NOTE TO USERS

Transition Metal-Catalyzed Bond Formations:
An Expansion of the Utility of Organotrifluoroborate Salts and Organoboronic Acids

by

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for the degree of Doctor of Philosophy
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Doctor of Philosophy, 2004
Tan Dai Quach
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Abstract

This thesis is a summary of the research conducted since September 1999 at the University of Toronto in the laboratory of Dr. Robert A. Batey. This manuscript is divided into four chapters. Chapter one provides a general introduction to the nature and reactivity of organotrifluoroborate salts. Their preparation from organoboron or organohalide precursors, as well as their use in a variety of synthetic transformations is reviewed. The preparation of novel tetra-*n*-butylammonium organotrifluoroborate salts within our own laboratory is also described.

Chapter two provides an overview of the classical copper-mediated Ullmann Reaction for carbon-carbon bond formation between aryl halides, as well as modern variations of the Ullmann-Goldberg Condensation for carbon-oxygen bond formation. Our contributions to this area of synthetic chemistry are described, including the copper-catalyzed cross-coupling of potassium aryl- and alkenyltrifluoroborates with unactivated alcohols and phenols, which were achieved in good to excellent yields by utilizing copper acetate monohydrate as catalyst under an atmosphere of oxygen in the presence of 4Å molecular sieves. Recent work into the copper-mediated/catalyzed cross-coupling of potassium organotrifluoroborate salts with activated carboxylate salts is also described.

Chapter three describes modern approaches to carbon-nitrogen bond formation through the Ullmann-Goldberg Condensation of organometalloid species with nitrogen-based

nucleophiles. The result of an investigation into the stoichiometric copper-mediated cross-coupling of potassium organotrifluoroborate salts and anilines is presented. In addition a novel reaction protocol for the ligandless and base free copper-catalyzed arylation of aliphatic amines is presented. The cross-coupling was found to work equally well with both potassium organotrifluoroborate salts and organoboronic acids.

Chapter four describes our efforts in the investigation of the mechanism of the cross-coupling. The various stages of the catalytic cycle are examined with particular focus upon the oxidation state of the copper species involved. The role of molecular sieves in the transformation is also explored, as experimental observations have suggested that they play a greater part than just as desiccant in the reaction. Finally, the result of a short study on the phenomenon of the deactivation of the catalytic transformation by the presence of quaternary ammonium species is also presented.

Acknowledgements

I should begin by thanking my research supervisor for the past five years: Dr. Robert A. Batey. Rob has strived to create an environment in his laboratory to foster both academic and intellectual development. Rob's supervision has offered both insight and guidance; while promoting an atmosphere of independent research and exploration. I should also thank the members of my advisory committee: Dr. Mark Lautens, Dr. Andrei Yudin, Dr. Jik Chin and Dr. Bob Morris for their insights and suggestions through my academic career. My deepest gratitude extends to Dr. Gregory Dake, who was kind enough to serve as my external examiner.

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Abbreviations

Å	angstroms
Ac	acyl moiety
Ar	aryl moiety
aq	aqueous
br	broad
Bu	butyl moiety
°C	degrees Celsius
cat	catalytic amount
Chx	cyclohexyl moiety
CI	chemical ionization
δ	chemical shift
Δ	heat
d	days or doublet (depending on context)
dd	doublet of doublets
ddd	doublet of doublet of doublets
ddt	doublet of doublet of triplets
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dq	doublet of quartets
dt	doublet of triplets
DMAP	*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EI	electron impact
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl moiety

Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
FCC	flash column chromatography
FID	Flame Ionization Detector
g	gram(s)
GC	gas chromatography
h	hour(s)
HF	hydrofluoric acid
HMPA	hexamethylphosphoric triamide
Hx	hexyl moiety
imid	imidazole
^{i}Pr	isopropyl moiety
IR	infrared spectroscopy
m	multiplet
M	molar
Me	methyl moiety
MeCN	acetonitrile
MeOH	methanol
min	minute(s)
µL	microlitre(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
MS	molecular sieves or mass spectroscopy (depending on context)
NMR	nuclear magnetic resonance spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	trifluoromethylsulfonate moiety
Ph	phenyl moiety

ppt	precipitate
PSSI	Programmed Split/Splitless Capillary Injector
pyr	pyridine
q	quartet
quant	quantitative
R	alkyl, alkenyl or alkynyl moiety
R_f	retention factor
rt	room temperature
s	singlet
t	triplet
TBA	tetra-*n*-butylammonium
TBAF	tetra-*n*-butylammonium fluoride
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
TMSCl	trimethylchlorosilane
TLC	thin layer chromatography
tt	triplet of triplets
X	generic halide

Chapter I

Organotrifluoroborate Salts

I.1 Introduction

I.1.1 General Introduction to Organopolyfluoroborates

Organometallic reagents have secured a pivotal role in modern synthetic chemistry.[1] Organolithium and organomagnesium halide compounds have been used for decades in a variety of applications from acting as strong bases to nucleophilic additions to electrophiles. In spite of their utility, the strengths of their basicity and nucleophilicity have limited their application in reactions containing sensitive functional groups. Chemists have spent decades searching for less reactive organometallic reagents that could tolerate a wider range of functionalities. Amongst the most notable of these discoveries are the organozinc,[1b] silicon,[1c] boron,[1d] and tin[1e] species; however, the use of these compounds is not without its drawbacks. For example, the toxicity of organostannanes and their by-products is well documented,[2] while organoboranes, especially the alkyl and alkynyl derivatives, are fairly unstable under normal atmospheric conditions due to a vacant orbital on the boron atom which is susceptible to attack by oxygen or water. A solution to the latter problem that has emerged from modern research is the use of organoborate reagents which are fully saturated at the boron atom. One class of these compounds which has gained the attention of several research groups over the past fifteen years are the tetravalent organotrifluoroborate salts. These salts often display greater stability to normal atmospheric conditions than their trivalent counterparts, while maintaining their reactivity in a variety of reaction classes.[3]

I.1.2 Properties of Organotrifluoroborate Salts

I.1.2.1 Physical Properties

Organotrifluoroborate salts show high stability towards atmospheric moisture and oxidation. They can be stored at room temperature indefinitely without noticeable degradation. This is not the case, however, for the majority of other organoboron reagents. For example, in the most ubiquitous class of boron compounds, the arylboronic acids show a relatively high degree of stability and have a long shelf-life, in contrast alkyl-, alkenyl- and alkynylboronic acids decompose within a matter of days to weeks when stored under normal atmospheric conditions. On the other hand, boronate esters prepared from boronic acids display much greater stability than their precursors, but usually at the sacrifice of their chemical reactivity.

The isolation and purification of the organotrifluoroborate salts are also much more facile than that of other organoboron reagents. The salts will usually precipitate out of the reaction mixture upon formation, and many of the products can be isolated by simple filtration. Purification of the products is accomplished by recrystallization in boiling acetonitrile, since most of the inorganic starting materials and by-products (KF, KHF_2 and $K^+BF_4^-$) are insoluble in the organic solvent. In contrast, the isolation of organoboronic acids often results in the formation of anhydride products like boroxines, which can be problematic when exact stoichiometric measures are required for reaction. As for the boronate esters, the diols used for their synthesis are difficult to remove from the reaction mixtures, and the chiral diols used for the preparation of asymmetric derivatives can be quite expensive.

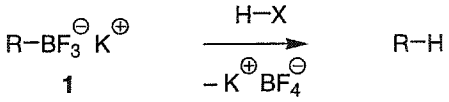
Potassium organotrifluoroborate salts, or more generally organotrifluoroborate salts containing an inorganic cation, are readily soluble only in polar solvents such as methanol, acetonitrile, acetone, DMF and DMSO. Some salts show slight solubility in water and THF, but all are insoluble in nonpolar organic solvents like dichloromethane, diethyl ether, and hydrocarbon solvents. In contrast, organotrifluoroborate salts containing an organic cation (e.g. tetraalkylammonium or tetraalkylphosphonium; *vide I.1.3.3*) are readily soluble in both polar and nonpolar organic solvents.

I.1.2.2 Chemical Reactivity

The tetravalent organotrifluoroborate moiety is electron-donating compared to the electron-withdrawing properties of trivalent organoborane moieties. Chemists have sought to exploit this difference in electronic properties in a variety of reactions with the main hypothesis being that the increased electron density at the boron centre would render the adjacent carbon substituent more nucleophilic. This increased nucleophilicity to the organic moiety would then aid in transmetallations or nucleophilic additions (*vide I.2*).[3]

The organotrifluoroborates are sensitive to both acids and bases. Under Brønsted acidic conditions, the reagents can undergo hydrodeboration resulting in carbon-boron bond scission. The comparative stability of various potassium organotrifluoroborate salts towards acid induced hydrodeboration was the subject of a recent study by the group of Frohn and coworkers. The results of their findings are summarized in Figure 1.[4] The organotrifluoroborate salts (**1**) were

found to be unreactive towards hydrodeboration in the presence of weak acids like acetic acid, while stronger acids like the anhydrous form of concentrated hydrofluoric acid was able to affect the hydrodeboration in a few minutes at room temperature. In the cases of the alkenyltrifluoroborates, the hydrodeboration was found to be stereospecific, where substitution of the proton would end up in the same position as the trifluoroborate moiety.



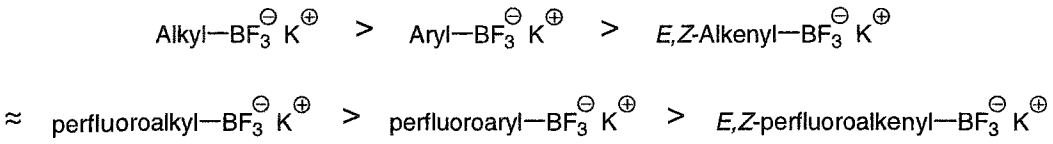


Figure 1 - Potassium Organotrifluoroborate Salts in Order of Decreasing Stability toward Acid Induced Hydrodeboration

In the presence of Lewis acids, and at high temperatures,[5] organotrifluoroborate salts can undergo a single boron-fluorine heterolysis to cleanly generate an organodifluoroborane species. In this manner, early work with organotrifluoroborate salts regarded them as "excellent means of storing and handling halo(organo)boranes, and of regenerating these compounds in a highly pure form." [5] A variety of Lewis acids have been used for this reaction including: gaseous BF_3,[6] $BF_3{\cdot}Et_2O$,[7,8] AsF_5,[9] TMSCl[10,11] and $SiCl_4$.[12] The resulting difluoroboranes were then utilized in further transformations (*vide I.2.1*).

Finally, in aqueous basic conditions, organotrifluoroborates can undergo one or more nucleophilic substitutions at boron. The fluoride substituents on boron are replaced by hydroxyl groups resulting in the formation various fluoroxyboronate species (Figure 2).[13-16]

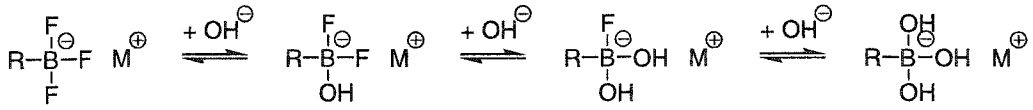
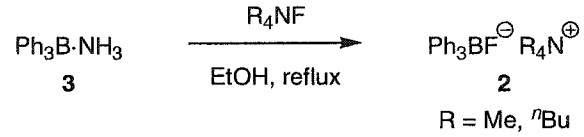


Figure 2 - Formation of Fluoroxyboronate Species under Aqueous Basic Conditions

I.1.3 Preparation of Organotrifluoroborate Salts

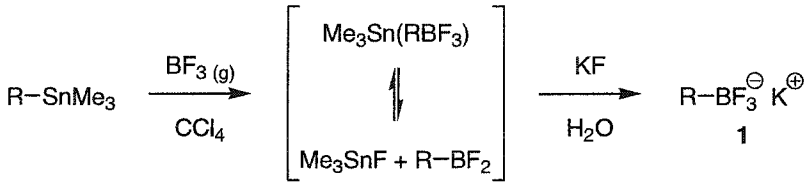
I.1.3.1 Classical Methods

Organopolyfluoroborate salts, or compounds of the general formula $[R_nBF_{4-n}]^-$ ($n \leq 3$), have been present in the chemical literature for over half a century. The first account of an organofluoroborate complex was reported by Fowler and Kraus in 1940.[17] They were able to prepare tetraalkylammonium derivatives of triphenylfluoroborate (**2**) by treatment of a triphenylborane-ammonia complex (**3**) with various tetraalkylammonium fluorides (Scheme 1). Fowler and Kraus' interest in the preparation of the salts was in their physical and crystalline properties, and no attempts were made to find a synthetic application for them.



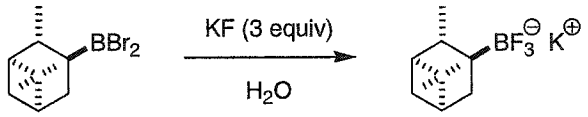
Scheme 1 - Preparation of Tetraalkylammonium Triphenylfluoroborates

The first appearance of organotrifluoroborate salts in the modern literature did not occur for another 20 years until the 1960s when Canadian researchers Chambers *et al.* described the preparation of various potassium organotrifluoroborate salts (**1**) from the corresponding organostannanes by reaction with gaseous boron trifluoride, and subsequent treatment of the intermediate(s) with potassium fluoride (Scheme 2).[18]



Scheme 2 - Preparation of Potassium Organotrifluoroborates from Organostannanes

An alternative method of generating the trifluoroborate salts came from the German group of Kaufmann *et al.* who discovered that treatment of organodihaloboranes with 3 equivalents of potassium fluoride would afford the trifluoroborate salts in good yields (Scheme 3).[19]

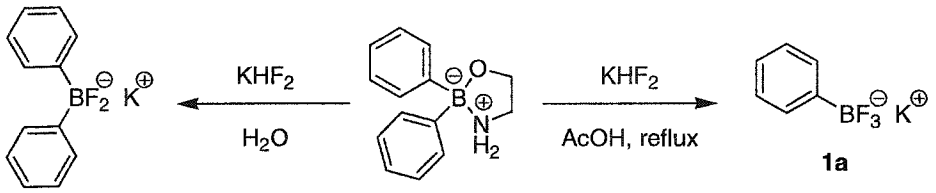


Scheme 3 - Preparation of Potassium Organotrifluoroborates from Organodihaloboranes

All of these classical methods of preparing the trifluoroborate salts require the formation of a highly reactive and unstable organodihaloborane intermediate. Hence, the use of trifluoroborate salts in organic synthesis was not popularized until the mid-1990s when Vedejs *et al.* reported a synthetic procedure capable of preparing the salts with much greater ease and efficiency that the previous methods.[10]

I.1.3.2 Preparation Methods Employing Potassium Hydrogen Difluoride

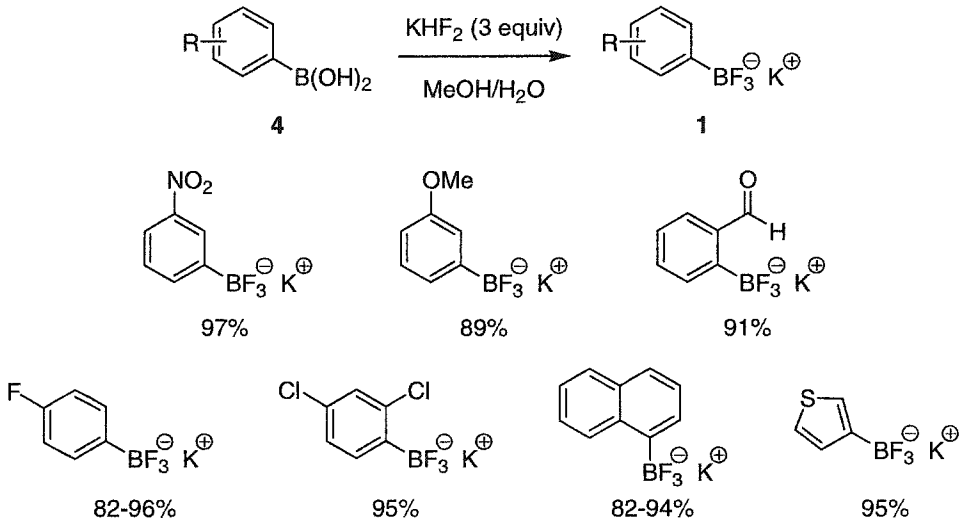
The initial reaction of potassium hydrogen difluoride (KHF_2) with an organoboron compound must be credited to Thierig and Umland in 1967, when they prepared potassium diphenyldifluoroborate from a diphenylborinic acid ethanolamine complex. They also observed that the same reactants, under harsher conditions, would produce potassium phenyltrifluoroborate (**1a**) (Scheme 4).[20] Their work, however, was not further explored in the substrate scope or limitations, and so the procedure was forgotten, for a time, in the obscurity of the chemical literature.



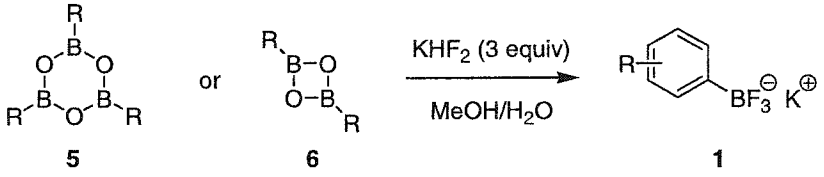
Scheme 4 - Initial Use of Potassium Hydrogen Difluoride as a Fluorinating Reagent for Boron

The possibility of using organotrifluoroborate as reagents was first described by Vedejs *et al.* in 1995, when they used KHF_2 as a fluorinating reagent for trivalent organoboron compounds.[10] Under their procedure, KHF_2 in aqueous methanol could displace the hydroxyl groups from boronic acids (**4**), a reaction that did not occur under the previous described methods utilizing KF. Hence, the highly air and moisture stable potassium organotrifluoroborate salts (**1**) could now be generated from commercially available boronic acids (**4**) in good to

excellent yields in one step. Research by various groups has greatly expanded the library of aryltrifluoroborate salts of the past decade, many of which are now commercially available (Scheme 5).[10,21-22] In addition, it was found that KHF_2 readily reacted with boroxines (**5**) and boronic acid dimers (**6**) that are often present in isolated samples of organoboronic acids (Scheme 6).

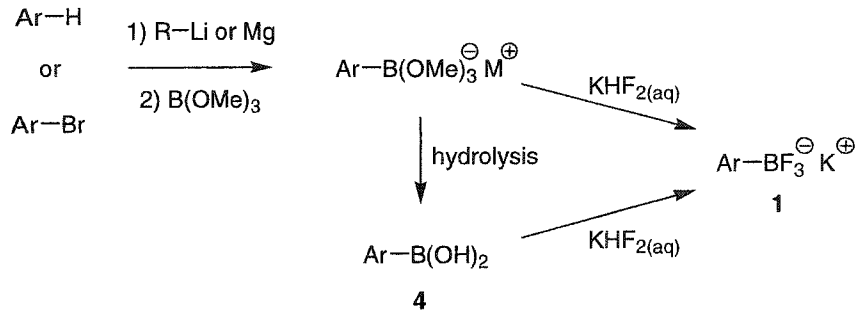


Scheme 5 - Preparation of Potassium Aryltrifluoroborate Salts from Commercially Available Arylboronic Acids



Scheme 6 - Reaction of Boroxines and Boronic Acid Dimers with Potassium Hydrogen Difluoride

The aryltrifluoroborate salts need not to be prepared directly from the purified boronic acids since KHF_2 also reacts with boronic acids prepared *in situ*, or with other boronate intermediates. Many more potassium aryltrifluoroborate salts have been prepared in this manner from their arene, aryl halide or organometallic precursors (Scheme 7).[10,21a,c,22,23]

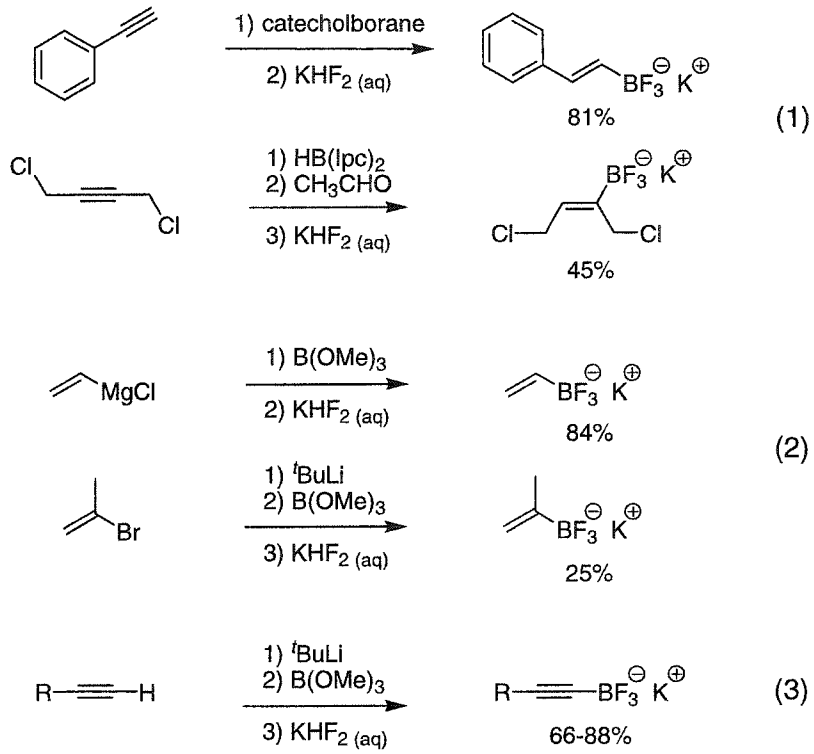


Scheme 7 - Preparation of Potassium Aryltrifluoroborate Salts from Other Arylboron Precursors

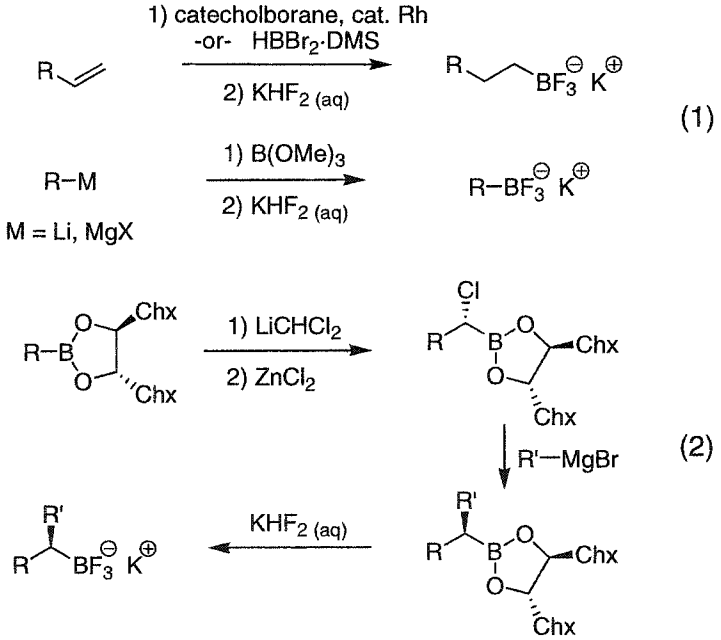
Potassium alkenyltrifluoroborates have been prepared from their commercially available alkenylboronic acid derivatives with KHF_2. In addition, standard procedures including hydroboration (Scheme 8, reaction 1) and trialkylborate trapping of organometallic intermediates (Scheme 8, reaction 2) can be used to generate the alkenylboron compounds *in situ*. Subsequent treatment with an aqueous solution of KHF_2 affords the trifluoroborate salts in moderate to good yields.[21,24-26] In the same manner, potassium alkynyltrifluoroborate salts have been prepared in good yields from their alkynyltrialkoxyboronate intermediates by Molander and coworkers (Scheme 8, reaction 3).[27]

Potassium alkyltrifluoroborate salts have also been prepared in a comparable manner. The alkylboron intermediates were generated by hydroboration of the alkenyl derivatives, or by trapping of organometallic species with trialkylborates (Scheme 9, reaction 1). More interesting, however, is the preparation of optically active alkyltrifluoroborate salts from the group of Matteson *et al.* They were able to successfully employ their own α-haloboronic ester technology to generate the chiral boronate esters which underwent fluorination in good yields without racemization (Scheme 9, reaction 2).[12]

In all of the above examples of preparation, several functional groups including halides, ketones, ethers and azides were able to survive the fluorination procedure unscathed. Aldehyde functionalities had to be protected as their acetal derivatives during hydroboration, but hydrolysis during the fluorination process would unmask the original functionality. Surprisingly, even silyl protecting groups on alcohols and alkynes were able to survive the presence of the fluoride source.[27]



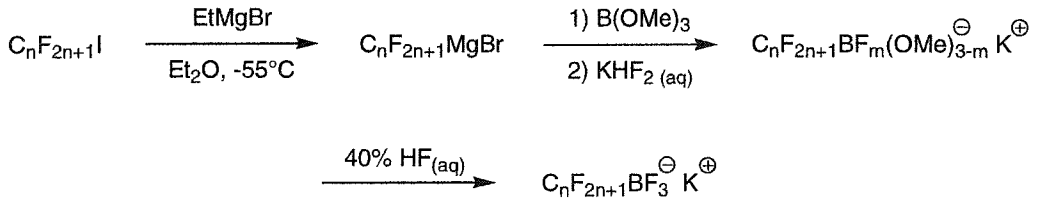
Scheme 8 - Preparation of Potassium Alkenyl- and Alkynyltrifluoroborate Salts



Scheme 9 - Preparation of Potassium Alkyltrifluoroborate Salts

I.1.3.3 Preparation Methods Employing Hydrofluoric Acid

Frohn and coworkers have reported the preparation of potassium perfluoroalkylborates from the perfluoroalkyl iodide precursors by first treating with ethylmagnesium bromide to affect a magnesium/halogen exchange, followed by trapping of the organometallic intermediate with trimethylborate. The tetracoordinate borate was then fluorinated with KHF_2, but conversion to the trifluoroborate salt was incomplete; instead, a mixture of fluorinated borates of the formula $R_fBF_n(OMe)_{3-n}^- K^+$ was formed. Complete fluorination to the trifluoroborate salt was accomplished by treating the reaction mixture with a 40 % solution of hydrofluoric acid (HF). The authors have speculated that the replacement of the electron-donating methoxy substituents on boron with electron-withdrawing fluorides, coupled with the already electron-withdrawing perfluorinated alkyl side-chain, increased the Lewis acidity of the borate making elimination of subsequent methoxide groups more difficult. Protonation on the oxygen by HF would facilitate the concomitant substitution of methoxide by fluoride (Scheme 10).[28]



Scheme 10 - Preparation of Potassium Perfluoroalkyltrifluoroborates with Hydrofluoric Acid

Treating organoboron compounds with HF to affect boron-fluoride bond formation was in no way a novel concept. More than a decade earlier, Kinder and Katzenellenbogen had reported the synthesis of organodifluoroboranes via the reaction of HF with organoboronic acids.[29] Their work with acylaminoboronic acids allowed an intramolecular coordination of the acyl moiety with the trivalent boron atom, thus the tetracoordinate borate complex formed was stable toward further fluorination by the aqueous HF solution, allowing them to isolate and characterize the normally unstable difluoroborane derivatives (Figure 3).

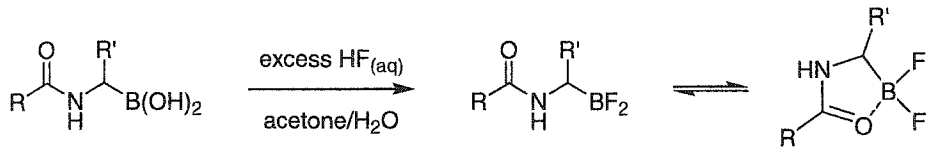
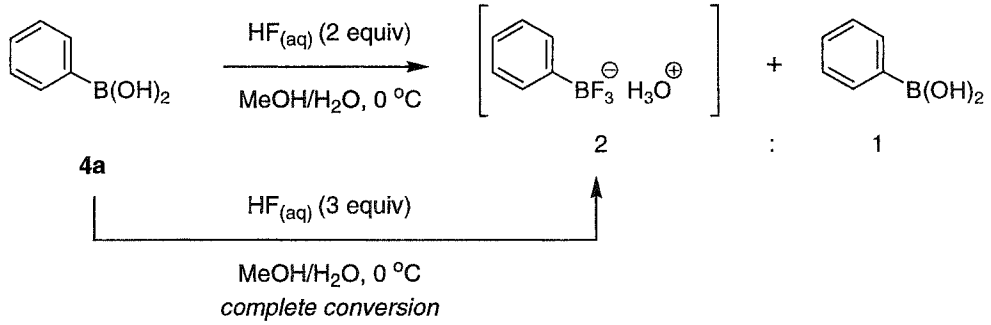


Figure 3 - Treatment of Acylaminoboronic Acids with Hydrofluoric Acid

I.1.3.3.1 Results and Discussion

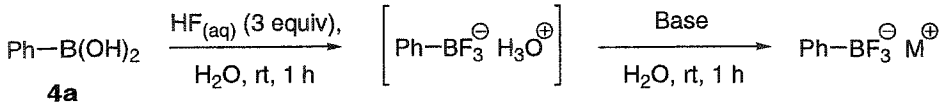
In an attempt to prepare phenyldifluoroborane, our group followed Kinder and Katzenellenbogen's protocol and treated phenylboronic acid (**4a**) with 2 equivalents of HF. The experiment resulted in an approximately 2:1 mixture of $PhB(OH)_2$ (^{11}B-NMR: δ 28.8 ppm) and $PhBF_3^-$ (^{11}B-NMR: δ 4.1 ppm) as determined by ^{11}B-NMR (Scheme 11). Under our conditions, where the organoboronic acid lacked a substituent capable of an intramolecular coordination with boron, the formation of a stable, coordinatively saturated organotrifluoroborate from the difluoroborane species occurred rapidly, consuming the HF limiting reagent before all of the boronic acid could be fluorinated. Indeed, treatment of **4a** with 3 equivalents of HF led to the complete conversion of all of the starting material to trifluoroborate species. All attempts to isolate the solid trifluoroborate salt with a hydronium counterion resulted in decomposition. Fortunately, treatment of the reaction mixture with KOH resulted in a counterion exchange to produce the isolable potassium phenyltrifluoroborate (**1a**).[15,30]



Scheme 11 - Treatment of Phenylboronic Acid with Hydrofluoric Acid

This two step method to preparing the trifluoroborates allowed for the control of the counterion on the salt by changing the species of base used to quench the hydronium intermediate generated. A series of $PhBF_3^-M^+$ salts was prepared with various counterions (Table 1). The species generated by reaction with LiOH was soluble in the aqueous layer, but evaporation of the aqueous solvent gave the crystalline solid **7a**. Compounds **1a, 8a** and **9a** containing inorganic counterions were insoluble in the aqueous reaction mixture and readily precipitated out of solution. Compounds **10a** and **11a** "oiled out" of the aqueous reaction mixture and were isolated by extraction with CH_2Cl_2. Evaporation of the organic solvent gave the corresponding crystalline solids.

Table 1 - Synthesis of Phenyltrifluoroborate Salts with Various Counterions



Entry	Base	Product	M	Yield (%)[a]
1	LiOH	**7a**	$Li^{\oplus}$	60
2	NaOH	**8a**	$Na^{\oplus}$	83
3	KOH	**1a**	$K^{\oplus}$	90
4	Cs_2CO_3	**9a**	$Cs^{\oplus}$	quant.
5	$^{n}Bu_4N^{\oplus}OH^{\ominus}$	**10a**	$^{n}Bu_4N^{\oplus}$	95
6	$^{n}Bu_4P^{\oplus}OH^{\ominus}$	**11a**	$^{n}Bu_4P^{\oplus}$	90

a) isolated yields.

All of the compounds prepared were crystalline solids upon isolation and purification, in fact, an X-ray crystal structure was obtained of tetra-*n*-butylammonium phenyltrifluoroborate (**10a**, Figure 4).[31] Unsurprisingly, the salts containing an inorganic counterion were only soluble in polar solvents, like acetonitrile and water, at elevated temperatures. Compounds **10a** and **11a** containing a large, organic counterion were found to be soluble in a wide range of polar and nonpolar solvents. Finally, all the salts have so far demonstrated the lengthy shelf-life (> 3 years) associated with the trifluoroborates without noticeable decomposition.

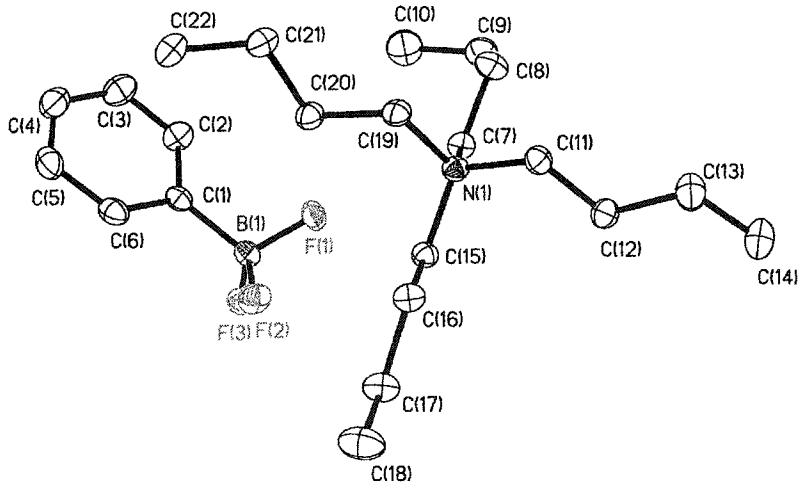
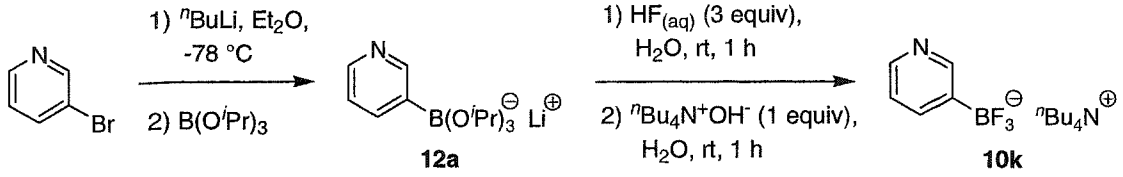


Figure 4 - Drawing of Tetra-*n*-butylammonium Phenyltrifluoroborate (10a) with 30 % Thermal Ellipsoids

It was also observed that a counterion exchange from potassium organotrifluoroborate salts could also be effected by treating the potassium salt with an aqueous solution of the organic base. This type of counterion exchange has previously been accomplished, but the reactions were slow with reaction times ranging from 18 h[10b] to several weeks.[32] Under our improved conditions the reaction is nearly instantaneous and the products are isolated and purified with ease. The scope of these counterion exchange protocols was explored by generating a number of tetra-*n*-butylammonium aryltrifluoroborate salts from their arylboronic acid (Table 2, entries 1-6), potassium aryltrifluoroborate (Table 2, entries 7-9), or lithium aryltrialkoxyboronate derivatives (Table 2, entry 10). The last example was synthesized directly from 3-bromopyridine by reaction with ^{n}BuLi and B(O^{i}Pr)$_3$ (Scheme 12).



Scheme 12 - Preparation of Tetra-*n*-butylammonium 3-Pyridyltrifluoroborate (10k)

An X-ray crystal structure of tetra-*n*-butylammonium ferrocenyltrifluoroborate was obtained, showing the interaction of two independent ferrocenyltrifluoroborate anions in each asymmetrical unit cell (**10g**, Figure 5).[33]

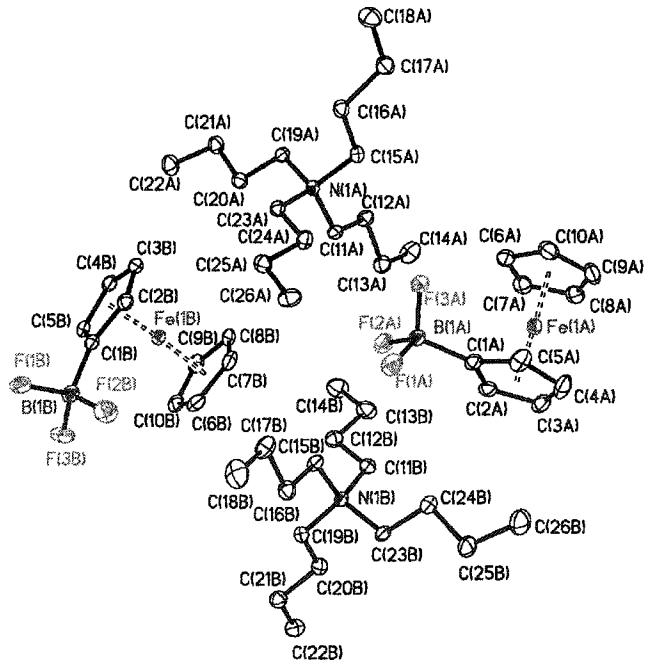
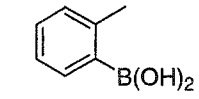
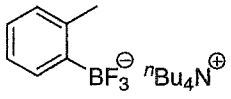
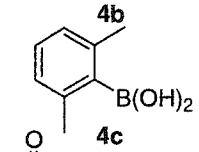
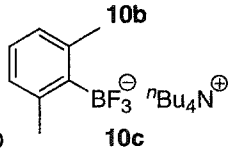
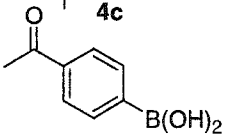
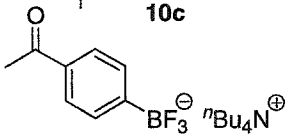
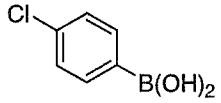
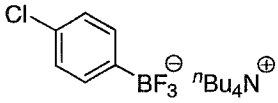
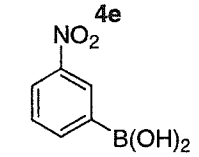
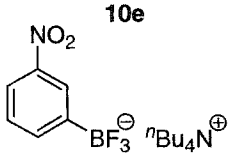
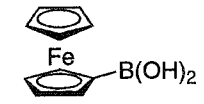
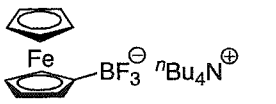
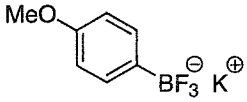
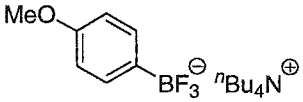
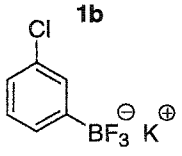
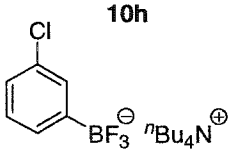
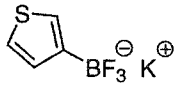
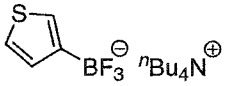
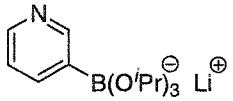
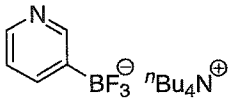


Figure 5 - Drawing of Tetra-*n*-butylammonium Ferrocenyltrifluoroborate (10g) with 30 % Thermal Ellipsoids

Table 2 - Synthesis of Tetra-*n*-butylammonium Aryltrifluoroborates via Counterion Exchange

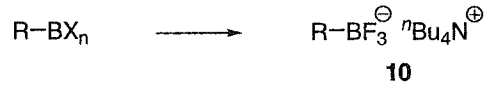
10

Entry	Boron Reagent	Conditions[a]	Product	Yield (%)[b]
1	 **4b**	A	 **10b**	97
2	 **4c**	A	 **10c**	90
3	 **4d**	A	 **10d**	quant.
4	 **4e**	A	 **10e**	97
5	 **4f**	A	 **10f**	97
6	 **4g**	A	 **10g**	80
7	 **1b**	B	 **10h**	92
8	 **1c**	B	 **10i**	97
9	 **1d**	B	 **10j**	95
10	 **12a**	A	 **10k**	90

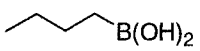
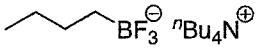
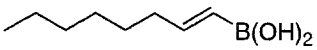
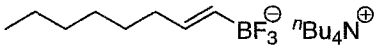
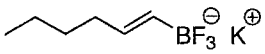
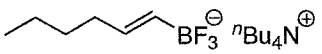
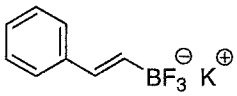
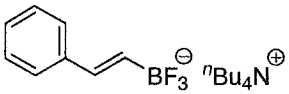
a) Conditions A: 1) $HF_{(aq)}$ (3 equiv), H_2O, rt, 1 h. ii) $^nBu_4N^+OH^-$ (1 equiv), H_2O, rt, 1 h. Conditions B: $^nBu_4N^+OH^-$ (1 equiv), H_2O, rt, 1 min. b) isolated yields.

Alkyl- and alkenylboron compounds were also subjected to the counterion exchange protocols resulting in good to excellent yields of the corresponding tetra-*n*-butylammonium alkyl/alkenyltrifluoroborate salts (Table 3).

Table 3 - Synthesis of Tetra-*n*-butylammonium Alkyl- and Alkenyltrifluoroborates via Counterion Exchange



10

Entry	Boron Reagent	Conditions[a]	Product	Yield (%)[b]
1	 **4h**	A	 **10l**	82
2	 **4i**	A	 **10m**	95
3	 **1e**	B	 **10n**	90
4	 **1f**	B	 **10o**	90

a) Conditions A: 1) $HF_{(aq)}$ (3 equiv), H_2O, rt, 1 h. ii) $^nBu_4N^+OH^-$ (1 equiv), H_2O, rt, 1 h. Conditions B: $^nBu_4N^+OH^-$ (1 equiv), H_2O, rt, 1 min. b) isolated yields.

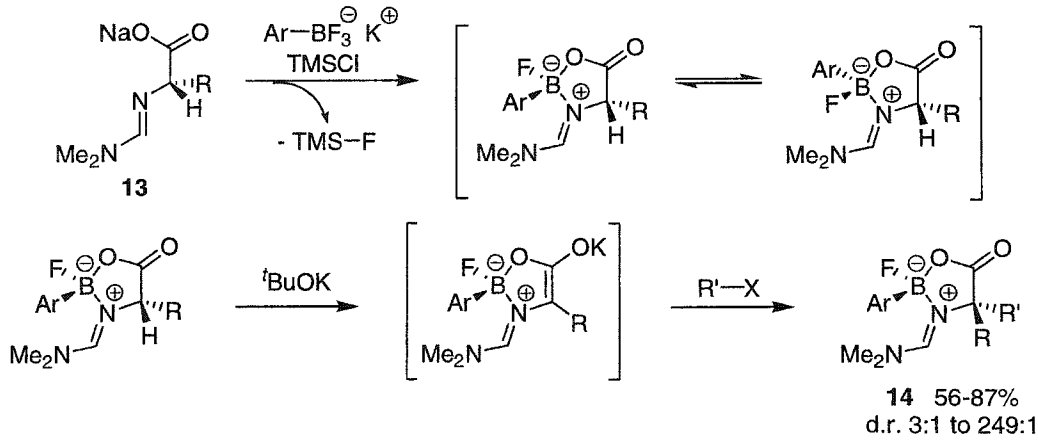
Hence, tetraalkylammonium organotrifluoroborate salts were prepared by two methods: (1) direct formation of the salts with the organic counterion via treatment of the organoboron precursor with HF followed by reaction with an organic base (e.g. $^nBu_4N^+OH^-$), or (2) initial formation of the potassium salt via KHF_2 and subsequent counterion exchange with $^nBu_4N^+OH^-$. The advantage of first method is that it was found to be the more mild of the two, as substrates that are sensitive to the harsh conditions of KHF_2 (e.g. Table 2, entries 6 and 10) could only be isolated after preparation following the first protocol.

I.2 Reactions of Organotrifluoroborate Salts

I.2.1 Generation and Use of Lewis Acidic Organodifluoroboranes

Organotrifluoroborate salts were first employed as stable equivalents to organodifluoroboranes. Upon reaction of the trifluoroborate salts with strong Lewis acids, one fluoride substituent on the boron centre can be removed. The increase in Lewis acidity of the remaining organodifluoroborane allowed reaction with other electron-donating species.

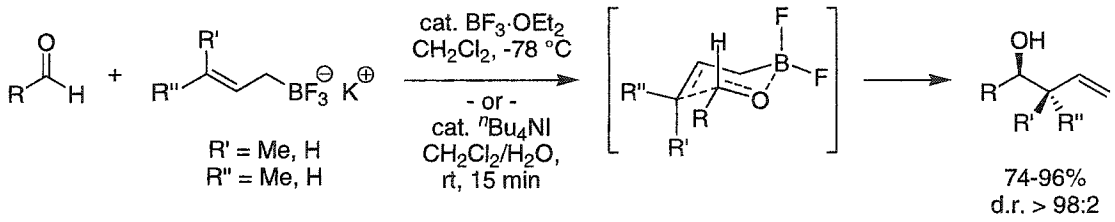
Vedejs and coworkers first used the trifluoroborates as chiral auxiliaries in the alkylation of amidinocarboxylates (**13**). Treatment of the aryltrifluoroborate with trimethylsilylchloride (TMSCl) generates an aryldifluoroborane *in situ* which then coordinates to **11** forming an oxazaborolidinone. While the oxazaborolidinone intermediate is in equilibrium with its epimer, it is possible to control the equilibrium and isolate a solution enriched in one of the epimeric forms. Enolization and alkylation of the oxazaborolidinone leads to the formation of the α,α'-dialkylated amino acid derivative **14** in good yields with high diastereoselectivities. The arylfluoroborate moiety retains the "chiral memory" of the original stereocentre, and diastereoselectivities can be altered by the nature of the aryltrifluoroborate salt employed.[10]



Scheme 13 - Potassium Aryltrifluoroborates as Chiral Auxiliaries in Amino Acid Alkylation

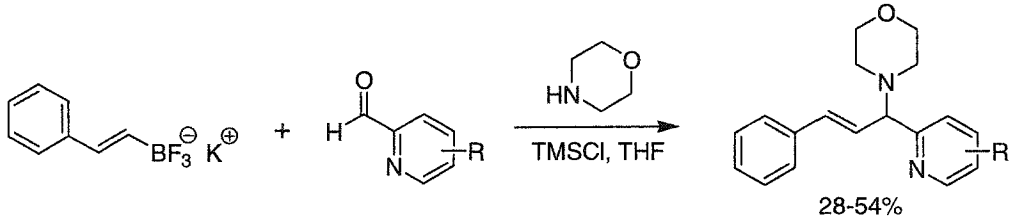
Our group's use of potassium organotrifluoroborate salts began with the reaction of potassium allyl- or crotyltrifluoroborates with aldehydes in the presence of a Lewis acid,[8] or in a biphasic medium under phase-transfer catalysis (Scheme 14).[34] The reaction was believed to proceed through a trivalent organodifluoroborane species which would allow coordination to the aldehyde in a Zimmerman-Traxler transition state. The product homoallylic alcohols were

generated with excellent diastereoselectivities.



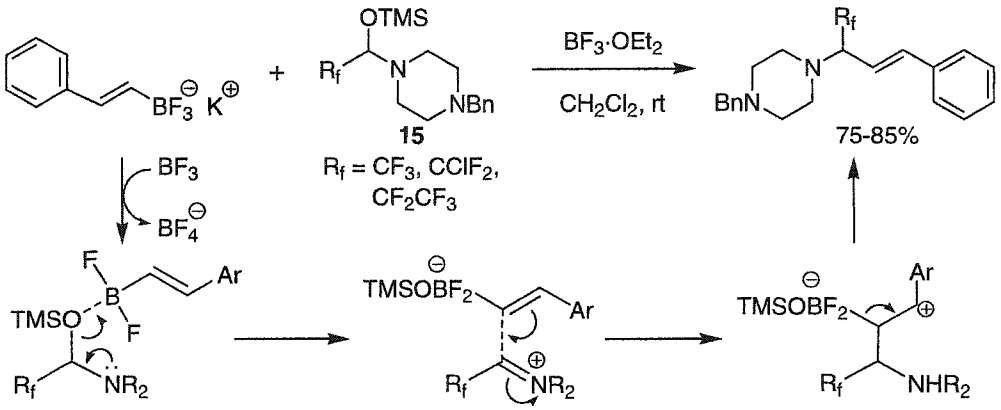
Scheme 14 - Allylation/Crotylation of Aldehydes Under Lewis Acid or Phase-Transfer Catalysis

Analogous to the reaction of trifluoroborate salts with aldehydes is the 1,2-addition to imines in the trifluoroborate variant of the Boronic Mannich reaction. Bryce *et al.* reacted heterocyclic aldehydes with potassium *E*-styryltrifluoroborate in the presence of morpholine and TMSCl.[11] They speculate that the difluoroborane generated then added to the iminium formed from the amine and the aldehyde in this multi-component coupling reaction. Although the products were only isolated in moderate yields, the trifluoroborate salts fared better than their boronic acid counterparts which gave only trace amounts of the product with heterocyclic aldehydes. The reaction also required the presence of a heteroatom α to the aldehyde moiety, the purpose of which is probably to intramolecularly direct the nucleophile into the iminium ion.



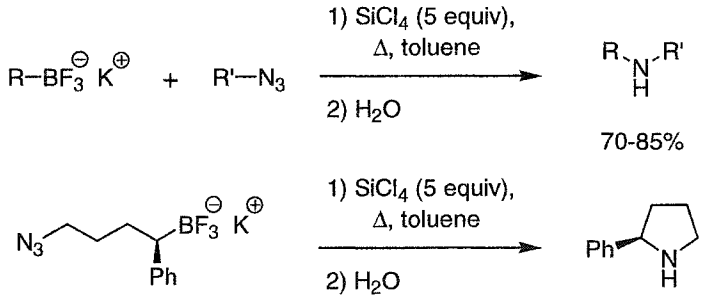
Scheme 15 - Potassium Organotrifluoroborate Salts in Boronic Mannich Reactions

Another variant of the addition of trifluoroborates to iminium species comes from Billard and Langlois.[7] Their addition of vinyltrifluoroborates to perfluorinated alkyl aldehyde hemiaminals (**15**) is believed to go through the Lewis acidic difluoroborane species. The difluoroborane facilitates the deoxygenation of the starting hemiaminal for the formation of the iminium ion. Addition of the alkenyl(siloxy)difluoroborate followed by the subsequent elimination of the boron moiety affords the final product (Scheme 16).



Scheme 16 - Potassium Alkenyltrifluoroborates Reaction with Fluorinated Iminium Species

Matteson and Kim have recently reported the use of tetrachlorosilane ($SiCl_4$) as the Lewis acid of choice to defluorinate trifluoroborate salts in their synthesis of secondary amines.[12] Both the inter- and intramolecular condensations of azidoalkanes with the activated trifluoroborate salts were reported (Scheme 17).

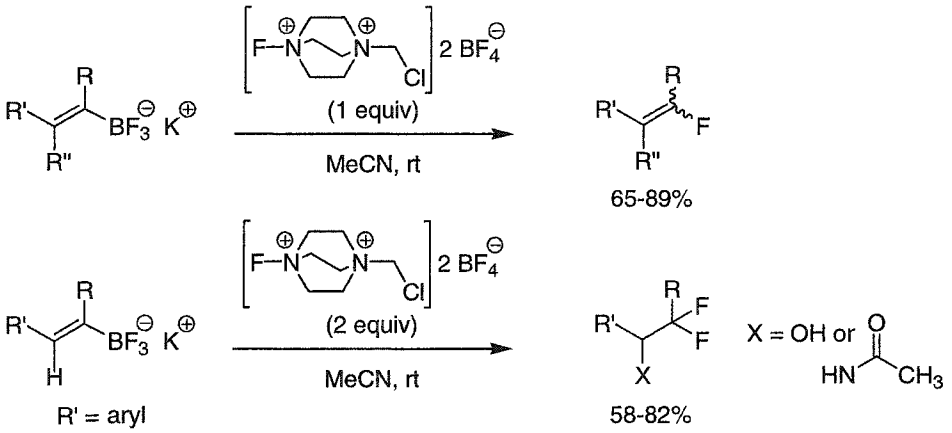


Scheme 17 - Potassium Organotrifluoroborates in Secondary Amine Synthesis

I.2.2 Direct Reactions with Electrophiles

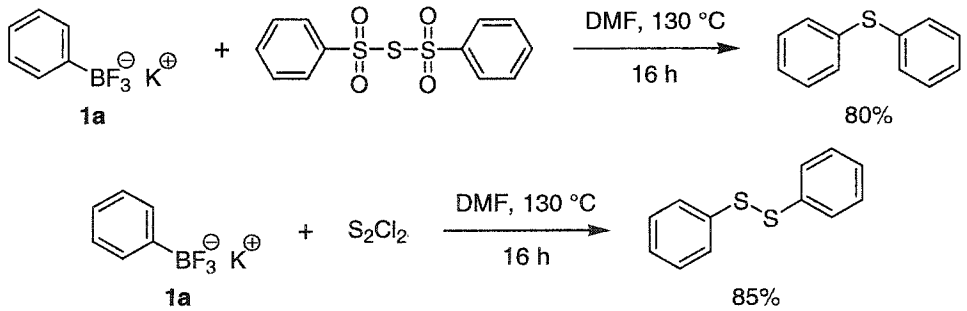
The reaction of trifluoroborate salts with electrophiles is not limited to those that proceed through a difluoroborane intermediate. One of the first applications of trifluoroborates was by Petasis *et al.*, who synthesized alkenyl fluorides from vinyltrifluoroborates and Selectfluor™ (**16**).[24] The corresponding boronic acids gave much slower reaction rates, as well as a mixture of products including the fluorine free alkenes. The reaction was thought to undergo an addition/elimination mechanism via a carbocation intermediate which explains the rate enhancement of the trifluoroborate salts and the mixture of *E/Z*-isomers produced. Interestingly, when the reaction was run with 2 equivalents of Selectfluor™, the alkenyl fluoride produced

after the first reaction would react further to produce a second carbocation intermediate which is then quenched by the solvent (Scheme 18). The second reaction only works when the cation produced was benzylic in nature (i.e. R' = aryl).



Scheme 18 - Electrophilic Fluorination of Potassium Vinyltrifluoroborate Salts

Another example of an uncatalyzed reaction between trifluoroborate salts and electrophiles comes from the work of Kerverdo and Gingras.[35] Their reaction of potassium trifluoroborate salts with various electrophilic sulfur compounds resulted in the formation of organosulfides and disulfides. Hence, the treatment of potassium phenyltrifluoroborate (**1a**) with bis(phenylsulfonyl)sulfide in DMF at 130 °C afforded the diphenyl sulfide, and reaction of **1a** with monochlorosulfide under the same conditions gave the corresponding diphenyl disulfide, both in good yields (Scheme 19). Other organoborate species including cesium triphenylfluoroborate and tetra-*n*-butylammonium tetraphenylborate were examined in the study, but the trifluoroborates gave the best results.



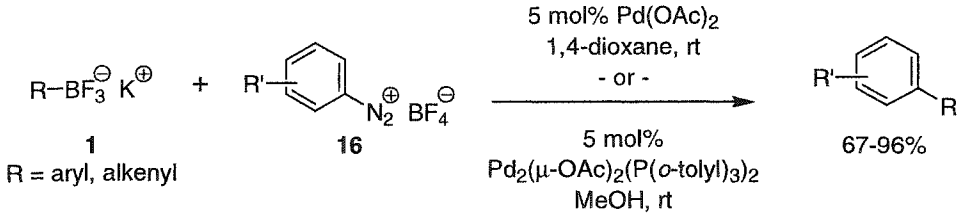
Scheme 19 - Sulfuration of Potassium Organotrifluoroborate Salts

I.2.3 Transition Metal-Catalyzed Reactions

I.2.3.1 Palladium-Catalyzed Transformations

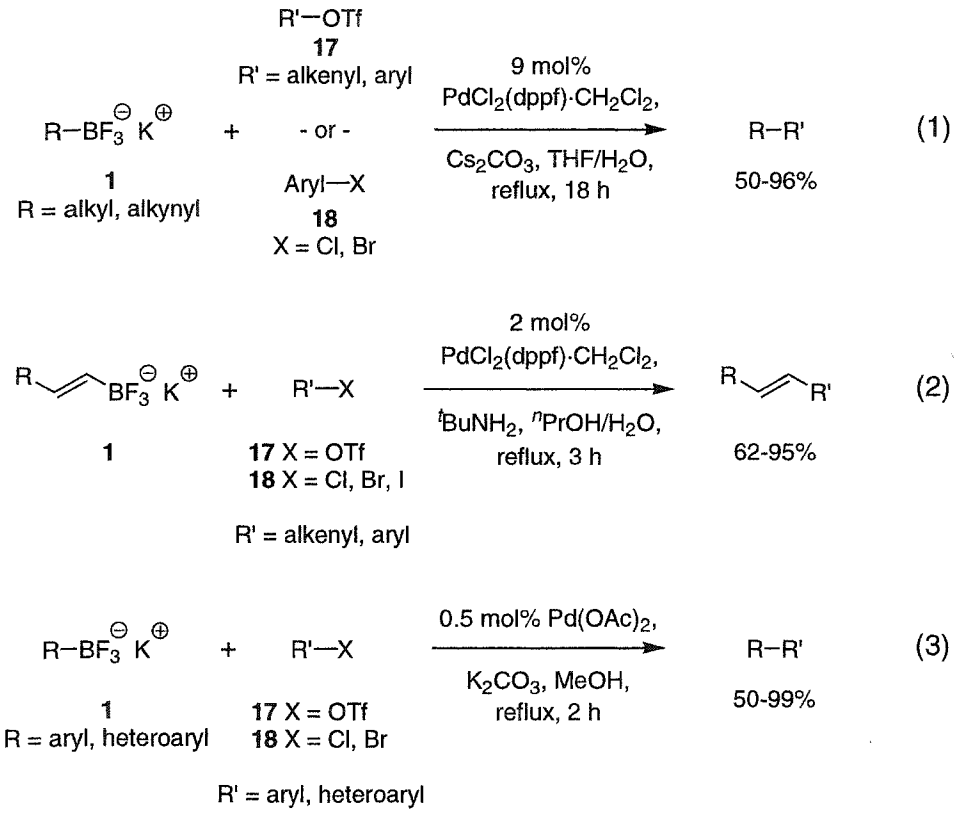
The first transmetallation of the organic moiety from the boron of trifluoroborates to a palladium catalyst was reported by Genêt and Darses in 1997.[21a] Their use of trifluoroborate salts in a palladium-catalyzed Suzuki-Miyaura type cross-coupling[36] to arene diazonium salts (**16**) paved the way for an explosion of interest into the synthetic utility of the salts. Within the past half a decade, several groups including those of Molander, Frohn, Chen and ourselves, have made many contributions to, what is arguably, the fastest growing and most developed area of trifluoroborate chemistry.

Genêt and Darses had hypothesized that the trifluoroborate salts would offer greater reactivity in the Suzuki-Miyaura cross-coupling due to the increased nucleophilicity of the organic moiety.[21a] Their work was influenced by the observation previously made by Wright and coworkers, who reported that fluoride salts (NaF, KF, CsF, Et_4NF, Bu_4NF) could be used to promote Suzuki-Miyaura cross-couplings of boronic acids. Wright's reaction was hypothesized to generate an organotrifluoroborate or other fluoroxyboronate species *in situ* due to the high affinity of fluoride ions to boron.[13] Indeed, Genêt's hypothesis was proven correct as the trifluoroborate salts turned out to be more efficient cross-coupling partners than the corresponding boronic acids. Under their optimized conditions, potassium aryl- and alkenyltrifluoroborate salts (**1**) could be cross-coupled to arene diazonium salts (**16**) with catalytic $Pd(OAc)_2$ in 1,4-dioxane, or with palladacycle $Pd_2(\mu\text{-}OAc)_2(P(o\text{-tolyl})_3)_2$ in methanol at room temperature (Scheme 20). Recently, Frohn *et al.* have extended this methodology to include perfluorinated organotrifluoroborate salts.[37a] A variety of functional groups are tolerated under these mild conditions including aryl halides and triflates which are typical organic electrophiles used in these types of cross-coupling reactions.



Scheme 20 - Suzuki-Miyaura Cross-Coupling of Potassium Aryl- and Alkenyltrifluoroborates with Arene Diazonium Salts

Molander's group has made a significant number of contributions to the field of potassium organotrifluoroborate chemistry, both in the synthesis of the salts themselves and in their application towards palladium-catalyzed cross-couplings. Potassium alkyl-,[26,38] alkenyl-,[25] alkynyl-,[27] aryl- and heteroaryltrifluoroborate salts[22] have all been shown to cross-couple with a

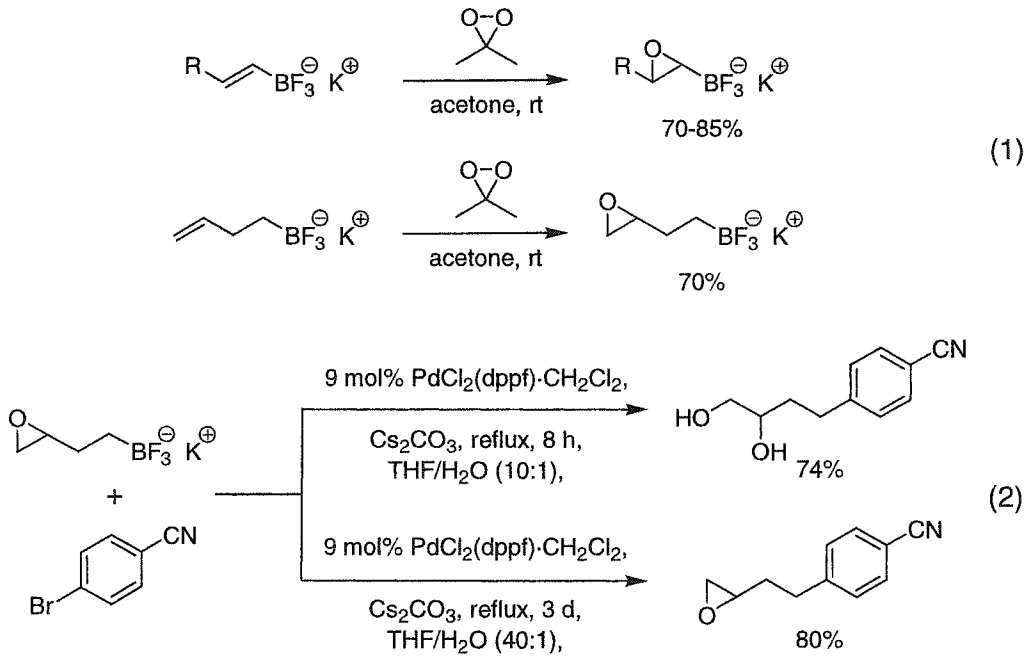


Scheme 21 - Suzuki-Miyaura Cross-Coupling of Potassium Organotrifluoroborates with Organotriflates and Organohalides

variety of organotriflates (**17**) and organohalides (**18**) under fairly mild conditions (Scheme 21). Frohn and coworkers have developed the perfluorinated organotrifluoroborate variant of these reactions as well.[37b]

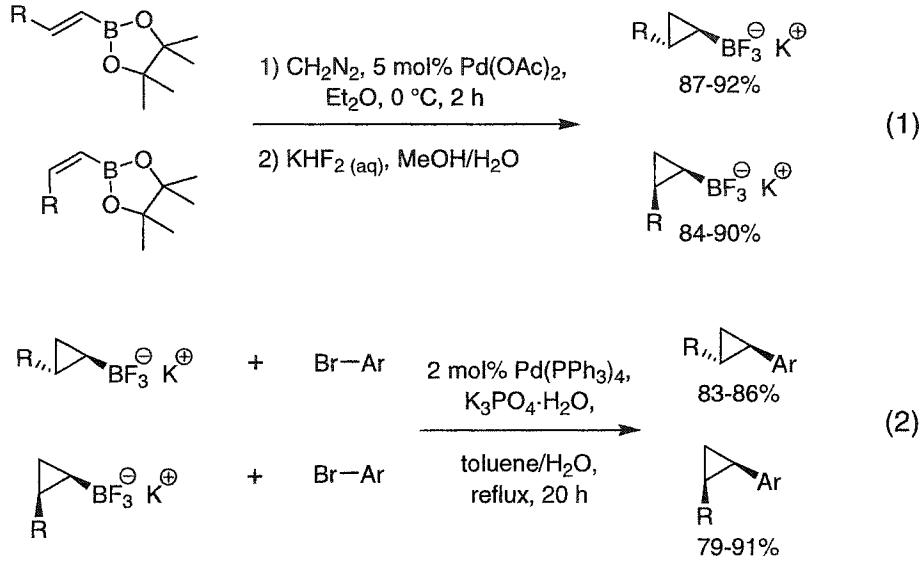
A recent report from Molander's group describes the epoxidation of alkenyltrifluoroborate salts with dimethyldioxirane (DMDO). The epoxidation was found to be successful on double bonds within the carbon chain as well as those directly attached to the trifluoroborate moiety (Scheme 21, reaction 1).[38] More interestingly, it was discovered that the epoxidized salts could undergo Suzuki-Miyaura cross-couplings to aryl halides. Under their standard procedures, the

epoxide moiety would ring open during the reaction; however, by increasing the solvent/ cosolvent ratio of THF/water from 10:1 to 40:1, they were able to obtain the cross-coupled product with the epoxide moiety intact (Scheme 22, reaction 2). The only example of such a cross-coupling had the epoxide moiety in a terminal position on the alkyl side chain; no examples of a direct epoxide cross-coupling were reported.



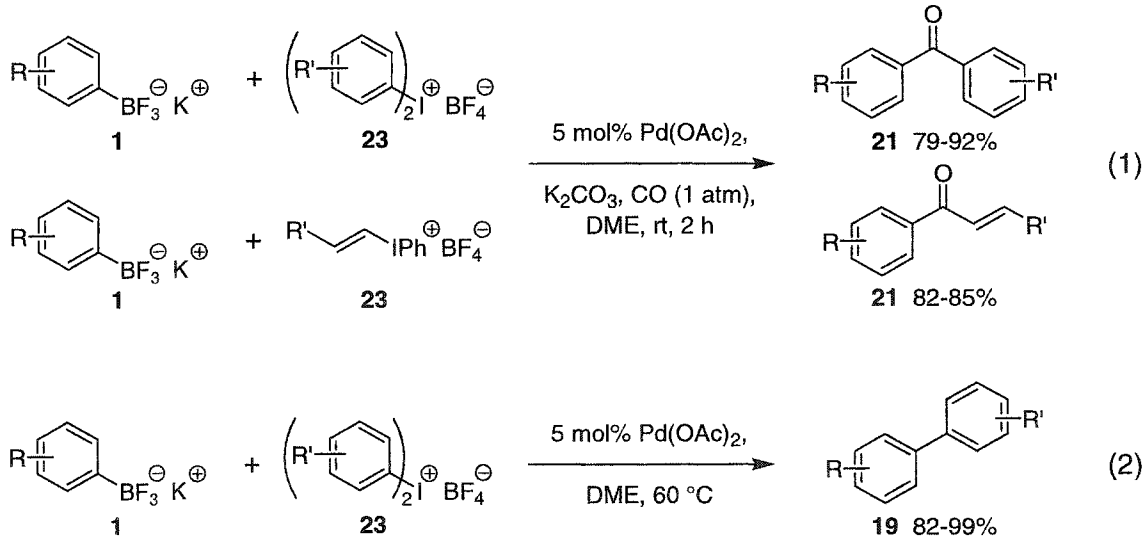
Scheme 22 - Preparation and Suzuki-Miyaura Cross-Coupling of Epoxidized Potassium Organotrifluoroborate Salts

Expanding on the subject of variation and application of trifluoroborate salts is a recently published paper by Deng and associates.[39] They were able to cyclopropanate the pinacol esters of alkenylboronic acids, convert the products to trifluoroborate salts, and subsequently cross-couple them to aryl bromides. As expected, cyclopropanation of the alkenes occurred stereospecifically, and the cross-couplings took place with retention of the stereocentres (Scheme 23).



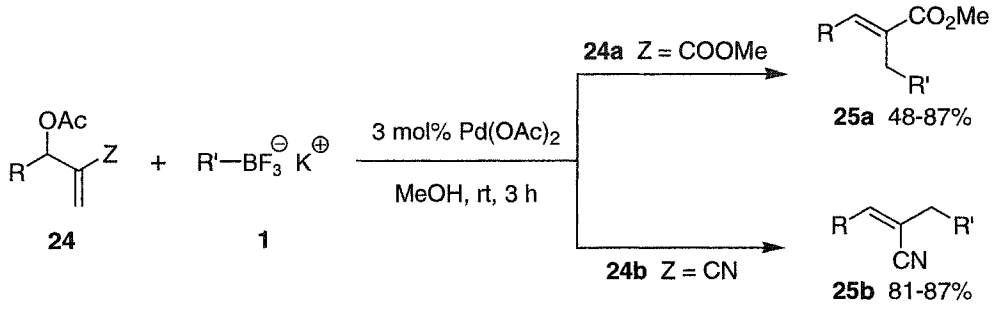
Scheme 23 - Preparation and Suzuki-Miyaura Cross-Coupling of Potassium Cyclopropyltrifluoroborate Salts

Chen and Xia have reported ketone formation by the carbonylative cross-coupling of tetrafluoroborate iodonium salts (**23**) to potassium aryltrifluoroborates (**1**) under an atmosphere of carbon monoxide.[40a] In this manner, diaryl ketones and chalcones were prepared in excellent yields under fairly mild conditions (Scheme 24, reaction 1). Unsurprisingly, in the absence of the carbon monoxide, the standard direct cross-coupling to the iodonium salt was also achieved. As in the case of Genêt's cross-couplings to the arene diazonium salts, the addition of a base was not required for the reaction to proceed with these highly reactive substrates (Scheme 24, reaction 2).[40b]



Scheme 24 - Suzuki-Miyaura Cross-Coupling of Potassium Aryl- and Alkenyltrifluoroborates with Aryl- and Alkenyliodonium Salts

The most recent report of the use of trifluoroborates in a palladium-catalyzed reaction comes from the group of Kabalka *et al.*, who employed the salts as nucleophilic cross-coupling partners to Baylis-Hillman acetates (**24**) in palladium-catalyzed π-allyl chemistry.[41] A variety of aryl-, heteroaryl-, and alkenyltrifluoroborates were shown to undergo the cross-coupling in moderate to good yields. Interestingly, the stereoconfiguration of the major products of the reaction could be controlled by the nature of the electron-withdrawing moiety on the Baylis-Hillman adduct. Hence, products of 3-acetoxy-2-methylenealkanoates (**24a**) are generated as the *E*-isomers (**25a**), and products of 3-acetoxy-2-methylenealkanenitriles (**24b**) are generated as the *Z*-isomers (**25b**, Scheme 26).



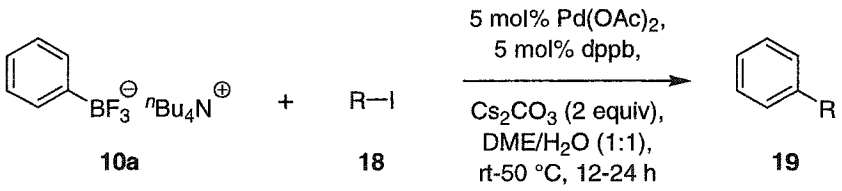
Scheme 25 - Palladium-Catalyzed Cross-Coupling of Baylis-Hillman Acetates with Potassium Organotrifluoroborate Salts

I.2.3.1.1 Results and Discussion

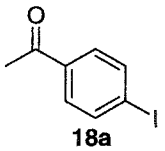
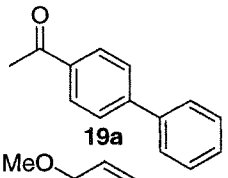
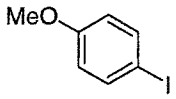
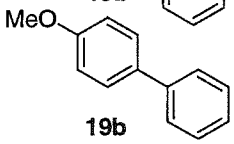
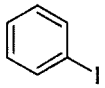
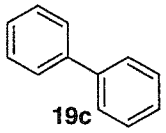
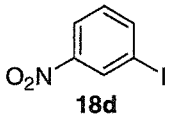
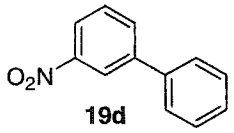
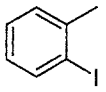
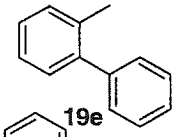
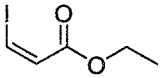
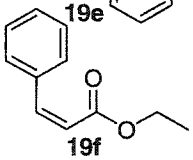
Our own contribution to the field of palladium-catalyzed Suzuki-Miyaura cross-couplings of trifluoroborate salts came in the application of the tetra-*n*-butylammonium derivatives.[15,30] Under our optimized conditions, tetra-*n*-butylammonium organotrifluoroborate salts (**10**) were cross-coupled to a variety of organobromides (Table 4) and organoiodides (Table 5) in moderate to excellent yields. Variation of the organo moiety on the boron substrate was also possible; hence, aryl-, heteroaryl-, and alkenyltrifluoroborates were successful cross-coupled to a variety of organobromides (Table 6). The reactions were performed in a biphasic solvent system of 1,2-dimethoxyethane (DME) and water at room temperature or 50 °C. The catalytic system utilized 5 mol % $Pd(OAc)_2$ with dppb as ligand. The addition of two equivalents of the Cs_2CO_3 base was vital to the success of the reaction, as formation of a fluoroxyboronate intermediate was necessary for transmetallation to the palladium catalyst.[13-15,30,42] Potassium organotrifluoroborate

salts also underwent cross-coupling under these optimized conditions; however, due to their limited solubility in organic media the addition of 10 mol % of a phase-transfer catalyst like tetra-*n*-butylammonium iodide (TBAI) was required to achieve comparable yields.

Table 4 - Suzuki-Miyaura Cross-Coupling of Tetra-*n*-butylammonium Phenyltrifluoroborate with Various Organoiodides

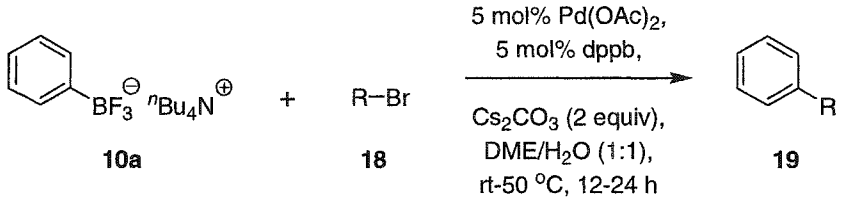


10a 18 19

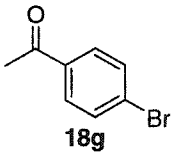
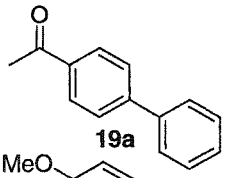
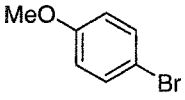
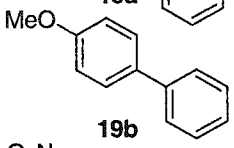
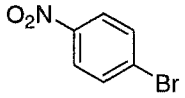
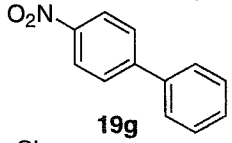
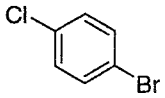
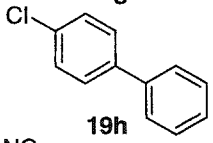
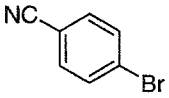
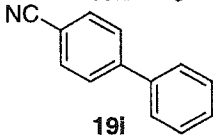
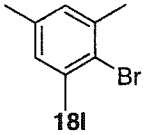
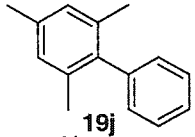
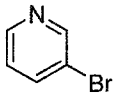
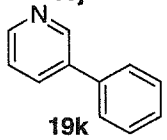
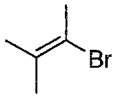
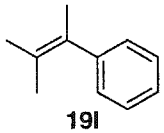
Entry	Arylhalide	Temp (°C)	Time (h)	Product	Yield (%)[a]
1	 18a	rt.	12	 19a	92 (3)[b]
2	 18b	50	24	 19b	82
3	 18c	rt.	12	 19c	quant.
4	 18d	50	24	 19d	76
5	 18e	rt.	12	 19e	97
6	 18f	50	24	 19f	55

a) isolated yields. b) yield of homocoupled product of the organohalide.

Table 5 - Suzuki-Miyaura Cross-Coupling of Tetra-*n*-butylammonium Phenyltrifluoroborate with Various Organobromides

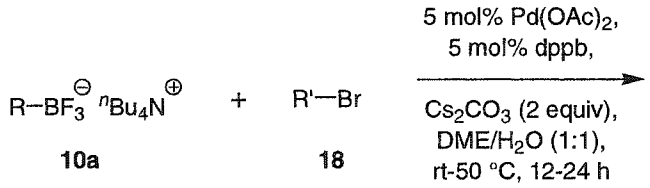


10a **18** **19**

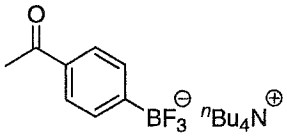
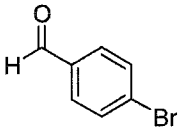
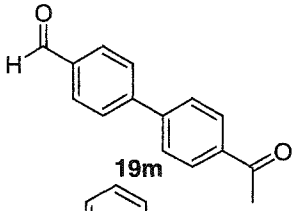
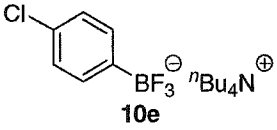
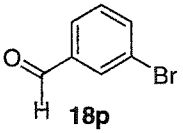
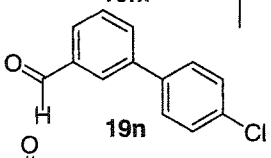
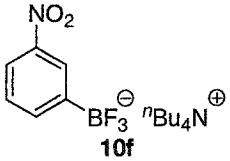
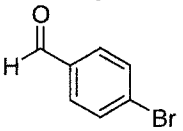
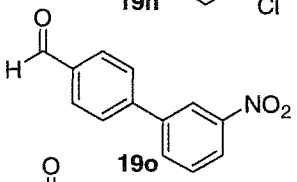
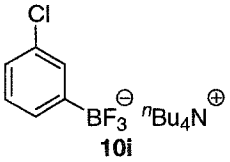
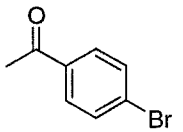
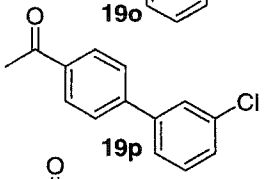
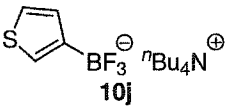
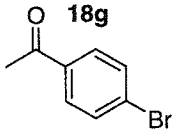
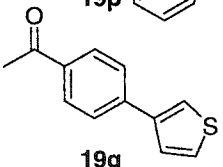
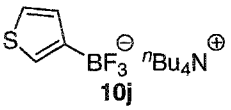
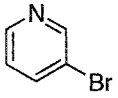
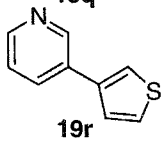
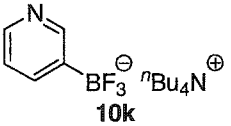
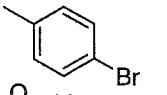
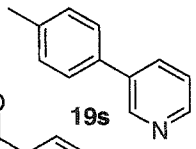
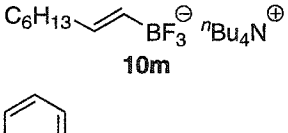
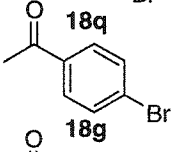
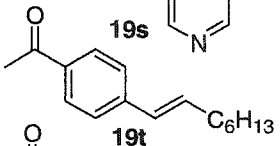
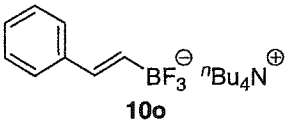
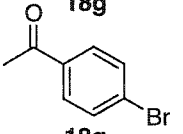
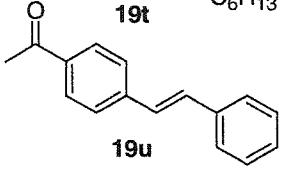
Entry	Arylhalide	Temp (°C)	Time (h)	Product	Yield (%)[a]
1	 **18g**	rt.	12	 **19a**	95 (3)[b]
2	 **18h**	50	24	 **19b**	79
3	 **18i**	50	24	 **19g**	79 (5)[b]
4	 **18j**	50	12	 **19h**	96
5	 **18k**	rt.	12	 **19i**	93
6	 **18l**	50	24	 **19j**	85
7	 **18m**	50	24	 **19k**	93
8	 **18n**	rt.	12	 **19l**	91

a) isolated yields. b) yield of homocoupled product of the organohalide.

Table 6 - Suzuki-Miyaura Cross-Coupling of Tetra-*n*-butylammonium Organotrifluoroborates with Various Organobromides

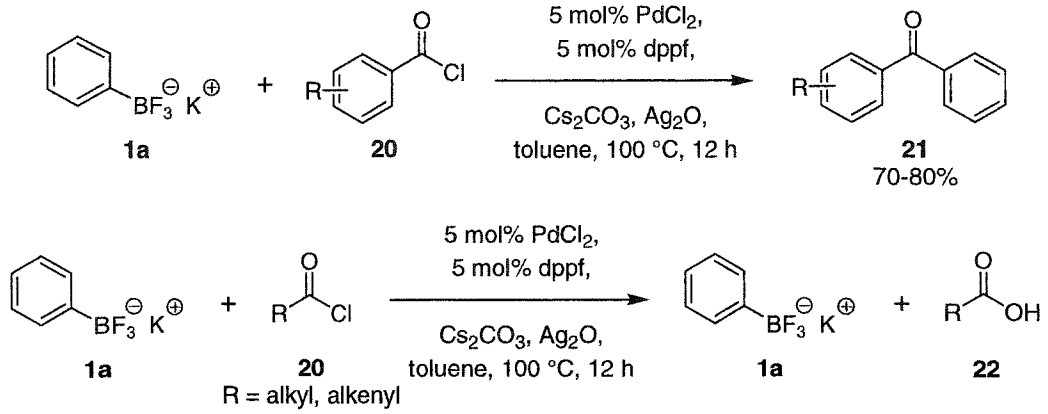


10a **18** **19**

Entry	Borate	Arylbromide	Product	Yield (%)[a]
1	 **10d**	 **18o**	 **19m**	75
2	 **10e**	 **18p**	 **19n**	60
3	 **10f**	 **18o**	 **19o**	78
4	 **10i**	 **18g**	 **19p**	92
5	 **10j**	 **18g**	 **19q**	91
6	 **10j**	 **18m**	 **19r**	88
7	 **10k**	 **18q**	 **19s**	69
8	 **10m**	 **18g**	 **19t**	87
9	 **10o**	 **18g**	 **19u**	55

a) isolated yields.

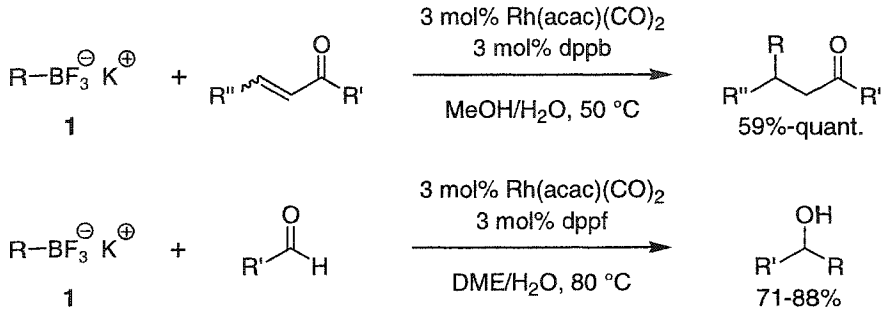
We have also reported the palladium-catalyzed, silver-mediated cross-coupling of potassium aryltrifluoroborates (**1**) with acid chlorides (**20**). The optimized conditions allowed for the formation of the cross-coupled ketones (**21**) to occur in good yields with aryl acid chlorides, but reaction with alkyl- or alkenyl acid chlorides afforded little or none of the desired cross-coupled product; instead, the acid chlorides were hydrolyzed to the corresponding carboxylic acids (**22**, Scheme 26). Unfortunately, the tetra-*n*-butylammonium organotrifluoroborates had no reactivity under these conditions, though it is unclear why this was the case.[15]



Scheme 26 - Palladium-Catalyzed, Silver-Mediated Cross-Coupling of Potassium Phenyltrifluoroborate with Acid Chlorides

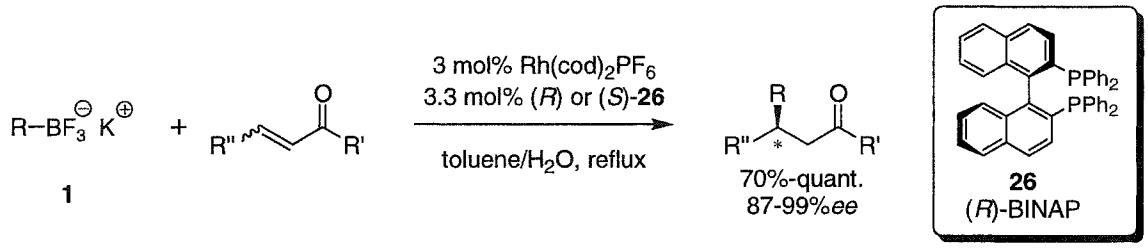
I.2.3.2 Rhodium-Catalyzed Transformations

Organotrifluoroborate salts, like their boronic acid counterparts, have been demonstrated to transmetallate to rhodium species. Our group was the first to report a trifluoroborate variant of the rhodium-catalyzed 1,4-addition of an organoboron reagent to an α,β-unsaturated enone, as well as, the direct 1,2-addition of trifluoroborates to aldehydes in the presence of rhodium (Scheme 27).[43] In both cases, the reactions with the trifluoroborate salts were faster than those carried out with the corresponding boronic acids under otherwise identical conditions. In addition, both reactions with the trifluoroborates were found to proceed efficiently with electron-poor substituents, whereas previous studies with the corresponding boronic acids were unsuccessful. For example, 3-nitrophenylboronic acid had no reactivity in the rhodium-catalyzed Michael addition to methyl vinyl ketone, but the corresponding trifluoroborate afford the product in 59 % yield. Likewise, nitro-substituted benzaldehyde derivatives were unreactive in 1,2-additions with organoboronic acids, but addition of the trifluoroborate salts was achieved in good yields (82-88 %).



Scheme 24 - Rhodium-Catalyzed Addition of Potassium Organotrifluoroborate Salts to α,β-Unsaturated Enones and Aldehydes

The application of trifluoroborate salts to the asymmetric variant of these rhodium-catalyzed Michael additions, also known as Miyaura-Hayashi reactions,[44] was reported by Genêt *et al.*[45] Their use of the bidentate phosphorus ligand, BINAP (**26**), allowed for enantioselectivities in excess of 98 % with near quantitative yields of the β-substituted products (Scheme 28).



Scheme 25 - Rhodium-Catalyzed Asymmetric Addition of Potassium Organotrifluoroborate Salts to α,β-Unsaturated Enones

I.2.4 Conclusions

Research performed on the reaction of organotrifluoroborate salts led to the development of a new protocol for the formation of organotrifluoroborate salts. Under this protocol, the nature of the cationic counterion can be controlled by the choice of base used in a counterion exchange. The tetraalkylammonium organotrifluoroborate salts produced are found to be readily soluble in both polar and nonpolar organic solvents, unlike their potassium organotrifluoroborate counterparts. A counterion exchange protocol was also developed that allowed the exchange of inorganic counterions with organic moieties to produce the tetraalkylammonium salts. The tetraalkylammonium salts were found to undergo Pd-catalyzed cross-coupling reactions with a variety of aryl- and alkenyl halides containing a broad range of functional groups under mild conditions and ambient temperatures to give good to excellent yields of the cross-coupled

products. In addition, the potassium organotrifluoroborate salts were found to undergo Ag_2O assisted Pd-catalyzed cross-couplings with aryl acid chlorides at elevated temperatures to give the cross-coupled ketones in moderate to good yields.

Clear precedence has been set, by us and others, for the ability of trifluoroborate salts to transmetallate onto transition-metal catalysts. It is this premise that has encouraged our further exploration into the synthetic utilities of this interesting class of organoboron compounds.

I.3 Experimental Procedures

I.3.1 General Synthetic Methods

MeCN and CH_2Cl_2 were distilled from CaH_2 under argon. Toluene, THF and Et_2O were distilled from sodium metal/benzophenone ketyl under argon. All other commercial solvents and reagents were used as received from the Aldrich Chemical Company, Fischer Scientific Ltd., Strem or BDH. All glassware was oven dried at 210 °C and allowed to cool under a stream of dry nitrogen.

Silica gel (60 Å, 230-400 mesh) used in flash column chromatography was obtained from Silicycle and used as received. Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel plates (Ultra Pure Silica Gel Plates purchased from Silicycle), visualized with a Spectroline UV_{254} lamp, and stained with a 20 % phosphomolybdic acid in ethanol solution. Solvent systems associated with R_f values and flash column chromatography are reported as v/v ratios.

Melting points were obtained using a Fisher-Johns melting point apparatus, and are uncorrected. ^1H and ^{13}C NMR were recorded at 400 or 300 MHz and 100 or 75 MHz respectively on Varian Unity 400, Gemini 300 or Mercury 300 spectrometers. ^{11}B NMR was recorded at 160 or 96 MHz on Varian Unity 500 or Gemini 300 spectrometers respectively. ^{19}F NMR was recorded at 282 or 375 MHz on Varian Mercury 300 or Unity 400 spectrometers respectively. Proton chemical shifts were internally referenced to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), D_2O (δ 4.79 ppm) or CD_3CN (δ 1.94 ppm). Carbon chemical shifts were internally referenced to the dueterated solvent signals in $CDCl_3$ (δ 77.20 ppm). Boron chemical shifts were externally referenced to $BF_3{\cdot}OEt_2$ (δ 0.00 ppm). Fluorine chemical shifts were externally referenced to $CFCl_3$ (δ 0.00 ppm). FT-IR spectra were recorded on a Perkin-Elmer Spectrum 1000, with samples loaded as neat films on NaCl plates or as pressed KBr discs. Low and high resolution mass spectra were recorded on a Bell and Howell 21-490 spectrometer and an AEI MS3074 spectrometer respectively.

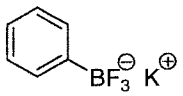
References following the compounds names indicate literature articles where ^1H and/or ^{13}C NMR data have been previously reported.

I.3.2 Synthetic Methods and Characterization Data of Organotrifluoroborate Salts

Representative Procedure for the Synthesis of Organotrifluoroborates with Various Counterions from Boronic Acids (4)

To a solution of $PhB(OH)_2$ (0.520 g, 4.27 mmol) in MeOH (ca. 1 mL) was added a 5.0M aqueous solution of HF (2.65 mL, 13.3 mmol) via a polypropylene syringe with vigorous stirring over a 1 minute period at room temperature. The reaction mixture was then cooled to 0 °C and KOH (0.240 g, 4.27 mmol) was slowly added over a 1 minute period. The reaction was again warmed to room temperature and stirred for another hour as the water insoluble product precipitated out of solution. The product was isolated by filtration as the white crystalline solid **1a** in 90 % yield (0.710 g, 3.84 mmol).

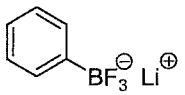
Potassium Phenyltrifluoroborate (1a) (Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020-3027.)



1a

Isolated as a white crystalline solid in 90 % yield: ^{1}H NMR (300 MHz, D_2O) δ 7.70 - 7.60 (2H, m), 7.48 - 7.39 (3H, m); ^{13}C NMR (75 MHz, D_2O) δ 131.5, 131.5, 128.3, 128.1, 128.0 (one signal absent); ^{11}B NMR (96 MHz, D_2O) δ 4.40 (q, J = 54.0 Hz); ^{19}F NMR (282 MHz, D_2O) δ -142.06 (q, J = 48.0 Hz).

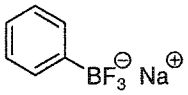
Lithium Phenyltrifluoroborate (7a)



7a

Isolated as a white solid and recrystallized in methanol as transparent crystals in 60 % yield: ^{1}H NMR (300 MHz, D_2O) δ 7.79 (2H, d, J = 7.0 Hz), 7.56 (1H, t, J = 7.0 Hz), 7.48 (2H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, D_2O) δ 157.9, 131.5, 128.5, 126.8, 125.9 (one signal absent); ^{11}B NMR (96 MHz, D_2O) δ 3.80 (br s); ^{19}F NMR (282 MHz, D_2O) δ -144.20 (q, J = 14.0 Hz).

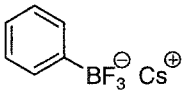
Sodium Phenyltrifluoroborate (8a)



8a

Isolated as a white powder in 83 % yield: ^{1}H NMR (300 MHz, CD_3CN) δ 7.45 (2H, d, J = 7.0 Hz), 7.22 - 7.09 (3H, m); ^{13}C NMR (75 MHz, CD_3CN) δ 158.8, 132.4, 129.4, 127.7, 126.8 (one signal absent); ^{11}B NMR (96 MHz, CD_3CN) δ 4.09 (br s); ^{19}F NMR (282 MHz, CD_3CN) δ -145.85 (br s).

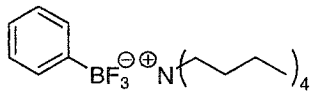
Cesium Phenyltrifluoroborate (9a)



9a

Isolated as a white powder in quantitative yield: mp = 218 - 219 °C (MeCN); ^{1}H NMR (300 MHz, CD_3CN) δ 7.70 - 7.60 (2H, m), 7.48 - 7.39 (3H, m); ^{13}C NMR (75 MHz, CD_3CN) δ 131.5, 131.5, 128.3, 128.1, 128.0 (one signal absent); ^{11}B NMR (96 MHz, CD_3CN) δ 3.87 (q, J = 56.0 Hz); ^{19}F NMR (282 MHz, CD_3CN) δ -138.66 (q, J = 48.0 Hz).

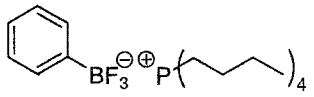
Tetra-*n*-butylammonium Phenyltrifluoroborate (10a) (Wang, C.; Mo, Y.; Jang, M.; Janzen, A. F. *Can. J. Chem.* **1993**, *71*, 525-528.)



10a

Isolated as a pale yellow, crystalline solid in 95 % yield: mp = 74 - 75 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (2H, d, J = 6.5 Hz), 7.15 - 7.00 (3H, m), 2.90 - 2.80 (8H, m), 1.40 - 1.18 (16H, m), 0.89 (12H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.6, 126.4, 125.3, 57.6, 23.3, 19.1, 13.3 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 3.30 (br s); ^{19}F NMR (282 MHz, $CDCl_3$) δ -142.03 (br s); IR (film) ν 2964, 2876, 1636, 1487, 1431, 1382, 1269, 1192, 1071, 950, 908, 751, 706, 598 cm^{-1}; LRMS (FAB): *m/z* = 145 (100), 144 (25), 91 (22); HRMS (FAB): *m/z* calcd. for ($C_6H_5BF_3^-$) = 145.0436, found = 145.0449.

Tetra-*n*-butylphosphonium Phenyltrifluoroborate (11a)



11a

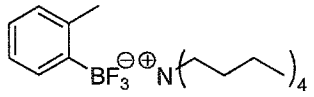
Isolated as a white crystalline solid in 90 % yield: mp = 46 - 47 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (2H, d, J = 6.5 Hz), 7.19 - 7.04 (3H, m), 2.00 - 1.87 (8H, m), 1.47 - 1.25 (16H, m), 0.90 (12H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.8, 126.8, 125.6, 23.9 (d, J = 15.0 Hz), 23.6 (d, J = 5.0 Hz), 18.3 (d, J = 47.5 Hz), 13.5 (d, J = 1.0 Hz) (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 3.33 (br s); ^{19}F NMR (282 MHz, $CDCl_3$) δ -141.43 (s); IR (film) ν 2959, 2873, 1466, 1191, 1122, 972, 950, 909, 754, 707 cm^{-1}.

Synthesis of Tetra-*n*-butylammonium Organotrifluoroborates (10) from Boronic Acids (4)

Method A: To a solution of $PhB(OH)_2$ (0.520 g, 4.27 mmol) in MeOH (ca. 1 mL) was added a 5.0M aqueous solution of HF (2.65 mL, 13.3 mmol) via a polypropylene syringe with vigorous stirring over a 1 minute period at room temperature. The reaction mixture was then cooled to 0 °C and a 1.54M aqueous solution of $^nBu_4N^+OH^-$ (2.76 mL, 4.27 mmol) was slowly added over a 5 minute period. The reaction was again warmed to room temperature and stirred for another hour. The biphasic reaction mixture was then diluted with CH_2Cl_2 (10 mL), the layers separated, and the aqueous phase further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the pale yellow, crystalline solid **10a** in 95 % yield (1.57 g, 4.06 mmol).

Method B: To a suspension of 4-$MeO(C_6H_4)BF_3^-K^+$ (0.910 g, 4.27 mmol) in CH_2Cl_2 (ca. 5 mL) in a separatory funnel was added a 1.54M aqueous solution of $^nBu_4N^+OH^-$ (2.76 mL, 4.27 mmol). The mixture was shaken and the layers were immediately separated. The aqueous phase was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the white, crystalline solid **10h** in 92 % yield (1.62 g, 3.93 mmol).

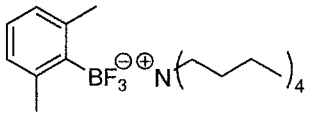
Tetra-*n*-butylammonium 2-Methylphenyltrifluoroborate (10b)



10b

Prepared via method A; isolated as a pale yellow, crystalline solid in 97 % yield: mp = 76 - 77 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, d, J = 6.5 Hz), 7.00 - 6.89 (3H, m), 2.95 - 2.84 (8H, m), 2.42 (3H, s), 1.44 - 1.22 (16H, m), 0.91 (12H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 132.3, 128.8, 125.9, 123.8, 58.1, 23.8, 22.1, 19.6, 13.7 (one signal absent); ^{11}B NMR (96 MHz, $CDCl_3$) δ 3.17 (br s); ^{19}F NMR (282 MHz, $CDCl_3$) δ -139.81 (br s); IR (film) ν 2963, 2875, 1595, 1488, 1381, 1266, 1176, 1053, 980, 967, 948, 936, 886, 748 cm^{-1}; LRMS (ESI): *m/z* (rel. intensity) = 160 (8), 159 (100), 158 (24), 139 (1).

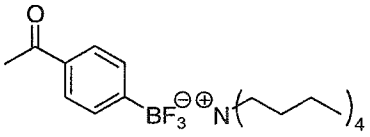
Tetra-*n*-butylammonium 2-Methylphenyltrifluoroborate (10c)



10c

Prepared via method A; isolated as a pale beige, crystalline solid in 90 % yield: mp = 72 - 74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 - 6.76 (3H, m), 2.95 - 2.86 (8H, m), 2.45 (6H, s), 1.48 - 1.24 (16H, m), 0.94 (12H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 127.0, 125.1, 58.1, 24.0, 23.9, 23.9, 19.8, 14.0 (one signal absent); ^{11}B NMR (96 MHz, $CDCl_3$) δ 3.75 (br s); ^{19}F NMR (282 MHz, $CDCl_3$) δ -130.26 (br s); IR (film) ν 2962, 2875, 2360, 1587, 1565, 1458, 1380, 1238, 1166, 1094, 1036, 962, 940, 769, 740 cm^{-1}; LRMS (ESI): *m/z* (rel. intensity) = 174 (9), 173 (100), 172 (24), 105 (2), 97 (6).

Tetra-*n*-butylammonium 4-Acetylphenyltrifluoroborate (10d)

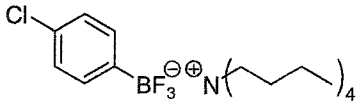


10d

Prepared via method A; isolated as a pale yellow solid in quantitative yield: mp = 59 - 61 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (2H, d, J = 8.0 Hz), 7.43 (2H, d, J = 8.0 Hz), 2.85

- 2.75 (8H, m), 2.32 (3H, s), 1.30 - 1.15 (8H, m), 1.06 (8H, sextet, J = 7.0 Hz), 0.69 (12H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 134.1, 131.2, 126.0, 57.5, 22.9, 18.7, 12.8 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 2.28 (br s); ^{19}F NMR (282 MHz, $CDCl_3$) δ -142.70 (s); IR (film) ν 2965, 2877, 1674, 1485, 1382, 1272, 1192, 1118, 948, 828, 735 cm^{-1}; LRMS (FAB): *m/z* = 187 (100), 186 (26), 144 (5).

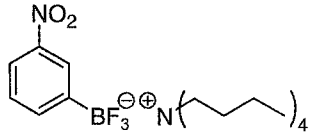
Tetra-*n*-butylammonium 4-Chlorophenyltrifuoroborate (10e)



10e

Prepared via method A; isolated as an orange-yellow solid in 97 % yield: mp = 44 - 45 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, d, J = 8.0 Hz), 7.13 (2H, d, J = 8.0 Hz), 3.00 - 2.89 (8H, m), 1.49 - 1.23 (16H, m), 0.93 (12H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 132.0, 126.8, 58.3, 23.8, 19.6, 13.7 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 2.28 (br s); ^{19}F NMR (282 MHz, $CDCl_3$) δ -142.19 (br s); IR (film) ν 2963, 2876, 1583, 1485, 1382, 1185, 1118, 970, 950, 819, 732 cm^{-1}; LRMS (ES): *m/z* = 181 (34), 180 (15), 179 (100), 178 (28), 113 (4), 111 (10).

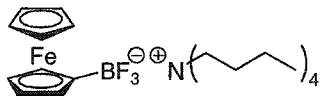
Tetra-*n*-butylammonium 3-Nitrophenyltrifluoroborate (10f)



10f

Prepared via method A; isolated as a yellow solid in 97 % yield: mp = 35 - 36 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (1H, d, J = 2.0 Hz), 7.93 (2H, m), 7.35 (1H, t, J = 8.0 Hz), 3.13 - 3.05 (8H, m), 1.58 - 1.46 (8H, m), 1.32 (8H, sextet, J = 7.5 Hz), 0.92 (12H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 138.6, 127.7, 126.2, 120.7, 58.5, 23.7, 19.6, 13.5 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 2.45 (br s); ^{19}F NMR (282 MHz, $CDCl_3$) δ -142.91 (br s); IR (film) ν 2965, 2877, 1519, 1473, 1345, 1274, 1193, 994, 902, 809, 735 cm^{-1}; LRMS (ES): *m/z* = 191 (8), 190 (100), 189 (25), 122 (16), 92 (4).

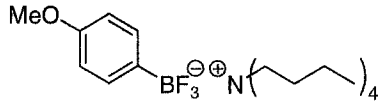
Tetra-*n*-butylammonium Ferrocenyltrifluoroborate (10g)



10g

Prepared via method A; isolated as a green crystalline solid in 80 % yield: mp = 104 - 105 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (2H, br s), 4.17 (7H, br s), 3.12 - 2.95 (8H, m), 1.57 - 1.45 (8H, m), 1.45 - 1.30 (8H, m), 0.97 (12H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.8, 58.6, 24.1, 19.8, 13.8 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 3.93 (br s); ^{19}F NMR (375 MHz, $CDCl_3$) δ -139.33 (br s); IR (film) ν 3084, 2961, 2875, 1633, 1472, 1381, 1310, 1271, 1204, 1103, 1053, 976, 856, 812, 735, 701, 632 cm^{-1}; LRMS (FAB): *m/z* = 253 (100), 252 (24), 251 (6), 113 (17).

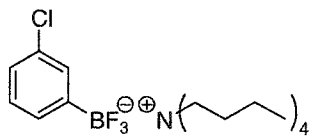
Tetra-*n*-butylammonium 4-Methoxyphenyltrifluoroborate (10h)



10h

Prepared via method B; isolated as a white crystalline solid in 92 % yield: mp = 94 - 95 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, d, J = 8.0 Hz), 6.74 (2H, d, J = 8.0), 3.75 (3H, s), 3.05 - 2.95 (8H, m), 1.50 - 1.40 (8H, m), 1.32 (8H, sextet, J = 7.5 Hz), 0.94 (12H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 133.0, 112.5, 58.4, 55.1, 23.9, 19.7, 13.8 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 3.29 (br s); ^{19}F NMR (375 MHz, $CDCl_3$) δ -141.38 (s); IR (film) ν 2960, 2874, 1644, 1601, 1490, 1278, 1178, 1123, 1036, 999, 970, 951, 935, 826, 816 cm^{-1}; LRMS (FAB): *m/z* = 175 (100), 174 (22), 160 (13).

Tetra-*n*-butylammonium 3-Chlorophenyltrifluoroborate (30g)

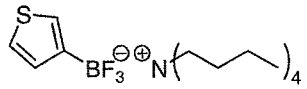


10i

Prepared via method B; isolated as a pale yellow crystalline solid in 97 % yield: mp = 53 - 54 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (1H, s), 7.42 (1H, d, J = 7.0 Hz), 7.14 - 7.02 (2H,

m), 3.00 - 2.90 (8H, m), 1.50 - 1.24 (16H, m), 0.94 (12H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9, 131.8, 129.9, 128.4, 125.6, 58.4, 23.9, 19.8, 13.8 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 2.67 (br s); ^{19}F NMR (375 MHz, $CDCl_3$) δ -141.38 (s); IR (film) ν 2962, 2875, 2360, 1560, 1488, 1465, 1382, 1260, 1189, 1106, 968, 889, 780, 755, 702, 668, 616, 602 cm^{-1}; LRMS (FAB): *m/z* = 181 (32), 180 (16), 179 (100), 178 (25), 145 (12), 144 (6), 97 (11).

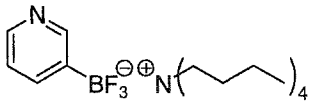
Tetra-*n*-butylammonium 3-Thiophenyltrifluoroborate (10j)



10j

Prepared via method B; isolated as a beige crystalline solid in 95 % yield: mp = 59 - 60 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 - 7.19 (2H, m), 7.14 - 7.09 (1H, m), 3.04 - 2.94 (8H, m), 1.53 - 1.28 (16H, m), 0.96 (12H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.2, 125.5, 122.9, 58.4, 24.0, 19.8, 13.9 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 2.72 (br s); ^{19}F NMR (375 MHz, $CDCl_3$) δ -137.49 (s); IR (film) ν 2963, 2874, 1489, 1467, 1383, 1204, 1143, 1107, 1043, 1004, 988, 870, 839, 776, 643, 600 cm^{-1}; LRMS (FAB): *m/z* = 153 (5), 152 (8), 151 (100), 150 (24).

Tetra-*n*-butylammonium 3-Pyridyltrifluoroborate (10k)

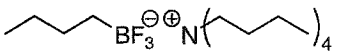


10k

Lithium 3-pyridyltriisopropylborate[46] (1.00 g, 3.65 mmol) was dissolved in a minimal amount of water (ca. 1 mL) to which a 5.0M solution of hydrofluoric acid (2.20 mL, 10.94 mmol) was added drop wise over 1 minute and the reaction mixture was stirred for a further 15 minutes. A 1.54M solution of tetra-*n*-butylammonium hydroxide (2.40 mL, 3.65 mmol) was added and the reaction was stirred for another 1 hour, and then cooled to 0 °C to encourage "oiling out" of the product from the aqueous layer. The reaction mixture was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an orange-yellow oil which solidifies upon refrigeration.

Isolated as an orange-yellow oil in 90 % yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (1H, s), 8.17 (1H, dd, J = 5.0, 2.0 Hz), 7.68 (1H, d, J = 7.5 Hz), 6.95 (1H, dd, J = 6.5, 5.0), 2.91 - 2.84 (8H, m), 1.39 - 1.22 (8H, m), 1.13 (8H, sextet, J = 7.0 Hz), 0.74 (12H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 146.0, 139.8, 122.5, 58.0, 23.4, 18.9, 13.2 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 2.79 (br s); ^{19}F NMR (282 MHz, $CDCl_3$) δ -142.30 (br s); IR (film) ν 2962, 1621, 1581, 1566, 1463, 1382, 1323, 1209, 1132, 996, 951, 808, 726 cm^{-1}; LRMS (ES): m/z = 147 (7), 146 (100), 145 (28), 97 (10).

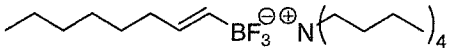
Tetra-*n*-butylammonium *n*-Butyltrifluoroborate (10l)



10l

Prepared via method A; isolated as a pale yellow oil in 82 % yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (2H, t, J = 6.5 Hz), 3.26 - 3.14 (8H, m), 1.68 - 1.53 (8H, m), 1.41 (8H, sextet, J = 7.5 Hz), 1.31 - 1.25 (4H, m), 0.98 (12H, t, J = 7.0 Hz), 0.84 (3H, t, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.6, 24.0, 19.8, 19.0, 14.2, 13.8, 13.7 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 2.51 (br s); ^{19}F NMR (375 MHz, $CDCl_3$) δ -140.45 (s); IR (film) ν 3520, 2961, 2885, 1638, 1477, 1382, 1278, 1117, 1072, 977, 886, 750, 617, 598 cm^{-1}.

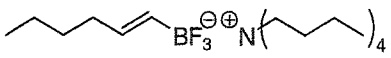
Tetra-*n*-butylammonium 1-Octenyltrifuoroborate (10m)



10m

Prepared via method A; isolated as a clear oil in 95 % yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (1H, dt, J = 17.0, 5.5 Hz), 5.22 (1H, d, J = 17.5 Hz), 3.04 - 2.96 (8H, m), 1.75 (2H, q, J = 5.5 Hz), 1.46 - 1.30 (8H, m), 1.28 - 1.12 (16H, m), 0.76 (12H, t, J = 7.0 Hz), 0.65 (3H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4, 135.3, 57.8, 35.6, 31.5, 29.3, 28.9, 23.4, 22.3, 19.2, 13.7, 13.2; ^{11}B NMR (160 MHz, $CDCl_3$) δ 2.82 (br s); ^{19}F NMR (375 MHz, $CDCl_3$) δ -138.90 (s); IR (film) ν 3510, 2960, 2875, 1637, 1467, 1381, 1277, 1107, 1071, 967, 885, 740, 616, 588 cm^{-1}; LRMS (FAB): m/z = 180 (9), 179 (100), 178 (26), 177 (5).

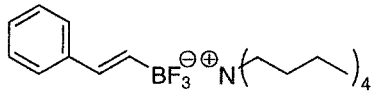
Tetra-*n*-butylammonium 1-Hexenyltrifuoroborate (10n)



10n

Prepared via method b; isolated as a clear oil in 90 % yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (1H, dt, *J* = 17.5, 5.0 Hz), 5.42 (1H, dq, *J* = 17.5, 5.0, 2.0 Hz), 3.22 - 3.11 (8H, m), 1.98 - 1.88 (2H, m), 1.63 - 1.49 (8H, m), 1.36 (8H, sextet, *J* = 7.0 Hz), 1.30 - 1.21 (4H, m), 0.93 (12H, t, *J* = 7.0 Hz), 0.82 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 99.8, 58.2, 35.5, 31.8, 23.6, 22.4, 19.4, 13.9, 13.4; ^{11}B NMR (96 MHz, $CDCl_3$) δ 2.42; ^{19}F NMR (375 MHz, $CDCl_3$) δ -140.23 (s); IR (film) ν 2961, 2927, 2875, 1637, 1486, 1467, 1381, 1277, 1242, 1107, 1071, 993, 968, 884, 740, 616 cm^{-1}; LRMS (FAB): *m/z* (rel. intensity) = 152 (7), 151 (100), 150 (26).

Tetra-*n*-butylammonium (*E*)-2-phenyl-1-ethenyltrifluoroborate (10o)



10o

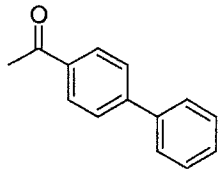
Prepared via method B; isolated as an amber oil in 90 % yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (2H, d, *J* = 8.0 Hz), 7.18 (2H, t, *J* = 8.0 Hz), 7.05 (1H, t, *J* = 8.0 Hz), 6.69 (1H, d, *J* = 18.0 Hz), 6.35 (1H, dq, *J* = 18.0, 3.5 Hz), 3.10 - 2.98 (8H, m), 1.50 - 1.37 (8H, m), 1.29 (8H, sextet, *J* = 7.0 Hz), 0.89 (12H, t, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 134.5, 134.4, 128.1, 125.9, 125.6, 58.2, 23.8, 19.6, 13.7 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 2.75 (br s); ^{19}F NMR (375 MHz, $CDCl_3$) δ -139.99 (s); IR (film) ν 3528, 2962, 2875, 1618, 1597, 1574, 1489, 1381, 1288, 1236, 1195, 1107, 1064, 994, 882, 828, 741, 695, 616, 528 cm^{-1}; LRMS (FAB): *m/z* = 172 (12), 171 (100), 170 (26), 151 (5).

I.3.3 Synthetic Methods and Characterization Data of Cross-Coupled Products

Representative Procedure for the Cross-Coupling of Tetra-*n*-butylammonium Organotrifluoroborates with Various Aryl- and Alkenyl Halides and Haloacrylates

To a stirred suspension of $PhBF_3^-{}^nBu_4N^+$ 0.390 g, 1.00 mmol), 4-Br(C_6H_4)$COCH_3$ (0.130 g, 0.660 mmol), dppb (14.2 mg, 0.030 mmol) and Cs_2CO_3 (0.430 g, 1.33 mmol) in DME (3.00 mL) was added water (3.00 mL) and $Pd(OAc)_2$ (7.50 mg, 0.030 mmol). The reaction mixture was stirred at room temperature for 12 hours, then transferred to a separatory funnel, diluted with water (30 mL), and extracted with CH_2Cl_2 (3 x 10 mL) . The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product mixture. The product (**19a**) was isolated by silica gel flash column chromatography (eluting with hexanes:EtOAc 9:1 ~ 3:1 gradient) as a white crystalline solid in 92 % yield (0.119 g, 0.607 mmol).

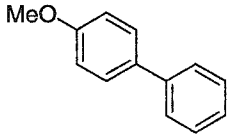
4-Acetylbiphenyl (19a) (Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830-1833.)



19a

Isolated as a white crystalline solid in 92 % yield from **18a**, and in 95 % yield from **18g**: R_f = 0.25 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 8.0 Hz), 7.69 (2H, d, *J* = 8.0 Hz), 7.63 (2H, d, *J* = 7.0 Hz), 7.52 - 7.37 (3H, m), 2.65 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 145.8, 139.9, 135.9, 129.0, 129.0, 128.3, 127.3, 127.3, 26.9.

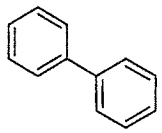
4-Methoxybiphenyl (19b) (Spivey, A. C.; Diaper, C. M.; Adams, H.; Rudge, A. J. *J. Org. Chem.* **2000**, *65*, 5253-5263.)



19b

Isolated as a white crystalline solid in 82 % yield from **18b**, and in 79 % yield from **18h**: R_f = 0.25 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 - 7.48 (4H, m), 7.38 (2H, t, *J* = 7.0 Hz), 7.27 (1H, tt, J = 7.0, 1.0 Hz), 6.95 (2H, ddd, *J* = 9.0, 5.0, 3.0 Hz), 3.82 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 140.9, 133.9, 128.8, 128.2, 126.8, 126.7, 114.3, 55.6.

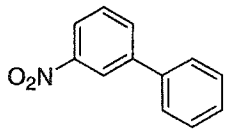
Biphenyl (19c) (Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830-1833.)



19c

Isolated as a clear crystalline solid in quantitative yield: $R_f = 0.8$ (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (4H, d, $J = 8.0$ Hz), 7.54 (4H, t, $J = 8.0$ Hz), 7.44 (2H, t, $J = 8.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 129.1, 127.6, 127.5.

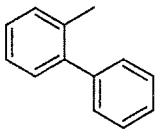
3-Nitrobiphenyl (19d) (Wang, L.; Chen, Z. C. *Synth. Commun.* **2000**, *30*, 3607-3612.)



19d

Isolated as a beige crystalline solid in 76 % yield: $R_f = 0.3$ (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (1H, t, $J = 1.0$ Hz), 8.19 (1H, ddd, $J = 8.0, 2.0, 1.0$ Hz), 7.91 (1H, dt, $J = 8.0, 1.0$ Hz), 7.62 (3H, m), 7.54 - 7.40 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 142.9, 138.7, 133.1, 129.7, 129.2, 128.6, 127.2, 122.1, 122.0.

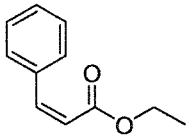
2-Methylbiphenyl (19e) (Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *J. Org. Chem.* **1999**, *64*, 6797-6803.)



19e

Isolated as a yellow oil in 97 % yield: $R_f = 0.75$ (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 - 7.25 (9H, m), 2.32 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 142.0, 135.4, 130.4, 129.9, 129.3, 128.1, 127.3, 126.8, 125.8, 20.7.

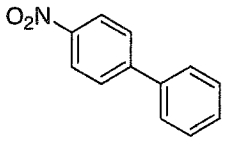
3-(*E*)-Phenylacrylic acid ethyl ester (19f) (Ando, K. *J. Org. Chem.* **1997**, *62*, 1934-1939.)



19f

Isolated as a pale yellow oil in 55 % yield: R_f = 0.6 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 - 7.56 (2H, m), 7.40 - 7.30 (3H, m), 6.94 (1H, d, *J* = 12.0 Hz), 5.96 (1H, d, *J* = 12.0 Hz), 4.16 (2H, q, *J* = 7.0 Hz), 1.22 (3H, t, *J* = 7.0 Hz).

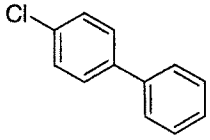
4-Nitrobiphenyl (19g) (Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830-1833.)



19g

Isolated as a pale yellow crystalline solid in 79 % yield: R_f = 0.2 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (2H, ddd, *J* = 9.0, 4.5, 2.5 Hz), 7.73 (2H, ddd, *J* = 9.0, 4.5, 2.5 Hz), 7.65 - 7.61 (2H, m), 7.54 - 7.42 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 147.1, 138.8, 129.2, 129.0, 127.8, 127.4, 124.2.

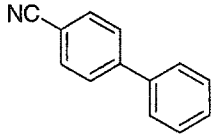
4-Chlorobiphenyl (19h) (Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684-1688.)



19h

Isolated as white crystalline solid in 96 % yield: R_f = 0.6 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 - 7.34 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 139.8, 133.6, 129.1, 129.1, 128.6, 127.8, 127.2.

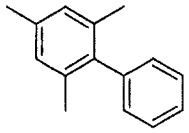
4-Cyanobiphenyl (19i) (Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561.)



19i

Isolated as a white crystalline solid in 93 % yield: R_f = 0.5 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (4H, ddd, *J* = 8.5, 6.5, 5.5 Hz), 7.59 (2H, m), 7.53 - 7.40 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 139.2, 132.6, 129.2, 128.7, 127.8, 127.3, 119.0, 111.0.

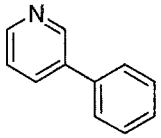
2,4,6- Trimethylbiphenyl (19j) (Anderson, J. C.; Namli, H; Roberts, C. A. *Tetrahedron* **1997**, *53*, 15123-15134.)



19j

Isolated as a clear oil in 85 % yield: $R_f = 0.7$ (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 - 7.33 (3H, m), 7.15 (2H, dd, J = 8.0, 1.5 Hz), 6.89 (2H, s), 2.43 (3H, s), 2.10 (6H, s).

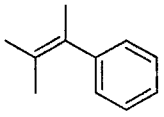
3-Phenylpyridine (19k) (Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron* **1993**, *49*, 9713-9720.



19k

Isolated as a yellow oil in 93 % yield: R_f = 0.4 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (1H, d, J = 2.0 Hz), 8.60 (1H, dd, J = 5.0, 2.0 Hz), 7.86 (1H, dt, J = 8.0, 2.0 Hz), 7.57 (2H, d, J = 7.0 Hz), 7.50 - 7.32 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 148.1, 137.7, 136.7, 134.4, 129.1, 128.1, 127.1, 123.6.

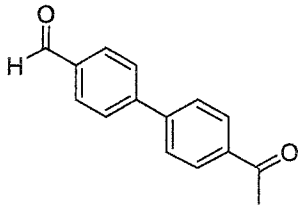
2-Methyl-3-phenylbut-2-ene (19l) (Hiegel, G. A.; Carney, J. R. *Synth. Commun.* **1996**, *26*, 2625-2632.)



19l

Isolated as a pale yellow solid in 91 % yield: $R_f = 0.8$ (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 - 7.10 (5H, m), 1.96 (3H, s), 1.82 (3H, s), 1.61 (3H, s).

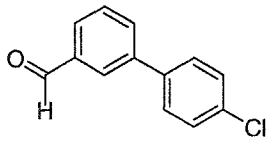
4'-Acetylbiphenyl-4-carbaldehyde (19m)



19m

Isolated as a pale yellow powder in 75 % yield: R_f = 0.7 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (1H, s), 8.07 (2H, d, *J* = 8.5 Hz), 7.99 (2H, m), 7.79 (2H, m), 7.73 (2H, d, *J* = 8.5 Hz), 2.66 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 191.4, 145.5, 143.9, 136.6, 135.6, 130.1, 128.8, 127.7, 127.4, 26.6; IR (film) ν 3019, 2360, 1700, 1676, 1602, 1357, 1266, 1210, 1169, 1004, 815, 765 cm^{-1}; LRMS (EI): *m/z* = 225 (13), 224 (50), 223 (11), 211 (10), 210 (51), 209 (100), 182 (6), 181 (16), 154 (7), 153 (36), 152 (56), 151 (24), 150 (11), 127 (8), 126 (8), 104 (6); HRMS (EI): *m/z* calcd. for ($C_{15}H_{12}O_2^+$) = 224.0837, found = 224.0837.

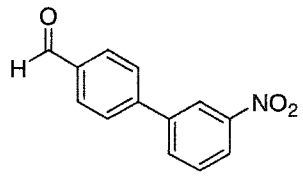
4'-Chlorobiphenyl-3-carbaldehyde (19n)



19n

Isolated as a clear crystalline solid in 60 % yield: R_f = 0.5 (9:1 hexanes:EtOAc), mp = 186 - 188 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (1H, s), 8.06 (1H, t, *J* = 2.0 Hz), 7.87 (1H, dt, *J* = 7.5, 1.0 Hz), 7.83 (1H, ddd, *J* = 7.5, 2.0, 1.0 Hz), 7.61 (1H, t, *J* = 7.5 Hz), 7.59 - 7.52 (2H, m), 7.44 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 141.1, 138.3, 137.2, 134.4, 133.0, 129.8, 129.4, 129.3, 128.6, 128.0; IR (film) Λ 3019, 2400, 1696, 1603, 1480, 1440, 1306, 1215, 1093, 1013, 926, 771, 685, 669, 651 cm^{-1}; LRMS (EI): *m/z* = 219 (5), 218 (39), 217 (41), 216 (100), 215 (73), 204 (9), 189 (9), 188 (10), 187 (25), 153 (20), 152 (99), 151 (24), 150 (13), 126 (7), 107 (8); HRMS (EI): *m/z* calcd. for ($C_{13}H_9ClO^+$) = 216.0342, found = 216.0342.

3'-Nitrobiphenyl-4-carbaldehyde (19o)

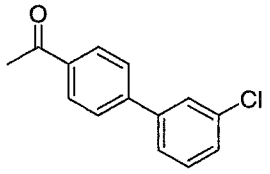


19o

Isolated as pale beige flakes in 78 % yield: R_f = 0.7 (9:1 hexanes:EtOAc), mp = 96 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (1H, s), 8.49 (1H, t, *J* = 2.0 Hz), 8.27 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz), 8.03 (2H, d, *J* = 8.0 Hz), 7.98 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz), 7.81 (2H, d, *J* = 8.0 Hz), 7.69 (1H, t, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 148.9, 144.8, 141.5, 136.1, 133.4,

130.7, 130.2, 128.0, 123.3, 122.3; IR (film) ν 3447, 3019, 1700, 1604, 1534, 1352, 1216, 771, 669 cm^{-1}; LRMS (EI): *m/z* = 228 (18), 227 (100), 226 (88), 210 (11), 209 (11), 181 (7), 180 (12), 153 (22), 152 (60), 151 (23), 150 (8), 139 (37), 126 (6), 93 (16); HRMS (EI): *m/z* calcd. for ($C_{13}H_9NO_3^+$) = 227.0582, found = 227.0579.

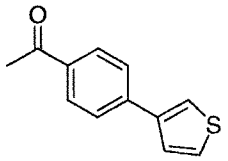
4-Acetyl-3'-chlorobiphenyl (19p) (Hantanaka, Y.; Goda, K.; Okahara, Y.; Hiyama, T. *Tetrahedron* **1994**, *50*, 8301-8316.)



19p

Isolated as an orange oil in 92 % yield: R_f = 0.5 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 8.5 Hz), 7.64 (2H, d, *J* = 8.5 Hz), 7.59 (1H, s), 7.49 (1H, dt, *J* = 7.0, 2.0 Hz), 7.42 - 7.34 (2H, m), 2.64 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 144.4, 141.8, 136.4, 135.0, 130.4, 129.2, 128.4, 127.5, 127.4, 125.6, 26.8.

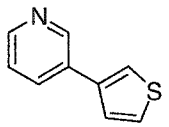
1-(4-thiophen-3-ylphenyl)-1-ethanone (19q) (Rieke, R. D.; Kim, S. H.; Wu, X. *J. Org. Chem.* **1997**, *62*, 6921-6927.)



19q

Isolated as a white powder in 91 % yield: R_f = 0.6 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (2H, ddd, *J* = 8.5, 4.0, 2.0 Hz), 7.68 (2H, ddd, *J* = 8.5, 4.0, 2.0 Hz), 7.57 (1H, dd, *J* = 2.5, 2.0 Hz), 7.45 - 7.40 (2H, m), 2.62 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 141.2, 140.3, 135.8, 129.2, 126.9, 126.5, 126.3, 122.2, 26.7.

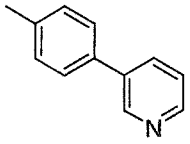
3-thiophen-3-ylpyridine (19r) (Novak, I.; Ng, S. C.; Mok, C. Y.; Huang, H. H.; Fang, J.; Wang, K. K. T. *J. Chem. Soc. Perkin Trans. 2* **1994**, *8*, 1771-1776.)



19r

Isolated as a beige powder in 88 % yield: R_f = 0.7 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (1H, d, *J* = 2.0 Hz), 8.52 (1H, dd, *J* = 5.0, 2.5 Hz), 7.84 (1H, ddd, *J* = 8.0, 2.5, 2.0 Hz), 7.50 (1H, dd, *J* = 3.0, 1.5 Hz), 7.42 (1H, dd, *J* = 5.0, 3.0 Hz), 7.38 (1H, dd, *J* = 5.0, 1.5 Hz), 7.30 (1H, ddd, *J* = 8.0, 5.0, 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 147.8, 138.9, 133.5, 131.6, 127.1, 126.0, 123.7, 121.5.

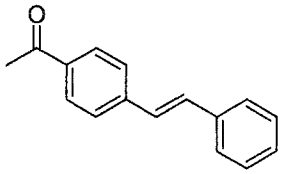
3-(4-methylphenyl)pyridine (19s) (Inada, K.; Miyaura, N. *Tetrahedron* **2000**, *56*, 8661-8664.)



19s

Isolated as a yellow-orange solid in 69 % yield: R_f = 0.7 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.83 (1H, d, *J* = 1.5 Hz), 8.56 (1H, dd, *J* = 5.0, 1.5 Hz), 7.84 (1H, ddd, *J* = 8.0, 2.5, 1.5 Hz), 7.48 (2H, d, *J* = 8.0 Hz), 7.34 (1H, ddd, *J* = 8.0, 5.0, 1.5 Hz), 7.28 (2H, d, *J* = 8.0 Hz), 2.41 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.4, 148.3, 138.2, 136.7, 135.1, 134.2, 129.6, 127.1, 123.7, 21.3.

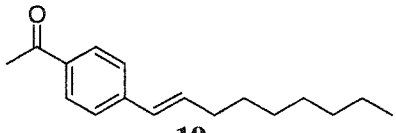
1-*trans*-stilben-4-ylethanone (19t) (Bezou, P.; Hilberer, A.; Hadziioannou, G. *Synthesis* **1996**, *4*, 449-451.)



19t

Isolated as a white powder in 55 % yield: R_f = 0.7 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (2H, d, *J* = 8.5 Hz), 7.58 - 7.49 (4H, m), 7.36 (2H, t, *J* = 7.0 Hz), 7.28 (1H, t, *J* = 7.0 Hz), 7.20 (1H, d, *J* = 16.5 Hz), 7.10 (1H, d, *J* = 16.5 Hz), 2.58 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6, 142.1, 136.8, 136.1, 131.6, 129.0, 128.9, 128.4, 127.6, 127.0, 126.6, 26.9.

1-(4-acetylphenyl)-1-octene (19u) (Hantanaka, Y.; Fukushima, S.; Hiyama, T. *Tetrahedron* **1992**, *48*, 2113-2126.)



19u

Isolated as a light yellow oil in 87 % yield: R_f = 0.8 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.5 Hz), 7.79 (2H, d, *J* = 8.5 Hz), 6.44 - 6.30 (2H, m), 2.55 (3H, s), 2.26 - 2.18 (2H, m), 1.52 - 1.24 (8H, m), 0.89 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 142.8, 135.5, 134.6, 129.0, 128.8, 126.0, 33.3, 31.8, 29.2, 29.0, 26.6, 22.7, 14.2; IR (film) Λ 2926, 2855, 1682, 1648, 1602, 1563, 1466, 1410, 1357, 1268, 1181, 1111, 1074, 1013, 966, 855, 809, 724, 705, 592 cm^{-1}; LRMS (EI): *m/z* = 231 (21), 230 (89), 216 (16), 215 (77), 148 (14), 147 (22), 146 (67), 145 (16), 134 (19), 133 (11), 132 (13), 131 (100), 129 (10), 128 (11), 117 (24), 116 (14), 115 (37), 91 (14); HRMS (EI): *m/z* calcd. for ($C_{16}H_{22}O^+$) = 230.1671, found = 230.1675.

I.4 References

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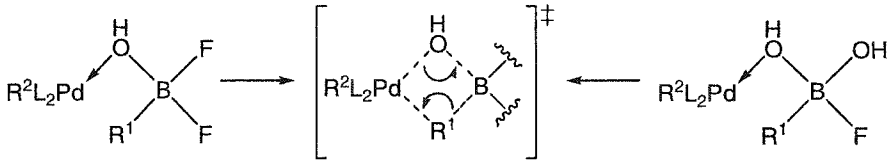

28 **27** **29**

Scheme 26 - Hydroxo-μ_2-Bridged Transition State Arising from Fluoroxyboronates

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Chapter II

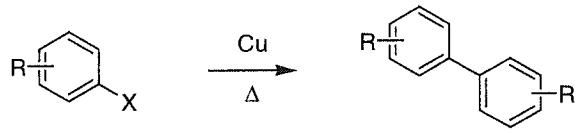
Organoboron Compounds in Copper-Mediated Carbon-Oxygen Bond Forming Reactions

II.1 Introduction

II.1.1 General Introduction to the Ullmann Reaction

It is fitting that the work of Fritz Ullmann at the dawn of the twentieth century has reached a second Renaissance now as we cross the threshold of the twenty-first century. Ullmann's pioneering discovery of a copper-mediated coupling of aryl halides for the preparation of symmetrical and unsymmetrical biaryl systems had initially enjoyed widespread usage in large scale syntheses and industrial applications.[1] The scope and limitations of this methodology has been the subject of multiple reviews over the past two decades.[2,3]

Fritz Ullmann
(1875–1939)

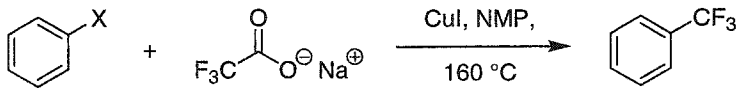


X = F, Cl, Br, I

18 **19**

Figure 6 - The Ullmann Reaction

In general, the order of reactivity for ease of halogen displacement from the aromatic ring is I > Br > Cl >> F, which is opposite of the trend observed in uncatalyzed nucleophilic aromatic substitutions (S_NAr).[3] Substituents present on the aromatic ring can have a great effect on the reactivity of the aryl halide. Nitro moieties and carbonyl groups that can potentially chelate to copper have a strong activating effect, but only when *ortho* to the halogen atom. Hydrogen, alkyl and alkoxyl moieties are activating substituents in any position. Electron-donating substituents, like hydroxyls, amines and amides inhibit the reaction as expected for nucleophilic aromatic substitutions. Carboxylic acids, but not esters, also inhibit the reaction as various side reactions occur in their presence. Reductive dehalogenation of the starting material is often the main product isolated from these reaction mixtures. In addition, copper mediated decarboxylation of the carboxylates can generate organocuprate intermediates, which can then undergo cross-coupling with the aryl halide (Scheme 30).[3]



47-88 %

Scheme 30 - Copper-Mediated Decarboxylation and Cross-Coupling of Sodium Trifluoroacetate

Both the disfavour and the recent resurgence in the popularity of copper-mediated processes can be attributed to the evolution of green chemistry. The main objective of which is to reduce or eliminate the use or generation of hazardous substances in the design, manufacture and application of chemical products. The requirement of stoichiometric amounts of metallic copper along with the need to run the reactions at elevated temperatures, often in excess of 200 °C, led to the search for other transition-metal catalyzed transformations. Despite the discovery that other forms of copper salts could also be employed in the reaction, in some instances even catalytically, the use of copper in synthesis waned in the 1970s in favour of other more reactive transition-metal complexes. Indeed, transition-metal complexes of palladium and nickel have been shown to promote the homocoupling of aryl halides under much milder conditions than copper. However, other factors limit their utilization on a large scale basis. For example, Pd and Ni catalysts often require the addition of phosphine ligands which are themselves nucleophilic in nature and can lead to undesired side products in the reaction. Recent developments in high yielding, and reliable copper-mediated/catalyzed processes at mild reaction temperatures have once again placed copper at the forefront of methodological research as a benign alternative to the more costly and often toxic heavy metals.[4]

There have been numerous alternative transition metal-catalyzed strategies for unsymmetrical biaryl synthesis involving the cross-coupling of aromatic electrophiles (e.g. halides, triflates, diazonium salts etc.) and arylmetalloid nucleophiles. The work in this field is far too vast to cover for the purposes of this introduction, but has been the topic of a recent comprehensive review by Lemaire *et al.*[2a] The individual cross-coupling strategies themselves have been the subject of dozens of texts and reviews over the past decade alone (Figure 7).[5-9] Current research into the iron-catalyzed cross-couplings of Grignard reagents with aryl halides mainly by the groups of Kochi[10] and Fürstner[11] has provided a viable alternative to the access of biaryl systems (Scheme 31, reaction 1). Finally, nucleophilic aromatic substitution (Scheme 31, reaction 2), and radical couplings via radical initiators or photochemistry (Scheme 31, reaction 3) have also been utilized to access biaryl systems.[2a]

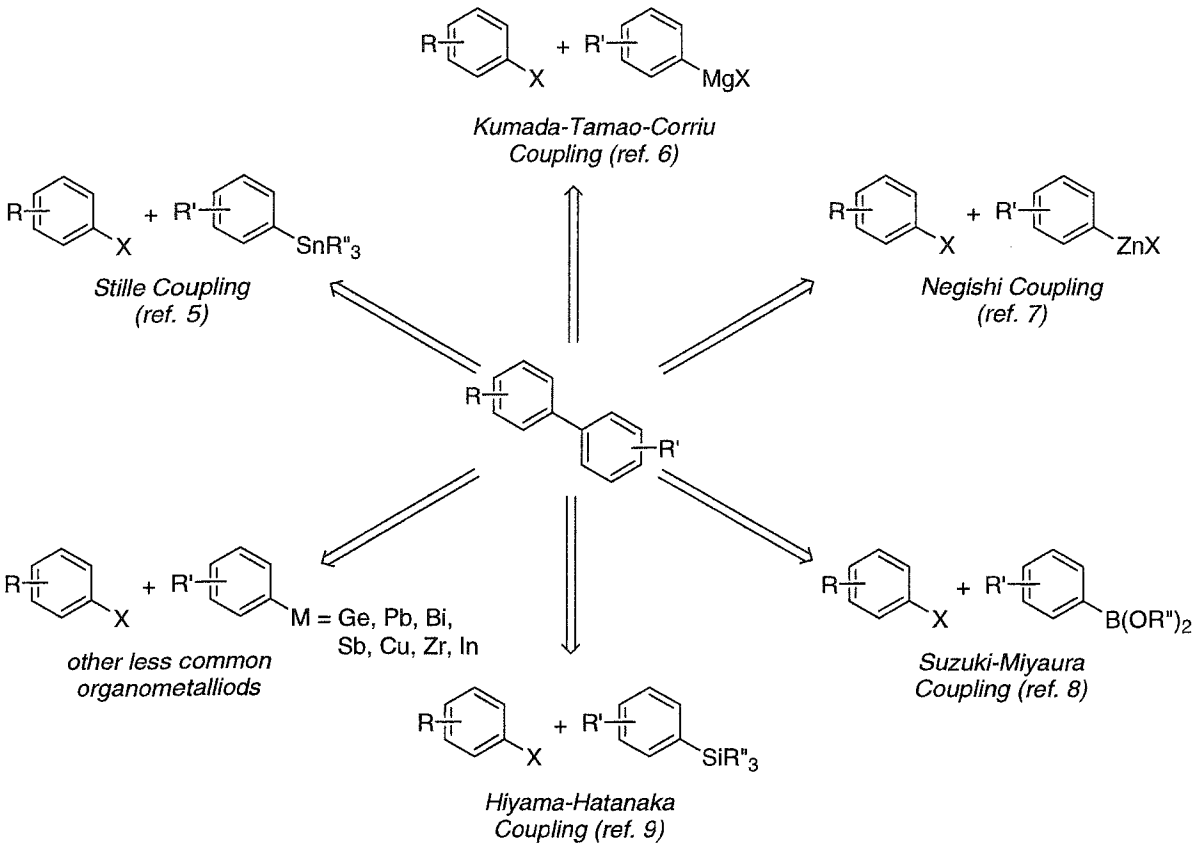
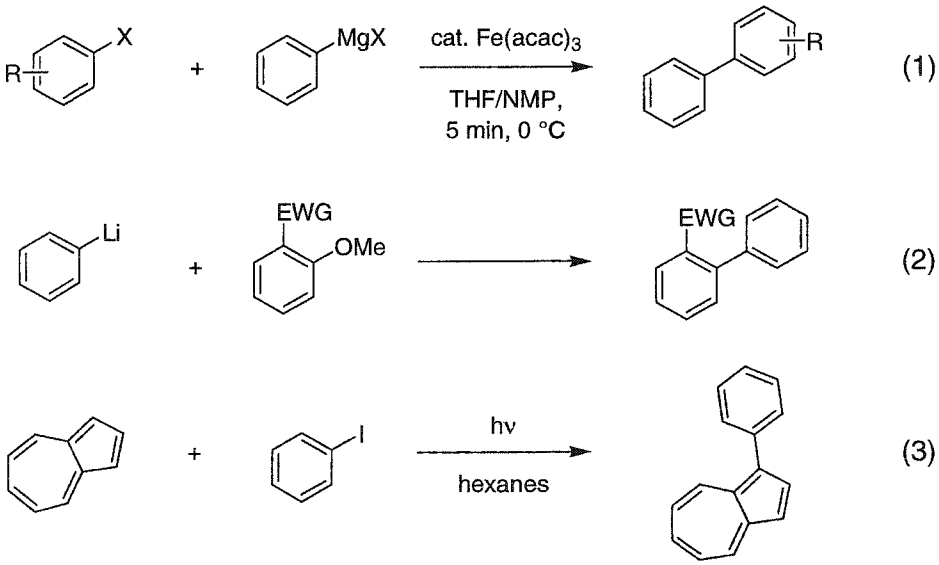


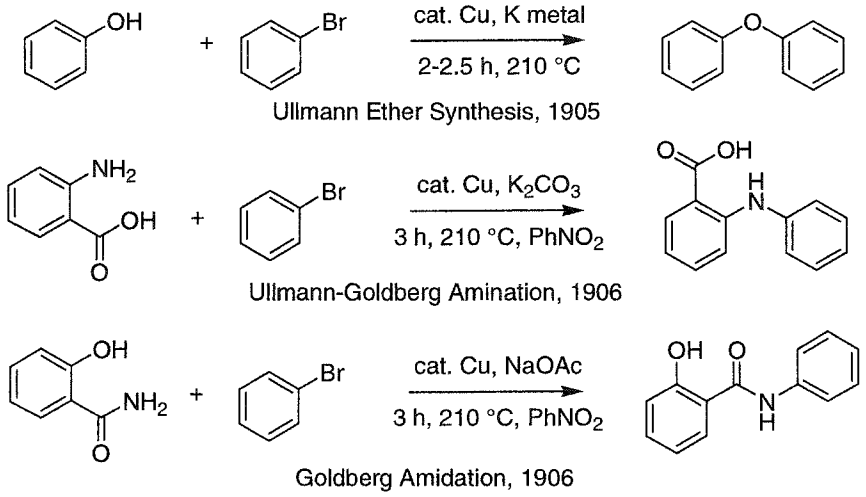
Figure 7 - Common Ni and/or Pd-catalyzed Cross-Coupling Strategies for Biaryl Synthesis



Scheme 31 - Alternative Methods of Aryl-Aryl Cross-Coupling

II.1.1.1 Ullmann and Goldberg Condensations

Ullmann's copper-mediated coupling reaction is not limited to carbon-carbon bond formation from aryl halides. Early work by Ullmann and Goldberg explored the copper-mediated/catalyzed cross-coupling of arylbromides with alcohols,[12] amines,[1c,13] and amides[13] (Scheme 32). This type of copper-mediated cross-coupling has since been known as the Ullmann Condensation.



Scheme 32 - Copper-Catalyzed Cross-Coupling of Arylbromides with Oxygen and Nitrogen Nucleophiles

The discovery that arylcopper intermediates are subject to facile nucleophilic attack helped to broaden the scope and utility of the reaction, and provided a relatively inexpensive methodology for the formation of carbon-heteroatom bonds on a large scale. Several nucleophiles (summarized in Figure 8) have been reported to undergo copper-mediated/catalyzed cross-couplings with aryl halides.[3] However, the success of this methodology has been hampered by two main side reactions: homocoupling and reductive dehalogenation of the aryl

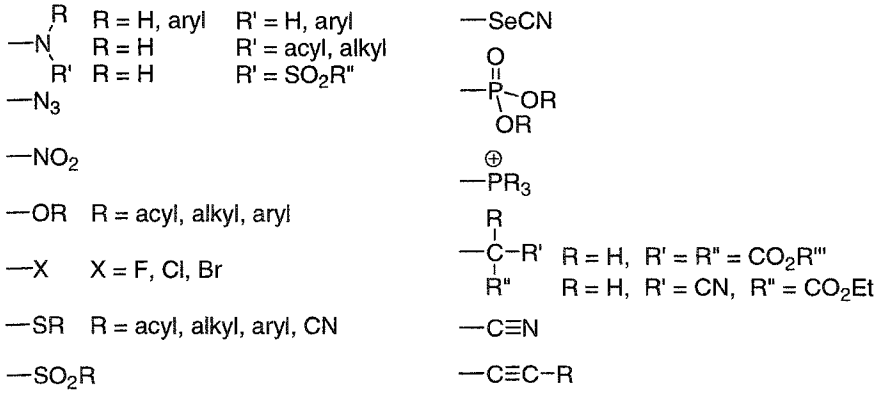


Figure 8 - Nucleophiles Reported to Undergo Ullmann Condensations with Aryl Halides

halide are competitive with the nucleophilic substitution.

Transition metal-catalyzed Ullmann-type condensations between electrophilic aryl halides and carbon-based or heteroatomic nucleophiles have been the main interest of several research groups over the past ten years (Figure 9). The most notable contributions in this field have come from the groups of Hartwig[14] and Buchwald[15] in palladium and nickel catalysis, and Buchwald in the area of copper catalysis.[16] Indeed, this area of synthesis has expanded so quickly that it has warranted no fewer than four major reviews in the past year and a half.[2a,17-19] Specific reactions in this field relevant to the work presented in this thesis will be referenced in the following sections; however, a general review of this topic is beyond the scope of this introduction.

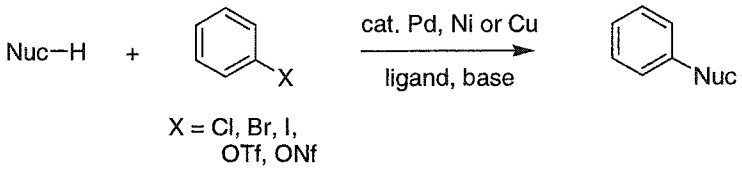


Figure 9 - Hartwig/Buchwald Coupling of Nucleophiles with Aryl Halides

II.1.1.2 Catalysts and Ligands

A wide spectrum of copper sources ranging from powdered copper metal to air-sensitive copper(I) salts to the air stable copper(II) salts have been screened in these cross-coupling reactions. Both oxidation states of the copper halides (CuCl, CuBr, CuI, $CuCl_2$, $CuBr_2$), $Cu(OPiv)_2$, $Cu(NO_3)_2$, $Cu(acac)_2$, $Cu(OCOCF_3)_2$, $Cu(OTf)_2$ and $CuSO_4$ have all been used to varying degrees of success. However, the best results have been obtained by employing $Cu(OAc)_2$ as copper source. Due to the facile disproportionation between the various oxidation states of copper, the success of the reactions does not appear to depend on the initial oxidation state of the copper source as does transformations catalyzed by palladium. Instead the success of the reactions is more closely related to the solubility of the copper reagent in the reaction medium. To this end, most transformations in polar solvents, at or near room temperature, have favoured the use of $Cu(OAc)_2$ or $CuSO_4$ as the reagent of choice; whereas transformations in nonpolar solvents at refluxing temperatures often employ CuI.

The choice of ligand to the copper catalyst has a profound effect on the success of the reaction. There are been exhaustive studies performed on the effect various ligands have on the

yield of copper-catalyzed cross-couplings of aryl halides with alkoxides[20] and amines.[16b] Ligands to copper can be either mono- or bidentate, and are based on the interaction between copper an the highly coordinating lone pair electrons of heteroatoms such as nitrogen, oxygen and phosphorus, and carbenes (Figure 10).

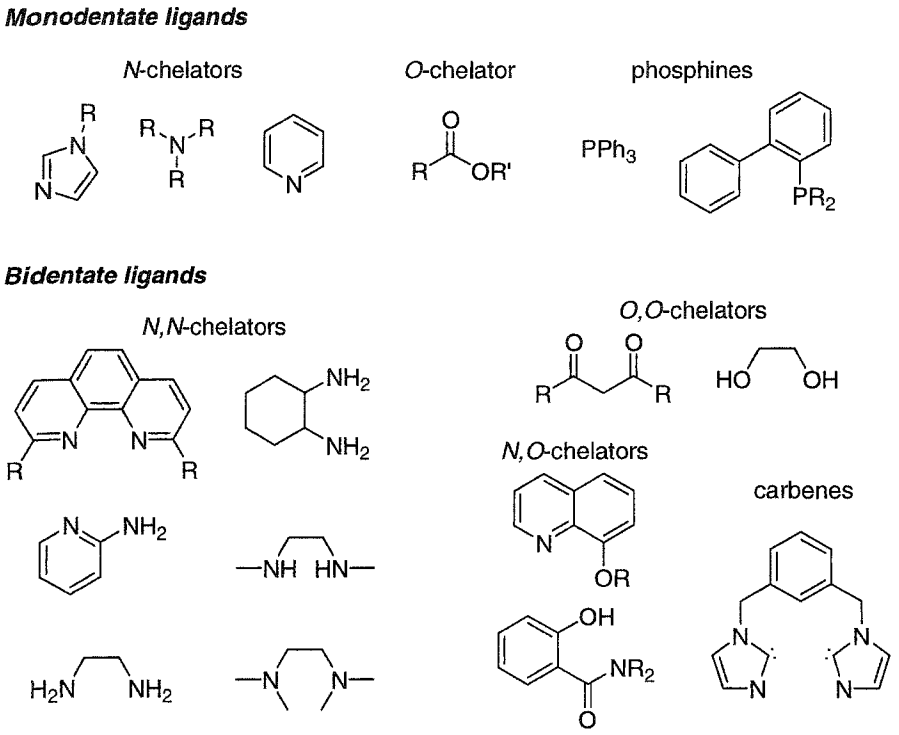


Figure 10 - Ligands Employed in Copper-Catalyzed Cross-Couplings

II.1.1.3 Organometalloids as Aryl Donors in Cross-Coupling

The unique properties of copper have provided access to a wide range of cross-coupling reactions. The original Ullmann reaction involved the coupling of two aryl halides, both electrophilic substrates. While the Ullmann condensation in turn, is a "traditional" coupling involving both an electrophilic aryl halide and a nucleophile. Another branch of research in Ullmann condensations has focussed on the cross-coupling of organometalloid species, often considered nucleophilic in nature, with heteroatomic (particularly *O*, *N*, *S* and *Se*-based) nucleophiles. Like that of organometalloid cross-couplings with aryl halides, the Ullmann condensation of organometalloids with heteroatomic nucleophiles offers a variety of pathways to analogous products (Figure 11). It is this third type of Ullmann condensation, the coupling of two nucleophilic species, which the work presented in this thesis is based upon.

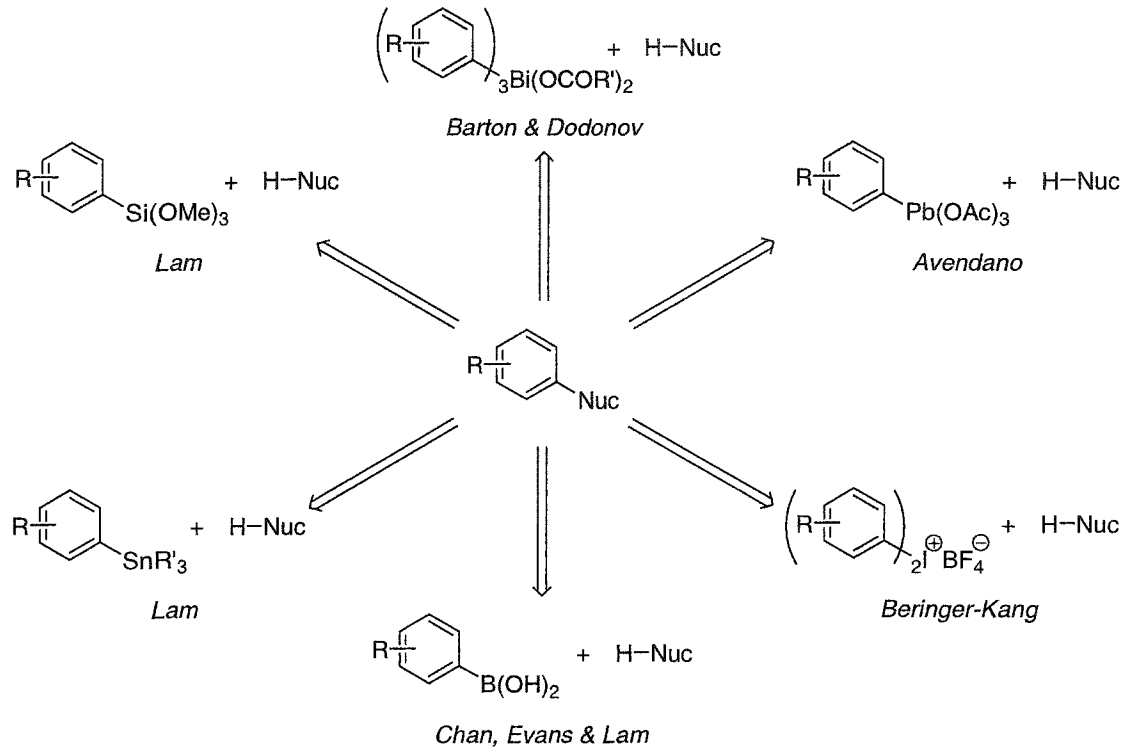


Figure 11 - Modified Ullmann Condensations between Organometalloids and Heteroatomic Nucleophiles

II.1.2 Ullmann Condensations of Organometalloids and Oxygen-Based Nucleophiles

Various organometalloids have been employed in cross-coupling reactions with both activated and unactivated oxygen-based nucleophiles (Figure 12). The remainder of this chapter

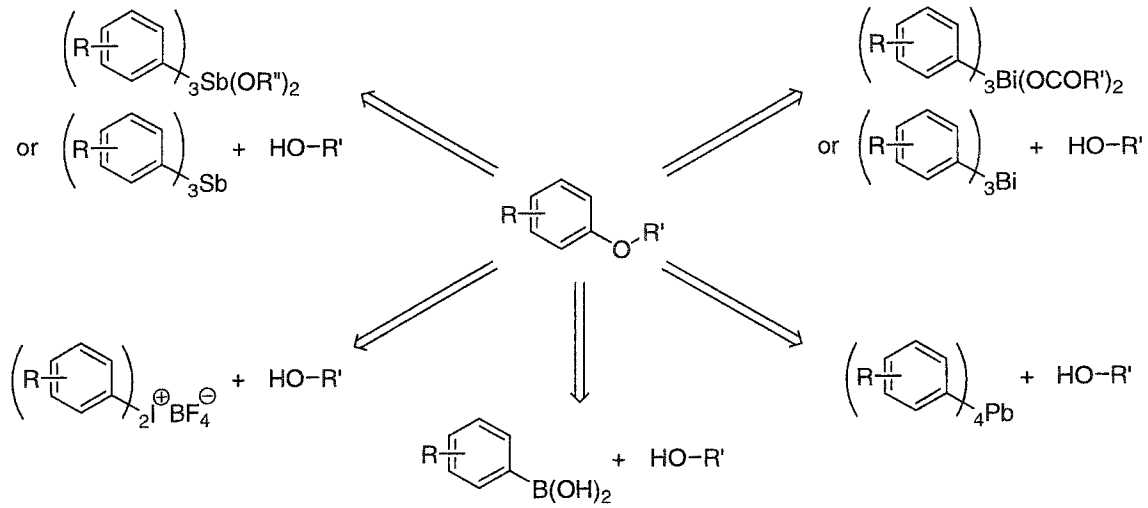


Figure 12 - Organometalloids Utilized for Copper-Mediated Arlyation of Oxygen-Based Nucleophiles

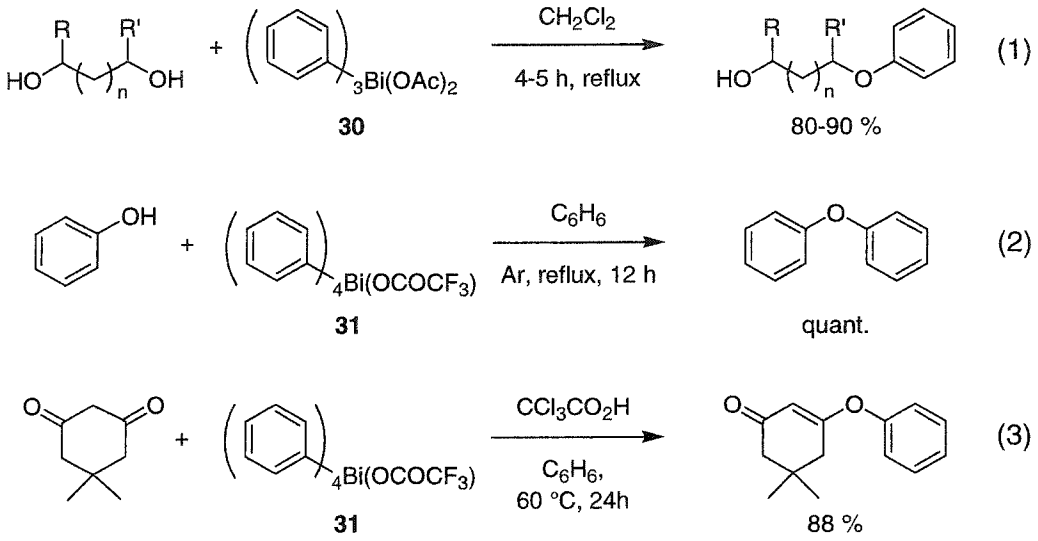
will focus upon the formation of carbon-oxygen bonds via copper-mediated or catalyzed Ullmann condensations. The following chapter will focus upon the formation of carbon-nitrogen bonds through an analogous strategy. It should be noted that research by various groups has also investigated the formation of carbon-sulfur[21,22] and carbon-selenium[22a] bonds utilizing this strategy. However, the particulars of these works are beyond the scope of this introduction and will not be discussed in detail.

II.1.2.1 Organobismuth Reagents

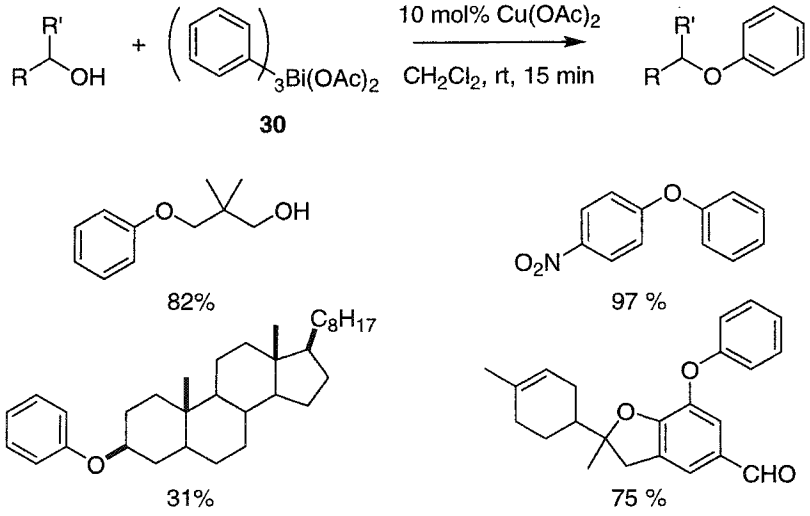
David and Thieffry were the first to report the reactivity of triphenylbismuth diacetate (**30**) in the arylation of aliphatic diols. Their conditions required refluxing the diol and the arylbismuth reagent in dichloromethane. Good to excellent yields of the corresponding monoarylated glycols were obtained after 4-5 hours (Scheme 33, reaction 1).[23] However, their reaction was not without its faults, Barton and coworkers soon discovered that the reaction had several serious limitations. First, the reaction was highly specific to diols, or alcohols with coordinating functional groups within close proximity of the hydroxyl moiety. Second, the reaction was solvent specific to dichloromethane. Finally, the reaction had a 2 hour induction period and a requirement for photochemical activation (i.e. experiments run overnight in the dark did not react).[24c] Barton had previously described the uncatalyzed arylation of phenols[24a] and enolates[24b] using the pentavalent bismuth reagent **31** (Scheme 33, reactions 2 and 3).

Barton also discovered that addition of catalytic amounts of copper salts would result in a great enhancement of the reaction rate and consequently the generality of David and Thieffry's protocol. The phenylations could now be performed at room temperature in most organic solvents with shorter reaction times, and without the need for photochemical induction. The substrate scope was broadened to include simple and complex alcohols and phenols, with or without coordinating groups near the reactive hydroxyl moiety (Scheme 34).[24] Barton's finding was echoed simultaneously, but independently, by the work of Dodonov's group from Russia.[25]

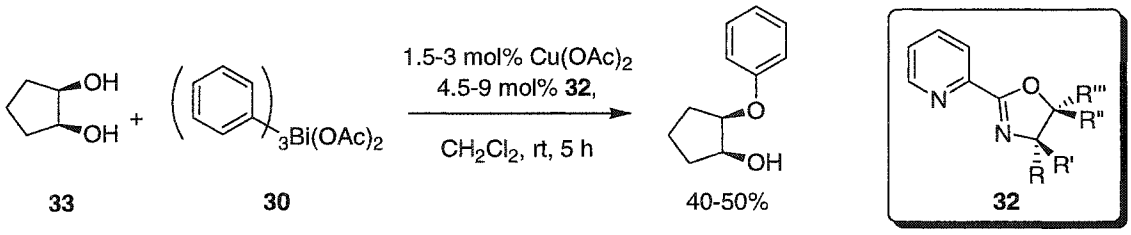
Others have also made use of organobismuth reagents both for the preparation of small molecule libraries and for the synthesis of complex molecules. As methods for the preparation of other functionalized polyarylbismuth reagents were developed, so too were those reagents utilized in cross-coupling reactions.[26] One interesting use of the organobismuth reagents is the enantioselective arylation of racemic diols. Brunner et al. employed chiral pyridinaloxazoline



Scheme 33 - Uncatalyzed Phenylation of Aliphatic Diols, Phenols and Enolates with Triphenylbismuth Diacetate



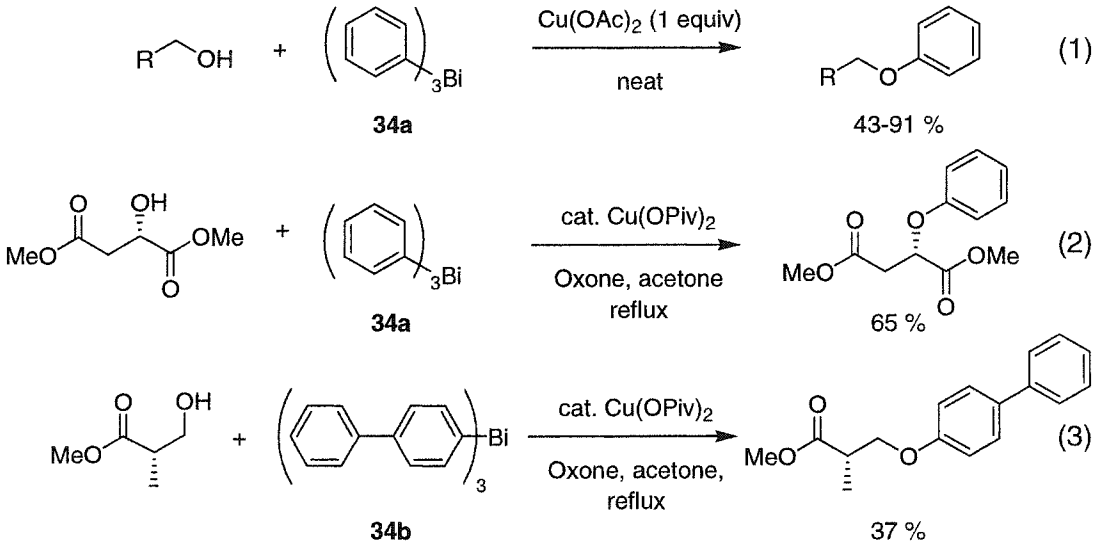
Scheme 34 - Copper-Catalyzed Phenylation of Alcohols and Phenols with Triphenylbismuth Diacetate



Scheme 35 - Copper-Catalyzed Enantioselective Arylation of *Meso* Diols with Triphenylbismuth Diacetate

compounds (**32**) as ligands to the copper-catalyst. They were able to achieve enantiomeric excesses of up to 50 % from reaction of the *meso* diol **33**. Unfortunately, the yields obtained were significantly lower than those acquired in the absence of the ligand (Scheme 35).[27]

Triarylbismuthane reagents (**34**) have also been employed in the formation of carbon-oxygen bonds. The reactions required a stoichiometric amount of copper for the transformation to occur (Scheme 36, reaction 1). [25c,d] However, if one equivalent of the chemical oxidant Oxone™ (potassium peroxymonosulfate: 2 $KHSO_5$, $KHSO_4$, K_2SO_4) was added to the reaction mixture then a catalytic amount of the copper salt could be employed. The reaction presumably goes through a pentavalent arylbismuth species generated *in situ* (Scheme 36, reaction 2 and 3).[28]

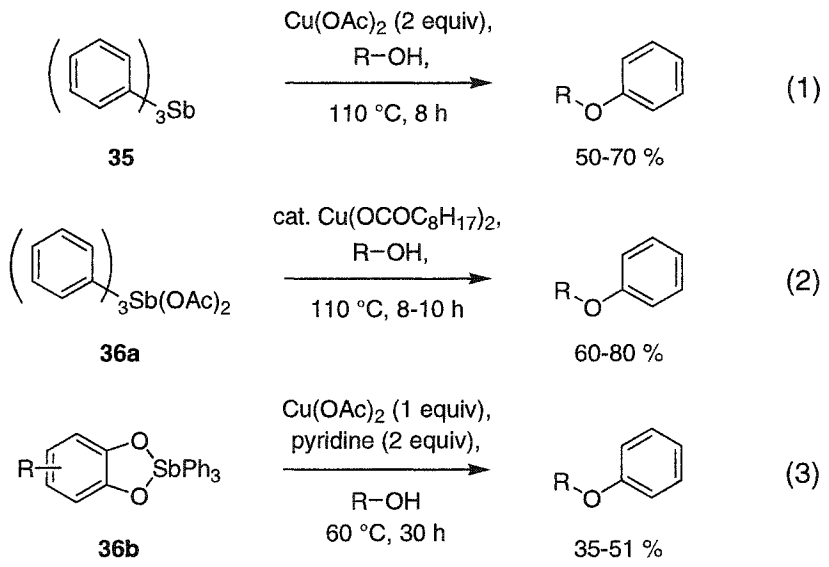


Scheme 36 - Arylation of Alcohols with Triphenylbismuthane and Oxone™

II.1.2.2 Organoantimony Reagents

Like trivalent arylbismuths, triarylantimony reagents (**35**) can only be cross-coupled to alcohols under stoichiometric conditions with copper. The arylation of simple primary alcohols was found to proceed in moderate to good yields (Scheme 37, reaction 1).[29b] Pentavalent arylantimony reagents (**36**) permit the use of catalytic amounts of the copper salt under an atmosphere of oxygen, but only when $Cu(OAc)_2$ is replaced with $Cu(OCOC_8H_{17})_2$ (copper dipelargonate) (Scheme 37, reaction 2).[29a] Pentaphenylantimony can also be used to arylate simple alcohols.[29c] All reports of arylations with organoantimony reagents have utilized the alcohols in solvent quantities with reaction temperatures well above 100 °C; hence very little study and application of arylantimony reagents has been reported. By far, the mildest set of

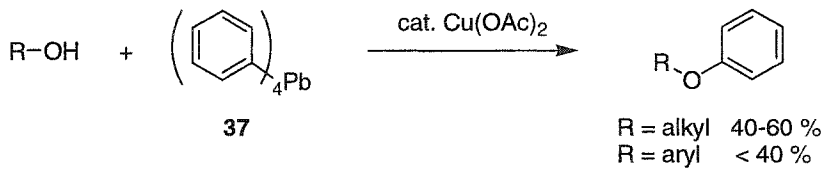
conditions comes from the use of the more exotic triphenylbenzoastibolanes (**36b**), though the yields of the corresponding aryl ethers are lower as well (Scheme 37, reaction 3).[2a]



Scheme 37 - Arylation of Alcohols with Arylantimony Reagents

II.1.2.3 Organolead Reagents

The efficiency of cross-coupling reactions of aryllead reagents is closely related to the nucleophilicity of the cross-coupling partner. Aryllead triacetates commonly used in the copper-catalyzed arylation of nitrogen-based nucleophiles (*vide* III.1.2.2) do not react with the less nucleophilic oxygen-based substrates. However, Dodonov *et al.* have reported that tetraphenyllead (**37**) can react with primary and secondary alcohols in moderate yields, and phenols in low yield. Phenyl transfer from the lead reagent is more efficient in the arylation of alcohols, with 1-2 of the phenyl moieties reacting (i.e. less than one equivalent of the lead reagent per equivalent of the alcohol is required). The reaction of phenols is much less efficient often requiring 1.5-2 equivalents of the lead reagent per equivalent of the phenol (Scheme 38).[30]

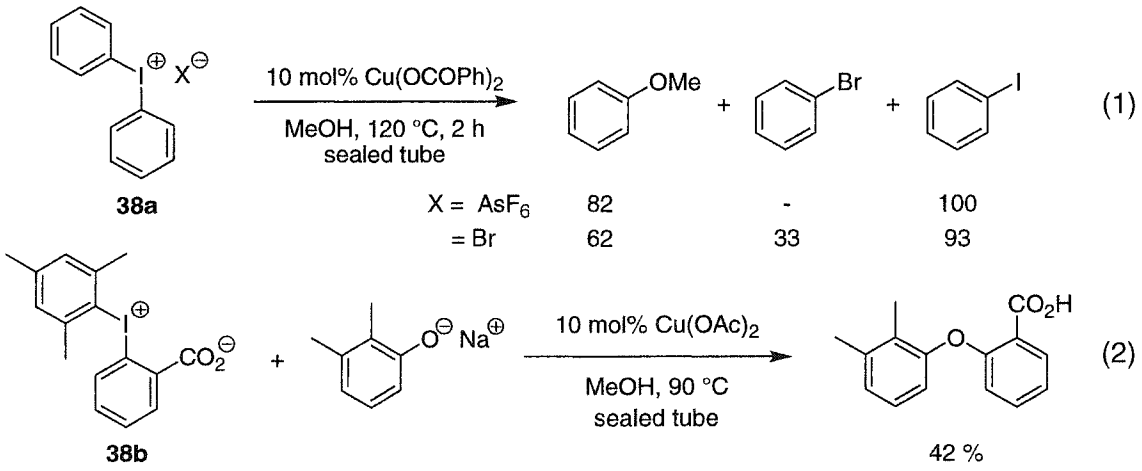


Scheme 38 - Arylation of Alcohols and Phenols with Tetraphenyllead

II.1.2.4 Organoiodine Reagents

The use of diaryliodonium salts (**38**) in copper-catalyzed Ullmann condensations for the

formation of carbon-oxygen bonds has been plagued with problems. First, high yields of the aryl ethers can only be obtained when the alcohol cross-coupling partner is employed in great excess, usually greater than 4 equivalents. Secondly, the nature of the counterion on the iodonium reagent plays a significant role in the reaction. The best yields were observed when non-nucleophilic counterions were present. In the presence of nucleophilic counterions, significant quantities of the cross-over side products were isolated. In addition, the iodine present in the reaction mixture can also act as a cross-coupling partner (Scheme 39, reaction 1).[31] An interesting aspect of diaryliodonium chemistry comes from the work of Scherrer and Beatty. They observed that reaction of the unsymmetrical salt **38b** with an activated phenol resulted in selective transfer of the electron-deficient phenyl-2-carboxylate moiety over that of the electron-rich and sterically hindered 2,4,6-trimethylphenyl moiety (Scheme 39, reaction 2).[32]

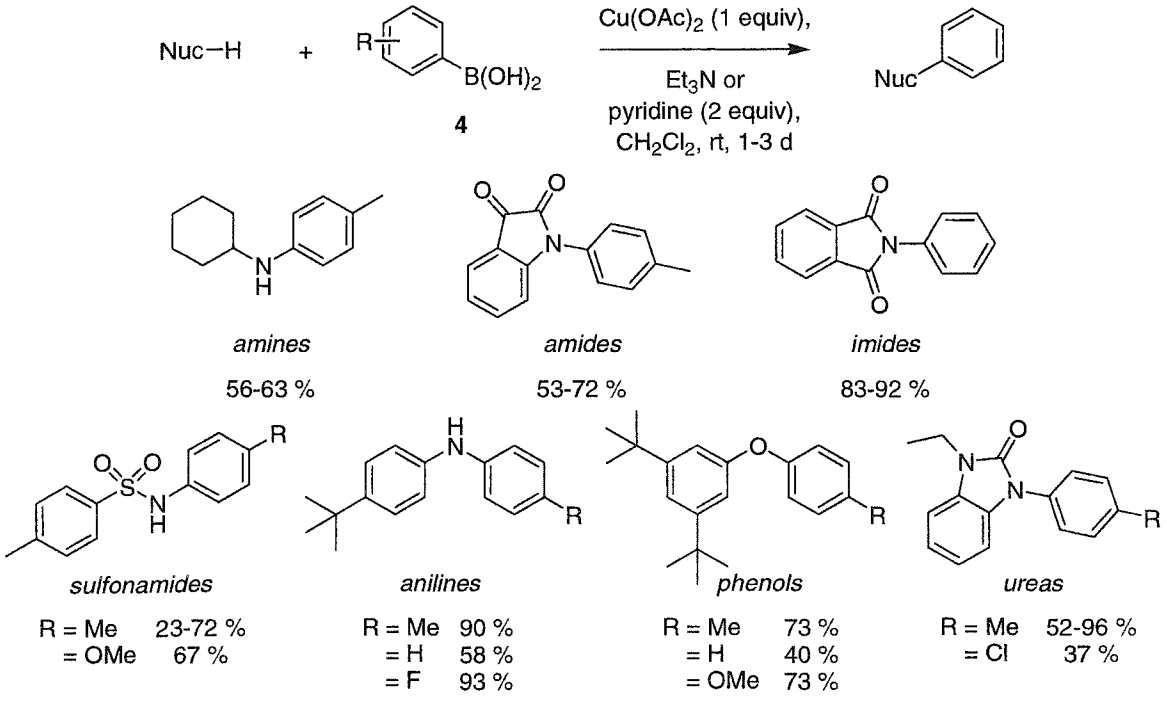


Scheme 39 - Arylation of Alcohols and Phenols with Diaryliodonium Salts

II.1.2.5 Organoboron Reagents

Organoboronic acids (**4**) are perhaps the most comprehensively studied organometalloid reagents in Ullmann-type cross-couplings. The collection of carbon-nitrogen bond forming reactions employing organoboronic acids as the aryl donor is quite large (*vide* III.1.2.7). In contrast, developments in this field of carbon-oxygen bond forming reactions have been relatively sparse within the past decade. The simultaneous, but independent reports by Chan,[33] Evans[34] and Lam[35] in 1998 initiated and gave momentum to the development of modern day Ullmann condensations. Their work offered a simplistic, yet reliable, alternative to carbon-heteroatom bond formation under much milder conditions than traditional approaches.

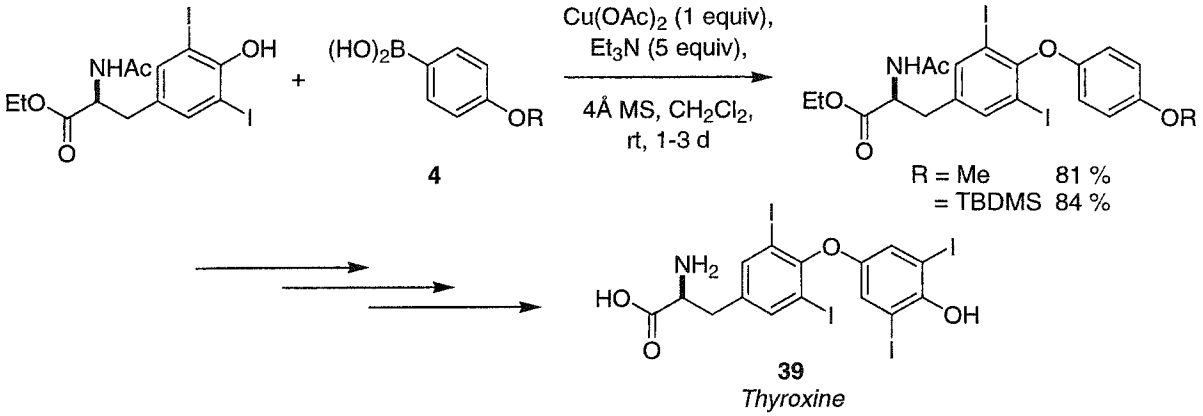
Chan and coworkers first described *N*- and *O*-arylations under these novel reaction conditions at a meeting of the American Chemical Society in June 1997; their report published soon after clearly demonstrated the ability of organoboronic acids to act as aryl donors for cross-coupling with a variety of oxygen and nitrogen-based nucleophiles.[33] Chan's protocol proved to be broadly applicable to a wide range of substrates, and tolerant to a variety of functional groups. The method employed a stoichiometric equivalent of $Cu(OAc)_2$ and two equivalents of a base. The reaction yield was found to be sensitive to the nature of the base added (in their study Et_3N or pyridine); however, no correlation between the nucleophile employed and the choice of base used was evident (Scheme 40). Finally, Chan's protocol offered a much more atom economical alternative to previous aryl donors, as the sole aryl moiety present in the starting material was transferred in the cross-coupling. Previous reagents often contained two to five aryl moieties in the organometalloid reagent, and only one was transferred to the product.



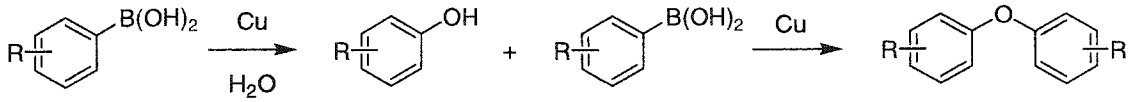
Scheme 40 - Arylation of Various Oxygen and Nitrogen-Based Nucleophiles with Arylboronic Acids

Chan's findings attracted the interest of Evans and coworkers, who optimized the protocol and employed it as the key step in a formal synthesis of thyroxine (**39**, Scheme 41). Evans was able to optimize the reaction conditions for arylation of phenols in the preparation of diaryl ethers. Like that of Chan, their protocol required the presence of excess arylboronic acid (used in

a 2-3:1 ratio of boron to the phenolic substrate) due a competitive side reaction, namely the arylation of water (Scheme 42), which consumed a significant portion of the starting material. Despite their attempts to keep the reaction under anhydrous conditions, water was found to be present in the reaction mixture via the formation of triarylboroxines.[36] They found that addition of molecular sieves to the reaction mixture helped to suppress the formation of the phenol and diaryl ether. Optimal cross-coupling conditions employed one equivalent of $Cu(OAc)_2$ and five equivalents of a base in CH_2Cl_2 at room temperature for 24 hours. Although the reaction was found to be fairly general for the phenol component of the cross-coupling, a highly coordinating substituent in the *ortho*-position of the arylboronic acid severely depressed the reaction yields. No reaction with aliphatic alcohols was reported. Evans also suggested a speculative mechanism analogous to that proposed by Barton for the amine arylation reaction (*vide* IV.1.2.1).[34]

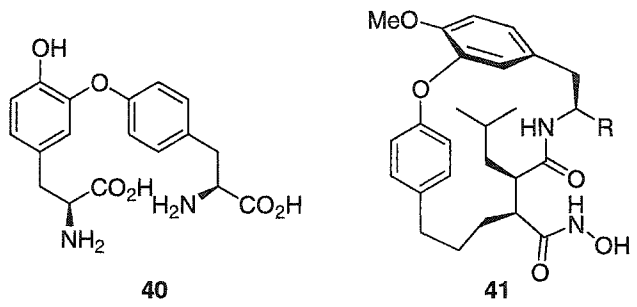


Scheme 41 - Arylation of Phenol Derivatives Toward the Synthesis of Thyroxine



Scheme 42 - Undesired Side Reaction: Arylation of Water and Subsequent Self-coupling of Arylboronic Acids

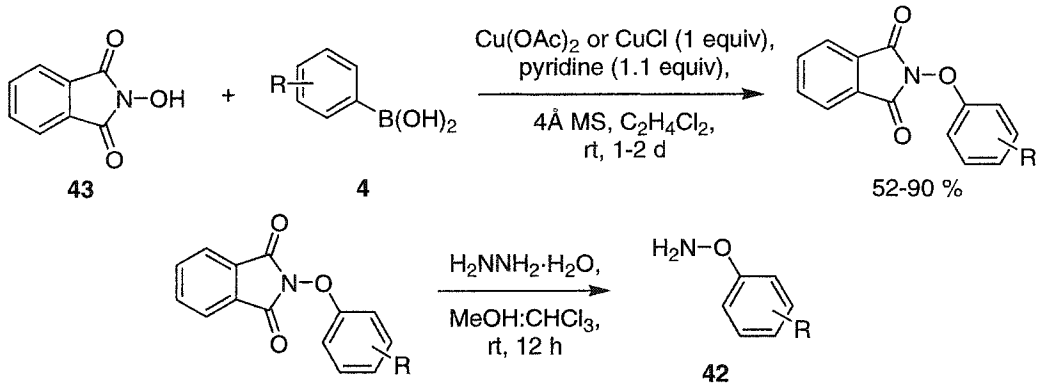
Others have also exploited this methodology toward the synthesis of interesting natural products. Jung and Lazarova utilized this modified Ullmann condensation as the key bond-forming step in their preparation of isodityrosine (**40**), a key structural unit in several biologically active natural products.[37] Decicco, Song and Evans used this cross-coupling in their preparation of several metalloproteinase inhibitors containing a macrocyclic diaryl ether motif (**41**, Figure 13).[34b]



40 41

Figure 13 - Natural Products Containing a Diaryl Ether Motif

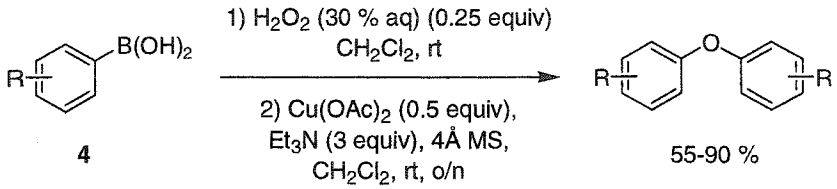
An expansion of the substrate scope of these copper-mediated carbon-oxygen bond formations comes from the work of Petrassi, Sharpless and Kelly. They make use of this protocol as a simple route to preparing aryloxyamines (**42**) from the arylation and subsequent deprotection of *N*-hydroxyphthalimides (**43**, Scheme 43).[37] The reaction worked well with both oxidation states of copper, but the counterions on the copper reagent played a significant role in the reactivity; hence, only $Cu(OAc)_2$, CuCl and CuBr·DMS successfully mediated the transformation.



43 4 52-90 % 42

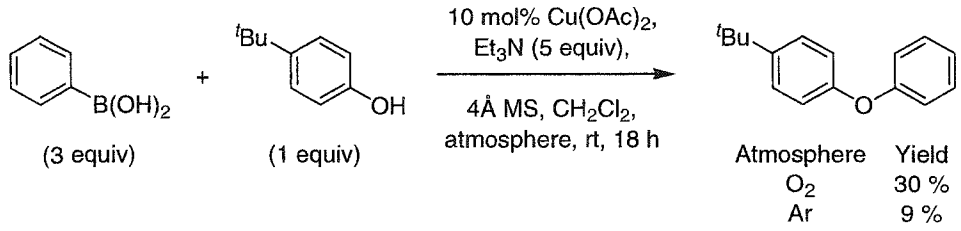
Scheme 43 - Arylation of *N*-hydroxyphthalimides for the Preparation of Aryloxyamines

Finally, Petasis *et al.* have reported a one-pot protocol for the oxidative homocoupling of arylboronic acids under copper mediation for the synthesis of symmetrical diaryl ethers. They exploited the sensitivity of organoboronic acids toward chemical oxidations; hence, treatment of one equivalent of the boronic acids with a quarter equivalent of aqueous hydrogen peroxide generated the phenolic cross-coupling partner *in situ*. Subsequent addition of the copper salt, base and molecular sieves afforded the desired diaryl ethers in good to excellent yields (Scheme 44).[38]



Scheme 44 - One-Pot Synthesis of Symmetrical Diaryl Ethers from Arylboronic Acids

It should also be noted that to this point, all protocols involving organoboronic acids in carbon-oxygen bond formations have been stoichiometric in the copper reagent used. Evans had proposed a mechanism wherein the copper species changed oxidation states during the course of the reaction (*vide* IV.1.2.1). The mechanism ended with a reductive elimination occurring from either a Cu(II) or Cu(III) intermediate to produce the cross-coupled product, and a Cu(0) or Cu(I) species respectively. Thus, it was speculated that if an oxidant could be used to regenerate the higher oxidation state copper species then the reaction could be rendered catalytic in copper. Indeed when run under an atmosphere of oxygen or air, some catalytic turnover was observed when a substoichiometric amount of copper reagent was used. For example, when 0.1 equivalents of $Cu(OAc)_2$ was used to 1 equivalent of the phenol derivative, the reaction gave a 30 % yield of the diaryl ether when run under oxygen, and only 9 % of the diarylether when run under argon (Scheme 45).[34]



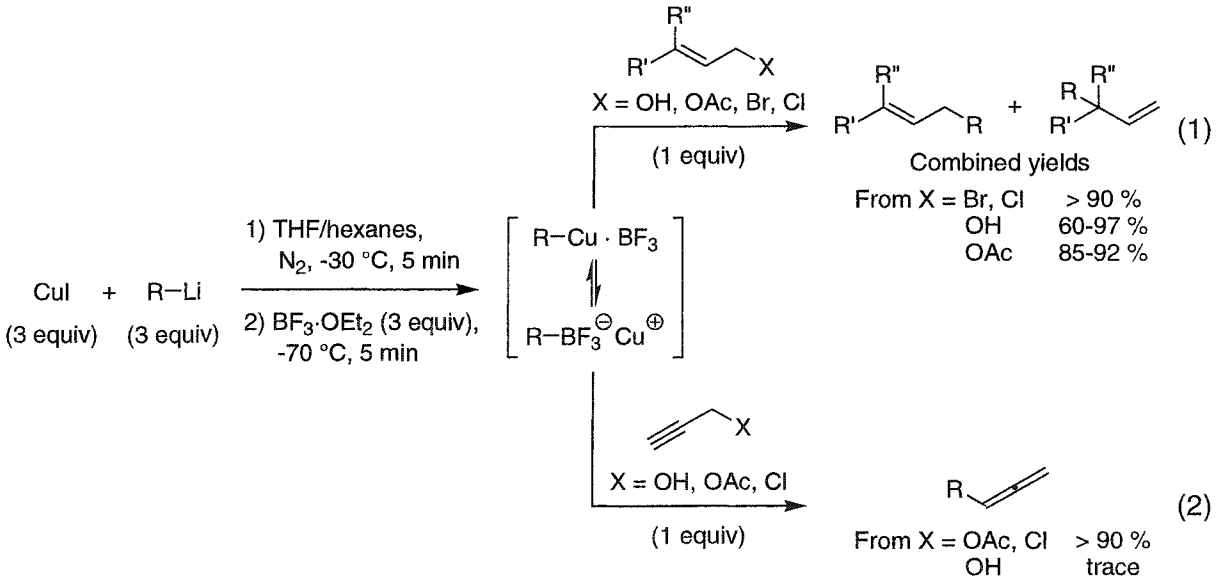
Scheme 45 - Early Attempts at Copper-Catalyzed *O*-Arylations with Boronic Acids

II.2 Results and Discussion

II.2.1 Copper-Catalyzed Cross-Coupling of Organotrifluoroborate Salts with Alcohols and Phenols

This project is an extension to our group's exploration of transmetallation reactions between organotrifluoroborate salts and various transition metals. Following the success of the Pd-catalyzed cross-coupling of tetraalkylammonium organotrifluoroborate salts with aryl halides, our attention turned toward copper promoted transformations, which at the time had been largely undeveloped.

In the early 1980s, Yamamoto *et al.* reported a new class of substitution reactions with organocuprates under Lewis acid mediation. Reaction of organocuprates with a Lewis acid generated an R-Cu·BF_3 complex which could undergo S_N2 or S_N2' reactions with allylic acetates, bromides and chlorides to afford a mixture of the α- and γ-substituted products in good to excellent yields (Scheme 46, reaction 1). Interestingly, unactivated alcohols also underwent the substitution reaction rather than the expected deprotonation. Propargylic acetates and chlorides reacted to afford the γ-substituted allenes exclusively in excellent yields, but propargyl alcohols did not react (Scheme 46, reaction 2). Yamamoto speculated that the intermediate generated from reaction of the organolithium with CuI possessed an "ate" complex structure (i.e. an organotrifluoroborate) which would be stable at low temperatures.[40]



Scheme 46 - Reaction of RCu·BF_3 with Allylic and Propargylic Electrophiles

Our initial forage into the realm of copper-mediated transformations involving organoboron compounds was an attempt to provide a facile method of generating the cuprous organotrifluoroborate species (**44**) via counterion exchange from the potassium salts (Figure 14). Unfortunately, the products were too unstable for isolation, or more likely, they were never formed.

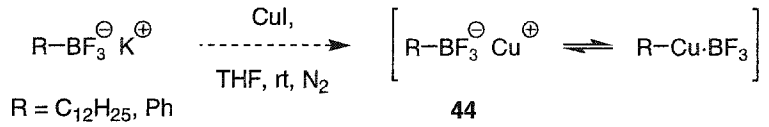
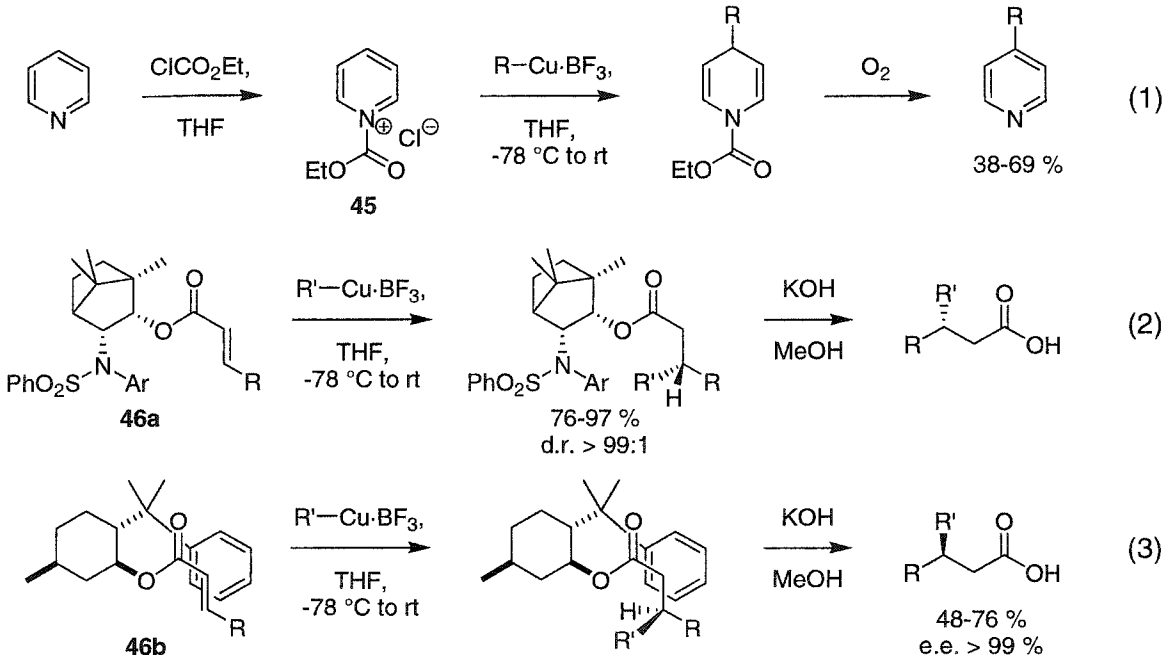


Figure 14 - Attempt to Prepare Cuprous Organotrifluoroborates via Counterion Exchange

Previous work by various groups had reported the trapping of Yamamoto's nucleophilic R-Cu·BF_3 species with Michael acceptors like *N*-acylpyridinium salts (**45**),[41] and α,β-unsaturated esters (**46**, Scheme 47). In the latter examples, diastereoselective additions could be affected with the use of chiral auxiliaries on the esters.[42,43]



Scheme 47 - Conjugate Additions of RCu·BF_3 to Michael Acceptors

Despite our attempts to trap the cuprous trifluoroborates with 2-cyclohexenone under various conditions, none were successful, and only unreacted starting materials were recovered from the reaction mixture (Figure 15).

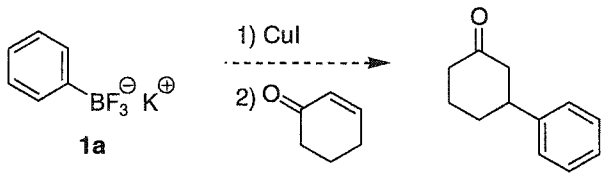
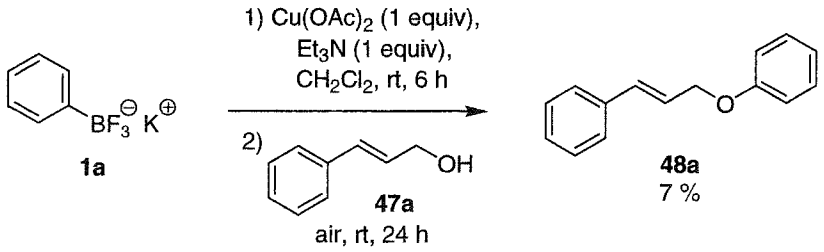


Figure 15 - Attempt at Copper-Mediated 1,4-Conjugate Addition of Potassium Phenyltrifluoroborate to 2,3-Cyclohexenone

The first sign of a copper-promoted reaction with organotrifluoroborate salts occurred while attempting to reproduce an S_N2 or S_N2' substitution result as in Yamamoto's work; hence, **1a** was stirred in a solution of $Cu(OAc)_2$ and Et_3N in CH_2Cl_2. Addition of (*E*)-cinnamyl alcohol (**47a**) with continuous stirring for 24 hours produced a new compound, albeit in low yield. It was serendipitously discovered that instead of the expected α or γ-substituted product, the reaction afforded the cross-coupled aryl allyl ether **48a** (Scheme 48).

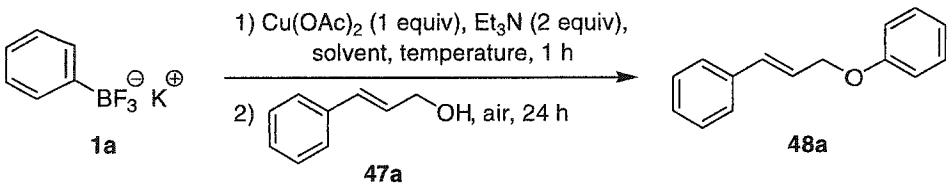


Scheme 48 - Reaction of Potassium Phenyltrifluoroborate with (*E*)-Cinnamyl Alcohol

II.2.1.1 Optimization of the Reaction Conditions

Once it was realized that a cross-coupling arylation of the alcohol had occurred rather than the planned nucleophilic substitution, studies were initiated to optimize the reaction conditions. Starting from Chan's unoptimized reaction conditions for the arylation of phenols,[33b] one equivalent of anhydrous $Cu(OAc)_2$ and 2 equivalents of Et_3N were employed as the initial conditions in the reaction of **1a** with (*E*)-cinnamyl alcohol (**47a**). The reaction solvent and temperature were the first factors examined. Even from these early studies it was evident that the choice of solvent would have a profound effect on the reaction. While polar solvents were favoured in the cross-coupling, solvents that held a high coordinative affinity towards copper hampered the reaction even at high temperatures (Table 7, entries 5-9). Switching from the trifluoroborate salts to the boronic acids did not produce a significant increase in the reaction yield (Table 7, entry 1 vs. entry 2).

Table 7 - Early Optimization Studies of Solvent and Temperature Effects for the Arylation of (*E*)-Cinnamyl Alcohol



1a **47a** **48a**

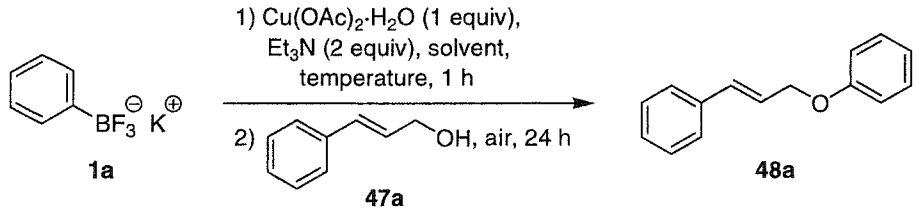
Entry	Solvent	Temperature	Yield (%)[a]
1	CH_2Cl_2	rt	7
2	CH_2Cl_2	rt	18[b]
3	Et_2O	rt	30
4	Et_2O	40 °C	31
5	THF	rt	-
6	DME	rt	9
7	DME	80 °C	15
8	1,4-dioxane	80 °C	3
9	MeCN	80 °C	-

a) isolated yields. b) from phenylboronic acid (**4a**).

Evans had reported that the presence of molecular sieves was necessary for high yields of the biaryl ethers under his optimized conditions; hence, the next logical step was to examine the effect that various additives and desiccants would have on the reaction yield. The use of $Cu(OAc)_2 \cdot H_2O$ effectively added one equivalent of water to the reaction mixture, thereby increasing the yield of the undesired by-products in the reaction (i.e. phenol and biaryl ether from the arylation of water). Switching to the more expensive anhydrous $Cu(OAc)_2$ did improve the reagent yield over that of the monohydrous reagent in the absence of any other additives (Table 8, entry 1 vs. entry 6). However, the addition of activated molecular sieves to the reaction mixture (1 gram per millimole of **47a**) mimicked that of the anhydrous results. The size of the pores in the molecular sieves did not appear to affect the reaction yield; however, their physical form did. Hence, the powdered form of the molecular sieves afforded significantly higher yields than that of the beaded variety (Table 8, entries 2-4 vs. entry 5). The molecular sieves may be

playing a greater role in the reaction than as just a desiccant (*vide* IV.2.1.2), as the use of finely powdered $MgSO_4$ did not have the same effect as that of the molecular sieves (Table 8, entry 8). Buchwald had recently described the use of myristic acid ($C_{13}H_{27}CO_2H$) to aid the dissolution of $Cu(OAc)_2$ in toluene in his arylation of amines and anilines with arylboronic acids (*vide* III.1.7).[44] In our case, addition of two equivalents of myristic acid to the reaction mixture only served to lower the yields of the alkyl aryl ether, as the mixture became so viscous that mechanical agitation of the reaction became difficult (Table 8, entry 9). Finally, as had previously been observed, changing the reaction solvent while increasing the temperature did not produce higher yields of the product (Table 8, entry 10).

Table 8 - Effect of Various Additives and Desiccants on the Arylation of (*E*)-Cinnamyl Alcohol

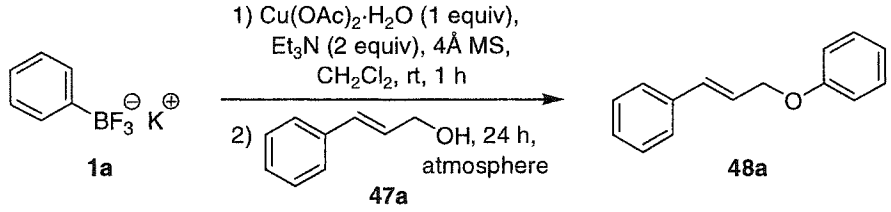


Entry	Solvent	Temperature	Additive	Yield (%)[a]
1	CH_2Cl_2	rt	-	5
2	CH_2Cl_2	rt	3Å MS (beads)	26
3	CH_2Cl_2	rt	4Å MS (beads)	29
4	CH_2Cl_2	rt	10Å MS (beads)	30
5	CH_2Cl_2	rt	4Å MS (powdered)	53
6	CH_2Cl_2	rt	-	22[b]
7	CH_2Cl_2	rt	4Å MS (powdered)	43[b]
8	CH_2Cl_2	rt	$MgSO_4$	27
9	CH_2Cl_2	rt	4Å MS (powdered) myristic acid (2 equiv)	14
10	DME	80 °C	4Å MS (powdered)	19

a) isolated yields. b) *anhydrous* $Cu(OAc)_2$ (1 equiv).

The breakthrough came in recognizing the need for excess equivalents of the borate salt in order to compensate for substrate loss do to the competing side reactions. Both Chan and Evans had previously reported this observation.[33b,34a] Doubling the stoichiometry of the trifluoroborate salt increased the yield to 96 % (Table 9, entry 2). Addition of greater than two equivalents of the salt actually lowered the effectiveness of the reaction, as the insolubility of the trifluoroborate salts in dichloromethane resulted in a viscous slurry which made stirring difficult; both the desired alkyl aryl ether **48a** and the side products were observed to be in lower concentration via isolation and TLC, respectively (Table 9, entry 3). Changing from the trifluoroborate salt to boronic acid **4a** did not improve the yield of the desired product (Table 9, entries 4 and 5). The increased solubility of the boronic acids makes them readily available to react with the water present in the reaction mixture, a more reactive cross-coupling partner than the unactivated alcohols. Hence, greater amounts of the side products were isolated in both those reactions.

Table 9 - Increasing the Equivalents of the Borate Component of the Cross-Coupling



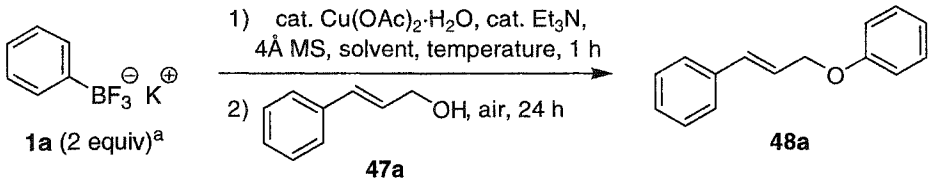
Entry	Equivalents of 1a	Atmosphere	Yield (%)[a]
1	1.0	air	53
2	2.0	air	96
3	3.0	air	83
4	2.0	air	54[b]
5	3.0	air	84[b]

a) isolated yields. b) from phenylboronic acid (**4a**).

Having established a set of standard conditions for the arylation of unactivated alcohols under a stoichiometric amount of copper, an investigation into developing a catalytic variant of the reaction was initiated. Reducing the catalyst/ligand loading to half and even one quarter of

an equivalent, compared to the alcohol, still maintained the high yield of the arylation (Table 10, entries 1-3). However, when the catalyst/ligand loadings were dropped to 10 mol % or lower the reaction yield dropped significantly and disproportionately. In fact, only a trace of the cross-coupled product and side products were observed by TLC when 5 mol % $Cu(OAc)_2 \cdot H_2O$ was employed (Table 10, entry 4 and 5). The solvent specificity of the reaction is once again illustrated in the last three entries of Table 10. Switching to other chlorinated solvents in order to achieve higher reaction temperatures only served to decrease the reaction yield (Table 10, entry 6) or prevent reaction altogether (Table 10, entries 7 and 8).

Table 10 - Reducing the Catalyst/Ligand Loading of the Cross-Coupling



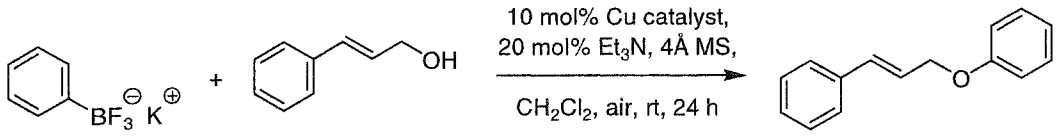
1a (2 equiv)[a] **47a** **48a**

Entry	Equivalents of Cu[a]	Equivalents of Et_3N[a]	Solvent	Temperature	Yield (%)[b]
1	1.00	2.00	CH_2Cl_2	rt	96
2	0.50	1.00	CH_2Cl_2	rt	98
3	0.25	0.50	CH_2Cl_2	rt	87
4	0.10	0.20	CH_2Cl_2	rt	32
5	0.05	0.10	CH_2Cl_2	rt	trace
6	0.10	0.05	$CHCl_3$	50 °C	50
7	0.10	0.05	CCl_4	70 °C	-
8	0.10	0.05	$Cl_2CHCHCl_2$	100 °C	-

a) to one equivalent of **47a**. b) isolated yields.

An in-depth study of the nature of the catalyst/ligand system was performed in trying to increase the yield of the catalytic reaction. Of the various copper species employed in the reaction, only three showed any reactivity at all: $Cu(OAc)_2 \cdot H_2O$, anhydrous $Cu(OAc)_2$, $CuSO_4 \cdot 5H_2O$ gave yields between 20-32 % when 10mol % of the catalyst was used with 20 mol % Et_3N as ligand. Other copper(I) and copper(II) salts gave neither the desired product, nor the side products (Scheme 49). One of the major factors that may have contributed to the failure of those

reactions is the salts' insolubility in dichloromethane. It was also discovered at this time that the induction period given to dissolve the trifluoroborate salts and the catalyst/ligand system before addition of the alcoholic substrate was unnecessary. Thus, all further reactions were performed with addition of the alcohol last, but without a significant period of time between the initial stirring of the reaction and the alcohol's addition.



1a (2 equiv) + **47a** (1 equiv) → **48a**

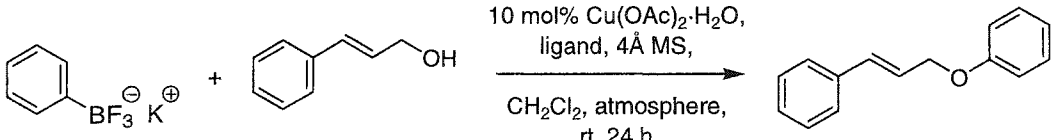
Cu catalyst = $Cu(OAc)_2 \cdot H_2O$, anhydrous $Cu(OAc)_2$, $CuSO_4 \cdot 5H_2O$ — 20-32 %

= CuO_2, $Cu(acac)_2$, $Cu(OTf)_2$, $CuBr_2$, $CuCl_2$, CuBr, CuBr·DMS, CuCl, CuI, Cu_2O, CuCN, CuSCN — 0 %

Scheme 49 - Catalyst Study for Optimization of the Arylation of (*E*)-Cinnamyl Alcohol

A much greater effect was observed when the ligand was changed in the reaction. Unsurprisingly, other aliphatic amines used as ligand to copper produced little noticeable improvement to the yield, regardless of the mono- or bidentate nature of the ligand (Table 11, entries 2, 3, 7 and 8). However, when nitrogen-based heterocycles were employed, a profound effect on the reaction yield was observed. Indeed, imidazole, pyridine and DMAP increased the yield of the desired cross-coupled product greater than two-fold over that of Et_3N; even the bidentate 1,10-phenathroline afforded a slightly higher yield (Table 11, entries 4-6 and 9). Finally, the atmospheric conditions of the reaction were confirmed to play an important role in the turnover of the catalyst. It is hypothesized that molecular oxygen takes part in the regeneration of the active copper species in the transformation (*vide* IV.2.1). Accordingly, the highest yields for the most active catalyst/ligand systems were obtained when run under open air (Table 11, entries 4-6), or under a blanket of oxygen (Table 10, entries 15 and 16); whereas reaction under a blanket of nitrogen gave little or no turnover of the catalyst as expected (Table 11, entries 10-13).

Table 11 - Optimization of Ligand and Atmospheric Conditions for the Arylation of (*E*)-Cinnamyl Alcohol



1a (2 equiv) + **47a** (1 equiv) → **48a**

Entry	Molar % of Ligand	Ligand	Atmosphere	Yield (%)[a]
1	-	-	air	9
2	20	Et_3N	air	32
3	20	DIPEA	air	19
4	20	imidazole	air	73
5	20	pyridine	air	84
6	20	DMAP	air	77
7	10	DMEDA	air	-
8	10	TMEDA	air	41
9	10	1,10-phenathroline	air	51
10	20	Et_3N	N_2	23
11	20	imidazole	N_2	1
12	20	pyridine	N_2	10
13	20	DMAP	N_2	27
14	20	Et_3N	O_2	33
15	20	pyridine	O_2	85
16	20	DMAP	O_2	89

a) isolated yields.

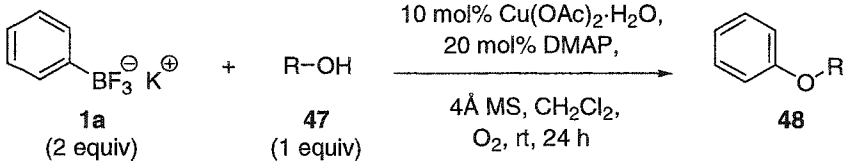
II.2.1.2 Scope and Limitations of the Oxygen-Based Nucleophile

The optimized reaction conditions for the arylation of unactivated aliphatic alcohols employed 10 mol % $Cu(OAc)_2 \cdot H_2O$, 20 mol % DMAP and 4Å molecular sieves (0.75 g per millimole of alcohol) in CH_2Cl_2 at room temperature under an atmosphere of dried oxygen gas. The choice to use DMAP in place of pyridine was made due to the ease of physical manipulation of the crystalline material. The optimized conditions were used to explore the generality of the substrate scope, and limitations of the reaction.

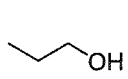
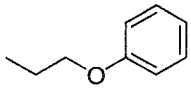
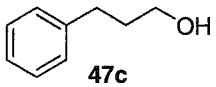
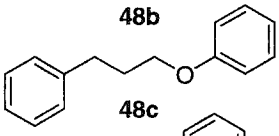
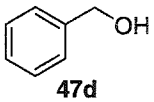
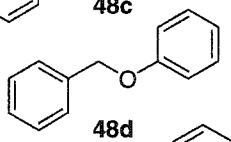
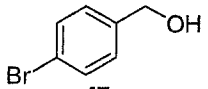
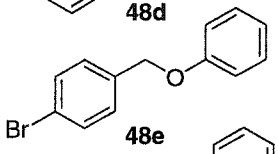
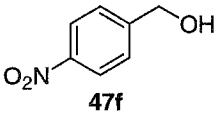
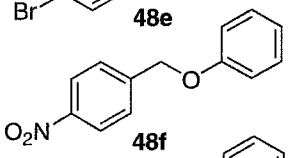
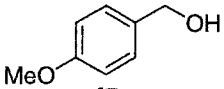
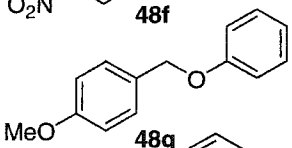
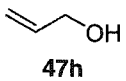
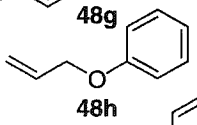
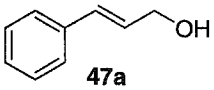
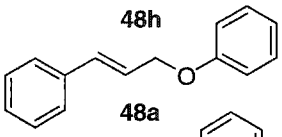
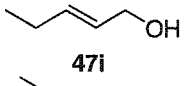
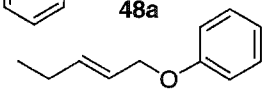
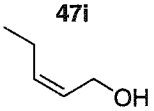
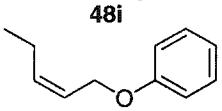
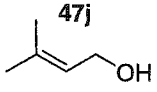
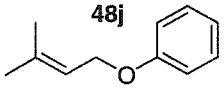
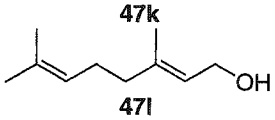
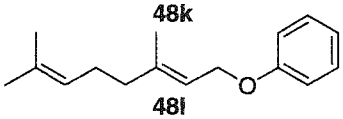
Primary aliphatic alcohols worked well in the reaction, with all but a few examples affording good to excellent yields of the alkyl aryl ethers (Tables 12a and 12b). Benzylic alcohols showed good reactivity in the cross-coupling, regardless of the presence of electron-donating or electron-withdrawing substituents on the aromatic ring (Table 12a, entries 3-6). Allylic alcohols were found to survive the arylation without isomerization of the double bond (Table 12a, entries 8-9 and 12). Alkyne functionalities are tolerated in the reaction, but only when substituted on both ends of the triple bond. Hence, 2-butynol (**47m**) was arylated in excellent yield, whereas homopropargyl alcohol (**47n**) underwent the arylation while concomitantly undergoing a copper-catalyzed oxidative homocoupling of the terminal alkyne moieties (Table 12b, entries 1-2). This copper-mediated coupling of terminal alkynes is known as the Eglinton reaction, and has been reported to proceed under conditions catalytic in copper in the presence of molecular oxygen.[45]

The presence of other heteroatoms on the alcoholic cross-coupling partners was received with mixed results. Interestingly, alkyl halides survived the essentially neutral cross-coupling conditions without nucleophilic substitution at the halide moiety, thereby demonstrating the potential of this protocol for preparation of substrates not possible under classical Williamson ether synthesis conditions (Table 12b, entries 3-5). The trimethylsilyl moiety was not tolerated in the reaction, as only a poor yield of the alkyl aryl ether was isolable (Table 12b, entry 6). It is speculated that the fluorophilic silicon moiety reacted with the trifluoroborate component resulting in the decomposition of either or both substrates. Heterocyclic moieties can be tolerated as demonstrated by the arylation of furfuryl alcohol (**47s**) in excellent yields (Table 12b, entry 7). In another example of the mildness of the reaction conditions, the stereocentre present in ester **47t** was not racemized to any detectable degree while undergoing the arylation (Table

Table 12a - Copper-Catalyzed Arylation of Primary Aliphatic Alcohols[a]

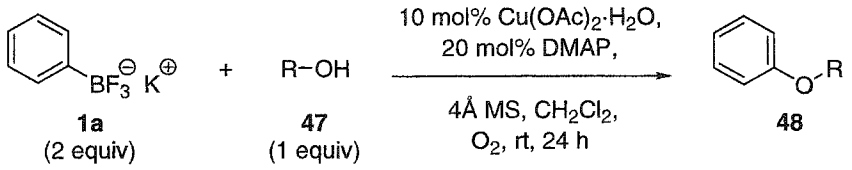


1a (2 equiv) + **47** (1 equiv) → **48**

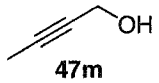
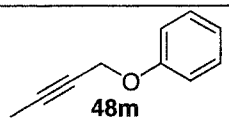
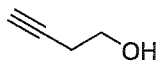
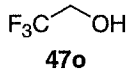
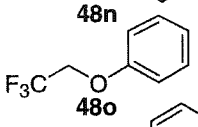
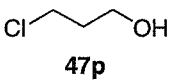
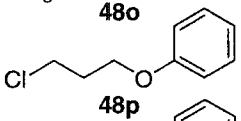
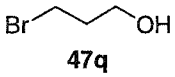
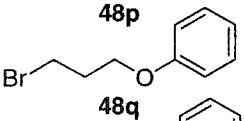
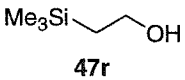
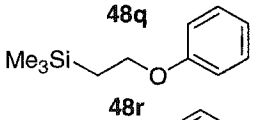
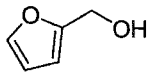
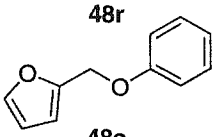
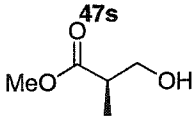
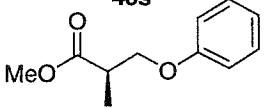
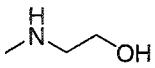
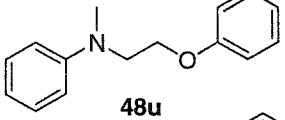
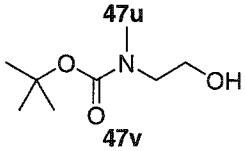
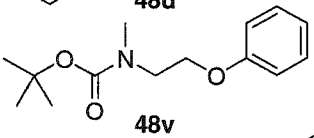
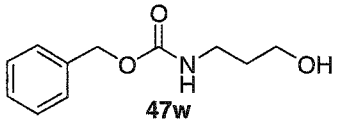
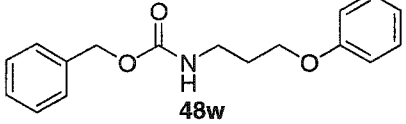
Entry	1° Alcohol	Product	Yield (%)[b]
1	 **47b**	 **48b**	78
2	 **47c**	 **48c**	95
3	 **47d**	 **48d**	71
4	 **47e**	 **48e**	94
5	 **47f**	 **48f**	75
6	 **47g**	 **48g**	80
7	 **47h**	 **48h**	93
8	 **47a**	 **48a**	89
9	 **47i**	 **48i**	74
10	 **47j**	 **48j**	83
11	 **47k**	 **48k**	83
12	 **47l**	 **48l**	87

a) reaction times are not optimized for individual substrates. b) isolated yields.

Table 12b - Copper-Catalyzed Arylation of Primary Aliphatic Alcohols[a]



1a (2 equiv) + **47** (1 equiv) → **48**

Entry	1° Alcohol	Product	Yield (%)[b]
1	 **47m**	 **48m**	91
2	 **47n**	 **48n**	61
3	 **47o**	 **48o**	82
4	 **47p**	 **48p**	95
5	 **47q**	 **48q**	93
6	 **47r**	 **48r**	25
7	 **47s**	 **48s**	90
8	 **47t**	 **48t**	90
9	 **47u**	 **48u**	30
10	 **47v**	 **48v**	93
11	 **47w**	 **48w**	85

a) reaction times are not optimized for individual substrates. b) isolated yields.

12b, entry 8). Finally, free N-H moieties were not tolerated in the cross-couplings as competing arylation on both the oxygen and nitrogen moieties was observed (Table 12b, entry 9). However, if the amine was selectively protected, then reaction of the hydroxyl group could occur in good to excellent yields without further complication (Table 12b, entries 10 and 11).

Secondary alcohols did not fare as well in the cross-coupling as the reaction was found to be sensitive to steric hindrance around the hydroxyl moiety. Though not as reactive as primary alcohols, the corresponding alkyl aryl ethers from secondary alcohols were still isolated in moderate to good yields (Table 13, entries 1-4). In addition, the steroid stigmasterol (**49e**) was arylated in 49 % yield, thus demonstrating that this methodology would be applicable to the synthesis of complex molecules (Table 13, entry 5). However, not all substrates were able to undergo the arylation reaction. The highly electron deficient 1,1,1,3,3,3-hexafluoropropanol (**51**) showed no reactivity in the cross-coupling, neither did the sterically hindered (±)-menthol (**52**). Unsurprisingly, tertiary alcohols like **53** did not react either.

As with the secondary alcohols, arylation of phenolic substrates was met with varying degrees of success. The reaction has to contend with both the steric hindrance around the hydroxyl moiety as well as the electronic properties of the molecule. While the arylation of *p*-cresol (**49f**) proceed smoothly, a more electron deficient substrate like 4-cyanophenol (**49g**) gave a poor yield of the corresponding diaryl ether (Table 13, entries 6 and 7). As expected, the phenol-like pyrones **54** and **55** gave none of the desired aryl ether.

In the final class of unreactive substrates are those molecules with highly coordinating

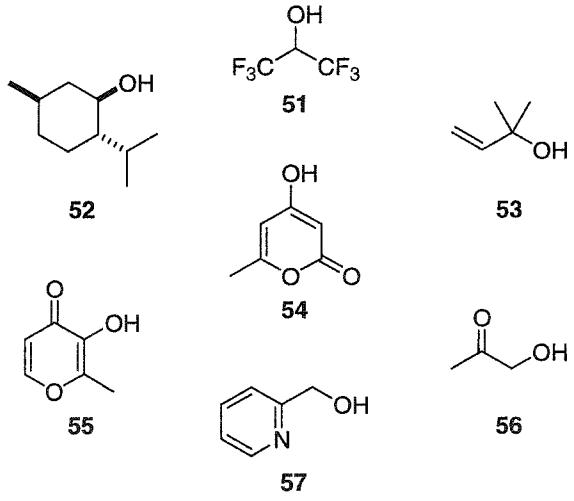
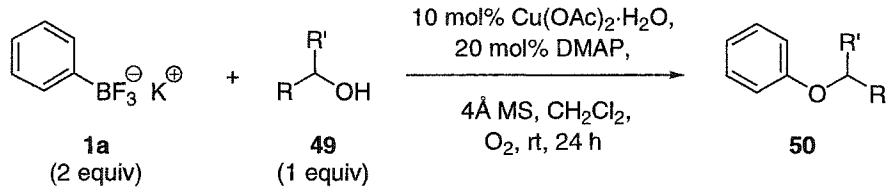


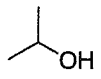
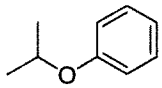
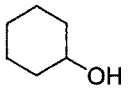
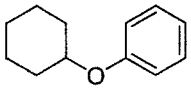
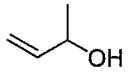
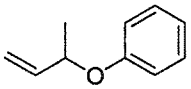
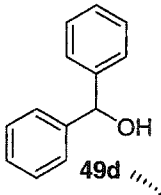
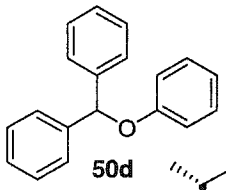
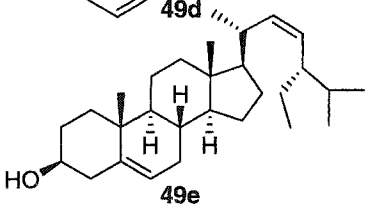
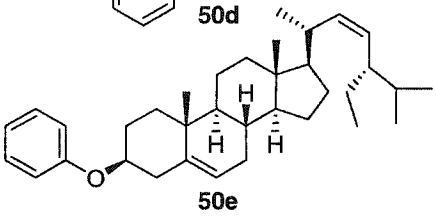
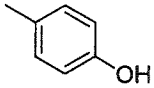
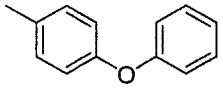
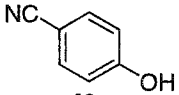
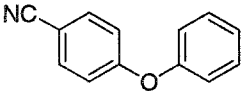
Figure 16 - Unreactive Substrates in Copper-Catalyzed Arylations

functional groups within close proximity, usually in the α or β position, of the reactive hydroxyl moiety (e.g. **55**, **56** and **57**, Figure 16). These substrates coordinate too tightly to the copper catalyst and do not permit the reaction to proceed. Unlike the amine substrates containing proximal coordinating functional groups which will undergo the arylation at higher temperatures (*vide* III.2.2.2), these oxygen-based compounds showed no reactivity at all.

Table 13 - Copper-Catalyzed Arylation of Secondary Aliphatic Alcohols and Phenols[a]



1a (2 equiv) + **49** (1 equiv) → **50**

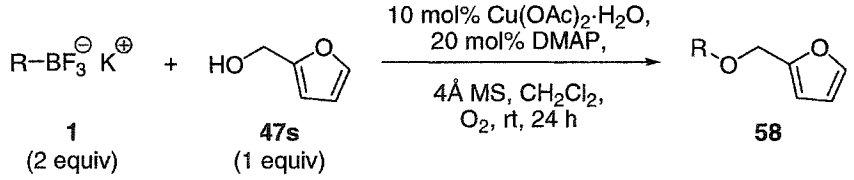
Entry	2° Alcohol	Product	Yield (%)[b]
1	 **49a**	 **50a**	71
2	 **49b**	 **50b**	67
3	 **49c**	 **50c**	69
4	 **49d**	 **50d**	75
5	 **49e**	 **50e**	48
6	 **49f**	 **50f**	82
7	 **49g**	 **50g**	15

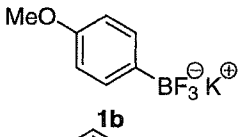
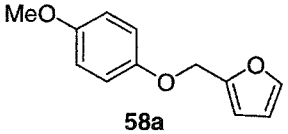
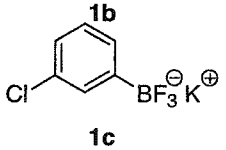
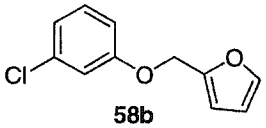
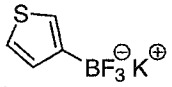
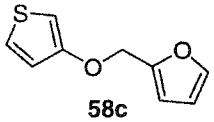
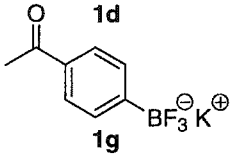
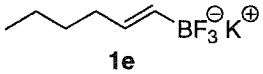
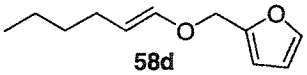
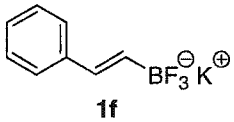
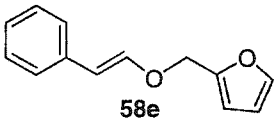
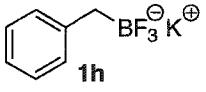
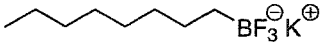
a) reaction times are not optimized for individual substrates. b) isolated yields.

II.2.1.3 Scope and Limitations of the Organoboron Component

Furfuryl alcohol (**47s**) was used as the alcohol standard in order to probe the limitations of the trifluoroborate component of the reaction. The electron-rich potassium 4-methoxyphenyltrifluoroborate was found to readily participate in the cross-coupling to provide a quantitative yield of the corresponding alkyl aryl ether **58a** (Table 14, entry 1). In contrast, electron-deficient aryltrifluoroborates gave much poorer results. The highly electron-deficient

Table 14 - Scope of Borate Component in Copper-Catalyzed Etherifications



Entry	Borate	Product	Yield[b]
1	 **1b**	 **58a**	quant.
2	 **1c**	 **58b**	71[c]
3	 **1d**	 **58c**	76
4	 **1g**	-	-
5	 **1e**	 **58d**	55
6	 **1f**	 **58e**	61
7	 **1h**	-	-
8	 **1i**	-	-

a) reaction times are not optimized for individual substrates.
b) isolated yields. c) 48 h reaction time.

4-acetylphenyltrifluoroborate (**1g**) did not undergo the cross-coupling, and only unreacted starting materials were isolated at the end of the reaction period (Table 14, entry 4). A slightly less electron-deficient substrate, the inductively electron-withdrawing 3-chloro derivative (**1c**), was able to undergo the transformation, but reasonable yields of the aryl ether were achieved only after doubling the reaction time (Table 14, entry 2). Heterocyclic trifluoroborate salts were tolerated in the reaction as evidenced by the cross-coupling of potassium 3-thienyltrifluoroborate (**1d**; Table 14, entry 3). Alkenyltrifluoroborates reacted to provide the corresponding alkyl vinyl ethers in moderate yields (Table 14, entries 5 and 6). It is unclear whether the lower yields are due to the instability of the products towards isolation, or due to a lowered reactivity of the borate. Alkyltrifluoroborates did not react under these conditions to provide the resulting dialkyl ethers (Table 14, entries 7 and 8).

In the cases of the unreactive borates (i.e. Table 14, entries 2, 7 and 8), it is believed that the reaction failed at the transmetallation step of the catalytic cycle (*vide* IV.2.1). If the organic moiety on the trifluoroborate had successfully transferred to copper, but the cross-coupling with the alcohol component had been problematic, other side products should have been observed; namely the products of cross-coupling with water, or homocoupled and hydrodeborated products (Figure 17). However, isolation of all post-reaction species revealed only the unreacted alcohol and the corresponding boronic acids (generated via hydrolysis of the trifluoroborate during flash column chromatography) in near quantitative yields. Hence, a problematic transmetallation from boron to copper was concluded.

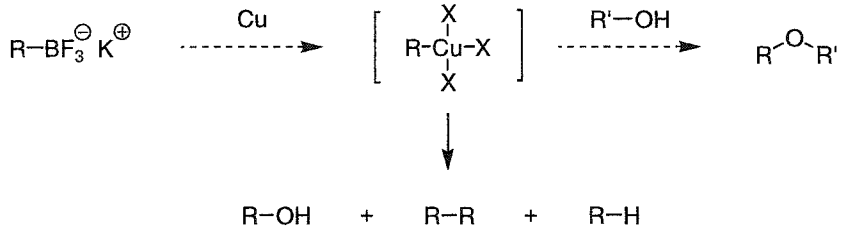
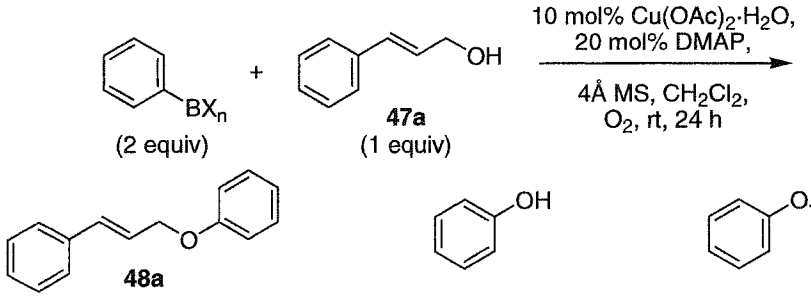


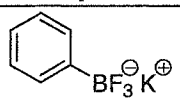
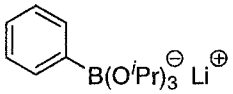
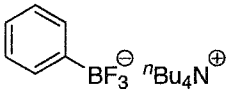
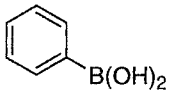
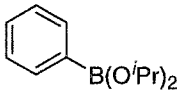
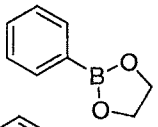
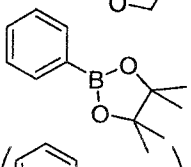
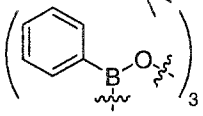
Figure 17 - Generation of Expected Side Products from an Organocuprate Intermediate

The type of organoboron compound used in the reaction also played an important role in the success of the transformation. A variety of organoboron compounds commonly used in synthesis were subjected to the optimized cross-coupling conditions with (*E*)-cinnamyl alcohol (**47a**). Over all potassium phenyltrifluoroborate gave the best yield of the aryl allyl ether with the least amount of by-products (Table 15, entry 1). In comparison, the other saturated borate salts

did not fair well in the reaction. The lithium trialkoxyborate was fairly unreactive providing only a low yield of the cross-coupled product, and little of the side products; however, it was not possible to recover the unreacted starting material (Table 15, entry 2). The tetra-*n*-butyl ammonium derivative was expected to react well under the optimized condition due to its greater solubility in CH_2Cl_2. Surprisingly, however, the salt gave no reaction whatsoever and complete

Table 15 - Various Organoboron Compounds in the Arylation of (*E*)-Cinnamyl Alcohol



Entry	Organoboron Compound	Yield of 48a (%)[a]	Yield of PhOH (%)[a]	Yield of Ph_2O (%)[a]	Starting Material (%)[a]
1		89	5	33	18
2		45	0	11	0
3		-	-	-	200
4		65	15	46	33
5		60	trace	20	40[b]
6		59	2	20	0[c]
7		11	trace	trace	36
8	 (0.66 equiv)	70	trace	trace	0

a) isolated yields; maximum total = 200 % (based on 2 equivalents of borane).
b) recovered 5 % of PhO^iPr. c) recovered 53 % of $(PhOCH_2)_2$.

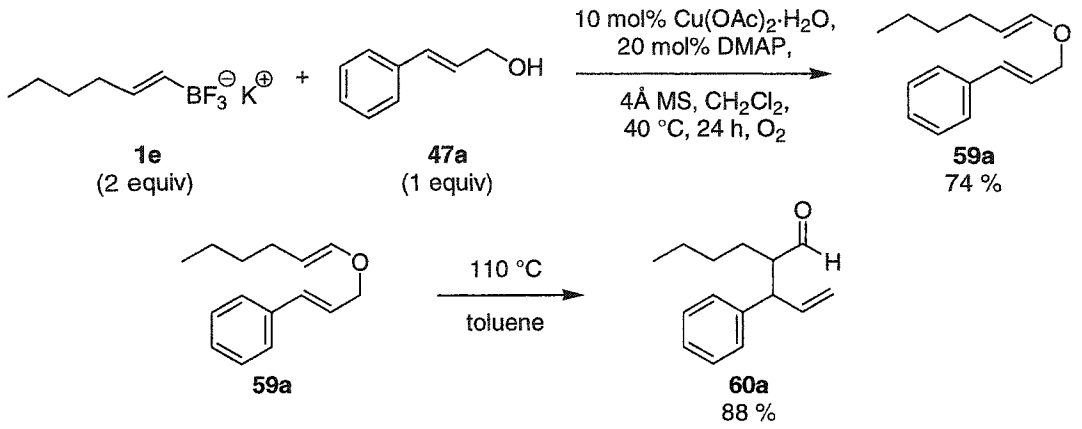
recovery of the unreacted starting material was possible. It is unclear why the reaction did not proceed, but later mechanistic studies have demonstrated that the transformation is highly intolerant of the presence of an ammonium cation (*vide* IV.2.2). The boronic acid was able to undergo the transformation, but gave greater amounts of the side products (Table 15, entry 4). It is speculated that the increased solubility of the boronic acid is actually detrimental to the overall reaction. If the arylation of water and phenol is faster than the reaction of the aliphatic alcohol then the presence of greater amounts of the boronic acid in solution would favour the formation of the side products. In addition, the trimerization of the boronic acids to form boroxines liberates water in the process; hence, increasing the chances of the undesired cross-couplings. Even reaction of the boronic acid in an anhydrous environment would not solve this problem as the formation of boroxines cannot be controlled. Indeed if the triphenylboroxine is preformed and then subjected to the reaction, a higher yield of the desired ether is obtained with only trace amounts of the side products present (Table 15, entry 8). In contrast, reaction of the less soluble trifluoroborate salts did not produce the excess water thereby resulting in lower yields of the side products.

Unsurprisingly, the boronate esters were able to undergo the cross-coupling. The most reactive substrates being the isopropanol and ethylene glycol derivatives (Table 15, entries 5 and 6); however, arylation of the alkoxide moieties were competitive with the main reaction. Finally, the pinacol derived boronate ester did not react well in the transformation. Steric hindrance by the multiple methyl substituents may have prevented the reagents interaction with the copper catalyst (Table 15, entry 7).

II.2.1.4 A Facile Route Toward Substrates for Claisen Rearrangements

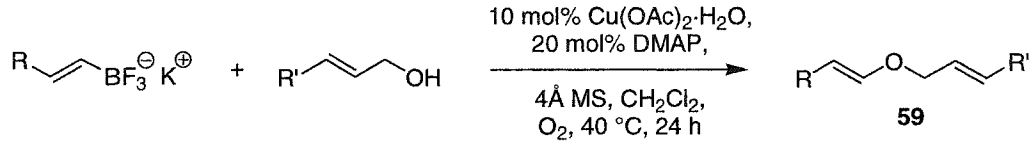
The discovery that alkenyltrifluoroborate salts could also be used in the copper-catalyzed cross-couplings led to the investigation of utilizing this protocol as a facile route towards allyl vinyl ethers (**59**), substrates for the [3,3]-sigmatropic Claisen rearrangement.[46] Indeed, initial experiments indicated that these ethers could be prepared via this cross-coupling strategy and could undergo [3,3]-sigmatropic rearrangement under thermal conditions (Scheme 50).

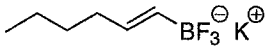
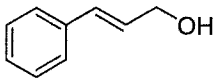
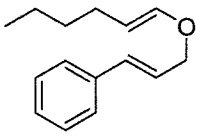
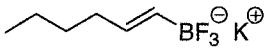
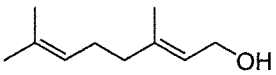
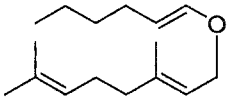
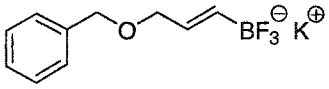
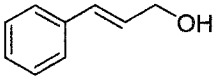
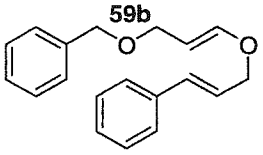
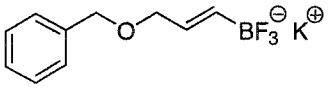
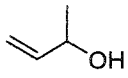
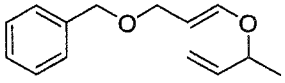
A small series of allyl vinyl ethers was prepared using this methodology to explore the versatility of the reaction. The reaction worked well for simple substrates (Table 16, entry 1);



Scheme 50 - Synthesis and Thermal Claisen Rearrangement of 1-Hexenyl-(*E*)-Cinnamyl Ether

Table 16 - Copper-Catalyzed Vinylation of Allylic Alcohols

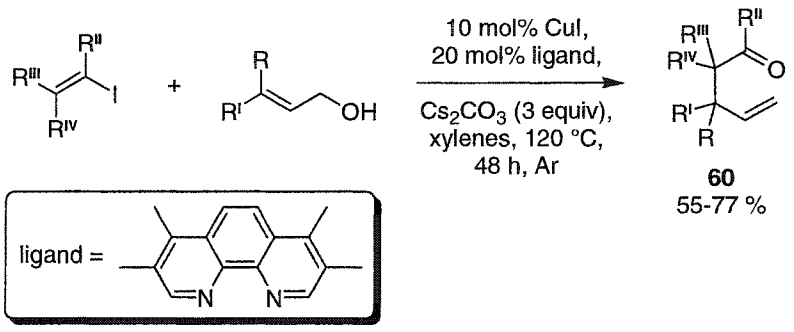


Entry	Borate	Alcohol	Product	Yield (%)[a]
1	 **1e**	 **47a**	 **59a**	74
2	 **1e**	 **47l**	 **59b**	48
3	 **1j**	 **47a**	 **59c**	30
4	 **1j**	 **49c**	 **59d**	28

a) isolated yields.

however, the isolated yields of more complex molecules dropped significantly (Table 16, entries 2-4). During the course of this investigation, Buchwald and Nordmann reported a one-pot copper-catalyzed domino allylic alcohol vinylation-Claisen rearrangement;[47] wherein vinyl

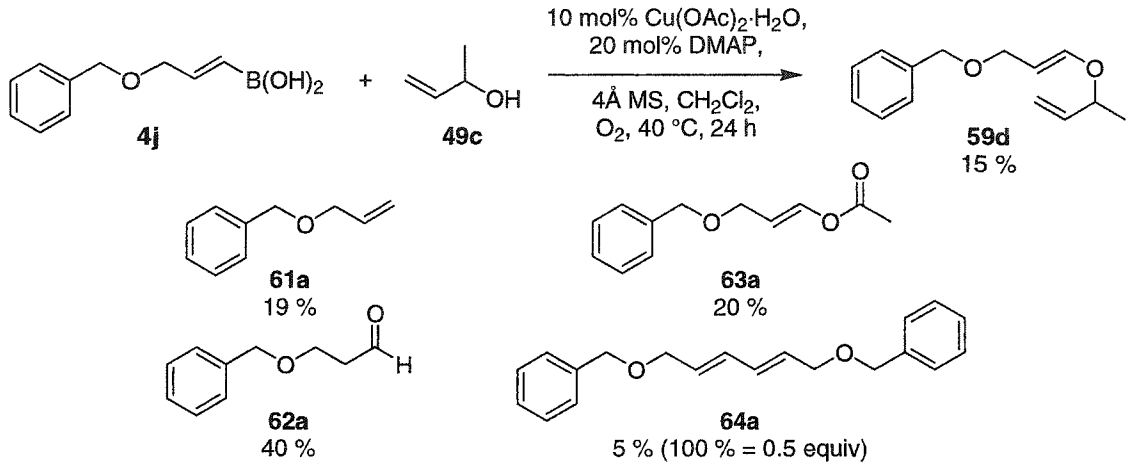
iodides were cross-coupled to allylic alcohols under copper-catalysis, the subsequent allyl vinyl ethers then underwent a thermal Claisen rearrangement to provide the corresponding γ-vinyl ketones or aldehydes (Scheme 51). Fortunately for us, analysis of the by-products from our less successful cross-coupling protocol led to other avenues of pursuit.



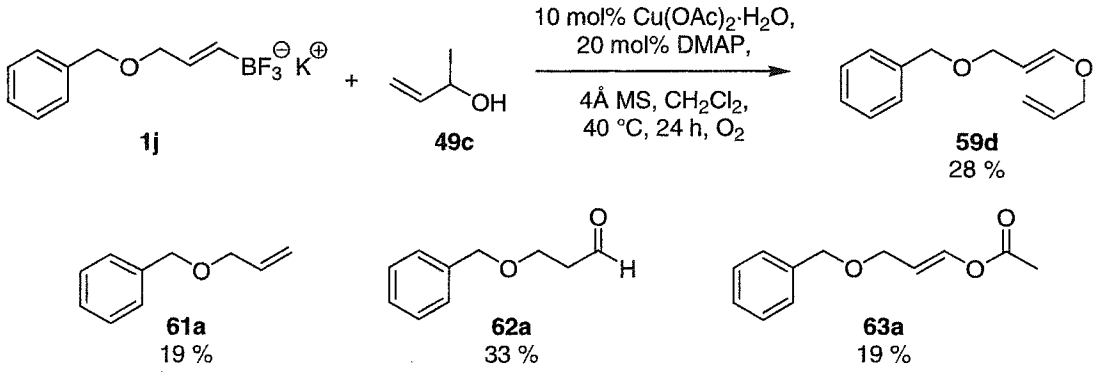
Scheme 51 - Copper-Catalyzed Domino Allylic Alcohol Vinylation-Claisen Rearrangement

II.2.2 Copper-Catalyzed Cross-Coupling of Organotrifluoroborate Salts with Carboxylates

Attempts to prepare substrate **59d** via the copper-catalyzed cross-coupling of 3-benzyloxy-1-propenylboronic acid and 3-buten-2-ol (**49e**) in good yield were unsuccessful under the previously established reaction conditions. Although good mass recovery from the reaction mixture was observed, the desired cross-coupled product was not the major component isolated (Scheme 52). Instead, no less than five compounds were recovered from the reaction mixture. The presence of allyl benzyl ether (**61a**) and 3-benzyloxypropionaldehyde (**62a**) can be rationalized by the hydrodeboration of the starting material, and vinylation of water followed by tautomerization of the resulting enol, respectively. The diene **64a** would have come from a homocoupling of the boronic acid starting material. Of greater interest is the isolation of the 3-benzyloxy-1-propenyl acetate (**63a**) which could only have resulted from the cross-coupling of the vinylboronic acid and the acetate ligands on the copper pre-catalyst. It should also be noted that similar results were obtained when potassium 3-benzyloxy-1-propenyltrifluoroborate was employed instead of the boronic acid, with the exception that the homocoupled product was not observed (Scheme 53).



Scheme 52 - Side Product Analysis of the Copper-Catalyzed Vinylation of 3-Buten-2-ol with 3-Benzyloxy-1-Propenylboronic Acid

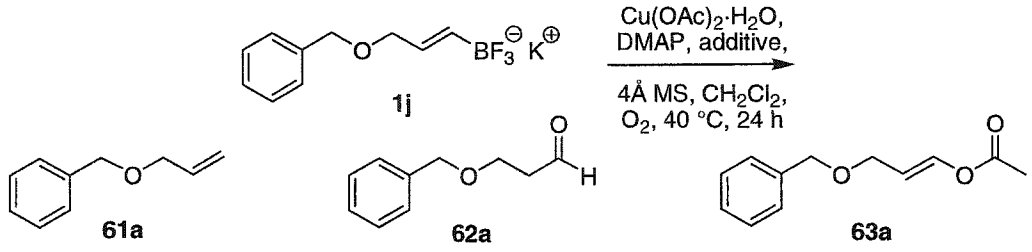


Scheme 53 - Side Product Analysis of the Copper-Catalyzed Vinylation of 3-Buten-2-ol with Potassium 3-Benzyloxy-1-Propenyltrifluoroborate

II.2.2.1 Optimization of the Reaction Conditions

An investigation was undertaken to optimize the yield of this transformation after having obtained proof-of-concept of this unprecedented cross-coupling between an organotrifluoroborate salt and a weakly nucleophilic carboxylate. Yields of the acetoxylated product could be increased by increasing the catalyst loading (Table 17, entry 2). However, the reaction employing a stoichiometric amount of the copper salt also required adding 2 equivalents of the DMAP ligand; as before the reaction mixture turned out to be a viscous sludge resulting in a decrease in the yield of the desired product (Table 17, entry 1). The addition of an external source of the acetate moiety demonstrated that the reaction could be catalytic in the copper salt (Table 17, entries 3-4). Reaction with the sodium salt was less effective than that of the potassium counterpart; perhaps the difference in solubility in CH_2Cl_2 between the salts distinguishes their reactivity.

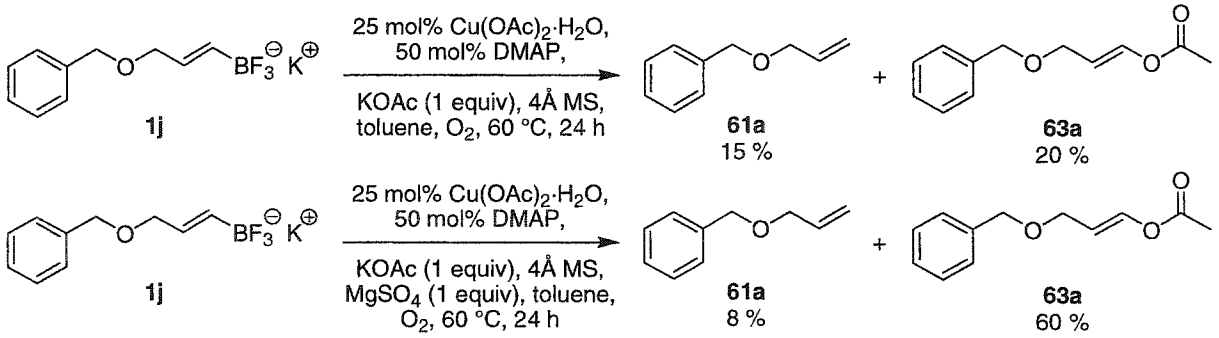
Table 17 - Optimization of Copper-Catalyzed Acetoxylation of Potassium Organotrifluoroborate Salts



Entry	Equivalents of $Cu(OAc)_2 \cdot H_2O$	Equivalents of DMAP	Additive	Yield of 61a (%)[a]	Yield of 62a (%)[a]	Yield of 63a (%)[a]
1	1.0	2.0	-	8	4	40
2	0.50	1.0	-	21	-	24
3	0.25	0.50	NaOAc (1.0 eq)	20	trace	11
4	0.25	0.50	KOAc (1.0 eq)	trace	-	61

a) isolated yields.

The reactions were performed in toluene with the temperature raised to 60 °C in hopes of increasing the reactivity; in addition, a desiccant was added to the reaction mixture in an attempt to decrease the amount of the hydrodeborated and aldehyde by-products produced (Scheme 54). As expected changing the medium did not improve the yields of this solvent-specific reaction; however, the use of freshly distilled toluene did reduce the formation of the aldehyde by-product (only trace amounts of the aldehyde were visible by ^{1}H-NMR of the crude reaction mixture). The use of 1 equivalent of $MgSO_4$ as a desiccant in addition to the molecular sieves aided the transformation tremendously; giving a yield similar to that of the reaction in CH_2Cl_2, but without the aldehyde by-product.



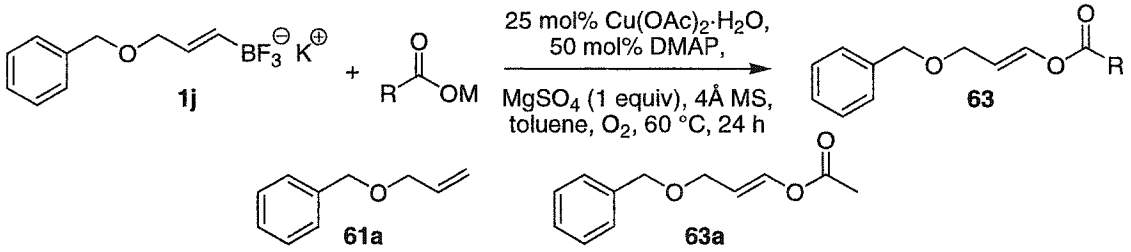
Scheme 54 - Attempts to Increase Reactivity while Decreasing By-product Formation

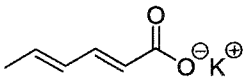
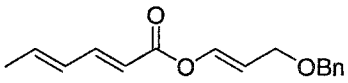
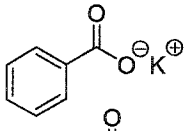
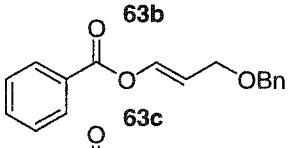
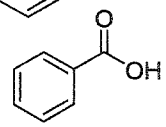
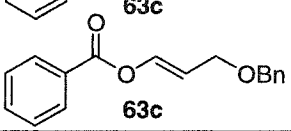
II.2.2.2 Scope and Limitations

At this point a series of potassium carboxylate salts (Table 18) and potassium organotrifluoroborate salts (Table 19) were employed as cross-coupling partners. The purpose of these experiments was two-fold: first, it needed to be established that this methodology was applicable to all forms of carboxylate cross-couplings and not limited only to the acetate moiety which was introduced as the copper salt pre-catalyst; second, the potassium 3-benzyloxy-1-propenyltrifluoroborate is an unusual cross-coupling partner, in that the oxygen atom γ to boron may be aiding the substrate's coordination to the copper catalyst. The cross-coupling needed to be proven with more "typical" organoboron compounds.

As before, reaction of potassium 3-benzyloxy-1-propenyltrifluoroborate with other carboxylate derivatives in the presence of $Cu(OAc)\cdot H_2O$/DMAP yielded three isolable products: the desired cross-coupled vinyl ester (**63**), the hydrodeborated starting material (**61a**), and the acetoxylated starting material (**63a**). Though the yields were moderate at best, it was established that this cross-coupling could be achieved (Table 18). In addition, but unsurprisingly, it was discovered that in the presence of an unactivated carboxylate (i.e. the free carboxylic acid) the reaction afforded mainly the hydrodeborated starting material.

Table 18 - Copper-Catalyzed Vinylation of Carboxylates and Carboxylic Acids

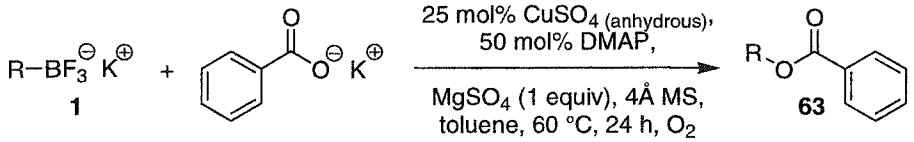


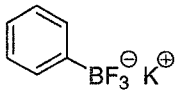
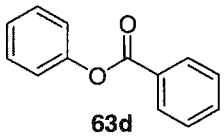
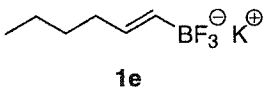
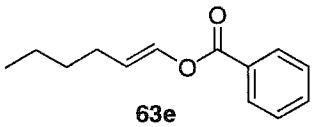
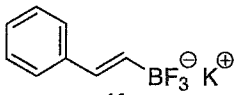
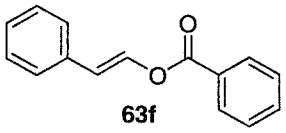
Entry	R-CO_2M	Product	Yield (%)[a]	Yield of 61a (%)[a]	Yield of 63a (%)[a]
1		 **63b**	52	8	20
2		 **63c**	50	6	28
3		 **63c**	13	41	7

a) isolated yield.

In the reactions of various trifluoroborate salts with potassium benzoate, $Cu(OAc)\cdot H_2O$ was replaced by anhydrous $CuSO_4$ in an attempt to minimize the amount of the acetoxyvinyl ester (**63a**) produced (Table 19). All the cross-couplings were successful, albeit in low yields; and the remainder of the reaction mixture was mainly unreacted starting material.

Table 19 - Early Attempts at Copper-Catalyzed Vinylation of Potassium Benzoate



Entry	Borate	Product	Yield (%)[a]
1	 **1a**	 **63d**	10
2	 **1e**	 **63e**	23
3	 **1f**	 **63f**	12

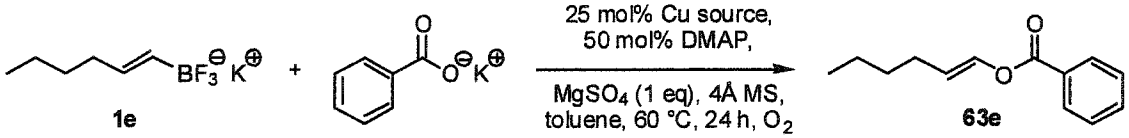
a) isolated yield.

II.2.2.3 Revisiting the Optimization Process

A series of reactions were performed to probe the effect of the copper source on the reaction yield. These reactions utilized potassium 1-hexenyltrifluoroborate as a more common representative of the trifluoroborate salts. Copper sources from all three commercially available copper oxidation states (i.e. Cu(0), Cu(I) and Cu(II)) were employed. The copper(I) salts (Table 20, entries 1-7) appeared to be slightly greater yielding than the copper(II) salts (Table 20, entries 9-14), but the differences were minor. Interestingly, copper(0) powder also worked in the reaction; however, it is possible that the metal had oxidized over time, thereby containing various amounts of the other copper species (Table 20, entry 8). The results suggest that the reaction is not catalytic in copper, or that little or no catalytic turnover is achieved under these conditions. It should also be noted that none of the copper species were soluble in toluene at room temperature,

but upon heating the salts do eventually dissolve as evidenced by the slow colour change in the reaction mixture over time (Figures 18a and 18b).

Table 20 - The Effect of Various Copper Salts on the Copper-Catalyzed Vinylation of Potassium Benzoate



1e 63e

Entry	Cu Source	Yield (%)[a]	Entry	Cu Source	Yield (%)[a]
1	Cu_2O	20	8	Cu (powdered)	17
2	CuCl	32	9	$CuSO_4 \cdot 5H_2O$	26
3	CuBr	35	10	$CuSO_4$ anhydrous	23
4	CuBr·DMS	26	11	$CuBr_2$	11
5	CuI	25	12	$CuCl_2$	19
6	CuCN	20	13	$Cu(acac)_2$	17
7	CuSCN	21	14	$Cu(OTf)_2$	30

a) isolated yield.

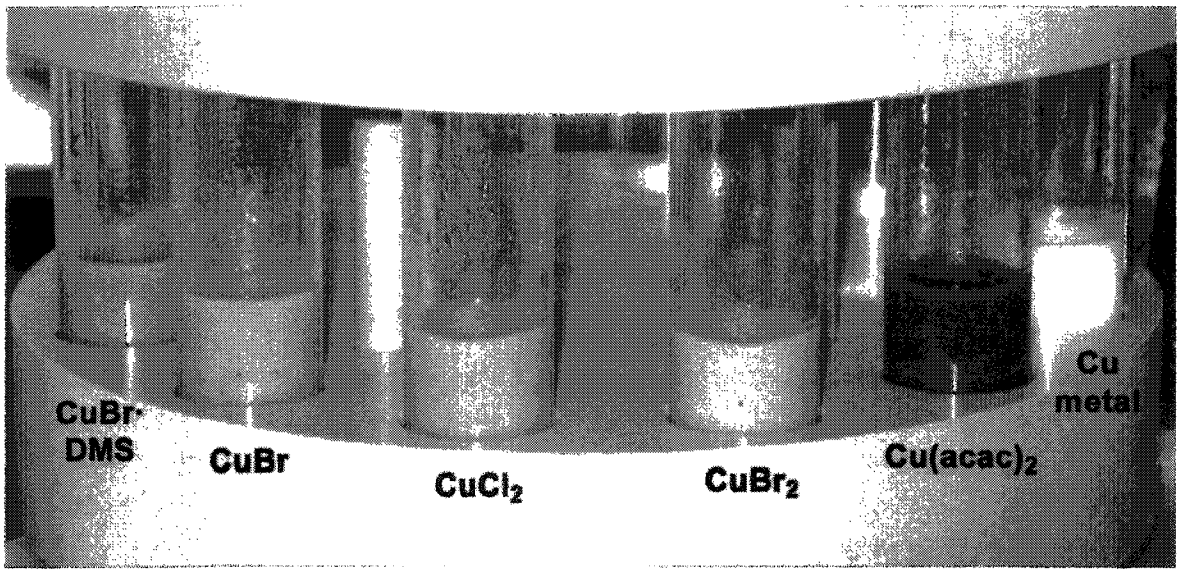


Figure 18a - Colorimetric Comparison of Various Copper Salts Interacting with DMAP in Toluene

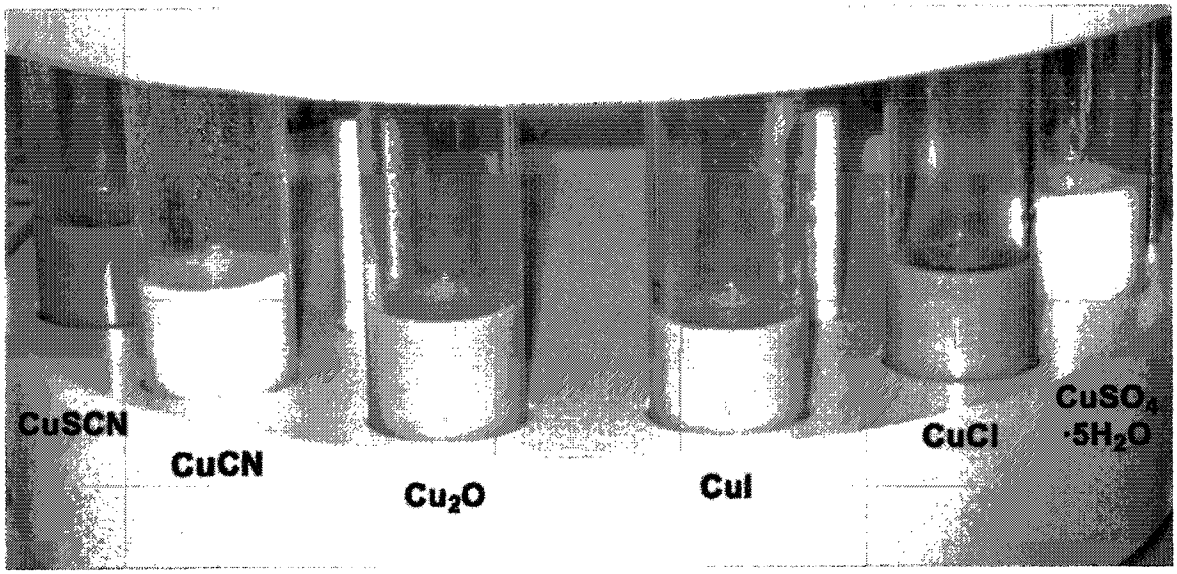
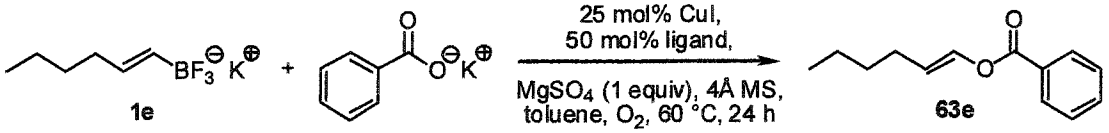


Figure 11b - Colorimetric Comparison of Various Copper Salts Interacting with DMAP in Toluene

Like that of the alcohol arylation reactions, the ligand used in the reaction proved to have a greater effect on the outcome than the choice of copper species. In fact, only the DMAP and TMEDA ligands gave any appreciable yield of the vinyl ester (Table 21, entries 3 and 6). Triethylamine, 1,10-phenanthroline and pyridine gave trace amounts of the product visible by TLC but not isolable (Table 21, entries 1, 4 and 5), and DIPEA and imidazole gave no reaction at all (Table 21 entries 2 and 7). This profound difference in reactivity was unlike that observed in

Table 21 - Optimization of Ligand for Copper-Catalyzed Vinylation of Potassium Benzoate



Entry	Ligand	Yield (%)[a]
1	Et_3N	trace
2	DIPEA	-
3	TMEDA (25 mol %)	7
4	1,10-phenanthroline (25 mol %)	trace
5	pyridine	trace
6	DMAP	25
7	imidazole	-

a) isolated yields.

the previous work with the alcohol cross-couplings. In addition, the various choices of ligands produced differently coloured reaction mixtures (Figures 19a and 19b).

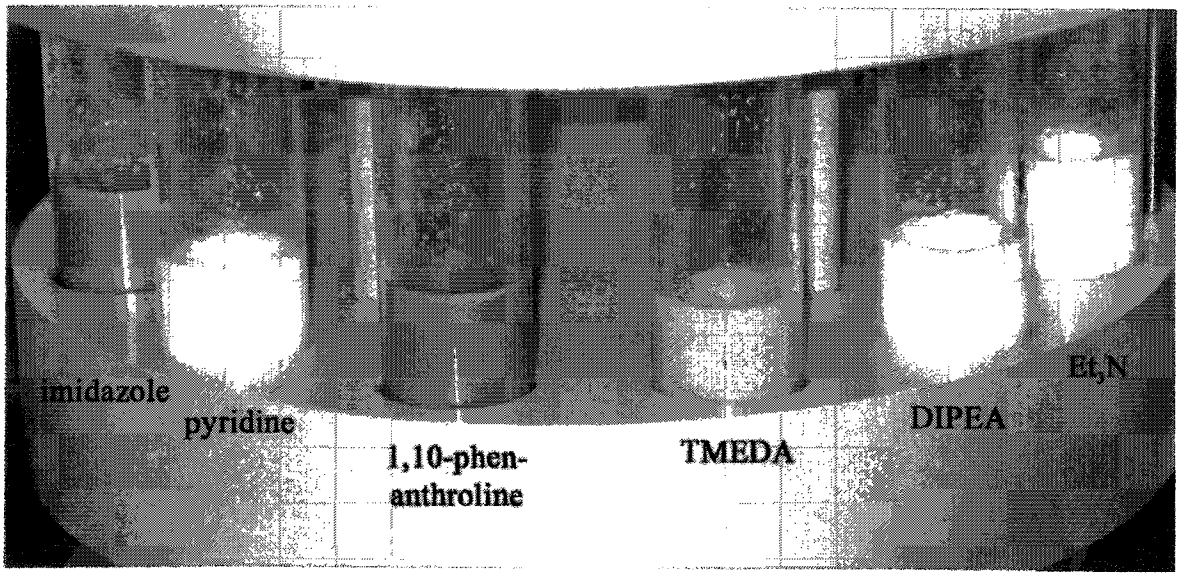


Figure 19a - Colorimetric Comparison of Various Nitrogen-Based Ligands Interacting with CuI in Toluene

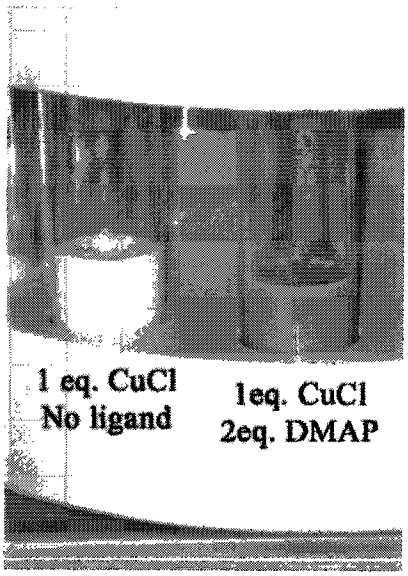


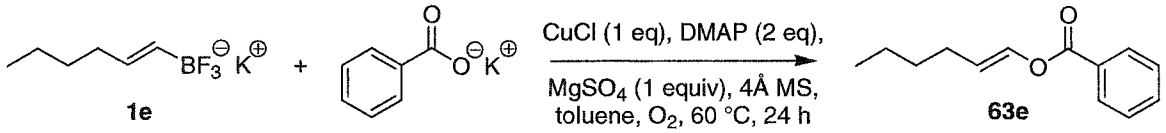
Figure 19b - Colorimetric Comparison of Various Nitrogen-Based Ligands Interacting with CuCl in Toluene

Continuing with the hypothesis that the reaction required a stoichiometric amount of copper, the copper loading was increased to one full equivalent with 2 equivalents of DMAP as ligand. Unfortunately, under the standard volume of solvent used the reaction mixture was a

very viscous sludge. As a result, the yield dropped significantly from what would have been expected (Table 22, entry 1). A series of experiments were run in an attempt to rectify this apparent problem. Although a slight trend relating the reaction yield to the dilution of the reaction mixture was observed, the yields were never greater than those of the catalytic reactions. Dilution of the copper/ligand concentration may have been beneficial for mechanical agitation of the reaction, but the resulting dilution of substrate concentrations may have countered this advantage.

As it currently stands this protocol for the preparation of vinyl esters is a work in progress. The reactions conditions are far from optimized, but proof-of-concept that this type of cross-coupling is possible has been achieved. It should also be noted that the $Cu(OAc)_2 \cdot H_2O$-catalyzed reactions gave the highest yields of the cross-coupled products in a catalytic capacity, despite the generation of the acetoxylated starting materials. Perhaps it is still the best copper source for the reaction, and the use of multiple equivalents of the trifluoroborate salt may compensate for the need to sacrifice a portion of the starting material.

Table 22 - The Effect of Reaction Mixture Concentration on the Copper-Mediated Vinylation of Potassium Benzoate



Entry	Solvent Volume (mL)	Concentration of Cu (mol/L)	Dilution Factor	Yield (%)[a]
1	4.0	0.130	1	10
2	8.0	0.065	2	13
3	12.0	0.043	3	18
4	16.0	0.033	4	20
5	20.0	0.026	5	22
6	24.0	0.022	6	23

a) isolated yields.

II.2.3 Conclusions and Continuing Work

A new protocol for the copper-catalyzed cross-coupling of potassium organotrifluoroborate salts with unactivated alcohols under mild and essential neutral reaction conditions has been developed. A variety of primary and secondary alcohols containing various functional groups have been demonstrated to undergo the reaction to form aryl alkyl ethers without complications. Secondary alcohols in general afforded lower yields than the primary alcohols as the reaction is sensitive to steric hindrance around the reactive hydroxyl moiety. Tertiary alcohols did not participate in the cross-coupling. Alkenyl isomerization and stereocentre racemization of the starting materials were not detected. The reaction, however, is not without some minor limitations. It is intolerant of competing nucleophilic moieties in the reaction mixture. For example, free N-H groups will also undergo the cross-coupling reaction. However, prior protection of these functional groups will allow the hydroxyls to react freely. In addition, substrates with highly coordinating functional groups within close proximity to the reactive hydroxyl centre will bind too tightly to the copper catalyst for reaction to occur. Both electron-rich or electronically neutral potassium aryl- and vinyltrifluoroborates were able to undergo the cross-coupling, but electron-poor potassium aryl- and alkyltrifluoroborate salts did not.

Proof-of-concept has been obtained for the copper-mediated/catalyzed cross-coupling of organotrifluoroborate salts with activated carboxylates to form vinylated esters. Currently, the reaction is plagued by side product formation including the hydrodeboration of the starting material and cross-coupling with water. Early examples suggest that both aryl- and vinyltrifluoroborate salts can undergo the cross-coupling. The reaction conditions have not been optimized for general utilization of this protocol, but the concept of this strategy for the preparation of esters, especially vinylic esters, is novel and certainly warrants further study.

Mechanistic investigations have been initiated to understand the nature of these copper-mediated cross-couplings. These results are discussion in detail in Chapter 4.

II.3 Experimental Procedures

II.3.1 General Synthetic Methods

MeCN and CH_2Cl_2 were distilled from CaH_2 under argon. Toluene, THF and Et_2O were distilled from sodium metal/benzophenone ketyl under argon. All other commercial solvents and reagents were used as received from the Aldrich Chemical Company, Fischer Scientific Ltd., Strem or BDH. All glassware was oven dried at 210 °C and allowed to cool under a stream of dry nitrogen for air-sensitive reactions, or cooled in open air for reactions performed under oxygen or under an open atmosphere. Oxygen gas (UHP/zero grade) was purchased from Air Products and dried through a column of Drierite (anhydrous $CaSO_4$) prior to connection to a manifold for delivery into the reaction flask. The gas is delivered through Tygon tubing fitted with a 20 gauge needle at an approximate flow rate of 38 mL/min. A bubbler (filled with silicon oil) was connected to the reaction vessels to prevent build-up of oxygen pressure during the reaction period.

Silica gel (60 Å, 230-400 mesh) used in flash column chromatography was obtained from Silicycle and was used as received. Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel plates (Ultra Pure Silica Gel Plates purchased from Silicycle), visualized with a Spectroline UV_{254} lamp, and stained with a 20 % phosphomolybdic acid in ethanol solution. Solvent systems associated with R_f values and flash column chromatography are reported as v/v ratios.

Melting points were obtained using a Fisher-Johns melting point apparatus, and are uncorrected. ^1H and ^{13}C NMR were recorded at 400 or 300 MHz and 100 or 75 MHz respectively on Varian Unity 400, Gemini 300 or Mercury 300 spectrometers. Proton chemical shifts were internally referenced to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), D_2O (δ 4.79 ppm) or CD_3CN (δ 1.94 ppm). Carbon chemical shifts were internally referenced to the dueterated solvent signals in $CDCl_3$ (δ 77.20 ppm). FT-IR spectra were recorded on a Perkin-Elmer Spectrum 1000, with samples loaded as neat films on NaCl plates or as pressed KBr discs. Low and high resolution mass spectra were recorded on a Bell and Howell 21-490 spectrometer and an AEI MS3074 spectrometer respectively.

References following the compounds names indicate literature articles where ^1H and/or ^{13}C NMR data have been previously reported.

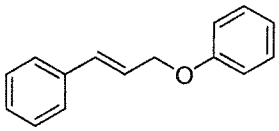
II.3.2 Synthetic Methods and Characterization Data of Aryl- / Alkenylated Alcohols and Phenols

Representative Procedure for the Cross-Coupling of Potassium Phenyltrifluoroborate (1a) with Aliphatic Alcohols (47)

A suspension of $PhBF_3^-K^+$ (0.368 g, 2.00 mmol), $Cu(OAc)_2 \cdot H_2O$ (20.0 mg, 0.100 mmol), DMAP (25.0 mg, 0.200 mmol) and powdered 4Å molecular sieves (0.750 g) in CH_2Cl_2 (8.00 mL) was stirred for 5 minutes at room temperature. To this stirring suspension was added (*E*)-cinnamyl alcohol (0.134 g, 1.00 mmol). The stirred reaction mixture was then sealed with a rubber septum under a blanket atmosphere of oxygen. Following a period of 24 h, the crude reaction mixture was filtered through a plug of Celite to remove the molecular sieves and any insoluble by-products, and then concentrated *in vacuo* to afford the crude product mixture. The product (**48a**) was isolated by silica gel column chromatography (eluting with hexanes:EtOAc 9:1 ~ 3:1 gradient) as a white crystalline solid in 89 % yield (0.188 g, 0.890 mmol).

Products of Experiments Summarized in Tables 12a & 12b

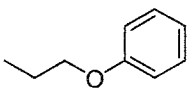
(*E*)-Cinnamylphenyl ether (48a) (Keinan, E.; Sahai, M.; Roth, Z. *J. Org. Chem.* **1985**, *50*, 3558-3566.)



48a

Isolated as a white, crystalline solid in 89 % yield: R_f = 0.6 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (2H, d, *J* = 7.0 Hz), 7.44 - 7.28 (5H, m), 7.11 - 6.95 (3H, m), 6.80 (1H, d, *J* = 16.0 Hz), 6.48 (1H, dt, *J* = 16.0, 6.0 Hz), 4.75 (2H, dd, *J* = 6.0, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 136.5, 133.1, 129.6, 128.7, 128.0, 126.7, 124.6, 121.0, 114.9, 68.8.

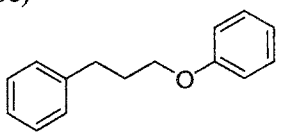
Phenylpropyl ether (48b) (Chen, C. T.; Marder, S. R.; Cheng, L. T. *J. Am. Chem. Soc.* **1994**, *116*, 3117-3118.)



48b

Isolated as a clear liquid in 78 % yield: R_f = 0.8 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 - 7.28 (2H, m), 7.00 - 6.90 (3H, m), 3.95 (2H, t, *J* = 7.0 Hz), 1.85 (2H, sextet, *J* = 7.0 Hz), 1.09 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.0, 129.4, 120.5, 114.5, 69.6, 23.0, 11.0.

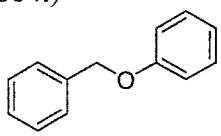
Phenyl-(3-phenylpropyl) ether (48c)



48c

Isolated as a light yellow oil in 95 % yield: R_f = 0.7 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 - 7.24 (7H, m), 7.04 - 6.94 (3H, m), 4.03 (2H, t, *J* = 6.5 Hz), 2.90 (2H, t, *J* = 7.5 Hz), 2.22-2.14 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.8, 141.5, 129.4, 128.5, 128.4, 125.9, 120.6, 114.5, 66.9, 32.5, 31.2; IR (film) ν 3062, 3027, 2946, 2870, 1736, 1600, 1586, 1497, 1470, 1454, 1389, 1301, 1246, 1172, 1080, 1039, 940, 882, 806, 752 cm^{-1}; LRMS (EI): *m/z* = 213 (12), 212 (67), 119 (21), 118 (80), 117 (44), 94 (22), 92 (12), 91 (100); HRMS (EI): *m/z* calcd. for ($C_{15}H_{16}O^+$) = 212.1201, found = 212.1206.

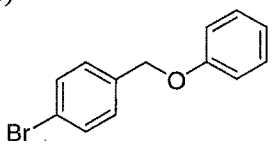
Benzylphenyl ether (48d) (Forrester, J.; Jones, R. V. H.; Newton, L.; Preston, P. N. *Tetrahedron* **2001**, *57*, 2871-2884.)



48d

Isolated as a white, crystalline solid in 71 % yield: R_f = 0.7 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 - 7.25 (7H, m), 7.02 - 6.93 (3H, m), 5.09 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 137.1, 129.5, 128.6, 127.9, 127.5, 121.0, 114.9, 70.1.

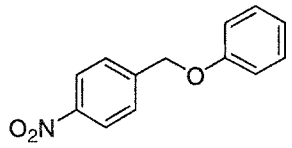
(4-Bromobenzyl)phenyl ether (48e)



48e

Isolated as a white, crystalline solid in 94 % yield: R_f = 0.5 (3:1 hexanes:toluene); mp = 91 - 92 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52 (2H, d, *J* = 8.0 Hz), 7.34 - 7.25 (4H, m), 7.02 - 6.94 (3H, m), 5.03 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.4, 136.1, 131.7, 129.5, 129.1, 121.2, 121.2, 114.8, 69.4; IR (film) ν 3080, 3048, 2922, 2878, 1916, 1600, 1490, 1456, 1406, 1384, 1240, 1079, 1032, 1016, 994, 871, 811, 753, 691 cm^{-1}; LRMS (EI): *m/z* = 264 (21), 262 (22), 172 (12), 171 (98), 170 (14), 169 (100), 90 (30); HRMS (EI): *m/z* calcd. for ($C_{13}H_{11}BrO^+$) = 261.9993, found = 261.9994.

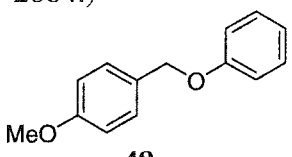
(4-Nitrobenzyl)phenyl ether (48f) (Maslak, P.; Guthrie, R. D. *J. Am. Chem. Soc.* **1986**, *108*, 2628-2636.)



48f

Isolated as a white, crystalline solid in 75 % yield: R_f = 0.3 (9:1 hexanes:toluene); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (2H, d, *J* = 8.5 Hz), 7.61 (2H, d, *J* = 8.5 Hz), 7.32 (2H, t, *J* = 7.5 Hz), 7.05 - 6.96 (3H, m), 5.19 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.0, 147.4, 144.5, 129.6, 127.5, 123.8, 121.5, 114.8, 68.7; LRMS (EI): *m/z* = 230 (23), 229 (93), 137 (15), 136 (100), 106 (42), 90 (28); HRMS (EI): *m/z* calcd. for ($C_{13}H_{11}NO_3^+$) = 229.0739, found = 229.0734.

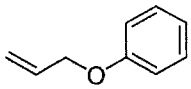
(4-Methoxybenzyl)phenyl ether (48g) (Forrester, J.; Jones, R. V. H.; Newton, L.; Preston, P. N. *Tetrahedron* **2001**, *57*, 2871-2884.)



48g

Isolated as a white, crystalline solid in 80 % yield: R_f = 0.4 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 - 7.28 (4H, m), 7.03 - 6.92 (5H, m), 5.01 (2H, s), 3.84 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.3, 158.7, 129.4, 129.2, 129.1, 120.9, 114.9, 114.0, 69.9, 55.5.

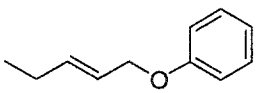
Allylphenyl ether (48h) (Annunziata, A.; Galli, C.; Marinelli, M.; Pau, T. *Eur. J. Org. Chem.* **2001**, *7*, 1323-1330.)



48h

Isolated as a clear oil in 93 % yield: R_f = 0.8 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 - 7.28 (2H, m), 7.00 - 6.91 (3H, m), 6.09 (1H, ddt, *J* = 17.5, 10.5, 5.5 Hz), 5.44 (1H, dd, *J* = 17.5, 1.5 Hz), 5.31 (1H, dd, *J* = 10.5, 1.5 Hz), 4.55 (2H, dt, *J* = 5.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 133.5, 129.6, 121.0, 117.7, 114.8, 68.8.

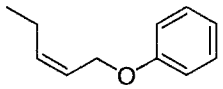
(*E*)-Pent-2-enylphenyl ether (48i)



48i

Isolated as a clear oil in 74 % yield: R_f = 0.4 (3:1 hexanes:toluene); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (2H, d, *J* = 8.0 Hz), 6.98 - 6.90 (3H, m), 5.91 (1H, dt, *J* = 15.5, 6.0 Hz), 5.72 (1H, ddd, *J* = 15.5, 6.0, 1.0 Hz), 4.49 (2H, dd, *J* = 6.0, 1.0 Hz), 2.14 (2H, qdd, *J* = 7.5, 7.5, 1.0 Hz), 1.06 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.6, 137.1, 129.4, 123.8, 120.7, 114.7, 68.9, 25.7, 13.6; IR (film) ν 2964, 1600, 1496, 1461, 1381, 1301, 1241, 1172, 1078, 1030, 1011, 968, 881, 753, 691 cm^{-1}; LRMS (EI): *m/z* = 162 (8), 95 (12), 94 (100), 77 (8); HRMS (EI): *m/z* calcd. for ($C_{11}H_{14}O^+$) = 162.1045, found = 162.1037.

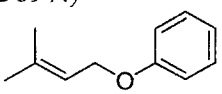
(Z)-Pent-2-enylphenyl ether (48j)



48j

^{1}H NMR analysis of the starting material reveals a 1:20 ratio of E:Z geometric isomers which is carried through to the cross-coupled products. Isolated as a clear oil in 83 % yield: R_f = 0.6 (3:1 hexanes:toluene); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 - 7.25 (2H, m), 6.98 - 6.90 (3H, m), 5.70 - 5.65 (2H, m), 4.60 (2H, d, *J* = 5.5 Hz), 2.23 - 2.15 (2H, m), 1.05 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.6, 136.0, 129.4, 124.2, 120.7, 114.7, 64.0, 21.5, 14.5; IR (film) ν 3028, 2965, 2874, 1600, 1586, 1496, 1300, 1242, 1172, 1078, 1031, 1011, 991, 881, 753, 691 cm^{-1}; LRMS (EI): *m/z* = 162 (30), 95 (12), 94 (100), 77 (13).

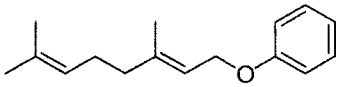
(3-Methylbut-2-enyl)phenyl ether (48k) (Johnston, B. D.; Czyzewska, E.; Oehlschlager, A. C. *J. Org. Chem.* **1987**, *52*, 3693-3697.)



48k

Isolated as a clear oil in 83 % yield: R_f = 0.8 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 - 7.25 (2H, m), 7.15 - 6.92 (3H, m), 5.53 (1H, tt, *J* = 7.0, 1.0 Hz), 4.43 (2H, d, *J* = 7.0 Hz), 1.83 (3H, s), 1.78 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 138.0, 129.4, 120.6, 119.8, 114.7, 64.9, 26.2, 18.6.

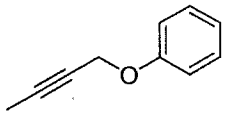
Geranylphenyl ether (48l) (Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131-8140.)



48l

Isolated as a clear oil in 87 % yield: R_f = 0.6 (4:1 hexanes:toluene); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 - 7.26 (2H, m), 7.00 - 6.91 (3H, m), 5.53 (1H, tq, *J* = 7.0, 1.5 Hz), 5.18 - 5.00 (1H, m), 4.57 (2H, d, *J* = 6.0 Hz), 2.23 - 2.08 (4H, m), 1.78 (3H, s), 1.73 (3H, s), 1.66 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 140.9, 131.7, 129.3, 123.8, 120.6, 119.6, 114.7, 65.0, 39.9, 26.7, 26.0, 18.1, 17.0.

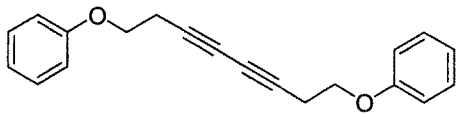
(2-Butynyl)phenyl ether (48m) (Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218-4227.)



48m

Isolated as a clear oil in 92 % yield: R_f = 0.7 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (2H, t, *J* = 7.5 Hz), 7.02 - 6.94 (3H, m), 4.66 (2H, q, *J* = 2.0 Hz), 1.88 (3H, t, *J* = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 129.4, 121.2, 114.8, 83.8, 74.3, 56.6, 4.1.

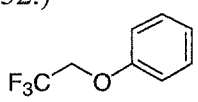
1,8-diphenoxy-octa-3,5-diyne (48n)



48n

Isolated as a beige, needle-like, crystalline solid in 61 % yield: R_f = 0.7 (9:1 hexanes: EtOAc); mp = 133 - 135 °C (hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (4H, t, *J* = 8.0 Hz), 6.96 (2H, t, *J* = 8.0 Hz), 6.89 (4H, d, *J* = 8.0 Hz), 4.09 (4H, t, *J* = 7.0 Hz), 2.76 (4H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.2, 129.5, 121.2, 114.7, 74.1, 66.8, 65.8, 20.7; IR (film) ν 2936, 1597, 1499, 1470, 1390, 1304, 1246, 1176, 1082, 1041, 883, 812, 752, 689 cm^{-1}; LRMS (EI): *m/z* = 291 (18), 290 (68), 289 (15), 262 (19), 261 (16), 183 (41), 182 (17), 181 (23), 157 (15), 153 (16), 133 (52), 107 (34), 77 (100); HRMS (EI): *m/z* calcd. for ($C_{20}H_{18}O_2^+$) = 290.1307, found = 290.1307.

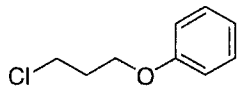
Phenyl-2,2,2-trifluoroethyl ether (48o) (Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633-3652.)



48o

Isolated as a clear oil in 82 % yield: R_f = 0.7 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 - 7.30 (2H, m), 7.10 - 7.02 (1H, m), 6.99 - 6.93 (2H, m), 4.36 (2H, q, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 129.7, 122.5, 115.0, 66.1 (q, J = 35.5 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -73.98 (3F, t, J = 8.0 Hz).

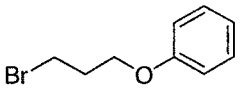
(3-Chloropropyl)phenyl ether (48p) (Foubelo, F.; Saleh, S. A.; Yus, M. *J. Org. Chem.* **2000**, *65*, 3478-3483.)



48p

Isolated as a clear oil in 95 % yield: R_f = 0.7 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 - 7.26 (2H, m), 7.00 - 6.90 (3H, m), 4.13 (2H, t, J = 6.0 Hz), 3.77 (2H, t, J = 6.0 Hz), 2.26 (2H, quintet, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.6, 129.5, 120.9, 114.6, 64.4, 41.9, 32.7.

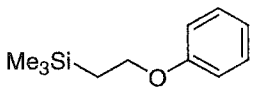
(3-Bromopropyl)phenyl ether (48q) (Reinholz, E.; Becker, A.; Hagenbruch, B.; Schaefer, S.; Schmitt, A. *Synthesis* **1990**, *11*, 1069-1071.)



48q

Isolated as a clear oil in 93 % yield: R_f = 0.7 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 - 7.31 (2H, m), 7.03 - 6.94 (3H, m), 4.14 (2H, t, J = 6.0 Hz), 3.65 (2H, t, J = 6.0 Hz), 2.36 (2H, quintet, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.8, 129.7, 121.1, 114.6, 65.3, 32.5, 30.3.

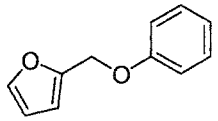
2-Trimethylsilyl-1-phenoxyethane (48r) (Ciommer, B.; Schwarz, H. *J. Organomet. Chem.* **1983**, *244*, 319-328.)



48r

Isolated as a clear oil in 25 % yield: R_f = 0.9 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (2H, t, J = 7.5 Hz), 6.98 - 6.86 (3H, m), 4.09 (2H, t, J = 8.0 Hz), 1.16 (2H, t, J = 8.0 Hz), 0.11 (9H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.8, 129.4, 120.4, 114.6, 65.5, 18.1, -0.8.

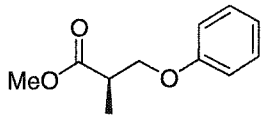
2-Phenoxymethyl furan (48s) (Katritzky, A. R.; Abdel-Megeed, M. F.; Lhommet, G.; Ramsden, C. A. *J. Chem. Soc. Perkin Trans. 1* **1979**, 426-429.)



48s

Isolated as a clear oil in 90 % yield: R_f = 0.6 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (1H, dd, *J* = 2.0, 1.0 Hz), 7.35 - 7.28 (2H, m), 7.04 - 6.96 (3H, m), 6.45 (1H, dd, *J* = 3.5, 0.5 Hz), 6.39 (1H, dd, *J* = 3.5, 2.0 Hz), 5.02 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.2, 150.2, 143.0, 129.4, 121.2, 114.9, 110.5, 109.9, 62.6.

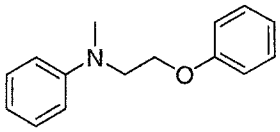
(R)-2-Methyl-3-phenoxypropionic acid methyl ester (48t) (Toda, S.; Miyamoto, M.; Kinoshita, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3600-3606.)



48t

Isolated as a clear oil in 90 % yield: R_f = 0.5 (9:1 hexanes:EtOAc); $[\alpha]_D^{22}$ = -13.2 ° (c = 3.1, CH_2Cl_2) for >99 % ee (Chiralcel OD, 1 % isopropanol/hexanes, 1.0 mL/min, retention times for R and S enantiomers are 8.26 and 9.98 min respectively) with determination of the absolute stereochemistry by comparison of the specific rotation with the literature value; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 - 7.25 (2H, m), 6.99 - 6.87 (3H, m), 4.20 (1H, dd, *J* = 9.0, 6.5 Hz), 4.00 (1H, dd, *J* = 9.0, 6.5 Hz), 3.73 (3H, s), 2.97 (1H, sextet, *J* = 7.0 Hz), 1.32 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.4, 158.5, 129.4, 121.0, 114.7, 69.7, 52.1, 40.1, 14.4.

Methyl-(2-phenoxyethyl)phenyl amine (48u)

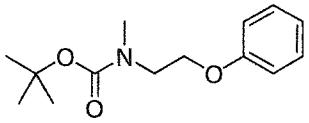


48u

Isolated as a clear oil in 30 % yield: R_f = 0.5 (9:1 hexanes: EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 - 7.25 (4H, m), 7.01 - 6.90 (3H, m), 6.83 - 6.73 (3H, m), 4.17 (2H, t, *J* = 6.0 Hz), 3.80 (2H, t, *J* = 6.0 Hz), 3.09 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.8, 149.1, 129.6, 129.5, 121.0, 116.6, 114.6, 112.3, 65.2, 52.1, 39.3; IR (film) ν 3027, 2923, 1599, 1497, 1368, 1301, 1245,

1172, 1077, 1034, 992, 884, 749, 691 cm^{-1}; LRMS (EI): *m/z* = 228 (9), 227 (48), 212 (11), 121 (14), 120 (100), 105 (8), 104 (8), 91 (5), 77 (19); HRMS (EI): *m/z* calcd. for ($C_{15}H_{17}NO^+$) = 227.1310, found = 227.1307.

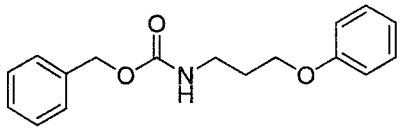
Methyl-(2-phenoxyethyl)carbamic acid *tert*-butyl ester (48v)



48v

Isolated as a clear oil in 93 % yield: R_f = 0.6 (9:1 hexanes: EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (2H, t, *J* = 7.5 Hz), 6.94 (1H, t, *J* = 7.5 Hz), 6.89 (2H, d, *J* = 7.5 Hz), 4.09 (2H, t, *J* = 5.5 Hz), 3.60 (2H, t, *J* = 5.5 Hz), 2.99 (3H, s), 1.47 (9H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.5, 155.5, 129.4, 120.8, 114.4, 79.7, 66.5 (broad), 48.6, 36.1 (broad), 28.8; IR (film) ν 2976, 1697, 1600, 1497, 1391, 1366, 1303, 1246, 1157, 1046, 882, 754 cm^{-1}; LRMS (EI): *m/z* = 251 (5), 196 (11), 179 (17), 178 (90), 158 (31), 120 (19), 108 (14), 107 (11), 103 (10), 102 (100), 94 (15), 77 (29); HRMS (EI): *m/z* calcd. for ($C_{14}H_{21}NO_3$ + H^+) = 252.1600, found = 252.1609.

(3-Phenoxypropyl)carbamic acid benzyl ester (48w)

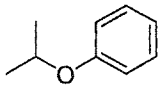


48w

Isolated as a clear oil in 85 % yield: R_f = 0.4 (3:1 hexanes: EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 - 7.25 (7H, m), 6.98 - 6.86 (3H, m), 5.12 (2H, s), 5.08 (1H, s, broad), 4.03 (2H, t, *J* = 6.0 Hz), 3.42 (2H, q, *J* = 6.0 Hz), 2.02 (2H, quintet, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.5, 156.3, 136.5, 129.4, 128.5, 128.0, 120.9, 114.5, 66.8, 65.9, 39.0, 29.7 (one signal absent); IR (film) ν 3336, 3064, 3033, 2949, 2878, 1702, 1600, 1587, 1530, 1498, 1471, 1455, 1243, 1173, 1142, 1080, 1041, 754, 693 cm^{-1}; LRMS (EI): *m/z* = 193 (12), 192 (84), 177 (7), 121 (5), 108 (9), 107 (9), 94 (20), 92 (10), 91 (100), 77 (15); HRMS (EI): *m/z* calcd. for ($C_{17}H_{19}NO_3^+$) = 285.1365, found = 285.1374.

Products of Experiments Summarized in Table 13

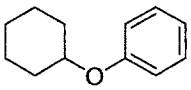
Isopropylphenyl ether (50a) (Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633-3652.)



50a

Isolated as a clear oil in 71 % yield: R_f = 0.8 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 - 7.24 (2H, m), 6.98 - 6.88 (3H, m), 4.57 (1H, septet, *J* = 6.0 Hz), 1.37 (6H, d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.8, 129.4, 120.5, 115.9, 69.9, 22.5.

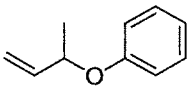
Cyclohexylphenyl ether (50b) (Tateiwa, J.; Nishimura, T.; Horiuchi, H.; Uemura, S. *J. Chem. Soc. Perkin Trans.1* **1994**, *23*, 3367-3372.)



50b

Isolated as a clear oil in 67 % yield: R_f = 0.8 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 - 7.25 (2H, m), 6.98 - 6.90 (3H, m), 4.27 (1H, m), 2.10 - 1.98 (2H, m), 1.91 - 1.80 (2H, m), 1.68 - 1.50 (3H, m), 1.48 - 1.28 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 129.4, 120.5, 116.1, 75.5, 32.2, 26.0, 24.2.

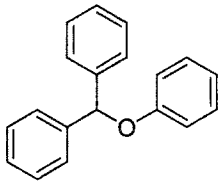
(1-Methylallyl)phenyl ether (50c)



50c

Isolated as a clear oil in 69 % yield: R_f = 0.8 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 - 7.30 (2H, m), 6.96 - 6.89 (3H, m), 5.93 (1H, ddd, *J* = 17.5, 10.5, 6.0 Hz), 5.28 (1H, dd, *J* = 17.5, 1.0 Hz), 5.18 (1H, dd, *J* = 10.5, 1.0 Hz), 4.82 (1H, qdd, *J* = 6.0, 6.0, 1.0 Hz), 1.46 (3H, d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.9, 139.2, 129.3, 120.7, 116.1, 115.6, 74.7, 21.7; IR (film) ν 3040, 2981, 1585, 1488, 1287, 1239, 1164, 1072, 1024, 990, 928, 866, 797, 750 cm^{-1}.

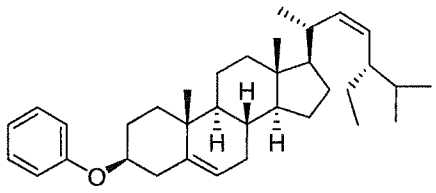
Benzhydrylphenyl ether (50d)



50d

Isolated as a clear liquid in 75 % yield: R_f = 0.6 (9:1 hexanes: EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 - 7.26 (12H, m), 7.07 - 6.95 (3H, m), 6.30 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.3, 141.4, 129.5, 128.8, 127.9, 127.1, 121.1, 116.2, 81.8; IR (film) ν 3062, 3029, 1597, 1586, 1493, 1454, 1306, 1235, 1172, 1078, 1029, 916, 880, 817, 753, 699, 655 cm^{-1}; LRMS (EI): *m/z* = 262 (43), 260 (10), 183 (25), 168 (24), 167 (100), 166 (17), 165 (39), 152 (20), 65 (12); HRMS (EI): *m/z* calcd. for ($C_{19}H_{16}O^+$) = 260.1201, found = 260.1196.

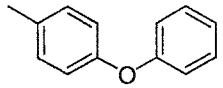
***O*-Phenyl stigmasterol (50e)**



50e

Isolated as a clear crystal in 48 % yield: R_f = 0.9 (9:1 hexanes: EtOAc); $[\alpha]_D^{22}$ = -40.7 ° (c = 1.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 - 7.23 (2H, m), 6.94 - 6.88 (3H, m), 5.40 (1H, d, *J* = 5.0 Hz), 5.17 (1H, dd, *J* = 15.0, 8.5 Hz), 5.02 (1H, dd, *J* = 15.0, 8.5 Hz), 4.18 - 4.07 (1H, m), 2.54 - 2.36 (2H, m), 2.11 - 1.90 (4H, m), 1.76 - 1.66 (2H, m), 1.65 - 1.34 (8H, m), 1.33 - 1.12 (6H, m), 1.10 - 1.02 (9H, m), 0.90 - 0.80 (9H, m), 0.73 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.6, 140.3, 138.3, 129.5, 129.3, 122.3, 120.6, 116.0, 77.2, 57.2, 56.3, 51.5, 50.5, 42.6, 40.8, 40.0, 39.1, 37.6, 37.2, 32.3, 32.3, 29.3, 28.6, 25.8, 24.8, 21.6, 21.5, 21.5, 19.9, 19.4, 12.7, 12.5; IR (film) ν 3037, 2950, 2851, 2361, 1583, 1486, 1379, 1366, 1290, 1230, 1152, 1088, 1037, 1021, 972, 866, 839, 806, 758, 693 cm^{-1}; LRMS (EI): *m/z* = 488 (1), 397 (18), 396 (27), 395 (64), 255 (28), 159 (15), 147 (17), 139 (41), 121 (19), 109 (15), 107 (16), 105 (20), 97 (23), 95 (24), 94 (17), 93 (22), 91 (18), 83 (100), 77 (10); HRMS (EI): *m/z* calcd. for ($C_{35}H_{52}O^+$) = 488.4018, found = 488.4027.

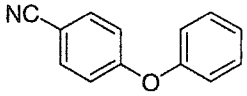
Phenyl-*p*-tolyl ether (50f) (Haga, N.; Takayanagi, H. *J. Org. Chem.* **1996**, *61*, 735-745.)



50f

Isolated as a clear oil in 82 % yield: R_f = 0.60 (5:1 hexanes:toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 - 7.41 (2H, m), 7.30 - 7.05 (7H, m), 2.48 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 154.9, 133.0, 130.4, 129.8, 123.4, 119.3, 118.5, 20.9.

4-Cyanodiphenyl ether (50g) (Gujadhur, R.; Venkataraman, D. *Synth. Commun.* **2001**, *31*, 2865-2880.)

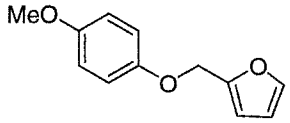


50g

Isolated as a thick, yellow oil in 77 % yield: R_f = 0.70 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (2H, ddd, *J* = 9.5, 5.0, 2.5 Hz), 7.42 (2H, t, *J* = 7.5 Hz), 7.23 (1H, tt, *J* = 7.0, 1.0 Hz), 7.06 (2H, ddd, *J* = 7.5, 3.5, 1.0 Hz), 7.00 (2H, ddd, *J* = 9.5, 5.0, 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 155.0, 134.3, 130.4, 125.3, 120.6, 119.0, 118.1, 106.0.

Products of Experiments Summarized in Table 14

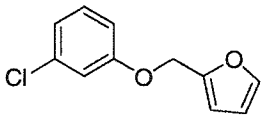
2-(4-Methoxyphenoxymethyl) furan (58a)



58a

Isolated as a clear, crystalline solid in quantitative yield: R_f = 0.4 (9:1 hexanes: EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44 (1H, dd, *J* = 2.0, 1.0 Hz), 6.93 (2H, d, *J* = 9.0 Hz), 6.84 (2H, d, *J* = 9.0 Hz), 6.41 (1H, d, *J* = 3.0 Hz), 6.38 (1H, dd, *J* = 3.0, 2.0 Hz), 4.95 (2H, s), 3.78 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.1, 152.4, 150.5, 142.9, 116.2, 114.6, 110.5, 109.8, 63.5, 55.9; IR (film) ν 2933, 2834, 1592, 1508, 1464, 1371, 1232, 1150, 1108, 1037, 1010, 923, 825, 780, 744 cm^{-1}; LRMS (EI): *m/z* = 204 (32), 123 (18), 95 (10), 82 (8), 81 (100); HRMS (EI): *m/z* calcd. for ($C_{12}H_{12}O_3^+$) = 204.0786, found = 204.0779.

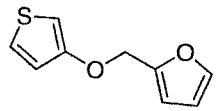
2-(3-Chlorophenoxymethyl) furan (58b)



58b

Isolated as a clear oil in 71 % yield: R_f = 0.5 (3:1 hexanes: toluene); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (1H, dd, *J* = 2.0, 1.0 Hz), 7.21 (1H, t, *J* = 8.0 Hz), 7.02 - 6.96 (2H, m), 6.88 (1H, ddd, *J* = 8.0, 2.5, 1.0 Hz), 6.44 (1H, d, *J* = 3.0 Hz), 6.40 (1H, dd, *J* = 3.0, 2.0 Hz), 4.99 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.9, 149.6, 143.2, 134.8, 130.2, 121.4, 115.4, 113.4, 110.6, 110.3, 62.7; IR (film) ν 3123, 3070, 2933, 2874, 1594, 1477, 1371, 1284, 1247, 1151, 1099, 1073, 1011, 924, 898, 768, 744, 680 cm^{-1}; LRMS (EI): *m/z* = 210 (6), 208 (8), 143 (5), 141 (16), 128 (11), 113 (7), 111 (13), 81 (100); HRMS (EI): *m/z* calcd. for ($C_{11}H_9ClO_2^+$) = 208.0291, found = 208.0293.

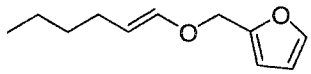
2-(Thiophen-3-yloxymethyl) furan (58c)



58c

Isolated as a yellow oil in 76 % yield: R_f = 0.5 (3:1 hexanes: toluene); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (1H, dd, *J* = 2.0, 1.0 Hz), 7.18 (1H, dd, *J* = 5.0, 3.0 Hz), 6.80 (1H, ddd, *J* = 5.0, 1.5, 1.0 Hz), 6.45 (1H, d, *J* = 3.5 Hz), 6.41 - 6.37 (2H, m), 4.97 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.9, 150.0, 143.1, 124.7, 119.7, 110.6, 110.2, 98.3, 64.5; IR (film) ν 3117, 2927, 1542, 1503, 1422, 1392, 1359, 1235, 1174, 1150, 1072, 1008, 953, 923, 874, 817, 752, 626 cm^{-1}; LRMS (EI): *m/z* = 180 (23), 82 (8), 81 (100); HRMS (EI): *m/z* calcd. for ($C_{12}H_{12}O_3^+$) = 180.0245, found = 180.0245.

2-Hex-1-enyloxymethyl furan (58d)

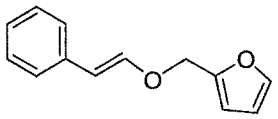


58d

Isolated as a clear oil in 55 % yield: R_f = 0.7 (9:1 hexanes: EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41 (1H, t, *J* = 1.5 Hz), 6.35 (2H, d, *J* = 1.5 Hz), 6.28 (1H, dt, *J* = 12.5, 1.0 Hz), 4.91 (1H, dt, *J* = 12.5, 7.5 Hz), 4.64 (2H, s), 1.98 - 1.88 (2H, m), 1.38 - 1.26 (4H, m), 0.94 - 0.86 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.6, 145.1, 142.9, 110.4, 109.6, 105.7, 63.5, 33.0, 27.7, 22.4, 14.3;

IR (film) ν 2958, 2926, 2858, 1672, 1653, 1503, 1456, 1369, 1290, 1226, 1157, 1126, 1080, 1016, 933, 885, 813, 738 cm^{-1}; LRMS (EI): *m/z* = 180 (7), 149 (9), 105 (11), 97 (7), 85 (10), 83 (6), 82 (8), 81 (100), 57 (13), 53 (9); HRMS (EI): *m/z* calcd. for ($C_{11}H_{16}O_2^+$) = 180.1150, found = 180.1154.

2-Styryloxymethyl furan (58e)



58e

Isolated as a clear oil in 61 % yield: R_f = 0.6 (9:1 hexanes: EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46 (1H, dd, *J* = 2.0, 1.0 Hz), 7.29 - 7.23 (4H, m), 7.18 - 7.06 (1H, m), 7.05 (1H, d, *J* = 13.0 Hz), 6.44 (1H, d, *J* = 3.0 Hz), 6.39 (1H, dd, *J* = 3.0, 2.0 Hz), 5.99 (1H, d, *J* = 13.0 Hz), 4.85 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.0, 147.0, 143.2, 136.0, 128.6, 125.9, 125.2, 110.6, 110.2, 107.4, 64.3; IR (film) ν 3024, 2924, 1733, 1654, 1637, 1598, 1501, 1448, 1371, 1330, 1276, 1227, 1153, 1072, 1016, 993, 921, 884, 816, 748, 694 cm^{-1}; LRMS (EI): *m/z* = 200 (3), 170 (5), 135 (17), 120 (8), 107 (46), 105 (39), 91 (17), 90 (9), 89 (11), 82 (18), 81 (100), 77 (37).

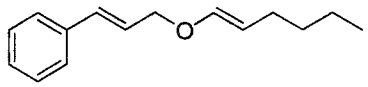
II.3.3 Synthetic Methods and Characterization Data of Claisen Rearrangement Substrates and Products

Representative Procedure for the Cross-Coupling of Potassium Alkenyltrifluoroborates with Allylic Alcohols (47)

A suspension of potassium 1-hexenyltrifluoroborate (0.380 g, 2.00 mmol), $Cu(OAc)_2 \cdot H_2O$ (20.0 mg, 0.100 mmol), DMAP (25.0 g, 0.200 mmol) and powdered 4Å molecular sieves (0.750 g) in CH_2Cl_2 (8.00 mL) was stirred for 5 minutes at room temperature. To this stirred suspension was added the solid (*E*)-cinnamyl alcohol (0.134 g, 1.00 mmol). The reaction mixture was then sealed with a rubber septum and stirred under a blanket atmosphere of oxygen. Following a period of 24 h, the crude reaction mixture was filtered through a plug of Celite to remove the molecular sieves and any insoluble by-products, and then concentrated *in vacuo* to afford the crude product mixture. The product (**59a**) was isolated by silica gel column chromatography (eluting with hexanes:EtOAc 9:1 ~ 3:1 gradient) as a clear oil in 74 % yield (0.158 g, 0.732 mmol).

Products of Experiments Summarized in Table 16

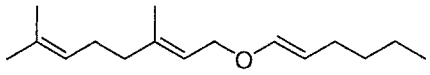
(*E*)-Cinnamyl-1-hexenyl ether (59a)



59a

Isolated as a clear oil in 74 % yield: R_f = 0.60 (5:1 hexanes:toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (2H, d, *J* = 7.0 Hz), 7.40 (2H, t, *J* = 7.0 Hz), 7.33 (1H, t, *J* = 7.0 Hz), 6.72 (1H, d, *J* = 16.0 Hz), 6.38 (1H, dt, *J* = 16.0, 6.0 Hz), 6.35 (1H, d, *J* = 12.5 Hz), 4.95 (1H, dt, *J* = 12.5, 7.5 Hz), 4.43 (2H, dd, *J* = 6.0, 1.5 Hz), 2.06 - 1.96 (2H, m), 1.46 - 1.34 (4H, m), 0.97 (3H, t, *J* = 5.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 136.7, 132.8, 128.7, 128.0, 126.7, 125.1, 105.4, 70.0, 33.0, 27.6, 22.2, 14.1; IR (film) ν 3027, 2956, 2925, 2854, 1671, 1651, 1495, 1450, 1378, 1211, 1166, 965, 930, 735, 692 cm^{-1}; LRMS (EI): *m/z* (rel. intensity) = 216 (23), 161 (10), 160 (82), 159 (51), 149 (18), 147 (14), 131 (19), 129 (72), 117 (100), 115 (19), 91 (12); HRMS (EI): *m/z* calcd. for (M^+) = 216.1514, found = 216.1510.

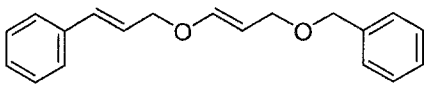
1-Hex-1-enyloxy-3,7-dimethyl-octa-2,6-diene (59b)



59b

Isolated as a clear oil in 48 % yield: R_f = 0.40 (3:1 hexanes:toluene); ^{1}H NMR (300 MHz, C_6D_6) δ 6.33 (1H, d, *J* = 12.5 Hz), 5.51 (1H, m), 5.14 (1H, m), 4.84 (1H, dt, *J* = 12.5, 7.5 Hz), 4.15 (2H, d, *J* = 6.5 Hz), 2.14 - 1.86 (6H, m), 1.65 (3H, s), 1.51 (3H, s), 1.48 (3H, s), 1.34 - 1.26 (4H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 147.1, 140.0, 131.8, 124.8, 121.5, 104.4, 66.3, 40.2, 33.8, 28.4, 27.1, 26.2, 22.8, 18.1, 16.8, 14.5; IR (film) ν 3052, 2959, 2923, 2857, 1653, 1450, 1380, 1329, 1266, 1209, 1167, 930, 825, 741 cm^{-1}; LRMS (EI): *m/z* (rel. intensity) = 236 (4), 235 (21), 149 (9), 137 (14), 136 (7), 105 (9), 95 (9), 93 (12), 91 (10), 69 (100); HRMS (EI): *m/z* calcd. for (M^+) = 236.2140, found = 236.2137.

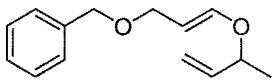
3-Benzyloxy-1-(*E*)-cinnamyloxy-1-propene (59c)



59c

Isolated as a clear oil in 30 % yield: R_f = 0.60 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, CD_3CN) δ 7.41 - 7.21 (10H, m), 6.63 (1H, d, *J* = 16.0 Hz), 6.54 (1H, d, *J* = 12.5 Hz), 6.29 (1H, dt, *J* = 16.0, 6.0 Hz), 5.05 (1H, dt, *J* = 12.5, 7.5 Hz), 4.49 (2H, s), 4.40 (2H, dd, *J* = 6.0, 1.0 Hz), 3.95 (2H, d, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, CD_3CN) δ 150.4, 138.5, 136.4, 133.3, 128.7, 128.5, 128.1, 128.0, 127.7, 126.7, 124.2, 100.6, 71.5, 70.0, 67.8; LRMS (EI): *m/z* (rel. intensity) = 280 (1), 189 (3), 159 (2), 134 (2), 117 (100), 107 (4), 91 (35), 77 (8).

[3-(1-Methyl-allyloxy)-allyloxymethyl]benzene (59d)

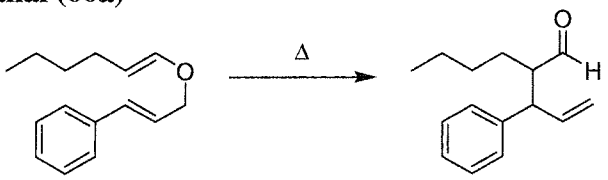


59d

Isolated as a clear oil in 28 % yield: R_f = 0.60 (9:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 - 7.32 (5H, m), 6.44 (1H, d, *J* = 12.5 Hz), 5.89 (1H, ddd, *J* = 17.0, 10.5, 6.5 Hz), 5.34 - 5.15 (3H, m), 4.56 (2H, s), 4.40 (1H, m), 3.99 (2H, d, *J* = 7.5 Hz), 1.40 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 137.3, 135.1, 128.7, 127.8, 127.2, 114.8, 97.5, 73.7, 72.5, 69.3, 19.8; IR (film) ν 3025, 2995, 2932, 2875, 1635, 1405, 1392, 1308, 1290, 1266, 1176, 903, 852, 714 cm^{-1}; LRMS (EI): *m/z* (rel. intensity) = 219 (16), 218 (10), 137 (14), 93 (12), 91 (10), 81 (34), 69 (100).

Representative Synthetic Method and Characterization Data of Aldehyde Generated via Claisen Rearrangement

2-(1-Phenyl-allyl)hexanal (60a)



59a **60a**

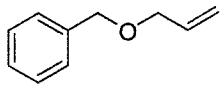
A solution of the 1-hexenyl cinnamyl ether (0.060 g, 0.277 mmol) in d_8-toluene (1.00 mL) was sealed in a 5 mm NMR tube and heated to 110 °C for 24 hours until quantitative conversion of the starting ether was observed. The aldehyde was isolated as a clear oil via silica gel column chromatography in 88 % yield: R_f = 0.60 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (1H, d, *J* = 4.0 Hz), 7.4 - 7.2 (5H, m), 6.07 - 5.94 (1H, m), 5.16 - 5.06 (2H, m), 3.58 (1H, t, *J* = 9.5 Hz), 2.70 (1H, ddt, *J* = 9.5, 7.0, 4.0 Hz), 1.59 - 1.12 (6H, m), 0.82 (3H, t, *J* = 6.5 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 141.2, 139.3, 128.9, 128.2, 127.0, 116.4, 56.3, 50.8, 29.2, 27.5, 22.7, 13.9; IR (film) ν 3029, 2957, 2930, 2860, 1724, 1600, 1493, 1454, 992, 920, 760, 701 cm^{-1}; LRMS (EI): *m/z* (rel. intensity) = 216 (24), 201 (37), 185 (27), 173 (77), 160 (11), 159 (10), 118 (17), 117 (100), 116 (6), 115 (21), 91 (16); HRMS (EI): *m/z* calcd. for (M^+) = 216.1514, found = 216.1511.

II.3.4 Synthetic Methods and Characterization Data of Aryl-/Alkenylated Carboxylates

Side Products Isolated During Attempted Preparation of Allyl Vinyl Ethers

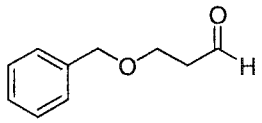
Allyl benzyl ether (61a) (Grobelny, Z.; Stolarzewicz, A.; Maercker, A.; Demuth, W. *J. Organomet. Chem.* **1999**, *590*, 153-157.)



61a

Isolated as a clear oil: R_f = 0.70 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.24 (5H, m), 5.95 (1H, ddd, *J* = 17.5, 10.5, 6.0 Hz), 5.29 (1H, dq, *J* = 17.5, 1.5 Hz), 5.20 (1H, dq, *J* = 10.5, 1.5, Hz), 4.52 (2H, s), 4.02 (2H, dt, *J* = 6.0, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 134.9, 128.5, 127.9, 127.7, 117.3, 72.3, 71.3.

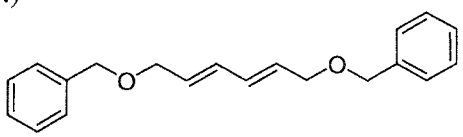
3-Benzyloxypropionaldehyde (62a) (Gutke, H. J.; Oesterreich, K.; Spitzner, D.; Braun, N. A. *Tetrahedron* **2001**, *57*, 997-1004.)



62a

Isolated as a clear oil: R_f = 0.20 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (1H, t, *J* = 2.0 Hz), 7.38 - 7.22 (5H, m), 4.52 (2H, s), 3.80 (2H, t, *J* = 6.0 Hz), 2.68 (2H, dt, *J* = 6.0, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 138.0, 128.6, 127.9, 127.8, 73.4, 63.9, 44.0.

1,6-Dibenzyloxy-2,4-hexadiene (64a) (Ghosal, S.; Luke, G. P.; Kyler, K. S. *J. Org. Chem.* **1987**, *52*, 4296-4298.)



64a

Isolated as a pale yellow oil: $R_f = 0.60$ (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.22 (10H, m), 6.28 (2H, ddd, J = 15.0, 10.5, 1.0 Hz), 5.81 (2H, m), 4.53 (4H, s), 4.08 (4H, dd, J = 6.0, 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.8, 132.6, 129.4, 128.9, 127.6, 72.6, 69.5.

Products of Experiments Summarized in Table 18 and 19

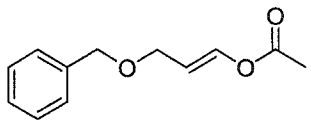
Procedure A: Cross-Coupling of a Potassium Organotrifluoroborate with an Activated Carboxylate Salt in Dichloromethane

A mixture of potassium 3-benzyloxy-1-propenyltrifluoroborate (0.255 g, 1.00 mmol), potassium acetate (99.0 mg, 1.00 mmol), $Cu(OAc)_2 \cdot H_2O$ (50.0 mg, 0.250 mmol), DMAP (61.0 mg, 0.500 mmol), magnesium sulphate (0.120 g, 1.00 mmol) and powdered 4Å molecular sieves (0.750 g) was suspended in CH_2Cl_2 (8.00 mL). The reaction mixture was then sealed with a rubber septum, heated to 40 °C, and stirred under a blanket atmosphere of oxygen. Following a period of 24 h, the crude reaction mixture was filtered through a plug of Celite to remove the molecular sieves and any insoluble by-products, and then concentrated *in vacuo* to afford the crude product mixture. The product (**63a**) was isolated by silica gel column chromatography (eluting with hexanes:toluene 4:1 ~ 1:1 gradient) as a clear oil in 61 % yield (0.129 g, 0.624 mmol).

Procedure B: Cross-Coupling of a Potassium Organotrifluoroborate with an Activated Carboxylate Salt in Toluene

A mixture of potassium 1-hexenyltrifluoroborate (0.190 g, 1.00 mmol), potassium benzoate (0.160 g, 1.00 mmol), anhydrous $CuSO_4$ (40.0 mg, 0.250 mmol), DMAP (61.0 m g, 0.500 mmol), magnesium sulphate (0.120 g, 1.00 mmol) and powdered 4Å molecular sieves (0.750 g) was suspended in toluene (8.00 mL). The reaction mixture was then sealed with a rubber septum, heated to 60 °C, and stirred under an atmosphere of oxygen (delivered via an oxygen tank connected to a manifold and dried by passage through a column of Drierite). Following a period of 24 h, the crude reaction mixture was filtered through a plug of Celite to remove the molecular sieves and any insoluble by-products, and then concentrated *in vacuo* to afford the crude product mixture. The product (**63e**) was isolated by silica gel column chromatography (eluting with hexanes:toluene 4:1 ~ 1:1 gradient) as a clear oil in 50 % yield (49.0 mg, 0.239 mmol).

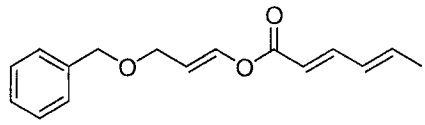
3-Benzyloxy-propenyl acetate (63a)



63a

Prepared via procedure A and isolated as a clear oil in 61 % yield: R_f = 0.40 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, CD_3CN) δ 7.38 - 7.24 (6H, m), 5.57 (1H, dt, *J* = 12.5, 7.0 Hz), 4.50 (2H, s), 4.01 (2H, dd, *J* = 7.0, 1.5 Hz), 2.13 (3H, s); ^{13}C NMR (75 MHz, CD_3CN) δ 168.1, 138.8, 138.2, 128.6, 127.9, 127.8, 110.8, 72.1, 66.6, 20.8; IR (film) ν 3065, 3032, 2859, 1756, 1677, 1497, 1455, 1372, 1217, 1069, 934, 740, 699, 598 cm^{-1}; LRMS (EI): *m/z* (rel. intensity) = 205 (3), 163 (18), 150 (31), 149 (20), 147 (13), 146 (57), 134 (15), 115 (36), 108 (22), 107 (40), 105 (53), 100 (12), 99 (26), 92 (61), 91 (100), 77 (5); HRMS (EI): *m/z* calcd. for ($M-H^+$) = 205.0865, found = 205.0864.

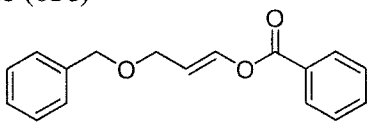
3-Benzyloxy-propenyl sorbate (63b)



63b

Prepared via procedure B and isolated as a clear oil in 52 % yield: R_f = 0.55 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 - 7.24 (7H, m), 6.28 - 6.15 (2H, m), 5.79 (1H, d, *J* = 15.5 Hz), 5.62 (1H, dt, *J* = 12.5, 7.5 Hz), 4.51 (2H, s), 4.03 (2H, dd, *J* = 7.5, 1.5 Hz), 1.87 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 147.3, 141.2, 139.0, 138.2, 129.9, 128.6, 127.9, 127.8, 117.4, 110.5, 71.9, 66.7, 18.9; IR (film) ν 3065, 3030, 2914, 2854, 1728, 1673, 1643, 1615, 1496, 1377, 1361, 1331, 1239, 1185, 1142, 1001, 933, 867, 738, 698 cm^{-1}; LRMS (EI): *m/z* (rel. intensity) = 258 (1), 202 (1), 167 (5), 163 (10), 152 (10), 146 (6), 105 (7), 96 (14), 95 (100), 91 (42), 77 (9); HRMS (ESI): *m/z* calcd. for ($M+Na^+$) = 281.1148, found = 281.1145.

3-Benzyloxy-propenyl benzoate (63c)

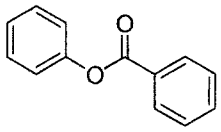


63c

Prepared via procedure B and isolated as a clear oil in 50 % yield: R_f = 0.50 (9:1

hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (2H, d, J = 8.0 Hz), 7.62 - 7.56 (2H, m), 7.47 (2H, t, J = 8.0 Hz), 7.38 - 7.26 (5H, m), 5.77 (1H, dt, J = 12.5, 7.0 Hz), 4.55 (2H, s), 4.10 (2H, dd, J = 7.0, 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 139.1, 138.2, 133.8, 130.2, 129.0, 128.7, 128.6, 128.0, 127.9, 111.4, 72.1, 66.7; IR (film) ν 3033, 2856, 1734, 1676, 1602, 1495, 1453, 1362, 1316, 1264, 1178, 1122, 1069, 1023, 933, 910, 734, 709 cm^{-1}; LRMS (EI): *m/z* (rel. intensity) = 268 (1), 212 (13), 163 (15), 146 (19), 106 (28), 105 (100), 91 (25), 77 (45); HRMS (EI): *m/z* calcd. for (M^+) = 268.1099, found = 268.1098.

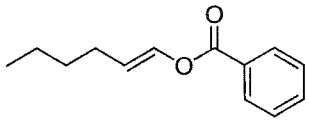
Phenyl benzoate (63d) (Lee, C. K.; Yu, J. S.; Kim, S. H. *J. Heterocycl. Chem.* **1998**, *35*, 835-842.)



63d

Prepared via procedure A and isolated as a white, crystalline solid in 17 % yield: R_f = 0.60 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (2H, dd, J = 7.0, 1.5 Hz), 7.64 (1H, tt, J = 7.0, 1.5 Hz), 7.54 - 7.40 (4H, m), 7.30 - 7.20 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 151.2, 133.8, 130.4, 129.8, 129.7, 128.7, 126.1, 121.9.

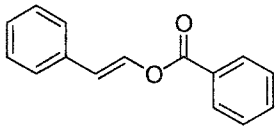
(*E*)-1-Hexenyl benzoate (63e) (Doucet, H.; Hoefer, J.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc. Chem. Commun.* **1993**, *10*, 850-851.)



63e

Prepared via procedure B and isolated as a clear oil in 23 % yield: R_f = 0.70 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (2H, dd, J = 7.5, 1.5 Hz), 7.58 (1H, tt, J = 7.5, 1.5 Hz), 7.46 (2H, t, J = 7.5 Hz), 7.32 (1H, dt, J = 12.5, 1.5 Hz), 5.61 (1H, dt, J = 12.5, 7.5 Hz), 2.07 (2H, dq, J = 7.5, 1.5 Hz), 1.47 - 1.31 (4H, m), 0.92 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 135.7, 133.5, 130.0, 129.5, 128.6, 115.8, 31.9, 27.2, 22.3, 14.0.

(*E*)-β-Benzoyloxystyrene (63f) (Rotem, M.; Shvo, Y. *J. Organomet. Chem.* **1993**, *448*, 189-204.)



63f

Prepared via procedure B and isolated as a white, crystalline solid in 21 % yield: $R_f = 0.60$ (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (2H, dd, J = 8.5, 1.5 Hz), 8.17 (1H, d, J = 12.5 Hz), 7.70 (1H, tt, J = 6.5, 1.5 Hz), 7.60 - 7.30 (7H, m), 6.66 (1H, d, J = 12.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 136.6, 134.3, 133.9, 130.2, 129.0, 128.9, 128.8, 127.7, 126.5, 116.0.

II.4 References

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Chapter III

Organoboron Compounds in Copper-Mediated Carbon-Nitrogen Bond Forming Reactions

III.1 Introduction

III.1.1 General Introduction to Carbon-Nitrogen Bond Formation via Cross-Coupling Strategies

The importance of carbon-nitrogen bond formation in synthetic chemistry can not be over stated. The prevalence of nitrogen-based compounds and alkaloids throughout the pharmaceutical, agricultural, cosmetic, materials, dye and textile industries outline the importance of carbon-nitrogen bond forming strategies.

The introduction of amino moieties into organic molecules has been well established in the historical literature. Classical strategies have mainly been based on the introduction of a masked amine equivalent to the molecule followed by reaction to free the amine functionality; examples of this range from the simple Gabriel amine synthesis to the more complex Hofmann and Curtius rearrangements. The introduction of azido, cyano and nitro moieties followed by reduction to the free amine are also commonly used methods of preparing primary amines.

The further functionalization of amines is often more problematic. Simple nucleophilic substitutions for the formation of secondary and tertiary amines are difficult to control as the more substituted the amine becomes, the more nucleophilic it is. Thus reaction of aliphatic amines with alkyl halides often only generates the quaternary ammonium salts. To this end, many reactions have been developed for the preparation of secondary and tertiary amines. Some of the more common amongst these strategies include reductive aminations, the Mannich reaction and others based upon the formation of imine or iminium intermediates. The development of organometallic chemistry and the use of transition-metal catalysis in organic synthesis have allowed for the more recently described hydroaminations to introduce nitrogen functionality into molecules.

The use of transition metals to catalyze the cross-coupling of molecules that otherwise would not be reactive toward each other can be traced back to the Ullmann and Goldberg condensations (*vide* II.1.1, Scheme 32).[1,2] Modern research mainly by the groups of Hartwig and Buchwald have made the amination of aryl halides a practical and reliable tool in the chemists' repertoire to generate aniline derivatives. Hartwig[3] and Buchwald[4] have shown that the cross-coupling of arylchlorides, bromides, iodides and sulfonates can occur under palladium and nickel catalysis, and Buchwald has employed copper catalysts to the same end (Figure 20).[5]

This strategy for the formation of carbon-nitrogen bonds has exploded in popularity, and interest in it has warranted several recent major reviews.[6-8]

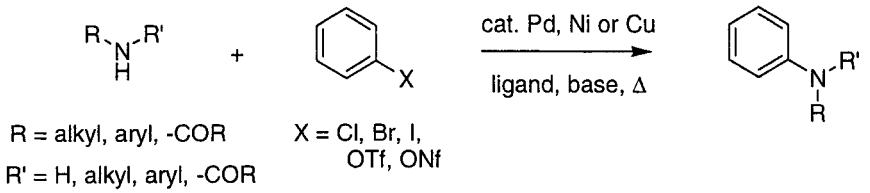


Figure 20 - Hartwig/Buchwald Amination/Amidation of Aryl Halides and Sulfonates

III.1.2 Ullmann Condensations of Organometalloids and Nitrogen-Based Nucleophiles

The aryl halides employed as the aryl donors in the aforementioned cross-couplings are electrophilic in nature. However, as with the *O*-arylation reactions, the arylation of nitrogen-based compounds can also be performed via the coupling of two nucleophilic species. Hence, the copper-mediated/catalyzed Ullmann condensation of organometalloids with nitrogen- based nucleophiles offers a diverse array of possible pathways for the preparation of aniline derivatives (Figure 21). This introduction will briefly summarize the use of organometalloid and pseudo-metalloid species in the copper-promoted arylation of nitrogen-based compounds. Particular attention will be paid towards the use of organoboron reagents in both copper-mediated and copper-catalyzed processes.

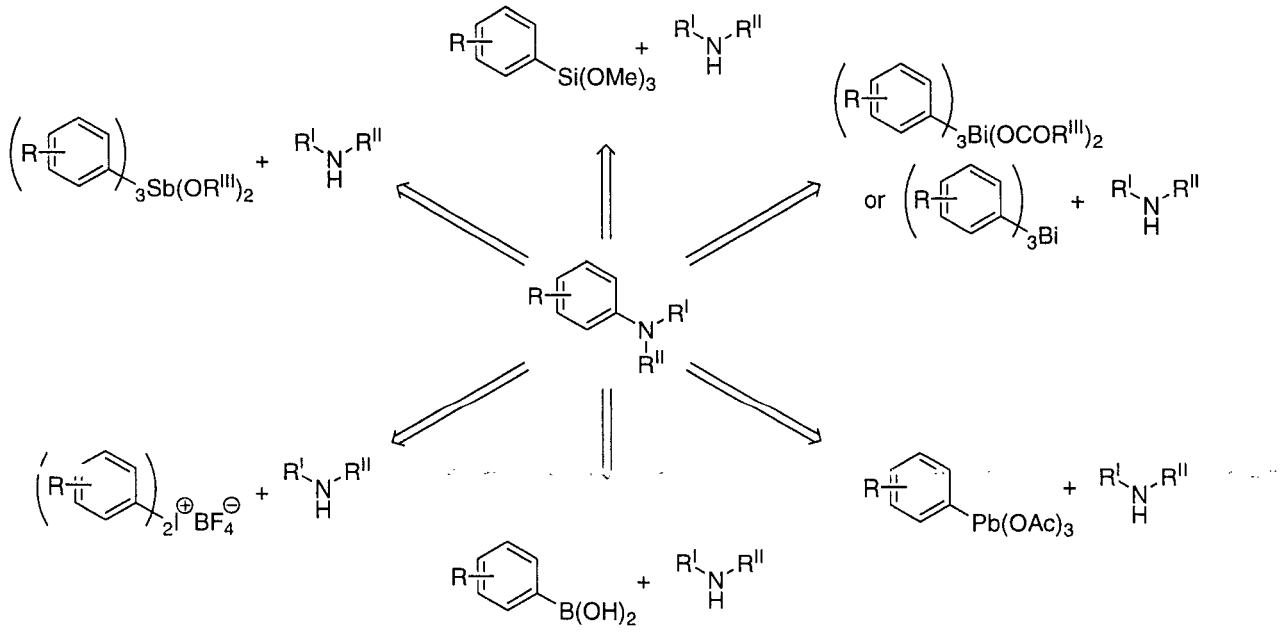
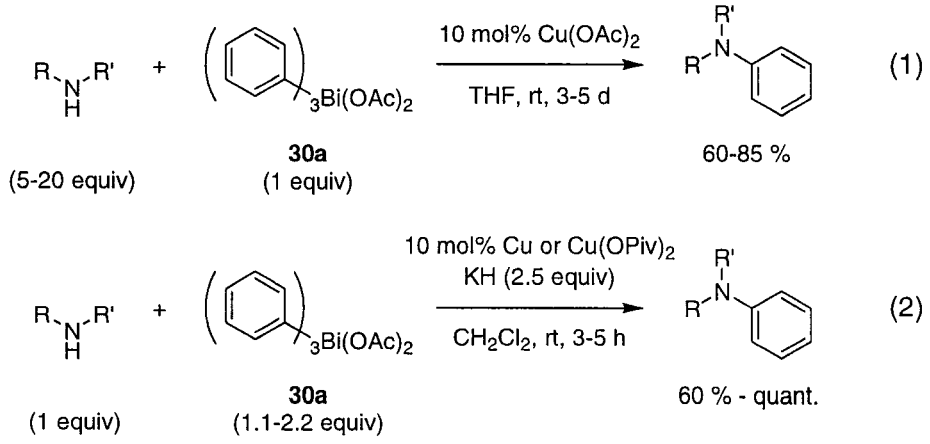


Figure 21 - Organometalloids Utilized for Copper-Mediated Arlyation of Nitrogen-Based Nucleophiles

III.1.2.1 Organobismuth Reagents

The use of triphenylbismuth diacetate (**30a**) in the arylation of simple primary and secondary aliphatic amines and aniline was first reported by Dodonov and coworkers.[9] They reacted a large excess of the amine with one equivalent of **30a** in the presence of a catalytic amount of $Cu(OAc)_2$ in THF. The reaction afforded moderate to good yields (based on transfer of one aryl moiety from each molecule of **30a**) of the monoarylated amines after 3 to 5 days (Scheme 55, reaction 1). The more sterically hindered diphenylamine gave only trace amounts (< 3 %) of the triarylated compound.

Barton *et al.* discovered that the same reaction could be performed much faster and in greater yields by simply changing the ethereal solvent to CH_2Cl_2. Their optimized conditions required only one equivalent of the amine to a slight excess of the arylbismuth reagent in the presence of catalytic copper. Interestingly, they employed ground metallic copper powder as the catalyst which gave greater yields than the traditionally used $Cu(OAc)_2$; $Cu(OPiv)_2$ also proved to be successful in catalyzing the reaction. In addition, the use of 2.5 equivalents of KH as base in the reactions gave quantitative yields of the monoarylated products in several examples (Scheme 55, reaction 2).[10]

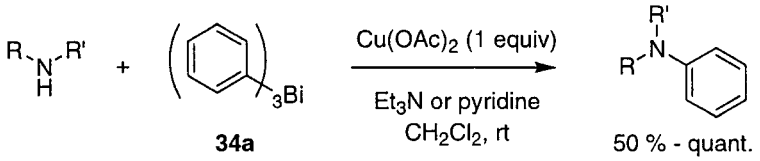


Scheme 55 - Copper-Catalyzed Phenylation of Aliphatic Amines and Anilines with Triphenylbismuth Diacetate

Several groups have made use of this protocol and have helped to define its scope to cover amides and a variety of nitrogen heterocycles including: imidazoles, pyrazoles, triazoles, and quinolines. Amino acid esters, but not the free amino acids, would also react under the standard conditions.[10-11] Steric hindrance around the nitrogen atom was found to play an important role in determining the success of the reaction. For hindered substrates, i.e. amines

with quaternary carbons α to nitrogen, or *ortho*-substituted anilines, the reaction required 2 or more equivalents of the bismuth reagent and longer reaction times in order to obtain comparable yields. A more reactive arylbismuth reagent, triphenylbismuth bis(trifluoroacetate), was also discovered.[10b] This reagent was able to perform the arylations in greater yields in much faster reaction times (< 1 h) than their diacetate counterparts; however, these substrates were more difficult to prepare.

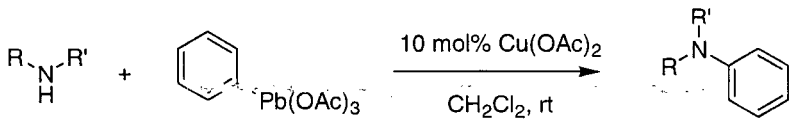
Triphenylbismuthane (**34a**) has also been employed in the arylation of nitrogen nucleophiles. As with the alcohol arylations, these reactions also required a stoichiometric amount of copper for the transformation to occur. In addition, one or more equivalents of a base, usually Et_3N or pyridine, were necessary to obtain high yields of the cross-coupled products (Scheme 56).[12]



Scheme 56 - Arylation of Amines with Triphenylbismuthane

III.1.2.2 Organolead Reagents

The reaction of aryllead reagents in copper-catalyzed cross-couplings is characterized by longer reaction times, higher temperatures and lower yields than those obtained using arylbismuth reagents. In addition, only electron-rich and electron-neutral aryllead reagents showed any reactivity at all; electron-poor substrates did not participate in the cross-coupling. Aryllead triacetates (**64**) were used to arylate aniline derivatives in good yields,[12a-d] but arylation of amines occurred in moderate yields at best.[13] Nitrogen heterocycles[12e,f, 14a,c] and amides[14b,d] were also able to undergo the cross-coupling (Scheme 57). The less "atom economical" tetraphenyllead reagents (**35**) used in the arylation of alcohols have not been reported for the arylation of nitrogen-based nucleophiles.

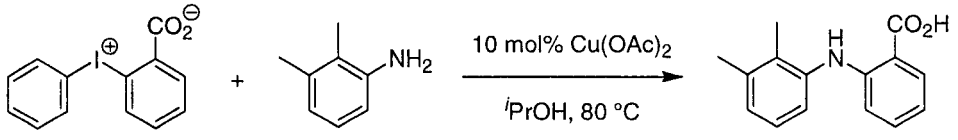


R, R' = H, aryl	70-95 %
R, R' = H, alkyl	17-55 %
R, R' = COR	75-98 %
Heterocycles	50-98 %

Scheme 57 - Copper-Catalyzed *N*-Phenylation with Phenyllead Triacetate

III.1.2.3 Organoiodine Reagents

Relatively few examples of the use of diaryliodonium salts (**36**) in copper-catalyzed Ullmann condensations with nitrogen-based compounds have been reported.[15-19] The reaction with nitrogen nucleophiles faces the same limitations as that of reaction with the oxygen-based nucleophiles (*vide* II.1.2.4). The most successful report made use of unsymmetrical diaryliodonium salts to arylate anilines in the preparation of *N*-aryl anthranilinic acid derivatives (**65**, Scheme 58). Transfer of the electron-poor aryl moiety was reported in each case.[17]

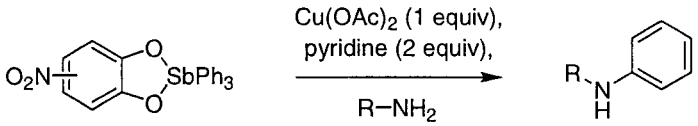


36c **65a** 90%

Scheme 58 - Preparation of Anthranilic Acid Derivatives with Diaryliodonium Salts

III.1.2.4 Organoantimony Reagents

Triarylantimony reagents (**37**) and pentavalent arylantimony reagents (**38**) are poor substrates for the arylation of nitrogen nucleophiles. The reactions are mediated by a stoichiometric amount of the copper reagent. By far the best results were obtained when electron-poor nitro-substituted triphenylbenzoastibolanes (**38c**) were employed to arylate aliphatic amines. The results varied according to the cross-coupling partner and isolated yields of the *N*-aryl amines ranged from 25-85 % (Scheme 59).[18]



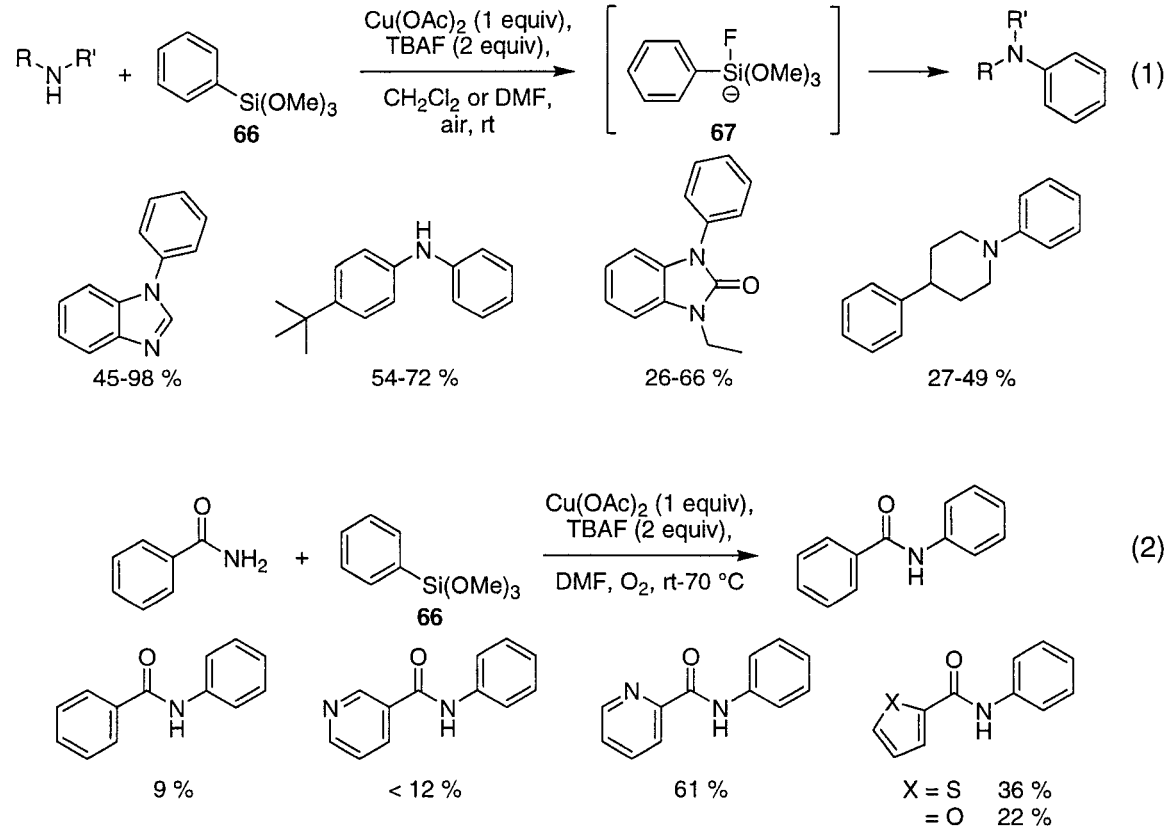
38c 25-85 %

Scheme 59 - Copper-Mediated Arylation of Amines with Triphenylbenzoastibolanes

III.1.2.5 Organosilicon Reagents

Lam and coworkers have reported the cross-coupling of arylsilicon reagents with nitrogen heterocycles and amides under stoichiometric copper conditions. Reaction of the tetravalent aryltrialkoxysilanes (**66**) with TBAF generated a hypervalent organosilicate (**67**) which would then undergo transmetallation to the copper salt leading to the arylation of the nitrogen-based nucleophiles. Moderate to good yields of the corresponding *N*-arylated heterocycles were

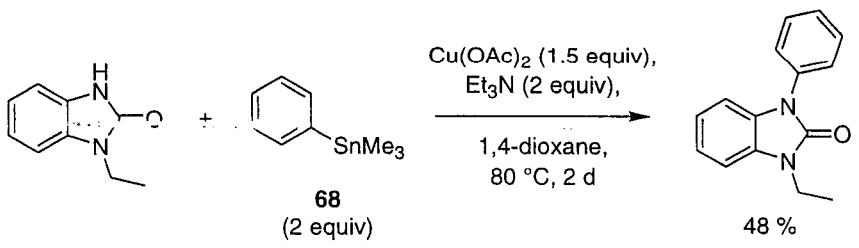
achieved at room temperature using either DMF or CH_2Cl_2 as solvent (Scheme 60, reaction 1).[19a] Standard aromatic amides afforded poor yields of product; however, the presence of a coordinating heteroatom α to the carbonyl group significantly increased the reaction yields (Scheme 60, reaction 2).[19b]



Scheme 60 - Copper-Mediated Arylation of Nitrogen-Based Nucleophiles with Arylsilicon Reagents

III.1.2.6 Organotin Reagents

Only one example of a copper-promoted *N*-arylation by organostannanes has been reported. The reaction was very slow and low yielding, affording only 48 % of the arylated product after reaction for 2 days at 80 °C (Scheme 61). [15]

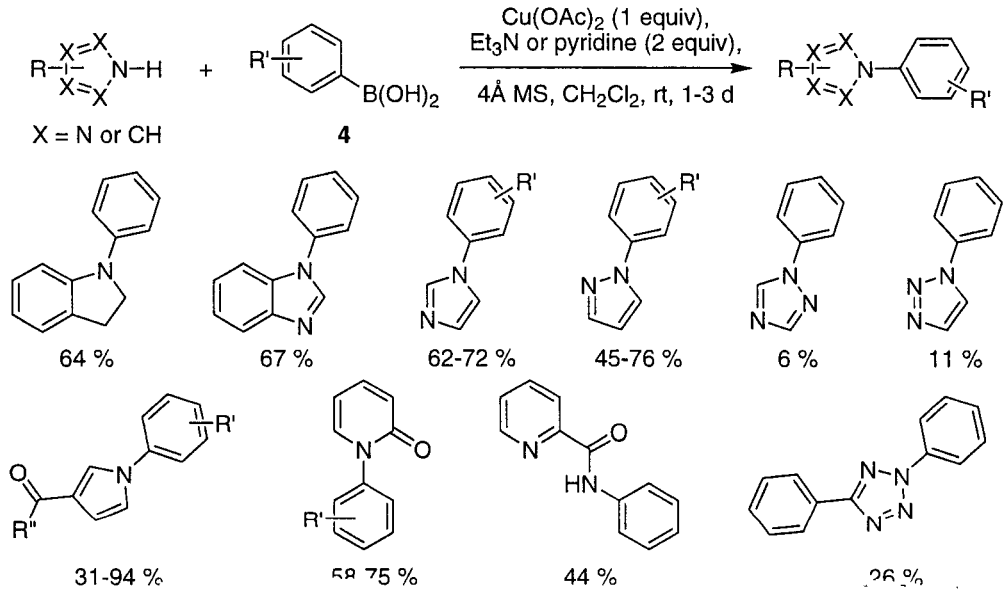


Scheme 61 - Arlyation of *N*-Ethylbenzimidazolinone with Phenyltrimethylstannane

III.1.2.7 Organoboron Reagents

The use of organoboronic acids (**4**) in copper-promoted carbon-nitrogen bond forming reactions is by far the most extensively investigated area of this field. The simultaneous published reports by Chan[20] and Lam[21a] in 1998 renewed both the industrial and academic synthetic community's interest in copper-meditated cross-coupling reactions and have led to the development of modern day Ullmann condensations. Their protocol has since been proven to be a facile and reliable method for carbon-heteroatom bond formation.

The initial work by Chan and coworkers has already been covered in this thesis (*vide* II.1.2.5). Lam and coworkers' contribution included the expansion of the protocol for arylation of a variety of nitrogen-based nucleophilic heterocycles and amides (Scheme 62). The reaction yields were not observed to be dependent upon the electronic properties of the arylboron compound, as both electron-rich and electron-poor arylboronic acids gave similar yields. The nucleophilicity of the cross-coupling partner, however, had a large impact on the yield of the desired product. Thus, more nucleophilic species like imidazoles and pyrazoles afforded good to excellent yields of the cross-coupled products, and less nucleophilic species like triazoles and tetrazoles gave only poor yields of the arylated products.[21a]



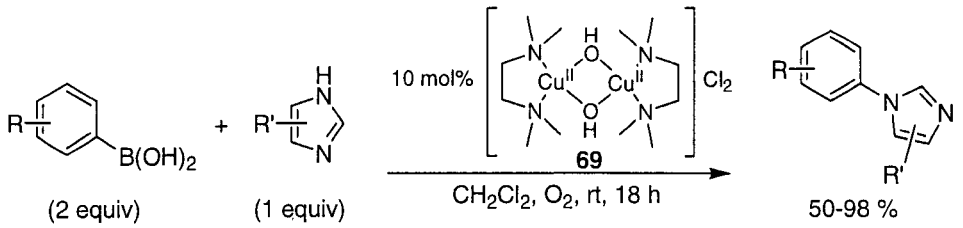
Scheme 62 - Arylation of Nitrogen-Based Nucleophilic Heterocycles and Amides with Arylboronic Acids[21]

Recent research from Lam's group at Bristol-Myers Squibb have expanded this methodology to cover the arylation of amino acid esters which were found not to racemize under

these mild conditions.[21b] Exploration of the nature of the boron cross-coupling partner has led to the discovery that both aryl- and alkenylboronic acids participate in the cross-coupling, as do boronate esters and boroxines.[21c,d] In addition, Combs and Lam have reported the use of this protocol on solid support for the arylation of nitrogen heterocycles, sulfonamides and aliphatic amines.[22] Others have also made use of these conditions to arylate a variety of nitrogen-based nucleophiles.[23-27]

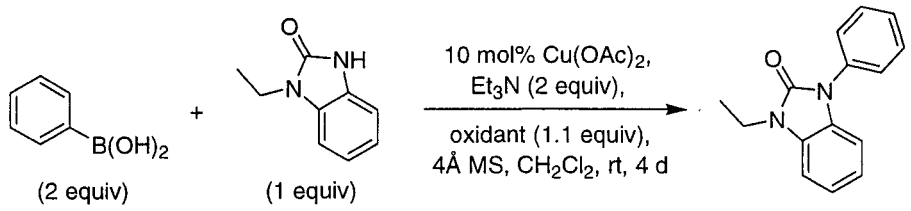
Chan and Lam's original conditions required stoichiometric amounts of the copper salt with 1-2 equivalents of $Cu(OAc)_2$ being employed per equivalent of the nucleophile. In addition, 2-5 equivalents of Et_3N or pyridine were used to activate the cross-coupling partner, or as ligand to the copper reagent. Evans had previously observed catalytic activity when a substoichiometric amount of the copper reagent was employed in the reaction under an atmosphere of oxygen (*vide* II.1.2.5); however, no other attempts to render the reaction truly catalytic in copper were made.[28]

Several other groups have attempted to find the optimal set of conditions for catalytic turnover to occur. The first example of an efficient set of conditions for the copper-catalyzed cross-coupling of imidazole derivatives with arylboronic acids came from Collman and coworkers.[29] Their use of the dimeric Cu(II) complex, $[Cu(OH)\cdot TMEDA]_2Cl_2$ (**69**), gave good to excellent yields of *N*-arylated imidazole derivatives at room temperature with as low as 10 mol % catalyst loadings (Scheme 63). Later work by Collman and coworkers showed that the reaction could be run in water,[29b] and that the dimeric Cu(II) complex **69**, though commercially available, could also be generated by mixing Cu(I)X salts (X = Br, Cl, I, OTf) with bidentate diamines under an atmosphere of oxygen. This discovery lead to the generation and screening of a variety of dimeric Cu(II) complexes; however, none showed the same reactivity as the original TMEDA complex.[29c] Collman's proposed catalytic cycle for this transformation is discussed further in Chapter 4 (*vide* IV.1.2.2). A serious drawback of this $[Cu(OH)\cdot TMEDA]_2Cl_2$ catalytic system is its limitation to imidazole derivatives as the only nucleophiles capable of undergoing the cross-coupling. The reaction fails when simple amines, anilines or phenol derivatives are used.[30]



Scheme 63 - Diamine·Copper Complex-Catalyzed Arylation of Imidazoles

A more generalized approach to a catalytic reaction comes from Lam and coworkers.[30] They made use of an external oxidant to regenerate the active copper catalyst. A number of chemical oxidants were screened to find the optimal reagent that would oxidize Cu(II) to Cu(III), or Cu(I) to Cu(II), without oxidizing the arylboronic acid to phenol in the process (Scheme 64). The reaction was found to be tolerant of a variety of nucleophilic substrates including amines, anilines, sulfonamides, imidazoles, and phenols. Of the oxidants screened, pyridinium *N*-oxide and TEMPO were found to give the best results with the widest range of nucleophiles while yielding a minimal amount of oxidation to the arylboronic acid; however, no general oxidant was found to be suitable for all the nucleophiles screened. In fact, different oxidants gave varying yields with different nucleophiles with no obvious correlations.

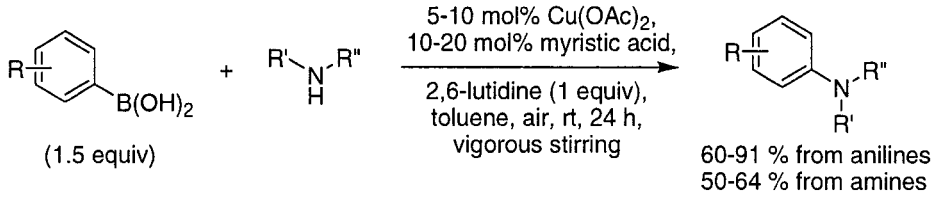


pyridium *N*-oxide	>	TEMPO	>	NMO	>	di-*t*-butyl nitroxide	>	(1R)-(10-camphor-sulfonyl)oxaziridine	>	$NaBO_3 \cdot H_2O$	>	$K_3Fe(CN)_6$	>	*m*CPBA
69%		64%		62%		55%		48%		31%		11%		6%

Scheme 64 - Regeneration of the Active Copper Species via Chemical Oxidation

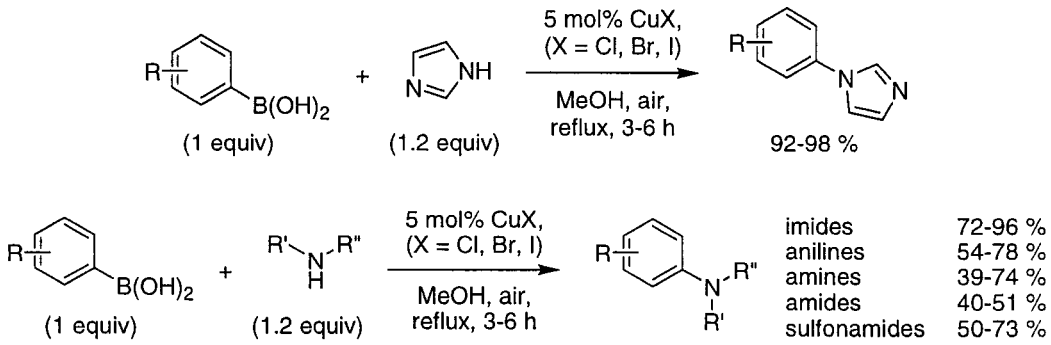
Buchwald and coworkers have reported a catalytic variant of these Ullmann-type couplings (Scheme 65). Their procedure adds a catalytic amount of myristic acid ($C_{13}H_{27}COOH$) to allow the $Cu(OAc)_2$ catalyst to dissolve more easily in the organic solvent. The reaction is run in high concentration using a minimal amount of solvent in an oversized reaction vessel (e.g. 100 mL round bottom flask for 2 mL reaction volume) with vigorous stirring. This is necessary to maximize the surface area of the reaction mixture as the reactions are performed under an open atmosphere, and air serves as the oxidant to copper. Anilines reacted to provide good to

excellent yields of the arylated product, while primary and secondary amines underwent the cross-coupling only moderately. Early attempts with imidazoles gave only low yields (< 30 %) of the cross-coupled product.[31] Interestingly, Buchwald's conditions did not require the presence of molecular sieves to avoid by-product formation.



Scheme 65 - Copper-Catalyzed Arylation of Amines and Anilines in Toluene

Most recently, the Chinese group of Xie *et al.* have reported a copper-catalyzed, ligandless and base free protocol for the arylation of imidazoles,[32a] amines, amides, imides, and sulfonamides[32b] with arylboronic acids that is similar to our own (*vide infra*). Their conditions combine a catalytic amount of a copper(I) halide salt, the arylboronic acid and a slight excess of the nucleophile in dry methanol; the reaction mixture is then refluxed under an open atmosphere for several hours. Imidazoles were reported to arylate in excellent yields, while the other nitrogen-based nucleophiles afforded moderate to good yields of the cross-coupled products (Scheme 66).

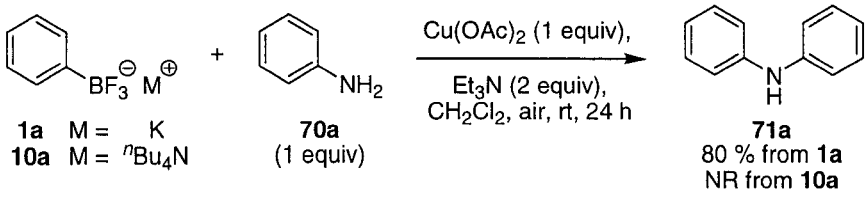


Scheme 66 - Copper-Catalyzed Arylation of Nitrogen Nucleophiles in Methanol

III.2 Results and Discussion

III.2.1 Copper-Mediated Cross-Coupling of Organotrifluoroborate Salts with Anilines

The investigation of copper-promoted carbon-nitrogen bond formations with the organotrifluoroborate salts is a natural extension of the previous *O*-arylation project. Initial experiments using 1 equivalent of each cross-coupling partner, a stoichiometric amount of $Cu(OAc)_2 \cdot H_2O$ and 2 equivalents of Et_3N under Chan's conditions gave a good yield of the phenylated product **71a** from the potassium trifluoroborate salt (Scheme 66), but once again, no reaction from the TBA^+ salts. A series of experiments were then performed to optimize the reaction conditions. Since the TBA^+ derivatives gave no trace of the cross-coupled product after two attempts, all further optimization experiments were performed with the potassium salts.



1a M = K
10a M = ^{n}Bu$_4$N

70a
(1 equiv)

71a
80 % from **1a**
NR from **10a**

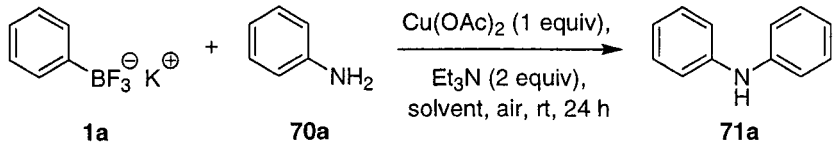
Scheme 67 - Initial Attempt at Arylation of Aniline via Copper-Mediation

III.2.1.1 Optimization of the Reaction Conditions

The nature of the solvent was the first aspect explored in the optimization reactions. The results of these experiments contrasted greatly with that of the *O*-arylation optimizations. Of the solvents examined, those known to coordinate well with Cu gave the best results (Table 23, entries 1, 4, and 5). Water and CH_2Cl_2 gave good yields of the product individually (Table 23, entries 1 and 2); however, when a combination of both solvents was used, the reaction gave a poor yield of **71a** (Table 23, entry 3), most likely due to partitioning of the reactants in separate layers of the reaction mixture.

EtOAc gave the best result from the solvent trials, and was used as the solvent of choice for the copper source experiments. The copper reagent was found to have a profound effect on the efficacy of the cross-coupling. In general, Cu(I) sources, although useful in other organic transformations, did not promote these cross-couplings well (Table 24, entries 1-6). In the case of the Cu(I) halides, a side reaction was promoted leading to azobenzene (**72**) as the major

Table 23 - Solvent Studies for Arylation of Anilines with Potassium Organotrifluoroborates

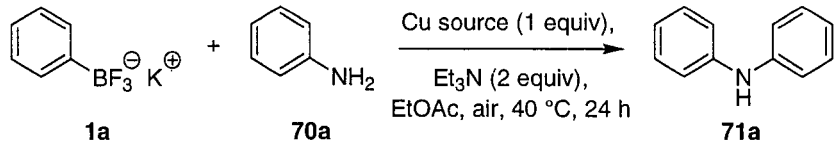


1a (1 equiv) + **70a** (1 equiv) → **71a**

Entry	Solvent	Yield (%)[a]
1	H_2O	77
2	CH_2Cl_2	80
3	CH_2Cl_2 : H_2O (1 : 1)	19
4	MeCN	83
5	EtOAc	84
6	acetone	25
7	DME	29

a) isolated yield.

Table 24 - Effect of the Copper Species on the Arylation of Aniline



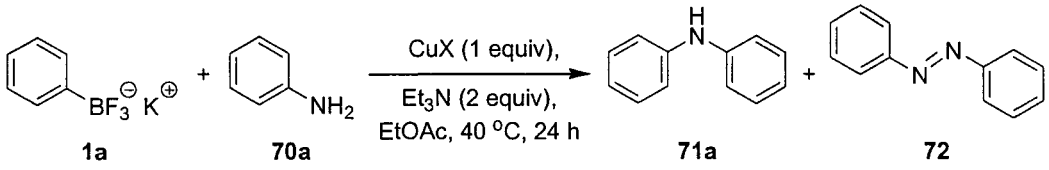
1a (1 equiv) + **70a** (1 equiv) → **71a**

Entry	Cu(I) Source	Yield (%)[a]	Entry	Cu(II) Source	Yield (%)[a]
1	CuBr·DMS	low[b]	7	$Cu(OAc)_2 \cdot H_2O$	84
2	CuCl	low[b]	8	$Cu(acac)_2$	-
3	CuI	17[b]	9	$CuBr_2$	-
4	CuCN	-	10	$CuCl_2$	-
5	CuSCN	-	11	$CuSO_4 \cdot 5H_2O$	74
6	Cu_2O	10	12	$CuSO_4$ (anhydrous)	12

a) isolated yield. b) major product: azobenzene (**72**, *vide* Table 25).

product isolated (Table 24, entries 1-3 and Table 25, entries 1-3).[33] Only two of the Cu(II) species examined showed any reactivity, fortunately they gave the cross-coupled product in good yield (Table 24, entries 7 and 12). Interestingly, the pentahydrate form of $CuSO_4$ gave a good yield, while its anhydrous counterpart gave a poor yield (Table 24, entry 11 versus 12).

Table 25 - Cu(I) Halide Promoted Homocoupling of Anilines



1a 70a 71a 72

Entry	Cu(I) Source	Yield of 71a (%)[a]	Yield of 72 (%)[a]
1	CuI	17	55
2	CuBr·DMS	15	60
3	CuCl	12	66

a) isolated yield.

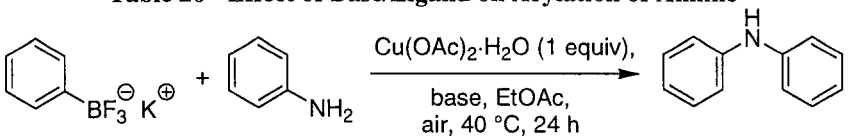
The results of the solvent studies showed that the reactions with the organotrifluoroborates were tolerant of the presence of water, unlike their boronic acids counterparts.[28] In Evans' work, molecular sieves had to be used to sequester the water produced from triarylboroxine formation. Since organotrifluoroborate salts are not as susceptible to the side reactions, it was unnecessary to use molecular sieves in order to achieve the same results. Combining this solvent observation with the copper source studies suggests that water may be required for the activation of the trifluoroborate salts for transmetallation to copper through a fluoroxyboronate species (*vide* I.2.3.1, Chapter 1, reference 42, and IV.2.1.2.1).

On a final note, the reaction temperature was raised from room temperature to 40 °C in an attempt to increase the yields from the less reactive catalysts; however, this change in temperature did not appear to have an impact on the yield of the reaction (Table 24, entry 7 versus Table 23, entry 5).

From Chan and Lam's observations, the exact role of the amine base in the reaction is not clearly understood. Although it is speculated to act as a ligand to the copper reagent,[29c] it is unclear as to why 5 to 10 equivalents of the base are required to obtain the best results in Evans'

synthesis of biaryl ethers.[28] The reaction was attempted employing three of the common bases reported in the literature as good ligands to copper.[34] The control reaction, without addition of a base, gave low yields of the desired product. This reaction relied on the solvent alone to act as the ligand to copper (Table 26, entry 1). Et_3N was found to be a better ligand than pyridine, but only 2 equivalents were required for the desired effect (Table 26, entries 3 versus 5); addition of excess base did not influence the reaction yields (Table 26, entries 4 and 6). The use of 1,10-phenanthroline completely inhibited the reaction, as the ligand chelated so well to the copper reagent that it was effectively sequestered from the reaction; only the unreacted substrates were isolated in the end (Table 26, entry 7). Attempts at using a polymer supported base to simplify the work-up and isolation procedure of the reaction were met with either a low yield or no reaction at all (Table 26, entries 8-10). The close proximity of multiple functional groups on the polymer support capable of chelation to copper likely acted to segregate the catalyst from the

Table 26 - Effect of Base/Ligand on Arylation of Aniline



1a **70a** **71a**

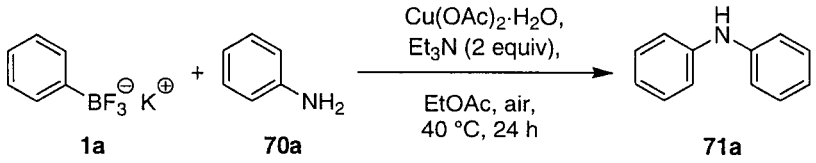
Entry	Base	Functionality	Equiv of Base	Yield (%)[a]
1	no base	-	-	20
2	Et_3N	-	1.0	40
3	Et_3N	-	2.0	84
4	Et_3N	-	5.0	85
5	pyridine	-	2.0	37
6	pyridine	-	5.0	40
7	1,10-phenanthroline	-	1.0	-
8	Amberlyst A-21	3° amine	-	18
9	Amberlite IRA-400 (OH)	4° ammonium	-	-
10	DOWEX IX2-100 (Cl)	4° ammonium	-	-

a) isolated yield.

rest of the reaction, or perhaps the presence of the ammonium cations acted to shut down the reaction as previously observed. In any case, only starting materials were recovered from these reactions.

In the case of aniline arylations, the effect of the amount of the organoboron reagent used on the reaction outcome was a serendipitous discovery. In an attempt to prepare the diarylated product, 2 equivalents of **1a** were used in the reaction. Instead of the expected triphenylamine product, **71a** was isolated in a quantitative yield (Table 27, entry 1). It is presumed that the diarylated compound is too sterically hindered for a second arylation to take place. Working backwards by lowering the amount of **1a** used, it was discovered that only 1.1 equivalents of the organotrifluoroborate was necessary for comparable yields. It is hypothesized that though organotrifluoroborate salts do not undergo the arylation of water as readily as their boronic acid counterparts, some of those side reactions do occur, and hence a slight excess of the reagent is necessary for complete conversion of the starting aniline. In all of the previous reactions, only the diphenylamine (**71a**) and the unreacted aniline (**70a**) were isolated in the end. Phenol and diphenyl ether were never isolated, but may have been present at concentrations too low to be detectable by TLC and NMR. Finally, attempts to render this particular set of conditions catalytic in the copper reagent were unsuccessful (Table 27, entries 5 and 6).

Table 27 - Effect of Excess Organotrifluoroborate and Reduced Catalyst Loading on the Arylation of Aniline



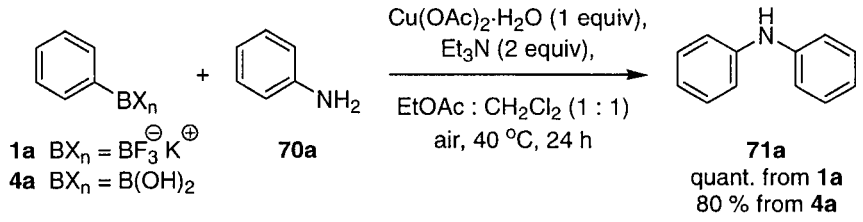
1a **70a** **71a**

Entry	Equiv of 1a	Equiv of $Cu(OAc)_2 \cdot H_2O$	Yield (%)[a]
1	2.0	1.0	quant.
2	1.5	1.0	quant.
3	1.1	1.0	95
4	1.0	1.0	80
5	1.2	0.5	45
6	1.2	0.1	9

a) isolated yield.

III.2.1.2 Scope and Limitations

As the scope and limitations of the reaction were explored, it was soon discovered that many of the aniline substrates were insoluble in EtOAc. Although not an obstacle at first, it was decided that any future problems could be pre-empted by using a 1:1 mixture of CH_2Cl_2:EtOAc for further investigations. With this set of "re-optimized" reaction conditions at hand (Scheme 68), the scope and limitations of the reaction were investigated. The optimized conditions were found to offer greater yields with the organotrifluoroborate salts than those of their boronic acid counterparts whose reactions also generated diphenyl ether and phenol in significant quantities.

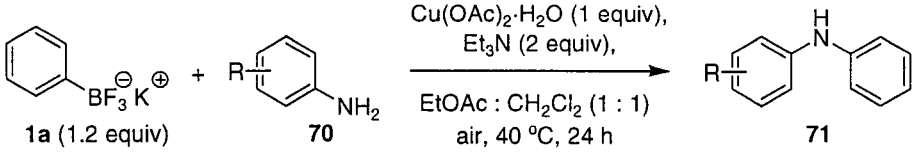


Scheme 68 - Optimized Conditions for the Arylation of Aniline with Potassium Aryltrifluoroborate Salts

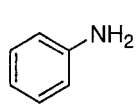
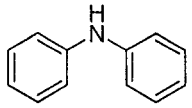
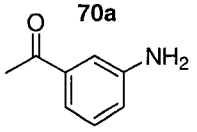
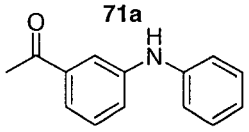
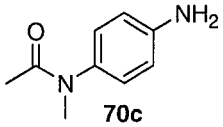
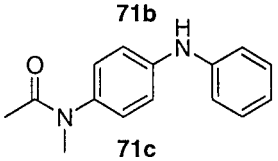
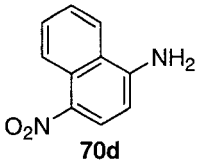
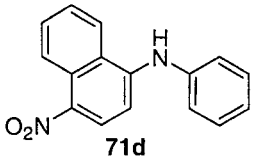
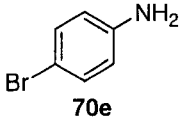
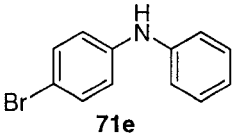
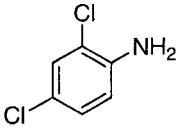
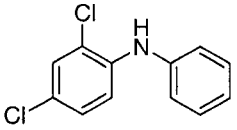
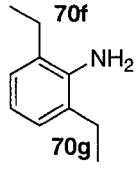
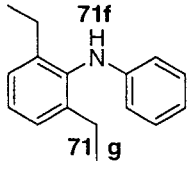
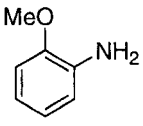
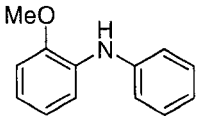
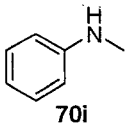
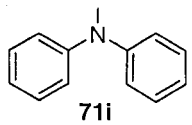
A variety of aniline derivatives were found to cross-couple with potassium phenyl-trifluoroborate (**1a**) in good to excellent yields. The reaction is tolerant of numerous functional groups including electron-withdrawing (Table 28, entries 2 and 4), and electron-donating substituents (Table 28, entries 3, 7 and 8). Halogen containing aniline derivatives did not undergo competitive Ullmann homocoupling under these mild conditions, but instead gave excellent yields of the *N*-arylated products (Table 28, entries 5 and 6). Steric hindrance *ortho* to the amine moiety only slightly lowered the isolated yield of the product (Table 28, entries 6-8). *N*-methylaniline is the only example of arylation of a secondary amine to give a tertiary amine product (Table 28, entry 9). In all cases, monoarylation of the starting material was the only reaction observed. The triaryl derivatives were never present in the reaction mixtures; an observation which is consistent with the established literature results.[20-22, 31]

Aniline derivatives participated well in the cross-coupling reaction, but primary and secondary amines did not. Of the amines attempted, only the primary amines homoveratrylamine (**73a**) and benzyl amine (**73b**), and the secondary amine piperidine (**75a**) afforded the arylated products (Table 29, entries 1-3), albeit in moderate yields. When simple aliphatic amines were employed in the reaction, none of the desired products or the unreacted starting materials were

Table 28 - Stoichiometric Copper-Mediated Phenylation of Aniline Derivatives



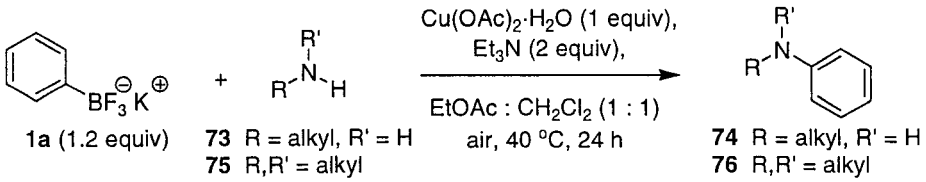
1a (1.2 equiv) **70** **71**

Entry	Aniline	Product	Yield (%)[a]
1	 **70a**	 **71a**	98
2	 **70b**	 **71b**	96
3	 **70c**	 **71c**	92
4	 **70d**	 **71d**	72
5	 **70e**	 **71e**	95
6	 **70f**	 **71f**	86
7	 **70g**	 **71 g**	75
8	 **70h**	 **71h**	88
9	 **70i**	 **71i**	80

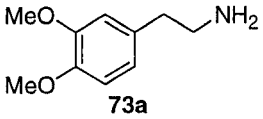
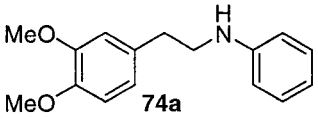
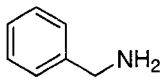
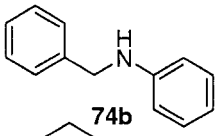
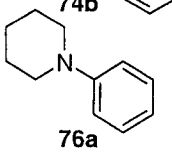
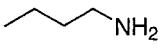
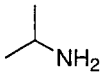
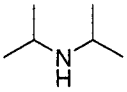
a) isolated yields.

recovered. In fact, the sole compound recovered from the reaction mixture was diphenylamine (**71a**) in near quantitative yields (Table 29, entries 4-6). Even when the reactions were performed under Chan and Lam's original conditions this observation was found to be consistent.

Table 29 - Stoichiometric Copper-Mediated Phenylation of Primary and Secondary Amines



1a (1.2 equiv) | **73** R = alkyl, R' = H; **75** R,R' = alkyl | **74** R = alkyl, R' = H; **76** R,R' = alkyl

Entry	Amine	Product	Yield (%)[a]
1	 **73a**	 **74a**	95
2	 **73b**	 **74b**	77
3	 **75a**	 **76a**	65
4	 **73c**	-	0[b]
5	 **73d**	-	0[b]
6	 **75b**	-	0[b]

a) isolated yields. b) nearly quantitative yields of Ph_2NH (**71a**) were isolated.

III.2.1.2.1 Copper-Promoted *N*-Dealkylations

It is believed that the production of the diphenylamine (**71a**) is due to a competitive copper-mediated *N*-dealkylation. Hence, the cross-coupling between **1a** and an amine (**73** or **75**) would proceed as expected to form the *N*-arylated product, but this alkylarylamine could then undergo a subsequent copper-promoted *N*-dealkylation. The resultant aniline then participated in a second cross-coupling with a second equivalent of the organoboron reagent, thus affording the diarylated product (Figure 22).

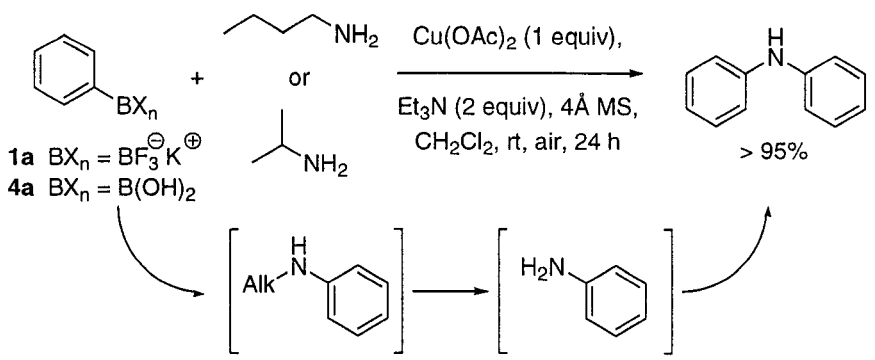


Figure 22 - Arylation and Subsequent Copper-Promoted *N*-Dealkylation of Aliphatic Amines

This hypothesis is supported by the observations of Tolman *et al.*, who observed that bis(μ-oxo)dicopper(III) complexes (**77**) promoted the oxidative C-N bond scission of aliphatic amines (Figure 23).[35] X-ray crystal structures of several bis(μ-oxo)dicopper(III) complexes (**77**) were obtained; the crystallographic data suggested the existence of a C–H···O hydrogen bond between a hydrogen α to the coordinating nitrogen atom and the oxo bridge. The authors suggested a rapid equilibrium in solution between the hydrogen bonded and nonbonded forms of **77**. The *N*-dealkylation could then proceed through various pathways. Path A is analogous to the classical cytochrome P450 rebound mechanism,[36] as it involves a rate-determining hydrogen atom abstraction followed by fast collapse of the resulting carbon radical (**78**) with the hydroxyl

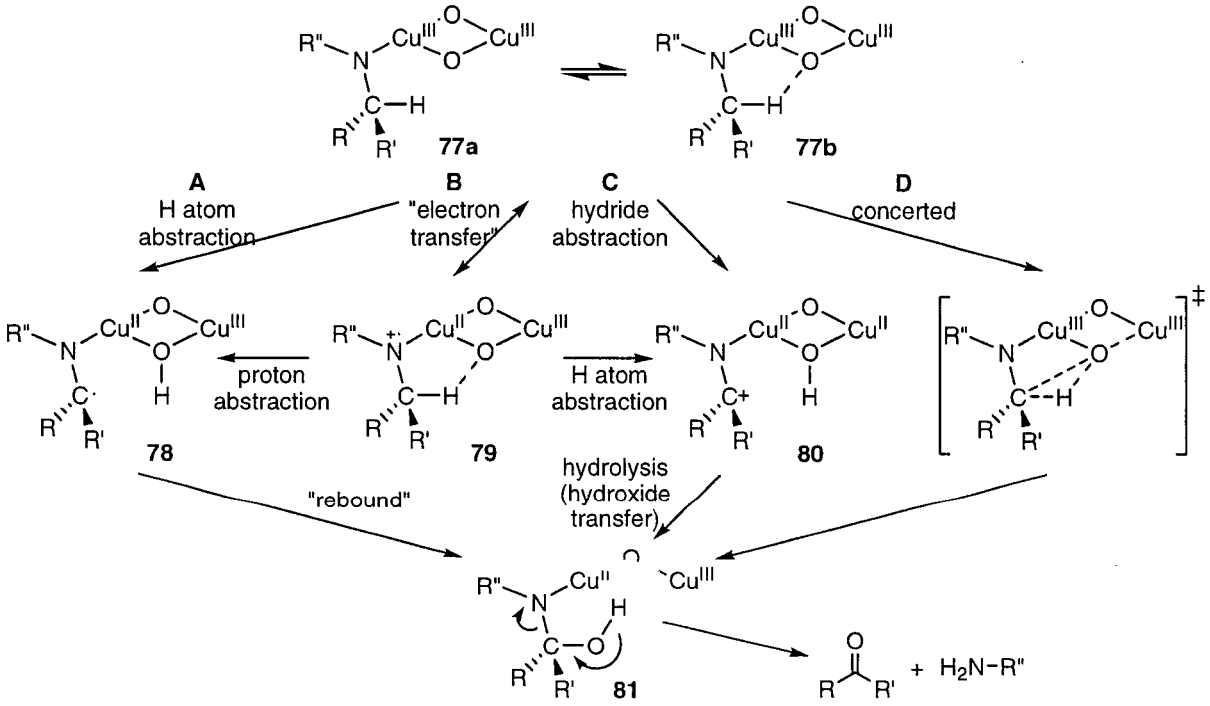


Figure 23 - *N*-Dealkylation Promoted by Bis(μ-oxo)dicopper Complexes

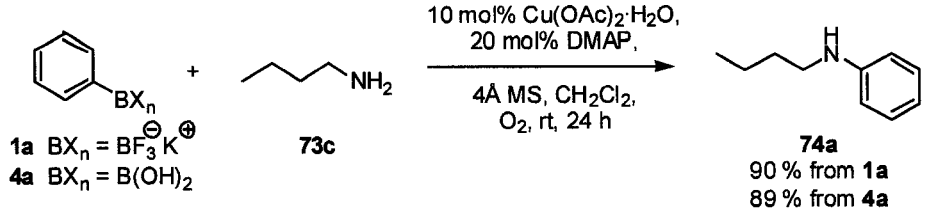
unit to afford aminol **81**. Path B is an electron transfer from nitrogen to copper generating a radical cation on nitrogen, thus intermediate **79** is perceived more as a resonance structure of **77** than as a distinct species in itself. A proton abstraction from **79** would then yield the radical **78**; alternatively, **79** can also undergo a hydrogen atom abstraction to generate the carbocation **80**, which is also accessible from **77** through path C: a hydride abstraction. Regardless of how they had arisen, both radical **78** and carbocation **80** can then collapse to the aminol **81**. An E2-type elimination from **81** would then lead to the ketone (or aldehyde) and the *N*-dealkylated amine products. Finally, aminol **81** can also be arrived at through the concerted pathway D.[37]

This copper-promoted *N*-dealkylation helps to explain why examples of *N*-arylation of aliphatic amines are sparse in the literature. Under Chan and Lam's stoichiometric conditions, the bis(μ-oxo)dicopper complexes can be formed via interaction of the copper reagent and water liberated through the formation of boroxines from the boronic acids. Typically only primary amines with bulky substituents and secondary amines were able to survive the conditions for arylation. In the case of Buchwald's arylation protocol, a few examples for primary amine arylation were reported. The catalytic amounts of copper may have aided in the prevention of the bis(μ-oxo)dicopper complex formation; however, the relatively concentrated reaction conditions (e.g. 2 mL of solvent for 1 mmol amine substrate) would have off set much of the benefits of lower catalyst loading. Thus, the arylation of aliphatic amines were achieved only in moderate yields. No mention was made of any side products of the reaction.[31]

The undesired side reaction could be exploited for the synthesis of symmetrical diarylamines, as simple aliphatic amines can be used as a surrogate for ammonia in the cross-coupling. However, it was still desirable to find a set of conditions for reliable arylation of aliphatic amines. We believed that the arylation of aliphatic amines could be achieved in greater yields if formation of the bis(μ-oxo)dicopper complexes could be prevented via a two-pronged approach: reduction of the amount of copper present and dilution of the reaction mixture. Hence, development of a catalytic protocol for the copper-mediated cross-coupling of organoboron compounds and amines was initiated.

III.2.2 Copper-Catalyzed Cross-Coupling of Organotrifluoroborate Salts and Organoboronic Acids with Aliphatic Amines

Following on the heels of our successful development of an *O*-arylation protocol, *n*-butylamine (**73c**) was subjected to the previously optimized reaction conditions. The reaction proved to be gratifyingly successful as excellent yields of the monoarylated *N*-butyl aniline (**74c**) was isolated from both the potassium phenyltrifluoroborate salt (**1a**) and phenylboronic acid (**4a**), thus confirming our hypothesis that the *N*-dealkylation could be prevented (Scheme 69).



Scheme 69 - Phenylation of *n*-Butylamine via Previously Optimized Conditions

III.2.2.1 Re-examination of Optimized Conditions

A quick investigation into the necessity of each component of the reaction mixture revealed that the use of DMAP as ligand to copper was redundant. The ligand is hypothesized to serve two purposes in the reaction: first, to aid in the solubility of the copper catalyst and second, to act as an electron-rich ligand to activate an organocuprate intermediate towards reductive elimination (*vide* IV.1.1.6). However, in the arylation of amine substrates, the nucleophile itself is a better ligand to the copper reagent than that of the DMAP additive, as evidenced by the colour change in the reaction media after addition of the amine to a pre-dissolved and stirring mixture of the Cu/DMAP system (Figure 24). Omission of the DMAP ligand from the reaction mixture did not have a significant impact on the success of the arylation.

Vessel A - 4Å MS, 10 mol% $Cu(OAc)_2 \cdot H_2O$ and 20 mol% DMAP dissolved in CH_2Cl_2.

Vessel B - Same as vessel A plus 1 equivalent $n BuNH_2$.

Figure 21 - Amine Chelation to Copper Catalyst Causing Colour Change in Reaction Mixture

Finally, heat was found to play a greater role in these cross-couplings than in the reaction of the oxygen-based nucleophiles. Several substrates that underwent the arylation poorly at room temperature, fared much better with slight warming of the reaction to 40 °C. Hence, it was found that the optimal set of conditions for *N*-arylation was the reaction of 2 equivalents of the organoboron compound to 1 equivalent of the amine in CH_2Cl_2 with 10 mol % $Cu(OAc)_2 \cdot H_2O$ and 4Å molecular sieves. Running the reaction at 40 °C for a period of 24 h usually gave good to excellent yields of the corresponding monoarylated products.

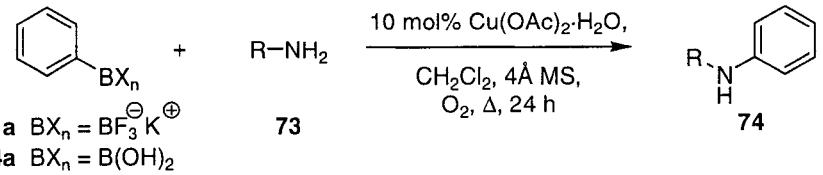
III.2.2.2 Scope and Limitations

Unsurprisingly, the arylation of amines occurred in greater yields than that of the reaction of the alcohols. The amines are better ligands to copper and the difference in the nucleophilicity between the oxygen and nitrogen-based substrates was the major factor that distinguished and characterized their reactivities. Simple aliphatic amines were able to undergo the reaction to afford the monoarylated products without noticeable *N*-dealkylated side products, or the generation of diarylamine. In addition, none of the diarylated products were observed in any of the cross-couplings performed despite the presence of 2 equivalents of the boron reagent for each equivalent of the nucleophile. Interestingly, the arylboronic acids were found to be the superior cross-coupling partner in these *N*-arylations, often giving slightly greater yields than reactions with the trifluoroborate salts. Perhaps the more reactive nucleophiles favoured a more soluble, and hence more readily available, cross-coupling partner.

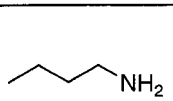
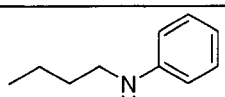
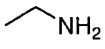
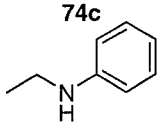
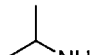
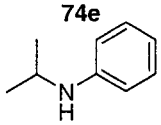
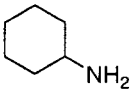
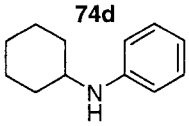
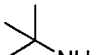
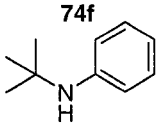
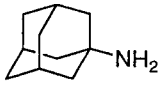
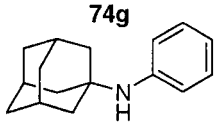
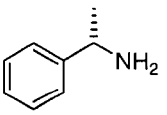
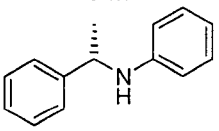
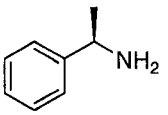
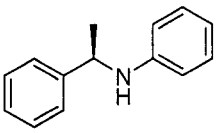
n-Butylamine (**73c**) was arylated in excellent yields, while the much more volatile ethylamine (**73e**) did not survive well under the optimized conditions (Table 30a, entries 1 and 2). Nevertheless, a small quantity of *N*-ethyl aniline (**74e**) was isolated. The product yield could perhaps be increased by employing an excess of the nucleophile, or by running the cross-coupling under a sealed system. As with the reaction of alcohols, the arylation of amines was found to be sensitive to steric hindrance around the amino moiety; however, the increased nucleophilicity of the amine substrates compared to the alcohols helped to overcome this problem. Hence, isopropylamine (**73d**) gave excellent yields of the arylated product, while cyclohexylamine (**73f**) produced a lower yield (Table 30a, entries 3 and 4). Fascinatingly, amines with quaternary carbons α to nitrogen still participated in the cross-coupling, *t*-

butylamine (**73g**) and adamantylamine (**73h**) afforded moderate yields of the corresponding anilines (Table 30a, entries 5 and 6). In contrast, tertiary alcohols did not participate in the cross-coupling even at higher temperatures (*vide* II.2.1.2). Finally, stereocentres were not racemized as demonstrated by the arylation of both enantiomers of α-methylbenzylamine (Table 30a, entries 7 and 8).

Table 30a - Copper-Catalyzed Arylation of Primary Aliphatic Amines[a]

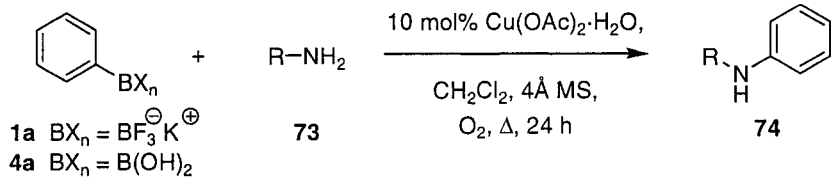


1a $BX_n = BF_3^{\ominus}K^{\oplus}$
4a $BX_n = B(OH)_2$
73
74

Entry	1° Amine	Temp. (°C)	Product	Yield from 1a (%)[b]	Yield from 4a (%)[b]
1	 **73c**	rt	 **74c**	89	92
2	 **73e**	rt	 **74e**	13	-
3	 **73d**	rt	 **74d**	98	98
4	 **73f**	rt 40	 **74f**	79 -	- 85
5	 **73g**	rt 40	 **74g**	26 -	- 39
6	 **73h**	40	 **74h**	57	67
7	 **73i**	rt	 **74i**	91[c]	-
8	 **73j**	rt	 **74j**	78[c]	-

a) reaction times are not optimized for individual substrates. b) isolated yields.
c) epimerization of the stereocentre did not occur under the reaction conditions.

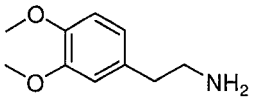
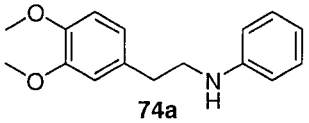
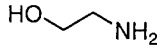
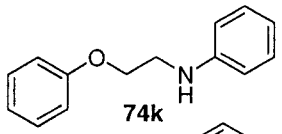
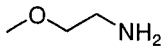
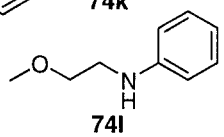
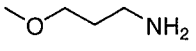
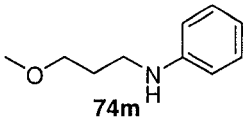
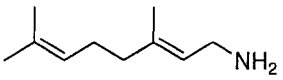
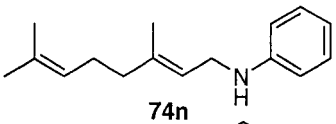
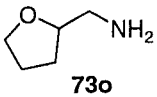
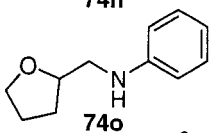
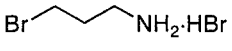
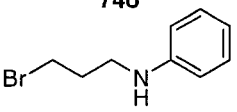
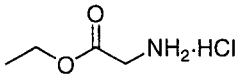
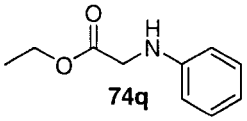
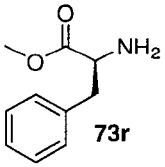
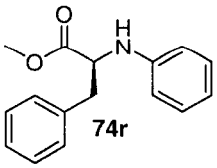
Table 30b - Copper-Catalyzed Arylation of Primary Aliphatic Amines and Ammonium Salts[a]



1a $BX_n = BF_3^{\ominus}K^{\oplus}$
4a $BX_n = B(OH)_2$

73

74

Entry	1° Amine	Temp. (°C)	Product	Yield from 1a (%)[b]	Yield from 4a (%)[b]
1	 **73a**	rt 40	 **74a**	90 -	- 95
2	 **73k**	40	 **74k**	13	15
3	 **73l**	rt 40	 **74l**	32 79	- 94
4	 **73m**	rt 40	 **74m**	78 -	- 85
5	 **73n**	40	 **74n**	80	89
6	 **73o**	40	 **74o**	83	91
7	 **73p**	40	 **74p**	-	86[d]
8	 **73q**	40	 **74q**	-	84[d]
9	 **73r**	40	 **74r**	-	90[c,d]

a) reaction times are not optimized for individual substrates. b) isolated yields. c) epimerization of the stereocentre did not occur under the reaction conditions. d) ammonium salt was pretreated with Amberlyst A-21 in MeCN for 30 min prior to addition to the reaction mixture. Yield reported is over both steps.

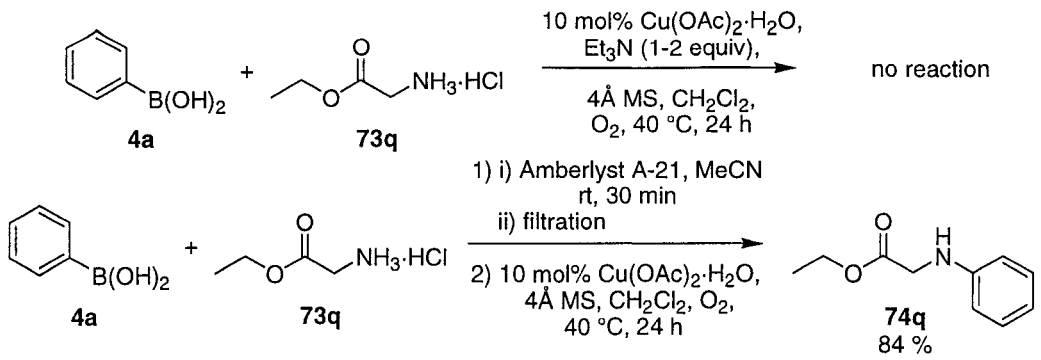
Ethanolamine (**73k**) was subjected to the reaction conditions with hopes that in the absence of DMAP, the catalytic system would be too deactivated for *O*-arylation, thereby permitting mono-*N*-arylation to occur in presence of a free hydroxyl. Unfortunately, this particular substrate did not participate well in the cross-coupling and only a low yield of the *N*- and *O*-diarylated product **74k** was obtained (Table 30b, entry 1). Protection of the hydroxyl moiety (e.g. as the methyl ether) allowed the reaction to proceed. 2-Methoxy-ethylamine (**73l**) is a strongly chelating ligand to copper, forming a gel like material when the two are mixed in solution. Reaction of this substrate at room temperature produced only a low yield of the arylated product; however, heating the reaction mixture to 40 °C allowed solvation of the copper complex and the arylation to proceed as expected. 3-Methoxy-propylamine (**73m**) did not encounter the same obstacle being a poorer ligand for copper (Table 30b, entry 3 versus 4).

Both allyl amines (**73n**) and heterocyclic amines (**73o**) were able to undergo the cross-coupling in excellent yields (Table 30b, 5 and 6) and in the case of the geranylamine (**73n**) isomerization of the alkene was not detected. As in the arylation of alcohols, the alkyl halide substituents were also able to undergo the cross-coupling without the expected nucleophilic substitution on the halide moiety (Table 30b, entry 7).

One of the more useful aspects of this methodology is the arylation of amino acid derivatives (Table 30b, entries 8 and 9). The neutral reaction conditions permit amino acid esters to be arylated without epimerization of the acid sensitive stereocentre. However, the substrates did require esterification of the carboxylate, as the free acids were unable to undergo the reaction. Lam *et al.* had reported the same observation in their stoichiometric copper-mediated arylation of amino acid esters.[21b]

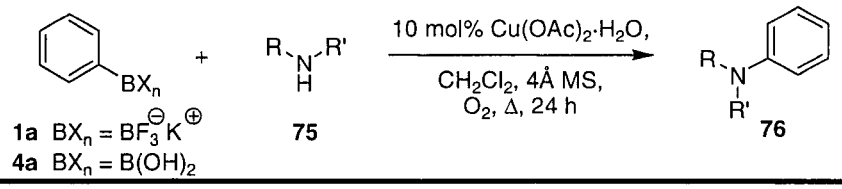
It should also be noted that only free amines can be employed in the cross-coupling reaction. Ammonium halide salts had to be pre-activated by treatment with the basic resin Amberlyst A-21 before addition to the reaction mixture. *In situ* activation of the ammonium salt by adding one or more equivalents of base did not have the same effect (Scheme 70).

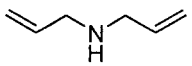
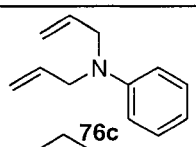
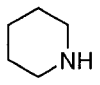
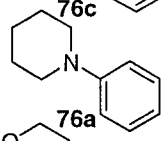
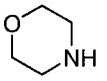
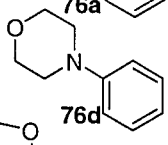
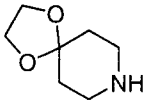
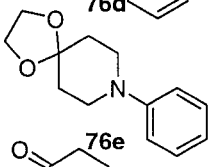
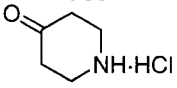
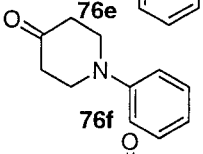
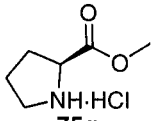
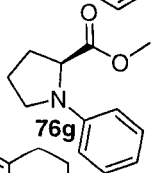
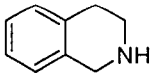
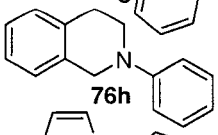
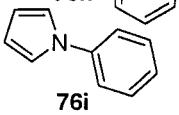
Secondary amines worked well in the cross-coupling. Once again the increased nucleophilicity of the substrates helped to compensate for the extra steric hindrance around the reactive nitrogen moiety. A variety of nitrogen heterocycles were arylated to afford high yields of the cross-coupled products. Two of the more interesting examples include: proline methyl



Scheme 70 - Activation and Cross-Coupling of Ammonium Halide Salts

Table 31 - Copper-Catalyzed Arylation of Secondary Aliphatic Amines and Ammonium Salts[a]



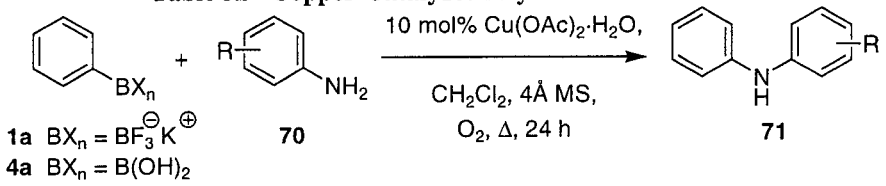
Entry	2° Amine	Temp. (°C)	Product	Yield from 1a (%)[b]	Yield from 4a (%)[b]
1	 **75c**	40	 **76c**	56	61
2	 **75a**	rt 40	 **76a**	78 -	- 86
3	 **75d**	40	 **76d**	81	90
4	 **75e**	40	 **76e**	87	86
5	 **75f**	40	 **76f**	-	83[d]
6	 **75g**	40	 **76g**	-	74[c,d]
7	 **75h**	rt	 **76h**	72	72
8	 **75i**	40	 **76i**	80	89

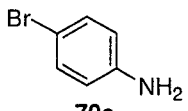
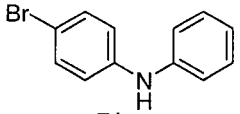
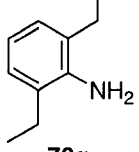
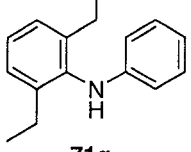
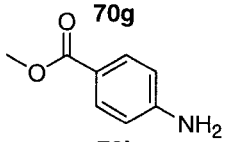
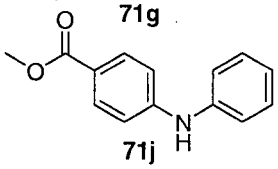
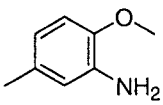
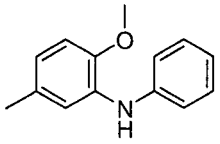
a) reaction times are not optimized for individual substrates. b) isolated yields. c) epimerization of stereocentre was not detected. d) ammonium salt was pretreated with Amberlyst A-21 in MeCN for 30 min prior to addition to the reaction mixture. Yield reported is over both steps.

ester (**75g**) where epimerization of the stereocentre did not occur (Table 31, entry 6), and pyrrole (**75i**) as it had previously been reported that only pyrrole derivatives with electron-withdrawing substituents were able the participate in the stoichiometric arylations (Table 31, entry 8).[26]

Anilines did not react as well in the cross-coupling. The combined effect of steric hindrance around the amino functionality and the lowered nucleophilicity of the substrate resulted in lower yields of the diarylamine products (Table 32). Additionally, competitive oxidative homocoupling of the anilines to azobenzene derivatives (10-15 %) occurred under these conditions.[33]

Table 32 - Copper-Catalyzed Arylation of Anilines[a]



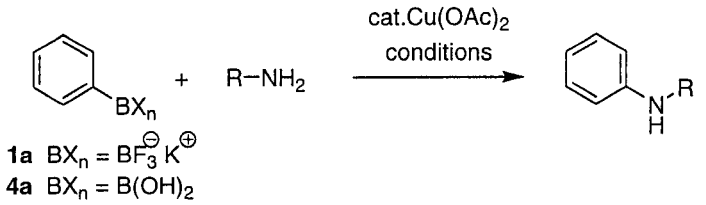
Entry	Aniline	Temp. (°C)	Product	Yield from 1a (%)[b]	Yield from 4a (%)[b]
1	 **70e**	40	 **71e**	30	53
2	 **70g**	40	 **71g**	34	49
3	 **70j**	40	 **71j**	35	40
4	 **70k**	40	 **71k**	51	66

a) reaction times are not optimized for individual substrates. b) isolated yields.

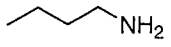
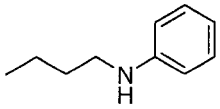
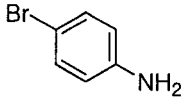
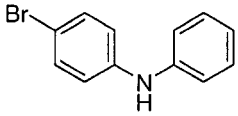
A comparison of our conditions with those of Buchwald's revealed that the two are complementary (Table 33). While Buchwald's conditions give excellent yields of the arylated anilines, the arylation of *n*-butylamine (**73c**) produces only 47 % of the product. The lower yields obtained under the Buchwald protocol using aliphatic amines is due, at least in part, to the fact that the higher concentration of Cu present results in undesired *N*-dealkylation side reactions.

Indeed, in our hands, 26 % of diphenylamine was isolated in the reaction of *n*-butylamine (**73c**) under Buchwald's conditions. The failure of the trifluoroborate salt to react under Buchwald's conditions is due to its insolubility in toluene at room temperature.

Table 33 - Comparison of Copper-Catalyzed Arylation Methods



1a $BX_n = BF_3^{\ominus}K^{\oplus}$
4a $BX_n = B(OH)_2$

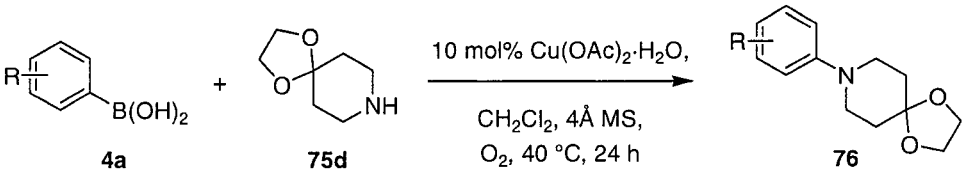
Entry	Nucleophile	Conditions[a]	Product	Yield from 1a (%)[b]	Yield from 4a (%)[b]
1	 **73c**	A	 **74c**	89	92
		B		0	47
2	 **70e**	A	 **71e**	30	53
		B		0	91

a) reaction conditions: A = 10 mol% $Cu(OAc)_2 \cdot H_2O$, CH_2Cl_2, 4Å MS, 40 °C, O_2, 24 h;
B = 10 mol% $Cu(OAc)_2$, 20 mol% myristic acid, 2,6-lutidine (1 equiv), toluene, rt, air (Ref. 31).
b) isolated yields.

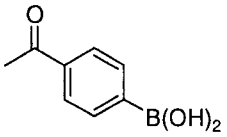
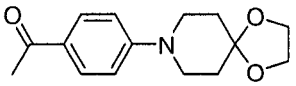
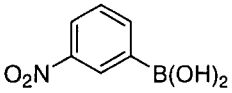
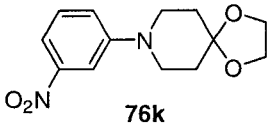
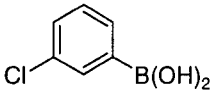
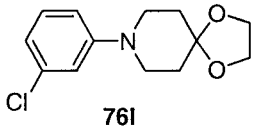
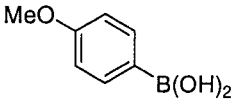
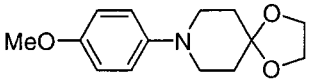
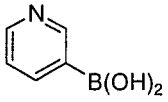
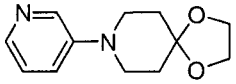
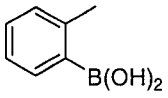
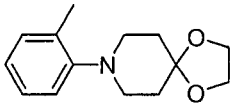
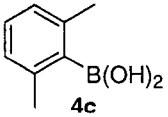
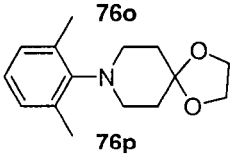
Several other nitrogen-based nucleophiles were subjected to the arylation conditions without success. The lowered nucleophilicity of imidazoles, carbamates, and ureas made them unfavourable for arylation under these conditions.

Since both the boronic acids and the trifluoroborate salts gave similar yields in the arylation of amines, it was decided that development of a protocol for the more readily available boronic acids was desirable. In contrast to that of the *O*-arylations, the electronic properties of the aryl moiety on the boronic acid did not play a significant role in the cross-coupling. Both electron-rich and electron-poor arylboronic acids gave excellent yields of the corresponding anilines (Table 32, entries 1-4). Even the heterocyclic boronic acid **4j** gave a moderate yield of the arylated amine (Table 32, entry 5). Steric hindrance around the boron moiety proved to be a greater obstacle to the cross-coupling, as yields dropped significantly in the reaction of *ortho*-tolylboronic acid (**4b**) and only a trace of product observable by ^1H NMR of the crude reaction mixture was afforded with 2,6-dimethylphenylboronic acid (**4c**; Table 33, entries 6 and 7).

Table 34 - Copper-Catalyzed *N*-Arylation of 1,4-Dioxa-8-azaspiro[4.5]decane[a]

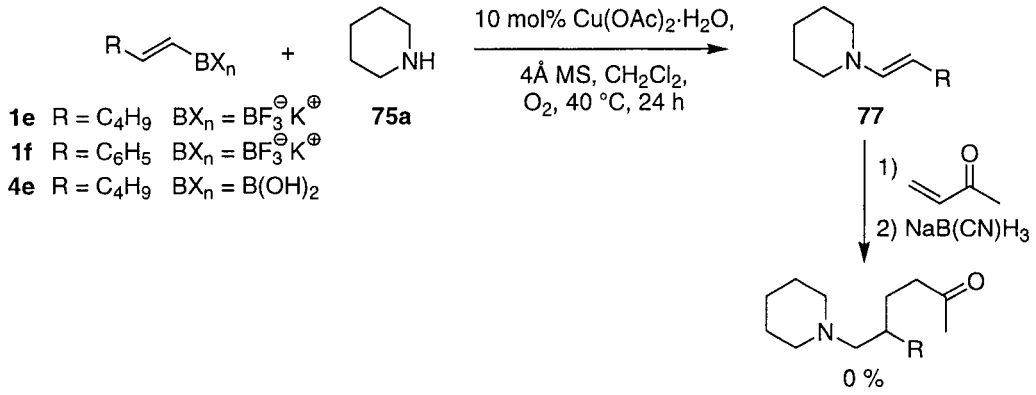


4a **75d** **76**

Entry	Borate	Product	Yield (%)[b]
1	 **4d**	 **76j**	93
2	 **4f**	 **76k**	84
3	 **4h**	 **76l**	85
4	 **4i**	 **76m**	95
5	 **4j**	 **76n**	55
6	 **4b**	 **76o**	61
7	 **4c**	 **76p**	trace

a) reaction times are not optimized for individual substrates. b) isolated yields.

Finally, alkenylboronic acids and potassium alkenyltrifluoroborate salts did not undergo the cross-coupling reaction in our hands under these catalytic conditions (Scheme 71). Attempts to either isolate enamine **77**, or trap it *in situ* with an electrophile were unsuccessful. Lam *et al.*have reported the vinylation of various nitrogen heterocycles and amides using their stoichiometric conditions; however, the yields were low to moderate at best.



Scheme 71 - Attempted Copper-Catalyzed Vinylation of Piperidine

III.2.3 Conclusions and Continuing Work

The protocol for the copper-catalyzed cross-coupling of potassium organotrifluoroborate salts and organoboronic acids with unactivated nucleophiles under mild and essential neutral conditions has been extended to include the arylation of primary and secondary amines containing various functional groups in good to excellent yields. Secondary amines in general afforded only slightly lower yields than the primary amines as the reaction's sensitivity to steric hindrance around the reactive amino moiety is somewhat compensated for by the increased nucleophilicity of the nitrogen-based nucleophile. Alkenyl isomerization and stereocentre racemization of the starting materials were not detected. All of the arylboronic acids examined underwent the cross-coupling, regardless of the electronic nature of the aryl moiety.

The reaction did not work as well with the less nucleophilic and more sterically hindered anilines resulting in generally lower yields. This protocol was found to be complimentary to Buchwald's previously reported copper-catalyzed arylations of anilines with arylboronic acids, as that system worked well for aniline derivatives, but poorly for simple aliphatic amines.

Further research into expanding this catalytic protocol for the cross-coupling of other nucleophiles with organoboron compounds from us and others in this field is expected.

III.3 Experimental Procedures

III.3.1 General Synthetic Methods

MeCN and CH_2Cl_2 were distilled from CaH_2 under argon. Toluene, THF and Et_2O were distilled from sodium metal/benzophenone ketyl under argon. All other commercial solvents and reagents were used as received from the Aldrich Chemical Company, Fischer Scientific Ltd., Strem or BDH. All glassware was oven dried at 210 °C and allowed to cool under a stream of dry nitrogen. Oxygen gas (UHP/zero grade) was purchased from Air Products and dried through a column of Drierite (anhydrous $CaSO_4$) prior to connection to a manifold for delivery into the reaction flask. The gas is delivered through Tygon tubing fitted with a 20 gauge needle at an approximate flow rate of 38 mL/min. A bubbler (filled with silicon oil) was connected to the reaction vessels to prevent build-up of oxygen pressure during the reaction period.

Silica gel (60 Å, 230-400 mesh) used in flash column chromatography was obtained from Silicycle and used as received. Analytical thin-layer chromatography (TLC) was performed on pre-coated Ultra Pure Silica Gel Plates (purchased from Silicycle), visualized with a Spectroline UV_{254} lamp, and stained with a 20 % phosphomolybdic acid in ethanol solution. Solvent systems associated with R_f values and flash column chromatography are reported as v/v ratios.

Melting points were obtained using a Fisher-Johns melting point apparatus, and are uncorrected. Specific optical rotations were determined on a Perkin-Elmer 243B Polarimeter under the conditions indicated using the sodium D line (589 nm). Sample concentrations are reported as grams per 100 mL solvent. Analytical chiral HPLC (of **74r** and **76g**) was performed on a Chiralcel OD column (4.6 x 250 mm) obtained from Daicel Chemical Industries, Ltd. ^1H and ^{13}C NMR were recorded at 400 or 300 MHz and 100 or 75 MHz respectively on Varian Unity 400, Gemini 300 or Mercury 300 spectrometers. Proton chemical shifts were internally referenced to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.20 ppm). FT-IR spectra were recorded on a Perkin-Elmer Spectrum 1000, with samples loaded as neat films on NaCl plates or as pressed KBr discs. Low and high resolution mass spectra were recorded on a Bell and Howell 21-490 spectrometer and an AEI MS3074 spectrometer respectively.

References following the compounds names indicate literature articles where ^1H and/or ^{13}C NMR data have been previously reported.

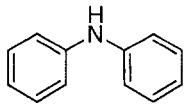
III.3.2 Synthetic Methods and Characterization Data of Arylated Amines and Anilines Under Stoichiometric Copper Conditions

Representative Procedure for the Cross-Coupling of Potassium Phenyltrifluoroborate (1a) with Aniline Derivatives (70)

To a stirring suspension of $PhBF_3^-K^+$ (0.221 g, 1.20 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.200 g, 1.00 mmol) in a 1:1 (v/v) solution of CH_2Cl_2 (4.0 mL) and EtOAc (4.0 mL) was added $PhNH_2$ (93.1 mg, 1.00 mmol) and Et_3N (0.202 g, 2.00 mmol) drop wise via syringe. The stirred reaction mixture was heated to 40 °C for 24 h, then transferred to a separatory funnel, diluted with CH_2Cl_2 (10 mL), and extracted with 1M HCl (30 mL). The organic layer was collected, and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product mixture. The product (**71a**) was isolated by silica gel flash column chromatography (eluting with hexanes:EtOAc 3:1 ~ 1:1 gradient) as an amber crystalline solid in 98 % yield (0.166 g, 0.980 mmol).

Products of Experiments Summarized in Table 28

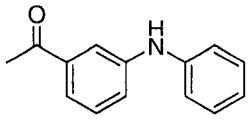
Diphenylamine (71a) (Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575-5580.)



71a

Isolated as an amber crystalline solid in 98 % yield: R_f = 0.3 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (4H, t, *J* = 7.5 Hz), 7.10 (4H, d, *J* = 7.5 Hz), 6.96 (2H, d, *J* = 7.5 Hz), 5.70 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.3, 129.5, 121.2, 118.0.

***N*-(3-Acetylphenyl)aniline (71b)** (Itier, J.; Casadevall, A. *Bull. Soc. Chim. Fr.* **1969**, 2342-2355.)

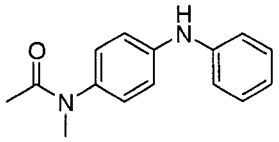


71b

Isolated as an amber crystalline solid in 96 % yield: R_f = 0.5 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (1H, t, *J* = 2.0 Hz), 7.44 (1H, dt, *J* = 5.5, 2.0 Hz), 7.33 - 7.22 (4H, m),

7.07 (2H, d, J = 7.5 Hz), 6.96 (1H, t, J = 7.5 Hz), 5.99 (1H, br s), 2.54 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.5, 144.0, 142.4, 138.4, 129.6, 129.6, 121.9, 121.6, 120.8, 118.6, 116.6, 26.8.

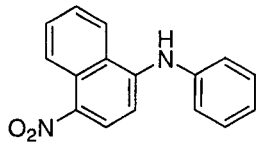
N-Methyl-N-(4-phenylamino-phenyl)acetamide (71c)



71c

Isolated as a pale yellow crystalline solid in 92 % yield: R_f = 0.6 (3:1 hexanes:EtOAc), mp = 103 - 105 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (2H, t, J = 8.5 Hz), 7.15 - 6.94 (7H, m), 6.19 (1H, br s), 3.23 (3H, s), 1.89 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 143.3, 142.4, 136.8, 129.5, 128.0, 121.9, 118.8, 117.6, 37.4, 22.4; IR (film) ν 3418, 3054, 2986, 2305, 1651, 1599, 1516, 1422, 1264, 1143, 896, 743 cm^{-1}; LRMS (EI): m/z = 241 (20), 240 (100), 199 (11), 198 (72), 197 (60), 185 (30), 183 (30), 169 (12), 168 (11), 167 (22), 164 (26), 122 (27), 121 (22), 107 (18), 94 (11), 93 (12), 92 (17), 77 (16); HRMS (EI): m/z calcd. for ($C_{15}H_{16}N_2O^+$) = 240.1263, found = 240.1274.

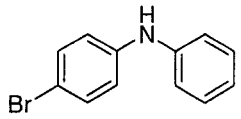
(4-Nitronaphthanlen-1-yl)phenylamine (71d)



71d

Isolated as a bright red crystalline solid in 72 % yield: R_f = 0.8 (3:1 hexanes:EtOAc), mp = 156 - 157 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.95 (1H, dt, J = 8.5, 0.5 Hz), 8.32 (1H, d, J = 9.0 Hz), 8.05 (1H, d, J = 8.5 Hz), 7.74 (1H, ddd, J = 8.5, 7.0, 1.0 Hz), 7.60 (1H, ddd, J = 8.5, 7.0, 1.0 Hz), 7.43 (2H, t, J = 7.5 Hz), 7.29 (2H, d, J = 7.5 Hz), 7.21 (1H, t, J = 7.5 Hz), 7.09 (1H, d, J = 9.0 Hz), 6.77 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.1, 140.1, 137.8, 134.5, 130.1, 128.2, 127.8, 126.7, 125.1, 124.9, 123.9, 122.8, 120.8, 106.3; IR (film) ν 3368, 1593, 1568, 1538, 1454, 1265, 1174, 1147, 995, 824, 742, 699, 571 cm^{-1}; LRMS (EI): m/z = 265 (28), 264 (100), 235 (14), 234 (54), 219 (10), 218 (40), 217 (60), 216 (29), 189 (11), 140 (11), 109 (14), 77 (23); HRMS (EI): m/z calcd. for ($C_{16}H_{12}N_2O_2^+$) = 264.0899, found = 264.0906.

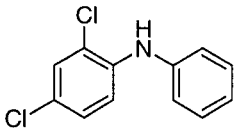
4-Bromodiphenylamine (71e) (Barchiesi, E.; Bradamante, S.; Pagani, G. A. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1091-1096.)



71e

Isolated as a transparent crystalline solid in 95 % yield: R_f = 0.4 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 - 7.22 (4H, m), 7.06 - 6.88 (5H, m), 5.63 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.6, 142.5, 132.3, 129.6, 121.8, 119.2, 118.4, 112.7.

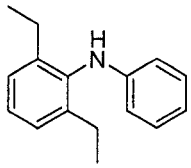
(2,4-Dichlorophenyl)phenylamine (71f) (Rioux-Lacoste, C.; Viel, C. *Bull. Soc. Chim. Fr.* **1974**, 2463-2470.)



71f

Isolated as a white crystalline solid in 86 % yield: R_f = 0.7 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 - 7.32 (3H, m), 7.20 - 7.05 (5H, m), 6.06 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.2, 139.4, 129.7, 129.5, 127.7, 124.3, 123.3, 121.9, 120.7, 116.2.

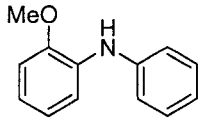
(2,6-Diethylphenyl)phenylamine (71g) (Moser, P.; Sallmann, A.; Wiesenberg, I. *J. Med. Chem.* **1990**, *33*, 2358-2368.)



71g

Isolated as an amber oil in 75 % yield: R_f = 0.7 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 - 7.05 (5H, m), 6.71 (1H, tt, *J* = 7.5, 1.0 Hz), 6.47 (2H, dd, *J* = 8.5, 1.0 Hz), 5.13 (1H, br s), 2.58 (4H, q, *J* = 7.5 Hz), 1.14 (6H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.5, 142.5, 137.0, 129.9, 129.4, 126.8, 126.7, 119.1, 118.1, 113.4, 24.9, 14.9; IR (film) ν 3396, 3044, 2965, 2872, 1603, 1497, 1453, 1411, 1374, 1306, 1237, 1175, 1106, 1077, 1026, 994, 866, 798, 747, 693 cm^{-1}; LRMS (EI): *m/z* = 226 (29), 225 (100), 211 (24), 210 (92), 208 (20), 196 (18), 194 (14), 193 (13), 182 (15), 181 (32), 180 (53), 170 (15), 168 (11), 167 (13), 148 (12), 134 (13), 91 (12), 77 (19); HRMS (EI): *m/z* calcd. for ($C_{16}H_{19}N^+$) = 225.1518, found = 225.1519.

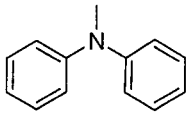
(2-Methoxyphenyl)phenylamine (71h) (Takeuchi, H.; Taniguchi, T.; Ueda, T. *J. Chem. Soc. Perkin Trans. 2*, **2000**, 295 - 300.)



71h

Isolated as an orange oil in 88 % yield: R_f = 0.6 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 - 7.21 (3H, m), 7.11 (2H, dd, *J* = 8.5, 1.0 Hz), 6.94 - 6.82 (4H, m), 6.12 (1H, br s), 3.82 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.4, 142.8, 133.1, 129.4, 121.2, 120.9, 120.0, 118.6, 114.8, 110.6, 55.7.

***N*-Methyldiphenylamine (71i)** (Gribble, G. W.; Nutaitis, C. F. *Synthesis*, **1987**, *8*, 709-711.)

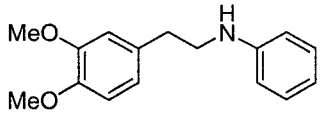


71i

Isolated as a yellow oil in 80 % yield: R_f = 0.6 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (4H, dd, *J* = 8.5, 7.5 Hz), 7.02 (4H, dd, *J* = 8.5, 1.0 Hz), 6.95 (2H, tt, J = 7.5, 1.0 Hz), 3.31 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.3, 129.4, 121.5, 120.7, 40.5.

Products of Experiments Summarized in Table 29

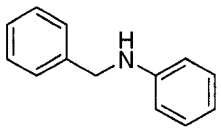
[2-(3,4-Dimethoxyphenyl)ethyl]phenylamine (74a) (Ninomiya, I.; Yasui, J.; Kiguchi, T. *Heterocycles* **1977**, *6*, 1855-1856.)



74a

Isolated as a clear oil in 95 % yield: R_f = 0.2 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (2H, t, *J* = 7.5 Hz), 6.86 - 6.68 (4H, m), 6.62 (2H, d, *J* = 7.5 Hz), 3.88 (3H, s), 3.87 (3H, s), 3.70 (1H, br s), 3.40 (2H, t, *J* = 7.0 Hz), 2.88 (2H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.1, 148.2, 147.8, 131.9, 129.4, 120.8, 117.6, 113.2, 112.2, 111.5, 56.1, 56.0, 45.2, 35.1; IR (film) ν 3394, 2932, 2360, 1603, 1513, 1465, 1419, 1319, 1261, 1235, 1179, 1156, 1140, 1027, 809, 750, 693 cm^{-1}; LRMS (EI): *m/z* = 257 (12), 152 (23), 151 (8), 107 (12), 106 (100), 77 (15); HRMS (EI): *m/z* calcd. for ($C_{16}H_{19}NO_2^+$) = 257.1416, found = 257.1418.

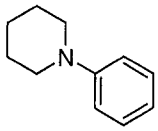
***N*-Benzylaniline (74b)** (Chandrasekhar, S.; Venkat R. M.; Chandraiah, L. *Synth. Commun.* **1999**, *29*, 3981-3988.)



74b

Isolated as a white solid in 77 % yield: R_f = 0.5 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 - 7.22 (5H, m), 7.15 (2H, t, *J* = 7.0 Hz), 6.70 (1H, dt, *J* = 7.0, 1.0 Hz), 6.61 (2H, dd, *J* = 7.0, 1.0 Hz), 4.29 (2H, s), 3.98 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.3, 139.6, 129.4, 128.8, 127.6, 127.4, 117.7, 113.0, 48.4.

***N*-Phenylpiperidine (76a)** (Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 44, 12829-12842.)



76a

Isolated as a clear oil in 65 % yield: R_f = 0.4 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (2H, dt, *J* = 7.5, 1.0 Hz), 6.94 (2H, dd, *J* = 7.5, 1.0 Hz), 6.82 (1H, dt, *J* = 7.5, 1.0 Hz), 3.16 (4H, dd, *J* = 5.5, 5.5 Hz), 1.76 - 1.66 (4H, m), 1.62 - 1.53 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.5, 129.2, 119.4, 116.7, 50.9, 26.1, 24.5.

III.3.3 Synthetic Methods and Characterization Data of Arylated Amines and Anilines Under Catalytic Copper Conditions

Representative Procedure for the Cross-Coupling of Potassium Phenyltrifluoroborate (1a) with Aliphatic Amines (73)

A suspension of $PhBF_3^-K^+$ (0.368 g, 2.00 mmol), $Cu(OAc)_2 \cdot H_2O$ (20.0 mg, 0.100 mmol), and powdered 4Å molecular sieves (0.750 g) in CH_2Cl_2 (8.0 mL) was stirred for 5 minutes at room temperature. To this stirred suspension was added *n*-butylamine (0.072 g, 99.0 μL, 1.00 mmol). The reaction mixture was then sealed with a rubber septa (heated to 40 °C if necessary), and stirred under a blanket atmosphere of O_2. Following a period of 24 h, the crude reaction mixture was filtered through a plug of Celite to remove the molecular sieves and any insoluble by-products and then concentrated *in vacuo* to afford the crude product mixture. The product (**74c**) was isolated by silica gel column chromatography (eluting with hexanes:EtOAc 9:1 ~ 3:1 gradient) as a pale yellow oil in 89 % yield (0.133 g, 0.89 mmol).

Representative Procedure for the Cross-Coupling of Phenylboronic Acid (4a) with Aliphatic Amines (73)

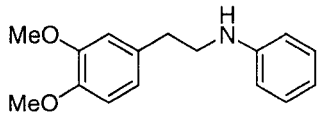
The above procedure was followed with substitution of $PhB(OH)_2$ (0.244 g, 2.00 mmol) in place of the $PhBF_3^-K^+$. The product (**74c**) was isolated as a pale yellow oil in 92 % yield (0.137 g, 0.89 mmol).

Representative Procedure for the Activation of Amine Hydrohalide Salts and Subsequent Cross-Coupling with $PhB(OH)_2$

To a stirred solution of 3-bromopropylamine hydrobromide (0.219 g, 1.00 mL) in acetonitrile (10.0 mL) was added Amberlyst A-21 resin (0.750 g). The suspension was stirred at room temperature for 30 min, then filtered and washed with CH_2Cl_2 to remove the resin. The filtrant was collected and concentrated *in vacuo*. The residue was then redissolved in acetonitrile (1.0 mL) and added to a prestirred suspension of $PhB(OH)_2$ (0.244 g, 2.00 mmol), $Cu(OAc)_2 \cdot H_2O$ (20.0 mg, 0.100 mmol), and powdered 4Å molecular sieves (0.750 g) in CH_2Cl_2 (7.0 mL). The reaction mixture was then sealed with a rubber septa, heated to 40 °C, and stirred under a blanket atmosphere of O_2. Following a period of 24 h, the crude reaction mixture was filtered through a plug of Celite to remove the molecular sieves and any insoluble by-products, and then concentrated *in vacuo* to afford the crude product mixture. The product (**3l**) was isolated by silica gel column chromatography (eluting with hexanes:EtOAc 9:1 ~ 3:1 gradient) as a clear oil in 86 % yield (0.184 g, 0.860 mmol).

Products of Experiments Summarized in Table 30a & 30b

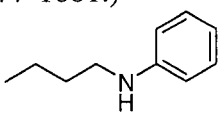
[2-(3,4-Dimethoxyphenyl)ethyl]phenylamine (74a) (Ninomiya, I.; Yasui, J.; Kiguchi, T. *Heterocycles* **1977**, *6*, 1855-1856.)



74a

Isolated as a clear oil in 90 % yield from $PhBF_3^-K^+$ at room temperature and in 95 % yield from $PhB(OH)_2$ at 40 °C: for characterization data *vide supra*.

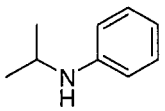
***n*-Butylphenylamine (74c)** (Alberti, A.; Cane, F.; Dembech, P.; Lazzari, D.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1996**, *61*, 1677-1681.)



74c

Reactions were performed at room temperature. Isolated as a pale yellow oil in 89 % yield from $PhBF_3^-K^+$ and in 92 % yield from $PhB(OH)_2$: R_f = 0.80 (3:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (2H, ddd, *J* = 8.5, 7.5, 1.0 Hz), 6.74 (1H, t, *J* = 7.5, 1.0 Hz), 6.65 (2H, dd, *J* = 8.5, 1.0 Hz), 3.62 (1H, br s), 3.15 (2H, t, *J* = 7.0 Hz), 1.65 (2H, quintet, *J* = 7.0 Hz), 1.48 (2H, sextet, *J* = 7.0 Hz), 1.01 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 129.4, 117.2, 112.8, 43.8, 31.8, 20.5, 14.1.

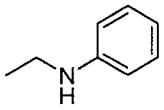
Isopropylphenylamine (74d) (Shaffer, C. L.; Morton, M. D.; Hanzlik, R. P. *J. Am. Chem. Soc.* **2001**, *123*, 8502-8508.



74d

Reactions were performed at room temperature. Isolated as a clear oil in 98 % yield from both $PhBF_3^-K^+$ and $PhB(OH)_2$: R_f = 0.70 (9:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, ddd, *J* = 8.0, 7.5, 1.0 Hz), 6.75 (1H, tt, *J* = 7.5, 1.0 Hz), 6.66 (2H, dd, *J* = 8.0, 1.0 Hz), 3.71 (1H, septet, *J* = 6.5 Hz), 3.50 (1H, br s), 1.28 (6H, d, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 129.4, 117.1, 113.3, 44.3, 23.1.

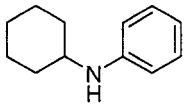
Ethylphenylamine (74e) (Kumar, H. M. S.; Reddy, B. V. S.; Anjaneyulu, S.; Yadav, J. S. *Tetrahedron Lett.* **1999**, *40*, 8305-8306.



74e

Isolated as a pale yellow oil in 13 % yield from $PhBF_3^-K^+$ at room temperature: R_f = 0.60 (3:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (2H, ddd, *J* = 8.5, 7.5, 1.5 Hz), 6.74 (1H, tt, *J* = 7.5, 1.0 Hz), 6.65 (2H, ddd, *J* = 8.6, 1.5, 1.0 Hz), 3.58 (1H, br s), 3.20 (2H, q, *J* = 7.0 Hz), 1.30 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 129.4, 117.4, 112.9, 38.6, 15.1.

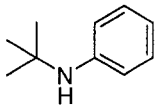
Cyclohexylphenylamine (74f) (Kawakami, T.; Sugimoto, T.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *J. Org. Chem.* **1995**, *60*, 2677-2682.)



74f

Isolated as a clear oil in 79 % yield from $PhBF_3^-K^+$ at room temperature; and in 85 % yield from $PhB(OH)_2$ at 40 °C: R_f = 0.60 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (2H, ddd, *J* = 8.5, 7.5, 2.0 Hz), 6.67 (1H, tt, *J* = 7.5, 1.0 Hz), 6.61 (2H, ddd, *J* = 8.5, 2.0, 1.0 Hz), 3.53 (1H, br s), 3.27 (1H, tt, *J* = 10.0, 4.0 Hz), 2.14 - 2.02 (2H, m), 1.84 - 1.62 (3H, m), 1.48 - 1.10 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 129.4, 117.0, 113.3, 51.9, 33.7, 26.1, 25.2.

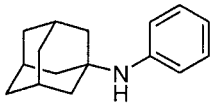
***t*-Butylphenylamine (74g)** (Arnauld, T.; Barton, D. H. R.; Doris, E. *Tetrahedron* **1997**, *53*, 4137-4144.)



74g

Isolated as a light beige oil in 26 % yield from $PhBF_3^-K^+$ at room temperature; and in 39 % yield from $PhB(OH)_2$ at 40 °C: R_f = 0.40 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (2H, t, *J* = 7.5 Hz), 6.8 - 6.72 (3H, m), 3.34 (1H, br s), 1.34 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 129.1, 118.5, 117.7, 51.7, 30.3.

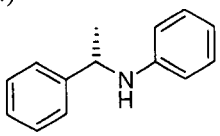
Adamantan-1-ylphenylamine (74h) (Olifirov, D. I.; Koshchii, V. A.; Kozlikovskii, Y. B. *J. Org. Chem. USSR (Engl. Transl.)*, **1992**, *28*, 152-157.)



74h

Reactions were performed at 40 °C. Isolated as a pale beige solid in 57 % yield from $PhBF_3^-K^+$ and in 67 % yield from $PhB(OH)_2$: R_f = 0.60 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 - 7.13 (2H, m), 6.83 - 6.77 (3H, m), 3.31 (1H, br s), 2.12 (3H, m), 1.88 (6H, d, *J* = 3.0 Hz), 1.77 - 1.71 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 128.9, 119.3, 119.2, 52.4, 43.6, 36.6, 29.9; LRMS (EI): *m/z* (rel.intensity) = 229 (9), 227 (51), 171 (15), 170 (100), 135 (41), 133 (9), 107 (5), 94 (5), 93 (21), 92 (11), 91 (7), 77 (12); HRMS (EI): *m/z* calcd. for (M^+) = 227.1674, found = 227.1673.

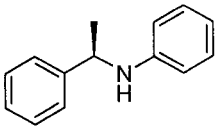
(*S*)-*N*-(1-Phenylethyl)aniline (74i) (Landor, S. R.; Sonola, O. O.; Tatchell, A. R. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1658-1661.)



74i

Product was isolated as a clear oil in 91 % yield from $PhBF_3^-K^+$ at room temperature: $R_f = 0.44$ (9:1 hexanes:EtOAc); $[\alpha]_D^{22} = +5.15$ ° (c = 10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 - 7.15 (5H, m), 7.07 (2H, t, *J* = 7.5 Hz), 6.63 (1H, t, *J* = 7.5 Hz), 6.49 (2H, d, *J* = 7.5 Hz), 4.46 (1H, q, *J* = 7.0 Hz), 3.98 (1H, br s), 1.48 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 145.4, 129.2, 128.8, 127.0, 126.0, 117.4, 113.4, 53.6, 25.2.

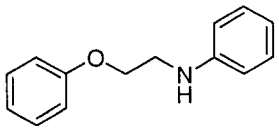
(*R*)-*N*-(1-Phenylethyl)aniline (74j) (Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F. M. *Chem. Europ. J.* **1997**, *3*, 887-892.)



74j

Product was isolated as a clear oil in 78 % yield from $PhBF_3^-K^+$ at room temperature: $R_f = 0.44$ (9:1 hexanes:EtOAc); $[\alpha]_D^{22} = -5.19$ ° (c = 5.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 - 7.15 (5H, m), 7.07 (2H, t, *J* = 7.5 Hz), 6.63 (1H, t, *J* = 7.5 Hz), 6.49 (2H, d, *J* = 7.5 Hz), 4.46 (1H, q, *J* = 7.0 Hz), 3.98 (1H, br s), 1.48 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 145.4, 129.2, 128.8, 127.0, 126.0, 117.4, 113.4, 53.6, 25.2.

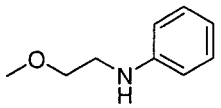
(2-Phenoxyethyl)phenylamine (74k) (Jios, J. L.; Romanelli, G. P.; Autino, J. C.; Magiera, D.; Duddeck, H. *Z. Naturforsch. B* **2002**, *57*, 226-232.)



74k

Reactions were performed at 40 °C. Isolated as a pale yellow oil in 13 % yield from $PhBF_3^-K^+$ and in 15 % yield from $PhB(OH)_2$: $R_f = 0.40$ (9:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (2H, t, *J* = 7.5 Hz), 7.19 (2H, t, *J* = 7.5 Hz), 6.93 (1H, t, *J* = 7.5 Hz), 6.91 (2H, d, *J* = 8.0 Hz), 6.74 (1H, t, *J* = 7.5 Hz), 6.67 (2H, d, *J* = 8.0 Hz), 4.15 (2H, t, *J* = 5.5 Hz), 4.10 (1H, br s), 3.52 (2H, t, *J* = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 148.1, 129.8, 129.5, 121.3, 118.1, 114.7, 113.4, 66.5, 43.5.

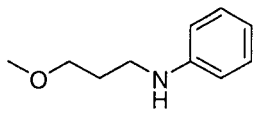
(2-Methoxyethyl)phenylamine (74l)



74l

Isolated as a clear oil in 32 % yield from $PhBF_3^-K^+$ at room temperature; and in 79 % yield from $PhBF_3^-K^+$ and 94 % yield from $PhB(OH)_2$ at 40 °C: R_f = 0.40 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (2H, t, *J* = 7.5 Hz), 6.70 (1H, t, *J* = 7.5 Hz), 6.61 (2H, d, *J* = 7.5 Hz), 4.02 (1H, br s), 3.57 (2H, t, *J* = 5.0 Hz), 3.37 (3H, s), 3.26 (2H, t, *J* = 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 129.3, 117.7, 113.2, 71.1, 58.8, 43.5; IR (film) ν 3051, 2925, 2891, 1603, 1506, 1472, 1319, 1259, 1193, 1117, 1071, 1025, 871, 750, 693 cm^{-1}; LRMS (EI): *m/z* (rel.intensity) = 152 (9), 151 (48), 107 (14), 106 (100), 94 (7), 77 (24); HRMS (EI): *m/z* calcd. for (M^+) = 151.0997, found = 151.0991.

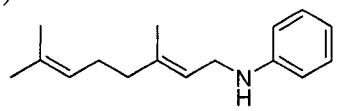
(3-Methoxypropyl)phenylamine (74m)



74m

Isolated as a clear oil in 78 % yield from $PhBF_3^-K^+$ at room temperature; and in 85 % yield from $PhB(OH)_2$ at 40 °C: R_f = 0.50 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (2H, ddd, *J* = 7.5, 3.0, 1.0 Hz), 6.70 (1H, tt, *J* = 7.5, 1.0 Hz), 6.63 (2H, dd, *J* = 7.5, 1.0 Hz), 3.94 (1H, br s), 3.53 (2H, t, *J* = 6.0 Hz), 3.37 (3H, s), 3.24 (2H, t, *J* = 6.0 Hz), 1.90 (2H, quintet, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 129.4, 117.3, 112.9, 71.4, 58.9, 41.9, 29.5; IR (film) ν 3394, 3051, 3021, 2924, 2871, 1604, 1508, 1478, 1433, 1389, 1321, 1262, 1180, 1117, 749, 693 cm^{-1}; LRMS (EI): *m/z* (rel.intensity) = 166 (6), 165 (37), 107 (13), 106 (100), 104 (6), 93 (11), 77 (18); HRMS (EI): *m/z* calcd. for (M^+) = 165.1154, found = 165.1150.

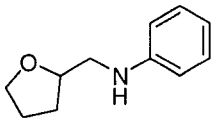
(3,7-Dimethylocta-2,6-dienyl)phenylamine (74n) (Ranu, B. C.; Majee, A.; Sarkar, A. *J. Org. Chem.* **1998**, *63*, 370-373.)



74n

Reactions were performed at 40 °C. Isolated as a yellow oil in 80 % yield from $PhBF_3^-K^+$ and in 89 % yield from $PhB(OH)_2$: R_f = 0.75 (3:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (2H, ddd, *J* = 8.5, 7.5, 2.0 Hz), 6.82 (1H, tt, *J* = 7.5, 1.0 Hz), 6.72 (2H, ddd, *J* = 8.5, 2.0, 1.0 Hz), 5.49 - 5.41 (1H, m), 5.25 - 5.18 (1H, m), 3.81 (2H, d, *J* = 6.5 Hz), 3.67 (1H, br s), 2.28 - 2.14 (4H, m), 1.82 (3H, s), 1.81 (3H, s), 1.73 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 139.1, 131.8, 129.3, 124.1, 121.7, 117.4, 113.0, 42.1, 39.7, 26.6, 25.9, 17.9, 16.5.

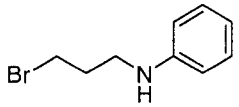
Phenyl(tetrahydrofuran-2-ylmethyl)amine (74o)



74o

Reactions were performed at 40 °C. Isolated as a pale yellow oil in 83 % yield from $PhBF_3^-K^+$ and in 91 % yield from $PhB(OH)_2$: R_f = 0.33 (3:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (2H, ddd, *J* = 8.5, 7.5, 2.0 Hz), 6.74 (1H, tt, *J* = 7.5, 1.0 Hz), 6.66 (2H, ddd, *J* = 8.5, 2.0, 1.0 Hz), 4.15 (1H, dddd, *J* = 7.0, 7.0, 7.0, 4.0 Hz), 4.05 (1H, br s), 3.92 (1H, ddd, *J* = 8.0, 7.0, 7.0 Hz), 3.81 (1H, ddd, *J* = 8.0, 7.0, 7.0 Hz), 3.28 (1H, dd, *J* = 12.5, 4.0 Hz), 3.10 (1H, dd, *J* = 12.5, 7.5 Hz), 2.11 - 1.90 (3H, m), 1.74 - 1.62 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 129.3, 117.5, 113.1, 77.6, 68.1, 48.2, 29.2, 25.9; IR (film) ν 3390, 3051, 3021, 2971, 2869, 1603, 1506, 1459, 1433, 1378, 1360, 1320, 1256, 1180, 1070, 749, 693 cm^{-1}; LRMS (EI): *m/z* (rel.intensity) = 178 (7), 177 (27), 107 (17), 106 (100), 77 (16); HRMS (EI): *m/z* calcd. for (M^+) = 177.1154, found = 177.1156.

(3-Bromopropyl)phenyl amine (74p)

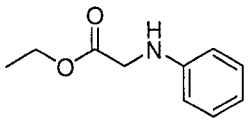


74p

The amine hydrobromide salt was pretreated with Amberlyst A-21 resin. Reaction was performed at 40 °C. Isolated as a clear oil in 86 % yield from $PhB(OH)_2$ over both steps: R_f = 0.30 (9:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (2H, ddd, *J* = 7.5, 2.0, 1.5 Hz), 6.83 (1H, tt, *J* = 7.5, 1.5 Hz), 6.73 (2H, dd, *J* = 7.5, 2.0 Hz), 3.95 (1H, br s), 3.60 (2H, t, *J* = 6.5

Hz), 3.42 (2H, t, J = 6.5 Hz), 2.24 (2H, quintet, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 129.5, 117.8, 113.0, 42.1, 32.1, 31.4; IR (film) ν 3410, 3051, 3021, 2961, 1603, 1507, 1431, 1322, 1255, 1180, 1100, 991, 870, 751, 693 cm^{-1}; LRMS (EI): *m/z* (rel.intensity) = 215 (19), 213 (18), 107 (15), 106 (100), 104 (7), 77 (27); HRMS (EI): *m/z* calcd. for (M^+) = 213.0153, found = 213.0151.

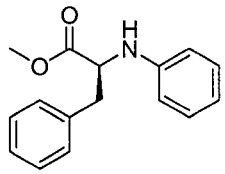
***N*-Phenyl-glycine ethyl ester (74q)** (Anderson, W. K.; Bhattacharjee, D.; Houston, D. M.; *J. Med. Chem.* **1989**, *32*, 119-127.)



74q

The amine hydrochloride salt was pretreated with Amberlyst A-21 resin. Reaction was performed at 40 °C. Isolated as a clear crystalline solid in 84 % yield from $PhB(OH)_2$ over both steps: R_f = 0.50 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (2H, t, J = 7.5 Hz), 6.76 (1H, dt, J = 7.5, 1.0 Hz), 6.62 (2H, dd, J = 7.5, 1.0 Hz), 4.28 (1H, br s), 4.25 (2H, q, J = 7.0 Hz), 3.91 (2H, s), 1.31 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 147.2, 129.5, 118.4, 113.2, 61.5, 46.1, 14.4.

(*S*)-*N*-Phenyl-phenylalanine methyl ester (74r) (Tunge, J. A.; Gately, D. A.; Norton, J. R. *J. Am. Chem. Soc.* **1999**, *121*, 4520-4521.)



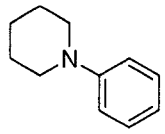
74r

The amine hydrochloride salt was pretreated with Amberlyst A-21 resin. Reaction was performed at 40 °C. Product was isolated as a light beige oil in 90 % yield from $PhB(OH)_2$ over both steps: R_f = 0.40 (3:1 hexanes:EtOAc); $[\alpha]_D^{22}$ = +25.88 ° (c = 10, CH_2Cl_2) for >99 % ee (Chiralcel OD, 10 % ethanol/hexanes, 1.0 mL/min, retention times for R and S enantiomers are 7.16 and 9.78 min respectively) with determination of the absolute stereochemistry by comparison of the specific rotation with the literature value; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 - 7.28 (7H, m), 6.90 (1H, t, J = 7.5 Hz), 6.75 (2H, d, J = 7.5 Hz), 4.53 (1H, t, J = 6.5 Hz), 4.36

(1H, br s), 3.79 (3H, s), 3.28 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 146.4, 136.4, 129.4, 129.3, 128.6, 127.0, 118.4, 113.6, 57.7, 52.0, 38.6.

Products of Experiments Summarized in Table 31

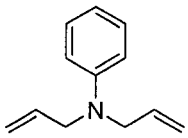
***N*-Phenylpiperidine (76a)** (Brenner, E.; Schneider, R.; Fort, Y.; *Tetrahedron*, **1999**, *55*, 12829-12842.)



76a

Isolated as a clear oil in 78 % yield from $PhBF_3^-K^+$ at room temperature; and in 86 % yield from $PhB(OH)_2$ at 40 °C: for characterization data *vide supra.*

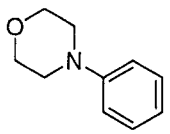
***N,N*-Diallylaniline (76c)** (Yang, S. C.; Hung, C. W. *Synthesis* **1999**, *10*, 1747-1752.)



76c

Isolated as a clear oil in 74 % yield: R_f = 0.6 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (2H, ddd, *J* = 9.0, 6.0, 2.0 Hz), 6.73 - 6.64 (3H, m), 5.86 (2H, ddt, *J* = 17.0, 10.0, 5.0 Hz), 5.18 (2H, dq, *J* = 17.0, 2.0 Hz), 5.14 (2H, dq, *J* = 10.0, 2.0 Hz), 3.92 (4H, dt, *J* = 5.0, 2.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.7, 134.0, 129.1, 116.3, 115.9, 112.4, 52.8.

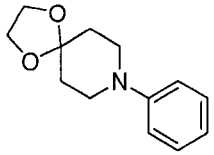
4-Phenylmorpholine (76d) (Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* **2001**, *66*, 186-191.)



76d

Reactions were performed at 40 °C. Isolated as a pale light beige, crystalline solid in 81 % yield from $PhBF_3^-K^+$ and in 90 % yield from $PhB(OH)_2$: R_f = 0.45 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (2H, ddd, *J* = 9.0, 7.5, 1.5 Hz), 6.96 - 6.88 (3H, m), 3.91 - 3.85 (4H, m), 3.20 - 3.15 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 129.3, 120.2, 115.8, 67.1, 49.5.

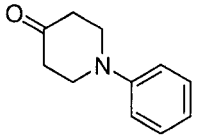
8-Phenyl-1,4-dioxa-8-azaspiro[4.5]decane (76e)



76e

Reactions were performed at 40 °C. Isolated as a clear oil in 87 % yield from $PhBF_3^-K^+$ and in 86 % yield from $PhB(OH)_2$: R_f = 0.40 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (2H, ddd, *J* = 7.5, 2.0, 1.5 Hz), 7.04 (2H, dd, *J* = 7.5, 2.0 Hz), 6.93 (1H, dt, *J* = 7.5, 1.5 Hz), 4.07 (4H, s), 3.42 (4H, dd, *J* = 6.0, 6.0 Hz), 1.94 (4H, dd, *J* = 6.0, 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 129.2, 119.5, 116.7, 107.3, 64.4, 47.8, 34.6; IR (film) ν 2956, 2882, 2828, 1599, 1497, 1466, 1365, 1228, 1143, 1105, 1037, 962, 946, 929, 896, 757, 693, 529 cm^{-1}; LRMS (EI): *m/z* (rel.intensity) = 220 (18), 219 (100), 218 (10), 174 (28), 158 (20), 133 (18), 132 (55), 106 (11), 105 (73), 104 (25), 77 (21); HRMS (EI): *m/z* calcd. for (M^+) = 219.1259, found = 219.1265.

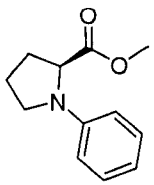
1-Phenylpiperidin-4-one (76f) (Hermant, R. M.; Bakker, N. A. C.; Scherer, T.; Krijnen, B.; Verhoeven, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 1214-1221.)



76f

The amine hydrochloride salt was pretreated with Amberlyst A-21 resin. Reaction was performed at 40 °C. Isolated as a light beige solid in 83 % yield from $PhB(OH)_2$ over both steps: R_f = 0.33 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (2H, ddd, *J* = 7.5, 2.0, 1.5 Hz), 6.97 (2H, dd, *J* = 7.5, 2.0 Hz), 6.91 (1H, dt, *J* = 7.5, 1.5 Hz), 3.60 (4H, dd, *J* = 6.0, 6.0 Hz), 2.54 (4H, t, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 149.3, 129.6, 120.0, 116.0, 49.0, 40.9.

***N*-Phenyl-L-proline methyl ester (76g)** (Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* **2001**, *66*, 186-191.)

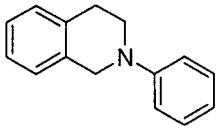


76g

The amine hydrochloride salt was pretreated with Amberlyst A-21 resin. Reaction was

performed at 40 °C. Isolated as a pale yellow oil in 74 % yield from $PhB(OH)_2$ over both steps: R_f = 0.50 (3:1 hexanes:EtOAc); $[\alpha]_D^{22}$ = -13.81 ° (c = 1.0, $CHCl_3$) for >99 % ee (Chiralcel OD, 10 % ethanol/hexanes, 1.0 mL/min, retention times for R and S enantiomers are 6.19 and 8.77 min respectively) with determination of the absolute stereochemistry by comparison of the specific rotation with the literature value; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (2H, ddd, *J* = 7.5, 2.0, 1.5 Hz), 6.81 (1H, dt, *J* = 7.5, 1.5 Hz), 6.64 (2H, dd, *J* = 7.5, 2.0 Hz), 4.34 (1H, dd, *J* = 8.0, 2.0 Hz), 3.80 (3H, s), 3.70 - 3.66 (1H, m), 3.49 - 3.40 (1H, m), 2.45 - 2.07 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 146.8, 129.4, 116.8, 112.0, 60.9, 52.2, 48.4, 31.0, 24.0.

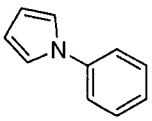
2-Phenyl-1,2,3,4-tetrahydroisoquinoline (76h) (Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1996**, *52*, 8545-8564.)



76h

Reactions were performed at room temperature. Isolated as a clear oil in 72 % yield from both $PhBF_3^-K^+$ and $PhB(OH)_2$: R_f = 0.50 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.13 (6H, m), 7.02 (2H, d, *J* = 7.5 Hz), 6.87 (1H, t, *J* = 7.5 Hz), 4.45 (2H, s), 3.60 (2H, t, *J* = 6.0 Hz), 3.03 (2H, t, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 134.4, 129.2, 129.0, 128.5, 126.5, 126.3, 126.0, 118.7, 115.2.

1-Phenylpyrrole (76i) (Lee, C. K.; Jun, J. H.; Yu, J. S. *J. Heterocycl. Chem.* **2000**, *37*, 15-24.)

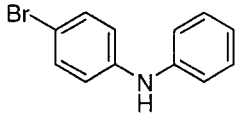


76i

Reactions were performed at 40 °C. Isolated as a clear, crystalline solid in 80 % yield from $PhBF_3^-K^+$ and in 89 % yield from $PhB(OH)_2$: R_f = 0.60 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 - 7.48 (4H, m), 7.38 - 7.31 (1H, m), 7.20 (2H, t, *J* = 2.0 Hz), 6.46 (2H, t, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140. 9, 129.7, 125.8, 120.7, 119.5, 110.6.

Products of Experiments Summarized in Table 32

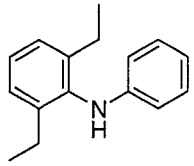
4-Bromodiphenylamine (71e) (Barchiesi, E.; Bradamante, S.; Pagani, G. A. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1091-1096.)



71e

Reactions were performed at 40 °C. Isolated as a clear, crystalline solid in 30 % yield from $PhBF_3^-K^+$ and in 53 % yield from $PhB(OH)_2$: for characterization data *vide supra*.

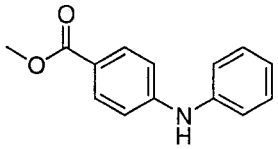
(2,6-Diethylphenyl)phenylamine (71g) (Moser, P.; Sallmann, A.; Wiesenberg, I. *J. Med. Chem.* **1990**, *33*, 2358-2368.)



71g

Reactions were performed at room temperature. Product was isolated as an amber oil in 34 % yield from $PhBF_3^-K^+$ and in 49 % yield from $PhB(OH)_2$: for characterization data *vide supra*.

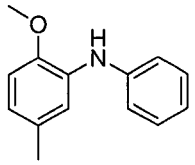
4-Anilinobenzoic acid methyl ester (71j)



71j

Reactions were performed at room temperature. Isolated as a beige, crystalline solid in 35 % yield from $PhBF_3^-K^+$ and in 40 % yield from $PhB(OH)_2$: R_f = 0.60 (1:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.5 Hz), 7.34 (2H, t, J = 8.0 Hz), 7.17 (2H, d, J = 8.0 Hz), 7.07 (1H, t, J = 8.0 Hz), 6.99 (2H, d, J = 8.5 Hz), 6.07 (1H, br s), 3.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 148.3, 141.0, 131.7, 129.7, 123.3, 121.3, 120.6, 114.8, 51.9; IR (film) ν 3343, 1695, 1591, 1521, 1496, 1434, 1328, 1282, 1172, 1109, 850, 769, 747, 693 cm^{-1}; LRMS (EI): *m/z* (rel.intensity) = 228 (24), 227 (100), 197 (21), 196 (95), 168 (23), 167 (56), 166 (14), 98 (11), 77 (15); HRMS (EI): *m/z* calcd. for (M^+) = 227.0946, found = 227.0919.

(2-Methoxy-5-methylphenyl)phenylamine (71k)

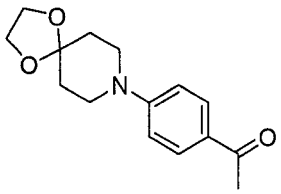


71k

Reactions were performed at room temperature. Isolated as an orange oil in 51 % yield from $PhBF_3^-K^+$ and in 66 % yield from $PhB(OH)_2$: R_f = 0.60 (3:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (2H, t, *J* = 7.5 Hz), 7.17 (3H, m), 6.97 (1H, tt, *J* = 7.5, 1.0 Hz), 6.80 (1H, d, *J* = 8.0 Hz), 6.67 (1H, dd, *J* = 8.0, 1.0 Hz), 6.13 (1H, br s), 3.88 (3H, s), 2.29 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 143.0, 132.9, 130.4, 129.4, 121.2, 120.3, 118.8, 115.6, 110.7, 55.9, 21.2; IR (film) ν 3410, 3047, 2935, 2860, 2833, 1594, 1526, 1496, 1463, 1413, 1311, 1293, 1244, 1221, 1176, 1156, 1079, 1033, 956, 865, 795, 748, 725, 708, 694, 620 cm^{-1}; LRMS (EI): *m/z* (rel.intensity) = 214 (19), 213 (100), 199 (15), 198 (89), 197 (17), 183 (33), 170 (26), 155 (11), 154 (11), 77 (12); HRMS (EI): *m/z* calcd. for (M^+) = 213.1154, found = 213.1160.

Products of Experiments Summarized in Table 34

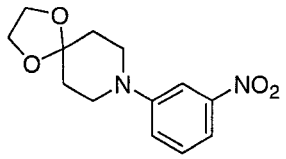
8-(4-Acetylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (76j) (Ogawa, K.; Kaji, M.; Kagawa, H.; Sagawa, M.; Kakuta, A. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **1994**, *50*, 95-97.)



76j

Reaction was performed at 40 °C. Isolated as a clear, crystalline solid in 93 % yield from $PhB(OH)_2$: R_f = 0.10 (3:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (2H, ddd, *J* = 10.0, 5.0, 3.0 Hz), 6.85 (2H, ddd, *J* = 10.0, 5.0, 3.0 Hz), 3.98 (4H, s), 3.50 (4H, dd, *J* = 6.0, 6.0 Hz), 2.50 (3H, s), 1.78 (4H, dd, *J* = 6.0, 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 153.6, 130.6, 127.2, 113.6, 107.1, 64.6, 46.0, 34.4, 26.2.

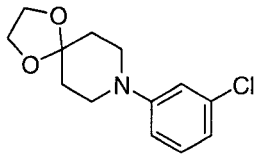
8-(3-Nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (76k)



76k

Reaction was performed at 40 °C. Isolated as a bright yellow oil in 84 % yield from $PhB(OH)_2$: R_f = 0.25 (3:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (1H, t, *J* = 2.0 Hz), 7.57 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz), 7.32 (1H, t, *J* = 8.0 Hz), 7.16 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz), 3.97 (4H, s), 3.40 (4H, dd, *J* = 6.0, 6.0 Hz), 1.78 (4H, dd, *J* = 6.0, 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 149.4, 129.8, 121.5, 113.3, 110.0, 106.9, 64.5, 47.0, 34.3; IR (film) ν 2960, 2886, 1616, 1526, 1349, 1234, 1144, 1112, 1036, 946, 856, 737, 674 cm^{-1}; LRMS (EI): *m/z* (rel.intensity) = 265 (19), 264 (93), 219 (46), 204 (12), 203 (35), 178 (24), 177 (48), 151 (13), 150 (100), 149 (10), 132 (12), 105 (15), 104 (15), 99 (17), 77 (15); HRMS (EI): *m/z* calcd. for (M^+) = 264.1110, found = 264.1109.

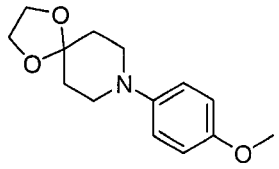
8-(3-Chlorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (76l)



76l

Reaction was performed at 40 °C. Isolated as a clear oil in 85 % yield from $PhB(OH)_2$: R_f = 0.30 (3:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (1H, t, *J* = 8.0 Hz), 6.89 (1H, t, *J* = 2.0 Hz), 6.82 - 6.75 (2H, m), 3.98 (4H, s), 3.33 (4H, dd, *J* = 6.0, 6.0 Hz), 1.81 (4H, dd, *J* = 6.0, 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 135.0, 130.2, 119.0, 116.3, 114.4, 107.2, 64.5, 47.4, 34.5; IR (film) ν 2958, 2883, 1595, 1563, 1487, 1466, 1365, 1231, 1144, 1097, 1037, 945, 768, 683 cm^{-1}; LRMS (EI): *m/z* (rel.intensity) = 255 (37), 254 (21), 253 (100), 210 (10), 208 (30), 194 (11), 192 (21), 168 (16), 167 (18), 166 (42), 141 (26), 140 (15), 139 (74), 138 (20), 111 (13); HRMS (EI): *m/z* calcd. for (M^+) = 253.0869, found = 253.0870.

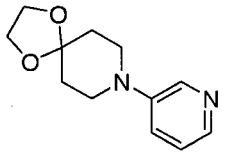
8-(4-Methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (76m)



76m

Reaction was performed at 40 °C. Isolated as a clear, crystalline solid in 95 % yield from $PhB(OH)_2$: mp = 60 - 61 °C (hexanes); R_f = 0.20 (3:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (2H, ddd, *J* = 9.0, 3.0, 1.0 Hz), 6.82 (2H, ddd, *J* = 9.0, 3.0, 1.0 Hz), 3.98 (4H, s), 3.76 (3H, s), 3.18 (4H, dd, *J* = 5.5, 5.5 Hz), 1.86 (4H, dd, *J* = 5.5, 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 145.7, 119.1, 114.4, 107.2, 64.4, 55.6, 49.5, 35.0; IR (film) ν 2956, 2821, 1512, 1466, 1442, 1417, 1368, 1288, 1249, 1224, 1180, 1115, 1036, 949, 896, 832, 704 cm^{-1}; LRMS (EI): *m/z* (rel.intensity) = 250 (26), 249 (100), 235 (11), 234 (51), 204 (12), 188 (10), 163 (13), 162 (42), 136 (12), 135 (63), 133 (18), 121 (11), 120 (41), 99 (11), 92 (10); HRMS (EI): *m/z* calcd. for (M^+) = 249.1365, found = 249.1361.

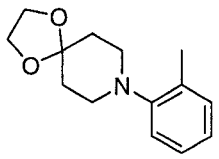
8-(Pyridin-3-yl)-1,4-dioxa-8-azaspiro[4.5]decane (76n)



76n

Reaction was performed at 40 °C. Isolated as light orange oil in 55 % yield from $PhB(OH)_2$: R_f = 0.10 (1:1 CH_2Cl_2:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (1H, s), 8.05 (1H, d, *J* = 3.5 Hz), 7.18 (1H, ddd, *J* = 8.5, 3.5, 1.5 Hz), 7.11 (1H, dd, *J* = 8.5, 3.5 Hz), 3.98 (4H, s), 3.34 (4H, dd, *J* = 5.5, 5.5 Hz), 1.82 (4H, dd, *J* = 5.5, 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 140.5, 139.2, 123.6, 122.9, 107.0, 64.5, 47.2, 34.5; IR (film) ν 2958, 2884, 1672, 1582, 1488, 1426, 1365, 1235, 1144, 1102, 1052, 1035, 946, 930, 799, 708, 670, 614 cm^{-1}; LRMS (EI): *m/z* (rel.intensity) = 221 (14), 220 (82), 175 (32), 159 (26), 134 (17), 133 (55), 107 (15), 106 (100), 105 (29), 99 (20); HRMS (EI): *m/z* calcd. for (M^+) = 220.1212, found = 220.1217.

8-*o*-Tolyl-1,4-dioxa-8-azaspiro[4.5]decane (76o)



76o

Reaction was performed at 40 °C. Isolated as a pale yellow oil in 61 % yield from $PhB(OH)_2$: R_f = 0.33 (9:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 - 7.18 (2H, m), 7.07 (1H, dd, *J* = 7.5, 1.0 Hz), 6.99 (1H, dt, *J* = 7.5, 1.0 Hz), 4.02 (4H, s), 3.01 (4H, dd, *J* = 5.5, 5.5 Hz), 2.34 (3H, s), 1.91 (4H, dd, *J* = 5.5, 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 132.8, 131.1, 126.6, 123.1, 119.4, 107.3, 64.4, 50.3, 35.8, 17.9; IR (film) ν 2955, 2880, 2823, 1599, 1493, 1470, 1363, 1328, 1217, 1142, 1101, 1038, 931, 899, 762, 724, 666 cm^{-1}; LRMS (EI): *m/z* (rel. intensity) = 234 (22), 233 (100), 232 (16), 188 (41), 172 (19), 147 (15), 146 (55), 132 (17), 119 (42), 118 (44), 91 (18); HRMS (EI): *m/z* calcd. for (M^+) = 233.1416, found = 233.1411.

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Chapter IV

Mechanistic Investigations

IV.1 Introduction

IV.1.1 Classical Mechanisms of Copper-Mediated Ullmann Reactions

The mechanism of copper-mediated transformations in general, and the Ullmann reaction in particular, have captured the interest of various research groups for decades. Despite multiple attempts at mechanistic elucidation, relatively little is known about the exact mechanism of the Ullmann transformation.[1-6] It is likely that the reaction proceeds in multiple steps with the generation of one or more arylcopper intermediates (Figure 25). In support of this is the observation that arylcopper compounds can be prepared independently and reacted with aryl halides to obtain the same cross-coupled biaryl products.[7]

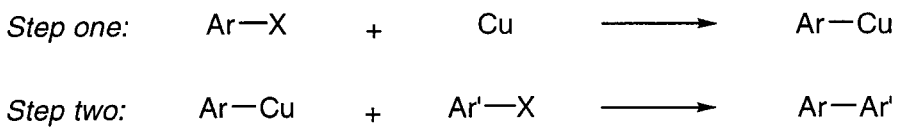


Figure 25 - Postulated Ullmann Mechanism via an Organocuprate Intermediate

Complicating the mechanistic investigation even further is the observation that a wide variety of copper complexes in all three stable oxidation states (0, +1 and +2) can apparently catalyze the reaction. In addition, several examples of stable copper(III) complexes have recently been reported in the literature.[8-10] In fact, no less than six reaction mechanisms have been proposed to explain the Ullmann reaction and its side products. However, little direct experimental evidence has been obtained to support the existence of these mechanistic pathways; instead, most of the mechanisms proposed are results of indirect observations based upon empirical observations. In addition, all of the mechanisms, except for the oxidative addition/reductive elimination mechanism, were proposed for reactions that were stoichiometric in the copper reagent. Thus much of the earlier literature was more concerned with the one way transformation of the starting materials into products, and less concerned with the balancing of chemical equations and accounting of all species involved in the reaction. Only in the modern literature where copper-catalyzed reactions are introduced are there more complete mechanistic pictures where it becomes necessary to account for the fate of the species involved in the catalytic cycles.

IV.1.1.1 σ-Complex Intermediate Mechanism

This mechanism describes the formation of a σ-complex between the metal catalyst and the lone pairs of electrons on the halogen atom. This coordinated complex then leads to polarization of the carbon-halogen bond and is followed by nucleophilic attack, either intramolecularly (Figure 26, reaction 1) or intermolecularly (Figure 26, reaction 2), to afford the substituted product.

Early mechanistic studies into the copper-mediated Ullmann condensations led to the proposal of this type of σ-complex intermediate. Castro and Stephens were the first to purpose this mechanism to explain the cross-coupling of aryl iodide with cuprous acetylides (Figure 27).[11] A similar mechanism was proposed by Bacon and Hill in their substitution reactions on various aryl halides by treatment with different Cu(I) salts (Figure 28).[12]

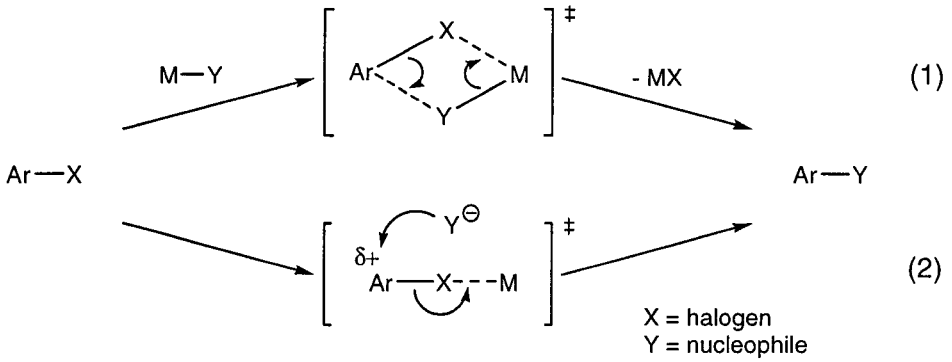


Figure 26 - σ-Complex Intermediate Mechanism

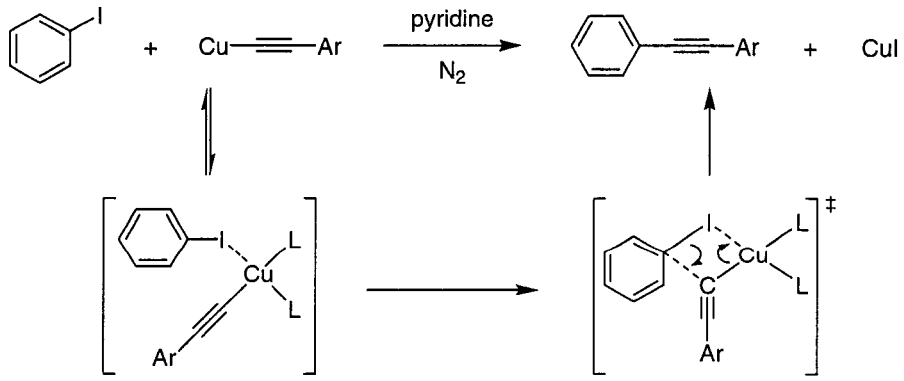


Figure 27 - Cross-Coupling of Aryl Iodide with Cuprous Acetylides

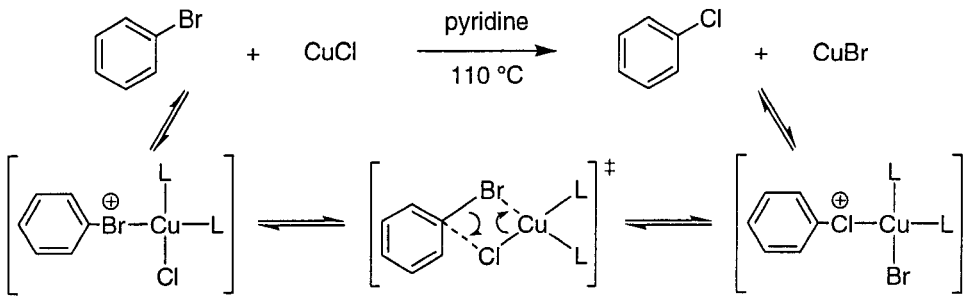


Figure 28 - Reaction of Arylbromides with Cuprous Chloride

IV.1.1.2 π-Complex Intermediate Mechanism

Transition metals are known to form π-complexes with aromatic compounds.[13] The metal centre acts as a strong electron withdrawing substituent on the aryl ring, allowing for a facile nucleophilic attack to follow. Substitution can occur via an addition/elimination mechanism leading to products substituted in a position *ortho* to the original halide (Figure 29, reaction 1), or via direct displacement of the leaving group leading to the *ipso*-substituted product (Figure 29, reaction 2). The first pathway has been shown to occur when π-complexed iron salts are reacted with silyl enol ethers,[14] thus it has been speculated that such a mechanism would also be possible for copper-mediated transformations;[15] however, no such example has been reported to date.

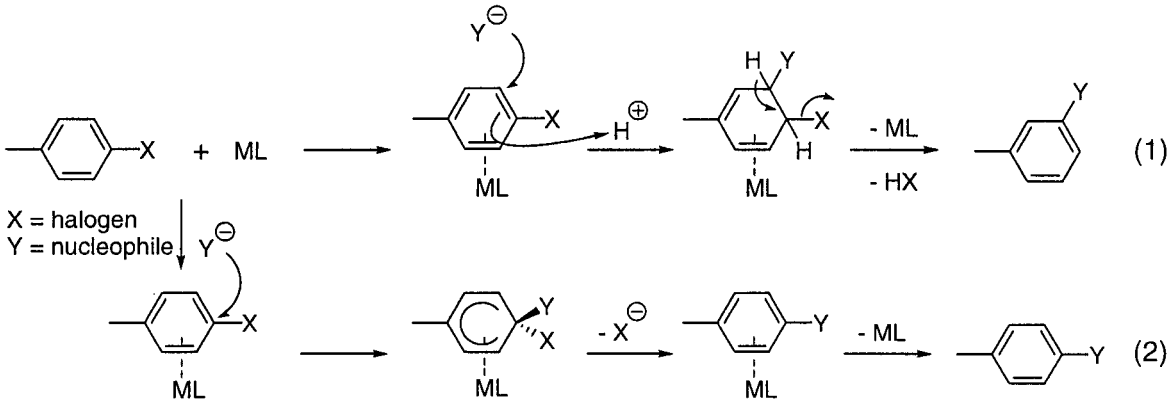


Figure 29 - π-Complex Intermediate Mechanism

Ma and Xia have invoked a π-complex mechanism to explain their copper(I)-catalyzed arylation of β-amino acids under refluxing DMF.[16] In their case, the amino acid acts as a bidentate ligand to the copper catalyst. Coordination of an aryl halide produces the π-complex intermediate which allows for an intramolecular nucleophilic attack by the amine functionality (Figure 30).

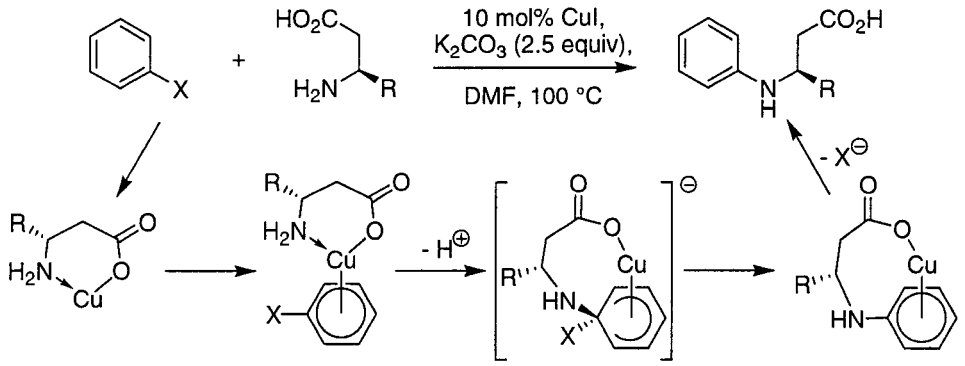


Figure 30 - Cuprous Iodide-Catalyzed Arylation of β-Amino Acids

IV.1.1.3 $S_{RN}1$: Unimolecular Radical Nucleophilic Substitution

SET (single electron transfer) mechanisms have been used to explain the experimental observations of many transition metal-catalyzed reactions.[17] The transition metal catalyst serves as a single electron donor to initiate the reaction by generating a radical anion centred on the halide atom of the aryl halide. Propagation begins with a homolytic scission of the carbon-halide bond to produce a carbon-centred radical. This carbon-centred radical can then couple with a nucleophile to give a second radical anion species. Transfer of an electron from this second radical anion to another molecule of the aryl halide affords both the cross-coupled product and regenerates the radical anion of the aryl halide which continues in the propagation step of the radical chain mechanism. The reaction terminates when a radical anion, either from the starting material or from the product, transfers an electron back to the metal catalyst (Figure 31).

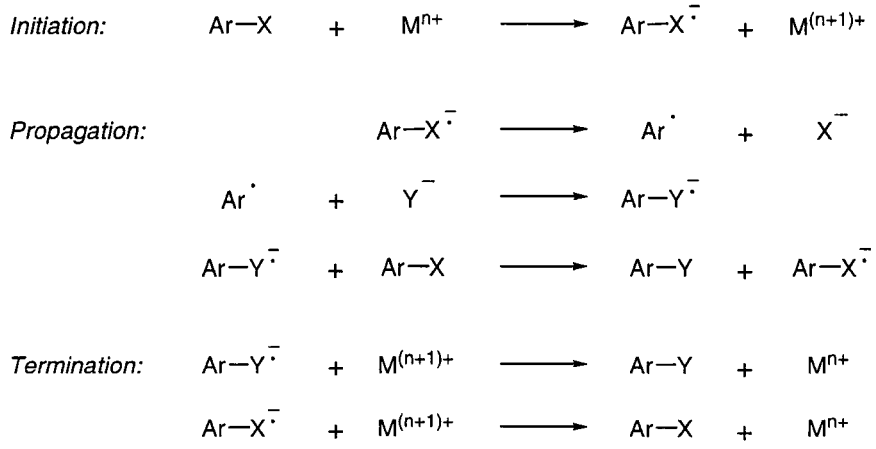


Figure 31 - $S_{RN}1$: Unimolecular Radical Nucleophilic Substitution

Bunnett suggested this mechanism to describe the formation of aniline in the reaction of aryliodides with potassium amide. He noticed the reaction could be inhibited by the presence of

radical scavengers (e.g. molecular oxygen and di-*tert*-butyl nitroxide), or stimulated by the presence of solvated electrons via dissolving metals in liquid ammonia.[18]

IV.1.1.4 $S_{ON}2$: Bimolecular Oxidative Nucleophilic Substitution

The $S_{ON}2$ mechanism is similar to the $S_{RN}1$ mechanism, but involves the formation of an intermediate radical cation on the aryl halide, rather than radical anion. In addition, the propagation step involves an intermediate composed of both the aryl halide and the incoming nucleophile (Figure 32). The mechanism was originally proposed by Alder to explain radical transformations that occurred under oxidative conditions.[19] Eberson used this argument to explain the nucleophilic substitution reactions of various aryl halides in the presence of potassium copper(III)biuretate (Figure 33).[20]

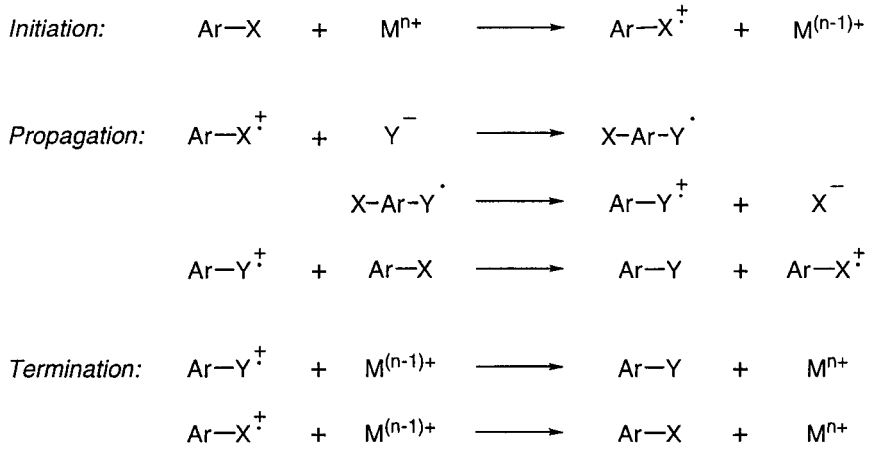


Figure 32 - $S_{ON}2$: Bimolecular Oxidative Nucleophilic Substitution

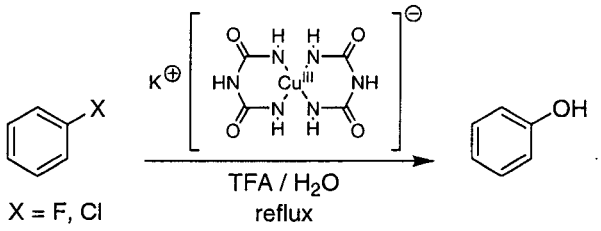


Figure 33 - Potassium Copper(III) Bisbiuretate Mediated Hydrolysis of Aryl Halides

IV.1.1.5 S_HAr: Homolytic Aromatic Substitution

The last in a series of three SET mechanisms is the S_HAr mechanism. This type of mechanism is most commonly observed when reaction of the nucleophile and the metal reagent results in the generation of a radical on the nucleophile.[21] This radical nucleophile then reacts

with the aryl halide in the same manner as described above to afford the cross-coupled product. The *ipso*-substituted product is always isolated (Figure 34).

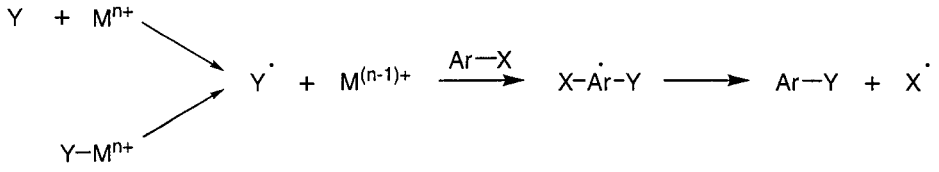


Figure 34 - S_HAr: Homolytic Aromatic Substitution

IV.1.1.6 Oxidative Addition/Reductive Elimination

Arguably one of the more favoured mechanisms applied to transition-metal catalyzed reactions in the modern literature, this mechanism begins with the oxidative insertion of the metal catalyst into the labile carbon-halogen bond. It has been speculated that oxidative addition may involve successive one electron transfers or a concerted electron pair process.[15] Coordination of the nucleophile to the metal centre allows for a reductive elimination, thus regenerating the initial oxidation state of the metal catalyst while concomitantly affording the cross-coupled product (Figure 35).

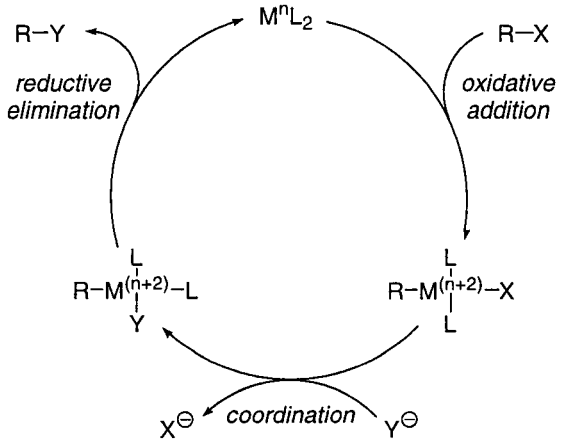


Figure 35 - Oxidative Addition/Reductive Elimination

IV.1.2 Modern Mechanisms of Copper-Mediated Ullmann Condensations with Organometalloids

The proposed mechanisms for the copper-mediated Ullmann condensation of organometalloids with heteroatomic nucleophiles often involve the formation of tetracoordinate organocuprate intermediates that are arrived at through transmetallation and oxidative addition pathways. Investigators had been able to rule out radical reaction mechanisms early on, as the

presence of radical scavenger additives (e.g. 1,1-diphenylethylene) did not inhibit the reactions.[22]

The modern use of organometalloid species in the cross-coupling, instead of the aryl halides, do not allow for oxidative addition of the electrophilic species to activate the metal catalysis. Hence, in the general mechanism for these transformations, the nucleophiles initially coordinate to the metal centre. A transmetallation of the organo moiety from the organometallic reagent provides a tetracoordinate intermediate which affords the cross-coupled product via a reductive elimination (Figure 36). The reduced metal species is now inactive in the transformation and the general catalytic cycle is interrupted. Hence, the problem at hand is the reoxidation of the lower oxidation state metal species to the reactive species of the higher oxidation state.

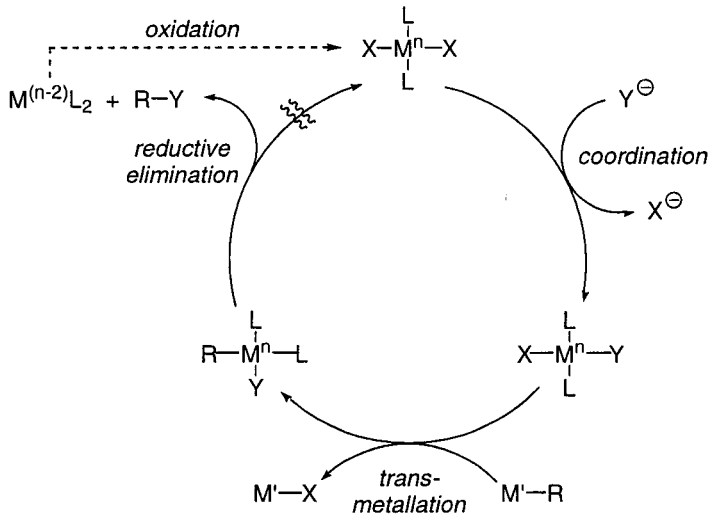


Figure 36 - General Mechanism for Stoichiometric Cross-Coupling of Organometalloids with Heteroatomic Nucleophiles

IV.1.2.1 Evans/Lam's Cu(I)/Cu(II)/Cu(III) Mechanism

Evans and coworkers were the first to speculate on the mechanism of their copper-mediated cross-coupling of arylboronic acids with phenols.[23] They proposed analogous pathways for the Ullmann condensation for both organometalloids (Figure 37a) and aryl halides (Figure 37b). Both reactions begin with interaction of a copper reagent with one of the cross-coupling partners to generate a tetracoordinate organocuprate intermediate. The organometalloid transmetallates an aryl moiety to copper in path A, thus the oxidation state of the Cu(II) centre remains unchanged. In contrast, path B shows the aryl halide undergoing an oxidative addition by the copper reagent; hence, the Cu(I) centre is oxidized to a Cu(III) species. Coordination of

the incoming nucleophile produces a second tetracoordinate intermediate containing both cross-coupling partners. A reductive elimination from this second organocuprate intermediate affords the diaryl ether product and a Cu(0) species in from path A, or a Cu(I) species from path B. The ambiguity in this mechanistic picture lies in the crossing of the two pathways at the second (or possibly the first) organocuprate intermediate.

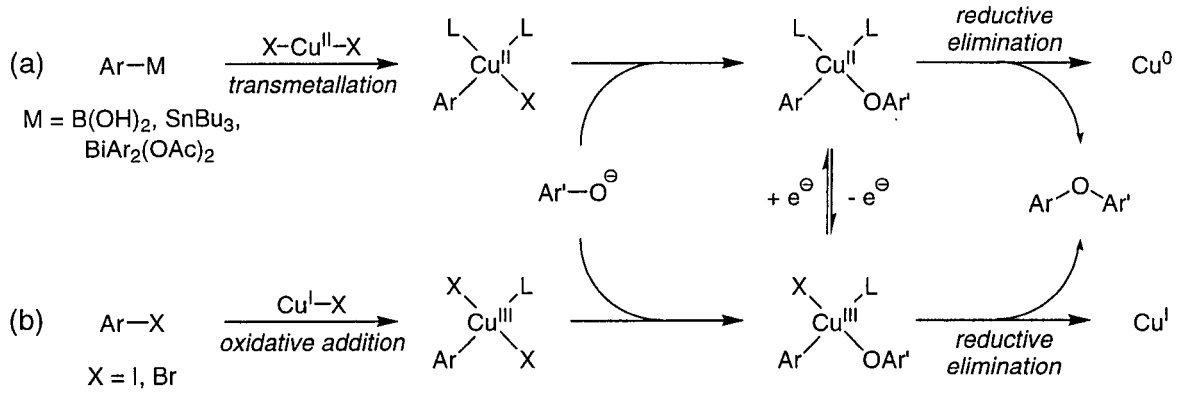


Figure 37 - Evans' Proposed Mechanism for Copper-Mediated Ullmann Condensations of Organometalloids with Phenols

Copper's ability to readily disproportionate between various oxidation states provides a crossing point between the two pathways. Indeed the two copper species may exist in an equilibrium controlled by the reduction potential of the copper couple. Therefore it remains unclear as to which organocuprate species is responsible for the final step of the sequence of events. In addition, the disproportionation between oxidation states is not limited to the Cu(II)/Cu(III) transition, but also applies to Cu(0)/Cu(I) and Cu(I)/Cu(II) systems; hence, even analysis of the copper residues at the end of the reaction would not provide a definitive elucidation of the active species. However, two putative details have been accepted by those exploring this field. The first is that coordination of the heteroatomic nucleophile to a Cu(II) centre decreases the reduction potential of the Cu(II)/Cu(III) couple, thereby making the transition between the oxidation states easier.[15] The second is that reductive elimination from a highly energetic Cu(III) species occurs faster than the reductive elimination from a Cu(II) species.[15,22-24] Indeed, Evans' observation that running the reaction under an atmosphere of oxygen affords greater yields of the cross-coupled product, gives credence to the proposed Cu(III) intermediate.[23]

Lam and coworkers have also proposed a mechanistic pathway that is identical to Evans

for their arylation/vinylation of nitrogen nucleophiles (Figure 38). Their main contribution to this field, however, is their analysis of the post-reaction copper residues. They found that only trace amounts of Cu(0) could be detected at the end of the reaction, even when stoichiometric amounts of the copper reagent were employed. This observation led them to conclude that reductive elimination most likely occurred from a Cu(III) intermediate, thus generating Cu(I), rather than a Cu(II) to Cu(0) transition occuring.[24]

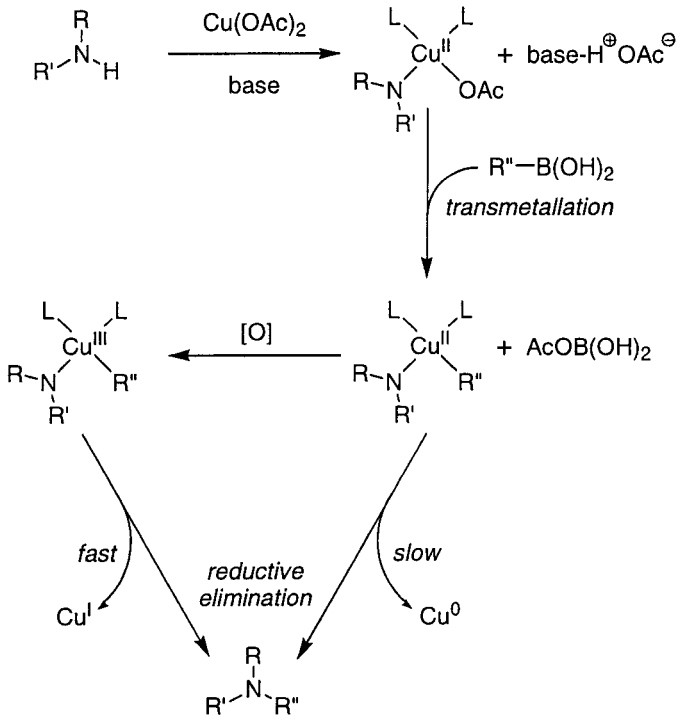


Figure 38 - Lam's Proposed Mechanism for Copper-Mediated Ullmann Condensations of Organoboronic Acids with Nitrogen-Based Nucleophiles

IV.1.2.2 Collman and Zhong's $[Cu(OH)\cdot TMEDA]_2Cl_2$ Catalytic Cycle

Collman and Zhong used the copper complex $[Cu(OH)\cdot TMEDA]_2Cl_2$ (**69**) (first as the commercially available reagent,[25a,b] then later generated by reaction of CuCl and TMEDA in aqueous ethanol)[25c] as a catalyst for the arylation of imidazoles (*vide* III.1.2.7). In their proposed catalytic cycle (Figure 39), the dimeric copper complex is first cleaved by the transmetallation of the aryl moiety from the boronic acid. The tetracoordinate intermediate **78** then coordinates to the incoming imidazole nucleophile to give the pentacoordinate copper species **79**. This Cu(II) complex is then oxidized to the more reactive Cu(III) complex **80**, while half an equivalent of molecular oxygen is concomitantly reduced to water (proton transfer from imidazole balances the chemical formula). The Cu(III) complex **80** quickly undergoes a reductive elimination to afford

the arylated imidazole product and the Cu(I) complex **81**. A second oxidation by molecular oxygen regenerates the initial Cu(II) complex **69**, returning to the beginning of the catalytic cycle.

It is interesting to note that complex **69** has the same structure as the bis(μ-oxo)dicopper complex that Tollman *et al.* had hypothesized to be responsible for catalytic *N*-dealkylation of amines (*vide* III.2.1.2.1).[26] Perhaps this is the reason why Collman's protocol only works for the arylation of imidazole and its derivatives.

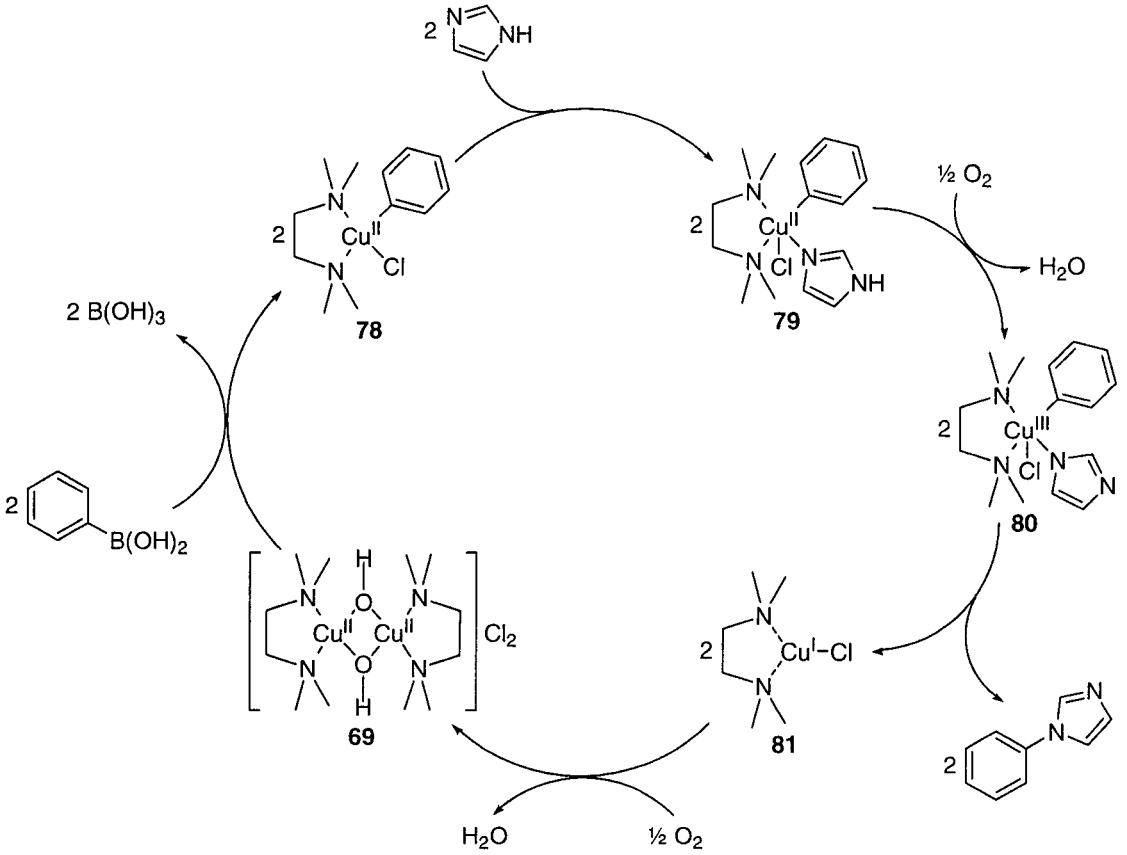


Figure 39 - Proposed Mechanism $[Cu(OH)\cdot TMEDA]_2Cl_2$ Complex-Catalyzed Arylation of Imidazoles

IV.1.3 Side Products of the Ullmann Condensation

IV.1.3.1 Phenols, Diaryl Ethers and Hydroborated Arenes

Several side reactions compete directly with the desired cross-coupling in the Ullmann condensation; therefore, the use of more than one equivalent of the boronic acid cross-coupling partner, regardless of whether the reaction is catalytic or stoichiometric in the copper reagent, is necessary to obtain high yields of the arylated product. The first by-product, phenol, can be

produced through one of two pathways (Figure 40, reactions 1 and 2). In the first pathway, molecular oxygen is reduced to hydrogen peroxide as Cu(II) is oxidized to Cu(III). The peroxide, under basic conditions, can cause boronic acids to undergo oxygen insertion/hydrolysis reactions to give phenol.[27] In the second pathway, water present in the reaction mixture acts a competing nucleophile in the cross-coupling; hence, phenol arises through the arylation of water. Even under anhydrous reaction conditions (i.e. the use of stoichiometric anhydrous $Cu(OAc)_2$ under an inert atmosphere), the production of phenol is observed when boronic acids are employed as cross-coupling partners. This is due to the fact that water is released in the trimerization of boronic acids into boroxines. Evans *et al.* observed that the use of molecular sieves to absorb excess water helped to increase the yield of the desired cross-coupled products while reducing the unwanted phenol production.[23] The phenol produced is nucleophilic enough to act as a competing cross-coupling partner. Thus, significant amounts of diphenyl ether are also isolated from reaction mixtures (Figure 40, reaction 3).

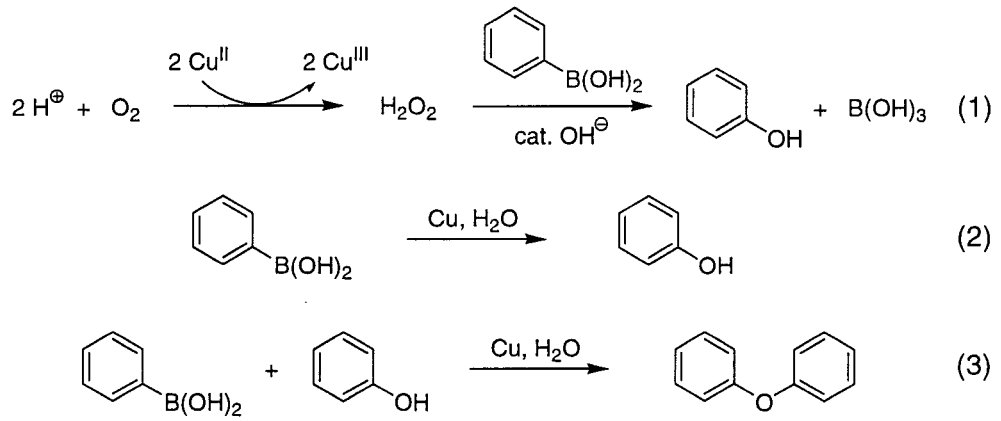
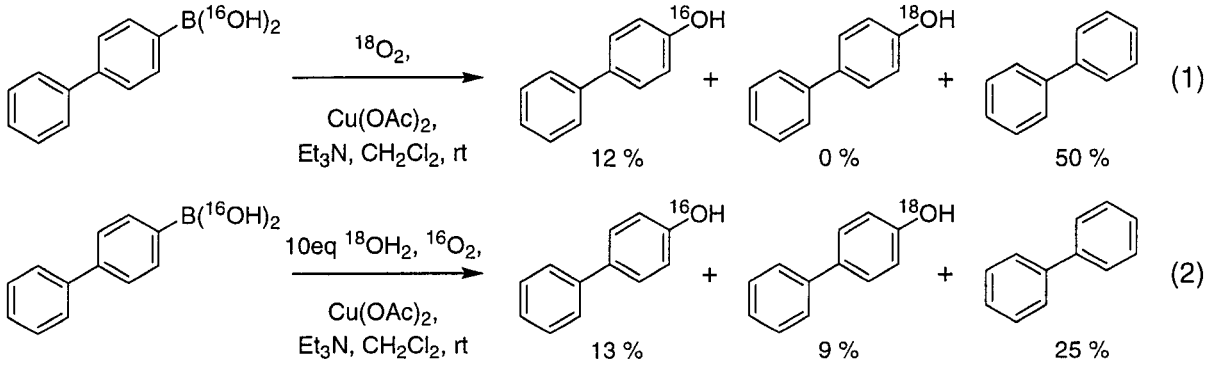


Figure 40 - Production and Arylation of Phenol

Through the use of isotopic labelling studies, Lam and coworkers were able to provide evidence that the production of phenol most likely came from the arylation of water, instead of the oxidation of the boronic acid by molecular oxygen. An arylboronic acid was subjected to two reactions under their standard protocol in the absence of a nucleophilic cross-coupling partner. One reaction was run under an atmosphere of $^{18}O_2$, while the other introduced the ^{18}O isotope through labelled water (Scheme 72). The only phenol derivative isolated came from the reaction in the presence of the isotopically labelled water (Scheme 72, reaction 2); while none of the isotopically labelled phenol was observed in the first reaction. Hence, it was concluded that the phenol side products came about through the arylation of water and not via oxidation by

molecular oxygen. Moreover, a second side reaction was observed in their studies. Significant quantities of the hydrodeborated starting material were also isolated. It is believed that reaction of the boronic acid with water, without the copper catalyst, lead to that side product.

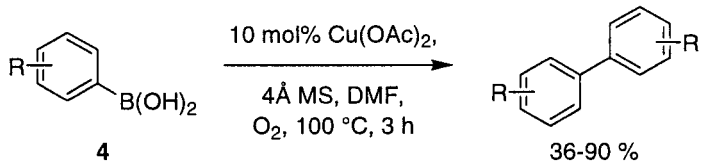


Scheme 72 - Reactions of Arylboronic Acids under Ullmann Conditions in the Absence of a Nucleophile

IV.1.3.2 Biaryls via Oxidative Dimerization

Other side products often isolated from the Ullmann condensation of arylboronic acids are symmetrical biaryl compounds resulting from the oxidative homocoupling of the organoboron component. Demir and coworkers have investigated the conditions for this undesired side reaction of the Ullmann condensation. They have recently described a set of optimized conditions for the preparation of the symmetrical biaryls through this protocol. In the reaction, the arylboronic acid **4** is treated with 10 mol % of the copper reagent in the presence of molecular sieves in DMF at 100 °C under an atmosphere of oxygen (Scheme 73).[28]

Electron rich arylboronic acids were found to give high yields of the corresponding biaryl compounds, while electron-deficient arylboronic acids afforded only low to moderate yields. Steric hindrance around the reactive boron centre via substitution in the *ortho*-position of the aromatic rings was not tolerated. Only poor yields of the corresponding biaryls were achieved regardless of the electronic properties of the aromatic ring. In fact, di-*ortho* substituted (i.e. in 2 and 6 positions of the aromatic ring) boronic acids gave none of the homocoupled product under the reaction conditions.



Scheme 73 - Symmetrical Biaryls via Oxidative Dimerization of Arylboronic Acids

IV.2 Results and Discussion

IV.2.1 Proposed Catalytic Cycle for Copper-Catalyzed Cross-Coupling of Organotrifluoroborate Salts with Heteroatomic Nucleophiles

The proposed catalytic cycle for the copper-catalyzed arylation of heteroatomic nucleophiles with organoboron compounds in general, and potassium organotrifluoroborate salts in particular, is based upon the generally accepted principles described above. The specific copper oxidation states that are involved in the transformation remain unknown; however, a combination of two catalytic cycles encompasses all of the commonly known reactive species of copper (Figure 41). In addition, the exact sequence of events is unknown with the exception that coordination/activation of the nucleophile to copper which is believe to occur first (*vide infra*). It should also be mentioned that the spatial orientation of the copper complexes are not known, and structures drawn do not imply specific stereochemistries.

The catalytic cycle begins with a copper (II) reagent, in this case $Cu(OAc)_2$. Interaction of the copper species with a ligand dissolves the sparingly soluble copper reagent in CH_2Cl_2. Addition of the nucleophile to this reaction mixture produces an immediate colour change to the stirring solution (*vide* III.2.2.1). This colour change is believed to be a result of coordination of the nucleophile to the copper species, with concomitant ligand exchange, to generate the first organocuprate intermediate **82**. This copper(II) intermediate can then react with the organoborate species to pick-up the aryl moiety through a transmetallation event, thus forming the second copper(II) intermediate **83**. A reductive elimination from **83** would provide the cross-coupled product, whilst generating a copper(0) species. Two single electron transfers from the copper(0) metal to molecular oxygen would result in the regeneration of the copper(II) active species, while reducing the oxygen to water, thus continuing the catalytic cycle.

To complicate matters, copper's ability to disproportionate between stable oxidation states allows access to a second catalytic cycle. The copper(II) intermediate **83** can oxidize to generate copper(III) species **84**. Thus, **84** can undergo a reductive elimination to produce the cross-coupled product and a copper(I) species. This copper(I) species can then interact with a molecule of the nucleophile to provide organocuprate **85**, also a copper(I) species. A transmetallation event from the organoboron compound would give the copper(I) intermediate **86**, which can then be reoxidized to the copper(III) intermediate **84** with the concurrent reduction

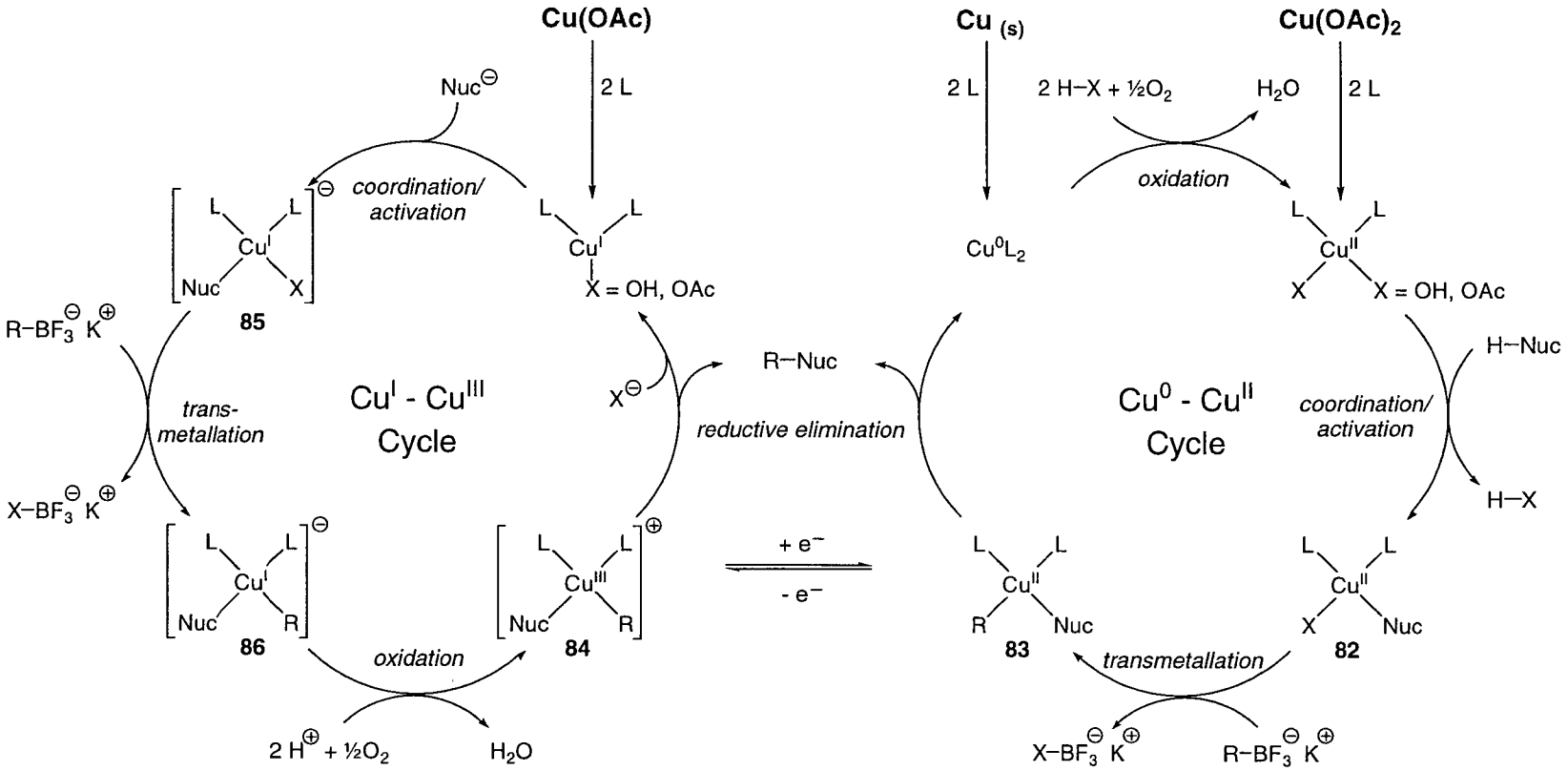
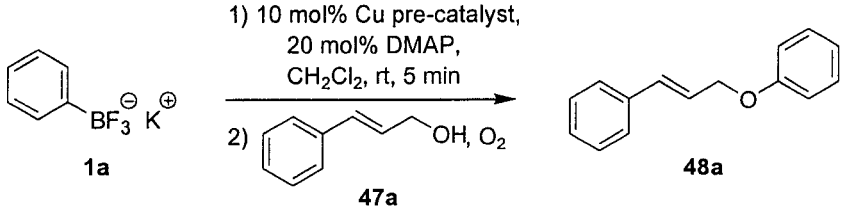


Figure 41 - Proposed Catalytic Cycle for Copper-Catalyzed Cross-Coupling of Organotrifluoroborate Salts with Heteroatomic Nucleophiles

of molecular oxygen to water to complete the second catalytic cycle.

Indeed, all three oxidation states of copper were able to be employed as the pre-catalyst in the reaction (Table 35). Both the copper(I) and copper(II) pre-catalysts afforded similar yields of the cross-coupled product under identical conditions. Surprisingly, the metallic copper species also gave some of the product, but only after stirring for 7 days. It is unclear whether the reactivity was due to oxidation of the copper(0) species to one of the other more reactive oxidation states *in situ*, or whether the copper sample already contained some of the higher oxidation state species through natural oxidation while in storage.

Table 35 - Various Copper Oxidation States as Pre-catalyst to Arylation



1a 47a 48a

Entry	Cu source	Time	Yield (%)[a]
1	$Cu(OAc)_2 \cdot H_2O$	24 h	89
2	CuOAc	24 h	78
3	Cu metal	7 d	10

a) isolated yields.

IV.2.1.1 Activation of the Nucleophile and the Role of Water

If the catalytic cycle proposed above is correct, then one molecule of water is being generated and consumed in each turn of the cycle. A closer examination of right side of the catalytic cycle with the generic ligand on copper described as a hydroxyl group, as depicted in Figure 42, reveals the fate of the water in the reaction.

The reaction begins with activation of the $Cu(OAc)_2$ pre-catalyst by hydroxide displacement of the acetate ligands. Coordination of the incoming nucleophile to copper liberates one of the hydroxyl moieties, which can then act as base to activate the nucleophile, thus generating a molecule of water. Transmetallation of the aryl moiety from the organotrifluoroborate salt could then displace the second hydroxyl ligand on copper. This

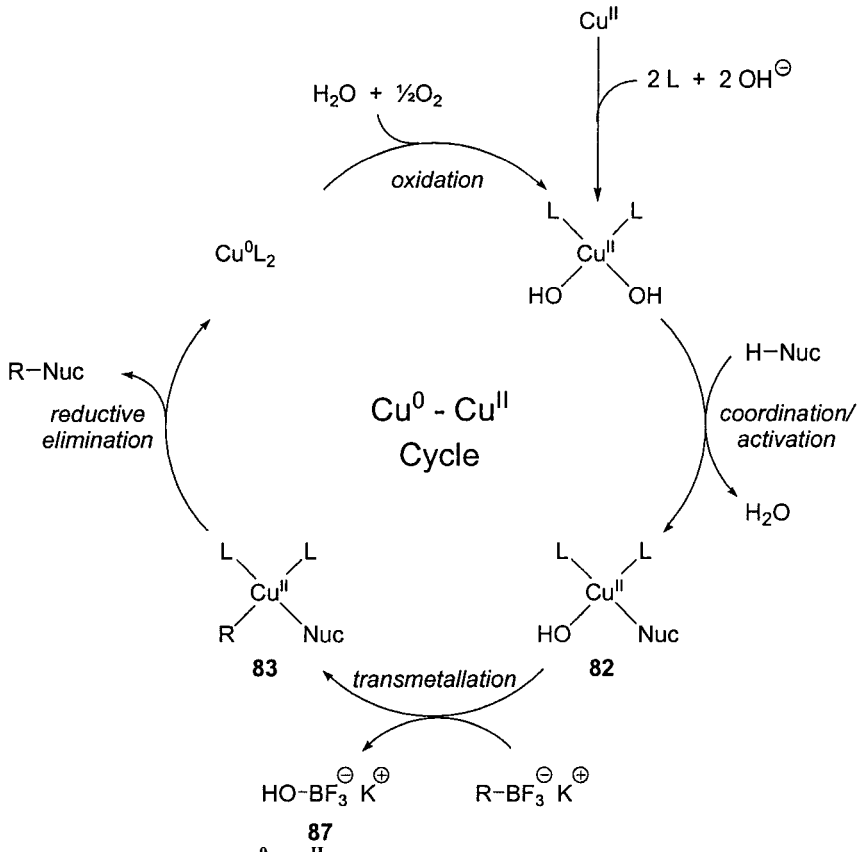


Figure 42 - Cu^0-Cu^{II} Catalytic Cycle Redrawn with X = OH

hydroxyl can then coordinate to the now trivalent BF_3 moiety to afford the fluoroxyboronate **87** (observable by ^{11}B and ^{19}F NMR), most likely this ligand exchange between copper and boron occurs in a concerted fashion. The catalytic cycle continues as intermediate **83** reductively eliminates to form the cross-coupled product and copper(0). The single molecule of water formed at the beginning of the catalytic cycle can now react with the copper(0) and molecular oxygen to regenerate the reactive $CuL_2(OH)_2$ species to begin the cycle again; thus, the water produced in the reaction is also consumed by the reaction.

An analogous catalytic cycle between copper(I) and copper(III) can be drawn from the left half of Figure 41, using a hydroxyl moiety in place of the generic ligand X (Figure 43).

It is worth reiterating that water can also act as a competing nucleophile in the reaction (*vide* IV.1.3.1). In an ideal reaction, the water would remain in the catalytic cycle and no by-products would be observed, but in reality, significant quantities of phenol and diphenyl ether can be isolated at the end of the reaction. In addition, the catalyst of choice, $Cu(OAc)_2 \cdot H_2O$, initially introduces at least 10 mol % of water into the reaction mixture.

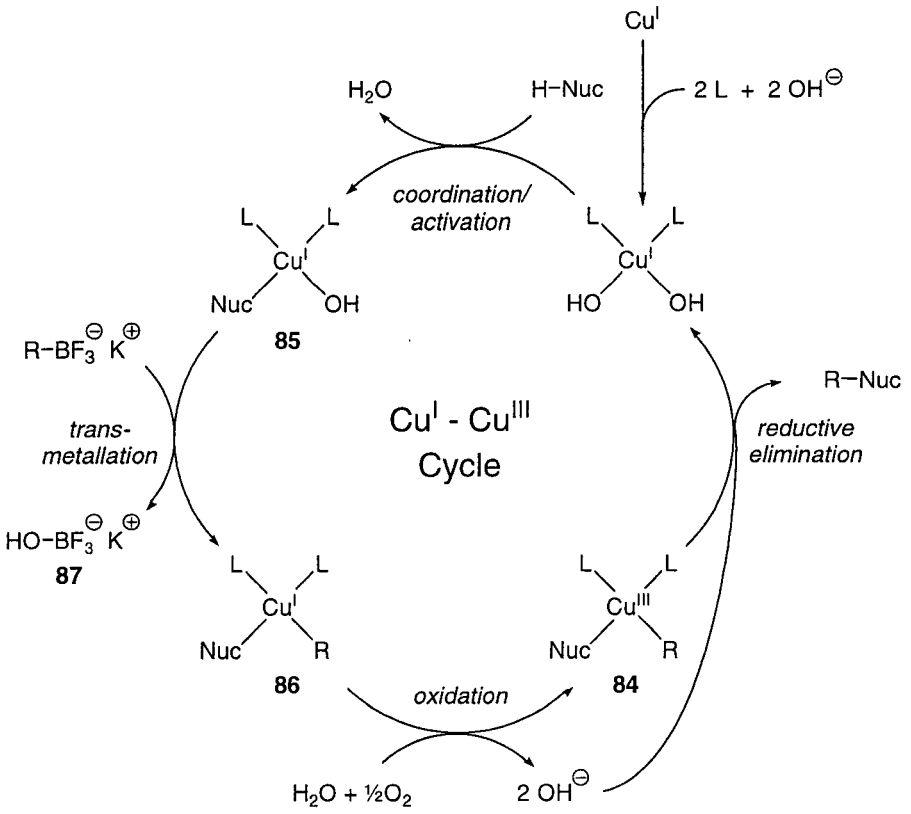


Figure 43 - Cu^{I}-Cu^{III} Catalytic Cycle Redrawn with X = OH

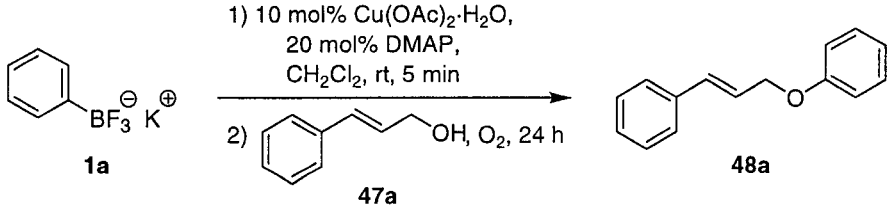
IV.2.1.2 The Role of Molecular Sieves

If the above supposition on the role of water is correct, then the obvious question is what role, if any, do the molecular sieves play in the reaction? During the optimization process of the arylation of aliphatic alcohols (*vide* II.2.1.1), it was believed that the molecular sieves acted as desiccant to remove water as a potential cross-coupling partner. Indeed, Evans and coworkers had stated in their paper that the presence of molecular sieves greatly enhanced the yields of the desired cross-coupled products over that of phenol and diphenyl ether.[23] However, if the molecular sieves only act as a desiccant then their replacement by another chemical desiccant should provide similar reactivity in the transformation. The results of control reactions run under the optimized conditions did not support this latter theory (Table 36).

There was not an obvious correlation between size of the pores in the molecular sieves and the reaction yields (Table 36, entries 1-3). However, it was observed that the beaded molecular sieves gave lower yields than the powdered variety (Table 36, entry 4). The use of a chemical desiccant in place of the molecular sieves did not give the same reaction. Only poor

yields of the cross-coupled product were obtained when the reaction was performed with CaH_2 or $MgSO_4$ (Table 36, entries 5 and 6). No reaction occurs in the absence of molecular sieves, the desired cross-coupling or otherwise, and only unreacted starting material is recovered at the end of the experiment. Hence, it was concluded that molecular sieves must be playing a greater role in the reaction than just as a desiccant to remove excess water.

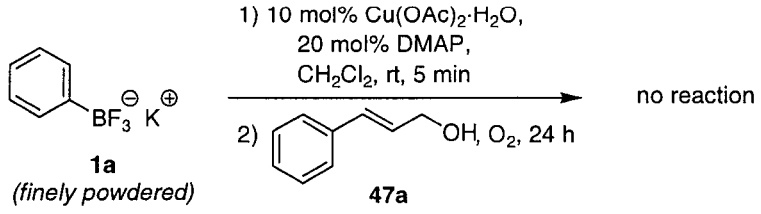
Table 36 - Control Reactions with Variance of the Desiccant



Entry	Additive	Yield (%)[a]
1	3Å MS (beads)	68
2	4Å MS (beads)	70
3	10Å MS (beads)	56
4	4Å MS (powdered)	89
5	$MgSO_4$	9
6	CaH_2	11
7	-	0[b]

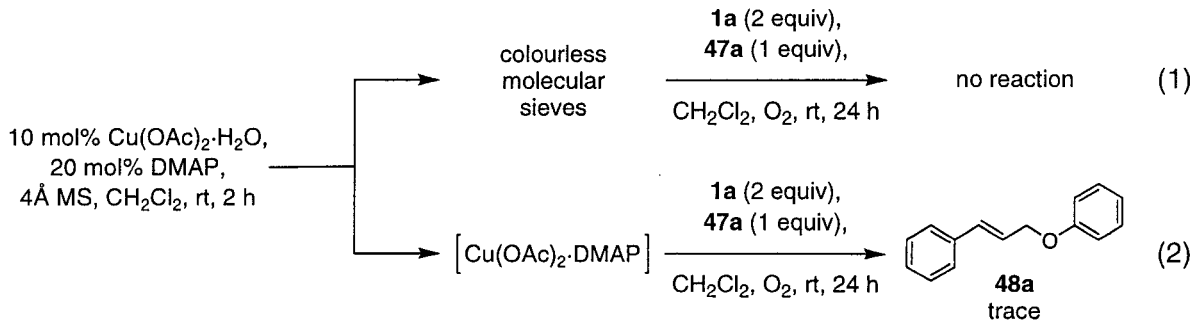
a) isolated yields. b) no side products observed; only unreacted **1a** recovered after reaction.

The mechanical aspect of the molecular sieves was investigated on the theory that the sieves were acting to grind the potassium trifluoroborate salts in the reaction mixture in order to aid their solubility in CH_2Cl_2. The use of finely powdered **1a** in the absence of molecular sieves did not produce any of the desired product, nor the side products (Scheme 74).



Scheme 74 - Finely Powdered Organotrifluoroborate Salt in the Absence of Molecular Sieves

The possibility that the molecular sieves were interacting with the copper complex in such a manner as to create the active species in the transformation was also explored. The copper catalyst and DMAP ligand were pre-stirred with molecular sieves in CH_2Cl_2 for several hours. Physical separation of the heterogeneous reaction mixture resulted in a sample of the molecular sieves, and a blue solution of the copper/ligand complex. These separate components were then subjected to parallel reactions under the standard conditions for the cross-coupling of **1a** and **47a** (Scheme 75). As expected, the experiment containing only the pre-treated molecular sieves did not show any reactivity (Scheme 75, reaction 1). Had the copper reagent interacted with the molecular sieves to form an active complex for catalysis, it is reasonable to expect the pre-treated molecular sieves would catalyze the reaction without addition of any more catalyst. However, an absence of reactivity in the experiment demonstrated that none of the copper reagent was present in the sample of molecular sieves. The second experiment, run in the absence of molecular sieves, afforded only trace amounts of the desired product visualized by TLC, but not isolated. The limited reactivity is probably due to minute amounts of the powdered molecular sieves previously dissolved in the CH_2Cl_2 solution (Scheme 75, reaction 2).



Scheme 75 - Investigation of Molecular Sieves/Copper Catalyst Interaction

IV.2.1.2.1 The Transmetallation Hypothesis

A more thorough investigation by gas chromatographic analysis of all the components in the crude reaction mixtures of the arylation of both alcohols and amines provided greater insight into the possible role of the molecular sieves. A series of reactions were run in parallel to examine the effect of the various components of the reaction. The choice of the arylboron reagent employed, the nucleophilic cross-coupling partner, the stoichiometry of the copper reagent, and the presence of molecular sieves were varied in each reaction (Figure 44). One equivalent of naphthalene was added to each reaction as an internal standard for gas

chromatography. An aliquot of each crude reaction mixture was taken, filtered through a small plug of silica gel to remove the copper reagent then injected into the GC and analyzed without further work-up. The data summarized in Tables 37 and 38 represent an average of two runs with yields normalized to the naphthalene signal. The specific experimental parameters can be found in the following section (*vide* IV.3.1).

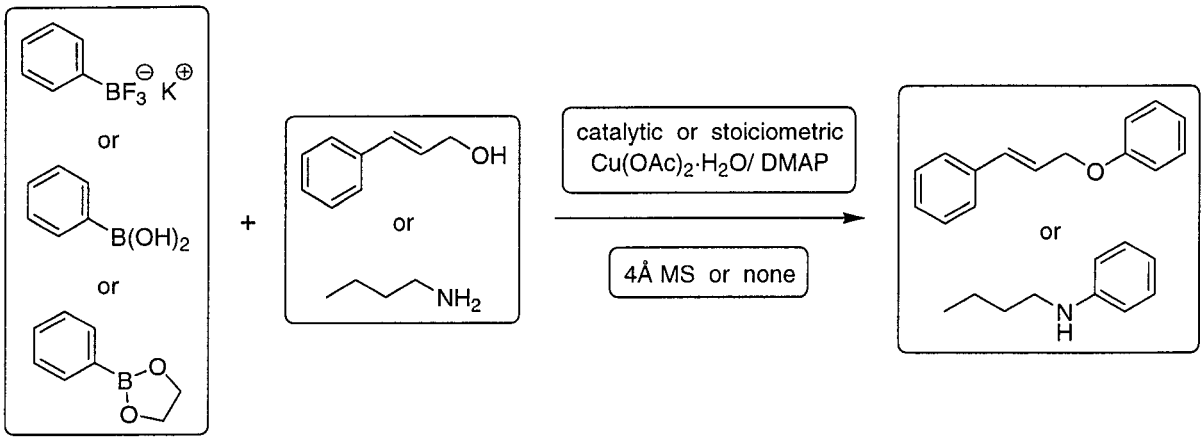


Figure 44 - Parameters Varied in Control Reactions of Arylations

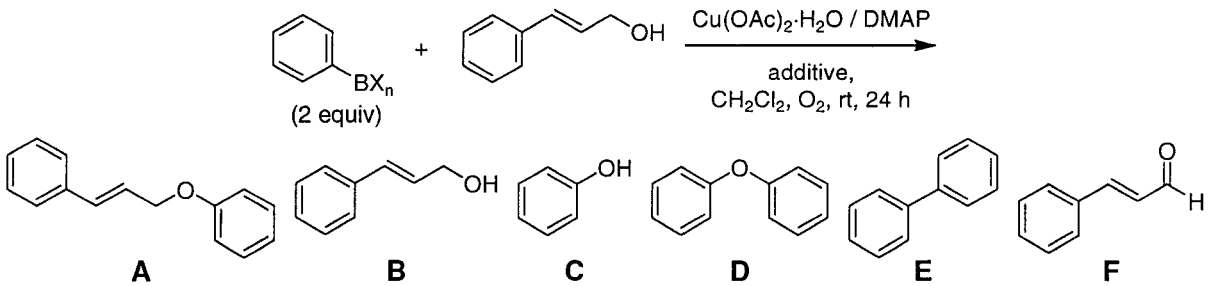
There are a few general observations from the series of parallel reactions that are worth noting. Firstly, the reactions that were stoichiometric in copper and ligand tend to give lower yields than the catalytic reactions. Without changing the volume of solvent used in the reaction, the stoichiometric reactions were highly concentrated slurries which made mechanical agitation of the mixtures difficult. Secondly, besides the desired arylated nucleophile, the crude reaction mixtures also contained phenol (i.e. arylation of water), diphenyl ether (i.e. arylation of phenol) and biphenyl (i.e. oxidative homocoupling of the borate). Finally, the amounts of phenol and diphenyl ether present is much greater in the stoichiometric reactions, as expected, due to the presence of one equivalent of water in the reaction from the monohydrate copper reagent.

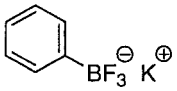
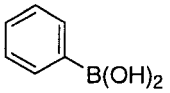
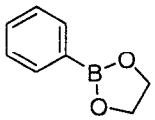
The arylation of (*E*)-cinnamyl alcohol was plagued with side products. The slow reactivity of the comparatively weaker nucleophile allowed other species to complicate the reaction, thus greater amounts of the arylated water by-products were observed here than in the *N*-arylation reactions. In addition, the presence of copper under these oxidative conditions allowed for oxidation of the cinnamyl alcohol to cinnaldehyde in significant quantities in some cases (the commercially obtained sample of cinnamyl alcohol contains < 5 % of the aldehyde as determined by ^{1}H NMR). This copper-catalyzed aerobic oxidation of primary and secondary

alcohols has been extensively studied by Markó and coworkers.[29]

The reaction of the aryltrifluoroborate salts gave the best yields for the desired cross-coupled product under catalytic conditions in the presence of molecular sieves (Table 37, entry 1). In contrast, the absence of molecular sieves gave none of the desired product, and only traces of the side products that would have come from the borate component of the reaction (Table 37, entry 2). This leads to the conclusion that no interaction between the aryltrifluoroborate and the

Table 37 - Control Reactions for the Arylation of (*E*)-Cinnamyl Alcohol under Oxygen



Entry	Borate	Amount of Cu[a]	Additive	A (%)[b]	B (%)[b]	C (%)[b]	D (%)[b]	E (%)[b]	F (%)[b]
1		cat.	4Å MS	79	2	22	23	-	19
2		cat.	-	2	90	-	trace[c]	-	8
3		stoich.	4Å MS	66	16	29	47	-	18
4		stoich.	-	13	57	-	2	-	27
5		cat.	4Å MS	52	34	24	11	41	3
6		cat.	-	5	83	13	-	12	10
7		stoich.	4Å MS	73	6	50	34	2	10
8		stoich.	-	71	14	15	36	trace[c]	14
9		cat.	4Å MS	61	20	17	23	-	16
10		cat.	-	22	56	2	6	-	19
11		stoich.	4Å MS	51	36	22	18	trace[c]	12
12		stoich.	-	24	62	5	19	-	14

a) cat. = 10 mol% $Cu(OAc)_2 \cdot H_2O$, 20 mol% DMAP; stoich. = 1 equiv. $Cu(OAc)_2 \cdot H_2O$, 2 equiv. DMAP
b) GC yields; an average of two runs; normalized to naphthalene response ratios. c) trace < 1 %.

copper reagent occurred in the absence of the sieves. Even under stoichiometric conditions in the absence of the sieves, only a slightly greater yield of the cross-coupled product was observed with trace amounts of the side products (Table 37, entry 4).

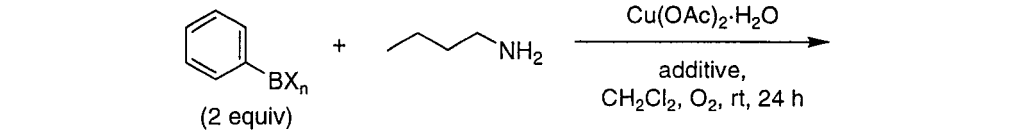
The more surprising results came from the reactions of the arylboronic acids and the arylboronate esters. Both arylboron compounds were able to produce significant amounts of the phenol and diphenyl ether by-products even in the absence of the molecular sieves (Table 37, entries 6, 8, 10 and 12). This suggests that an interaction between these boron reagents and copper is not necessarily mediated by the molecular sieves. Another peculiarity observed in these reactions is that the production of the oxidatively dimerized product, biphenyl, only occurs when the arylboronic acids are employed, but not when the trifluoroborate salt or the boronate ester is used. It is unclear why this phenomenon only occurs with the boronic acids, but it should be noted that the aryl moiety of the boronic acids is more "electron-deficient" than that of the trifluoroborate salts or the boronate esters, as evidenced by the chemical shifts of the *ortho* protons on the ^{1}H-NMR spectrum (i.e. δ 8.20 ppm versus δ 7.85 ppm and δ 7.82 ppm respectively).

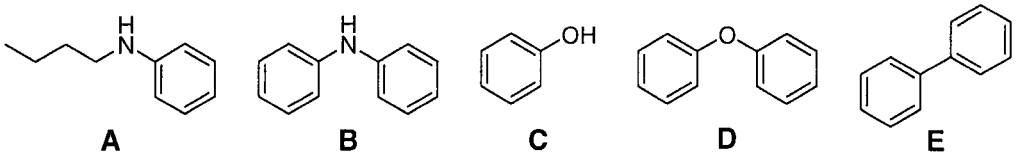
The arylation of *n*-butylamine gave similar results to those of the alcohol with the exception that lower quantities of the side products were observed (Table 38). Once again the stoichiometric reactions resulted in a thickening of the mixture making smooth stirring difficult to achieve. In addition, the increased copper loading resulted in greater quantities of the *N*-dealkylated product, diphenyl amine. As before, the reactivity of the trifluoroborate salt was severely diminished in the absence of the sieves, but boronic acid and the boronate ester still displayed limited reactivity. And once again, the reactions of the boronic acid were the only ones that gave any significant amount of the homocoupled biphenyl product.

The ability of the boronic acid and the boronate ester to react in the absence of the molecular sieves suggests that their structural differences may be key to their reactivity. If Matos and Soderquist's proposed hydroxo-μ_2-bridged transition state (*vide* I.2.3.1 and Chapter 1, reference 42) for transmetallation of organoboron compounds to palladium were true for transmetallation to transition metals in general, then perhaps the hydroxyl/alkoxyl moieties from the boronic acids and boronate esters are responsible for their reactivity. Thus, being able to coordinate to the copper reagent, the boronic acids and the boronate esters can undergo

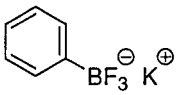
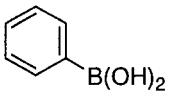
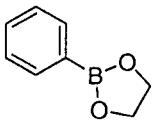
transmetallation to copper, whereas the trifluoroborate salts cannot (Figure 45).

Table 38 - Control Reactions for the Arylation of *n*-Butylamine under Oxygen





A B C D E

Entry	Borate	Amount of Cu[a]	Additive	A (%)[b]	B (%)[b]	C (%)[b]	D (%)[b]	E (%)[b]
1		cat.	4Å MS	87	2	1	4	trace[c]
2		cat.	-	1	-	-	-	-
3		stoich.	4Å MS	58	37	8	13	4
4		stoich.	-	17	trace[c]	trace[c]	2	-
5		cat.	4Å MS	64	21	1	5	5
6		cat.	-	68	18	1	7	1
7		stoich.	4Å MS	70	25	5	7	trace[c]
8		stoich.	-	58	22	4	9	1
9		cat.	4Å MS	53	-	-	trace[c]	trace[c]
10		cat.	-	9	-	-	trace[c]	trace[c]
11		stoich.	4Å MS	49	32	2	2	trace[c]
12		stoich.	-	16	1	trace[c]	1	trace[c]

a) cat. = 10 mol% $Cu(OAc)_2 \cdot H_2O$; stoich. = 1 equiv. $Cu(OAc)_2 \cdot H_2O$. b) GC yields; an average of two runs; normalized to naphthalene response ratios. c) trace < 1 %.

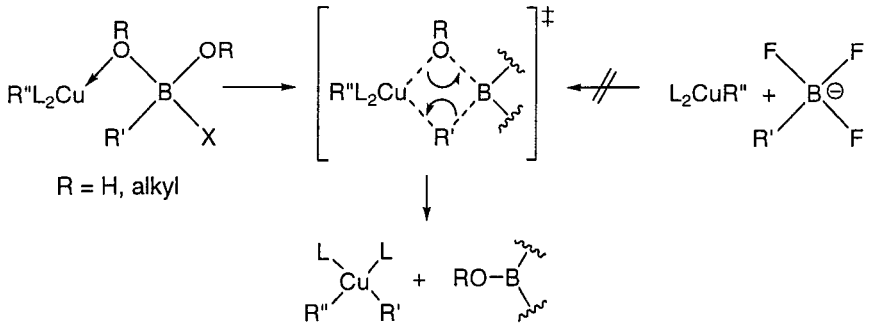


Figure 45 - Hydroxo-μ_2-Bridged Transition State for the Transmetallation from Boron to Copper

While the hydroxo-μ_2-bridged transition state explains the observed reactivity of the boronic acids and boronate esters and the trifluoroborate salts' inability to react, it does not explain why the trifluoroborate salts (and organoboron compounds in general) appear to be activated in the presence of the molecular sieves. For this explanation, the fluorophilic nature of silicon must be invoked.

It has been established that under basic aqueous conditions hydroxide-fluoride exchange can occur on the boron of trifluoroborate salts to generate various fluoroxyboronate species (*vide* I.1.2.2). It has also been observed that treatment with silica gel will hydrolyze trifluoroborate salts back to their corresponding boronic acids; hence, trifluoroborate salts cannot be purified via flash column chromatography. It is therefore plausible to hypothesize that the molecular sieves, basically a solid matrix of alumino-silicates,[30] is acting to hydrolyze the trifluoroborate salts to a fluoroxyboronate species capable of transmetallation to copper (Figure 46). Although there is no precedence for this transformation in the literature, it is a thermodynamically allowable transformation based on a calculation of their average bond strengths (Figure 47).[31]

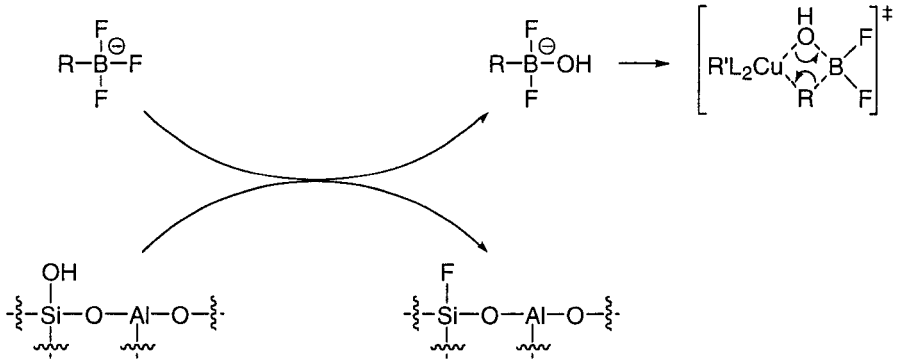


Figure 46 - Molecular Sieves Promoted Hydrolysis of Trifluoroborate Salts

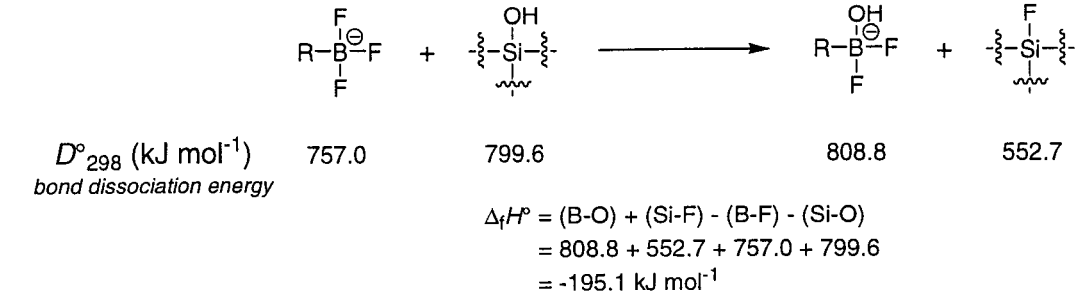


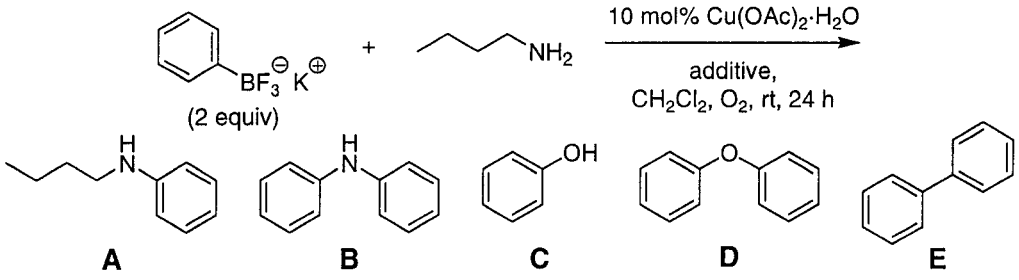
Figure 47 - Thermodynamically Allowable Hydrolysis of Trifluoroborate Salts

To test this hypothesis, a variety of silica and alumina sources were screened against the optimized reaction conditions in place of the molecular sieves; the resultant crude reaction mixtures were then analyzed by gas chromatography (Table 39). Phenol was not directly observed in any of the reaction mixtures; however, diaryl ether, the by-product arising from phenol, was produced in reactions where the solid matrix contained significant amounts of water (Table 39, entries 2, 3, 8-10). Unsurprisingly, no biphenyl was observed in any of the reactions either, but this was expected as biphenyl is rarely seen in the reaction of the trifluoroborate salts (*vide supra*). None of the reactions gave as high a yield of the desired product as reaction in the presence of molecular sieves, but this may be a result of the kinetics of the new systems, rather than a reflection of their reactivity.

Of the silicon based materials, silica gel, Florisil (a magnesium-silicate composition), silicon oil and hexamethyl disiloxane were able to mediate the reaction to some degree (Table 39, entries 2-5). The best results were obtained from Florisil whose molecular composition is not unlike the molecular sieves themselves (Table 39, entry 3). Trimethylsilylacetate and potassium trimethylsilanoate did not mediate the reaction at all, most likely due to their lack of a free hydroxyl group on the silicon centre and their insolubility in CH_2Cl_2 (Table 39, entries 6 and 7). The aluminum oxide based materials were also able to mediate the reaction to some degree (Table 39, entries 7-9). Unsurprisingly, both the basic and neutral materials fared bettered than the acid material; as reaction of the latter would have also mediated the hydrodeboration of the starting material.

While these experiments lend credence to the theory of a molecular sieves induced

Table 39 - Use of Other Silicon and Aluminum-Based Materials in Place of Molecular Sieves



Entry	Additive[a]	A (%)[b]	B (%)[b]	C (%)[b]	D (%)[b]	E (%)[b]
1	4Å molecular sieves	87	2	1	4	trace[c]
2	silica gel 60 (230-400 mesh, 50-70Å)	33	5	-	20	-
3	Florisil ($MgO_{3.75}SiO_2 \cdot nH_2O$)	53	trace[c]	-	6	-
4	silicon oil	29	trace[c]	-	trace[c]	-
5	$(Me_3Si)_2O$	19	1	-	trace[c]	-
6	Me_3SiOAc	trace[c]	1	-	trace[c]	-
7	$Me_3SiO^{\ominus}K^{\oplus}$	-	trace[c]	-	trace[c]	-
8	Al_2O_3 - Brockmann I (basic)	45	trace[c]	-	5	-
9	Al_2O_3 - Brockmann I (acidic)	19	trace[c]	-	15	-
10	Al_2O_3 - Brockmann I (neutral)	35	trace[c]	-	2	-

a) 0.75 g of the additive was employed. b) GC yields; an average of two runs; normalized to naphthalene response ratios. c) trace < 1 %.

hydrolysis of the trifluoroborate salts, they do not definitively prove it. Another possible role that the molecular sieves can play in the reaction is that of a surrogate metal to facilitate transmetallation from boron to copper. Thus, the aryl moiety would first transmetallate to silicon before ending up on the reactive copper species (Figure 48). Certainly, this type of secondary metal-assisted transmetallation has been proposed in other organometallic transformations; for example the use of copper salts in the palladium-catalyzed Sonogashira couplings for aryl halides with terminal alkynes,[32] and the use of chromium salts in the nickel-catalyzed Nozaki-Hiyama-Kishi addition of vinyl iodides to aldehydes.[33] Indeed, organosilicates have been employed in

Ullmann condensations to nitrogen-based nucleophiles (*vide* III.1.2.5).

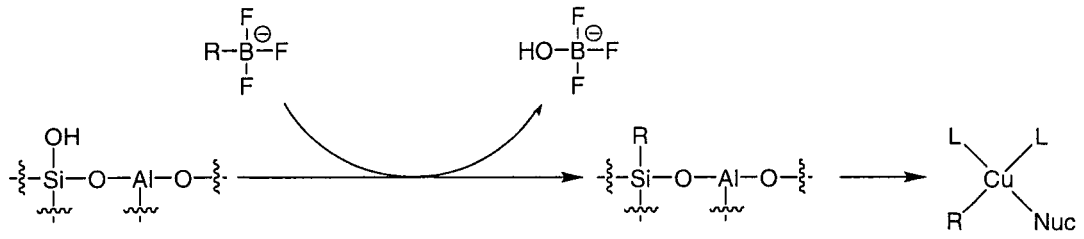
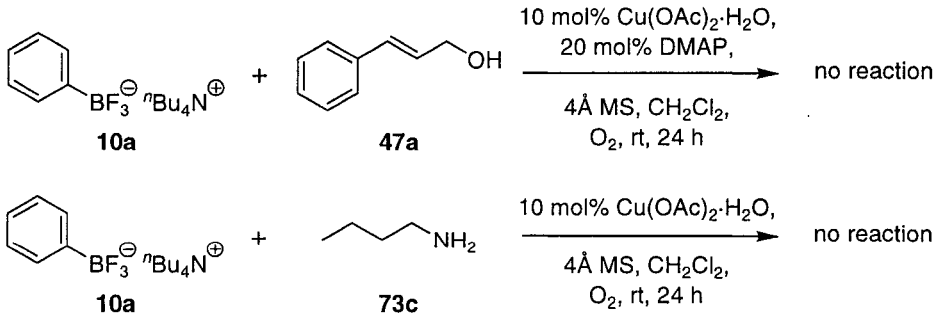


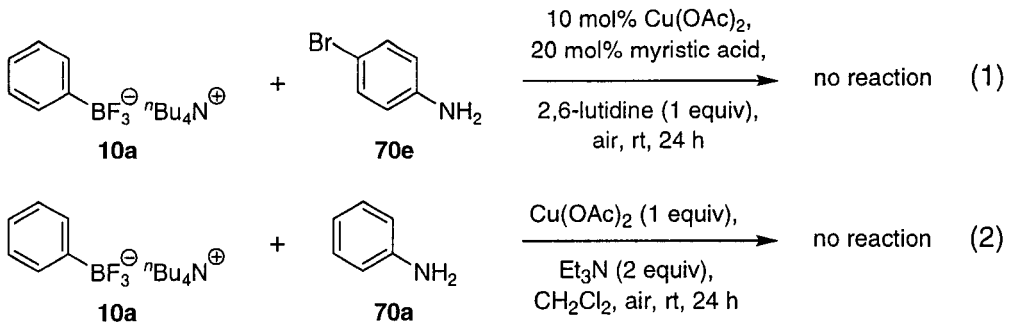
Figure 48 - Molecular Sieves-Assisted Transmetallation from Boron to Copper

IV.2.2 The Ammonium Cation Phenomenon

The copper-catalyzed Ullmann condensation was found to be highly intolerant of quaternary ammonium species. This was first observed when tetra-*n*-butylammonium phenyltrifluoroborate (**10a**) was employed as the aryl donor in the cross-coupling. The premise was that a more soluble organoboron reagent in the organic media would allow for faster reaction times. However, in both the attempted arylations of **47a** and **73c**, none of the desired cross-coupled products were obtained, and no by-products were observed either. In fact, in both reactions the nucleophiles and the borate were recovered quantitatively (Scheme 76). Even under Buchwald's conditions (Scheme 77, reaction 1; *vide* III.1.2.7),[34] and our previously optimized stoichiometric conditions for the arylation of anilines (Scheme 77, reaction 2; *vide* III.2.1), the reaction did not proceed.

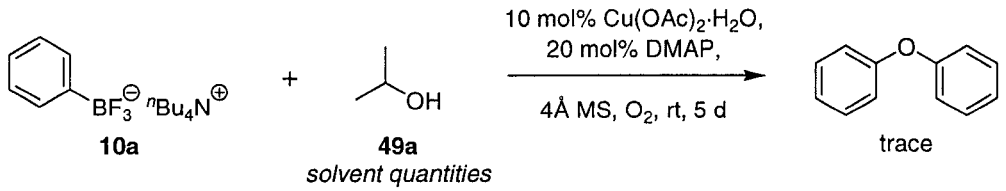


Scheme 76 - Unreactivity of Tetra-*n*-butyl Ammonium Aryltrifluoroborate Salts under Copper-Catalyzed Conditions



Scheme 77 - Unreactivity of Tetra-*n*-butyl Ammonium Aryltrifluoroborate Salts under Other Optimized Conditions

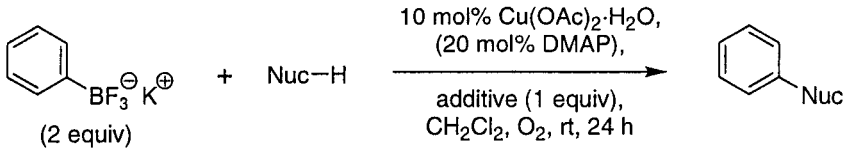
At first the lack of reactivity was believed to be a result of a close ion pair formed between the ammonium species and the trifluoroborate salt. If that had been the case, then the use of a more polar solvent would have aided in breaking the association of the ions. However, when the reaction was run with MeCN as the solvent for the arylation of **47a**, again no reaction was observed. Switching the nucleophile to isopropanol (**49a**) and using it as solvent in the reaction did not achieve any desired cross-coupling either. The use of nucleophiles in solvent quantities is not ideal for the cross-coupling; nevertheless, previous reactions have shown that at least some yield of the desired arylated product can be obtained. However, in the case of the tetra-*n*-butylammonium salt, only a trace of biphenyl ether was detected (by TLC) even after 5 days of stirring (Scheme 78).

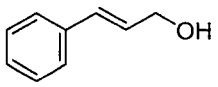
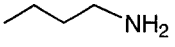


Scheme 18 - Isopropanol as Solvent/Nucleophile in an Attempt to Break Close Ion Pairings

In a final attempt to ascertain the cause of this inactivity, the effect of an added quaternary ammonium species to a working reaction was probed. Once again, the presence of the ammonium species was reconfirmed to render the catalytic system inactive. Both the tetraalkylammonium derivatives (Table 40, entries 1, 2 and 4) and ammonium chloride itself (Table 40, entries 3 and 6) were found to have the same effect. Surprisingly, the addition of two equivalents of Et_3N to the reaction mixture appeared to reactivate transformation (Table 40, entry 5). At this point the precise reason for the cessation of the reaction in the presence of an ammonium species remains a mystery.

Table 40 - The Effect of Quaternary Ammonium Additives to the Cross-Coupling of Potassium Phenyltrifluoroborate Salts



Entry	Nucleophile	Additive	Yield (%)[a]
1		$^{n}Bu_4N^{\oplus}\ I^{\ominus}$	no reaction
2		$^{n}Bu_4N^{\oplus}\ Br^{\ominus}$	no reaction
3		$NH_4^{\oplus}\ Cl^{\ominus}$	no reaction
4		$^{n}Bu_4N^{\oplus}\ I^{\ominus}$	no reaction
5		$^{n}Bu_4N^{\oplus}\ I^{\ominus}$ + Et_3N (2 equiv)	60 %
6		$NH_4^{\oplus}\ Cl^{\ominus}$	no reaction

a) isolated yields.

IV.2.3 Conclusions

The copper-catalyzed Ullmann condensation of organoboron compounds with heteroatomic nucleophiles is a powerful method of carbon-heteroatom bond formation. The protocols that have been developed by others, as well as the contributions that have been made in our laboratory, have allowed for quick and facile access to a variety of interesting molecules. This methodology has been readily accepted and applied in industrial applications, especially in the generation of small molecule libraries for biological screening.

However, the reaction is not without its faults. In addition to the main cross-coupling, a variety of other side reactions compete to consume the starting material. The organoboron component of the reaction can undergo cross-coupling to water/hydroxide to generate phenol, which in itself is a good nucleophile for another cross-coupling side reaction. Organoboronic acids are also prone to oxidative homocoupling under these conditions to give biphenyl.

As for the nucleophiles themselves, the alcohols can be oxidized to the corresponding aldehydes under very similar copper-catalyzed conditions. The protocols for metal-catalyzed aerobic oxidations are often more vigorous than those of the Ullmann condensations, nevertheless some of the alcoholic substrates have afforded traces of the oxidized product. The arylated products of aliphatic amines on the other hand, may undergo a copper complex-mediated *N*-dealkylation under stoichiometric copper conditions, or in concentrated solutions, thus giving rise to the generation of aniline, yet another nucleophile capable of undergoing a side reaction to compete with the intended cross-coupling.

Finally, the exact mechanism of the transformation remains unknown. Several groups have suggested plausible mechanisms based upon basic organometallic transformation theories. More work is expected in this field to elucidate the nature of the intermediates involved in this reaction.

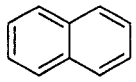
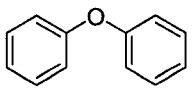
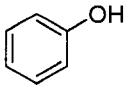
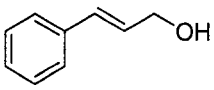
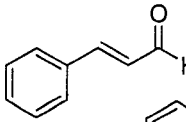
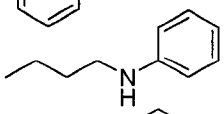
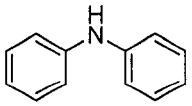
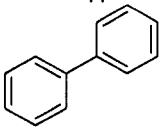
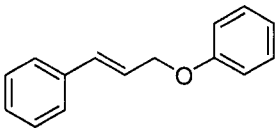
IV.3 Experimental Procedures

IV.3.1 Parameters for Gas Chromatographic Analysis of Crude Reaction Mixtures

The crude reaction mixtures were analyzed on a Perkin Elmer AutoSystem XL Gas Chromatographer equipped with a Flame Ionization Detector (FID). The column used was an HP-5 (Crosslinked 5 % Ph Me Silicone; column ID: 0.25 mm; length: 60 m; film thickness: 0.25 μm; phase ratio: 250). All gases used in chromatography were purchased from BOC (formerly Air Products). Helium (UHP/Zero grade) was used as the carrier gas after purification by passage through a Supelco Carrier Gas Purifier. Air (Ultra-Pure Carrier Grade) and hydrogen (UHP/Zero grade) were employed as the combustible gases. The samples were manually injected into a Programmed Split/Splitless Capillary Injector (PSSI) at an initial temperature of 260 °C. The experiment was run for 16 minutes with a carrier gas pressure of 14.0 psi with a detector sampling rate of 1.56 pts/sec. The oven zones were set at an initial temperature of 50 °C with a ramp of 20 °C per minute up to 250 °C then holding constant for a final 6 minutes.

Naphthalene was used as an inert internal standard for all reactions. GC yields reported normalized to the naphthalene signal with the following predetermined response ratios:

Table 41 - Retention Times and Response Ratios of Various Compounds Observed in Copper-Catalyzed Arylation of Nucleophiles

Compound	Retention Time R_f (min)	Response Ratio to Naphthalene	Compound	Retention Time R_f (min)	Response Ratio to Naphthalene
	7.8	1.00		9.7	1.25
	5.5	0.390		13.3	0.326
	8.1	0.640			
	8.9	1.86		14.0	1.26
	9.4	1.24		14.9	1.29

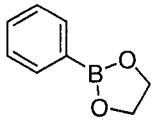
IV.3.2 Characterization Data of Synthesized Reactants and Observed/ Isolated By-Products

Synthesized Reactants

Representative Procedure for the Preparation of Cyclic Boronate Esters from the Boronic Acid Precursors

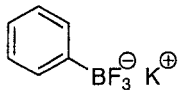
To a stirring solution of phenylboronic acid (**4a**, 7.17 g, 58.8 mmol) in toluene was added ethylene glycol (3.65 g, 58.8 mmol). The reaction flask was fitted with a Dean-Stark apparatus and heated to reflux for a period of 20 hours. The reaction was then filtered and concentrated *in vacuo* to afford the crude product mixture. The product 2-phenyl[1,3,2]dioxaborolane was purified via distillation, and obtained in 97 % yield (8.44 g, 57.0 mmol).

2-Phenyl[1,3,2]dioxaborolane (Wong, K. T.; Chien, Y. Y.; Liao, Y. L.; Lin, C. C.; Chou, M. Y.; Leung, M. *J. Org. Chem.* **2002**, *67*, 1041-1044.)



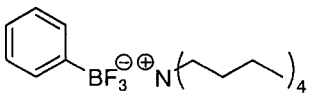
Isolated as a clear oil: bp = 69-72 °C (1 torr); d = 1.089 g/mL; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (2H, dd, *J* = 7.5, 1.5 Hz), 7.46 (1H, tt, *J* = 7.5, 1.5 Hz), 7.37 (2H, tt, *J* = 7.5, 1.5 Hz), 4.32 (4H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.9, 131.6, 127.9, 66.1 (one signal absent).

Potassium Phenyltrifluoroborate (1a) (Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020-3027.)



Isolated as a white crystalline solid: ^{1}H NMR (300 MHz, D_2O) δ 7.70 - 7.60 (2H, m), 7.48 - 7.39 (3H, m); ^{13}C NMR (75 MHz, D_2O) δ 131.5, 131.5, 128.3, 128.2, 128.0 (one signal absent); ^{11}B NMR (96 MHz, D_2O) δ 4.40 (q, *J* = 54.0 Hz); ^{19}F NMR (282 MHz, D_2O) δ -142.06 (q, *J* = 48.0 Hz).

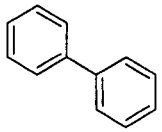
Tetra-*n*-butylammonium Phenyltrifluoroborate (10a) (Wang, C.; Mo, Y.; Jang, M.; Janzen, A. F. *Can. J. Chem.* **1993**, *71*, 525-528.)



Isolated as a pale yellow, crystalline solid: mp = 74-75 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (2H, d, J = 6.5 Hz), 7.15 - 7.00 (3H, m), 2.90 - 2.80 (8H, m), 1.40 - 1.18 (16H, m), 0.89 (12H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.6, 126.4, 125.3, 57.6, 23.3, 19.1, 13.3 (one signal absent); ^{11}B NMR (160 MHz, $CDCl_3$) δ 3.30 (br s); ^{19}F NMR (282 MHz, $CDCl_3$) δ -142.03 (br s); IR (film) ν 2964, 2876, 1636, 1487, 1431, 1382, 1269, 1192, 1071, 950, 908, 751, 706, 598 cm^{-1}; LRMS (FAB): *m/z* = 145 (100), 144 (25), 91 (22); HRMS (FAB): *m/z* calcd. for ($C_6H_5BF_3^-$) = 145.0436, found = 145.0449.

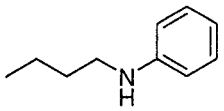
Products

Biphenyl (19c) (Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830-1833.)



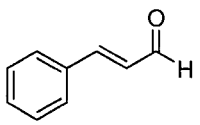
Isolated as a clear crystalline solid: R_f = 0.8 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (4H, d, J = 8.0 Hz), 7.54 (4H, t, J = 8.0 Hz), 7.44 (2H, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 129.1, 127.6, 127.5.

***n*-Butylphenylamine (74c)** (Alberti, A.; Cane, F.; Dembech, P.; Lazzari, D.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1996**, *61*, 1677-1681.)



Isolated as a pale yellow oil: R_f = 0.6 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (2H, ddd, J = 8.5, 7.5, 1.0 Hz), 6.74 (1H, tt, J = 7.5, 1.0 Hz), 6.65 (2H, dd, J = 8.5, 1.0 Hz), 3.62 (1H, br s), 3.15 (2H, t, J = 7.0 Hz), 1.65 (2H, quintet, J = 7.0 Hz), 1.48 (2H, sextet, J = 7.0 Hz), 1.01 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 129.4, 117.2, 112.8, 43.8, 31.8, 20.5, 14.1.

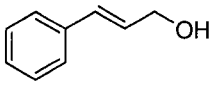
(*E*)-Cinnamaldehyde (Ragagnin, G. Betzemeier, B. Quici, S. Knochel, P. *Tetrahedron* **2002**, *58*, 3985-3992.)



Isolated as a white crystalline solid: R_f = 0.3 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$)

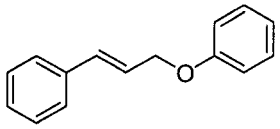
δ 9.65 (1H, d, J = 7.5 Hz), 7.54-7.50 (2H, m), 7.43-7.37 (3H, m), 6.69 (1H, d, J = 16.0 Hz), 6.65 (1H, dd, J = 16.0, 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 152.5, 133.7, 131.1, 128.9, 128.4, 128.2.

(*E*)-Cinnamyl alcohol (Nudelman, N.S.; Schulz, H.G.; Garcia, G.V. *J. Phys. Org. Chem.* **1998**, *11*, 722-730.)



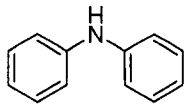
Isolated as a white crystalline solid: R_f = 0.4 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.25 (5H, m), 6.57 (1H, d, J = 16.0 Hz), 6.31 (1H, dt, J = 16.0, 5.5 Hz), 4.27 (2H, d, J = 5.5 Hz), 2.02 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 131.2, 128.7, 128.5, 127.8, 126.5, 63.8.

(*E*)-Cinnamylphenyl ether (48a) (Keinan, E.; Sahai, M.; Roth, Z. *J. Org. Chem.* **1985**, *50*, 3558-3566.)



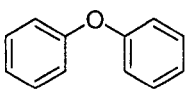
Isolated as a white, crystalline solid: R_f = 0.6 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (2H, d, J = 7.0 Hz), 7.44 - 7.28 (5H, m), 7.11 - 6.95 (3H, m), 6.80 (1H, d, J = 16.0 Hz), 6.48 (1H, dt, J = 16.0, 6.0 Hz), 4.75 (2H, dd, J = 6.0, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 136.5, 133.1, 129.6, 128.7, 128.0, 126.7, 124.6, 121.0, 114.9, 68.8.

Diphenylamine (71a) (Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575-5580.)



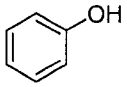
Isolated as an amber crystalline solid: R_f = 0.3 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (4H, t, J = 7.5 Hz), 7.10 (4H, d, J = 7.5 Hz), 6.96 (2H, d, J = 7.5 Hz), 5.70 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.3, 129.5, 121.2, 118.0.

Diphenyl ether (Castellano, S.; Sun, C.; Kostelnik, R. *Tetrahedron Lett.* **1967**, *8*, 5205-5209.)



Isolated as a clear crystalline solid: R_f = 0.7 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (2H, dd, *J* = 8.0, 7.5 Hz), 6.98 (1H, dd, *J* = 7.5, 1.0 Hz), 6.93 (2H, dd, *J* = 8.0, 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 129.6, 123.1, 118.8.

Phenol (Abraham, R. J.; Reid, M. *J. Chem. Soc., Perkin Trans. 2*, **2002**, 1081-1091.)



Isolated as a clear crystalline solid: R_f = 0.5 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (2H, t, *J* = 7.5 Hz), 6.93 (1H, t, *J* = 7.5 Hz), 6.82 (2H, d, *J* = 7.5 Hz), 5.35 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 129.5, 120.8, 115.8.

IV.4 References

(1) (a) Arai, S.; Hashimoto, Y.; Yamagishi, T.; Hida, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3143-3149. (b) Arai, S.; Hida, M.; Yamagishi, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 277-282.

(2) Bethell, D.; Jenkins, I. L.; Quan, P. M. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1789-1795.

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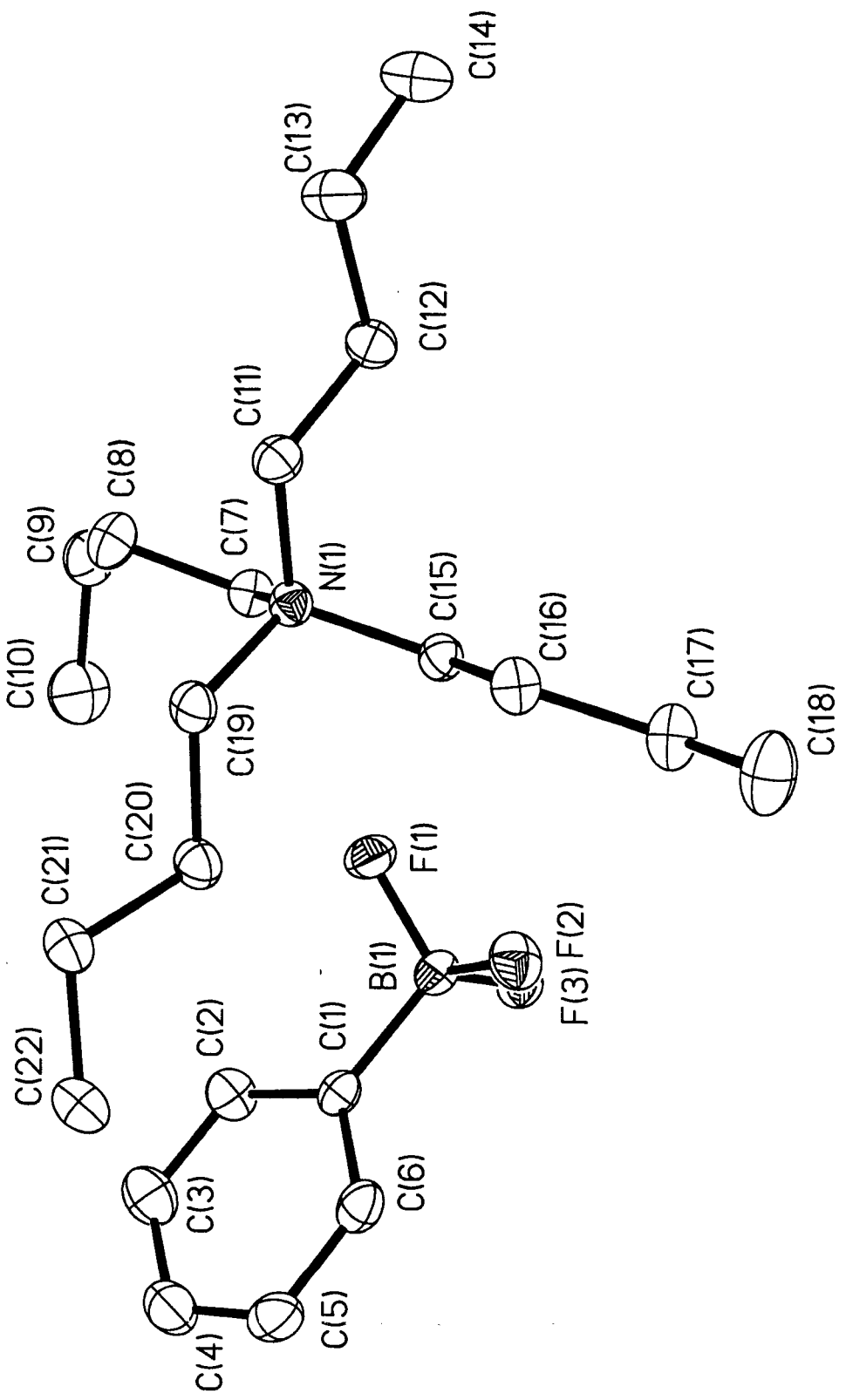
Appendix A

X-ray Crystal Structure Data

Appendix A.1

X-ray Crystal Structure Data for Tetra-*n*-butylammonium Phenyltrifluoroborate (10a)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C(13)
C(12)
C(11)
C(8)
C(9)
C(7)
N(1)
C(15)
C(16)
C(17)
C(18)
C(10)
C(19)
C(20)
C(21)
F(1)
B(1)
F(3)
F(2)
C(22)
C(2)
C(1)
C(3)
C(6)
C(5)
C(4)

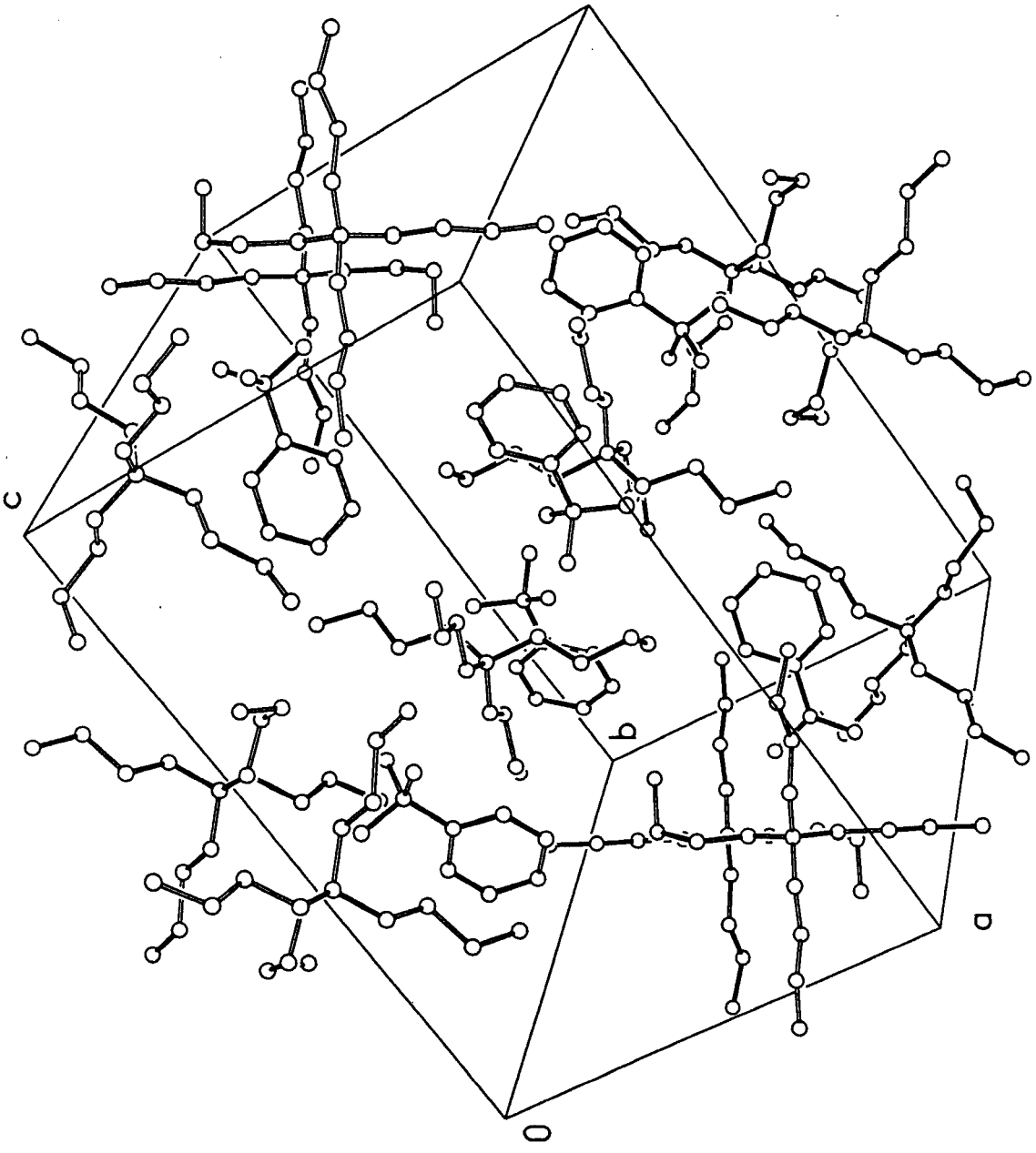

c
b
a

Table 1. Crystal data and structure refinement for k0041.

Identification code	k0041	
Empirical formula	C22 H41 B F3 N	
Formula weight	387.37	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbcn	
Unit cell dimensions	a = 13.5626(6) Å	$\alpha = 90°$.
	b = 17.1534(7) Å	$\beta = 90°$.
	c = 20.3567(7) Å	$\gamma = 90°$.
Volume	4735.9(3) $Å^3$	
Z	8	
Density (calculated)	1.087 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	1696	
Crystal size	0.40 x 0.35 x 0.34 mm^3	
Theta range for data collection	2.58 to 25.37°.	
Index ranges	0<=h<=16, 0<=k<=20, 0<=l<=24	
Reflections collected	20559	
Independent reflections	4341 [R(int) = 0.029]	
Completeness to theta = 25.37°	99.5 %	
Absorption correction	multi-scan (Denzo-SMN)	
Max. and min. transmission	0.9741 and 0.9696	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4341 / 0 / 249	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2sigma(I)]	R1 = 0.0508, wR2 = 0.1130	
R indices (all data)	R1 = 0.0923, wR2 = 0.1298	
Extinction coefficient	0.0013(6)	
Largest diff. peak and hole	0.194 and -0.178 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for k0041. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	993(1)	730(1)	4262(1)	48(1)
F(2)	2584(1)	922(1)	4596(1)	51(1)
F(3)	1507(1)	1942(1)	4553(1)	42(1)
C(1)	2126(1)	1419(1)	3484(1)	34(1)
C(2)	1427(2)	1470(1)	2980(1)	48(1)
C(3)	1668(2)	1652(1)	2344(1)	60(1)
C(4)	2628(2)	1804(1)	2181(1)	58(1)
C(5)	3350(2)	1749(1)	2650(1)	56(1)
C(6)	3095(2)	1548(1)	3297(1)	45(1)
B(1)	1807(2)	1247(1)	4227(1)	37(1)
N(1)	1508(1)	-1463(1)	4592(1)	32(1)
C(7)	503(1)	-1099(1)	4459(1)	35(1)
C(8)	-192(2)	-1560(1)	4019(1)	49(1)
C(9)	-1094(2)	-1072(1)	3847(1)	52(1)
C(10)	-876(2)	-380(2)	3413(1)	71(1)
C(11)	1405(2)	-2268(1)	4892(1)	36(1)
C(12)	898(1)	-2312(1)	5554(1)	38(1)
C(13)	740(2)	-3157(1)	5749(1)	52(1)
C(14)	197(2)	-3255(1)	6385(1)	60(1)
C(15)	2037(1)	-907(1)	5052(1)	33(1)
C(16)	3080(1)	-1132(1)	5245(1)	39(1)
C(17)	3492(2)	-536(1)	5726(1)	47(1)
C(18)	4538(2)	-726(2)	5945(1)	64(1)
C(19)	2086(2)	-1567(1)	3959(1)	35(1)
C(20)	2372(2)	-836(1)	3587(1)	38(1)
C(21)	2752(2)	-1064(1)	2909(1)	41(1)
C(22)	3241(2)	-390(1)	2551(1)	48(1)

Table 3. Bond lengths [Å] and angles [°] for k0041.

F(1)-B(1)	1.418(2)
F(2)-B(1)	1.409(3)
F(3)-B(1)	1.425(2)
C(1)-C(6)	1.387(3)
C(1)-C(2)	1.399(3)
C(1)-B(1)	1.600(3)
C(2)-C(3)	1.372(3)
C(3)-C(4)	1.368(3)
C(4)-C(5)	1.371(3)
C(5)-C(6)	1.404(3)
N(1)-C(15)	1.516(2)
N(1)-C(11)	1.517(2)
N(1)-C(19)	1.519(2)
N(1)-C(7)	1.523(2)
C(7)-C(8)	1.522(3)
C(8)-C(9)	1.523(3)
C(9)-C(10)	1.508(3)
C(11)-C(12)	1.515(2)
C(12)-C(13)	1.517(3)
C(13)-C(14)	1.500(3)
C(15)-C(16)	1.518(3)
C(16)-C(17)	1.521(3)
C(17)-C(18)	1.523(3)
C(19)-C(20)	1.515(2)
C(20)-C(21)	1.525(3)
C(21)-C(22)	1.519(3)
C(6)-C(1)-C(2)	115.50(18)
C(6)-C(1)-B(1)	123.04(18)
C(2)-C(1)-B(1)	121.44(18)
C(3)-C(2)-C(1)	123.1(2)
C(4)-C(3)-C(2)	119.9(2)
C(3)-C(4)-C(5)	119.9(2)
C(4)-C(5)-C(6)	119.6(2)

C(1)-C(6)-C(5)	122.0(2)
F(2)-B(1)-F(1)	107.99(16)
F(2)-B(1)-F(3)	107.20(16)
F(1)-B(1)-F(3)	106.08(16)
F(2)-B(1)-C(1)	112.03(17)
F(1)-B(1)-C(1)	111.91(16)
F(3)-B(1)-C(1)	111.32(16)
C(15)-N(1)-C(11)	111.58(13)
C(15)-N(1)-C(19)	110.75(14)
C(11)-N(1)-C(19)	106.36(13)
C(15)-N(1)-C(7)	106.01(13)
C(11)-N(1)-C(7)	111.19(14)
C(19)-N(1)-C(7)	111.03(13)
C(8)-C(7)-N(1)	116.54(15)
C(7)-C(8)-C(9)	110.32(17)
C(10)-C(9)-C(8)	114.17(19)
C(12)-C(11)-N(1)	116.41(14)
C(11)-C(12)-C(13)	110.13(16)
C(14)-C(13)-C(12)	113.74(18)
N(1)-C(15)-C(16)	116.13(15)
C(15)-C(16)-C(17)	109.74(16)
C(16)-C(17)-C(18)	112.73(18)
C(20)-C(19)-N(1)	117.29(14)
C(19)-C(20)-C(21)	109.00(15)
C(22)-C(21)-C(20)	112.68(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for k0041. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	50(1)	38(1)	54(1)	-3(1)	8(1)	-11(1)
F(2)	56(1)	50(1)	47(1)	5(1)	-11(1)	8(1)
F(3)	45(1)	35(1)	45(1)	-8(1)	5(1)	-3(1)
C(1)	34(1)	26(1)	43(1)	-5(1)	-2(1)	2(1)
C(2)	45(1)	53(1)	46(1)	2(1)	-2(1)	7(1)
C(3)	68(2)	64(2)	47(1)	7(1)	-4(1)	11(1)
C(4)	82(2)	49(1)	44(1)	-1(1)	11(1)	-3(1)
C(5)	51(2)	52(1)	66(2)	-18(1)	22(1)	-12(1)
C(6)	39(1)	42(1)	52(1)	-15(1)	2(1)	-2(1)
B(1)	36(1)	32(1)	43(1)	-2(1)	-3(1)	-1(1)
N(1)	35(1)	29(1)	32(1)	-3(1)	1(1)	2(1)
C(7)	33(1)	35(1)	38(1)	0(1)	-2(1)	4(1)
C(8)	44(1)	47(1)	56(1)	-7(1)	-11(1)	-2(1)
C(9)	36(1)	69(2)	52(1)	-2(1)	-10(1)	-1(1)
C(10)	57(2)	83(2)	72(2)	14(1)	-24(1)	1(1)
C(11)	41(1)	29(1)	39(1)	0(1)	0(1)	2(1)
C(12)	38(1)	37(1)	38(1)	3(1)	1(1)	2(1)
C(13)	57(2)	45(1)	56(1)	6(1)	9(1)	-4(1)
C(14)	65(2)	52(1)	62(2)	17(1)	11(1)	-1(1)
C(15)	37(1)	30(1)	33(1)	-2(1)	-1(1)	1(1)
C(16)	38(1)	41(1)	38(1)	-3(1)	-2(1)	4(1)
C(17)	47(1)	49(1)	46(1)	-7(1)	-9(1)	4(1)
C(18)	48(2)	77(2)	66(2)	-16(1)	-17(1)	4(1)
C(19)	38(1)	33(1)	34(1)	-5(1)	3(1)	3(1)
C(20)	46(1)	36(1)	34(1)	-2(1)	2(1)	2(1)
C(21)	49(1)	40(1)	33(1)	-1(1)	0(1)	7(1)
C(22)	53(1)	53(1)	37(1)	3(1)	7(1)	5(1)

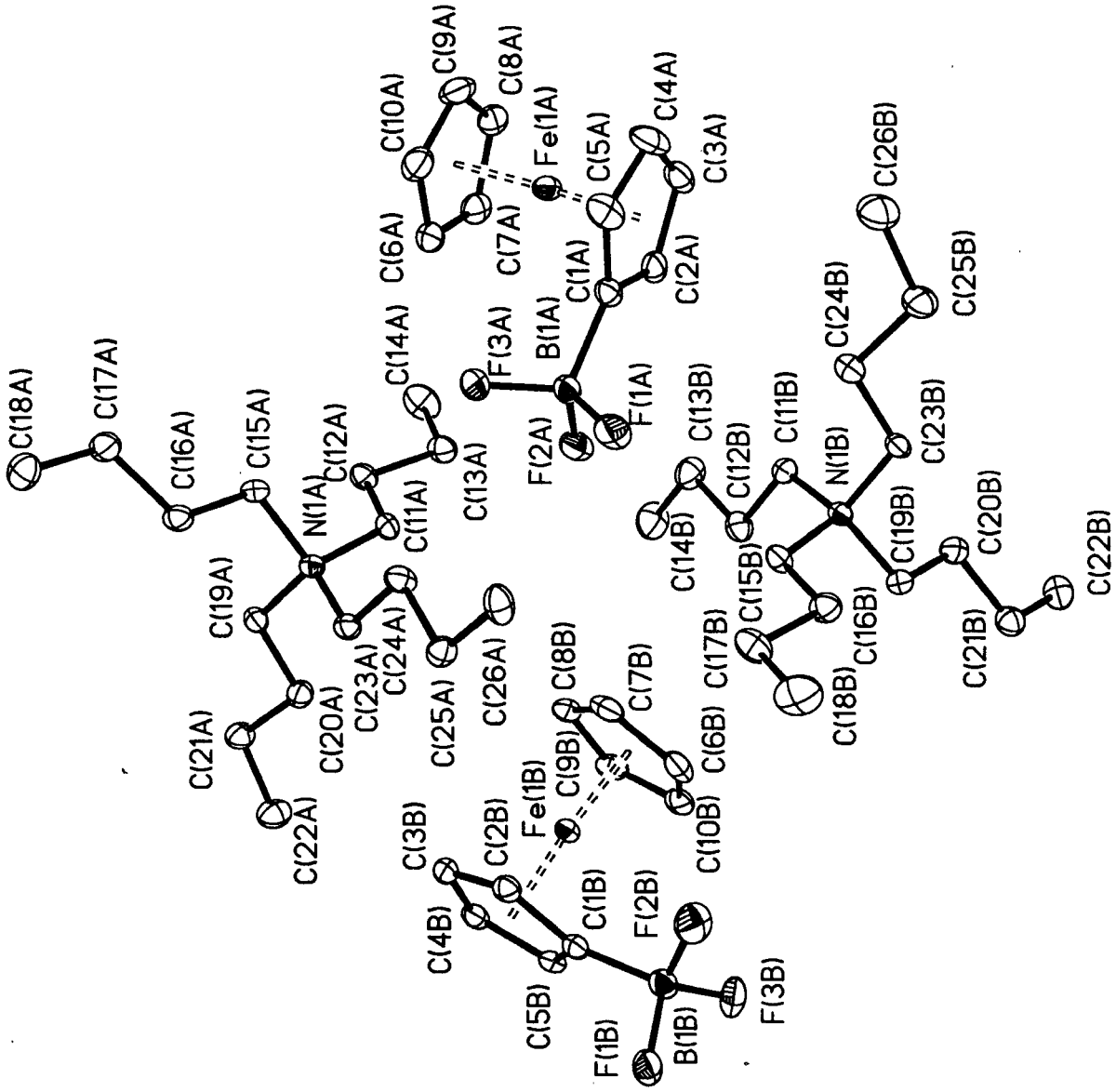
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for k0041.

	x	y	z	U(eq)
H(2A)	755	1374	3083	57
H(3A)	1169	1673	2017	71
H(4A)	2793	1948	1744	70
H(5A)	4019	1845	2538	67
H(6A)	3603	1500	3616	54
H(7A)	171	-1014	4886	42
H(7B)	609	-581	4257	42
H(8A)	-402	-2042	4247	59
H(8B)	156	-1712	3611	59
H(9A)	-1581	-1409	3623	63
H(9B)	-1399	-883	4259	63
H(10A)	-1494	-119	3297	106
H(10B)	-545	-558	3012	106
H(10C)	-447	-15	3648	106
H(11A)	1035	-2600	4580	44
H(11B)	2072	-2496	4938	44
H(12A)	254	-2041	5532	45
H(12B)	1307	-2048	5889	45
H(13A)	366	-3422	5397	63
H(13B)	1390	-3416	5785	63
H(14A)	85	-3811	6468	89
H(14B)	-438	-2984	6360	89
H(14C)	589	-3034	6744	89
H(15A)	1640	-857	5458	40
H(15B)	2058	-387	4842	40
H(16A)	3502	-1152	4848	47
H(16B)	3079	-1655	5450	47
H(17A)	3059	-514	6117	57
H(17B)	3486	-15	5517	57
H(18A)	4754	-343	6272	96

H(18B)	4981	-708	5564	96
H(18C)	4554	-1249	6138	96
H(19A)	2698	-1856	4064	42
H(19B)	1691	-1899	3661	42
H(20A)	2891	-551	3831	46
H(20B)	1792	-489	3543	46
H(21A)	3232	-1495	2956	49
H(21B)	2194	-1259	2642	49
H(22A)	3425	-556	2107	72
H(22B)	3833	-229	2792	72
H(22C)	2780	49	2525	72

Appendix A.2

X-ray Crystal Structure Data for Tetra-*n*-butylammonium Ferrocenyltrifluoroborate (10g)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B(1A)
F(3A)
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C(3B)
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C(8B)
C(7B)
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C(6B)
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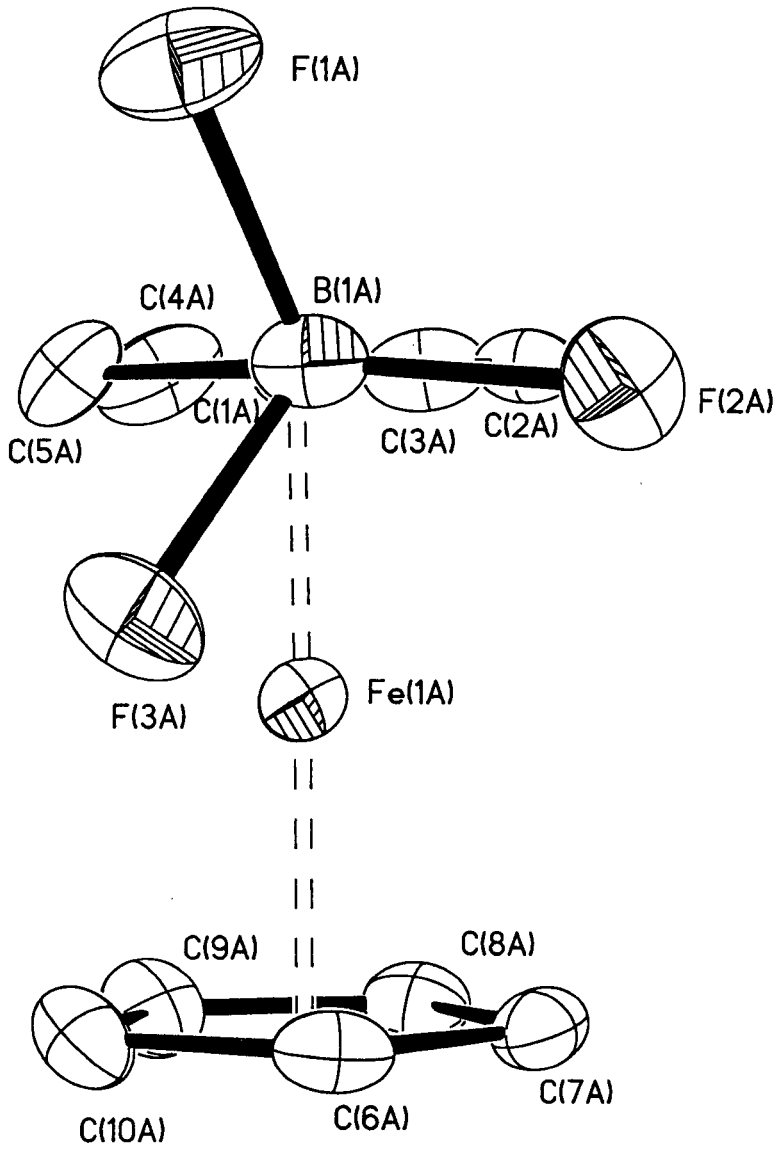
F(2B)
C(10B)
F(1B)
B(1B)
F(3B)
C(13B)
C(12B)
C(11B)
C(14B)
C(15B)
C(17B)
C(18B)
N(1B)
C(24B)
C(26B)
C(25B)
C(23B)
C(19B)
C(16B)
C(20B)
C(21B)
C(22B)


F(1A)
C(4A)
B(1A)
C(1A)
C(5A)
C(3A)
C(2A)
F(2A)
F(3A)
Fe(1A)
C(9A)
C(8A)
C(7A)
C(10A)
C(6A)

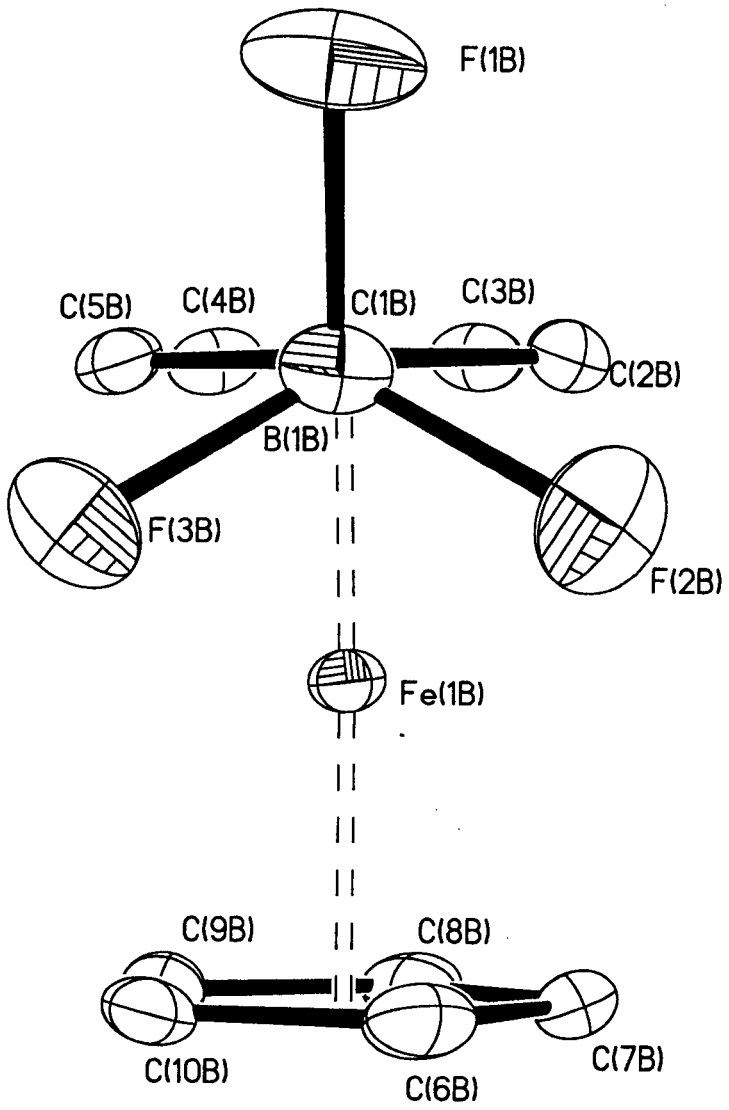

F(1B)
C(5B)
C(4B)
C(1B)
C(3B)
C(2B)
B(1B)
F(3B)
F(2B)
Fe(1B)
C(9B)
C(8B)
C(10B)
C(6B)
C(7B)

Table 1. Crystal data and structure refinement for k00122.

Identification code	k00122	
Empirical formula	C26 H45 B F3 Fe N	
Formula weight	495.29	
Temperature	150(1) K	
Wavelength	0.71070 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.9310(2) Å	α= 87.4994(14)°.
	b = 15.5450(4) Å	β= 87.9357(17)°.
	c = 17.9230(5) Å	γ = 75.3339(16)°.
Volume	2673.31(11) $Å^3$	
Z	4	
Density (calculated)	1.231 Mg/m^3	
Absorption coefficient	0.598 mm^{-1}	
F(000)	1064	
Crystal size	0.25 x 0.15 x 0.15 mm^3	
Theta range for data collection	2.61 to 27.51°.	
Index ranges	0<=h<=12, -19<=k<=20, -23<=l<=23	
Reflections collected	33767	
Independent reflections	12237 [R(int) = 0.041]	
Completeness to theta = 27.51°	99.6 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.9156 and 0.8648	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12237 / 0 / 578	
Goodness-of-fit on F^2	1.023	
Final R indices [I>2sigma(I)]	R1 = 0.0480, wR2 = 0.1072	
R indices (all data)	R1 = 0.0877, wR2 = 0.1226	
Extinction coefficient	0.0007(4)	
Largest diff. peak and hole	0.383 and -0.436 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for k00122. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Fe(1A)	3593(1)	3127(1)	10240(1)	30(1)
F(1A)	3722(2)	3681(1)	7788(1)	53(1)
F(2A)	2555(2)	2671(1)	8224(1)	47(1)
F(3A)	4874(2)	2435(1)	8442(1)	46(1)
C(1A)	3216(3)	3627(2)	9157(1)	32(1)
C(2A)	1957(3)	3761(2)	9600(1)	36(1)
C(3A)	2043(3)	4274(2)	10224(2)	45(1)
C(4A)	3358(4)	4470(2)	10184(2)	53(1)
C(5A)	4072(3)	4072(2)	9530(2)	45(1)
C(6A)	4452(3)	1806(2)	10125(2)	41(1)
C(7A)	3261(3)	1940(2)	10606(2)	40(1)
C(8A)	3489(3)	2425(2)	11222(1)	43(1)
C(9A)	4823(3)	2590(2)	11117(2)	48(1)
C(10A)	5422(3)	2207(2)	10435(2)	46(1)
B(1A)	3601(3)	3094(2)	8397(2)	33(1)
N(1A)	5379(2)	95(1)	7503(1)	25(1)
C(11A)	4056(2)	564(2)	7923(1)	29(1)
C(12A)	3686(2)	81(2)	8627(1)	32(1)
C(13A)	2303(2)	611(2)	8960(1)	36(1)
C(14A)	1877(3)	156(2)	9667(2)	52(1)
C(15A)	6609(2)	34(2)	8003(1)	28(1)
C(16A)	8042(2)	-296(2)	7626(1)	32(1)
C(17A)	9166(2)	-627(2)	8192(1)	37(1)
C(18A)	10599(3)	-933(2)	7822(2)	46(1)
C(19A)	5352(2)	-848(2)	7322(1)	27(1)
C(20A)	4179(2)	-933(2)	6840(1)	32(1)
C(21A)	4240(3)	-1908(2)	6732(1)	36(1)
C(22A)	3248(3)	-2042(2)	6151(2)	46(1)
C(23A)	5511(2)	619(2)	6779(1)	28(1)
C(24A)	5704(3)	1547(2)	6865(1)	33(1)
C(25A)	5707(3)	2022(2)	6104(1)	33(1)

C(26A)	5920(3)	2955(2)	6173(2)	41(1)
Fe(1B)	1319(1)	1387(1)	5297(1)	25(1)
F(1B)	1890(2)	2372(1)	2955(1)	57(1)
F(2B)	1839(2)	3163(1)	3992(1)	55(1)
F(3B)	-100(2)	2764(1)	3653(1)	49(1)
C(1B)	1833(2)	1564(2)	4186(1)	27(1)
C(2B)	3055(2)	1278(2)	4625(1)	30(1)
C(3B)	3072(2)	442(2)	4993(1)	32(1)
C(4B)	1855(2)	194(2)	4787(1)	31(1)
C(5B)	1109(2)	880(2)	4292(1)	29(1)
C(6B)	442(3)	2638(2)	5638(2)	41(1)
C(7B)	1410(3)	2170(2)	6169(2)	41(1)
C(8B)	975(3)	1410(2)	6436(1)	38(1)
C(9B)	-260(3)	1411(2)	6069(1)	37(1)
C(10B)	-593(2)	2163(2)	5579(1)	39(1)
B(1B)	1348(3)	2476(2)	3700(2)	34(1)
N(1B)	-603(2)	4790(1)	7408(1)	26(1)
C(11B)	-680(2)	4129(2)	8051(1)	30(1)
C(12B)	-1041(3)	3279(2)	7862(1)	36(1)
C(13B)	-1033(3)	2702(2)	8579(2)	47(1)
C(14B)	-1521(3)	1879(2)	8464(2)	56(1)
C(15B)	675(2)	4395(2)	6921(1)	31(1)
C(16B)	951(2)	4986(2)	6266(1)	36(1)
C(17B)	2321(3)	4552(2)	5872(2)	45(1)
C(18B)	2680(3)	5147(2)	5238(2)	61(1)
C(19B)	-1900(2)	4975(2)	6936(1)	30(1)
C(20B)	-3284(2)	5274(2)	7350(1)	36(1)
C(21B)	-4472(2)	5479(2)	6811(2)	38(1)
C(22B)	-5887(3)	5732(2)	7217(2)	44(1)
C(23B)	-507(2)	5664(2)	7730(1)	29(1)
C(24B)	740(2)	5628(2)	8204(1)	33(1)
C(25B)	668(3)	6556(2)	8466(2)	45(1)
C(26B)	1758(3)	6575(2)	9025(2)	59(1)

Table 3. Bond lengths [Å] and angles [°] for k00122.

Fe(1A)-C(6A)	2.031(3)
Fe(1A)-C(7A)	2.032(3)
Fe(1A)-C(10A)	2.037(3)
Fe(1A)-C(2A)	2.038(3)
Fe(1A)-C(5A)	2.039(3)
Fe(1A)-C(3A)	2.039(3)
Fe(1A)-C(4A)	2.040(3)
Fe(1A)-C(9A)	2.042(3)
Fe(1A)-C(8A)	2.043(3)
Fe(1A)-C(1A)	2.071(2)
F(1A)-B(1A)	1.414(3)
F(2A)-B(1A)	1.411(3)
F(3A)-B(1A)	1.414(3)
C(1A)-C(5A)	1.425(4)
C(1A)-C(2A)	1.431(3)
C(1A)-B(1A)	1.608(3)
C(2A)-C(3A)	1.419(4)
C(3A)-C(4A)	1.414(4)
C(4A)-C(5A)	1.429(4)
C(6A)-C(10A)	1.413(4)
C(6A)-C(7A)	1.414(4)
C(7A)-C(8A)	1.420(4)
C(8A)-C(9A)	1.416(4)
C(9A)-C(10A)	1.427(4)
N(1A)-C(15A)	1.522(3)
N(1A)-C(19A)	1.522(3)
N(1A)-C(23A)	1.522(3)
N(1A)-C(11A)	1.522(3)
C(11A)-C(12A)	1.520(3)
C(12A)-C(13A)	1.528(3)
C(13A)-C(14A)	1.523(3)
C(15A)-C(16A)	1.529(3)
C(16A)-C(17A)	1.512(3)
C(17A)-C(18A)	1.520(3)

C(19A)-C(20A)	1.510(3)
C(20A)-C(21A)	1.522(3)
C(21A)-C(22A)	1.515(4)
C(23A)-C(24A)	1.518(3)
C(24A)-C(25A)	1.522(3)
C(25A)-C(26A)	1.528(3)
Fe(1B)-C(6B)	2.030(2)
Fe(1B)-C(10B)	2.035(2)
Fe(1B)-C(5B)	2.036(2)
Fe(1B)-C(7B)	2.041(2)
Fe(1B)-C(2B)	2.042(2)
Fe(1B)-C(4B)	2.042(2)
Fe(1B)-C(9B)	2.047(2)
Fe(1B)-C(3B)	2.047(2)
Fe(1B)-C(8B)	2.058(2)
Fe(1B)-C(1B)	2.061(2)
F(1B)-B(1B)	1.422(3)
F(2B)-B(1B)	1.409(3)
F(3B)-B(1B)	1.399(3)
C(1B)-C(5B)	1.430(3)
C(1B)-C(2B)	1.433(3)
C(1B)-B(1B)	1.605(4)
C(2B)-C(3B)	1.427(3)
C(3B)-C(4B)	1.423(3)
C(4B)-C(5B)	1.428(3)
C(6B)-C(10B)	1.418(4)
C(6B)-C(7B)	1.419(4)
C(7B)-C(8B)	1.416(4)
C(8B)-C(9B)	1.413(4)
C(9B)-C(10B)	1.408(4)
N(1B)-C(15B)	1.523(3)
N(1B)-C(11B)	1.524(3)
N(1B)-C(19B)	1.525(3)
N(1B)-C(23B)	1.526(3)
C(11B)-C(12B)	1.509(3)
C(12B)-C(13B)	1.534(4)

C(13B)-C(14B)	1.504(4)
C(15B)-C(16B)	1.518(3)
C(16B)-C(17B)	1.521(3)
C(17B)-C(18B)	1.523(4)
C(19B)-C(20B)	1.512(3)
C(20B)-C(21B)	1.514(3)
C(21B)-C(22B)	1.526(3)
C(23B)-C(24B)	1.516(3)
C(24B)-C(25B)	1.520(3)
C(25B)-C(26B)	1.508(4)

C(6A)-Fe(1A)-C(7A)	40.75(10)
C(6A)-Fe(1A)-C(10A)	40.66(11)
C(7A)-Fe(1A)-C(10A)	68.63(11)
C(6A)-Fe(1A)-C(2A)	119.64(11)
C(7A)-Fe(1A)-C(2A)	107.81(11)
C(10A)-Fe(1A)-C(2A)	153.86(11)
C(6A)-Fe(1A)-C(5A)	122.47(11)
C(7A)-Fe(1A)-C(5A)	159.43(11)
C(10A)-Fe(1A)-C(5A)	106.09(12)
C(2A)-Fe(1A)-C(5A)	67.67(11)
C(6A)-Fe(1A)-C(3A)	156.11(12)
C(7A)-Fe(1A)-C(3A)	122.32(12)
C(10A)-Fe(1A)-C(3A)	162.83(12)
C(2A)-Fe(1A)-C(3A)	40.73(10)
C(5A)-Fe(1A)-C(3A)	68.30(11)
C(6A)-Fe(1A)-C(4A)	160.47(12)
C(7A)-Fe(1A)-C(4A)	158.01(11)
C(10A)-Fe(1A)-C(4A)	124.74(13)
C(2A)-Fe(1A)-C(4A)	68.23(12)
C(5A)-Fe(1A)-C(4A)	41.00(10)
C(3A)-Fe(1A)-C(4A)	40.55(12)
C(6A)-Fe(1A)-C(9A)	68.45(11)
C(7A)-Fe(1A)-C(9A)	68.41(12)
C(10A)-Fe(1A)-C(9A)	40.95(11)
C(2A)-Fe(1A)-C(9A)	163.90(10)

C(5A)-Fe(1A)-C(9A)	121.45(12)
C(3A)-Fe(1A)-C(9A)	126.96(11)
C(4A)-Fe(1A)-C(9A)	109.05(13)
C(6A)-Fe(1A)-C(8A)	68.58(11)
C(7A)-Fe(1A)-C(8A)	40.78(11)
C(10A)-Fe(1A)-C(8A)	68.74(11)
C(2A)-Fe(1A)-C(8A)	126.49(11)
C(5A)-Fe(1A)-C(8A)	157.71(12)
C(3A)-Fe(1A)-C(8A)	109.93(11)
C(4A)-Fe(1A)-C(8A)	123.00(11)
C(9A)-Fe(1A)-C(8A)	40.58(11)
C(6A)-Fe(1A)-C(1A)	104.37(10)
C(7A)-Fe(1A)-C(1A)	122.85(10)
C(10A)-Fe(1A)-C(1A)	117.89(10)
C(2A)-Fe(1A)-C(1A)	40.74(9)
C(5A)-Fe(1A)-C(1A)	40.57(11)
C(3A)-Fe(1A)-C(1A)	69.14(10)
C(4A)-Fe(1A)-C(1A)	69.21(11)
C(9A)-Fe(1A)-C(1A)	154.66(11)
C(8A)-Fe(1A)-C(1A)	161.35(11)
C(5A)-C(1A)-C(2A)	105.3(2)
C(5A)-C(1A)-B(1A)	126.7(2)
C(2A)-C(1A)-B(1A)	128.0(2)
C(5A)-C(1A)-Fe(1A)	68.52(15)
C(2A)-C(1A)-Fe(1A)	68.39(13)
B(1A)-C(1A)-Fe(1A)	127.47(17)
C(3A)-C(2A)-C(1A)	109.9(2)
C(3A)-C(2A)-Fe(1A)	69.70(16)
C(1A)-C(2A)-Fe(1A)	70.87(14)
C(4A)-C(3A)-C(2A)	107.7(2)
C(4A)-C(3A)-Fe(1A)	69.76(16)
C(2A)-C(3A)-Fe(1A)	69.57(14)
C(3A)-C(4A)-C(5A)	107.3(3)
C(3A)-C(4A)-Fe(1A)	69.70(16)
C(5A)-C(4A)-Fe(1A)	69.46(15)
C(1A)-C(5A)-C(4A)	109.8(2)

C(1A)-C(5A)-Fe(1A)	70.91(14)
C(4A)-C(5A)-Fe(1A)	69.54(15)
C(10A)-C(6A)-C(7A)	108.4(2)
C(10A)-C(6A)-Fe(1A)	69.92(16)
C(7A)-C(6A)-Fe(1A)	69.66(14)
C(6A)-C(7A)-C(8A)	108.1(2)
C(6A)-C(7A)-Fe(1A)	69.59(15)
C(8A)-C(7A)-Fe(1A)	70.02(15)
C(9A)-C(8A)-C(7A)	107.7(2)
C(9A)-C(8A)-Fe(1A)	69.69(15)
C(7A)-C(8A)-Fe(1A)	69.20(15)
C(8A)-C(9A)-C(10A)	108.2(3)
C(8A)-C(9A)-Fe(1A)	69.74(16)
C(10A)-C(9A)-Fe(1A)	69.36(16)
C(6A)-C(10A)-C(9A)	107.5(2)
C(6A)-C(10A)-Fe(1A)	69.42(15)
C(9A)-C(10A)-Fe(1A)	69.70(15)
F(2A)-B(1A)-F(1A)	107.2(2)
F(2A)-B(1A)-F(3A)	107.8(2)
F(1A)-B(1A)-F(3A)	107.7(2)
F(2A)-B(1A)-C(1A)	111.2(2)
F(1A)-B(1A)-C(1A)	110.7(2)
F(3A)-B(1A)-C(1A)	112.1(2)
C(15A)-N(1A)-C(19A)	107.89(17)
C(15A)-N(1A)-C(23A)	111.46(17)
C(19A)-N(1A)-C(23A)	109.11(16)
C(15A)-N(1A)-C(11A)	108.26(16)
C(19A)-N(1A)-C(11A)	111.23(17)
C(23A)-N(1A)-C(11A)	108.91(16)
C(12A)-C(11A)-N(1A)	115.95(18)
C(11A)-C(12A)-C(13A)	109.62(19)
C(14A)-C(13A)-C(12A)	111.9(2)
N(1A)-C(15A)-C(16A)	115.08(18)
C(17A)-C(16A)-C(15A)	111.61(19)
C(16A)-C(17A)-C(18A)	111.9(2)
C(20A)-C(19A)-N(1A)	116.11(18)

C(19A)-C(20A)-C(21A)	110.55(19)
C(22A)-C(21A)-C(20A)	113.2(2)
C(24A)-C(23A)-N(1A)	115.78(18)
C(23A)-C(24A)-C(25A)	110.32(19)
C(24A)-C(25A)-C(26A)	111.4(2)
C(6B)-Fe(1B)-C(10B)	40.83(10)
C(6B)-Fe(1B)-C(5B)	127.24(11)
C(10B)-Fe(1B)-C(5B)	106.00(10)
C(6B)-Fe(1B)-C(7B)	40.79(11)
C(10B)-Fe(1B)-C(7B)	68.33(10)
C(5B)-Fe(1B)-C(7B)	166.71(11)
C(6B)-Fe(1B)-C(2B)	114.40(10)
C(10B)-Fe(1B)-C(2B)	145.68(11)
C(5B)-Fe(1B)-C(2B)	67.97(9)
C(7B)-Fe(1B)-C(2B)	109.46(10)
C(6B)-Fe(1B)-C(4B)	167.24(11)
C(10B)-Fe(1B)-C(4B)	130.02(11)
C(5B)-Fe(1B)-C(4B)	40.99(9)
C(7B)-Fe(1B)-C(4B)	151.55(11)
C(2B)-Fe(1B)-C(4B)	68.54(9)
C(6B)-Fe(1B)-C(9B)	68.20(10)
C(10B)-Fe(1B)-C(9B)	40.34(10)
C(5B)-Fe(1B)-C(9B)	116.21(10)
C(7B)-Fe(1B)-C(9B)	67.86(10)
C(2B)-Fe(1B)-C(9B)	172.95(10)
C(4B)-Fe(1B)-C(9B)	110.47(10)
C(6B)-Fe(1B)-C(3B)	148.80(11)
C(10B)-Fe(1B)-C(3B)	170.35(11)
C(5B)-Fe(1B)-C(3B)	68.43(10)
C(7B)-Fe(1B)-C(3B)	118.81(10)
C(2B)-Fe(1B)-C(3B)	40.84(9)
C(4B)-Fe(1B)-C(3B)	40.73(10)
C(9B)-Fe(1B)-C(3B)	133.99(10)
C(6B)-Fe(1B)-C(8B)	68.35(11)
C(10B)-Fe(1B)-C(8B)	68.05(10)
C(5B)-Fe(1B)-C(8B)	150.17(11)

C(7B)-Fe(1B)-C(8B)	40.41(10)
C(2B)-Fe(1B)-C(8B)	133.60(10)
C(4B)-Fe(1B)-C(8B)	119.45(10)
C(9B)-Fe(1B)-C(8B)	40.25(10)
C(3B)-Fe(1B)-C(8B)	112.56(10)
C(6B)-Fe(1B)-C(1B)	104.13(10)
C(10B)-Fe(1B)-C(1B)	112.02(10)
C(5B)-Fe(1B)-C(1B)	40.84(9)
C(7B)-Fe(1B)-C(1B)	128.72(10)
C(2B)-Fe(1B)-C(1B)	40.89(9)
C(4B)-Fe(1B)-C(1B)	69.51(9)
C(9B)-Fe(1B)-C(1B)	145.92(10)
C(3B)-Fe(1B)-C(1B)	69.36(9)
C(8B)-Fe(1B)-C(1B)	168.98(10)
C(5B)-C(1B)-C(2B)	105.5(2)
C(5B)-C(1B)-B(1B)	127.0(2)
C(2B)-C(1B)-B(1B)	127.4(2)
C(5B)-C(1B)-Fe(1B)	68.64(12)
C(2B)-C(1B)-Fe(1B)	68.83(12)
B(1B)-C(1B)-Fe(1B)	125.36(15)
C(3B)-C(2B)-C(1B)	109.7(2)
C(3B)-C(2B)-Fe(1B)	69.79(12)
C(1B)-C(2B)-Fe(1B)	70.28(12)
C(4B)-C(3B)-C(2B)	107.6(2)
C(4B)-C(3B)-Fe(1B)	69.44(13)
C(2B)-C(3B)-Fe(1B)	69.37(12)
C(3B)-C(4B)-C(5B)	107.3(2)
C(3B)-C(4B)-Fe(1B)	69.84(13)
C(5B)-C(4B)-Fe(1B)	69.28(13)
C(4B)-C(5B)-C(1B)	109.9(2)
C(4B)-C(5B)-Fe(1B)	69.73(13)
C(1B)-C(5B)-Fe(1B)	70.52(13)
C(10B)-C(6B)-C(7B)	107.6(2)
C(10B)-C(6B)-Fe(1B)	69.77(14)
C(7B)-C(6B)-Fe(1B)	70.00(14)
C(8B)-C(7B)-C(6B)	108.2(2)

C(8B)-C(7B)-Fe(1B)	70.45(14)
C(6B)-C(7B)-Fe(1B)	69.21(14)
C(9B)-C(8B)-C(7B)	107.6(2)
C(9B)-C(8B)-Fe(1B)	69.47(14)
C(7B)-C(8B)-Fe(1B)	69.13(14)
C(10B)-C(9B)-C(8B)	108.6(2)
C(10B)-C(9B)-Fe(1B)	69.37(13)
C(8B)-C(9B)-Fe(1B)	70.28(13)
C(9B)-C(10B)-C(6B)	108.0(2)
C(9B)-C(10B)-Fe(1B)	70.30(14)
C(6B)-C(10B)-Fe(1B)	69.39(13)
F(3B)-B(1B)-F(2B)	108.4(2)
F(3B)-B(1B)-F(1B)	106.7(2)
F(2B)-B(1B)-F(1B)	106.3(2)
F(3B)-B(1B)-C(1B)	112.4(2)
F(2B)-B(1B)-C(1B)	111.7(2)
F(1B)-B(1B)-C(1B)	111.0(2)
C(15B)-N(1B)-C(11B)	108.26(17)
C(15B)-N(1B)-C(19B)	109.35(17)
C(11B)-N(1B)-C(19B)	111.24(17)
C(15B)-N(1B)-C(23B)	111.11(17)
C(11B)-N(1B)-C(23B)	108.69(17)
C(19B)-N(1B)-C(23B)	108.20(17)
C(12B)-C(11B)-N(1B)	117.1(2)
C(11B)-C(12B)-C(13B)	108.8(2)
C(14B)-C(13B)-C(12B)	113.0(3)
C(16B)-C(15B)-N(1B)	115.49(19)
C(15B)-C(16B)-C(17B)	110.1(2)
C(16B)-C(17B)-C(18B)	111.9(2)
C(20B)-C(19B)-N(1B)	116.40(19)
C(19B)-C(20B)-C(21B)	110.7(2)
C(20B)-C(21B)-C(22B)	111.9(2)
C(24B)-C(23B)-N(1B)	116.59(18)
C(23B)-C(24B)-C(25B)	109.1(2)
C(26B)-C(25B)-C(24B)	113.4(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for k00122. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Fe(1A)	38(1)	30(1)	24(1)	-2(1)	-2(1)	-11(1)
F(1A)	79(1)	44(1)	28(1)	4(1)	12(1)	-8(1)
F(2A)	48(1)	46(1)	48(1)	-15(1)	-3(1)	-9(1)
F(3A)	41(1)	51(1)	36(1)	-11(1)	1(1)	8(1)
C(1A)	41(1)	25(1)	28(1)	1(1)	2(1)	-6(1)
C(2A)	41(1)	30(1)	30(1)	5(1)	1(1)	0(1)
C(3A)	68(2)	32(2)	29(1)	-4(1)	6(1)	0(1)
C(4A)	93(2)	34(2)	36(2)	-9(1)	2(2)	-24(2)
C(5A)	60(2)	35(2)	46(2)	-3(1)	9(1)	-24(1)
C(6A)	53(2)	32(1)	34(1)	1(1)	-7(1)	-1(1)
C(7A)	49(2)	34(2)	39(2)	7(1)	-7(1)	-13(1)
C(8A)	51(2)	43(2)	30(1)	6(1)	-1(1)	-4(1)
C(9A)	53(2)	58(2)	34(2)	0(1)	-17(1)	-15(1)
C(10A)	36(1)	57(2)	41(2)	1(1)	-5(1)	-4(1)
B(1A)	39(2)	29(2)	27(1)	-2(1)	2(1)	-2(1)
N(1A)	29(1)	26(1)	19(1)	-2(1)	0(1)	-4(1)
C(11A)	27(1)	29(1)	26(1)	-4(1)	3(1)	0(1)
C(12A)	33(1)	32(1)	30(1)	-3(1)	5(1)	-9(1)
C(13A)	31(1)	44(2)	34(1)	-6(1)	5(1)	-9(1)
C(14A)	52(2)	61(2)	46(2)	-7(2)	23(2)	-19(2)
C(15A)	32(1)	33(1)	20(1)	-2(1)	-2(1)	-9(1)
C(16A)	29(1)	41(2)	26(1)	-4(1)	1(1)	-9(1)
C(17A)	33(1)	44(2)	33(1)	-1(1)	-2(1)	-9(1)
C(18A)	32(1)	53(2)	52(2)	0(1)	-1(1)	-10(1)
C(19A)	29(1)	24(1)	27(1)	-3(1)	1(1)	-4(1)
C(20A)	33(1)	29(1)	34(1)	0(1)	-5(1)	-7(1)
C(21A)	44(2)	32(1)	35(1)	-1(1)	-8(1)	-13(1)
C(22A)	57(2)	42(2)	43(2)	-3(1)	-12(1)	-21(1)
C(23A)	33(1)	28(1)	21(1)	-1(1)	1(1)	-7(1)
C(24A)	45(2)	31(1)	25(1)	-3(1)	3(1)	-12(1)
C(25A)	33(1)	36(1)	28(1)	3(1)	1(1)	-8(1)

C(26A)	43(2)	30(1)	47(2)	5(1)	10(1)	-4(1)
Fe(1B)	26(1)	26(1)	22(1)	-5(1)	2(1)	-4(1)
F(1B)	74(1)	43(1)	36(1)	12(1)	18(1)	15(1)
F(2B)	74(1)	34(1)	60(1)	8(1)	-9(1)	-21(1)
F(3B)	38(1)	40(1)	59(1)	12(1)	-1(1)	5(1)
C(1B)	30(1)	27(1)	23(1)	-5(1)	3(1)	-4(1)
C(2B)	26(1)	35(1)	27(1)	-5(1)	4(1)	-7(1)
C(3B)	33(1)	34(1)	24(1)	-2(1)	1(1)	3(1)
C(4B)	43(1)	25(1)	24(1)	-4(1)	6(1)	-6(1)
C(5B)	33(1)	31(1)	21(1)	-8(1)	2(1)	-5(1)
C(6B)	47(2)	29(1)	43(2)	-11(1)	10(1)	-3(1)
C(7B)	34(1)	51(2)	39(2)	-25(1)	4(1)	-10(1)
C(8B)	42(2)	45(2)	22(1)	-9(1)	2(1)	1(1)
C(9B)	35(1)	48(2)	31(1)	-10(1)	9(1)	-15(1)
C(10B)	27(1)	52(2)	32(1)	-15(1)	5(1)	1(1)
B(1B)	38(2)	31(2)	31(2)	-1(1)	7(1)	-5(1)
N(1B)	31(1)	23(1)	23(1)	-3(1)	0(1)	-5(1)
C(11B)	35(1)	27(1)	26(1)	2(1)	-2(1)	-6(1)
C(12B)	39(1)	29(1)	41(2)	-2(1)	-1(1)	-10(1)
C(13B)	54(2)	35(2)	55(2)	7(1)	-14(1)	-15(1)
C(14B)	57(2)	43(2)	70(2)	6(2)	-10(2)	-19(1)
C(15B)	34(1)	27(1)	31(1)	-8(1)	4(1)	-4(1)
C(16B)	32(1)	45(2)	30(1)	-3(1)	2(1)	-8(1)
C(17B)	44(2)	47(2)	44(2)	-14(1)	13(1)	-13(1)
C(18B)	51(2)	91(3)	43(2)	-2(2)	14(2)	-22(2)
C(19B)	32(1)	30(1)	27(1)	-2(1)	-5(1)	-7(1)
C(20B)	37(1)	39(2)	30(1)	-4(1)	-1(1)	-6(1)
C(21B)	35(1)	37(2)	41(2)	-6(1)	-2(1)	-10(1)
C(22B)	37(1)	41(2)	55(2)	-3(1)	-2(1)	-12(1)
C(23B)	40(1)	21(1)	25(1)	-4(1)	1(1)	-5(1)
C(24B)	33(1)	33(1)	34(1)	-7(1)	3(1)	-9(1)
C(25B)	60(2)	35(2)	45(2)	-5(1)	-9(1)	-10(1)
C(26B)	61(2)	58(2)	63(2)	-15(2)	-10(2)	-24(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for k00122.

	x	y	z	U(eq)
H(2AA)	1146	3519	9491	43
H(3AA)	1304	4463	10620	54
H(4AA)	3720	4824	10545	63
H(5AA)	5036	4093	9364	54
H(6AA)	4581	1486	9646	49
H(7AA)	2407	1730	10526	48
H(8AA)	2824	2620	11650	51
H(9AA)	5264	2925	11459	58
H(10A)	6357	2220	10215	55
H(11A)	4151	1155	8061	35
H(11B)	3269	664	7579	35
H(12A)	4429	13	8995	38
H(12B)	3611	-520	8504	38
H(13A)	2385	1212	9078	44
H(13B)	1568	682	8586	44
H(14A)	988	515	9864	78
H(14B)	2594	95	10042	78
H(14C)	1776	-434	9551	78
H(15A)	6536	-370	8437	34
H(15B)	6541	631	8197	34
H(16A)	8023	-784	7292	38
H(16B)	8263	195	7315	38
H(17A)	8957	-1128	8494	44
H(17B)	9167	-143	8534	44
H(18A)	11296	-1142	8206	69
H(18B)	10816	-435	7531	69
H(18C)	10607	-1419	7490	69
H(19A)	6244	-1132	7067	33
H(19B)	5300	-1187	7798	33
H(20A)	4249	-631	6348	38

H(20B)	3275	-639	7080	38
H(21A)	5201	-2221	6580	43
H(21B)	4015	-2180	7215	43
H(22A)	3336	-2680	6105	69
H(22B)	3477	-1785	5668	69
H(22C)	2291	-1747	6303	69
H(23A)	6312	275	6483	33
H(23B)	4663	670	6488	33
H(24A)	6596	1507	7111	40
H(24B)	4941	1892	7185	40
H(25A)	4810	2066	5862	39
H(25B)	6460	1670	5783	39
H(26A)	5916	3242	5675	62
H(26B)	6815	2912	6404	62
H(26C)	5166	3308	6483	62
H(2BA)	3773	1619	4677	36
H(3BA)	3803	96	5336	39
H(4BA)	1577	-359	4956	38
H(5BA)	201	888	4063	35
H(6BA)	476	3204	5360	49
H(7BA)	2256	2345	6327	49
H(8BA)	1460	953	6812	46
H(9BA)	-801	950	6140	45
H(10B)	-1416	2333	5249	46
H(11C)	233	3968	8296	36
H(11D)	-1379	4435	8423	36
H(12C)	-352	2953	7493	43
H(12D)	-1973	3417	7639	43
H(13C)	-75	2526	8770	57
H(13D)	-1641	3061	8962	57
H(14D)	-1494	1537	8938	83
H(14E)	-911	1514	8093	83
H(14F)	-2477	2049	8286	83
H(15C)	1502	4249	7240	37
H(15D)	570	3831	6725	37
H(16C)	991	5571	6448	43

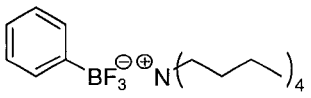
H(16D)	182	5084	5911	43
H(17C)	2258	3982	5669	53
H(17D)	3076	4420	6237	53
H(18D)	3567	4847	4998	92
H(18E)	2760	5708	5438	92
H(18F)	1944	5270	4869	92
H(19C)	-1833	5439	6550	36
H(19D)	-1896	4427	6674	36
H(20C)	-3299	5813	7629	43
H(20D)	-3401	4801	7715	43
H(21C)	-4419	4950	6512	45
H(21D)	-4378	5974	6464	45
H(22D)	-6627	5859	6850	66
H(22E)	-5951	6262	7506	66
H(22F)	-5992	5238	7554	66
H(23C)	-502	6098	7309	35
H(23D)	-1361	5897	8036	35
H(24C)	1611	5406	7908	39
H(24D)	740	5216	8641	39
H(25C)	781	6943	8027	54
H(25D)	-265	6804	8694	54
H(26D)	1656	7189	9172	88
H(26E)	2686	6345	8799	88
H(26F)	1640	6205	9467	88

Appendix B

Selected Spectra of Novel Compounds

Appendix B.1

Novel Organotrifluoroborate Salts



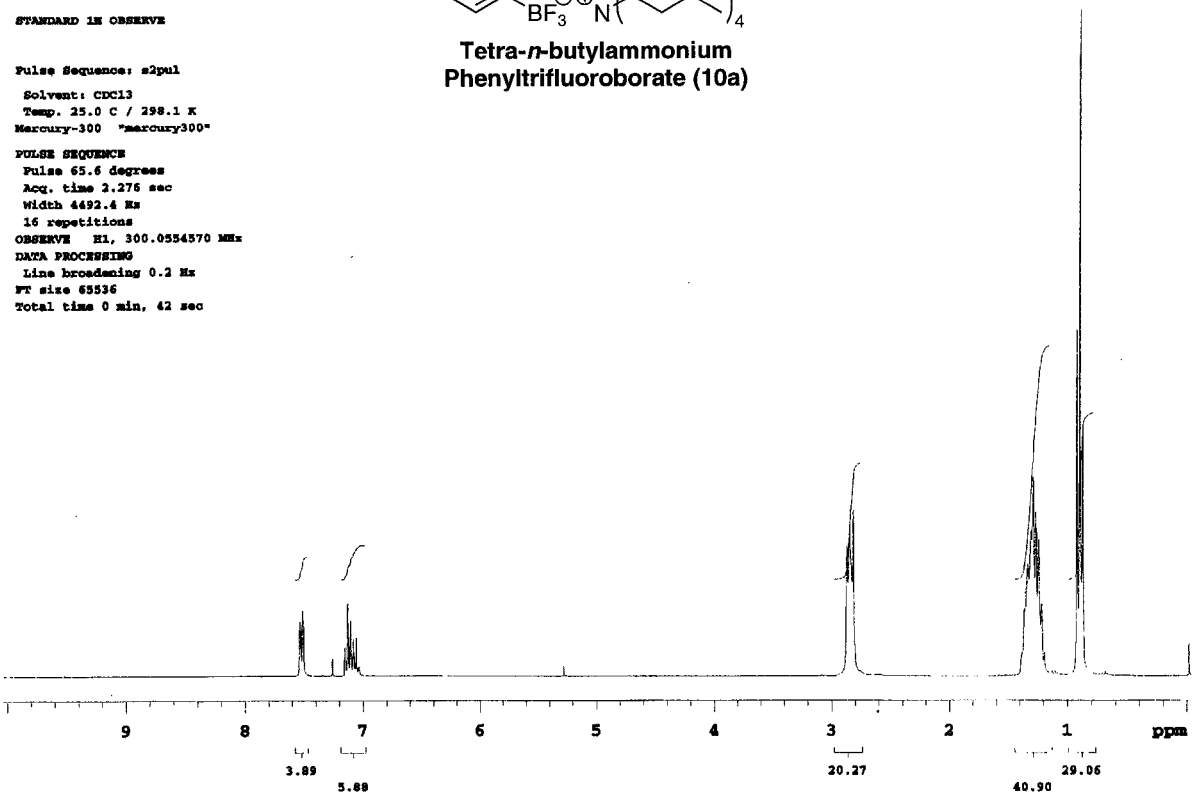
Tetra-*n*-butylammonium Phenyltrifluoroborate (10a)

STANDARD 1H OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"

PULSE SEQUENCE
Pulse 65.6 degrees
Acq. time 2.275 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0554570 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec



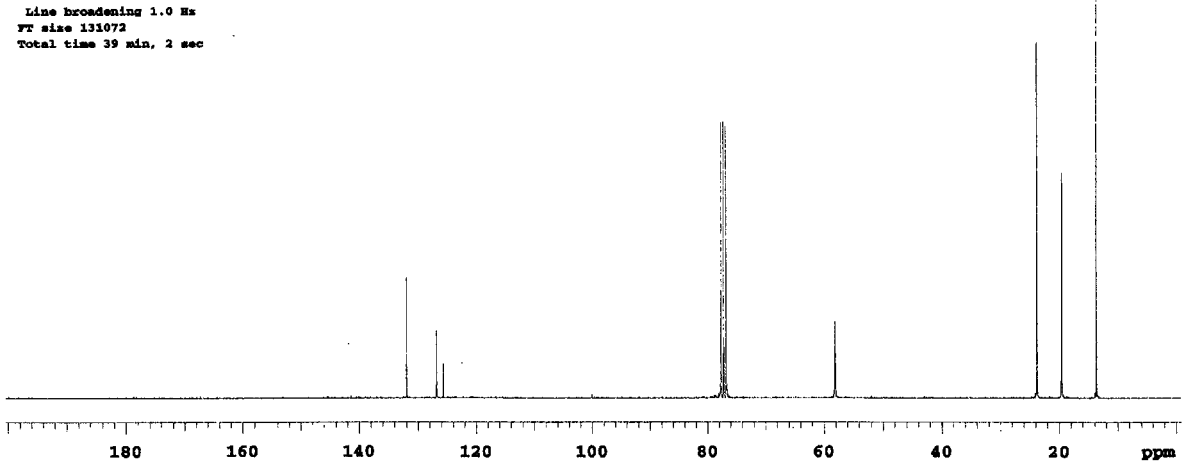
13C OBSERVE

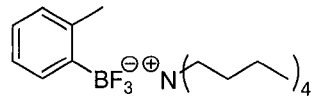
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"

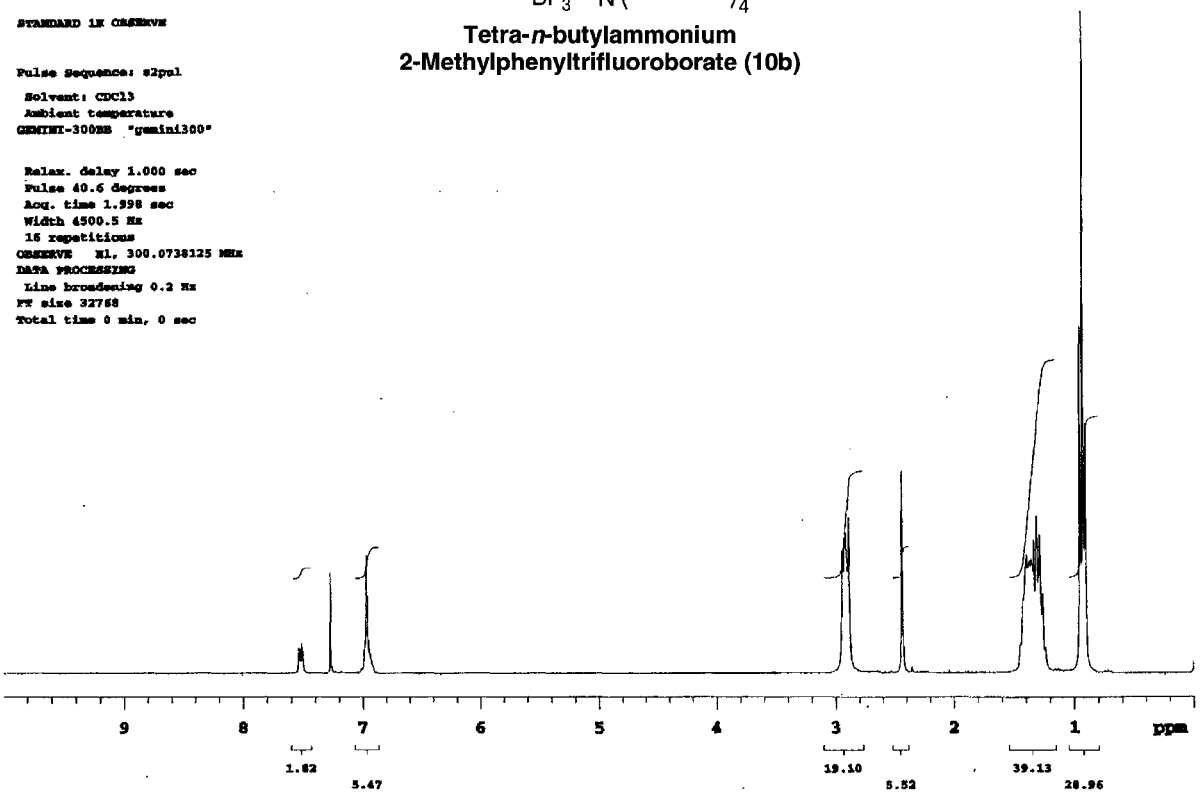
PULSE SEQUENCE
Pulse 30.0 degrees
Acq. time 1.747 sec
Width 18761.7 Hz
64 repetitions
OBSERVE C13, 75.4489947 MHz
DECOUPLE H1, 300.0569294 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 39 min, 2 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	9955.763	131.954	26.2
2	9568.705	126.823	14.7
3	9482.533	125.681	7.5
4	5856.440	77.621	59.8
5	5824.376	77.196	59.7
6	5792.598	76.775	58.8
7	4383.501	58.099	16.7
8	1791.185	23.740	76.5
9	1475.984	19.563	49.0
10	1034.246	13.708	139.5

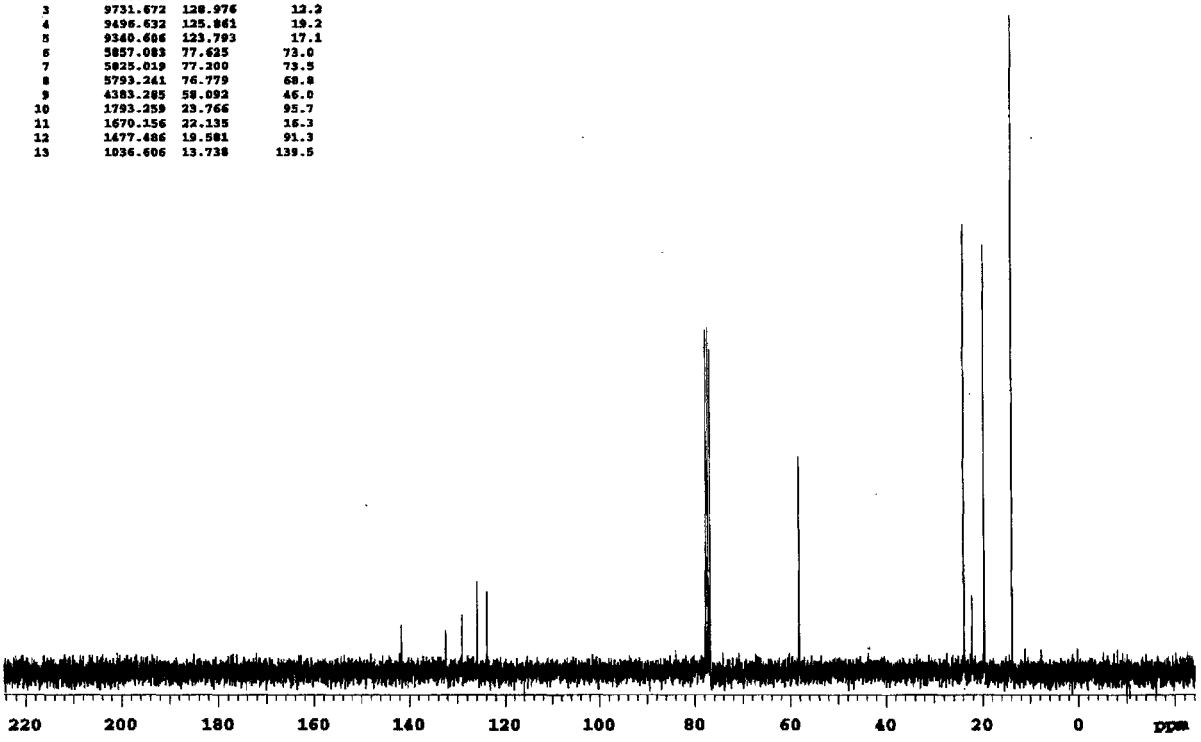


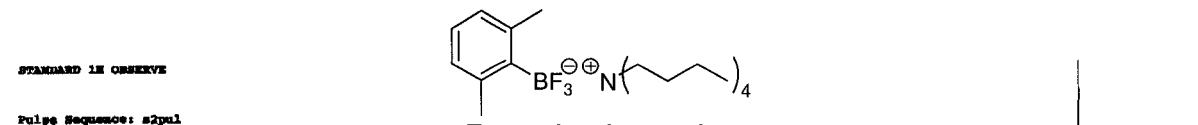


Tetra-*n*-butylammonium 2-Methylphenyltrifluoroborate (10b)

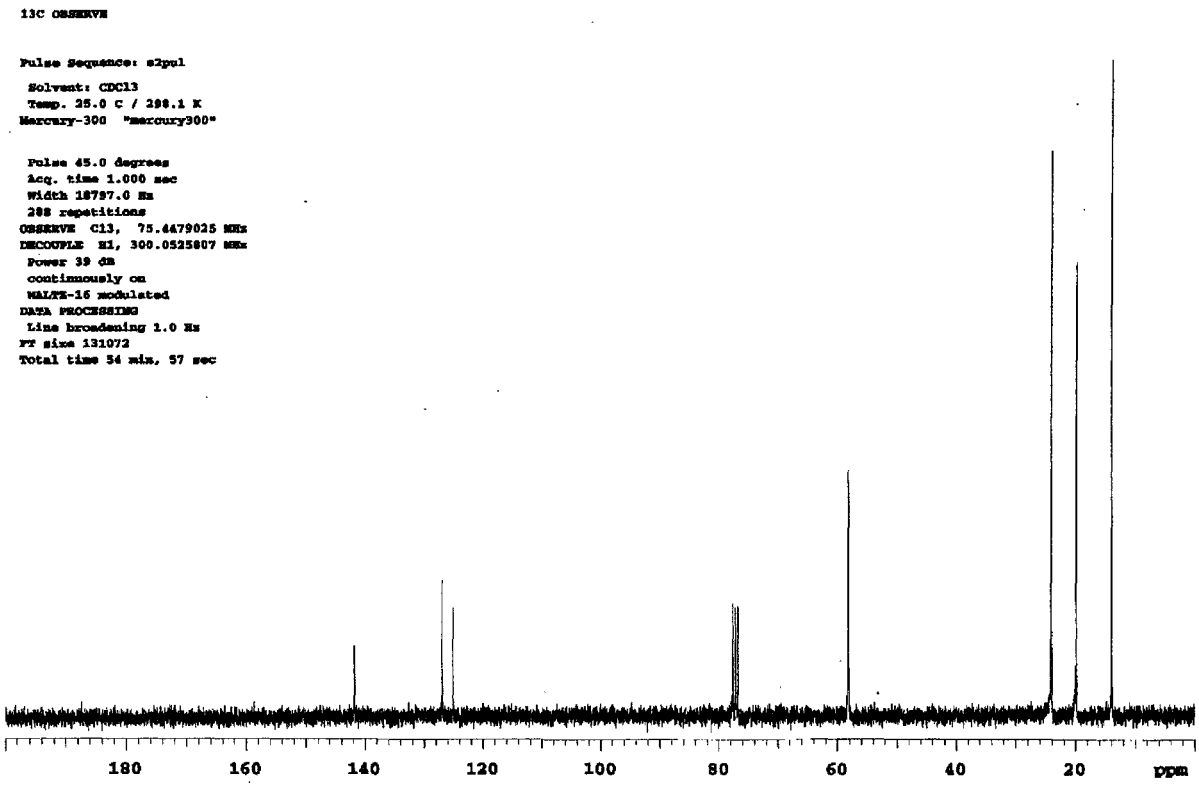


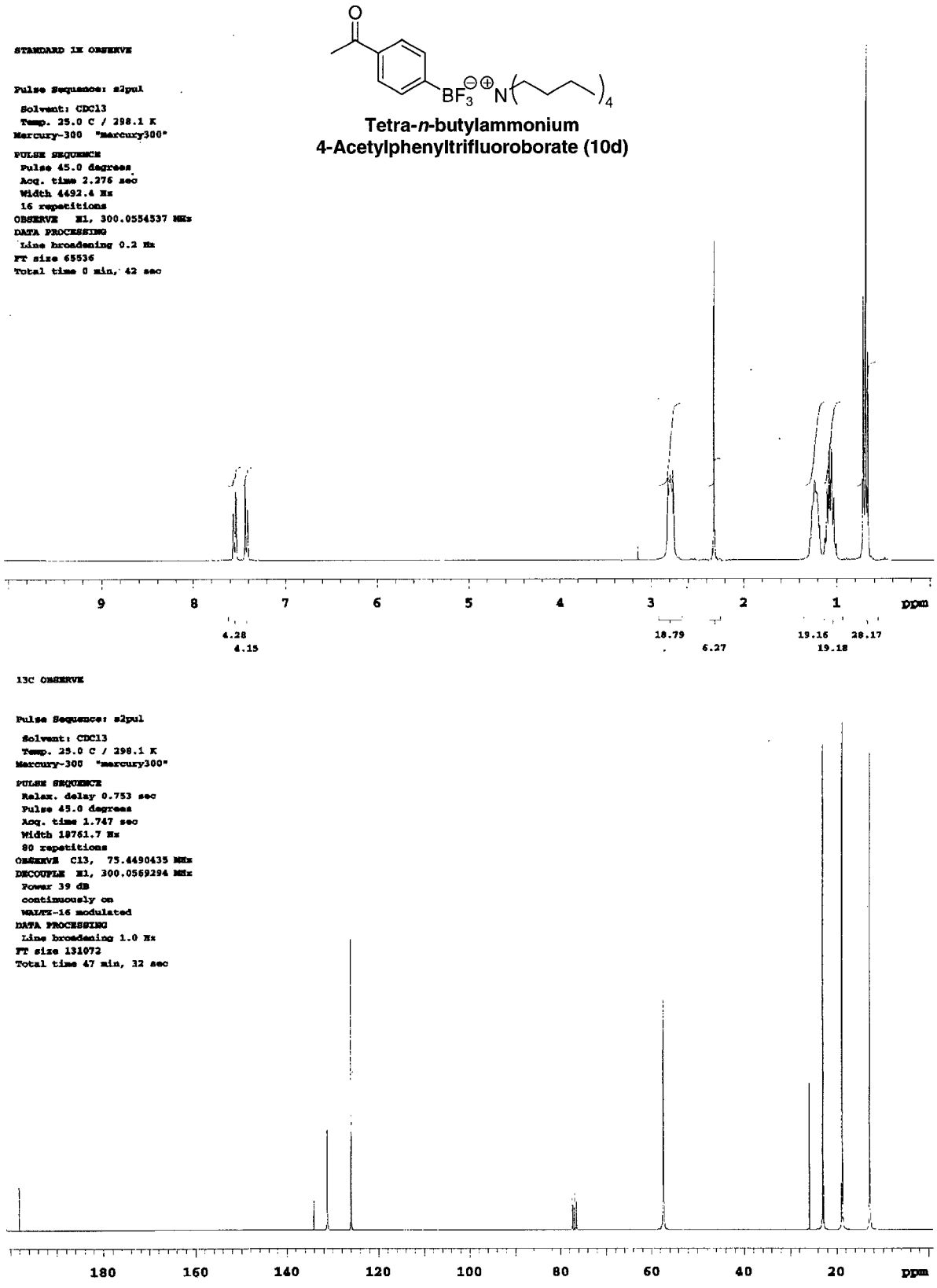
INDEX	FREQUENCY	PPM	HEIGHT
1	10688.438	141.656	10.0
2	9985.035	132.333	8.9
3	9731.672	128.976	12.2
4	9496.632	125.861	19.2
5	9340.606	123.793	17.1
6	5857.083	77.625	73.0
7	5825.019	77.200	73.5
8	5793.241	76.779	68.8
9	4383.285	58.092	46.0
10	1793.259	23.766	95.7
11	1670.156	22.135	16.3
12	1477.486	19.581	91.3
13	1036.606	13.738	139.5

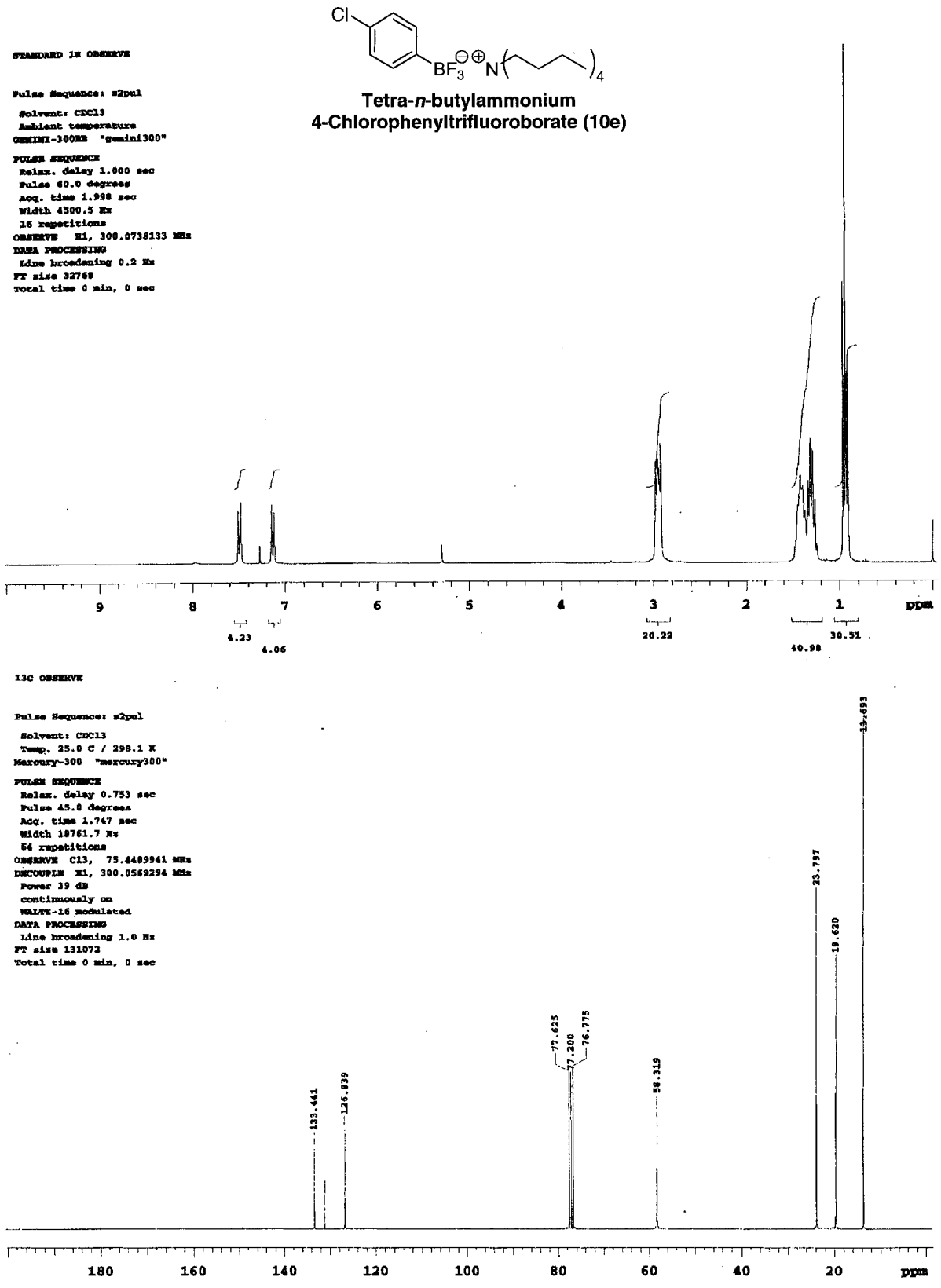


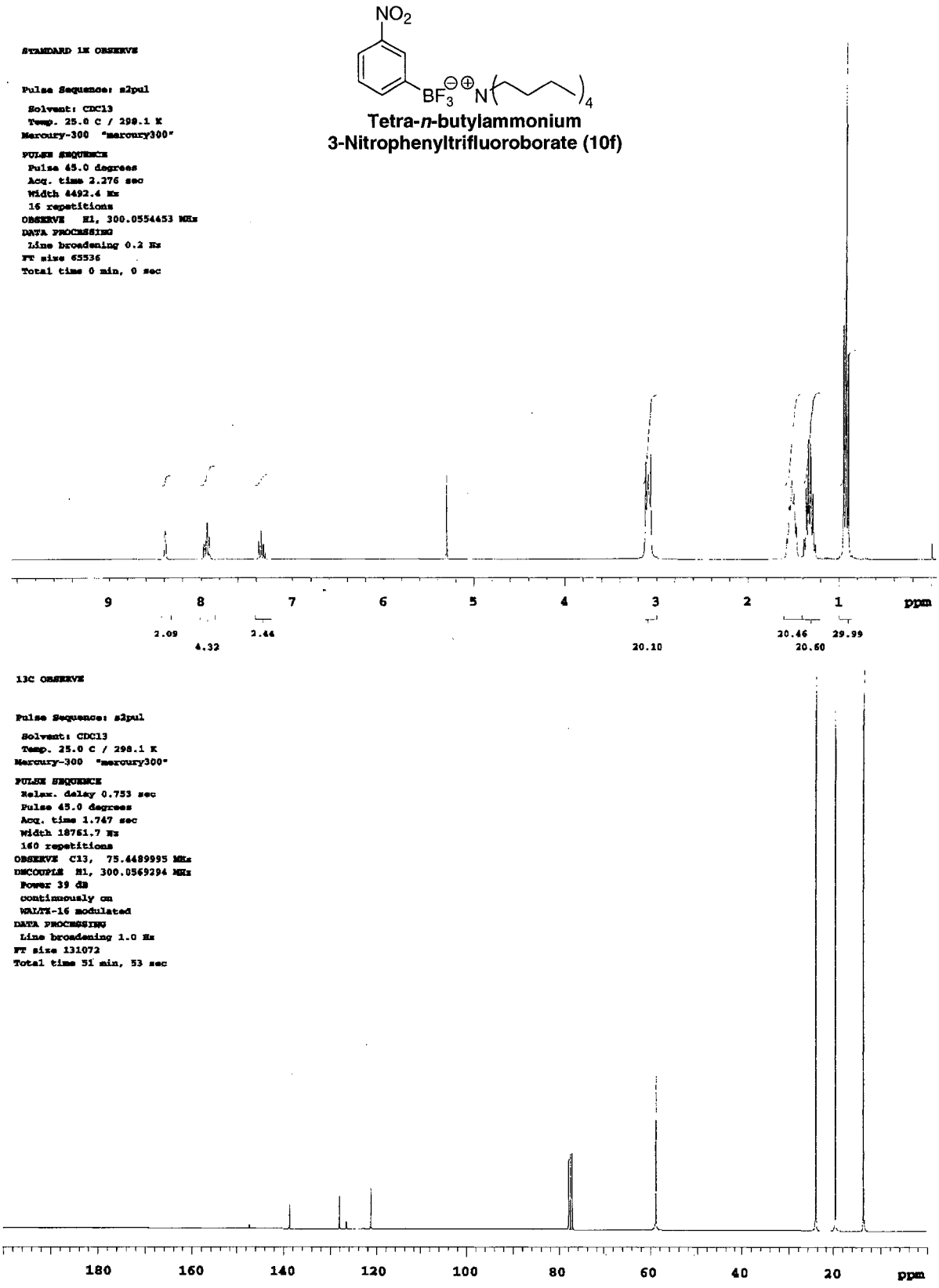


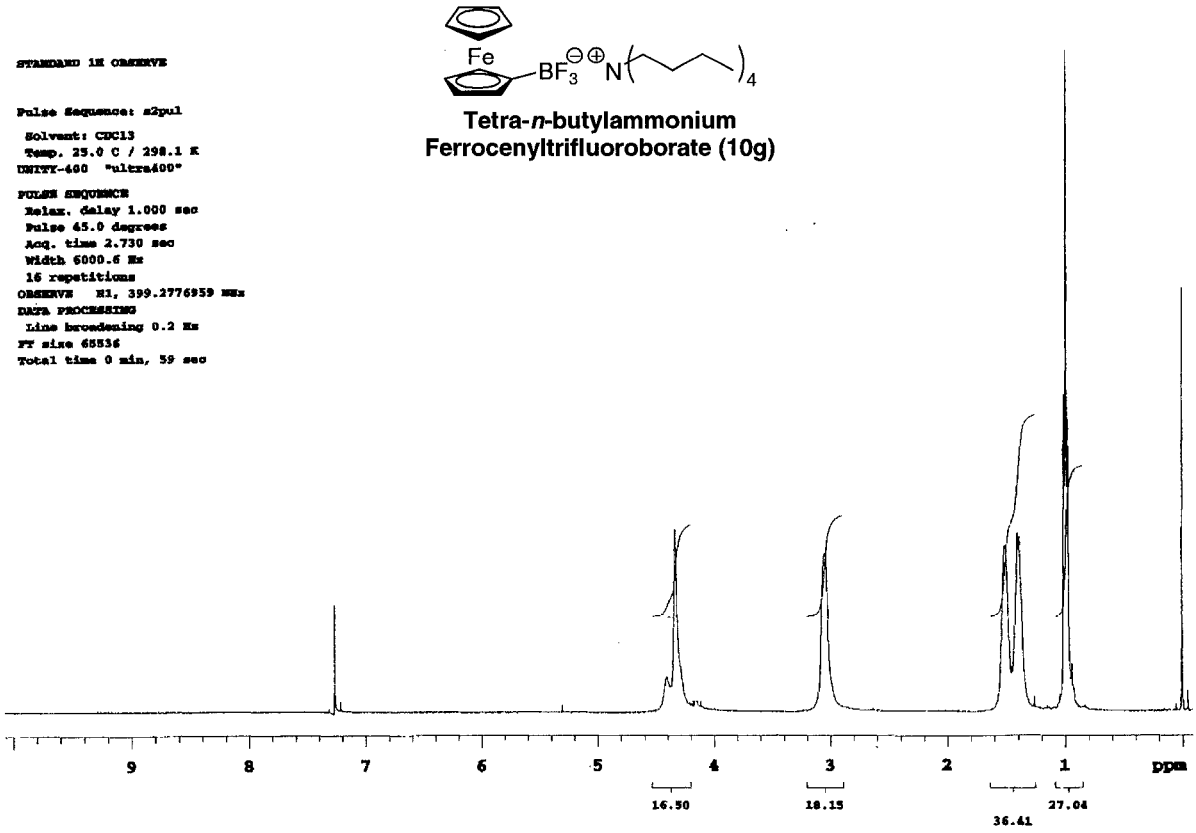
Tetra-*n*-butylammonium 2,6-Dimethylphenyltrifluoroborate (10c)




STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0554537 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec
Tetra-n-butylammonium
4-Acetylphenyltrifluoroborate (10d)
9
8
7
6
5
4
3
2
1
ppm
4.28
4.15
18.79
6.27
19.16
19.18
28.17
13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Relax. delay 0.753 sec
Pulse 45.0 degrees
Acq. time 1.747 sec
Width 18761.7 Hz
80 repetitions
OBSERVE C13, 75.4490435 MHz
DECOUPLE H1, 300.0569294 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 47 min, 32 sec
180
160
140
120
100
80
60
40
20
ppm


Cl
BF3
N
4
Tetra-n-butylammonium
4-Chlorophenyltrifluoroborate (10e)
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "gemini300"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 60.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0738133 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 0 sec
9
8
7
6
5
4
3
2
1
ppm
4.23
4.06
20.22
40.98
30.51
13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Relax. delay 0.753 sec
Pulse 45.0 degrees
Acq. time 1.747 sec
Width 18761.7 Hz
64 repetitions
OBSERVE C13, 75.4489941 MHz
DECOUPLE H1, 300.0569294 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 0 min, 0 sec
33.693
23.797
19.620
77.625
77.200
76.775
58.319
133.441
126.839
180
160
140
120
100
80
60
40
20
ppm


NO2
BF3
N
4
Tetra-n-butylammonium
3-Nitrophenyltrifluoroborate (10f)
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0554453 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 0 sec
9
8
7
6
5
4
3
2
1
ppm
2.09
4.32
2.44
20.10
20.46
20.60
29.99
13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Relax. delay 0.753 sec
Pulse 45.0 degrees
Acq. time 1.747 sec
Width 18761.7 Hz
160 repetitions
OBSERVE C13, 75.4489995 MHz
DECOUPLE H1, 300.0569294 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 51 min, 53 sec
180
160
140
120
100
80
60
40
20
ppm



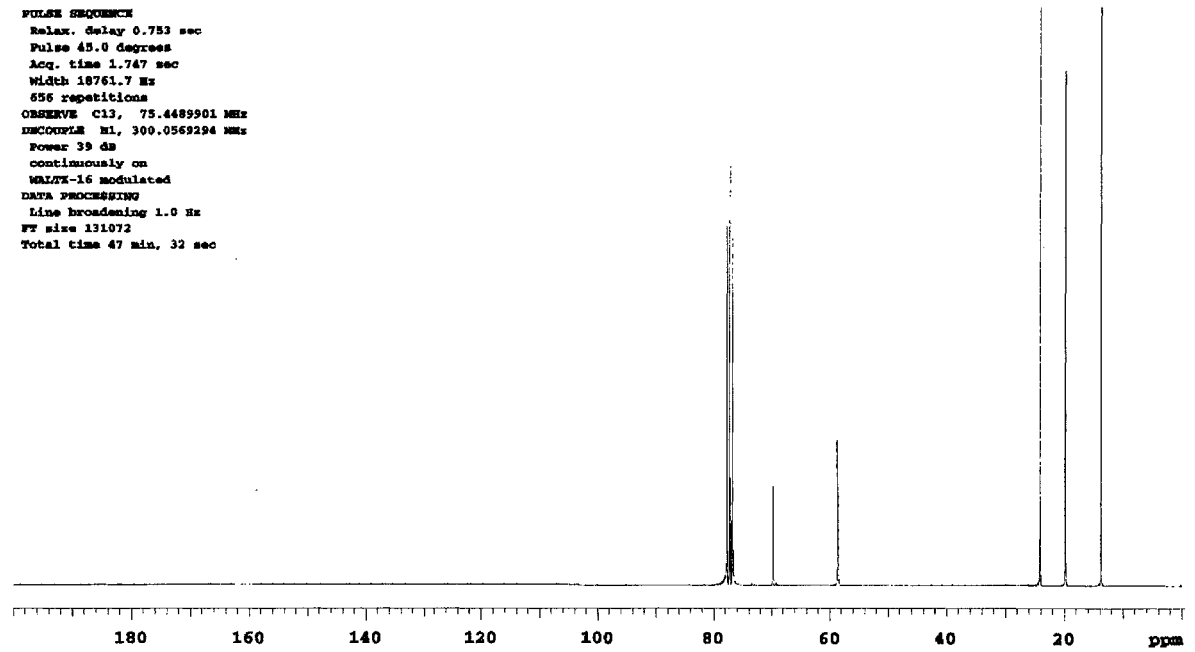
Tetra-*n*-butylammonium Ferrocenyltrifluoroborate (10g)

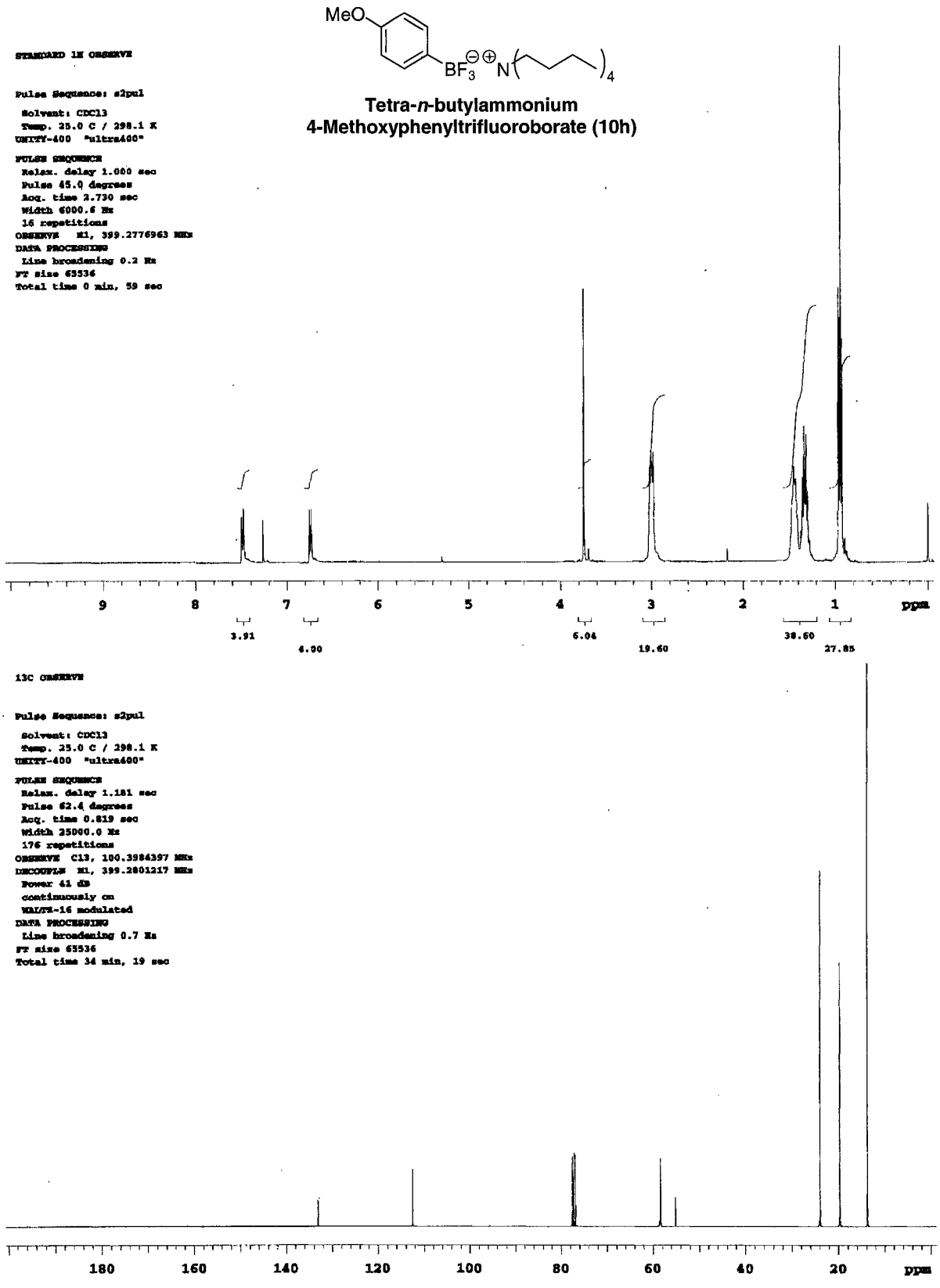
STANDARD 1H OBSERVE

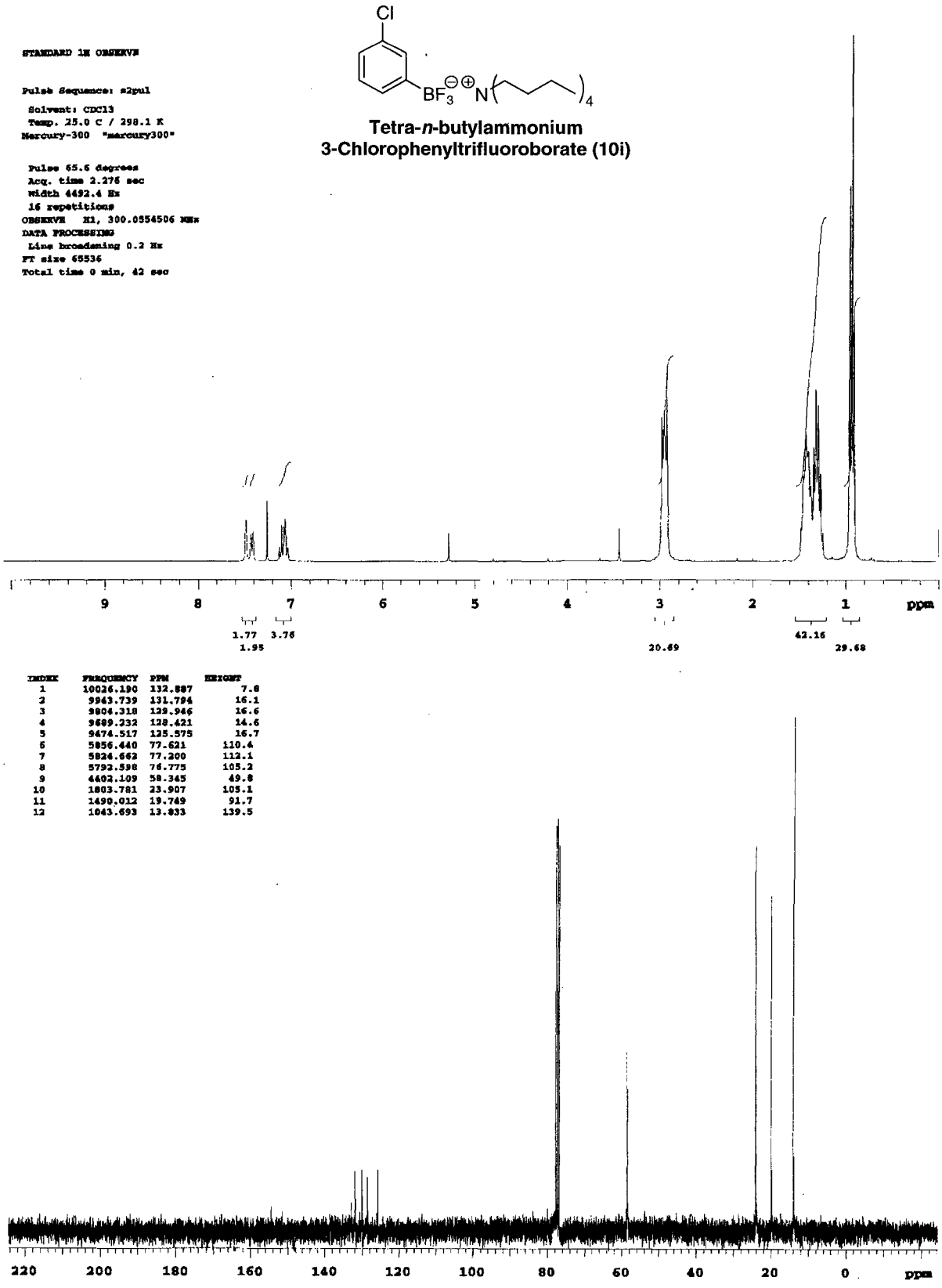
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
UNITY-400 "ultra400"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.730 sec
Width 6000.6 Hz
16 repetitions
OBSERVE H1, 399.2776959 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 59 sec

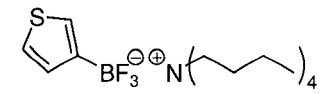
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Relax. delay 0.753 sec
Pulse 45.0 degrees
Acq. time 1.747 sec
Width 18761.7 Hz
656 repetitions
OBSERVE C13, 75.4489901 MHz
DECOUPLE H1, 300.0569294 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 47 min, 32 sec



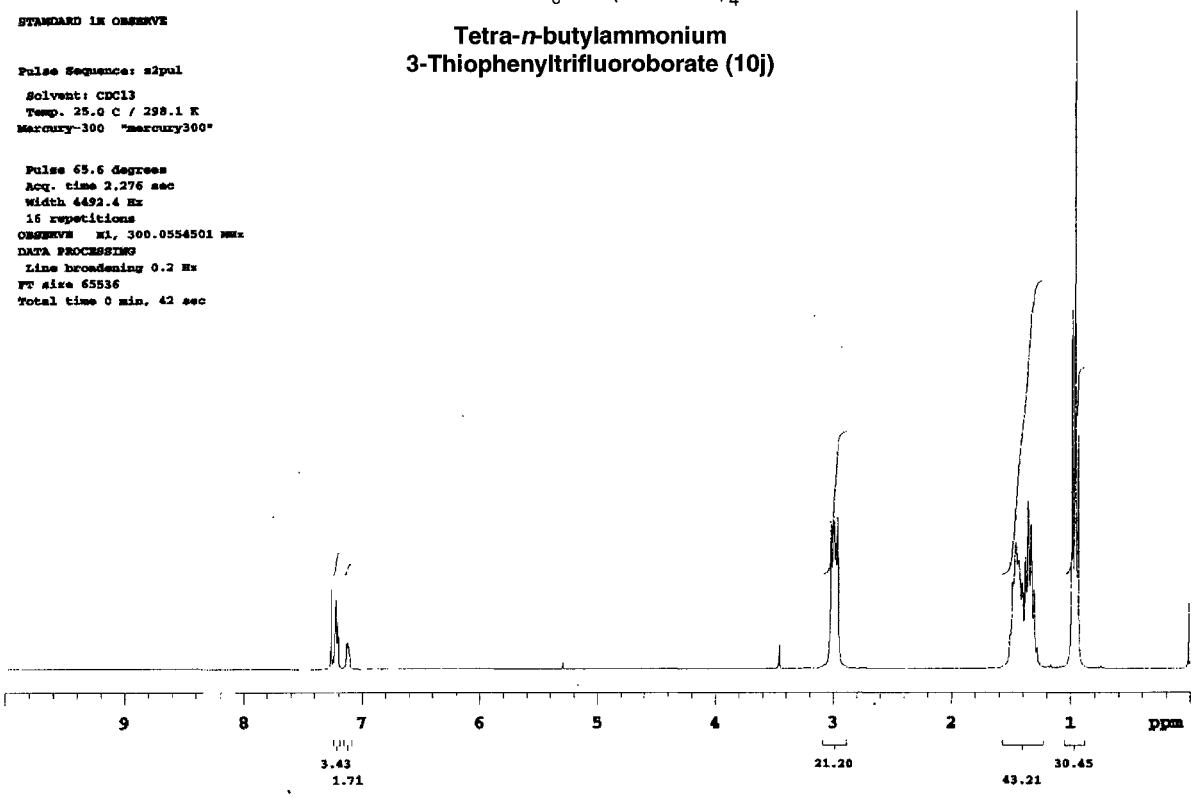

MeO
BF3
N
4
Tetra-n-butylammonium
4-Methoxyphenyltrifluoroborate (10h)
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
UNITY-400 "ultra400"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.730 sec
Width 6000.6 Hz
16 repetitions
OBSERVE H1, 399.2776963 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 59 sec
9
8
7
6
5
4
3
2
1
ppm
3.91
4.00
6.04
19.60
38.60
27.85
13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
UNITY-400 "ultra400"
PULSE SEQUENCE
Relax. delay 1.181 sec
Pulse 62.4 degrees
Acq. time 0.819 sec
Width 25000.0 Hz
176 repetitions
OBSERVE C13, 100.3984397 MHz
DECOUPLE H1, 399.2801217 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.7 Hz
FT size 65536
Total time 34 min, 19 sec
180
160
140
120
100
80
60
40
20
ppm


Cl
BF3
N
4
Tetra-n-butylammonium
3-Chlorophenyltrifluoroborate (10i)
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 65.6 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0554506 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec
9
8
7
6
5
4
3
2
1
ppm
1.77
3.76
1.95
20.69
42.16
29.68
INDEX FREQUENCY PPM HEIGHT
1 10026.190 132.887 7.8
2 9963.739 131.794 16.1
3 9804.318 129.946 16.6
4 9689.232 128.421 14.6
5 9474.517 125.575 16.7
6 5856.440 77.621 110.4
7 5824.662 77.200 112.1
8 5792.598 76.775 105.2
9 4402.109 58.345 49.8
10 1803.781 23.907 105.1
11 1490.012 19.749 91.7
12 1043.693 13.833 139.5
220
200
180
160
140
120
100
80
60
40
20
0
ppm

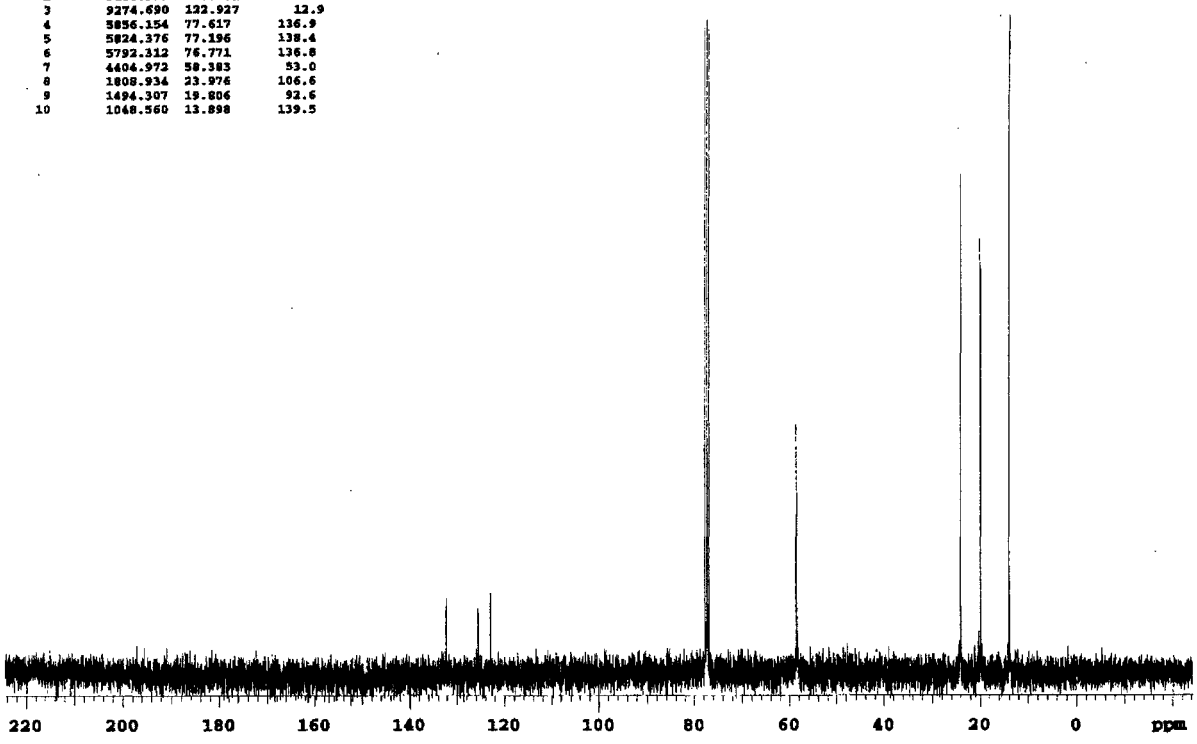


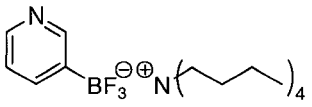
Tetra-*n*-butylammonium 3-Thiophenyltrifluoroborate (10j)

```
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Mercury-300  "mercury300"

 Pulse 65.6 degrees
 Acq. time 2.276 sec
 Width 4492.4 Hz
 16 repetitions
OBSERVE    H1, 300.0554501 MHz
DATA PROCESSING
 Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec
```



INDEX	FREQUENCY	PPM	HEIGHT
1	9876.372	132.200	12.1
2	9465.929	125.461	9.7
3	9274.690	122.927	12.9
4	5856.154	77.617	136.9
5	5824.376	77.196	138.4
6	5792.312	76.771	136.8
7	4404.972	58.383	53.0
8	1808.934	23.976	106.6
9	1494.307	19.806	92.6
10	1048.560	13.898	139.5





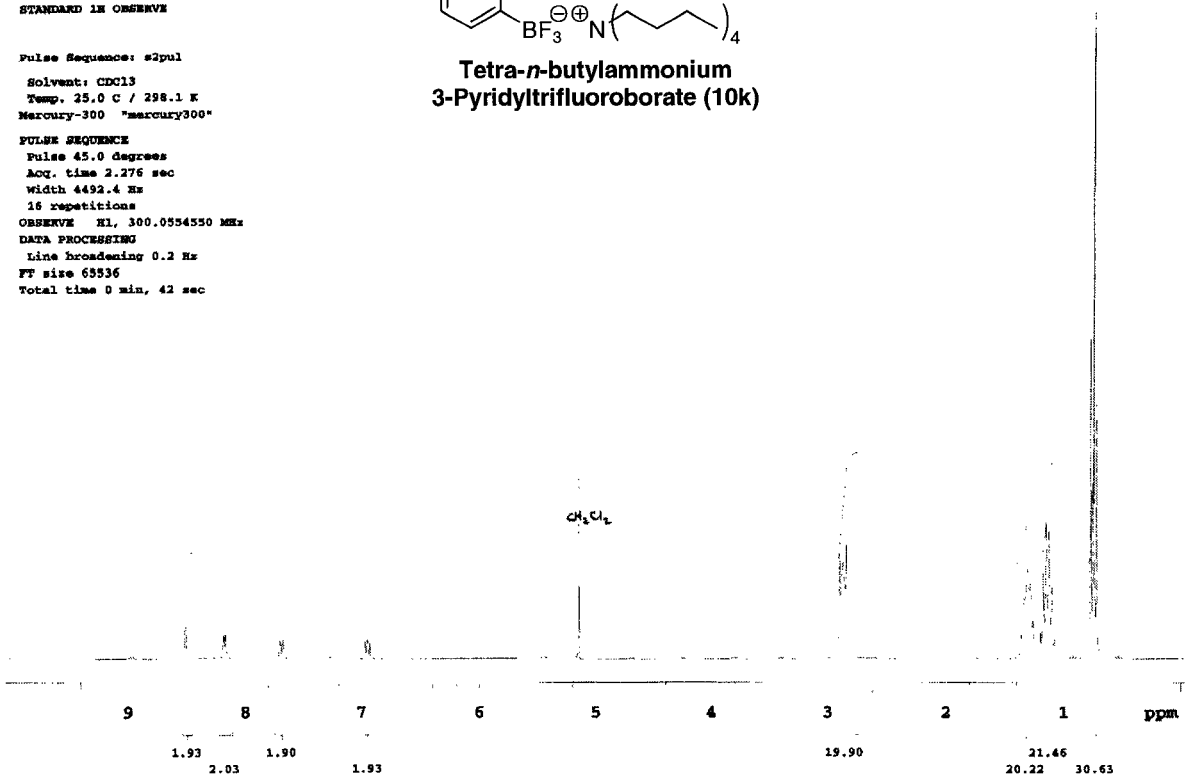
Tetra-*n*-butylammonium 3-Pyridyltrifluoroborate (10k)

STANDARD 1H OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"

PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0554550 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec

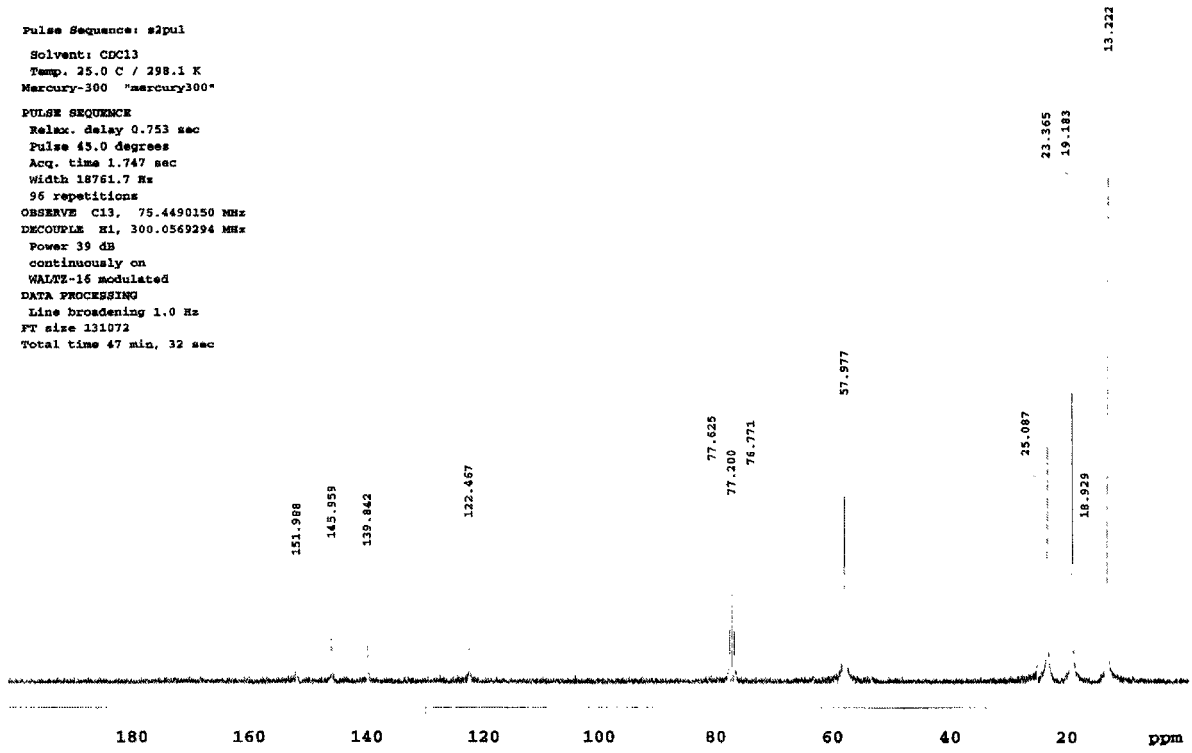


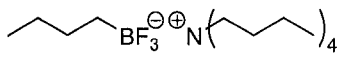
13C OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"

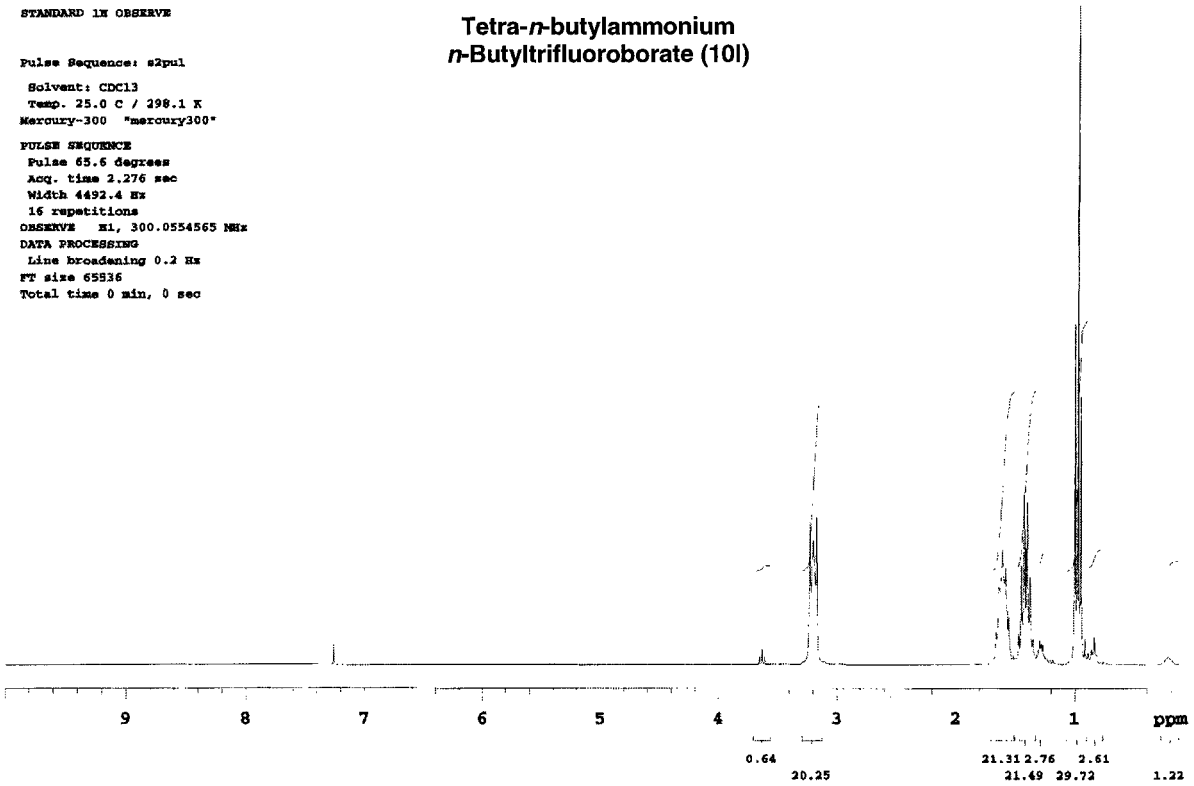
PULSE SEQUENCE
Relax. delay 0.753 sec
Pulse 45.0 degrees
Acq. time 1.747 sec
Width 18761.7 Hz
96 repetitions
OBSERVE C13, 75.4490150 MHz
DECOUPLE H1, 300.0569294 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 47 min, 32 sec





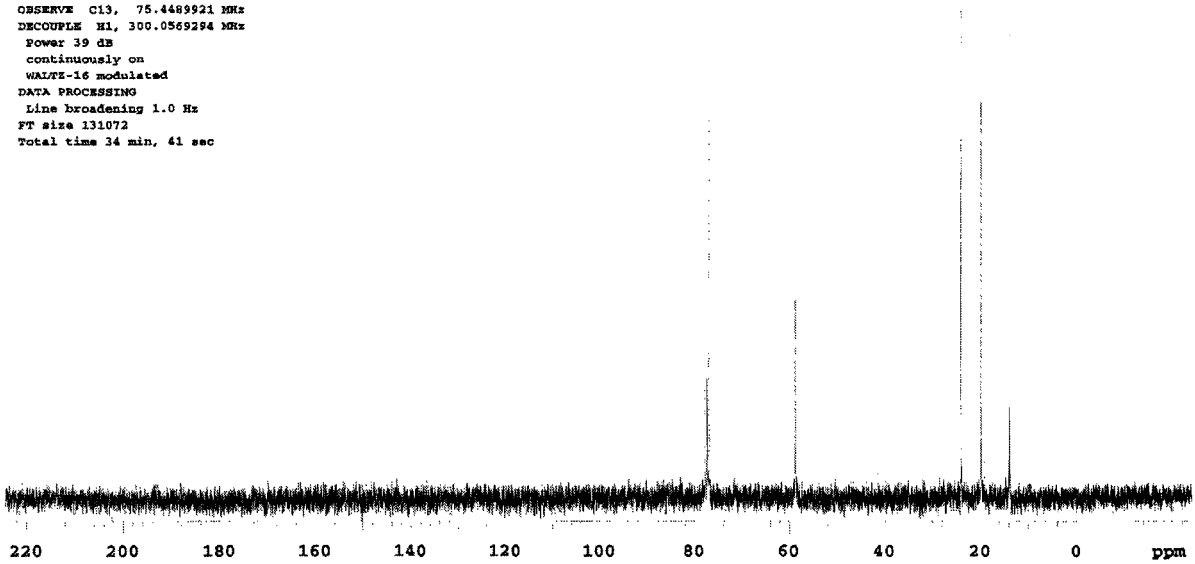
Tetra-*n*-butylammonium *n*-Butyltrifluoroborate (10l)

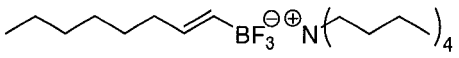
```
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Mercury-300  "mercury300"
PULSE SEQUENCE
 Pulse 65.6 degrees
 Acq. time 2.276 sec
 Width 4492.4 Hz
 16 repetitions
OBSERVE   H1, 300.0554565 MHz
DATA PROCESSING
 Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 0 sec
```




```
13C OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Mercury-300  "mercury300"
PULSE SEQUENCE
 Pulse 29.1 degrees
 Acq. time 1.747 sec
 Width 18761.7 Hz
 256 repetitions
OBSERVE   C13,  75.4489921 MHz
DECOUPLE  H1, 300.0569294 MHz
 Power 39 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 34 min, 41 sec
```

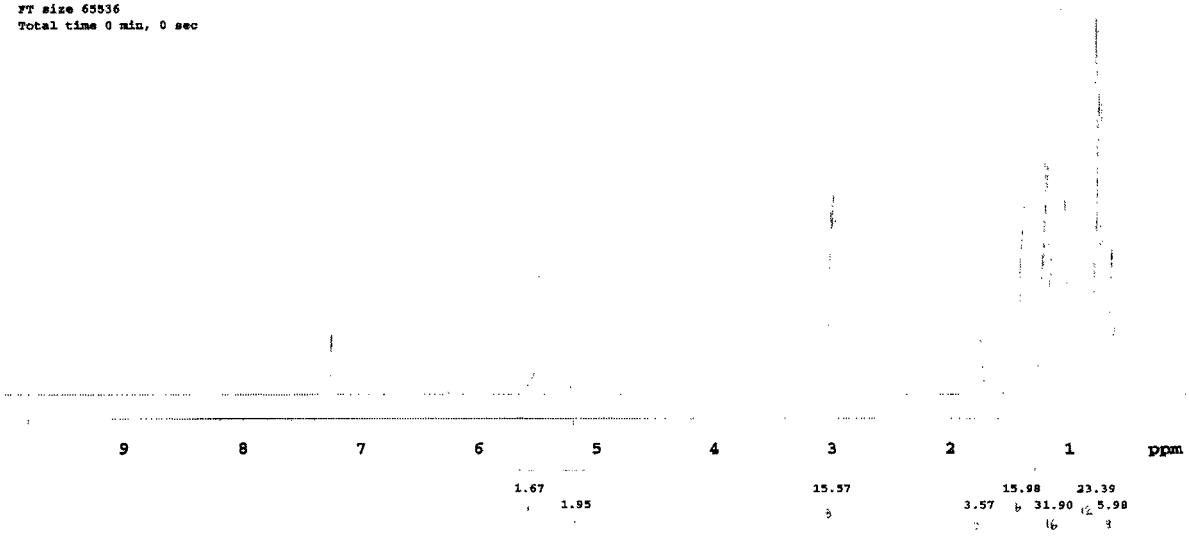
INDEX	FREQUENCY	PPM	HEIGHT
1	5856.726	77.625	119.7
2	5824.662	77.200	123.1
3	5792.598	76.775	121.5
4	4423.581	58.630	45.7
5	1807.503	23.957	104.6
6	1490.012	19.749	87.3
7	1035.677	13.727	139.5



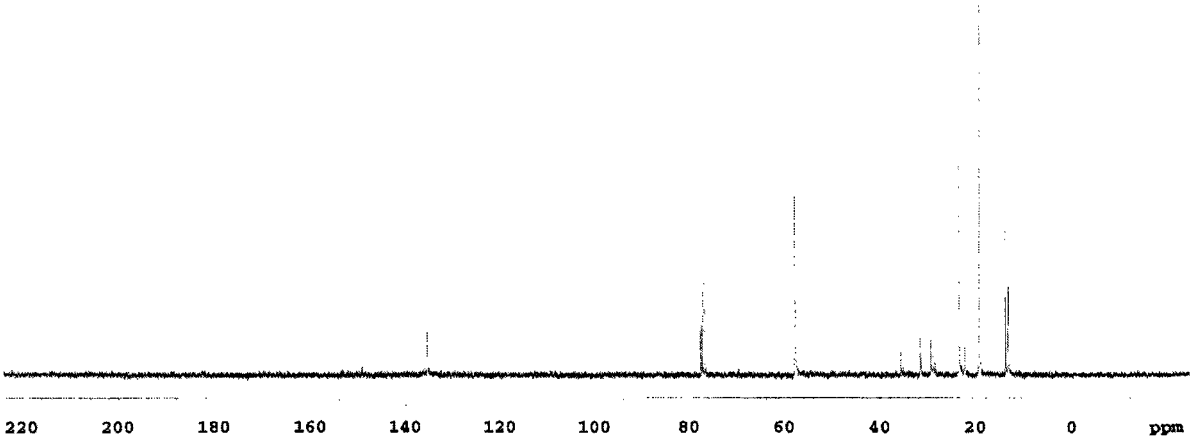


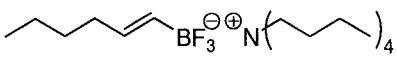
Tetra-*n*-butylammonium 1-Octenyltrifluoroborate (10m)

```
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Mercury-300  "mercury300"

 Pulse 22.9 degrees
 Acq. time 2.276 sec
 Width 4492.4 Hz
 16 repetitions
OBSERVE   H1, 300.0554525 MHz
DATA PROCESSING
 Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 0 sec
```



INDEX	FREQUENCY	PPM	HEIGHT
1	10215.427	135.395	9.4
2	10211.133	135.338	9.9
3	5857.015	77.629	20.0
4	5839.552	77.397	10.5
5	5824.665	77.200	22.7
6	5792.315	76.771	20.4
7	4360.028	57.788	42.4
8	2684.112	35.575	22.7
9	2377.500	31.511	34.1
10	2212.600	29.326	22.5
11	2176.528	28.848	32.9
12	1766.567	23.414	78.7
13	1678.677	22.249	33.7
14	1447.645	19.187	90.5
15	1034.248	13.708	34.0
16	998.176	13.230	139.5





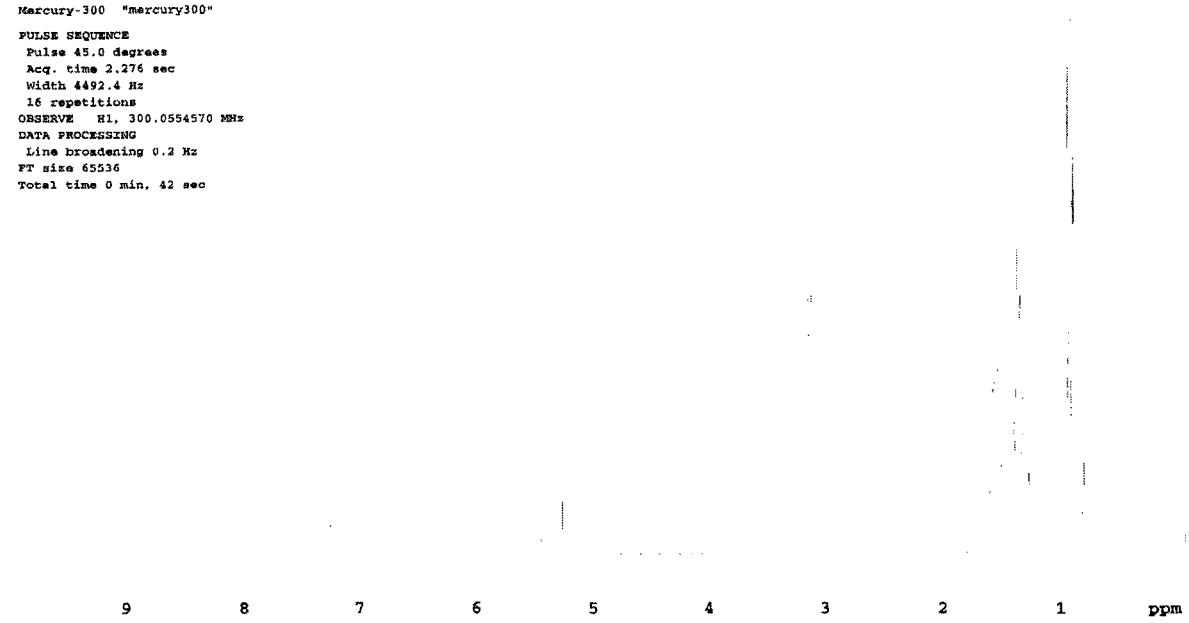
Tetra-*n*-butylammonium 1-Hexenyltrifluoroborate (10n)

STANDARD 1H OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"

PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0554570 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec

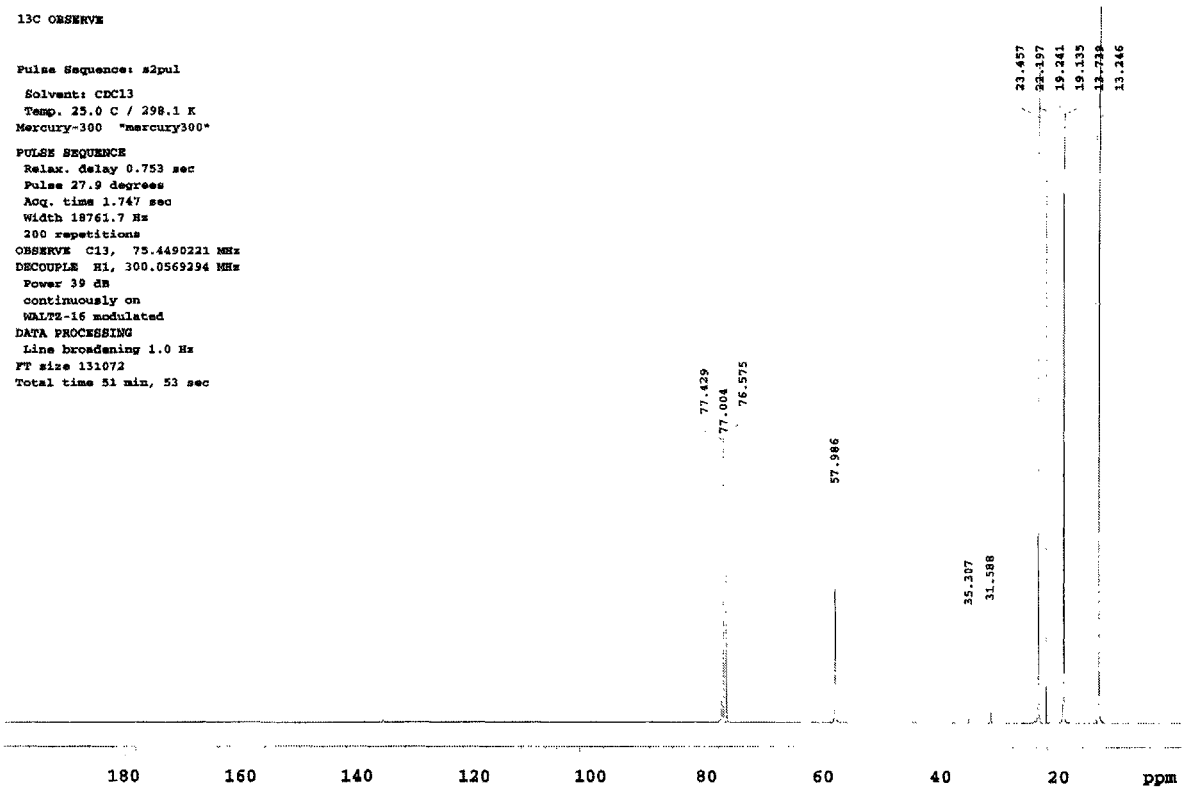


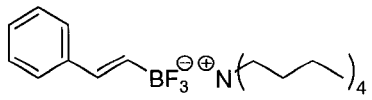
13C OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"

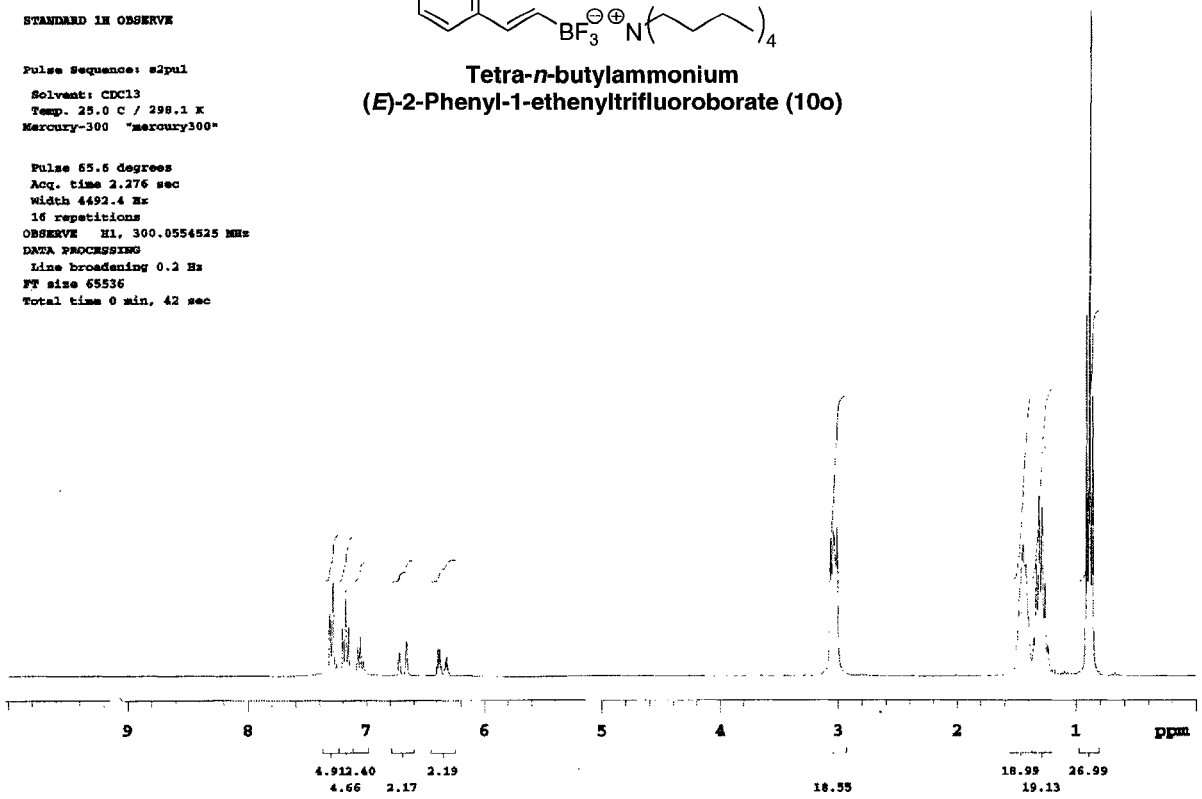
PULSE SEQUENCE
Relax. delay 0.753 sec
Pulse 27.9 degrees
Acq. time 1.747 sec
Width 18761.7 Hz
200 repetitions
OBSERVE C13, 75.4490221 MHz
DECOUPLE H1, 300.0569294 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 51 min, 53 sec



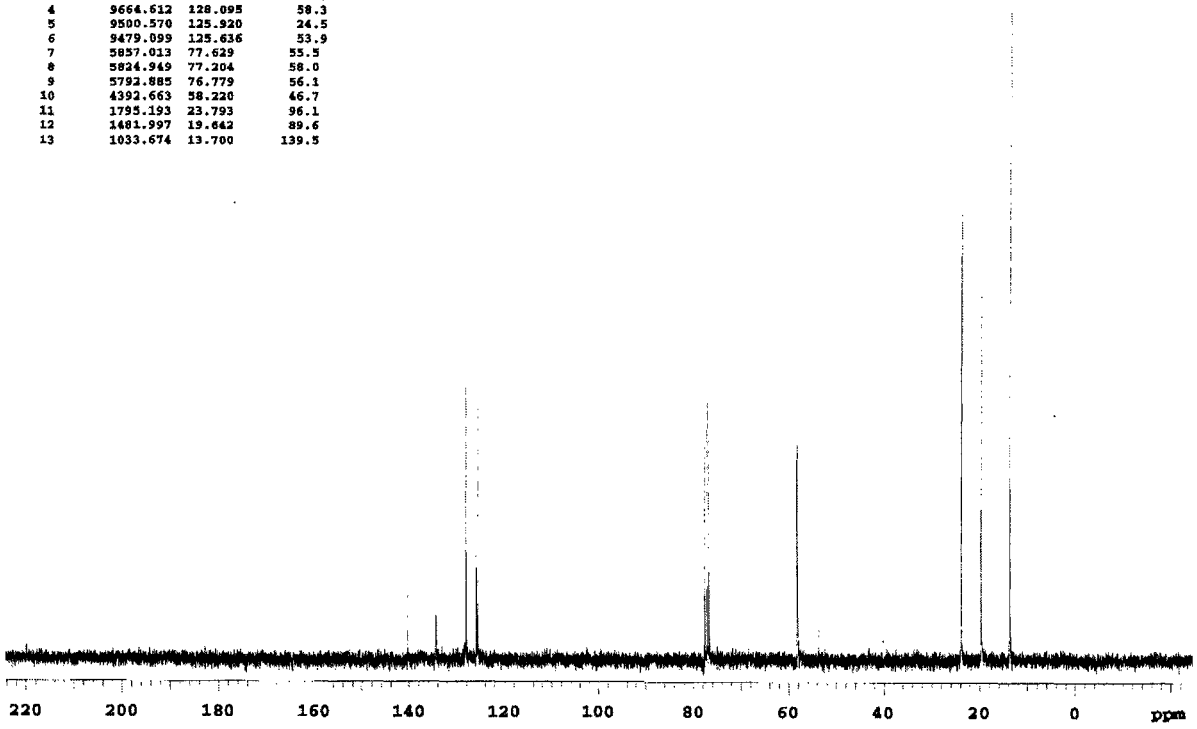


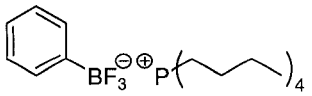
Tetra-*n*-butylammonium
(*E*)-2-Phenyl-1-ethenyltrifluoroborate (10o)

```
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Mercury-300  "mercury300"

 Pulse 65.6 degrees
 Acq. time 2.276 sec
 Width 4492.4 Hz
 16 repetitions
OBSERVE   H1, 300.0554525 MHz
DATA PROCESSING
 Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec
```



INDEX	FREQUENCY	PPM	HEIGHT
1	10591.032	140.373	15.5
2	10144.713	134.458	9.2
3	10140.418	134.401	9.3
4	9664.612	128.095	58.3
5	9500.570	125.920	24.5
6	9479.099	125.636	53.9
7	5857.013	77.629	55.5
8	5824.949	77.204	58.0
9	5792.885	76.779	56.1
10	4392.663	58.220	46.7
11	1795.193	23.793	96.1
12	1481.997	19.642	89.6
13	1033.674	13.700	139.5

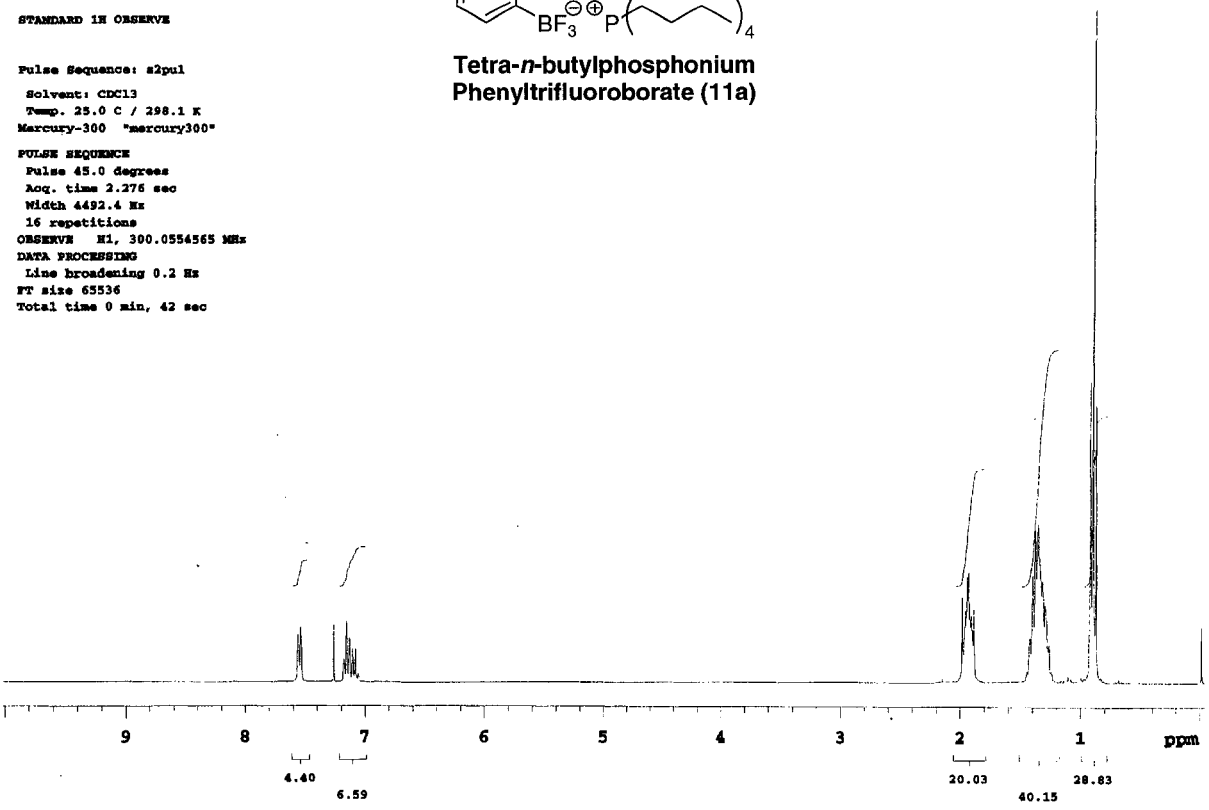




Tetra-*n*-butylphosphonium Phenyltrifluoroborate (11a)

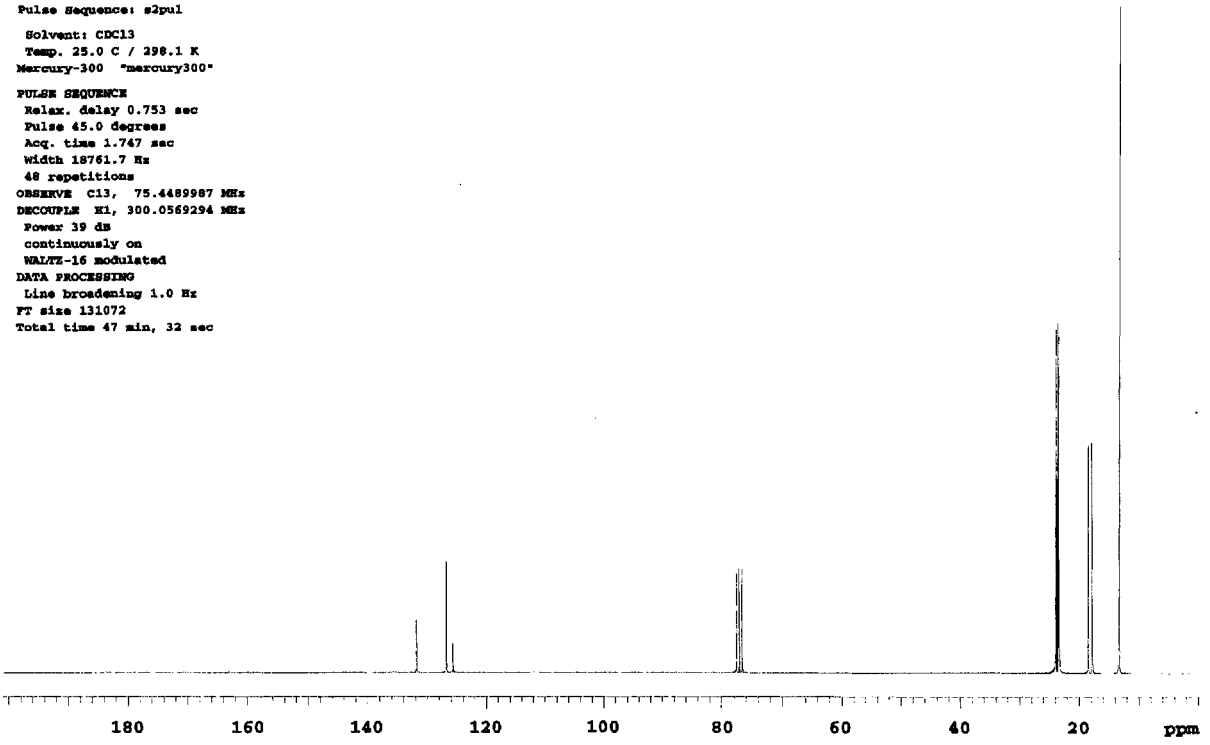
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0554565 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec



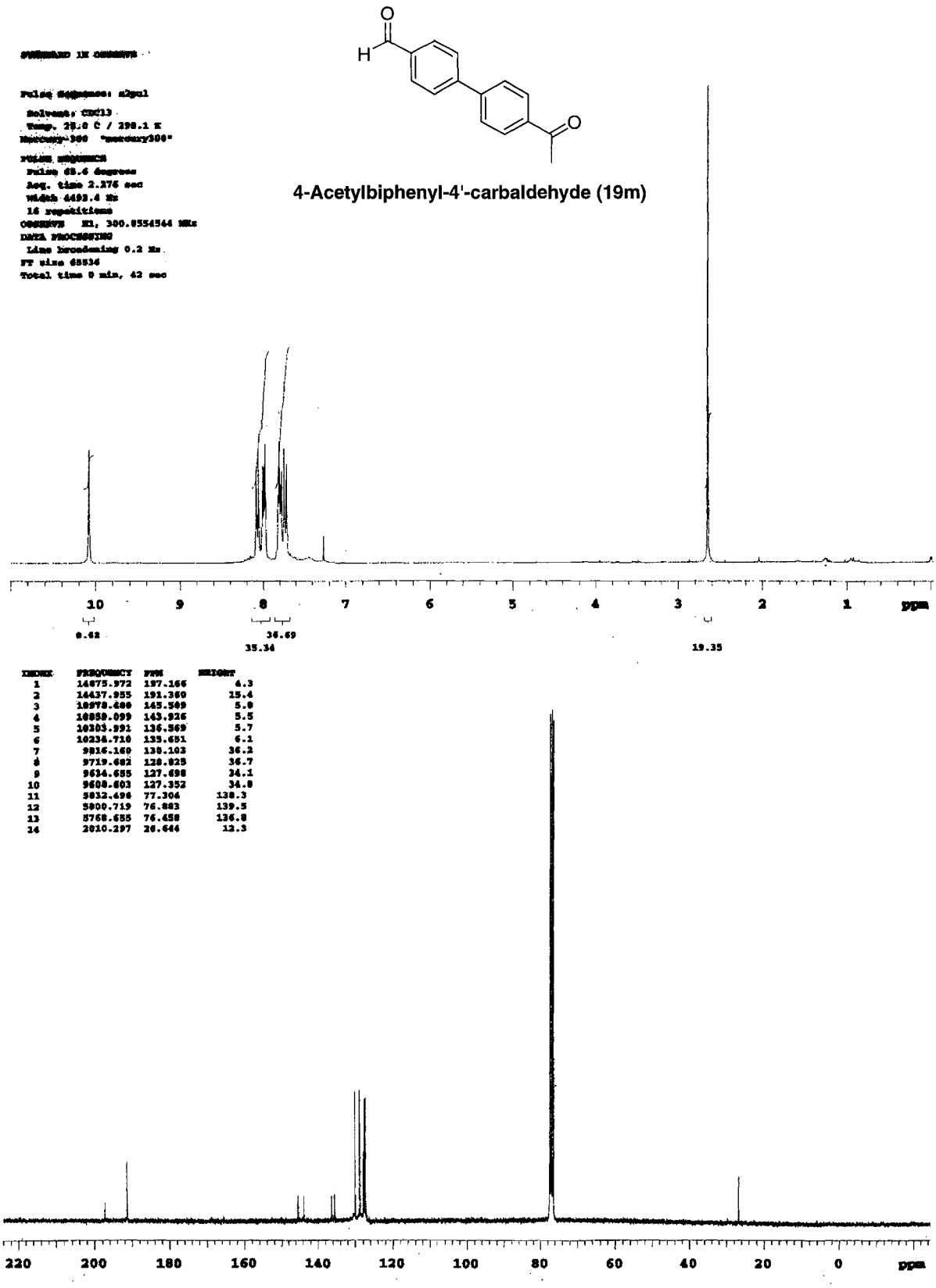
13C OBSERVE

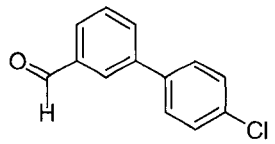
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Relax. delay 0.753 sec
Pulse 45.0 degrees
Acq. time 1.747 sec
Width 18761.7 Hz
48 repetitions
OBSERVE C13, 75.4489987 MHz
DECOUPLE H1, 300.0569294 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 47 min, 32 sec



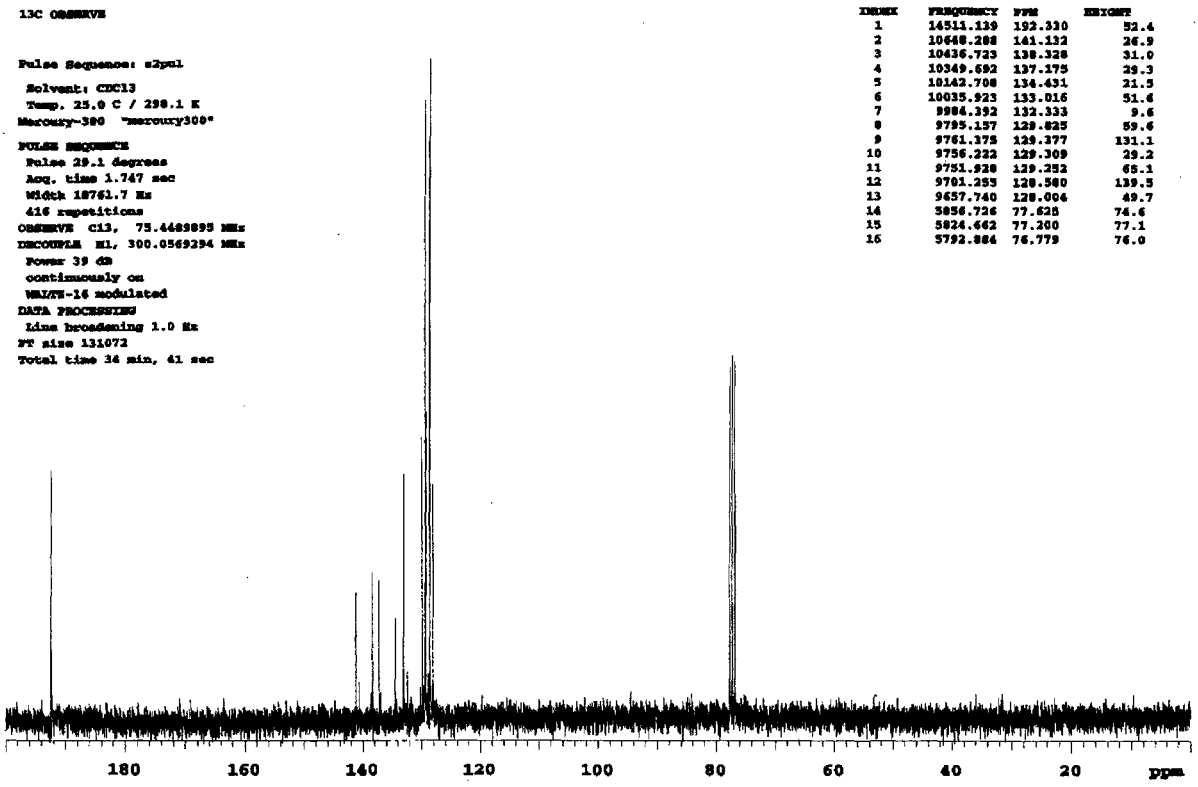
Appendix B.2

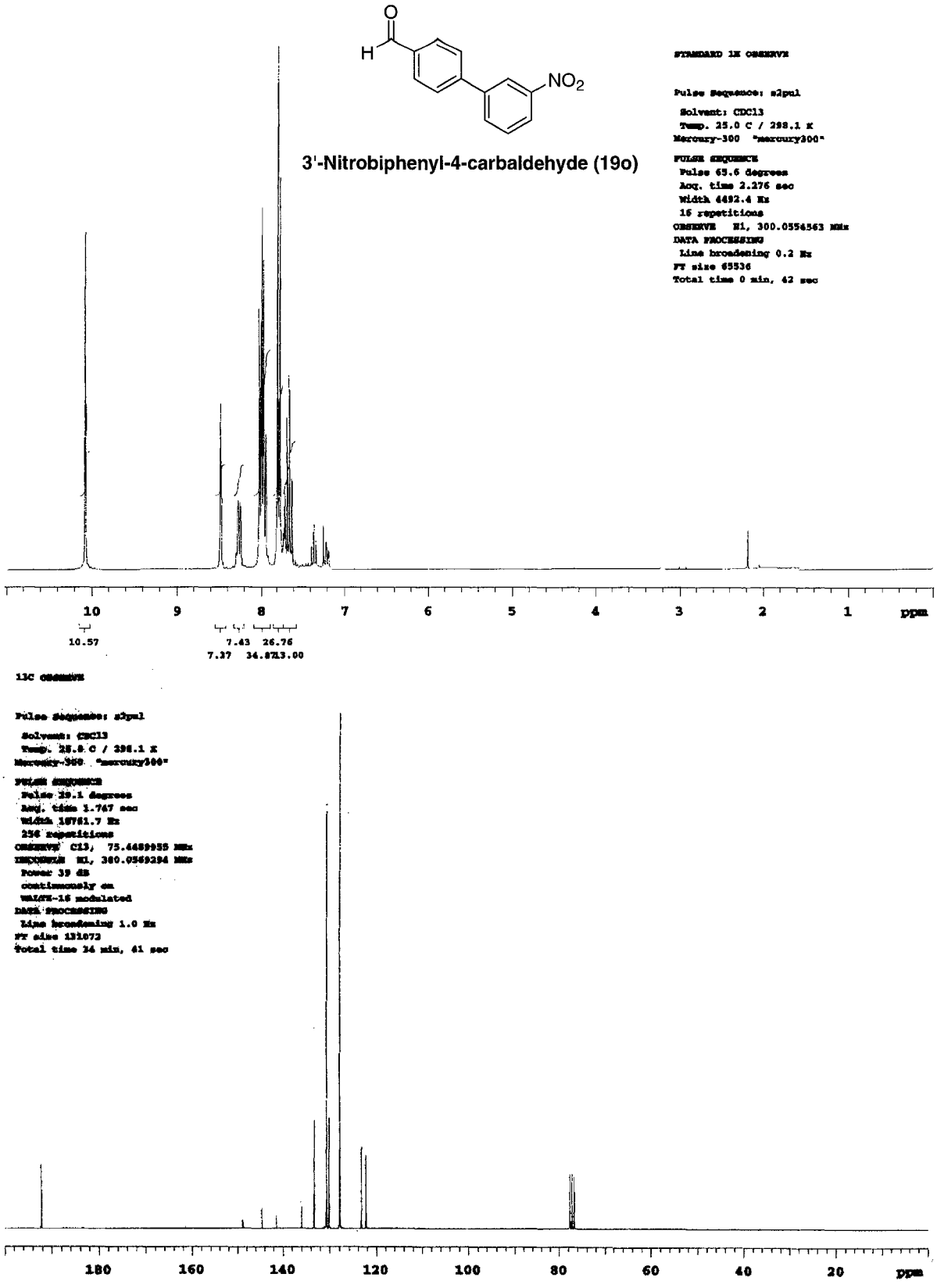
Novel Products of Suzuki-Miyaura Cross-Couplings


4-Acetylbiphenyl-4'-carbaldehyde (19m)
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Pulse 45.6 degrees
Acq. time 2.276 sec
Width 4493.4 Hz
16 repetitions
Total time 0 min, 42 sec
10 9 8 7 6 5 4 3 2 1 ppm
0.42
36.69
35.34
19.35
1 14675.972 197.166 4.3
2 14437.955 191.360 15.4
3 10978.480 145.569 5.0
4 10858.099 143.926 5.5
5 10303.991 136.369 5.7
6 10238.710 133.651 6.1
7 9816.160 128.103 36.2
8 9719.682 128.025 36.7
9 9634.685 127.698 34.1
10 9608.603 127.352 34.8
11 5812.496 77.306 138.3
12 5809.719 76.883 139.5
13 5768.655 76.458 136.8
14 2010.297 26.644 12.3
220 200 180 160 140 120 100 80 60 40 20 0 ppm



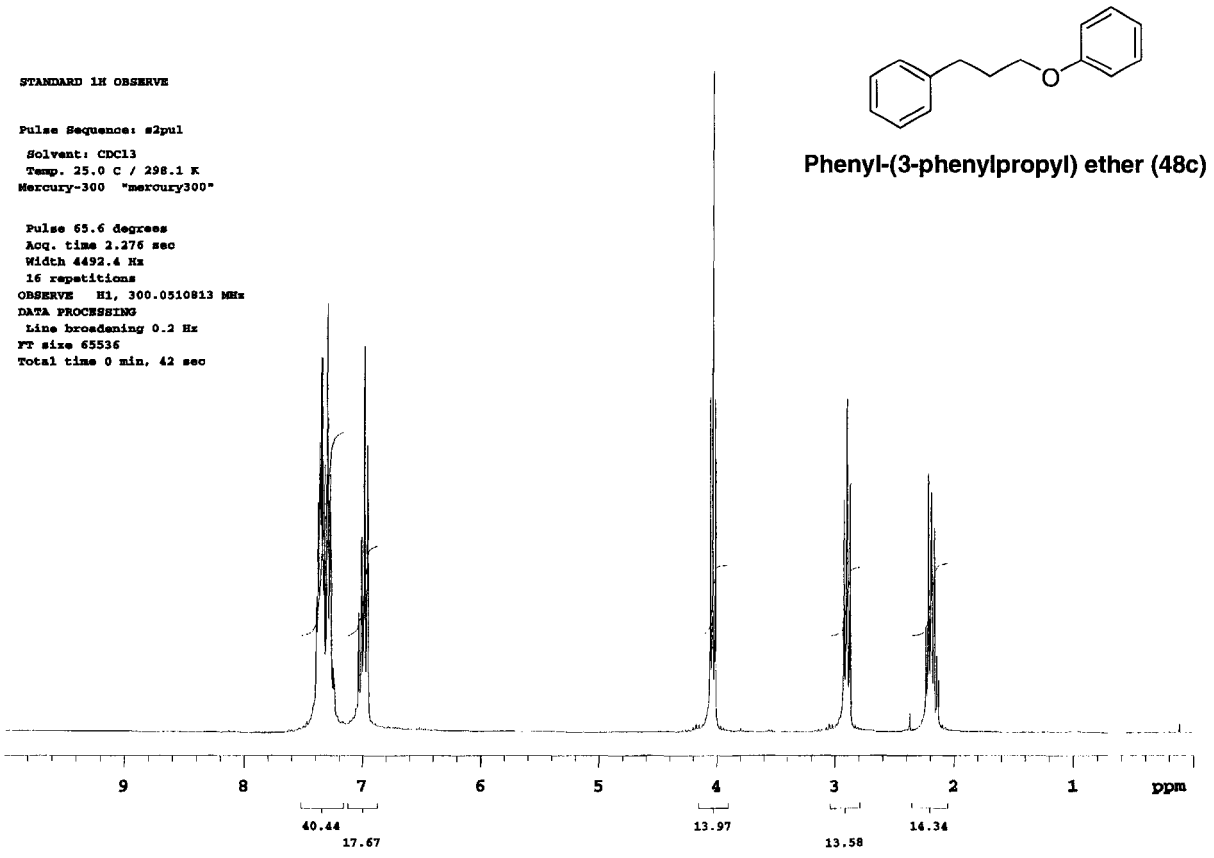
4'-Chlorobiphenyl-3-carbaldehyde (19n)

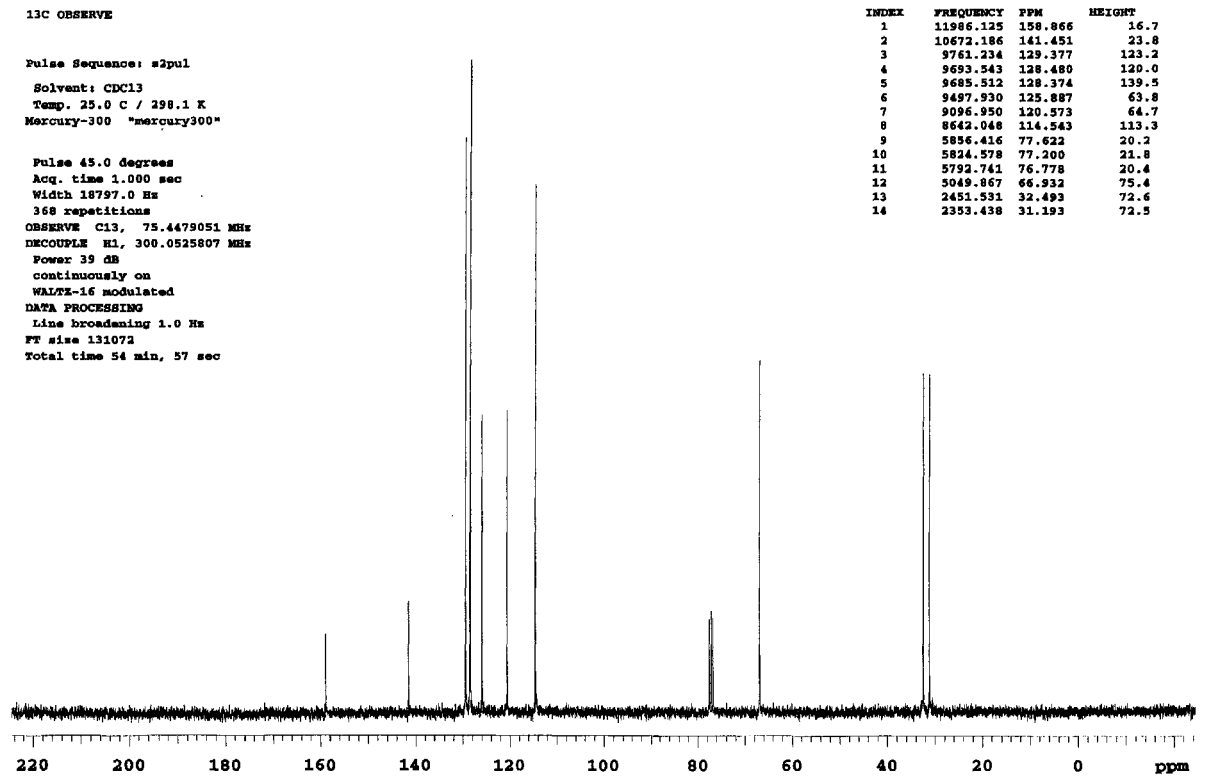



O
H
NO2
3'-Nitrobiphenyl-4-carbaldehyde (19o)
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Pulse 65.6 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0556563 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec
10
9
8
7
6
5
4
3
2
1
ppm
10.57
7.43
26.76
7.37
34.87
13.00
13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Pulse 29.1 degrees
Acq. time 1.747 sec
Width 18761.7 Hz
256 repetitions
OBSERVE C13, 75.4489955 MHz
DECOUPLE H1, 300.0569294 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 24 min, 41 sec
180
160
140
120
100
80
60
40
20
ppm

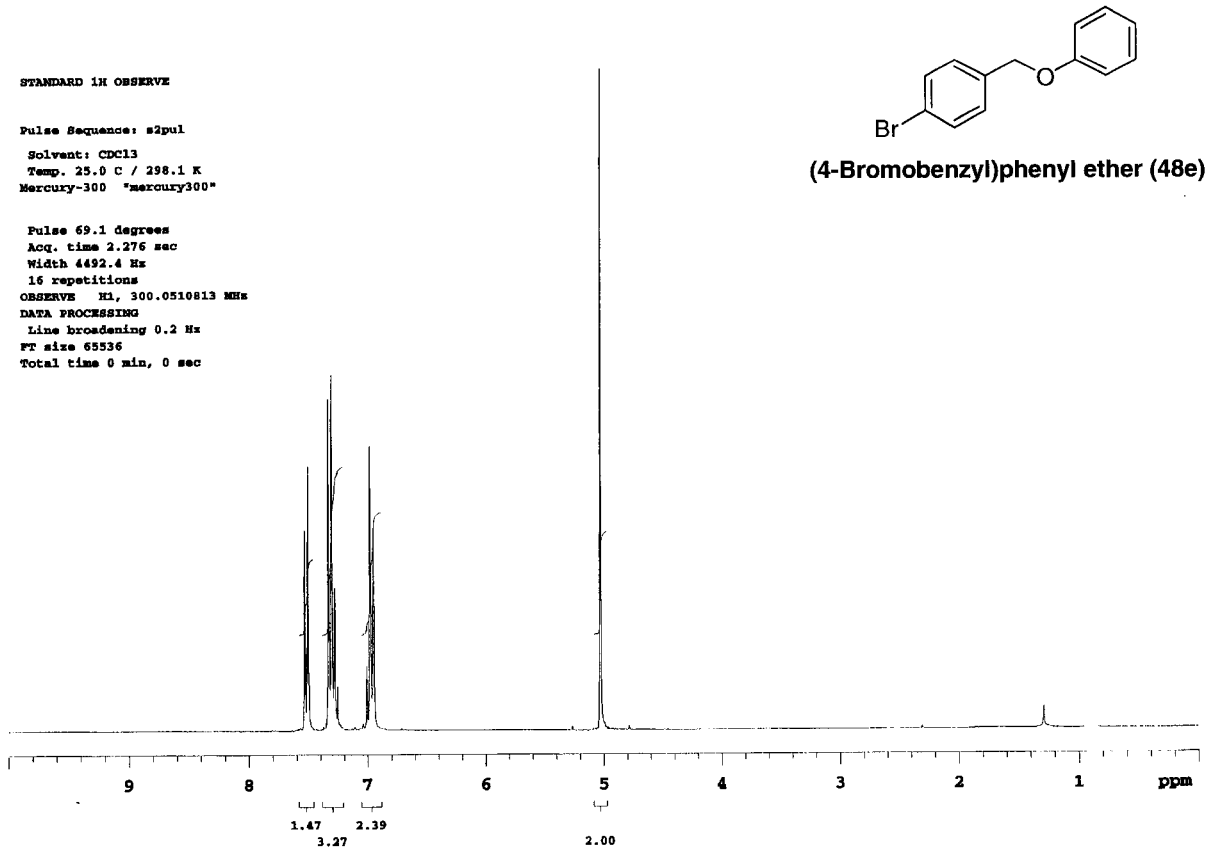
Appendix B.3

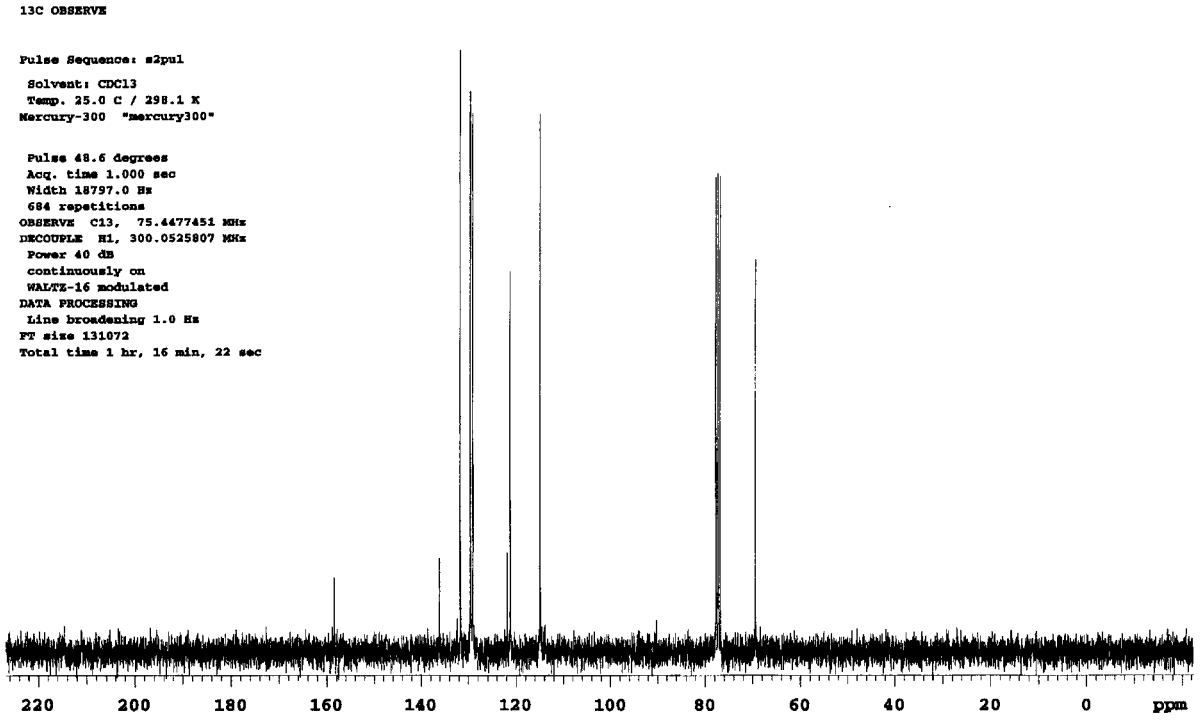
Novel Products from Arylation/Vinylation of Aliphatic Alcohols and the Vinylation of Carboxylates

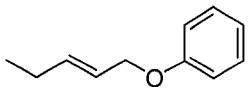




INDEX	FREQUENCY	PPM	HEIGHT
1	11986.125	158.866	16.7
2	10672.186	141.451	23.8
3	9761.234	129.377	123.2
4	9693.543	128.480	120.0
5	9685.512	128.374	139.5
6	9497.930	125.887	63.8
7	9096.950	120.573	64.7
8	8642.048	114.543	113.3
9	5856.416	77.622	20.2
10	5824.578	77.200	21.8
11	5792.741	76.778	20.4
12	5049.867	66.932	75.4
13	2451.531	32.493	72.6
14	2353.438	31.193	72.5


STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 69.1 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0510813 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 0 sec
Br
O
(4-Bromobenzyl)phenyl ether (48e)
9
8
7
6
5
4
3
2
1
ppm
1.47
2.39
3.27
2.00


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 48.6 degrees
Acq. time 1.000 sec
Width 18797.0 Hz
684 repetitions
OBSERVE C13, 75.4477451 MHz
DECOUPLE H1, 300.0525807 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 16 min, 22 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

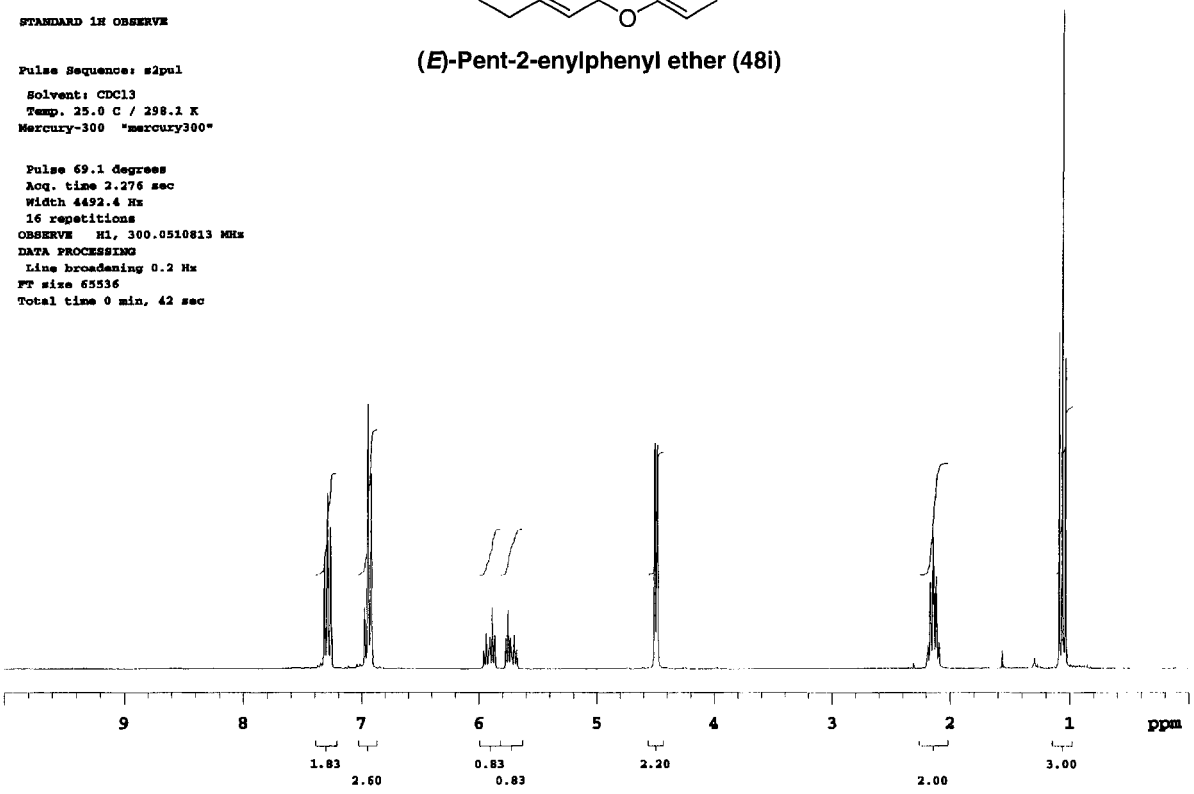


(*E*)-Pent-2-enylphenyl ether (48i)

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"

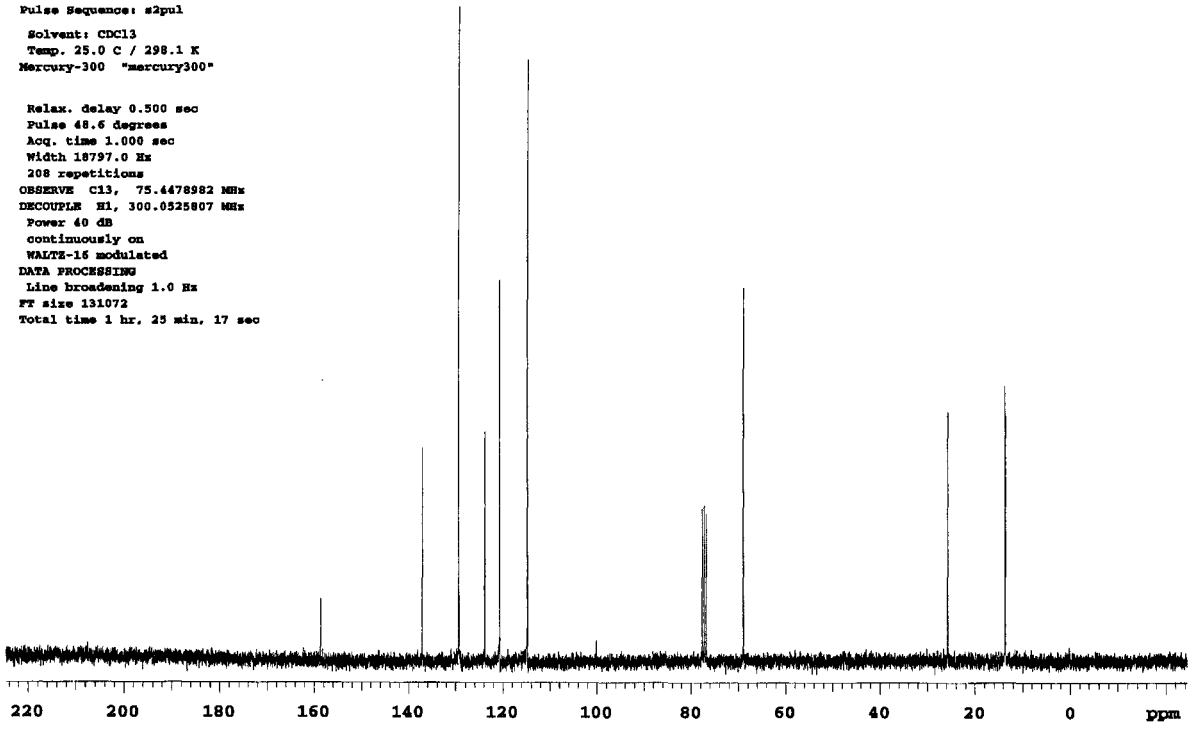
Pulse 69.1 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0510813 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec

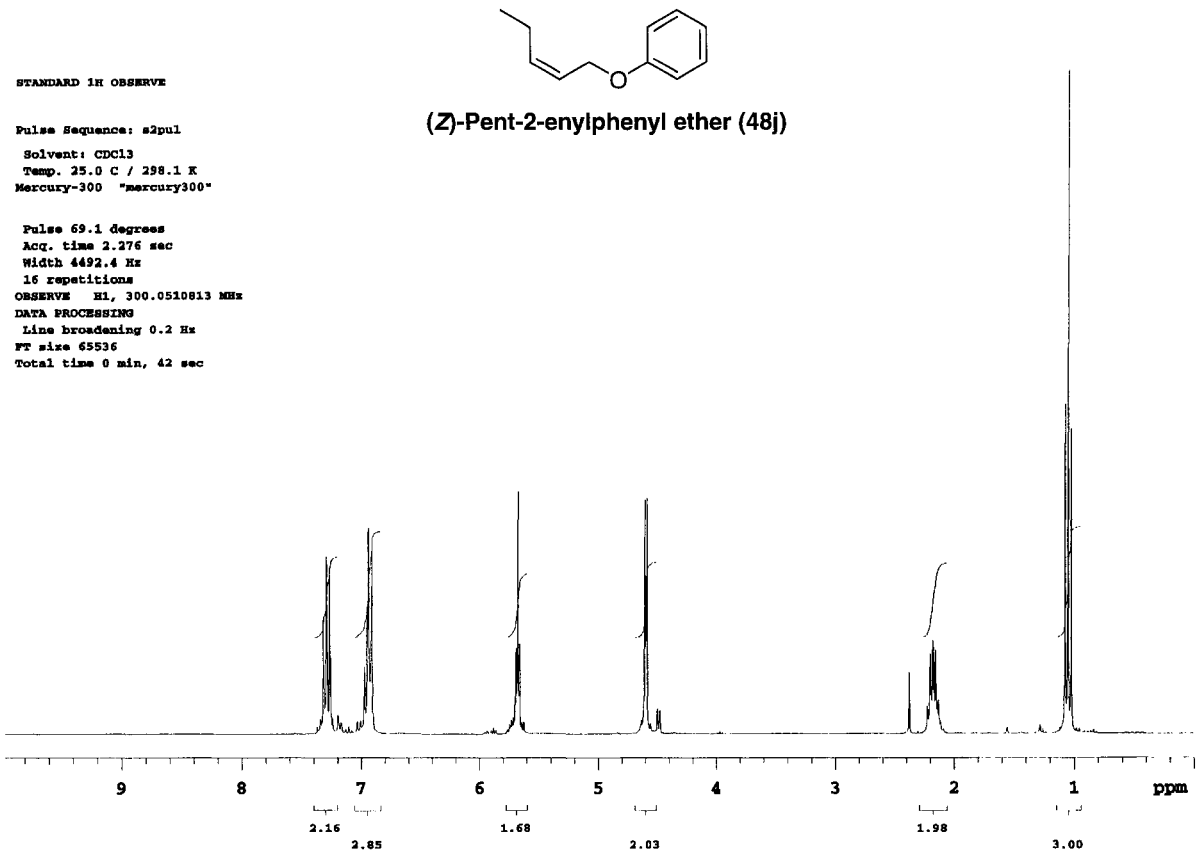


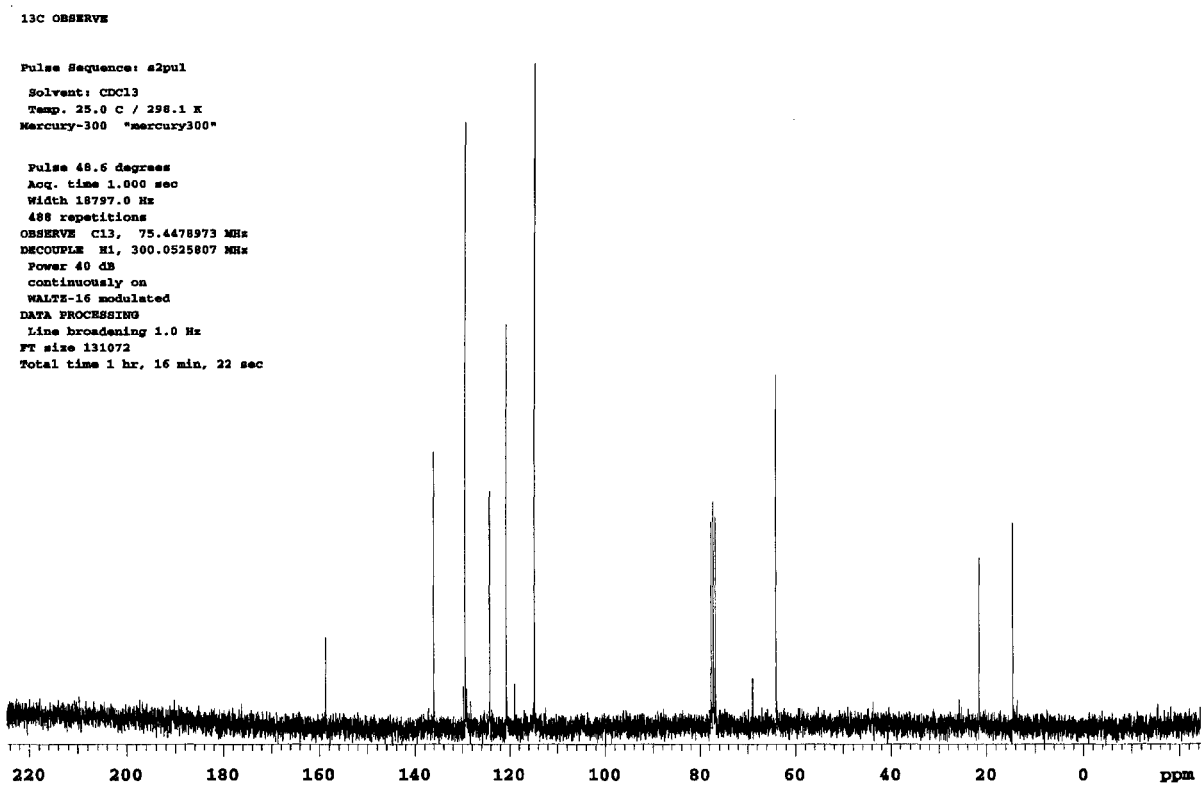
13C OBSERVE

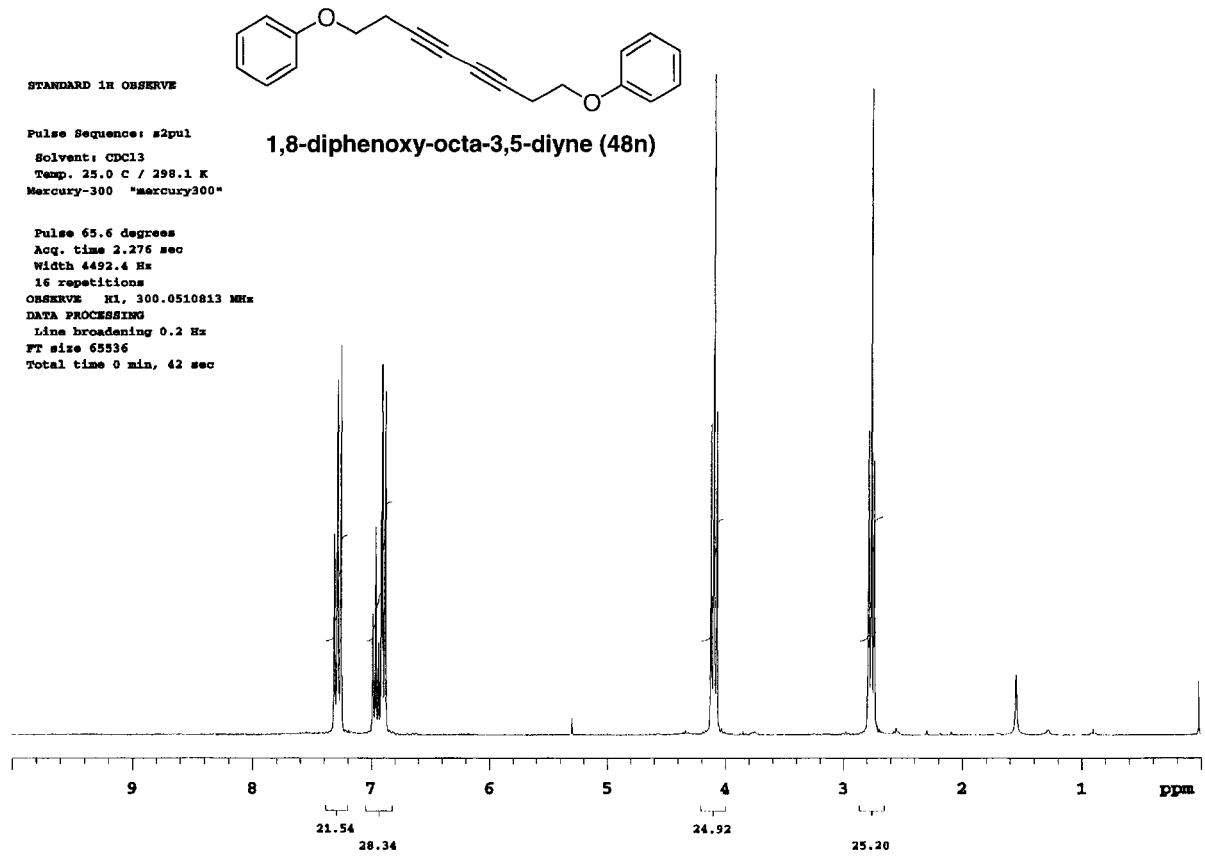
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"

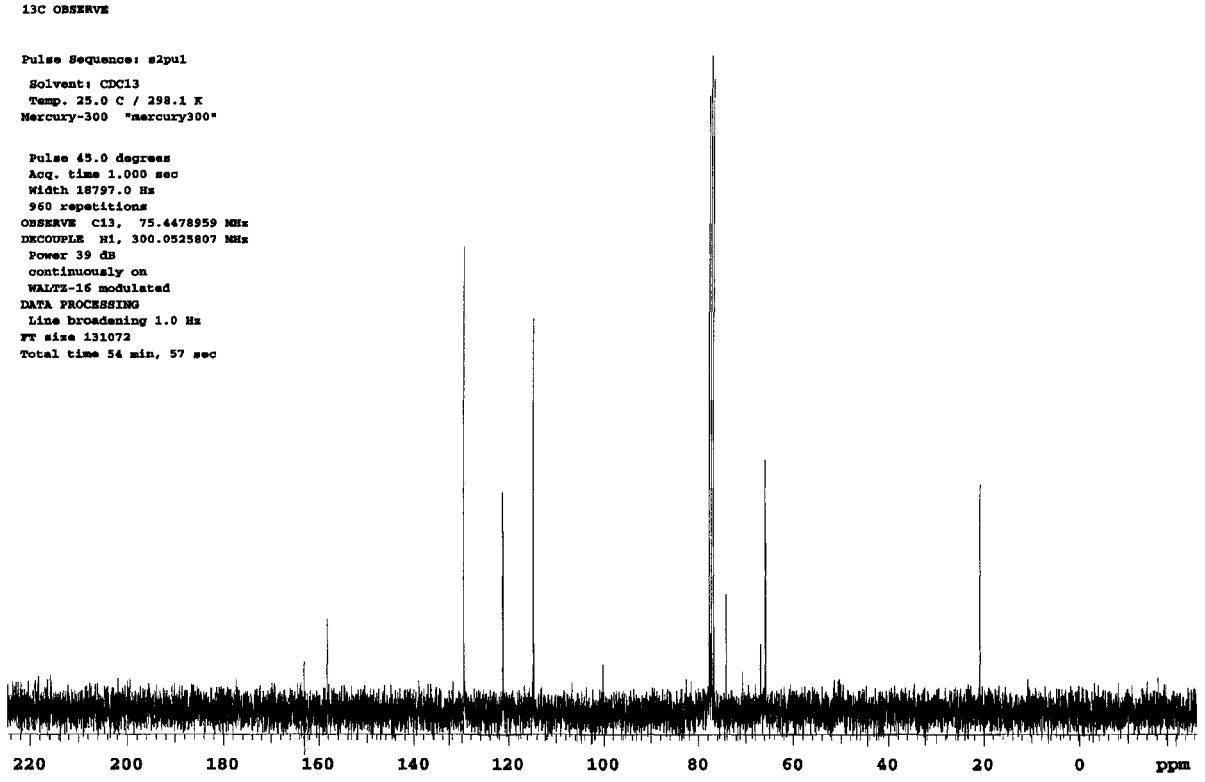
Relax. delay 0.500 sec
Pulse 48.6 degrees
Acq. time 1.000 sec
Width 18797.0 Hz
208 repetitions
OBSERVE C13, 75.4478982 MHz
DECOUPLE H1, 300.0525807 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 25 min, 17 sec

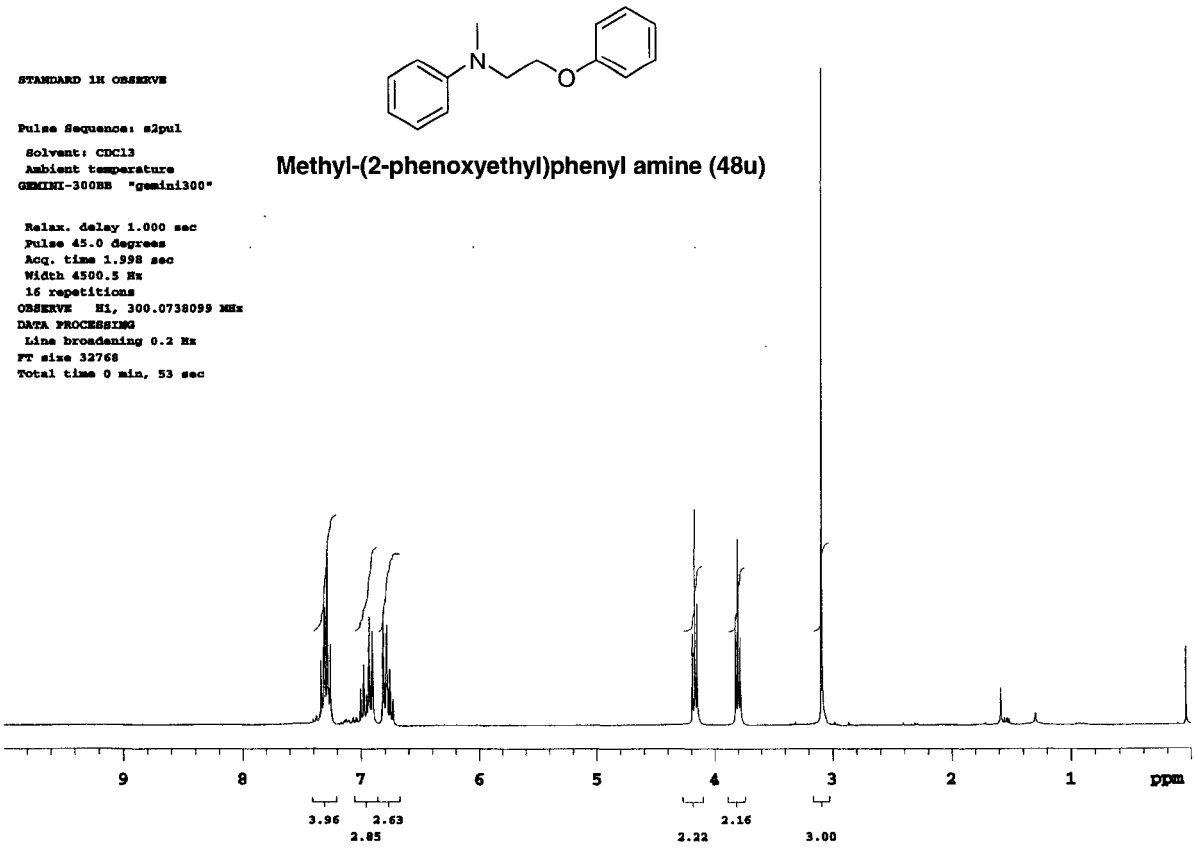


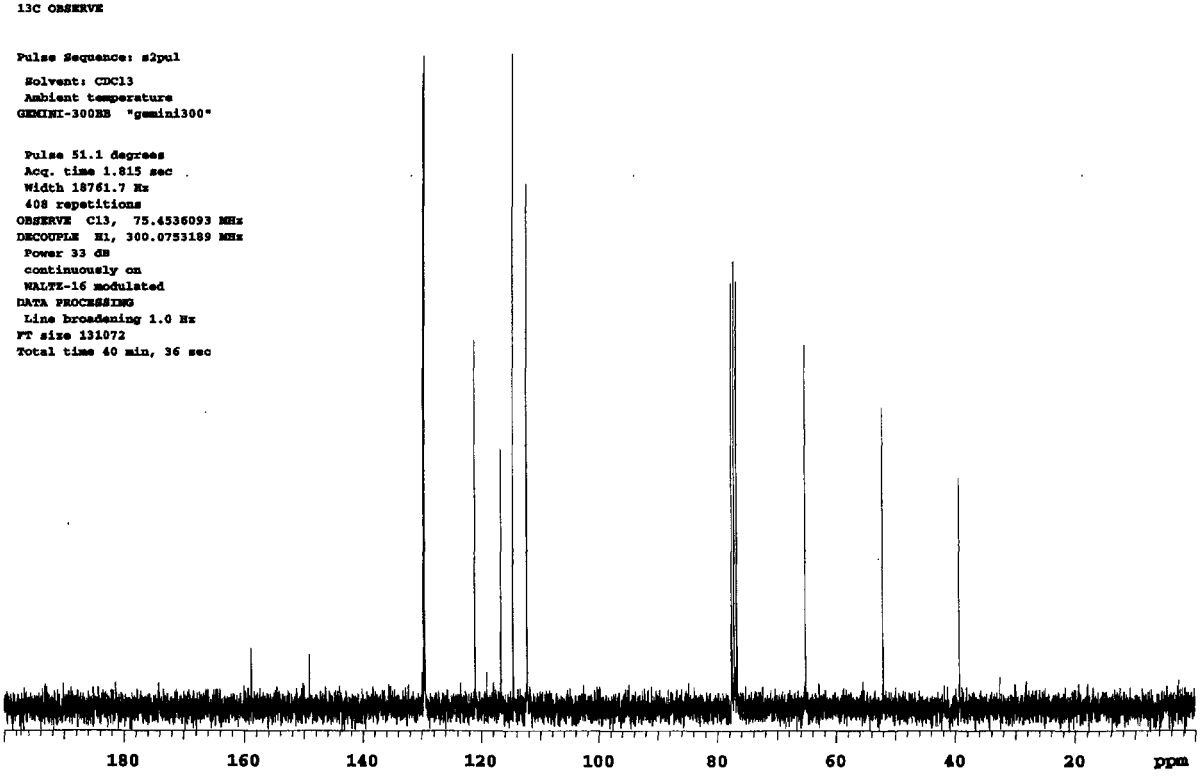

(Z)-Pent-2-enylphenyl ether (48j)
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 69.1 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0510813 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec
9
8
7
6
5
4
3
2
1
ppm
2.16
2.85
1.68
2.03
1.98
3.00

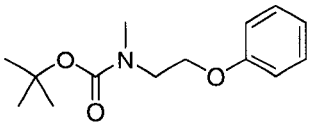

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 48.6 degrees
Acq. time 1.000 sec
Width 18797.0 Hz
488 repetitions
OBSERVE C13, 75.4478973 MHz
DECOUPLE H1, 300.0525807 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 16 min, 22 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm


1,8-diphenoxy-octa-3,5-diyne (48n)
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 65.6 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0510813 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec
9
8
7
6
5
4
3
2
1
ppm
21.54
28.34
24.92
25.20


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 45.0 degrees
Acq. time 1.000 sec
Width 18797.0 Hz
960 repetitions
OBSERVE C13, 75.4478959 MHz
DECOUPLE H1, 300.0525807 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 54 min, 57 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm


STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "gemini300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0738099 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 53 sec
Methyl-(2-phenoxyethyl)phenyl amine (48u)
9
8
7
6
5
4
3
2
1
ppm
3.96
2.63
2.85
2.22
2.16
3.00


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "gemini300"
Pulse 51.1 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
408 repetitions
OBSERVE C13, 75.4536093 MHz
DECOUPLE H1, 300.0753189 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 40 min, 36 sec
180
160
140
120
100
80
60
40
20
ppm

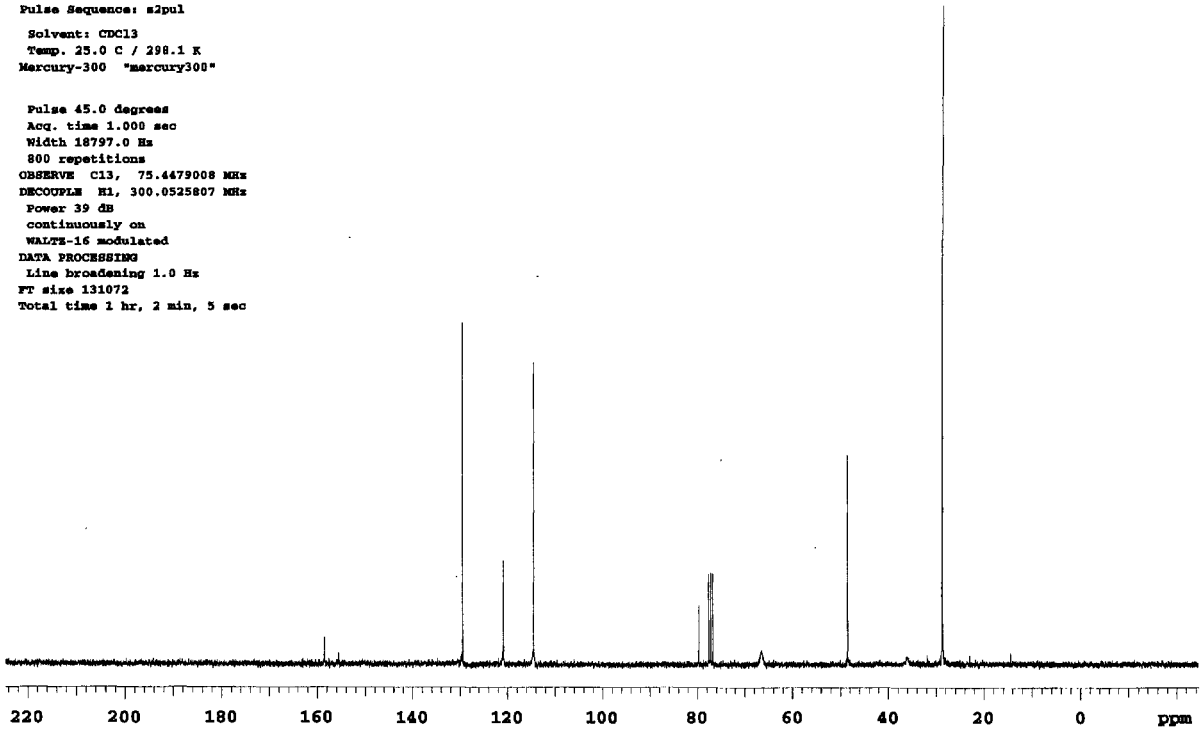


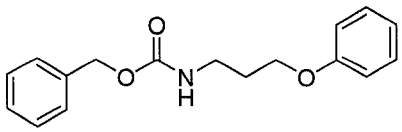
Methyl-(2-phenoxyethyl)carbamic acid *t*-butyl ester (48v)

```
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Mercury-300  "mercury300"

 Pulse 65.6 degrees
 Acq. time 2.276 sec
 Width 4492.4 Hz
 16 repetitions
OBSERVE   H1, 300.0510813 MHz
DATA PROCESSING
 Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 0 sec
```

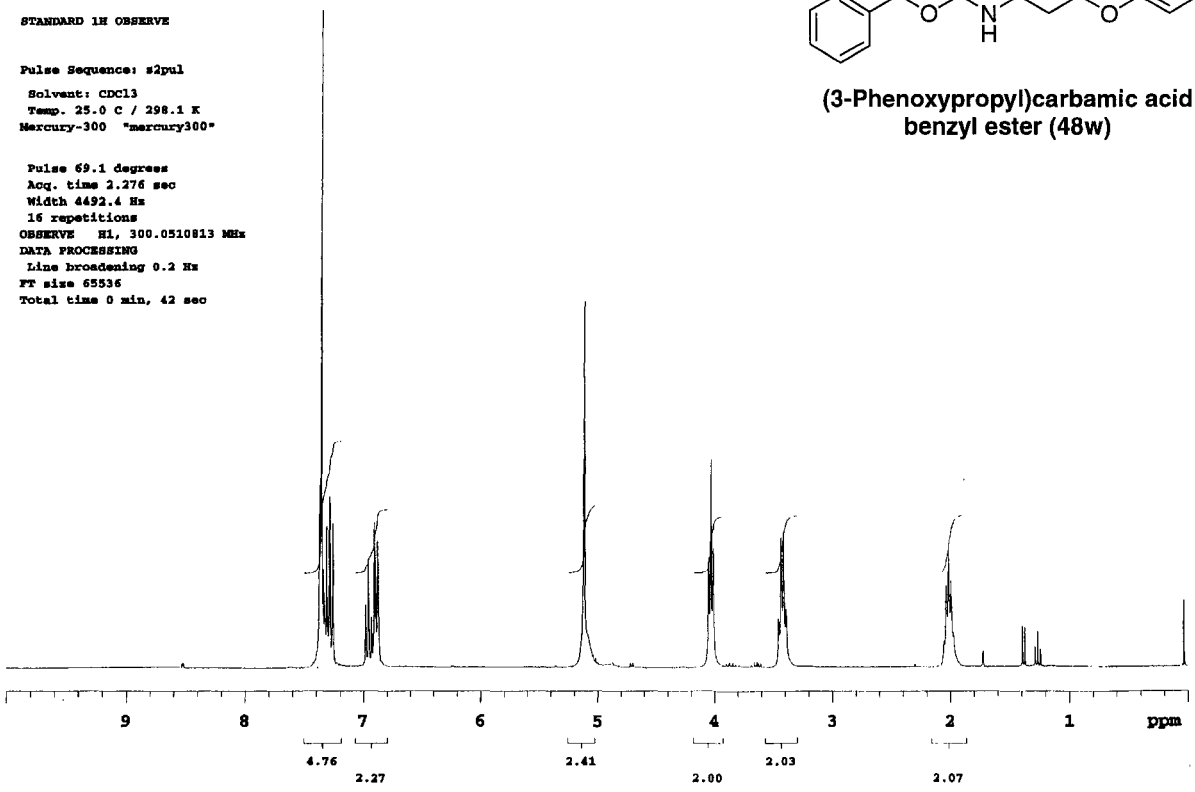


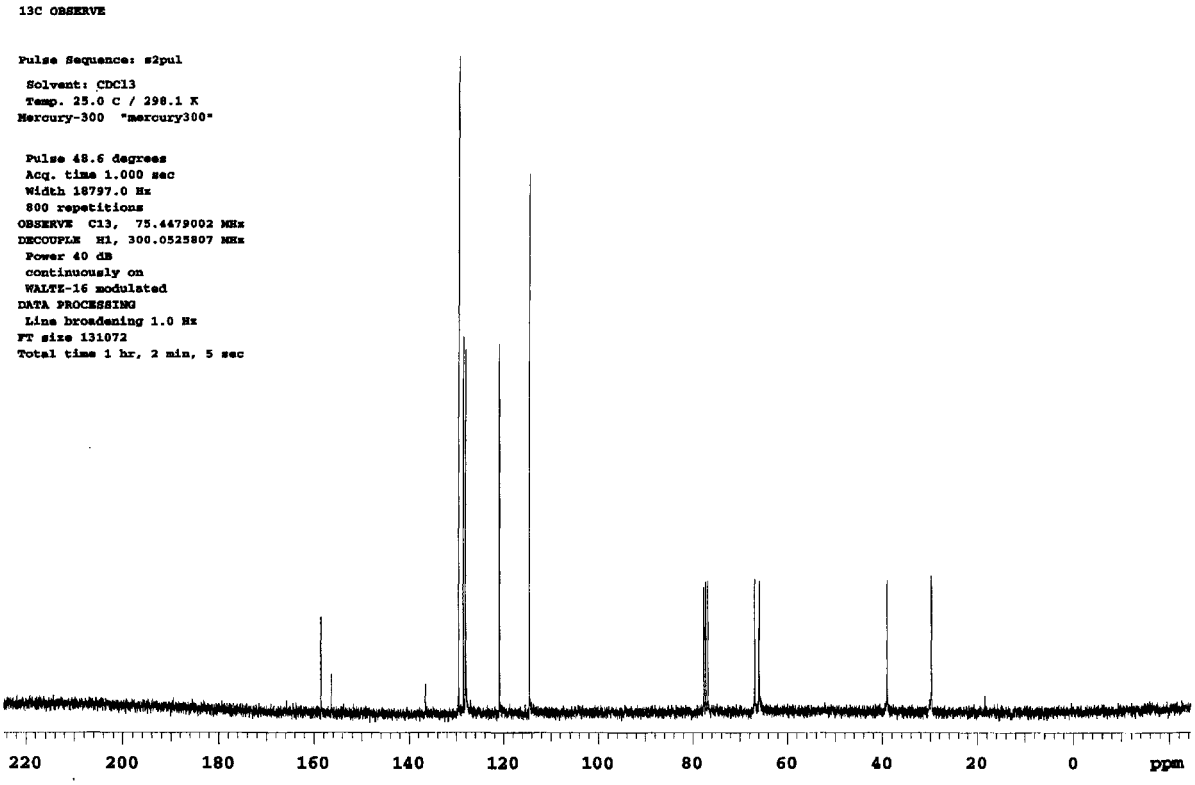
```
13C OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Mercury-300  "mercury300"

 Pulse 45.0 degrees
 Acq. time 1.000 sec
 Width 18797.0 Hz
 800 repetitions
OBSERVE   C13,   75.4479008 MHz
DECOUPLE  H1, 300.0525807 MHz
 Power 39 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 2 min, 5 sec
```

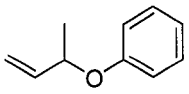




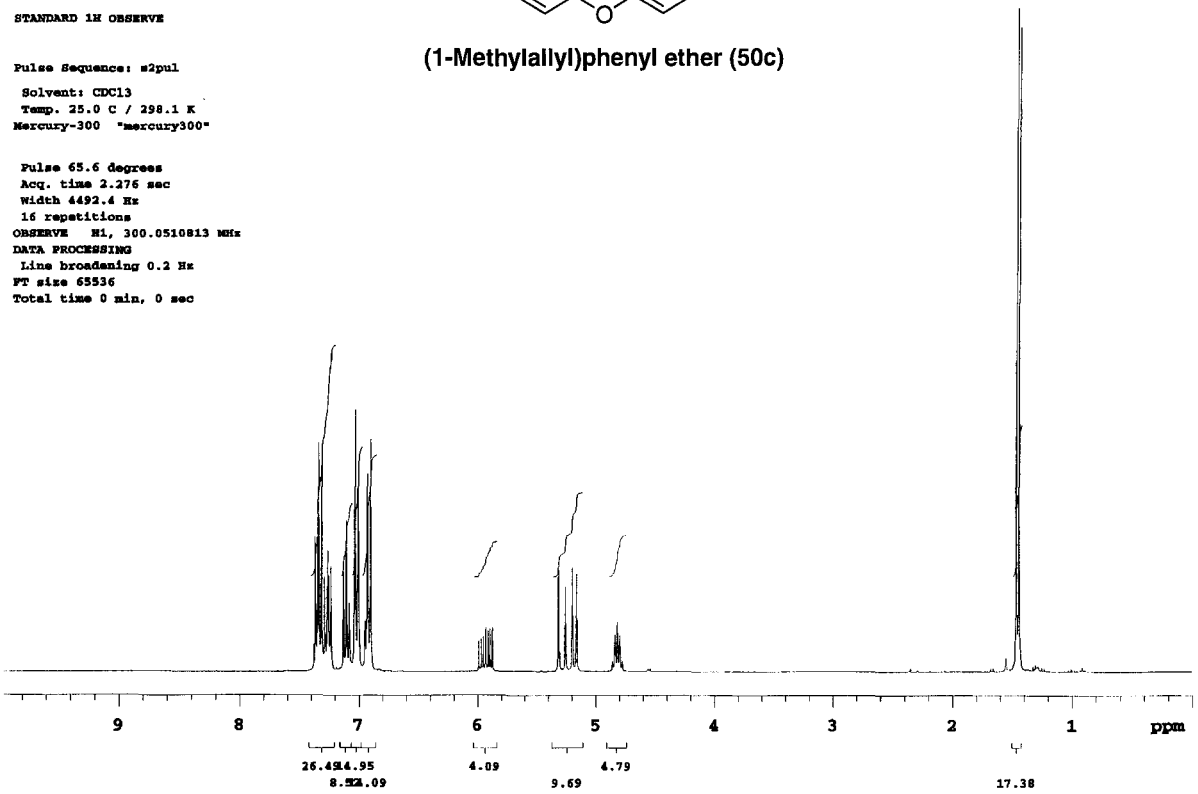
(3-Phenoxypropyl)carbamic acid benzyl ester (48w)

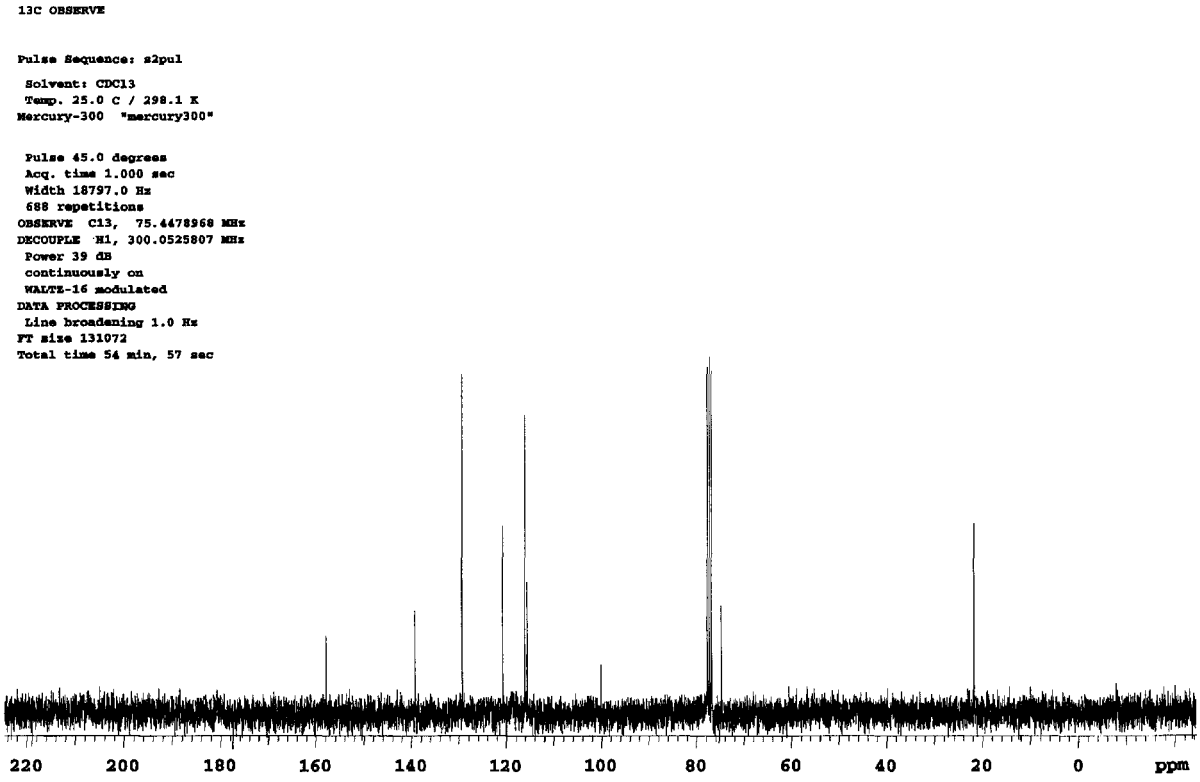




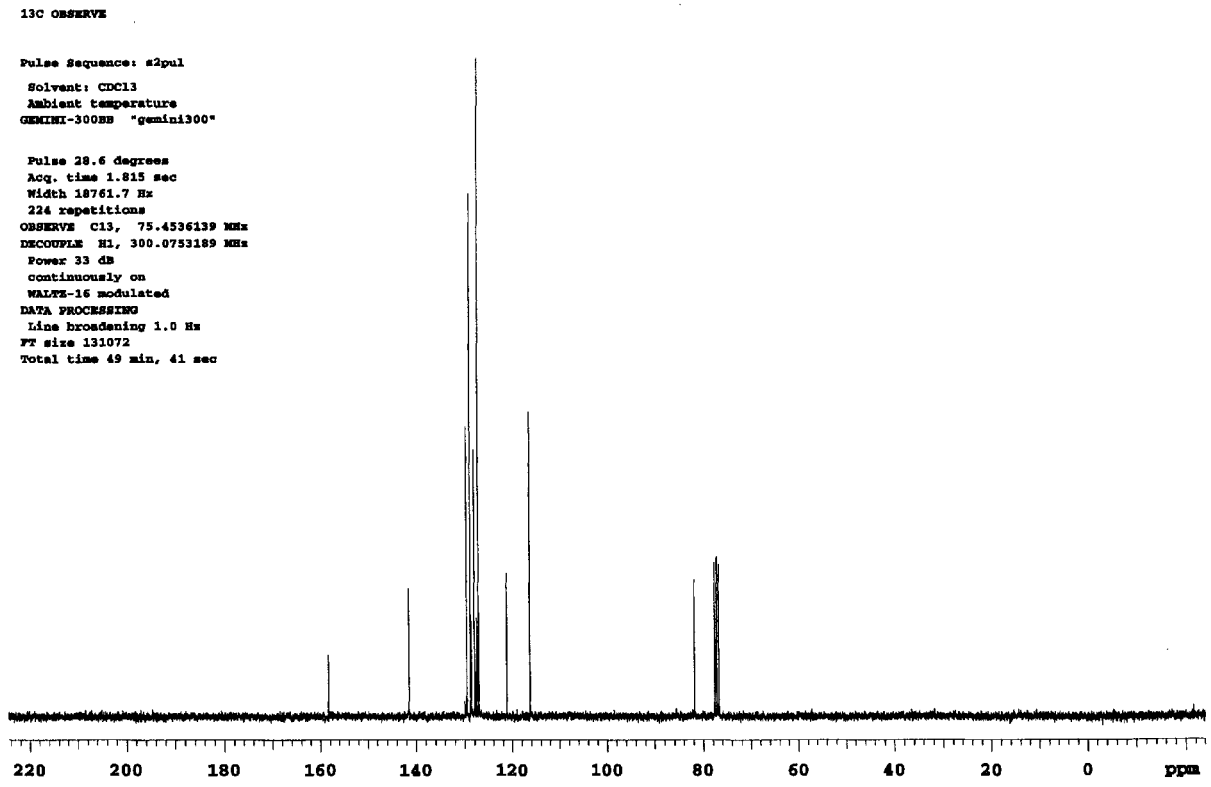


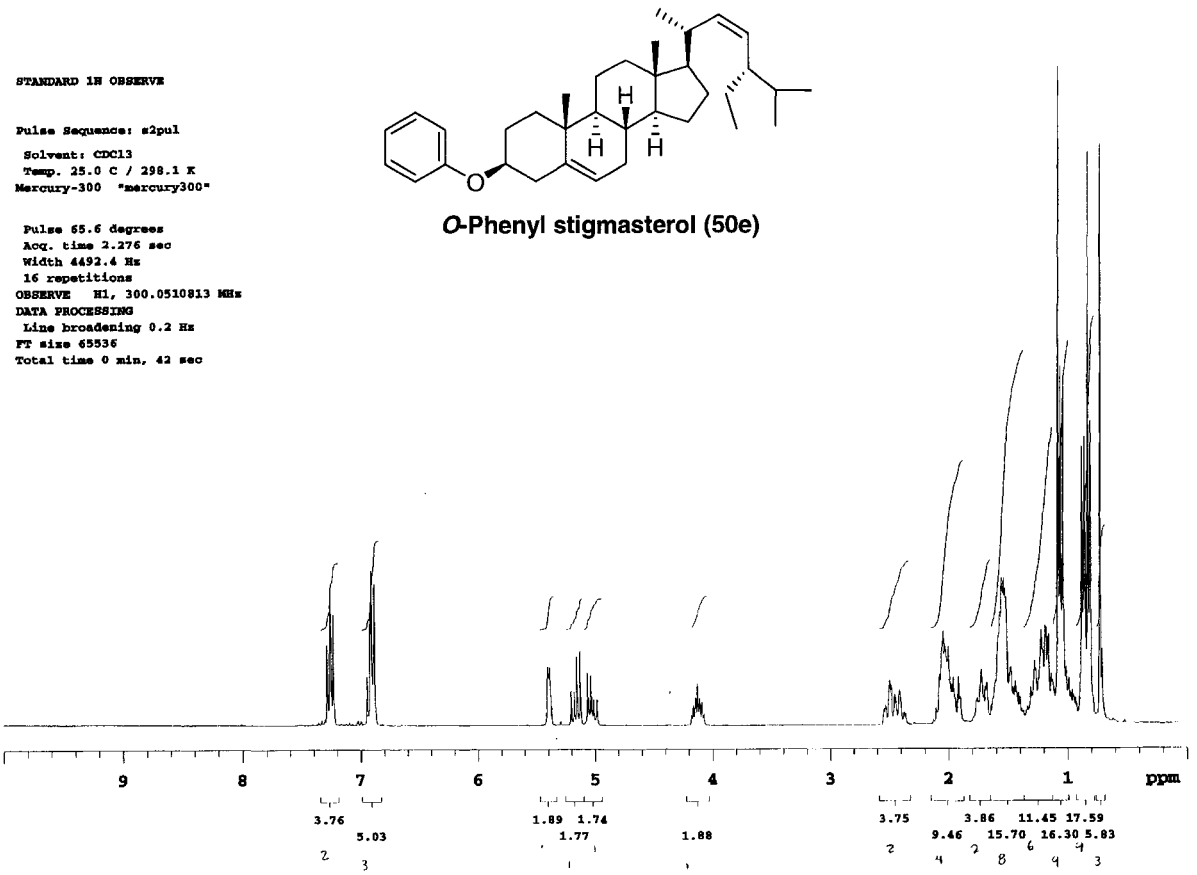
(1-Methylallyl)phenyl ether (50c)

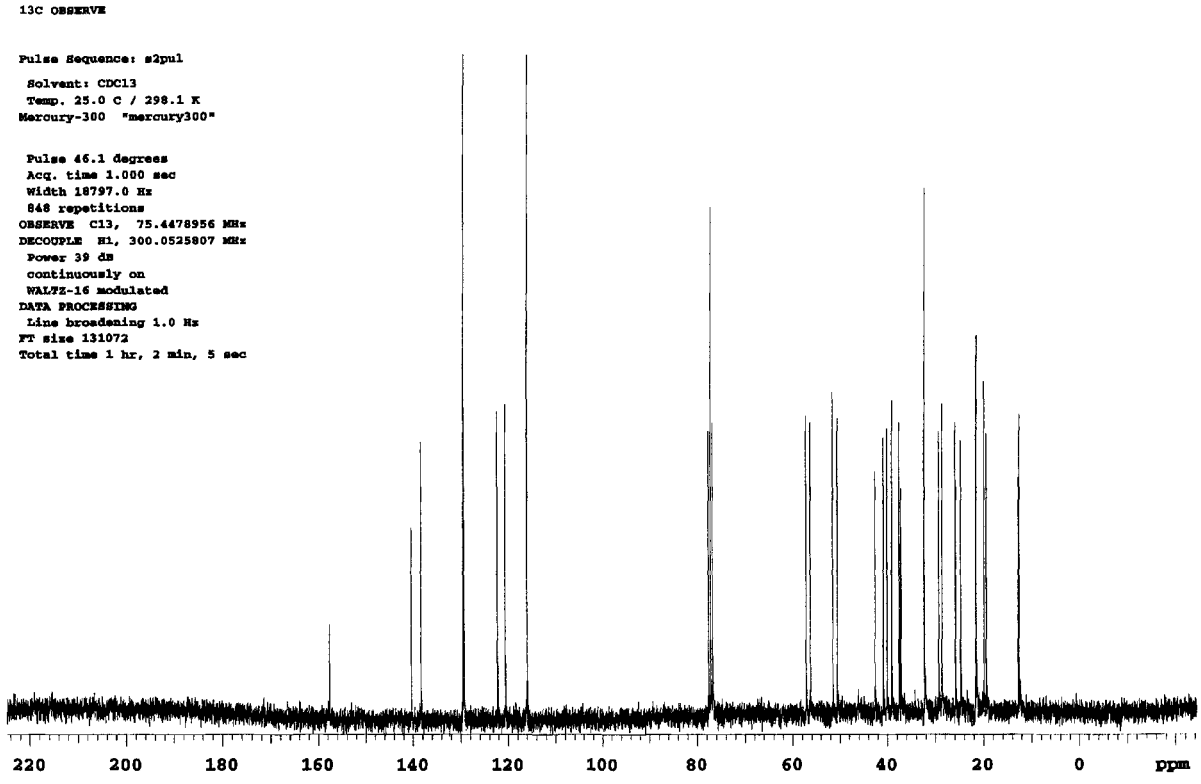


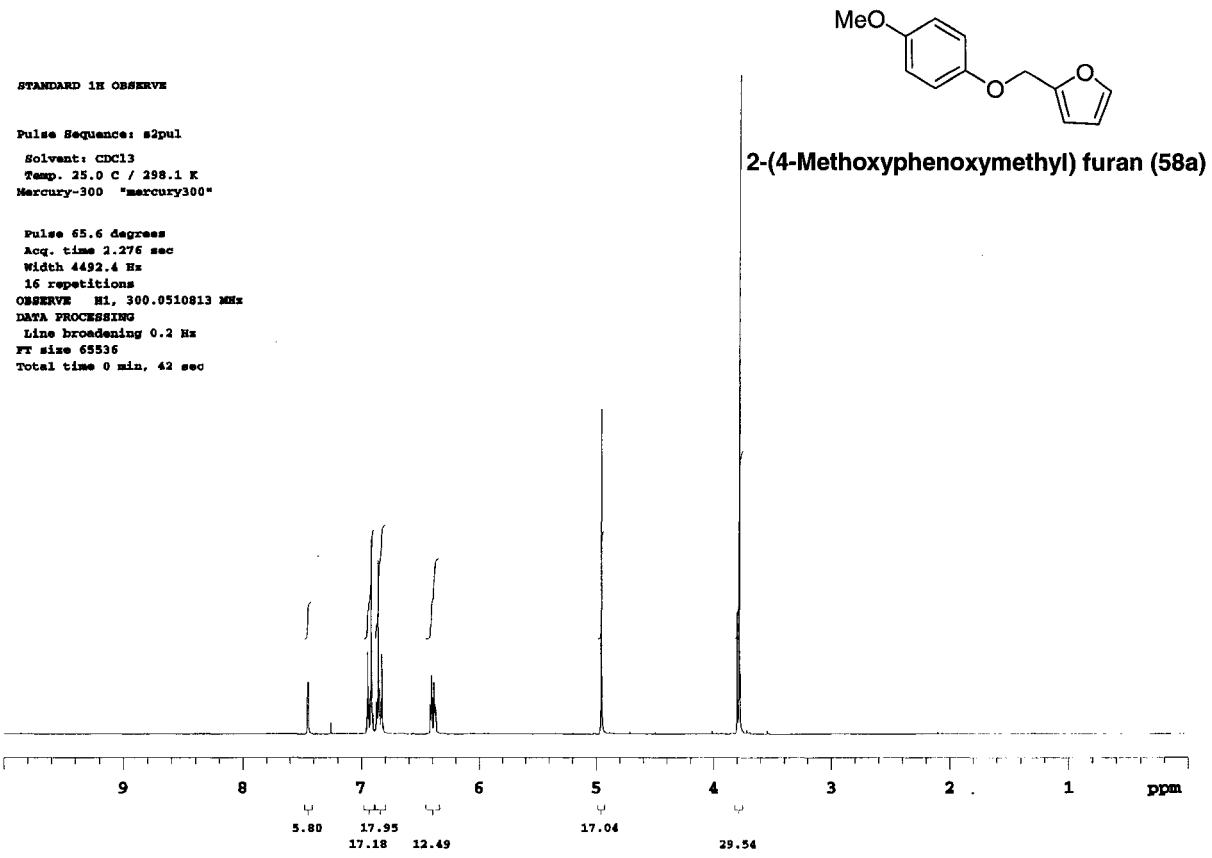


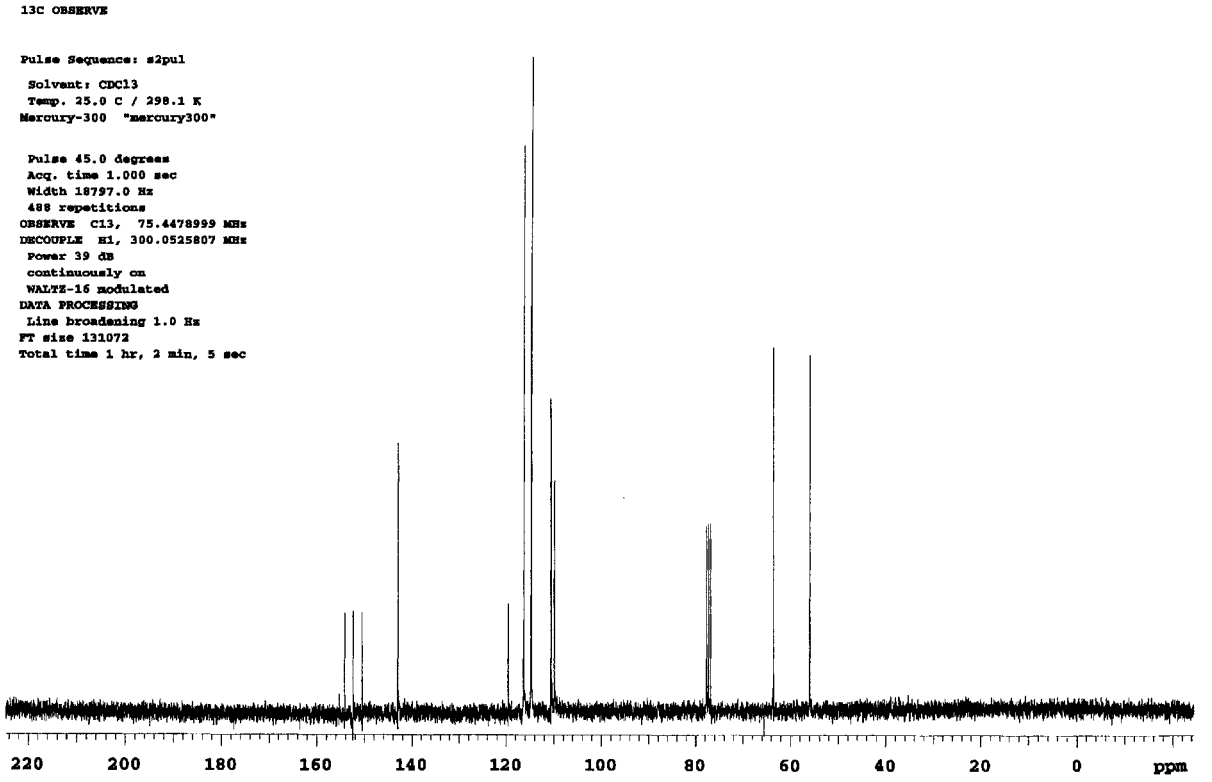
Benzhydrylphenyl ether (50d)

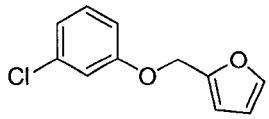



STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 65.6 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0510813 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec
H
H
H
O
O-Phenyl stigmasterol (50e)
9
8
7
6
5
4
3
2
1
ppm
3.76
5.03
1.89
1.74
1.77
1.88
3.75
3.86
11.45
17.59
9.46
15.70
16.30
5.83

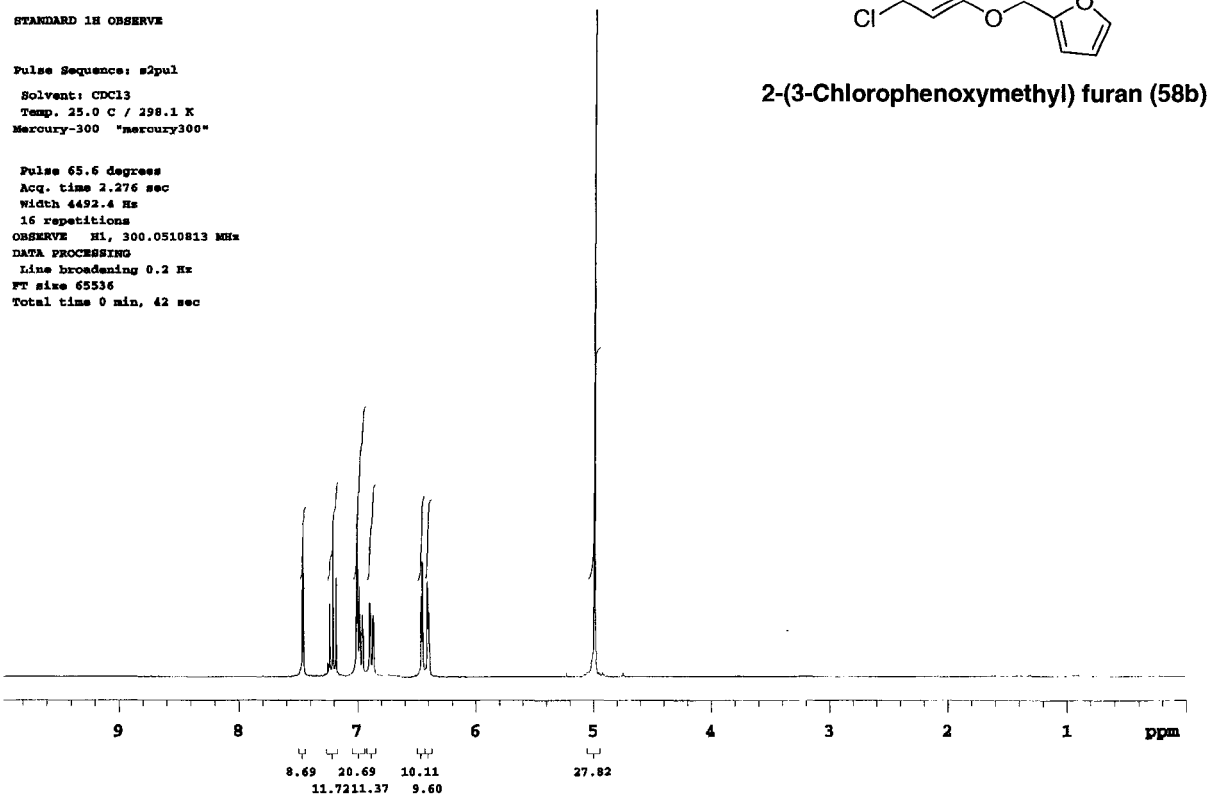

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 46.1 degrees
Acq. time 1.000 sec
Width 18797.0 Hz
848 repetitions
OBSERVE C13, 75.4478956 MHz
DECOUPLE H1, 300.0525807 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 2 min, 5 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

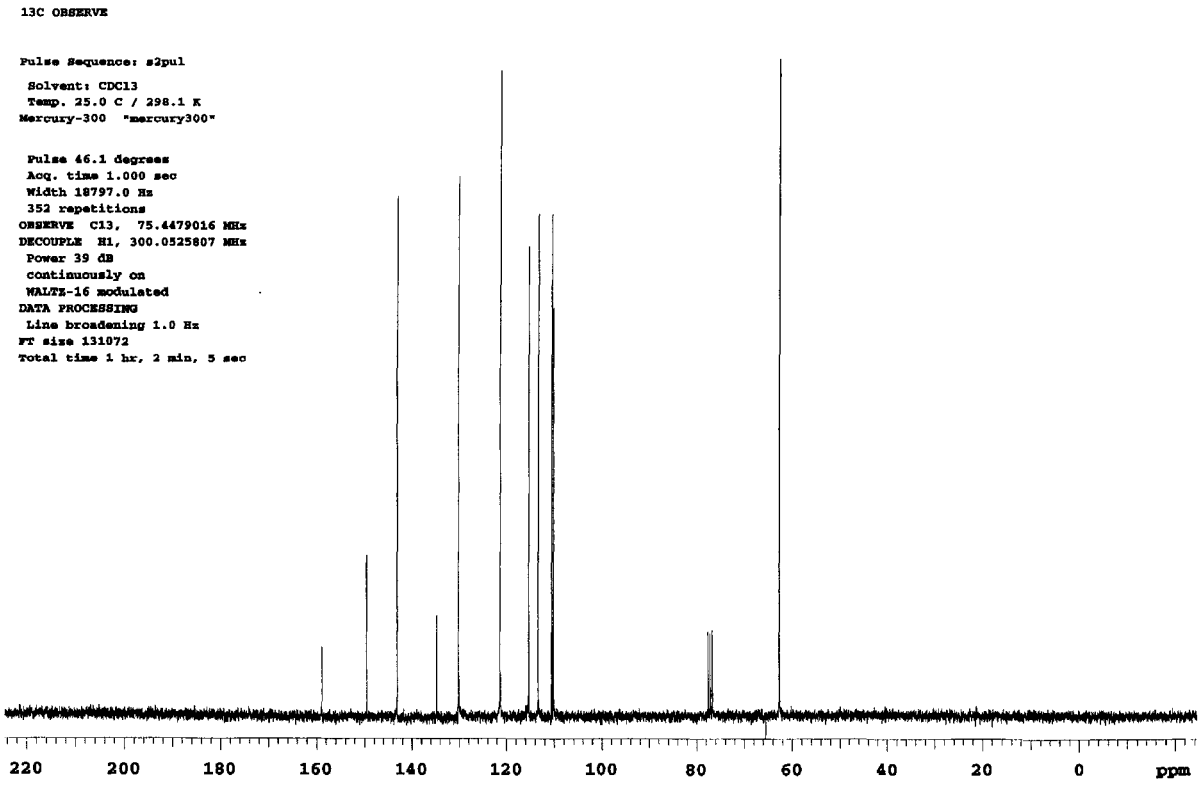

MeO
O
O
2-(4-Methoxyphenoxymethyl) furan (58a)
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 65.6 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0510813 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec
9
8
7
6
5
4
3
2
1
ppm
5.80
17.95
17.18
12.49
17.04
29.54

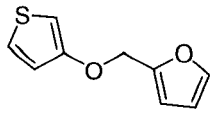

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 45.0 degrees
Acq. time 1.000 sec
Width 18797.0 Hz
488 repetitions
OBSERVE C13, 75.4478999 MHz
DECOUPLE H1, 300.0525807 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 2 min, 5 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm



2-(3-Chlorophenoxymethyl) furan (58b)

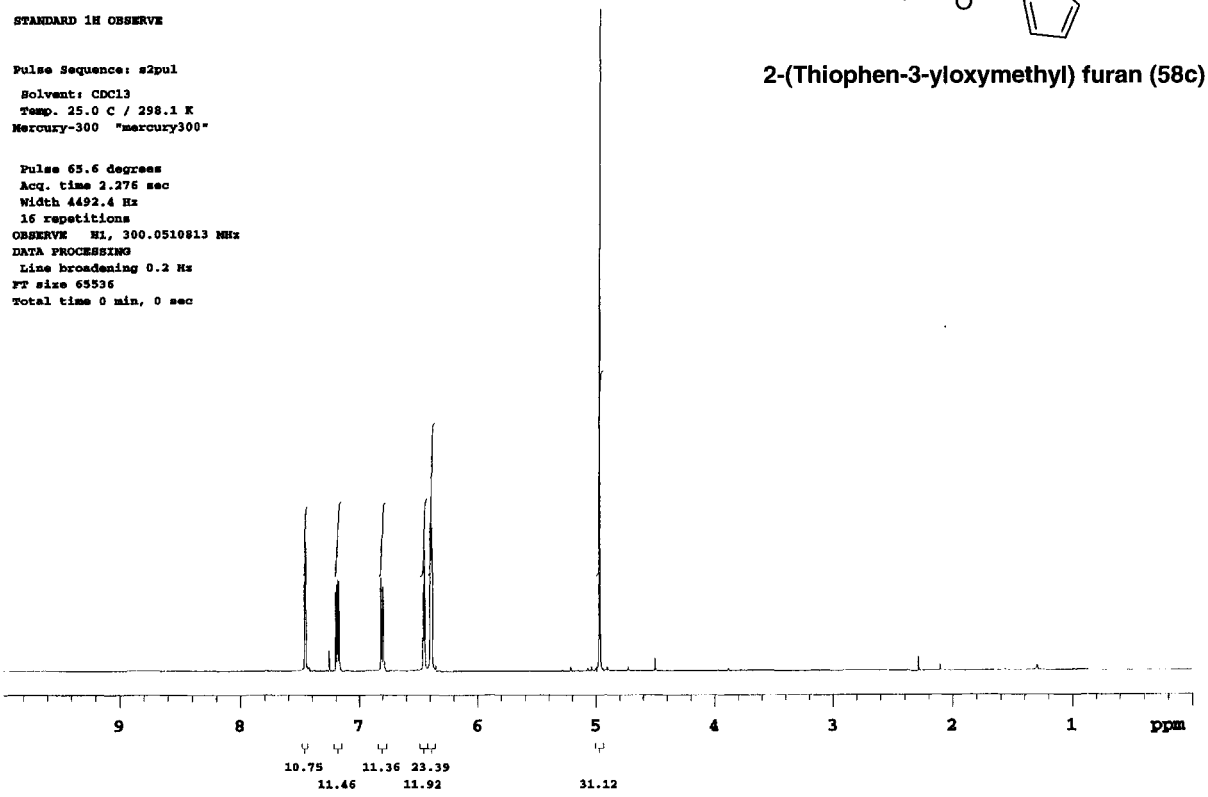




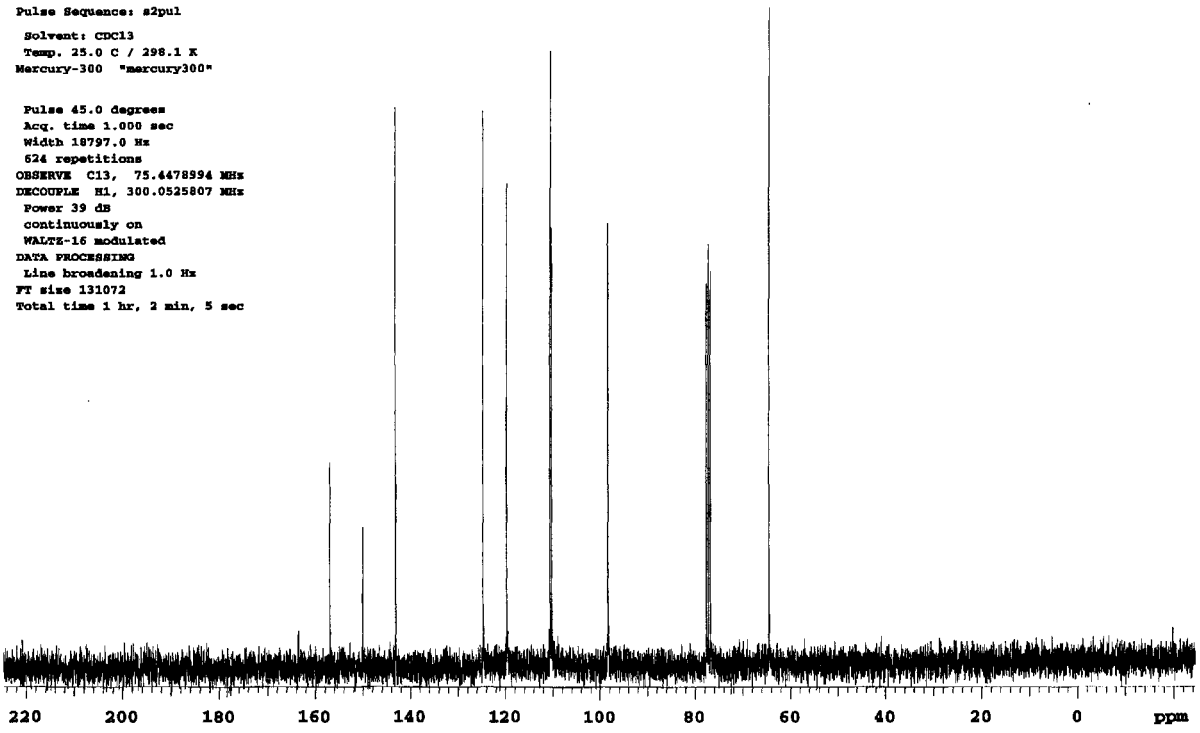


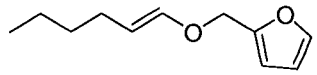
2-(Thiophen-3-yloxymethyl) furan (58c)

```
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Mercury-300  "mercury300"

 Pulse 65.6 degrees
 Acq. time 2.276 sec
 Width 4492.4 Hz
 16 repetitions
OBSERVE   H1, 300.0510813 MHz
DATA PROCESSING
 Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 0 sec
```

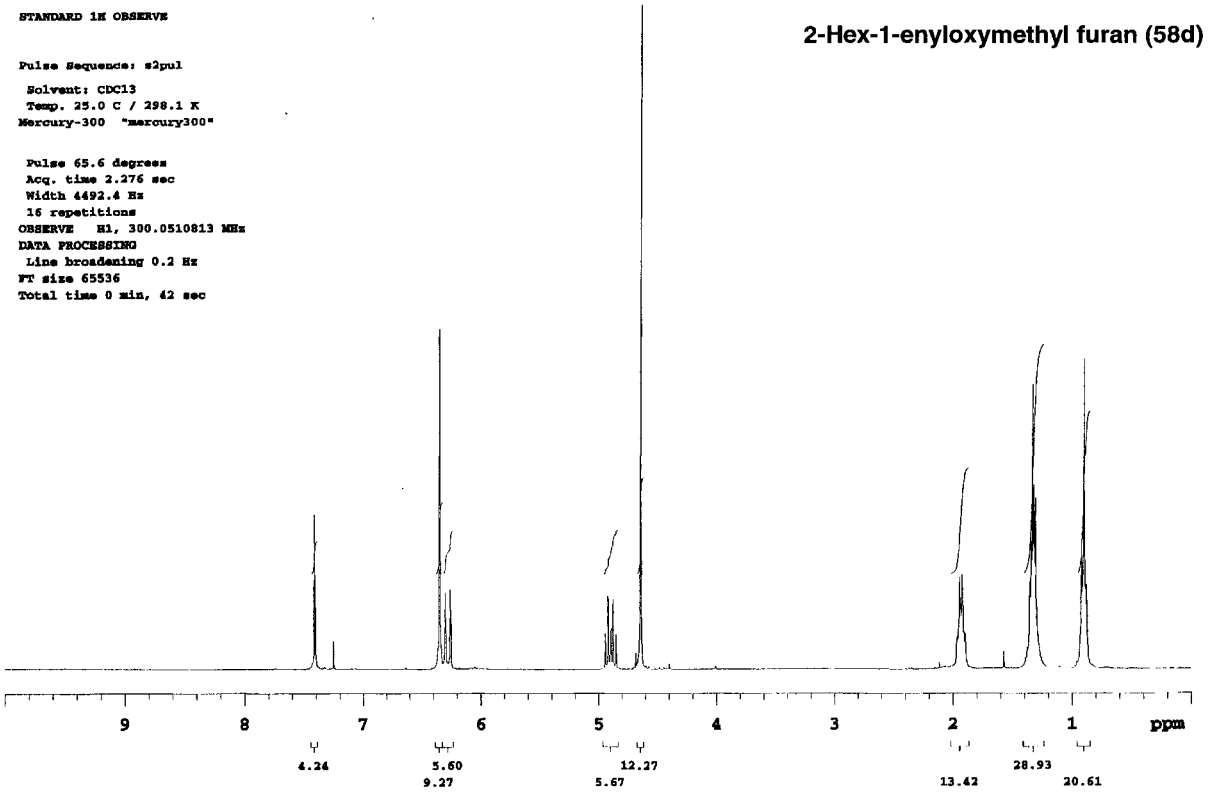


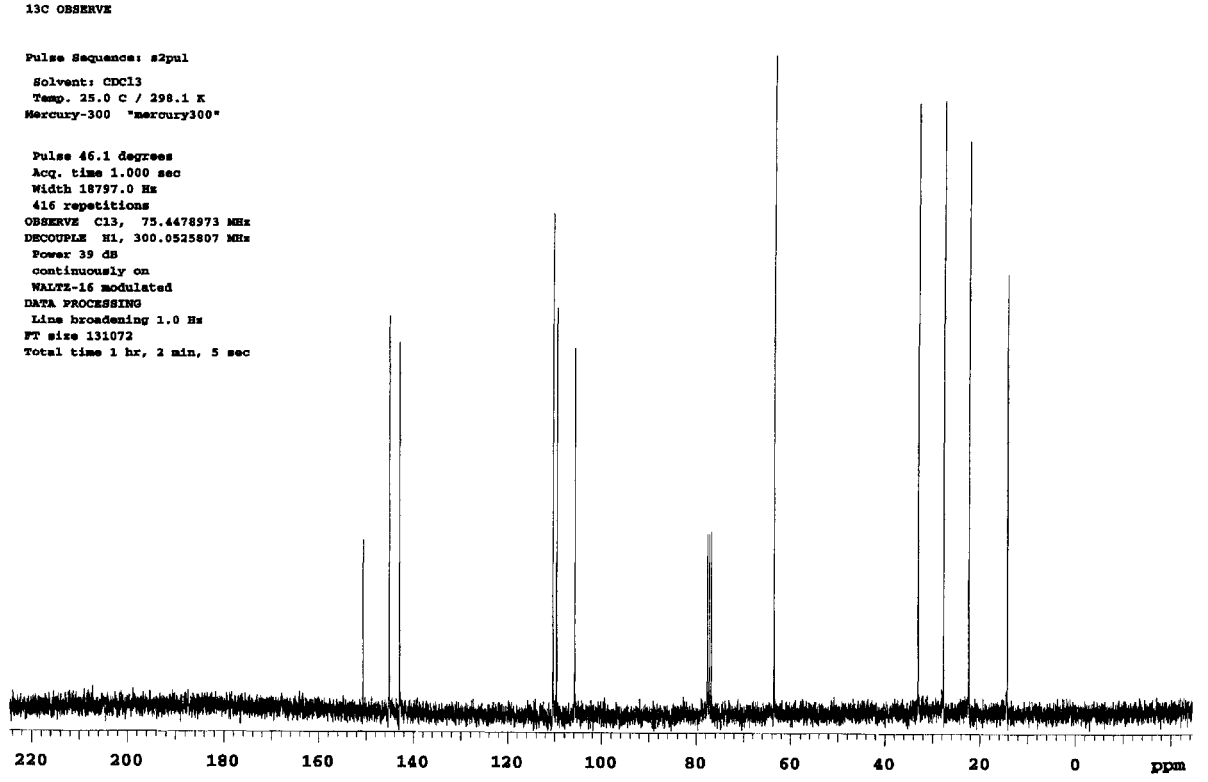

```
13C OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Mercury-300  "mercury300"

 Pulse 45.0 degrees
 Acq. time 1.000 sec
 Width 18797.0 Hz
 624 repetitions
OBSERVE   C13,  75.4478994 MHz
DECOUPLE  H1, 300.0525807 MHz
 Power 39 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 2 min, 5 sec
```

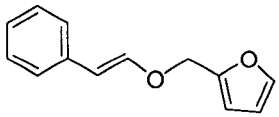




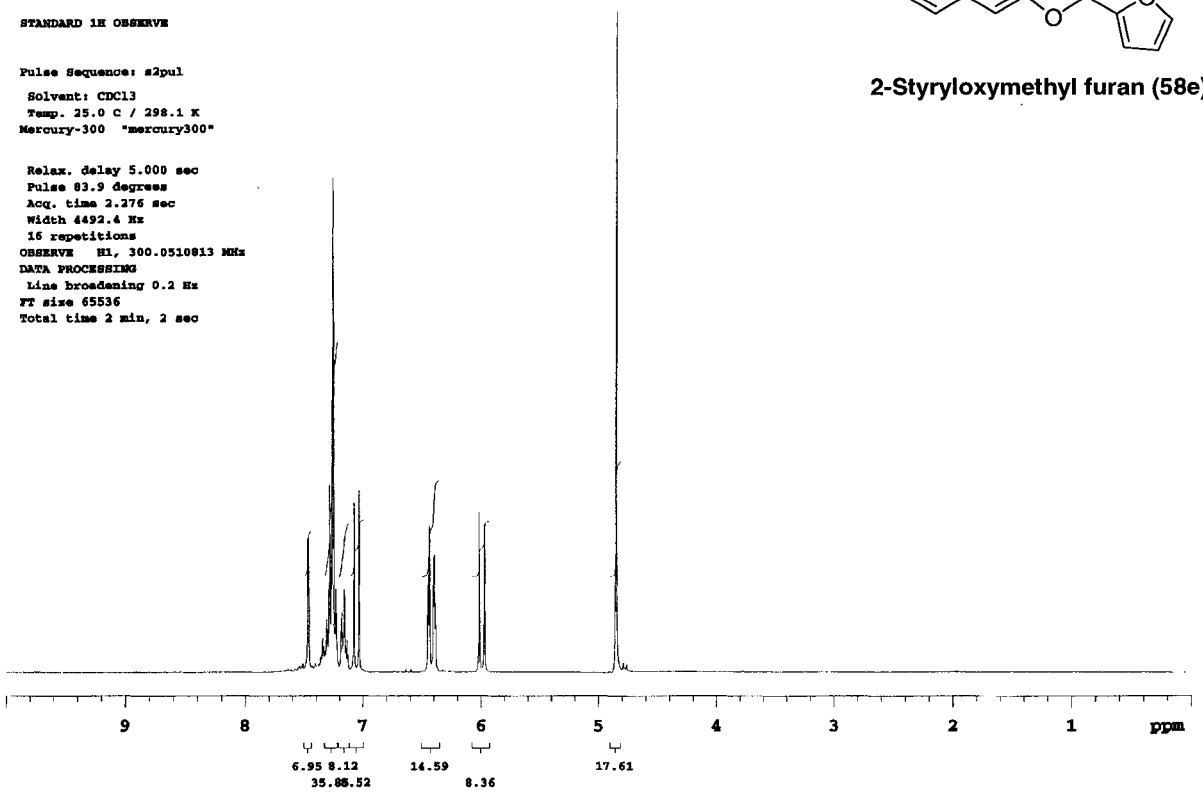
2-Hex-1-enyloxymethyl furan (58d)

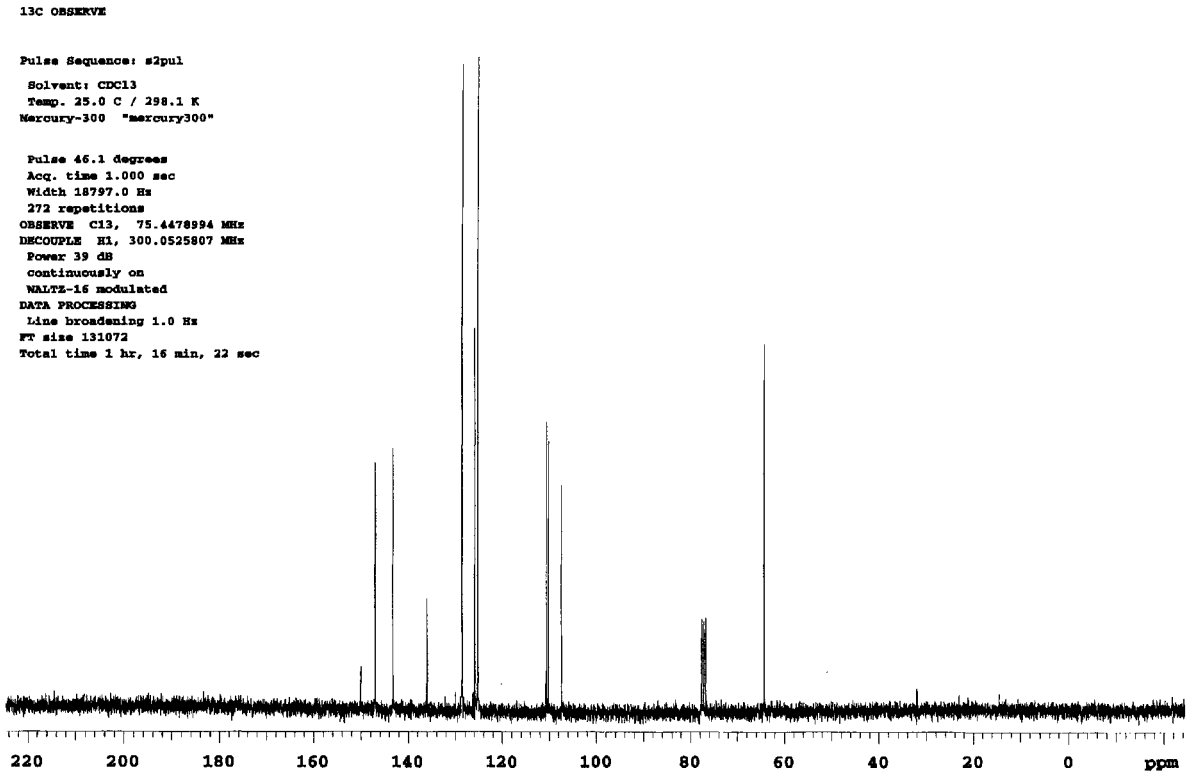


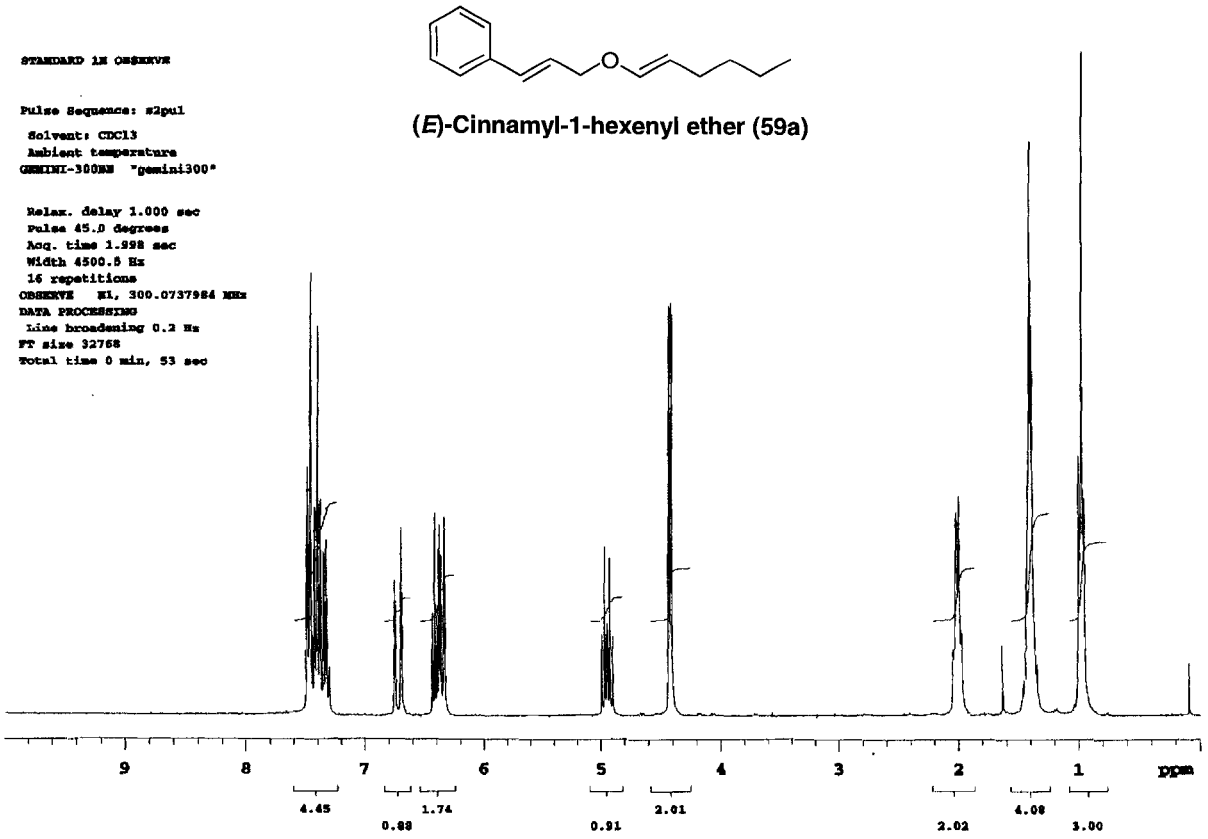


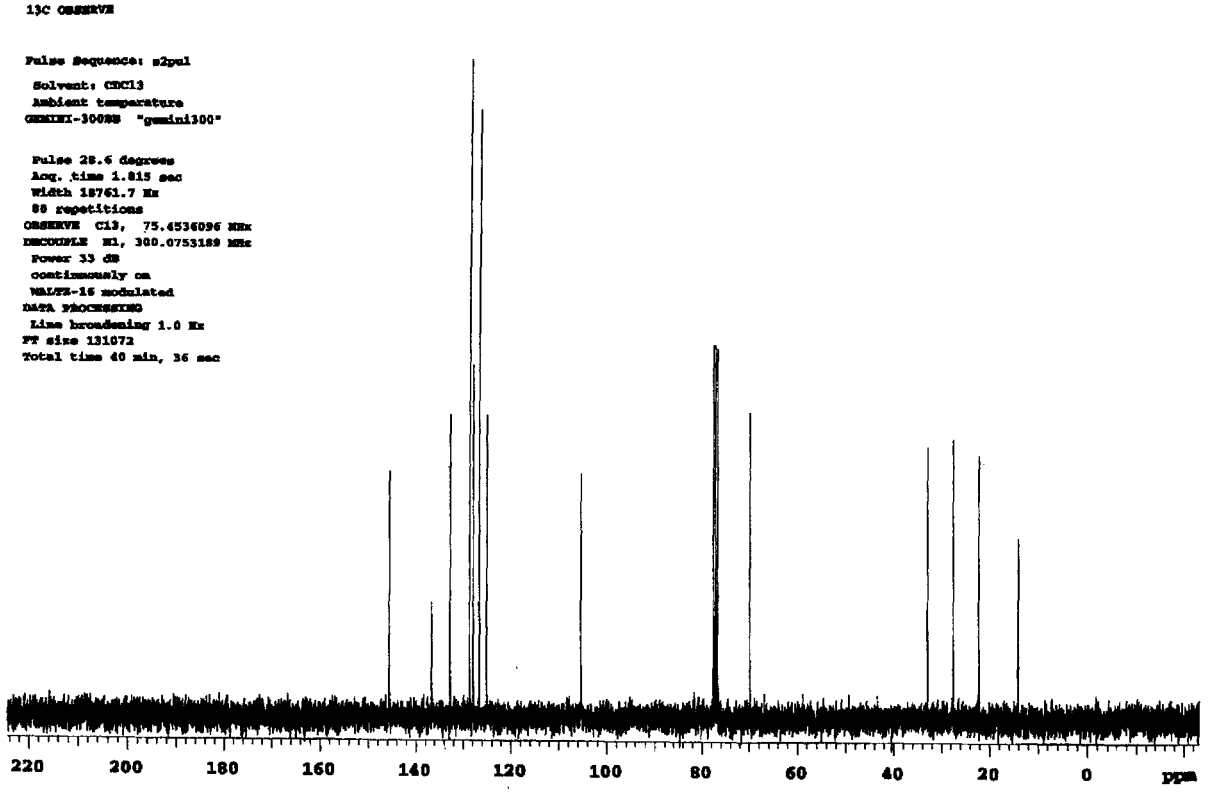


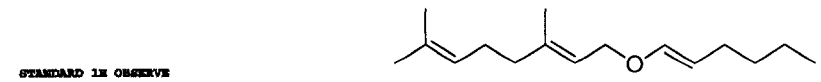
2-Styryloxymethyl furan (58e)



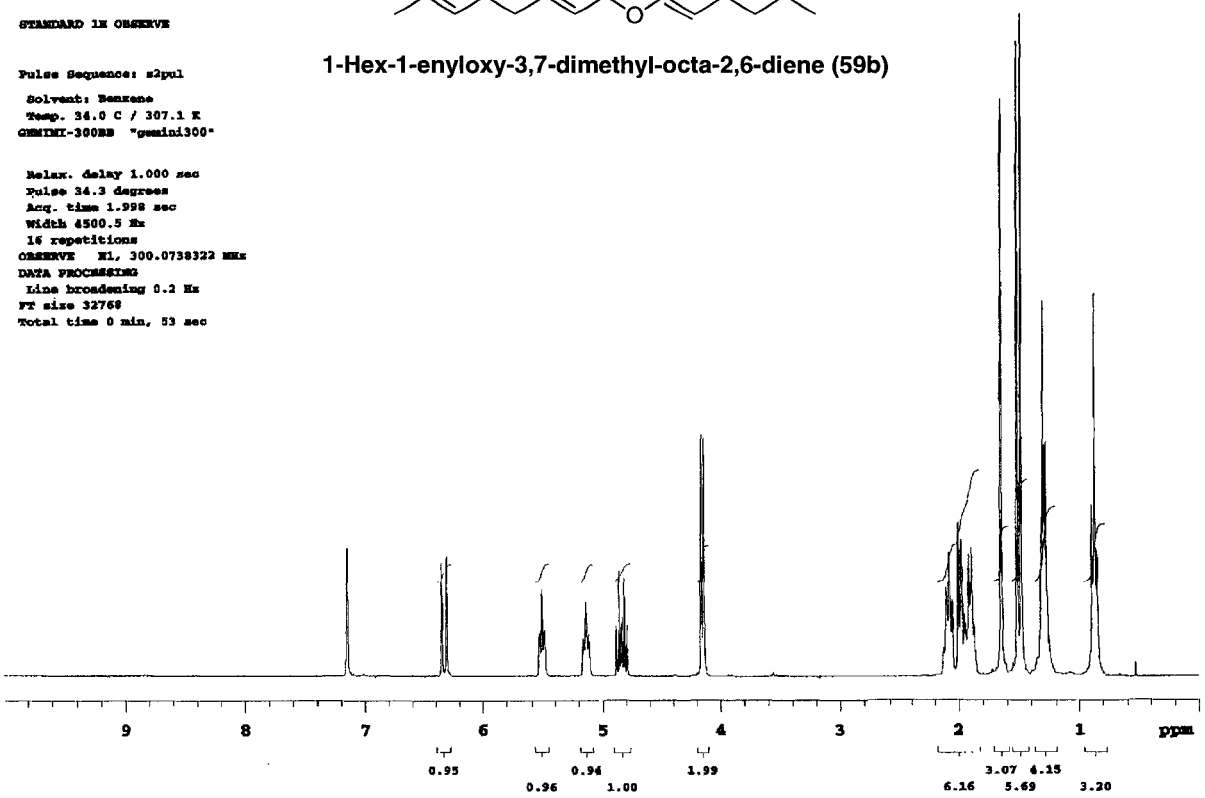


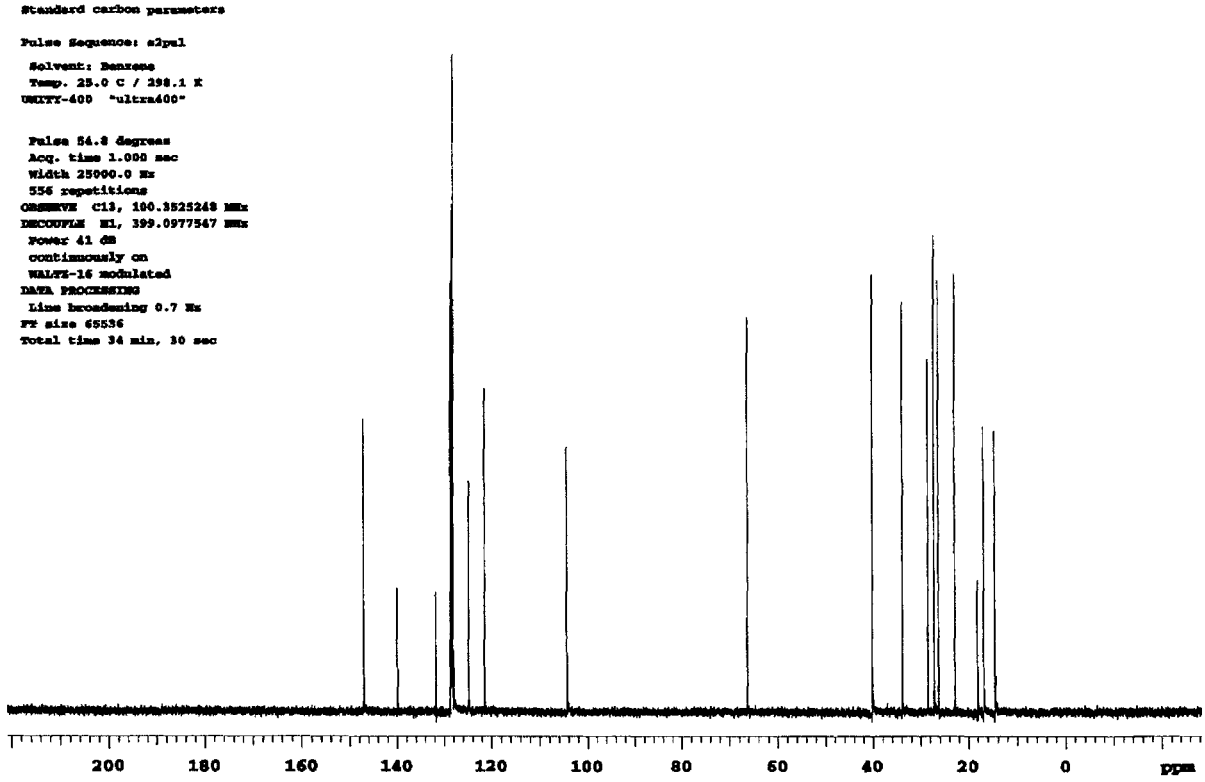

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "gemini300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0737984 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 53 sec
(E)-Cinnamyl-1-hexenyl ether (59a)
9
8
7
6
5
4
3
2
1
ppm
4.45
0.88
1.74
0.91
2.01
2.02
4.08
3.00

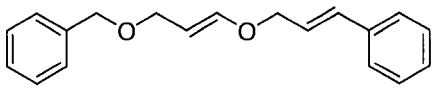

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "gemini300"
Pulse 28.6 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
88 repetitions
OBSERVE C13, 75.4536096 MHz
DECOUPLE H1, 300.0753189 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 40 min, 36 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm



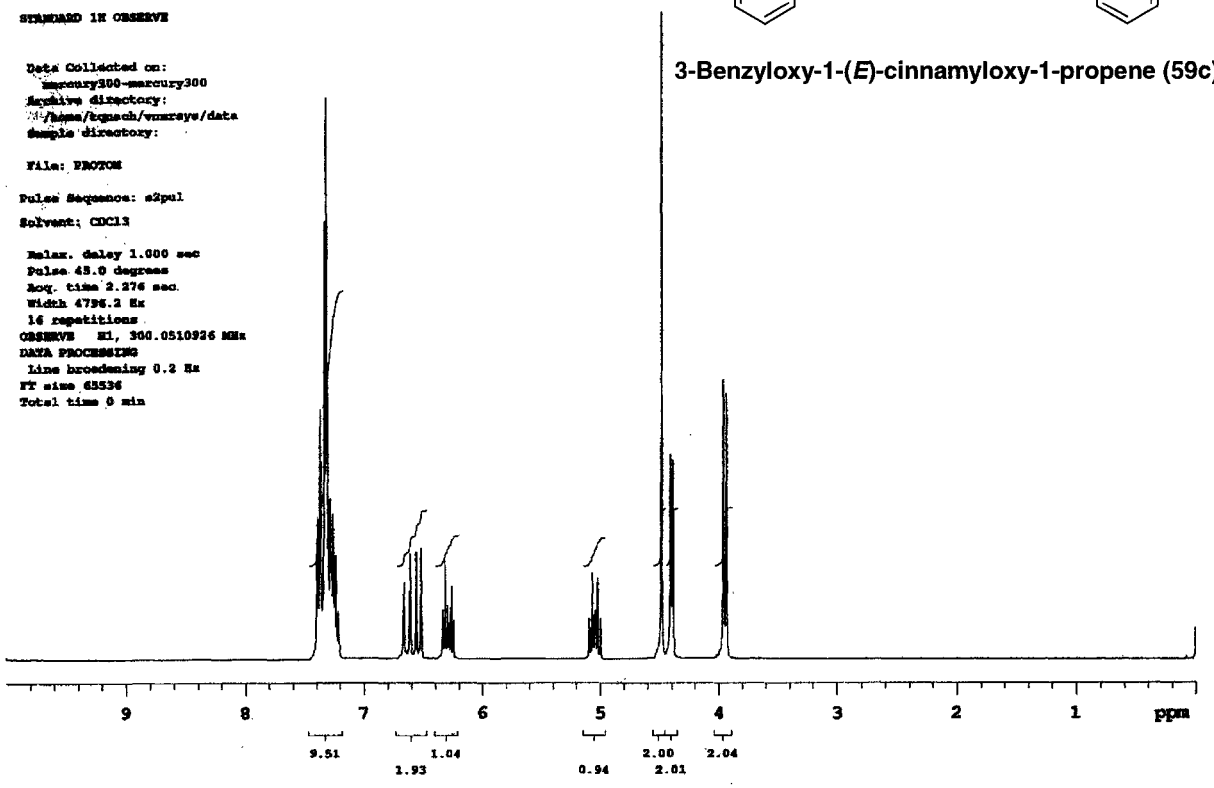
1-Hex-1-enyloxy-3,7-dimethyl-octa-2,6-diene (59b)

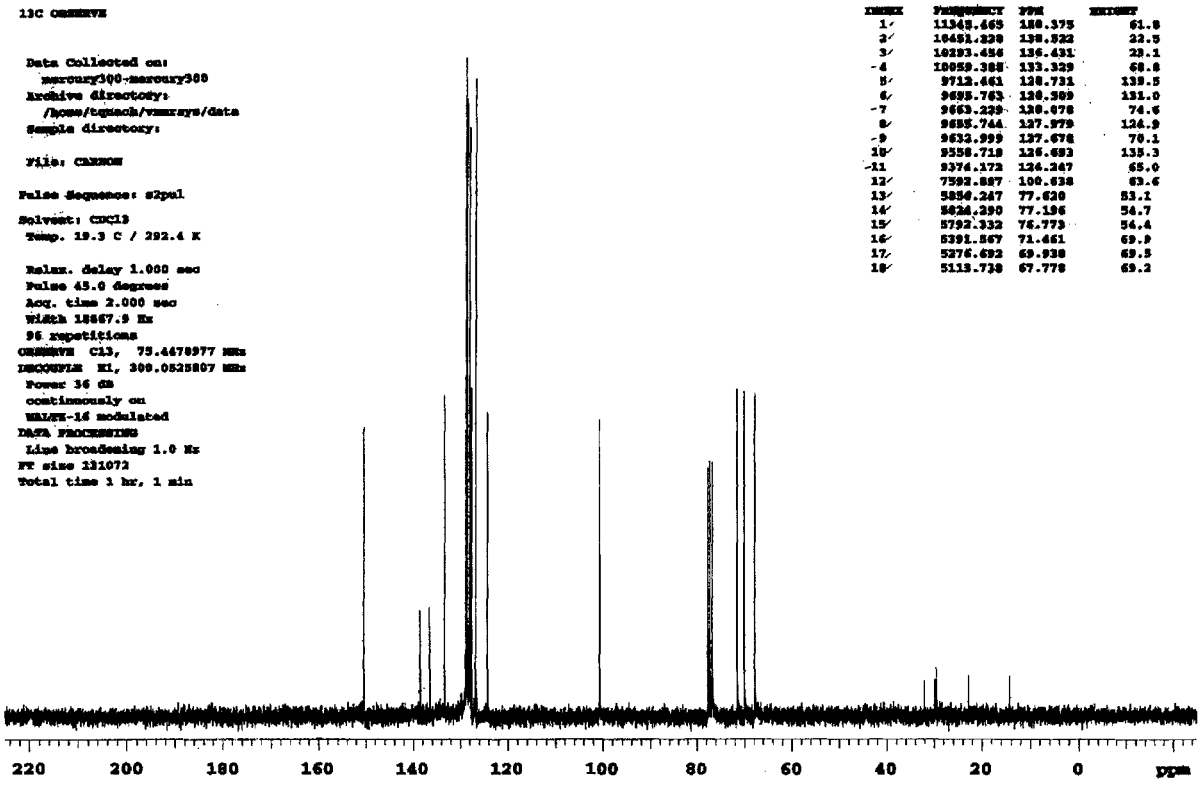


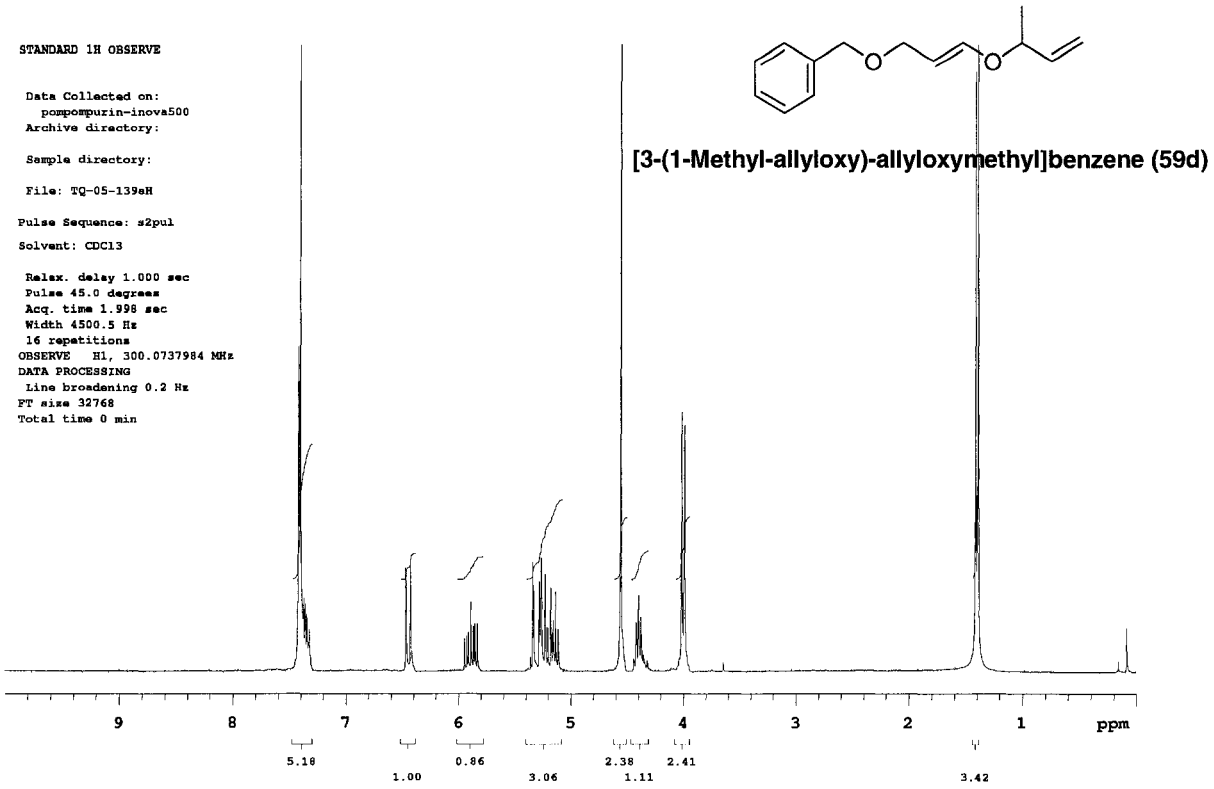


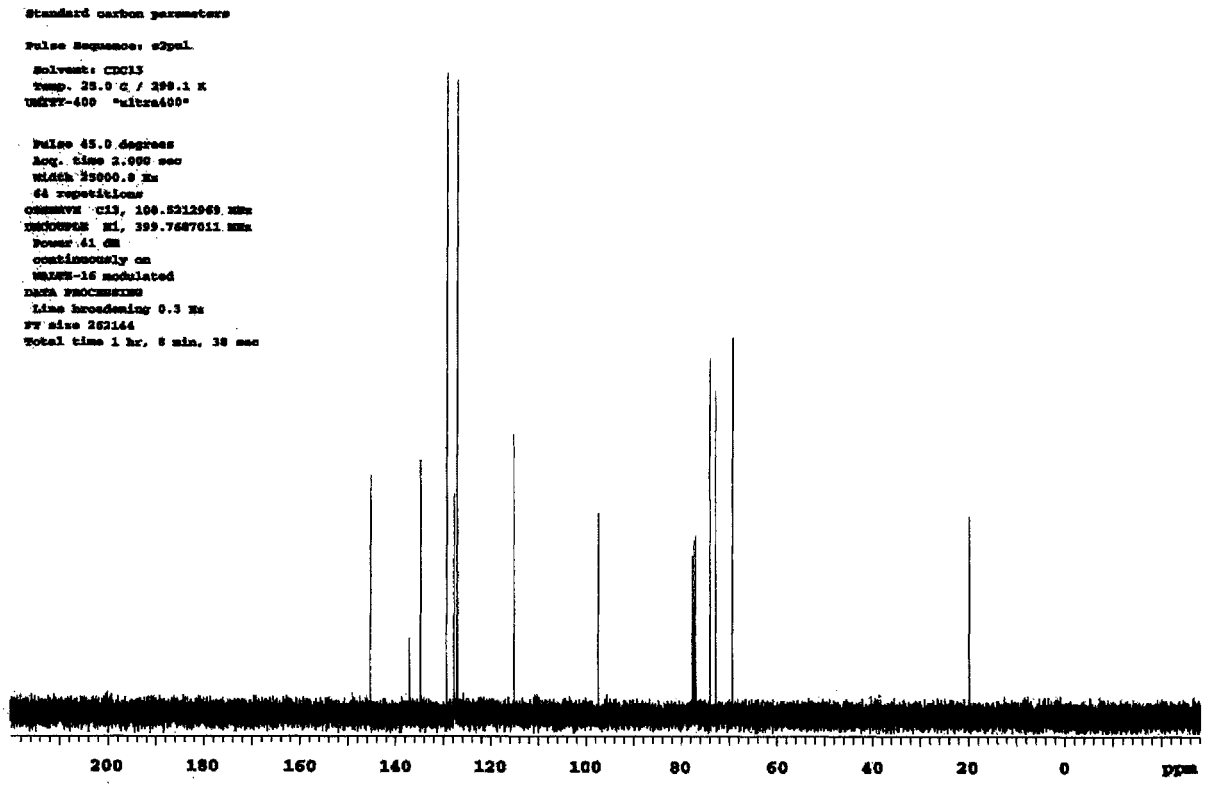


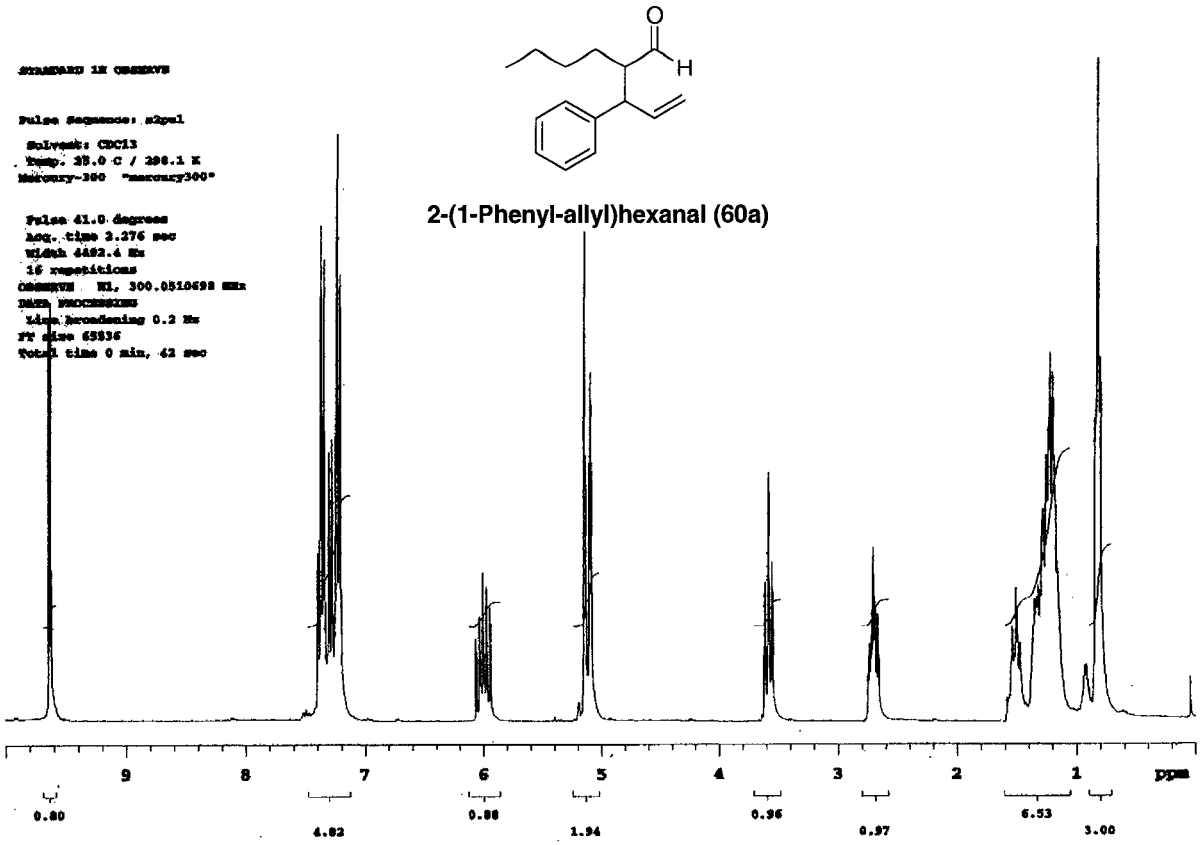
3-Benzyloxy-1-(*E*)-cinnamyloxy-1-propene (59c)



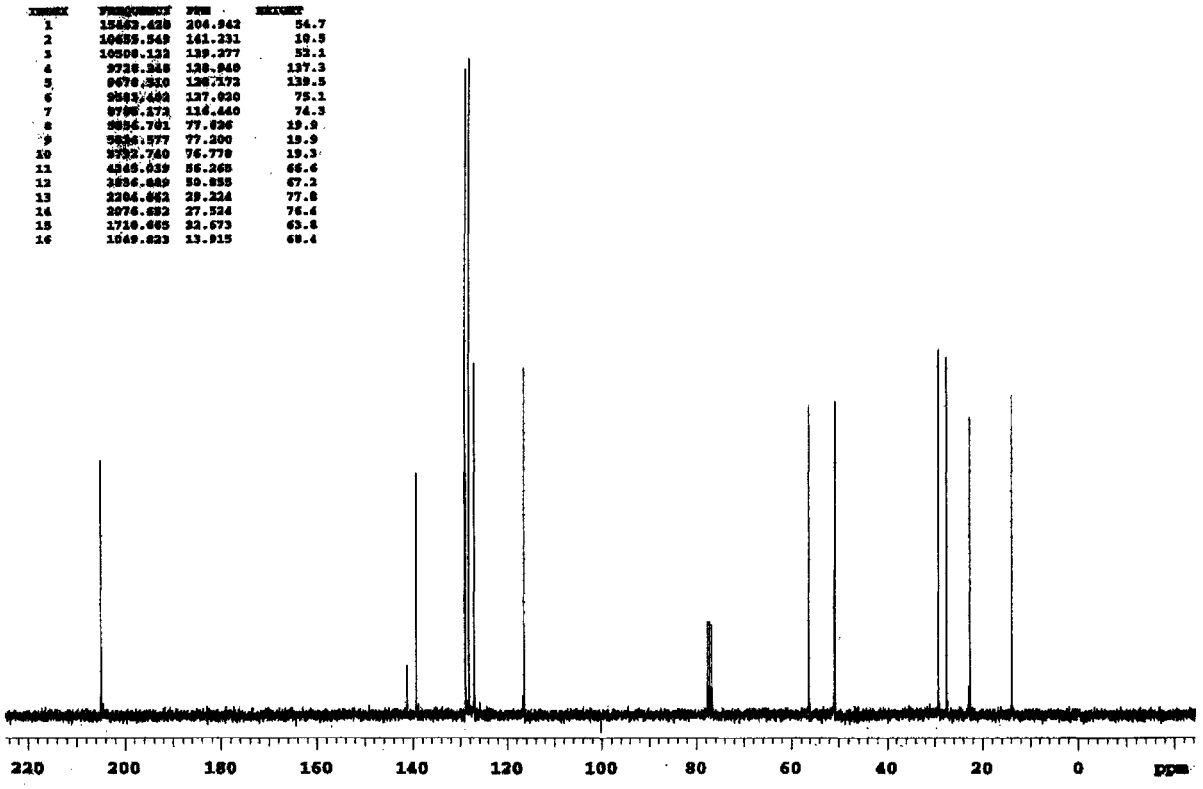


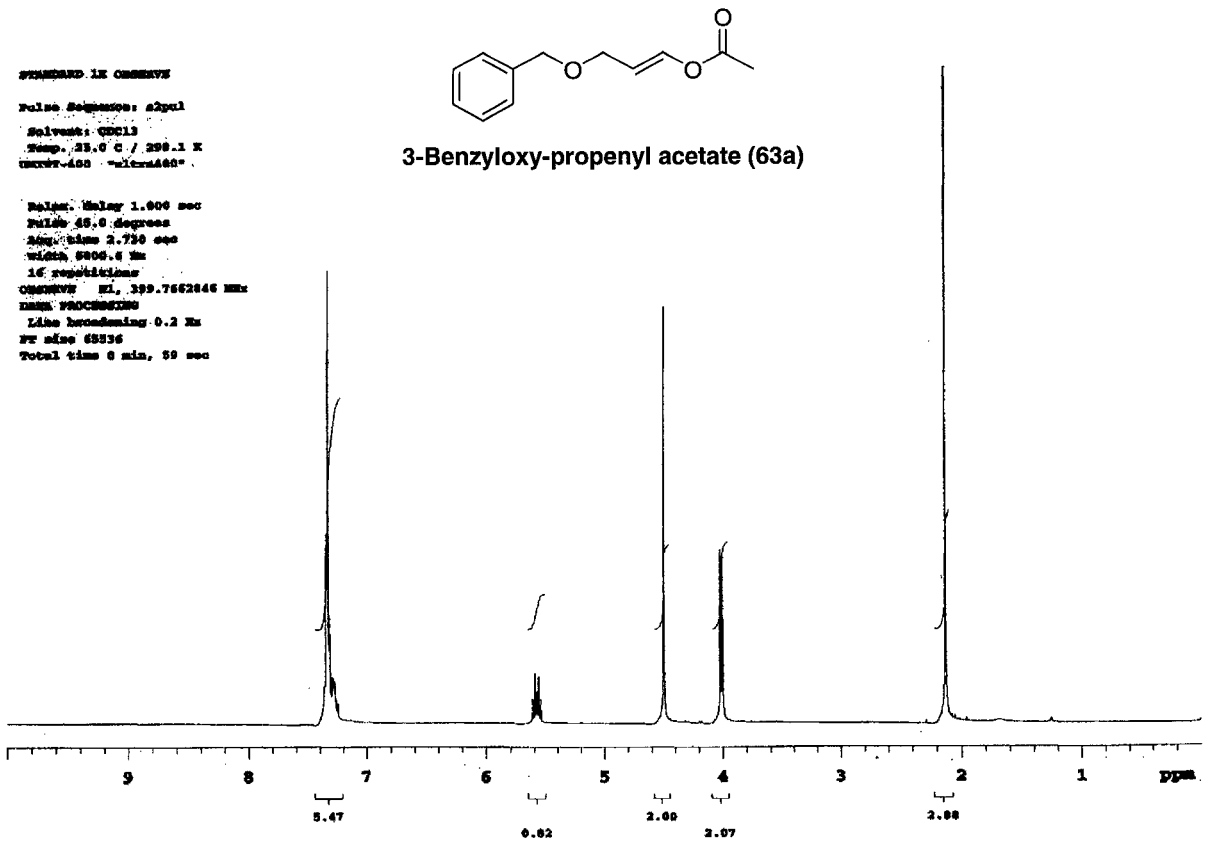

STANDARD 1H OBSERVE
Data Collected on:
pompompurin-inova500
Archive directory:
Sample directory:
File: TQ-05-139aH
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0737984 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min
[3-(1-Methyl-allyloxy)-allyloxymethyl]benzene (59d)
9
8
7
6
5
4
3
2
1
ppm
5.18
1.00
0.86
3.06
2.38
1.11
2.41
3.42

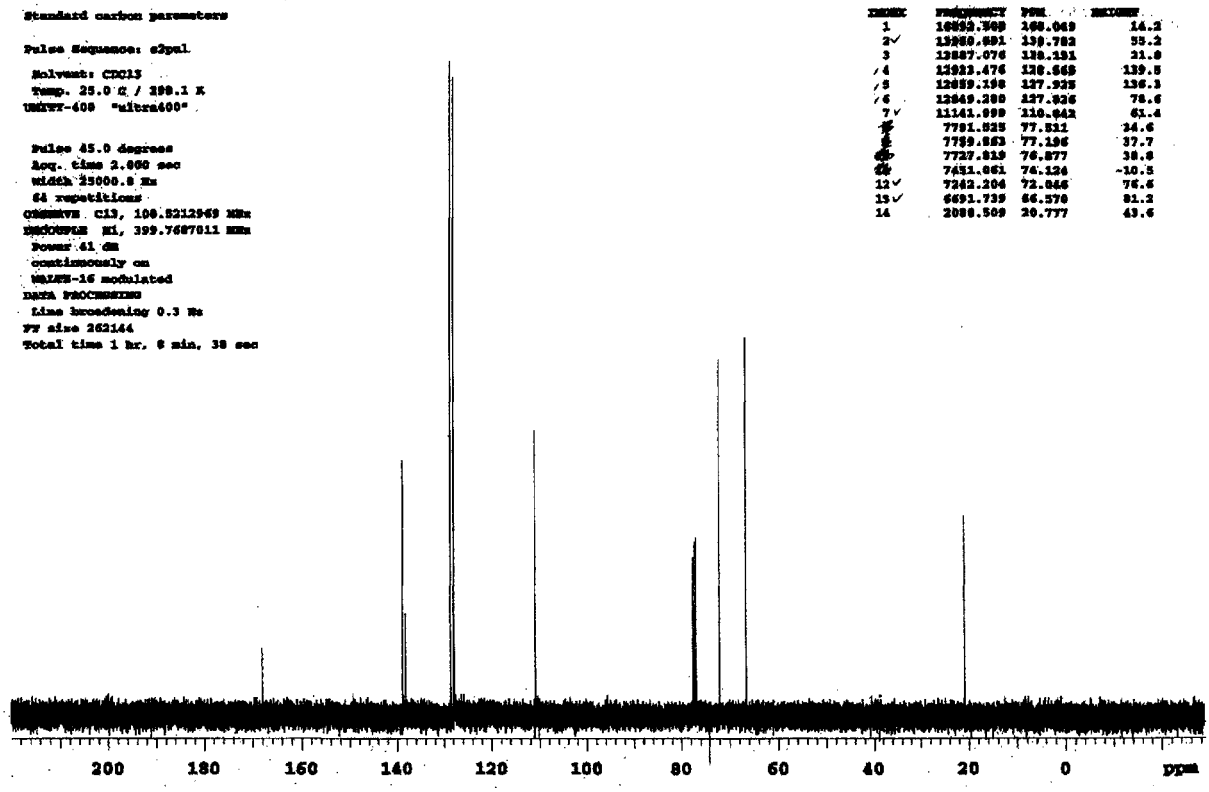

Standard carbon parameters
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "ultra400"
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 25000.0 Hz
64 repetitions
OBSERVE C13, 100.5212969 MHz
DECOUPLE H1, 399.7687011 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 262144
Total time 1 hr, 8 min, 38 sec
200
180
160
140
120
100
80
60
40
20
0
ppm

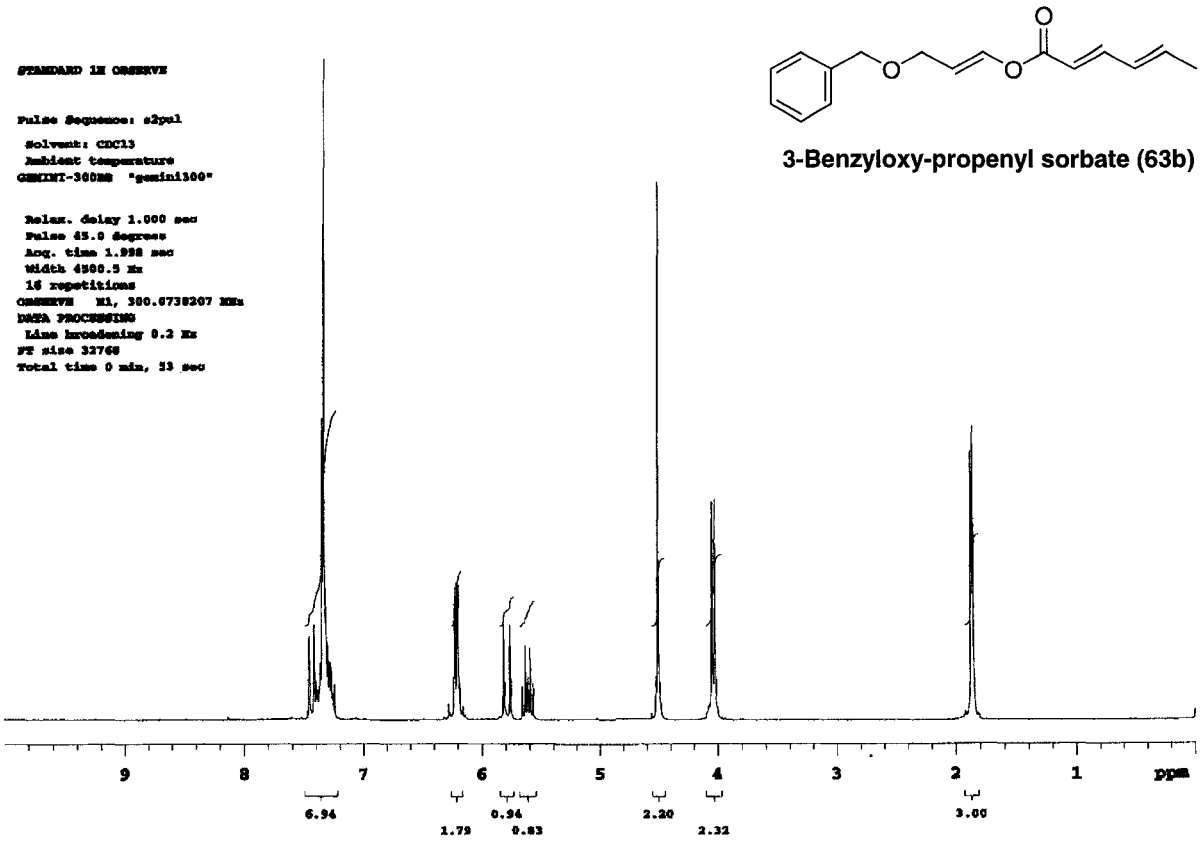


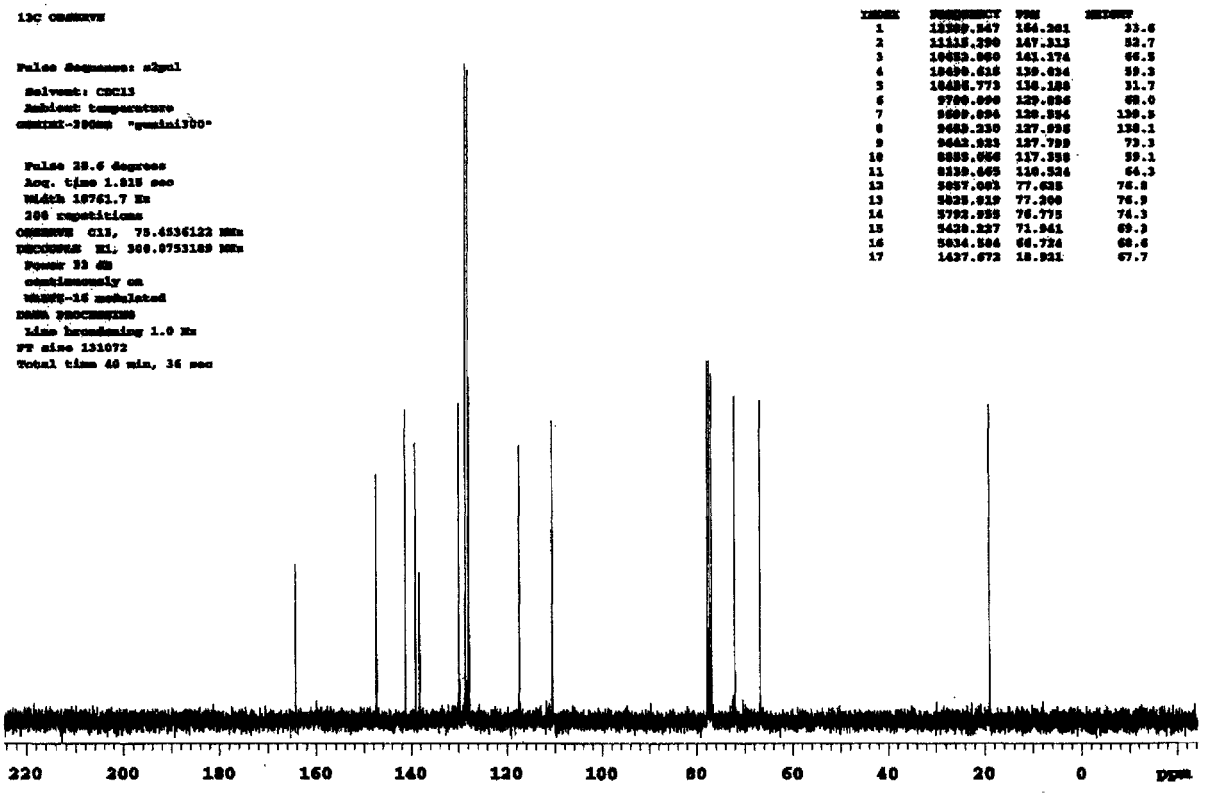
2-(1-Phenyl-allyl)hexanal (60a)

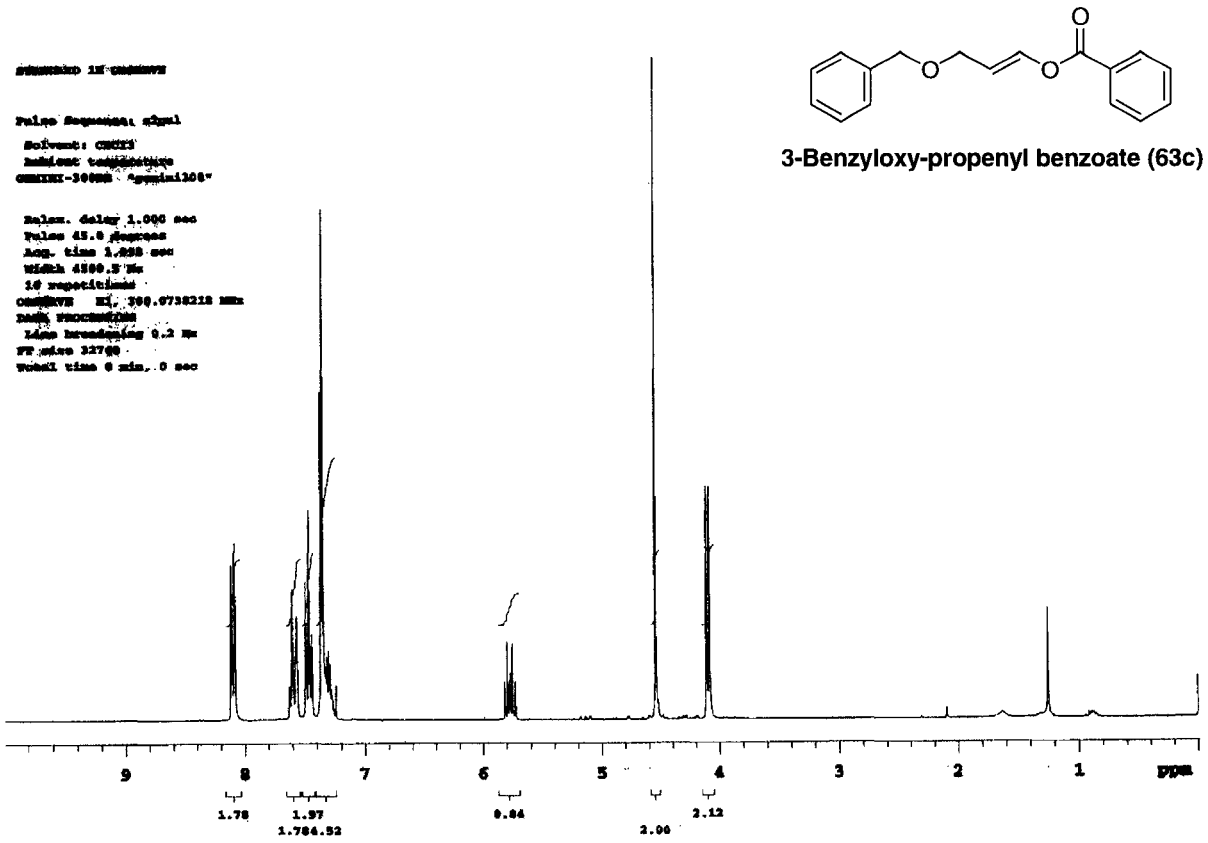


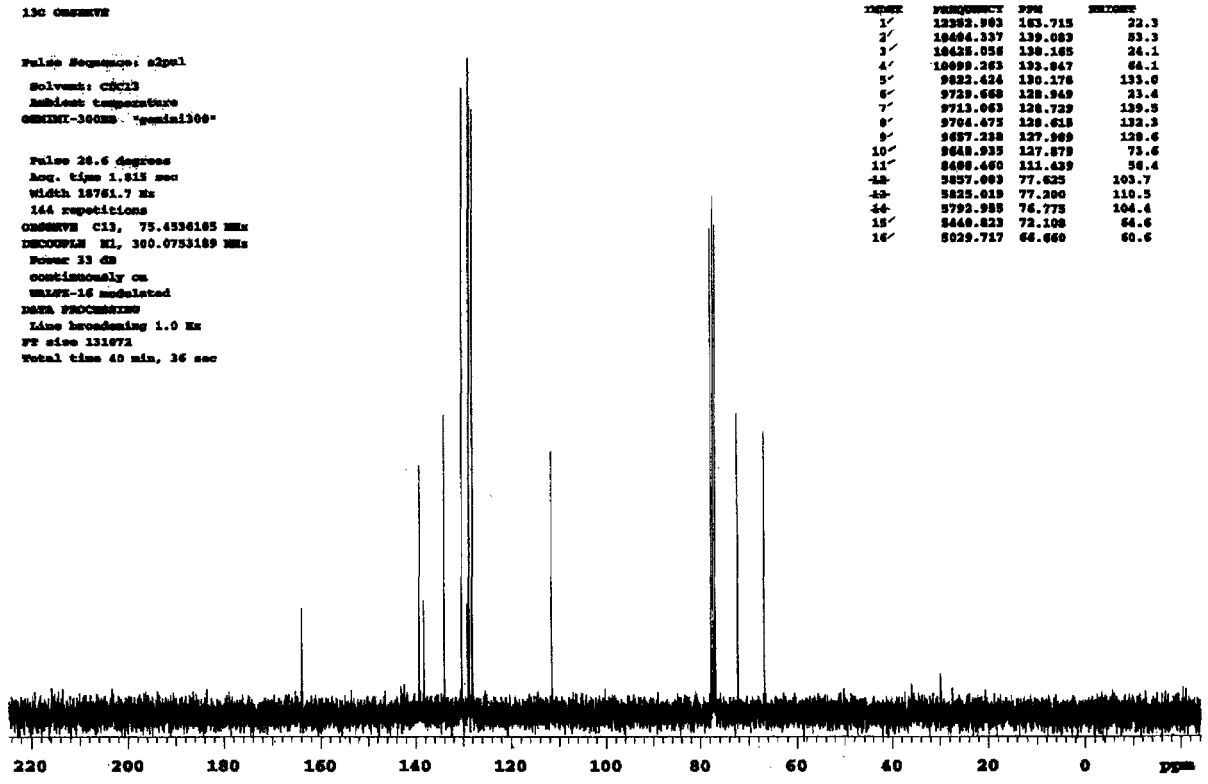

3-Benzyloxy-propenyl acetate (63a)
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Pulse 45.0 degrees
Acq. time 2.730 sec
Width 5806.6 Hz
16 repetitions
OBSERVE H1, 399.7662846 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 59 sec
9
8
7
6
5
4
3
2
1
ppm
5.47
0.82
2.00
2.07
2.88


Standard carbon parameters
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 25000.0 Hz
64 repetitions
OBSERVE C13, 100.5212969 MHz
DECOUPLE H1, 399.7687011 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 262144
Total time 1 hr, 8 min, 38 sec
INDEX FREQUENCY PPM INTENSITY
1 16852.748 168.049 14.2
2✓ 13860.691 138.782 55.2
3 13887.076 138.191 21.8
4 13923.476 136.668 139.5
5 13859.198 127.925 136.3
6 13849.280 127.826 76.6
7✓ 11141.099 110.942 61.4
7791.525 77.511 14.6
7759.563 77.196 37.7
7727.819 76.877 38.8
7451.661 74.124 -10.5
12✓ 7262.204 72.246 76.6
13✓ 6691.739 66.570 81.2
14 2088.509 20.777 43.6
200
180
160
140
120
100
80
60
40
20
0
ppm


3-Benzyloxy-propenyl sorbate (63b)
9
8
7
6
5
4
3
2
1
ppm
6.94
1.79
0.94
0.83
2.20
2.32
3.00

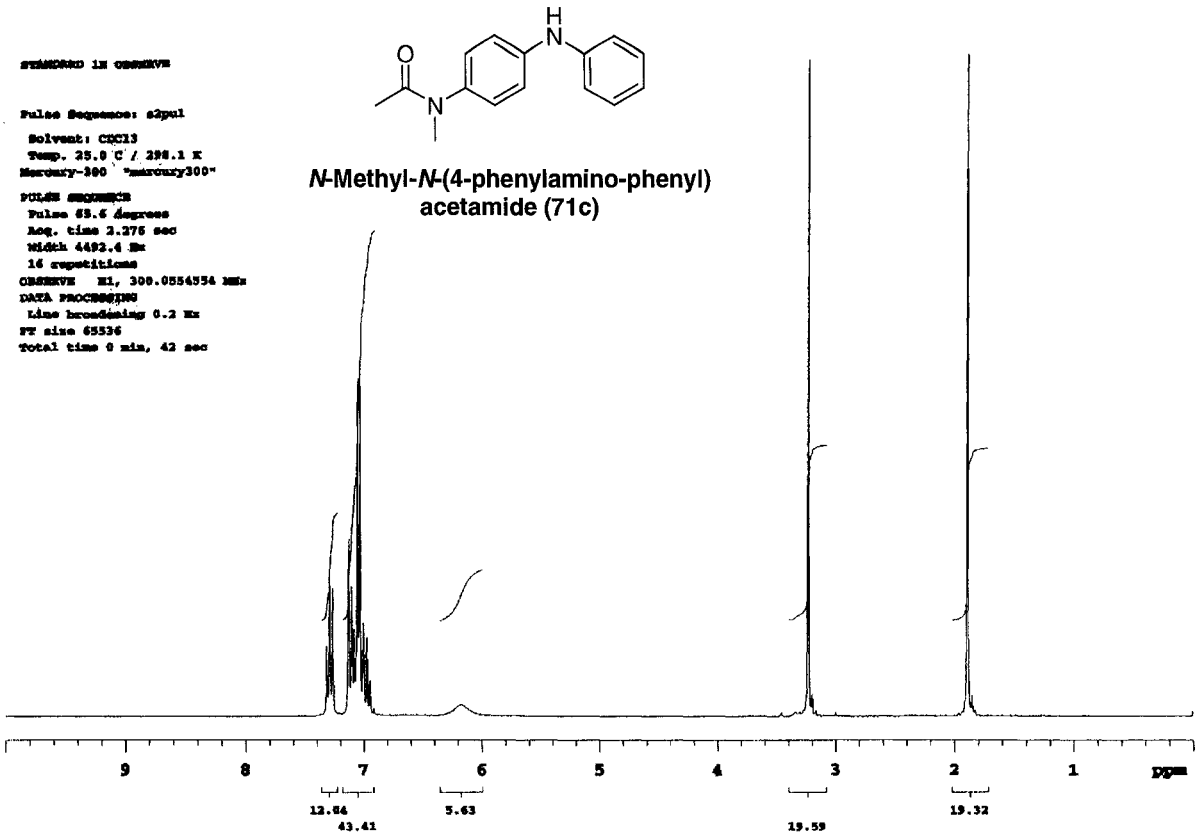

220
200
180
160
140
120
100
80
60
40
20
0
ppm

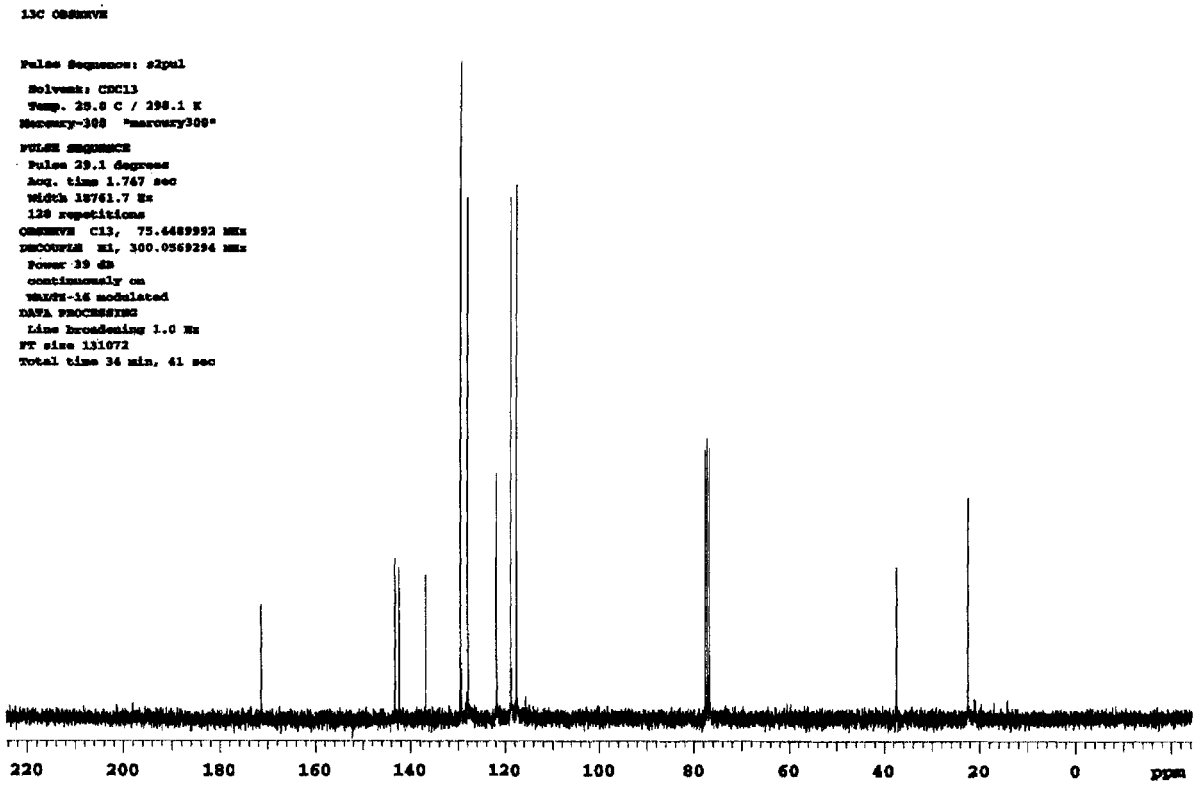

3-Benzyloxy-propenyl benzoate (63c)
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.638 sec
Width 4500.5 Hz
16 repetitions
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 0 sec
9
8
7
6
5
4
3
2
1
ppm
1.78
1.97
1.784.52
0.84
2.00
2.12

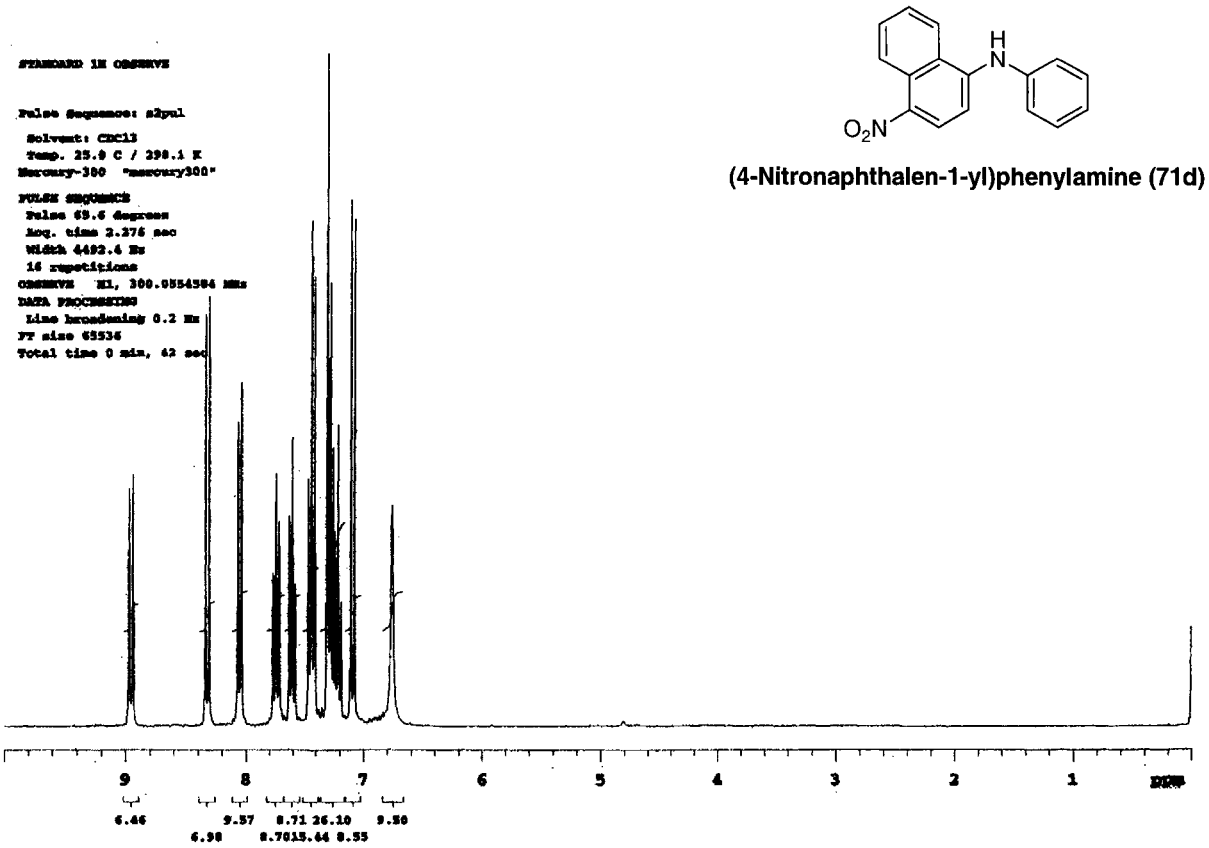

13C CHLOROFORM
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Pulse 28.6 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
144 repetitions
OBSERVE C13, 75.4536185 MHz
DECOUPLE H1, 300.0753189 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
Line broadening 1.0 Hz
FT size 131072
Total time 40 min, 36 sec
INDEX FREQUENCY PPM HEIGHT
1 12382.963 163.715 22.3
2 10494.337 139.083 53.3
3 10428.058 138.185 24.1
4 10099.263 133.847 64.1
5 9822.424 130.178 133.0
6 9729.668 128.949 23.4
7 9713.063 128.729 139.5
8 9704.673 128.618 132.3
9 9687.238 127.969 128.6
10 9648.935 127.879 73.6
11 8408.460 111.439 58.4
12 5857.003 77.625 103.7
13 5825.019 77.200 110.5
14 5792.985 76.775 104.4
15 5440.823 72.108 64.6
16 5029.717 66.660 60.6
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Appendix B.4

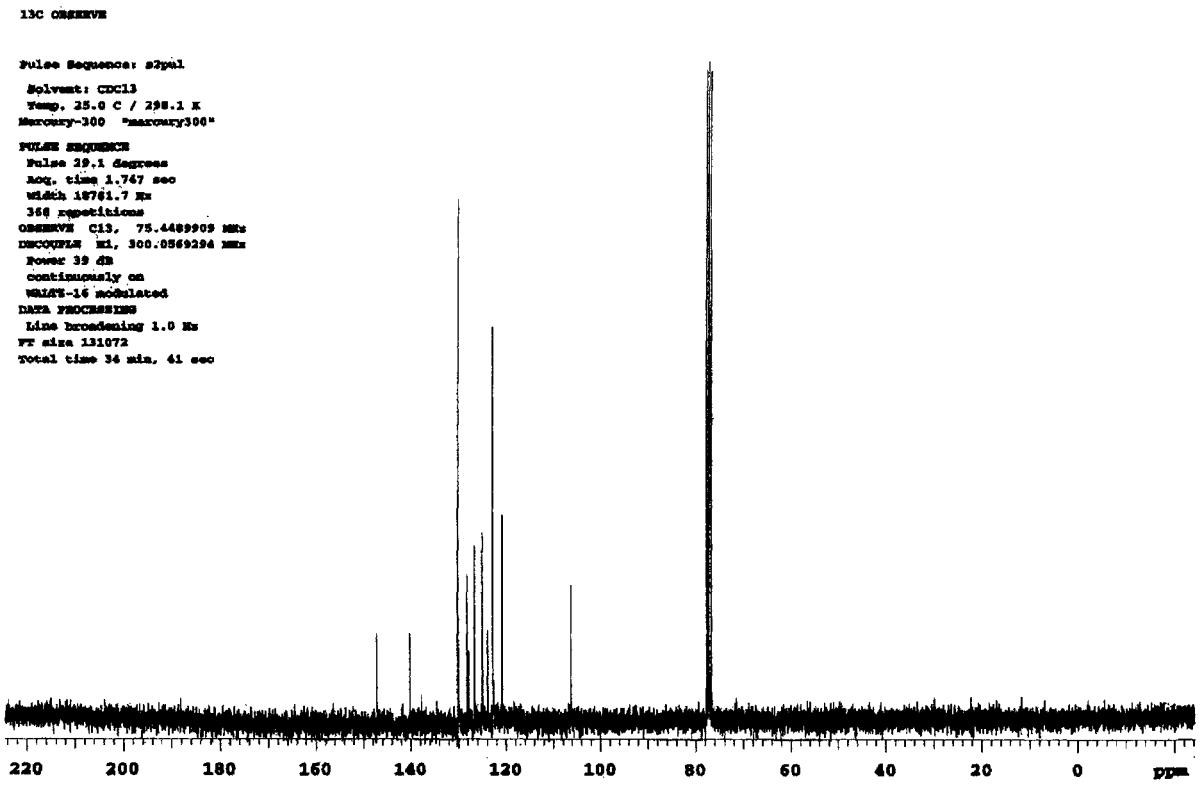
Novel Products from Arylation of Anilines and Aliphatic Amines

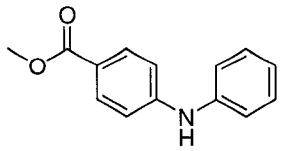

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Pulse 45.6 degrees
Acq. time 2.275 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0554554 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec
N-Methyl-N-(4-phenylamino-phenyl) acetamide (71c)
9
8
7
6
5
4
3
2
1
ppm
12.84
43.41
5.63
19.59
19.32


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
PULSE SEQUENCE
Pulse 29.1 degrees
Acq. time 1.767 sec
Width 18761.7 Hz
128 repetitions
OBSERVE C13, 75.4689992 MHz
DECOUPLE H1, 300.0569294 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 34 min, 41 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

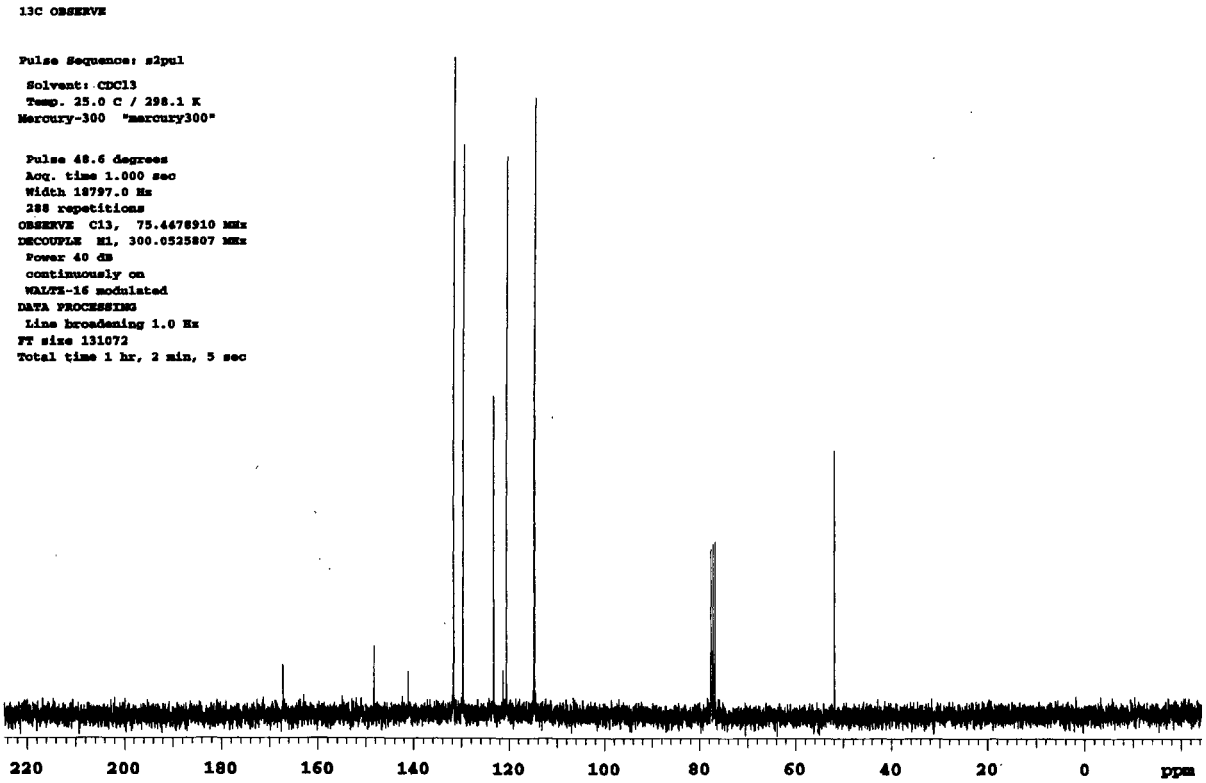


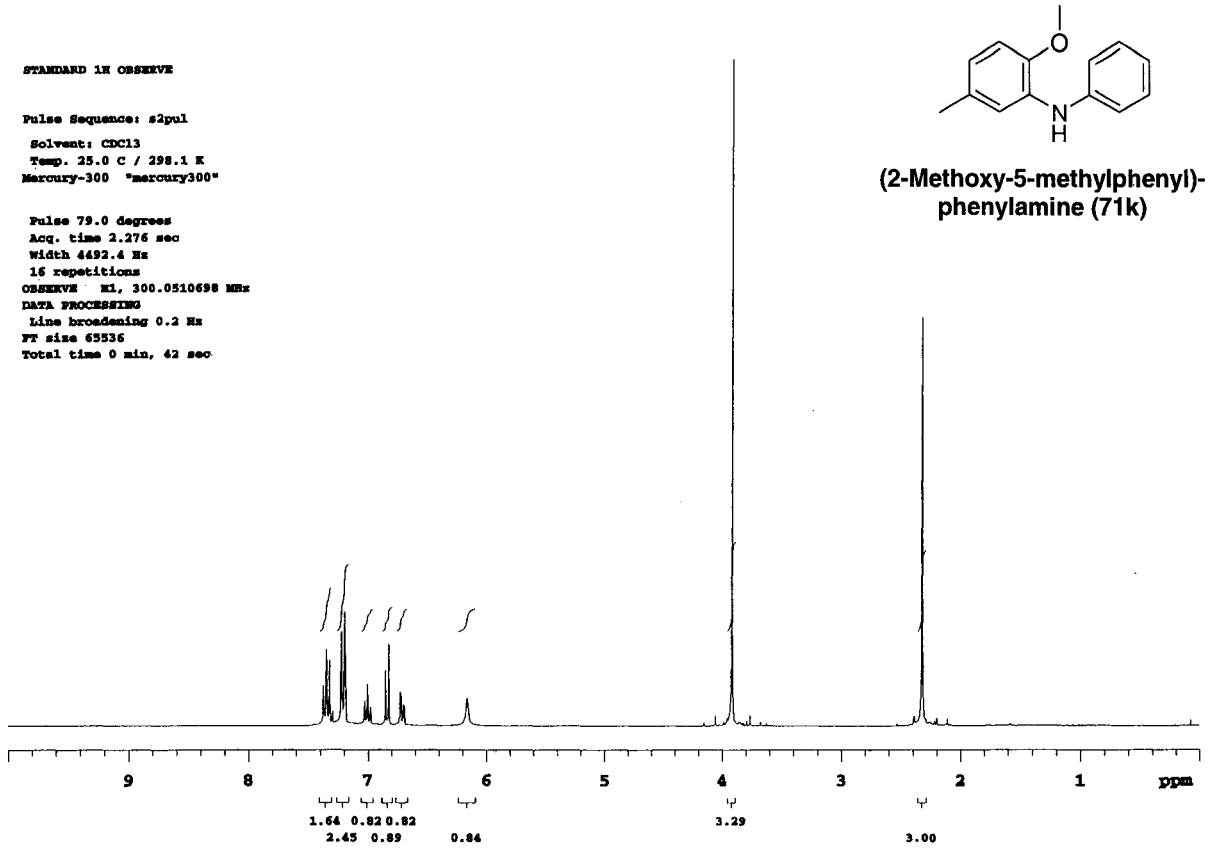
(4-Nitronaphthalen-1-yl)phenylamine (71d)

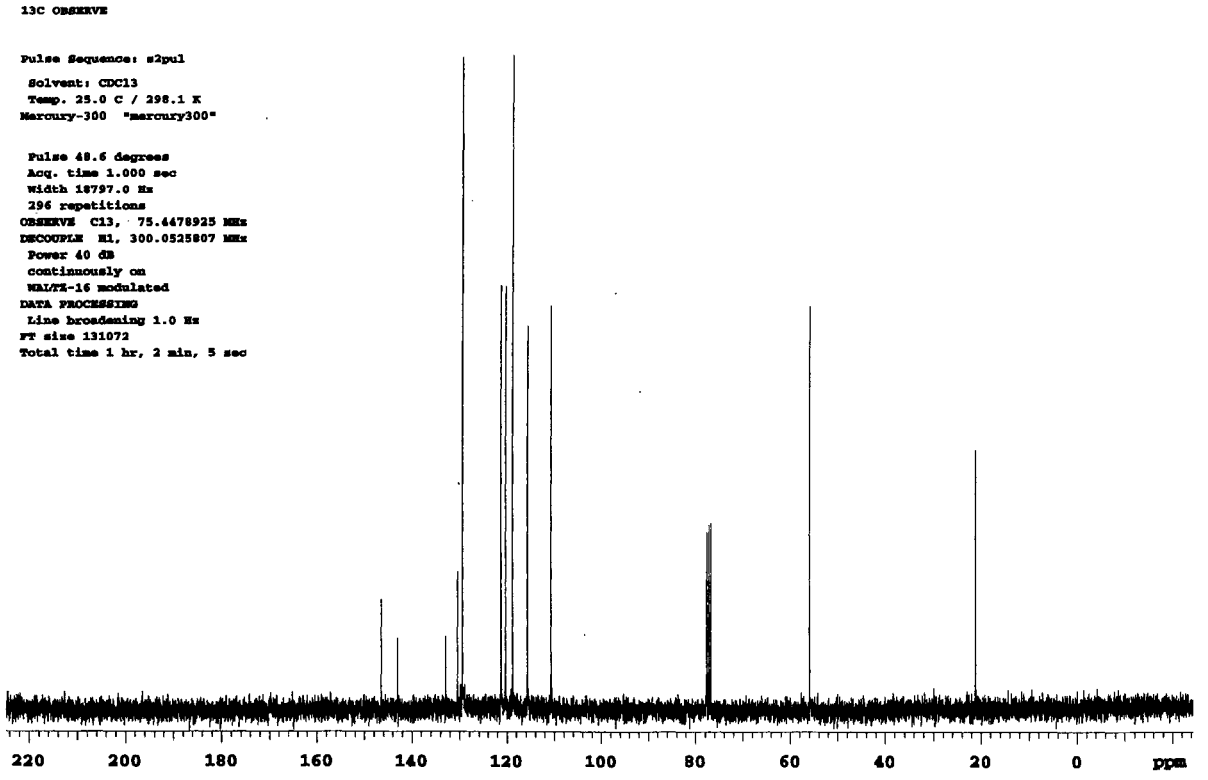


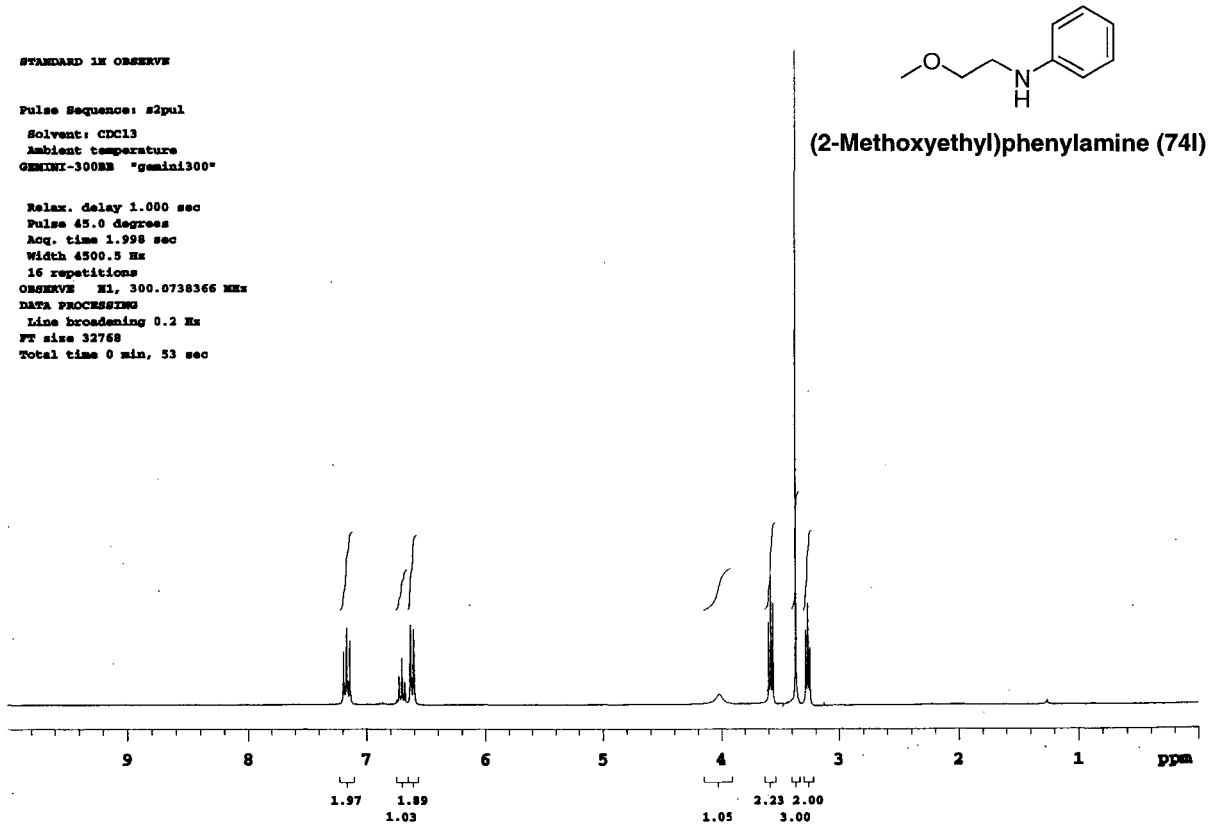


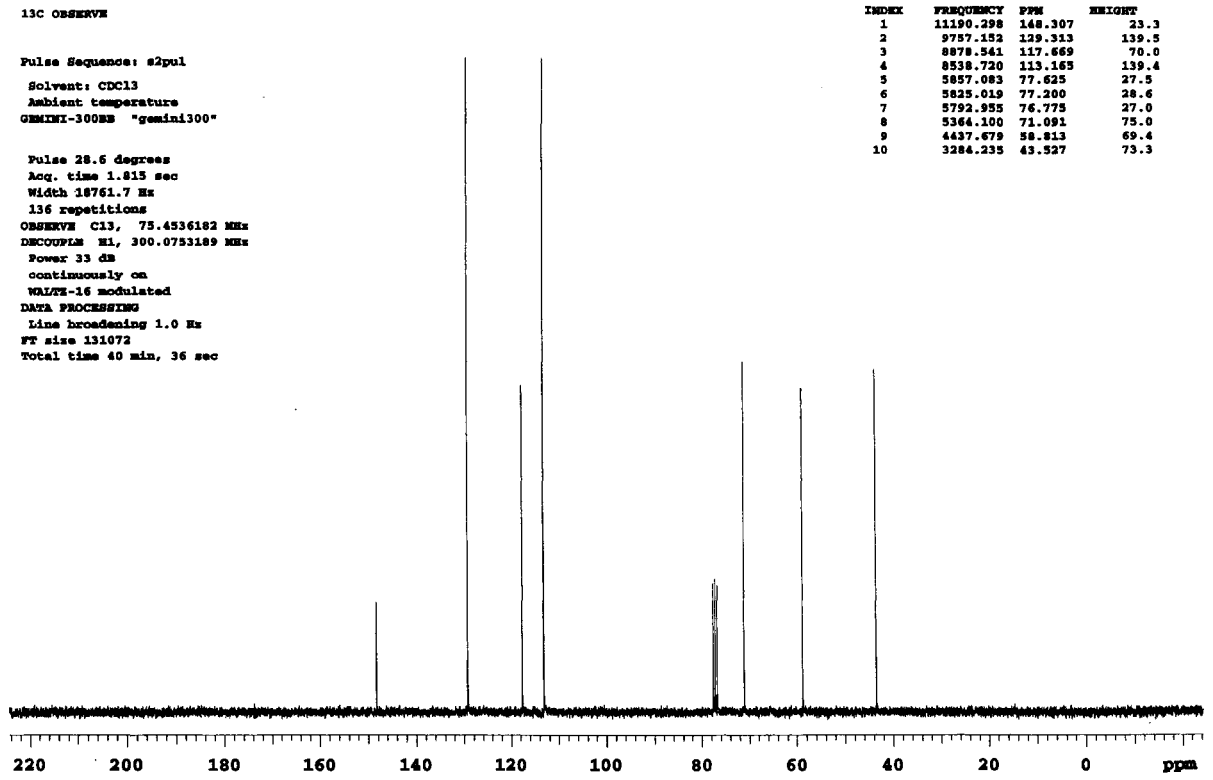
4-Anilinobenzoic acid
methyl ester (71j)

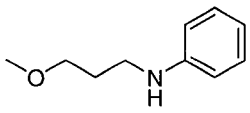



STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 79.0 degrees
Acq. time 2.276 sec
Width 4492.4 Hz
16 repetitions
OBSERVE H1, 300.0510698 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 42 sec
O
N
H
(2-Methoxy-5-methylphenyl)-
phenylamine (71k)
9
8
7
6
5
4
3
2
1
ppm
1.64 0.82 0.82
2.45 0.89
0.84
3.29
3.00


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Mercury-300 "mercury300"
Pulse 48.6 degrees
Acq. time 1.000 sec
Width 18797.0 Hz
296 repetitions
OBSERVE C13, 75.4678925 MHz
DECOUPLE H1, 300.0525807 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 2 min, 5 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

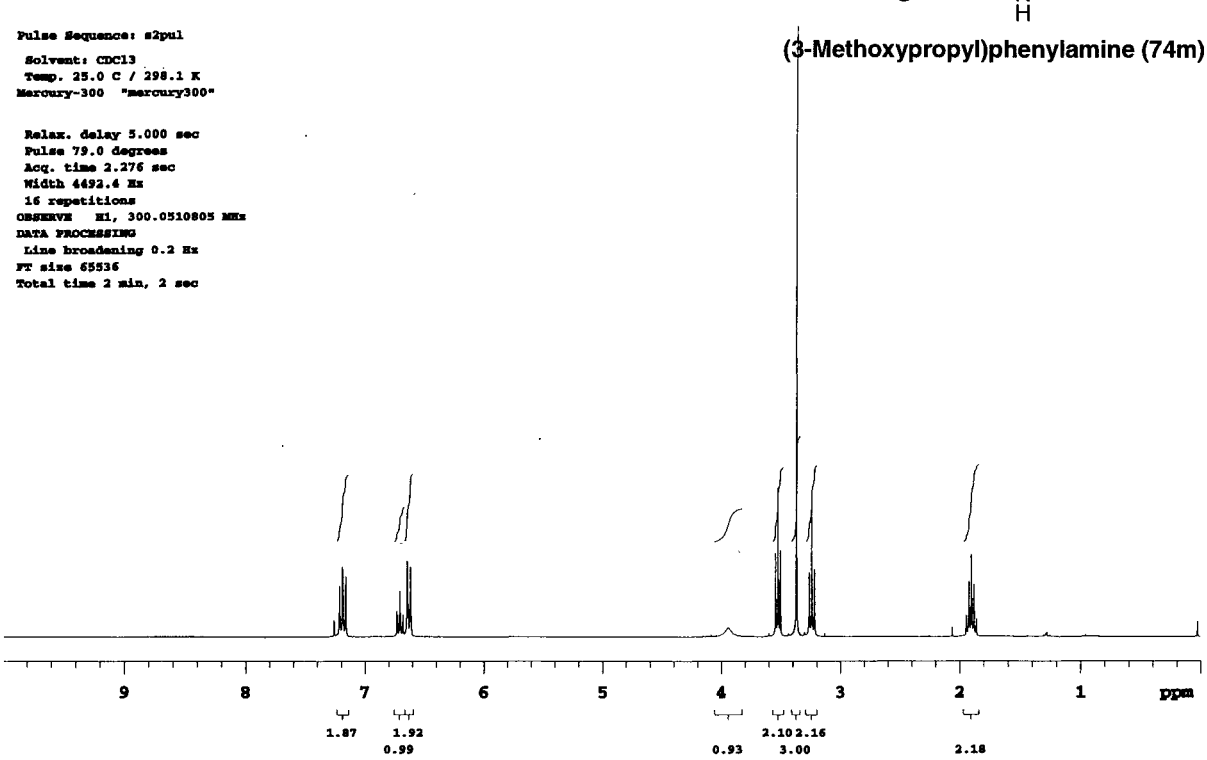

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "gemini300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0738366 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 53 sec
(2-Methoxyethyl)phenylamine (74l)
9
8
7
6
5
4
3
2
1
ppm
1.97
1.89
1.03
1.05
2.23
2.00
3.00


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "gemini300"
Pulse 28.6 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
136 repetitions
OBSERVE C13, 75.4536182 MHz
DECOUPLE H1, 300.0753189 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 40 min, 36 sec
INDEX FREQUENCY PPM HEIGHT
1 11190.298 148.307 23.3
2 9757.152 129.313 139.5
3 8878.541 117.669 70.0
4 8538.720 113.165 139.4
5 5857.083 77.625 27.5
6 5825.019 77.200 28.6
7 5792.955 76.775 27.0
8 5364.100 71.091 75.0
9 4437.679 58.813 69.4
10 3284.235 43.527 73.3
220
200
180
160
140
120
100
80
60
40
20
0
ppm



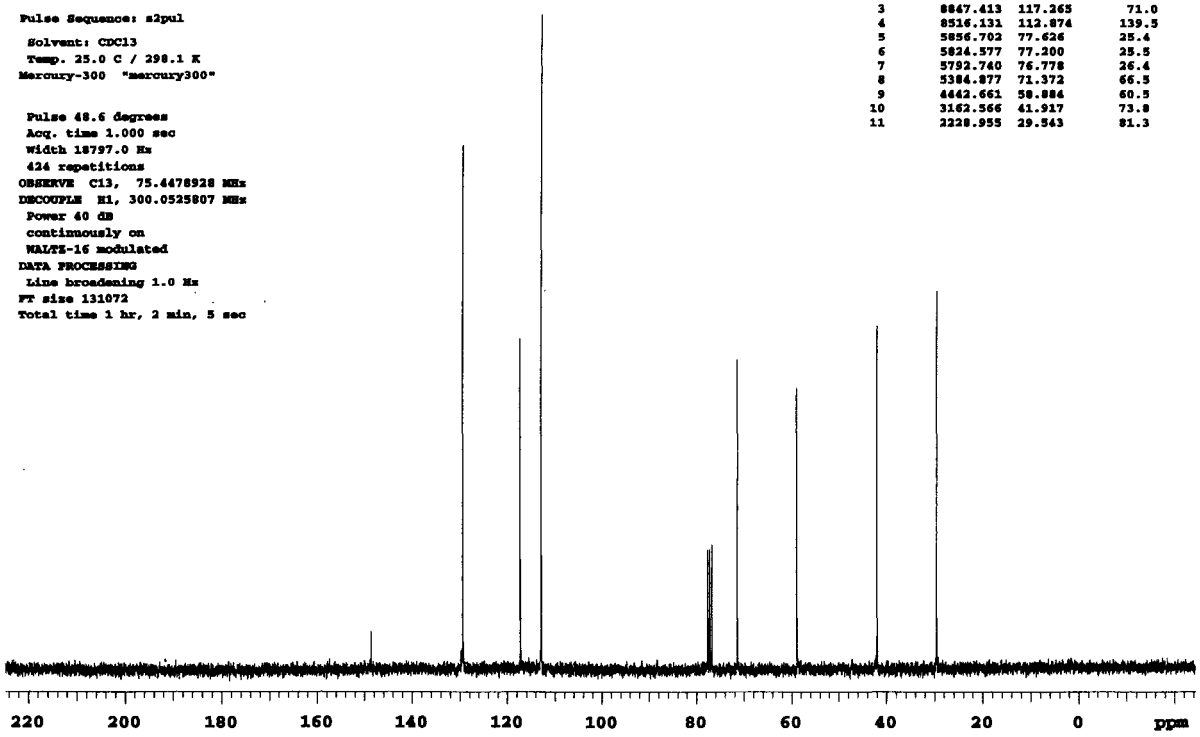
(3-Methoxypropyl)phenylamine (74m)

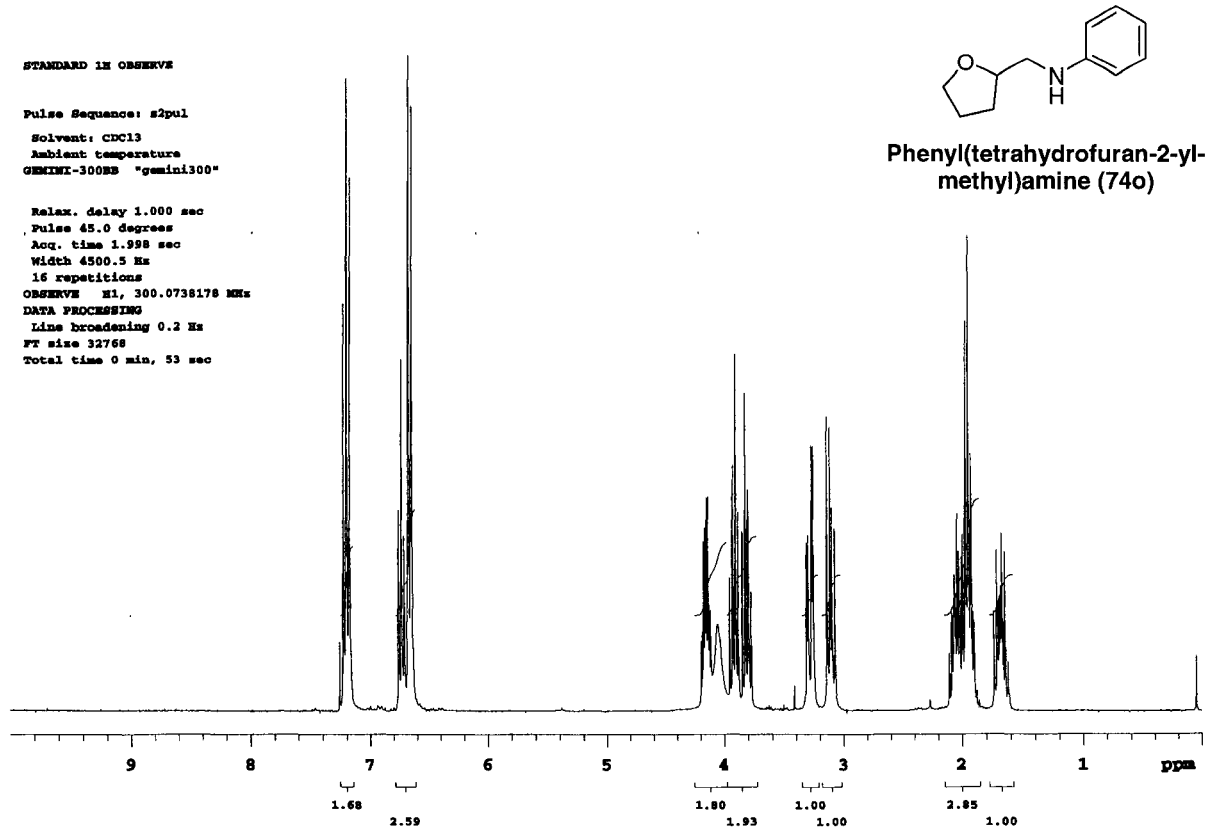
```
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Mercury-300  "mercury300"

 Relax. delay 5.000 sec
 Pulse 79.0 degrees
 Acq. time 2.276 sec
 Width 4492.4 Hz
 16 repetitions
OBSERVE   H1, 300.0510805 MHz
DATA PROCESSING
 Line broadening 0.2 Hz
FT size 65536
Total time 2 min, 2 sec
```

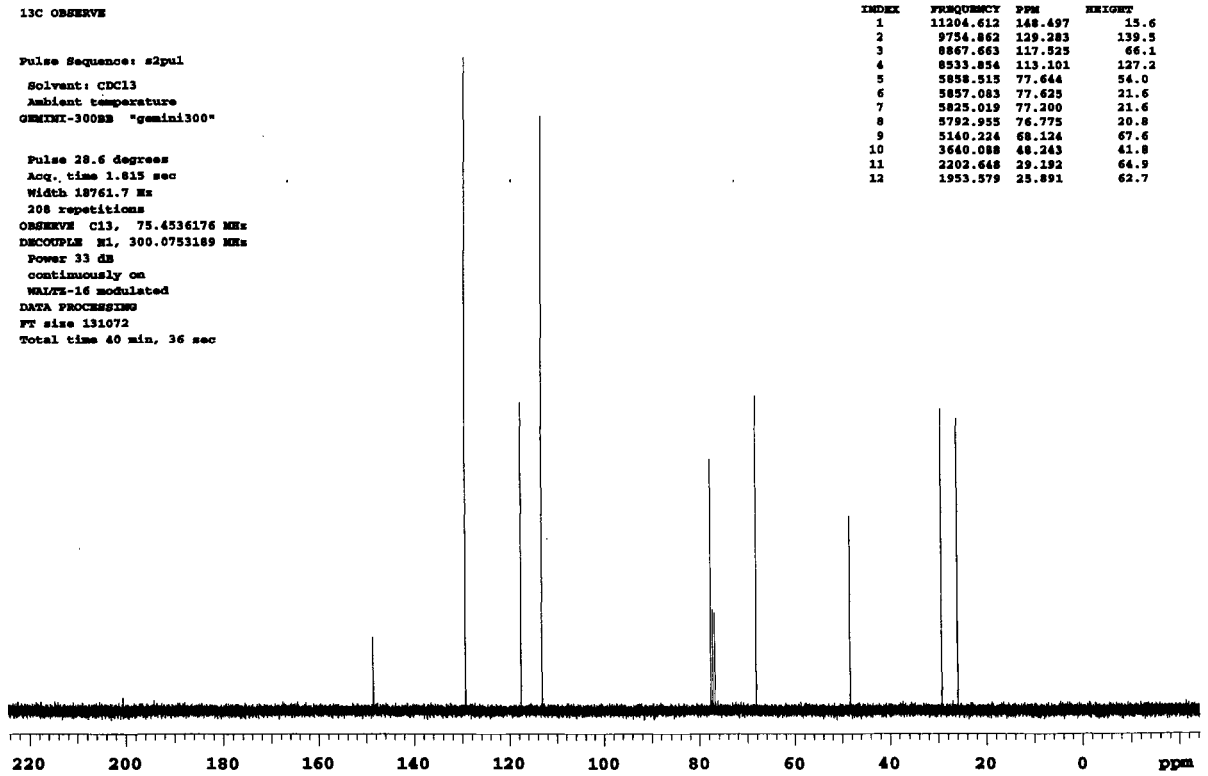


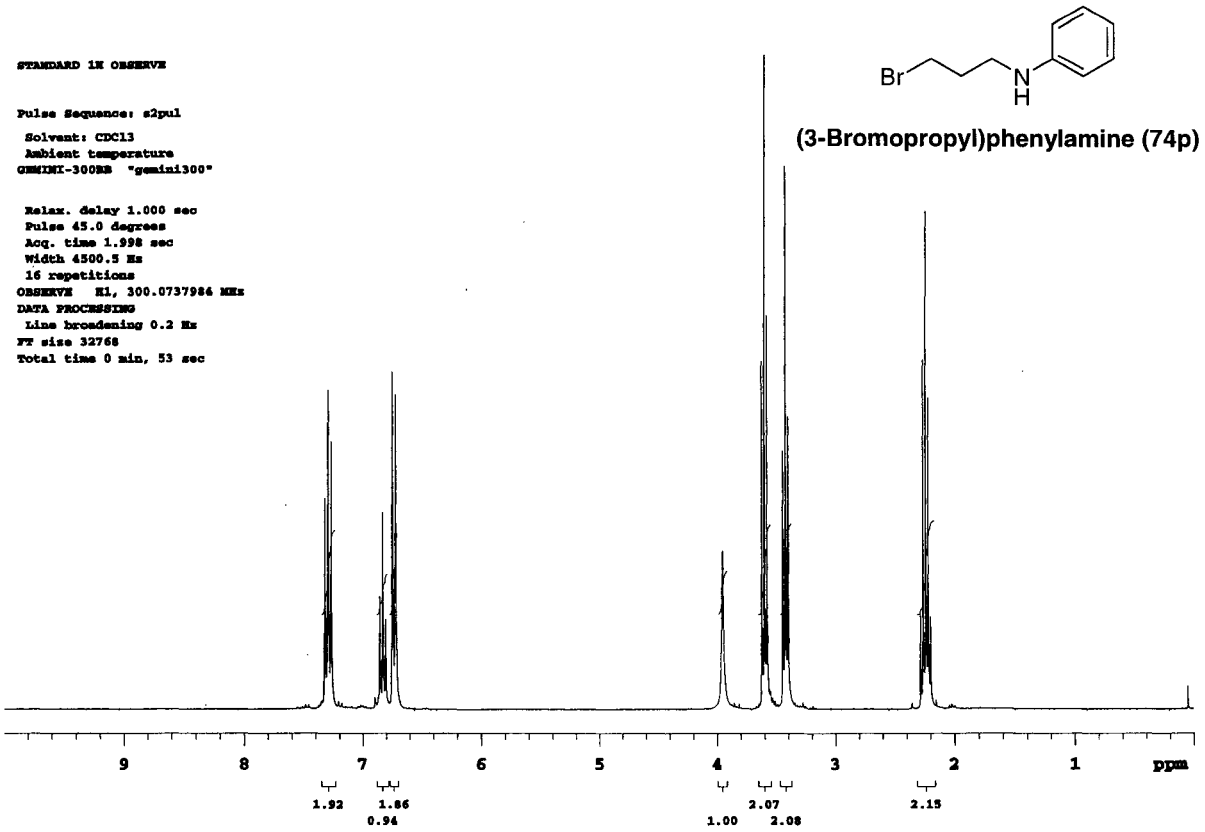

```
13C OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Mercury-300  "mercury300"

 Pulse 48.6 degrees
 Acq. time 1.000 sec
 Width 18797.0 Hz
 424 repetitions
OBSERVE   C13,   75.4478928 MHz
DECOUPLE  H1, 300.0525807 MHz
 Power 40 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 2 min, 5 sec
```

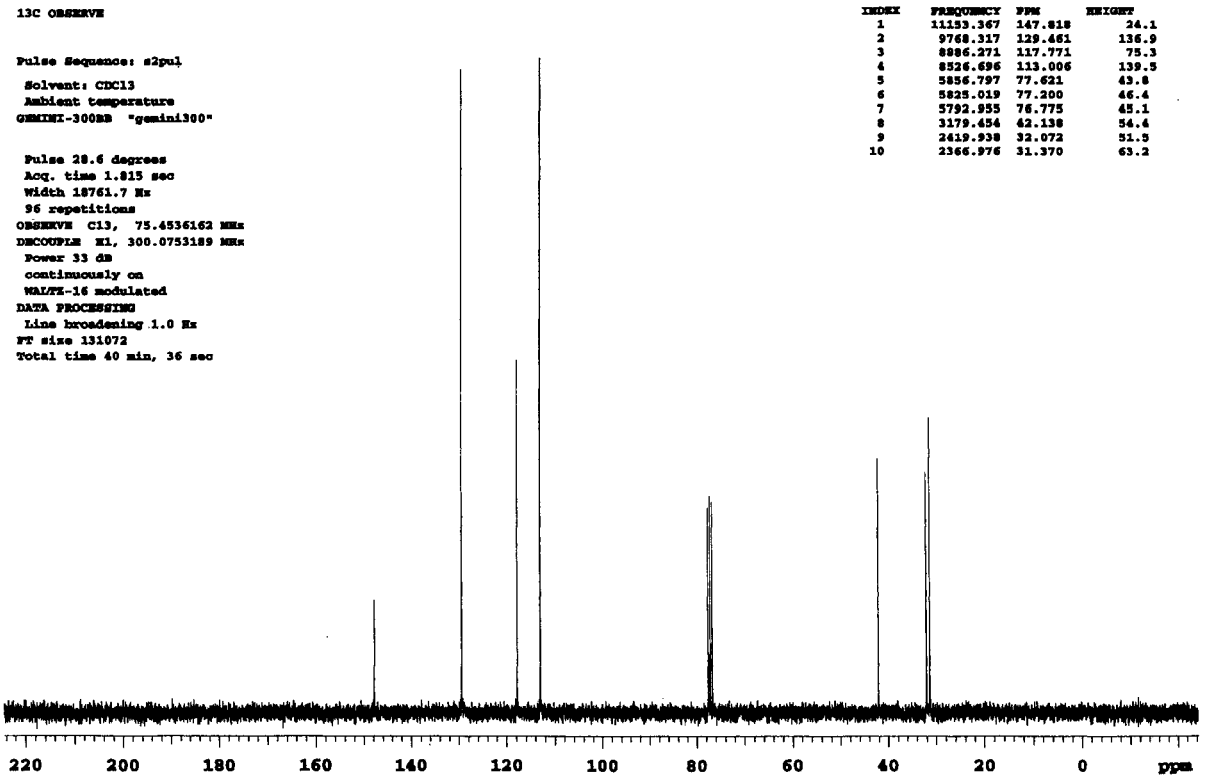
INDEX	FREQUENCY	PPM	HEIGHT
1	11216.290	148.663	7.9
2	9760.659	129.370	112.0
3	8847.413	117.265	71.0
4	8516.131	112.874	139.5
5	5856.702	77.626	25.4
6	5824.577	77.200	25.5
7	5792.740	76.778	26.4
8	5384.877	71.372	66.5
9	4442.661	58.884	60.5
10	3162.566	41.917	73.8
11	2228.955	29.543	81.3

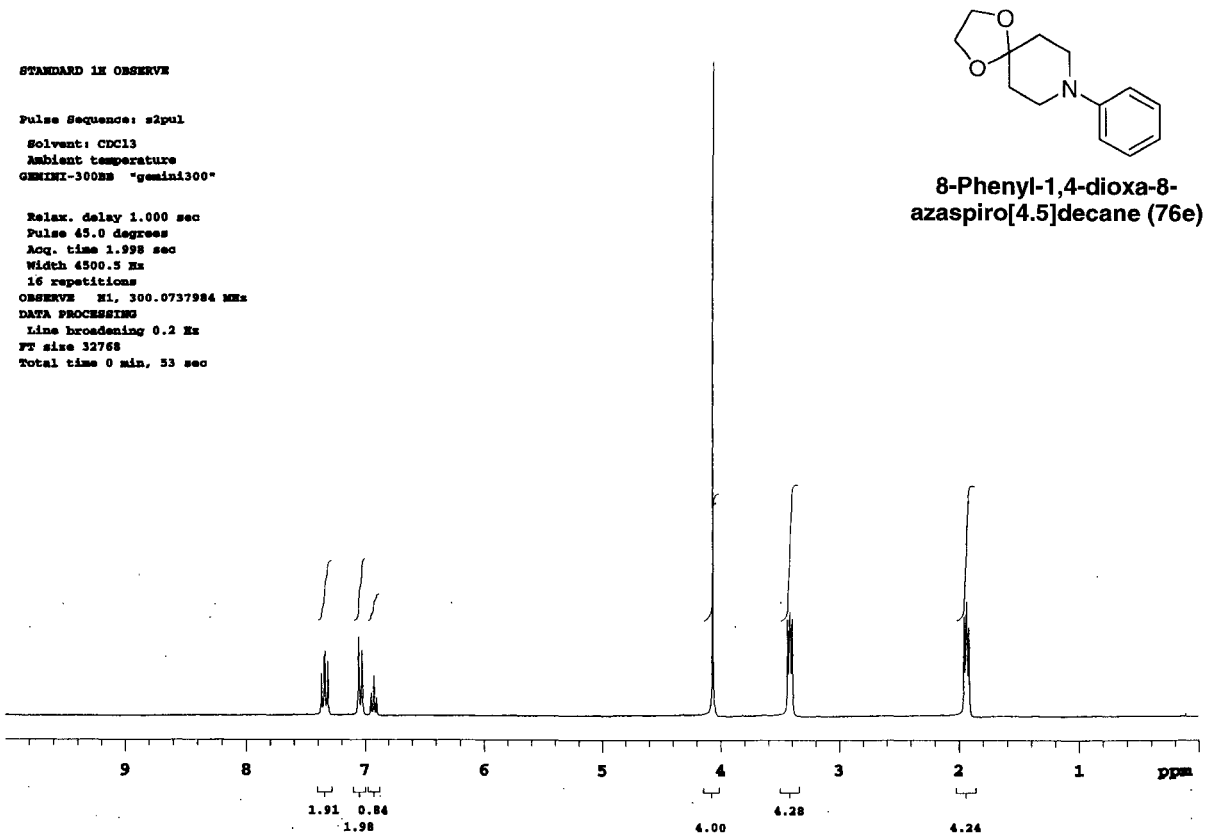



STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "gemini300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0738178 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 53 sec
Phenyl(tetrahydrofuran-2-yl-methyl)amine (74o)
9
8
7
6
5
4
3
2
1
ppm
1.68
2.59
1.80
1.93
1.00
1.00
2.85
1.00

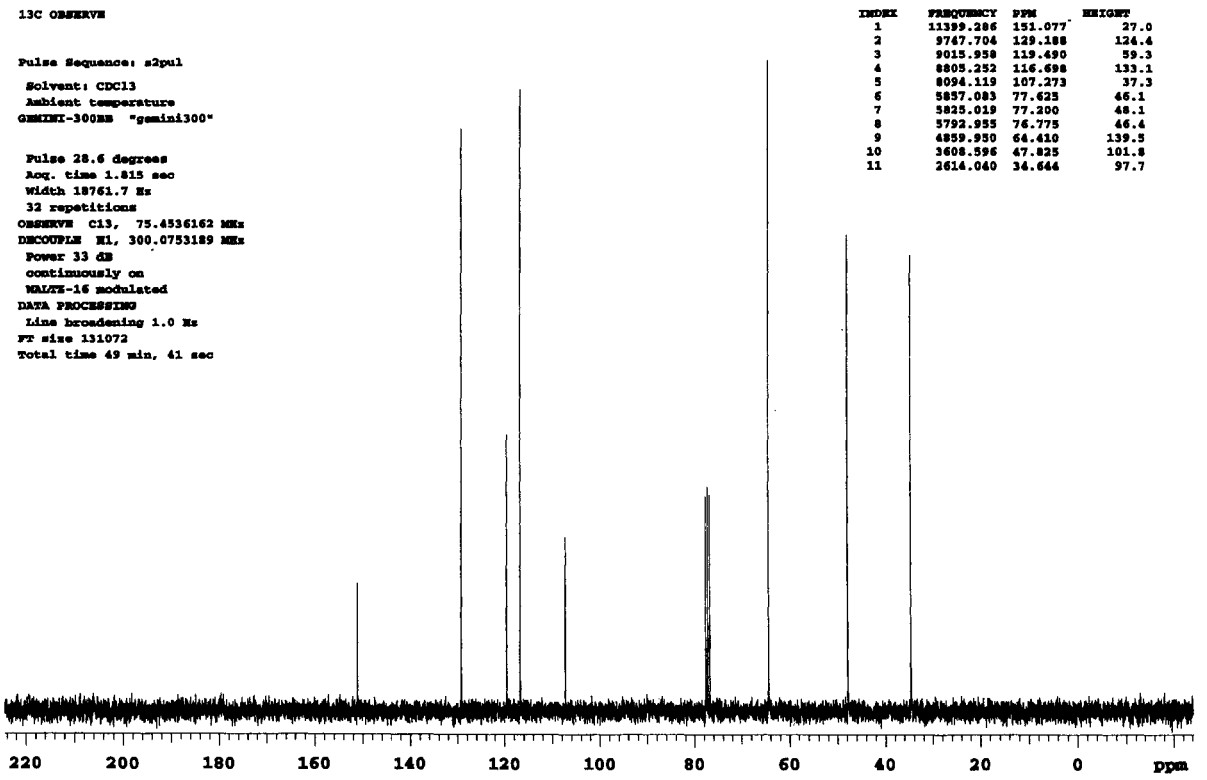

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "gemini300"
Pulse 28.6 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
208 repetitions
OBSERVE C13, 75.4536176 MHz
DECOUPLE H1, 300.0753189 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
FT size 131072
Total time 40 min, 36 sec
INDEX FREQUENCY PPM HEIGHT
1 11204.612 148.497 15.6
2 9754.862 129.283 139.5
3 8867.663 117.525 66.1
4 8533.854 113.101 127.2
5 5858.515 77.644 54.0
6 5857.083 77.625 21.6
7 5825.019 77.200 21.6
8 5792.955 76.775 20.8
9 5140.224 68.124 67.6
10 3640.088 48.243 41.8
11 2202.648 29.192 64.9
12 1953.579 25.891 62.7
220
200
180
160
140
120
100
80
60
40
20
0
ppm

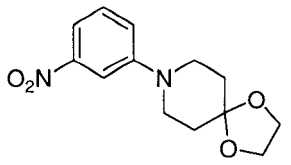

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "gemini300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0737986 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 53 sec
Br
N
H
(3-Bromopropyl)phenylamine (74p)
9
8
7
6
5
4
3
2
1
ppm
1.92
1.86
0.94
1.00
2.07
2.08
2.15


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "gemini300"
Pulse 28.6 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
96 repetitions
OBSERVE C13, 75.4536162 MHz
DECOUPLE H1, 300.0753189 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 40 min, 36 sec
INDEX FREQUENCY PPM HEIGHT
1 11153.367 147.818 24.1
2 9768.317 129.461 136.9
3 8886.271 117.771 75.3
4 8526.696 113.006 139.5
5 5856.797 77.621 43.8
6 5825.019 77.200 46.4
7 5792.955 76.775 45.1
8 3179.454 42.138 54.4
9 2419.938 32.072 51.5
10 2366.976 31.370 63.2
220
200
180
160
140
120
100
80
60
40
20
0
ppm



8-Phenyl-1,4-dioxa-8-azaspiro[4.5]decane (76e)





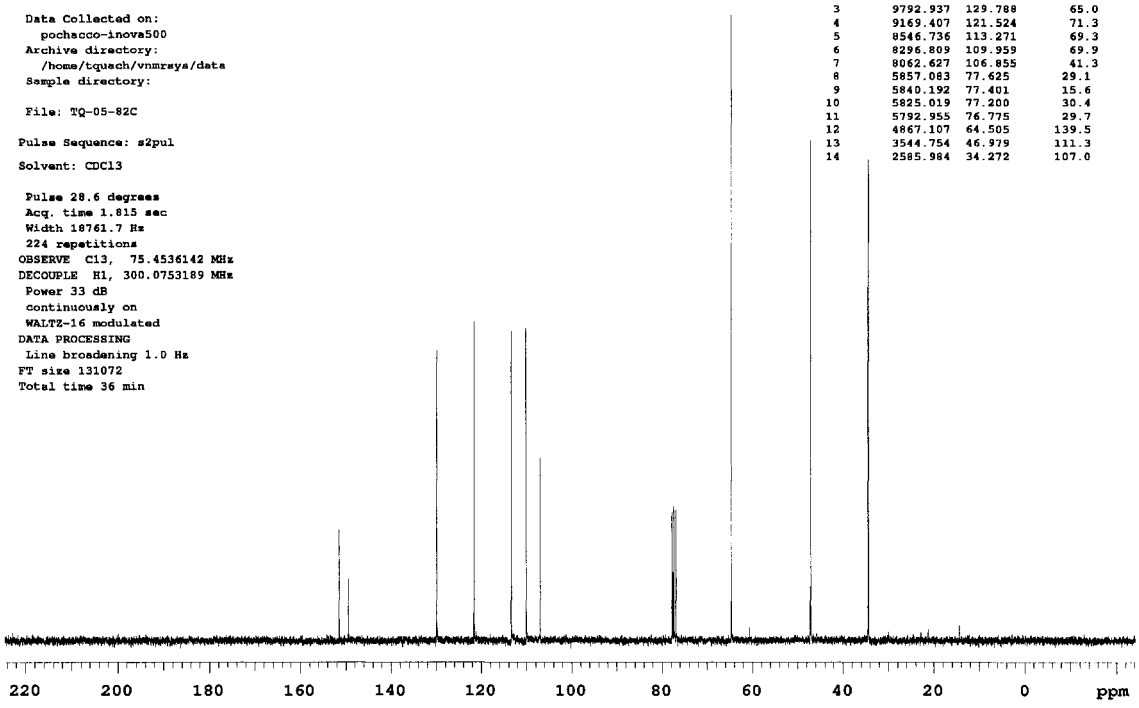
8-(3-Nitro-phenyl)-1,4-dioxa-8-azaspiro[4.5]decane (76k)

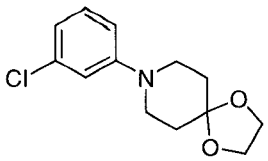
```
STANDARD 1H OBSERVE

 Data Collected on:
   pochacco-inova500
 Archive directory:
   /home/tquach/vnmrsys/data
 Sample directory:

 File: TQ-05-82H

Pulse Sequence: s2pul
Solvent: CDCl3

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 4500.5 Hz
 16 repetitions
OBSERVE   H1, 300.0738184 MHz
DATA PROCESSING
 Line broadening 0.2 Hz
FT size 32768
Total time 0 min
```



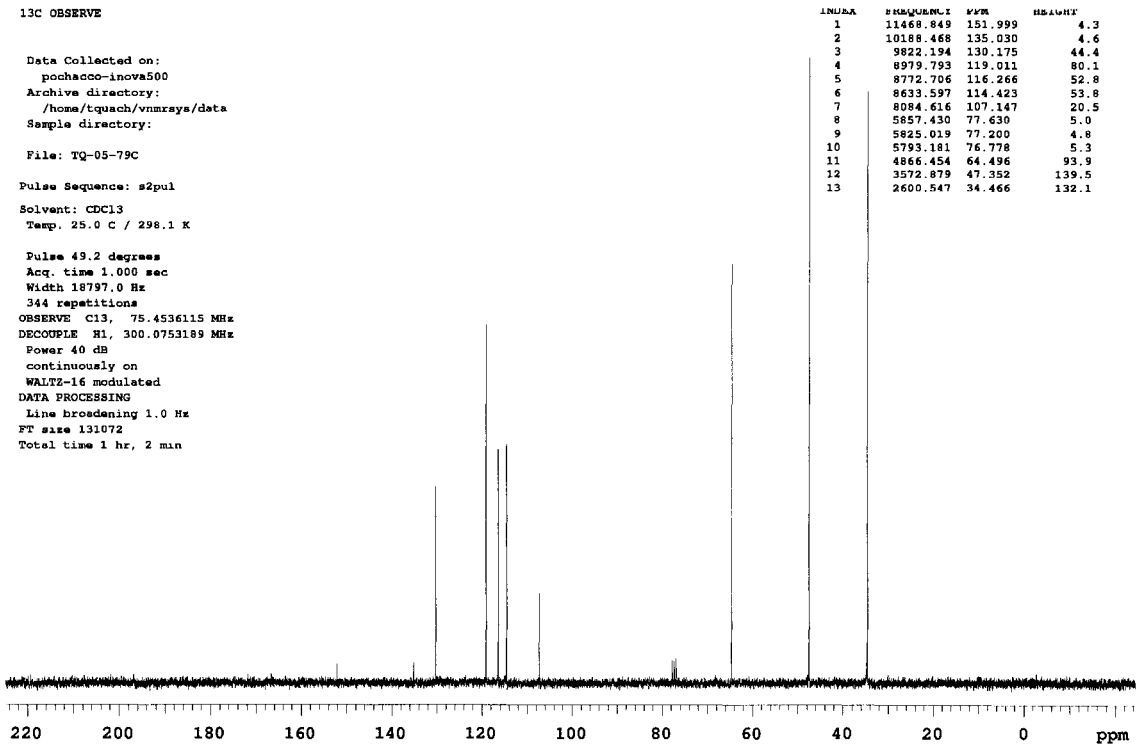
```
13C OBSERVE

 Data Collected on:
   pochacco-inova500
 Archive directory:
   /home/tquach/vnmrsys/data
 Sample directory:

 File: TQ-05-82C

Pulse Sequence: s2pul
Solvent: CDCl3

 Pulse 28.6 degrees
 Acq. time 1.815 sec
 Width 18761.7 Hz
 224 repetitions
OBSERVE   C13,   75.4536142 MHz
DECOUPLE  H1,  300.0753189 MHz
 Power 33 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 36 min
```

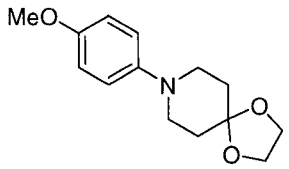
INDEX	FREQUENCY	PPM	HEIGHT
1	11419.326	151.342	25.3
2	11268.739	149.347	13.8
3	9792.937	129.788	65.0
4	9169.407	121.524	71.3
5	8546.736	113.271	69.3
6	8296.809	109.959	69.9
7	8062.627	106.855	41.3
8	5857.083	77.625	29.1
9	5840.192	77.401	15.6
10	5825.019	77.200	30.4
11	5792.955	76.775	29.7
12	4867.107	64.505	139.5
13	3544.754	46.979	111.3
14	2585.984	34.272	107.0





8-(3-Chloro-phenyl)-1,4-dioxa-8-azaspiro[4.5]decane (76l)





8-(4-Methoxy-phenyl)-1,4-dioxa-8-azaspiro[4.5]decane (76m)

STANDARD 1H OBSERVE

Data Collected on:
pochacco-inova500
Archive directory:
/home/tquach/vnmrsys/data
Sample directory:

File: TQ-05-81H

Pulse Sequence: s2pul

Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0738184 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min

13C OBSERVE

Data Collected on:
pochacco-inova500
Archive directory:
/home/tquach/vnmrsys/data
Sample directory:

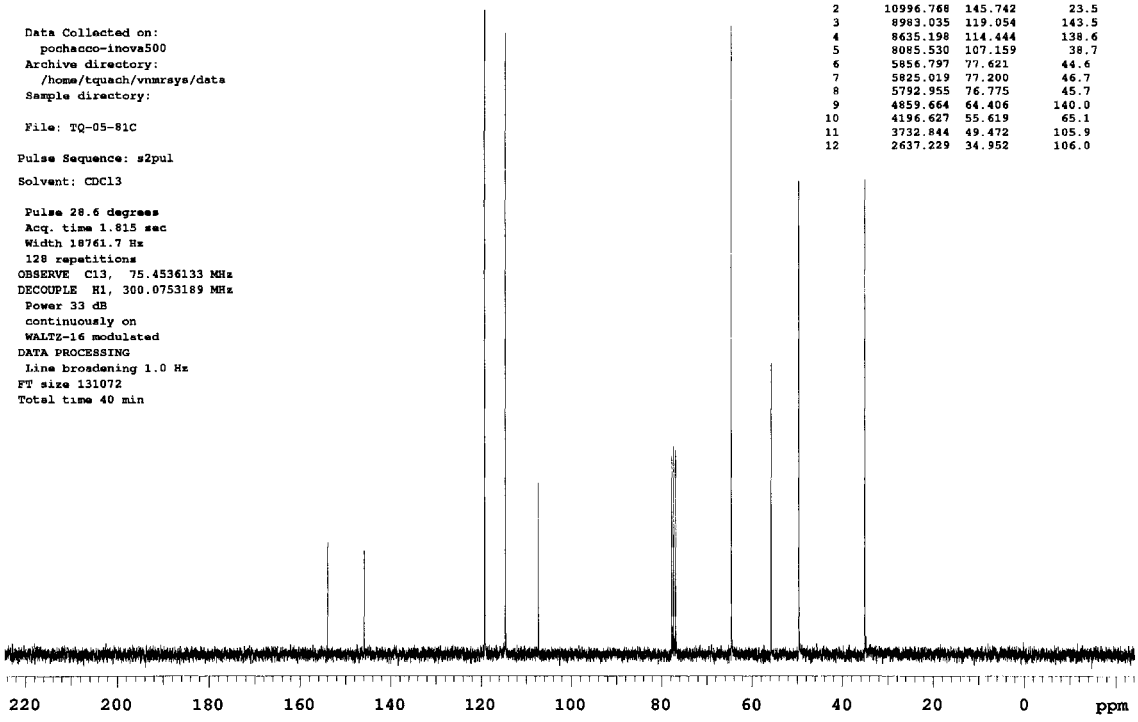
File: TQ-05-81C

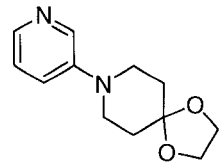
Pulse Sequence: s2pul

Solvent: CDCl3

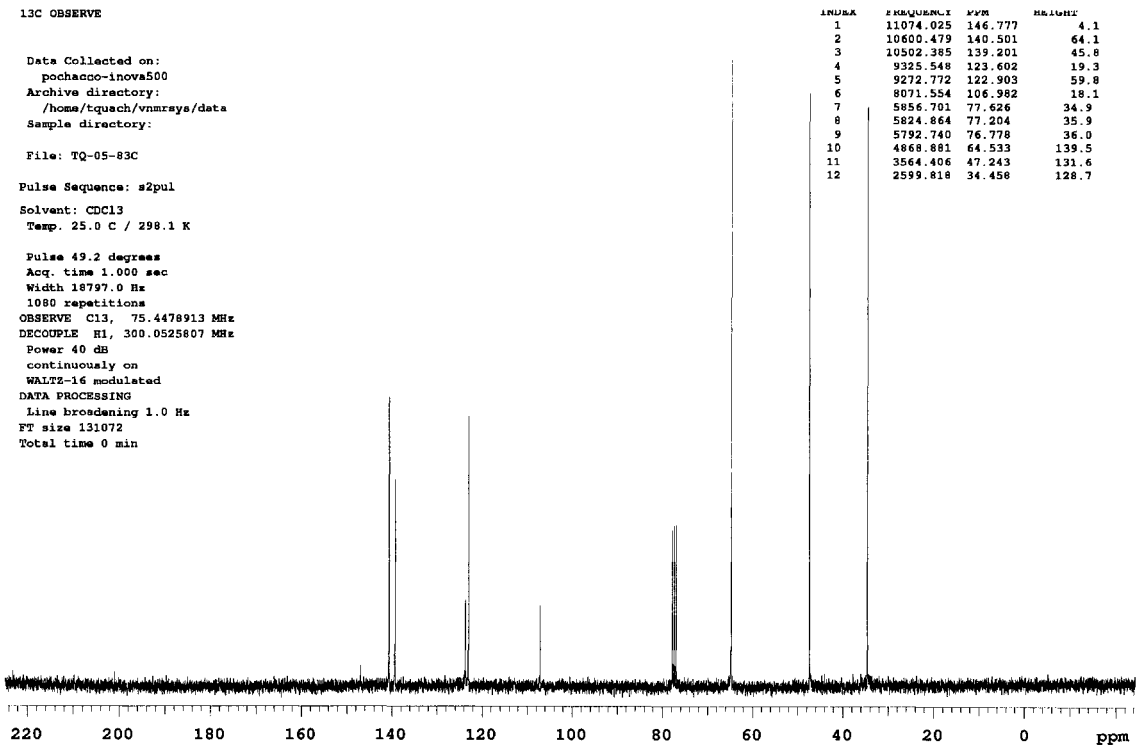
Pulse 28.6 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
128 repetitions
OBSERVE C13, 75.4536133 MHz
DECOUPLE H1, 300.0753189 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 40 min

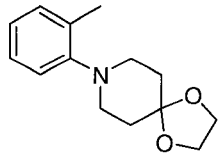
INDEX	FREQUENCY	PPM	HEIGHT
1	11606.556	153.824	25.4
2	10996.768	145.742	23.5
3	8983.035	119.054	143.5
4	8635.198	114.444	138.6
5	8085.530	107.159	38.7
6	5856.797	77.621	44.6
7	5825.019	77.200	46.7
8	5792.955	76.775	45.7
9	4859.664	64.406	140.0
10	4196.627	55.619	65.1
11	3732.844	49.472	105.9
12	2637.229	34.952	106.0



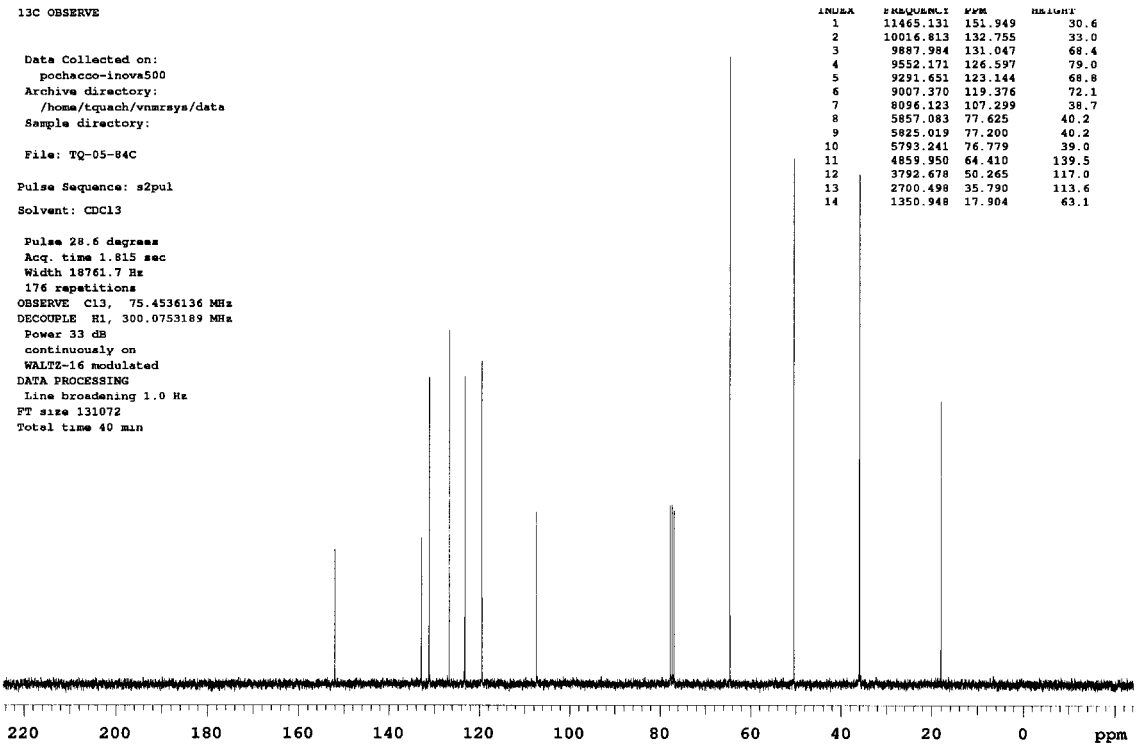


8-Pyridin-3-yl-1,4-dioxa-8-azaspiro[4.5]decane (76n)





8-*o*-Tolyl-1,4-dioxa-8-azaspiro[4.5]decane (76o)



INDEX	FREQUENCY	PPM	HEIGHT
1	11465.131	151.949	30.6
2	10016.813	132.755	33.0
3	9887.984	131.047	68.4
4	9552.171	126.597	79.0
5	9291.651	123.144	68.8
6	9007.370	119.376	72.1
7	8096.123	107.299	38.7
8	5857.083	77.625	40.2
9	5825.019	77.200	40.2
10	5793.241	76.779	39.0
11	4859.950	64.410	139.5
12	3792.678	50.265	117.0
13	2700.498	35.790	113.6
14	1350.948	17.904	63.1