A Two Part Research Report: Aromatic Nucleophilic Fluoroal Koxylation via Cationic Phase Transfer Catalysis and Reactions of Unsymmetrical Vinamidinium Salts with Organometallic Reagents

Joseph E. Coury
University of Central Florida

This Masters Thesis (Open Access) is brought to you for free and open access by STARS. It has been accepted for inclusion in Retrospective Theses and Dissertations by an authorized administrator of STARS. For more information, please contact STARS@ucf.edu.

STARS Citation
https://stars.library.ucf.edu/rtd/4721
A TWO PART RESEARCH REPORT
AROMATIC NUCLEOPHILIC FLUOROALKOXYLATION
VIA CATIONIC PHASE TRANSFER CATALYSIS AND
REACTIONS OF UNSYMMETRICAL VINAMIDINIUM
SALTS WITH ORGANOMETALLIC REAGENTS

BY
JOSEPH EDWARD COURY
B.S., The Florida State University, 1983

RESEARCH REPORT
Submitted in partial fulfillment of the requirements
for the Master of Science degree in Industrial Chemistry
in the Graduate Studies Program for the College of Arts and Sciences
University of Central Florida
Orlando, Florida

Fall Term
1984
This report discusses research which was conducted in two areas: the study of aromatic nucleophilic fluoroalkoxylation assisted via cationic phase transfer catalysis and the study of unsymmetrical vinamidinium salts and their reactions with organometallic reagents.

Sodium alkoxides have been successfully used to fluoroalkoxylate activated halo-aryl and heteroaryl substrates under phase transfer catalysis conditions. Optimum reaction conditions incorporated tetra-n-butyl-phosphonium bromide as the catalyst and refluxing toluene as the solvent medium. Different quarternary phosphonium and ammonium salts have been evaluated as catalysts: also, the effects of activating groups, leaving groups, and nucleophiles have been reported.

The reaction of 3-dimethylamino-3-phenyl-prop-2-en-l-ylidenedimethylliminium perchlorate with organolithium and Grignard reagents has also been studied in an effort to define the reaction in terms of which electrophilic site of the salt is susceptible to nucleophilic attack to the greatest extent. The results reported reveal that the reaction occurs at the 1-position in all cases producing the \( \alpha, \beta \)-unsaturated ketone after acid hydrolysis.

Finally, this report reveals the experimental procedures used as well as the spectral and physical data of all new compounds synthesized. Explanations of the data are offered and recommendations for future research in both areas are given.
ACKNOWLEDGEMENTS

I am deeply indebted to Dr. John T. Gupton III for his guidance, support, and understanding during my graduate research. His expertise and knowledge in the field of chemistry proved to be invaluable in enabling me to present this research report.

As members of my graduate committee, I am also indebted to Dr. Graeme Baker and Dr. Guy Mattson for their time and patience.

In addition, I would like to thank my fellow graduate students and co-workers for making my graduate career at the University of Central Florida a pleasant one. Finally, I wish to thank my family and my girlfriend Alison for their love, understanding, and support throughout my college years.
TABLE OF CONTENTS

ACKNOWLEDGEMENTS ........................................ iii
LIST OF TABLES ................................................. iv
LIST OF FIGURES ............................................... vii
LIST OF ABBREVIATIONS ........................................ viii

PART I
AROMATIC NUCLEOPHILIC FLUOROALKOXYLATION
VIA CATIONIC PHASE TRANSFER CATALYSIS

INTRODUCTION .................................................. 1
EXPERIMENTAL .................................................. 6
A. Feasibility Study and Optimization ...................... 6
B. Activating Group Study ................................... 12
C. Leaving Group Study ...................................... 16
D. Regioselectivity Study .................................... 17
E. Nucleophile Study ......................................... 19
DISCUSSION OF RESULTS ..................................... 20
CONCLUSIONS .................................................. 28
RECOMMENDATIONS ............................................. 29

PART II
REACTIONS OF UNSYMmetrical VINAMIDINIUM
SALTS WITH ORGANOMETALLIC REAGENTS

INTRODUCTION .................................................. 31
<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Experimental data for the evaluation of catalyst effectiveness</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Experimental data for the determination of optimum reaction conditions</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>Experimental data for non-heterocyclic substrates</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Experimental data for heterocyclic substrates</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>Experimental data for the evaluation of the extent of the activation at the o-, m-, and p- positions</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>Experimental data for the evaluation of leaving groups</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>Experimental data for determining the feasibility of polysubstitution and regioselective monosubstitution of activated dihaloarenes and dihaloheteroarenes</td>
<td>17</td>
</tr>
<tr>
<td>8</td>
<td>Experimental data for the determination of the effect of the nucleophile on the fluoroalkoxylation of activated benzenes</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>Experimental data for the preparation of trans-1-benzoyl ethenes</td>
<td>37</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

I. DOWCO-416 and a DOWCO-416 trifluoroethoxylated analog ... 1
II. Flecainide acetate ................................................. 2
III. The reaction of sodium methoxide with unactivated and activated benzene systems ........................................... 3
IV. Reported studies of the effect of substrate, leaving group, and nucleophile on aromatic nucleophilic fluoroalkoxylation ........................ 3
V. The reaction of aromatic tetrachlorides with alkyl thiolates under PTC conditions .............................. 4
VI. Nucleophilic displacement of activated halogen by thiophenoxide ion .................................................. 5
VII. The two resonance structures of the iminium ion .... 31
VIII. A simple amidine system ............................................. 31
IX. A simple vinamidinium system ...................................... 32
X. The reaction of vinamidinium salts with electrophiles and nucleophiles .................................................. 33
XI. The Eschenmoser reagent .............................................. 34
XII. 3-Substituted-2-phenyl-acroleins from the reaction of organometallic reagents with 2-arylvaminadinium salts. . 34
XIII. 3-Dimethylamino-3-phenyl-prop-2-en-1-ylidene-dimethyliminium perchlorate ................................................. 35
XIV. Proposed synthetic route to the α,β-unsaturated ketones or aldehydes from a 1-arylvaminadinium salt .... 35
XV. Synthesis of a 1-arylvaminadinium salt from acetophenone . 36
XVI. Suggested mechanism for the reaction of organometallic reagents with an unsymmetrical vinamidinium salt .... 43
### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>American Chemical Society</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Centigrade</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wavenumbers (IR spectrum)</td>
</tr>
<tr>
<td>δ</td>
<td>delta (NMR spectrum)</td>
</tr>
<tr>
<td>d</td>
<td>doublet (NMR spectrum)</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>E⁺</td>
<td>electrophile</td>
</tr>
<tr>
<td>equ</td>
<td>equivalents</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>g</td>
<td>grams</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>hr</td>
<td>hours</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz (cycles per second-NMR spectrum)</td>
</tr>
<tr>
<td>in</td>
<td>inches</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (NMR spectrum)</td>
</tr>
<tr>
<td>lit</td>
<td>literature</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (NMR spectrum)</td>
</tr>
<tr>
<td>M⁺</td>
<td>molecular ion (mass spectrum)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>m/e</td>
<td>mass to charge ratio (mass spectrum)</td>
</tr>
<tr>
<td>Me₂NH</td>
<td>dimethylamine</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>ml</td>
<td>milliliters</td>
</tr>
<tr>
<td>mm</td>
<td>millimeters</td>
</tr>
<tr>
<td>mol</td>
<td>moles</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PTC</td>
<td>phase transfer catalyst</td>
</tr>
<tr>
<td>R-M</td>
<td>organometallic reagent</td>
</tr>
<tr>
<td>Rₜ</td>
<td>retention time (GC analysis)</td>
</tr>
<tr>
<td>rxn</td>
<td>reaction</td>
</tr>
<tr>
<td>RBF</td>
<td>round-bottom flask</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR spectrum)</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR spectrum)</td>
</tr>
<tr>
<td>TBPB</td>
<td>tetra-n-butylphosphonium bromide</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>UNK</td>
<td>unknown</td>
</tr>
<tr>
<td>w/w</td>
<td>weight/weight</td>
</tr>
</tbody>
</table>
PART I

AROMATIC NUCLEOPHILIC FLUOROALKOXYLATION
VIA CATIONIC PHASE TRANSFER CATALYSIS

INTRODUCTION

The practical application of fluoronated organic compounds has flourished since the early 1930's and the development of "Freons" as refrigerants. Today, fluoronated materials are finding use as polymers, propellants, blood substitutes, pharmaceuticals, and pesticides.1-3

Fluoroalkoxy aromatics are particularly interesting in that they have been found to be important intermediates in the synthesis of potentially effective insecticides such as the fluoronated DOWCO-416 analogs4-5 (Figure I).

Figure I. DOWCO-416 and a DOWCO-416 trifluoroethoxylated analog.

At the 1984 Annual ACS Meeting, it was announced that the first fluorine-containing drug for the treatment of cardiac arrhythmias had been recommended for approval by a drug advisory committee of the Food and Drug Administration.6 The effectiveness of Fleca

\[ \text{Figure I. DOWCO-416 and a DOWCO-416 trifluoroethoxylated analog.} \]

At the 1984 Annual ACS Meeting, it was announced that the first fluorine-containing drug for the treatment of cardiac arrhythmias had been recommended for approval by a drug advisory committee of the Food and Drug Administration. The effectiveness of Fleca

Acetate (Figure 2) is due to the two 2,2,2-trifluoroethoxy substituents. Analogs of the drug not containing fluorine are not nearly as effective. The new drug is a perfect example of the practicality of introducing fluorine, particularly fluoroalkoxide, into aromatic systems.

![Figure II. Flecainide Acetate](image)

In the past, fluoroalkoxy aromatics have been synthesized by reactions of electrophilic haloalkyl fluoride, fluoroalkene, or a fluoroalkyl sulfonate with a nucleophilic phenol derivative.\(^2,7-9\)

Shaw and Kornblum\(^{10,11}\) have reported direct introduction of alkoxy groups to unactivated and activated halobenzenes. Shaw's work involved the reaction of unactivated halobenzenes with sodium methoxide in HMPA at 90\(^\circ\)C to give the corresponding methyl phenyl ethers. Kornblum studied activated nitrobenzenes with sodium methoxide at 25\(^\circ\)C to give the corresponding methoxy nitrobenzenes (Figure III).

Based on Shaw's and Kornblum's work, Gupton, Idoux and co-workers\(^{12-14}\) undertook a comprehensive investigation of the reaction of sodium 2,2,2-trifluoroethoxide with unactivated and activated halo-aryl and heteroaryl substrates in HMPA or DMF to yield the
2,2,2-trifluoroethoxy aryl and heteroaryl products. Their investigation included the effect of solvent and time on trifluoroethoxylation as well as the effect of substrate, leaving group, and various fluoroalkoxide ions in aromatic fluoroalkoxylation (Figure IV).

![Chemical structures](image)

**Figure III.** The reaction of sodium methoxide with unactivated and activated benzene systems.

![Chemical structures](image)

**Figure IV.** Reported studies of the effect of substrate, leaving group, and nucleophile on aromatic nucleophilic fluoroalkoxylation.
Analagous to the preparation of fluoroalkoxy aromatics is the synthesis of aryl thioethers. A recent report by Rolla and co-workers\textsuperscript{15} on the reaction of alkyl thiolates with dichlorobenzenes in water, catalyzed by dicyclohexano-18-crown-6, prompted Brunelle\textsuperscript{16} to report results in a similar area. Brunelle reported the reaction of alkyl thiolates and aromatic di-, tri-, and tetrachlorides under phase transfer catalyst (PTC) conditions in toluene solution (Figure V).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure_v.png}
\caption{The reaction of aromatic tetrachlorides with alkyl thiolates under PTC conditions.}
\end{figure}

A number of different phase transfer catalysts were evaluated by Brunelle, with the quarternary phosphonium salts proving the most effective.

Reeves and co-workers\textsuperscript{17} reported a similar study on the preparation of aryl thioethers by the phase transfer catalyzed displacement of halogen from activated aromatic rings by thiophenoxide ion (Figure VI). As with Brunelle's work, Reeves also evaluated a number of phase transfer catalysts with tetra-n-butylammonium bromide proving to be the most effective.
Figure VI. Nucleophilic displacement of activated halogen by thiophenoxide ion.

From these observations, we propose to investigate the reaction of sodium fluoroalkoxides with activated halo-aryl and heteroaryl substrates under PTC conditions in a toluene solvent system. An initial feasibility and optimization study will be performed including the evaluation of certain quarternary phosphonium and ammonium salts as phase transfer catalysts. If successful, different activating groups as well as the extent of activation at the o-, m-, and p- positions will be studied. Also included will be the determination of the effect of leaving group and nucleophile on the nucleophilic displacement reaction, and the determination of the regioselectivity of the reaction under PTC conditions.

Substrates will be chosen to yield expected products identical to those previously reported by Gupton and Idoux\textsuperscript{12-14} in order to simplify structural determination. Characterization of any new compounds will be done by NMR, IR, and mass spectrometry. Purity will be assessed by GC.
PART I

EXPERIMENTAL

A. Feasibility Study and Optimization

\[
\text{NO}_2^+ \text{Cl}^- + \text{HOCH}_2\text{CF}_3 \text{NaH} \xrightarrow{\text{PTC} \text{toluene} 110^\circ C} \text{NO}_2^+ \text{OCH}_2\text{CF}_3 + \text{NaCl} + \text{H}_2
\]

Table 1

Experimental data for the evaluation of catalyst effectiveness

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solid-Liquid&lt;sup&gt;a&lt;/sup&gt; conversion (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Solid-Liquid&lt;sup&gt;a&lt;/sup&gt; yield (%)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Liquid-Liquid&lt;sup&gt;b&lt;/sup&gt; conversion (%)</th>
<th>Liquid-Liquid&lt;sup&gt;b&lt;/sup&gt; yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tetra-n-butylphosphonium bromide (TBPB)</td>
<td>44.9</td>
<td>UNK&lt;sup&gt;e&lt;/sup&gt;</td>
<td>30.4</td>
<td>19.3</td>
</tr>
<tr>
<td>2</td>
<td>benzyltriethylammonium chloride</td>
<td>8.5</td>
<td>1.5</td>
<td>15.3&lt;sup&gt;g&lt;/sup&gt;</td>
<td>9.7</td>
</tr>
<tr>
<td>3</td>
<td>tetrabutylammonium hydrogen sulfate</td>
<td>25.7</td>
<td>15.8</td>
<td>--&lt;sup&gt;f&lt;/sup&gt;</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>benzyltrimethylammonium chloride</td>
<td>16.0</td>
<td>13.9</td>
<td>14.5</td>
<td>9.4</td>
</tr>
<tr>
<td>5</td>
<td>methyltricaprylammonium chloride</td>
<td>8.5</td>
<td>4.9</td>
<td>6.8&lt;sup&gt;g&lt;/sup&gt;</td>
<td>4.7</td>
</tr>
<tr>
<td>6</td>
<td>Adogen 464&lt;sup&gt;h&lt;/sup&gt;</td>
<td>25.0</td>
<td>20.9</td>
<td>10.9&lt;sup&gt;g&lt;/sup&gt;</td>
<td>9.1</td>
</tr>
<tr>
<td>7</td>
<td>tetrabutylammonium hydroxide</td>
<td>--&lt;sup&gt;i&lt;/sup&gt;</td>
<td>--</td>
<td>43.5</td>
<td>26.0</td>
</tr>
</tbody>
</table>
a) For "solid-liquid" trials, the physical form of the catalyst was not changed before addition to the reaction vessel.
b) For "liquid-liquid" trials, the catalyst was added to the reaction vessel as a 40% (w/w) aqueous solution. With regard to catalysts not soluble in water (e.g. Adogen 464), water was added directly to the vessel separately from the catalyst.
c) The conversions for all of the entries in Table 1 were determined by GC. Standards of authentic samples of the starting material and product provided response factors which were used in the determination of the conversion values.

**Instrument Conditions**

i) column type: 1/8" by 6' 3% SB-2401-DB  
ii) column temperature: 170°  
iii) injector temperature: 200°  
iv) flow rate: 50 ml/min  

d) The percent yields refer to crude yields based on the theoretical 100% conversion of starting materials.
e) The crude product was lost after the GC analysis and a crude yield could not be determined.
f) Any effects of the anion on catalysis were assumed negligible. The "liquid-liquid" conversion values for tetrabutylammonium hydroxide were considered characteristic of the effectiveness of the tetrabutylammonium cation.
g) The base incorporated into the reaction was NaOH instead of NaH.
h) Adogen 464 is a trademark of Ashland Chemical Company. The catalyst is a methyltrialky1(\text{C}_8-\text{C}_{10})ammonium chloride. The MW was estimated to be that of methyltrinonylammonium chloride.
i) The catalyst was procured from Aldrich Chemical Company as a 40\% (w/w) aqueous solution.

\[
\text{NO}_2 + \text{HOCH}_2\text{CF}_3 + \text{Base} \xrightarrow{\text{PTC}} \text{toluene} \xrightarrow{110^\circ\text{C}} \text{NO}_2 + \text{NaCl} + \text{H}_2\text{O (or H}_2) + \text{OCH}_2\text{CF}_3
\]

Table 2

Experimental data for the determination of optimum reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mole %\textsuperscript{a}</th>
<th>Base</th>
<th>Reaction time (hr)</th>
<th>Conv. (%)\textsuperscript{b}</th>
<th>Yield (%)\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tetra-n-butylphosphonium bromide\textsuperscript{d}</td>
<td>10</td>
<td>NaH</td>
<td>24</td>
<td>44.9</td>
</tr>
<tr>
<td>2</td>
<td>same</td>
<td>10</td>
<td>NaH</td>
<td>72</td>
<td>53.3</td>
</tr>
<tr>
<td>3</td>
<td>same</td>
<td>30</td>
<td>NaH</td>
<td>24</td>
<td>97.8</td>
</tr>
<tr>
<td>4</td>
<td>same</td>
<td>10</td>
<td>NaOH</td>
<td>24</td>
<td>49.0</td>
</tr>
<tr>
<td>5</td>
<td>same</td>
<td>30</td>
<td>NaOH</td>
<td>72</td>
<td>87.9</td>
</tr>
<tr>
<td>6</td>
<td>same</td>
<td>50</td>
<td>NaH</td>
<td>24</td>
<td>95.2</td>
</tr>
<tr>
<td>7</td>
<td>same</td>
<td>30</td>
<td>NaOH\textsuperscript{e}</td>
<td>44</td>
<td>98.7</td>
</tr>
<tr>
<td>8</td>
<td>tetra-n-butylammonium hydroxide</td>
<td>30</td>
<td>NaOH</td>
<td>24</td>
<td>47.1</td>
</tr>
<tr>
<td>9</td>
<td>same</td>
<td>30</td>
<td>NaOH</td>
<td>72</td>
<td>60.4</td>
</tr>
</tbody>
</table>
a) The mole percentage value is relative to the amount of p-chloro-nitrobenzene present at the beginning of the reaction.
b) The conversions for all the entries in Table 2 were determined by GC. See (c) below Table 1 for instrument conditions.
c) The percent yields refer to crude yields based on theoretical 100% conversion of starting material.
d) The catalyst was added to the reaction vessel as a solid – not as a 40% (w/w) aqueous solution.
e) Here, water was removed from the reaction mixture azeotropically as the reaction proceeded.
f) The catalyst here was added as a 40% (w/w) aqueous solution.
Graph illustrating conversion vs. time for two catalysts.

Data for graph:

<table>
<thead>
<tr>
<th>Time</th>
<th>Tetra-n-butylphosphonium bromide</th>
<th>Tetra-n-butylammonium hydroxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.58</td>
<td>25.54</td>
<td>19.03</td>
</tr>
<tr>
<td>1.08</td>
<td>39.12</td>
<td>21.25</td>
</tr>
<tr>
<td>1.58</td>
<td>49.30</td>
<td>28.10</td>
</tr>
<tr>
<td>2.08</td>
<td>59.87</td>
<td>26.02</td>
</tr>
<tr>
<td>2.58</td>
<td>60.98</td>
<td>32.48</td>
</tr>
<tr>
<td>3.08</td>
<td>73.36</td>
<td>35.74</td>
</tr>
<tr>
<td>3.58</td>
<td>72.50</td>
<td>45.96</td>
</tr>
<tr>
<td>4.08</td>
<td>77.91</td>
<td>42.45</td>
</tr>
<tr>
<td>72.00</td>
<td>87.90</td>
<td>60.40</td>
</tr>
</tbody>
</table>
a) See entry 5 in Table 2 for reaction conditions.
b) See entry 9 in Table 2 for reaction conditions.
c) Conversions were determined by GC with samples taken directly from the reaction pot and injected. The instrument conditions were the same as those in (c) below Table 1.
d) The time \((t)\) was measured relative to the time that a steady reflux could be seen.

4-(2,2,2-trifluoroethoxy)nitrobenzene

To a one-neck 500 ml RBF equipped with a magnetic stirrer and heating mantle was added 1.2 g \((0.030 \text{ mol})\) 60% \((\text{w/w})\) oil dispersed NaH and 10 ml of hexane. The base/hexane mixture was stirred for 10 min, and the hexane-oil layer removed by suction. Seventy-five ml of toluene was added to the flask, followed by 5.35 g \((0.050 \text{ mol})\) of 2,2,2-trifluoroethanol, and the mixture was allowed to stir for 1 hr. While stirring, 2.55 g \((0.0075 \text{ mol})\) of tetra-n-butylphosphonium bromide was added in one portion followed by addition of 4.00 g \((0.025 \text{ mol})\) 4-chloronitrobenzene in one portion. The flask was then equipped with a condenser, flushed with nitrogen, and heated to reflux. After 24 hr, the reaction mixture was cooled to room temperature and the contents of the flask were extracted with 2 x 50 ml portions of water. The drying agent was removed by filtration and the toluene layer removed in vacuo leaving 4.7 g \((83.3\% \text{ yield})\) of a tan solid. The spectral data \((\text{NMR and IR})\) and melting point matched that of an
authentic sample of 4-(2,2,2-trifluoroethoxy)nitrobenzene. See reference 12 for spectral data and physical characteristics of the fluoroalkoxylated nitrobenzene.

B. Activating Group Study

\[
\begin{array}{c}
\text{Cl} \quad \text{HOCH}_2\text{CF}_3 \quad \text{NaOH} \\
\text{TBPB} \quad \text{toluene} \quad \text{110}^\circ\text{C} \\
\text{OCH}_2\text{CF}_3
\end{array}
\]

Table 3

Experimental data for non-heterocyclic substrates\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(-X)</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(-\text{NO}_2)</td>
<td>65.2(^c)</td>
</tr>
<tr>
<td>2</td>
<td>(-\text{CN})</td>
<td>95.0(^d)</td>
</tr>
<tr>
<td>3</td>
<td>4-\text{ClPhSO}_2^-</td>
<td>46.4(^e)</td>
</tr>
<tr>
<td>4</td>
<td>(-\text{CF}_3)</td>
<td>(_f)</td>
</tr>
</tbody>
</table>

a) See reference 12 for spectral details and physical constants of the products.
b) The percent yields refer to purified yields where purification involved silica gel filtration, distillation, or both.
c) The product here was purified by recrystallization from isopropanol/water.
d) The mole percentage of PTC was increased to 50 and reaction time increased to 96 hr to push the reaction to 100% completion. NaH was
also used as the base to prevent formation of the benzamide by the hydrolysis of the nitrile.

e) The amounts of alcohol and base were increased to obtain the ditrifluoroalkoxylated product.

f) GC analysis revealed less than 5% of the substrate had been converted to product.

Table 4

Experimental data for heterocyclic substrates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate 1" /></td>
<td>-c</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate 2" /></td>
<td>74.9</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate 3" /></td>
<td>91.6</td>
</tr>
</tbody>
</table>

a) See reference 12 for spectral details and physical constants of the products.

b) The percent yields refer to purified yields unless otherwise noted. The products were purified by silica gel filtration, distillation, or both.

c) The conversion of starting material to product was less than 100%. A 64.9% conversion was achieved, yet only a 5% crude yield was realized due to loss of material through vacuum during work-up.
Experimental data for the evaluation of the extent of activation at the o-, m-, and p- positions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>-Y</th>
<th>-X</th>
<th>Conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-CN</td>
<td>2-Cl</td>
<td>70.2</td>
<td>67.7</td>
</tr>
<tr>
<td>2</td>
<td>-CN</td>
<td>3-Cl</td>
<td>1.4</td>
<td>0.64</td>
</tr>
<tr>
<td>3</td>
<td>-CN</td>
<td>4-Cl</td>
<td>95.0</td>
<td>95.0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>-CN</td>
<td>4-Cl&lt;sup&gt;d&lt;/sup&gt;</td>
<td>59.9</td>
<td>41.7</td>
</tr>
<tr>
<td>5</td>
<td>-CN</td>
<td>4-Cl&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3-NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> The conversions for all of the entries in Table 5 were determined by GC. Standards of authentic samples of the starting material and product provided response factors which were used in the determination of the conversion values. The instrument conditions were the same as those found in (c) below Table 1 except that a column temperature of 150°C was utilized.

<sup>b</sup> The percent yields refer to crude yields based on the theoretical 100% conversion of starting material unless otherwise specified.

<sup>c</sup> The percent yield refers to a purified yield (via silica gel filtration). See (c) below Table 3 for special reaction conditions.
d) Here, one equivalent of NaF was added in an attempt to assist the catalysis and increase the conversion to 100%.

e) Here, one equivalent of CuCl and one equivalent of pyridine was added to the reaction mixture in an attempt to assist the catalysis and increase the conversion to 100%. Only trace amounts of product were found.

f) GC analysis revealed less than 5% conversion of starting material to product. NaOH was used as the base with azeotropic removal of water from the reaction mixture.

**2-(2,2,2-Trifluoroethoxy)lepidine**

To a one-neck 500 ml RBF equipped with a magnetic stirrer was added 1.2 g (0.030 mol) powdered NaOH, 5.0 g (0.050 mol) CF₃CH₂OH, and 75 ml toluene. While stirring, 2.55 g (0.0075 mol) tetra-n-butyolphosphonium bromide was added in one portion followed by 4.44 g (0.025 mol) of 2-chlorolepidine. The flask was then equipped with a condenser and Dean-Stark apparatus and the system was flushed with N₂. The reaction mixture was brought to reflux and the reaction allowed to run for 24 hr. The reaction mixture was then cooled to room temperature and filtered into a chromatographic column 1 inch in diameter filled with a 3 inch layer of 200 mesh preparative column silica gel. Following addition of the reaction mixture, 150 ml of ethyl acetate was used as an eluant. The product, toluene, and ethyl acetate were collected at the bottom of the column. The solvents were removed in vacuo leaving a clear liquid residue which
was then placed under vacuum (0.08 mm Hg) for further drying. Upon
drying 5.0 g of clear liquid residue remained. The residue was
distilled (Kugelrohr) affording 4.6 g of a clear liquid (74.9% yield,
bp 80°C at 0.08 mm Hg) whose NMR spectrum and GC R<sub>T</sub> were identical
to that of 2-(2,2,2-trifluoroethoxy)-lepidine.

C. Leaving Group Study

![Chemical Reaction Image]

Table 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>-X</th>
<th>Conversion (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5 hr</td>
</tr>
<tr>
<td>1</td>
<td>-NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>100.0</td>
</tr>
<tr>
<td>2</td>
<td>-F</td>
<td>100.0</td>
</tr>
<tr>
<td>3</td>
<td>-Cl</td>
<td>83.1&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>-Br</td>
<td>100.0&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>-I</td>
<td>75.0&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Water was azeotropically removed from the reaction mixture.
<sup>b</sup> The conversion values for all of the entries in Table 4 were
determined by GC. Standards of authentic samples of the starting
material and product provided response factors which were used in the
determination of values. The instrument conditions were the same as
those found in (c) below Table 1 except that a column temperature of
180°C was utilized. See reference 12 for spectral details and
physical constants of the products.
c) Only a small amount of by-product, believed to be the di(trifluoro­
ethoxy)benzene was found along with the product.
d) A substantial amount of by-product, believed to be a di(trifluoro­
ethoxy)benzene, was found along with the expected product. The
structural characterization of the by-product has not been performed.

D. Regioselectivity Study

Table 7

Experimental data for determining the feasibility of polysubstitution
and regioselective monosubstitution of activated dihaloarenes and
dihaloheteroarenes^a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate" /></td>
<td><img src="image2" alt="Product" /></td>
<td>73.6</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate" /></td>
<td><img src="image4" alt="Product" /></td>
<td>54.0^d</td>
</tr>
</tbody>
</table>
Table 7 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product$^b$</th>
<th>Yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><img src="image1.png" alt="Substrate Image" /></td>
<td><img src="image2.png" alt="Product Image" /></td>
<td>100.0$^e$</td>
</tr>
<tr>
<td>4</td>
<td><img src="image3.png" alt="Substrate Image" /></td>
<td><img src="image4.png" alt="Product Image" /></td>
<td>76.7</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Substrate Image" /></td>
<td><img src="image6.png" alt="Product Image" /></td>
<td>92.1</td>
</tr>
</tbody>
</table>

a) Disubstitution was brought about by use of 4.0 equivalents of alcohol and 2.4 equivalents base instead of the usual stoichioimetric amounts used for monosubstitution (i.e. 2.0 equ. alcohol and 1.2 equ. base).
b) Spectral data and physical constants of the products matched those of authentic samples (see references 13 and 14).
c) The percent yields refer to purified yields where purification involved silica gel filtration, distillation, or both.
d) Mono- and disubstituted products were found after a reaction time of 34 hr. The crude product was further reacted with more base and alcohol for an additional 24 hr to effect 100% conversion to the disubstituted product.
e) Here, the reaction was done at 50°C for 0.5 hr instead of the normal reaction conditions of 110°C for 24 hr.
E. Nucleophile Study

\[
\begin{align*}
\text{NO}_2 & \quad \text{Cl} \quad + \quad \text{NaOH} \quad + \quad \text{HOR}_F \quad \xrightarrow{\text{TBPB}} \quad \text{NO}_2 \quad \text{OR}_F \quad + \quad \text{NaCl} \quad + \quad \text{H}_2\text{O} \\
\text{toluene} &
\end{align*}
\]

Table 8

Experimental data for the determination of the effect of the nucleophile on the fluoroalkoxylation of activated halobenzenes\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(-\text{R}_F)</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(-\text{CH}_2\text{CF}_3)</td>
<td>97.4(^c)</td>
</tr>
<tr>
<td>2</td>
<td>(-\text{CH}_2\text{CF}_2\text{CF}_2\text{CF}_3)</td>
<td>85.0(^d,e)</td>
</tr>
</tbody>
</table>

\(a\) Water was azeotropically removed from the reaction mixture.

\(b\) The percent yields refer to purified yields where purification involved silica gel filtration, distillation, or both.

\(c\) The reaction time here was 2 hr instead of the normal reaction time of 24 hr.

\(d\) Fifty mole percent of catalyst and a reaction time of 96 hr was utilized instead of the usual reaction conditions of 30 mole \(\%\) and a reaction time of 24 hr.

\(e\) 2-(2,2,3,3,4,4,4-heptafluorobutoxy)nitrobenzene; bp 70-75\(^\circ\)C (0.1 mm Hg); NMR (\(\text{CDCl}_3\)) \(\delta\) 4.5 (t, \(J=8\) Hz, 2H), 7.2 (m, 2H), 7.5 (d of t, \(J=6\) Hz, 2Hz, 1H); IR (neat) 3080, 2950, 1605, 1530, 1355, 1230, 1055, 860, 742 cm\(^{-1}\); mass spectrum \(m/e\) 321 (\(M^+\)).
DISCUSSION OF RESULTS

For all five studies conducted on aromatic fluoroalkoxylation via phase transfer catalysts, the results relatively paralleled those of Gupton and Idoux.\textsuperscript{12-14} In all cases, nucleophilic substitution occurred at the halogen on the activated aromatic system.

Once the basic reaction conditions were decided upon (i.e. solvent and reaction temperature) a number of phase transfer catalysts were evaluated at a concentration of 10 mole \% based on the amount of starting substrate. The lower catalyst concentration provided conversions less than 100\% in order that all the catalysts could be effectively evaluated. The results of the evaluation were not surprising. As with Brunelle's work,\textsuperscript{16} the phosphonium catalyst proved to be the most efficient; however, the catalyst was more effective under "solid-liquid" conditions than "liquid-liquid" conditions.

The search for optimum reaction conditions consisted mainly of varying catalyst concentration. An increase above 30 mole \% was found to be a waste of catalyst with respect to the p-chloronitrobenzene substrate. Unexpectedly, a change from \textit{NaH} as base to \textit{NaOH} brought about slightly lower conversion values. Apparently, water produced from the reaction of the alcohol with the base brought about "liquid-liquid" reaction conditions - and thus, lower conversions.
The problem was easily corrected by removing the water azeotropically from the reaction mixture - an advantage in the use of toluene as the solvent.

The time study incorporating tetra-n-butylyphosphonium bromide and tetra-n-butylammonium hydroxide as the catalysts clearly shows the phosphonium salt's higher reactivity relative to the ammonium salt. Conversion values determined during the study would undoubtedly have been better if water had been removed from the reaction mixture.

Experimental data compiled during the activating group study revealed trends similar to those found by Gupton and Idoux. The nitro- and p-chlorophenylsulfonyl- groups were most effective at a catalyst concentration of 30 mole%. Catalyst concentration and reaction time had to be increased with respect to the benzonitrile substrate, but the result was a higher yield. Also, NaH was required as the base to eliminate chances of hydrolysis of the nitrile to the benzamide. The benzoyl trifluoride only presented negligible conversion.

Heterocyclic substrates seemed to afford cleaner reactions which were easier to work up. The best yield was afforded by 2-chloroquinoline, followed by the lepidine (i.e. 2-chloro-4-methylquinoline). Slight deactivation by the methyl group of lepidine most likely brought about the lower yield. Somewhat disconcerting was the pyrazine's lower conversion. Here, deactivation by two methyl groups may have been responsible for the lower conversion. A higher catalyst concentration and a longer reaction period may have brought about 100% conversion. The use of benzene (i.e. a lower boiling solvent)
may also have prevented loss of material through distillation work-up, thus increasing the yield of the reaction.

Experimental data on the evaluation of the extent of activation at the o-, m-, and p- positions clearly shows the consequences of an o-, p- activating group. Under identical conditions, reaction predominates at the ortho- position (presumably by some sort of inductive effect) over the para- position, while the meta- position appears to be almost invulnerable. Even m-dinitrobenzene, where the nitro group is generally a good leaving group in alkoxide aromatic substitution,\textsuperscript{10-18} afforded less than 5\% conversion.

During the activating group study, it became noticeable that the crude products contained catalyst that was not easily removed by distillation. Decomposition of the catalyst upon heating brought about undesirable products, and another method of purification was clearly needed to afford sufficiently pure products. Brunelle\textsuperscript{16} had used a thin pad of silica gel to remove the catalyst from the crude product. It was decided to pass the whole crude reaction mixture through a short column of 200 mesh preparative column silica gel, followed by eluant, in an attempt to remove catalyst and excess alcohol. The first attempts were successful and solvents with higher polarity such as ethyl acetate could be used to elute the product in a shorter period of time. The procedure provides a very simple method for reaction work-up and circumvents the need of an aqueous separation procedure. The eluant and toluene can easily be removed in vacuo leaving the product of sufficiently high purity. If for
some reason product purity was sub-standard, the product could be purified by distillation (Kugelrohr) easily in the absence of catalyst.

The leaving group study brought about some surprising results. The leaving groups behaved as expected where \(-\text{NO}_2, -\text{F}>-\text{Cl}>-\text{Br}>-\text{I}\) with respect to the leaving tendency. Ortho- activation apparently permits the reaction to proceed more quickly than with the para- substituted nitrobenzene - as could be expected from the evaluation of activation at the o-, m-, and p- positions. However, a curious side product was detected by GC for the Cl-, Br-, and I- substrates. The side product in all three instances had the same retention time and is presumably the di(trifluoroethoxy)benzene. The amount of by-product increased with increasing size of the halogen (i.e. the I- substrate allowed for the most by-product). Further work is planned to separate the two products and structurally characterize the side product. The decreased reaction rate of the iodo- substrate relative to the other halo- substrates can be explained by the previously reported adverse effects of iodide ion on phase transfer catalysis.\(^\text{17}\)

The PTC assisted reaction of trifluoroethoxide ion with the aromatic substrates is typical of a two-step \(S_n\text{Ar}\) reaction where the first step is rate determining (i.e. fluoro- is generally the poorest leaving group of the halogens when the second step is rate determined).\(^\text{19}\)

Results of the regioselectivity study also closely paralleled those of Gupton and coworkers\(^\text{13}\) using HMPA and DMF reaction conditions without phase transfer catalysis. Polysubstitution was effected at both activated halogens of 2,6-dichlorobenzonitrile and 3,6-dichloropyradizine. Regioselective substitution was observed at the para-
position rather than the meta- position for 3,4-dichloronitrobenzene. The 4- position of quinoline was easily substituted while the 7-position seems to have remained invulnerable under normal reaction conditions. Also shown was that the better leaving group, -F, could be selectively substituted rather than -Cl if reaction temperature and reaction time were decreased.

Since the effect of -F on the nucleophilicity of the alkoxide ion was assumed negligible when the halogen is located more than two C–C bond lengths away from the oxygen, only one alcohol other than the already well-studied 2,2,2-trifluoroethanol was investigated. The relatively less reactive heptafluorobutanol was easily deprotonated and incorporated onto the nitrobenzene. Of all the trifluoroalkoxylated products, the heptafluorobutoxy nitrobenzene was the only one not structurally characterized by earlier investigators (the spectral and physical data of all other products were identical to that previously reported). The compound was structurally characterized by NMR, IR, and mass spectrometry. The NMR spectrum of the product was very similar to that of the o-(2,2,2-trifluoroethoxy) nitrobenzene with respect to the aromatic region.
H_a could be found furthest downfield as a doublet of doublets (ortho-meta coupled) centered at δ 7.8. H_c is found further upfield as a doublet of triplets (ortho-ortho-meta coupled) centered at δ 7.5. H_b and H_d could be found together as a multiplet centered at δ 7.2. 

Ortho coupling constants are on the order of 6 Hz while meta-coupling constants are smaller at 2 Hz. The methylene protons split into a triplet (J=8Hz) by the adjacent -F, are upfield at δ 4.5.

The IR spectrum of o-(2,2,3,3,4,4,4-heptafluorobutoxy)nitrobenzene showed characteristic bands of fluoroalkoxylated benzenes. The strong asymmetric O–N–O stretch at 1530 cm⁻¹ could be easily seen as well as the strong symmetric O–N–O stretch at 1355 cm⁻¹. An absorption band at 1055 cm⁻¹ is due to the aryl alkyl ether C–O–C symmetrical stretch. The asymmetrical band is found at 1230 cm⁻¹. The broadened characteristic absorption band of C–F is found between 1400-1500 cm⁻¹.

The results of all five aromatic fluoroalkoxylation studies parallel those of Gupton and Idoux¹²-¹⁴ very closely; yet, there are a few stark contrasts between the two methods of effecting the aromatic nucleophilic substitution. The activating group study provided results which relatively paralleled those of Gupton and Idoux with the exceptions that the cyano- and trifluoromethyl- groups
were not quite as active under PTC/toluene reaction conditions as they were under HMPA or DMF reaction conditions. With respect to heterocyclic substrates, yields were appreciably greater under PTC conditions.

The greatest difference between the results accumulated on substitution at the o-, m-, and p- positions was the activity of the meta position. Even with an excellent leaving group such as -NO₂, under PTC conditions, the position is relatively inactive. Gupton and Idoux have reported respectable yields of m-trifluoroalkoxylated benzonitriles and nitrobenzenes.¹²

Another interesting occurrence under PTC conditions was the formation of the as yet unknown by-product during fluoroalkoxylation of o-chloro, bromo-, and iodo- nitrobenzenes. Work is already underway on the trifluoroethoxylation of o-dihalobenzenes via phase transfer catalysis. Discussion will be withheld, however, until more data can be obtained and reported at a later date.

Results of the regioselectivity studies done under PTC conditions paralleled those under HMPA or DMF conditions with only slight differences in yields. With respect to the nucleophile studies, however, HMPA conditions were originally ineffective at promoting the substitution of halogen by nucleophiles containing more than four fluorines. Since then, HMPA conditions have been optimized to permit introduction of the heptafluorobutoxy group into 3,4-dichloronitrobenzene and dioxane has been used as a solvent medium for introducing the group into 3,6-dichloropyridazine.
Regarding experimental procedures, that of the PTC reactions (see preparation of 2-(2,2,2-trifluoroethoxy)lepidine) is superior to that of the fluoroalkoxylation reactions in HMPA or DMF. The advantages include:

i) the use of a cheaper, more convenient, and less toxic solvent

ii) the use of a cheaper and more convenient base

iii) no need for a water work-up or biphasic separation

iv) easy and rapid work-up with efficient removal of catalyst

v) formation of products of sufficient purity (i.e. greater than 95%) where recrystallization or distillation is rarely needed

vi) lower reaction temperatures and thus milder reaction conditions
PART I

CONCLUSIONS

Sodium alkoxides have been successfully used to fluoroalkoxylate activated halo-aryl and heteroaryl substrates under phase transfer catalyst conditions using toluene as the solvent system. The catalyst found to be the most effective at promoting the aromatic nucleophilic substitution was tetra-n-butylphosphonium bromide under "solid-liquid" reaction conditions.

The simplicity of the reaction procedure, the milder reaction conditions, the use of cheap, available starting materials, and a non-toxic solvent makes this new synthetic method particularly attractive over previous methods for introducing the fluoroalkoxy group into aromatic systems.
PART I

RECOMMENDATIONS

The following are suggestions for future research in the area of PTC assisted aromatic nucleophilic fluoroalkoxylation:

1. One particular phase transfer catalyst not evaluated was tricyclohexyl-n-dodecyl phosphonium bromide. Brunelle\textsuperscript{16} found this catalyst to be particularly effective. Brunelle reports that the effectiveness may be due to steric hindrance. Further investigations can be made using the tricyclohexyl-n-dodecyl catalyst along with other phosphonium salts tailor-made to help researchers better understand why some catalysts are more effective than others.

2. All work done in this report is relative to activated benzene systems. Some data has already been compiled on non-activated systems but not reported here. The effectiveness of phase transfer catalysis in promoting fluoroalkoxylation of non-activated systems should be studied. Substrates such as nitrobenzene and orthodihalobenzenes would provide useful synthetic routes to fluorinated benzenes if successful.

3. The silica gel filtration technique of purification reported here is very practical for a laboratory scale reaction. An investigation should be made into the recovery of the catalyst from the silica gel in such a manner that the separation procedure may be more industrially appealing.
4. Reeves\textsuperscript{17} conducted his reactions in an aqueous medium. Investigation into the possibility of using an aqueous medium instead of an organic solvent system should be made. Here, the catalyst would be responsible for transferring the organic substrate into the aqueous phase for reaction with the water soluble alkoxide.
PART II
REACTIONS OF UNSYMMETRICAL VINAMIDINIUM SALTS WITH ORGANOMETALLIC REAGENTS

INTRODUCTION

Increasing interest has been placed in vinamidine and vinamidinium salt chemistry. Their synthetic usefulness arises from their enhanced reactivity with electrophiles and nucleophiles due to their stabilized "push-pull" character. The study of vinamidines and vinamidinium salts arose from investigations concerning the iminium ion depicted below in Figure VII in its two resonance forms.

Figure VII. The two resonance structures of the iminium ion.

Amidine systems are those systems where an amino group is bonded to the carbon atom of the iminium ion above (Figure VIII).

Figure VIII. A simple amidine system.
Here, the system is referred to as a "push-pull" alkene system where an electron-donating group is attached to one end of the double bond while an electron-withdrawing group is attached to the other end. This alkene exhibits greater stability relative to other alkenes due to the delocalization of electrons from the donor group through the double bond to the acceptor group.

If the size of the amidine system is increased to represent its vinylog, a vinamidinium system exists in its two resonance forms (Figure IX).

![Figure IX. A simple vinamidinium system.](image)

The vinamidinium system may be substituted at the α, β, and γ positions as well as being mono- or dialkylated at the nitrogen positions. The most common counter ions found with the vinamidinium systems are the chloride and perchlorate ions.

The synthetic utility of the vinamidinium system is illustrated in Figure X. Since the α and β carbon atoms of a vinamidinium salt are electrophilic and nucleophilic, respectively, the salt will undergo substitution reactions with electrophiles and nucleophiles to form σ complexes.
The reactions of nucleophiles with vinamidinium salts have been of special interest if results reported in the literature are of any indication. Vinamidinium salts have been shown to react with nucleophiles to form pyrazoles, oxazoles, pyrimidines, diazepines, quinolines, quinolizines, etc.

With respect to the reaction of vinamidinium salts with organometallic reagents, very little work has been done. The reaction of simple iminium salts, such as the Eschenmoser reagent (Figure XI) with Grignard and lithium reagents has been reported to produce dialkylaminoalkanes.
Reactions involving organometallic reagents with actual vinamidinium salts, however, have not been evaluated in great detail. Meyers\textsuperscript{25} and Moriya\textsuperscript{26} have carried out reactions of cyclic iminium analogs of vinamidinium salts with Grignard and lithium reagents to produce dialkylaminoalkanes. To date, the only work done on acyclic vinamidinium salts has been done by Gupton and Polaski.\textsuperscript{27} Their work involved the reactions of various organometallic reagents with 3-dimethylamino-2-phenyl-prop-2-en-1-yliden-dimethyliminium perchlorate to produce 3-substituted-2-phenyl-acroleins after acid work-up (Figure XII).

![Figure XI. The Eschenmoser reagent.](image)

![Figure XII. 3-Substituted-2-phenyl-acroleins from the reaction of organometallic reagents with 2-arylvinamidinium salts.](image)
Being symmetrical, the 2-arylvinamidinium salt presents two equivalent electrophilic sites for the nucleophile to attack.

From these observations, we propose to investigate the reaction of Grignard and lithium reagents with a 1-arylvinamidinium system - specifically, 3-dimethylamino-3-phenyl-prop-2-en-l-yliden-dimethyliminium perchlorate (Figure XIII).

![Figure XIII. 3-Dimethylamino-3-phenyl-prop-2-en-l-yliden-dimethyliminium perchlorate.](image)

This system offers two non-equivalent electrophilic sites for nucleophilic attack, and upon acid work-up should produce the α, β-unsaturated ketone, aldehyde, or both (Figure XIV).

![Figure XIV. Proposed synthetic route to the α, β-unsaturated ketones or aldehydes from a 1-arylvinamidinium salt.](image)
The 1-arylvinamidinium salt will initially be synthesized from a procedure paralleling that of Liebscher\textsuperscript{28} (Figure XV). Subsequent reaction conditions with the organometallic reagents will parallel those of Gupton and Polaski.\textsuperscript{27}

![Chemical structure](image)

Figure XV. Synthesis of a 1-arylvinamidinium salt from acetophenone.

Various alkyl- and aryl- organometallic reagents will be used in order to help define the reaction in terms of which electrophilic site is most susceptible to nucleophilic attack. The reagents used may also help explain whether electronic or steric factors predominate during the reaction.

Characterization of new compounds will be done by NMR, IR, and mass spectrometry. Purity will be assessed by GC.
PART II

EXPERIMENTAL

A. Preparation of Trans-1-benzoyl-ethenes

Table 9

Experimental data for the preparation of trans-1-benzoyl ethenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-M</th>
<th>Yield (%)</th>
<th>mp/bp</th>
<th>°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CH₂CH₂CH₂-Li</td>
<td>47.9c</td>
<td>bp 95-100</td>
<td>0.15 mm</td>
</tr>
<tr>
<td>2</td>
<td>CH₂MgCl</td>
<td>89.5d</td>
<td>mp 76-78</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CH₃-MgBr</td>
<td>41.0c</td>
<td>mp 92-94</td>
<td>bp 125</td>
</tr>
<tr>
<td>4</td>
<td>CH₂O-MgBr</td>
<td>35.6e</td>
<td>mp 63-65</td>
<td>bp 140</td>
</tr>
</tbody>
</table>

37
a) The percent yield refers to the purified yield where the purification involved distillation, recrystallization, or both.
b) Boiling point values were determined on a Kugelrohr apparatus.
c) See the experimental procedure for spectral data.
d) Here, 0.017 mol of the vinamidinium salt was used as compared to the typical amount of 0.010 mol. The reaction mixture was allowed to stir at 0-10°C for 2-3 hr and then at room temperature overnight. NMR (CDCl$_3$) $\delta$ 3.85 (m, 2H), 6.5 (broadened t, 2H), 7.0-7.6 (m, 8H), 8.0 (d of d, J=3Hz, J=6Hz, 2H); IR (CHCl$_3$) 3000, 1675, 1595, 1575, 1490, 1445, 1265, 980, and 695 cm$^{-1}$.
e) Here, only 0.008 mol of the vinamidinium salt was used as compared to the typical amount of 0.010 mol. Also, the reaction was allowed to reflux for 48 hr instead of the typical 3 hr reflux period. NMR (CDCl$_3$) $\delta$ 3.8 (s, 3H), 6.9 (d, J=9Hz, 2H), 7.2-7.6 (m, 7H), 8.0 (d of d, J=3Hz, J=6Hz, 2H); IR (CHCl$_3$) 3000, 1655, 1598, 1510, 1255, 1170, 1032, 1015, 830, and 690 cm$^{-1}$.

3-Chloro-3-phenyl-prop-2-en-1-yliden-dimethyliminium perchlorate

To a 250 ml three-neck RBF immersed in an ice bath and equipped with a thermometer, condenser, and magnetic stirrer was added 33.7 g (0.22 mol) phosphorous oxychloride and 29.2 g (0.4 mol) dimethylformamide. The mixture was then allowed to stir at room temperature. After 1 hr, 12.0 g (0.1 mol) acetophenone was dripped into the reaction mixture in such a manner that the reaction temperature remained between 35-70°C. The reaction was then allowed to run at
55°C once the exothermic reaction had subsided. After 5 hr, the reaction mixture was poured into 500 ml ice-cold methanol and 25 ml of 70% (w/w) aqueous perchloric acid was added. After the mixture had cooled to 0°C, crystallization was induced by scratching the sides of the flask. The bright yellow crystals were then collected by vacuum filtration and air dried to afford 13.7 g (46.6% yield) of the perchlorate salt (mp 181-182°C; lit. mp 181-182°C).

3-Dimethylamino-3-phenyl-prop-2-en-l-yliden-dimethyliminium perchlorate29 (VAS)

To 150 ml ethanol in a 250 ml one-neck RBF was added 6.00 g (0.26 mol) Na metal. The metal was allowed to dissolve completely and the excess ethanol was removed in vacuo. To the sodium ethoxide remaining was added 59.4 g (0.85 mol) ethanol followed by 21.1 g (0.26 mol) dimethylamine hydrochloride after the ethoxide had been completely dissolved in the alcohol. The resulting mixture was then filtered into a 250 ml one-neck RBF equipped with a magnetic stirrer and containing 8.8 g (0.03 mol) of 3-chloro-3-phenyl-prop-2-en-l-yliden-dimethyliminium perchlorate. The flask was stoppered and the mixture allowed to stir overnight at room temperature. The resulting yellow crystals were collected by vacuum filtration and air dried to afford 7.4 g (82% yield) of the dimethylaminated perchlorate salt (mp 144°C; lit. mp 144°C).
Trans-1-benzoyl-1-hexene

To a dry 250 ml three-neck RBF equipped with magnetic stirrer, condenser, thermometer, and rubber septum was added 3.0 g (0.01 mol) VAS and 50 ml dry THF. The system was flushed with nitrogen and the mixture was cooled in an ice/saltwater bath, after which 13.2 ml (0.021 mol) of 1.6 M n-butyl lithium in THF was added via syringe. The reaction mixture was allowed to stir overnight at room temperature. Any excess organometallic reagent was then destroyed by the addition of a few ml of methanol. The mixture was cooled in an ice/saltwater bath and 35 ml of 10% (w/w) aqueous HCl added. The mixture was stirred for 30 min, neutralized with 10% (w/w) NaOH, and saturated with NaCl. After saturation, the contents of the flask were extracted with 3 x 50 ml chloroform. The chloroform extracts were combined, treated with brine, and dried over anhydrous magnesium sulfate. The drying agent was removed and the mixture concentrated in vacuo. The residue was placed in a dry 250 ml one-neck RBF equipped with a magnetic stirrer. To the flask was added 30 ml methanol and 7.25 g (0.05 mol) methyl iodide. After stirring for 1 hr at room temperature the mixture was concentrated in vacuo and 30 ml of a saturated aqueous NaHCO₃ solution was added along with 30 ml chloroform. The contents of the flask were stirred for 10 min, the phases separated, and the aqueous phase extracted twice more with 2 x 50 ml chloroform. All three chloroform extracts were combined and dried over anhydrous magnesium sulfate. The drying agent was removed and the mixture concentrated in vacuo leaving a dark red liquid. The residue was
then fractionally distilled (Kugelrohr) to afford 0.9 g (47.9% yield) of a yellow liquid (bp 95-100°C, 0.15 mm Hg): NMR (CDCl₃) δ 0.95 (broad t, 3H), 1.43 (m, 4H), 2.30 (m, 2H), 6.75 (d, J=14Hz, 1H), 6.90-7.60 (m, 4H), 7.95 (d of d, J=3 Hz, J=6Hz, 2H); IR (thin film) 3050, 2955, 2920, 2860, 1668, 1645, 1618, 1445, 1340, 1280, 1220, 1000, 980, 785, 760, and 692 cm⁻¹; mass spectrum m/e 188 (M⁺).

Trans-1-benzoyl-2-(4-methylphenyl)ethene

To a dry 250 ml three-neck RBF equipped with magnetic stirrer, condenser, and thermometer was added 0.50 g (0.021 mol) magnesium turnings. The system was flushed with nitrogen, and a solution of 3.6 g (0.021 mol) p-bromotoluene in 50 ml dry THF was added dropwise over a 20 min period. The exothermic reaction was allowed to subside and the mixture allowed to reflux for 3 hr. The reaction mixture was then cooled in an ice/saltwater bath and 3.0 g (0.010 mol) VAS was added in one portion. The contents of the flask were then brought to reflux for 3 hr and allowed to stir overnight at room temperature. Afterwards, any excess organometallic reagent was destroyed by the addition of a few ml of methanol. The flask contents were cooled in an ice/saltwater bath, 35 ml 10% (w/w) aqueous HCl solution was added, and the mixture was stirred for 30 min. The mixture was then neutralized with 10% (w/w) aqueous NaOH, saturated with NaCl, and extracted with 3 x 50 ml chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate, the drying agent was removed, and the mixture was concentrated in vacuo. The residue was fractionally distilled to yield a
yellow solid (bp 125-130°C, 0.4 mm Hg) which was recrystallized from a 50:50 methanol/water mixture to afford 0.9 g (41% yield) of a white solid (mp 92-94°C): NMR (CDCl₃) δ 2.34 (s, 3H), 7.20 (broad d, J=8Hz, 3H), 7.30-7.80 (m, 6H), 8.00 (d of d, J=3Hz, J=6Hz, 2H); IR (CHCl₃) 3000, 1658, 1600, 1510, 1332, 1178, 1018, 814, 692, and 658 cm⁻¹.
DISCUSSION OF RESULTS

As can be seen by the results located in the Experimental section, attack by the organometallic reagent on the vinamidinium salts occurred exclusively at the 1-position - producing the $\alpha$, $\beta$-unsaturated ketone upon acid hydrolysis. The following mechanism (Figure XVI) is suggested to explain the observed mode of reaction. Attack at the least substituted, electrophilic carbon atom seems to indicate that steric factors play a large role in the reaction.

Figure XVI. Suggested mechanism for the reaction of organometallic reagents with an unsymmetrical vinamidinium salt.

For all four entries in Table 10, purification of the product was done by distillation (Kugelrohr), recrystallization, or both. Entries 1, 3, and 4 were not as clean as anticipated due to the presence of low-boiling contaminants thought to be solvent decomposition products.
GC analysis revealed that the same contaminants were common to all three entries. With respect to entries 3 and 4, the products were easily separated from the impurities by distillation (Kugelrohr) due to their much greater molecular weight (i.e. greater boiling point). With respect to entry 1, NMR and GC analysis seemed to confirm the presence of a dimethylaminated intermediate (i.e. from complete hydrolysis). Subsequent methylation with iodomethane followed by a bicarbonate wash afforded a crude reaction mixture without the presence of the intermediate. A careful, fractional distillation (Kugelrohr) was needed to purify the product due to its considerably lower boiling point. Reaction conditions were changed for entry 2 in such a way that a lower reaction temperature was utilized (see (d) below Table 10). These new conditions seemed to afford a very clean reaction mixture containing only expected product and a diphenylethane impurity. The impurity arises from coupling of the Grignard reagent with itself and is presumably already present within the reagent bottle. (The organometallic reagent here was added as a preformed Grignard reagent in THF). Further work needs to be done to insure that the lower reaction temperature is what actually afforded the cleaner crude reaction mixtures.

The NMR spectra of the four products were characteristic of substituted benzoyl ethenes. All four spectra showed a doublet of doublets for $H_a$ centered at $\delta$ 8.0 with coupling constants of 3Hz
and 6Hz. Absorptions for H_b and H_c occurred between δ 7.0-7.06 within a multiplet which was more complex for those products containing an additional aromatic ring.

![Chemical Structure](image)

Chemical shifts for both vinylic protons, H_d and H_e, were affected by the substituent group, R. For entry 1, H_d absorption occurs further upfield as a doublet centered at δ 6.75. If resolution is good, H_e can be seen as a doublet of triplets downfield of H_d. Otherwise, a multiplet can be described for H_b, H_c, and H_e centered between δ 6.90-7.60. The remaining n-butyl protons of entry 1 exhibit characteristic absorptions much further upfield with those protons adjacent to the unsaturation centered at δ 2.3 while the others are found as multiplets at δ 1.43 and δ 0.95.

The aromatic region of the NMR spectrum of entry 2 (i.e. H_a, H_b, H_c) is similar to that of entry 1. H_e, however, is shifted further upfield and its absorption is found centered at δ 6.5 along with that of H_d in the form of a broadened triplet. The chemical shift of these protons, further upfield than those of entry 1, is due to partial shielding by the phenyl ring in the allylic position. The methylene protons of entry 2 are seen as a doublet of triplets, if resolution is good, centered at δ 3.85 (otherwise a multiplet can be described).
The NMR spectrum of entry 3, again, shows identical chemical shifts for \( Ha, Hb, \) and \( Hc \). The peaks corresponding to \( Hd \) and the two protons ortho- to the methyl group are found as a broadened doublet at \( \delta 7.20 \) integrating for 3H. The peaks corresponding to \( Hd \) and the two protons meta- to the methyl group are found along with those of \( Hb \) and \( Hc \) as a multiplet at \( \delta 7.30-7.80 \). The methyl protons are found as a sharp singlet at \( \delta 2.20 \).

The spectrum of entry 4 is very similar to that of entry 3. Both vinylic protons, however, are found as two doublets along with \( Hb, Hc \), and a doublet corresponding to the two protons meta- to the methoxy group, i.e. \( \delta 7.2-7.6 \) (m, 7H). The two protons ortho- to the methoxy group are found as a doublet upfield at \( \delta 6.9 \). The methoxy protons are located as a sharp singlet at \( \delta 3.8 \).

The IR spectra of entries 1-4 exhibit characteristic absorption of trans-\( \alpha,\beta \)-unsaturated ketones. Cross-conjugated carbonyl absorption in all cases occurs at lower wavenumbers between 1650-1675 cm\(^{-1}\). Particularly strong \( C=\overset{\cdot}{\overset{\cdot}{\overset{\cdot}{C}}} \) absorption is seen at 1595-1620 cm\(^{-1}\), especially for those products containing two aryl rings. The \( C=C \) stretch is greater for those products (entries 3 and 4) where the aryl ring is in conjugation with the double bond. Strong, typical, conjugated trans-trans olefinic absorption occurs near 1000 cm\(^{-1}\) in all cases. The other typical trans-trans \( C=C \) stretch can be seen as a shoulder on the intense \( C=O \) stretch near 1670 cm\(^{-1}\). Absorptions typical of the substituent groups, \( R \), also occurred in all cases.
CONCLUSIONS

Grignard and lithium organometallic reagents have been successfully reacted with 3-dimethylamino-3-phenyl-prop-2-en-1-yliden-dimethyliminium perchlorate to produce the trans-1-benzoyl ethenes. It has been shown that alkyl-, aryl-, and benzyl-organometallic reagents react exclusively at the 1-position (i.e. the less substituted position) to give α,β-unsaturated ketones after acid hydrolysis.
PART II

RECOMMENDATIONS

The following are suggestions for future research in the area of organometallic reactions involving unsymmetrical vinamidinium salts.

1. Liebscher reports the reactions of a number of nitrogen nucleophiles (e.g. pyridine, morpholine, pyrollidine, etc.) with arylchloropropeniminium systems to produce the unsymmetrical vinamidinium salts. Investigations can be made into the reaction of these salts with organometallic reagents to see if the regioselectivity of the reaction can be changed (i.e. reaction of the nucleophile at the 3-position instead of the 1-position).

2. In addition, the nature of the aryl group may be changed by using substituted acetophenones to produce the unsymmetrical vinamidinium salts. The possible incorporation of strong electron-withdrawing or electron-releasing substituents may alter the electrophilicity of the carbon at the 3-position of the salt, hence altering the regioselectivity of the reaction.

3. Reaction conditions should be altered in an attempt to minimize the formation of the low-boiling contaminants within the crude reaction mixture. Lower reaction temperatures (e.g. 0-25°C) and a milder acidic work-up (e.g. NH₄Cl) should be investigated.
4. The chloropropeniminium salt itself is an interesting substrate. Its reaction with organometallic reagents should be studied in an attempt to see if it also produce the $\alpha,\beta$-unsaturated ketones upon acid work-up. Reaction may occur at the 3-position. If so, a convenient method will have been found to selectively alkylate (or arylate) at the 1- or 3- position by merely choosing the appropriate starting substrate.
INSTRUMENTATION AND EQUIPMENT

Infrared spectra were recorded on a Perkin-Elmer Model 457 infrared spectrophotometer. Samples were run as thin films, nujol mulls, or CHCl₃ solutions. NMR spectra were obtained in CDCl₃ or Me₂SO-d₆ solutions using (CH₃)₄Si as an internal standard at 60 MHz with a Varian EM-360 spectrometer. GC traces were obtained on a Shimadzu Model GC-7A gas chromatograph coupled with a Shimadzu Model C-R1B recorder. Removal of solvents in vacuo was performed using a Rinco Rotovapor rotary evaporator. All boiling and melting points are uncorrected. Melting points were recorded on a Fischer-Johns melting point apparatus. Most starting materials used were purchased from Aldrich Chemical Company, Milwaukee, Wisconsin.
BIBLIOGRAPHY


29. The procedure is a modification of that found in reference 28.