Polyfluoro-Pyridyl Glycosyl donors

Christopher . Hargreaves

University of Durham

A Thesis Entitled

Polyfluoro-Pyridyl Glycosyl Donors

Submitted by

Christopher A. Hargreaves MChem (Hons) Dunelm

(Ustinov College)

Department of Chemistry

A Candidate for the Degree of Doctor of Philosophy

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Tho' we are not now that strength which in old days

Moved earth and heaven; that which we are, we are;

One equal temper of heroic hearts,

Made weak by time and fate, but strong in will

To strive, to seek, to find, and not to yield.

Ulysses, Alfred Lord Tennyson

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Memorandum

The work presented within this thesis was carried out at the University of Durham between October 2002 and August 2005. The thesis is the work of the author, except where acknowledged by reference, and has not been submitted for any other degree. The copyright of this thesis lies solely with the author and no quotation from it should be published without prior written consent and information derived from it should be acknowledged.

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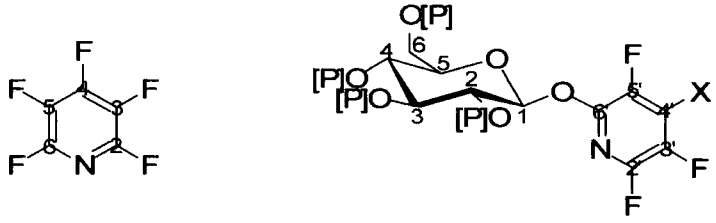


All the compounds detailed in this thesis are numbered utilising the above system, with the ring substituents being number according to the position they occupy on the parent ring system.

Nomenclature and Abbreviations

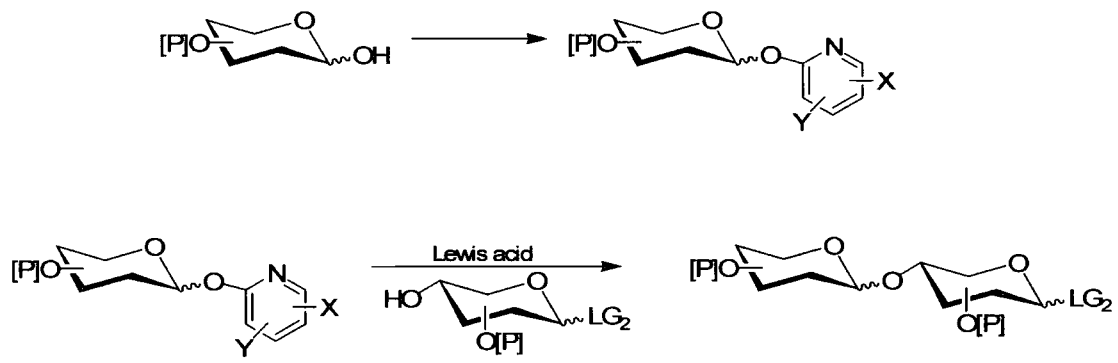
Bn	Benzyl group
Bz	Benzoyl group
DAST	(Diethylamino)sulphur trifluoride
DMSO	Dimethyl sulfoxide
DMTST	Dimethyl (methyl thio) sulfonium triflate
GA	Glycosyl acceptor
GD	Glycosyl donor
GLU	Glucose moiety
HFP	Hexafluoropropene
HPLC	High pressure liquid chromatography
IDCP	Bis (2,4,6-collidine) iodonium perchlorate
LA	Lewis acid
LDA	Lithium diisopropylamide
LG	Leaving group
NBS	N-Bromosuccinimide
NIS	N-Iodosuccinimide
Nu	Nucleophile
O[P]	Generic hydroxyl protecting group
OAc	Acetyl group
TDAE	Tetrakis(dimethylamino)ethylene
Tf	Triflate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethyl silane
HPFC	High pressure flash chromatography

Abstract

Carbohydrates are one of the most structurally and functionally diverse classes of naturally occurring compounds and it is well established that they play an essential role in a vast array of biological processes.

The synthesis of stereochemically defined oligosaccharides by a series of glycosylation processes, involving the reaction between a glycosyl donor and acceptor, is of paramount importance in synthetic carbohydrate chemistry and glycobiology. However, despite the importance of glycosylation chemistry and the development of sophisticated methodologies, there remains no general and stereoselective strategy that has been universally adopted for the syntheses of oligosaccharides.

In this thesis we present the synthesis and function of a novel family of glycosyl donors, in which fluorinated pyridine systems are utilised as the leaving group. In systems of this type it proved possible to 'tune' the glycosylation capability of the donor *via* variation of the substituents present on the pyridine ring and the type of Lewis acid activator used.



The formation of a glycosidic bond with control of the stereochemistry at the anomeric centre is usually difficult. Interestingly glycosyl donor systems of this type provide a high degree of stereoselectivity, providing diastereomeric excesses in the region of 80 to 98%. It has been determined that polyfluoro-pyridyl glycosyl donors do not react *via* the established S_N1 glycosylation process but *via* an unique S_N2 process which gives rise to the high degree of stereoselectivity observed.

Contents

1 Polyfluoro-Pyridyl Glycosyl Donors

Carbohydrates are one of the most structurally and functionally diverse classes of naturally occurring compound[1-6] and it is well established that they play an essential role in a vast array of biological processes. For almost 150 years the importance of sugars has driven research for creating bonds between them, however, a universal methodology for the synthesis of oligosaccharides remains elusive. The lack of easy access to oligosaccharides has hindered their investigation and development; consequently, general methodologies for the synthesis of oligosaccharides are imperative if the area of glycobiology is to be expanded.

Recently, promising improvements have been made with the development of hetaryl glycosyl donors[7, 8] and this study aims to expand upon this area by proposing a methodology that utilises fluorinated heterocycles to couple two or more saccharides (Figure 1.1).

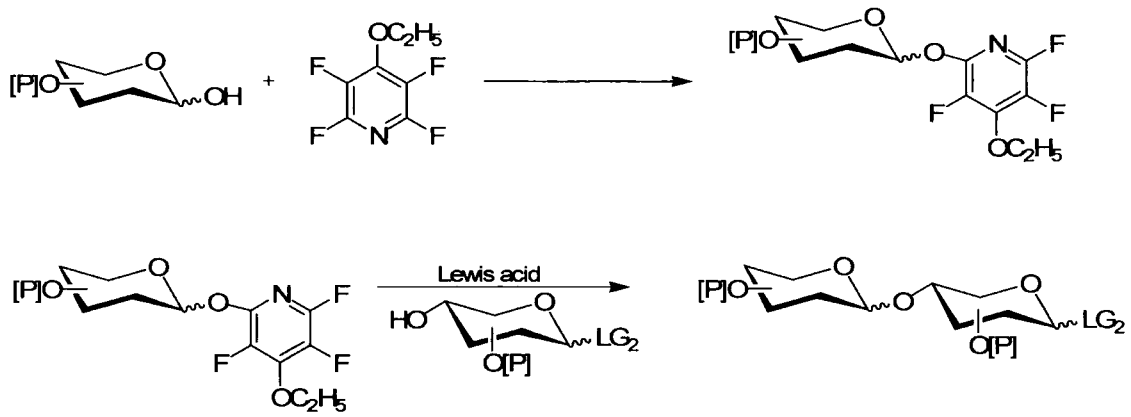


Figure 1.1. A schematic representation of the use of hetaryl glycosyl donors in oligosaccharide synthesis.

In principle, the reactivity of systems of this type will be tuneable by varying the substituents on the heterocyclic ring and the Lewis acid activator used, providing a high degree of control. However, before we can investigate the synthesis and reactions of such systems a knowledge of both carbohydrate and fluorine chemistry, with a particular emphasis on perfluoroheteroaromatic chemistry, is required and to that end the following two chapters will provide an overview of these two unique areas of chemistry.

1.1 Fluorine in Nature

Fluorinated organic compounds are rarely found in nature, fewer than twenty compounds are currently known.[9-13] A selection of these naturally occurring fluorine containing compounds can be seen in Figure 1.2.

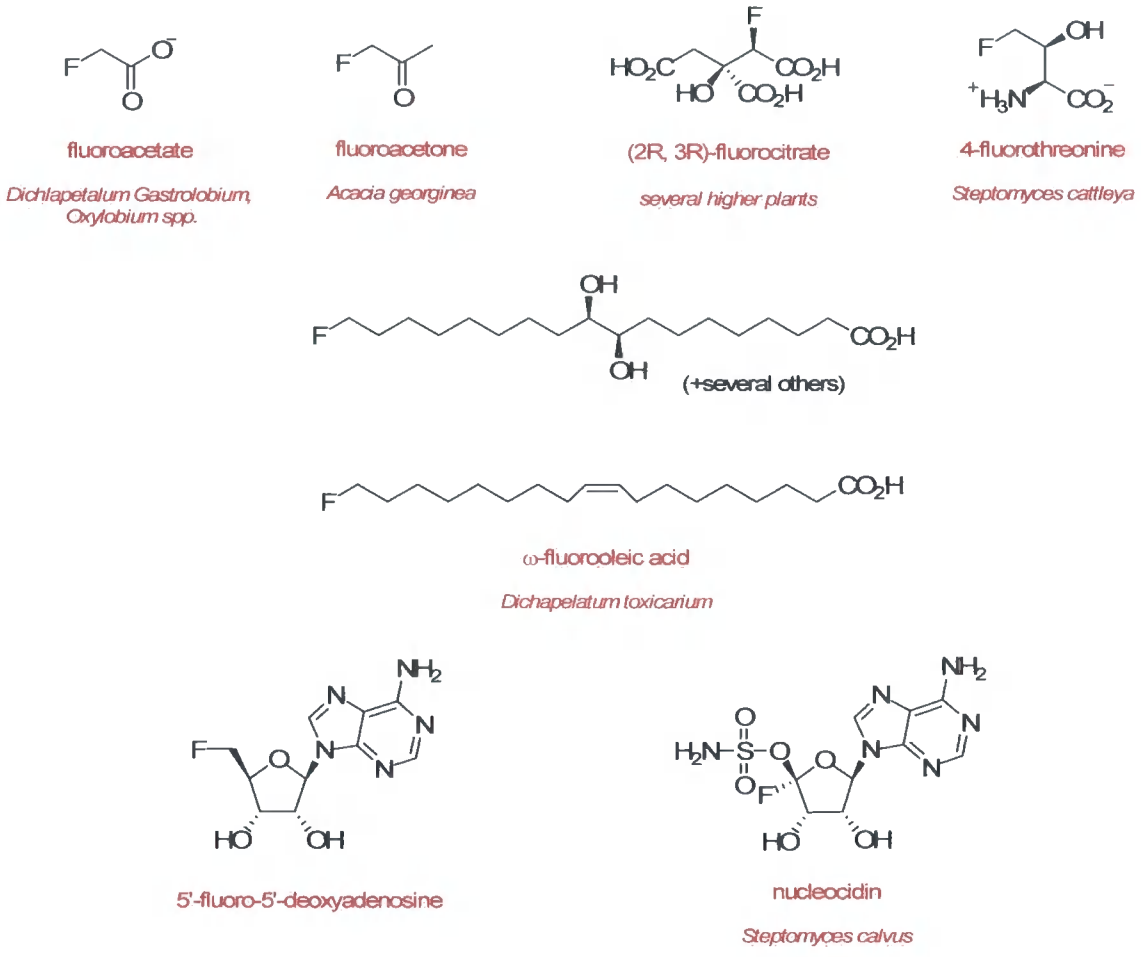


Figure 1.2. Naturally occurring fluorinated compounds.

Natural products containing chlorine, bromine and iodine are more numerous in nature. The apparent absence of fluorinated compounds is surprising since fluorine is widespread and has been estimated as the 13th most abundant element in the earth's crust,[13, 14] whereas chlorine has been estimated as the 20th, bromine the 46th and iodine the 60th. Nature, however, has generally found it difficult to incorporate fluorine into organic molecules, probably due to the strong energy of solvation of fluoride ion in water.

Fluorine can also be found in a variety of mineral deposits in the form of various inorganic compounds, the most important being fluorspar (CaF_2, fluorite) which is the principle source of fluorine for industrial fluorocarbon production.[15] Other simple fluorine containing minerals are known, some examples are villaumite (NaF), sellarite (MgF_2), fluoropatite ($Ca_5(PO_4)_3F$) and yttocerite ($Ca_3Ce_2Y_2F_6$).[16]

1.2 Properties of Carbon-Fluorine Bonds

The introduction of one or more fluorine atoms into an organic compound can impart unique chemical and physical properties to the compound, compared to the corresponding non-fluorinated derivatives. This arises due to the nature of the fluorine atom and its bonds to carbon; there are several factors which contribute to the distinct behaviour of fluorine as a substituent.[13, 14, 17-19]

- Fluorine is the most reactive halogen, and arguably the most reactive element in the periodic table, combining with all other elements except the lighter noble gases. The high reactivity of fluorine can be attributed to a combination of the very weak F-F bond (159 $kJmol^{-1}$) and the very strong bonds of fluorine to most other atoms (Table 1.1).[13, 20]

- Fluorine is the most electronegative atom in the periodic table (Pauling scale), therefore, carbon-fluorine bonds are more polarised and ionic in character than other carbon-halogen bonds.[17, 21, 22]

- Fluorine forms the strongest single bond to carbon (485 $kJmol^{-1}$),[17] often resulting in compounds that posses enhanced thermal stability.[13]

- The presence of fluorine in an organic compound also serves to strengthen the bonds between other proximate atoms in the molecule, for example, the C-C bond dissociation energies of CH_3CH_3, CH_3CH_2F and CH_3CF_3 are 372, 423 and 413 $kJmol^{-1}$ respectively.[13]

- Fluorine has a relatively small Van der Waals radius giving it a steric size similar to that of oxygen; this means that the introduction of a fluorine atom into a compound does not perturb the structure any more than that of an oxygen atom.

- Fluorine posses three tightly bound, non-bonding electron pairs, which results in weak intermolecular reactions between perfluorinated compounds.

Property	F	Cl	Br	I	H	O
Electronegativity (Pauling scale)	4.0	3.2	2.8	2.5	2.1	3.4
C-X bond length (Å)	1.35	1.77	1.94	2.14	1.09	1.43
C-X bond dissociation energy ($kJmol^{-1}$)	485	339	285	213	413	358
Van der Waals radii (Å)	1.47	1.75	1.85	1.98	1.20	1.52

Table 1.1. Properties of C-X bonds.

1.3 Applications of Fluorinated Compounds

The unique properties of fluorine containing compounds, such as enhanced chemical and thermal stabilities, have been utilised for numerous industrial applications and some examples are illustrated in Figure 1.3.[13-15, 17, 19, 23-25]

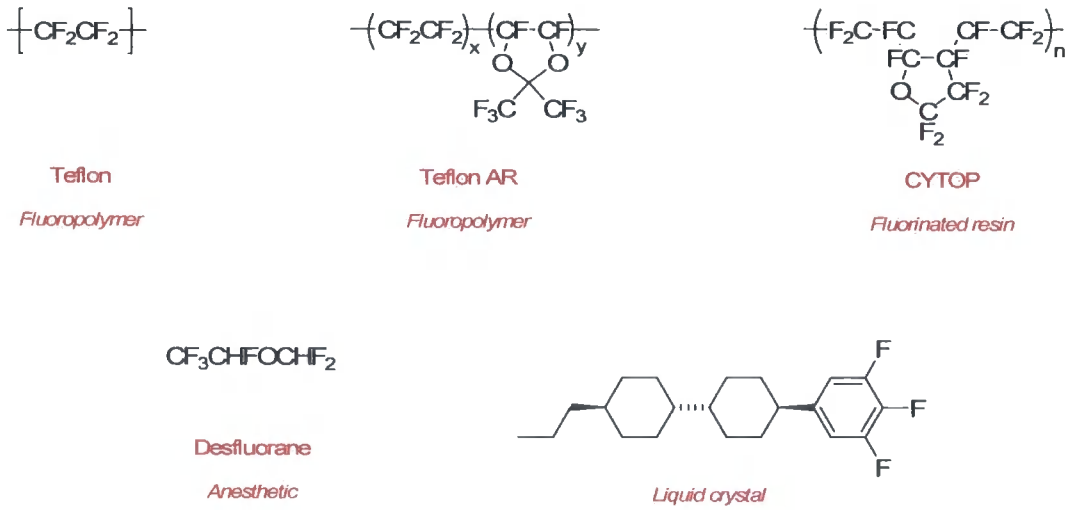


Figure 1.3. Some industrial fluorinated compounds.

The application of fluorine containing compounds to the pharmaceutical and agrochemical fields is relatively new. The first compound to demonstrate the importance of fluorine substituents in enhancing the effectiveness of drugs was 9-α-fluorohydrocortisone acetate, developed by Fried in 1954 (Figure 1.4).[26] Until the 1970s, however, fluorinated compounds were only rarely encountered in medicinal and agrochemicals, whereas, at present there are over 220 fluorinated life-science products in use in the US, a selection of these can been seen in Figure 1.4.[13, 25, 27, 28]

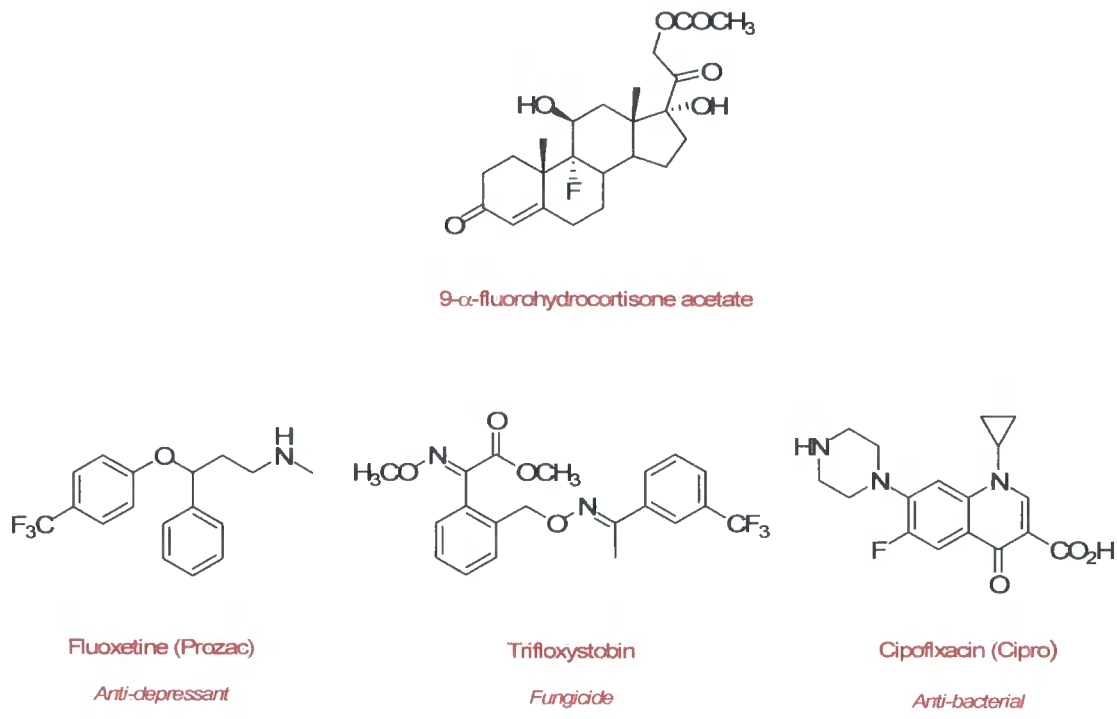


Figure 1.4. Examples of fluorine containing pharmaceutical and agro-chemicals.

1.4 The Chemistry of Polyfluoroaromatic Compounds

The purpose of this study was to develop a methodology that utilised fluorinated heterocyclic leaving groups to couple two or more saccharide units together (Figure 1.1). Subsequent chapters will detail the synthesis of highly substituted heterocyclic compounds derived from perfluorinated systems. Therefore, it is desirable to discuss some of the aspects that govern the chemistry of highly-fluorinated heteroaromatic compounds since they form the basis of the methodology developed in this thesis.

1.4.1 Synthesis

Most of the synthetic methods that are utilised for incorporating other halogens into organic compounds are not appropriate for the synthesis of fluorinated molecules; however, several different routes to the synthesis of highly fluorinated heteroaromatic compounds exist.

One of the first methods for synthesising perfluorinated aromatic compounds consisted of perfluorination of the parent hydrocarbon followed by defluorination over iron or nickel under vigorous conditions.[29, 30] Recently more efficient techniques have been developed utilising hot sodium oxalate ($Na_2C_2O_4$) for defluorination under milder conditions.[31]

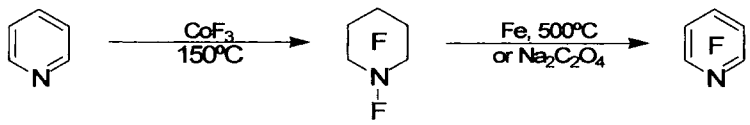


Figure 1.5

This approach has been used to synthesise a wide range of aromatic and heteroaromatic systems, however, its effectiveness is severely limited due to the relatively low yields of perfluorinated compound isolated and the difficulty of the defluorination stage which often results in complex mixtures of compounds.

One of the most practical routes to highly fluorinated aromatic systems involves the nucleophilic displacement of chloride by fluorine using alkali-metal fluorides.

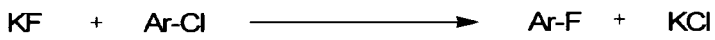


Figure 1.6

The reactivity of the alkali metal fluorides decreases in the series CsF › KF » NaF (*i.e.* with increasing lattice energy) and, because the nucleophilicity of fluorine diminishes substantially upon solvation, reactions are usually carried out in either a dipolar aprotic solvent or in the absence of solvent.[29, 32-36] It has been determined that optimum results

are obtained in the absence of solvent with reactions occurring at high temperature in an autoclave.[36]

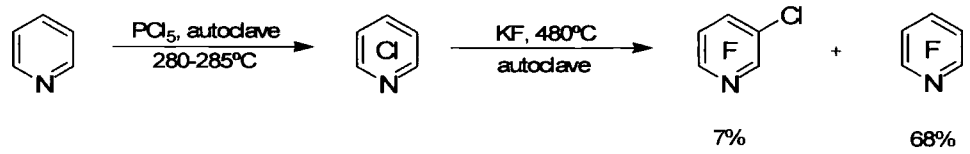


Figure 1.7

Numerous highly fluorinated aromatic and heteroaromatic compounds have been synthesised in this manner and the conditions for their synthesis have been documented in several reviews.[29, 34, 37, 38]

1.4.2 Nucleophilic Aromatic Substitution

Fluorine is characterised by its high electron affinity, the introduction of fluorine into an aromatic or heteroaromatic compound significantly alters the electronic properties and reactivity of the system compared to their hydrocarbon analogues. Due to the high electronegativity of fluorine, highly fluorinated aromatic compounds are very electron deficient species and are therefore susceptible to nucleophilic attack.[34, 39-42] The substitution of fluorine by a nucleophile in highly fluorinated aromatic systems proceeds *via* a well established two-stage mechanism[34, 40-44] in which the first stage (k_1) is rate limiting with the second stage consisting of the cleavage of the carbon-fluorine bond (k_2).

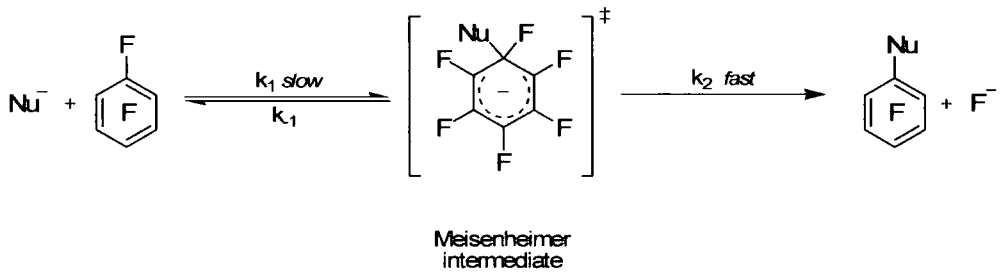


Figure 1.8. The two stage process of nucleophilic substitution in highly fluorinated aromatic systems.

The fact that perfluorobenzene is much more reactive than perchlorobenzene is consistent with there being little or no bond breaking in the rate-determining stage.[41]

An important feature of nucleophilic substitution in highly fluorinated aromatic compounds is their poly-functionality, *i.e.* a nucleophile can substitute a fluorine atom located *ortho-*, *meta-* or *para-* to a substituent other than fluorine (Figure 1.9). Kinetic studies for substitution reactions of various fluoroaromatic compounds (Table 1.2) have determined that a fluorine atom *para-* to the site of attack is slightly deactivating, whereas fluorine atoms *ortho-* and *meta-* to the site of attack are activating with respect to hydrogen atoms at the same position.

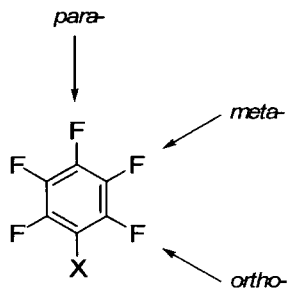


Figure 1.9

	Ortho	*Meta*	*Para*
		CH_3O^-/CH_3OH, 58°C	
Benzene derivatives	57	106	0.43
Pyridine derivatives	79	30	0.33
		NH_3/dioxane, 25°C	
Pyridine derivatives	31	23	0.26

Table 1.2. Comparison of k_F/k_H.

The electron distribution at the transition state can explain the observed substitution patterns in fluorinated aromatic species.[40, 41, 44, 45] The stability of the carbanionic Meisenheimer intermediate is significant in determining the regioselectivity of nucleophilic attack in fluorinated heterocycles, there are two situations to consider:[21, 39, 40, 44, 46, 47]

- Fluorine directly attached to the carbanion centre. $^{-}$:C–F
- Fluorine attached to a carbon adjacent to the carbanion centre. $^{-}$:C–C–F

The effect of a fluorine atom attached to a carbon atom adjacent to the carbanion is highly carbanion stabilising, due to the Iσ electron withdrawing effect.[39, 46]

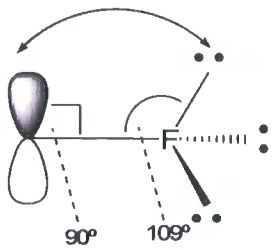
$^{-}$:C→C→F

Stabilising

For a fluorine atom attached directly to a carbanion centre there are two opposing effects to consider: electron withdrawing effects (Iσ) and electron pair repulsion (Iπ), the resultant of these two effects determines the effect of a fluorine atom upon the carbanion.

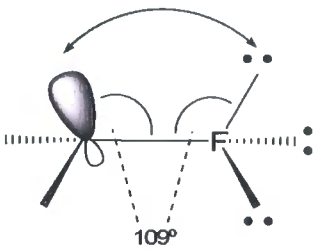
The electron withdrawing (Iσ) effect of fluorine is strongly carbanion stabilising and arises from the high electronegativity of fluorine.[21, 39]

Electron pair (Iπ) repulsion arises due to the interaction between the lone-pairs of electrons on the fluorine atom and the non-bonding electron pair at the carbanion site, the magnitude of this effect is dependant upon the geometry at the carbanion centre.



sp^2 hybridised system

Destabilising



sp^3 hybridised system

Stabilising

Figure 1.10

It has been established that the Iπ repulsion effect is greater for planar sp^2 hybridised carbanion centres, due to the proximity of the non-bonding electron pairs on the carbon and fluorine atoms. Consequently, for sp^2 hybridised systems the destabilising Iπ effect

overshadows the Iσ stabilising effect resulting in the overall destabilisation of the carbanion,[21, 39, 48, 49] whereas, for sp^3 hybridised systems the Iσ effect is dominant resulting in stabilisation of the carbanion centre.

The activating and deactivating effects of the fluorine atoms can now be explained by examining the stabilising and destabilising effects of the fluorine substituents on the Meisenheimer intermediate. In the case of a fluorine atom *para-* to the site of attack (Figure 1.11), delocalisation of charge generates a carbanion centre with a fluorine atom directly attached to it, which has been demonstrated to be destabilising in planar (sp^2 hybridised) systems.

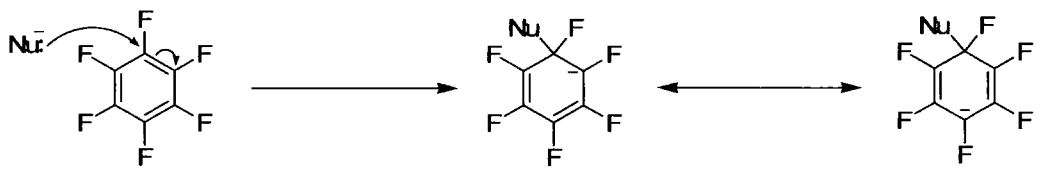


Figure 1.11

The same effect would also be expected for fluorine atoms *ortho-* to the site of attack, however, kinetic studies have shown that fluorine atoms in this position are in fact activating.[40, 41, 44, 45] Consequently, the activating effect of the *ortho*-fluorine atoms is predominantly a polar influence (Iσ) on the initial state, enhancing the electrophilic character of the carbon atom under attack. This inductive effect activates the initial state to such an extent that it effectively supplants the deactivating influence observed in the Meisenheimer intermediate (Figure 1.12).

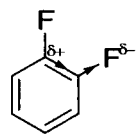


Figure 1.12

The activating effect of a fluorine atom *meta-* to the site of attack can be explained simply by examining the Meisenheimer intermediate, in this instance the

negative charge is delocalised adjacent to the carbon-fluorine bond in the *meta*-position (Figure 1.13) which has been demonstrated to be highly stabilising.[39, 46]

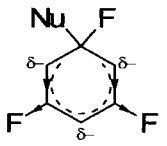


Figure 1.13

The site of nucleophilic attack can now be rationalised by minimising the number of deactivating *para*-fluorine atoms while at the same time maximising the number of activating *ortho*- and *meta*-fluorine atoms.[40-42, 44-47]

It has been established that both *ortho*- and *meta*-fluorine atoms are activating, with respect to hydrogen, however, the extent to which each contributes is dependant upon the system. In hexafluorobenzene, for example, *meta*-fluorine atoms exhibit a greater activating influence than *ortho*-fluorine atoms while for more reactive systems, such as pentafluoropyridine, the activating influence of *ortho*-fluorine atoms takes precedence.[41, 44, 46, 47] This is further confirmation that the activating influence of fluorine *ortho*- to the site of attack can be attributed to the enhancement of the electrophilic character of the carbon centre under attack in the initial state. On this basis, a more reactive system should lead to an earlier transition state (Hammond postulate[50]) which means a greater contribution from the initial state to the structure of the transition state. This in turn implies that the inductive effect of *ortho*-fluorine is more significant than the activating effect of the *meta*-fluorine atoms. Conversely, in a less reactive system, the transition state will more closely resemble the product, thereby decreasing the significance of the *ortho*-fluorine activating effect, allowing the *meta*-fluorine activating effect to become dominant.

1.4.3 Pentafluoropyridine

Polyfluoro-nitrogen-heteroaromatic systems are all activated, relative to the corresponding benzenoid compounds, towards nucleophilic aromatic substitution due to the activating effect of the ring nitrogen (Figure 1.14).[34]

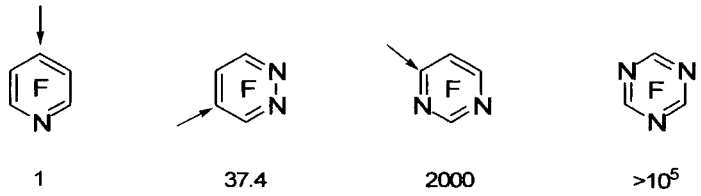


Figure 1.14. The relative rate constants for attack by NH_3/aq. dioxane, 25°C

In the case of pentafluoropyridine, the ring nitrogen would be expected to direct *ortho-* and *para-* to itself, however, it has been found that nucleophilic substitution occurs exclusively at the 4-position, *para-* to the ring nitrogen. The site of nucleophilic attack in polyfluorinated pyridines is governed by a combination of the directing effects of the ring nitrogen and the activating/deactivating effects of the fluorine substituents, *i.e.* the number of fluorine atoms *ortho-* and *meta-* to the site of attack is maximised (Figure 1.15).[40-42, 44]

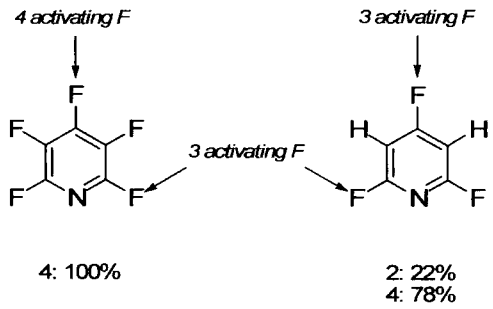


Figure 1.15. The sites of nucleophilic substitution by aqueous ammonia.

In systems where several possible sites of nucleophilic attack have the same number of activating/deactivating fluorine substituents the activating effect of the ring nitrogen determines the ratio of attack.[43, 45]

Another effect of the fluorine substituents in pentafluoropyridine is their influence upon the base strength of the ring nitrogen, the electron-withdrawing effect of the fluorine atoms *ortho-* to the ring nitrogen render pentafluoropyridine almost entirely non-basic and in fact acid salts are only formed by protonation with extremely powerful super acids.[51-53]

1.4.4 Reactions of Pentafluoropyridine

The reactions of pentafluoropyridine with an array of carbon, nitrogen, oxygen and sulphur centred nucleophiles have been investigated,[29, 34, 36, 51, 54-65] some examples are displayed in Figure 1.16, and such reactions are central to much of the work in this thesis. Reactions between pentafluoropyridine and nucleophilic species can be vigorous and are usually carried out using equimolar stoichiometries or excess nucleophile under very mild conditions.

The range of nucleophilic species found to undergo mono-substitution with pentafluoropyridine is vast, even bulky hindered nucleophiles such as *tert*-butoxide and LDA have been found to undergo nucleophilic substitution to give the mono-substituted compounds.[64]

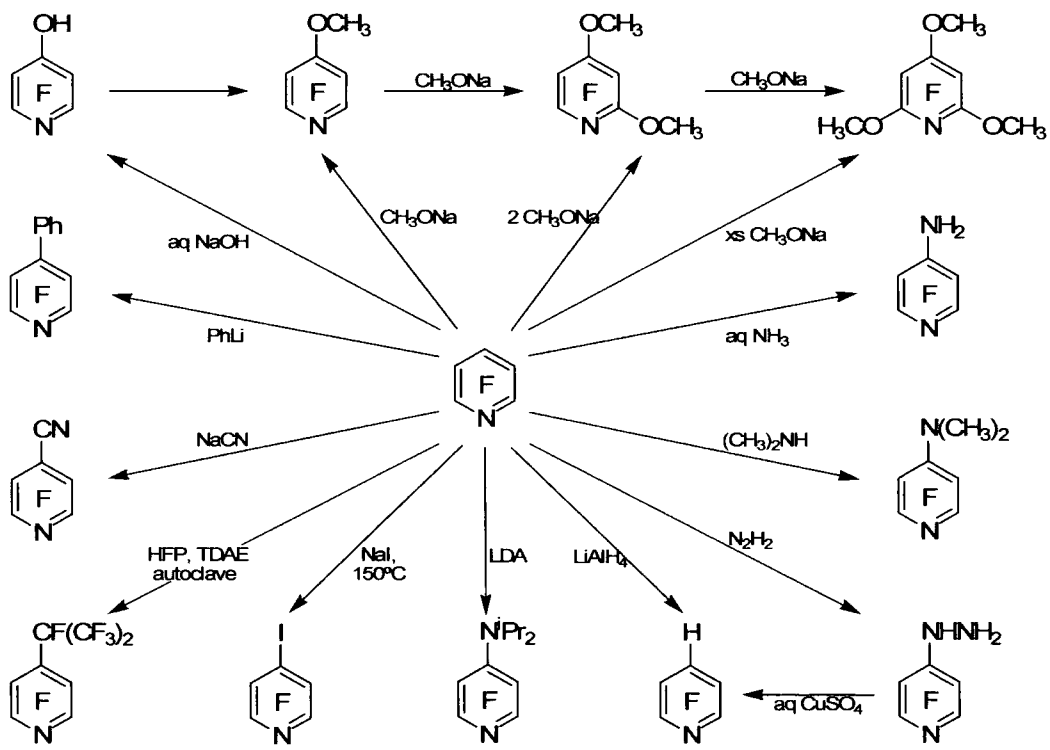


Figure 1.16. Selected nucleophilic substitution reactions of pentafluoropyridine.[51, 54-56]

A great extent of this research has been focussed upon the synthesis of mono-substituted perfluoropyridine derivatives and, surprisingly, there has been little research into sequential poly-substitution reactions. Trimethoxylation of pentafluoropyridine

yielding the 2,4,6-trimethoxy derivative[24, 51, 64] and, more recently, a series of reactions of tetrafluoro-4-(perfluoropropan-2-yl)pyridine[66-70] are the exceptions (Figure 1.17).

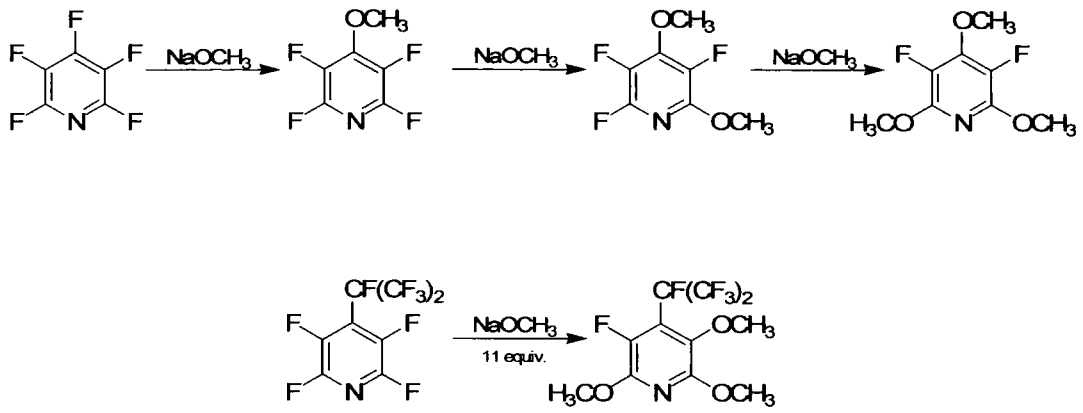


Figure 1.17. Highly substituted pyridine derivatives from the sequential nucleophilic substitution of pentafluoropyridine.

These studies have confirmed that the order of activation towards nucleophilic substitution follows the sequence 4-fluorine › 2-fluorine » 3-fluorine which is consistent with the carbanion stabilisation rules presented previously. However, due to the limited nature of this research little is known regarding the factors that influence reactivity and substituent compatibilities. Nucleophilic substitution at the 3-position is rare and has only been observed with the tetrafluoro-4-(perfluoropropan-2-yl)pyridine systems.[24, 51, 64, 66-70]

1.5 Summary

Organofluorine compounds have been found to be extremely useful compounds and materials; however, they do not occur naturally and hence they must be prepared by a variety of synthetic methods.

Many nucleophilic aromatic substitution reactions of pentafluoropyridine have been carried out providing a vast array of experimental information, however, studies concerning sequential poly-substitution reactions have not been examined, demonstrating that there is still a great deal of work required in this area in order to determine the factors that influence reactivity. Consequently, before sequential nucleophilic substitution can be used to generate substituted pyridines, a systematic

study to establish the regiochemistry of sequential substitution reactions and assess the robustness of the substituents towards further nucleophilic substitution reactions is required.

2 Carbohydrate Chemistry

Carbohydrates are one of the most structurally and functionally diverse classes of naturally occurring compound[1-6] and it is well established that they play an essential role in a vast array of biological processes.[5, 71-74] As well as their roles in metabolism, biosynthesis and as a structural component, there is ever-increasing recognition of their role as messengers in communication processes.[3, 6, 75, 76] The fact that oligosaccharides can function as ligands in biological recognition, usually through their binding to protein receptor sites, is now beyond dispute.[77-80] As part of glycoproteins, glycolipids and other conjugates, carbohydrates are the key elements in a variety of processes such as bacterial and viral adhesion and intercellular recognition.[3, 5, 71-73, 81, 82] The function of these molecules and detailed mechanisms of these events are still poorly understood and, as such, carbohydrates remain the least exploited of the three major classes of biomolecules.

For almost 150 years the importance of carbohydrates has driven the search for methods for creating bonds between saccharides, both as mechanistic probes and as potential therapeutic agents.[2, 3] Unlike the synthesis of peptides and nucleotides, the synthesis of oligosaccharides is much more complicated – mostly because of the inherent properties of the molecules themselves, but also due to the lack of a single set of 'optimum' reaction conditions for the stereospecific formation of the oxygen bridges between two saccharide residues, the glycosidic bond. The comparison of the number of possible isomers of di-, tri-, tetra- and penta-saccharides with those of the corresponding peptides and nucleotides, given in Table 2.1, clearly demonstrates the relative complexity of oligosaccharide synthesis.

Oligomer	Composition*	Number of possible isomers	
		Peptide or nucleotide	Saccharide
Dimer	AA/AB	½	11/20
Trimer	AAA/ABC	1/6	120/720
Tetramer	AAAA/ABCD	1/24	1424/34560
Pentamer	AAAAA/ABCDE	1/120	17872/2144640

Table 2.1. Isomeric possibilities for sequences for biopolymers.[83]

*A, B, C... represent a distinct peptide, nucleotide or saccharide residue.

Several efficient methodologies for glycosidic bond synthesis and, hence oligosaccharides are now available, but typically each has its own idiosyncrasies that are characteristic to a specific systems.[1, 3, 4, 7, 8, 84] The lack of easy access to oligosaccharides has created a technological bottleneck; therefore, general methods for the synthesis of oligosaccharides are an urgent requirement if the area of glycobiology is to be expanded. A general discussion concerning glycosylation strategies will follow since this thesis is concerned with the development of new methodologies based upon the synthesis and application of highly fluorinated heterocyclic glycosyl donors.

2.1 Glycosylation Strategies

In general, glycosylation involves the controlled coupling of a glycosyl donor, which is usually a protected carbohydrate system bearing a leaving group at the anomeric carbon atom (C_1), with a suitably protected glycosyl acceptor bearing one unprotected hydroxyl group (Figure 2.1). Complicated protecting group strategies[85-93] and suitable procedures for the activation[94-100] of the anomeric carbon atom are required and ideally the coupling stage should occur stereoselectively with respect to the formation of an α or β linkage between the saccharide units.

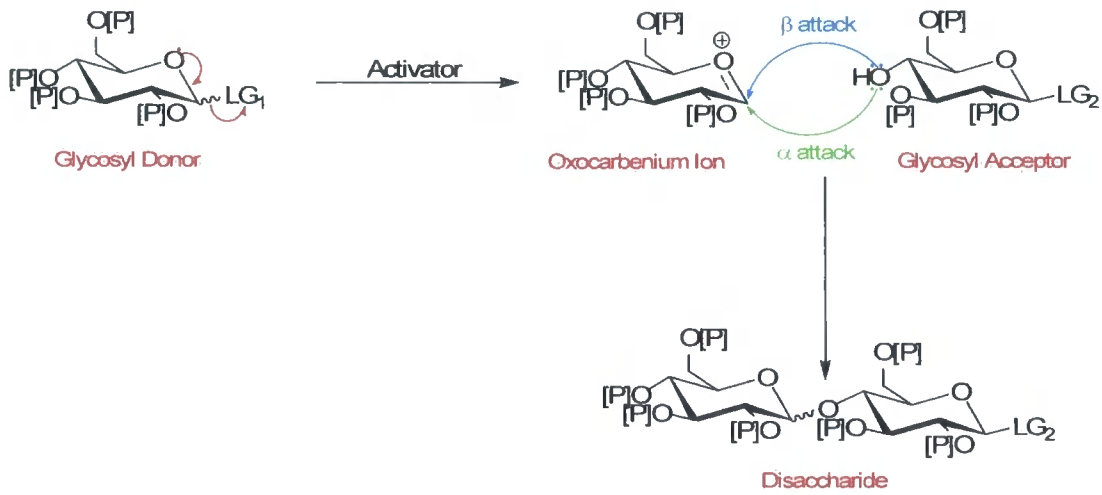


Figure 2.1. The glycosylation process.

The reactivity of a glycosyl donor system is dependant upon the nature of the protecting groups, for example, benzyl protecting groups generally activate the system,

whereas benzoyl groups are deactivating towards glycosylation, and the leaving group ability of the substituent (LG) located at the anomeric carbon.[90-93] The nature of the leaving group can have a striking effect on the reactivity of a glycosyl donor since the rate-limiting step in all glycosylation reactions involves the development of positive charge at the anomeric site. Glycosyl donors are roughly classified into 14 groups based upon the type of anomeric functional group and their activation methods. The choice of glycosyl donor is dependant upon: the required stereochemistry of the glycosyl linkage, the reactivity and the stability of the saccharide under the reaction conditions and the required chemoselectivity of the oligosaccharide product. Table 2.2 provides an overview of some common glycosyl donors along with their methods of activation. The number of glycosyl donors available is beyond the scope of this introduction into carbohydrate chemistry and has been reviewed thoroughly;[1, 3, 4, 101, 102] instead several classes of glycosyl donor will be examined in more detail providing an insight into this significant area of research.

Glycosyl Donor leaving group	Activator	Comments
Br	Br^-, $HgCN_2$, AgOTf	Most commonly used donor. The rates of reaction can be modulated by the choice of activator
Cl	$HgCN_2$, $HgBr_2$, AgOTf	More stable and less flexible than the bromide
F	AgOTf/$SnCl_2$, Tf_2O, DMTST	Efficient donors under mild conditions, react with thioglycosides in good yields
OAc	DMTST, TfOH	Mild conditions
SR/SeR	DMTST, TfOH	Rapid, high yielding and Stereoselective
SOR	Tf_2O	Rapid glycosylation of unreactive acceptors

Table 2.2. Several of the most common glycoside donors.[1, 3, 83, 84, 97, 100-104]

2.2 The Stereoselectivity of Glycosylation

The key step in deciding a strategy for oligosaccharide synthesis is often dependant upon the required stereochemistry of the glycosidic linkage, to this end, linkages are classified according to the stereochemistry of the C_1 - C_2 bond, *cis* (α) or *trans* (β), of the unit being transferred (Figure 2.2). Several of the glycosyl donor systems can influence the stereoselectivity of the glycosylation process; however, this is usually insufficient so several methodologies for controlling the stereoselectivity of glycosidic bond formation have been developed.

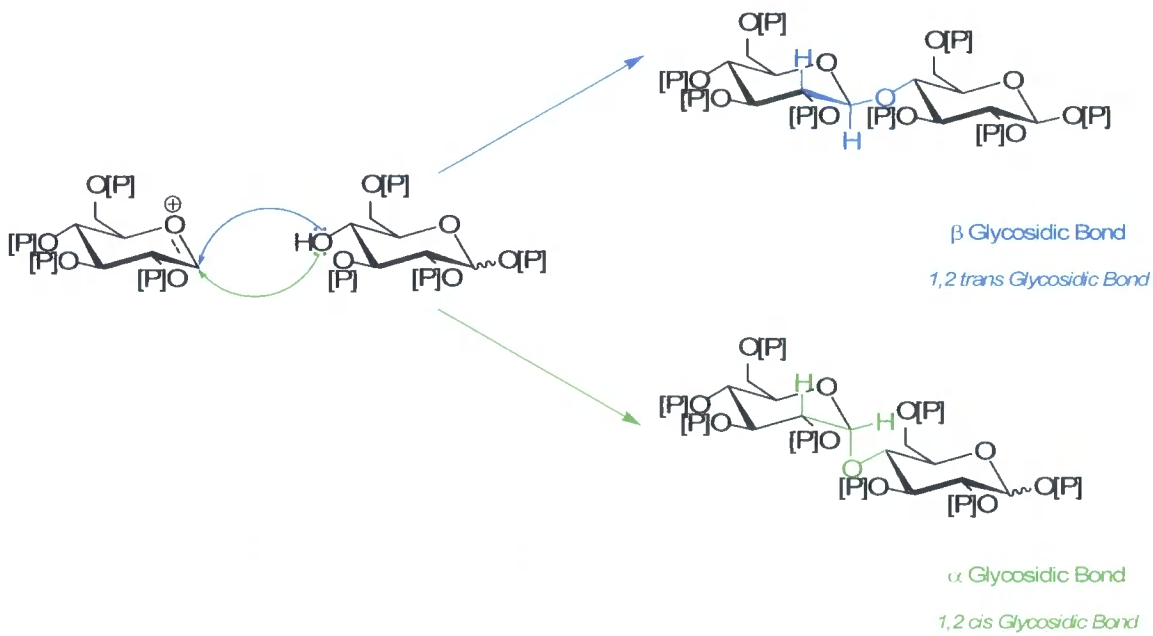


Figure 2.2. Stereoselectivity considerations in the glycosylation process.

There are several glycosylation strategies for influencing the stereochemistry of glycosidic bond formation depending upon the type of linkage required, two of the most common are:[1-3, 83]

- Anchimeric assistance or neighbouring group participation (NGP) for the construction of 1,2-*trans* linkages.

- *In situ* anomerisation for the synthesis of 1,2-*cis* linkages.

2.2.1 Neighbouring Group Participation

β Glycosyl linkages can be readily formed through anchimeric assistance from participatory groups, such as an ester (acetate, benzoate or pivalate) at the C_2 position. After the leaving group has departed from the glycosyl donor, the neighbouring group active substituent at the C_2 position stabilises the oxocarbenium ion to give a dioxocarbenium ion (Figure 2.3).

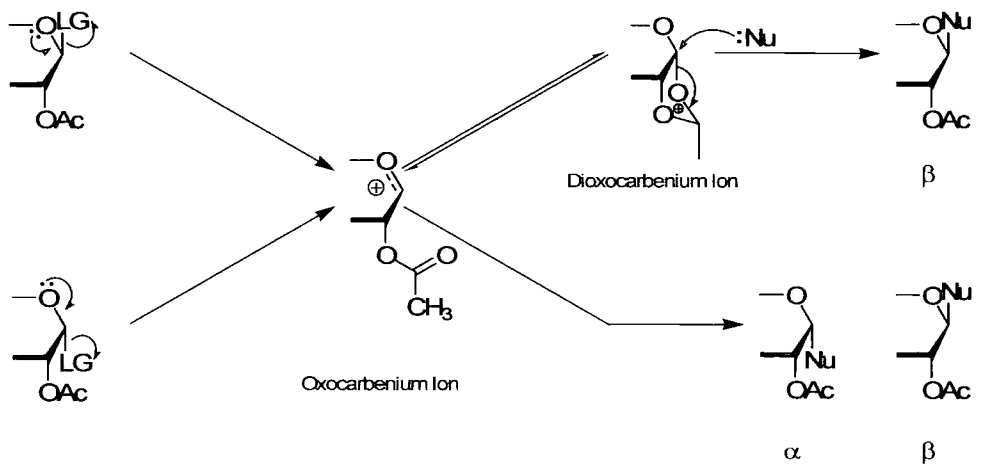


Figure 2.3. Stereochemical control utilising neighbouring group participation.

Nucleophilic ring opening of the dioxocarbenium ion at the C_1 position results in the formation of the β glycoside only since the nucleophile can only access the upper face of the dioxocarbenium ion. In reactions with only moderately reactive alcohols, the oxocarbenium ion can also react resulting in the loss of control over the stereochemistry of glycosidic bond formation.[1, 3] This strategy is used routinely to generate β glycosidic bonds with a high level of success, however, it does limit the range of protecting groups available.[105-110]

2.2.2 Non-Participatory Glycosylation

In the absence of C_2 NGP, stereoselectivity is considerably less and the formation of a glycosyl cation (favoured by polar solvents) means that absolute control of the stereochemistry of glycosidic bond formation is lost (Figure 2.4). Stereoelectronic effects dictate that such cations will tend to form mixtures of both α and β glycosyl

linkages, however, their interception either by counterions (resulting in either covalent intermediates or intimate ion pairs) or certain solvent molecules may dramatically affect the stereochemistry.[3, 4, 102, 111, 112]

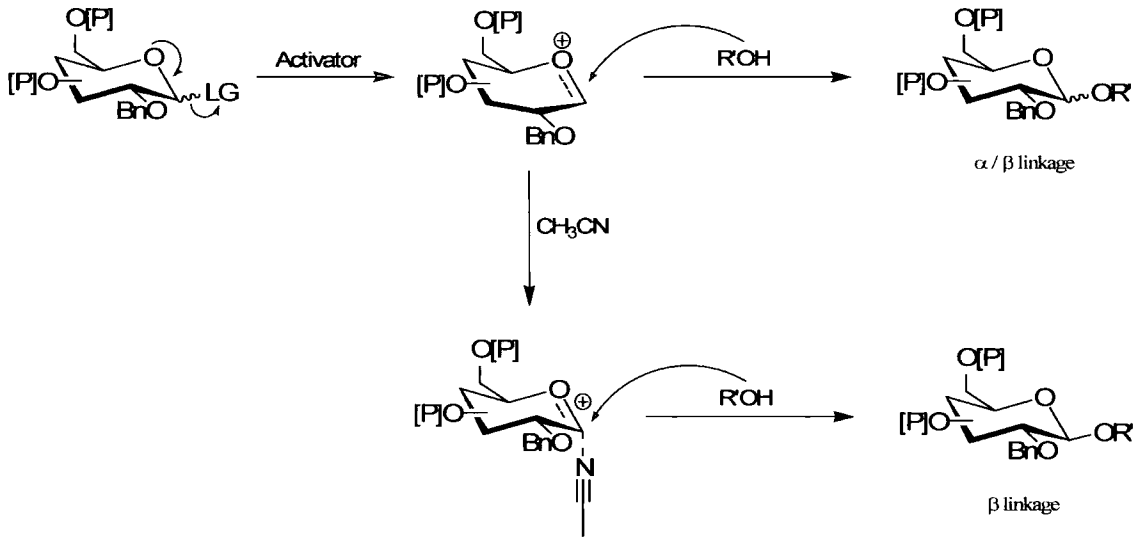


Figure 2.4. Non-participatory glycosylation.

This strategy can successfully enhance the formation of one isomer, however, the effect of a particular solvent is usually characteristic of the donor system being used.[111, 113, 114]

2.2.3 *In Situ* Anomerisation

The synthesis of α glycosides by the previous two methods is problematic due to the formation of anomeric mixtures, the separation of which is time consuming and expensive, or the preferential formation of β glycosidic bonds. To avoid these difficulties, the synthesis of α glycosides can be carried out using the *in situ* anomerisation methodology (Figure 2.5).[1, 104, 115]

The α glycoside (**i**) exists in equilibrium with the β glycoside (**ii**); the equilibrium reaction is catalysed by anion species, such as halides, and is usually carried out in solvents of low polarity. The ion pairs (**iii**) and (**v**) are generated from the α and β glycosides respectively, the two ion pairs are in equilibrium *via* the ion (**vi**).[104]

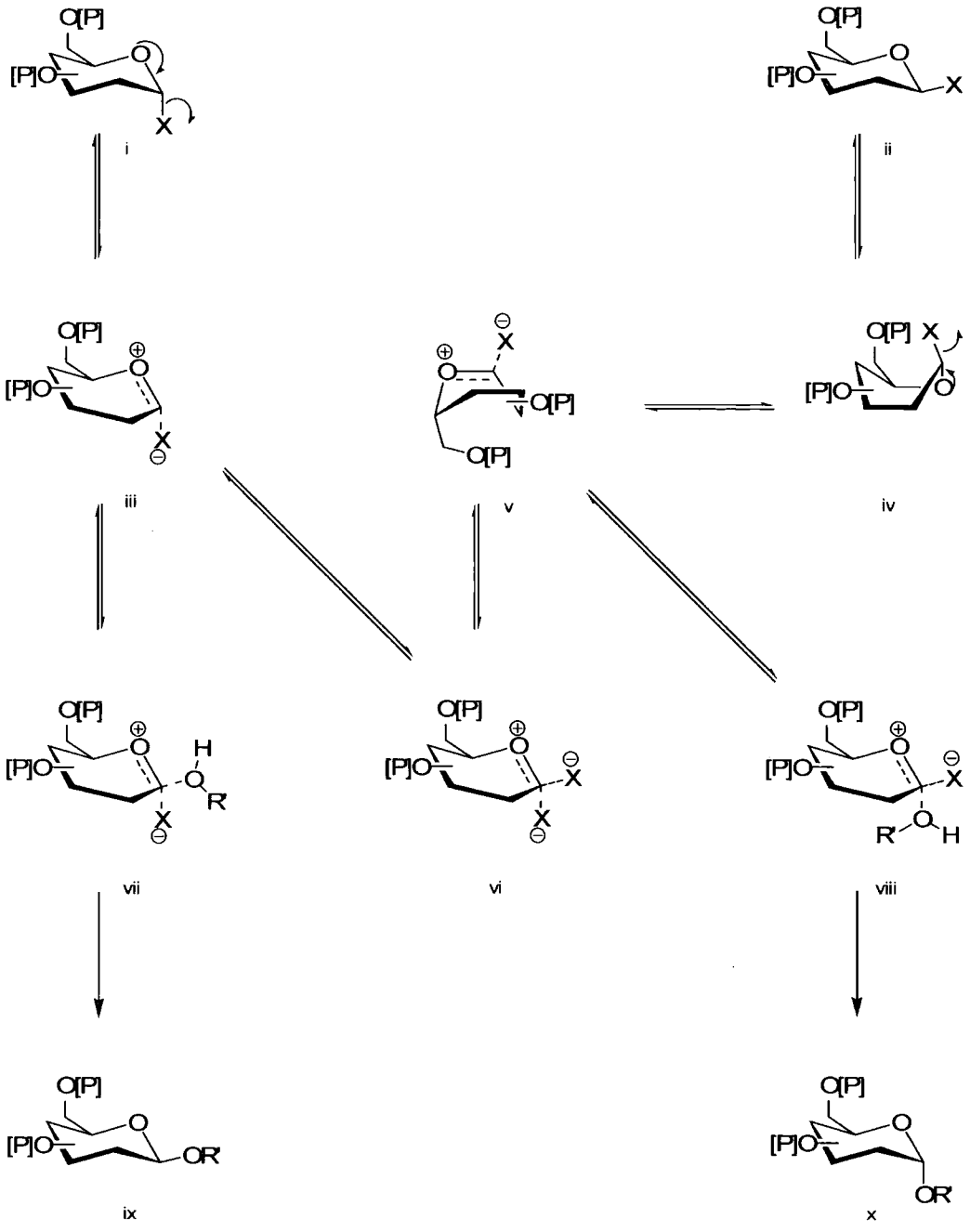


Figure 2.5. The *in situ* anomerisation strategy to generate α glycosyl linkage.

The glycosylation reaction can now proceed *via* one of two routes:

- firstly, with inversion *via* (**ii**) → (**v**) → (**viii**) → (**x**), or
- secondly *via* (**i**) → (**iii**) → (**vii**) → (**ix**).

The energy barrier for the nucleophilic reaction occurring by the first mechanism is lower than that for the second,[1] therefore, the formation of the α glycoside (**x**) is faster than that of the β glycoside (**ix**). This enables control of the reaction by exploiting the differences in the reaction rates of the two processes, effectively allowing the selective synthesis of α glycosidic linkages. The main problem of this approach is that it is often quite difficult to completely control the reaction rates of the two processes and hence anomeric mixtures are often produced.

2.3 Glycosyl Donor Systems

As stated previously, the number of glycoside donors available is vast and far beyond the scope of this introduction into carbohydrate chemistry; instead several classes of glycoside donor will be examined in more detail providing an insight into this immense area of chemistry.

2.3.1 Glycosyl Halides

The use of glycosyl bromides and chlorides as glycosyl donors was first introduced by Koenigs and Knorr in 1903[83, 84] and they still remain one of the most efficient and versatile classes of glycosyl donor. Glycosylation conditions and reaction rates can be modified over a wide range by varying the choice of halide and activator used demonstrating the versatility of this class of donor system (Table 2.3).[1, 3, 83, 84, 102, 104, 116]

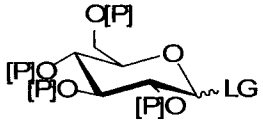
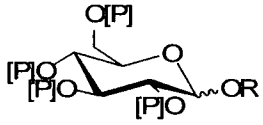
Glycosyl donor	Activator*	Glycosyl acceptor
	$Ag(SO_3CF_3)$ / Ag_2CO_3 $AgClO_4$ / Ag_2CO_3 $HgBr_2$ / molecular sieve $Hg(CN)_2$ / $HgBr_2$	
[P] – Bn › Bz › Ac LG – I › Br › Cl › F	$Hg(CN)_2$ $(C_2H_5)_4NBr$ / molecular sieve	CH_3OH » RCH_2OH › 6-OH › 3-OH › 2-OH › 4-OH

Table 2.3. The reactivities of the glycosyl halides and their corresponding activators.

* activator reactivity is listed in descending order, *i.e.* from the most to the least active.

Recent developments with this class of glycosyl donor have centred on the use of glycosyl fluorides, although they are less reactive than the glycosyl donors created from the other halides, they possess higher thermal and chemical stabilities compared to the lower stabilities of other glycosyl halides. The drawback of this class of donors is that they often require significant quantities of highly toxic heavy metal activators, which is unfavourable and hinders their application in the synthesis of bioactive compounds.

2.3.2 Heterocyclic Glycosyl Donors

Of particular interest to this report is the recent development of a series of heterocyclic glycosyl donors.[3, 7, 8, 117-125] In systems of this type, the C_1 hydroxyl group is selectively alkylated using N-heterocyclic chlorides or fluorides to form a hetaryl glycosyl donor, which under mild acid activation form pyridinones (Figure 2.6). The reaction of hetaryl donors is comparable to that of trichloroacetimidates forming amides, which have been well documented.[3, 7, 8, 109, 126]

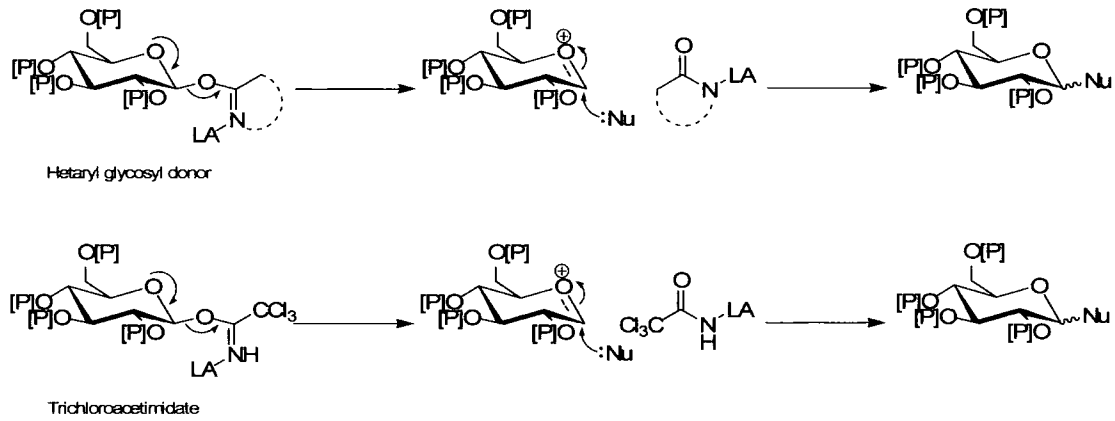


Figure 2.6. The reaction pathway of hetaryl and trichloroacetimidate glycosyl donors.

Hetaryl glycosyl donors are usually generated *via* nucleophilic substitution of the halogen on the parent heterocycle by a saccharide moiety. Several electron poor halogenated azines have been reacted with glucose to produce hetaryl glycosides; several of which are shown in Table 2.4.

The ease of formation and potential for leaving group tuning in these systems holds great promise, but has yet to be addressed systematically. As shown in Figure 2.7 hetaryl glycosyl donors can function both in enzyme catalysed and Lewis acid activated

glycosylations,[117] this technique also provides a convenient route for the joining of oligosaccharides to heterocycles enabling the synthesis of potentially novel pharmaceutical compounds.[120]

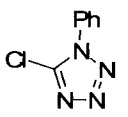
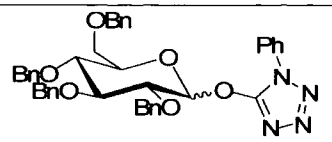
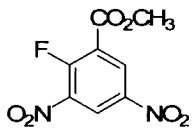
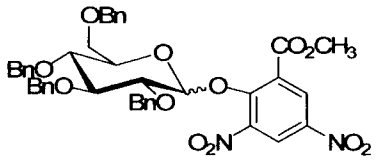
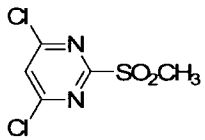
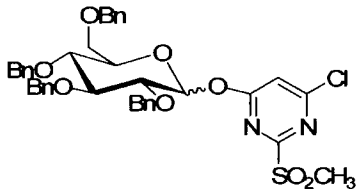
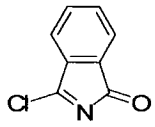
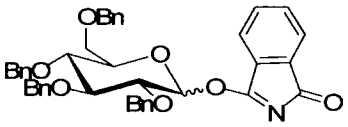
Parent heterocycle	Glycosyl donor	Stereochemistry of glycosylation (α:β)
		1:19 [125]
		2.1:1 [121-123]
		4:1 [7]
		2:1 [8]

Table 2.4. Examples of hetaryl glycosyl donors.

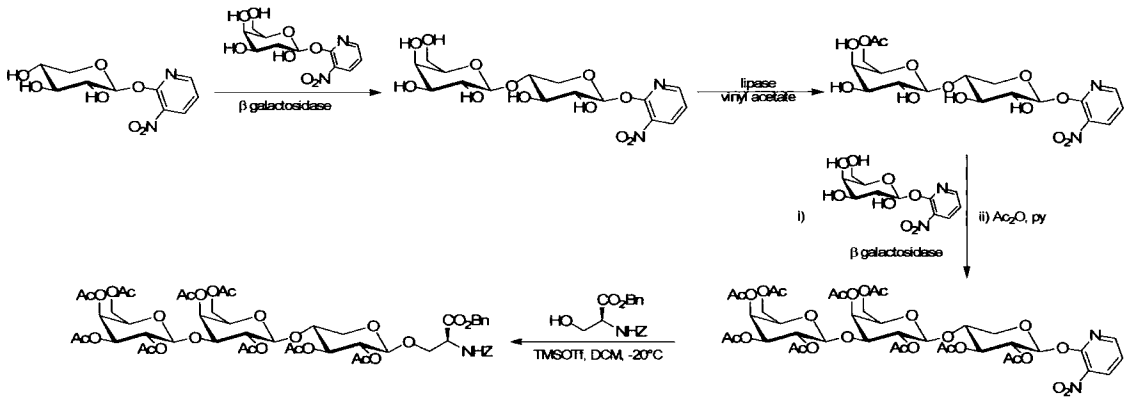


Figure 2.7. Reaction showing the versatility of hetaryl glycosyl donors and their use in enzyme and acid promoted glycosylations.

2.4 Chemoselectivity

In the majority of glycosylation strategies a large percentage of the synthetic effort is directed towards the preparation of the monomeric glycosyl donors and acceptors. Ideally the assembly of these units to construct an oligomer should involve the minimum number of synthetic steps and each reaction should proceed with high stereoselectivity and high yield. Previously, we have examined how to couple the monomeric units in a stereoselective manner, now we shall examine the various strategies utilised to construct complex oligosaccharides efficiently.

2.4.1 Orthogonal Glycosylation Strategies

In standard glycosylation strategies, the conversion of common saccharide building block into a glycosyl donor requires several manipulations at the anomeric centre and this presents a major drawback that is especially undesirable when coupling larger oligosaccharides. Ideally the anomeric substituent of an oligosaccharide should be able to act as both a protecting group and also as a glycosyl donor under various conditions. This is the basis for the orthogonal glycosylation strategy, by varying the type of activator used during the reaction, a group that acted as a protecting group earlier in the reaction can be activated becoming the glycosyl donor (Figure 2.8).

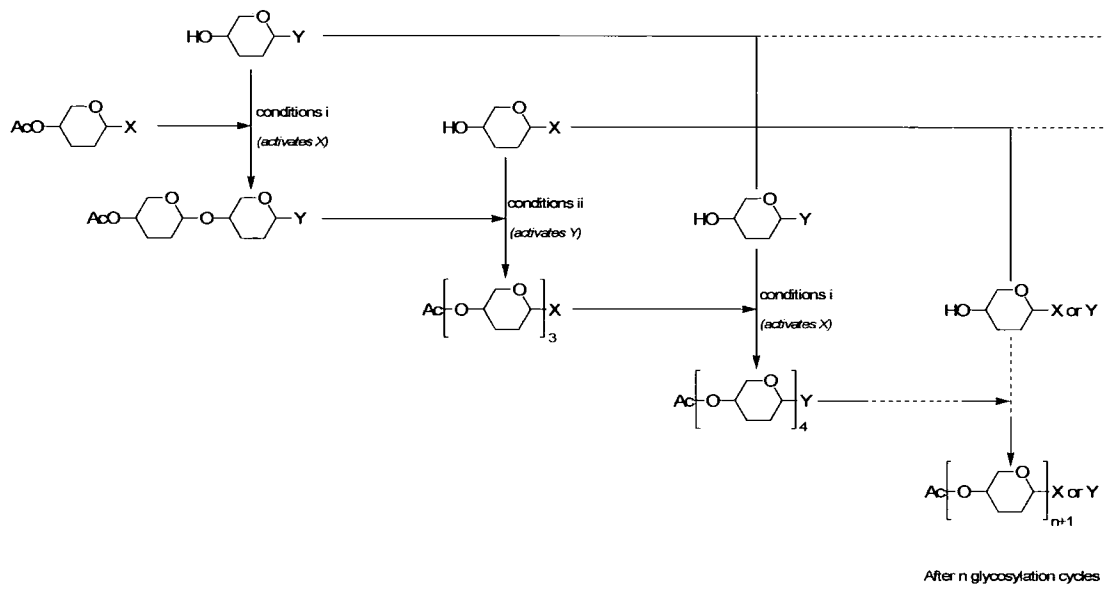


Figure 2.8. A schematic of the orthogonal glycosylation strategy.[3, 4, 127]

The thioglycoside donors have been utilised extensively for orthogonal strategies due to their variable reactivities and the variety of activators available. For example, a common set of conditions for orthogonal glycosylation uses the phenylthio group for X, activated using NBS-DAST, and the fluoride for Y, activated by Cp_2HfCl_2-$AgClO_4$ (Figure 2.9). This orthogonal glycosylation strategy exploits the fact that a fluorine substituent can be activated without affecting a thioglycoside at the anomeric carbon.

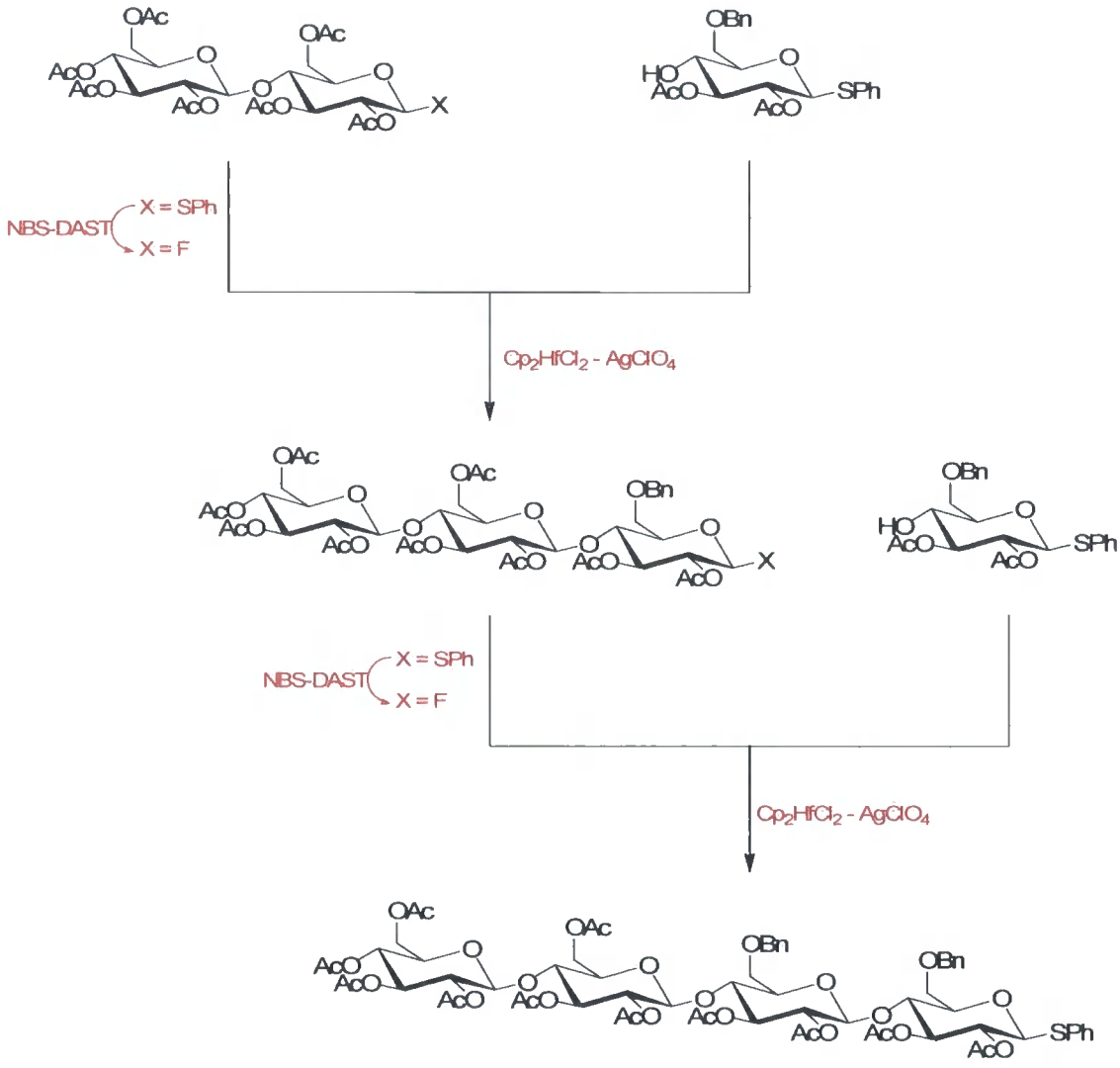


Figure 2.9. An orthogonal synthesis of a tetrasaccharide utilising thio- and fluoro-glycosyl donors.[4, 97]

2.4.2 Armed-Disarmed Strategies

Whether the mechanism of a given glycosylation reaction possesses partial or complete S_N1 character, the rate-limiting step typically involves the development of positive charge in the transition state. As a consequence, the electronic effects of the substituents of a given glycosyl donor can markedly effect its reactivity. Consequently, electron donating substituents, such as those found in ether protected donors, tend to stabilise the rate limiting transition state of glycosylation. This results in an increase of the reactivity of the donor so such donors are termed 'armed'. Conversely, electron withdrawing substituents, such as ester, give rise to 'disarmed' donors.[3, 4, 84]

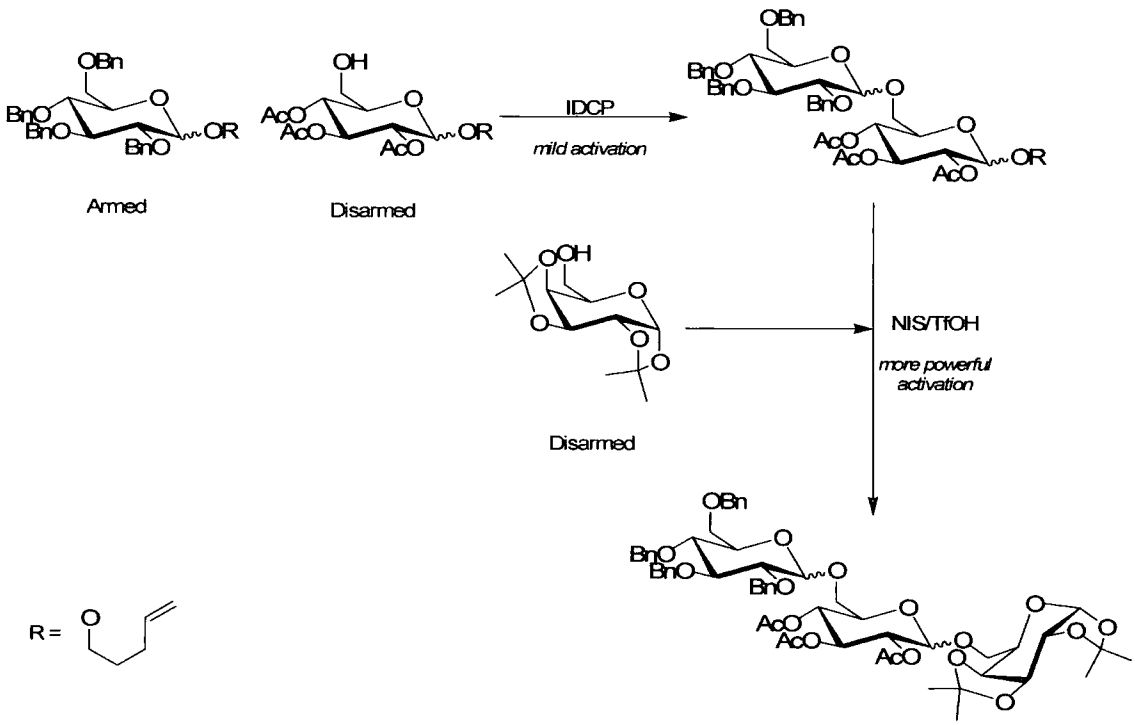


Figure 2.10. The use of the armed-disarmed strategy in the synthesis of a trisaccharide.

This methodology enables the coupling of two saccharides which have the same leaving group at the anomeric centre with high selectivity by exploiting the fact that one is 'armed' and the other is 'disarmed' (Figure 2.10).

2.4.3 Active-Latent Strategies

It was proposed by Ley *et al.*[128] that the armed-disarmed glycosylation strategy could gain versatility by tuning the glycosyl donor leaving group ability, *i.e.* switching the donor reactivity on or off *via* alteration of the leaving group substituent (Figure 2.11). In this strategy the nature of the leaving group controls the reactivity of the system, for example, a reactive thioglycoside donor can react with a less reactive thioglycoside protected acceptor, which in turn, can act as a glycosyl donor under more forcing reaction conditions. This approach has been used successfully in several multi-component one-pot syntheses where chemoselectivity is achieved by the use of varying levels of donor reactivity, allowing a controlled cascade of glycosylation reactions with different donor systems.[3, 4, 84, 123]

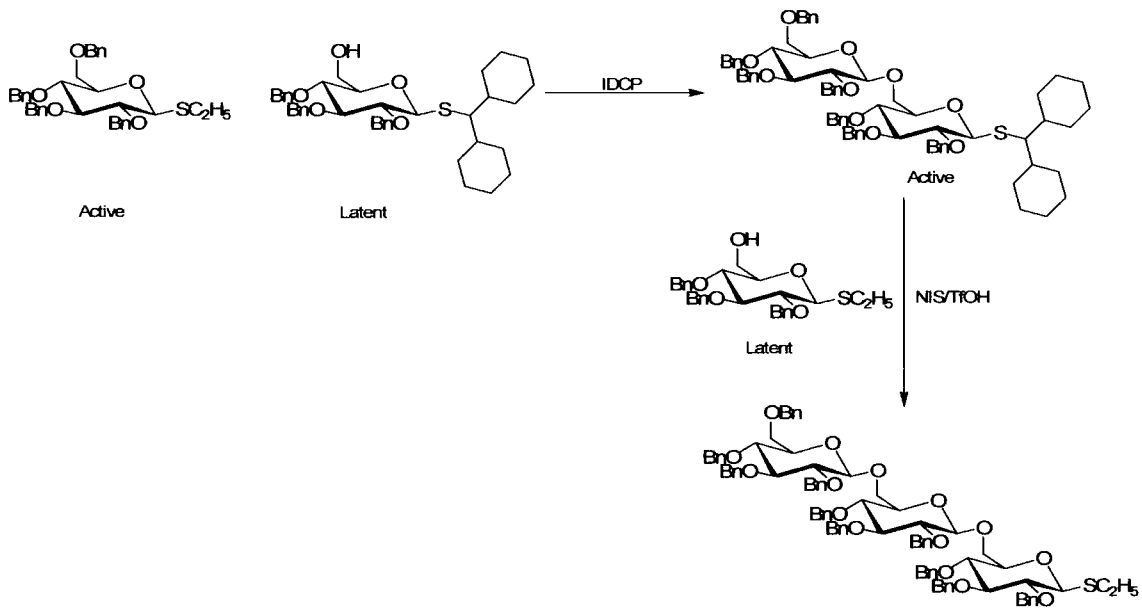


Figure 2.11. The use of the active-latent strategy in the synthesis of a trisaccharide.

2.5 Multi-Component Synthesis

One-pot glycosylations to form two or more glycosidic bonds by the chemoselective addition of glycosyl donors is an attractive strategy for the synthesis of oligosaccharides since it does not require the purification of intermediate compounds. Multi-component syntheses utilise layers of reactivity available through tuning of the glycosyl donors and

all of the previously mentioned strategies in order to establish a controlled cascade of glycosylation reactions.[3, 4, 112, 123, 129-131] The order of activation of the glycosyl donors not only relies on their leaving groups but also upon the combination of their protecting groups and activators providing access to a large assortment of reactivities.

Figure 2.12 details the synthesis of a trisaccharide from a mixture of monosaccharides,[130] treatment of the mixture with zinc chloride followed by NIS and a catalytic amount of triflic acid resulted in the exclusive formation of the trisaccharide with a yield of 46%. This reaction was found to proceed in a sequential manner with the glycal epoxide (**ii**) coupling to the unprotected hydroxyl group on the glucosamine (**i**) to give the disaccharide. This was followed by the addition of (**iii**), with NIS and a catalytic amount of triflic acid, which couples to the disaccharide to give the trisaccharide.

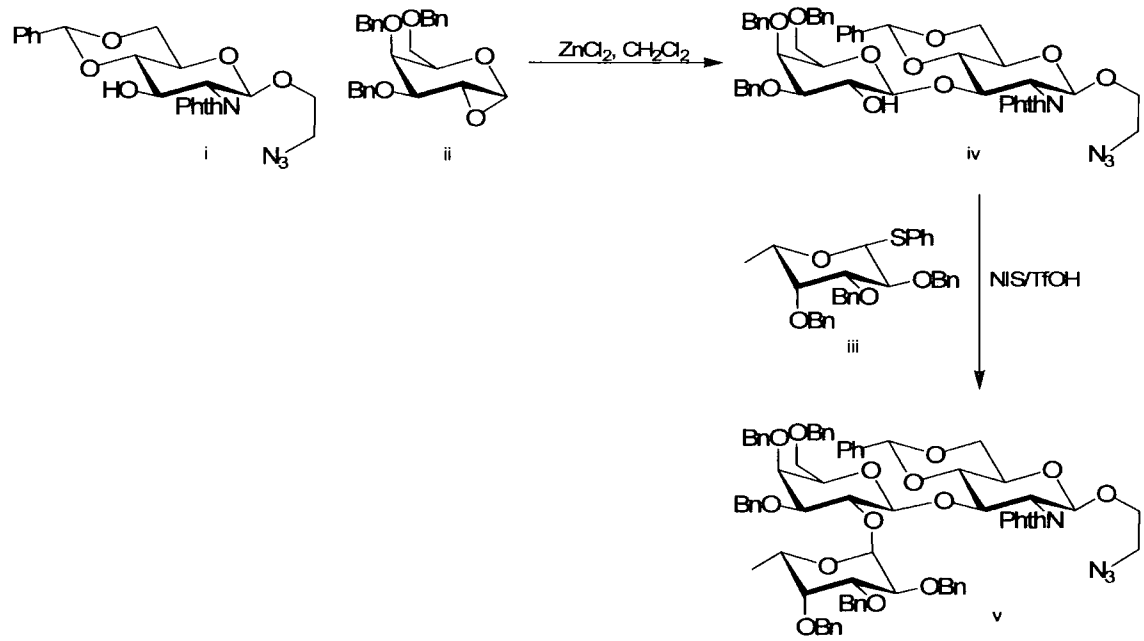


Figure 2.12. The synthesis of a trisaccharide using a one-pot methodology.

This type of glycosylation strategy allows the construction of several glycosidic linkages *via* a one-pot procedure; however, this sort of reaction only gives satisfactory results when the individual glycosylation reactions are highly diastereoselective. Several oligosaccharides have been synthesised utilising this strategy, providing an efficient and selective route to a wide range of target compounds.[129-131]

2.6 Summary

Many strategies for the synthesis of oligosaccharides exist, yet these can be highly specific and sometimes unpredictable. The main driving force in the area of carbohydrate chemistry is the development of a generalised methodology which will make the synthesis of oligosaccharides more predictable and routine. In spite of considerable progress in the development of new glycosylation techniques there still exists a requirement for a general glycosylation methodology, especially one which provides increased control over the stereochemistry of glycosyl bond formation while still being simple and robust enough to be used routinely in organic synthesis.

3 Polyfluoro-Pyridyl-Glycosyl Donors

The synthesis of oligosaccharides, by linking a series of monosaccharide units together *via* glycosidic bonds, remains a key research challenge. As discussed in the previous chapters, many strategies for the synthesis of oligosaccharides exist; however, these are generally highly specific and unpredictable. Future developments in glycosylation methodology will, therefore, require the synthesis of families of new glycosyl donors with adjustable reactivity in which the electronic demand of the leaving group can 'tune' the reactivity of each donor in conjunction with specific activating agents.

The purpose of this study was to develop a glycosylation methodology that utilises heterocyclic leaving groups in glycosyl donors (Figure 3.1).[7, 8, 121, 122]

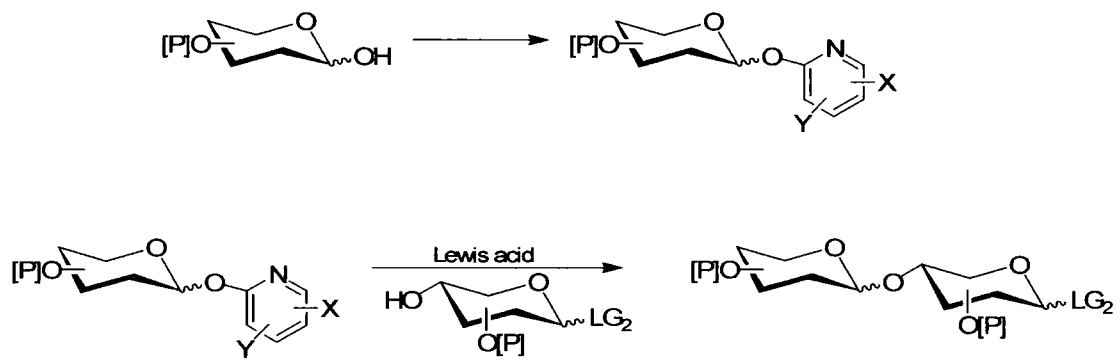


Figure 3.1. Glycosylation using hetaryl glycosyl donors.

For this approach to be effective, a simple method for the synthesis of a range of polyfunctional pyridine systems was required, along with a procedure for the attachment of a saccharide moiety to the heterocyclic ring. However, the range of readily accessible pyridine systems is relatively narrow due to the low reactivity of pyridine, severely hindering the variety of pyridyl-glycosyl donors possible.

As discussed previously, fluorinated heteroaromatic systems are very electron deficient systems that are highly reactive towards nucleophiles and, in principle, all the fluorine atoms could be displaced by nucleophiles in a sequential process, although this chemistry has not been established. Simple tri-substituted systems have been reported involving the reaction of pentafluoropyridine with a sequence of three nucleophiles (Figure 3.2) indicating the possibilities of this approach.[24, 51, 64]

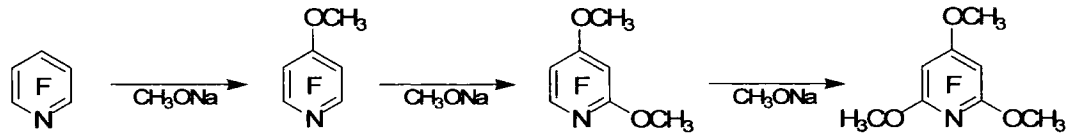


Figure 3.2. Sequential nucleophilic substitution of pentafluoropyridine.

Utilising this approach we can envisage the sequential nucleophilic substitution strategy depicted in Figure 3.3 where an appropriately protected carbohydrate derivative is utilised as a nucleophile to generate a highly functionalised hetaryl glycosyl donor.

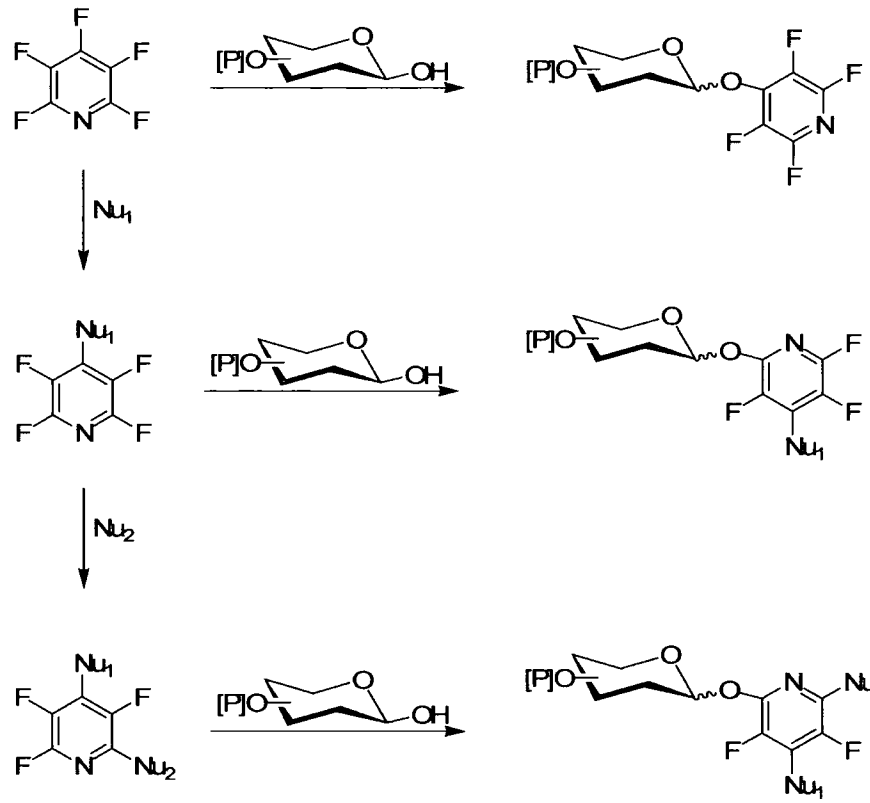


Figure 3.3. Strategy for the synthesis of families of glycosyl donors from pentafluoropyridine (**1**).

In principle this approach would allow the synthesis of a family of glycosyl donors bearing different functionalities on the pyridine ring. In these cases the leaving group ability of the pyridine ring would, theoretically, be dependant upon both the substituents present on the ring and the type of Lewis acid activator utilised. This concept was

separated into three areas of research, which will be examined in the subsequent chapters.

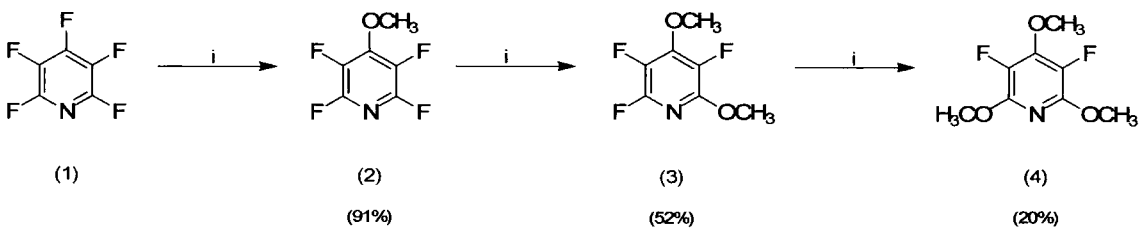
Firstly, we will investigate the synthesis of poly-substituted heteroaromatic compounds from pentafluoropyridine (**1**), as seen previously, studies concerning such sequential poly-substitution reactions have not been developed to any real extent.[24, 51, 64, 66-70] Secondly, the information obtained from the systematic investigation of the reactivity of (**1**) will be used to synthesise a series of glycosyl donors as depicted in Figure 3.3. Finally, we will examine the reactions of this novel class of glycosyl donors in order to determine their glycosylation potential.

4 Nucleophilic Aromatic Substitution of Pentafluoropyridine

The glycosyl donor synthetic strategy detailed in the previous chapter (Figure 3.3) is dependant upon a sequence of nucleophilic substitution reactions utilising pentafluoropyridine (**1**) as a scaffold. However, as seen previously, studies concerning such sequential poly-substitution reactions have not been developed to any real extent.[24, 51, 64, 66-70] Consequently, before undertaking the synthesis of pyridyl-glycosyl donors, the reactions of (**1**) with a series of oxygen and nitrogen nucleophiles was studied to establish the viability of the poly-substitution strategy, determine the regiochemistry of sequential substitution reactions and assess the robustness of the substituents towards further nucleophilic substitution reactions. We began our model studies by investigating the reactions of (**1**) with a series of oxygen nucleophiles, since such systems are analogous to oxygen nucleophiles derived from carbohydrate systems.

4.1 Reactions with Oxygen Nucleophiles

The reaction of (**1**) with sodium methoxide proceeded in accordance with literature reports[24, 51, 64] yielding the 4-methoxy derivative (**2**) which reacted sequentially with two further equivalents of sodium methoxide to give (**3**) and (**4**) in a stepwise manner (Figure 4.1)



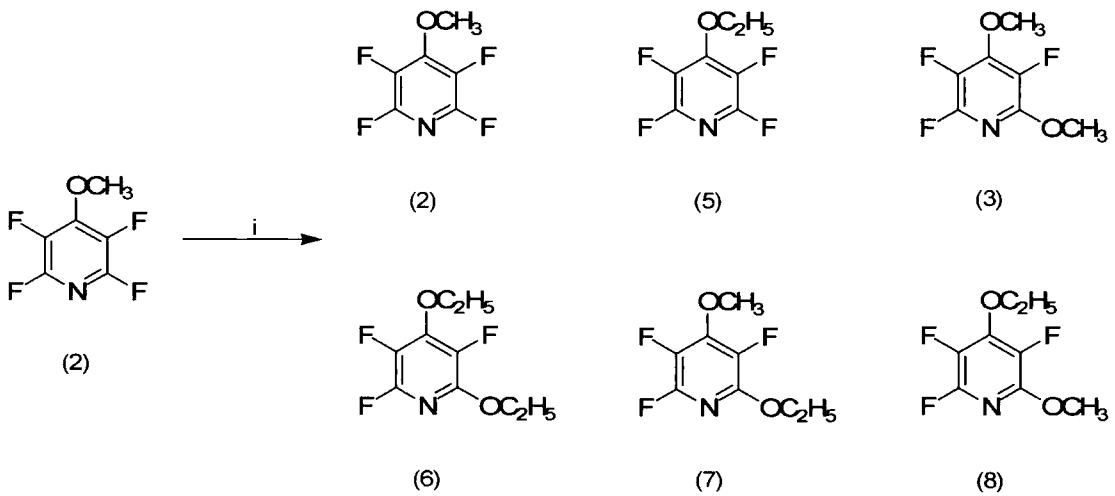
(1) (2) (91%) (3) (52%) (4) (20%)

Figure 4.1. *Reagents and Conditions:* i, CH_3ONa (1 equiv.), CH_3OH, reflux.

This proved consistent with the expected order of activation towards nucleophilic attack (Section 1.4.4), with the fluorine atom in the 4-position being the most susceptible towards nucleophilic substitution, followed by replacement of the fluorine atoms in the 2- and 6-positions. The substitution of fluorine also results in a decline in the reactivity of the system, evident from the reduction in the yields from (**2**) → (**4**).

The standard literature procedure for isolating mono-substituted compounds of this type from the reaction mixture involves an aqueous/organic extraction procedure[51, 55, 56, 66-68, 70, 132] which generally provided isolated yields in the region of 50-60%. An alternative procedure was developed that utilised solid phase resins to remove or neutralise the unreacted nucleophilic species. In this procedure, the addition of Amberlite resin (sodium form) replaced the extraction stage increasing the isolated yields to greater than 90%. Amberlite resin is highly acidic, effectively neutralising any alkoxide present in the reaction mixture converting it back into the parent alcohol. Filtration to remove the resin and sodium fluoride, formed during the neutralisation, followed by concentration under reduced pressure directly yielded the substituted pyridines in high purity.

In order to investigate the compatibility of the methoxy substituent towards further nucleophilic substitution reactions, (**2**) was reacted with sodium ethoxide (Figure 4.2). However, in contrast to the reaction with sodium methoxide, the reaction of (**2**) with sodium ethoxide gave a complex mixture of products arising from the displacement of methoxide from the activated 4-position.



Solvent	Compound ratio					
	2	3	5	6	7	8
Ethanol	4	5	3	10	77	1
THF	5	18	3	9	62	3

Figure 4.2. *Reagents and Conditions:* i, C_2H_5ONa (1 equiv.), C_2H_5OH or THF, reflux.

Compounds (**3**), (**5**), (**6**) and (**8**) arose from the displacement of the methoxy substituent from the 4-position and subsequent reaction with either sodium ethoxide or the liberated methoxide anion. Varying the solvent appears to have little effect upon the degree of displacement of the methoxy substituent at the 4-postion, as observed from the ratios of compounds (**5**), (**6**) and (**8**). Changing the solvent did appear to have an effect on the extent of nucleophilic attack by the liberated methoxide ion; this is not surprising since ethanol is a protic solvent which would neutralise the methoxide ion, effectively removing it from the reaction, accounting for the decreased amounts of compound (**3**).

The displacement of the methoxy substituent can be explained by examination of the Meisenheimer intermediates for attack at the 2- and 4-positions (Figure 4.3). The most stable carbanionic intermediate is formed from attack at the 4-position, combined with the good leaving group ability of methoxide explains why nucleophilic substitution at the 4-position of (**2**) occurs. These results demonstrate that methoxy substituents are inappropriate for the purposes of our glycosyl donor synthesis strategy.

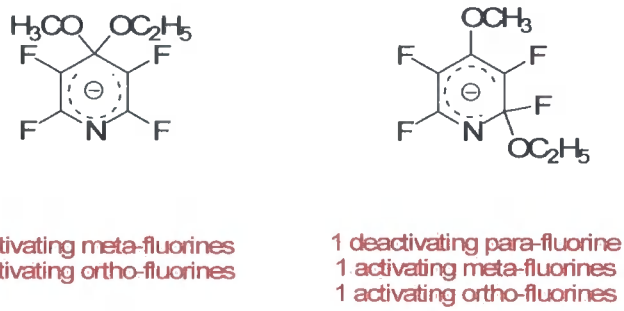


Figure 4.3. Comparison of the Meisenheimer intermediates for attack at the 2- and 4-positions of (**2**)

In contrast, however, reactions of 4-ethoxy-2,3,5,6-tetrafluoropyridine (**5**) were found to be selective (Figure 4.4) and both the 2,4-diethoxy-3,5,6-trifluoropyridine (**6**) and 4-ethoxy-2,3,5-trifluoro-6-methoxypyridine (**8**) systems were prepared by reaction of (**5**) with sodium ethoxide and sodium methoxide respectively. The synthesis of the tri-substituted system (**9**) also proved possible indicating that this is a viable approach for the synthesis of glycosyl donors when the substituents on the pyridine ring are not labile.

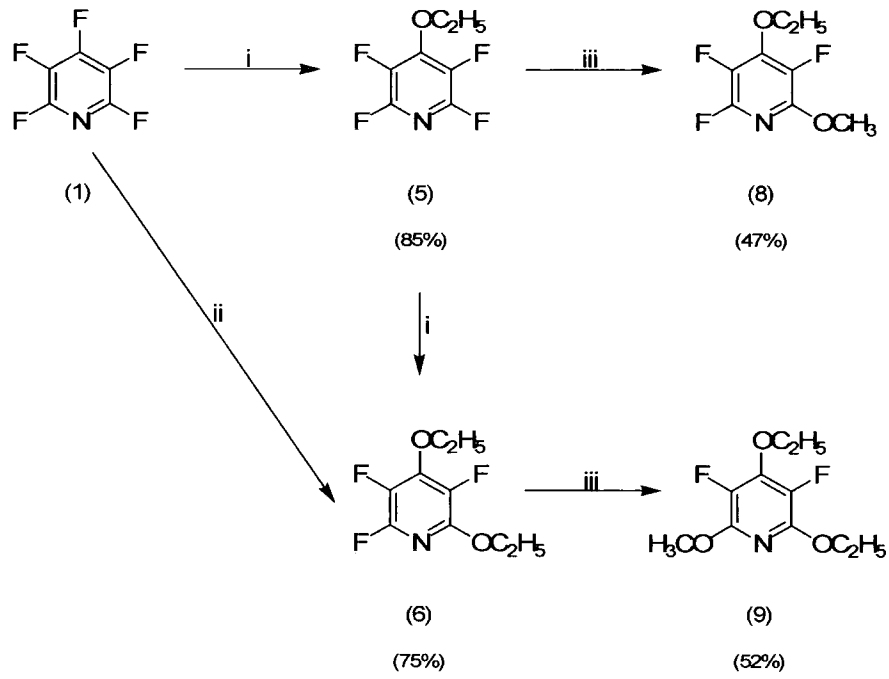


Figure 4.4. *Reagents and Conditions:* i, C_2H_5ONa (1.2 equiv.), C_2H_5OH, reflux; ii, C_2H_5ONa (2.2 equiv.), C_2H_5OH, reflux; iii, CH_3ONa (1.2 equiv.), CH_3OH, reflux.

The selectivity observed when using ethoxy substituents can be attributed to their inferior leaving group ability, compared to the methoxy substituent, which diminishes the likelihood of substitution occurring at the site occupied by the ethoxy group.

4.2 Reactions with Nitrogen Nucleophiles

In order to increase the range of poly-substituted pyridine systems available by the sequential nucleophilic substitution approach, the reactions of (**1**) with primary and secondary amine nucleophiles was investigated (Figure 4.5), methylamine and diethylamine gave (**10**) and (**11**) respectively. Two equivalents of the amine were required in both cases to provide mono-substitution, compared to only one equivalent being required for the alkoxides. It is postulated that one equivalent of amine acts as a nucleophile substituting the fluorine atom in the 4-position, while the second equivalent of amine acts as a base to neutralise the hydrogen fluoride generated as a by-product in these reactions. Nucleophilic substitution was possible with only one equivalent of amine when there was another base present in the reaction, consistent with the above theory (Figure 4.5 condition iii).

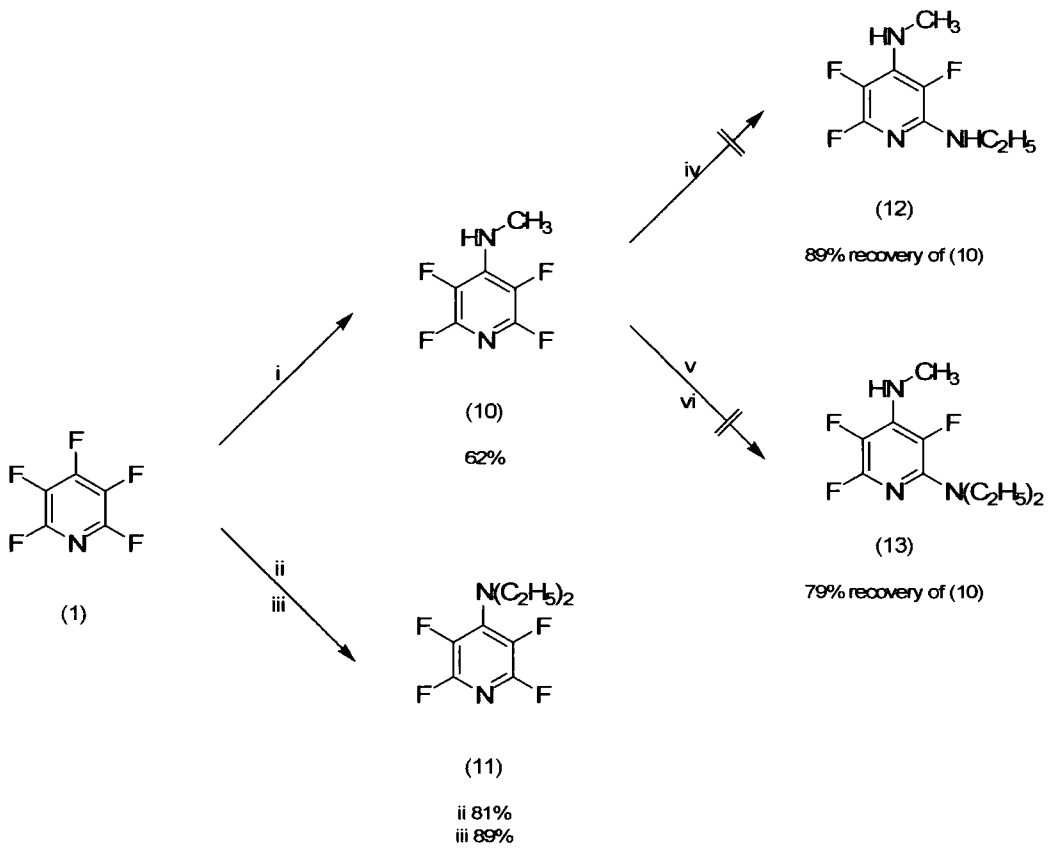


Figure 4.5. *Reagents and Conditions:* i, CH_3NH_2 (2.2 equiv.), THF, stir, rt; ii, $(C_2H_5)_2NH$ (2.2 equiv.), THF, reflux; iii, $(C_2H_5)_2NH$ (1 equiv.), $NaHCO_3$ (2 equiv.), THF, reflux; iv, $C_2H_5NH_2$ (2.2 equiv.), THF, reflux; v, $(C_2H_5)_2NH$ (2.2 equiv.), THF, reflux; vi, $(C_2H_5)_2NH$ (3.2 equiv.), THF, reflux.

In order to increase the degree of functionality on the pyridine ring, (**10**) was reacted with ethylamine and diethylamine in an attempt to form the 2,4-disubstituted compounds (**12**) and (**13**) respectively (Figure 4.5). However, (**10**) failed to react with either of the amine nucleophiles; it is proposed that the amines were primarily acting as a base, instead of a nucleophile, interacting with the acidic secondary amine substituent on the heterocyclic ring resulting in the reduction of the nucleophilicity of the system (Figure 4.6). The presence of the hydrogen bonded system (**14**) was inferred from a broadening of the observed ^{19}F NMR signals.

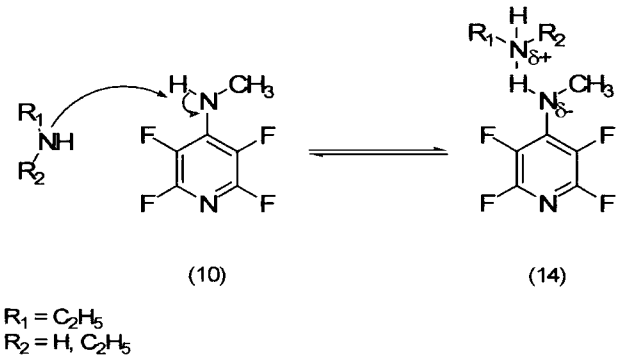


Figure 4.6. Interaction of (**10**) with amines.

In contrast, the reaction of (**15**) with butylamine and diethylamine proceeded as expected to give exclusively the 2,4-disubstituted products (**16**) and (**17**) in moderate yield (Figure 4.7). Electronically methylamine and *iso*propylamine groups are similar, so the difference in the reactivities of (**10**) and (**15**) may be attributed to the increased steric bulk around the nitrogen atom in (**15**), which restricts access by an amine and hence reduces the degree of association, enabling nucleophilic attack.

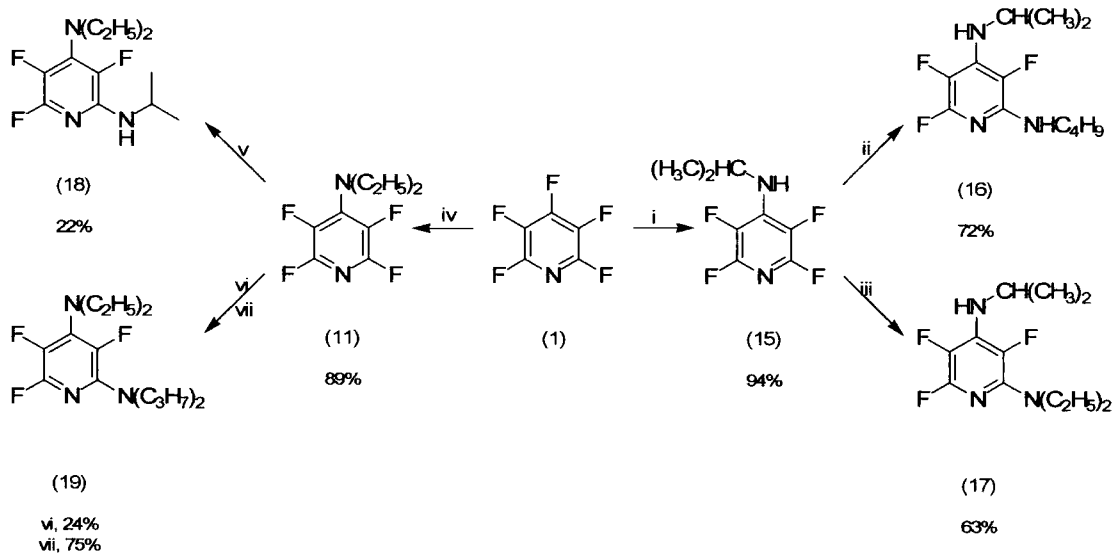


Figure 4.7. *Reagents and Conditions:* i, $(CH_3)_2CHNH_2$ (2.2 equiv.), THF, reflux; ii, $C_4H_9NH_2$ (3.2 equiv.), THF, reflux; iii, $(C_2H_5)_2NH_2$ (11.2 equiv.), THF, reflux; iv, $(C_2H_5)_2NH$ (2.2 equiv.), THF, reflux; v, $(CH_3)_2CHNH_2$ (2.2 equiv.), THF, reflux; vi $(C_3H_7)_2NH$ (6 equiv.), THF, reflux; vii, $(C_3H_7)_2NH$ (1.2 equiv.), ^{t}BuLi (1.2 equiv.), THF, reflux.

Compound (**11**) was also found to react with both primary and secondary amines to generate the di-substituted compounds (**18**) and (**19**) (Figure 4.7). The introduction of a second nitrogen-centred nucleophile into (**11**) was found to be considerably more difficult than for (**15**), an excess of reagent and prolonged heating was required to afford reasonable quantities of (**18**) and (**19**). This evidence suggests that the diethylamine substituent deactivates the pyridine ring towards further nucleophilic substitution to a greater degree than an *iso*propylamine or an oxygen substituent in the same position, therefore, a more activated nucleophile is required to facilitate substitution in such systems. To this end, an alternative procedure was developed that involved the generation of the lithium salt of the amine prior to nucleophilic attack as this was expected to increase the nucleophilicity of the amine and hence improve the rate of nucleophilic substitution. This procedure resulted in a three fold increase in the yield of (**19**) in addition to a reduction in reaction time and the quantity of nucleophile required (Figure 4.7 condition vii).

4.3 More Complex Substitution Patterns

The range of multi-substituted pyridines developed thus far has been limited to systems utilising the same family of nucleophiles (*i.e.* both oxygen or both nitrogen nucleophiles). In order to fulfil the requirements of the glycosyl donor methodology (Figure 3.3) a much wider range of substituted pyridines is required and, to that end, the synthesis of heterocycles utilising a mixture of carbon, nitrogen and oxygen nucleophiles was carried out.

4.3.1 Oxygen, Nitrogen Systems

The reaction of (**2**) with diethylamine failed to produce the expected 2,4-disubstituted compound in practical quantities (Figure 4.8) due to the dealkylation of the methoxy substituent to give *2,3,5,6-terafluoropyridin-4-olatediethyl-ammonium* (**20**). This result may be explained by the high rate of S_N2 nucleophilic attack at a methyl group compared to higher chain length alkyl groups (Table 4.1), for example, the rate of attack at a methyl site is thirty times that for a methylene site.[133] This provides further evidence for the incompatibility of methyl-based substituents with this approach.

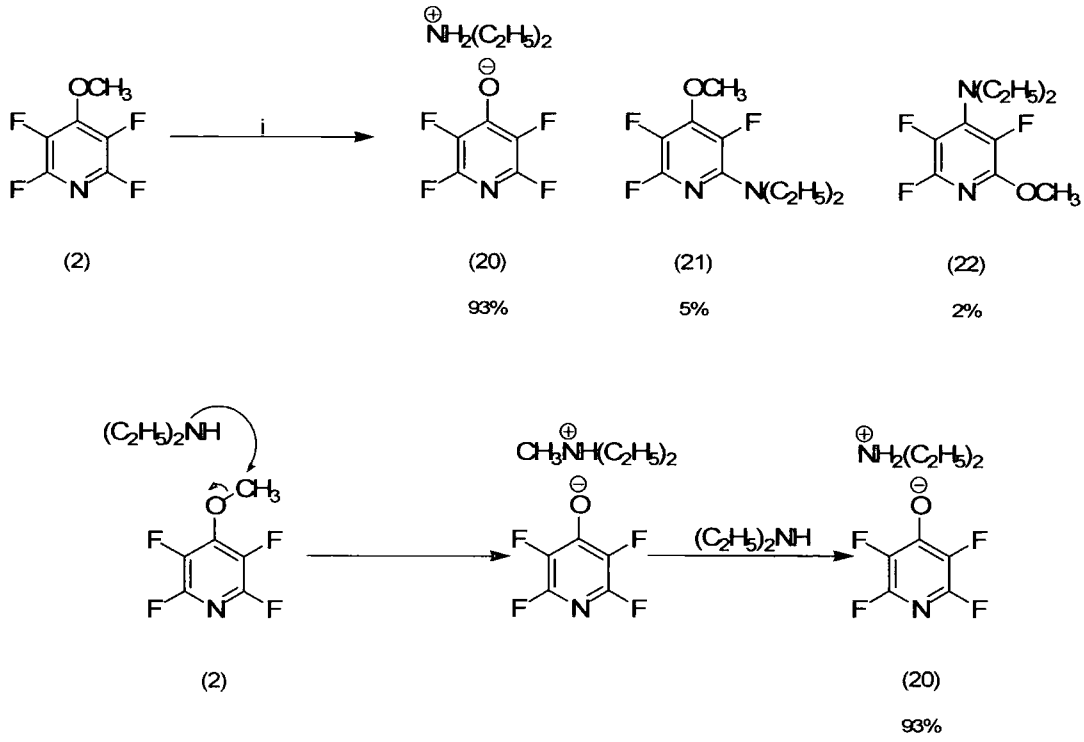


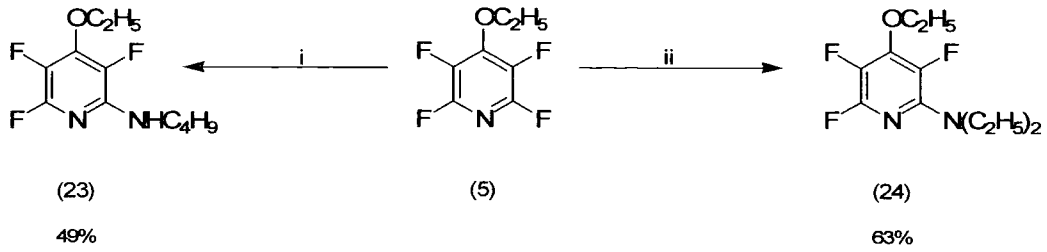
Figure 4.8. *Reagents and Conditions:* i, $HN(C_2H_5)_2$ (2.2 equiv), THF, reflux.

The structure of compound (**20**) was confirmed by NMR spectroscopy and mass spectrometry. It is postulated that the counter ion observed in (**20**) results from the second equivalent of amine, present in the reaction mixture, displacing the counter ion that was formed during the reaction.

	CH_3-X	CH_3CH_2-X	$(CH_3)_2CH$-X
k_{S_N2} rel.	30	1	0.025

Table 4.1. Comparison of the relative rates of nucleophilic attack by S_N2 processes of alkyl chlorides with the iodine ion.[133]

The kinetic data indicates that the prospect of dealkylation occurring is diminished when higher alkyl groups are utilised. This was confirmed by the fact that the reaction of (**5**) with butylamine and diethylamine proceeded as desired with the nucleophile substituting the fluorine atom at the 2-position of the pyridine ring (Figure 4.9).



(23)

49%

(5)

(24)

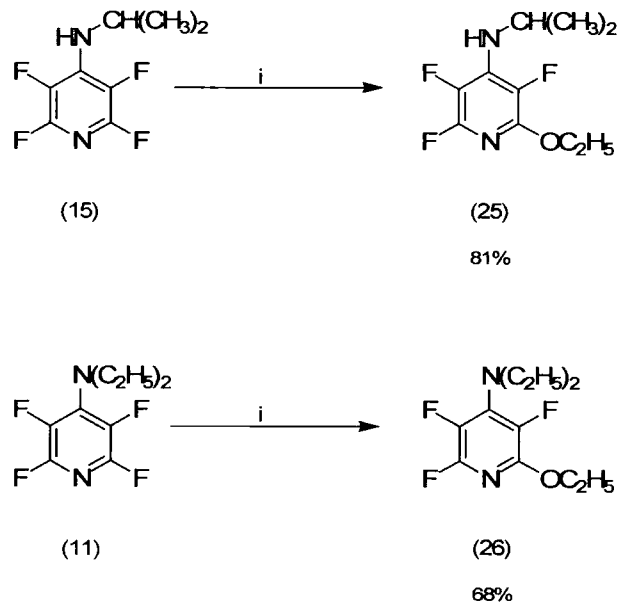
63%

Figure 4.9. *Reagents and Conditions:* i, $H_2NC_4H_9$ (2.2 equiv), THF, reflux; ii, $HN(C_2H_5)_2$ (2.2 equiv.), THF, reflux.

The yields obtained from these reactions were comparable to the reactions detailed previously in Sections 4.1 and 4.2.

4.3.2 Nitrogen, Oxygen Systems

In order to provide a model for the coupling of a saccharide unit with an amine substituted pyridine, compounds (**15**) and (**11**) were reacted with sodium ethoxide (Figure 4.10). These reactions proceeded in the same way as the oxygen, oxygen systems detailed in Section 4.1.



(15)

(25)

81%

(11)

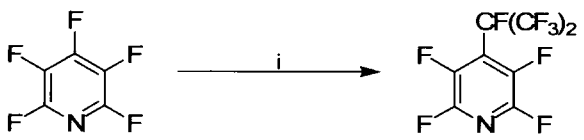
(26)

68%

Figure 4.10. *Reagents and Conditions:* i, $NaOC_2H_5$ (1.2 equiv), C_2H_5OH, reflux.

4.3.3 Electron Poor Perfluoroalkyl Systems

The nucleophilic substitution reactions detailed in the previous sections demonstrate the potential use of this methodology for the synthesis of highly substituted pyridine systems in a controlled and highly efficient manner. So far, all of the substituents added to the pentafluoropyridine scaffold have been less electron withdrawing than fluorine and so in order to provide access to more electron deficient systems, perfluoroalkyl groups were utilised as a substituent (Figure 4.11). Chambers and co-workers[66-68] developed an efficient route to perfluoroalkylated heteroaromatics using tetrakis(dimethylamino)ethylene (TDAE) as a catalyst in the absence of solvent.



(1) (27)

28%

Figure 4.11. *Reagents and Conditions:* i, hexafluoropropene (HFP) (1 equiv.), TDAE (0.02 equiv.), autoclave, 60 °C.

The proposed mechanism for the formation of perfluoroalkylated heteroaromatic compounds is shown in Figure 4.12. Under anhydrous reaction conditions, TDAE reacts with HFP displacing a fluoride ion from the alkene, effectively acting as an *in situ* source of fluoride ion. The liberated fluoride ion reacts with another HFP molecule to give the nucleophilic fluorocarbanion (**28**) which then reacts with (**1**) to give *2,3,5,6-tetrafluoro-4-(perfluoropropan-2-yl)pyridine* (**27**).

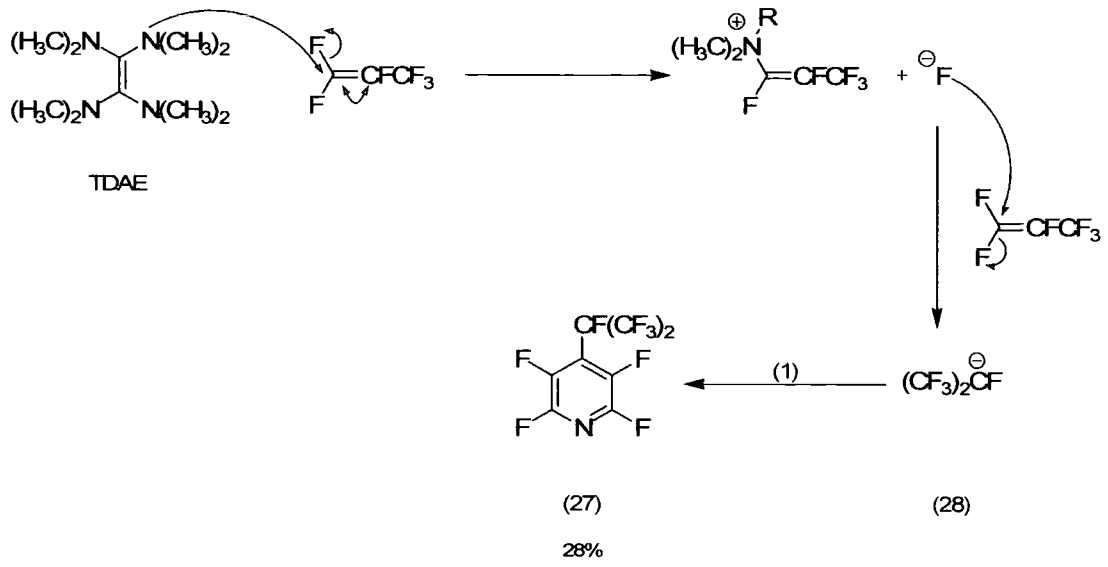


Figure 4.12. Mechanism for the formation of perfluoroalkylated heteroaromatics.

In principle, nucleophilic substitution in (**27**) could occur at either the 2- or 3-positions, in both cases the Meisenheimer intermediate has functionalities which could stabilise the generated anion (Figure 4.13). However, it has been reported previously that nucleophilic substitution occurs exclusively at the 2/6-position with alkoxide ions.[67, 68]

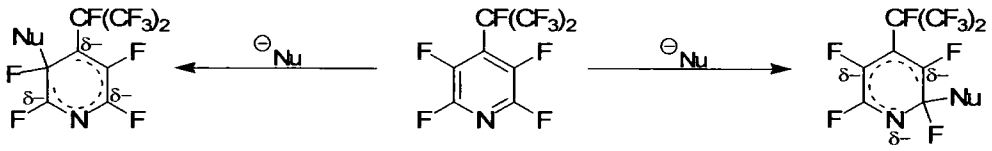


Figure 4.13. The two possible sites for nucleophilic attack in (**27**).

The reactions of (**27**) with oxygen and nitrogen centred nucleophiles proceeded as previously observed (Figure 4.14) to give the 2,4-disubstituted compounds (**29**) to (**31**) in moderate to good yields. Interestingly the reactions of (**27**) proceed much more rapidly than the reactions of (**5**), (**11**) and (**15**) indicating that these systems are more electron deficient than the previously developed substituted heterocycles.

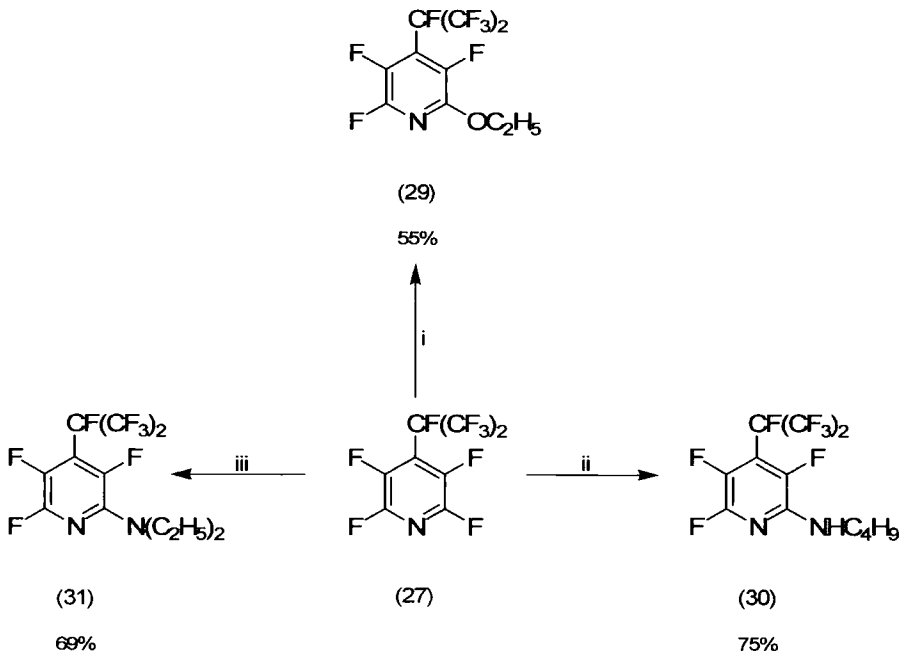


Figure 4.14. *Reagents and Conditions:* i, $NaOC_2H_5$ (1.2 equiv), C_2H_5OH, reflux; ii, $H_2NC_4H_9$ (2.2 equiv), THF, reflux; iii, $HN(C_2H_5)_2$ (2.2 equiv.), THF, reflux.

4.4 One-Pot Multi-Component Reactions

It has been shown that sequential nucleophilic substitution of (**1**) provides a versatile and efficient route to the synthesis of a variety of highly substituted pyridine based compounds. In order to increase the efficiency of this methodology the applicability of sequential nucleophilic substitution pertaining to a one-pot synthetic strategy was investigated (Figure 4.15).

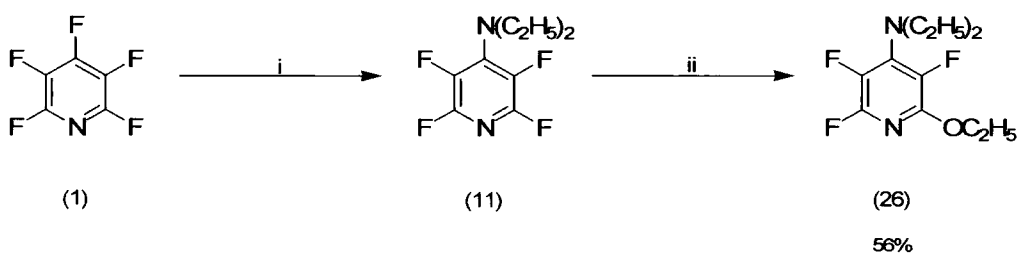


Figure 4.15. *Reagents and Conditions:* i, $HN(C_2H_5)_2$ (1 equiv.), $NaHCO_3$ (2 equiv.), THF, reflux; ii, C_2H_5ONa (1 equiv.), THF, reflux.

Firstly, (**1**) was reacted with diethylamine to give the mono-substituted compound (**11**) as seen previously; this was followed by the addition of sodium ethoxide to the reaction medium to give the di-substituted compound (**26**) in moderate yield. In order to control the regiochemistry of the reaction it was determined that the use of excess amine in the first stage was not possible, therefore, the alternative procedure was used (Figure 4.5 condition iii), where an excess of sodium hydrogen carbonate replaces the second equivalent of amine. ^{19}F NMR provided a probe to determine when complete conversion of (**1**) into (**11**) had occurred, enabling the correct timing for the addition of the sodium ethoxide solution.

This further emphasises the applicability of this approach to the rapid synthesis of a multitude of poly-substituted pyridine compounds.

4.5 Summary

In this chapter we have conducted a systematic study into the chemistry of pentafluoropyridine (**1**) with a range of oxygen and nitrogen centred nucleophiles; the purpose of which was to examine the possibility of utilising (**1**) as a scaffold for the synthesis of a range of poly-substituted pyridine derivatives as models for the development of hetaryl glycosyl donors (Figure 3.3).

In general (**1**) was found to readily undergo nucleophilic aromatic substitution to provide mono- di- and tri-substituted compounds with excellent regiochemical control and moderate to good yields, for the nucleophiles studied (Figure 4.16). The orientation of nucleophilic attack was found to be highly selective, with the order of activation following the sequence 4-position › 2-position » 3-position, which proved consistent with earlier limited investigations.

Several limitations were discovered with this approach, specifically the incompatibility of methoxy and methylamine substituents towards further nucleophilic substitution reactions. This is not of great concern since it does not significantly reduce the range of poly-substituted pyridine motifs accessible by this strategy. The ease of nucleophilic substitution was also found to decrease with each substitution of fluorine. This was unsurprising, but resulted in an increase in the severity of the conditions required for several reactions. This may result in some problems when utilising nucleophiles derived from saccharides due to their low thermal tolerances.

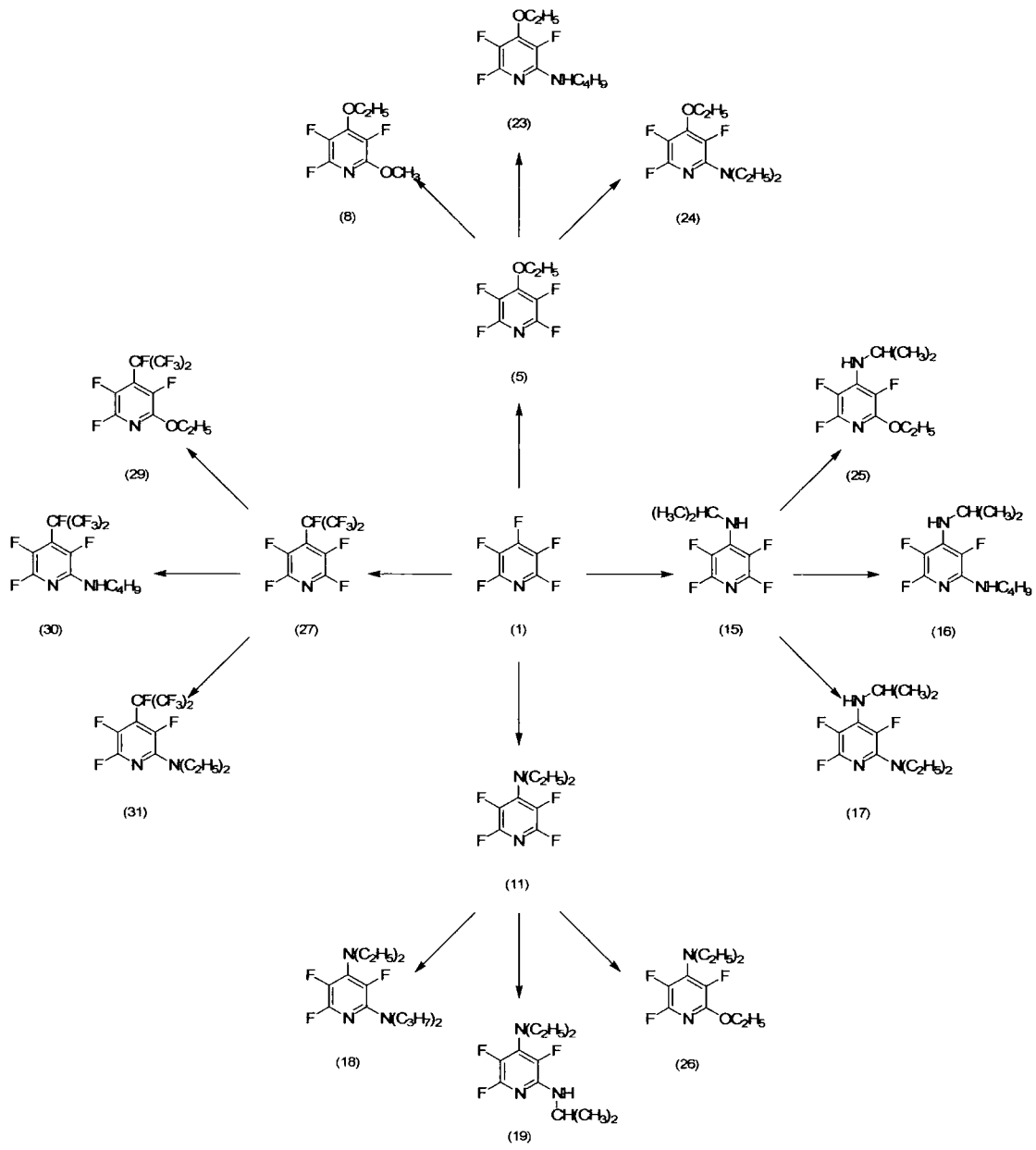


Figure 4.16. Schematic representation of the use of (**1**) for the synthesis of poly-substituted pyridine systems.

Overall, the synthesis of poly-substituted pyridines *via* sequential nucleophilic aromatic substitution of (**1**) has proved to be a viable, versatile and effective strategy. This synthetic strategy allows the rapid synthesis of heterocyclic compounds in a controlled manner, using either multi-stage or one-pot methodologies. It has been established that a range of mono-, di- and tri-substituted pyridine compounds can be synthesised in this way, demonstrating the potential applicability of this approach to the synthesis of 'tuneable' hetaryl glycosyl donors.

5 Polyfluoro-Pyridyl Glycosyl Donor Synthesis

The glycosyl donor synthetic strategy detailed in Figure 5.1 is dependent upon a sequence of nucleophilic substitution reactions utilising pentafluoropyridine (**1**) as a scaffold. In the previous chapter we conducted a systematic study of the chemistry of pentafluoropyridine (**1**) with an array of oxygen and nitrogen centred nucleophiles, demonstrating that the synthesis of multi-substituted pyridines *via* the sequential nucleophilic aromatic substitution of (**1**) is a viable and effective strategy.

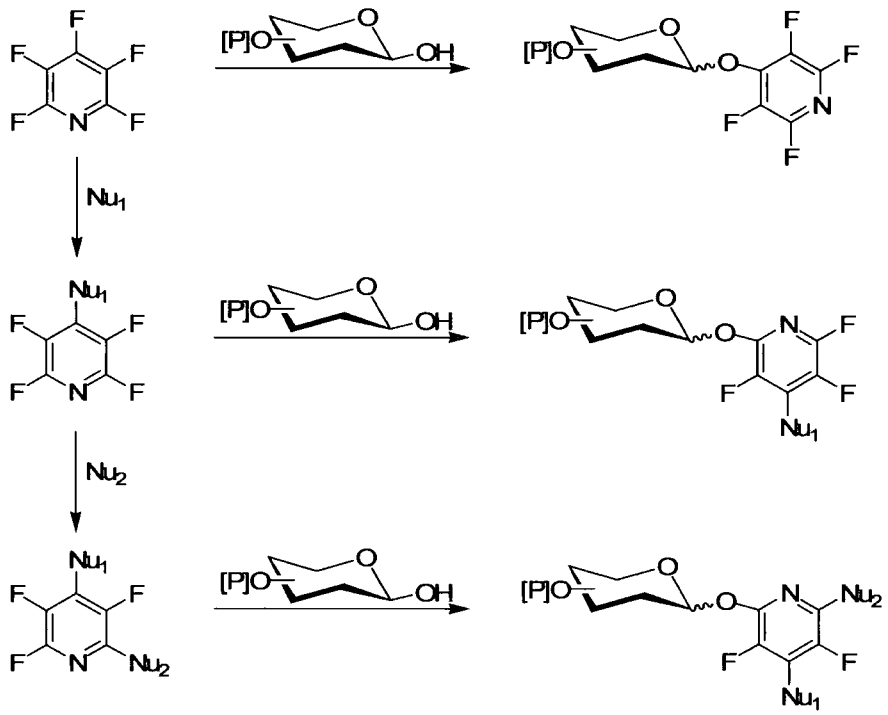


Figure 5.1. Strategy for the synthesis of families of glycosyl donors from pentafluoropyridine (**1**).

In principle, if an appropriately protected carbohydrate derivative was to be used as a nucleophile a family of glycosyl donors, bearing different functionalities on the pyridine ring, could be constructed readily. In the following chapters we detail the synthesis of a short range of glycosyl donors and demonstrate the applicability of these systems in a variety of glycosylation reactions.

Direct O-hetarylation of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (**32**) with electron deficient heteroaromatic compounds, leading directly to hetaryl

glucopyranosides, has recently been shown to be quite effective.[7, 8, 121-123, 125, 134] This approach provides a convenient manner to link sugar residues through a glycosidic linkage onto heterocycles. The synthesis of several aryl- and hetaryl glycosides has been reported previously,[3, 7, 8, 83, 121-123] Schmidt *et al*[7, 8] have recently prepared a related system by the reaction of a glucose derivative with pentafluoropyridine (**1**) and effected glycosylation using strong Lewis acid promotion.

In the previous chapter we saw that (**1**) reacts readily with a range of oxygen nucleophiles, since such systems are analogous to the nucleophiles generated from carbohydrate systems it should prove possible to use the same approach for the attachment of a saccharide to the pyridine ring.

5.1 Mono-Substituted Donor Synthesis

The reaction of (**1**) with (**32**) was firstly carried out according to the experimental procedure detailed by Schmidt et al[7, 8] (Figure 5.2, condition i), where (**1**) was added to a solution of (**32**) in dry dichloromethane and stirred at room temperature for 1-3 hours. This procedure failed to generate the heterocyclic glycosyl donor (**33**), providing complete recovery of the starting material. This is unsurprising since the reactions of (**1**) with simple alkoxides usually required heating before nucleophilic aromatic substitution occurred.

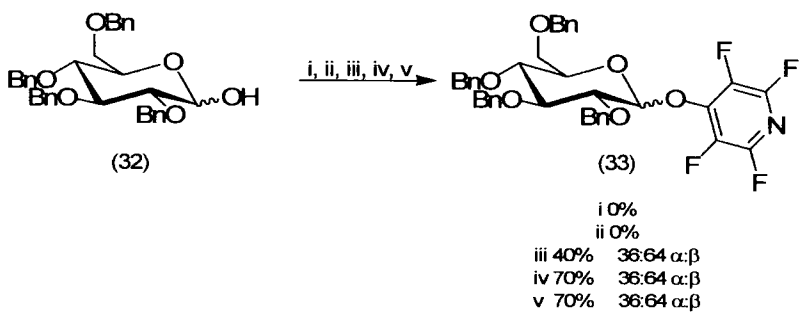


Figure 5.2. *Reagents and Conditions:* i, (**1**) (1 equiv.), NaH (1.2 equiv.), CH_2Cl_2, stir rt; ii (**1**) (1 equiv.), NaH (1.2 equiv.), CH_2Cl_2, 40°C, iii, (**1**) (1 equiv.), NaH (1.2 equiv.), THF, 70°C; iv, (**1**) (1 equiv.), Na (1.2 equiv.), THF, 70°C; v, (**1**) (1 equiv.), ^nBuLi (1.2 equiv.), THF, 70°C.

Utilising the optimised reaction conditions developed in the previous chapter, (**33**) was generated readily. Purification by high pressure flash chromatography (HPFC) allowed the rapid isolation of the α and β anomers in good yields. Typically isolation of the glycosyl donor from unreacted (**32**) and (**1**) was achieved in under an hour utilising HPFC.

Analysis of the ^{1}H NMR spectrum of (**33**) allowed the identification of the α and β anomers (Figure 5.3) by the observation of a unique set of signals for each of the isomers. The most important signal to identify was the peak arising from the C_1 hydrogen atom since this allowed the ratio of the α and β anomers to be determined. The hydrogen atom at the anomeric centre can be easily assigned since it occurs downfield of the other ring hydrogen atoms due to deshielding by the two oxygen atoms and the electron deficient pyridine ring.

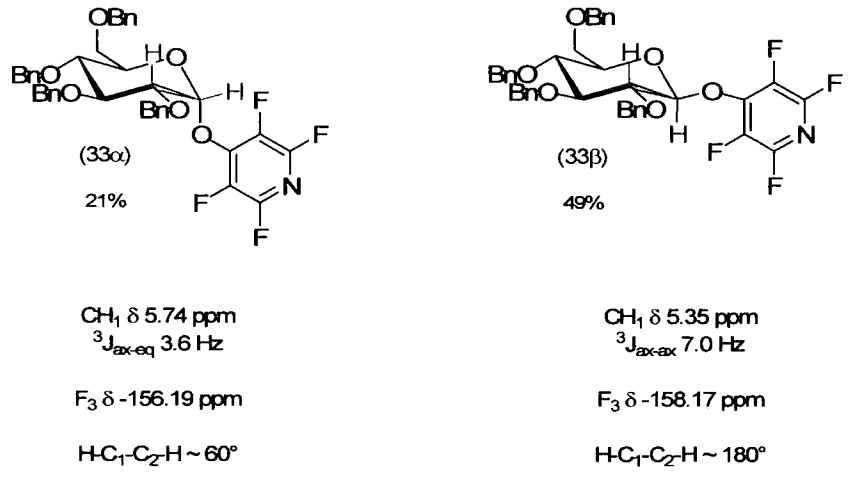


Figure 5.3. The α and β isomers of (2,3,5,6-tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxy)-pyridine (**33**).

A doublet signal was observed at δ 5.74 ppm, this is consistent with the existence of a hydrogen atom that is bonded to a carbon atom attached to two oxygen atoms (the anomeric carbon, C_1). The coupling constant (J) for this doublet was 3.6 Hz, this is due to a smaller axial-equatorial dihedral angle at H-C_1-C_2-H (approximately 60°), which proves consistent with the α isomer. A second doublet was also observed centred at δ 5.35 ppm. This proton signal exhibits a significantly larger coupling constant, J = 7.0 Hz, which proves consistent with a larger axial-axial coupling expected from the β isomer, in which the angle at H-C_1-C_2-H is approximately 180°.

We observed that the α and β anomers had distinctive ^{19}F NMR spectra (Figure 5.4) which allowed the very convenient determination of the ratio of the two anomers in the reaction mixture. Signals at δ -156.19 ppm and δ -158.17 ppm were observed for the α and β anomers, corresponding to the fluorine atoms at the 3` and 5` positions. The ratio values obtained from the ^{19}F NMR were consistent with the α:β ratios determined by ^{1}H NMR, optical polarimetry and literature values for the equilibrium concentrations of the two anomers of glucose (Table 5.1).[135, 136] Consequently, ^{19}F NMR provides a unique probe for the monitoring of systems of this type, allowing the rapid determination of anomeric ratios without the isolation of the compounds.

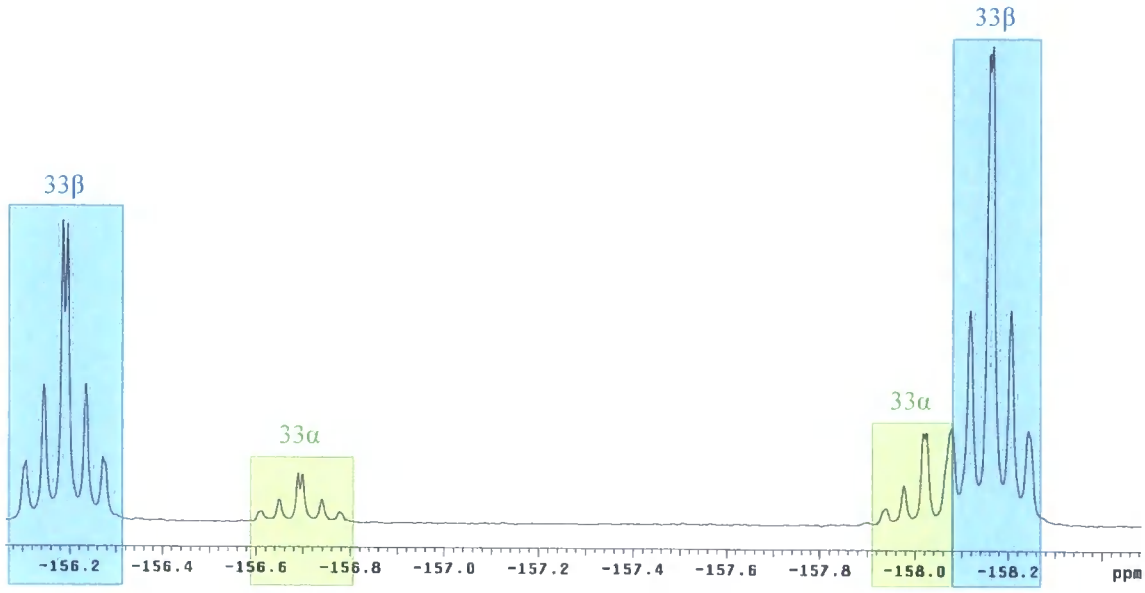


Figure 5.4. ^{19}F NMR of compound (**33**) showing the α and β anomers.

Percentage anomer (%)	α	B
^{1}H NMR	37	63
^{13}C NMR	35	65
^{19}F NMR	35	65
Optical polorimetry	36	64
Literature values[135, 136]	36	64

Table 5.1. Relative amounts of the α and β anomers of (**33**) in the reaction mixture as determined from ^{1}H and ^{19}F NMR.

^{13}C NMR was also used to characterise compound (**33**), unique signals resulting from the carbon atom at the anomeric centre allowed the identification of the two anomers and the α:β anomer ratios determined were consistent with the ratios determined by ^{1}H and ^{19}F NMR (Table 5.1). However, in order to acquire accurate integral data the ^{13}C NMR had to be carried out for a prolonged period of time due to slow relaxation of the ^{13}C nuclei which proved to be inefficient.

5.2 Di-Substituted Donor Synthesis

The reaction of (**32**) with the mono-substituted pyridine cores (**5**), (**11**), (**15**) and (**27**) proceeded as expected to generate the corresponding hetaryl glycosyl donors in good to moderate yields (Figure 5.5).

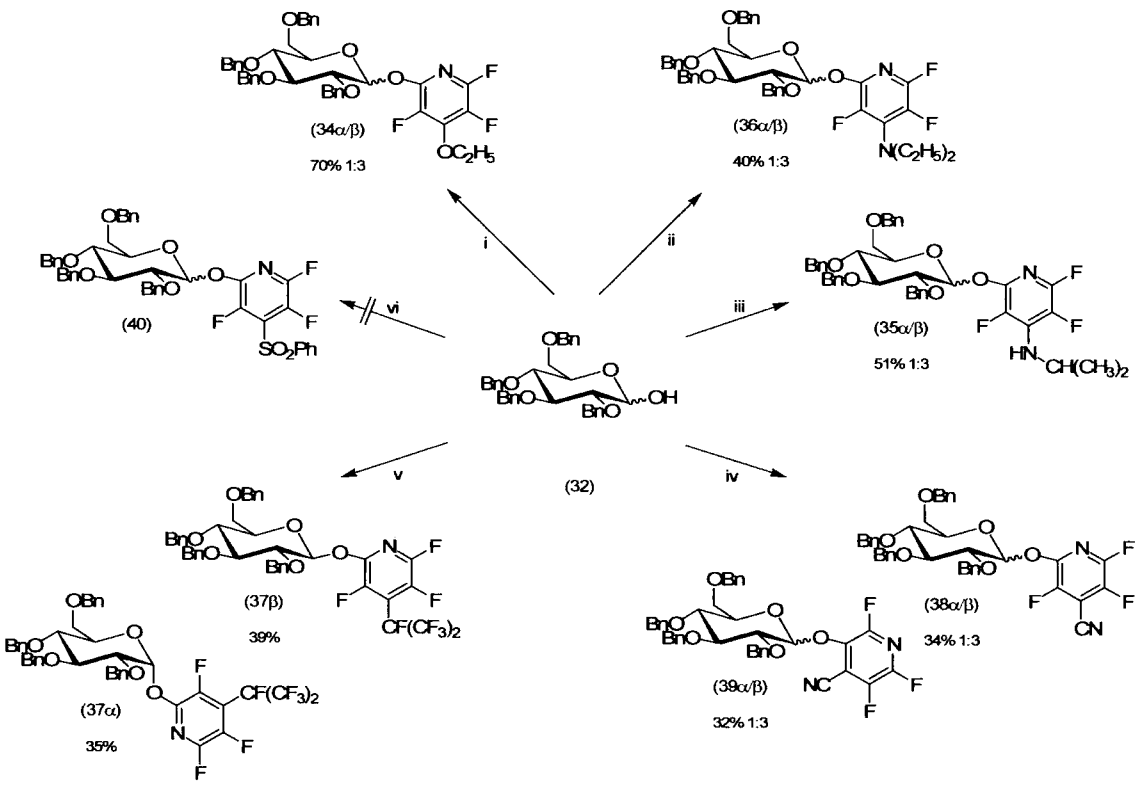


Figure 5.5. *Reagents and Conditions:* i, (**5**) (1 equiv.), NaH (1.2 equiv.), THF, reflux; ii, (**11**) (1 equiv.), NaH (1.2 equiv.), THF, reflux; iii, (**26**) (1 equiv.), NaH (1.2 equiv.), THF, reflux; iv, (**41**) (1 equiv.), NaH (1.2 equiv.), THF, reflux; v, (**27**) (1 equiv.), NaH (1.2 equiv.), THF, reflux; vi, (**42**) (1 equiv.), NaH (1.2 equiv.), THF, reflux.

Separation of the α and β anomers of the di-substituted pyridine systems by chromatography proved more difficult than for (**33**) with only (**37α**) and (**37β**) being separated, the other compounds were isolated as anomeric mixtures.

Characterisation of both the α and β anomers from the anomeric mixture was still possible by utilising their unique NMR signals in a similar manner to that used for compound (**33**). Characterisation of the di-substituted pyridine systems was achieved by identifying the anomeric carbon and hydrogen atoms using ^{13}C and ^{1}H NMR (Figure 5.6), utilising these signals it was possible to assign the neighbouring atoms sequentially using COSY and HETCOR 2-dimensional NMR techniques.

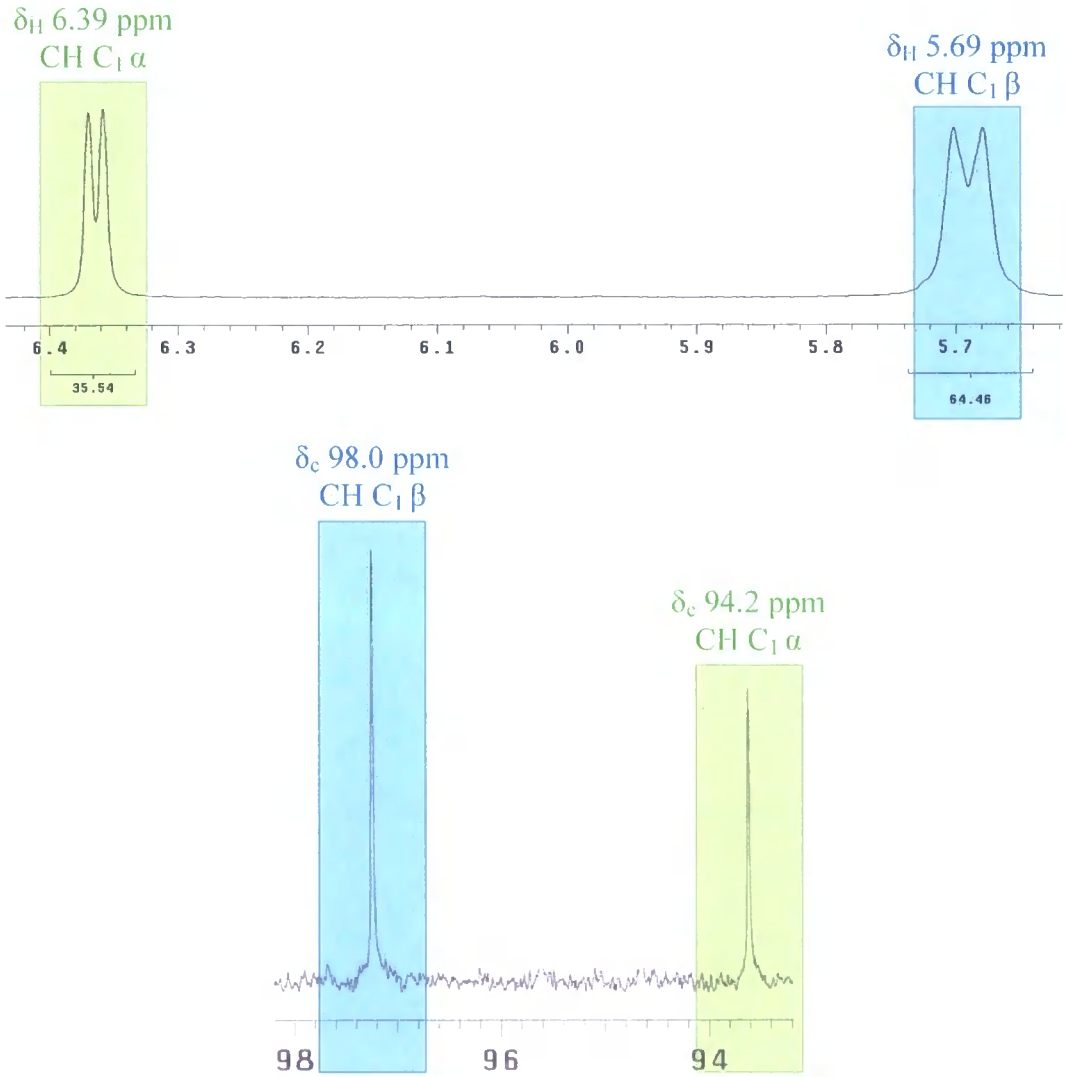


Figure 5.6. ^{1}H and ^{13}C NMR of compound (**34**) showing the unique signals from the anomeric hydrogen and carbon atoms.

We also observed that the α and β anomers had distinctive ^{19}F NMR spectra (Figure 5.7), analogous to (**33**), which allowed the relative amounts of the α and β anomers to be determined. The ratios determine by ^{19}F NMR proved consistent with the ratios determined from the mono-substituted pyridine system and the cited equilibrium values for the ratio of the α and β anomers of D-glucose in solution (Table 5.1).

Figure 5.7. ^{19}F NMR of compound (**34**) showing the α and β anomers.

Interestingly the reaction of (**32**) with *2,3,5,6-tetrafluoro-pyridine-4-carbonitrile* (**41**) yielded two different glycosyl donors due to nucleophilic substitution of fluorine at the 2- and 3-positions, compounds (**38α/β**) and (**39α/β**) respectively. Nucleophilic substitution of fluorine at the 2-position was expected as observed from previous reactions. Nucleophilic substitution of fluorine at the 3-position arose due to the *ortho*-activating effect of the cyano substituent at the 4-position (Figure 5.8).

Figure 5.8. The ortho-activating effects of a 4-cynao substituent.

The cyano substituent at the 4-position provides stabilisation of the Meisenheimer complex when nucleophilic substitution occurs at the 3-position in a similar way to the ring nitrogen when attack occurs at the 2-position. In addition to this, the cyano

substituent is also highly electron withdrawing activating the site *ortho* to it in the initial state, comparable to the *ortho* activating effect of fluorine detailed in Chapter two. The ratio of nucleophilic aromatic substitution at the 2- and 3-postions was 1:1, the number of activating and deactivating fluorine atoms is the same for attack at either position indicating that the cyano group exerts an activating effect comparable to that of the ring nitrogen.

The reaction of (**32**) with *4-benzenesulfonyl-2,3,5,6-tetrafluoro-pyridine* (**42**) failed to produce the expected hetaryl glycosyl donor due to displacement of the benzenesulfonyl substituent. This resulted in a complex mixture of compounds arising from the displacement of the benzenesulfonyl substituent and subsequent nucleophilic attack from both the liberated benzenesulfonyl and 2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxide in a comparable process to that observed in Figure 4.2. The failure of this reaction demonstrates the incompatibility of the benzenesulfonyl group with the current polyfluoro-pyridyl glycosyl donor methodology.

5.3 Tri-Substituted Donor Synthesis

In order to increase the tuning aspect of this family of donors, (**32**) was reacted with equimolar quantities of the di-substituted pyridine derivatives synthesised in the previous chapter (Figure 4.16). The reaction of (**32**) with the majority of the di-substituted pyridine derivatives failed to generate the expected hetaryl glycosyl donors with the only exception being the more activated system (**30**) (Figure 5.9). This result is unsurprising since the synthesis of many of the di-substituted pyridine derivatives required an excess of reagents and prolonged heating to afford reasonable quantities. Prolonged heating and increased reaction concentration failed to facilitate the formation of the expected glycosyl donors, instead resulting in the decomposition of (**32**).

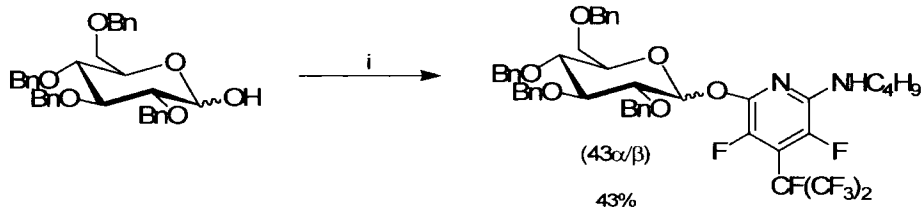


Figure 5.9. *Reagents and Conditions:* (**30**) (1 equiv.), NaH (1.2 equiv.), THF, reflux.

The systems based upon *2,3,5,6-tetrafluoro-4-(perfluoropropan-2-yl)pyridine* (**27**) were more activated towards nucleophilic substitution compared to the other substituted pyridines. This can be attributed to the electron withdrawing effect of the perfluoropropan-2-yl substituent which reduces the electron density of the pyridine ring causing it to be more susceptible to nucleophilic attack.

5.4 Summary

In this chapter we have detailed the synthesis of a novel family of potential glycosyl donors. The synthesis of compounds (**33**) to (**40**) demonstrates that protected glucose moieties can be readily attached to a substituted pyridine ring utilising the same techniques developed in the previous chapter for the synthesis of highly functionalised pyridine derivatives. Systems of this type have also been found to be quite stable, with little degradation of the glycosyl donors being observed after periods of up to two years with no special handling or storage protection.

It was also determined that ^{19}F NMR provides an excellent probe for measuring the α and β anomer ratios which can not be achieved for any class of donor system previously developed.

6 Glycosylation Reactions of Polyfluoro-Pyridyl Glycosyl Donors

The chemical synthesis of oligosaccharides is much more complicated than the synthesis of other biomolecules, such as peptides and nucleotides, due to the lack of a single set of 'optimum' reaction conditions for the stereoselective formation of a glycosidic bond between two saccharide residues.[83] As discussed in Chapter two, several efficient methodologies for the synthesis of glycosidic bonds are now available, however, these are generally unpredictable and characteristic to specific systems.[1, 3, 4, 7, 8, 84] The lack of easy access to oligosaccharides has slowed the development of the area of glycobiology, resulting in carbohydrates being the least exploited of the three major classes of biomolecules. The purpose of this thesis was to develop a new glycosylation methodology that utilised highly fluorinated heterocyclic leaving groups in glycosyl donors in an attempt to create a more versatile and selective class of glycosyl donor (Figure 6.1).[7, 8, 121-123, 125, 137, 138]

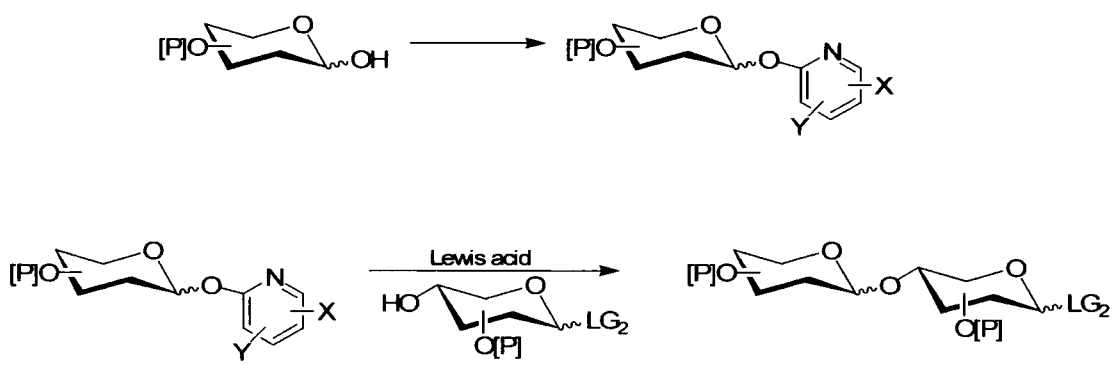


Figure 6.1. Glycosylation using hetaryl glycosyl donors.

In the previous two chapters we developed a synthetic methodology for the synthesis of a wide range of poly-substituted heteroaromatic compounds onto which a saccharide moiety could be grafted to create potential glycosyl donors. Utilising this methodology a series of potential glycosyl donors, (**33**) to (**39**), was synthesised and in the following chapter we will detail the glycosylation potential of this family of hetaryl glycosyl donors with a variety of substrates.

6.1 Model Glycosylation Reactions

The compounds synthesised in the previous chapter display the same structural motif as many classes of glycosyl donor, implying that they should also possess analogous glycosyl donor properties. In order to determine the glycosyl donor properties of hetaryl glycosyl donors of this type, compounds (**33**) to (**39**) were reacted with hexan-1-ol and cyclohexanol, as simple carbohydrate mimics, in the presence of a Lewis acid (boron trifluoride diethyletherate) in the initial studies of this reaction (Figure 6.2).

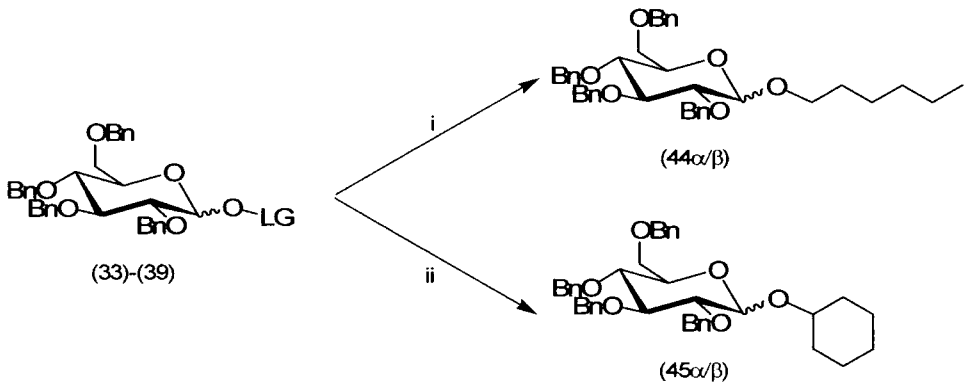


Figure 6.2. *Reagents and Conditions:* i, (**33**) to (**39**) (1 equiv.), hexan-1-ol (1 equiv.), $BF_3.(C_2H_5)_2O$ (1.5 equiv.), CH_3CN, stir, rt; ii, (**33**) to (**39**) (1 equiv.), cyclohexanol (1 equiv.), $BF_3.(C_2H_5)_2O$ (1.5 equiv.), CH_3CN, stir, rt.

Under boron trifluoride activation in acetonitrile solution, these O-benzyl protected glycosyl donors afforded the known saccharides (**44α/β**)[139, 140] and (**45α/β**)[139-143] in good to high yields with a high degree of stereoselectivity (Table 6.1).

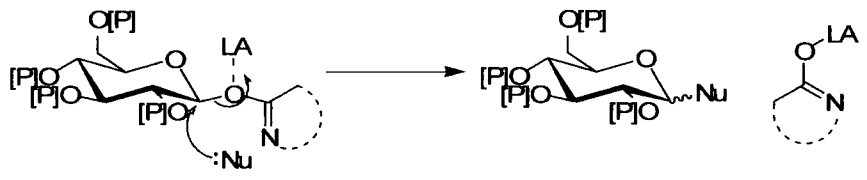


Figure 6.3. The reaction pathway of hetaryl glycosyl donors

It is postulated that during the glycosylation process the Lewis acid coordinates to the oxygen atom which forms the glycosidic bond between the saccharide and the

electron withdrawing pyridine ring. This facilitates the formation of the new glycosidic bond by increasing the leaving group ability of the pyridine ring (Figure 6.3).

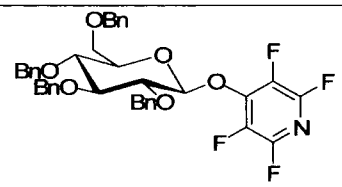
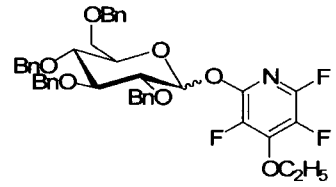
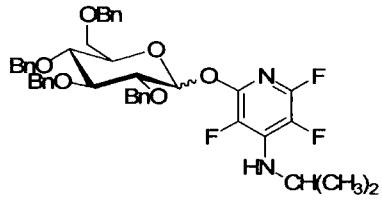
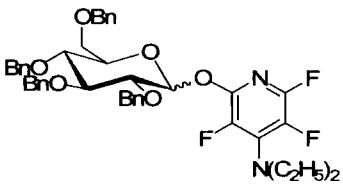
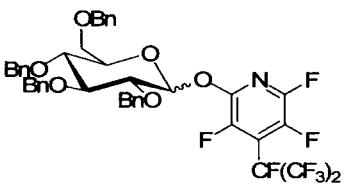
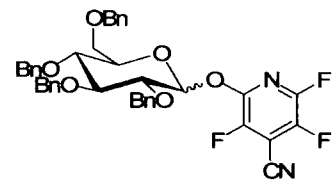
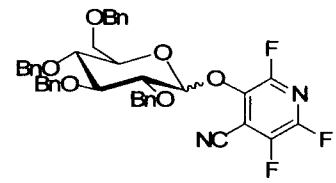
	Donor		Acceptor: Hexanol		Acceptor: Cyclohexanol	
		α:β ratio	Yield [%]	44α/β	Yield [%]	45α/β
33β		0:1	78	19:1	59	49:1
34α/β		4:7	69	7:4	67	7:4
35α/β		4:7	94	7:4	87	7:4
36α/β		4:7	0	-	0	-
37α/β		4:7	94	7:4	83	7:4
38α/β		4:7	64	7:4	-	-
39α/β		4:7	60	7:4	-	-

Table 6.1. Glycosylation of donors (**33**) to (**39**) with hexan-1-ol and cyclohexanol.

During the model glycosylation reactions it was possible to monitor the progress of glycosylation using ^{19}F NMR spectroscopy. By observing the disappearance of the signals arising from the fluorine atoms on the heterocyclic leaving group, it was possible to determine the progress of the reaction. This provided a unique reaction probe which offers many advantages over traditional techniques, such as TLC and HPLC, which are generally slower and less efficient.

The saccharides (**44α/β**) and (**45α/β**) were isolated from unreacted polyfluoro-pyridyl glycosyl donor and acceptor by high pressure flash chromatography (HPFC). This was found to be an efficient and rapid technique for the isolation of such compounds, typically allowing their separation within an hour.

Once the saccharides had been isolated it was possible to determine the ratio of the α and β anomers by comparison of the ^{1}H NMR integrals arising from the hydrogen atom at the C_1 position, since a unique signal is observed for each anomer.

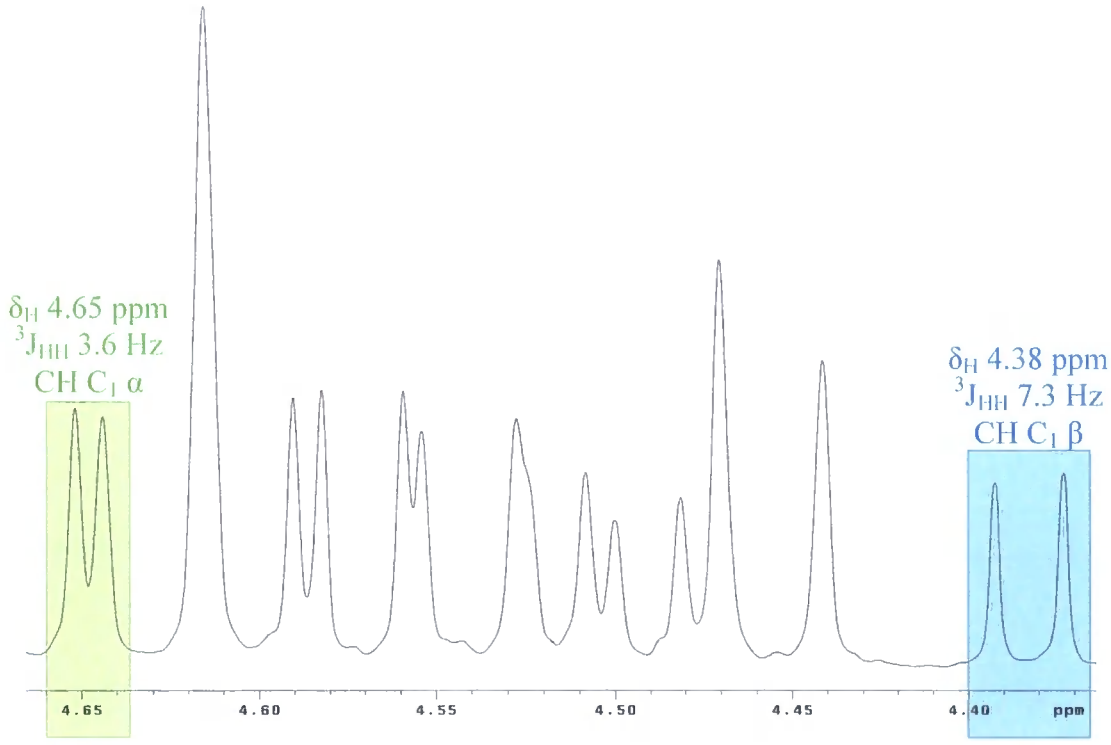


Figure 6.4. ^{1}H NMR of compound (**44α/β**) showing the ratio of the α and β anomers.

It was possible to identify the signals arising from the C_1 hydrogen atom of the α anomers of (**44**) and (**45**) due to their coupling constant (J) of 3.6 and 3.5 Hz respectively. Coupling constants of this magnitude are characteristic of a smaller axial-

equatorial dihedral angle at H-C_1-C_2-H (approximately 60°). In contrast the signals arising from the β anomers exhibit a significantly larger coupling constant, J = 7.3 and 7.7 Hz, which proves consistent with a larger axial-axial coupling. The anomer ratios ascertained by optical polarimetry were consistent with those determined utilising the ^{1}H NMR integrals confirming the validity of using ^{1}H NMR to determine the anomer ratios. Utilising the unique NMR signals arising from the α and β anomers, it was possible to fully characterise compounds (**44α/β**) and (**45α/β**), spectroscopic data proved consistent literature values[139-143] confirming the glycosylation potential of polyfluoro-pyridyl glycosyl donor systems.

Interestingly the model glycosylation reactions of donors (**33**) to (**39**), with hexanol and cyclohexanol, displayed an unusually high degree of stereoselectivity (Table 6.1). This implies that the glycosylation reactions are not proceeding *via* the expected S_N1 mechanism, an alternative glycosylation mechanism will be discussed in Section 6.1.1.

In contrast to the other polyfluoro-pyridyl glycosyl donors the reaction of diethylamino-pyridine derivative (**36α/β**) with hexanol failed to generate the expected saccharide (**44**). It is hypothesised that instead of promoting the glycosylation process, boron trifluoride underwent a one-electron transfer process to generate a radical cationic species (Figure 6.5).[144-146] The formation of a radical cation was proposed due to a quenching of the NMR signals usually observed during the ^{19}F NMR reaction monitoring. The formation of the radical cation would not only neutralise the Lewis acid, by altering its oxidation state, and hence restrict the expected glycosylation process, it would also alter the electron density of the pyridine ring, reducing its leaving group ability.

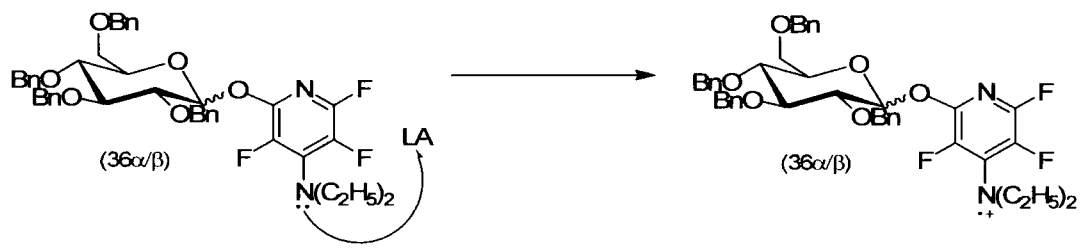


Figure 6.5. Theorised radical cation formation from the reaction of (**36**) with a Lewis acid.

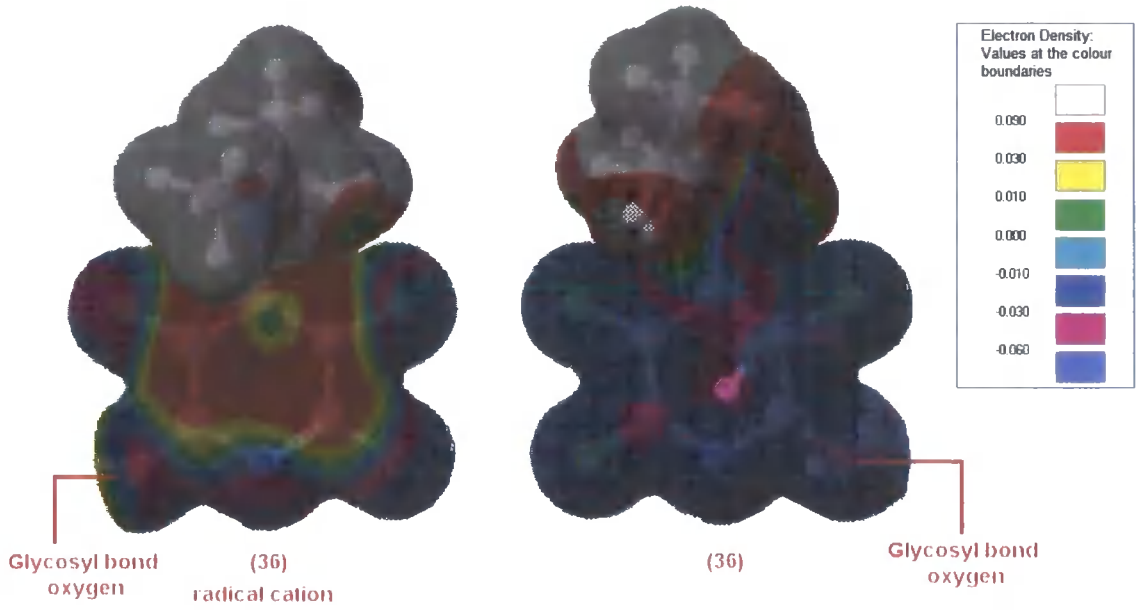


Figure 6.6. An electron density plot for compound (**36**) and the radical cation generated during glycosylation derived *via* molecular modelling.

In order to determine the effect of forming a radical cation upon the electron density of the glycosidic bond oxygen the electron density of (**36**) and the radical cation were calculated (Figure 6.6). Figure 6.6 shows that the formation of a radical cation would remove electron density from the glycosidic bond oxygen, diminishing its ability to coordinate to the Lewis acid and hence its action as a glycosyl donor. This clearly demonstrates that a diethylamine substituent on the pyridine ring inhibits the glycosylation process.

6.1.1 The Stereochemistry of Glycosylation using Polyfluoro-Pyridyl Donors

The formation of a glycosidic bond with control of the stereochemistry at the anomeric centre is usually difficult, as discussed in Section 2.2. Interestingly the model glycosylation reactions of donors (**33**) to (**39**), with hexanol and cyclohexanol, displayed an unusually high degree of stereoselectivity (Table 6.1). This was most evident for the reactions of donor (**33**), where pure β anomer was used for the glycosylation reactions, in this case the glycosylation reactions predominantly yielded the α anomers of (**44**) and (**45**) with a diastereomeric excess of 95 and 98% respectively.

This is surprising since the established mechanism for the glycosylation process is an S_N1 reaction proceeding *via* an oxocarbenium ion (Figure 6.7).

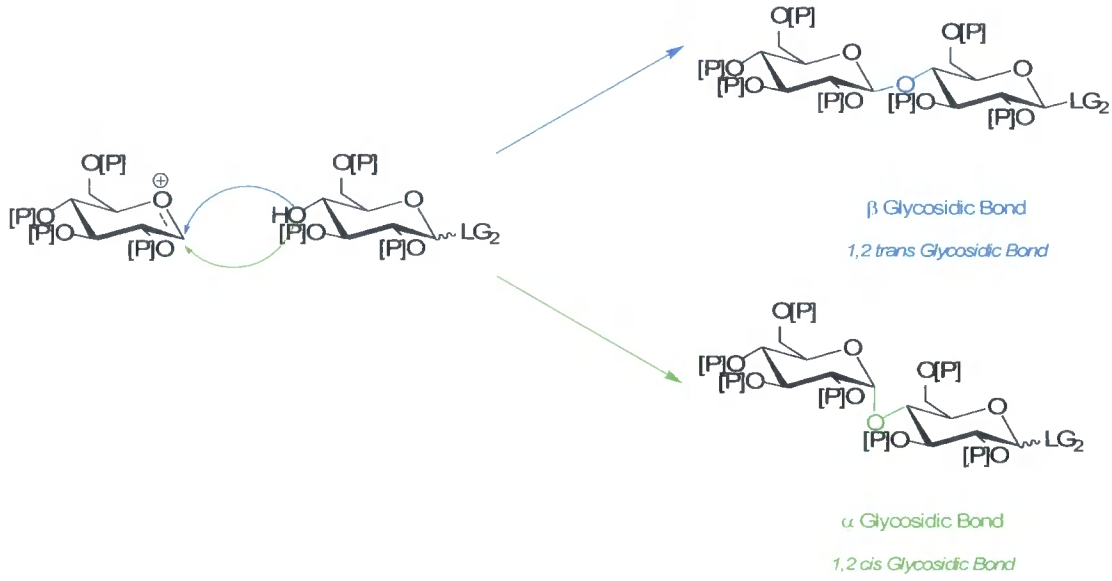


Figure 6.7. Stereoselectivity considerations in the glycosylation process.

As previously discussed in Chapter two, a mechanism of this type is expected to produce a mixture of α and β anomers unless anchimeric assistance is utilised.

In the glycosylation reactions of this class of donor, it appears that the stereochemistry at the anomeric carbon (C_1) was inverted with respect to the initial configuration of the donor. This was observed for donors (**34**) to (**39**), where a 4:7 ratio of the α and β anomers was utilised for the glycosylation reactions, resulting in a 7:4 ratio of α and β products. This inversion of configuration is characteristic of an S_N2 reaction, where the nucleophile (or glycosyl acceptor in this case) must approach the site of substitution from the side opposite the leaving group (Figure 6.8).

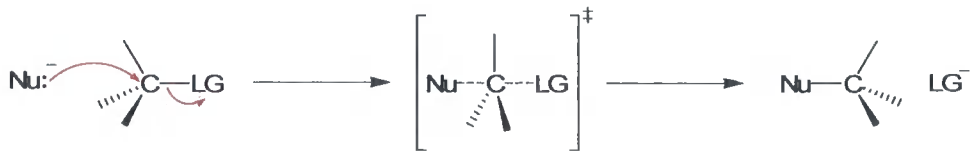


Figure 6.8. Schematic representation of the inversion of configuration observed with S_N2 reactions.

Therefore, for this class of donor it seems that the glycosylation process must proceed *via* the S_N2 mechanism detailed in Figure 6.9, rather than the expected S_N1 process. In this mechanism, instead of being cleaved to form an oxocarbenium ion, the leaving group remains attached to the glucose moiety. The heterocyclic leaving group effectively blocks one face of the glucose moiety, forcing the glycosyl acceptor to attack the free face which results in the observed inversion of configuration at the C_1 position

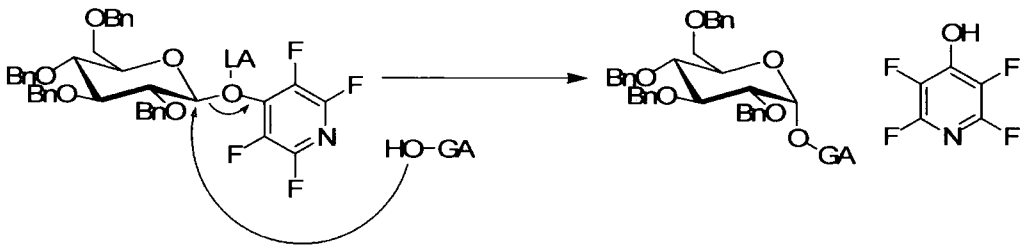


Figure 6.9. Proposed S_N2 mechanism for glycosylation utilising polyfluoro-pyridyl glycosyl donors.

This new glycosylation pathway could have far reaching implications for the synthesis of oligosaccharides as it enables the synthesis of glycosidic bonds with control over their stereochemistry.

6.1.2 NMR Reaction Monitoring

During the glycosylation process pyridin-ol compounds were generated from the displacement of the substituted pyridine leaving groups from the glucose moiety (Figure 6.9). The appearance of NMR signals attributed to these pyridin-ol compounds provided an effective probe for monitoring the progress of the glycosylation reactions using ^{19}F NMR spectroscopy, by analysing a sample of the reaction mixture at timed intervals it was possible to observe signals arising from the formation of the pyridin-ol compounds and the disappearance of signals due to the glycosyl donor (Figure 6.10).

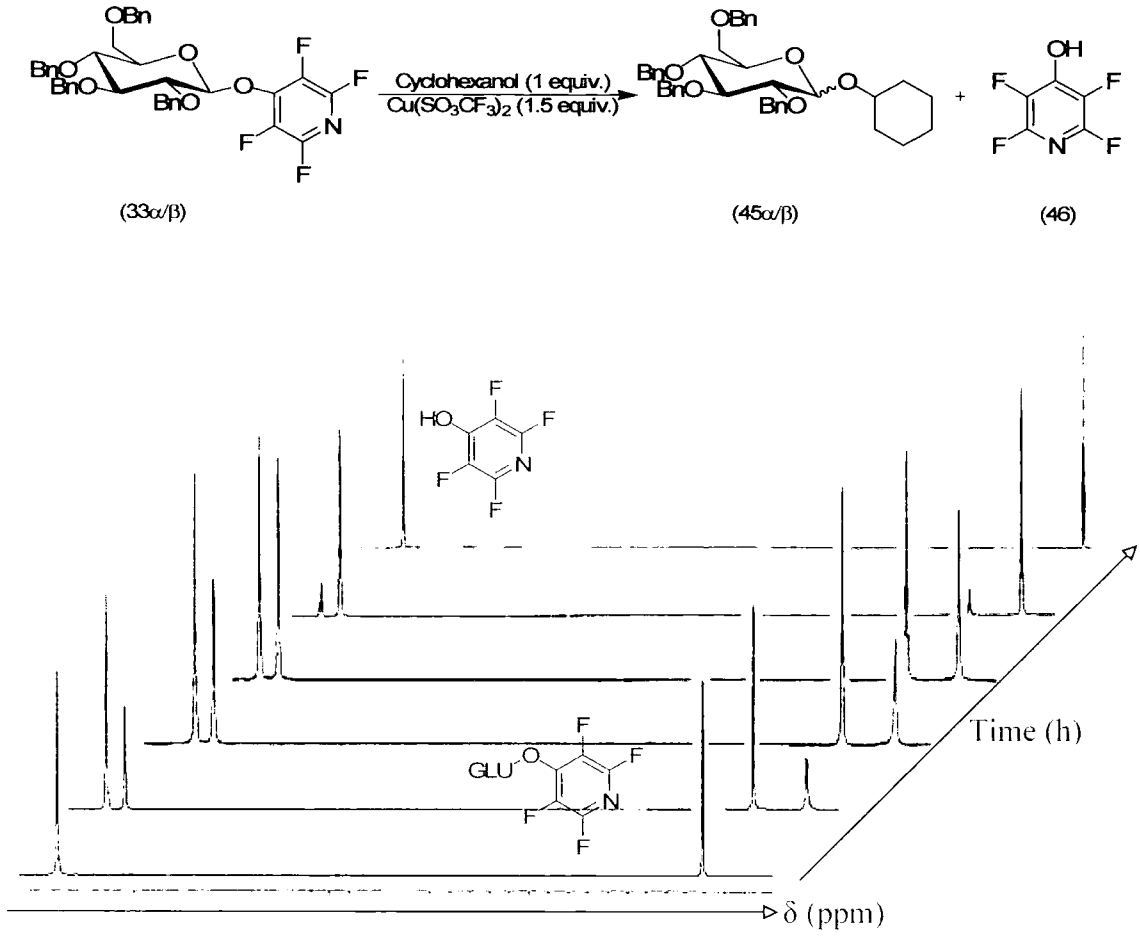
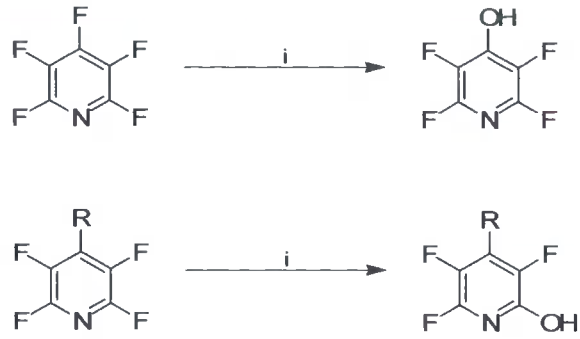
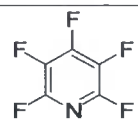
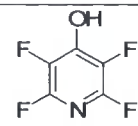
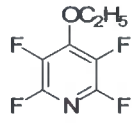
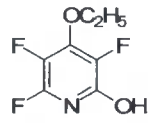
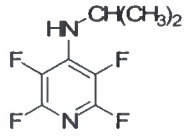
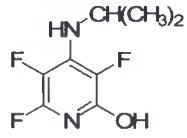
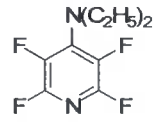
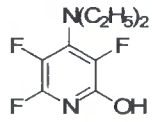
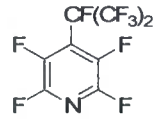
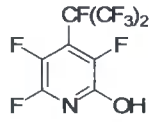


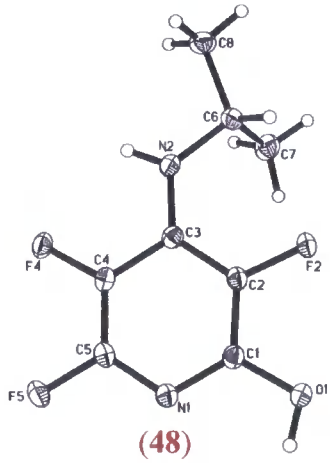
Figure 6.10. Time resolved ^{19}F NMR of the reaction between (**33**) and cyclohexanol.

In order to use the pyridin-ol compounds as a reaction probe, it was necessary to synthesise the pyridin-ol compounds unambiguously by nucleophilic aromatic substitution of the parent pyridine to confirm that they are formed as reaction by-products.

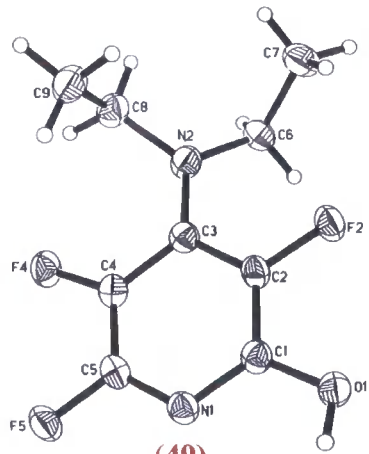
Reaction of the parent pyridines with sodium hydroxide in 2-methylypropan-2-ol generated the pyridin-ol compounds in good yields (Figure 6.11). The structure of the pyridin-ol compounds was confirmed by x-ray crystallography and their ^{19}F NMR spectroscopic data proved consistent with the data obtained from the glycosylation reactions. Interestingly, the x-ray crystallographic data displayed no double bond character for the carbon-oxygen bond at the C_1 position which is consistent with the proposed reaction mechanism (Section 6.1.1) since it provides an indication of the nature of the heterocyclic leaving groups.



Parent pyridine		Pyridin-ol compound		Yield [%]
(1)		(46)		70
(5)		(47)		68
(15)		(48)		80
(11)		(49)		83
(27)		(50)		72



(48)



(49)

Figure 6.11. *Reagents and Conditions:* i, **(1)**, **(5)**, **(11)**, **(15)**, **(27)** (1 equiv.), sodium hydroxide (2.2 equiv.), 2-methylpropan-2-ol, reflux.

The ability to monitor reactions of this type rapidly *via* standard NMR techniques provides a significant advantage over existing donor species where monitoring of the progress of glycosylation is usually achieved *via* thin layer chromatography (TLC), which only provides qualitative information, or by isolation of the reaction products by HPLC. HPLC analysis does provide quantitative data, but it can be time consuming and requires characterisation of the isolated products. NMR analysis on the other hand, can provide quantitative data in a much shorter time.

The simple model glycosylation reactions detailed in this section demonstrate that this class of compound exhibit glycosyl donor characteristics with both primary and secondary alcohol acceptors. More importantly it appears that this class of glycosyl donor utilises an S_N2 type glycosylation mechanism rather than the previously documented S_N1 glycosylation mechanism. This provides this class of donor with an unusually high degree of stereoselectivity over the formation of glycosidic bonds.

6.2 Tuning Glycosyl Donor Reactivity

In the previous section it was established that polyfluoro-pyridyl systems display glycosyl donor properties, forming glycosidic bonds with a high degree of stereoselectivity. However, to be effective glycosyl donors, polyfluoro-pyridyl systems must display a wide range of reactivities under various conditions in order to enable their use in the various glycosylation strategies detailed in Section 2.4. In donor systems of this type the glycosylation potential of the donors was hoped at the onset to be dependant upon the leaving group ability of the pyridine ring and the type of Lewis acid used to promote the reaction. In order to determine the effect of the ring substituents and Lewis acids upon the rate of glycosylation the O-benzyl glycosyl donors (**33**) - (**35**) and (**37**) were reacted with cyclohexanol, under the glycosylation conditions utilised in the previous section, and screened against a variety of Lewis acid activators (Figure 6.12).

The progress of the reactions was monitored over time using ^{19}F NMR spectroscopy to determine the relative amounts of donor and pyridin-ol present in the reaction mixtures (full data can be found in appendix A). This proved to be an effective and easily performed method for determining the relative effectiveness of the glycosyl donor / Lewis acid combinations.

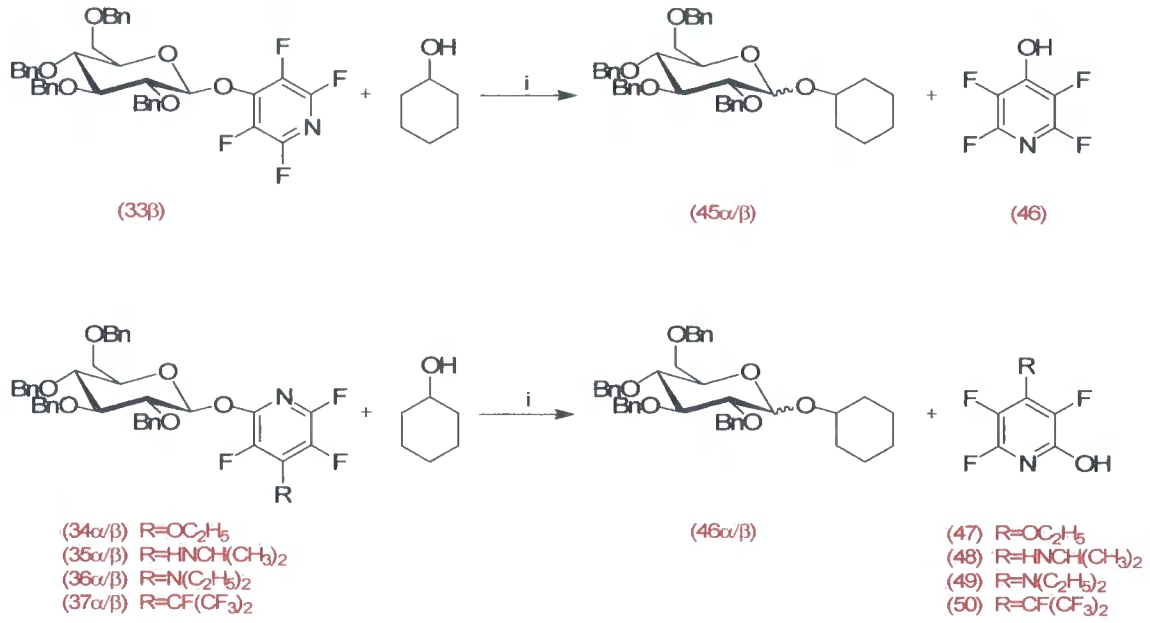


Figure 6.12. *Reagents and Conditions:* i, (**33**) to (**37**) (1 equiv.), cyclohexanol (1 equiv.), Lewis acid (1.5 equiv.), CH_3CN, stir, rt.

All of the polyfluoro-pyridyl donor systems developed in Chapter five were screened against 12 Lewis acids, including copper(II)triflate, aluminium(III)chloride, boron trifluoride diethyletherate and titanium(IV)chloride (full data can be found in appendix A). Donor (**36**) failed to generate any usable screening data due to the quenching of the NMR signal resulting from the formation of a radical cationic species (Figure 6.5).

The screening of the glycosyl donors with a range of Lewis acids revealed that glycosylation only occurred when certain donor / Lewis acid combinations were used (Table 6.2), these 'match-pairs' of donors and Lewis acids appear ideal for orthogonal (Section 2.4.1) and active-latent (Section 2.4.3) glycosylation strategies. However, in this format the data provides limited information regarding the relative reactivities of the 'match' donor / Lewis acid combinations, therefore, the data was used to determine the initial rate constants for the glycosylation reactions.

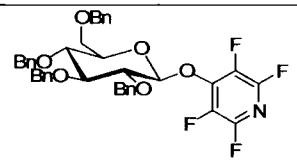
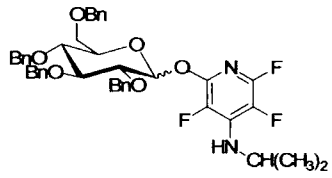
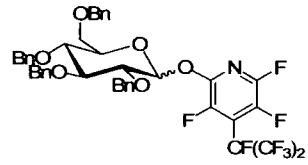
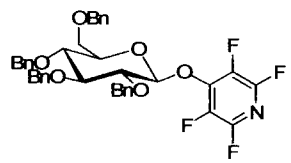
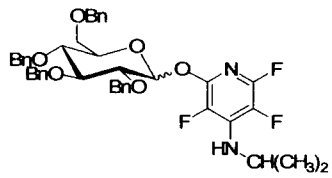
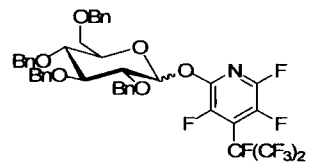
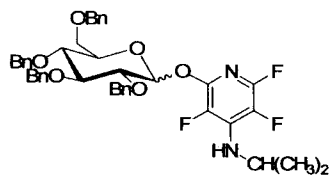
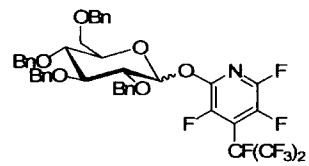
Donor		Lewis acid	Percentage conversion after t (h)					
			2	4	6	12	24	48
	(**33**)	$Cu(SO_3CF_3)_2$	18	30	41	58	73	100
	(**35**)	$Cu(SO_3CF_3)_2$	0	0	0	0	0	0
	(**37**)	$Cu(SO_3CF_3)_2$	0	0	0	0	0	0
	(**33**)	$TiCl_4$	11	22	28	42	55	71
	(**35**)	$TiCl_4$	-	-	7	12	20	31
	(**37**)	$TiCl_4$	0	0	0	0	0	0
	(**35**)	$AlCl_3$	35	51	61	81	95	100
	(**37**)	$AlCl_3$	23	42	47	51	62	78

Table 6.2. Comparison of the percentage conversion of several glycosyl donors with various Lewis acid activators.

6.2.1 Kinetic Study of the Glycosyl Donor Reactivity

The progress of the screen reactions was monitored over time using ^{19}F NMR spectroscopy, from the NMR peak integrals it was possible to calculate the concentrations of glycosyl donor and pyridin-ol in the reaction mixtures. The glycosylation was assumed to obey second order kinetics, *i.e.* displays a dependence on both the donor and acceptor concentrations, due to the S_N2 nature of the reaction mechanism. Second order kinetics follows the following rate equation:[147-149]

$$rate \propto [donor][acceptor]$$

$$rate = \frac{d[donor]}{dt} = \frac{d[acceptor]}{dt} = -k[donor][acceptor]$$

For the reactivity screens we set $[donor]_0 = [acceptor]_0$ which reduces the equation to:

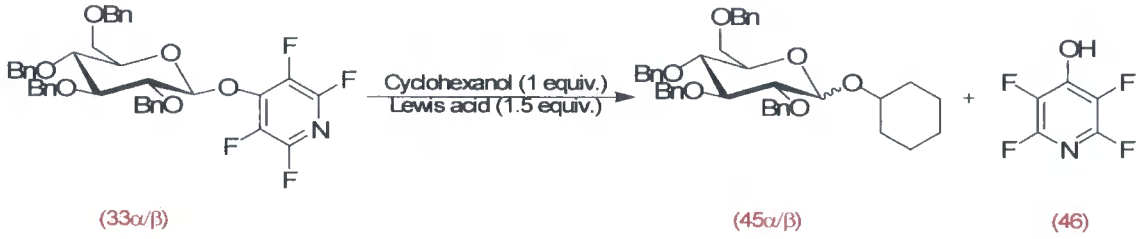
$$rate = \frac{d[donor]}{dt} = -k[donor]^2$$

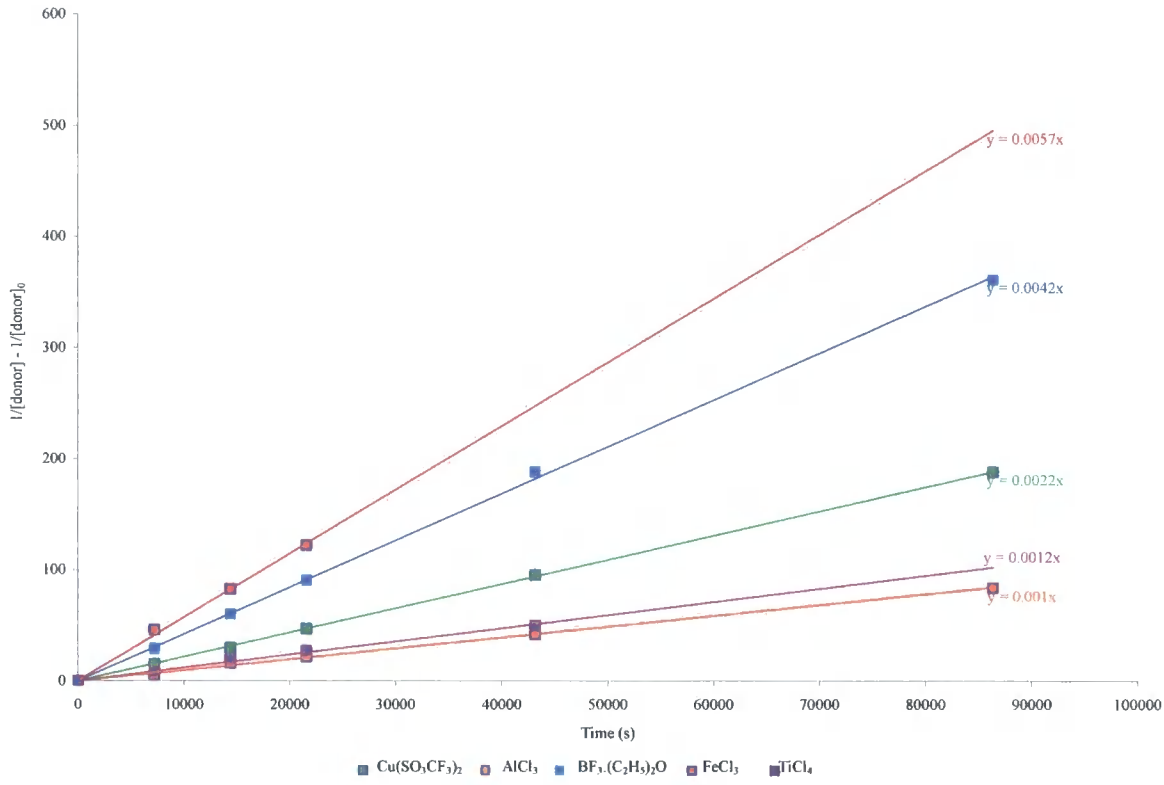
$$\equiv kt = \frac{1}{[donor]} - \frac{1}{[donor]_0}$$

$[donor]$	=	concentration of donor	$moldm^{-3}$
$[donor]_0$	=	initial concentration of donor	$moldm^{-3}$
k	=	rate constant	$dm^3mol^{-1}s^{-1}$
t	=	time	s

A plot of $\frac{1}{[donor]} - \frac{1}{[donor]_0}$ vs. t gave a straight line of gradient k. The results for donors (**33**), (**34**), (**35**) and (**37**) are detailed on the following pages.

2,3,5,6-Tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine (**33**)

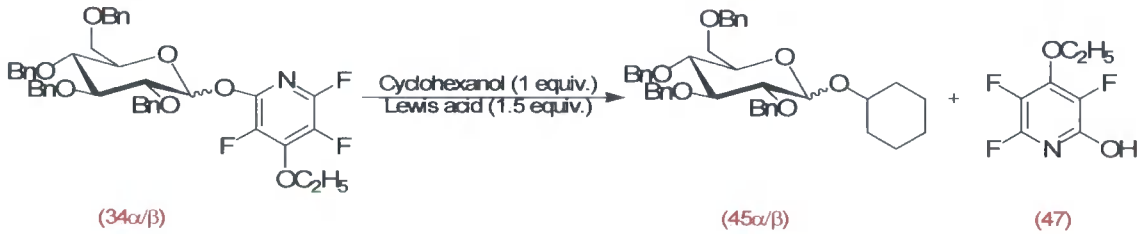




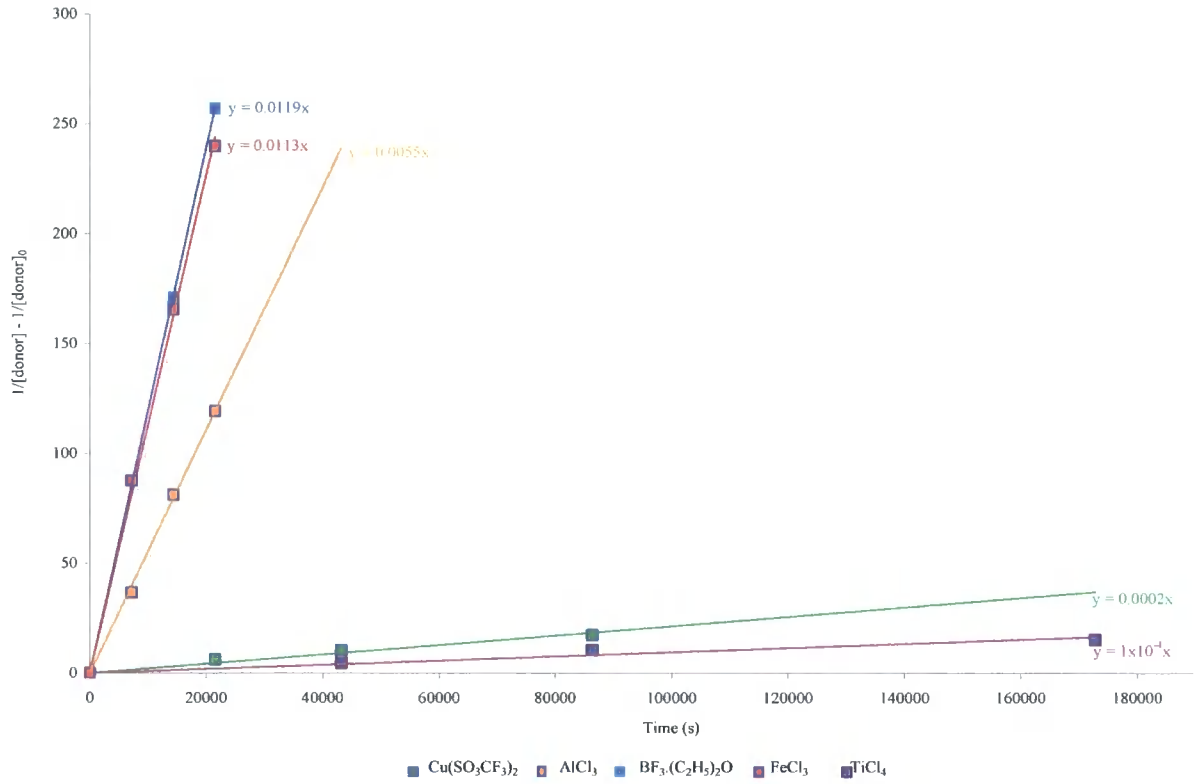
[(**33**)] / moldm^{-3} (x 10^{-3})	Time (h)	0	2	4	6	12	24	k / dm^{3}mol^{-1}s^{-1} (x 10^{-3})
	$Cu(SO_3CF_3)_2$	14.5	11.9	11.0	8.6	6.1	3.9	2.4
	$AlCl_3$	14.5	13.5	11.7	11.0	9.0	6.5	1.0
	$BF_3.(C_2H_5)_2O$	14.5	10.2	7.7	6.3	3.9	2.3	4.2
	$FeCl_3$	14.5	8.7	6.6	5.2	5.2	5.2	5.3
	$TiCl_4$	14.5	12.9	11.3	10.4	8.4	6.5	1.2

Figure 6.13. Kinetic data for the reaction of (**33**) with cyclohexanol.

4-Ethoxy-2,3,5-tetrafluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine (**34**)



(34α/β) (45α/β) (47)

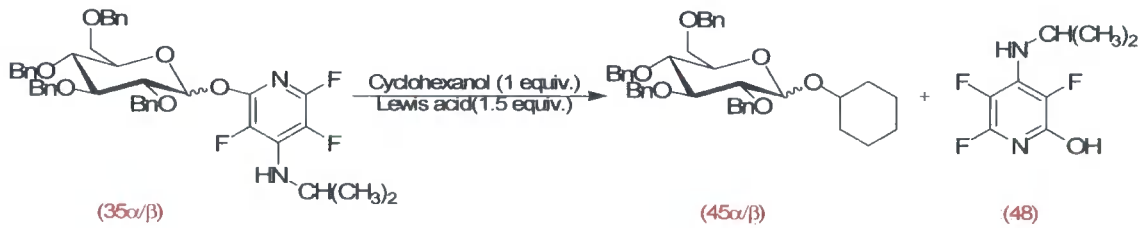


	Time (h)	0	2	4	6	12	24	k / $dm^3mol^{-1}s^{-1}$ (x 10^{-3})
[(**34**)] / $moldm^{-3}$ (x 10^{-3})	$Cu(SO_3CF_3)_2$	14.0	14.0*	14.0*	12.9	12.2	11.3	0.2
	$AlCl_3$	14.0	9.2	6.5	5.2	2.5	2.0	5.5
	$BF_3.(C_2H_5)_2O$	14.0	6.3	4.1	3.0	2.1	1.7	11.9
	$FeCl_3$	14.0	6.3	4.2	3.2	2.2	2.2	11.3
	$TiCl_4$	14.0	14.0*	14.0*	14.0*	13.1	12.2	0.1

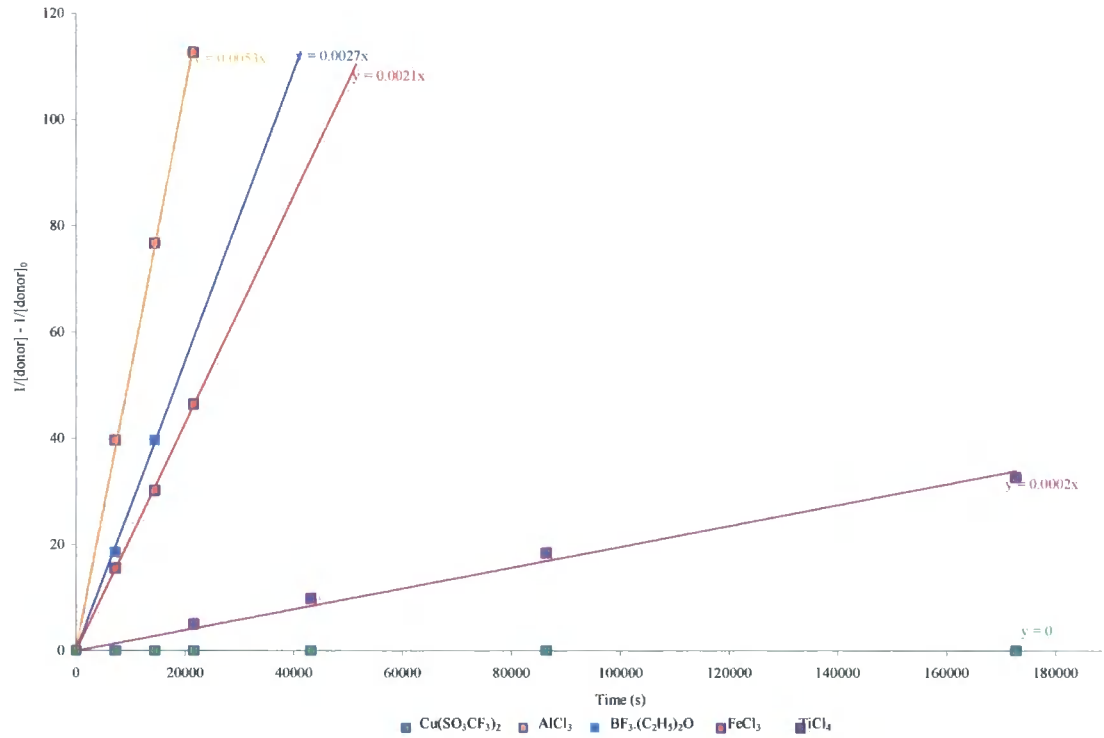
Figure 6.14. Kinetic data for the reaction of (**34**) with cyclohexanol.

* progress of the glycosylation reaction was below the detection threshold.

2,3,5-Trifluoro-N-isopropyl-6-(2,3,4,6-tetra-O-benzyl-D-glucopranosyloxy)pyridin-4-amine (**35**)



(35α/β) (45α/β) (48)

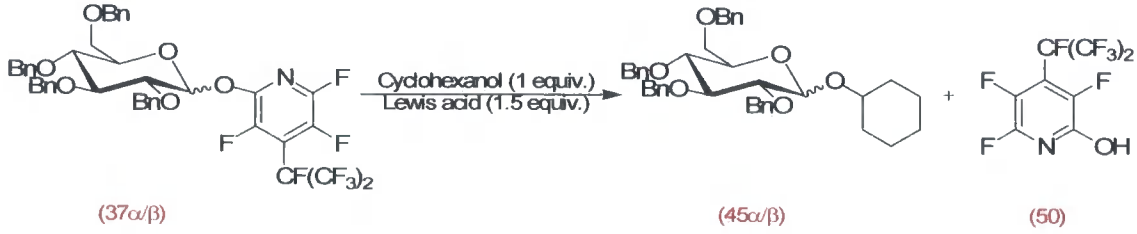


	Time (h)	0	2	4	6	12	24	k / $dm^3mol^{-1}s^{-1}$ (x 10^{-3})
[**35**)] / $moldm^{-3}$ (x 10^{-3})	$Cu(SO_3CF_3)_2$	13.7	13.7	13.7	13.7	13.7	13.7	0.0
	$AlCl_3$	13.7	8.9	6.7	5.4	2.6	0.7	5.3
	$BF_3.(C_2H_5)_2O$	13.7	10.9	8.9	6.2	3.6	1.1	2.7
	$FeCl_3$	13.7	11.3	9.7	8.4	8.0	8.0	2.1
	$TiCl_4$	13.7	13.7*	13.7*	12.8	12.1	11.0	0.2

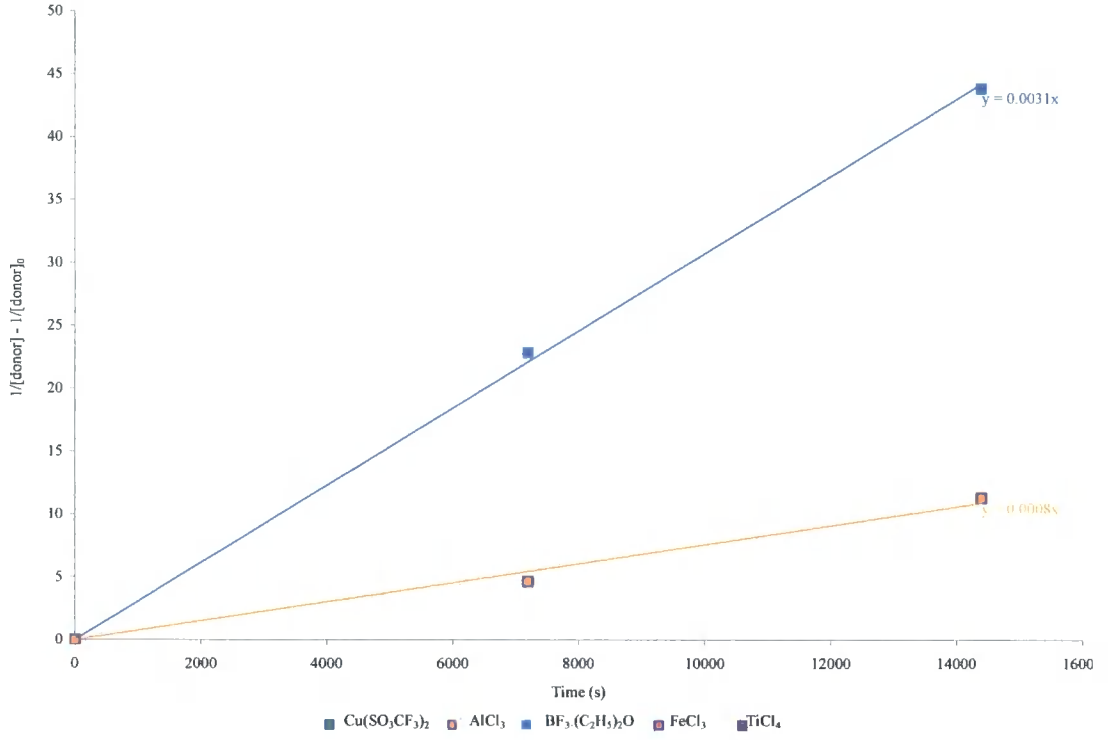
Figure 6.15. Kinetic data for the reaction of (**35**) with cyclohexanol.

* Progress of the glycosylation reaction was below the detection threshold.

2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-β-$_D$-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridine (**37**)



(37α/β) (45α/β) (50)



	Time (h)	0	2	4	6	12	24	k / $dm^3mol^{-1}s^{-1}$ ($x 10^{-3}$)
[(**37**)] / $moldm^{-3}$ ($x 10^{-3}$)	$Cu(SO_3CF_3)_2$	64.0	64.0	64.0	64.0	64.0	64.0	0.0
	$AlCl_3$	64.0	49.3	37.1	33.9	31.3	24.3	0.8
	$BF_3.(C_2H_5)_2O$	64.0	26.0	16.8	14.5	9.3	0	3.1
	$FeCl_3$	64.0	64.0	64.0	64.0	64.0	64.0	0.0
	$TiCl_4$	64.0	64.0	64.0	64.0	64.0	64.0	0.0

Figure 6.16. Kinetic data for the reaction of (**37**) with cyclohexanol.

The initial rate constants calculated above allowed us to prepare a scale of reactivity for this class of glycosyl donor. Table 6.3 displays the relative rate constants for the 'matched' glycosyl donor / Lewis acid combinations with respect to the least reactive combinations (donor (**34**) and $TiCl_4$).

	k_{rel}			
	(**33**)	(**34**)	(**35**)	(**37**)
$Cu(SO_3CF_3)_2$	24	2	0	0
$AlCl_3$	10	55	53	8
$BF_3.(C_2H_5)_2O$	42	119	27	31
$FeCl_3$	53	113	21	0
$TiCl_4$	12	1	2	0

Table 6.3. The relative rate constants for glycosyl donors (**33**) – (**35**) and (**37**).

The relative rate constants for the donor / activator combinations range over a factor of 100, providing a wide range of reactivity from a small selection of donors. This clearly demonstrates the reactivity tuning potential of this family of glycosyl donor. Ideally reactivity ranges over a factor of 1000 are desirable,[150-153] however, from such a small sample set the relative reactivity range of 100 demonstrates the versatility of this class of donors and it is expected that the analysis of a much larger set of donors would provide a range of reactivities over the preferred factor of 1000.

Interestingly there appears to be little relationship between the relative rate constants and the substituents on the pyridine ring, as demonstrated by donor (**34**) which displays relative rate constants over a factor of 100. Instead it appears as if the reactivity is purely dependant upon creating a compatible donor / Lewis acid pairing.

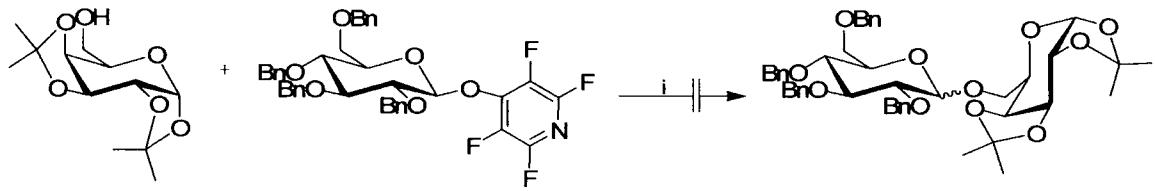
The model glycosylation reactions detailed in the previous sections demonstrates that the new class of donors synthesised in Chapter five are effective glycosyl donors providing excellent yields of the coupled saccharides (**44**) and (**45**).

The most important discovery during this investigation was that this class of donor does not react *via* the standard S_N1 type glycosylation mechanism. Instead an S_N2 type glycosylation mechanism is observed which provides high levels of stereoselectivity, enabling the selective synthesis of α or β glycosidic linkages. As

discussed in Chapter two the stereoselective formation of glycosidic bonds is a key requirement for the effective synthesis of oligosaccharides. It is also interesting to note that this class of donor provides stereoselectivity even when a non-participatory solvent (Section 2.2.2) is used which favours the formation of the opposite anomer, demonstrating the robustness of this approach.

6.3 Glycosylation Reactions between Two Saccharides

The model glycosylation reactions detailed in the previous sections demonstrate the potential usefulness of polyfluoro-pyridyl glycosyl donors in the synthesis of complex oligosaccharides. So far the polyfluoro-pyridyl donors have only been coupled with simple alcohols, hexanol and cyclohexanol, and although these reactions have proved successful the donors ability to form an oligosaccharide is still unknown. To this end, glycosyl donor (**33**) was reacted with the glycosyl acceptor 1,2:3,4-di-O-*iso*propylidene-α-$_D$-galactopyranose (**54**) utilising the same conditions as the model glycosylation reactions (Figure 6.17). However, under these conditions glycosylation failed to occur, allowing complete recovery of the glycosyl donor.



(54) (33β) (55α/β)

Figure 6.17. *Reagents and Conditions:* i, $Cu(SO_3CF_3)_2$ (1.5 equiv.), CH_3CN, stir, rt.

6.3.1 Optimisation of the Glycosylation Process

Since the glycosylation conditions utilised previously failed to yield the disaccharide (**55**) a systematic study into the reaction conditions required in order to achieve glycosylation was carried out. It was quickly established that the reaction required heating before glycosylation would occur, upon heating the reaction to a temperature of 40°C it was possible to observe the formation of (**46**) and the depletion of (**33**) in the reaction mixture by ^{19}F NMR, indication that glycosylation was occurring.

The first step in optimising the reaction conditions required for glycosylation was to determine the optimum concentration of acceptor and donor required. This was achieved by reacting various amounts of (**33**) and (**54**), where [(**33**)] = [(**54**)], with a fixed quantity of Lewis acid (Figure 6.18, Table 6.4)

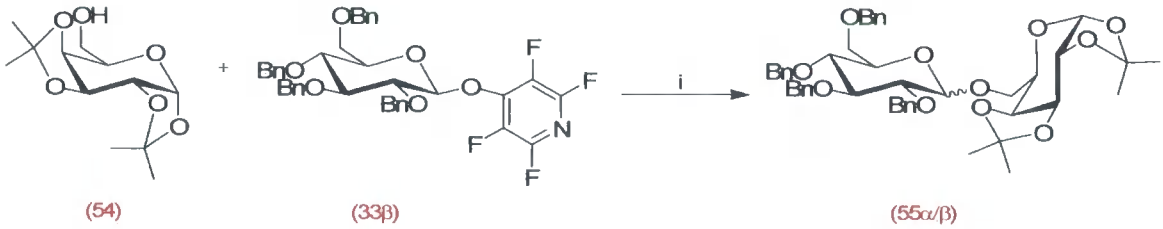


Figure 6.18. *Reagents and Conditions:* i, $Cu(SO_3CF_3)_2$ (1.5 equiv.), CH_3CN, stir, 40°C.

A plot of [(**33**)] vs. percentage conversion allows the optimum donor concentration to be ascertained by determining the concentration which yielded the greatest percentage conversion (Figure 6.19)

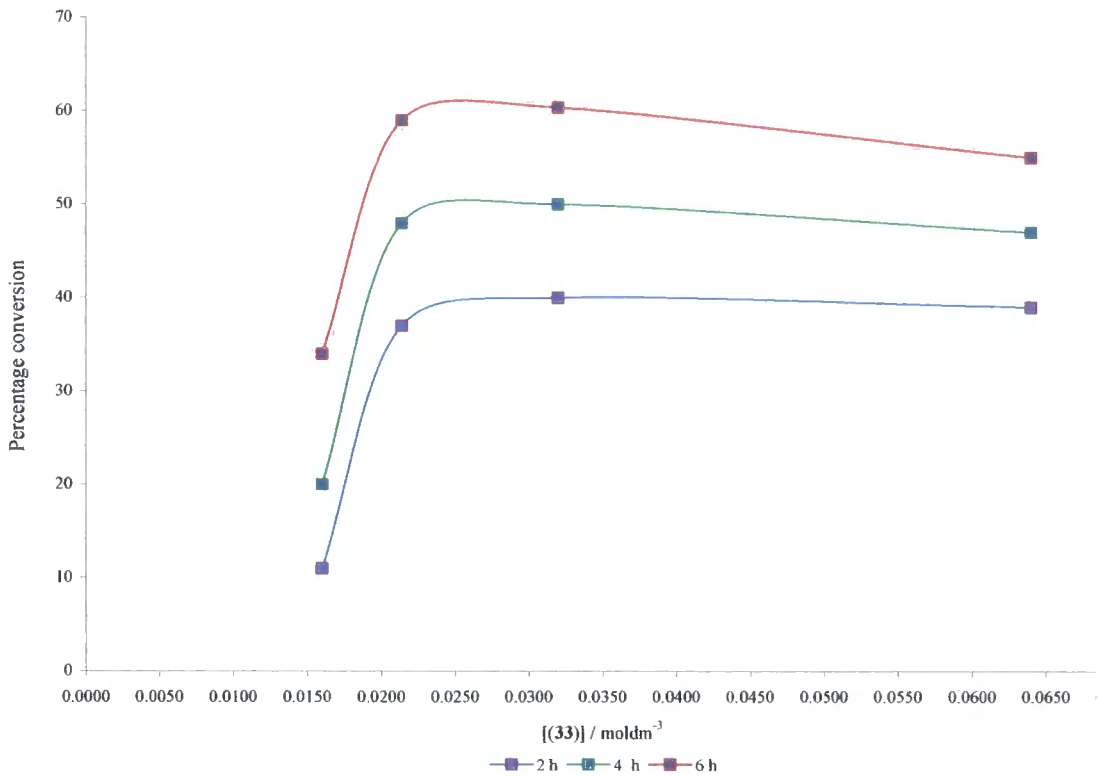


Figure 6.19. A plot of [(**33**)] vs. percentage conversion.

[(**33**)] ($x10^{-2}$) / $moldm^{-3}$	Percentage conversion after t (h)			
	0	2	4	6
1.6	0	11	20	34
2.1	0	37	48	59
3.2	0	40	50	60
6.4	0	39	47	54

Table 6.4. Optimisation data for Figure 6.17.

From Figure 6.19 it is clear that the optimum donor and acceptor concentration is 0.026 $moldm^{-3}$, since concentrations above this value provide no increase in conversion. At high donor and acceptor concentrations reduced conversion is observed, compared to the optimum concentration, due to the increased viscosity of the reaction mixture.

The next stage in optimising the glycosylation conditions was to determine the effect of the Lewis acid concentration upon the glycosylation process. This was achieved by reacting a donor / acceptor solution of fixed concentration with increasing amounts of Lewis acid and monitoring the formation of (**46**) in the reaction *via* ^{19}F NMR (Table 6.5).

$[Cu(SO_3CF_3)_2]$ ($x\ 10^{-2}$) / $moldm^{-3}$	Percentage conversion after t / h				
	0	2	4	6	12
1.6	0	0	0	0	0
3.2	0	0	0	0	4
6.4	0	0	0	0	11
9.6	0	0	0	9	20
12.8	0	3	7	17	28
16.0	0	8	16	24	36

Table 6.5. Optimisation data for Figure 6.19.

A plot of $[Cu(SO_3CF_3)_2]$ vs. percentage conversion (Figure 6.20) demonstrates that increasing the concentration of Lewis acid in the glycosylation reaction increases the rate of glycosylation.

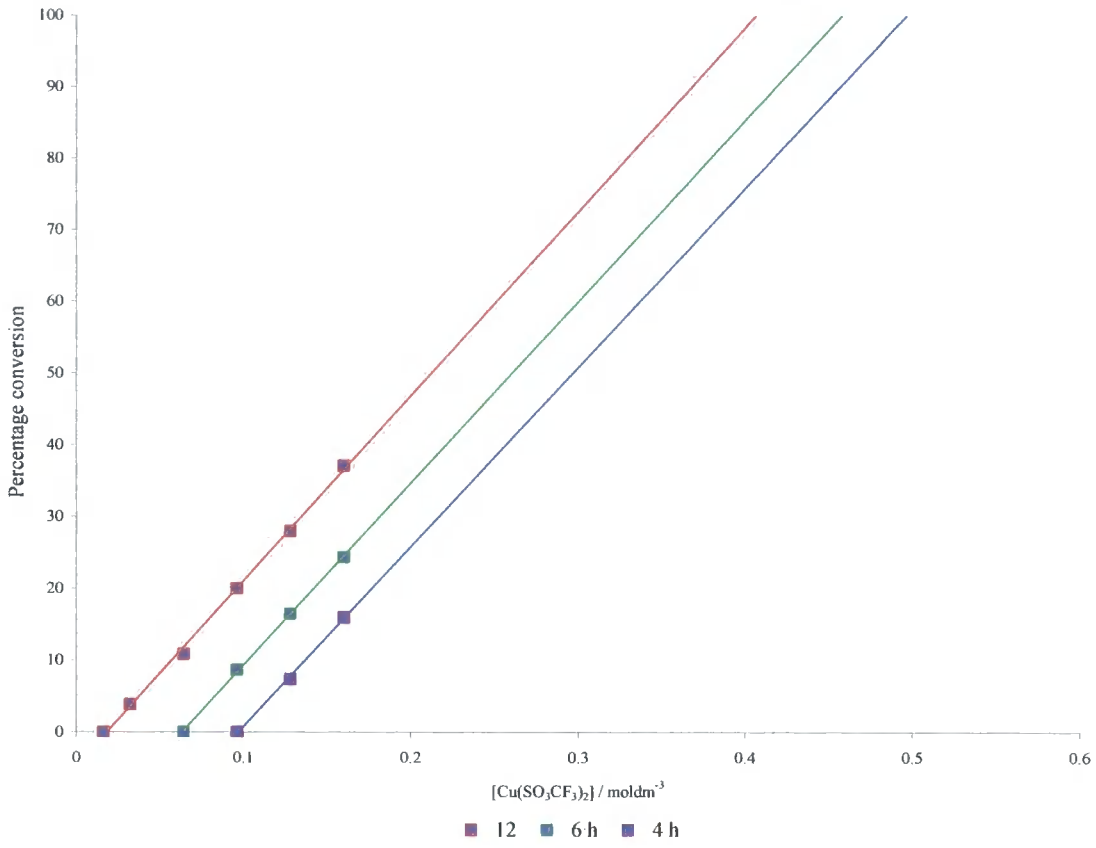


Figure 6.20. A plot of $[Cu(SO_3CF_3)_2]$ vs. percentage conversion.

The reactivity screens detailed above allow us to propose a set of optimised reaction conditions for the glycosylation reactions involving polyfluoro-pyridyl glycosyl donors. It has been established that the reaction requires a donor and acceptor concentration of 0.026 moldm^{-3}, an excess of Lewis acid and heating to a temperature of 40°C in order to achieve glycosylation in acceptable levels.

6.3.2 Optimised Glycosylation

Utilising the optimised glycosylation conditions from the previous section, glycosyl donor (**33**) was reacted with the glycosyl acceptor (**54**) (Figure 6.21), ^{19}F NMR spectroscopy showed the formation of (**46**) and the depletion of (**33**) in the reaction mixture. Compound (**55**) was not, however, isolated from the reaction medium; instead

a complex mixture of compounds was observed which resisted separation by column chromatography.

It appears as if the acidic conditions utilised to promote the glycosylation reaction also catalysed the deprotection of the acetal protecting groups on the acceptor, resulting in a complete loss of regiochemistry and the formation of a complex mixture of oligosaccharides.

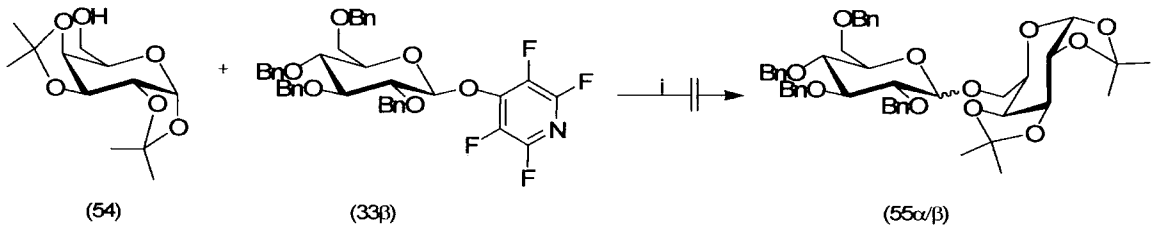


Figure 6.21. *Reagents and Conditions:* i, $Cu(SO_3CF_3)_2$ (1.5 equiv.), CH_3CN, stir, 40°C.

In order to inhibit the deprotection of the glycosyl acceptor, the glycosylation reaction was buffered with *2,4,6-tri-tert-butylpyrimidine* (**56**) (Figure 6.22),[154] which effectively stopped the acid catalysed deprotection of the glycosyl acceptor without effecting the glycosylation process. A slight reduction in the rate of glycosylation was observed when the reaction was buffered with (**56**), however, this was considered an acceptable loss since the reaction proceeded with complete control of the regiochemistry of the disaccharide formed.

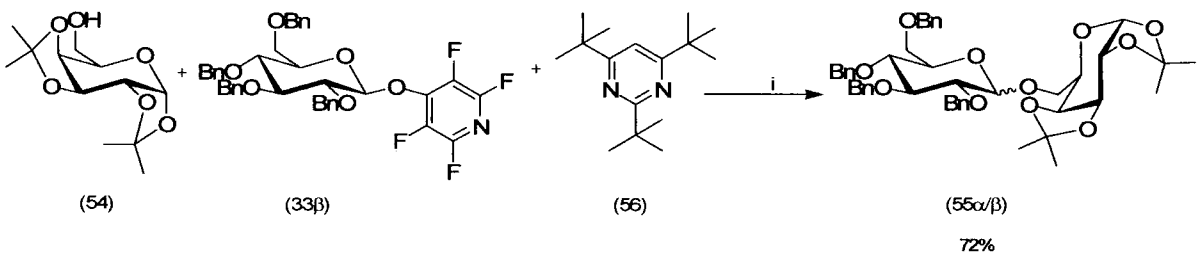


Figure 6.22. *Reagents and Conditions:* i, (**54**) (1.0 equiv.), (**33**) (1.0 equiv.), $Cu(SO_3CF_3)_2$ (1.5 equiv.), (**56**) (1.6 equiv.), CH_3CN, stir, 40°C.

Under these modified conditions the glycosylation reaction proceeded efficiently to give compound (**55**) in moderate yield. There was, however, a slight reduction in the

stereoselectivity of the glycosylation process, compared to the model reactions, with (**55α**) being isolated with a diastereomeric excess of 80%.

The stereoselectivity observed in this reaction is a improvement upon that achieved by many of the existing groups of glycosyl donor, especially considering it can be predetermined by using either the α or β anomer of the glycosyl donor. This class of donor also provides an effective route for the synthesis of α glycosidic linkages, which, as we saw in Chapter two, are extremely difficult to synthesise selectively in practical quantities.

6.4 Applicable Glycosylation Strategies

The range of reactivity available from this class of donor makes them ideal candidates for the glycosylation strategies detailed in Sections 2.4.1 and 2.4.3. An orthogonal glycosylation strategy can be envisaged (Figure 6.23) where variation of the activator can be used to establish a controlled cascade of glycosylation reactions.

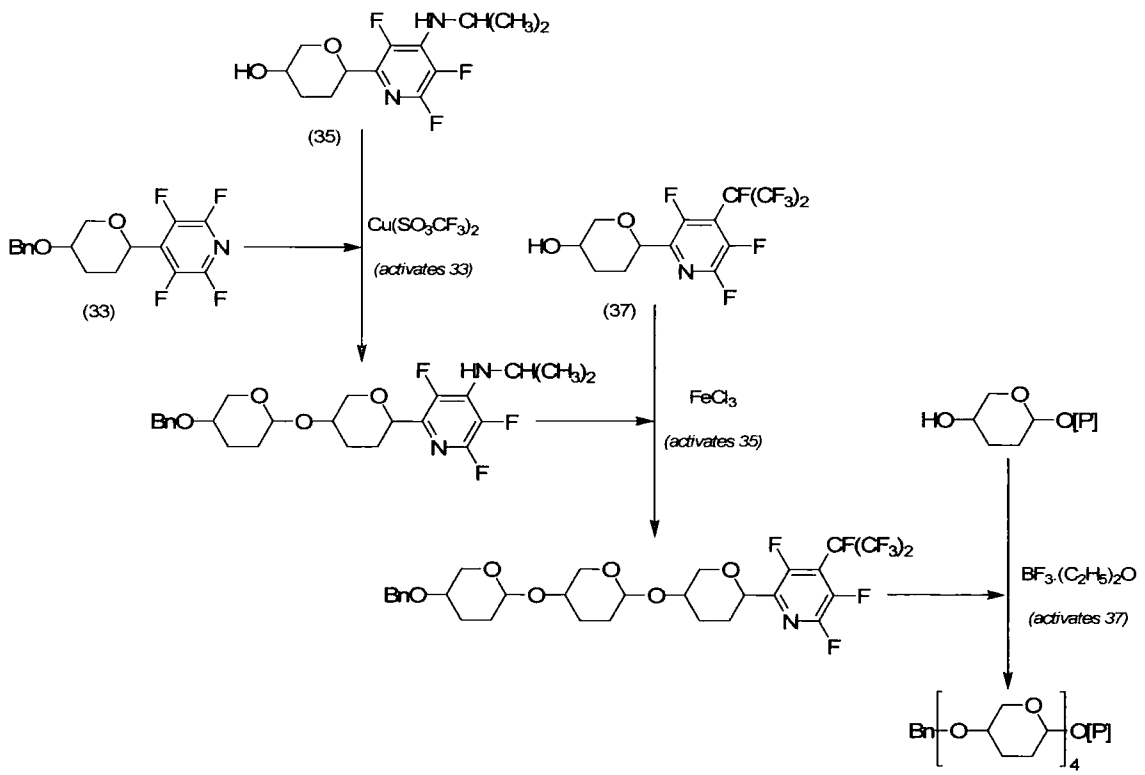


Figure 6.23. A schematic of an orthogonal glycosylation strategy using polyfluoro-pyridyl glycosyl donors.

In this proposed tetrasaccharide synthesis the anomeric substituents act as a protecting group until the correct Lewis acid is added to the reaction mixture. ^{19}F NMR spectroscopy would allow reaction monitoring, providing detailed information as to when to add the correct Lewis acid activator.

Unfortunately, time constraints have not allowed us to pursue this methodology for the synthesis of polysaccharides; however, initial indications are that this glycosylation strategy should allow the synthesis of polysaccharides in a controlled manner with good control of the stereochemistry of the glycosidic linkages.

6.5 Summary

In this chapter we have conducted a systematic study into the glycosylation capabilities of a novel family of glycosyl donors with a variety of substrates. The synthesis of compounds (**44**), (**45**) and (**55**) clearly demonstrates that the new class of donors synthesised in Chapter five are effective glycosyl donors providing excellent yields of coupled saccharides.

Probably the most important discovery during this investigation was that this class of donor does not appear to react *via* the standard S_N1 type glycosylation mechanism. Instead an S_N2 type glycosylation mechanism is observed, which can be confirmed by kinetic studies and stereochemical evidence, which provides high levels of stereoselectivity, enabling the selective synthesis of α or β glycosidic linkages. As discussed in Chapter two the stereoselective formation of glycosidic bonds is a key requirement for the effective synthesis of oligosaccharides which this class of donors has successfully fulfilled. It is also interesting to note that this class of donor provides stereoselectivity even when a non-participatory solvent (Section 2.2.2) is used which favours the formation of the opposite anomer, demonstrating the robustness of this approach.

The other prerequisite for an effective glycosylation methodology is that it must display a wide-range of reactivities under various conditions in order to access the chemoselective glycosylation strategies (Section 2.4). The small set of polyfluoro-pyridyl donors screened display variable reactivity over a factor of 100, ideally reactivity ranges over a factor of 1000 are desired.[150-153] However, from such a small sample set the relative reactivity range of 100 demonstrates the versatility of this class

of donors and it is expected that the analysis of a much larger set of donors would provide a range of reactivities over the preferred factor of 1000.

7 Summary of Polyfluoro-Pyridyl Glycosyl Donors

Carbohydrates are one of the most structurally and functionally diverse classes of naturally occurring compound and it is well established that they play a vital role in a vast array of biological processes. In spite of this, carbohydrates are the least exploited of the three major classes of biomolecules due to the difficulty of synthesising oligosaccharides with control of the chemo- and stereo-chemistry. As discussed in Chapter two, several efficient methodologies for the synthesis of glycosidic bonds are now available; however, these are generally unpredictable and characteristic to particular systems.

The purpose of this thesis was to develop a new glycosylation methodology that utilised heterocyclic leaving groups in glycosyl donors (Figure 7.1) in an attempt to address the limitations of the existing strategies.

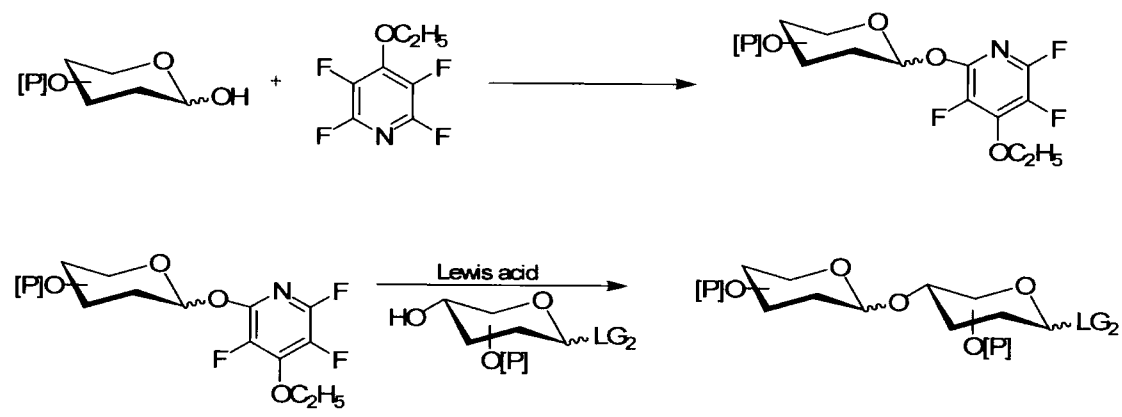


Figure 7.1. A schematic representation of the use of hetaryl glycosyl donors in oligosaccharide synthesis.

This approach required a simple procedure for the synthesis of a range of polyfunctional heterocyclic cores, along with a procedure for the attachment of a saccharide moiety to the heterocyclic ring. In Chapter three an approach utilising polyfluorinated heterocycles was proposed, which would allow the construction of such systems by nucleophilic aromatic substitution.

Since studies concerning the sequential nucleophilic substitution of highly fluorinated heterocycles have not been developed to any real extent, we conducted a systematic study into the chemistry of pentafluoropyridine (**1**) with a range of oxygen

and nitrogen centred nucleophiles (Chapter four). In general (**1**) was found to undergo nucleophilic aromatic substitution to provide mono-, di- and tri-substituted compounds with excellent control of the regiochemistry in excellent yields.

In general the synthesis of poly-substituted pyridines *via* nucleophilic aromatic substitution was demonstrated to be a versatile and effective synthetic strategy which allowed the synthesis of an array of highly substituted pyridine cores for the development of polyfluoro-pyridyl glycosyl donors.

Utilising the nucleophilic aromatic substitution methodology developed for the synthesis of poly-functional pyridines it was possible to develop a family of hetaryl glycosyl donors of the type shown in Figure 7.2. The synthesis of compounds (**33**) to (**40**) demonstrated that an appropriately protected glucose moiety could be grafted onto a substituted pyridine core *via* nucleophilic attack from a glucopyranosyl anion. This proved to be an efficient method for the synthesis of an array of polyfluoro-pyridyl glycosyl donors displaying a range of substituents on the pyridine ring (Figure 7.2)

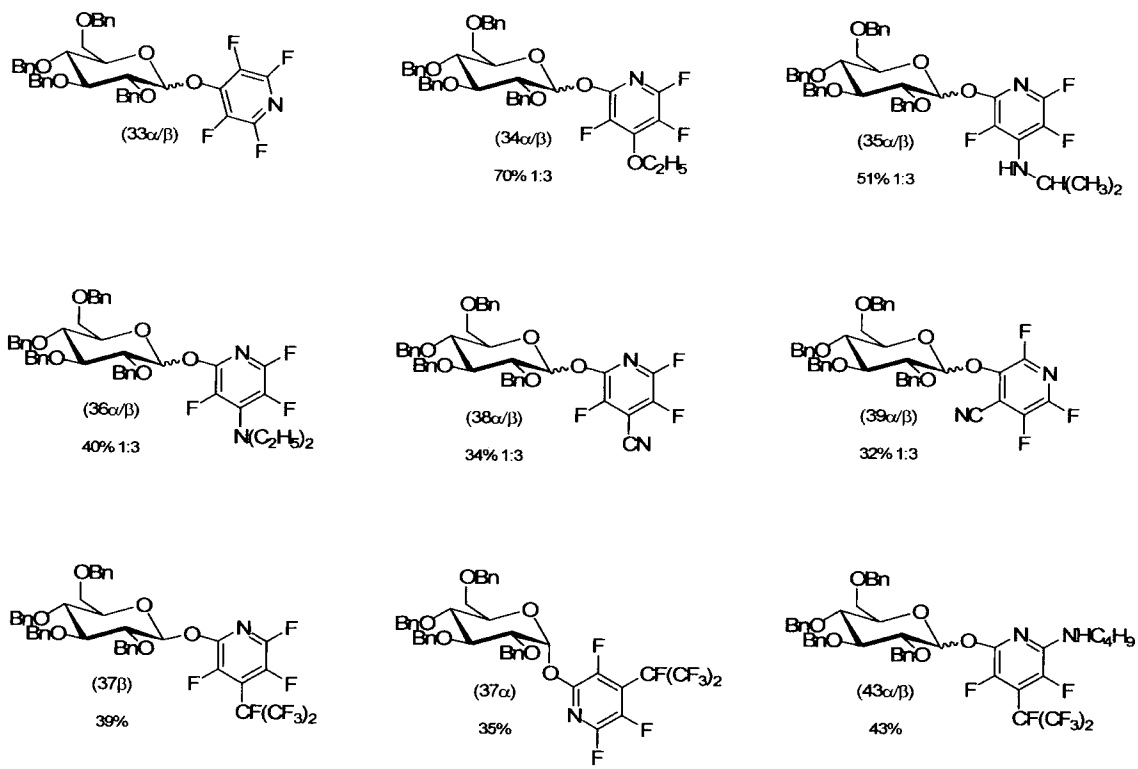


Figure 7.2. The polyfluoro-pyridyl glycosyl donors synthesised *via* this approach.

In order to determine the glycosyl donor properties of this class of donors a systematic study into their glycosylation capabilities was conducted with a variety of acceptors. The synthesis of compounds (**44**), (**45**) and (**55**) clearly demonstrate that polyfluoro-pyridyl glycosyl donors were effective in glycosylation reactions.

The most important discovery from this investigation was that the donors do not appear to react *via* the standard S_N1 glycosylation mechanism. Instead an S_N2 type mechanism is observed which provides inversion of the configuration of the anomeric carbon (C_1) on the glycosyl donor allowing the stereoselective formation of glycosidic bonds (Figure 7.3).

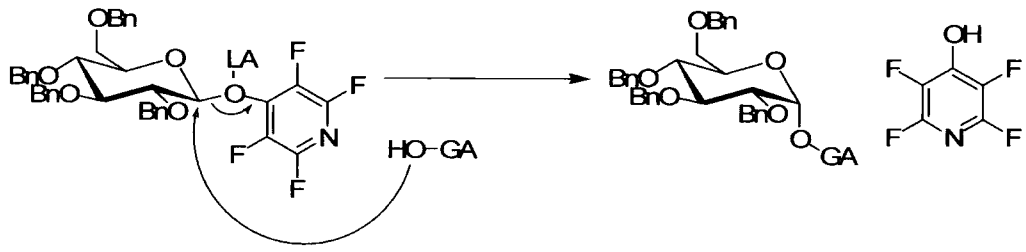


Figure 7.3. Proposed S_N2 mechanism for glycosylation utilising polyfluoro-pyridyl glycosyl donors.

Glycosyl donors of this type also display a moderate range of reactivities which are tuneable *via* alteration of the Lewis acid used and the substituents present on the pyridine ring. In principle, this range of reactivity should enables polyfluoro-pyridyl systems to utilise various multi-component glycosylation strategies to control the chemoselectivity during oligosaccharide synthesis.

Polyfluoro-pyridyl glycosyl donors display many advantages over existing glycosylation methodologies, primary due to the high levels of stereoselectivity observed when they are used in glycosylation reactions. They are simple to synthesise and stable for prolonged periods of time, illustrating their potential for commercial applications. The small set of donors investigated in this thesis appear to address many of the limitations observed with previous methodologies and provide a promising new approach for the synthesis of complex oligosaccharides.

8 Experimental

8.1 Instrumentation

Reagents

Unless otherwise stated, all chemicals were used as received from the suppliers: Aldrich, Apollo, Lancaster and Sigma. All solvents were dried according to literature procedures and column chromatography was performed using silica gel (particle size 0.040-0.063 mm).

High pressure flash chromatography

HPFC was performed on a Biotage Horizon flash chromatography system equipped with UV detector and solvent gradient modules.

Elemental analysis

Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser.

Gas liquid chromatography

Chromatographic analyses were performed on a Hewlett Packard 5890 Series II gas liquid chromatograph equipped with a 25 m cross-linked methyl silicone or 5% phenyl methyl silicone capillary with a flame ionisation detector.

Mass spectrometry

Mass spectra were recorded on a Fisions VG Trio 1000 mass spectrometer coupled with a Hewlett Packard 5890 Series II gas chromatograph (for EI^+) or a Micromass LTC (for ES^+).

Melting point analysis

Melting points were obtained using Gallenkamp melting point apparatus and are not corrected.

NMR spectroscopy

NMR spectra were recorded in deuteriochloroform as solvent, unless otherwise stated, utilising the following spectrometers: Varian Unity 300, Varian VXR 400S or Unity

Inova 500. ^{1}H spectra were recorded at 400 MHz, ^{13}C spectra were recorded at 100 MHz and ^{19}F NMR were recorded at 376 MHz. Reactions were monitored by ^{19}F NMR at 282 MHz. All spectra were obtained using either tetramethylsilane (TMS), chloroform, acetonitrile and/or trichlorofluoromethane as internal references. Coupling constants are given in Hertz.

COSY, HETCOR and DEPT spectra were recorded deuteriochloroform as solvent, unless otherwise stated, utilising a Unity Inova 500 spectrometer.

Optical Polorimetry

Optical rotations were recorded in chloroform utilising an Optical Activity AA-10 automatic polarimter using the D-line of sodium as the light source and a temperature of 20°C. The observed rotation was then used to calculate the specific rotation ($[\alpha]_D^{20}$) utilising the following equation:

$$[\alpha]_D^{20} = \frac{[\alpha]_{obs}}{lc}$$

$[\alpha]_D^{20}$	=	specific rotation	°
$[\alpha]_{obs}$	=	observed rotation	°
l	=	pathlength	dm
c	=	concentration	gdm^{-1}

X-ray analysis

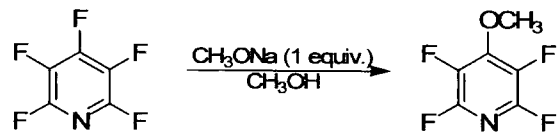
Crystal structures were obtained were collected at T=120°K using a Bruker SMART-CCD 6000 diffractometer. Structural elucidation (direct methods) and refinement by full matrix least squares on F^2 for all data using SHELLXTL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically.

Molecular Modelling

Molecular modelling calculations were carried out using CACHe worksystems version 6.1.1. Calculations were carried out by firstly optimising the molecular geometry of the molecule by performing a minimise gradient calculation in MOPAC using PM5 parameters. This was followed by the determination of the electron density isosurface of the molecule utilising PM5 parameters.

8.2 Experimental to Chapter 4

2,3,5,6-Tetrafluoro-4-methoxypyridine (2)

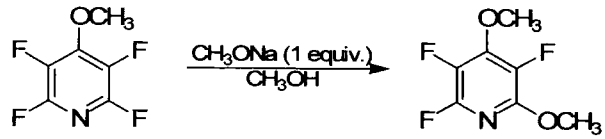


(1) (2)

Under an atmosphere of dry argon, sodium metal (0.410 g, 17.7 mmol) was added to methanol (20 mL) and stirred until hydrogen evolution subsided. The sodium methoxide solution was added dropwise to pentafluoropyridine (**1**) (3.000 g, 17.7 mmol) over 30 min. The reaction mixture was then heated at reflux temperature for 20h before cold water (50 mL) was added. The mixture was extracted with dichloromethane (4 x 20 mL), dried ($MgSO_4$) and evaporated to yield crude material (1.84 g). Distillation at reduced pressure yielded *2,3,5,6-tetrafluoro-4-methoxypyridine (2)* (1.72 g, 53 %) as a colourless oil; bp 28 °C, 0.85mbar. (Found: C, 39.7; H, 1.6; N, 7.6. $C_6H_3F_4NO$ requires C, 39.8; H, 1.7; N, 7.7%); δ_H 4.29 (3H, t, $^5J_{HF}$ 2.6, O*CH*$_3$); δ_C 61.6 (t, $^4J_{CF}$ 4.5, CH_3), 134.8 (ddm, $^1J_{CF}$ 248.8, $^2J_{CF}$ 23.6.7, C3), 144.4 (dtm, $^1J_{CF}$ 248.8, $^2J_{CF}$ 23.6, C2), 147.895 (m, C4); δ_F -91.44 (2F, m, 2-F), -160.48 (2F, m, 3-F); m/z (EI^+) 181 (M^+, 100), 180 (49), 151 (70), 138 (82), 132 (40), 100 (69), 93 (69), 74 (55), 31 (17); spectroscopic data is consistent with literature values.[51, 56, 155]

Under an atmosphere of dry argon, sodium metal (3.402 g, 0.15 mol) was added to methanol (165 mL) and stirred until hydrogen evolution subsided. The sodium methoxide solution was added dropwise, while stirring, to pentafluoropyridine (24.95 2 g, 0.15 mol) over 30 minutes, followed by heating at reflux temperature for 14h. The reaction mixture was allowed to cool to room temperature and neutralised with ion-exchange resin (Amberlite IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g), filtered and the filtrate concentrated under reduced pressure. Purification by reduced pressure distillation yielded *2,3,5,6-tetrafluoro-4-methoxypyridine (2)* (24.516 g, 91%) as a colourless oil. Spectroscopic data were consistent with previously recorded results.

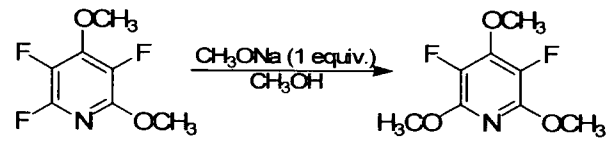
2,3,5-Trifluoro-4,6-dimethoxypyridine (3)



(2) (3)

Sodium metal (1.272 g, 55.2 mmol) was added to methanol (50 mL) under an argon atmosphere and stirred at room temperature until hydrogen evolution was complete. The methoxide solution was then added dropwise to 2,3,5,6-tetrafluoro-4-methoxypyridine (**2**) (9.992 g, 55.2 mmol) with stirring over 30 minutes; the resulting mixture was heated at reflux temperature over 15h. Water (50 mL) was added and the mixture extracted in dichloromethane (4 x 20 mL), the organic extracts were dried ($MgSO_4$) and evaporated to give a crude product which was purified by reduced pressure distillation to yield *2,3,5-trifluoro-4,6-dimethoxypyridine (3)* as a colourless liquid (5.582 g, 52%); bp 29 °C, 0.9 mbar; (Found C, 43.7; H, 3.3; N, 7.1. $C_7H_6F_3NO_2$ requires C, 43.5; H, 3.1; N, 7.3%); δ_H 3.93 (3H, s, 2-O*CH*$_3$), 4.20 (3H, t, $^5J_{HF}$ 2.6, 4-O*CH*$_3$); δ_C 54.6 (s, 2-O*CH*$_3$), 61.5 (t, $^4J_{CF}$ 4.3, 4-O*CH*$_3$), 132.1 (dd, $^1J_{CF}$ 246.3, $^2J_{CF}$ 19.3, C3), 136.1 (dd, $^1J_{CF}$ 246.3, $^3J_{CF}$ 6.5, C5), 145.0 (ddd, $^1J_{CF}$ 246.3, $^2J_{CF}$ 19.3, $^4J_{CF}$ 4.3, C2), 146.291 (m, C6), 146.589 (tm, $^2J_{CF}$ 19.3, C4); δ_F -94.39 (1F, t, $^{3/5}J_{FF}$ 23.2, 2-F), -161.72 (1F, d, $^5J_{FF}$ 23.2, 5-F), -168.11 (1F, d, $^3J_{FF}$ 23.2, 3-F); m/z (EI^+) 193 (M^+, 100), 192 (62), 164 (80), 163 (40), 162 (14), 150 (31)); spectroscopic data is consistent with literature values.[36, 51, 56]

3,5-Difluoro-2,4,6-trimethoxypyridine (4)

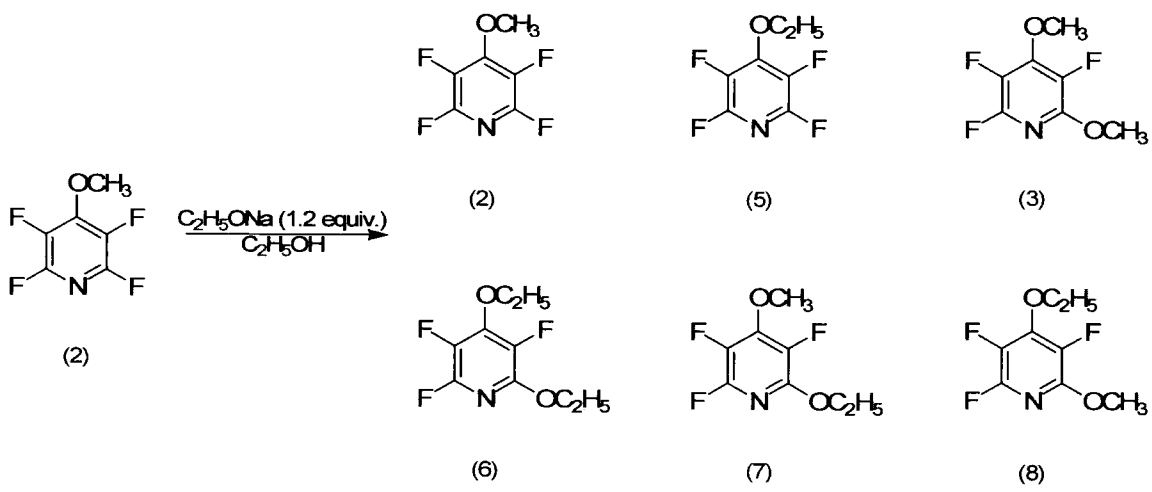


(3) (4)

Sodium methoxide (0.281 g, 5.2 mmol) in methanol (10 mL) was added to 2,4-dimethoxy-3,5,6-trifluoropyridine (**3**) (1.021 g, 5.3 mmol) over 30 minutes and the

mixture stirred at reflux temperature for 65h. Water (25 mL) was added and the mixture was extracted into dichloromethane (4 x 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give a crude product which was purified by sublimation at 40 °C, 1.2 mbar to yield *3,5-difluoro-2,4,6-trimethoxypyridine (4)* (0.214 g, 20%) as a white crystalline solid; mp 52-53°C. (Found: C, 46.6; H, 4.3; N, 6.7. $C_8H_9F_2NO_3$ requires C, 46.8; H, 4.4; N, 6.8%); δ_H 4.15 (3H, t, $^5J_{HF}$ 2.4, 4-O*CH*$_3$), 3.95 (6H, s, 2/6-O*CH*$_3$); δ_C 54.0 (s, 2/6 O*CH*$_3$), 61.4 (t, $^4J_{CF}$ 3.9, 4-O*CH*$_3$), 133.7 (d, $^1J_{CF}$ 248.5, C3), 145.1 (t, $^2J_{CF}$ 9.9, C4), 146.1 (dd, $^2J_{CF}$ 9.9, $^4J_{CF}$ 3.9, C-2); δ_F -169.05 (2F, m, 3-F); m/z (EI^+) 205 (M^+, 100), 175 (29), 162 (60), 132 (20), 116 (34), 105 (40), 100 (18), 87 (21), 70 (21).

Reaction of 2,3,5,6-tetrafluoro-4-methoxypyridine (2) with sodium ethoxide



General Procedure. Under an argon atmosphere, sodium metal was added to a solution of ethanol (40 mL) and stirred until hydrogen evolution had subsided. The sodium ethoxide solution was added dropwise to 2,3,5,6-tetrafluoro-4-methoxypyridine (**2**) over 30 minutes at room temperature; the resulting mixture was heated at reflux temperature for 20h before being cooled to room temperature and water (50 mL) added. Extraction into dichloromethane (4 x 20 mL) enabled recovery of products. The organic phase was dried ($MgSO_4$) and the solvent removed on a rotary evaporator to give a crude product.

Solvent: ethanol. Sodium (0.635 g, 27.6 mmol) and 2,3,5,6-tetrafluoro-4-methoxy-pyridine (5.021 g, 27.6 mmol), yielded crude material (5.66 g) shown to contain 6

components by analytical g.l.c and ^{19}F NMR (ratio of peaks 4:3:5:10:76:1 corresponding *2,3,5,6-tetrafluoro-4-methoxypyridine (2)*, *4-ethoxy-2,3,5,6-tetrafluoropyridine (5)*, *2,3,5-trifluoro-4,6-dimethoxypyridine (3)*, *2,4-diethoxy-3,5,6-trifluoropyridine (6)*, *2-ethoxy-3,5,6trifluoro-4-methoxypyridine (7)* and *4-ethoxy-2,3,5-trifluoro-6-methoxypyridine (8)* respectively, which were identified by NMR spectroscopy, mass spectrometry and/or comparison to authentic samples. No further separation was attempted.

2,3,5,6-tetrafluoro-4-methoxypyridine (2). δ_F -91.6 (2F, m, 2-F), -160.8 (2F, m, 3-F); m/z (EI^+) 181 (M^+, 100), 151 (11), 138 (23), 100 (15), 91 (15), 74 (11), 59 (32), 43 (32), 31 (15).

4-ethoxy-2,3,5,6-tetrafluoropyridine (5). δ_F -91.82 (2F, m, 2-F), -160.31 (2F, m, 3-F); m/z (EI^+) 195 (M^+, 22), 181 (17), 167 (100), 119 (18), 93 (11), 29 (20).

2,3,5-trifluoro-4,6-dimethoxypyridine (3). δ_F -94.89 (1F, t, 2-F), -162.11 (1F, d, 5-F), -168.47 (1F, d, 3-F); m/z (EI^+) 193 (M^+, 100), 192 (69), 164 (94), 163 (65), 150 (35), 116 (22), 93 (21), 74 (27).

2,4-diethoxy-3,5,6-trifluoropyridine (6). δ_F -94.89 (1F, t, 6-F), -161.08 (1F, d, 3-F), -168.17 (1F, d, 5-F); m/z (EI^+) 221 (M^+, 25), 207 (30), 193 (33), 179 (69), 165 (100).

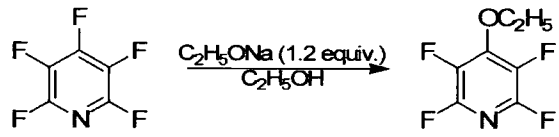
2-ethoxy-3,5,6trifluoro-4-methoxypyridine (7). δ_F -94.71 (1F, t, 6-F), -161.78 (1F, dd, 3-F), -168.79 (1F, dd, 5-F); m/z (EI^+) 207 (M^+, 32), 179 (100), 151 (34), 136 (48).

4-ethoxy-2,3,5-trifluoro-6-methoxypyridine (8). δ_F -94.71 (1F, t, 2-F), -161.41 (1F, d, 5-F), -167.86 (1F, d, 3-F); m/z (EI^+) 207 (M^+, 32), 179 (100), 151 (34), 136 (48).

Spectroscopic results are consistent with recorded results for these compounds.

Solvent: THF. Sodium (0.649 g, 28.2 mmol), ethanol (1.300 g, 28.2 mmol) and 2,3,5,6-tetrafluoro-4-methoxypyridine (4.942 g, 27.3 mmol), gave crude material (4.54 g) shown to contain 6 components by analytical g.l.c and ^{19}F NMR (ratio of peaks 5:3:18:9:61:3) corresponding to corresponding *2,3,5,6-tetrafluoro-4-methoxypyridine (2)*, *4-ethoxy-2,3,5,6-tetrafluoropyridine (5)*, *2,3,5-trifluoro-4,6-dimethoxypyridine (3)*, *2,4-diethoxy-3,5,6-trifluoropyridine (6)*, *2-ethoxy-3,5,6trifluoro-4-methoxypyridine (7)* and *4-ethoxy-2,3,5-trifluoro-6-methoxypyridine (8)* respectively.

4-Ethoxy-2,3,5,6-tetrafluoropyridine (5)

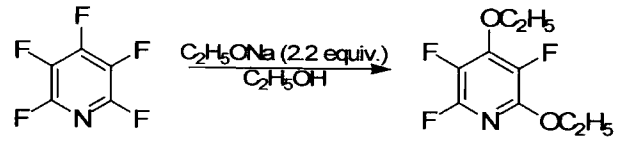


(1) (5)

Sodium metal (0.188 g, 8.2 mmol) was added to ethanol (10 mL) under an argon atmosphere and stirred at room temperature until hydrogen evolution was complete. The ethoxide solution was added to a stirred solution of pentafluoropyridine (**1**) (1.459 g, 8.6 mmol) over 30 min at room temperature; the resulting mixture was heated at reflux temperature for 3h before water (25 mL) was added. The mixture was extracted with dichloromethane (4 x 10 mL), dried ($MgSO_4$) and evaporated affording a liquid (1.80 g). Kugelrohr distillation yielded *4-ethoxy-2,3,5,6-tetrafluroropyridine (5)* (0.872 g, 55%) as a colourless liquid; bp 28 °C 2.4 mbar. (Found: C, 43.0; H, 2.5; N, 7.3. $C_7H_5F_4NO$ requires C, 43.1; H, 2.6; N, 7.2%); δ_H 1.84 (3H, t, $^3J_{HH}$ 7.2 , OCH_2CH_3), 4.94 (2H, qt, $^3J_{HH}$ 7.2, $^5J_{HF}$ 1.6, OCH_2CH_3); δ_C 15.6 (s, OCH_2CH_3), 70.8 (t, $^4J_{CF}$ 4.6, OCH_2CH_3), 135.1 (dm, $^1J_{CF}$ 246.2, C3), 144.40 (dm, $^1J_{CF}$ 246.2, C2), 147.3 (m, C4); δ_F -91.53 (2F, m, 2-F), -159.89 (2F, m, 3-F); m/z (EI^+) 195 (M^+, 82), 168 (24), 167 (100), 138(27), 119 (65), 100 (28), 93 (26), 74 (30), 29 (57), 27 (32).

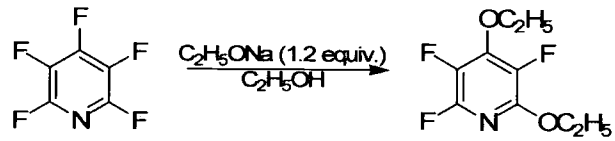
Under an atmosphere of dry argon, sodium metal (3.136 g, 0.14 mol) was added to methanol (130 mL) and stirred until hydrogen evolution subsided. The sodium methoxide solution was added to pentafluoropyridine (20.699 g, 0.12 mol) over 30 min at room temperature; the resulting mixture was heated at reflux temperature for 20h before Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 2.00 g) was added. The mixture was filtered and evaporated affording a liquid. Reduced pressure distillation yielded *4-ethoxy-2,3,5,6-tetrafluoropyridine (5)* (19.899 g, 85%) as a colourless oil. Spectroscopic data were consistent with previously recorded results.

2,4-Diethoxy-3,5,6-trifluoropyridine (6)



(1) (6)

Sodium metal (1.403 g, 60.9 mmol) was added to ethanol (25 mL) under an atmosphere of dry argon and stirred until hydrogen evolution was complete. The sodium ethoxide solution was added to pentafluoropyridine (**1**) (4.936 g, 29.2 mmol) over 30 minutes. The resulting mixture was heated at reflux temperature for 20h before water (50 mL) was added and the mixture extracted into dichloromethane (4 x 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give a crude product which was purified by reduced pressure distillation yielding *2,4-diethoxy-3,5,6-trifluoropyridine (6)* (4.859 g, 75%) as a colourless liquid; bp 42 °C 1.1 mbar; (Found C, 48.9; H, 4.5; N, 6.4. $C_9H_{10}F_3NO_2$ requires C, 48.9; H, 4.6; N, 6.3%); δ_H 1.39 (3H, t, $^3J_{HH}$ 7.0 , 2-OCH_2CH_3), 1.44 (3H, t, $^3J_{HH}$ 7.0, 4-OCH_2CH_3), 4.33 (2H, q, $^3J_{HH}$ 7.0, 2-OCH_2CH_3), 4.48 (2H, qt, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.5, 4-OCH_2CH_3); δ_C 14.5 (s, 2-OCH_2CH_3), 15.6 (s, 4-OCH_2CH_3), 63.4 (s, 2-OCH_2CH_3), 70.2 (t, $^4J_{CF}$ 3.1, 4-OCH_2CH_3), 132.2 (dd, $^1J_{CF}$ 245.8, $^2J_{CF}$ 22.1, C5), 136.3 (dd, $^1J_{CF}$ 245.8, $^3J_{CF}$ 6.9, C3), 144.8 (ddd, $^1J_{CF}$ 245.8, $^2J_{CF}$ 22.1, $^4J_{CF}$ 3.1, C6), 145.5 (m, C2), 146.1 (tm, $^2J_{CF}$ 22.1, C4), δ_F -94.50 (1F, t, $^{3/5}J_{FF}$ 23.6, 6-F), -160.70 (1F, d, $^5J_{FF}$ 23.6, 3-F), -167.79 (1F, d, $^3J_{FF}$ 23.6, 5-F); m/z (EI^+) 221 (M^+, 50), 206 (40), 193 (58), 178 (35), 165 (85), 148 (34), 145 (38), 137 (100), 116 (69), 93 (44), 74 (31), 29 (44).

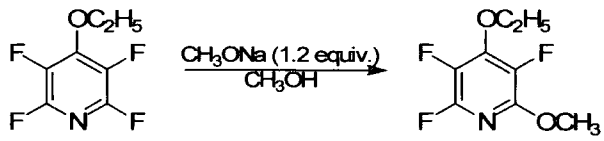


(5) (6)

Under an atmosphere of dry argon, sodium metal (0.232 g, 9.7 mmol) was added to methanol (5 mL) and stirred until hydrogen evolution subsided. The sodium methoxide solution was added to 4-ethoxy-2,3,5,6-tetrafluoropyridine (**5**) (1.503 g, 7.7 mmol) over

30 min at room temperature; the resulting mixture was heated at reflux temperature for 17h before Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added. The mixture was filtered and evaporated affording a liquid. Reduced pressure distillation yielded *2,4-diethoxy-3,5,6-trifluoropyridine (6)* (1.483 g, 87%) as a colourless oil. Spectroscopic data were consistent with previously recorded results.

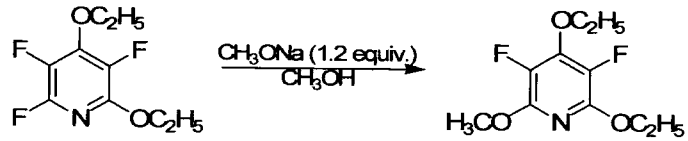
4-Ethoxy-2,3,5-trifluoro-6-methoxypyridine (8)



(5) (8)

Sodium metal (0.425 g, 18.5 mmol) was added to methanol (20 mL) with stirring under an atmosphere of dry argon until hydrogen evolution had subsided. This solution was then added dropwise over 30 minutes to 4-ethoxy-2,3,5,6-tetrafluoropyridine (**5**) (3.587 g, 18.4 mmol). The mixture was heated at reflux temperature for 17h before being cooled to room temperature and water (50 mL) added. Extraction into dichloromethane (4 x 20 mL) enabled recovery of the products. The organic phase was dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. Reduced pressure distillation gave *4-ethoxy-2,3,5-trifluoro-6-methoxypyridine (8)* (1.776 g, 47%) as a colourless oil; bp 84 °C 10.0 mbar; (Found C, 46.3; H, 3.9; N, 6.9. $C_8H_8F_3NO_2$ requires C, 46.4; H, 3.9; N, 6.8%); δ_H 1.41 (3H, t, $^3J_{HH}$ 7.0 , OCH_2CH_3), 3.89 (3H, s, OCH_3), 4.45 (2H, qt, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.5, OCH_2CH_3); δ_C 15.4 (s, OCH_2CH_3), 54.4 (s, OCH_3), 70.2 (t, $^4J_{CF}$ 4.4, OCH_2CH_3), 132.3 (dd, $^1J_{CF}$ 246.1, $^2J_{CF}$ 22.1, C5), 136.3 (dd, $^1J_{CF}$ 246.1, $^3J_{CF}$ 13.7, C3), 144.9 (ddd, $^1J_{CF}$ 246.1, $^2J_{CF}$ 22.1, $^4J_{CF}$ 4.4, C2), 145.5 (dt, $^2J_{CF}$ 22.1, $^3J_{CF}$ 13.7, C4), 146.4 (ddd, $^2J_{CF}$ 22.1, $^3J_{CF}$ 13.7, $^4J_{CF}$ 4.4, C2), δ_F -94.67 (1F, t, $^{3/5}J_{FF}$ 23.5, 2-F); -161.00 (1F, $^3J_{FF}$ 23.5, 3-F), -167.59 (1F, d, $^5J_{FF}$ 23.5, 5-F); m/z (EI^+) 207 (M^+, 66), 179 (40), 178 (52), 149 (100), 136 (15), 131 (26), 100 (21), 74 (17), 29 (28).

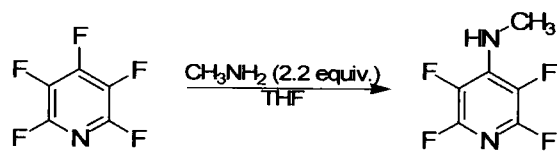
2,4-Diethoxy-3,5-difluoro-6-methoxypyridine (9)



(6) (9)

Under an atmosphere of dry argon, sodium metal (0.227 g, 9.9 mmol) was added to methanol (20 mL) and stirred until hydrogen evolution had subsided. The sodium ethoxide solution was added dropwise to 2,4-diethoxy-3,5,6-trifluoropyridine (**6**) (2.158 g, 9.8 mmol) over 30 minutes. The mixture was heated at reflux temperature for 71h before being cooled to room temperature and water (50 mL) added. Extraction into dichloromethane (2 x 20 mL), enabled recovery of products, the organic phase was dried ($MgSO_4$) and the solvent removed on a rotary evaporator. Sublimation at 42 °C, 0.6 mbar gave *2,4-diethoxy-3,5-difluoro-6-methoxypyridine (**9**)* (1.172 g, 52 %) as a white crystalline solid; mp 33-34 °C; (Found C, 51.2; H, 5.6; N, 6.0. $C_{10}H_{13}F_2NO_3$ requires C, 51.5; H, 5.6; N, 6.0%); δ_H 1.38 (3H, t, $^3J_{HH}$ 7.1, 2-OCH_2CH_3), 1.39 (tt, 3H, $^3J_{HH}$ 7.1, $^6J_{HF}$ 0.5, 4-OCH_2CH_3), 3.90 (3H, s, 6-OCH_3), 4.35 (2H, q, $^3J_{HH}$ 7.1, 2-OCH_2CH_3), 4.38 (2H, qt, $^3J_{HH}$ 7.1, $^5J_{HF}$ 1.4, 4-OCH_2CH_3); δ_C 14.7 (s, 2-OCH_2CH_3), 15.5 (s, 4-OCH_2CH_3), 53.7 (s, 6-OCH_3), 62.4 (s, 2-OCH_2CH_3), 69.8 (t, $^4J_{CF}$ 4.2, 4-OCH_2CH_3), 133.8 (d, $^1J_{CF}$ 247.9, C5), 134.0 (d, $^1J_{CF}$ 247.9, C3) 144.2 (t, $^2J_{CF}$ 10.2, C4), 145.8 (m, C2/6); δ_F -167.9 (1F, s, 5-F), -168.6 (1F, s, 3-F); m/z (EI^+) 233 (M^+, 71), 205 (44), 177 (71), 176 (82), 148 (100), 29 (22).

2,3,5,6-Tetrafluoro-N-methylpyridin-4-amine (10)

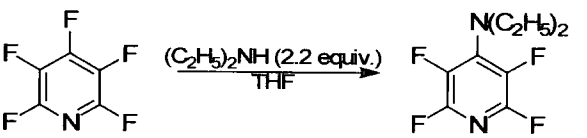


(1) (10)

A solution of methylamine (60 mL, 2.0 $moldm^{-3}$ solution in THF, 0.12 mol) in THF (50 mL), was added dropwise to pentafluoropyridine (**1**) (10.043 g, 59.4 mmol) at room

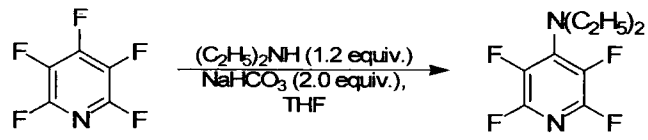
temperature over 30 minutes and the resulting mixture was stirred at room temperature for 28h. Water (50 mL) was added and the mixture extracted in dichloromethane (4 x 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated to give a crude product which was purified by recrystallisation from propan-2-ol yielding *2,3,5,6-tetrafluoro-N-methylpyridin-4-amine (**10**)* (6.60 g, 62%) as a white crystalline solid; mp 83-84 °C; (Found: C, 40.0; H, 2.3; N, 15.5. $C_6H_4F_4N_2$ requires C, 40.0; H, 2.3; N, 15.6%); δ_H 3.24 (3H, t, $^5J_{HF}$ 2.4, HN*CH*$_3$), 4.59 (1H, br s, *H*NCH$_3$); δ_C 32.3 (s, N*CH*$_3$), 131.4 (dm, $^1J_{CF}$ 242.4, C3), 138.64 (m, C4), 144.4 (dm, $^1J_{CF}$ 242.4, C2); δ_F -95.00 (2F, m, 2-F), -165.65 (2F, m, 3-F); m/z (EI$^+$) 180 (M$^+$, 85), 179 (100), 139 (31), 132 (79), 100 (22), 90 (15), 82 (34), 31 (16).

N,N-Diethyl-2,3,5,6-tetrafluoropyridin-4-amine (11)



(1) (11)

A solution of diethylamine (17.306 g, 0.24 mol), in acetonitrile (100 mL) was added dropwise to pentafluoropyridine (**1**) (20.025 g, 0.12 mol) at room temperature over 30 minutes and the resulting mixture was heated at reflux temperature for 16h. Water (50 mL) was added and the mixture extracted in dichloromethane (4 x 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated to give a crude product which was purified by reduced pressure distillation to yield *N,N-diethyl-2,3,5,6-tetrafluoropyridin-4-amine (**11**)* (19.262 g, 81%) as a colourless liquid; bp 52 °C, 1.5 mbar; (Found: C, 48.6; H, 4.5; N, 12.7. $C_9H_{10}F_4N_2$ requires C, 48.7; H, 4.5; N, 12.6%); δ_H 1.22 (6H, t, $^3J_{HH}$ 7.0, NCH$_2$*CH*$_3$), 3.43 (4H, qt, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.6, N*CH*$_2$CH$_3$); δ_C 13.9 (s, NCH$_2$*CH*$_3$), 46.7 (t, $^4J_{CF}$ 5.0, N*CH*$_2$CH$_3$), 134.5 (ddm, $^1J_{CF}$ 245.9, $^2J_{CF}$ 22.7 C3), 139.5 (m, C4), 145.3 (dtm, $^1J_{CF}$ 245.9, $^2J_{CF}$ 12.7, C2); δ_F -95.06 (2F, m, 2-F), -156.71 (2F, m, 3-F); m/z (EI$^+$) 222 (M$^+$, 23), 207 (82), 193 (10), 179 (100), 177 (11), 100 (9), 29 (27), 28 (22).

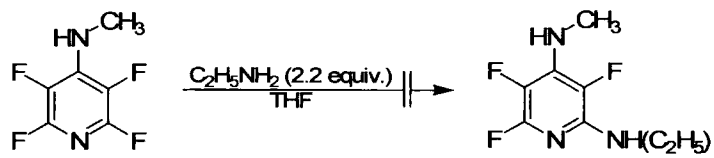


(1) (11)

A solution of diethylamine (0.836 g, 11.4 mmol), in THF (5 mL) was added dropwise to a solution of pentafluoropyridine (**1**) (2.025 g, 12.0 mmol) and sodium hydrogen carbonate (1.928 g, 22.9 mmol), in THF (5 mL), at room temperature over 30 minutes. The mixture was heated at reflux temperature for 15h before being cooled to room temperature. Water (50 mL) was added and the mixture extracted into dichloromethane (4 x 20 mL). The organic extracts were dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. Purification by reduced pressure distillation yielded *N,N-diethyl-2,3,5,6-tetrafluoropyridin-4-amine (11)* (2.241 g, 89%) as a colourless oil, spectroscopic data was consistent with previously recorded results.

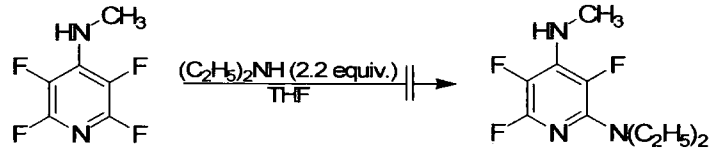
Attempted reaction of 2,3,4,5-tetrafluoro-N-methylpyridin-4-amine (10)

General procedure. The amine nucleophile in THF (50 mL) was added to 2,3,5,6-tetrafluoro-N-methylpyridin-4-amine (**10**) in a dropwise manner over 30 minutes. The resulting solution was heated at reflux temperature before water (50 mL) was added. The mixture was extracted with dichloromethane (4 x 20 mL), dried ($MgSO_4$) and concentrated to yield crude material which was analysed by ^{19}F NMR and gas chromatography mass spectrometry.



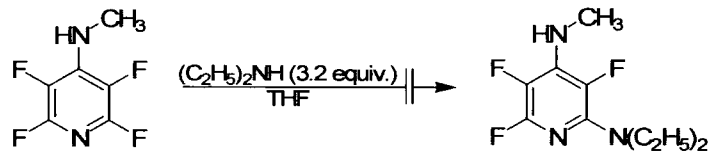
(10) (12)

Amine: ethylamine. Ethylamine (11 mL of 2.0 M solution in THF, 21.0 mmol) and 2,3,5,6-tetrafluoro-N-methylpyridin-4-amine (**10**) (1.882 g, 10.5 mmol) were stirred at reflux temperature for 22h gave *2,3,5,6-tetrafluoro-N-methylpyridin-4-amine (10)* (1.684 g, 89% recovery). Spectral data was consistent with previous results.



(10) (13)

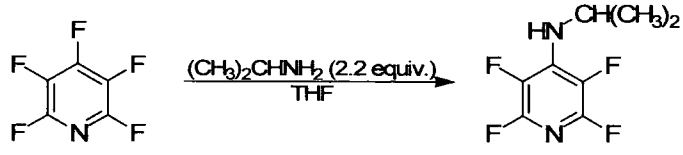
Amine: diethylamine. Diethylamine (0.843 g, 11.5 mmol) and 2,3,5,6-tetrafluoro-N-methylpyridin-4-amine (**10**) (1.013 g, 5.6 mmol) were stirred at reflux temperature for 24h gave *2,3,5,6-tetrafluoro-N-methylpyridin-4-amine (**10**)* (0.750 g, 74% recovery).



(10) (13)

Amine: diethylamine. Diethylamine (1.241 g, 17.0 mmol) and 2,3,5,6-tetrafluoro-N-methylpyridin-4-amine (**10**) (1.022 g, 5.7 mmol) were stirred at reflux temperature for 24h gave *2,3,5,6-tetrafluoro-N-methylpyridin-4-amine (**10**)* (0.858 g, 84% recovery).

2,3,5,6-Tetrafluoro-N-*iso*propylpyridin-4-amine (15)



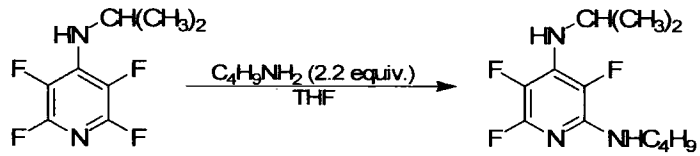
(1) (15)

A solution of *iso*propylamine (6.993 g, 0.12 mol) in acetonitrile (50 mL) was added dropwise to pentafluoropyridine (**1**) (9.962 g, 58.9 mmol) at room temperature over 30 minutes and the resulting mixture was stirred at room temperature for 16h. Water (50 mL) was added and the mixture extracted in dichloromethane (4 x 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated to give a crude product which was purified by reduced pressure distillation to yield *2,3,5,6-tetrafluoro-N-isopropylpyridin-4-amine (**15**)* (11.029 g, 90%) as a colourless liquid; bp 62 °C, 2.4 mbar; (Found: C, 46.0; H, 3.9;

N, 13.5. $C_8H_8F_4N_2$ requires C, 46.2; H, 3.9; N, 13.5%); δ_H 1.28 (6H, t, $^3J_{HH}$ 6.3, HNCH(CH_3)$_2$), 4.13 (1H, sext, $^3J_{HH}$ 6.3, HNCH(CH$_3$)$_2$), 4.38 (1H, Br s, HNCH(CH$_3$)$_2$); δ_C 24.0 (s, HNCH(CH_3)$_2$), 46.6 (t, $^4J_{CF}$ 8.7, HNCH(CH$_3$)$_2$), 131.0 (ddm, $^1J_{CF}$ 242.4, $^2J_{CF}$ 24.0 C3), 137.1 (m, C4), 144.4 (dtm, $^1J_{CF}$ 242.4, $^2J_{CF}$ 24.0, C2); δ_F -95.15 (2F, m, 2-F), -164.80 (2F, m, 3-F); m/z (EI$^+$) 208 (M$^+$, 77), 193 (100), 166 (61), 153 (52), 146 (56), 100 (58), 97 (54), 43 (52), 41 (54).

A solution of *iso*propylamine (7.693 g, 0.13 mol) in THF (50 mL) was added dropwise to pentafluoropyridine (**1**) (9.999 g, 59.1 mmol) at room temperature over 30 minutes and the resulting mixture was stirred at room temperature for 20h. Amberlite resin IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed. Reduced pressure distillation yielded *2,3,5,6-tetrafluoro-N-isopropylpyridin-4-amine (15)* (11.503 g, 94%) as a colourless oil. Spectroscopic data were consistent with previously recorded results.

N^2-Butyl-3,5,6-trifluoro-N^4-*iso*propylpyridine-2,4-diamine (16)

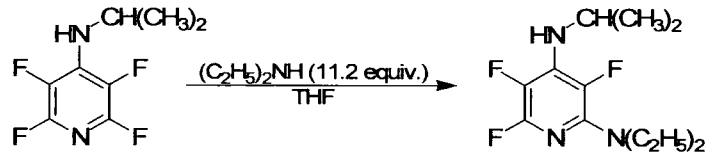


(15) (16)

A solution of butylamine (2.214 g, 30.3 mol) in THF (15 mL) was added dropwise to 2,3,5,6-tetrafluoro-N-*iso*propylpyridin-4-amine (**15**) (2.019 g, 9.7 mmol) at room temperature over 30 minutes and the resulting mixture was heated at reflux temperature for 72h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by reduced pressure distillation yielded *N^2-butyl-3,5,6-trifluoro-N^4-isopropylpyridine-2,4-diamine (16)* (1.832 g, 72%) as a colourless oil; bp 120-121 °C, 2.6 mbar; (Found: C, 55.0; H, 7.0; N, 16.2. $C_{12}H_{18}F_3N_3$ requires C, 55.2; H, 6.9; N, 16.1%); δ_H 0.92 (3H, t, $^3J_{HH}$ 7.1, HN(CH$_2$)$_3$$CH_3$), 1.22 (6H, d, $^3J_{HH}$ 7.1, HNCH(CH_3)$_2$), 1.38 (2H, hextet, $^3J_{HH}$ 7.1,

$HN(CH_2)_2CH_2CH_3$), 1.54 (2H, pentet, $^3J_{HH}$ 7.1, $NHCH_2CH_2CH_2CH_3$), 3.32 (2H, t, $^3J_{HH}$ 7.1, $NHCH_2(CH_2)_2CH_3$), 3.85 (1h, br s, NHC_4H_9), 4.02 (1H, m, $NHCH(CH_3)_2$), 4.18 (1H, br s, $NHCH(CH_3)_2$); δ_C 14.0 (s, $NH(CH_2)_3CH_3$), 20.2 (s, $NH(CH_2)_2CH_2CH_3$), 24.1 (s, $NHCH(CH_3)_2$), 32.1 (s, $NHCH_2CH_2CH_2CH_3$), 41.0 (s, $NHCH_2(CH_2)_2CH_3$), 46.2 (t, $^4J_{CF}$ 2.5 $NHCH(CH_3)_2$), 126.6 (ddd, $^1J_{CF}$ 233.2, $^2J_{CF}$ 21.8, $^3J_{CF}$ 6.4, C5), 131.9 (dd, $^1J_{CF}$ 233.2, $^3J_{CF}$ 6.4, C3), 133.6 (m, C4), 141.5 (ddd, $^2J_{CF}$ 21.8, $^3J_{CF}$ 6.4, $^4J_{CF}$ 2.4, C2), 146.7 (ddd, $^1J_{CF}$ 233.2, $^2J_{CF}$ 21.8, $^4J_{CF}$ 2.5, C6); δ_F -97.19 (1F, t, $^{3/5}J_{FF}$ 24.2, 6-F), -167.27 (1F, d, $^5J_{FF}$ 24.2, 3-F) ,-176.38 (1F, d, $^3J_{FF}$ 24.2, 5-F); m/z (EI^+) 261 (M^+, 70), 246 (25), 232 (21), 219 (28), 218 (100), 205 (131), 190 (69), 176 (99), 102 (26), 41 (28).

N^2,N^2-Diethyl-3,5,6-trifluoro-N^4-*iso*propylpyridine-2,4-diamine (17)

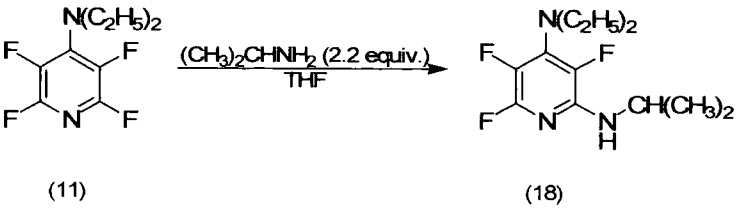


(15) (17)

A solution of diethylamine (7.907 g, 108.1 mmol) in THF (15 mL) was added dropwise to 2,3,5,6-tetrafluoro-N-*iso*propylpyridin-4-amine (**15**) (2.017 g, 9.7 mmol) at room temperature over 30 minutes and the resulting mixture was heated at reflux temperature for 10 days. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by reduced pressure distillation yielded *N^2,N^2-diethyl-3,5,6-trifluoro-N^4-isopropylpyridine-2,4-diamine (17)* (0.668 g, 26%) as a colourless oil; bp 91 °C, 2.9 mbar; (Found: C, 55.3; H, 6.8; N, 16.1. $C_{12}H_{18}F_3N_3$ requires C, 55.2; H, 6.9; N, 16.1%); δ_H 1.13 (6H, t, $^3J_{HH}$ 6.8, NCH_2CH_3), 1.22 (6H, d, $^3J_{HH}$ 6.8, $HNCH(CH_3)_2$), 3.35 (4H, qt, $^3J_{HH}$ 6.8, $^5J_{HF}$ 1.5, NCH_2CH_3), 3.89 (1H, br s, $NHCH(CH_3)_2$), 4.04 (1H, sext, $^3J_{HH}$ 6.8, $^5J_{HF}$ 1.5, $HNCH(CH_3)_2$); δ_C 13.8 (s, NCH_2CH_3), 24.2 (s, $HNCH(CH_3)_2$), 44.1 (d, $^4J_{CF}$ 4.3, $NHCH_2CH_3$), 46.2 (t, $^4J_{CF}$ 4.3 $HNCH(CH_3)_2$), 127.0 (dd, $^1J_{CF}$ 235.2, $^2J_{CF}$ 21.7, C5), 134.1 (dd, $^1J_{CF}$ 235.2, $^3J_{CF}$ 7.3, C3), 135.2 (dt, $^2J_{CF}$ 21.7, $^3J_{CF}$ 7.3, C4), 140.9 (ddd, $^2J_{CF}$ 21.7, $^3J_{CF}$ 7.3, $^4J_{CF}$ 4.3, C2), 145.7 (ddd, $^1J_{CF}$ 235.2, $^2J_{CF}$ 21.7, $^4J_{CF}$ 4.3, C6); δ_F -94.73 (1F, t, $^{3/5}J_{FF}$ 26.3, 6-F), -157.92

(1F, d, $^5J_{FF}$ 26.3, 3-F) ,-173.76 (1F, d, $^3J_{FF}$ 26.3, 5-F); m/z (EI^+) 261 (M^+, 75), 247 (24), 246 (100), 232 (33), 218 (79), 202 (22), 190 (32), 176 (83), 72 (31), 41 (17), 29 (24).

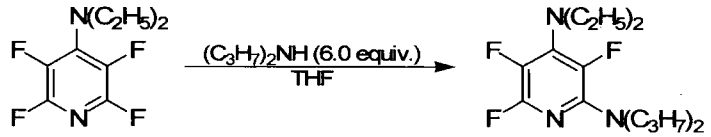
N^4,N^4-Diethyl-3,5,6-trifluoro-N^2-*iso*propylpyridine-2,4-diamine (18)



(11) (18)

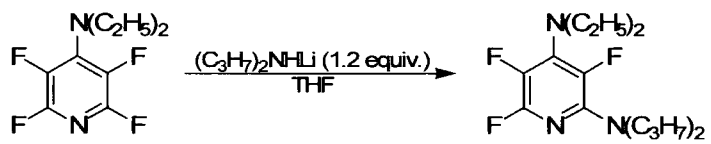
A solution of *iso*propylamine (1.171 g, 19.8 mmol) in THF (15 mL), was added dropwise to N,N-diethyl-2,3,5,6-tetrafluoropyridin-4-amine (**11**) (1.989 g, 9.0 mmol) at room temperature over 30 minutes and the resulting mixture was heated at reflux temperature for 10 days. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by reduced pressure distillation yielded *N^4,N^4-diethyl-3,5,6-trifluoro-N^2-isopropylpyridine-2,4-diamine (**18**)* (0.505 g, 22%) as a colourless oil; bp 119 °C, 7.0 mbar; (Found: C, 55.0; H, 6.9; N, 16.0. $C_{12}H_{18}F_3N_3$ requires C, 55.2; H, 6.9; N, 16.1%); δ_H 1.12 (6H, t, $^3J_{HH}$ 7.2, NCH_2CH_3), 1.20 (6H, d, $^3J_{HH}$ 7.2, $HNCH(CH_3)_2$), 3.30 (4H, qt, $^3J_{HH}$ 7.2, $^5J_{HF}$ 1.5, NCH_2CH_3), 4.09 (2H, br m, $HNCH(CH_3)_2$); δ_C 13.7 (s, $NCH(CH_3)_2$), 23.3 (s, NCH_2CH_3), 42.6 (s, $HNCH(CH_3)_2$), 46.4 (t, $^4J_{CF}$ 2.9, NCH_2CH_3), 130.5 (ddd, $^1J_{CF}$ 258.5, $^2J_{CF}$ 18.5, $^3J_{CF}$ 6.7, C5), 136.1 (dt, $^2J_{CF}$ 18.5.7, $^3J_{CF}$ 6.7, C4), 136.3 (dd, $^1J_{CF}$ 258.2, $^3J_{CF}$ 6.7, C3), 141.4 (ddd, $^2J_{CF}$ 18.5, $^3J_{CF}$ 6.7, $^4J_{CF}$ 2.9, C2), 147.1 (ddd, $^1J_{CF}$ 258.2, $^2J_{CF}$ 18.5, $^4J_{CF}$ 2.9, C6); δ_F -96.77 (1F, t, $^{3/5}J_{FF}$ 24.7, 6-F), -157.04 (1F, d, $^5J_{FF}$ 24.7, 3-F) ,-168.20 (1F, d, $^3J_{FF}$ 24.7, 5-F); m/z (EI^+) 261 (M^+, 33), 247 (28), 246 (100), 232 (14), 218 (15), 204 (16), 202 (21), 176 (15), 58 (13), 41 (11), 29 (17).

N^4,N^4-Diethyl-3,5,6-trifluoro-N^2,N^2-dipropylpyridine-2,4-diamine (19)



(11) (19)

A solution of dipropylamine (6.606 g, 65.3 mmol) in THF (15 mL), was added dropwise to N,N-diethyl-2,3,5,6-tetrafluoropyridin-4-amine (**11**) (2.112 g, 12.5 mmol) at room temperature over 30 minutes and the resulting mixture was heated at reflux temperature for 12 days. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by reduced pressure distillation yielded *N^4,N^4-diethyl-3,5,6-trifluoro-N^2,N^2-dipropylpyridine-2,4-diamine (**19**)* (0.880 g, 24%) as a colourless liquid; bp 77 °C, 0.5 mbar; (Found C, 59.1; H, 8.0; N, 13.8. $C_{15}H_{24}F_3N_3$ requires C, 59.4; H, 8.0; N, 13.9%); δ_H 0.89 (3H, t, $^3J_{HH}$ 7.2, $NCH_2CH_2\mathit{CH_3}$), 1.12 (3H, t, $^3J_{HH}$ 7.2, $NCH_2\mathit{CH_3}$), 1.57 (2H, sextet, $^3J_{HH}$ 7.2, $NCH_2\mathit{CH_2}CH_3$), 3.26 (2H, t, $^3J_{HH}$ 7.2, $N\mathit{CH_2}CH_2CH3$), 3.29 (2H, q, $^3J_{HH}$ 7.0, $N\mathit{CH_2}CH_3$); δ_C 11.5 (s, $NCH_2CH_2\mathit{CH_3}$), 13.6 (s, $NCH_2\mathit{CH_3}$), 21.7 (s, $NCH_2\mathit{CH_2}CH_3$), 46.4 (t, $^4J_{CF}$ 4.2, $N\mathit{CH_2}CH_3$), 52.3 (d, $^4J_{CF}$ 4.2, $N\mathit{CH_2}CH_2CH_3$), 131.7 (dd, $^1J_{CF}$ 240.3, $^2J_{CF}$ 23.8, C5), 137.7 (dt, $^2J_{CF}$ 23.8, $^3J_{CF}$ 6.9, C4), 139.2 (dd, $^1J_{CF}$ 240.3, $^3J_{CF}$ 6.9, C3), 142.3 (ddd, $^2J_{CF}$ 23.8, $^3J_{CF}$ 6.9, $^4J_{CF}$ 4.2, C2), 145.9 (dd, $^1J_{CF}$ 240.3, $^2J_{CF}$ 23.8, C6); δ_F -94.59 (1F, t, $^{3/5}J_{FF}$ 26.3, 6-F), -145.89 (1F, d, $^5J_{FF}$ 26.3, 3-F), -165.06 (1F, d, $^3J_{FF}$ 26.3, 5-F); m/z (EI^+) 303 (M^+, 20), 275 (15), 274 (100), 246 (12), 232 (62), 216 (6), 204 (9), 188 (13), 41 (7).

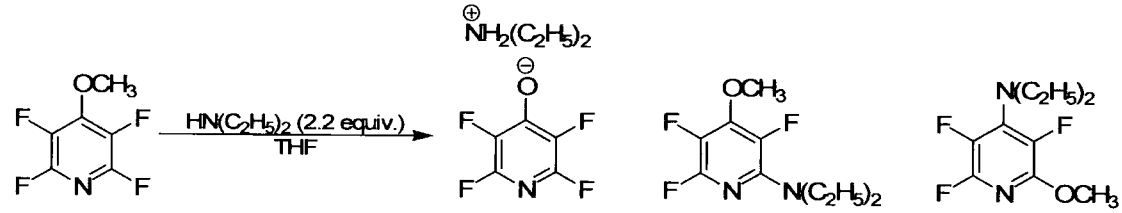


(11) (19)

Tert-butyl lithium (0.433 g, 6.8 mmol) was added to a solution of dipropylamine (0.684 g, 6.8 mmol) in THF (10 mL) at -78°C and stirred for 1h before being allowed to warm

to room temperature. This solution was then added dropwise to N,N-diethyl-2,3,5,6-tetrafluoropyridin-4-amine (**11**) (1.508 g, 6.8 mmol) at room temperature over 30 minutes and the resulting mixture was heated at reflux temperature for 18h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by reduced pressure distillation yielded *N^4,N^4-diethyl-3,5,6-trifluoro-N^2,N^2-dipropylpyridine-2,4-diamine* ***(19)*** (1.547 g, 75%) as a colourless liquid; spectroscopic data was consistent with previous results.

Reaction of 2,3,5,6-tetrafluoro-4-methoxypyridine with diethylamine



(2) (20) (21) (22)

A solution of diethylamine (4.031 g, 55.1 mmol) in THF (25 mL) was added to 2,3,5,6-tetrafluoro-4-methoxypyridine (**2**) (4.872 g, 27.0 mmol) at room temperature over 30 minutes; the resulting mixture was heated at reflux temperature for 20h before water (50 mL) was added. The mixture was filtered yielding *2,3,5,6-tetrafluoro-pyridin-4-olate-diethyl-ammonium* ***(20)*** which was recrystallised from DMSO (6.031 g, 93%) as a white crystalline solid; mp 220-222 °C (Found: C, 45.0; H, 5.1; N, 11.6. $C_9H_{12}F_4N_2O$ requires C, 45.0; H, 5.0; N, 11.7%); δ_H (DMSO) 1.71 (6H, t, $^3J_{HH}$ 7.2 , $NCH_2\mathit{CH_3}$), 2.93 (2H, q, $^3J_{HH}$ 7.2, $N\mathit{CH_2}CH_3$), 8.90 (br s, NH_2); δ_C (DMSO) 11.0 (s, $NCH_2\mathit{CH_3}$), 41.5 (s, $N\mathit{CH_2}CH_3$), 136.0 (dm, $^1J_{CF}$ 231.3, C3), 144.8 (dm, $^1J_{CF}$ 231.3, C2), 158.9 (m, C4); δ_F (DMSO) -103.87 (2F, m, 2-F), -173.55 (2F, m, 3-F); m/z (EI^+) 167 (100), 138 (21), 119 (59), 100 (21), 93 (35), 74 (61), 73 (40), 72 (30), 58 (88), 44 (44), 42 (23).

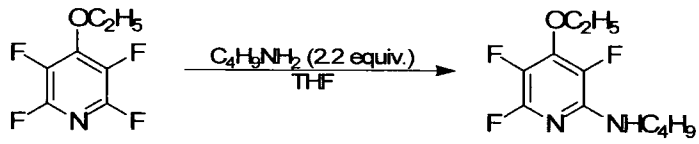
The filtrate was extracted into dichloromethane (4 x 10 mL), dried ($MgSO_4$) and evaporated to yield a colourless oil (0.93 g) shown to contain 2 components by ^1H and ^{19}F NMR (ratio of peaks 5:2). Further purification was not possible.

The major component was identified as *N,N-diethyl-3,5,6-trifluoro-4-methoxypyridin-2-amine* ***(21)***. δ_H 1.16 (6H, t, $^3J_{HH}$ 7.0, 2-$NCH_2\mathit{CH_3}$), 3.41 (4H, qd, $^3J_{HH}$

7.0, $^{5}J_{HF}$ 1.6, 2-NCH_2CH$_3$), 4.12 (3H, t, $^{3}J_{HH}$ 7.0, OCH_3); δ_F -91.57 (1F, t, $^{3/5}J_{FF}$ 26.0, 6-F), -156.02 (1F, d $^{5}J_{FF}$ 26.0, 3-F), -172.82 (1F, d, $^{3}J_{FF}$ 26.0, 5-F); m/z (EI$^+$) 234 (M$^+$, 34), 220 (11), 219 (93), 205 (20), 191 (100), 176 (10), 162 (10), 29 (13).

The minor component was identified as *N,N-diethyl-2,3,5-trifluoro-6-methoxypyridin-4-amine (22)*. δ_H 1.22 (6H, t, $^{3}J_{HH}$ 7.2, 4-NCH$_2$$CH_3$), 2.79 (4H, q, $^{3}J_{HH}$ 7.2, 4-NCH_2CH$_3$), 4.21 (3H, t, $^{3}J_{HH}$ 7.2, OCH_3); δ_F -94.37 (1F, t, $^{3/5}J_{FF}$ 24.2, 2-F), -161.71 (1F, d $^{5}J_{FF}$ 24.2, 5-F), -168.08 (1F, d, $^{3}J_{FF}$ 24.2, 3-F); m/z (EI$^+$) 234 (M$^+$, 34), 220 (11), 219 (93), 205 (20), 191 (100), 176 (10), 162 (10), 29 (13).

N-Butyl-4-ethoxy-3,5,6-trifluoropyridin-2-amine (23)

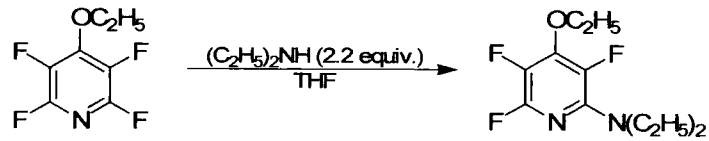


(5) (23)

A solution of butylamine (1.661 g, 22.7 mol) in THF (15 mL) was added dropwise to 4-ethoxy-2,3,5,6-tetrafluoropyridine (**5**) (1.980 g, 10.2 mmol) at room temperature over 30 minutes and the resulting mixture was heated at reflux temperature for 72h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by reduced pressure distillation yielded *N-butyl-4-ethoxy-3,5,6-trifluoro-pyridin-2-amine (23)* (1.231 g, 49%) as a colourless oil; bp 100 °C, 2.6 mbar; (Found: C, 53.0; H, 6.2; N, 11.5. $C_{11}H_{15}F_3N_2O$ requires C, 53.2; H, 6.1; N, 11.3%); δ_H 0.94 (3H, t, $^{3}J_{HH}$ 7.2, HN(CH$_2$)$_3$$CH_3$), 1.38 (2H, sextet, $^{3}J_{HH}$ 7.2, HN(CH$_2$)$_2$$CH_2CH_3$), 1.41 (3H, t, $^{3}J_{HH}$ 7.2, CH$_2$$CH_3$), 1.57 (2H, pent, $^{3}J_{HH}$ 7.2, NHCH$_2$$CH_2CH_2CH_3$), 3.35 (2H, qd, $^{3}J_{HH}$ 7.2, $^{5}J_{HF}$ 1.4, NHCH_2(CH$_2$)$_2$CH$_3$), 4.40 (1H, br s, *NH*C$_4$H$_9$), 4.41 (2H, qt, $^{3}J_{HH}$ 7.2, $^{5}J_{HF}$ 1.4, OCH_2CH$_3$); δ_C 13.9 (s, NH(CH$_2$)$_3$$CH_3$), 15.6 (s, OCH$_2CH_3$), 20.2 (s, NH(CH$_2$)$_2$$CH_2CH_3$), 31.9 (s, NHCH$_2$$CH_2CH_2CH_3$), 41.0 (s, NH$CH_2$(CH$_2$)$_2CH_3$), 69.9 (t, $^{4}J_{CF}$ 3.1 OCH_2CH$_3$), 129.1 (dd, $^{1}J_{CF}$ 240.6, $^{2}J_{CF}$ 21.3, C5), 135.3 (dd, $^{1}J_{CF}$ 240.6, $^{3}J_{CF}$ 9.4, C3), 142.1 (ddd, $^{2}J_{CF}$ 21.3, $^{3}J_{CF}$ 9.4, $^{4}J_{CF}$ 3.1, C2), 143.7 (m, C4), 147.0 (ddd, $^{1}J_{CF}$ 240.6, $^{2}J_{CF}$ 21.3, $^{4}J_{CF}$ 3.1, C6); δ_F -94.21 (1F, t, $^{3/5}J_{FF}$ 24.8, 6-F), -163.95 (1F, d, $^{3}J_{FF}$ 24.8, 3-F), -174.53 (1F, d,

$^5J_{FF}$ 24.8, 5-F); m/z (EI^+) 248 (M^+, 60), 206 (19), 205 (88), 179 (19), 177 (100), 164 (24), 41 (20), 29 (31).

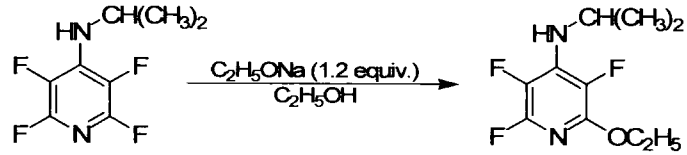
4-Ethoxy-N,N-diethyl-3,5,6-trifluoropyridin-2-amine (24)



(5) (24)

A solution of diethylamine (1.694 g, 23.2 mol) in THF (15 mL) was added dropwise to 4-ethoxy-2,3,5,6-tetrafluoropyridine (**5**) (2.006 g, 10.3 mmol) at room temperature over 30 minutes and the resulting mixture was heated at reflux temperature for 72h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by reduced pressure distillation yielded *4-ethoxy-N,N-diethyl-3,5,6-trifluoropyridin-2-amine (**24**)* (1.612 g, 63%) as a colourless oil; bp 62 °C, 3.3 mbar; (Found: C, 52.9; H, 6.1; N, 11.4. $C_{11}H_{15}F_3N_2O$ requires C, 53.2; H, 6.1; N, 11.3%); δ_H 1.15 (6H, t, $^3J_{HH}$ 7.1, NCH_2CH_3), 1.42 (3H, t, $^3J_{HH}$ 7.1, OCH_2CH_3), 3.40 (4H, qd, $^3J_{HH}$ 7.1, $^5J_{HF}$ 1.5, NCH_2CH_3), 4.38 (2H, qt, $^3J_{HH}$ 7.1, $^5J_{HF}$ 1.5, OCH_2CH_3); δ_C 13.8 (s, NCH_2CH_3), 15.6 (s, OCH_2CH_3), 44.1 (s, NCH_2CH_3), 70.0 (t, $^4J_{CF}$ 3.5, OCH_2CH_3), 129.5 (dd, $^1J_{CF}$ 241.9, $^2J_{CF}$ 18.6, C5), 137.2 (dd, $^1J_{CF}$ 241.9, $^3J_{CF}$ 7.0, C3), 141.6 (ddd, $^2J_{CF}$ 18.6, $^3J_{CF}$ 7.0, $^4J_{CF}$ 3.5, C2), 145.3 (ddd, $^1J_{CF}$ 241.9, $^2J_{CF}$ 18.6, $^4J_{CF}$ 3.5, C6), 145.3 (dt, $^2J_{CF}$ 18.6, $^3J_{CF}$ 7.0, C4); δ_F -91.74 (1F, t, $^{3/5}J_{FF}$ 26.6, 6-F), -155.32 (1F, d, $^3J_{FF}$ 26.6, 3-F) ,-172.15 (1F, d, $^5J_{FF}$ 26.6, 5-F); m/z (EI^+) 248 (M^+, 89), 233 (90), 219 (35), 205 (63), 203 (28), 191 (54), 188 (32), 177 (100), 175 (34), 149 (33), 148 (52), 135 (44), 72 (30), 29 (40), 27 (47).

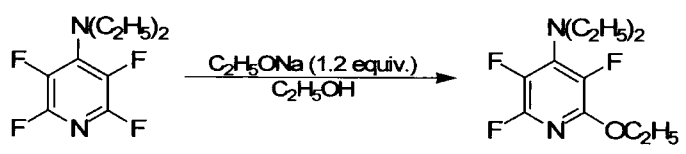
2-Ethoxy-3,5,6-trifluoro-N-*iso*propylpyridin-4-amine (25)



(15) (25)

Under an atmosphere of dry nitrogen sodium metal (0.303 g, 13.2 mmol) was added to ethanol (10 mL) and stirred until hydrogen evolution was complete. The ethoxide solution was added to a stirred solution of 2,3,5,6-tetrafluoro-N-*iso*propylpyridin-4-amine (**15**) (1.967 g, 9.5 mmol) in ethanol (5 mL) over 30 min at room temperature; the resulting mixture was heated at reflux temperature for 20h before Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added. The mixture was filtered and evaporated affording a liquid. Reduced pressure distillation yielded *2-ethoxy-3,5,6-trifluoro-N-isopropylpyridin-4-amine (25)* (1.785 g, 81%) as a colourless liquid; bp 71 °C, 3.1 mbar; (Found: C, 51.4; H, 5.7; N, 12.0. $C_{10}H_{13}F_3N_2O$ requires C, 51.3; H, 5.6; N, 12.0%); δ_H 1.23 (6H, d, $^3J_{HH}$ 6.6, HNCH(CH_3)$_2$), 1.36 (3H, t, $^3J_{HH}$ 76.6, OCH$_2CH_3$), 4.06 (2H, m, *H*NC*H*(CH$_3$)$_2$), 4.29 (2H, q, $^3J_{HH}$ 6.6, OCH_2CH$_3$); δ_C 14.6 (s, OCH$_2CH_3$), 24.1 (s, HNCH(CH_3)$_2$), 46.3 (t, $^4J_{CF}$ 2.9, HN*C*H(CH$_3$)$_2$), 62.8 (s, OCH_2CH$_3$), 128.9 (dd, $^1J_{CF}$ 238.3, $^2J_{CF}$ 18.2, C5), 132.5 (dd, $^1J_{CF}$ 238.3, $^3J_{CF}$ 7.5, C3), 135.4 (dt, $^2J_{CF}$ 18.2, $^3J_{CF}$ 7.5, C4), 145.4 (ddd, $^2J_{CF}$ 18.2, $^3J_{CF}$ 7.5, $^4J_{CF}$ 2.9, C2), 144.9 (ddd, $^1J_{CF}$ 238.3, $^2J_{CF}$ 18.2, $^4J_{CF}$ 2.9, C6); δ_F -97.37 (1F, t, $^{3/5}J_{FF}$ 23.0, 6-F); -165.25 (1F, $^5J_{FF}$ 23.0, 3-F), -170.99 (1F, d, $^3J_{FF}$ 23.0, 5-F); m/z (EI$^+$) 234 (M^+, 49), 219 (100), 191 (80), 43 (22).

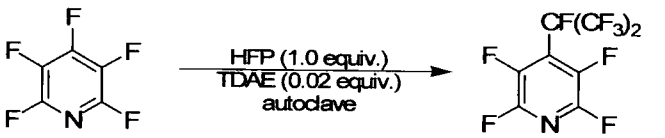
2-Ethoxy-N,N-diethyl-3,5,6-trifluoropyridin-4-amine (26)



(11) (26)

Under an atmosphere of dry argon, sodium metal (0.343 g, 14.9 mmol) was added to ethanol (20 mL) and stirred until hydrogen evolution had subsided. The sodium ethoxide solution was added dropwise to N,N-diethyl-2,3,5,6-tetrafluoropyridin-4-amine (**11**) (2.979 g, 13.4 mmol) over 30 minutes at room temperature. The resulting mixture was heated at reflux temperature for 16h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by reduced pressure distillation yielded *2-ethoxy-N,N-diethyl-3,5,6-trifluoropyridine-4-amine (**26**)* (2.249 g, 68%) as a colourless oil; bp 72 °C 1.1 mbar; (Found C, 53.0; H, 6.1; N, 11.2. $C_{11}H_{15}F_3N_2O$ requires C, 53.2; H, 6.1; N, 11.3%); δ_H 1.17 (6H, t, $^3J_{HH}$ 7.0, $NCH_2\mathit{CH_3}$), 1.39 (3H, t, $^3J_{HH}$ 7.0, $OCH_2\mathit{CH_3}$), 3.36 (4H, qt, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.1, NCH_2CH_3), 4.32 (2H, q, $^3J_{HH}$ 7.1, OCH_2CH_3); δ_C 13.8 (s, $NCH_2\mathit{CH_3}$), 14.7 (s, $OCH_2\mathit{CH_3}$), 46.4 (t, $^4J_{CF}$ 3.9, NCH_2CH_3), 62.9 (s, OCH_2CH_3), 132.9 (dd, $^1J_{CF}$ 242.7, $^2J_{CF}$ 23.7, C5), 136.7 (dd, $^1J_{CF}$ 242.7, $^3J_{CF}$ 5.0, C3), 137.9 (dd, $^2J_{CF}$ 23.7, $^3J_{CF}$ 5.0, C4), 145.6 (ddd, $^1J_{CF}$ 242.7, $^2J_{CF}$ 23.7, $^4J_{CF}$ 3.9, C6), 146.0 (ddd, $^2J_{CF}$ 23.7, $^3J_{CF}$ 5.0, $^4J_{CF}$ 3.9, C2); δ_F -97.30 (1F, t, $^{3/5}J_{FF}$ 23.3, 6-F), -155.52 (1F d, $^5J_{FF}$ 23.3, 3-F), -162.32 (1F, d, $^3J_{FF}$ 23.3, 5-F); m/z (EI^+) 248 (M^+, 80), 234 (32), 233 (97), 205 (82), 191 (62), 177 (100), 148 (32), 135 (19), 29 (41).

2,3,5,6-Tetrafluoro-4-(perfluoropropan-2-yl)pyridine (27)

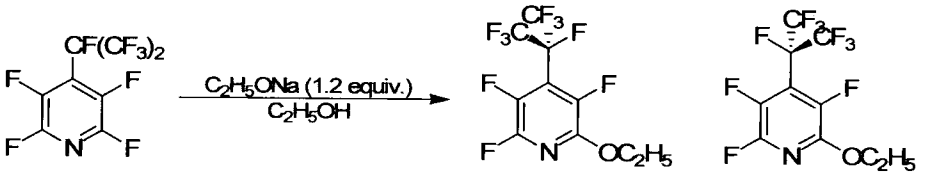


(1) (27)

A stainless steel autoclave was charged with pentafluoropyridine (**1**) (20.130 g, 0.1 mmol) and tetrakis(dimethylamino)ethylene (0.392 g, 2.0 mmol). The mixture was degassed, by freeze-thawing under vacuum, before hexafluoropropene (16.60 g, 0.1 mol) was transferred into the autoclave. The autoclave was sealed and heated to 60 °C for 24h in a thermostatically controlled rocking furnace. Fractional distillation yielded *2,3,5,6-tetrafluoro-4-(perfluoropropan-2-yl)pyridine (27)* (9.195 g, 28%) as a colourless liquid; bp 128 °C; (Found: C, 30.0; N, 4.4. $C_8F_{11}N$ requires C, 30.1; N, 4.4%); δ_C 91.8

(doublet of septets of triplets, $^{1}J_{CF}$ 251.9, $^{2}J_{CF}$ 28.5, $^{4}J_{CF}$ 2.5, *CF*$(CF_3)_2$), 119.4 (dd, $^{2}J_{CF}$ 28.5, $^{3}J_{CF}$ 11.1, C4), 119.8 (qd, $^{1}J_{CF}$ 251.9, $^{2}J_{CF}$ 28.5, CF(*CF_3*)$_2$), 144.8 (br dm, $^{1}J_{CF}$ 251.9, C2/3); δ_F -75.25 (6F, br s, CF_3), -86.64 (2F, s, 2-F), -135.13 (2F, s, 3-F), -180.46 (1F, m, CF) ; m/z (EI^+) 319 (M^+, 85), 300 (20), 250 (61), 231 (21), 201 (24), 200 (100), 181 (34), 162 (25), 131 (22), 117 (42), 100 (34), 93 (23), 69 (91). Spectroscopic data were consistent with literature values.[66-70]

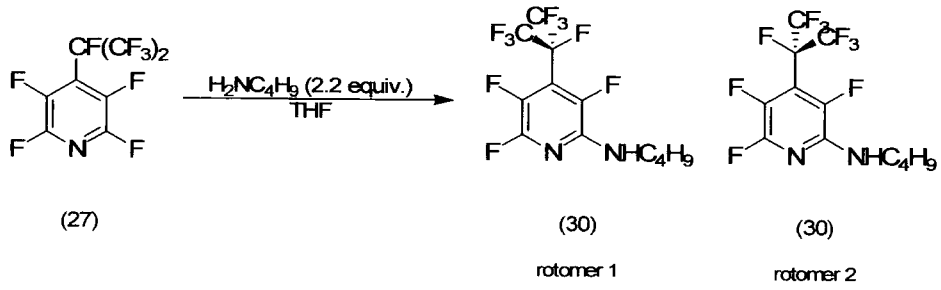
2-Ethoxy-3,5,6-trifluoro-4-(perfluoropropan-2-yl)pyridine (29)



(27) (29) rotomer 1 (29) rotomer 2

Under an atmosphere of dry nitrogen sodium metal (0.176 g, 7.7 mmol) was added to ethanol (15 mL) and stirred until hydrogen evolution was complete. The ethoxide solution was added to a stirred solution of 2,3,5,6-tetrafluoro-4-(perfluoropropan-2-yl)pyridine (**27**) (2.054 g, 6.4 mmol) over 30 min at room temperature; the resulting mixture was heated at reflux temperature for 30h before Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added. The mixture was filtered and evaporated affording a liquid. Reduced pressure distillation yielded *2-ethoxy-3,5,6-trifluoro-4-(perfluoropropan-2-yl)pyridine (**29**)* (1.199 g, 55%) as a colourless liquid; bp 76 °C 8.1 mbar; (Found: C, 34.6; H, 1.5; N, 4.3. $C_{10}H_5F_{10}NO$ requires C, 34.8; H, 1.5; N, 4.1%); δ_H 1.45 (3H, t, $^{3}J_{HH}$ 7.1, OCH_2CH_3), 4.43 (2H, q, $^{3}J_{HH}$ 7.1, OCH_2CH_3); δ_C 14.3 (s, OCH_2CH_3), 64.6 (s, OCH_2CH_3), 92.0 (d sept, $^{1}J_{CF}$ 270.5, $^{2}J_{CF}$ 25.7, CF), 116.6 (m, C4), 120.0 (qd, $^{1}J_{CF}$ 270.5, $^{2}J_{CF}$ 25.7, CF_3), 143.6-146.1 (broad overlapping multiplet, C2/3/5/6); δ_F (major rotomer) -75.00 (6F, m, CF_3), -90.97 (1F, br s, F6), -134.65 (1F, br s, F3), -150.52 (1F, br s, F5), -180.36 (1F, m, CF); δ_F (minor rotomer) -75.00 (6F, m, CF_3), -92.15 (1F, br s, F6), - 137.28 (1F, br s, F3), -147.27 (1F, br s, F5), -180.36 (1F, m, CF); ratio major:minor 6:5; m/z (EI^+) 345 (M^+, 55), 330 (36), 317 (94), 298 (36), 289 (49), 220 (100), 198 (35), 170 (44), 69 (88), 45 (35), 29 (66).

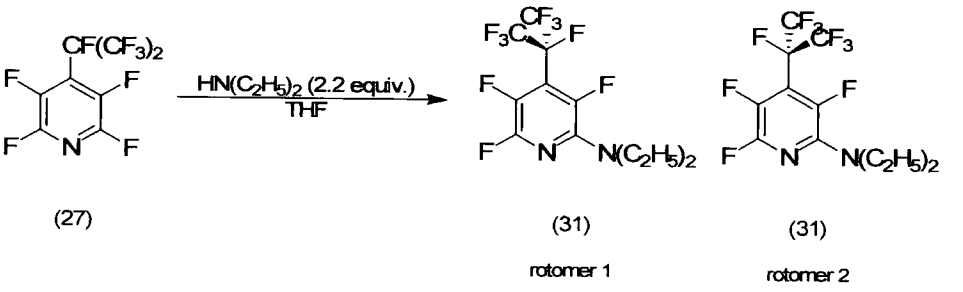
N-Butyl-3,4,6-trifluoro-4-(perfluoropropan-2-yl)pyridin-2-amine (30)



(27) (30) rotomer 1 (30) rotomer 2

A solution of butylamine (1.033 g, 14.1 mol) in THF (15 mL), was added dropwise to 2,3,5,6-tetrafluoro-4-(perfluoropropan-2-yl)pyridine (**27**) (2.030 g, 6.4 mmol) at room temperature over 30 minutes and the resulting mixture was heated at reflux temperature for 30h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by reduced pressure distillation yielded *N-butyl-3,4,6-trifluoro-4-(perfluoropropan-2-yl)pyridine-2-amine* ***(30)*** (1.782 g, 75%) as a colourless oil; bp 70 °C, 7.9 mbar; (Found: C, 38.6; H, 2.7; N, 7.8. $C_{12}H_{10}F_{10}N_2$ requires C, 38.7; H, 2.7; N, 7.5%); δ_H 0.96 (3H, t, $^3J_{HH}$ 7.1, $HN(CH_2)_3CH_3$), 1.42 (2H, sext, $^3J_{HH}$ 7.1, $HN(CH_2)_2CH_2CH_3$), 1.60 (2H, pent, $^3J_{HH}$ 7.1, $NHCH_2CH_2CH_2CH_3$), 3.41 (2H, qd, $^3J_{HH}$ 7.1, $^5J_{HF}$ 1.2, $NHCH_2(CH_2)_2CH_3$), 4.78 (1H, br s, NHC_4H_9); δ_C 13.8 (s, $NH(CH_2)_3CH_3$), 20.2 (s, $NH(CH_2)_2CH_2CH_3$), 31.6 (s, $NHCH_2CH_2CH_2CH_3$), 41.2 (s, $NHCH_2(CH_2)_2CH_3$), 91.9 (dm, $^1J_{CF}$ 288.3, CF), 114.1 (m, C4), 120.7 (qd, $^1J_{CF}$ 288.3, $^2J_{CF}$ 26.9, CF_3), 142.0-148.7 (br m, C2/3/5/6); δ_F (major rotomer) -75.62 (6F, m, CF_3), -92.40 (1F, br s, F6), - 141.92 (1F, br s, F3), -156.26 (1F, br s, F5), -180.32 (1F, m, CF); δ_F (minor rotomer) -75.62 (6F, m, CF_3), -91.28 (1F, br s, F6), - 139.22 (1F, br s, F3), -159.55 (1F, br s, F5), -180.32 (1F, m, CF); ratio major:minor 1:1; m/z (EI^+) 273 (M^+, 30), 372 (54), 352 (29), 353 (46), 343 (35), 329 (100), 316 (57), 311 (42), 274 (37), 260 (93), 241 (41), 220 (32), 210 (54), 197 (33), 160 (26), 69 (52), 55 (31), 41 (43), 39 (31), 29 (36), 27 (42).

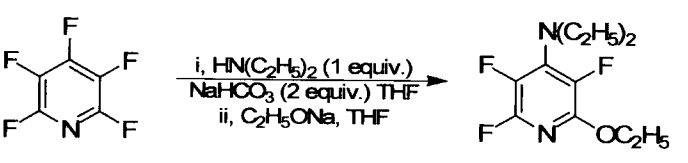
N,N-Diethyl-3,5,6-trifluoro-4-(perfluoropropan-2-yl)pyridin-2-amine (31)



(27) (31) rotomer 1 (31) rotomer 2

A solution of diethylamine (0.988 g, 13.5 mol) in THF (15 mL), was added dropwise to 2,3,5,6-tetrafluoro-4-(perfluoropropan-2-yl)pyridine (**27**) (2.137 g, 6.7 mmol) at room temperature over 30 minutes and the resulting mixture was heated at reflux temperature for 30h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by reduced pressure distillation yielded *N,N-diethyl-3,5,6-trifluoro-4-(perfluoropropan-2-yl)pyridin-2-amine (31)* (1.725 g, 69%) as a colourless oil; bp 80 °C, 8.3 mbar; (Found: C, 38.9; H, 2.6; N, 7.7. $C_{12}H_{10}F_{10}N_2$ requires C, 38.7; H, 2.7; N, 7.5%); δ_H 1.20 (6H, t, $^3J_{HH}$ 7.1, NCH_2CH_3), 3.46 (4H, qd, $^3J_{HH}$ 7.1, $^5J_{HF}$ 1.0, NCH_2CH_3); δ_C 13.6 (s, NCH_2CH_3), 44.8 (d, $^4J_{CF}$ 6.1 NCH_2CH_3), 119.6 (qd, $^1J_{CF}$ 288.8, $^2J_{CF}$ 27.4, CF_3); δ_F (major rotomer) -74.83 (6F, m, CF_3), -88.81 (1F, br s, F6), - 131.28 (1F, br s, F3), -156.41 (1F, d, $^4J_{FF}$ 87.3, F5), -178.68 (1F, d, $^4J_{FF}$ 87.3, CF); δ_F (minor rotomer) -74.83 (6F, m, CF_3), -90.11 (1F, br s, F6), - 133.62 (1F, d, $^4J_{FF}$ 99.9, F3), -152.83 (1F, br s, F5), -179.52 (1F, d, $^4J_{CF}$ 99.9, CF); ratio major:minor 3:2; m/z (EI^+) 372 (M^+, 55), 358 (37), 357 (100), 343 (33), 329 (98), 274 (38), 260 (49), 69 (48), 29 (65).

One-pot synthesis of 2-ethoxy-N,N-diethyl-3,5,6-trifluoropyridin-4-amine (26)



(1) (26)

A solution of diethylamine (1.294 g, 17.7 mmol) and sodium hydrogen carbonate (1.528 g, 18.2 mmol) in THF (20 mL) was added dropwise to pentafluoropyridine (3.041 g, 18.0 mmol) at room temperature over 30 minutes and heated to reflux temperature for 15h until complete conversion was observed by ^{19}F NMR. Under an atmosphere of dry argon, sodium metal (0.409 g, 17.8 mmol) was added to a solution of ethanol (0.818 g, 17.7 mmol) in THF (10 mL) and stirred until hydrogen evolution had subsided. The sodium ethoxide solution was added dropwise to the reaction mixture over 30 minutes and the mixture heated at reflux temperature for a further 32h, before being allowed to cool to room temperature. Water (50 mL) was added and the mixture was extracted into dichloromethane (4 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed on a rotary evaporator, affording a crude product (3.93 g). Purification reduced pressure distillation yielded *2-ethoxy-N,N-diethyl-3,5,6-trifluoropyridin-4-amine* (2.212 g, 56 %). Spectroscopic data were consistent with previously recorded results.

8.3 Experimental to Chapter 5

Attempted Synthesis of 2,3,5,6-tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)pyridine (33)

2,3,4,6-Tetra-O-benzyl-D-glucopyranose (**32**) (6.445 g, 11.9 mmol) was dissolved in dry dichloromethane (10 mL) and stirred with sodium hydride (0.290 g, 12.1 mmol) until hydrogen evolution had subsided. The resulting solution was added dropwise, while stirring at room temperature, to pentafluoropyridine (**1**) and then stirred for a further 36h. Analysis by ^{19}F NMR showed the reaction consisted of only *pentafluoropyridine (1)*. Spectroscopic data were consistent with previously recorded results and literature values.[51, 56, 156]

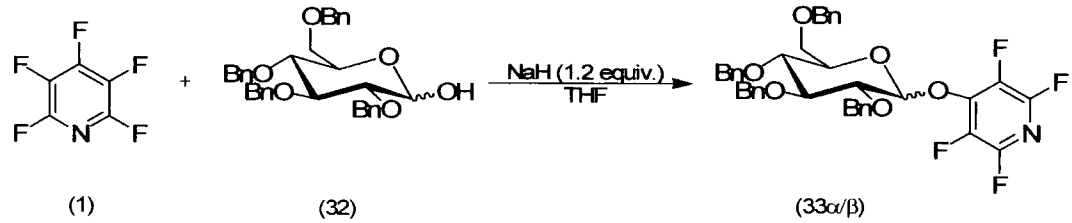
2,3,4,6-Tetra-O-benzyl-D-glucopyranose (**32**) (6.445 g, 11.9 mmol) was dissolved in dry dichloromethane (10 mL) and stirred with sodium hydride (0.290 g, 12.1 mmol) until hydrogen evolution had subsided. The resulting solution was added dropwise, while stirring at room temperature, to pentafluoropyridine (**1**) and then heated at 40°C for a further 36h. Analysis by ^{19}F NMR showed the reaction consisted of only

pentafluoropyridine (1). Spectroscopic data were consistent with previously recorded results and literature values.[51, 56, 156]

Procedure for the Synthesis of Donors (33) to (42)

General Method. 2,3,4,6-Tetra-O-benzyl-D-glucopyranose (**32**) was dissolved in dry THF (10 mL) and stirred with sodium metal or sodium hydride until hydrogen evolution had subsided. The resulting solution was added dropwise, while stirring at room temperature, to the fluoropyridine scaffold and then heated at reflux temperature. After, the reaction was allowed to cool to room temperature. Amberlite (Na form, 0.50 g) was added with stirring at room temperature for 30 minutes and the solvent removed on a rotary evaporator. Purification by HPFC using silica gel (1:10 ethyl acetate:hexane) yielded the expected glycosyl donors as an α/β mixture in the ratio of 36:64 (except for donors (**33β**) and (**37α/β**) which could be separated from the mixture of anomers as pure isomers).

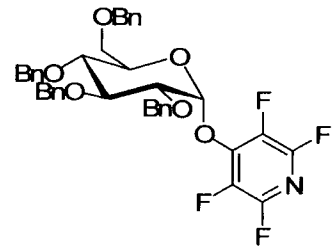
2,3,5,6-Tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)pyridine (33α)



(1) (32) (33α/β)

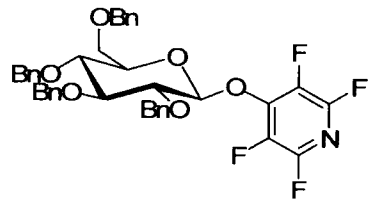
2,3,4,6-Tetra-O-benzyl-glucopyranose (**32**) (5.985 g, 11.1 mmol), butyl lithium (5.30 mL, 1.50 moldm^{-3}, 13.3 mmol) and pentafluoropyridine (1.883 g, 11.1 mmol) were heated at reflux temperature for 24h, affording *2,3,5,6-tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine* (1.587 g, 21%, 23:2 α:β) as a white syrup; shown to consist of two isomers in the ration of 7:4. Purification by HPFC allowed the separation of the β anomer from the anomeric mixture.

2,3,5,6-Tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)pyridine (33α)



(Found C, 67.8; H, 5.1; N, 2.0. $C_{39}H_{35}F_4NO_6$ requires C, 67.9; H, 5.1; N, 2.0%); δ_H 3.62 (1H, dd, $^3J_{HH}$ 3.0, CH_2 C6), 3.79 (1H, dd, $^3J_{H1H2}$ 3.0, $^3J_{H2H3}$ 10.8, CH C2), 3.80 (1H, dd, $^3J_{HH}$ 3.0, $^3J_{HH}$ 10.8, CH_2 C6), 3.82 (1H, t, $^3J_{HH}$ 10.8, CH C4), 4.09 (1H, dt, $^3J_{HH}$ 3.0, $^3J_{HH}$ 10.8, CH C5), 4.21 (1H, dt, $^3J_{HH}$ 10.8, CH C3), 4.46 (1H, d, $^2J_{HH}$ 11.2, O*CH*$_2$Ph C3), 4.56 (1H, d, $^2J_{HH}$ 11.2, O*CH*$_2$Ph C4), 4.60 (1H, d, $^2J_{HH}$ 11.2, O*CH*$_2$Ph C3), 4.75 (1H, d, $^2J_{HH}$ 11.2, O*CH*$_2$Ph C4), 4.87 (1H, d, $^2J_{HH}$ 11.2, O*CH*$_2$Ph C2), 4.91 (1H, d, $^2J_{HH}$ 11.2, O*CH*$_2$Ph C6), 4.95 (1H, d, $^2J_{HH}$ 11.2, O*CH*$_2$Ph C2), 5.04 (1H, d, $^2J_{HH}$ 11.2, O*CH*$_2$Ph C6), 5.87 (1H, d, $^3J_{H1H2}$ 3.0, CH C1), 7.18-7.43 (20H, m, 8 CH_2*Ph*); δ_C 67.8 (s, CH_2 C6), 73.1 (s, *CH* C4), 73.6 (s, O*CH*$_2$Ph C4), 74.2 (s, O*CH*$_2$Ph C6), 75.5 (s, O*CH*$_2$Ph C3), 76.1 (s, O*CH*$_2$Ph C2), 76.8 (s, CH C5), 79.5 (s, CH C2), 81.3 (s, CH C3), 100.7 (s, CH C1), 127.8-128.8 (m, CH_2*Ph*), 137.4 (s, OCH_2*C* C4), 137.6 (s, OCH_2*C* C3), 137.9 (s, OCH_2*C* C6), 138.5 (s, OCH_2*C* C2); δ_F -90.09 (2F, m, 2-F), -156.19 (2F, m, 3-F); m/z (ES^+) 712 (M^++Na^+, 100).

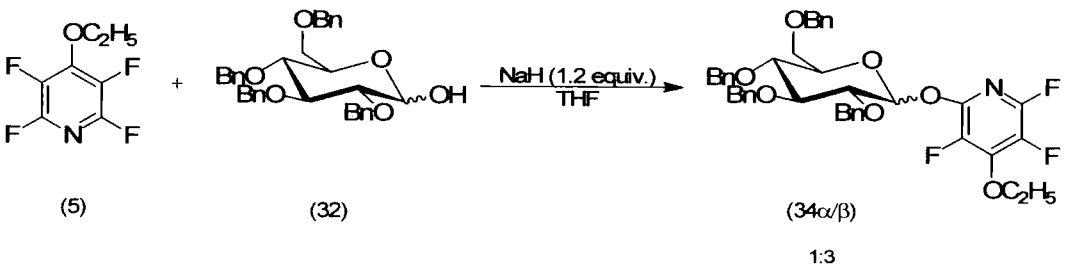
2,3,5,6-Tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyloxy)pyridine (33β)



2,3,5,6-Tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyloxy)pyridine ***(33β)*** (3.763 g, 49%) as a white solid; mp 79.5-80 °C; (Found C, 67.8; H, 5.2; N, 2.0. $C_{39}H_{35}F_4NO_6$ requires C, 67.9; H, 5.1; N, 2.0%); $[\alpha]_D^{20}$ +8 (c=1 $CHCl_3$); δ_H 3.50 (1H, m, CH C4), 3.63 (2H, m, CH_2 C6), 3.68 (3H, m, CH C2,C3,C5), 4.38 (2H, d, $^2J_{HH}$ 10.8,

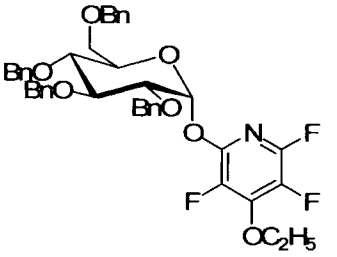
O*CH*$_2$Ph C3), 4.48 (1H, d, $^2J_{HH}$ 10.8, O*CH*$_2$Ph C4), 4.49 (1H, d, $^2J_{HH}$ 10.8, O*CH*$_2$Ph C4), 4.71 (1H, d, $^2J_{HH}$ 10.8, O*CH*$_2$Ph C6), 4.77 (1H, d, $^2J_{HH}$ 10.8, O*CH*$_2$Ph C6), 4.85 (1H, d, $^2J_{HH}$ 10.8, O*CH*$_2$Ph C2), 4.87 (1H, d, $^2J_{HH}$ 10.8, O*CH*$_2$Ph C2), 5.36 (1H, d, $^3J_{H1H2}$ 7.2, CH C1), 7.05-7.30 (20H, m, 8 CH$_2$*Ph*); δ_C 68.0 (s, CH$_2$ C6), 73.5 (s, O*CH*$_2$Ph C6), 75.2 (s, O*CH*$_2$Ph C4), 75.3 (s, O*CH*$_2$Ph C3), 75.8 (s, CH C4), 75.9 (s, O*CH*$_2$Ph C2), 77.1 (s, CH C3), 81.8 (s, CH C2), 84.3 (s, CH C5), 102.8 (s, CH C1), 127.8-128.2 (m, CH$_2$*Ph*), 137.7 (s, OCH$_2$*C* C4), 137.8 (s, OCH$_2$*C* C3), 137.9 (s, OCH$_2$*C* C6), 138.3 (s, OCH$_2$*C* C2); δ_F -90.44 (2F, m, 2-F), -158.17 (2F, m, 3-F); m/z (ES$^+$) 712 (M$^+$+Na$^+$, 100).

4-Ethoxy-2,3,5-tetrafluoro-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxy)pyridine (34αβ)



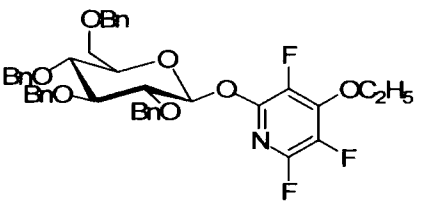
2,3,4,6-Tetra-O-benzyl-glucopyranose (**32**) (3.026 g, 5.6 mmol), sodium hydride (0.266 g, 6.66 mmol) and 4-ethoxy-2,3,5,6-tetrafluoropyridine (**5**) (1.028 g, 5.26 mmol) were heated at reflux temperature for 24h, affording *4-ethoxy-2,3,5-tetrafluoro-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxy)pyridine* (2.653 g, 70%) as a white syrup; shown to consist of two isomers in the ratio of 1:3. (Found: C, 68.8; H, 5.7; N, 2.0. $C_{41}H_{40}F_3NO_7$ requires C, 68.8; H, 5.6; N, 2.0%).

4-Ethoxy-2,3,5-tetrafluoro-6-(2,3,4,6-tetra-O-benzyl-α-$_D$-glucopyranosyloxy) pyridine (34α).



δ_H (CD_3CN) 1.38 (3H, t, $^3J_{HH}$ 7.0, OCH_2CH_3), 3.57 (1H, dd, $^2J_{HH}$ 11.0, $^3J_{HH}$ 2.0, CH_2 C6), 3.63 (1H, dd, $^2J_{HH}$ 11.0, $^3J_{HH}$ 2.0, CH_2 C6), 3.75 (1H, dd, $^3J_{H1H2}$ 3.6, $^3J_{H2H3}$ 9.7, CH C2), 3.80 (1H, t, $^3J_{HH}$ 9.7, CH C4), 3.88 (1H, dd, $^3J_{H5H6}$ 2.0, $^3J_{H4H5}$ 9.7, CH C5), 4.00 (1H, t, $^3J_{HH}$ 9.7, CH C3), 4.47 (2H, m, OCH_2CH_3), 4.33-4.52 (4H, m, OCH_2Ph C3/4), 4.65-4.92 (4H, m, OCH_2Ph C2/6), 6.39 (1H, d, $^3J_{H1H2}$ 3.6, CH C1), 7.20-7.37 (20H, m, OCH_2Ph); δ_C (CD_3CN) 15.8 (s, OCH_2CH_3), 69.5 (s, CH_2 C6), 71.5 (t, $^4J_{CF}$ 5.3, OCH_2CH_3), 73.5 (s, CH C4), 73.7 (s, OCH_2Ph C4), 73.8 (s, OCH_2Ph C6), 75.4 (s, OCH_2Ph C3), 76.1 (s, OCH_2Ph C2), 78.2 (s, CH C5), 80.4 (s, CH C2), 82.2 (s, CH C3), 94.2 (s, CH C1), 128.5-129.3 (m, OCH_2Ph), 134.1 (ddd, $^1J_{CF}$ 243.8, $^2J_{CF}$ 30.8, $^3J_{CF}$ 16.0, C3′), 137.8 (ddd, $^1J_{CF}$ 243.8, $^2J_{CF}$ 30.8, $^4J_{CF}$ 5.3, C5′), 139.2-139.9 (m, OCH_2C), 144.5 (tm, $^3J_{CF}$ 16.0, C6′), 145.6 (dd, $^1J_{CF}$ 243.8, $^2J_{CF}$ 30.8, C2′), 147.11 (tm, $^3J_{CF}$ 16.0, C4′); δ_F (CD_3CN) -93.64 (1F, t, J_{FF} 23.6, 2-F), -157.94 (1F, d, J_{FF} 23.6, 3-F), -164.52 (1F, d, J_{FF} 23.6, 5-F); m/z (ES^+) 738 (M^++Na^+,100), 739 (10).

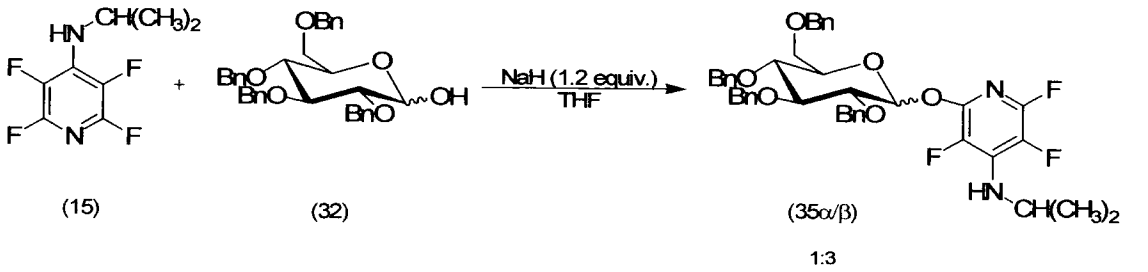
4-Ethoxy-2,3,5-tetrafluoro-6-(2,3,4,6-tetra-O-benzyl-β-$_D$-glucopyranosyloxy) pyridine (34β).



δ_H (CD_3CN) 1.40 (3H, t, $^3J_{HH}$ 7.0, OCH_2CH_3), 3.66 (2H, dd, $^2J_{HH}$ 10.0, $^3J_{H5H6}$ 2.8, CH_2 C6), 3.66-3.71 (3H, m, CH C2/3/4), 3.75 (1H, dt, $^3J_{H5H6}$ 2.8, $^3J_{H4H5}$ 9.8, CH C5), 4.47

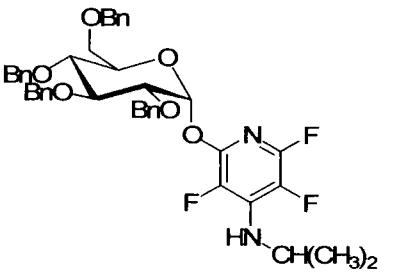
(2H, m, O$CH_2$$CH_3$), 4.33-4.52 (4H, m, O$CH_2$Ph C3/4), 4.65-4.92 (4H, m, OCH_2Ph C2/6), 5.39 (1H, d, $^3J_{H1H2}$ 3.6, CH C1), 7.20-7.37 (20H, m, OCH_2Ph); δ_C (CD_3CN) 15.8 (s, OCH_2CH_3), 69.6 (s, CH_2 C6), 71.5 (t, $^4J_{CF}$ 5.3, O$CH_2$$CH_3$), 73.7 (s, O$CH_2$Ph C3), 75.4 (s, O$CH_2$Ph C6), 75.6 (s, O$CH_2$Ph C4), 75.7 (s, CH C3), 76.0 (s, OCH_2Ph C2), 78.4 (s, CH C4), 82.2 (CH C2), 85.0 (s, CH C5), 98.0 (s, CH C1), 128.5-129.3 (m, OCH_2Ph), 134.2 (ddd, $^1J_{CF}$ 243.8, $^2J_{CF}$ 30.8, $^3J_{CF}$ 16.0, C3′), 137.8 (ddd, $^1J_{CF}$ 243.8, $^2J_{CF}$ 30.8, $^4J_{CF}$ 5.3, C5′), 139.2-139.9 (m, OCH_2C), 144.5 (tm, $^3J_{CF}$ 16.0, C6′), 145.6 (dd, $^1J_{CF}$ 243.8, $^2J_{CF}$ 30.8, C2′), 147.11 (tm, $^3J_{CF}$ 16.0, C4′); δ_F (CD_3CN) -93.62 (1F, t, J_{FF} 23.6, 2-F), -158.24 (1F, d, J_{FF} 23.6, 3-F), -164.21 (1F, d, J_{FF} 23.6, 5-F); m/z (ES^+) 738 (M^++Na^+,100), 739 (10).

2,3,5-Trifluoro-N-*iso*propyl-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopranosyloxy)pyridin-4-amine (35α/β)



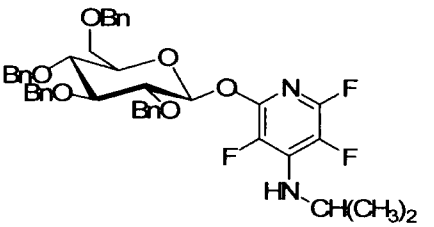
2,3,4,6-Tetra-O-benzyl-glucopyranose (**32**) (3.013 g, 5.6 mmol), sodium hydride (0.160 g, 6.66 mmol) and 2,3,5,6-tetrafluoro-N-*iso*propylpyridin-4-amine (**15**) (1.154 g, 5.55 mmol) were heated at reflux temperature for 24h, affording *2,3,5-trifluoro-N-isopropyl-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopranosyloxy)pyridin-4-amine (35α/β)* (2.064 g, 51%) as a white syrup; shown consist of two isomers in the ratio of 1:3. (Found: C, 69.3; H, 6.1; N, 3.7. $C_{42}H_{43}F_3N_2O_6$ requires C, 69.2; H, 6.0; N, 3.8%).

2,3,5-Trifluoro-N-*iso*propyl-6-(2,3,4,6-tetra-O-benzyl-α-D-glucopranosyloxy) pyridin-4-amine (35α).



δ_H (CD_3CN) 1.24 (6H, d, $^3J_{HH}$ 6.4, NCH(CH_3)$_2$), 3.59 (1H, dd, $^2J_{HH}$ 9.3, $^3J_{H5H6}$ 4.2, CH_2 C6), 3.64 (1H, dd, $^2J_{HH}$ 9.3, $^3J_{H5H6}$ 1.2, CH_2 C6), 3.72 (1H, dd, $^3J_{H2H3}$ 9.5, $^3J_{H1H2}$ 3.6, CH C2), 3.78 (1H, t, $^3J_{HH}$ 9.5, CH C4), 3.89 (1H, ddd, $^3J_{H4H5}$ 9.5, $^3J_{H5H6}$ 4.2, $^3J_{H5H6}$ 2.0, CH C5), 4.00 (1H, t, $^3J_{HH}$ 9.5, CH C3), 4.06-4.10 (2H, m, *H*NC*H*(CH_3)$_2$), 4.41 (4H, m, OCH_2Ph, C3/4), 4.71-4.95 (4H, m, OCH_2Ph C2/6), 6.37 (1H, d, $^3J_{H1H2}$ 3.6, CH C1), 7.20-7.38 (20H, m, OCH_2*Ph*); δ_C (CD_3CN) 23.9 (s, HNCH*(CH$_3$)$_2$*), 47.3 (m, NH*CH*(CH_3)$_2$), 64.7 (s, CH_2 C6), 73.3 (s, CH C4), 73.6 (s, OCH_2Ph C4), 73.7 (s, OCH_2Ph C6), 75.6 (s, OCH_2Ph C3), 75.7 (s, OCH_2Ph C2), 78.3 (s, CH C5), 80.4 (s, CH C2), 82.4 (s, CH C3), 93.7 (s, CH C1), 128.5-129.3 (m, OCH_2*Ph*), 130.6 (ddm, $^1J_{CF}$ 238.7, $^2J_{CF}$ 23.5, C3′), 133.7 (dd, $^1J_{CF}$ 238.7, $^4J_{CF}$ 4.8, C5′), 137.4 (td, $^3J_{CF}$ 12.1, $^4J_{CF}$ 4.8, C6′), 139.2-139.9 (m, OCH_2*C*), 143.9 (tm, $^3J_{CF}$ 12.1, C4′), 145.9 (dd, $^1J_{CF}$ 238.7, $^2J_{CF}$ 23.5, C2′); δ_F (CD_3CN) -95.97 (1F, t, J_{FF} 23.1, 2-F), -160.63 (1F, dd, J_{FF} 23.1, $^4J_{FF}$ 6.8, 3-F), -166.71 (1F, dd, J_{HH} 23.1, $^4J_{FF}$ 6.8, 5-F); m/z (ES^+) 751 (M^++Na^+,100), 752 (15).

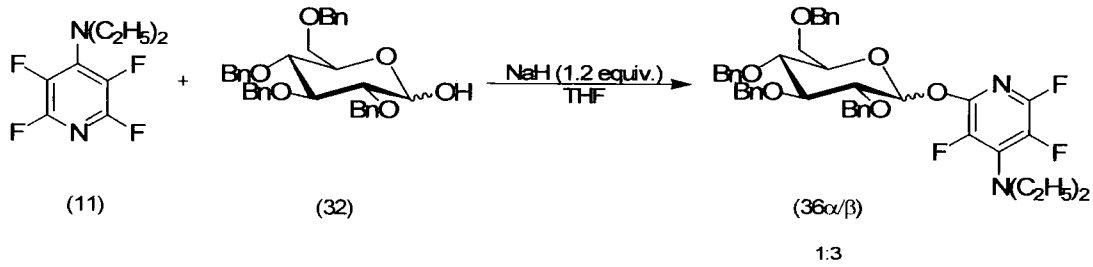
2,3,5-Trifluoro-N-*iso*propyl-6-(2,3,4,6-tetra-O-benzyl-β-D-glucopranosyloxy) pyridin-4-amine (35β).



δ_H (CD_3CN) 1.25 (6H, d, $^3J_{HH}$ 6.4, NCH*(CH$_3$)$_2$*), 3.67 (4H, m, CH C2/3/4/5), 3.64 (2H, dd, $^3J_{HH}$ 1.2, J_{HH} 9.2, CH_2 C6), 4.06-4.10 (2H, m, *H*NC*H*(CH_3)$_2$), 4.41-4.66 (4H, m,

O*CH*$_2$Ph C3/4), 4.71-4.95 (4H, m, O*CH*$_2$Ph C2/6), 5.80 (1H, d, $^3J_{H1H2}$ 8.0, CH C1), 7.20-7.38 (20H, m, OCH$_2$*Ph*); δ_C (CD_3CN) 23.9 (s, HNCH*(CH$_3$)$_2$*), 47.3 (m, NH*CH*(CH$_3$)$_2$), 69.6 (s, CH$_2$ C6), 73.7 (s, O*CH*$_2$Ph C3), 75.3 (s, O*CH*$_2$Ph C6), 75,5 (s, O*CH*$_2$Ph C4), 75.9 (s, CH C3), 76.1 (s, O*CH*$_2$Ph C2), 78.5 (s, CH C4), 82.3 (s, CH C2), 85.0 (s, CH C5), 97.7 (s, CH C1), 128.5-129.3 (m, OCH$_2$*Ph*), 130.6 (ddm, $^1J_{CF}$ 238.7, $^2J_{CF}$ 23.5, C3′), 133.7 (dd, $^1J_{CF}$ 238.7, $^4J_{CF}$ 4.8, C5′), 137.4 (td, $^3J_{CF}$ 12.1, $^4J_{CF}$ 4.8, C6′), 139.2 -139.9 (m, OCH$_2$*C*), 143.9 (tm, $^3J_{CF}$ 12.1, C4′), 145.9 (dd, $^1J_{CF}$ 238.7, $^2J_{CF}$ 23.5, C2′); δ_F (CD_3CN) -96.08 (1F, t, J_{FF} 22.6, 2-F), -161.20 (1F, dd, J_{FF} 22.6, $^4J_{FF}$ 6.8, 3-F), -166.48 (1F, dd, J_{HH} 22.6, $^4J_{FF}$ 6.8, 5-F); m/z (ES^+) 751 (M^++Na^+,100), 752 (15).

N,N-Diethyl-2,3,5-trifluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridin-4-amine (36α/β).

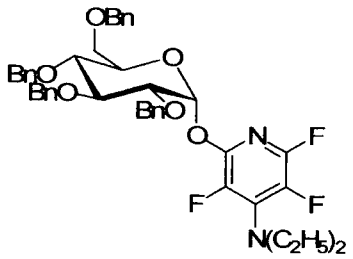


(11) (32) (36α/β)

1:3

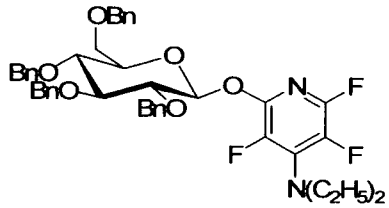
2,3,4,6-Tetra-O-benzyl-glucopyranose (**32**) (3.000 g, 5.6 mmol), sodium hydride (0.160 g, 6.66 mmol) and N,N-diethyl-2,3,5,6-tetrafluoropyridin-4-amine (**11**) (1.233 g, 5.6 mmol) were heated at reflux temperature for 24h, affording *N,N-diethyl-2,3,5-trifluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine-4-amine* ***(36α/β)*** (1.559 g, 40%) as a white syrup; shown to consist of two isomers in the ratio of 1:3. (Found: C, 69.5; H, 6.1; N, 3.6. $C_{43}H_{45}F_3N_2O_6$ requires C, 69.6; H, 6.1; N, 3.8%).

N,N-Diethyl-2,3,5-trifluoro-6-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy) pyridin-4-amine (36α).



δ_H (CD_3CN) 1.16 (6H, t, $^3J_{HH}$ 6.8, NCH_2CH_3), 3.38 (4H, q, $^3J_{HH}$ 6.8, NCH_2CH_3), 3.59 (1H, dd, $^2J_{HH}$ 11.0, $^3J_{H5H6}$ 2.0, CH_2 C6), 3.62-3.69 (2H, m, CH C4, CH_2 C6), 3.74 (1H, dd, $^3J_{H1H2}$ 3.6, $^3J_{H2H3}$ 9.6, CH C2), 3.90 (1H, ddd, $^3J_{H5H6}$ 2.0, $^3J_{H5H6}$ 2.4, $^3J_{H4H5}$ 9.6, CH C5), 4.00 (1H, t, $^3J_{HH}$ 9.6, CH C3), 4.45-4.65 (4H, m, OCH_2Ph C3/4), 4.75-4.97 (4H, m, OCH_2Ph C2/6), 6.40 (1H, d, $^3J_{H1H2}$ 3.6, CH C1), 7.23-7.37 (20H, m, OCH_2Ph); δ_C (CD_3CN) 14.1 (s, NCH_2CH_3), 47.1 (t, $^4J_{CF}$ 4.8, NCH_2CH_3), 69.6 (s, CH_2 C6), 73.3 (s, CH C4), 73.6 (s, OCH_2Ph C4), 73.6 (s, OCH_2Ph C6), 75.7 (s, OCH_2Ph C3), 76.1 (s, OCH_2Ph C2), 78.3 (s, CH C5), 80.4 (s, CH C2), 82.4 (s, CH C3), 93.8 (s, CH C1), 128.5-129.3 (m, OCH_2Ph), 134.4 (dd, $^1J_{FF}$ 242, $^2J_{FF}$ 23.9, C3′), 137.5 (dm, $^1J_{CF}$ 242.0, C5′), 139.43 (m, C6) 139.30-139.80 (m, OCH_2C), 144.7 (tm, $^3J_{CF}$ 15.1, C4′), 146.53 (dd, $^1J_{CF}$ 242.0, $^2J_{CF}$ 23.9, C2′); δ_F (CD_3CN) -96.21 (1F, t, J_{FF} 22.6, 2-F), -153.01 (1F, d, J_{FF} 22.6, 3-F), -159.46 (1F, d, J_{HH} 22.6, 5-F); m/z (ES^+) 765 (M^++Na^+,100), 766 (10).

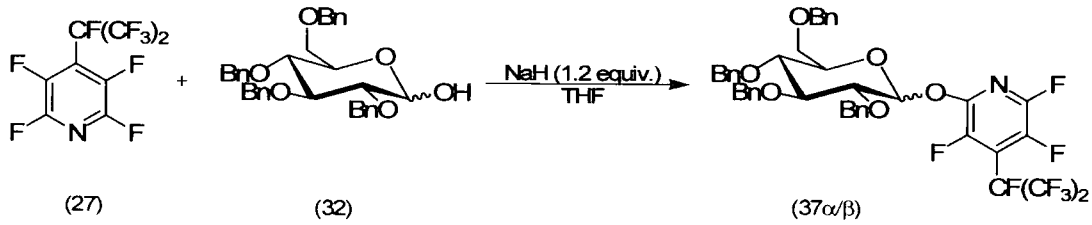
N,N-Diethyl-2,3,5-trifluoro-6-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyloxy) pyridin-4-amine (36β).



δ_H (CD_3CN) 1.18 (6H, t, $^3J_{HH}$ 6.8, NCH_2CH_3), 3.40 (4H, q, $^3J_{HH}$ 6.8, NCH_2CH_3), 3.60-3.70 (6H, m, CH C2/3/4/5, CH_2 C6), 4.45-4.65 (4H, m, OCH_2Ph C3/4), 4.75-4.97 (4H, m, OCH_2Ph C2/6), 5.83 (1H, d, $^3J_{H1H2}$ 7.6, CH C1), 7.23-7.37 (20H, m, OCH_2Ph); δ_C

(CD_3CN) 14.1 (s, NCH_2CH_3), 47.1 (t, $^4J_{CF}$ 4.8, NCH_2CH_3), 69.6 (s, CH_2 C6), 73.7 (s, OCH_2Ph C3), 75.3 (s, OCH_2Ph C6), 75.5 (s, OCH_2Ph C4), 76.0 (s, CH C3), 76.1 (s, OCH_2Ph C2), 78.5 (CH C4), 82.4 (s, CH C2), 85.0 (s, CH C5), 97.8 (s, CH C1), 128.5-129.3 (m, OCH_2Ph), 134.4 (dd, $^1J_{FF}$ 242, $^2J_{FF}$ 23.9, C3′), 137.5 (dm, $^1J_{CF}$ 242.0, C5′), 139.4 (m, C6′) 139.3-139.8 (m, OCH_2C), 144.7 (tm, $^3J_{CF}$ 15.1, C4′), 146.5 (dd, $^1J_{CF}$ 242.0, $^2J_{CF}$ 23.9, C2′); δ_F (CD_3CN) -96.29 (1F, t, J_{FF} 22.1, 2-F), -153.36 (1F, d, J_{FF} 22.1, 3-F), -159.27 (1F, d, J_{HH} 22.6, 5-F); m/z (ES^+) 765 (M^++Na^+,100), 766 (10).

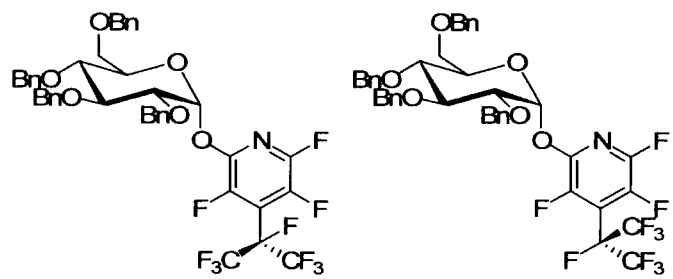
2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridine (37α/β).



(27) (32) (37α/β)

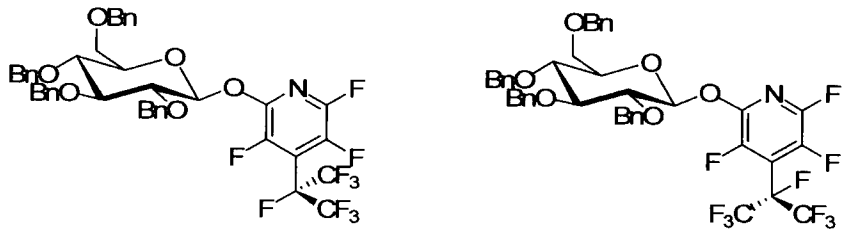
2,3,4,6-Tetra-O-benzyl-glucopyranose (**32**) (3.009 g, 5.6 mmol), sodium hydride (0.266 g, 6.6 mmol) and 2,3,5,6-tetrafluoro-4-(perfluoropropan-2-yl)pyridine (**27**) (1.755 g, 5.5 mmol) were heated at reflux temperature for 24h, affording *2,3,5-trifluoro-6-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridine (**37α**)* (1.608 g, 35%) and *2,3,5-trifluoro-6-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridine (**37β**)* (1.790 g, 39%) as white syrups after column chromatography.

2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridine (37α).



(Found C, 60.3; H, 4.4; N, 1.6. $C_{42}H_{35}F_{10}NO_6$ requires C, 60.1; H, 4.2; N, 1.7%); $[\alpha]_D^{20}$ +31 (c=1 $CHCl_3$); δ_H 3.63 (2H, dd, $^3J_{HH}$ 9.8, $^4J_{HH}$ 2.0, CH_2 C6), 3.81 (1H, dd, $^3J_{HH}$ 9.8, $^3J_{H1H2}$ 3.6, CH C2), 3.82 (1H, t, $^3J_{HH}$ 9.8, CH C4), 3.99 (1H, dm, $^3J_{HH}$ 9.8, CH C5), 4.15 (1H, t, $^3J_{HH}$ 9.8, CH C3),4.46-4.72 (4H, m, O*CH*$_2$Ph C3/4), 4.81-5.04 (4H, m, O*CH*$_2$Ph C2/6), 6.46 (1H, d, $^3J_{H1H2}$ 3.6, CH C1), 7.15-7.42 (20H, m, CH_2*Ph*); δ_C 68.0 (s, CH_2 C6), 73.1 (s, CH C4), 73.6 (s, O*CH*$_2$Ph C4), 73.8 (s, O*CH*$_2$Ph C6), 75.5 (s, O*CH*$_2$Ph C3), 76.0 (s, O*CH*$_2$Ph C2), 77.0 (s, CH C5), 79.5 (s, CH C2), 81.7 (s, CH C3), 94.7 (s, CH C1), 127.6-128.8 (m, OCH_2*Ph*), 137.7 (s, OCH_2*C* C4), 137.8 (s, OCH_2*C* C3), 138.0 (s, OCH_2*C* C6), 138.7 (s, OCH_2*C* C2); δ_F (major rotomer) -75.34 (6F, m, CF_3), -89.29 (1F, br s, 2-F), - 133.23 (1F, br s, 3-F), -146.14 (1F, br s, 5-F), -181.47 (1F, m, CF); δ_F (minor rotomer) -75.34 (6F, m, CF_3), -90.41 (1F, br s, 2-F), - 135.55 (1F, br s, 3-F), - 143.31 (1F, br s, 5-F), -181.47 (1F, m, CF); ratio major:minor 3:2; m/z (ES^+) 862 (M^++Na^+, 100), 863 (48), 864 (12).

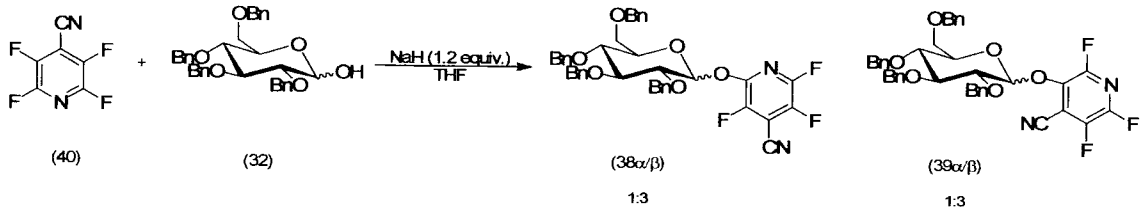
2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-β-$_D$-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridine (37β).



(Found C, 60.3; H, 4.4; N, 1.6. $C_{42}H_{35}F_{10}NO_6$ requires C, 60.1; H, 4.2; N, 1.7%); $[\alpha]_D^{20}$ +6 (c=1 $CHCl_3$); δ_H 3.70 (1H, m, CH C4), 3.77 (2H, m, CH_2 C6), 3.81 (3H, m, CH C2/3/5), 4.48 (1H, d, $^2J_{HH}$ 12.2, O*CH*$_2$Ph C3), 4.55 (1H, d, $^2J_{HH}$ 10.8, O*CH*$_2$Ph C4), 4.62 (1H, d, $^2J_{HH}$ 12.2, O*CH*$_2$Ph C3), 4.85 (1H, s, O*CH*$_2$Ph C6), 4.85 (1H, d, $^2J_{HH}$ 10.8, O*CH*$_2$Ph C4), 4.85 (1H, s, O*CH*$_2$Ph C6), 4.88 (1H, d, $^2J_{HH}$ 10.8, O*CH*$_2$Ph C2), 4.97 (1H, d, $^2J_{HH}$ 10.8, O*CH*$_2$Ph C2), 5.77 (1H, d, $^3J_{H1H2}$ 7.2, CH C1), 7.15-7.35 (20H, m, OCH_2*Ph*); δ_C 68.2 (s, CH2 C6), 73.6 (s, O*CH*$_2$Ph C 4), 75.2 (s, O*CH*$_2$Ph C3), 75.3 (s, O*CH*$_2$Ph C6), 75.6 (s, CH C4), 75.9 (s, O*CH*$_2$Ph C2), 77.3 (s, CH C3), 81.2 (s, CH C2), 84.7 (s, CH C5), 97.8 (s, CH C1), 127.9-128.1 (m, OCH_2*Ph*), 128.5-128.6 (m, OCH_2*Ph*), 137.9 (s, OCH_2*C* C4), 138.0 (s, OCH_2*C* C3), 138.1 (s, OCH_2*C* C6), 138.4 (s, OCH_2*C* C2); δ_F (major rotomer) -76.15 (6F, m, CF_3), -90.35 (1F, br s, 2-F), - 134.88

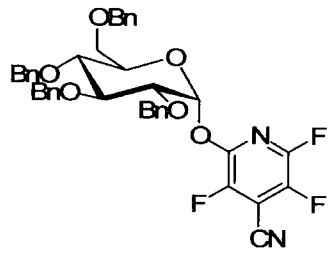
(1F, br s, 3-F), -147.08 (1F, br s, 5-F), -181.47 (1F, m, CF); δ_F (minor rotomer) -76.15 (6F, m, CF_3), -91.67 (1F, br s, 2-F), - 137.21 (1F, br s, 3-F), -144.18 (1F, br s, 5-F), -181.47 (1F, m, CF); ratio major:minor 6:5; m/z (ES^+) 862 (M^++Na^+, 100), 863 (48), 864 (12).

2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-α-$_D$-glucopyranosyloxy)pyridine-4-carbonitrile (38α/β, 39α/β).



2,3,4,6-Tetra-O-benzyl-glucopyranose (**32**) (3.051 g, 5.6 mmol), sodium hydride (0.266 g, 6.6 mmol) and 2,3,5,6-tetrafluoro-pyridine-4-carbonitrile (**41**) (0.925 g, 5.3 mmol) were heated at reflux temperature for 24h, affording a mixture of *2,3,5-trifluoro-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxy)pyridine-4-carbonitrile* ***(38α/β)*** (1.229 g, 34%) and *2,3,6-trifluoro-5-(2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxy)pyridine-4-carbonitrile* ***(39α/β)*** (1.180 g, 32%).

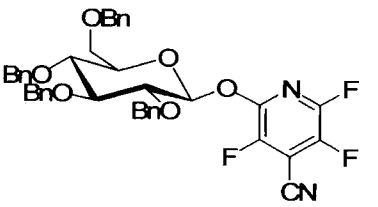
2,3,5-trifluoro-6-(2,3,4,6-tetra-O-benzyl-α-$_D$-glucopyranosyloxy)pyridine-4-carbonitrile (38α).



(Found C, 69.2; H, 5.4; N, 3.9. $C_{40}H_{35}F_3N_2O_6$ requires C, 69.0; H, 5.1; N, 4.0%); δ_H 3.64 (1H, dd, $^2J_{HH}$ 9.8, $^3J_{H5H6}$ 2.0, CH_2 C6), 3.71 (1H, dd, $^2J_{HH}$ 9.8, $^2J_{H5H6}$ 2.6, CH_2 C6), 3.80 (1H, dd, $^3J_{H1H2}$ 3.6, $^3J_{H2H3}$ 11, CH C2), 3.82 (1H, t, $^3J_{HH}$ 11, CH C4), 4.00 (1H, ddd, $^3J_{H4H5}$ 11, $^3J_{H5H6}$ 2.6, $^3J_{H5H6}$ 2.0, CH C5), 4.15 (1H, t, $^3J_{H2H3}$ 11, CH C3), 4.47-4.68 (4H, m, O*CH*$_2$Ph C3/4), 4.80-5.04 (4H, m, O*CH*$_2$Ph C2/6), 6.46 (1H, d, $^3J_{H1H2}$ 3.6, CH C1),

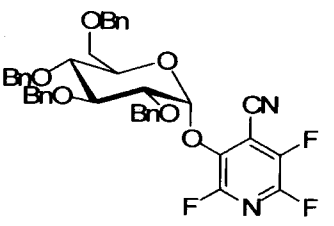
7.17-7.41 (20H, m, OCH_2Ph); δ_C 68.0 (s CH_2 C6), 73.2 (s, CH C4), 73.6 (s, OCH_2Ph C4), 73.8 (s, OCH_2Ph C6), 75.5 (s, OCH_2Ph C3), 76.00 (s, OCH_2Ph C2), 76.9 (s, CH C5), 79.4 (s, CH C2), 81.6 (s, CH C3), 95.2 (s, CH C1), 127.2-128.7 (m, OCH_2Ph), 137.5-139.0 (m, OCH_2C); δ_F -87.74 (1F, m, 2-F), -130.74 (1F, dd, $^4J_{FF}$ 26.1, J_{FF} 7.6, 3-F), -141.04 (1F, $^4J_{FF}$ 26.1, J_{FF} 7.6, 5-F); m/z (ES^+) 731 (M^++1.5 Na^+, 100).

2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyloxy)pyridine-4-carbonitrile (38β).



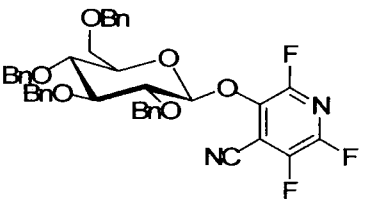
(Found C, 69.2; H, 5.4; N, 3.9. $C_{40}H_{35}F_3N_2O_6$ requires C, 69.0; H, 5.1; N, 4.0%); δ_H 3.75 (2H, dd, $^3J_{HH}$ 10.6, J_{HH} 1.9, CH_2 C6), 3.78-3.84 (2H, m, CH C3/4), 3.81 (1H, dt, $^3J_{HH}$ 10.6, J_{HH} 3.0, CH C5), 3.82 (1H, dd, $^3J_{H1H2}$ 7.6, $^3J_{H2H3}$ 10.6, CH C2), 4.47-4.68 (4H, m, OCH_2Ph C3, C4), 4.80-5.04 (4H, m, OCH_2Ph C2/6), 5.80 (1H, d, $^3J_{H1H2}$ 7.6, CH C1), 7.17-7.41 (20H, m, OCH_2Ph); δ_C 68.2 (s, CH_2 C6), 73.6 (s, OCH_2Ph C3), 75.1 (s, OCH_2Ph C6), 75.2 (s, OCH_2Ph C4), 75.6 (s, CH C3), 75.8 (s, OCH_2Ph C2), 77.1 (s, CH C4), 81.2 (s, CH C2), 84.6 (s, CH C5), 97.9 (s, CH C1), 127.2-128.7 (m, OCH_2Ph), 137.5-139.0 (m, OCH_2C); δ_F -87.74 (1F, m, 2-F), -131.04 (1F, dd, $^4J_{FF}$ 26.0, J_{FF} 7.5, 3-F), -140.87 (1F, $^4J_{FF}$ 26.0, J_{FF} 7.5, 5-F); m/z (ES^+) 731 (M^++1.5Na^+, 100).

2,3,6-Trifluoro-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)pyridine-4-carbonitrile (39α).



(Found C, 69.1; H, 5.2; N, 4.1. $C_{40}H_{35}F_3N_2O_6$ requires C, 69.0; H, 5.1; N, 4.0%); δ_H 3.66 (1H, dd, $^2J_{HH}$ 10.6, $^3J_{HH}$ 2.5, CH_2 C6), 3.70 (1H, dd, $^2J_{HH}$ 10.6, $^3J_{HH}$ 2.5, CH_2 C6), 3.78 (1H, dd, $^3J_{H2H3}$ 9.5, $^3J_{H1H2}$ 3.6, CH C2), 3.79 (1H, t, $^3J_{HH}$ 9.5, CH C4), 4.19 (1H, dt, $^3J_{HH}$ 9.8, $^3J_{H5H6}$ 2.6, CH C5), 4.25 (1H, t, $^3J_{HH}$ 9.5, CH C3), 4.40-4.68 (4H, m, O*CH*$_2$Ph C3/4), 4.78-5.08 (4H, m, O*CH*$_2$Ph C2/6), 5.72 (1H, d, $^3J_{H1H2}$ 3.6, CH C1), 7.15-7.40 (20H, m, OCH$_2$*Ph*); δ_C 67.8 (s, CH_2 C6), 73.6 (s, CH C4), 74.6 (s, O*CH*$_2$Ph C4), 75.3 (s, O*CH*$_2$Ph C6), 75.7 (s, O*CH*$_2$Ph C3), 76.1 (O*CH*$_2$Ph C2), 76.8 (s, CH C5), 79.9 (s, CH C2), 81.4 (s, CH C3), 102.0 (s, CH C1), 127.7-128.7 (m, OCH$_2$*Ph*), 137.2-138.5 (m, OCH$_2$*C*); δ_F -79.42 (1F, dd, J_{FF} 30.5, $^4J_{FF}$ 13.2, 6-F), -89.25 (1F, m, 2-F), -135.23 (1F, dd, J_{FF} 30.5, $^3J_{FF}$ 20.7, 3-F); m/z (ES$^+$) 731 (M^++1.5Na^+, 100).

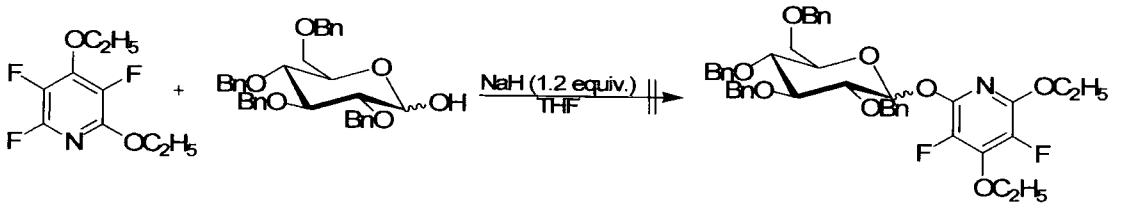
2,3,6-Trifluoro-5-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyloxy)pyridine-4-carbonitrile (39β).



(Found C, 69.1; H, 5.2; N, 4.1. $C_{40}H_{35}F_3N_2O_6$ requires C, 69.0; H, 5.1; N, 4.0%); δ_H 3.57 (2H, m, CH_2 C6), 3.78 (1H, dd, $^3J_{H1H2}$ 7.4, $^3J_{H2H3}$ 11.0, CH C2), 3.74-3.82 (3H, m, CH C3/4/5), 4.40-4.68 (4H, m, O*CH*$_2$Ph C3/4), 4.78-5.08 (4H, m, O*CH*$_2$Ph C2/6), 5,28 (1H, d, $^3J_{H1H2}$ 7.4, CH C1), 7.15-7.40 (20H, m, OCH$_2$*Ph*); δ_C 68.5 (s, CH_2 C6), 73.6 (s, O*CH*$_2$Ph C3), 73.7 (s, O*CH*$_2$Ph C4), 75.2 (s, O*CH*$_2$Ph C6), 75.4 (s, CH C3), 75.8 (s, O*CH*$_2$Ph C2), 77.1 (s, CH C4), 81.9 (s, CH C2), 84.2 (s, CH C5), 103.4 (s, CH C1), 127.7-128.7 (m, OCH$_2$*Ph*), 137.2-138.5 (m, OCH$_2$*C*); δ_F -80.92 (1F, dd, J_{FF} 30.4, $^4J_{FF}$ 13.4, 6-), -89.25 (1F, m, 2-F), -135.55 (1F, dd, J_{FF} 30.4, $^3J_{FF}$ 20.7, 3-F) ; m/z (ES$^+$) 731 (M^++1.5Na^+, 100).

Procedure for the Synthesis of Tri-substituted Donors

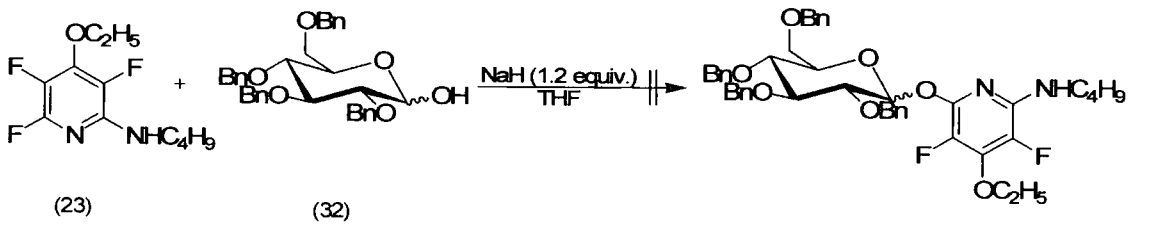
Attempted Synthesis of 4-ethoxy-3,5-difluoro-2-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)-6-propoxypyridine



(32)

2,3,4,6-Tetra-O-benzyl-glucopyranose (**32**) (1.002 g, 1.85 mmol) was dissolved in dry THF (5 mL) and stirred with sodium hydride (0.091 g, 2.28 mmol) until hydrogen evolution had subsided. The resulting solution was added dropwise, while stirring at room temperature, to 2,4-diethoxy-3,5,6-trifluoropyridine (**6**) (0.417 g, 1.37 mmol), then heated at reflux temperature. After 82h the reaction was shown to consist of only *2,4-diethoxy-3,5,6-trifluoropyridine (6)* by ^{19}F NMR. A further equivalent of 2,3,4,6-tetra-O-benzyl-glucopyranose (**32**) (1.001 g, 1.85 mmol) was dissolved in dry THF (5 mL) and stirred with sodium hydride (0.089 g, 2.23 mmol) until hydrogen evolution subsided. The resulting solution was added to the reaction mixture over 30 minutes. The reaction mixture was heated at reflux temperature for a further 72h, analysis by ^{19}F NMR showed the reaction consisted of only *2,4-diethoxy-3,5,6-trifluoropyridine (6)*. Spectroscopic data were consistent with previously recorded results.

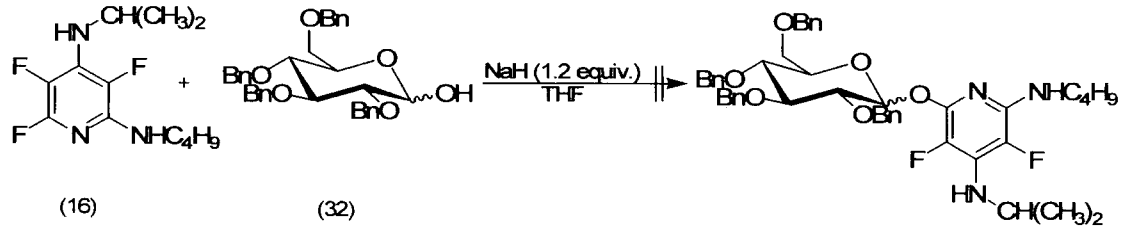
Attempted Synthesis of N-butyl-4-ethoxy-3,5-difluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridin-2-amine



(23) (32)

2,3,4,6-Tetra-O-benzyl-glucopyranose (**32**) (0.987 g, 1.83 mmol) was dissolved in dry THF (5 mL) and stirred with sodium hydride (0.091 g, 2.28 mmol) until hydrogen evolution had subsided. The resulting solution was added dropwise, while stirring at room temperature, to N-butyl-4-ethoxy-3,5,6-trifluoropyridin-2-amine (**23**) (0.435 g, 1.75 mmol), then heated at reflux temperature. After 82h the reaction was shown to consist of only *N-butyl-4-ethoxy-3,5,6-trifluoropyridin-2-amine (23)* by ^{19}F NMR. A further equivalent of 2,3,4,6-tetra-O-benzyl-glucopyranose (**32**) (0.993 g, 1.84 mmol) was dissolved in dry THF (5 mL) and stirred with sodium hydride (0.089 g, 2.23 mmol) until hydrogen evolution subsided. The resulting solution was added to the reaction mixture over 30 minutes. The reaction mixture was heated at reflux temperature for a further 72h, analysis by ^{19}F NMR showed the reaction consisted of only *4-ethoxy-2,3,5-trifluoro-6-propoxypyridine (23)*. Spectroscopic data were consistent with previously recorded results.

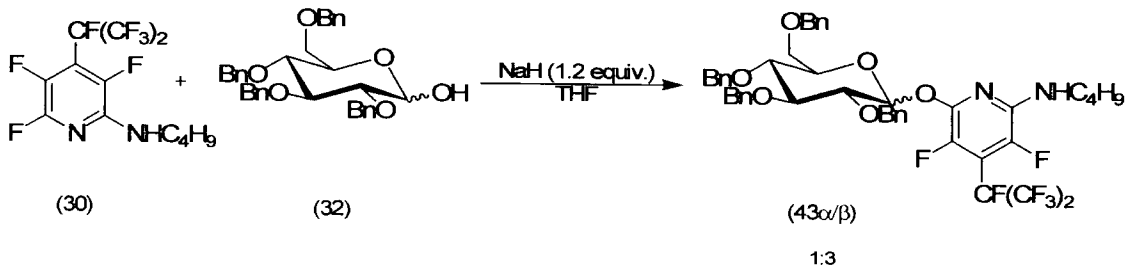
N^2-Butyl-3,5-difluoro-N^4-*iso*propyl-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy) pyridine-2,4-diamine



(16) (32)

2,3,4,6-Tetra-O-benzyl-glucopyranose (**32**) (1.078 g, 1.99 mmol) was dissolved in dry THF (5 mL) and stirred with sodium hydride (0.093 g, 2.33 mmol) until hydrogen evolution had subsided. The resulting solution was added dropwise, while stirring at room temperature, to N^2-butyl-3,5,6-trifluoro-N^4-*iso*propylpyridine-2,4-diamine (**16**) (0.143 g, 0.55 mmol), then heated at reflux temperature for 6.5 days. Analysis by ^{19}F NMR showed the reaction consisted of only *N^2-butyl-3,5,6-trifluoro-N^4-isopropylpyridine-2,4-diamine (16)*. Spectroscopic data were consistent with previously recorded results.

N-Butyl-3,4-difluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridin-2-amine (43α/β).

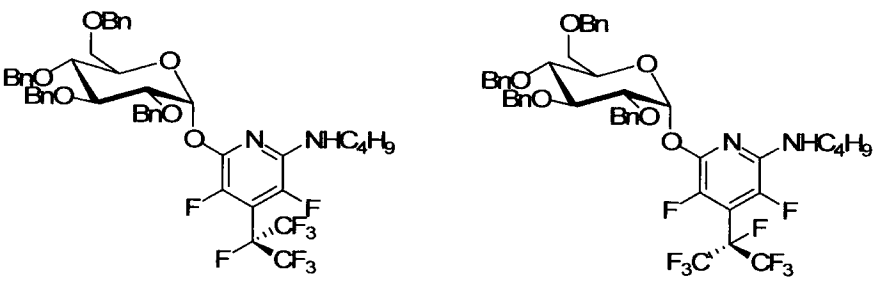


(30) (32) (43α/β)

1:3

2,3,4,6-Tetra-O-benzyl-glucopyranose (**32**) (1.059 g, 1.96 mmol) was dissolved in dry THF (5.0 mL) and stirred with sodium hydride (0.094 g, 2.35 mmol) until hydrogen evolution had subsided. The resulting solution was added dropwise, while stirring at room temperature, to N-butyl-3,4,6-trifluoro-4-(perfluoropropan-2-yl)pyridin-2-amine (**30**) (0.688 g, 1.73 mmol), then heated at reflux temperature for 72h. The reaction was allowed to cool to room temperature before Amberlite (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.50 g) was added with stirring at room temperature for 30 minutes and the solvent removed on a rotary evaporator. Purification by HPFC using silica gel (1:10 ethyl acetate:hexane) yielded *N-butyl-3,4-difluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridin-2-amine* ***(43α/β)*** (0.667 g, 43%, 26:74 α:β) as a mixture of anomers as a pale yellow syrup.

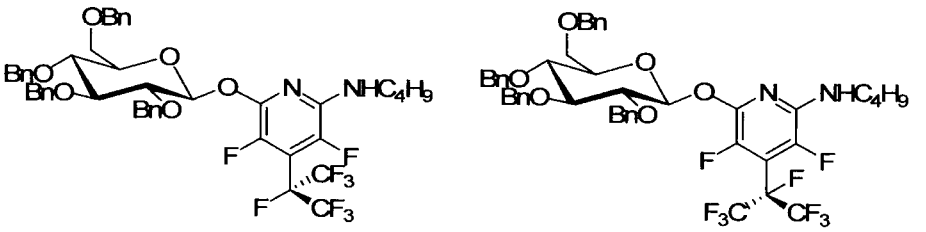
N-Butyl-3,4-difluoro-6-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridin-2-amine (43α).



(Found C, 62.2; H, 5.3; N, 2.9. $C_{46}H_{45}F_9N_2O_6$ requires C, 61.9; H, 5.1; N, 3.1%); δ_H 0.87 (3H, t, $^3J_{HH}$ 7.1, $HN(CH_2)_3CH_3$), 1.24-1.35 (2H, m, $HN(CH2)_2CH_2CH_3$), 1.44-1.53 (2H, m, $HNCH_2CH_2CH_2CH_3$), 3.17 (2H, q, $^3J_{HH}$ 7.1, $HNCH_2(CH_2)_2CH_3$), 3.58 (2H, dd,

$^3J_{HH}$ 2.2, $^3J_{HH}$ 9.2, CH_2 C6), 3.63-3.70 (3H, m, CH C2/3/5), 4.10 (1H, t, $^3J_{HH}$ 9.2 CH C4), 4.32-4.56 (4H, m, O*CH*$_2$Ph C3/4), 4.66-4.95 (4H, m, O*CH*$_2$Ph C2/6), 6.45 (1H, d, $^3J_{H1H2}$ 3.2, CH C1), 7.05-7.30 (20H, m, CH_2*Ph*); δ_C 14.0 (s, NH$(CH_2)_3$*CH*$_3$), 20.3 (s, HN$(CH_2)_2$*CH*$_2$$CH_3$), 31.7 (s, HNCH$_2$*CH*$_2$$CH_2CH_3$), 41.1 (s, HN*CH*$_2$$(CH_2)_2CH_3$), 68.0 (s, CH_2 C6), 72.2 (s, CH C4), 73.2 (s, O*CH*$_2$Ph), 73.6 (s, O*CH*$_2$Ph), 75.4 (s, O*CH*$_2$Ph), 76.0 (s, O*CH*$_2$Ph), 77.4 (s, CH C5), 79.3 (s, CH C2), 82.0 (s, CH C3), 93.2 (s, CH C1), 127.8-128.7 (m, OCH$_2$*Ph*), 137.9-138.8 (s, OCH$_2$*C*); δ_F (rotomer A) -75.86 (6F, m, CF_3), - 144.87 (1F, br s, 5-F), -152.56 (1F, br s, 3-F), -18.19 (1F, m, CF); δ_F (rotomer B) -75.86 (6F, m, CF_3), - 147.53 (1F, br s, 5-F), -155.74 (1F, br s, 3-F), -180.19 (1F, m, CF); ratio A:B 1:1; m/z (ES^+) 915 (M^++Na^+, 100).

N-Butyl-3,4-difluoro-6-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridin-2-amine (43β).



(Found C, 62.2; H, 5.3; N, 2.9. $C_{46}H_{45}F_9N_2O_6$ requires C, 61.9; H, 5.1; N, 3.1 δ_H 0.84 (3H, t, $^3J_{HH}$ 7.0, HN$(CH_2)_3$*CH*$_3$), 1.24-1.35 (2H, m, HN(CH2)$_2$*CH*$_2$$CH_3$), 1.44-1.53 (2H, m, HNCH$_2$*CH*$_2$$CH_2CH_3$), 3.26 (2H, q, $^3J_{HH}$ 7.0, HN*CH*$_2$$(CH_2)_2CH_3$), 3.53 (2H, dd, $^3J_{HH}$ 2.4, $^3J_{HH}$ 11.0, CH_2 C6), 3.63-3.70 (3H, m, CH C2/3/5), 4.11 (1H, t, $^3J_{HH}$ 11.0, CH C4), 4.32-4.56 (4H, m, O*CH*$_2$Ph C3/4), 4.66-4.95 (4H, m, O*CH*$_2$Ph C2/6), 5.70 (1H, d, $^3J_{H1H2}$ 7.0, CH C1), 7.05-7.30 (20H, m, CH_2*Ph*); δ_C 14.0 (s, NH$(CH_2)_3$*CH*$_3$), 20.3 (s, HN$(CH_2)_2$*CH*$_2$$CH_3$), 31.6 (s, HNCH$_2$*CH*$_2$$CH_2CH_3$), 41.1 (s, HN*CH*$_2$$(CH_2)_2CH_3$), 68.5 (s, CH_2 C6), 73.6 (s, O*CH*$_2$Ph), 75.3 (s, O*CH*$_2$Ph), 75.4 (s, O*CH*$_2$Ph), 75.7 (s, CH C4), 75.9 (s, O*CH*$_2$Ph), 77.6 (s, CH C3), 81.3 (s, CH C2), 84.9 (s, CH C5), 97.3 (s, CH C1), 127.8-128.7 (m, OCH$_2$*Ph*), 137.9-138.8 (s, OCH$_2$*C*); δ_F (rotomer A) -75.86 (6F, m, CF_3), - 145.53 (1F, br s, 5-F), -153.91 (1F, br s, 3-F), -180.19 (1F, m, CF); δ_F (rotomer B) -75.86 (6F, m, CF_3), - 148.67 (1F, br s, 5-F), -157.05 (1F, br s, 3-F), -180.19 (1F, m, CF); ratio A:B 1:1; m/z (ES^+) 862 (M^++Na^+, 100), 915 (100).

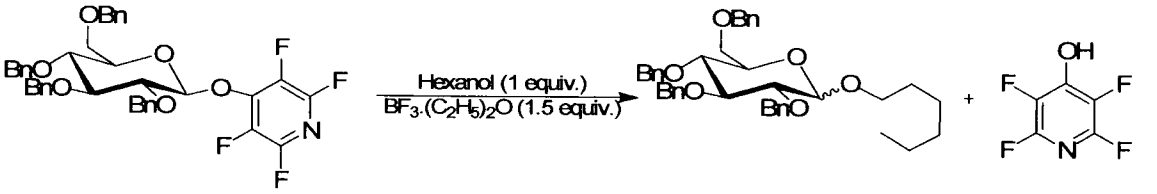
8.4 Experimental to Chapter 6

Glycosylation Reactions with Simple Alcohols

General procedure. Under an argon atmosphere the glycosyl donor and alcohol were dissolved in dry acetonitrile. Boron trifluoride diethyl etherate was added and the reaction stirred at room temperature. The pyridin-ol derivative was identified by ^{19}F NMR spectroscopy of the reaction mixture (consistent with authentic samples); but not isolated. The reaction mixture was then concentrated in vacuo, purification by high pressure flash chromatography (1:10 ethyl acetate:hexane) gave the corresponding saccharide.

Glycosyl Acceptor: Hexanol

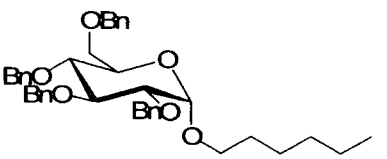
2,3,5,6-Tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine (33β).



(33β) (44α/β) (46)

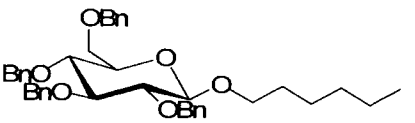
2,3,5,6-Tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine (0.342 g, 0.50 mmol, 100% β), hexan-1-ol (51 mg, 0.50 mmol) and boron trifluoride diethyl etherate (0.106 g, 0.75 mmol) were dissolved in acetonitrile (12.5 mL) and stirred at room temperature for 24h, affording *hexyl 2,3,4,6-tetra-O-benzyl-D-glycopyranoside* (0.243 g, 78%, 19:1 α:β). (Found: C, 76.7; H, 7.5. $C_{40}H_{48}O_6$ requires C, 76.9; H, 7.7%).

Hexyl 2,3,4,6-tetra-O-benzyl-α-D-glycopyranoside (44α).



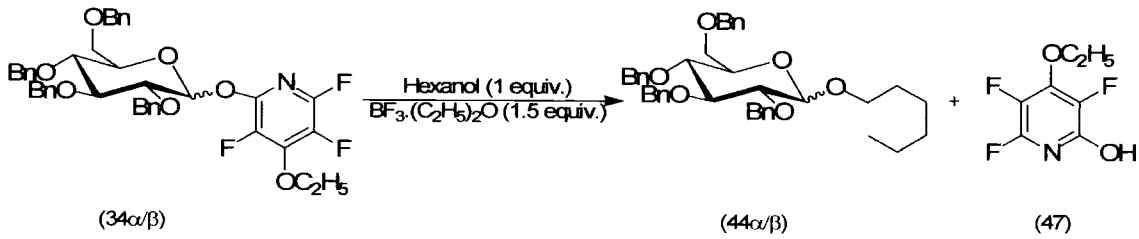
$[\alpha]_D^{20}$ +33° (c 0.5, $CHCl_3$); δ_H 0.87 (3H, m, $O(CH_2)_5CH_3$), 1.28 (6H, m, CH_2), 1.61 (2H, m, $OCH_2CH_2(CH_2)_3CH_3$), 3.44 (2H, t, $^3J_{HH}$ 7.2, $OCH_2(CH_2)_4CH_3$), 3.55 (1H, dd, $^3J_{H1H2}$ 3.4, $^3J_{H2H3}$ 9.8, CH C2), 3.61 (1H, dd, $^3J_{HH}$ 2.4, $^3J_{HH}$ 9.8, CH_2 C6), 3.70 (1H, dm, $^3J_{HH}$ 9.8, CH C3), 3.74 (1H, dd, $^3J_{HH}$ 9.8, $^3J_{HH}$ 2.4, CH_2 C6), 3.98 (1H, t, $^3J_{HH}$ 9.8, CH C4), 3.90 (1H, dd, $^3J_{HH}$ 9.8, $^3J_{HH}$ 2.4, CH C5), 4.44-5.02 (8H, m, OCH_2Ph), 4.65 (1H, d, $^3J_{H1H2}$ 3.2, CH C1), 7.11-7.38 (20H, m, OCH_2Ph); δ_C 14.2 (s, $O(CH_2)_5CH_3$), 22.7 (s, CH_2 hexyl), 25.9 (s, CH_2 hexyl), 29.5 (s, $OCH_2CH_2(CH_2)_3CH_3$), 31.8 (s, CH_2 hexyl), 67.8 (s, $OCH_2(CH_2)_4CH_3$), 68.3 (s, CH_2 C6), 70.2 (s, CH C4), 70.3 (s, OCH_2Ph), 73.6 (s, OCH_2Ph), 75.1 (s, OCH_2Ph), 75.8 (s, OCH_2Ph), 77.9 (s, CH C5), 80.2 (s, CH C2), 82.2 (s, CH C3), 97.9 (s, CH C1), 127.4-128.7 (m, OCH_2Ph), 138.1-139.1(m, OCH_2C); m/z (ES^+) 647 (M^++Na^+,100). Spectroscopic data were consistent with literature values.[139, 140]

Hexyl 2,3,4,6-tetra-O-benzyl-β-D-glycopyranoside (44β).



$[\alpha]_D^{20}$ +5° (c 0.5, $CHCl_3$); δ_H 0.87 (3H, m, $O(CH_2)_5CH_3$), 1.28 (6H, m, CH_2), 1.49 (2H, m, $OCH_2CH_2(CH_2)_3CH_3$), 3.42 (1H, dd, $^3J_{H2H3}$ 10.3, $^3J_{H1H2}$ 7.3, CH C2), 3.51-4.00 (2H, m, CH C3/5), 3.55 (1H, t, $^3J_{HH}$ 10.3 CH C4), 3.64 (1H, dd, , $^3J_{HH}$ 10.3, $^3J_{HH}$ 1.8CH_2 C6), 3.71 (2H, t, $^3J_{HH}$ 7.3, $OCH_2(CH_2)_4CH_3$), 3.75 (1H, dd, $^3J_{HH}$ 1.8, $^3J_{HH}$ 10.3, CH_2 C6), 4.44-5.02 (8H, m, OCH_2Ph), 4.38 (1H, d, $^3J_{H1H2}$ 7.3, CH C1), 7.11-7.38 (20H, m, OCH_2Ph); δ_C 14.2 (s, $O(CH_2)_5CH_3$), 22.7 (s, CH_2 hexyl), 25.9 (s, CH_2 hexyl), 29.9 (s, $OCH_2CH_2(CH_2)_3CH_3$), 31.7 (s, CH_2 hexyl), 68.6 (s, CH_2 C6), 69.1 (s, $OCH_2(CH_2)_4CH_3$), 73.2 (s, CH C4), 73.2 (s, OCH_2Ph), 73.6 (s, OCH_2Ph), 74.9 (s, OCH_2Ph), 75.3 (s, OCH_2Ph), 78.0 (s, CH C5), 82.4 (s, CH C2), 84.8 (s, CH C3), 103.8 (s, CH C1), 127.4-128.7 (m, OCH_2Ph), 138.1-139.1(m, OCH_2C); m/z (ES^+) 647 (M^++Na^+,100). Spectroscopic data were consistent with literature values.[139, 140]

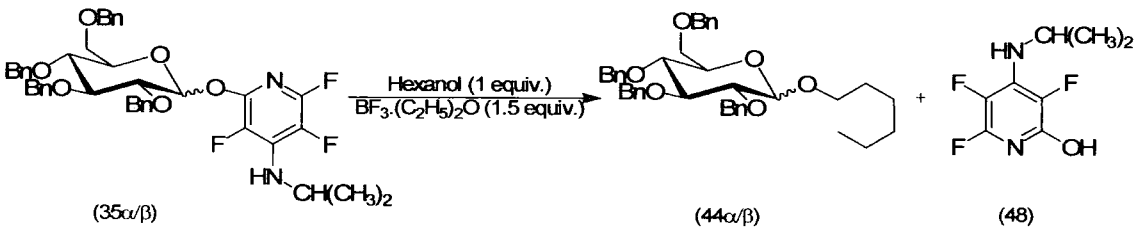
4-Ethoxy-2,3,5-tetrafluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine (34α/β).



(34α/β) (44α/β) (47)

4-Ethoxy-2,3,5-tetrafluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine (**34**) (0.374 g, 0.52 mmol, 36:64 α:β), hexan-1-ol (51 mg, 0.50 mmol) and boron trifluoride diethyl etherate (0.106 g, 0.75 mmol) were dissolved in acetonitrile (12.5 mL) and stirred at room temperature for 24h, affording *hexyl 2,3,4,6-tetra-O-benzyl-D-glycopyranoside* ***(44α/β)*** (0.225 g, 69%, 62:38 α:β), spectroscopic data is consistent with the values given above.

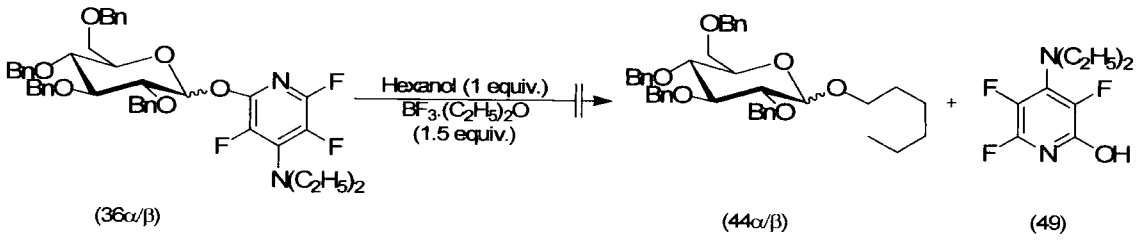
2,3,5-Trifluoro-N-*iso*propyl-6-(2,3,4,6-tetra-O-benzyl-D-glucopranosyloxy)pyridin-4-amine (35α/β).



(35α/β) (44α/β) (48)

2,3,5-trifluoro-N-*iso*propyl-6-(2,3,4,6-tetra-O-benzyl-D-glucopranosyloxy)pyridin-4-amine (**35α/β**) (0.378 g, 0.52 mmol, 36:64 α:β), hexan-1-ol (51 mg, 0.50 mmol) and boron trifluoride diethyl etherate (0.106 g, 0.75 mmol) were dissolved in acetonitrile (12.5 mL) and stirred at room temperature for 24h, affording *hexyl 2,3,4,6-tetra-O-benzyl-D-glycopyranoside* ***(44α/β)*** (0.305 g, 94%, 64:36 α:β), spectroscopic data is consistent with previous results.

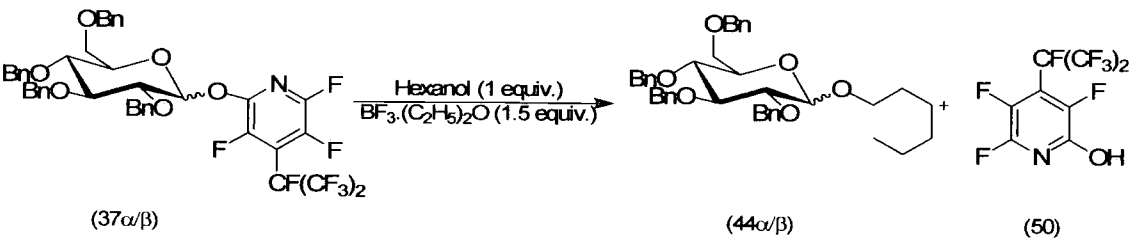
N,N-Diethyl-2,3,5-trifluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridin-4-amine (36α/β).



(36α/β) (44α/β) (49)

N,N-Diethyl-2,3,5-trifluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridin-4-amine (**36α/β**) (0.390 g, 0.53 mmol, 36:64 α:β), hexan-1-ol (51 mg, 0.50 mmol) and boron trifluoride diethyl etherate (0.106 g, 0.75 mmol) were dissolved in acetonitrile (12.5 mL) and stirred at room temperature for 24h, affording *N,N-diethyl-2,3,5-trifluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridin-4-amine (**36α/β**)* (0.342 g, 87% 36:64 α:β), spectroscopic data is consistent with previous results.

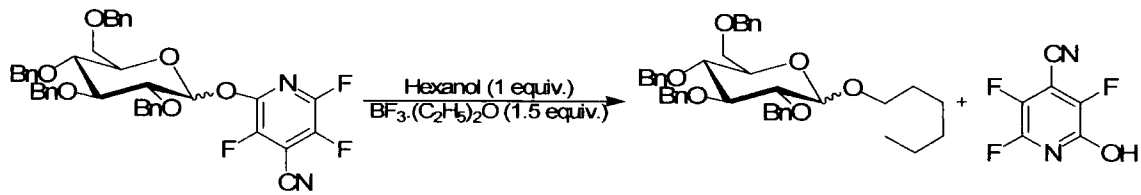
2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridine (37α/β).



(37α/β) (44α/β) (50)

2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridine (**37α/β**) (0.420 g, 0.50 mmol, 36:64 α:β), hexan-1-ol (51 mg, 0.50 mmol) and boron trifluoride diethyl etherate (0.106 g, 0.75 mmol) were dissolved in acetonitrile (12.5 mL) and stirred at room temperature for 24h, affording *hexyl 2,3,4,6-tetra-O-benzyl-D-glycopyranoside (**44α/β**)* (0.295 g, 94%, 63:37 α:β), spectroscopic data is consistent with previous results.

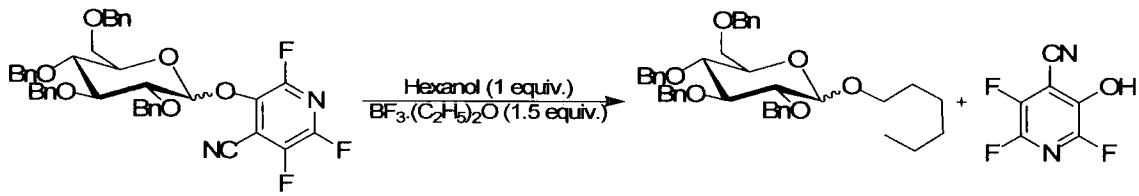
2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyloxy)pyridine-4-carbonitrile (38α/β).



(38α/β) (44α/β) (51)

2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine-4-carbonitrile (**38α/β**) (0.350 g, 0.50 mmol, 36:64 α:β), hexan-1-ol (51 mg, 0.50 mmol) and boron trifluoride diethyl etherate (0.106 g, 0.75 mmol) were dissolved in acetonitrile (12.5 mL) and stirred at room temperature for 24h, affording *hexyl 2,3,4,6-tetra-O-benzyl-D-glycopyranoside* ***(44α/β)*** (0.200 g, 64%, 64:36 α:β), spectroscopic data is consistent with previous results.

2,3,5-Trifluoro-5-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyloxy)pyridine-4-carbonitrile (39α/β).

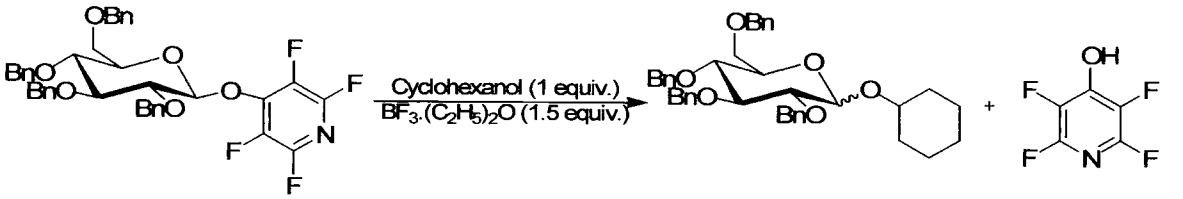


(39α/β) (44α/β) (52)

2,3,5-Trifluoro-5-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine-4-carbonitrile (**39α/β**) (0.139 g, 0.20 mmol, 36:64 α:β), hexan-1-ol (29 mg, 0.20 mmol) and boron trifluoride diethyl etherate (43 mg, 0.30 mmol) were dissolved in acetonitrile (12.5 mL) and stirred at room temperature for 24h, affording *hexyl 2,3,4,6-tetra-O-benzyl-D-glycopyranoside* ***(44α/β)*** (75 g, 60%, 70:30 α:β), spectroscopic data is consistent with previous results.

Glycosyl Acceptor: Cyclohexanol

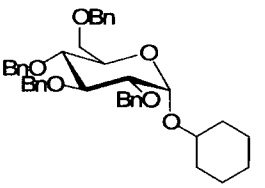
2,3,5,6-Tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-β-$_D$-glucopyranosyloxy)pyridine (33β).



(33α/β) (45α/β) (46)

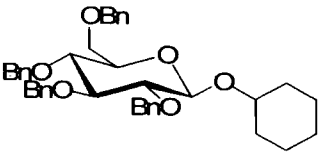
2,3,5,6-Tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-β-$_D$-glucopyranosyloxy)pyridine **(33β)** (1.519 g, 2.20 mmol, 100% β), cyclohexanol (0.204 g, 2.04 mmol) and boron trifluoride diethyl etherate (0.370 g, 2.60 mmol) were dissolved in acetonitrile (15.0 mL) and stirred at room temperature for 1h, affording *cyclohexyl 2,3,4,6-tetra-O-benzyl-$_D$-glycopyranoside **(45α/β)*** (0.746 g, 59%, 98:2 α:β) as a mixture of anomers. (Found: C, 77.4; H, 7.4. $C_{40}H_{46}O_6$ requires C, 77.1; H, 7.4%).

Cyclohexyl 2,3,4,6-tetra-O-benzyl-α-$_D$-glycopyranoside (45α).



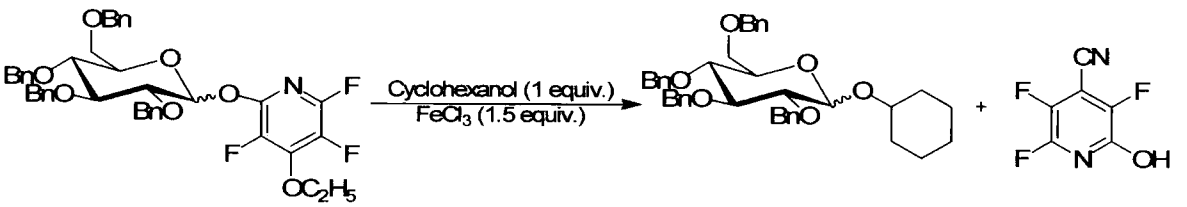
δ_H 1.18-2.10 (10H, CH_2 cyclohexyl), 3.48 (1H, m, OCH cyclohexyl), 3.58 (1H, dd, $^3J_{H2H3}$ 9.9, $^3J_{H1H2}$ 3.5, CH C2), 3.63 (1H, dm, $^3J_{HH}$ 9.9, CH C3), 3.67 (1H, dd, $^3J_{HH}$ 9.9, $^3J_{HH}$ 2.6, CH_2 C6), 3.91 (1H, dd, $^3J_{HH}$ 9.9, $^3J_{HH}$ 2.6, CH C5), 3.76 (1H, dd, $^3J_{HH}$ 9.9, $^3J_{HH}$ 2.6, CH_2 C6), 4.03 (1H, t, $^3J_{HH}$ 9.9, CH C4), 4.46-5.04 (8H, m, O*C*H_2Ph), 4.98 (1H, d, $^3J_{H1H2}$ 3.5, CH C1), 7.14-7.40 (20H, m, OCH$_2$*Ph*); δ_C 24.3, 24.6, 25.7, 31.6, 33.5, 68.7, 70.2, 73.1, 73.6, 75.3, 75.4, 75.8, 78.0, 80.8, 82.2, 94.8, 127.7-128.6, 138.1-139.1; m/z (ES^+) 645 (M^++Na^+,100). Spectroscopic data were consistent with literature values.[139-143]

Cyclohexyl 2,3,4,6-tetra-O-benzyl-β-$_D$-glycopyranoside (45β).



δ_H 01.18-2.10 (10H, CH_2 cyclohexyl), 3.47 (1H, dd, $^3J_{HH}$ 7.7, $^3J_{HH}$ 9.8, CH C2), 3.48 (1H, ddd, $^3J_{HH}$ 9.8, $^3J_{HH}$ 2.5, $^3J_{HH}$ 2.0, CH C5), 3.56 (1H, t, $^3J_{HH}$ 9.8, CH C3), 3.66 (1H, t, $^3J_{HH}$ 9.8, CH C4), 3.67 (1H, dd, $^3J_{HH}$ 9.8, $^3J_{HH}$ 2.6, CH_2 C6), 3.72 (1H, m, OCH cyclohexyl), 3.77 (1H, dd, $^3J_{HH}$ 2.6, $^3J_{HH}$ 9.8, CH_2 C6), 4.46-5.04 (8H, m, OCH_2Ph), 4.52 (1H, d, $^3J_{H1H2}$ 7.7, CH C1), 7.14-7.40 (20H, m, OCH_2Ph); δ_C 24.1, 24.3, 25.8, 32.3, 34.0, 69.3, 74.9, 75.0 (2C), 75.2, 75.8, 78.1, 82.4, 85.0,102.1, 127.7-128.6, 138.1-139.1; m/z (ES^+) 645 (M^++Na^+,100). Spectroscopic data were consistent with literature values.[139-143]

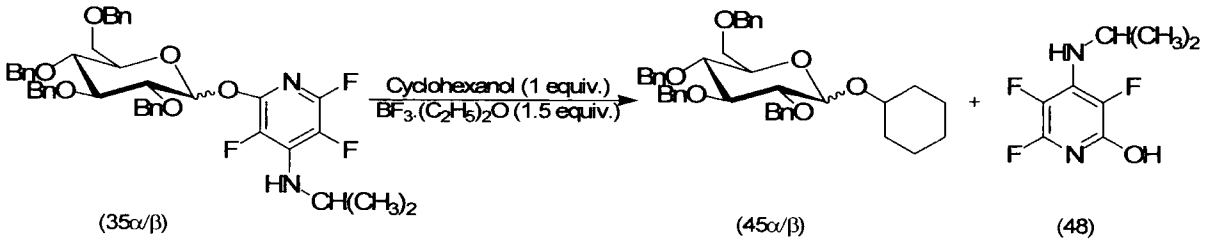
4-Ethoxy-2,3,5-tetrafluoro-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxy)pyridine.



(34α/β) (45α/β) (47)

4-Ethoxy-2,3,5-tetrafluoro-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxy)pyridine (**34α/β**) (1.576 g, 2.10 mmol, 36:64 α:β), cyclohexanol (0.210 g, 2.10 mmol) and iron(III)chloride (0.452 g, 2.79 mmol) were dissolved in acetonitrile (15.0 mL) and stirred at room temperature for 94h, affording *cyclohexyl 2,3,4,6-tetra-O-benzyl-$_D$-glycopyranoside* (***45α/β***) (0.873 g, 67%, 63:37 α:β). (Found: C, 77.2; H, 7.3. $C_{40}H_{46}O_6$ requires C, 77.1; H, 7.4%), spectroscopic data is consistent with previous results.

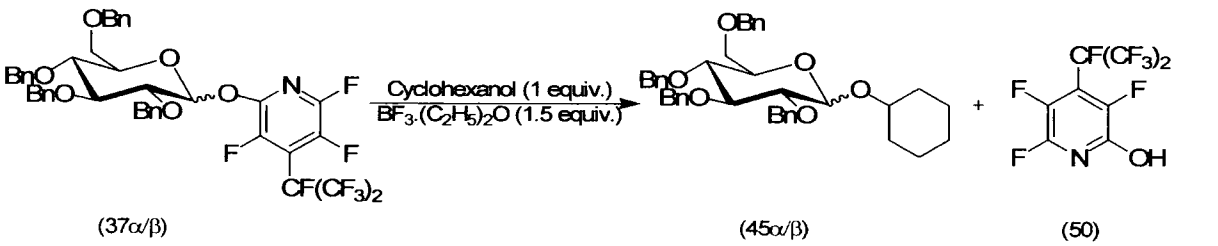
2,3,5-Trifluoro-N-*iso*propyl-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopranosyloxy)pyridin-4-amine (35α/β).



(35α/β) (45α/β) (48)

2,3,5-Trifluoro-N-*iso*propyl-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopranosyloxy)pyridin-4-amine (**35α/β**) (0.743 g, 1.02 mmol, 36:64 α:β), cyclohexanol (0.100 g, 1.00 mmol) and boron trifluoride diethyl etherate (0.213 g, 1.50 mmol) were dissolved in acetonitrile (7.5 mL) and stirred at room temperature for 24h, affording cyclo*hexyl 2,3,4,6-tetra-O-benzyl-$_D$-glycopyranoside* ***(45α/β)*** (0.542 g, 87%, 64:36 α:β); spectroscopic data is consistent with previous results.

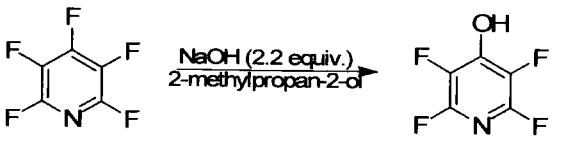
2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridine (37α/β).



(37α/β) (45α/β) (50)

2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridine (**37α/β**) (0.940 g, 1.12 mmol, 36:64 α:β), cyclohexanol (0.100 g, 1.00 mmol) and boron trifluoride diethyl etherate (0.213 g, 1.50 mmol) were dissolved in acetonitrile (12.5 mL) and stirred at room temperature for 24h, affording cyclo*hexyl 2,3,4,6-tetra-O-benzyl-$_D$-glycopyranoside* ***(45α/β)*** (0.517 g, 83%, 63:37 α:β); spectroscopic data is consistent with previous results.

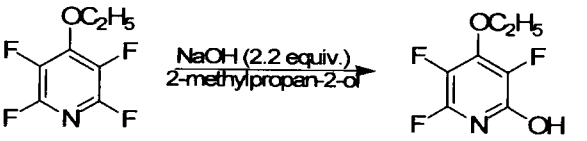
2,3,5,6-Tetrafluoropyridin-4-ol (46).



(1) (46)

A solution of sodium hydroxide (0.707 g, 17.69 mmol) in 2-methylpropan-2-ol (10 mL) was added dropwise to pentafluoropyridine (**1**) (1.513 g, 8.95 mmol) at room temperature, the resulting mixture was heated at reflux temperature for 48h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.25 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by vacuum sublimation at room temperature and 1.0 mbar pressure, yielded *2,3,5,6-tetrafluoropyridin-4-ol* ***(46)*** (1.046 g, 70%) as a while crystalline solid; mp 96-97°C. (Found: C, 36.2; H, 0.7; N, 8.6. C_5HF_4NO requires C, 36.0; H, 0.6; N, 8.4%); δ_C 132.9 (dd, $^1J_{CF}$ 253.6, C3), 142.59 (m, C2), 145.39 (m, C4); δ_F (pH 7) -90.74 (2F, m, 2-F), -163.73 (2F, m, 3-F); δ_F (pH 1) -103.26 (2F, m, 2-F), -158.20 (2F, m, 3-F); m/z (EI^+) 168 (M^++H, 42), 167 (M^+, 100), 148 (30), 138 (50), 120 (22), 119 (88), 100 (57), 93 (70), 88 (24), 75 (48), 74 (82), 71 (52), 62 (46), 31 (52).

4-Ethoxy-3,5,6-trifluoropyridin-2-ol (47).

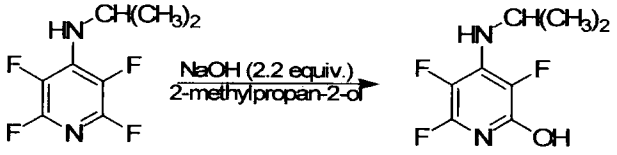


(5) (47)

A solution of sodium hydroxide (0.620 g, 15.51 mmol) in 2-methylpropan-2-ol (10 mL) was added dropwise to 4-ethoxy-2,3,5,6-tetrafluoropyridine (**5**) (1.513 g, 7.75 mmol) at room temperature, the resulting mixture was heated at reflux temperature for 48h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.25 g) was added

with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by sublimation at room temperature and 2.0 mbar, yielded *4-ethoxy-3,5,6-trifluoropyridin-2-ol (47)* (1.021 g, 68%) as a while crystalline solid; mp 106-107°C. (Found: C, 43.5; H, 3.1; N, 7.3. $C_7H_6F_3NO_2$ requires C, 43.5; H, 3.1; N, 7.3%); δ_H 1.48 (3H, t, $^3J_{HH}$ 7.1, OCH_2CH_3), 4.57 (2H, qt, $^3J_{HH}$ 7.1, $^5J_{HF}$ 1.4, OCH_2CH_3), 10.52 (1H, br s, OH); δ_C 15.6 (s, OCH_2CH_3), 70.5 (t, $^4J_{CF}$ 4.7, OCH_2CH_3), 131.9 (dd, $^1J_{CF}$ 246.8, $^2J_{CF}$ 19.0, C5), 135.3 (dd, $^1J_{CF}$ 246.8, $^4J_{CF}$ 4.7, C3), 145.32 (ddd, $^1J_{CF}$ 246.8, $^2J_{CF}$ 19.0, $^4J_{CF}$ 4.7, C6), 146.95 (dt, $^2J_{CF}$ 19.0, $^4J_{CF}$ 4.7, C2), 147.26 (m, C4); δ_F -98.21 (1F, t, $^{3/5}J_{FF}$ 21.3, 6-F), -160.81 (1F, d, $^5J_{FF}$ 21.3, 3-F), -168.28 (1F, d, $^3J_{FF}$ 21.3, 5-F); δ_F (CD_3CN) -94.55 (1F, t, $^{3/5}J_{FF}$ 24.1, 6-F), -159.86 (1F, d, $^5J_{FF}$ 24.1, 3-F), -167.40 (1F, d, $^3J_{FF}$ 24.1, 5-F); m/z (EI^+) 193 (M^+, 52), 165 (100), 137 (67), 117 (40), 106 (36), 82 (14), 29 (58).

3,5,6-Trifluoro-4-(*iso*propylamino)pyridin-2-ol (48).

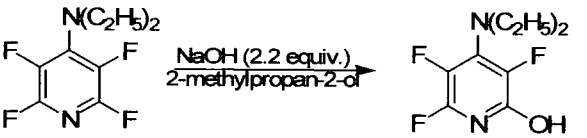


(15) (48)

A solution of sodium hydroxide (0.634 g, 15.85 mmol) in 2-methylpropan-2-ol (10 mL) was added dropwise to 2,3,5,6-tetrafluoro-N-*iso*propylpyridin-4-amine (**15**) (1.489 g, 7.15 mmol) at room temperature, the resulting mixture was heated at reflux temperature for 55h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.25 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by sublimation at room temperature and 2.2 mbar, yielded *2,5,6-trifluoro-4-(isopropylamino)pyridin-2ol (48)* (1.179 g, 80%) as a white crystalline solid; mp 170°C. (Found: C, 46.4; H, 4.6; N, 13.3. $C_8H_9F_3N_2O$ requires C, 46.6; H, 4.4; N, 13.6%); δ_H 1.28 (6H, d, $^3J_{HH}$ 6.3, $HNCH(CH_3)_2$), 4.15 (1H, sex t, $^3J_{HH}$ 6.3, $^5J_{HF}$ 1.8, $HNCH(CH_3)_2$), 4.25 (1H, s, $HNCH(CH_3)_2$), 11.11 (1H, br s, OH); δ_C 24.2 (s, $HNCH(CH_3)_2$), 46.5 (t, $^4J_{CF}$ 4.4, $HNCH(CH_3)_2$), 128.4 (dd, $^1J_{CF}$ 240.4, $^2J_{CF}$ 18.9, C5), 131.36 (dm, $^1J_{CF}$ 240.4, C3), 136.89 (dt, $^2J_{CF}$ 18.9, $^3J_{CF}$ 8.4, C2), 145.38 (ddd, $^1J_{CF}$ 240.4, $^2J_{CF}$ 18.9, $^4J_{CF}$ 4.4, C6),

146.35 (tm, $^{2}J_{CF}$ 18.9, C4); δ_F -101.55 (1F, t, $^{3/5}J_{FF}$ 21.0, 6-F), -165.91 (1F, d, $^{5}J_{FF}$ 21.0, 3-F), -172.37 (1F, d, $^{3}J_{FF}$ 21.0, 5-F); δ_F (CD_3CN) -97.90 (1F, t, J_{FF} 23.3, 6-F), -163.46 (1F, d, J_{FF} 23.3, 3-F), -170.00 (1F, d, J_{FF} 23.3, 5-F); m/z (EI^+) 206 (M^+, 44), 192 (12), 191 (100), 144 (20), 116 (21), 93 (13), 43 (26), 41 (25).

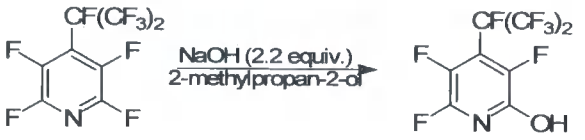
4-(Diethylamino)-3,5,6-trifluoropyridin-2-ol (49).



(11) (49)

A solution of sodium hydroxide (0.605 g, 15.13 mmol) in 2-methylpropan-2-ol (10 mL) was added dropwise to N,N-diethyl-2,3,5,6-tetrafluoropyridin-4-amine (**11**) (1.508 g, 6.79 mmol) at room temperature, the resulting mixture was heated at reflux temperature for 48h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.25 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by sublimation at 40 °C and 3.5 mbar yielded *4-(diethylamino)-3,5,6-triflouropyridin-2-ol* ***(49)*** (1.241 g, 83%) as a while crystalline solid; mp 104°C. (Found: C, 49.1; H, 5.0; N, 12.7. $C_9H_{11}F_3N_2O$ requires C, 49.1; H, 5.0; N, 12.7%); δ_H 1.21 (6H, t, $^{3}J_{HH}$ 7.0, $NCH_2\mathit{CH_3}$), 3.42 (4H, q, $^{3}J_{HH}$ 7.0, $N\mathit{CH_2}CH_3$), 10.95 (1H, br s, OH); δ_C 14.0 (s, $NCH_2\mathit{CH_3}$), 46.7 (t, $^{4}J_{CF}$ 3.8, $N\mathit{CH_2}CH_3$), 131.86 (dd, $^{1}J_{CF}$ 241.6, $^{2}J_{CF}$ 19.1, C5), 134.94 (dm, $^{1}J_{CF}$ 241.6, C3), 139.4 (dm, $^{3}J_{CF}$ 8.0, C2), 146.2 (ddd, $^{1}J_{CF}$ 241.6, $^{2}J_{CF}$ 19.1, $^{4}J_{CF}$ 3.8, C6), 147.1 (tm, $^{2}J_{CF}$ 19.1, C4); δ_F -101.50 (1F, t, $^{3/5}J_{FF}$ 20.4, 6-F), -156.88 (1F, d, $^{5}J_{FF}$ 20.4, 3-F), -164.23 (1F, d, $^{3}J_{FF}$ 20.4, 5-F); δ_F (CD_3CN) -97.37 (1F, t, $^{3/5}J_{FF}$ 23.1, 6-F), -154.49 (1F, d, $^{5}J_{FF}$ 23.1, 3-F), -162.00 (1F, d, $^{3}J_{FF}$ 23.1, 5-F); m/z (EI^+) 220 (M^+, 26), 205 (91), 177 (100), 29 (42).

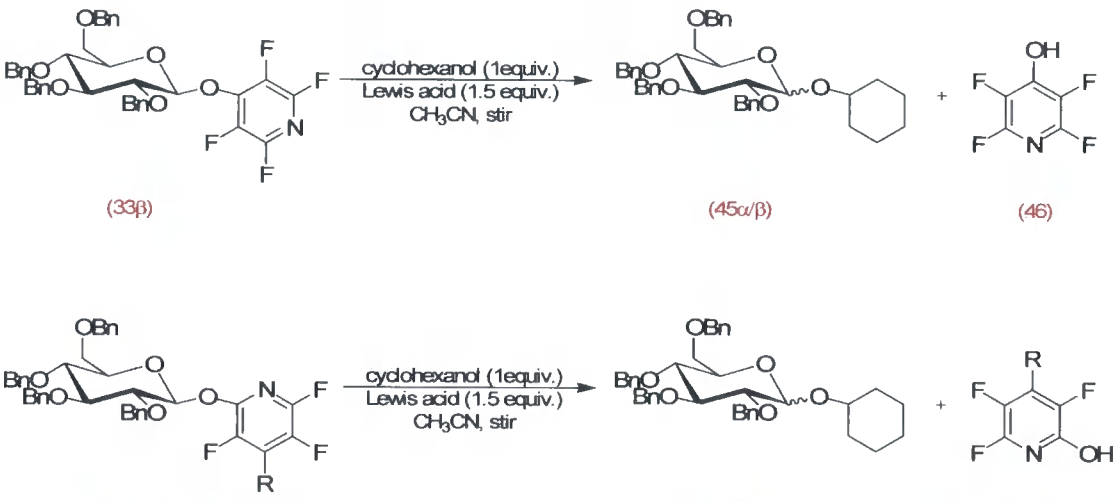
3,5,6-Trifluoro-4-(perfluoropropan-2-yl)pyridin-2-ol (50).



(27) (50)

A solution of sodium hydroxide (1.028 g, 3.2 mmol) in 2-methylpropan-2-ol (10 mL) was added dropwise to 2,3,5,6-tetrafluoro-4-(perfluoropropan-2-yl)pyridine (**27**) (0.133 g, 3.3 mmol) at room temperature, the resulting mixture was heated at reflux temperature for 50h. Amberlite resin (IR 120, Na^+ form, 16-50 mesh, 8% cross-linked, 0.25 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent removed on a rotary evaporator. Purification by sublimation at room temperature and 3.5 mbar yielded *3,5,6-trifluoro-4-(perfluoropropan-2-yl)pyridin-2-ol (**50**)* (0.729 g, 72%) as a while crystalline solid; mp 88-89 °C. Spectroscopic data correspond to literature values.[67, 68]

Glycosylation Screens: Lewis acid Evaluation



(33β) (45α/β) (46)

(34α/β) R=OC_2H_5
(35α/β) R=$HNCH(CH_3)_2$
(36α/β) R=$N(C_2H_5)_2$
(37α/β) R=$CF(CF_3)_2$

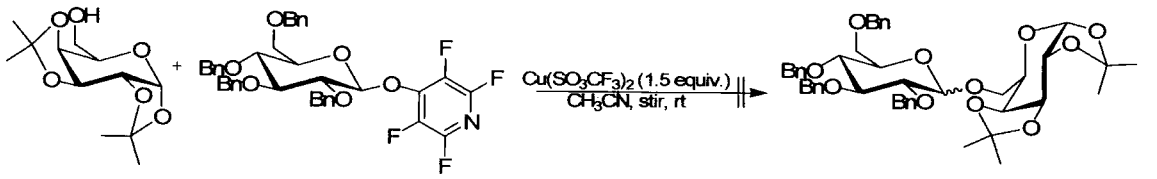
(46α/β)

(47) R=OC_2H_5
(48) R=$HNCH(CH_3)_2$
(49) R=$N(C_2H_5)_2$
(50) R=$CF(CF_3)_2$

General procedure. A selection of Lewis acids were evaluated as potential activators by reacting standard solutions of the glycosyl donors (**33β**) to (**37α/β**) (typically 0.08

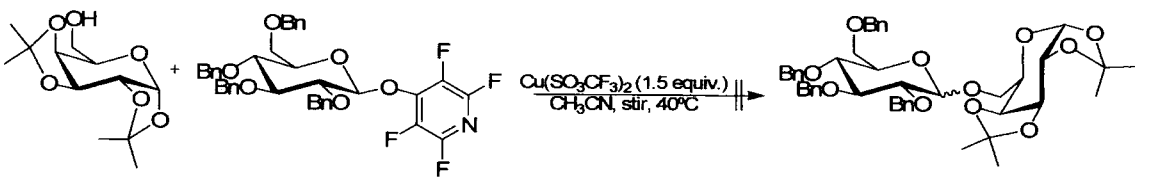
mmol) with cyclohexanol (1.0 equiv.) in acetonitrile. The glycosyl donor and cyclohexanol solutions were placed in 20 mL test tubes under an atmosphere of dry argon. The indicated Lewis acid was added (1.5 equiv.) with acetonitrile to give a total volume of 6 mL. The resulting mixture was stirred at room temperature with a NMR sample being removed after 2, 4, 6, 12, 24 and 48h to determine the ratio of glycosyl donor to hydroxyl-pyridine derivative. Collected data can be found in appendix A.

Attempted Synthesis of 6-O-(2',3',4',6'-tetra-O-benzyl-D-glucopyranosyl)-(1-6)-1,2:3,4-di-*iso*propylidene-α-D-galactopyranose (55α/β).



(54) (33β) (55α/β)

Under an argon atmosphere 2,3,5,6-tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyloxy)pyridine (**33β**) (0.713 g, 1.03 mmol, 8:92 α:β) and 1,2:3,4-di-O-*iso*propylidene-α-D-galactopyranose (**54**) (0.260 g, 1.0 mmol) were dissolved in dry acetonitrile (5 mL). A solution of copper(II)trifluoromethanesulfonate (0.579 g, 1.6 mmol) in acetonitrile (5 mL) was added and the reaction stirred at room temperature for 30h, affording *2,3,5,6-tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyloxy)pyridine (33β)* (0.328 g, 46% recovery), spectroscopic data is consistent with previous results.

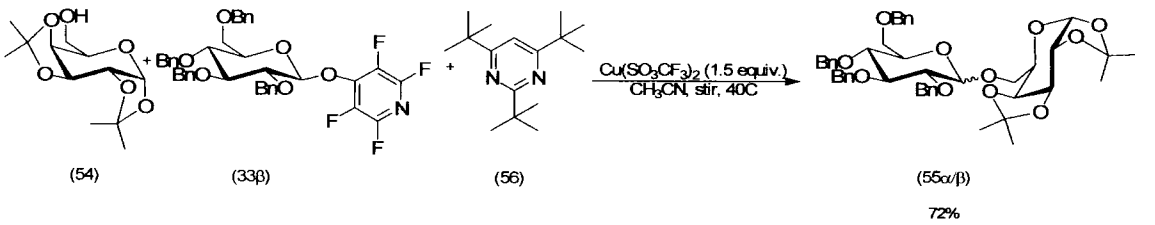


(54) (33β) (55α/β)

Under an argon atmosphere 2,3,5,6-tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine (**33**) (0.713 g, 1.03 mmol, 8:92 α:β) and 1,2:3,4-di-O-*iso*propylidene-α-D-galactopyranose (**54**) (0.260 g, 1.0 mmol) were dissolved in dry acetonitrile (5 mL). A solution of copper(II)trifluoromethanesulfonate (0.579 g, 1.6

mmol) in acetonitrile (5 mL) was added and the reaction stirred at 40°C for 48h, the reaction mixture was then concentrated in vacuo. Purification by column chromatography proved impossible due to the complex nature of the product mixture.

6-O-(2′,3′,4′,6′-tetra-O-benzyl-D-glucopyranosyl)-(1-6)-1,2:3,4-di-*iso*propylidene-α-D-galactopyranose (55α/β).



(54) (33β) (56) (55α/β) 72%

Under an argon atmosphere 2,3,5,6-tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine (**33α/β**) (0.713 g, 1.03 mmol, 8:92 α:β), 1,2:3,4-di-O-*iso*propylidene-α-D-galactopyranose (**54**) (0.260 g, 1.00 mmol) and 2,4,6-tri-*tert*-butylpyrimidine (**56**) (0.447 g, 1.8 mmol) were dissolved in dry acetonitrile (5.0 mL). A solution of copper(II)trifluoromethanesulfonate (0.579 g, 1.6 mmol) in acetonitrile (5.0 mL) was added and the reaction stirred at 50 °C for 72h, the reaction mixture was then concentrated in vacuo. Purification by column chromatography (1:10 ethyl acetate:hexane) yielded *6-O-(2′,3′,4′,6′-tetra-O-benzyl-D-glucopyranosyl)-(1-6)-1,2:3,4-di-isopropylidene-α-D-galactopyranose (**55α/β**)* (0.567 g, 72 %, 73:27 α:β). (Found: C, 70.3; H, 7.0. $C_{46}H_{54}O_{11}$ requires C, 70.6; H, 7.0.); δ_H 5.57 (1H, d, $^3J_{H1H2}$ 5.2 CH C1 α), 5.52 (1H, d, $^3J_{H1H2}$ 4.9 CH C1 β), 5.00 (1H, d, $^3J_{H1H2}$ 3.2 CH C1′ α), 4.45 (1H, d, $^3J_{H1H2}$ 7.6 CH C1′ β); δ_C 104.4 (s, CH C1′ β), 97.2 (s, CH C1′ α), 96.5 (s, CH C1 β), 96.4 (s, CH C1 α); m/z (ES^+) 805 (M^++Na^+,100). Spectroscopic data were consistent with literature values.[7, 8, 114, 139, 141-143]

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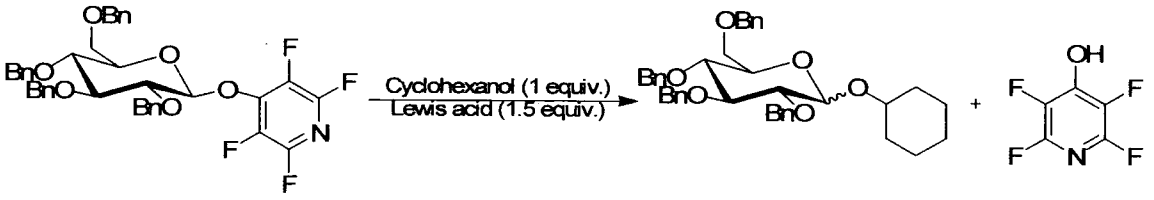
Appendix A. Glycosyl Donor Kinetics Data.

2,3,5,6-Tetrafluoro-4-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyloxy)pyridine (33β).

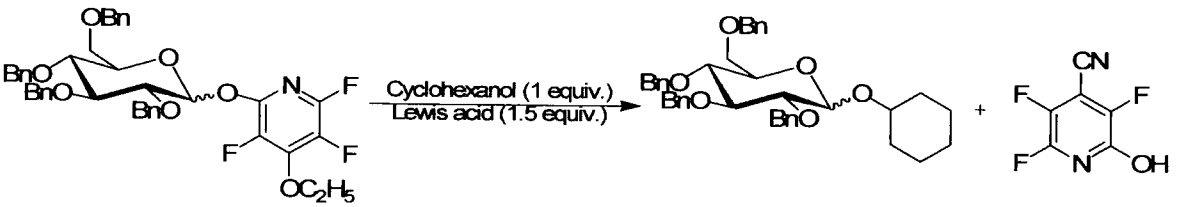


(33α/β) (45α/β) (46)

Lewis Acid	Percentage conversion after: (h)					
	2	4	6	12	24	48
$Cu(SO_3CF_3)_2$	18	28	43	60	75	100
$CuSO_3CF_3$	0	0	0	0	0	0
$NaSO_3CF_3$	0	0	0	0	0	0
$AlCl_3$	10	19	24	38	55	76
$Ni(acac)_2$	0	0	0	0	0	0
CuBr	0	0	0	0	0	0
$BF_3.Et_2O$	30	47	57	73	84	92
$FeCl_3$	40	55	61	62	64	64
$Pd(acetate)_2$	0	0	0	0	0	0
$AgNO_3$	0	0	0	0	0	0
$ZnCl_2$	0	0	0	0	0	0
$Ti^{IV}Cl_4$	11	23	28	42	55	71

[(**33β**)] (x 10^{-3}) /	Time (h)						
$moldm^{-3}$	0	2	4	6	12	24	48
$Cu(SO_3CF_3)_2$	14.5	11.9	10.1	8.6	6.1	3.9	0.0
$AlCl_3$	14.5	13.5	11.7	11.0	9.0	6.5	3.5
$BF_3.Et_2O$	14.5	10.2	7.7	6.3	3.9	2.3	1.1
$FeCl_3$	14.5	8.7	6.6	5.2	5.2	5.2	5.2
$Ti^{IV}Cl_4$	14.5	12.9	11.3	1.04	8.4	6.5	4.2

4-Ethoxy-2,3,5-tetrafluoro-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxy)pyridine (34α/β).

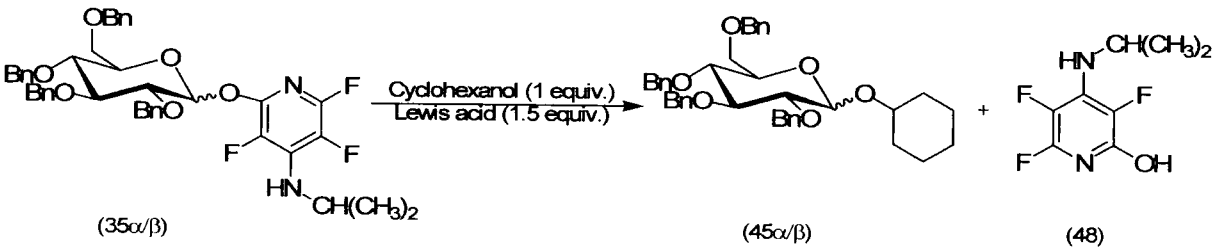


(34α/β) (45α/β) (47)

Lewis Acid	Percentage conversion after: (h)					
	2	4	6	12	24	48
$Cu(SO_3CF_3)_2$	0	0	8	14	18	24
$CuSO_3CF_3$	0	0	0	0	0	0
$NaSO_3CF_3$	0	0	0	0	0	0
$AlCl_3$	34	54	63	82	86	91
$Ni(acac)_2$	0	0	0	0	0	0
CuBr	0	0	0	0	0	0
$BF_3.Et_2O$	57	71	77	85	88	91
$FeCl_3$	55	76	82	84	84	84
$Pd(acetate)_2$	0	0	0	0	0	0
$AgNO_3$	0	0	0	0	0	0
$ZnCl_2$	0	0	0	0	0	0
$Ti^{IV}Cl_4$	0	0	0	6	14	17

[(**34β**)] (x 10^{-3}) /	Time (h)						
$moldm^{-3}$	0	2	4	6	12	24	48
$Cu(SO_3CF_3)_2$	14.0	14.0	14.0	12.9	12.2	11.3	10.6
$AlCl_3$	14.0	9.2	6.5	5.2	2.5	2.0	1.3
$BF_3.Et_2O$	14.0	6.3	4.1	3.0	2.1	1.7	1.3
$FeCl_3$	14.0	6.3	4.2	3.2	2.2	2.2	2.2
$Ti^{IV}Cl_4$	14.0	14.0	14.0	14.0	13.1	12.2	11.5

2,3,5-Trifluoro-N-*iso*propyl-6-(2,3,4,6-tetra-O-benzyl-D-glucopranosyloxy)pyridin-4-amine (35α/β).

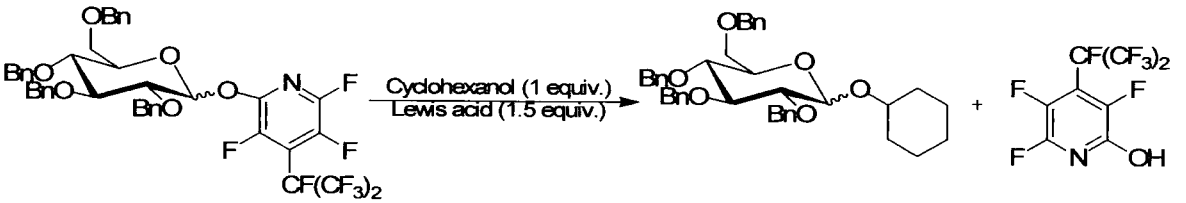


(35α/β) (45α/β) (48)

Lewis Acid	Percentage conversion after: (h)					
	2	4	6	12	24	48
$Cu(SO_3CF_3)_2$	0	0	0	0	0	0
$CuSO_3CF_3$	0	0	0	0	0	0
$NaSO_3CF_3$	0	0	0	0	0	0
$AlCl_3$	35	51	61	81	95	100
$Ni(acac)_2$	0	0	0	0	0	0
CuBr	0	0	0	0	0	0
$BF_3.Et_2O$	20	35	55	74	92	100
$FeCl_3$	18	29	39	42	42	45
$Pd(acetate)_2$	0	0	0	0	0	0
$AgNO_3$	0	0	0	0	0	0
$ZnCl_2$	0	0	0	0	0	0
$Ti^{IV}Cl_4$	0	0	7	12	20	31

[(**35β**)] (x 10^{-3}) /	Time (h)						
$moldm^{-3}$	0	2	4	6	12	24	48
$Cu(SO_3CF_3)_2$	13.7	13.7	13.7	13.7	13.7	13.7	13.7
$AlCl_3$	13.7	8.9	6.7	5.4	2.6	0.7	0.0
$BF_3.Et_2O$	13.7	10.9	8.9	6.2	3.6	1.1	0.0
$FeCl_3$	13.7	11.3	9.7	8.4	8.0	8.0	7.6
$Ti^{IV}Cl_4$	13.7	13.7	13.7	12.8	12.1	11.0	9.5

2,3,5-Trifluoro-6-(2,3,4,6-tetra-O-benzyl-$_D$-glucopyranosyloxy)-4-(perfluoropropan-2-yl)pyridine (37α/β).

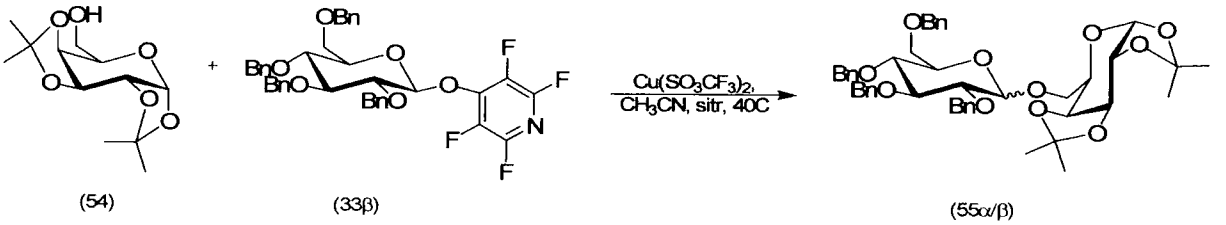


(37α/β) (45α/β) (50)

Lewis Acid	Percentage conversion after: (h)					
	2	4	6	12	24	48
$Cu(SO_3CF_3)_2$	0	0	0	0	0	0
$CuSO_3CF_3$	0	0	0	0	0	0
$NaSO_3CF_3$	0	0	0	0	0	0
$AlCl_3$	37	42	47	51	62	78
$Ni(acac)_2$	0	0	0	0	0	0
CuBr	0	0	0	0	0	0
$BF_3.Et_2O$	67	74	77	84	100	100
$FeCl_3$	0	0	0	0	0	0
$Pd(acetate)_2$	0	0	0	0	0	0
$AgNO_3$	0	0	0	0	0	0
$ZnCl_2$	0	0	0	0	0	0
$Ti^{IV}Cl_4$	0	0	0	0	0	0

[(**37β**)] (x 10^{-2}) /	Time (h)						
moldm^{-3}	0	2	4	6	12	24	48
$Cu(SO_3CF_3)_2$	6.4	6.4	6.4	6.4	6.4	6.4	6.4
$AlCl_3$	6.4	4.9	3.7	3.4	3.1	2.4	1.4
$BF_3.Et_2O$	6.4	2.6	1.7	1.5	0.9	0.0	0.0
$FeCl_3$	6.4	6.4	6.4	6.4	6.4	6.4	6.4
$Ti^{IV}Cl_4$	6.4	6.4	6.4	6.4	6.4	6.4	6.4

Appendix B. Glycosylation Optimisation Data.



(54) (33β) (55α/β)

Table B.1. Donor Concentration Optimisation

[(**33**)] (x 10^{-2}) / moldm^{-3}	Percentage conversion after (h)					
	0	2	4	6	24	48
1.6	0	11	20	34	91	100
2.1	0	37	48	59	94	97
3.2	0	40	50	60	87	93
6.4	0	39	47	55	85	93

Table B.2. Lewis acid Optimisation

[$Cu(SO_3CF_3)_2$] (x 10^{-2}) / moldm^{-3}	Percentage conversion after (h)					
	2 h	4 h	6 h	12	24	48
1.6	0	0	0	0	0	23
3.2	0	0	0	4	15	39
6.4	0	0	0	11	28	77
9.6	0	0	9	20	42	86
12.8	0	7	17	28	54	90
16.0	8	16	24	37	69	100

Appendix C. Crystallographic Data.

3,5,6-Trifluoro-4-(*iso*propylamino)pyridin-2-ol (48).

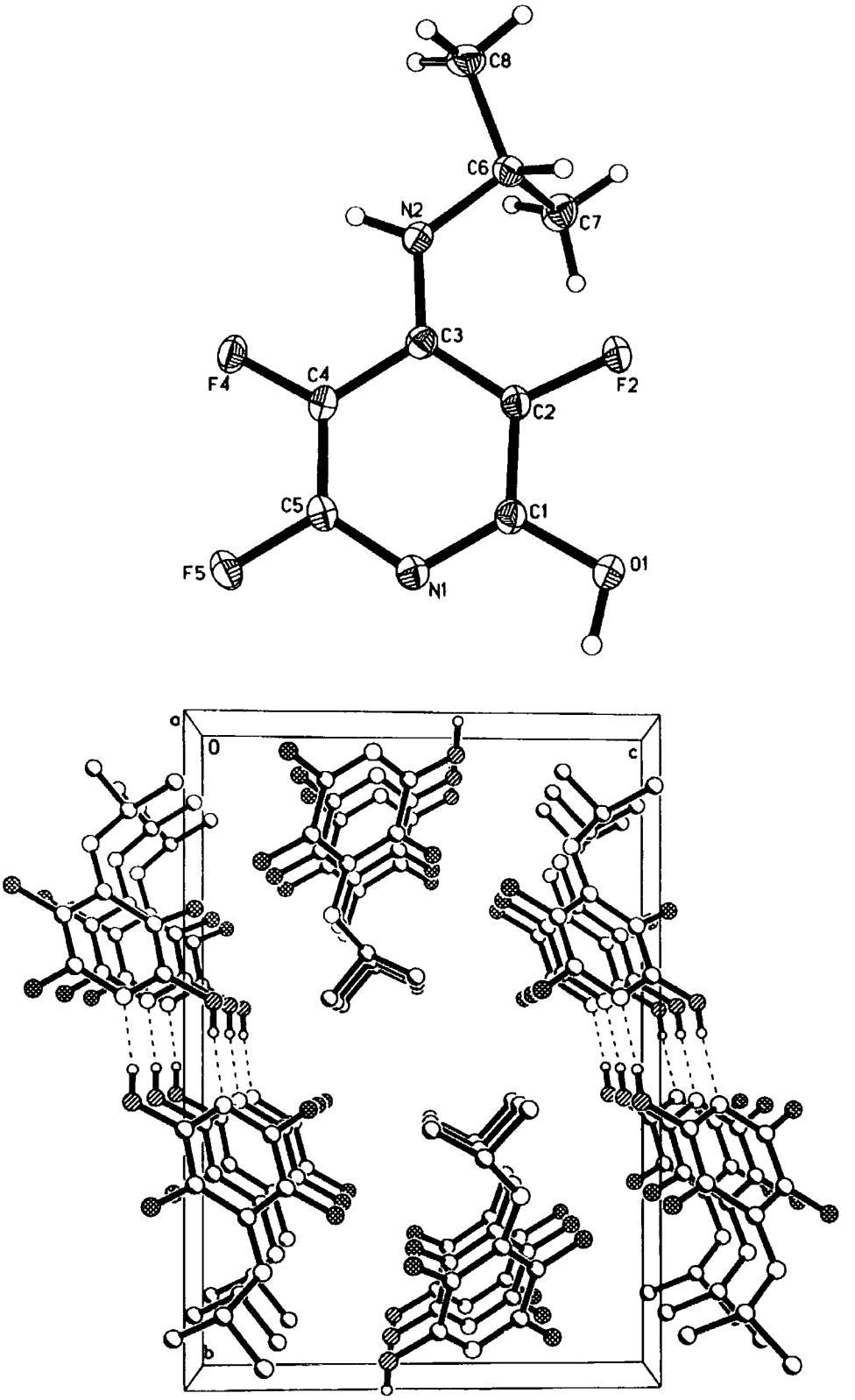


Table C.1.1. Crystal data and structure refinement for (**48**).

Empirical formula	$C_8H_9F_3N_2O$	
Formula weight	206.17	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/C$	
Unit cell dimensions	a = 4.5839(2) Å	α = 90°
	b = 16.3699(6) Å	β = 93.46(1)°
	c = 11.3986(4) Å	γ = 90°
Volume	853.71(6) $Å^3$	
Z	4	
Density (calculated)	1.604 Mg/m^3	
Adsorption coefficient	0.152 mm^{-1}	
F(000)	424	
Crystal size	0.52 x 0.42 x 0.3 mm^3	
Theta range for data collection	2.49 to 30.00°	
Index ranges	-6<=h<=6, -22<=k<=23, -10<=l<=16	
Reflections collected	7639	
Independent reflections	2447 [R(int) = 0.0388]	
Completeness to theta = 30.00°	98.4 %	
Adsorption correction	None	
Refinement method	Full-matrix least squares on F^2	
Data / restraints / parameter	2447 / 0 / 164	
Goodness-of-fit on F^2	1.139	
Final R indices [I›2sigma(I)]	R_1 = 0.0359, wR2 = 0.1105	
R indicies (all data)	R_1 = 0.0381, wR2 = 0.1128	
Extinction coefficient	0.025(5)	
Largest diff. peak and hole	0.468 and -0.316 e.$Å^{-3}$	

Table C.1.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3). U(eq) is defined as one third of the trace of the orthogonalised U^{ij} tensor.

Atom	x	y	z	U(eq)
F(2)	10483(1)	7094(1)	-199(1)	21(1)
F(4)	5116(1)	7326(1)	3236(1)	21(1)
F(5)	2699(1)	5854(1)	2648(1)	24(1)
O(1)	7736(2)	5707(1)	-688(1)	21(1)
N(1)	5179(2)	5767(1)	1001(1)	18(1)
N(2)	9165(2)	8011(1)	1895(1)	19(1)
C(1)	7103(2)	6094(1)	297(1)	16(1)
C(2)	8502(2)	6834(1)	533(1)	16(1)
C(3)	7931(2)	7290(1)	1554(1)	16(1)
C(4)	5858(2)	6927(1)	2259(1)	16(1)
C(5)	4636(2)	6190(1)	1954(1)	17(1)
C(6)	10922(2)	8550(1)	1188(1)	19(1)
C(7)	9087(2)	8912(1)	155(1)	26(1)
C(8)	12198(2)	9213(1)	2002(1)	24(1)

Table C.1.3. Anisotropic displacement parameters ($Å^2$ x 10^3). The anisotropic displacement factor exponent takes the form:$-2\pi^2[h^2a^{*2}U^{11} + \ldots + 2hka^*b^*U^{12}]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(2)	24(1)	22(1)	18(1)	-1(1)	9(1)	-5(1)
F(4)	26(1)	22(1)	14(1)	-2(1)	6(1)	1(1)
F(5)	28(1)	23(1)	22(1)	2(1)	11(1)	-5(1)
O(1)	27(1)	20(1)	17(1)	-4(1)	6(1)	-5(1)
N(1)	20(1)	17(1)	16(1)	1(1)	2(1)	-1(1)
N(2)	25(1)	18(1)	14(1)	-2(1)	3(1)	-4(1)
C(1)	19(1)	17(1)	14(1)	1(1)	2(1)	0(1)
C(2)	18(1)	17(1)	14(1)	2(1)	3(1)	-1(1)
C(3)	17(1)	16(1)	13(1)	2(1)	0(1)	1(1)

C(4)	19(1)	18(1)	12(1)	0(1)	2(1)	2(1)
C(5)	18(1)	19(1)	15(1)	3(1)	3(1)	0(1)
C(6)	19(1)	17(1)	20(1)	-2(1)	5(1)	-3(1)
C(7)	36(1)	22(1)	19(1)	3(1)	2(1)	-3(1)
C(8)	23(1)	22(1)	28(1)	-7(1)	3(1)	-4(1)

Table C.1.4. Selected bond lengths [Å] and angles [°]

F(2)-C(2)	1.3548(9)	N(1)-C(1)	1.339(1)	C(3)-C(4)	1.413(1)
F(4)-C(4)	1.3521(9)	N(2)-C(3)	1.355(1)	C(6)-C(5)	1.366(1)
F(5)-C(5)	1.342(1)	N(2)-C(6)	1.468(1)	C(6)-C(8)	1.523(1)
O(1)-C(1)	1.337(1)	C(1)-C(2)	1.393(1)	C(6)-C(7)	1.525(1)
N(1)-C(5)	1.325(1)	C(2)-C(3)	1.401(1)		

C(5)-N(1)-C(1)	116.49(7)	C(2)-C(3)-C(4)	113.80(7)
C(3)-N(2)-C(6)	126.76(8)	F(4)-C(4)-C(5)	121.11(8)
O(1)-C(1)-N(1)	119.86(7)	F(4)-C(4)-C(3)	118.43(7)
O(1)-C(1)-C(2)	117.90(8)	C(5)-C(4)-C(3)	120.46(8)
N(1)-C(1)-C(2)	122.24(8)	N(1)-C(5)-F(5)	115.68(7)
F(2)-C(2)-C(1)	117.26(7)	N(1)-C(5)-C(4)	125.12(8)
F(2)-C(2)-C(3)	120.87(7)	F(5)-C(5)-C(4)	119.20(8)
C(1)-C(2)-C(3)	121.86(8)	N(2)-C(6)-C(8)	107.28(7)
N(2)-C(3)-C(2)	127.07(8)	N(2)-C(6)-C(7)	111.24(7)
N(2)-C(3)-C(4)	119.13(8)	C(8)-C(6)-C(7)	111.53(8)

Table C.1.5. Selected torsion angles [°]

C(6)-N(2)-C(3)-C(2)	12.90(14)
C(6)-N(2)-C(3)-C(4)	-168.04(8)
C(3)-N(2)-C(6)-C(8)	-171.56(8)
C(3)-N(2)-C(6)-C(7)	66.22(11)

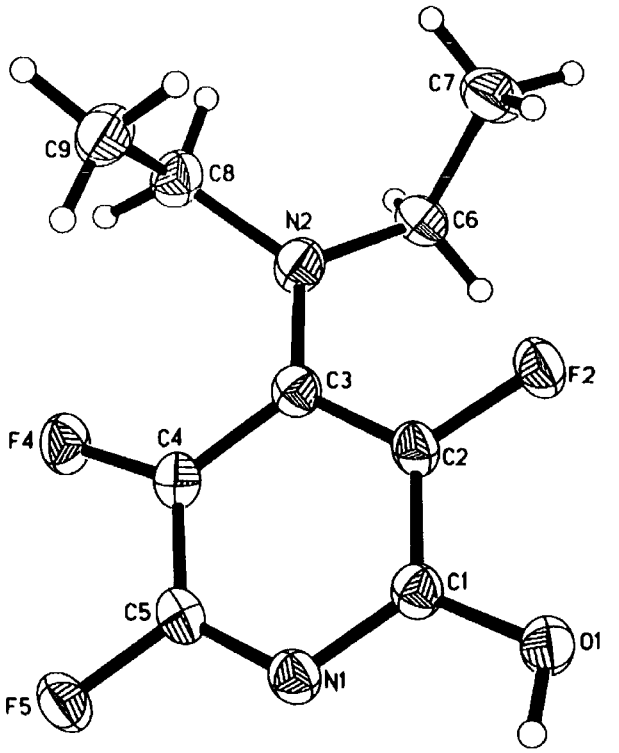
Table C.1.6. Hydrogen bonds [Å and °]

D-H....A	d(D-H)	d(H....A)	d(D....A)	<(DHA)
O(1)-H(1O)....N(1)#1	0.88(2)	1.90(2)	2.7711(10)	169.8(17)
N(2)-H(2N)....F(4)	0.43(17)	2.314(15)	2.7171(9)	109.8(13)

Table C.1.7. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3).

Atom	x	y	z	U(eq)
H(1O)	6660(40)	5262(12)	-729(17)	54(5)
H(2N)	8610(30)	81900(10)	2539(15)	35(4)
H(6)	12520(30)	8241(8)	887(12)	22(3)
H(71)	8040(30)	8483(10)	-282(15)	40(4)
H(72)	7620(30)	9298(8)	453(12)	21(3)
H(73)	10380(30)	9205(9)	-326(15)	35(4)
H(81)	13430(30)	9580(9)	1576(13)	28(3)
H(82)	10640(30)	9554(9)	2315(14)	30(3)
H(83)	13290(40)	8988(10)	2682(16)	44(4)

4-(Diethylamino)-3,5,6-trifluoropyridin-2-ol (49).



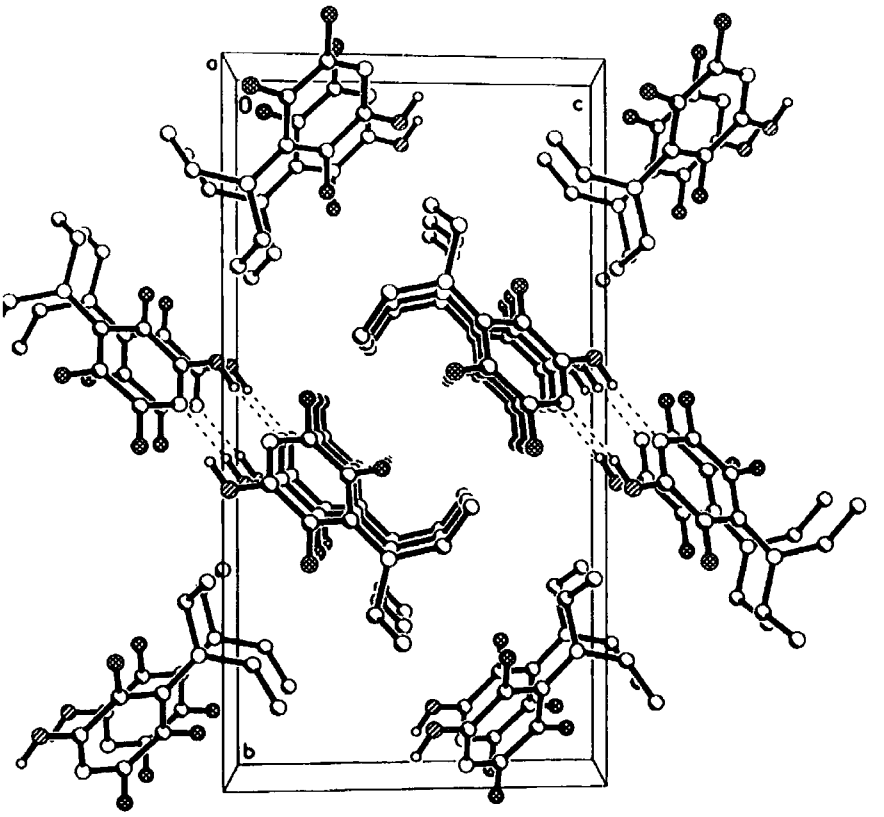


Table C.2.1. Crystal data and structure refinement for (**48**).

Empirical formula	$C_9H_{11}F_3N_2O$
Formula weight	220.20
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 5.1450(2) Å α = 90°
	b = 19.1493(6) Å β = 93.46(1)°
	c = 9.9069(3) Å γ = 90°
Volume	969.88(6) $Å^3$
Z	4
Density (calculated)	1.508 Mg/m^3
Adsorption coefficient	0.139 mm^{-1}
F(000)	456
Crystal size	0.48 x 0.25 x 0.22 mm^3
Theta range for data collection	2.33 to 29.00°
Index ranges	-7<=h<=6, -25<=k<=26, -13<=l<=13
Reflections collected	9334
Independent reflections	2563 [R(int) = 0.0421]
Completeness to theta = 30.00°	99.7 %
Adsorption correction	None
Refinement method	Full-matrix least squares on F^2
Data / restraints / parameter	2563 / 0 / 180
Goodness-of-fit on F^2	1.071
Final R indices [I>2sigma(I)]	R_1 = 0.0351, wR2 = 0.1225
R indicies (all data)	R_1 = 0.0385, wR2 = 0.1274
Largest diff. peak and hole	0.358 and -0.286 $e.Å^{-3}$

Table C.2.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3). U(eq) is defined as one third of the trace of the orthogonalised U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	-1713(2)	862(1)	4568(1)	29(1)
F(2)	-1795(1)	1824(1)	2649(1)	30(1)
F(4)	5275(1)	635(1)	912(1)	32(1)
F(5)	4883(1)	-320(1)	2842(1)	34(1)
N(1)	1632(2)	256(1)	3703(1)	25(1)
N(2)	1839(2)	1817(1)	718(1)	30(1)
C(1)	2(2)	804(1)	3661(1)	24(1)
C(2)	36(2)	1314(1)	2670(1)	24(1)
C(3)	1761(2)	1302(1)	1675(1)	23(1)
C(4)	3418(2)	711(1)	1757(1)	25(1)
C(5)	3244(2)	227(1)	2763(1)	26(1)
C(6)	1440(2)	2552(1)	1055(1)	26(1)
C(7)	-1067(2)	2865(1)	363(1)	37(1)
C(8)	2440(1)	1661(1)	-666(1)	31(1)
C(9)	623(2)	1122(1)	-1376(1)	35(1)

Table C.2.3. Anisotropic displacement parameters ($Å^2$ x 10^3). The anisotropic displacement factor exponent takes the form:$-2\pi^2[h^2a^{*2}U^{11} + \ldots + 2hka^*b^*U^{12}]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	37(1)	24(1)	30(1)	3(1)	13(1)	4(1)
F(2)	35(1)	21(1)	37(1)	3(1)	13(1)	7(1)
F(4)	29(1)	33(1)	36(1)	-1(1)	13(1)	4(1)
F(5)	33(1)	28(1)	41(1)	4(1)	9(1)	10(1)
N(1)	27(1)	21(1)	27(1)	-1(1)	4(1)	1(1)
N(2)	44(1)	20(1)	27(1)	0(1)	10(1)	-1(1)
C(1)	27(1)	20(1)	26(1)	-2(1)	4(1)	-1(1)
C(2)	27(1)	18(1)	27(1)	-3(1)	5(1)	1(1)

C(3)	26(1)	19(1)	25(1)	-2(1)	3(1)	-2(1)
C(4)	25(1)	24(1)	28(1)	-3(1)	6(1)	-1(1)
C(5)	25(1)	21(1)	31(1)	-2(1)	3(1)	2(1)
C(6)	25(1)	20(1)	32(1)	1(1)	2(1)	-2(1)
C(7)	30(1)	41(1)	41(1)	9(1)	3(1)	8(1)
C(8)	36(1)	30(1)	28(1)	2(1)	12(1)	-1(1)
C(9)	35(1)	41(1)	28(1)	-5(1)	5(1)	1(1)

Table C.2.4. Selected bond lengths [Å] and angles [°]

O(1)-C(1)	1.332(1)	N(1)-C(1)	1.341(1)	C(2)-C(3)	1.398(1)
F(2)-C(2)	1.355(1)	N(2)-C(3)	1.371(1)	C(3)-C(4)	1.414(1)
F(4)-C(4)	1.347(1)	N(2)-C(6)	1.467(1)	C(4)-C(5)	1.371(1)
F(5)-C(5)	1.341(1)	N(2)-C(8)	1.469(1)	C(6)-C(7)	1.515(1)
N(1)-C(5)	1.316(1)	C(1)-C(2)	1.387(1)	C(8)-C(9)	1.511(1)

C(5)-N(1)-C(1)	116.89(7)	N(2)-C(3)-C(4)	123.41(8)
C(3)-N(2)-C(6)	121.09(7)	C(2)-C(3)-C(4)	113.51(7)
C(3)-N(2)-C(8)	121.64(7)	F(4)-C(4)-C(5)	119.15(8)
C(6)-N(2)-C(8)	117.21(7)	F(4)-C(4)-C(3)	121.09(8)
O(1)-C(1)-N(1)	120.22(8)	C(5)-C(4)-C(3)	119.64(8)
O(1)-C(1)-C(2)	118.74(8)	N(1)-C(5)-F(5)	115.64(8)
N(1)-C(1)-C(2)	121.03(8)	N(1)-C(5)-C(4)	125.75(8)
F(2)-C(2)-C(1)	117.01(8)	F(5)-C(5)-C(4)	118.58(8)
F(2)-C(2)-C(3)	119.75(7)	N(2)-C(6)-C(7)	114.29(8)
C(1)-C(2)-C(3)	123.16(8)	N(2)-C(8)-C(9)	112.88(8)
N(2)-C(3)-C(2)	123.08(8)		

Table C.2.6. Hydrogen bonds [Å and °]

D-H....A	d(D-H)	d(H....A)	d(D....A)	<(DHA)
O(1)-H(1O)....N(1)#1	0.834(18)	1.908(18)	2.7382(10)	173.5(17)

Table C.2.7. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3).

Atom	x	y	z	U(eq)
H(1O)	-1660(30)	502(10)	5044(17)	58(4)
H(61)	1550(30)	2601(7)	1979(15)	36(3)
H(62)	2860(30)	2817(7)	777(14)	33(3)
H(71)	-1070(30)	2857(7)	-598(16)	40(3)
H(72)	-2560(30)	2646(8)	638(16)	46(4)
H(73)	-1260(30)	3349(10)	633(17)	64(5)
H(81)	2180(30)	2081(7)	-1172(14)	37(3)
H(82)	4260(30)	1508(8)	-745(14)	46(4)
H(91)	-1210(30)	1268(8)	-1385(14)	49(4)
H(92)	1010(30)	1051(8)	-2314(15)	45(3)
H(93)	790(30)	659(7)	-924(14)	37(3)