possible reactions of aliphatic diazonium salt.

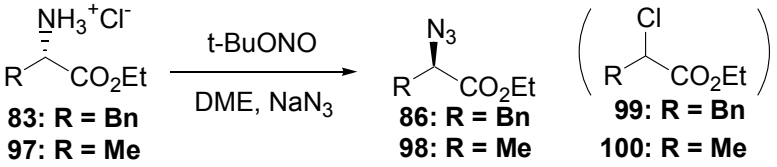
5.4.2 Diazotization of L-amino acid esters

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

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**.

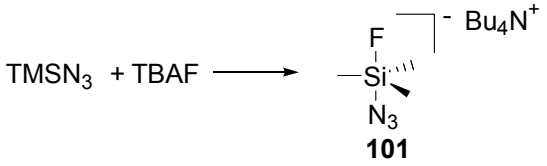


83: R = Bn **97: R = Me** **86: R = Bn** **98: R = Me** **99: R = Bn** **100: R = Me**

*Scheme 5.13 Diazotization of L-alanine and L-phenylalanine ethyl esters **83** and **97**.*

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)[36] 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.

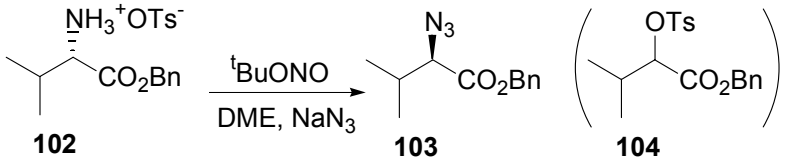


101

Scheme 5.14 Formation of soluble azide from trimethylsilylazide and tertiary butylammonium fluoride.

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.



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 couterions. 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.

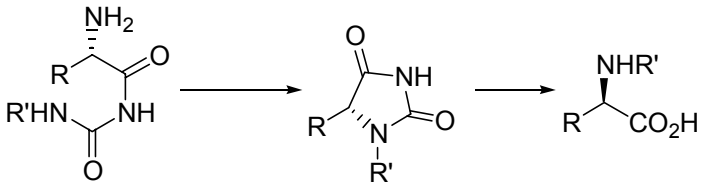
*Table 5.3: Yields and optical properties of the chloro and tosyl substituted products **99, 100** and **104***

Compound	Yield (%)	Optical activity, $[\alpha]_D$	Stereoselectivity
99	92	+ 4.7 (c = 2, EtOH)	31% retention[a]
100	90	+ 5.1 (c = 2, $CHCl_3$)	
104	44	+ 3.6 (c = 2, $CHCl_3$)	

[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 intramoleculary 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-Benzenedisulfonylchloride was prepared as described elsewhere[15]. DME and THF were distilled under nitrogen from sodium benzophenone ketyl and used immediately. DMF and dichloromethane were distilled over CaH_2. 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 400/100.61 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). X-ray: Enraf-Nonius CAD-4 diffractometer.

5.6.2 *N,N*-Benzene-1,2-disulfonylimide derivative of L-phenylalanine ethyl ester (**84**)

Benzene-1,2-disulfonyl chloride **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 **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 *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 **84**. M.p. 130-132°C. ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J = 7 Hz, 3H), 3.42 (dd, J = 15 and 11 Hz, 1H), 3.72 (dd, J = 5 and 15 Hz, 1H), 4.03 (q, J = 7 Hz, 2H), 4.95 (dd, J = 11 and 5 Hz, 1H), 7.35 (m, 5 H), 7.84 (m, 2H), 7.92 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$): 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 [*m/z* (rel. int.)]: 395 (M^+, 0.1%), 322 (13%), 304 (6%), 232 (5%), 220 (1.4), 176 (100%), 148 (15%), 131 (21%), 104 (4%), 91 (56%); IR (KBr, cm^{-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); $[\alpha]_D$ = -60.66 (c = 1, $CHCl_3$).

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 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): 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), 4.1 (m, 2H), 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); ^{13}C NMR (100.61 MHz, $CDCl_3$): 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 - BF_4, 15%), 410 (33%), 307 (PH_3Pyr, 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), 1621 (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); $[\alpha]_D$ = -1.75 (c = 2, $CHCl_3$).

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 ^{o}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**; $[\alpha]_D$ = -2.25 (c = 2, $CHCl_3$).

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

2,4,6-Triphenylpyridinium tetrafluoroborate **85** (2.5 g, 4.4 mmol) and NaN_3 (1.0 g, 15.4 mmol) in DMF were stirred and heated to 80^{o}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 Na_2SO_4. 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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%), 176 (35%), 141 (10%), 139 (M - $EtCO_2$, 30%), 131 (100%), 103 (61%), 91 (73%), 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, $CDCl_3$): δ 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, $CDCl_3$): δ 14.04, 21.52, 52.61, 62.06, 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

(m), 1743 (s), 1447 (m), 1373 (m), 1302 (w), 1270 (s), 1184 (s), 1143 (s), 1074 (m), 1021 (m), 992 (w) 858 (w) 691 (w); $[\alpha]_D$ = +5.1 (*c* = 2, $CHCl_3$); HRMS: calculated for $C_5H_9ClO_2$: 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 NaN_3 (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. ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75.47 MHz, $CDCl_3$): 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 (w), 1370 (m), 1276 (m), 1177 (s), 997 (s), 839 (m), 697 (w); $[\alpha]_D$ = +3.6 (*c* = 2, $CHCl_3$).

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Appendices

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Appendix 1: Paper I

Said, S. A., Fiksdahl, A. "Preparation and nucleophilic substitution of the *N,N*-1,2-naphthalenedisulfonylimide derivative of a chiral amine", *Tetrahedron: Asymmetry* **1999**, *10*, 2627-2633.

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TETRAHEDRON: *ASYMMETRY*

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

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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.

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]

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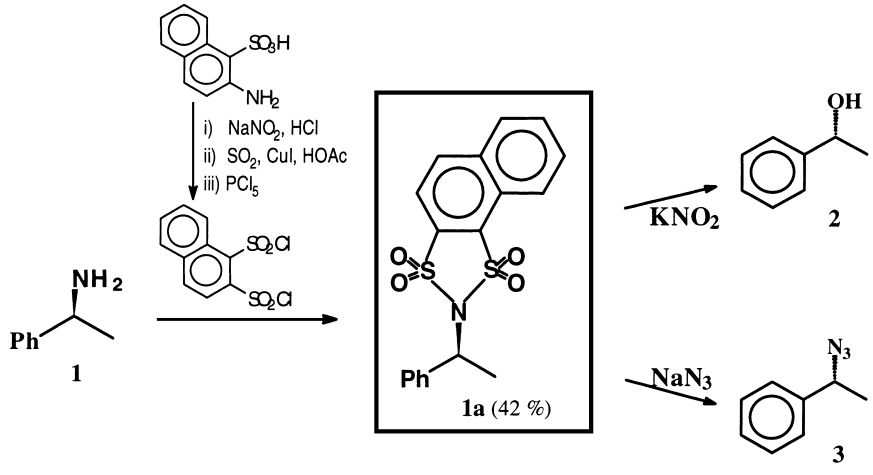
2. Results and discussion

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.[6] 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.[6] 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.



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 KNO_2 and 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[6] (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**.[1–5] This is particularly apparent at lower reaction temperatures. However, in contrast to what was observed for the *N*,*N*-1,2-benzenedisulfonylimides **8a**,**b**,[6] 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

	Substitution product, % ee/*R* (reaction conditions)	**Degree of Inversion**
	Alcohol 2[a]	
entry 1	20 % ee/*R* (KNO_2/18-cr-6, DMF, 0°C, 3 hrs)	60 %
entry 2	20 % ee/*R* (as above, 30% DMF/DMSO, 0°C,5 hrs)	60 %
entry 3	24 % ee/*R* (as above, DMF, 18°C, 24 hrs)	62 %
entry 4	20 % ee/*R* (as above, DMSO, 18°C, 24 hrs)	60 %
entry 5	24 % ee/*R* (KOH, DMF, 18°C, 24 hrs)	62 %
entry 6	26 % ee/*R* (NH_4OAc, DMF, 18°C, 24 hrs)	63 %
entry 7	26 % ee/*R* (NH_4OBz, DMF, 18°C, 24 hrs)	63 %
entry 8	20 % ee/*R* (KNO_2/18-cr-6, DMF, 80°C, 3 hrs)	60 %
entry 9	22 % ee/*R* (as above, DMSO, 80°C, 3 hrs)	61 %
	Azide 3[a]	
entry 10	40 % ee/*R* (NaN_3, 30 % DMF/DMSO, 0°C, 24 h)	70 %
entry 11	34 % ee/*R* (NaN_3, DMF, 18°C, 4 days)	67 %
entry 12	40 % ee/*R* (NaN_3, DMSO, 18°C, 24 h)	70 %
entry 13	20 % ee/*R* (NaN_3, DMF, 60°C, 24 h)	60 %
entry 14	36 % ee/*R* (NaN_3, DMSO, 60°C, 24 h)	68 %

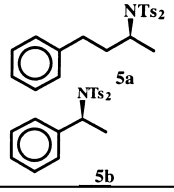
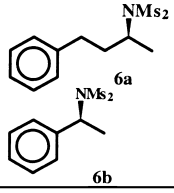
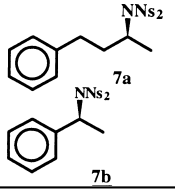
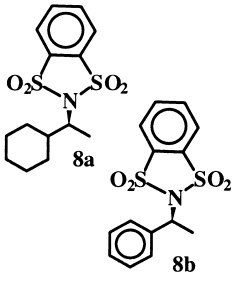
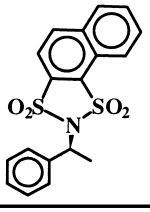
[a] The % enantiomeric excess of the alcohol product **2** and the azide product **3** is based on the direct chiral GLC analysis.

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[3] 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 (-NTs_2, **5a**,**b**) 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 KNO_2 and NaN_3 afforded the alcohol **2** and azide **3** with, respectively, 60–63% and 60–70% inversion of configuration.

Table 2
Comparison between nucleophilic substitution reactions of different *N,N*-disulfonylimides[1–6]

Nucleophilic Substitution of *N,N*-disulfonylimides	**Degree of inversion, (optimal reaction conditions)**	
	Alcohol product 	**Azide product** 
 **5a** **5b**	**100 %** (KNO_2,DMF, 120^{0}C, 72h) **100 %** (as above)	**100 %** (NaN_3, DMF,135^{0}C, 2h) **100 %** (as above)
 **6a** **6b**	**93 %** (as above) **82 %** (as above)	- -
 **7a** **7b**	**95 %** (as above) **82 %** (as above)	- -
 **8a** **8b**	**90 %** (KNO_2,DMF, 90^{0}C, 3d) **84 %** (KNO_2,30%DMF/DMSO, 0^{0}C, 24h)	**98 %** (NaN_3, DMSO,80^{0}C,4d) **94 %** (NaN_3,30%DMF/DMSO, 0^{0}C,24h)
 **1a**	**60-63 %** (Independent of reaction conditions, see Table 1)	**70 %** (Independent of reaction conditions, see Table 1)

This is lower than for the previously reported analogous *N*,*N*-1,2-benzenedisulfonylimides[6] (**8a**–**b**, 84–98%). 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**, -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 (*purum*); 2-aminonaphthalenesulfonic acid, Fluka (*pract*); sodium azide, Merck (*reinst*); sodium nitrite, Merck (>99%); potassium nitrite, Acros (>97%). Solvents: *pro analysi* quality. DMF and DMSO were dried over activated molecular sieve (4A). TLC: DC-Fertigplatten Kieselgel 60 F_{254} (0.25 mm). Detection: UV light at 254 nm or preferentially by 5% alcoholic molybdatophosphoric acid and heating. Flash chromatography: Kieselgel 60 (230–400 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 5–5.5 psi. Mps are uncorrected, and were measured on a Büchi apparatus. ^{1}H NMR: Bruker Avance DPX 300 MHz and 400 MHz NMR spectrometer, chemical shifts are reported in ppm downfield from TMS. 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% 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, $CDCl_3$): δ 7.65 (m, 2H), 7.93 (d, J=9.2 Hz, 1H), 8.06 (d, J=8.8 Hz, 1H), 8.19 (d, J=8.8 Hz, 1H), 8.92 (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 ($POCl_3$) were distilled off under vacuum. The yellowish solid was added ice water (100 ml) and the mixture was extracted with chloroform (3×50 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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), 1349 (s), 1326 (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 $C_{18}H_{15}NO_4S_2$, 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, $CDCl_3$): δ 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.

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Appendix 2: Paper II

Said, S. A., Fiksdahl, A., Carlsen, P. H. J. "Stereoselective synthesis of optically active phenyl ether", *Tetrahedron Lett.* **2000**, *41*, 5593-5596.

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Stereoselective synthesis of optically active phenyl ethers

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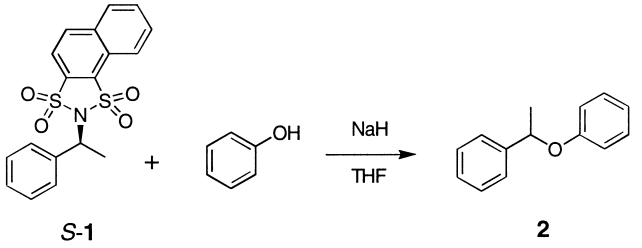
Abstract

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.

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



S-1 **2**

Scheme 1.

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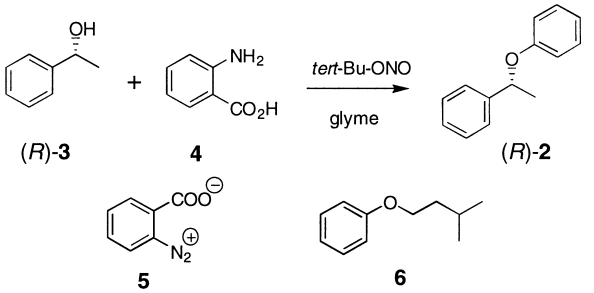
substitution procedures were tested. However, as expected, all were either unreactive or not stereoselective. The methods for the formation of the alkyl phenyl ether required mild, basic, neutral or eventually slightly acidic conditions. Strong acid conditions readily cleaved the benzylic ether bonds 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).



Scheme 2.

The crude reaction mixture contained **2** together with 9% of unreacted (*R*)-**3**.[15] 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, $CHCl_3$).

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 1
Measurements of the degree of inversion in the reaction between (*S*)-**1** and phenol

Reaction	**Product** (yield, %)	$[\alpha]_D^{20}$ (c=2.0, $CHCl_3$)	***e.e*** %	**Inversion** %
(*S*)-**1** to **2**	(*R*)-**2**, (57)	+ 4.05	46	73
(*R*)-**3** + **4** to **2**	(*R*)-**2**, (42)	+ 5.55	99	0

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

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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 $MgSO_4$, 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, $CHCl_3$).

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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, $CDCl_3$): 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, $CDCl_3$): 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 (Na_2SO_4) 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, $CHCl_3$). The product exhibited the following spectroscopic properties: ^{1}H NMR (300 MHz, $CDCl_3$): 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, $CDCl_3$): 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

Said, S. A., Fiksdahl, A. "Formation of chiral aryl ethers from enantiopure amine or alcohol substrates", *Tetrahedron: Asymmetry* **2001**, *12*, 893-896.

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TETRAHEDRON: *ASYMMETRY*

Formation of chiral aryl ethers from enantiopure amine or alcohol substrates

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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.

1. Introduction

We have previously shown[1–7] 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.[6,7] 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 benzyne route[8] from anthranilic acid **4** via diazotisation with *tert*-butylnitrite and thermal decomposition to benzyne 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-

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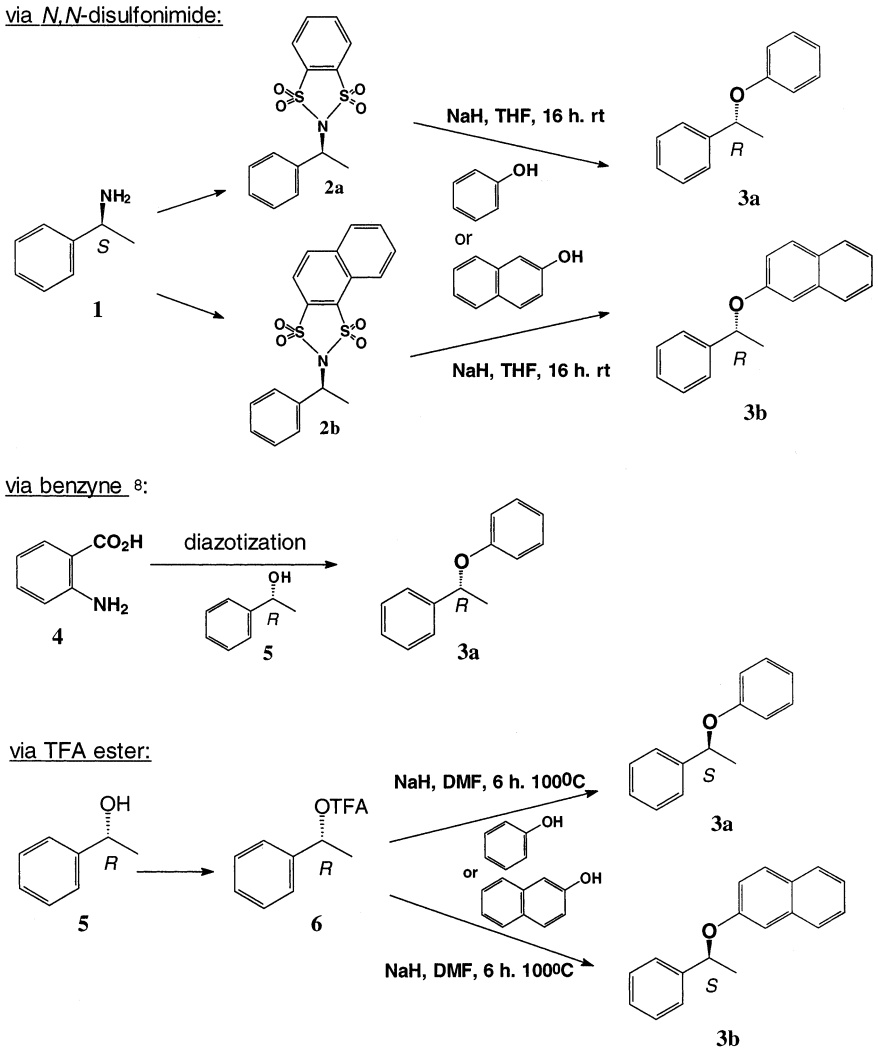
phenylethyl 2-naphthyl ether **3b** using the benzyne route[8] were also unsuccessful. However, the homochiral phenyl and 2-naphthyl ether reference compounds **3a** and **3b** could be prepared in 65–87% yield by nucleophilic substitution of the corresponding (*R*)-1-phenylethanol TFA ester[9] **6** (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 **3a**. The optical purity of the 2-naphthyl ether products (**3b** from **2a** and **2b**) was established based on comparison of optical rotation data with the homochiral reference compound **3b**. However, as mentioned above, this method is less



Scheme 1.

Table 1. Results for reactions are shown in Scheme 1

Starting material	Substrate	Nucleophile	Product (yield %)	$[\alpha]_D$ ($CHCl_3$)	Stereoselectivity
2a, **2b**	(*S*)-**2a**	PhO^-	(*R*)-**3a** (39)	+4.8 (*c*=2)	87% inv.[a]
	(*S*)-**2a**	2-$NaphthO^-$	(*R*)-**3b** (44)	+98 (*c*=0.2)	79% inv.[b]
	(*S*)-**2b**	PhO^-	(*R*)-**3a** (57)	+4.05 (*c*=2)	83% inv.[a]
	(*S*)-**2b**	2-$NaphthO^-$	(*R*)-**3b** (68)	+87 (*c*=0.2)	70% inv.[b]
4	**4**	(*R*)-**5**	(*R*)-**3a** (42)	+5.55 (*c*=2)	100% ret.[a]
6	(*R*)-**6**	PhO^-	(*S*)-**3a** (65)	−5.6 (*c*=2)	100% inv.[a]
	(*R*)-**6**	2-$NaphthO^-$	(*S*)-**3b** (87)	−124 (*c*=0.2)	100% inv.[c]

[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.

accurate and gives lower results than the more precise GLC method.

Based on previous experience,[7] 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.[7] The 1,2-naphthalenedisulfonylimide leaving group affords only a slightly lower degree of inversion than the corresponding 1,2-benzene leaving group in the formation of aryl ethers **3a** and **3b**. This is in contrast to our previous observations for the formation of azide and alcohol products,[6,7] which showed 20–25% lower stereoselectivity for the 1,2-naphthalene intermediate.
2. In the formation of the azide and alcohol products, alkyl substrates generally afford 5–15% higher stereoselectivity than benzylic substrates,[7] 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-, dimesyl- and dinosylimides.[1–7] 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.[1–7] All studies were focused on the degree of inversion for the reactions and no attempts were made to optimise the yields.
4. Two methods are presented for the formation of ethers **3a** and **3b** from amine and alcohol derivatives, respectively, by nucleophilic substitution with ArO^- to give inversion of configuration. Higher stereoselectivity is observed for the oxygen leaving group, -O-TFA (100% 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_N2 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.

3. Conclusion

Nucleophilic attack on *N*,*N*-1,2-benzenedisulfonylimides **2a** and *N*,*N*-1,2-naphthalenedisulfonylimides **2b** by aryloxide anions afforded (*R*)-1-phenylethyl phenyl ether **3a** and 2-naphthyl ether **3b** in 39–68% yield with 83–87 and 70–79% inversion of configuration, respectively. The homochiral phenyl and 2-naphthyl ethers **3a** and **3b** were prepared alternatively from the corresponding chiral alcohol via the TFA ester with 100% inversion of configuration. Phenyl ether **3a** has also been synthesised[8] via a benzyne route with complete retention of configuration.

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-disulfonyl chloride and naphthalene 1,2-disulfonyl chloride, respectively, as described elsewhere.[6,7] Phenol and 2-napthol were obtained from Merck, (*R*)-phenylethanol from Acros, TFA anhydride from Fluka, and NaH (>95%) from Aldrich. THF was distilled (N_2) from the sodium ketyl of benzophenone and was used immediately, while DMF was dried over activated molecular sieve (4 Å). All solvents were pro analysi quality. Chiral GLC analysis: Chrompack CP-CHIRADEX-CB fused silica WCOT (25 m, 0.32 mm; 0.32 μm), carrier gas pressure 5–5.5 psi. $^1H/^{13}C$ NMR: Bruker Avance DPX 300/75.47 MHz spectrometer; chemical shifts are reported in ppm downfield from TMS. MS: MAT 95 XL. IR: Nicolet 20SXC FT-IR spectrometer.

4.1. Preparation of (*R*)-1-phenylethyl phenyl ether 3a from (*S*)-*N*,*N*-1,2-naphtalenedisulfonyl-1-phenylethylamine 2b

The preparation of (*R*)-**3a** from (*S*)-**2b** and the characterisation of (*R*)-**3a** has been published elsewhere.[8] HRMS calcd for $C_{14}H_{14}O$: 198.1045; obsvd: 198.1042. Chiral GLC indicated a degree of inversion of 83% (*R*:*S* ratio 83:17).

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

The reaction was carried out as described elsewhere[8] 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. ^1H NMR (300 MHz, $CDCl_3$): δ 1.69 (d, $J=6.4$ Hz, 3H), 5.46 (q, $J=6.4$ Hz, 1H), 6.9 (d, $J=2$ 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, $CDCl_3$): δ 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* (% 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), 2869 (w), 1628 (s), 1600 (s), 1510 (m), 1485 (s), 1386 (m), 1258 (s), 1217 (s), 1181 (m), 1103 (m), 837 (m), 747 (m), 700 (s). HRMS calcd for $C_{18}H_{16}O$: 248.1201; obsvd: 248.1203. $[\alpha]_D$ +87 ($c=0.2$, $CHCl_3$). 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* ratio 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% yield) obtained after flash chromatography was characterised giving data in accordance with (*R*)-**3a** obtained from (*S*)-**2b** above. $[\alpha]_D$ +4.8 ($c=2$, $CHCl_3$). Chiral GLC indicated a degree of inversion of 87% (*R*:*S* ratio 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% yield) obtained after flash chromatography was characterised giving data in accordance with (*R*)-**3b** obtained from (*S*)-**2b** above. $[\alpha]_D$ +98 ($c=0.2$, $CHCl_3$). 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* ratio 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 g, 4.1 mmol) and triethylamine (0.68 mL, 4.9 mmol, 1.2 equiv.) in dichloromethane (10 mL) was carefully added trifluoroacetic anhydride (0.68 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 g, 90%), which was obtained after evaporation of the solvent, was purified by flash chromatography to give (*R*)-**6** as an oil (0.68 g, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (d, $J=6.6$ Hz, 3H), 6.04 (q, $J=6.6$ Hz, 1H), 7.36 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 22.0, 77.4, 114.7 (q, $J=286$ Hz), 126.3, 129.0, 129.1, 139.3, 157.3 (q, $J=42$ 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 ($c=2$, $CHCl_3$).

4.6. (*S*)-1-Phenylethyl phenyl ether 3a from (*R*)-1-phenylethyl trifluoroacetate 6[9]

A solution of phenol (97 mg, 1.03 mmol) and NaH (37 mg, 1.54 mmol, 1.5 equiv.) in DMF (10 mL) was stirred at rt until gas evolution ceased. (*R*)-**6** (150 mg, 0.7 mmol) in DMF (2 mL) was added and the mixture was heated for 6 h at 100°C. Water (25 mL) was added after cooling, and (*S*)-**3a** was obtained after extraction and flash chromatography (89 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 ($c=2$, $CHCl_3$). Chiral GLC indicated a degree of inversion of 100% (>99% 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**) from 2-naphthol (317 mg, 2.2 mmol), NaH (79 mg, 3.3 mmol, 1.5 equiv.) and (*R*)-**6** (320 mg, 1.47 mmol) to give (*S*)-**3b** (317 mg, 87% yield). The spectroscopic properties and GLC retention times were in agreement with those of (*R*)-**3b** prepared from the *N*,*N*-disulfonylimides (*S*)-**2a** and (*S*)-**2b**. $[\alpha]_D$ −124 ($c=0.2$, $CHCl_3$). 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 anthranilic acid 4 and (*R*)-1-phenylethanol 5

This method, via the benzyne intermediate, has been published elsewhere.[8]

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Appendix 4: Paper IV

Said, S. A., Fiksdahl, A. "Stereoselective transformation of amines via chiral 2,4,6-triphenylpyridinium intermediates", *Tetrahedron: Asymmetry* **2001**, *12*, 1947-1951.

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TETRAHEDRON: *ASYMMETRY*

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

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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.

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 RNH_2 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 RNH_2 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 BF_4^-, 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.

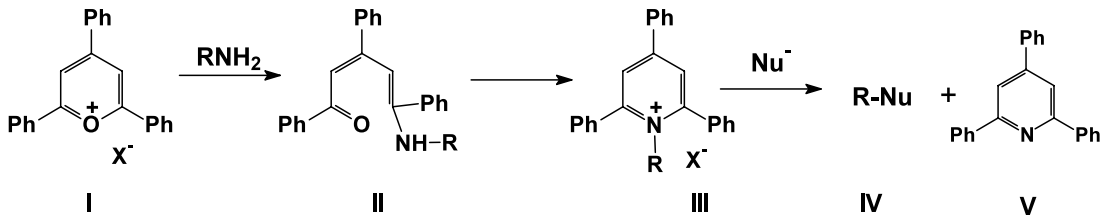

Figure 1.

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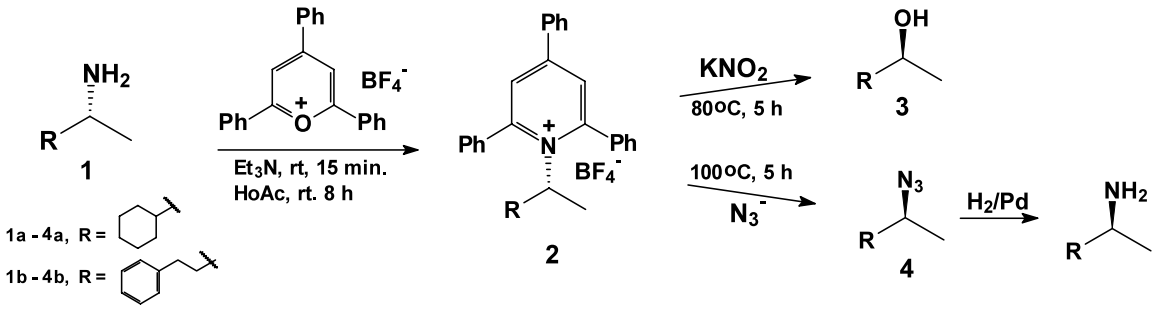
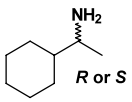
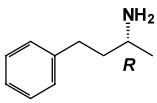


Scheme 1.

Table 1. Results for the reactions shown in Scheme 1

Starting material	Triphenyl-pyridinium intermediate 2 (yield %)	Stereoselectivity (yield %)	
		Alcohol 3[b] 	Azide 4[c] 
(*R*)-**1a** 	(*R*)-**2a** (84)	(*S*)-**3a**; >99% inv. (21)	(*S*)-**4a**; 97% inv. (37)
(*S*)-**1a**	(*S*)-**2a** (90)	(*R*)-**3a**; >99% inv. (17)	(*R*)-**4a**; 96% inv. (43)
(*R*)-**1b**[a] 	(*R*)-**2b**[a] (89)	(*S*)-**3b**[a]; >99% inv. (41)	(*S*)-**4b**[a]; 98% inv. (71)

[a] Substrate **1b** had e.e. of 96%. The % degree of inversion for product **3b** and **4b** has been corrected for this.

[b] Enantiomeric purity of the alcohol products **3a** and **3b** is based on chiral GLC.

[c] Enantiomeric purity of the azide products **4a** and **4b** 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 **1a** and **1b** reacted with 2,4,6-triphenylpyrylium tetrafluoroborate by fast ring opening to the vinylogous amide (**II**), which underwent slow ring closure to the 1-substituted 2,4,6-triphenylpyridinium cations **2a** and **2b** 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_3N 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.[12,15,17] 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 **2a**, **2b**. 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. ^{1}H NMR of the cyclohexyl intermediate **2a** showed a characteristic phenyl ring current effect[19] causing a high field resonance of two of the cyclohexyl protons as can be observed for (*S*)-**2a**; 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 **1a** and **1b** were nearly completely inverted by the nucleophilic substitution of the pyridinium intermediates **2a**, **2b** to give the alcohol **3a**, **3b** and azide **4a**, **4b** products. The azides **4a**, **4b** can be further reduced to the primary amines and thus afford the inverted amines. No attempts to optimize the yields of the substitution products **3a**, **3b** and **4a**, **4b** (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*-disulfonylderivative intermediates.[1–9] Triphenylpyridinium derivatives **2a**, **2b** showed comparable reactivity (80–100°C, 5 h) towards nucleophiles to ditosyl-, dimesyl- and dinosyl-imides[1–5] (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 ditosylimides[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 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 predried 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

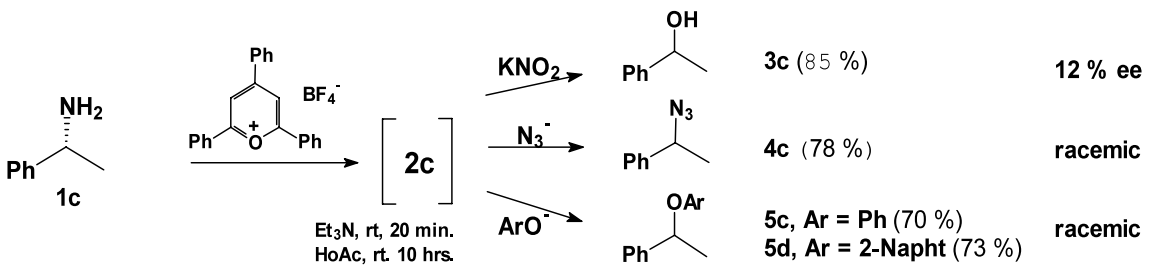
The stereoselective conversion of chiral primary amines into alcohols and azides with inversion of configuration has been demonstrated. The 2,4,6-triphenylpyridinium derivatives **2a**, **2b** of the chiral primary aliphatic amines **1a** and **1b** were formed from 2,4,6-triphenylpyrylium tetrafluoroborate 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*)-α-methoxyphenylacetic acid were obtained from Fluka, (*R*)-1-phenylethylamine, potassium nitrite, triethylamine and acetic acid from Acros, and (*R*)-1-methyl-3-phenylpropylamine was prepared by optical resolution using diastereomeric crystallization with (*S*)-*N*-acetylcystein 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 analysi 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



Scheme 2.

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; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 21.1, 25.4, 25.59, 25.62, 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 (Ph_3Pyr, 100%), 278 (1%), 230 (13%), 202 (6%), 110 (2%), 102 (2%), 81 (4%); IR (KBr, cm^{-1}): 3059 (w), 2929 (m), 2851 (m), 1619 (s), 1599 (m), 1562 (s), 1494 (m), 1411 (m), 1353 (s), 1082 (m), 1057 (s), 1034 (m), 892 (m), 763 (s), 702 (s), 532 (w), 521 (w). (*S*)-**2a**: $[\alpha]_D$ +61.7 (*c* 2.0, $CHCl_3$). (*R*)-**2a** was correspondingly prepared in 84% yield from (*R*)-**1a** and characterized; $[\alpha]_D$ −59.1 (*c* 2.0, $CHCl_3$).

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; ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75.47 MHz, $CDCl_3$): 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 (Ph_3Pyr, 100%), 278 (3%), 230 (29%), 202 (15%), 152 (11%), 132 (10%), 117 (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.); $[\alpha]_D$ −53.7 (*c* 2.0, $CHCl_3$).

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 KNO_2 (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 Na_2SO_4. 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.[4] 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 NaN_3 (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 solution was dried over Na_2SO_4. 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%). $[\alpha]_D$ −35.8 (*c* 2.0, $CHCl_3$). (*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.[6] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90–1.80 (m, 11H), 1.25 (d, $J=6.6$ Hz, 3H), 3.27 (quintet, $J=6.6$ Hz, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$): 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-methoxyphenylacetyl 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-phenylpropanol 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 nitrite 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] ^{13}C NMR (75.47 MHz, $CDCl_3$): 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.[3] Chiral GLC indicated an *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 NaN_3 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] ^{13}C NMR (75.47 MHz, $CDCl_3$): 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*)-α-methoxyphenylacetyl 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.[1]

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 KNO_2 (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.[4] 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 KNO_2 with NaN_3 (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.[2] 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 KNO_2 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.[8,9] 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).

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Appendix 5:

*X-ray data for compound **85***

URN:NBN:no-2330

Experimental

Crystal data

$C_{34}H_{30}BF_4NO_2$
$M_r = 571.40$
Monoclinic
$P2_1/c$
$a = 10.985$ (6) Å
$b = 15.501$ (6) Å
$c = 18.129$ (6) Å
$\beta = 106.41$ (3)°
$V = 2961$ (2) Å^3
$Z = 4$
$D_x = 1.282$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71069$ Å
Cell parameters from 25 reflections
$\theta = 10$–16°
$\mu = 0.095$ mm^{-1}
$T = 298$ (2) K
Block
Colourless
0.60 × 0.40 × 0.20 mm
Crystal source: ?

Data collection

Enraf–Nonius CAD-4 diffractometer

ω–2θ scans

Absorption correction:
ψ scan (ABSCALC in OSCAIL; McArdle & Daly, 1999),(North *et al.* 1986)

$T_{min} = 0.9275$, $T_{max} = 0.9628$

5579 measured reflections

5204 independent reflections

2672 reflections with >2sigma(I)
$R_{int} = 0.0151$
$\theta_{max} = 25.00°$
$h = 0 \rightarrow 13$
$k = 0 \rightarrow 18$
$l = -21 \rightarrow 20$
3 standard reflections
frequency: 120 min
intensity decay: 2%

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=$1/[\sigma^2(F_o^2) + (0.1651P)^2 + 0.1363P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = 0.147$
$\Delta\rho_{max} = 0.587$ e Å^{-3}
$\Delta\rho_{min} = -0.382$ e Å^{-3}
Extinction correction: *SHELXL*
Extinction coefficient: 0.0030 (19)
Scattering factors from *International Tables for Crystallography* (Vol. C)

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 *S*1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j$.

	Occupancy	x	y	z	$U_{\rm eq}$
N1	1	0.6088 (2)	0.71899 (17)	0.18078 (15)	0.0563 (7)
F1	1	0.5547 (2)	0.3731 (2)	0.40298 (17)	0.1219 (10)
F2	1	0.6883 (3)	0.4129 (2)	0.33782 (16)	0.1257 (10)
F3	1	0.7432 (3)	0.31117 (18)	0.42592 (19)	0.1258 (10)
F4	1	0.7282 (3)	0.4472 (2)	0.46010 (16)	0.1326 (11)
B1	1	0.6788 (4)	0.3869 (3)	0.4071 (2)	0.0688 (11)
C1	1	0.5006 (3)	0.67638 (19)	0.18171 (18)	0.0531 (8)
C2	1	0.4237 (3)	0.6440 (2)	0.11519 (17)	0.0574 (8)
C3	1	0.4505 (3)	0.6517 (2)	0.04530 (19)	0.0608 (9)
C4	1	0.5635 (3)	0.6927 (2)	0.0472 (2)	0.0646 (9)
C5	1	0.6407 (3)	0.7261 (2)	0.1130 (2)	0.0636 (9)
C6	1	0.6900 (3)	0.7625 (2)	0.25092 (19)	0.0661 (9)
C7	1	0.6229 (3)	0.8317 (3)	0.2846 (2)	0.0900 (13)
C8	1	0.7140 (3)	0.9039 (3)	0.3193 (2)	0.0765 (11)
C9	1	0.7493 (4)	0.9636 (3)	0.2743 (3)	0.0937 (13)
C10	1	0.8338 (5)	1.0284 (3)	0.3059 (3)	0.1022 (14)
C11	1	0.8803 (4)	1.0349 (3)	0.3820 (3)	0.0969 (14)
C12	1	0.8469 (4)	0.9781 (3)	0.4298 (3)	0.0912 (14)
C13	1	0.7634 (3)	0.9117 (3)	0.3985 (2)	0.0844 (12)
C14	1	0.4645 (3)	0.6669 (2)	0.25469 (18)	0.0583 (8)
C15	1	0.3667 (3)	0.7172 (2)	0.2646 (2)	0.0704 (9)
C16	1	0.3281 (4)	0.7076 (3)	0.3308 (2)	0.0877 (12)
C17	1	0.3860 (5)	0.6481 (3)	0.3853 (2)	0.0946 (14)
C18	1	0.4793 (4)	0.5966 (3)	0.3741 (2)	0.0864 (12)
C19	1	0.5186 (3)	0.6049 (2)	0.3082 (2)	0.0691 (9)
C20	1	0.7586 (3)	0.7732 (3)	0.1119 (2)	0.0722 (10)
C21	1	0.8764 (4)	0.7342 (3)	0.1379 (3)	0.1068 (16)
C22	1	0.9840 (4)	0.7799 (4)	0.1362 (4)	0.130 (2)
C23	1	0.9738 (5)	0.8624 (4)	0.1096 (3)	0.125 (2)
C24	1	0.8566 (5)	0.9001 (4)	0.0827 (3)	0.1201 (18)
C25	1	0.7490 (4)	0.8549 (3)	0.0834 (2)	0.0890 (12)
C26	1	0.3631 (4)	0.6196 (2)	−0.02777 (19)	0.0672 (9)
C27	1	0.4094 (5)	0.5775 (3)	−0.0814 (2)	0.0900 (13)
C28	1	0.3274 (6)	0.5491 (3)	−0.1490 (3)	0.1131 (17)
C29	1	0.2015 (6)	0.5629 (3)	−0.1634 (3)	0.1130 (18)
C30	1	0.1515 (5)	0.6048 (3)	−0.1115 (2)	0.0930 (13)
C31	1	0.23255 (19)	0.63326 (15)	−0.04167 (13)	0.0738 (10)
O22	0.50	0.80135 (19)	0.64528 (15)	0.29450 (13)	0.0729 (17)
O21	0.50	0.81275 (19)	0.70728 (15)	0.36601 (13)	0.180 (5)
O12	0.50	0.77075 (19)	0.72268 (15)	0.38830 (13)	0.184 (5)
C34	1	1.02396 (19)	0.64382 (15)	0.39332 (13)	0.246 (6)
C332	0.50	0.89126 (19)	0.59683 (15)	0.36751 (13)	0.109 (3)
C331	0.50	0.92616 (19)	0.64593 (15)	0.40861 (13)	0.181 (9)
O11	0.50	0.79642 (19)	0.61579 (15)	0.26043 (13)	0.102 (3)
C32	1	0.76452 (19)	0.69479 (15)	0.30153 (13)	0.159 (4)

Table *S*2. *Anisotropic displacement parameters* (Å²)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N1	0.0411 (14)	0.0638 (16)	0.0643 (16)	0.0041 (12)	0.0152 (12)	0.0035 (13)
F1	0.0737 (16)	0.129 (2)	0.166 (3)	−0.0184 (15)	0.0394 (16)	−0.0018 (19)
F2	0.154 (3)	0.140 (2)	0.0961 (18)	0.000 (2)	0.0570 (17)	0.0225 (17)

F3	0.1023 (19)	0.0925 (19)	0.169 (3)	0.0057 (15)	0.0155 (18)	0.0297 (17)
F4	0.149 (3)	0.116 (2)	0.108 (2)	−0.0300 (19)	−0.0040 (18)	−0.0307 (17)
B1	0.068 (3)	0.069 (3)	0.065 (3)	−0.015 (2)	0.012 (2)	0.000 (2)
C1	0.0449 (17)	0.0522 (17)	0.062 (2)	0.0040 (14)	0.0147 (14)	0.0022 (14)
C2	0.0528 (17)	0.062 (2)	0.061 (2)	−0.0050 (15)	0.0210 (15)	−0.0010 (15)
C3	0.065 (2)	0.0594 (19)	0.062 (2)	0.0058 (16)	0.0253 (16)	−0.0057 (15)
C4	0.064 (2)	0.072 (2)	0.065 (2)	0.0052 (18)	0.0298 (17)	−0.0030 (16)
C5	0.0509 (18)	0.066 (2)	0.079 (2)	0.0100 (16)	0.0257 (17)	0.0070 (17)
C6	0.0457 (17)	0.077 (2)	0.069 (2)	−0.0017 (16)	0.0053 (16)	0.0108 (18)
C7	0.056 (2)	0.130 (4)	0.081 (3)	−0.015 (2)	0.0156 (19)	−0.038 (2)
C8	0.054 (2)	0.109 (3)	0.065 (2)	−0.001 (2)	0.0128 (17)	−0.024 (2)
C9	0.091 (3)	0.106 (3)	0.081 (3)	0.015 (3)	0.020 (2)	−0.006 (3)
C10	0.106 (4)	0.085 (3)	0.122 (4)	0.015 (3)	0.042 (3)	0.007 (3)
C11	0.073 (3)	0.086 (3)	0.132 (4)	0.004 (2)	0.030 (3)	−0.020 (3)
C12	0.056 (2)	0.119 (4)	0.089 (3)	0.002 (2)	0.005 (2)	−0.037 (3)
C13	0.060 (2)	0.118 (3)	0.080 (3)	−0.013 (2)	0.0274 (19)	−0.024 (2)
C14	0.0523 (18)	0.069 (2)	0.0525 (18)	−0.0076 (16)	0.0128 (14)	−0.0008 (15)
C15	0.068 (2)	0.074 (2)	0.075 (2)	0.0037 (19)	0.0309 (18)	0.0035 (18)
C16	0.096 (3)	0.093 (3)	0.087 (3)	0.000 (2)	0.048 (2)	−0.011 (2)
C17	0.118 (4)	0.110 (4)	0.065 (3)	−0.018 (3)	0.043 (2)	−0.012 (2)
C18	0.103 (3)	0.095 (3)	0.060 (2)	−0.011 (3)	0.020 (2)	0.011 (2)
C19	0.069 (2)	0.069 (2)	0.066 (2)	−0.0045 (18)	0.0131 (17)	−0.0041 (17)
C20	0.0474 (18)	0.088 (3)	0.087 (2)	−0.0017 (18)	0.0283 (17)	0.011 (2)
C21	0.056 (2)	0.109 (3)	0.161 (4)	0.015 (2)	0.041 (3)	0.023 (3)
C22	0.053 (2)	0.165 (6)	0.180 (6)	0.017 (3)	0.049 (3)	0.042 (5)
C23	0.066 (3)	0.149 (5)	0.165 (5)	−0.019 (3)	0.040 (3)	0.033 (4)
C24	0.093 (4)	0.124 (4)	0.155 (5)	−0.007 (3)	0.055 (3)	0.043 (3)
C25	0.063 (2)	0.108 (3)	0.104 (3)	0.002 (2)	0.035 (2)	0.024 (3)
C26	0.083 (2)	0.064 (2)	0.060 (2)	−0.0082 (18)	0.0297 (18)	−0.0029 (16)
C27	0.123 (4)	0.085 (3)	0.069 (2)	0.013 (3)	0.040 (2)	−0.007 (2)
C28	0.161 (5)	0.106 (4)	0.074 (3)	0.004 (4)	0.037 (3)	−0.026 (3)
C29	0.163 (5)	0.096 (4)	0.066 (3)	−0.023 (4)	0.008 (3)	−0.019 (2)
C30	0.104 (3)	0.102 (3)	0.066 (2)	−0.034 (3)	0.013 (2)	−0.002 (2)
C31	0.076 (2)	0.081 (2)	0.067 (2)	−0.017 (2)	0.0235 (19)	−0.0026 (18)
O22	0.059 (3)	0.076 (4)	0.081 (4)	0.016 (3)	0.015 (3)	0.018 (4)
O21	0.264 (13)	0.103 (7)	0.101 (6)	−0.004 (8)	−0.068 (7)	0.010 (5)
O12	0.230 (10)	0.089 (5)	0.141 (6)	−0.053 (6)	−0.095 (7)	0.034 (5)
C34	0.096 (5)	0.217 (10)	0.344 (14)	0.015 (5)	−0.069 (7)	0.098 (9)
C332	0.095 (6)	0.090 (6)	0.117 (7)	0.013 (5)	−0.009 (6)	0.043 (6)
C331	0.30 (2)	0.098 (8)	0.064 (6)	0.007 (10)	−0.086 (9)	−0.005 (5)
O11	0.116 (5)	0.057 (3)	0.118 (6)	0.031 (3)	0.008 (4)	−0.032 (3)
C32	0.081 (4)	0.144 (6)	0.198 (8)	−0.045 (4)	−0.049 (4)	0.080 (6)

Table *S*3. *Geometric parameters (Å, °)*

N1—C1	1.364 (4)	C18—H18	0.9300
N1—C5	1.374 (4)	C19—H19	0.9300
N1—C6	1.492 (4)	C20—C25	1.359 (6)
F1—B1	1.360 (5)	C20—C21	1.385 (5)
F2—B1	1.352 (5)	C21—C22	1.386 (7)
F3—B1	1.363 (5)	C21—H21	0.9300
F4—B1	1.340 (5)	C22—C23	1.360 (8)
C1—C2	1.358 (4)	C22—H22	0.9300
C1—C14	1.492 (4)	C23—C24	1.371 (7)
C2—C3	1.384 (4)	C23—H23	0.9300
C2—H2	0.9300	C24—C25	1.377 (6)
C3—C4	1.386 (5)	C24—H24	0.9300
C3—C26	1.485 (5)	C25—H25	0.9300
C4—C5	1.355 (5)	C26—C27	1.382 (5)
C4—H4	0.9300	C26—C31	1.400 (4)
C5—C20	1.492 (5)	C27—C28	1.373 (6)
C6—C32	1.479 (4)	C27—H27	0.9300
C6—C7	1.524 (5)	C28—C29	1.351 (7)
C6—H6	0.9800	C28—H28	0.9300
C7—C8	1.514 (6)	C29—C30	1.378 (7)
C7—H7A	0.9700	C29—H29	0.9300
C7—H7B	0.9700	C30—C31	1.398 (4)
C8—C9	1.361 (6)	C30—H30	0.9300
C8—C13	1.390 (5)	C31—H31	0.9300
C9—C10	1.377 (7)	O22—O11	0.7581
C9—H9	0.9300	O22—C32	0.8932
C10—C11	1.334 (6)	O22—O21	1.5899
C10—H10	0.9300	O22—C332	1.5977
C11—C12	1.356 (6)	O21—O12	0.7339
C11—H11	0.9300	O21—C32	1.1553
C12—C13	1.390 (6)	O21—C331	1.5841
C12—H12	0.9300	O21—C332	1.9138
C13—H13	0.9300	O12—C32	1.6143
C14—C19	1.375 (5)	C34—C331	1.1834
C14—C15	1.379 (5)	C34—C332	1.5777
C15—C16	1.389 (5)	C34—H34A	0.9700
C15—H15	0.9300	C34—H34B	0.9700
C16—C17	1.370 (6)	C332—C331	1.0584
C16—H16	0.9300	C332—H332	0.9800
C17—C18	1.358 (6)	C331—H331	0.9800
C17—H17	0.9300	O11—C32	1.5248
C18—C19	1.387 (5)		
C1—N1—C5	119.5 (3)	C5—C4—H4	119.0
C1—N1—C6	121.4 (3)	C3—C4—H4	119.0
C5—N1—C6	119.0 (3)	C4—C5—N1	120.2 (3)
F4—B1—F2	109.6 (4)	C4—C5—C20	120.3 (3)
F4—B1—F1	110.3 (4)	N1—C5—C20	119.5 (3)
F2—B1—F1	109.6 (3)	C32—C6—N1	107.5 (3)
F4—B1—F3	110.1 (3)	C32—C6—C7	119.8 (3)
F2—B1—F3	108.6 (4)	N1—C6—C7	114.8 (3)
F1—B1—F3	108.7 (3)	C32—C6—H6	104.3
C2—C1—N1	119.6 (3)	N1—C6—H6	104.3
C2—C1—C14	119.8 (3)	C7—C6—H6	104.3
N1—C1—C14	120.7 (3)	C8—C7—C6	110.5 (3)
C1—C2—C3	122.8 (3)	C8—C7—H7A	109.5
C1—C2—H2	118.6	C6—C7—H7A	109.5
C3—C2—H2	118.6	C8—C7—H7B	109.6
C4—C3—C2	115.9 (3)	C6—C7—H7B	109.6
C4—C3—C26	121.6 (3)	H7A—C7—H7B	108.1
C2—C3—C26	122.4 (3)	C9—C8—C13	117.8 (4)
C5—C4—C3	122.0 (3)	C9—C8—C7	121.3 (4)

C13—C8—C7	120.9 (4)	C27—C28—H28	120.0
C8—C9—C10	121.3 (4)	C28—C29—C30	121.8 (4)
C8—C9—H9	119.4	C28—C29—H29	119.1
C10—C9—H9	119.4	C30—C29—H29	119.1
C11—C10—C9	120.1 (5)	C29—C30—C31	119.5 (5)
C11—C10—H10	119.9	C29—C30—H30	120.2
C9—C10—H10	120.0	C31—C30—H30	120.2
C10—C11—C12	121.2 (5)	C30—C31—C26	118.2 (3)
C10—C11—H11	119.4	C30—C31—H31	120.9
C12—C11—H11	119.4	C26—C31—H31	120.9
C11—C12—C13	119.1 (4)	O11—O22—C32	134.7
C11—C12—H12	120.5	O11—O22—O21	179.6
C13—C12—H12	120.4	C32—O22—O21	45.5
C12—C13—C8	120.4 (4)	O11—O22—C332	106.1
C12—C13—H13	119.8	C32—O22—C332	119.0
C8—C13—H13	119.8	O21—O22—C332	73.8
C19—C14—C15	120.0 (3)	O12—O21—C32	115.6
C19—C14—C1	121.6 (3)	O12—O21—C331	117.2
C15—C14—C1	118.1 (3)	C32—O21—C331	117.7
C14—C15—C16	119.4 (4)	O12—O21—O22	136.8
C14—C15—H15	120.3	C32—O21—O22	33.5
C16—C15—H15	120.3	C331—O21—O22	84.5
C17—C16—C15	120.2 (4)	O12—O21—C332	129.3
C17—C16—H16	119.9	C32—O21—C332	86.6
C15—C16—H16	119.9	C331—O21—C332	33.6
C18—C17—C16	120.3 (4)	O22—O21—C332	53.3
C18—C17—H17	119.9	O21—O12—C32	40.2
C16—C17—H17	119.9	C331—C34—C332	42.1
C17—C18—C19	120.4 (4)	C331—C34—H34A	119.3
C17—C18—H18	119.8	C332—C34—H34A	119.3
C19—C18—H18	119.8	C331—C34—H34B	119.3
C14—C19—C18	119.7 (4)	C332—C34—H34B	119.3
C14—C19—H19	120.2	H34A—C34—H34B	116.8
C18—C19—H19	120.2	C331—C332—C34	48.6
C25—C20—C21	120.0 (4)	C331—C332—O22	105.1
C25—C20—C5	119.1 (3)	C34—C332—O22	109.4
C21—C20—C5	120.8 (4)	C331—C332—O21	55.9
C20—C21—C22	119.3 (5)	C34—C332—O21	88.1
C20—C21—H21	120.3	O22—C332—O21	52.9
C22—C21—H21	120.3	C331—C332—H332	123.5
C23—C22—C21	120.3 (5)	C34—C332—H332	123.5
C23—C22—H22	119.9	O22—C332—H332	123.5
C21—C22—H22	119.9	O21—C332—H332	138.6
C22—C23—C24	120.0 (5)	C332—C331—C34	89.3
C22—C23—H23	120.0	C332—C331—O21	90.6
C24—C23—H23	120.0	C34—C331—O21	122.9
C23—C24—C25	120.2 (5)	C332—C331—H331	115.6
C23—C24—H24	119.9	C34—C331—H331	115.6
C25—C24—H24	119.9	O21—C331—H331	115.6
C20—C25—C24	120.2 (4)	O22—O11—C32	24.6
C20—C25—H25	119.9	O22—C32—O21	101.0
C24—C25—H25	119.9	O22—C32—C6	135.60 (18)
C27—C26—C31	120.5 (3)	O21—C32—C6	121.60 (17)
C27—C26—C3	120.8 (4)	O22—C32—O11	20.7
C31—C26—C3	118.7 (3)	O21—C32—O11	121.7
C28—C27—C26	120.1 (5)	C6—C32—O11	115.46 (18)
C28—C27—H27	120.0	O22—C32—O12	118.2
C26—C27—H27	120.0	O21—C32—O12	24.2
C29—C28—C27	119.9 (5)	C6—C32—O12	106.15 (18)
C29—C28—H28	120.0	O11—C32—O12	137.6
C5—N1—C1—C2	−2.2 (4)	C5—N1—C1—C14	179.3 (3)
C6—N1—C1—C2	174.4 (3)	C6—N1—C1—C14	−4.1 (4)

N1—C1—C2—C3	0.5 (5)	C27—C26—C31—C30	−1.2 (5)
C14—C1—C2—C3	179.0 (3)	C3—C26—C31—C30	178.3 (3)
C1—C2—C3—C4	1.7 (5)	O11—O22—O21—O12	179 **(100)**
C1—C2—C3—C26	−177.2 (3)	C32—O22—O21—O12	62.2
C2—C3—C4—C5	−2.4 (5)	C332—O22—O21—O12	−111.2
C26—C3—C4—C5	176.6 (3)	O11—O22—O21—C32	116 (6)
C3—C4—C5—N1	0.8 (5)	C332—O22—O21—C32	−173.4
C3—C4—C5—C20	−177.2 (3)	O11—O22—O21—C331	−57 (6)
C1—N1—C5—C4	1.5 (5)	C32—O22—O21—C331	−173.2
C6—N1—C5—C4	−175.1 (3)	C332—O22—O21—C331	13.4
C1—N1—C5—C20	179.6 (3)	O11—O22—O21—C332	−70 (6)
C6—N1—C5—C20	2.9 (4)	C32—O22—O21—C332	173.4
C1—N1—C6—C32	77.5 (3)	C331—O21—O12—C32	−145.7
C5—N1—C6—C32	−106.0 (3)	O22—O21—O12—C32	−32.7
C1—N1—C6—C7	−58.6 (4)	C332—O21—O12—C32	−107.9
C5—N1—C6—C7	118.0 (4)	C331—C34—C332—O22	93.4
C32—C6—C7—C8	83.4 (4)	C331—C34—C332—O21	44.0
N1—C6—C7—C8	−146.3 (3)	O11—O22—C332—C331	158.6
C6—C7—C8—C9	75.9 (5)	C32—O22—C332—C331	−26.4
C6—C7—C8—C13	−104.6 (4)	O21—O22—C332—C331	−21.0
C13—C8—C9—C10	1.6 (6)	O11—O22—C332—C34	107.7
C7—C8—C9—C10	−178.9 (4)	C32—O22—C332—C34	−77.3
C8—C9—C10—C11	−1.7 (7)	O21—O22—C332—C34	−71.9
C9—C10—C11—C12	0.6 (7)	O11—O22—C332—O21	179.6
C10—C11—C12—C13	0.4 (7)	C32—O22—C332—O21	−5.4
C11—C12—C13—C8	−0.5 (6)	O12—O21—C332—C331	−80.4
C9—C8—C13—C12	−0.6 (6)	C32—O21—C332—C331	158.9
C7—C8—C13—C12	180.0 (4)	O22—O21—C332—C331	155.3
C2—C1—C14—C19	101.3 (4)	O12—O21—C332—C34	−119.4
N1—C1—C14—C19	−80.2 (4)	C32—O21—C332—C34	119.9
C2—C1—C14—C15	−73.2 (4)	C331—O21—C332—C34	−39.1
N1—C1—C14—C15	105.3 (3)	O22—O21—C332—C34	116.2
C19—C14—C15—C16	3.2 (5)	O12—O21—C332—O22	124.3
C1—C14—C15—C16	177.8 (3)	C32—O21—C332—O22	3.6
C14—C15—C16—C17	−0.6 (6)	C331—O21—C332—O22	−155.3
C15—C16—C17—C18	−1.6 (7)	O22—C332—C331—C34	−102.7
C16—C17—C18—C19	1.2 (7)	O21—C332—C331—C34	−122.9
C15—C14—C19—C18	−3.7 (5)	C34—C332—C331—O21	122.9
C1—C14—C19—C18	−178.0 (3)	O22—C332—C331—O21	20.2
C17—C18—C19—C14	1.4 (6)	C332—C34—C331—O21	−90.2
C4—C5—C20—C25	75.7 (5)	O12—O21—C331—C332	121.0
N1—C5—C20—C25	−102.3 (4)	C32—O21—C331—C332	−23.9
C4—C5—C20—C21	−103.0 (5)	O22—O21—C331—C332	−19.7
N1—C5—C20—C21	79.0 (5)	O12—O21—C331—C34	−149.5
C25—C20—C21—C22	1.4 (7)	C32—O21—C331—C34	65.6
C5—C20—C21—C22	−179.9 (5)	O22—O21—C331—C34	69.8
C20—C21—C22—C23	0.3 (9)	C332—O21—C331—C34	89.5
C21—C22—C23—C24	−1.4 (10)	O21—O22—O11—C32	−116 (6)
C22—C23—C24—C25	0.7 (9)	C332—O22—O11—C32	173.9
C21—C20—C25—C24	−2.1 (7)	O11—O22—C32—O21	−179.5
C5—C20—C25—C24	179.2 (4)	C332—O22—C32—O21	7.3
C23—C24—C25—C20	1.1 (8)	O11—O22—C32—C6	−15.3 (2)
C4—C3—C26—C27	42.4 (5)	O21—O22—C32—C6	164.2 (2)
C2—C3—C26—C27	−138.7 (4)	C332—O22—C32—C6	171.4 (2)
C4—C3—C26—C31	−137.1 (3)	O21—O22—C32—O11	179.5
C2—C3—C26—C31	41.8 (5)	C332—O22—C32—O11	−173.3
C31—C26—C27—C28	0.2 (6)	O11—O22—C32—O12	162.3
C3—C26—C27—C28	−179.3 (4)	O21—O22—C32—O12	−18.2
C26—C27—C28—C29	0.6 (8)	C332—O22—C32—O12	−11.0
C27—C28—C29—C30	−0.4 (9)	O12—O21—C32—O22	−137.8
C28—C29—C30—C31	−0.6 (8)	C331—O21—C32—O22	7.7
C29—C30—C31—C26	1.3 (5)	C332—O21—C32—O22	−5.3

O12—O21—C32—C6	55.13 (18)	N1—C6—C32—O21	−162.19 (15)
C331—O21—C32—C6	−159.38 (18)	C7—C6—C32—O21	−28.7 (3)
O22—O21—C32—C6	−167.07 (18)	N1—C6—C32—O11	30.2 (3)
C332—O21—C32—C6	−172.37 (18)	C7—C6—C32—O11	163.6 (2)
O12—O21—C32—O11	−138.0	N1—C6—C32—O12	−141.68 (19)
C331—O21—C32—O11	7.5	C7—C6—C32—O12	−8.2 (3)
O22—O21—C32—O11	−0.2	O22—O11—C32—O21	0.6
C332—O21—C32—O11	−5.5	O22—O11—C32—C6	168.22 (17)
C331—O21—C32—O12	145.5	O22—O11—C32—O12	−23.4
O22—O21—C32—O12	137.8	O21—O12—C32—O22	48.4
C332—O21—C32—O12	132.5	O21—O12—C32—C6	−133.32 (15)
N1—C6—C32—O22	36.1 (3)	O21—O12—C32—O11	57.6
C7—C6—C32—O22	169.6 (2)		