RADIOLABELLING OF ORGANIC MOLECULES WITH SHORT-LIVED RADIONUCLIDES (^{11}C, ^{18}F)

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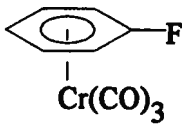
Abstract

The primary aim of this study was to develop new methods for the introduction of short-lived radionuclides (^{11}C, ^{18}F) into organic molecules. This was accomplished by the use of organometallic intermediates: (i) (η^6-arene)tricarbonylchromium complexes were used to facilitate aromatic nucleophilic substitution of the attached arene for the incorporation of [^{11}C]cyanide anion, and (ii) vinyl-tin derivatives were employed for electrophilic fluorination reactions to produce ^{19}F- and ^{18}F-labelled vinyl fluorides.

A range of simple (η^6-arene)tricarbonylchromium complexes were prepared as model systems. Fluorine was found to be the only leaving group that was readily displaced by cyanide. Non-radioactive and ^{11}C-labelled aryl nitriles were prepared in 10 minutes by reaction of complexes **1**, **4**, **5**, and **6** with [^{12}C]cyanide and [^{11}C]cyanide in DMSO at elevated temperature. Under the reaction conditions used, the aryl nitrile product was liberated from the chromium tricarbonyl moiety thereby obviating the need for a separate oxidative decomplexation step.

The reactivity of (*E*)-vinylstannanes **30**, **31**, **32**, **33**, and **34** was studied with elemental fluorine and acetyl hypofluorite under varied conditions. Generally, gaseous CH_3COOF was found to be the most effective fluorinating agent for the electrophilic cleavage of vinyl-tin bonds. For example, **31** was fluorinated with CH_3COOF, at room temperature, to yield an isomeric mixture of **39** and **40** in 41-42% yield; fluorination with F_2 proceeded in 9.0% yield at best. Subsequently, **31** was radiofluorinated with $CH_3COO^{18}F$ in 19% radiochemical yield (based on starting [^{18}F]F_2).



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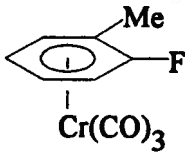

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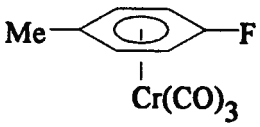

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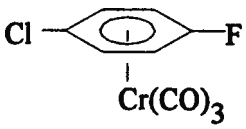

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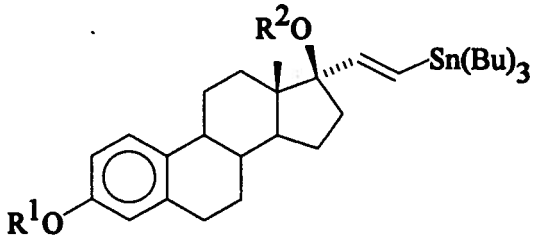

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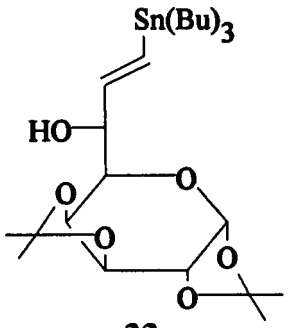
31 $R^1 = Me$, $R^2 = H$

32 $R^1 = R^2 = Me$



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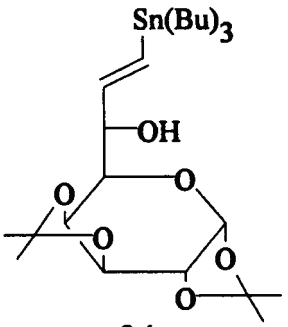

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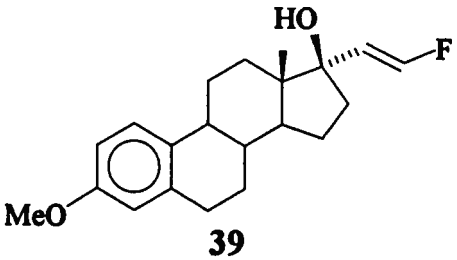

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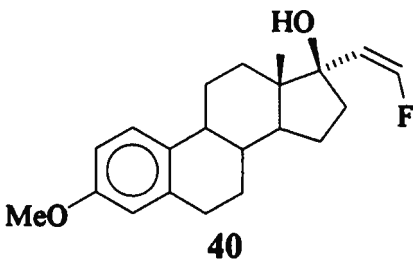

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Dedication

To my risen Lord

Chapter 1

GENERAL INTRODUCTION

1.1 Background

Organic molecules labelled with short-lived positron emitting nuclides have had a great impact on biomedical research.[1] Thus, for the first time, using positron emitting radiopharmaceuticals, quantitative in vivo measurements have been made of the human biochemical and physiological processes of the brain, heart, and other organs.[2] For example, it has been shown that regional brain metabolism can be correlated with functional activity in humans under normal circumstances,[3] during somatosensory stimulation,[4] and also in disease states such as schizophrenia[5] and senile dementia.[6] Other parameters of physiological function have also been measured which include blood volume, blood flow, oxygen- and glucose-metabolic rates, drug-receptor interactions, protein synthesis, amino acid transport, permeability of the blood-brain barrier, and tissue pH. These studies are intended to give a better understanding of disease states such as cancer, epilepsy, heart disease, stroke, movement disorders such as Parkinson's disease, and mental illness.[7,8]

The in vivo measurement of biochemical and physiological processes, using compounds labelled with short-lived positron emitting nuclides, is based on the use of Positron Emission Tomography (PET). In this technique, a positron emitting

radiopharmaceutical, with the desired biological activity, is administered to a living subject. Inside the body, the radiotracer decays by emitting a positron (β^+, positive electron), which travels a few millimetres, combines with an electron, its antimatter twin, and is thereby annihilated to produce two gamma-ray photons each of 511 keV. The two gamma-rays travel in opposite directions, nearly 180° apart, penetrating the surrounding tissue and are detected by a circular array of coincidence detectors surrounding the subject being imaged. Only timed coincidence annihilation events registered by paired detectors located 180° apart are recorded. From these, the spatial distribution of the radiotracer is reconstructed by computer, and is presented as a series of cross-sectional images.[7,9]

The successful application of PET as a medical research tool derives from the fact that PET allows the study of physiological and biochemical processes to be done in a quantitative, non-invasive manner, within a volume element of tissue in vivo. From the technical viewpoint, a key ingredient of this process is the positron emitting radiopharmaceutical itself.[10] One of the cornerstones of modern medicine is the understanding that all clinical symptoms result from biochemical reactions, and as a consequence, every pathology has an underlying biochemical defect.[7] Thus, the radiopharmaceutical acts as a biochemical probe and, by virtue of the attached positron emitting nuclide, the fate of the radiopharmaceutical can be spatially mapped using PET. As a result, the range of studies that can be performed using PET depends on the availability of compounds appropriate to the study, which can be labelled with positron emitting nuclides.[8,10]

To date, PET has been most extensively applied to problems in neurology, cardiology,

and oncology. As a result of the successes obtained in these studies, substantial efforts are being made to expand PET into new areas of research.[11,12] Therefore, to exploit the full potential of PET, continued development of new and improved methods of radiopharmaceutical synthesis are required.

1.2 Aspects of Labelling with Short-lived Isotopes

The goals of radiopharmaceutical synthesis have many elements in common with traditional synthetic organic chemistry. Both the radiochemist and organic chemist are concerned with developing syntheses which will yield in the most direct manner, the desired compound in the largest chemical yield possible. In addition, the radiochemist is concerned with obtaining high radiochemical yields. Radiochemical yield is defined as the amount of radioactivity incorporated into the product as a percentage of the initial quantity of radioactivity used. Both the radiochemist and organic chemist require the final compound to be isolated in a chemically pure state. However, radiolabelled compounds must also be radiochemically pure and free of other radionuclidic impurities.[13] Furthermore, organic compounds produced as pharmaceuticals and formulated for intravenous injection, whether radiolabelled or not, must also be sterile and pyrogen free.[14]

In order to ensure a successful radiopharmaceutical synthesis, several additional considerations hold which are not common to synthetic organic chemistry. The key aspects that need to be addressed by the radiochemist are as follows: (i) the physical properties of the radionuclide, (ii) the source and chemical form of the radionuclide, and (iii) the specific activity, stoichiometry, and reaction scale. These topics will now be

discussed in the above order.

The most important radionuclides used in PET are ^{11}C, ^{13}N, ^{15}O, and ^{18}F; their half-lives are listed in Table 1.1. All of these positron emitting nuclides possess short half-

Table 1.1: Characteristics of Radionuclides Used for PET

Radionuclide	Half-life (min)	% β^+ Decay[a]	Daughter
^{11}C	20.4	99.8	^{11}B, stable
^{13}N	9.96	100	^{13}C, stable
^{15}O	2.07	99.9	^{15}N, stable
^{18}F	109.7	96.9	^{18}O, stable

SOURCE: Reference 15.

[a] β^+ = positron emission.

lives*,[16] and emit high energy, body-penetrating radiation. These characteristics are important properties which make these radionuclides suitable for medical use. However, these same properties also give rise to problems for radiolabelling development. Most significantly, the half-life of the nuclide poses a limit on the time allowable for synthesis. The total synthesis time, beginning with the generation of the radionuclide and its incorporation into the substrate, followed by any further chemical modifications (i.e., removal of protecting groups, etc.) through to the final purification of the radiopharmaceutical, should be equivalent to no more than one or two half-lives of the radioisotope.[17,18] Clearly, the associated manipulative problems become particularly acute when using nuclides whose half-lives are on the order of minutes. The actual

* A radionuclide is usually defined as short-lived when its half-life is less than 15 h.

imaging of the patient must in turn be completed within about three or four half-lives of the radionuclide used.[19]

Another problem inherent in working with positron emitting nuclides is the obvious radiation hazard they pose, which unfortunately, exposes the radiochemist to a potentially serious health risk. Hence, for prudent safety reasons, it is necessary to work with adequate levels of shielding, use remote operations whenever possible, properly monitor the radiation level in the work area, and to work with care while handling radioactive compounds.[20]

The source and chemical form in which a given radioisotope is available has a significant impact on the development of a practical synthetic strategy. The first problem is the availability of the required positron emitting nuclide. In general, positron emitting nuclides are produced by nuclear reactions performed with a charged particle accelerator, generally a cyclotron.[21] Some positron emitters are available from a nuclide generator system, such as the $^{68}Ge/^{68}Ga$ (half-life of ^{68}Ga is 68.1 min) generator. Although such generators are very convenient as they allow shipment of radionuclides for long distances from the production site, unfortunately, few such generator systems exist for positron emitting isotopes.[22] Therefore, it is generally mandatory that accelerator produced nuclides be made on site, or within relatively short travelling distance (i.e., time) from the radiolabelling facilities.

The chemical form of a given radionuclide is the second problem that has to be considered. Radioisotopes, as obtained from a cyclotron or generator, are usually available in a limited range of chemical forms. Although the preparation of a

radioisotope is dependant on the nuclear reaction used, target design, and cyclotron characteristics, the chemical form of the radioisotope is determined by a number of factors—the most crucial factor is the chemical composition of the target and the energy deposition in the target;[17] this area of study is referred to as *target chemistry*. Therefore, if the reagent form of the radionuclide is inappropriate for a given radiolabelling procedure, then additional chemical manipulations are required to obtain the desired form of reagent. Since this increases the synthesis time and adds complexity to the experimental procedure, the best approach, whenever possible, is to directly prepare the radioisotope in the specific chemical form required for the radiolabelling step.

The last topic of this section is the issue of specific activity, stoichiometry, and reaction scale; these three subjects are closely related. Specific activity is defined as the quantity of radioactivity present, generally expressed in curies, per mole of compound. One curie of activity produces 3.70×10^{10} Bq (disintegrations per second);[23] the maximum specific activity of a radionuclide depends on its half-life (see Table 1.2), and is only attainable when no other isotope of the same element (i.e., carrier) is present; this ideal state is referred to as the *carrier-free* (CF) state. For some radioisotopes, this CF state can be approached only to within an order of magnitude so that some carrier is unavoidably present in most cases. For example, it is reported that in the production of $H^{11}CN$, the ratio of ^{11}C to ^{12}C is approximately 1:3000.[24] In light of this problem, additional terminology is needed for specifying the extent of dilution present in a radiopharmaceutical product. The *no carrier-added* (NCA) state, as applied to an element or compound, means that no carrier of the same element or compound has

Table 1.2: Physical Properties of Some Radionuclides

Nuclide	Half-life	Decay Mode[a]	Maximum energy (MeV)	Range[b] (mm)	Maximum specific activity (Ci/mol)
^{11}C	20.4 min	β^+(99+%)	0.96	4.108	9.22×10^9
^{15}O	2.07 min	β^+(99.9%)	1.72	8.2	9.08×10^{10}
^{13}N	9.96 min	β^+(100%)	1.19	5.39	1.89×10^{10}
^{18}F	109.7 min	β^+(97%)	0.635	2.39	1.71×10^9
^{3}H	12.35 y	β^-(100%)	0.0186	0.0072	2.90×10^4
^{14}C	5730 y	β^-(100%)	0.155	0.359	62.4

SOURCE: Reference 25.

[a]Decay modes: β^+=positron emission, β^-=beta particle emission.
[b]Maximum linear range in water.

been added during its preparation. The *carrier-added* (CA) state means a known amount of carrier has been added to the element or compound during its preparation.[17]

Especially when dealing with short-lived radiopharmaceuticals near their maximum specific activity, the mass of the product is not detectable by ordinary chemical or spectroscopic means. To illustrate this point, consider the mass of 1 mCi of ^{11}C as compared to ^{14}C, which is 1.5 pg (6.53×10^{10} atoms) as opposed to 0.22 mg (9.59×10^{18} atoms) of ^{14}C.[26] Therefore, the production of high specific activity radiopharmaceuticals in the CF or NCA states is highly desirable because the mass of the radiopharmaceuticals is then so small that when administered in vivo it is usually below the threshold where any physiological response is invoked, yet there is adequate radioactivity present (in the order of 0.1 to 0.5 μCi/g of tissue in the case of PET instruments) to be detected

with statistical significance.[24] Thus, even highly toxic molecules can be used for studies if adequate specific activities can be achieved.[17]

Working with small amounts of high specific activity radionuclides usually leads to problems regarding stoichiometry and reaction scale. When a labelling reaction is performed, in which both labelling reagent and substrate are used in approximately one to one ratio, everything may work well. However, when the concentration of the labelling reagent is reduced by several orders of magnitude, as during a high specific activity radiosynthesis, very different results may be observed. Since NCA radiosyntheses are performed on a very small scale, the amount of impurities present in the reagents and solvents may be comparable to, or even exceed, the quantity of the radionuclide used in the synthesis. These impurities may compete with the radiolabelling reagent in a given reaction, leading either to unwanted side-products, or even to complete prevention of the formation of the desired radiolabelled product.[27] If one of the impurities present in the synthesis is carrier, this will lower the specific activity of the radiolabelled product. This can be a very serious problem when very high specific activities are required, and as a result great care must be taken to exclude carrier from all possible sources, such as solvents, reagents, and substrates.[28]

In spite of the various difficulties and challenges involved in the area of radiopharmaceutical synthesis, much progress has actually been made. A variety of positron emitting radiopharmaceuticals have been developed and are currently being used in PET imaging, and some of the commonly used radiopharmaceuticals for PET

Table 1.3: Positron Emitting Radiopharmaceuticals Used Commonly in PET Imaging Procedures

Radiopharmaceutical	Application
[^{18}F]fluorodeoxyglucose	Cerebral glucose metabolism Myocardial glucose metabolism
[^{18}F]fluorodopa	Dopa uptake studies
[^{18}F]spiperone	Dopamine receptor binding
[^{18}F]-*N*-methylspiperone	Dopamine receptor binding
[^{18}F]-16α-fluoro-17β-estradiol	Estrogen receptor binding
[^{11}C]carbon dioxide	Tissue pH
[^{11}C]-1-butanol	Cerebral blood flow
[^{11}C]methionine	Amino acid metabolism
[^{11}C]palmitate	Myocardial metabolism
[^{11}C]acetate	Myocardial metabolism
[^{11}C]glucose	Cerebral glucose metabolism
[^{11}C]-*N*-methylspiperone	Dopamine receptor binding
[^{15}O]oxygen	Cerebral oxygen extraction and metabolism
[^{15}O]carbon monoxide	Cerebral blood volume Myocardial blood volume
[^{15}O]water	Cerebral blood flow Myocardial blood flow
[^{13}N]ammonia	Myocardial blood flow
SOURCES: References 7,8,10,29.	

are summarized in Table 1.3.

1.3 Objectives and Format of this Thesis

With the continuing development of PET, new and innovative synthetic methodologies

are needed to produce the required radiopharmaceuticals for future PET applications. The primary objective of this study was the exploration of new methods for the incorporation of positron emitting radionuclides—specifically ^{11}C and ^{18}F—into organic compounds.

Increasingly, the use of organometallic intermediates are providing new avenues to rapidly label organic molecules. The organic derivatives of some main group metals (B,[30] Si,[31,32] Ge,[33] Sn,[34,35] Hg,[36] Tl,[37]) have been studied and utilized for radiolabelling. Generally, their prime application has been to prepare compounds that are radiolabelled on the aromatic ring. Boron[30] and silicon[32] derivatives have also been successfully used for the preparation of radiolabelled alkyl halides. The common feature of these reactions is the exploitation of the reactivity of the polarized carbon-metal bond, in which the metal possesses a partial positive charge and the attached carbon possesses a partial negative charge; as a result, an organometallic compound is susceptible to electrophilic attack. This is important because the electrophilic cleavage of organometallic precursors can potentially be performed under mild conditions with short reaction times. Therefore, radionuclides that can be prepared in electrophilic reagent form, can in turn be used for the radiolabelling of organometallic precursors, in a regioselective manner.

Previous studies in this laboratory focussed on the development of labelling vinyl-tin derivatives with radioactive bromine (^{82}Br) and iodine (^{123}I and ^{131}I).[38] The use of vinyl-tin reagents was found to be very successful. This experience prompted our interest in extending the utility of vinyl-tin reagents to radiofluorinations with ^{18}F.

The organic derivatives of transition metals, however, exhibit very different patterns of reactivity as compared to those of the main group metals.[39] The fundamental reason for this is the presence of partly filled *d* or *f* orbitals. This leads to a variety of bonding interactions with organic ligands.[40] Transition metals are able to form complexes in which the metal is bonded to unsaturated organic molecules such as ethylene, cyclobutadiene, or benzene. The normal pattern of reactivity of unsaturated organic molecules when coordinated to transition metals is changed, whereby the unsaturated moieties can be attacked by a wide range of nucleophiles. The more electron-withdrawing the metal centre, the more facile is the nucleophilic addition.[41] This mode of reactivity could have significant potential for the application of radiolabelling. It was decided to explore the labelling of aromatic rings with ^{11}C using (η^6-arene)tricarbonyl-chromium complexes as synthetic intermediates.

The format of this thesis is as follows. Chapter 2 is devoted to the evaluation of (η^6-arene)tricarbonylchromium compounds as synthetic intermediates for the incorporation of ^{11}C, in the form of [^{11}C]cyanide, onto aromatic rings. At the beginning of the chapter, some introductory background information is presented regarding organochromium chemistry. Then, the preparation of (η^6-arene)tricarbonylchromium complexes used for this study will be described. This will be followed by an examination of the reactivity of the prepared chromium tricarbonyl complexes with non-radioactive cyanide. Lastly, radiolabelling studies with ^{11}C-labelled cyanide will be presented.

Chapter 3 is devoted to the development of electrophilic fluorination methodology that is applicable to vinyl-tin compounds with both non-radioactive fluorine and radiofluorine.

The chapter begins with an introduction to selective fluorination of organic molecules. This will be followed by a presentation of the synthesis of the vinyl-tin derivatives employed for this present study. Next, fluorination studies of the vinyl-tin precursors with elemental fluorine and acetyl hypofluorite will be described. Finally, radio-fluorination with ^{18}F of a selected vinyl-tin derivative will be presented.

In Chapter 4, the general conclusions developed from the studies described in Chapters 2 and 3 will be presented, along with suggestions for future work.

In Chapter 5, the experimental details are given for the work performed for this thesis. The general methods are described first, followed by the specific experimental descriptions for Chapters 2 and 3, respectively.

References

1. *Positron Emission Tomography*; Reivich, M., Alavi, A., Eds.; Alan R. Liss: New York, 1985; *Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart*; Phelps, M. E., Mazziotta, J. C., Schelbert, H. R., Eds.; Raven: New York, 1986.

2. Kellersohn, C. *Brit. J. Radiol.* **1981**, *54*, 91-102; Wagner, H. N. *J. Am. Med. Assoc.* **1986**, *256*, 2096-2097.

3. Reivich, M.; Kuhl, D.; Wolf, A. P.; Greenberg, J. H.; Phelps, M. E.; Ido, T.; Casella, V.; Fowler, J. S.; Hoffman, E. J.; Alavi, A.; Som, P.; Sokoloff, L. *Circ. Res.* **1979**, *44*, 127-137; Phelps, M. E.; Huang, S. C.; Hoffman, E. J.; Selin, C.; Sokoloff, L.; Kuhl, D. E. *Ann. Neurol.* **1979**, *6*, 371-388.

4. Alavi, A.; Reivich, M.; Greenberg, J. H.; Hand, P.; Rosenquist, A.; Wolf, A. P. *Semin. Nucl. Med.* **1981**, *11*, 24-31; Greenberg, J. H.; Reivich, M.; Alavi, A.; Hand, P.; Rosenquist, A.; Rintelman, W.; Stein, A.; Tusa, R.; Dann, R.; Christman, D.; Fowler, J. S.; MacGregor, B.; Wolf, A. P. *Science* **1981**, *212*, 678-680.

5. Farkas, T.; Reivich, M.; Alavi, A.; Greenberg, J. H.; Fowler, J. S.; MacGregor, R. R.; Christman, D. R.; Wolf, A. P. In *Cerebral Metabolism and Neural Function*; Passonneau, J. V., Hawkins, R. A., Lust, W. D., Welsh, R. A., Eds.; Williams and Wilkins: Baltimore, 1980; pp 403-408.

6. Ferris, S. H.; deLeon, M. J.; Wolf, A. P.; Farkas, T.; Christman, D. R.; Reisberg, B.; Fowler, J. S.; MacGregor, R.; Goldman, A.; George, A. E.; Rampal, S. *Neurobiol. of Aging* **1980**, *1*, 127-131.

7. Ter-Pogossian, M. M.; Raichle, M. E.; Sobel, B. E. *Sci. Am.* **1980**, *243*, 170-181.

8. Dagani, R. *Chem. Eng. News* **1981**, *59*(45), 30-37.

9. Links, J. M. In *Nuclear Imaging in Drug Discovery, Development, and Approval*; Burns, H. D., Gibson, R. E., Dannals, R. F., Siegl, P. K. S., Eds.; Birkhäuser: Boston, 1993; pp 22-23.

10. Jacobson, H. G. *J. Am. Med. Assoc.* **1988**, *259*, 1854-1860.

11. Ter-Pogossian, M. M. *J. Nucl. Med.* **1985**, *26*, 1487-1498.

12. Cox, P. H. In *Text of Radiopharmacy: Theory and Practice*; Sampson, C. B., Ed.; Gordon and Breach Science: New York, 1990; Chapter 16.

13. Theobald, A. E. In *Textbook of Radiopharmacy: Theory and Practice*; Sampson, C. B., Ed.; Gordon and Breach Science: New York, 1990; Chapter 7.

14. Nickoloff, E. L. In *The Chemistry of Radiopharmaceuticals*; Heindel, N. D., Burns, H. D., Honda, T., Brady, L. W., Eds.; Masson Publishing USA: New York, 1978; Chapter 5.

15. Wolf, A. P.; Fowler, J. S. In *Positron Emission Tomography*; Reivich, M., Alavi, A., Eds.; Alan R. Liss: New York, 1985; p 65.

16. Vaalburg, W.; Paans, A. M. J. In *Radionuclides Production*; Helus, F., Ed.; CRC: Boca Raton, 1983; Vol. 2, p 48.

17. Fowler, J. S.; Wolf, A. P. *The Synthesis of Carbon-11, Fluorine-18, and Nitrogen-13 Labeled Radiotracers for Biomedical Applications*; Nuclear Science Series, Monograph NAS-NS-3201; Technical Information Center, U.S. Department of Energy: Springfield, VA, 1982.

18. See reference 16; Vol. 2, Chapter 2.

19. Adam, M. J., TRIUMF, Vancouver, BC, personal communication.

20. Hesslewood, S. R. In *Textbook of Radiopharmacy: Theory and Practice*; Sampson, C. B., Ed.; Gordon and Breach Science: New York, 1990; Chapter 6.

21. Wolf, A. P.; Schlyer, D. J. In *Nuclear Imaging in Drug Discovery, Development, and Approval*; Burns, H. D., Gibson, R. E., Dannals, R. F., Siegl, P. K. S., Eds.; Birkhäuser: Boston, 1993; Chapter 3.

22. Robinson, G. D., Jr. In *Positron Emission Tomography*; Reivich, M., Alavi, A., Eds.; Alan R. Liss: New York, 1985; Chapter 4.

23. Short, M. D. In *Textbook of Radiopharmacy: Theory and Practice*; Sampson, C. B., Ed.; Gordon and Breach Science: New York, 1990; p 19.

24. See reference 17; pp 28-29.

25. Fowler, J. S.; Wolf, A. P. In *Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart*; Phelps, M. E., Mazziotta, J. C., Schelbert, H. R., Eds.; Raven: New York, 1986; p 393.

26. See reference 17; p 39.

27. See reference 17; pp 29-30.

28. Wilbur, D. S.; Garcia, S. R.; Adam, M. J.; Ruth, T. J. *J. Labelled Compd. Radiopharm.* **1984**, *21*, 767-779.

29. *Radiopharmaceuticals for Positron Emission Tomography: Methodological Aspects*; Stöcklin, G., Pike, V. W., Eds.; Kluwer Academic: Boston, 1993.

30. Kabalka, G. W. *Acc. Chem. Res.* **1984**, *17*, 215-221.

31. Wilbur, D. S.; Anderson, K. W.; Stone, W. E.; O'Brien, H. A., Jr. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 1171-1188.

32. Wilbur, D. S.; Svitra, Z. V. *J. Labelled Compd. Radiopharm.* **1983**, *20*, 619-626.

33. Moerlein, S. M.; Coenen, H. H. *J. Labelled Compd. Radiopharm.* **1984**, *21*, 1076-1077.

34. Adam, M. J.; Ruth, T. J.; Pate, B. D.; Hall, L. D. *J. Chem. Soc., Chem. Commun.* **1982**, 625-626.

35. Coleman, R. S.; Seevers, R. H.; Friedman, A. M. *J. Chem. Soc., Chem. Commun.* **1982**, 1276-1277.

36. Bo-Li, L.; Yu-Tai, J.; Zhong-Yum, P.; Maeda, M.; Kojima, M. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 1089-1096.

37. Gilliland, D. L.; Basmadjiam, G. P.; Marchand, A. P.; Hinkle, G. H.; Earlywine, A.; Ice, R. D. *J. Radioanal. Chem.* **1981**, *65*, 107-113.

38. Balatoni, J. A. M.Sc. Thesis, The University of British Columbia, Dec. 1985.

39. Coates, G. E.; Green, M. L. H.; Powell, P.; Wade, K. *Principles of Organometallic Chemistry*; Chapman and Hall: London, 1979.

40. Collman, J. P.; Hegedus, L. S. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1980.

41. Davies, S. G. *Organotransition Metal Chemistry: Applications to Organic Synthesis*; Pergamon: Toronto, 1982; Chapter 4.

Chapter 2

APPLICATION OF ORGANOCHROMIUM CHEMISTRY TO RADIOLABELLING

2.1 Introduction

The first (η^6-arene)tricarbonylchromium complex was reported in 1957, by Fischer and Ofele.[1] Since that time, literally hundreds of such complexes have been prepared, characterized, and studied with respect to the structure and reactivity of the arene ring while complexed to the metal centre.[2,3] (η^6-Arene)tricarbonylchromium compounds are air-stable, diamagnetic, crystalline solids, generally yellow to orange in colour. They are soluble in a variety of solvents, readily characterized by spectroscopic methods, and are easily purified by chromatographic and recrystallization techniques. As a result of the π-coordination of an arene to chromium, its reactivity is significantly altered.[4] These changes in arene reactivity are summarized in Figure 2.1.

The most significant change in arene reactivity is the increased ability of the coordinated arene to undergo nucleophilic aromatic substitution. It is this reaction which has been most studied and extensively employed in synthetic chemistry.[5] To a lesser degree, the steric effect of the attached chromium tricarbonyl moiety has been used for the stereoselective modifications of the aromatic side chain.[6] The other changes in arene reactivity have received less attention regarding their potential use for

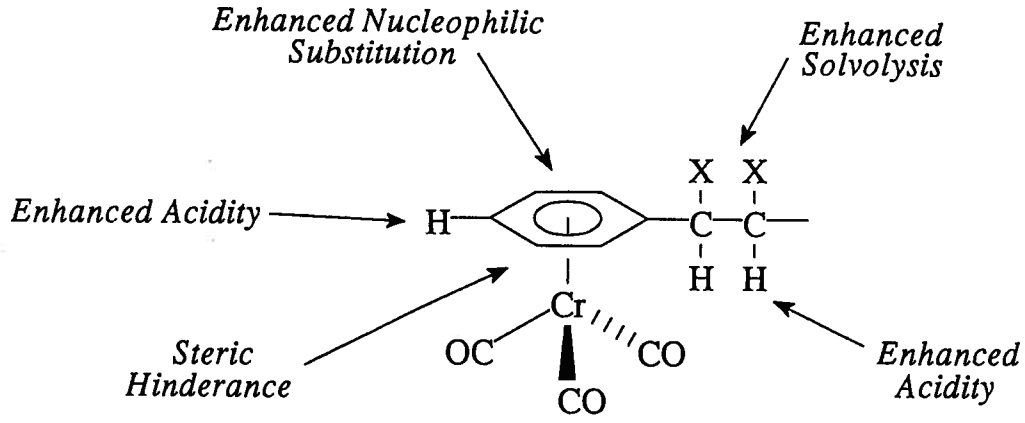
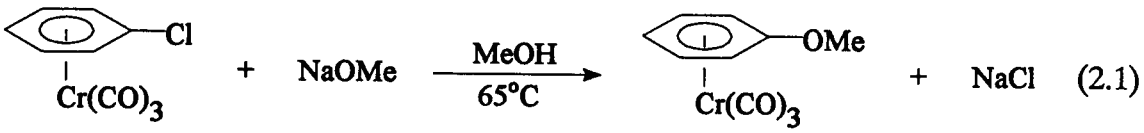


Figure 2.1: Changes in arene reactivity when complexed to chromium tricarbonyl. (Adapted from reference 7.)

synthesis.[8,9]

During early studies of the reactivity of (η^6-arene)tricarbonylchromium compounds, Nicholls and Whiting found that (η^6-chlorobenzene)tricarbonylchromium readily underwent substitution of chlorine by methoxide in very high yield.[10] Uncomplexed



(2.1)

chlorobenzene is unreactive toward methoxide under the same conditions. Later investigations have shown other nucleophiles to react similarly, such as sodium phenoxide, aniline,[11] and 2-methyl-2-propanethiol.[12] (η^6-Fluorobenzene)tricarbonyl-chromium also exhibits reactivity toward a variety of nucleophiles. Successful reactions with alkoxides, amines, thiolates, and cyanide have been reported.[12,13] It has been shown that fluorine is more readily displaced than chlorine, during aromatic nucleophilic substitution.[4]

Of greater interest for organic synthesis, is the reactivity of (η^6-arene)tricarbonyl-

chromium complexes with carbanions. Indeed, a variety of carbanions have been successfully used to alkylate the chromium tricarbonyl complexes of chlorobenzene and fluorobenzene; see Figure 2.2 for examples. Nucleophilic substitution for hydrogen can

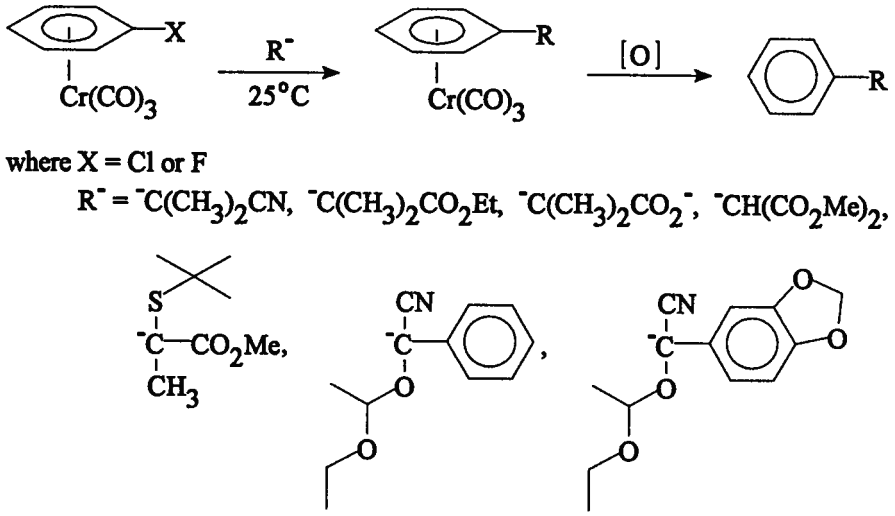


Figure 2.2: Examples of carbanions which react with (η^6-halobenzene)tricarbonyl-chromium complexes.

also occur directly on the η^6-arene ring, which opens up additional synthetic pathways. (η^6-Benzene)tricarbonylchromium, for example, reacts with a number of carbanions as shown in Figure 2.3. Furthermore, if the crude reaction intermediate is treated with excess strong acid, prior to oxidative demetallation, substituted 1,3-cyclohexadienes are obtained.[5]

Unfortunately, not all synthetically important carbanions work well with (η^6-arene)-tricarbonylchromium complexes. Grignard reagents, organocuprates, and alkylmercuric chlorides fail to react at low temperatures, while unidentified decomposition products are obtained upon heating. When strongly basic anions are used, such as methyl- or

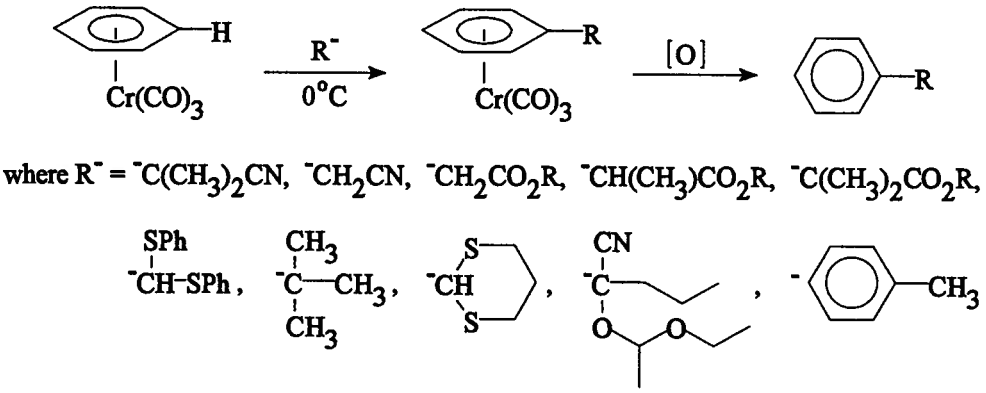


Figure 2.3: Examples of carbanions which react with (η^6-benzene)tricarbonylchromium.

butyllithium, proton abstraction results; this produces the lithiated η^6-arene complex. However, this can be a useful result, as the lithiated species can then be treated with different electrophiles, thus providing an additional route for ring modifications.[5]

An important feature of (η^6-arene)tricarbonylchromium chemistry has been the development of several methods for both complexing the chromium tricarbonyl group onto aromatic rings and being able to remove that same group efficiently when desired. A number of approaches have been developed to π-complex an arene with chromium tricarbonyl. Typically, chromium hexacarbonyl is either heated in neat arene, or with excess arene in a solvent (e.g., 1,4-dioxane, di-*n*-butyl ether), which affords the corresponding arene complex. After the desired chemistry has been accomplished, the final arene product can be readily recovered by mild oxidation. A variety of reagents have been successfully used for oxidative demetallation; aqueous Ce(IV), iodine, and exposure to sunlight and air, being the most common.[5,6,14] This is a vital consideration, if (η^6-arene)tricarbonylchromium complexes are to be useful in synthesis. The

introduction and subsequent removal of activating groups in organic chemistry presents difficult problems, not easily solved. Classical aromatic nucleophilic substitution suffers from this deficiency, as activating groups like nitro require drastic conditions for nitration, and lack mild and direct methods to remove the nitro group once its activating function is completed.[15] As a result, classical aromatic nucleophilic substitution has found limited application in complex organic synthesis. (η^6-Arene)tricarbonylchromium complexes potentially offer a significant improvement as synthetic intermediates since the chromium tricarbonyl moiety can be readily attached in most cases, then decomplexed in high yield once synthetic operations are done.

The synthesis of radiopharmaceuticals labelled with short-lived positron emitting nuclides requires special synthetic methods, due to the considerations presented earlier in Chapter 1. Prompted by the unique properties and reactivity of (η^6-arene)tricarbonyl-chromium complexes, we decided to explore the potential utility of these compounds for radiolabelling. There are about five reasons that would commend these organo-chromium compounds for radiolabelling work.

Firstly, most organic pharmaceuticals, either of potential interest for labelling or being currently used in nuclear medicine today, contain arene rings in their structures. Examples include 6-fluoro-3,4-dihydroxyphenylalanine (6-fluorodopa), the butyro-phenone neuroleptics, the estradiol class of steroids, benzodiazepines, and benzamides such as Raclopride (*S*-(-)-3,5-dichloro-*N*-[(1-ethyl-2-pyrrolidinyl)]methyl-2-hydroxy-6-methoxybenzamide).[16,17] Therefore, the presence of an aromatic ring provides a possible labelling site for attaching the radionuclide of interest. Secondly, medically useful

radioisotopes are generally produced in anionic, nucleophilic form.[18] Labelling reactions which can directly use the nucleophilic form of the radionuclide are advantageous, because this eliminates additional chemical manipulations and time to modify the reagent form of the radionuclide. Thirdly, (η^6-arene)tricarbonylchromium complexes facilitate nucleophilic substitution reactions on the aromatic ring. This established reactivity could allow the facile incorporation of nucleophilic radioisotopes onto aromatic rings. Fourthly, methods for complexing most arenes to the chromium tricarbonyl moiety, then later removing same, have been well established. This is in contrast to the use of traditional activating groups for nucleophilic aromatic substitution, such as nitro, which cannot be readily removed under mild conditions. Finally, the other modes of reactivity (see pp 1-2) exhibited by (η^6-arene)tricarbonylchromium compounds, adds additional synthetic options when designing a radiopharmaceutical synthesis.

In this chapter, the synthesis of a number of (η^6-arene)tricarbonylchromium complexes will be described. This will be followed by studies regarding the reactivity of the prepared chromium tricarbonyl compounds with cyanide. Lastly, the reactions of ^{11}C-labelled cyanide with some chromium tricarbonyl compounds will be presented.

2.2 Preparation of (η^6-Arene)tricarbonylchromium Complexes

2.2.1 Synthesis

The objective for this study was to prepare a range of simple (η^6-arene)-tricarbonylchromium complexes in order to study their suitability for radiolabelling. To accomplish this, commercially available arenes were selected to produce the

corresponding chromium tricarbonyl complexes using literature methods.

Five general methods have been developed for the synthesis of (η^6-arene)tricarbonyl-chromium compounds. The first method, as outlined in equation 2.2, is the direct

$$\text{Arene} + \text{Cr(CO)}_6 \xrightarrow[\text{solvent}]{\text{heat}} (\eta^6\text{-Arene})\text{Cr(CO)}_3 + 3\ \text{CO}\uparrow \qquad (2.2)$$

reaction of arene with $Cr(CO)_6$ under thermolysis conditions. This reaction has been carried out with various solvents ranging from neat arene to non-polar (e.g., decalin) to polar (e.g., diglyme*) solvents. The reaction must be conducted at relatively high temperatures to achieve decarbonylation of the metal carbonyl and obtain π-complexed product. The majority of (η^6-arene)tricarbonylchromium complexes have been prepared by this method. The second method involves a two-step process, in which during the first step $Cr(CO)_6$ has three carbon monoxide ligands replaced by more thermally labile ligands (L) such as pyridine, 4-methylpyridine, CH_3CN, or NH_3, as shown in equation 2.3.

$$\begin{aligned} 3\ \text{L} + \text{Cr(CO)}_6 &\xrightarrow{\text{heat}} \text{Cr(CO)}_3\text{L}_3 + 3\ \text{CO}\uparrow \ \text{(step 1)} \\ \text{Arene} + \text{Cr(CO)}_3\text{L}_3 &\xrightarrow[\text{solvent}]{\text{heat}} (\eta^6\text{-Arene})\text{Cr(CO)}_3 + 3\ \text{L (step 2)} \end{aligned} \qquad (2.3)$$

In the next step, the prepared complex, $Cr(CO)_3L_3$, is allowed to react with excess arene, using significantly lower temperatures, to obtain the desired product. The milder conditions of this methodology has allowed the preparation of chromium tricarbonyl complexes not obtainable by the first method described above. The third method is the

*Formally named bis(2-methoxyethyl) ether.

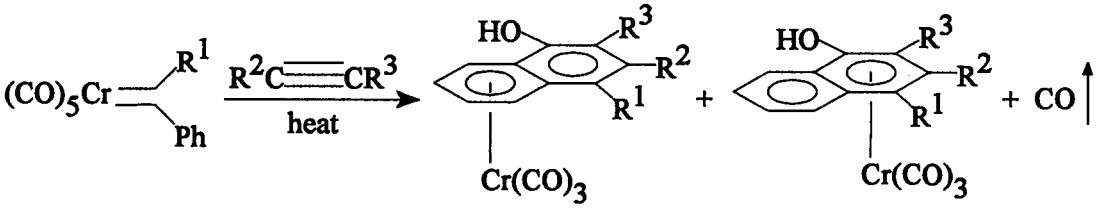
direct reaction of arene with $Cr(CO)_6$ via photolysis. Irradiation of the reaction mixture at room temperature accomplishes the desired decarbonylation. (η^6-Benzene)tricarbonylchromium and other complexes have been prepared using equation 2.4. The fourth

$$\text{Arene} + Cr(CO)_6 \xrightarrow[\text{solvent}]{\text{light}} (\eta^6\text{-Arene})Cr(CO)_3 + 3\ CO\uparrow \qquad (2.4)$$

method is arene exchange, which relies on the observation that (η^6-arene)-tricarbonylchromium complexes undergo exchange reactions in the presence of another arene at elevated temperatures (ca. 200°C), as outlined in equation 2.5. The use of donor solvents has allowed these exchange reactions to be conducted at lower

$$(\eta^6\text{-Arene}_A)Cr(CO)_3 + \text{Arene}_B \underset{}{\overset{\text{heat}}{\rightleftharpoons}} (\eta^6\text{-Arene}_B)Cr(CO)_3 + \text{Arene}_A \qquad (2.5)$$

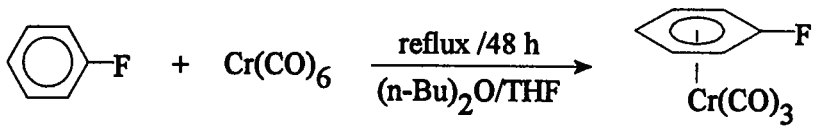
temperatures (ca. 140°C). However, the synthetic utility of this method has been limited by the high temperatures required, and by the low yields obtained. The final method is the reaction of alkynes with chromium pentacarbonyl carbenes, as illustrated in equation 2.6. A chromium tricarbonyl complex is formed from the condensation of an



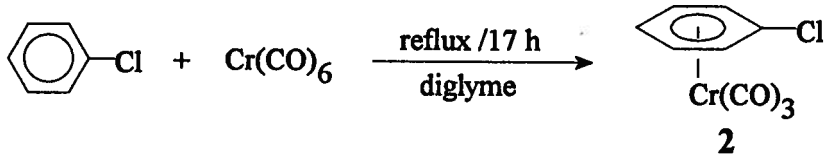
(2.6)

alkyne with a metal carbene. This novel method requires no arene starting material. A range of interesting π-complexed naphthalene and phenanthrene derivatives have been prepared by this route.[14,19]

Given the various synthetic options available, it was desirable to choose the simplest, most direct synthetic procedure to prepare the desired (η^6-arene)tricarbonylchromium complexes. The choice was made to prepare (η^6-fluorobenzene)tricarbonylchromium **1** by adapting the method of Mahaffy and Pauson,[20] and to prepare (η^6-chlorobenzene)-tricarbonylchromium **2** by the method of Nicholls and Whiting.[10]



1 (2.7)



2 (2.8)

Although (η^6-arene)tricarbonylchromium compounds are quite air-stable in solid form, their solutions are relatively air-sensitive. All preparations of these complexes, including workup and isolation, were conducted under inert atmosphere. Compound **1** was prepared in 68% yield according to equation 2.7 using an 8:1 mixture of di-*n*-butyl ether and tetrahydrofuran (THF). Mahaffy and Pauson reported a 90% yield for the synthesis of **1** under similar conditions.[20] Alternatively, **2** was obtained in an isolated yield of 47% (equation 2.8), based on the amount of $Cr(CO)_6$ consumed. This result is comparable to that of Nicholls and Whiting who reported a yield of 52%, after a reaction time of 3 h.[10]

When examining these initial experimental results, it became clear that working with

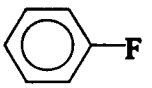
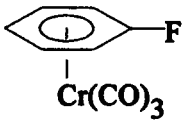
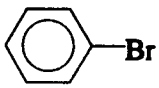
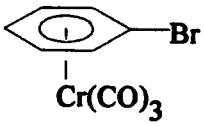
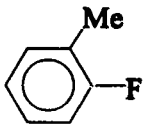
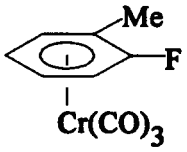
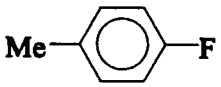
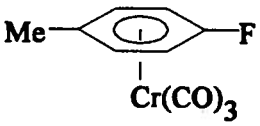
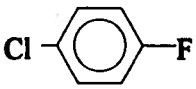
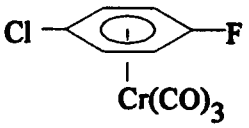
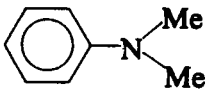
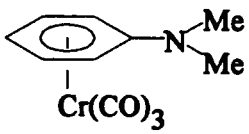
diglyme was less desirable, since it was very difficult to remove during workup. The butyl ether/THF mixture was readily removed to dryness, making workup much easier. More importantly, the method of Mahaffy and Pauson exhibited a potential for significantly better yields of chromium complexed product. As a consequence, it was decided to use the Mahaffy and Pauson reaction conditions for the preparation of other (η^6-arene)tricarbonylchromium compounds.

A number of chromium tricarbonyl complexes were successfully synthesized according to the general equation 2.9. The results obtained are summarized in Table 2.1. With

$$\text{Arene} + \text{Cr(CO)}_6 \xrightarrow[(\text{n-Bu})_2\text{O/THF}]{\text{reflux}} \text{Complex} + 3\ \text{CO}\uparrow \qquad (2.9)$$

additional work and experience, the preparative yield of **1** was improved to 80% (see Table 2.1). The reaction (equation 2.9) was found to be very sensitive to any traces of oxygen present in the reaction mixture. Regardless of how carefully the reaction apparatus, reagents, and solvents were handled under inert atmosphere, it was vital to employ freeze-pump-thaw degassing as a final step to ensure an oxygen-free environment for the reaction. The major drawback of the Mahaffy and Pauson procedure was the slowness of the reaction, thus requiring prolonged heating of the reactants (1-2 days) which can cause some decomposition of product complex. Unfortunately, this decomposition could result in further autocatalytic decomposition of any chromium tricarbonyl product formed. Some investigators have recently reported that the prime reason for decomposition of (η^6-arene)tricarbonylchromium during the reaction (equation 2.9) was due to the presence of impurities in the starting materials and

Table 2.1: Summary of Yields Obtained for Complexes Synthesized using Equation 2.9

Arene	Complex	Reaction Time	Yield
	 **1**	48 h	80 %
	 **3**	44 h	19 %
	 **4**	48 h	89 %
	 **5**	16.5 h	85 %
	 **6**	23 h	12 %
	 **7**	21 h	70 %

solvents used, and traces of atmospheric oxygen over the reaction mixture.[21]

A common problem with the direct reaction of arenes with $Cr(CO)_6$ is the volatility of $Cr(CO)_6$ itself, which results in sublimation of the metal carbonyl from the reaction mixture. Anticipating this problem, a special reaction apparatus was constructed* that allowed any sublimed $Cr(CO)_6$ to be mechanically returned to the reaction mixture. However, it was found that the use of di-*n*-butyl ether with 10-20% of THF present, effectively washed back sublimed $Cr(CO)_6$ to the reaction mixture. A regular Liebig condenser could then be used with conventional glassware to perform the synthetic reactions (see Experimental for details).

For our purposes, a paradoxical limitation of the Mahaffy and Pauson procedure, is that while electron-donating groups on the arene helps the reaction, electron-withdrawing groups slow the reaction.[22] It was found that fluorobenzene, 2-fluoro-toluene, and 4-fluorotoluene were successfully complexed, producing **1**, **4**, and **5** in high yield (80-89%). However, the corresponding complex of 4-chlorofluorobenzene (**6**) was made in only 12% yield. Persistent decomposition accompanied the preparation of **6**, thereby limiting the reflux time possible—allowing the reaction to proceed longer than overnight results in progressive decomposition and in little or no product formed. In addition, during the synthesis of **6**, a significant amount of **1** was obtained as a byproduct† which had to be separated using column chromatography.

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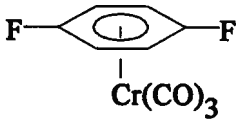
*The design of this reaction vessel was obtained from Dr. Peter Legzdins of the Chemistry Department, U.B.C., and is described in the Experimental.

†This would appear to result from a reductive dehalogenation process in which the fluorobenzene complex **1** is formed from 4-chlorofluorobenzene, probably via some

In addition to **6**, the preparations of (η^6-1,4-difluorobenzene)tricarbonylchromium **8** and (η^6-4-fluoroanisole)tricarbonylchromium **9** were attempted. In these two cases, only very small quantities (tens of milligrams) were obtained at best. Extensive



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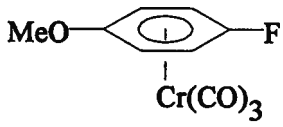


9

decomposition also accompanied these reactions. As a consequence of these disappointing results, other synthetic approaches were examined that would be more suitable for complexing arenes with electron-withdrawing substituents.

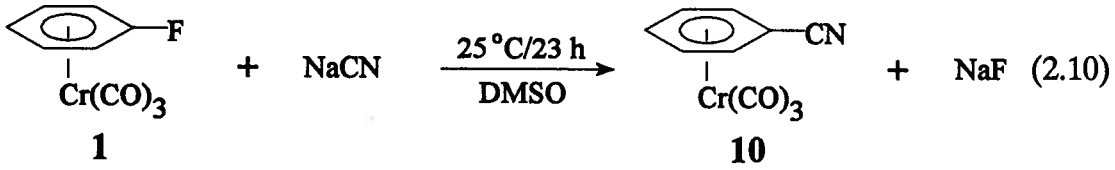
Limited trials of other synthetic methods also did not yield satisfactory results. It became clear that a sustained study would be required to resolve this problem and this was beyond the scope of time available for this work. Therefore, the chromium tricarbonyl complexes that could be prepared in adequate quantity were settled upon for the desired radiolabelling studies.

The direct reaction of benzonitrile with $Cr(CO)_6$ does not yield the corresponding chromium tricarbonyl complex.[10,23] However, Mahaffy and Pauson were able to synthesize (η^6-benzonitrile)tricarbonylchromium **10** indirectly by allowing the fluorobenzene complex **1** to react with a large excess of cyanide overnight in acetonitrile at 50°C. They obtained a 44% conversion of **10** from starting **1**.[23] Semmelhack has also

---

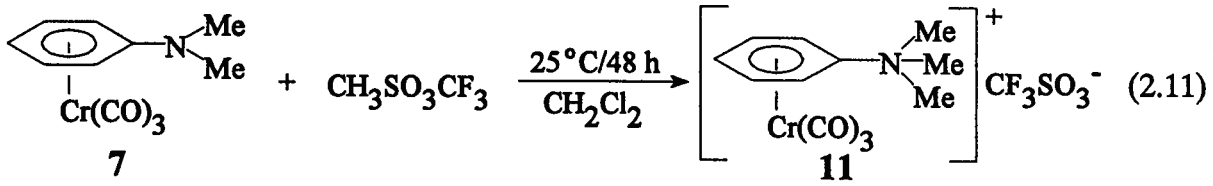
chromium species in solution. Similar results have been reported by Hudeček and Toma.[21]

reported, in a 1976 review, the successful reaction of cyanide anion with **1** at 25°C, obtaining a 94% yield.[5] Unfortunately, the experimental details of this work have never been published to the best of this author's knowledge. We were able to prepare **10** in 69% yield using different conditions, as outlined in equation 2.10.



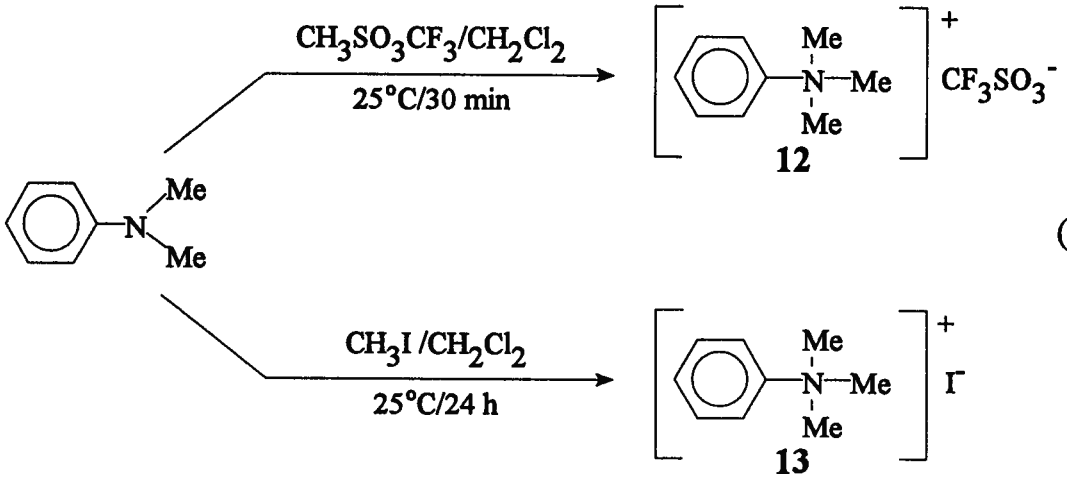
1 **10**

Of additional interest was the desire to prepare chromium tricarbonyl complexes in which the attached arene possessed groups of greater mobility toward aromatic nucleophilic substitution than halogen. Prompted by reports of radiolabelling studies using aromatics with dimethylsulfonium[24] and trimethylammonium leaving groups,[25,26] it was considered whether an analogous chromium tricarbonyl complex could be made. Bunnet and Herman successfully methylated (η^6-thioanisole)tricarbonylchromium with trimethyloxonium tetrafluoroborate to obtain (η^6-phenyldimethylsulfonium)tricarbonyl-chromium tetrafluoroborate in 89% yield.[27] However, they found that (η^6-*N*,*N*-dimethylaniline)tricarbonylchromium **7** could not be methylated by trimethyloxonium tetrafluoroborate.[27] In our efforts, we found that complex **7** can be methylated using methyltrifluoromethanesulfonate (commonly called methyl triflate) according to equation 2.11. (η^6-*N*,*N*,*N*-Trimethylanilinium)tricarbonylchromium trifluoromethanesulfonate **11** was produced in 59% yield. In order to compare the behaviour of this new complex **11** with the corresponding uncomplexed arene, *N*,*N*,*N*-trimethylanilinium trifluoromethane-



(2.11)

sulfonate **12** and *N,N,N*-trimethylanilinium iodide **13** were also synthesized as shown in equation 2.12. Compound **12** was prepared in 83% yield, while **13** was obtained in 56% yield.



(2.12)

2.2.2 Characterization

All of the (η^6-arene)tricarbonylchromium complexes, except for **11**, are known compounds. Their melting points were recorded and are presented in Table 2.2. The chromium tricarbonyl complexes tended to decompose to some degree during melting point determinations. The degree of decomposition would vary with the heating rate thereby making the melting points difficult to determine in some cases.

Table 2.2: Summary of Melting Points of Organochromium Complexes

Complex	Observed mp (°C)	Literature mp (°C)	Reference
1	117	116-117	27
2	100-101	101-102	20
3	101-105	120	28
4	71-72	73-74	29
5	59-60	61-62	29
6	61-62	—	none found
7	137-138	144	20
11	120-121	—	none found

The identification of the chromium tricarbonyl complexes was accomplished by mass spectrometry (MS). The principal fragmentation patterns of simple (η^6-arene)-tricarbonylchromium compounds using electron impact MS have been well established and are shown in Figure 2.4.[30,31] The fragmentation patterns exhibited by the synthesized chromium tricarbonyl complexes were consistent with the scheme depicted in Figure 2.4. Also, Müller and Göser reported that all (η^6-halobenzene)tricarbonyl-chromium compounds gave the Cr-halogen$^+$ ion on fragmentation (i.e., $[(C_6H_5X)Cr]^+ \rightarrow [CrX]^+ + C_6H_5\cdot$).[31] This ion was observed for each of the chromium tricarbonyl complexes with halogen-substituted aromatic rings. These characteristic features of the mass spectra, exhibited by the chromium tricarbonyl compounds, made product identification rapid and straight forward.

Complex **11** was previously an unknown compound and was characterized by elemental analysis and ^{1}H NMR spectroscopy. Compounds **12** and **13** were identified

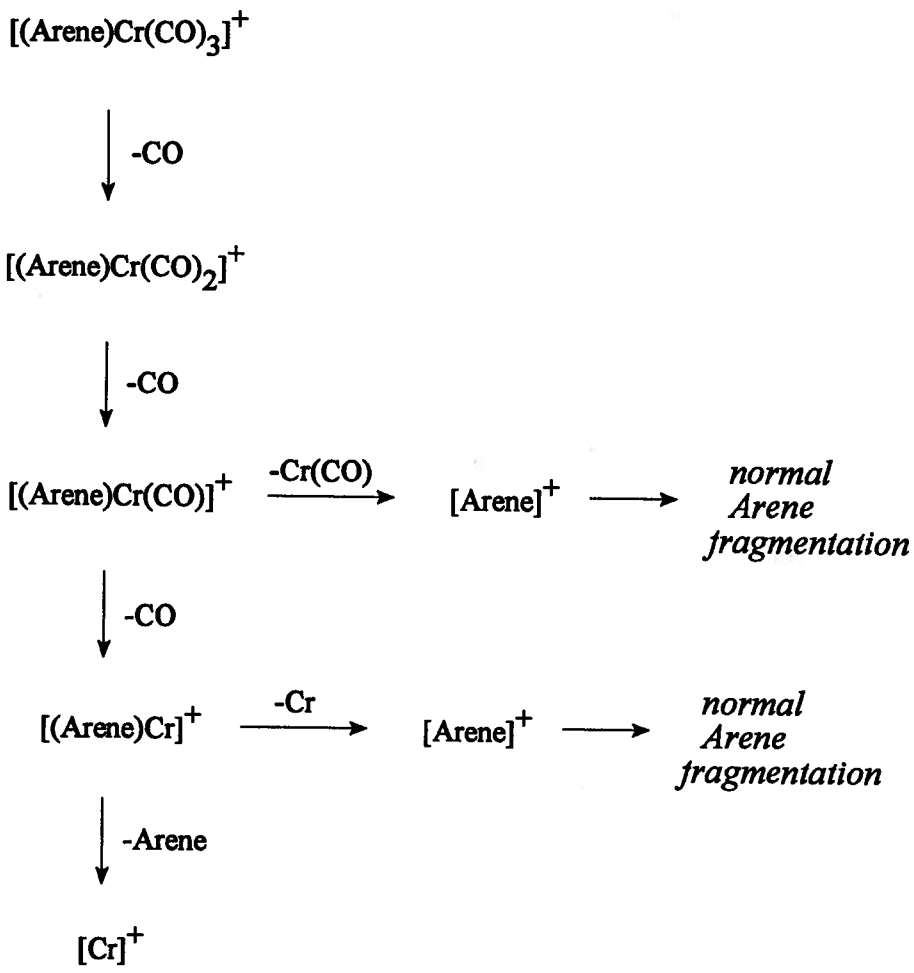


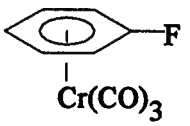
Figure 2.4: Principal fragmentation pattern of (η^6-arene)tricarbonylchromium compounds.

by ^{1}H NMR spectroscopy. MS could not be employed for analysis of these salt complexes (**11**, **12**, **13**). A satisfactory elemental analysis for C, H, N, and S was obtained for **11**. The ^{1}H NMR spectrum of **11** exhibited the aromatic proton resonances at 5.77 (H-3,5), 6.07 (H-4), 6.69 (H-2,6) ppm, and a singlet for the trimethylammonium group protons at 3.56 ppm. The ^{1}H NMR spectral data for **12** and **13** were found to be

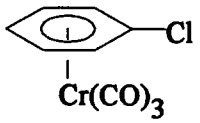
the same; the aromatic protons were observed at 7.58-7.68 (H-3,4,5) and 7.97 (H-2,6) ppm, and the trimethylammonium group protons at 3.61 ppm. These results showed the expected upfield shifts in proton resonances due to complexation with chromium tricarbonyl. This is a characteristic feature of the ^{1}H NMR spectra of chromium tricarbonyl complexes when compared to the uncomplexed arene.[4]

2.3 Reactions of Organochromium Compounds with Cyanide

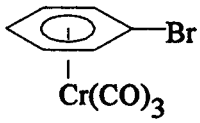
These studies began with investigating the reactivity of cyanide with (η^6-halobenzene)-tricarbonylchromium complexes **1**, **2**, and **3**. All substitution reactions were performed



1



2



3

under an argon or nitrogen atmosphere, using dried solvents. Complex **1** was allowed to react with excess sodium cyanide (ca. 10 equiv) in DMSO at 150°C* for 30 minutes. During heating, the initial yellow colour of the reaction mixture became dark red. After cooling, the reaction mixture was diluted with water, extracted with diethyl ether, then dried. The dried ether extracts were colourless. The ether extracts were concentrated and analyzed by gas chromatography (GC). GC analysis confirmed the presence of benzonitrile **14** as the only product obtained. This reaction was repeated under slightly different conditions, where complex **1** was treated with about 2 equivalents of sodium

*Reaction temperatures always refer to the oil bath temperature used.

cyanide at 155°C in DMSO for 20 minutes. After workup, GC analysis of the ether extracts exhibited two prominent peaks, a major peak due to **14** and a minor peak due to fluorobenzene. For comparison, uncomplexed fluorobenzene was allowed to react with sodium cyanide under the same conditions. GC analysis showed that only unreacted fluorobenzene was present.

These initial results clearly demonstrated that the fluorobenzene complex **1** underwent successful aromatic nucleophilic substitution with cyanide and that the reaction was rapid under the conditions employed. The control experiment with uncomplexed fluorobenzene confirmed that free fluorobenzene failed to react with cyanide, and that intact chromium tricarbonyl species underwent the substitution reaction.

The reactivity of the chlorobenzene complex **2** was examined next. Complex **2** was treated with sodium cyanide (ca. 0.5 equiv) in DMSO at 160°C for 15 minutes. After workup, the ether extracts were yellow in colour. GC analysis showed only the presence of chlorobenzene. The ether extracts were subsequently treated with iodine to decomplex any intact chromium tricarbonyl components, and the GC analysis was repeated. Chlorobenzene remained the only compound detected. For comparison, the reaction of **1** with sodium cyanide was repeated under the same conditions as used for **2**. GC analysis showed two significant peaks, one peak due to **14** and the other due to fluorobenzene. In like manner, the ether extracts were again treated with iodine to decomplex any chromium tricarbonyl components present. GC analysis gave the same results as observed prior to oxidative decomplexation.

Unfortunately, these results showed that **2** is either unreactive toward cyanide or is

possibly undergoing significant decomplexation under the reaction conditions used. However, **1** readily underwent substitution with cyanide using the analogous conditions employed for the reaction trial with **2**. Though disappointing, this observation was complimentary to previous studies that have shown that fluorine is more easily displaced during aromatic nucleophilic substitution than chlorine.[4] Therefore, these results suggested that chlorine is an inappropriate leaving group to use in future studies, and was thus abandoned.

Lastly, the potential of bromine as a leaving group was investigated using the bromobenzene complex **3**. Complex **3** was allowed to react with 0.5 equivalents of potassium cyanide in DMSO at 135°C for 10 minutes. After cooling, high pressure liquid chromatography (HPLC) was employed to directly examine the reaction mixture. HPLC analysis confirmed the absence of the desired product **14.** In contrast, **1** was treated with cyanide under identical conditions, and benzonitrile **14** was produced. HPLC analysis not only confirmed the presence of **14**, but the yield was also determined—these results will be presented and discussed later in this section.

These results also indicated that **3** is either unreactive toward cyanide or is possibly decomplexing under the reaction conditions employed. Bromine, as a consequence, would also appear to be an unsuitable leaving group for aromatic nucleophilic substitution. Therefore, the only useful halogen leaving group for reactions with cyanide was determined to be fluorine.

In order to further characterize the benzonitrile product **14**, obtained from the reaction of **1** with cyanide, isolated products from several small scale reactions were

combined. This combined product sample (dissolved in diethyl ether) was subjected to GC analysis, and only one component was observed with almost 99% purity. The ether was evaporated and the product sample was dissolved in deuterated chloroform for NMR spectroscopy. The room temperature ^{1}H NMR spectrum was recorded at 80 MHz.* In addition, the ^{1}H NMR spectrum of authentic **14** (commercially obtained) was recorded under the same conditions. The spectrum of the product sample exhibited a multiplet centered at 7.57 ppm that was the same as that observed for authentic **14**. Therefore, the ^{1}H NMR spectrum clearly identified the product sample as benzonitrile **14**. This is in addition to GC and HPLC studies which readily identified **14** by comparison of its retention time with that of authentic standard. Also, during HPLC studies, an aliquot of reaction mixture was taken and standard **14** was added to see if the assigned product peak would correspondingly increase in size. This was observed, and deemed as further evidence that the chromatographic assignment was correct. Furthermore, it was noted during the workup of the reactions of **1** with cyanide that the characteristic odour of **14** was present.

A number of general observations were made during the early studies regarding the reaction of **1** with cyanide. Reactions employing approximately 2 or more equivalents of cyanide for 15-30 minutes exhibited essentially a quantitative conversion of **1** to **14**, as determined by GC analysis. The temperatures used for these reactions were 150-155°C. Additional experiments were performed in which the reaction mixtures were

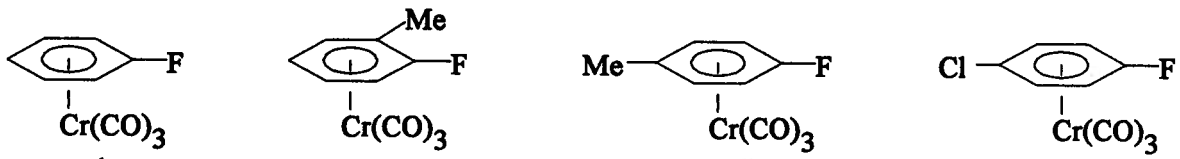
*These spectra were obtained on a departmental Bruker WP-80 spectrometer with tetramethylsilane used as an external standard.

heated for as little as one to three minutes and **14** was still produced, as observed by GC and HPLC analyses. Other reactions conducted used a large molar excess (up to 17-fold) of complex **1** relative to cyanide. Again, benzonitrile **14** was obtained, according to GC and HPLC analyses. Lastly, decomplexation of the aromatic nitrile takes place during the reaction under the conditions employed. This was demonstrated by examining a product mixture by GC (after workup) which showed no change in benzonitrile **14** concentration after treatment with iodine. Subsequently, this observation was further confirmed with additional experimental experience, which shall be presented at later stages of this discussion. As a consequence, no separate oxidative decomplexation step was needed to liberate the organic product. This result was not too surprising as it has been reported that (η^6-arene)tricarbonylchromium complexes can undergo displacement of the aromatic ring in donor solvents, such as pyridine, at elevated temperatures.[32]

These results further indicated just how facile and rapid the substitution reaction of **1** with cyanide actually is. Since the intent was to ultimately apply this chemistry for the incorporation of [^{11}C]cyanide into arenes, the studies to follow were designed to model this application. With excess cyanide and longer reaction times, excellent reaction yields could be assured. The half-life of ^{11}C, however, is 20.4 minutes, which places a premium on using the shortest reaction time possible. Also, it is highly desirable that the reaction be eventually compatible with high specific activity [^{11}C]cyanide, for the reasons discussed earlier in Chapter 1. Therefore, the decision was made to limit subsequent cyanide substitution reactions to 10 minutes and to use cyanide as the limiting reagent

(0.5 equiv).

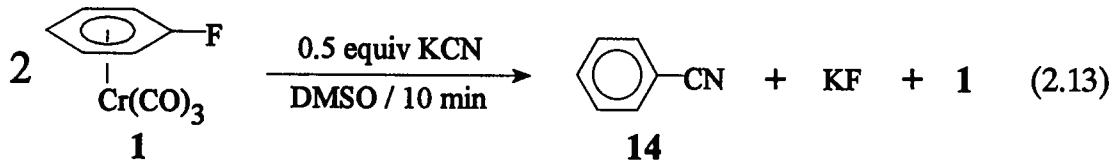
Within these parameters, the reactivity of the chromium tricarbonyl complexes **1**, **4**, **5**, and **6** was examined. The general procedure used is as follows. An aqueous solution



1 **4** **5** **6**

of cyanide, containing a known amount of KCN, was dispensed into a reaction vessel, and was carefully dried under a fast flow of inert gas. (This was done to model the handling necessary in using [^{11}C]cyanide, which is obtained as an aqueous solution after cyclotron production.) The (η^6-arene)tricarbonylchromium complex, dissolved in 1 mL of DMSO, was added to the dried cyanide. The mixture was heated for 10 minutes. Upon cooling, the reaction mixture was quantitatively transferred to a volumetric flask and diluted to a known volume with DMSO. This solution was analyzed by HPLC. The extent of product formation was determined using a calibration curve constructed using HPLC absorbance values of standard solutions of expected aryl nitrile product. The chemical yields were calculated using KCN as the limiting reagent. In order to optimize the results obtained for each of the complexes studied, the reaction temperatures were varied and the corresponding chemical yields were determined.

Complex **1** was treated with cyanide, as shown in equation 2.13, using reaction



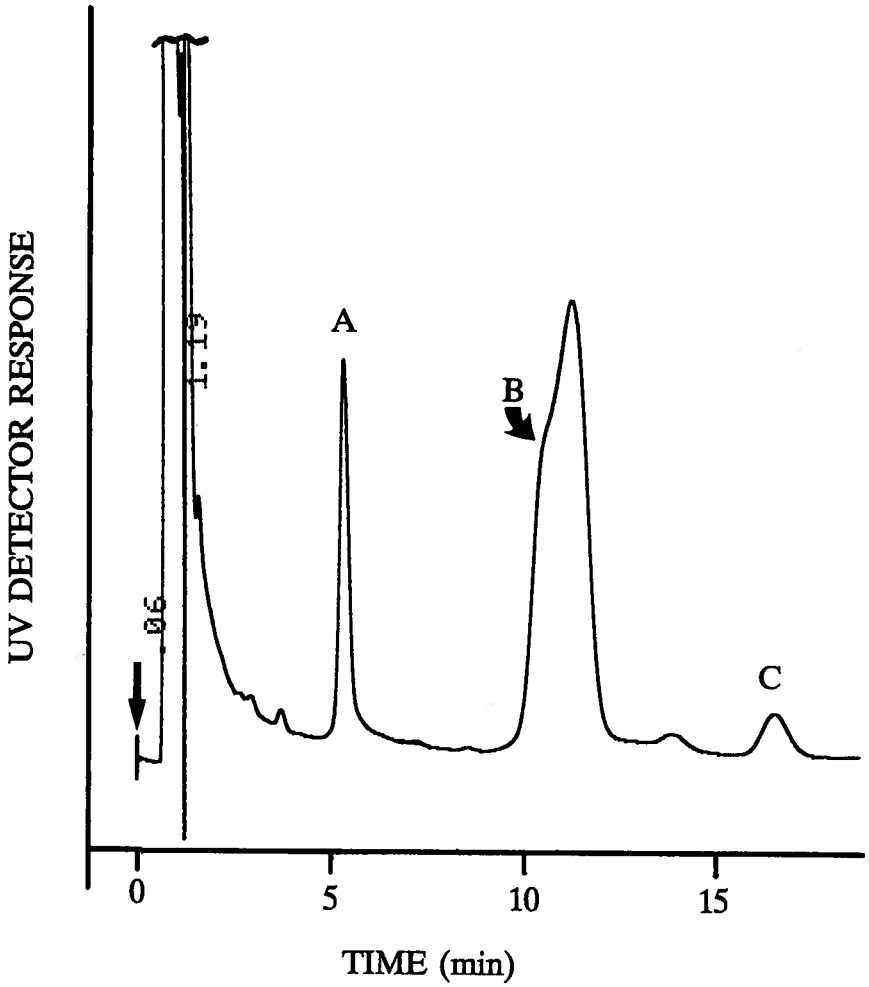
1 **14** (2.13)

temperatures ranging from 105-150°C. The results obtained are summarized in Table 2.3. The optimum temperature found for equation 2.13 was 135°C, giving a best yield of 41%. A representative HPLC chromatogram is shown in Figure 2.5. The chromatogram shows the presence of the desired product **14** (peak A), along with residual starting complex **1** (peak C) and free fluorobenzene (peak B) which is visible only as a shoulder of an unidentified peak. Injection of a solution, consisting of fluorobenzene standard added to an aliquot of reaction mixture, exhibited an increase of this shoulder (peak B) into a distinct peak at the same retention time, thereby confirming the assignment of peak B. Another control experiment was performed with uncomplexed fluorobenzene using 0.5 equivalents of cyanide at 135°C. Once again, only unreacted fluorobenzene was observed in the HPLC chromatogram.

Table 2.3: Chemical Yields Obtained for Complex **1**

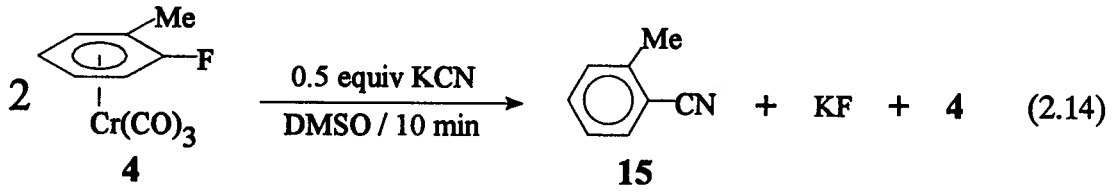
Temperature (°C)	Yield	no. of runs	Average Yield
150	23-33%	2	28%
135	40-41%	2	41%
120	31%	1	31%
115	32%	1	32%
105	12%	1	12%

Next, the reactions of complexes **4**, **5**, and **6** with cyanide were investigated. The reactivity of **4** (equation 2.14) was examined over a temperature range of 95-135°C. The results obtained are shown in Table 2.4. The best yields (41-43%) were observed at 105-115°C. The control reaction done with 2-fluorotoluene (uncomplexed) using 0.5 equiva-



The compounds are: (A, 5.4 min), **14**; (B, ~10.5 min), fluorobenzene; (C, 16.8 min), **1**. The HPLC conditions are: Waters 10 μm C-18 reverse phase RCM column; eluent: isocratic methanol/water, 1:1; flow rate, 2.5 mL/min; UV detection set at 280 nm.

Figure 2.5: HPLC chromatogram obtained from the analysis of the reaction of complex **1** with cyanide at 135°C. The yield of **14** was determined to be 40%.



(2.14)

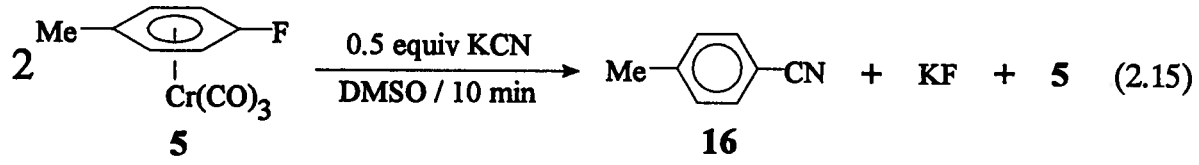
lents of cyanide at 135°C gave no reaction; unreacted 2-fluorotoluene was the only compound observed in the HPLC chromatogram. Two reaction trials (equation 2.14) were performed using only 1.5 mg of **4**, this being about a tenth of the usual quantity of complex used per reaction trial. This results in a five-fold excess of cyanide being

Table 2.4: Chemical Yields Obtained for Complex **4**

Temperature (°C)	Yield	no. of runs	Average Yield
135	29-36%	4	32%
125	28-29%	2	28.5%
115	41%	1	41%
105	41-43%	2	42%
95	26%	1	26%
135[a]	58%	1	58%
143[a]	58%	1	58%
[a]Only a tenth of the usual quantity of **4** was used, giving a stoichiometric ratio of 5:1, of KCN to **4**.			

present in these reactions. Yields of 58% were obtained at both 135 and 143°C. These results were significantly better than those obtained using 0.5 equivalents of cyanide (see Table 2.4).

The reaction of **5** with cyanide, as summarized in equation 2.15, was studied over the temperature range of 105-150°C. The chemical yields obtained are outlined in Table



(2.15)

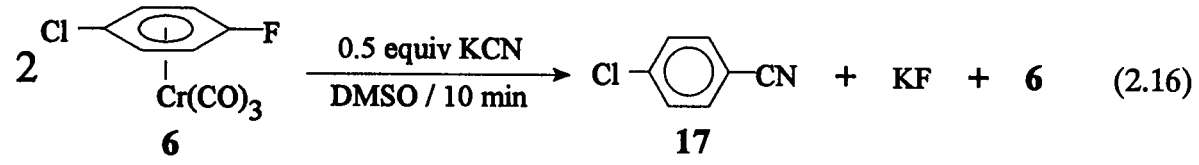
2.5. The best yields (26-29%) were obtained at 115°C, while the next best results (22-26%) were seen at 135°C. The control experiment performed using uncomplexed 4-

Table 2.5: Chemical Yields Obtained for Complex **5**

Temperature (°C)	Yield	no. of runs	Average Yield
150	21%	1	21%
135	22-26%	3	24%
125	21%	1	21%
115	26-29%	2	27.5%
105	11%	1	11%

fluorotoluene (0.5 equiv of KCN; 135°C) exhibited no reaction. HPLC analysis showed only the presence of unreacted 4-fluorotoluene.

The reaction of **6** with cyanide (equation 2.16) was examined at 115 and 135°C. These results are summarized in Table 2.6. The best yields (26-34%) were obtained at



(2.16)

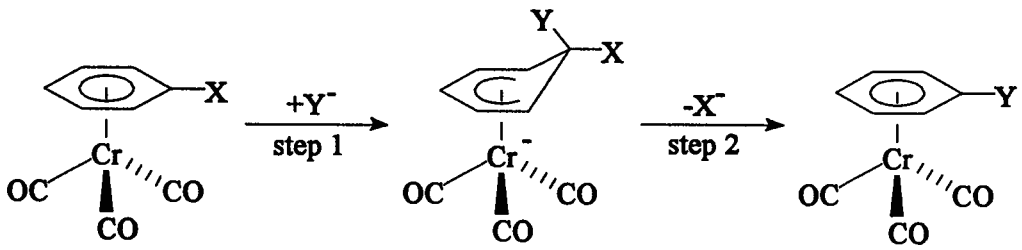
the reaction temperature of 115°C. The control reaction done with 4-chlorofluoro-benzene (uncomplexed) using 0.5 equivalents of cyanide at 135°C exhibited no reaction; unreacted 4-chlorofluorobenzene was the only compound observed in the HPLC chroma-togram. One reaction trial (equation 2.16) was heated (115°C) for five minutes, and gave

Table 2.6: Chemical Yields Obtained for Complex **6**

Temperature (°C)	Yield	no. of runs	Average Yield
135	21%	1	21%
115	26-34%	3	30%
115[a]	17%	1	17%
[a]A reaction time of 5 min was used.			

only about half the yield observed for a 10 minute reaction time (see Table 2.6). This indicates that reaction times shorter than 10 minutes would result in a significant sacrifice in chemical yield.

In the process of examining the chemical yields obtained for complexes **1**, **4**, **5**, and **6**, it would be interesting to discover any trends or systematic patterns of chemical behaviour. However, inspecting the results presented in Tables 2.3-2.6 indicates that there are no such patterns observable. What emerges is that each chromium tricarbonyl complex studied exhibits its own distinct pattern of reaction yields. The mechanism for nucleophilic substitution reactions of (η^6-arene)tricarbonylchromium systems is thought



(2.17)

to proceed by a two-step mechanism (equation 2.17),[5,33] analogous to classical aromatic

nucleophilic substitution.*,[34] The first step is addition of the nucleophile (Y^-) onto the aromatic ring, on the side opposite the chromium tricarbonyl moiety—this results in the *exo*-substituted, anionic η^5-cyclohexadienyl complex. The second step is expulsion of the halide leaving group (X^-), giving the final substitution product. If this mechanism is valid, it would be anticipated, from comparison to classical aromatic nucleophilic substitution, that electron-withdrawing groups would make the substitution reaction with cyanide more facile, while electron-donating groups would hinder same.[35] Using the fluorobenzene complex **1** as the baseline standard, it may be expected that the presence of the additional methyl group in **4** would hinder the reaction with cyanide, relative to **1**, and may lead to lower substitution yields during the short reaction time used. The best average yield for **1** was 41% obtained at 135°C, while **4** exhibited its best average yield of 42% at 105°C. As a result, **4** essentially equalled the best yield obtained by **1** at 30 degrees lower temperature. On the other hand, the results obtained by **5** were much more surprising. Since **4** and **5** are simply ortho- and para-isomers, respectively, similar chemical yields with cyanide might be anticipated for both complexes. However, **5** gave unexpectedly low yields, with a best average yield of 27.5% obtained at 115°C. In fact, the chemical yields obtained by **4** readily surpassed those of **5** at all temperatures investigated (see Tables 2.4 and 2.5). Complex **6**, which bears an extra chlorine substituent (relative to **1**), would be expected to produce the highest chemical yields with cyanide—yet this was not observed. A best average yield of 30% was exhibited at 115°C.

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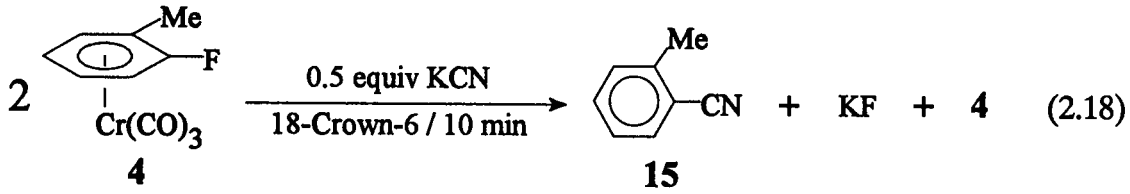
*The mechanism being specifically referred to here is addition-elimination, also called SNAr by March.

Unfortunately, circumstances did not permit the opportunity to conduct reactions at temperatures below 115°C. It is possible that higher chemical yields could be obtained for **6** at lower temperatures. Nonetheless, equal or better yields were obtained from **1** and **4** at both 115 and 135°C.

These results may be explained in part by the relative thermal stability of the complexes. Complex **6** was clearly more prone to decomposition in solution; this was particularly evident during its synthesis (see pages 27-28). Due to the presence of the chlorine substituent, in addition to the fluorine, there would be less electron density available on the aromatic ring to complex with the chromium tricarbonyl moiety, and the resulting complex would be anticipated to be less thermally stable relative to **1**. Therefore, the lower chemical yield for **6** at 135°C, compared to that of **1**, could stem from greater thermal breakdown of **6** at that temperature. The yields resulting from **1** and **6** at 115°C are quite comparable. As a result, **1** exhibits better yields at 135°C than **6** simply because it is likely the more thermally robust complex, and not from any greater intrinsic reactivity. On the other hand, both **4** and **5** would be expected to be somewhat more thermally stable than **1**. Complexes **4** and **5** were both prepared in higher yield than **1**, and were found to be as well behaved during storage and handling. However, as presented earlier, **4** exhibited better yields at lower temperatures as compared to **1**, but **5** exhibited significantly lower chemical yields at all reaction temperatures employed when compared to those of **4**. Since it would be reasonable to assume that both **4** and **5** would be of equivalent thermal stability, the reason for this marked difference in chemical yields obtained by **4** and **5** is unknown. For each

chromium tricarbonyl complex studied, the chemical yields obtained were found to be quite sensitive to reaction temperature, and hence must be optimized for each complex individually to achieve the best results possible.

In order to improve upon the chemical yields obtained thus far, it was decided to investigate the use of crown ethers. The presence of crown ethers with many ionic reagents have shown increased solubility and anion reactivity in aprotic organic solvents. Therefore, by employing a crown ether with potassium cyanide, it would be anticipated that the nucleophilicity of the cyanide anion would be enhanced.[36,37] Previously, 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) has been successfully used to help convert benzyl halides[38] and alkyl halides[39] to their corresponding nitriles in high yield. As a result, 18-crown-6 was chosen as the crown ether to use, to examine its potential benefit on the reaction of **4** with cyanide, as shown in equation 2.18. The same general



(2.18)

procedure was followed as described earlier, except for the addition of approximately 1.2 equivalents of 18-crown-6 to the reaction mixture prior to heating. The reactions were conducted over a temperature range of 95-135°C and the chemical yields were determined by HPLC analysis as before. The results obtained are summarized in Table 2.7. The best yields (40-44%) were now observed to occur throughout the temperature range of 105-135°C. These results did not surpass the previous best yields of 41-43%, obtained at 105-115°C, in the absence of 18-crown-6. When the reaction was repeated

at 105°C using approximately three equivalents of 18-crown-6, a slightly improved yield of 46% was obtained. However, the use of 18-crown-6 did significantly improve upon earlier reaction yields that were obtained at 95, 125, and 135°C (see Table 2.4)—increases of about 30-50% over earlier average chemical yields were exhibited.

Table 2.7: Chemical Yields Obtained for Complex **4** using 18-Crown-6

Temperature (°C)	Solvent	Yield	no. of runs	Average Yield
135	DMSO	41%	1	41%
125	"	42%	1	42%
115	"	40%	1	40%
105	"	40-44%	2	42%
105[a]	"	46%	1	46%
95	"	35%	1	35%
80	CH_3CN	3%	1	3%
95[b]	"	4%	1	4%

[a]About 3 equiv of 18-crown-6 was used.
[b]At this oil bath temperature, the CH_3CN was observed to be refluxing.

In addition to these results, a couple of reaction trials (equation 2.18) were conducted using acetonitrile as the solvent with one equivalent of 18-crown-6 added; these were done using oil bath temperatures of 80 and 95°C. As shown in Table 2.7, very poor yields were obtained. After chromatographic (HPLC) analysis, these reaction mixtures were simply set aside without any further manipulations. The following day these mixtures were reexamined by HPLC, which showed a significant increase in the concentration of 2-tolunitrile **15** (see Table 2.8). These reaction mixtures were again set

aside for about two weeks. Then HPLC analysis was performed again and a further increase in the concentration of **15** was observed (see Table 2.8). Initially, the results obtained using CH_3CN as the reaction solvent looked wholly unimpressive, but unexpectedly, good yields of **15** were produced with the passage of time. Experience with

Table 2.8: Chemical Yields Obtained for Equation 2.18 using Acetonitrile as the Solvent

Temperature (°C)	Yield	Time elapsed after initial HPLC analysis
80	3%	0
80	21%	~18 h
80	50%	~13.5 d
95	4%	0
95	21%	~16 h
95	46%	~13.5 d

DMSO as the reaction solvent has shown that after the reaction has been performed and the reaction mixture analyzed by HPLC, no further changes in nitrile product concentration was observed with subsequent reanalyses. Due to the elevated temperatures used for the reactions (equation 2.18) done in CH_3CN, it was expected that the chemical yields, determined initially, represented the total nitrile product formed (and decomplexed) during the 10 minute reaction time. What is not clear is whether the improved yields shown in Table 2.8 were due to the reaction continuing to occur at a slower rate at room temperature (during storage), or to the fact that the initially formed (η^6-2-tolunitrile)tricarbonylchromium species only decomplexed to a small extent at first,

then continued to slowly decomplex while being stored.* Unfortunately, this work was not followed up at the time.

The preliminary results obtained using 18-crown-6 shows promise for the use of crown ethers in the substitution reactions of chromium tricarbonyl complexes. In fact, other crown ethers and cryptands are available for potential use.[36,40] It is anticipated that some experimentation would be needed to find the optimum macrocycle to function in these substitution reactions with cyanide.

The identification of the aryl nitrile products formed from the reactions of complexes **4**, **5**, and **6** with cyanide was accomplished using chromatographic (HPLC) studies. Each of the nitrile products (2-tolunitrile **15**, 4-tolunitrile **16**, 4-chlorobenzonitrile **17**) were readily identified by comparison of their respective retention times with that of authentic standard. To further confirm the identity of the nitrile products **15**, **16**, and **17**, a separate set of reaction trials was conducted to isolate the organic products and analyze these by gas chromatography-mass spectrometry (GC-MS). These reactions were performed as described previously in the general procedure used for the earlier cyanide reactions (see page 38). Upon cooling, however, the reaction mixtures were diluted with water, then extracted with diethyl ether. The ether extracts were cooled to 0°C, then treated with iodine for two hours to oxidatively decomplex any chromium tricarbonyl species present. The treatment was quenched with the addition of aqueous sodium thiosulfate solution. The ether layer was further washed (aqueous $Na_2S_2O_3$ and saturated

*The reaction mixtures were kept in small, stoppered volumetric flasks, but these mixtures had been exposed to air during HPLC work. As a result, any chromium tricarbonyl species present could gradually undergo oxidative decomposition.

NaCl solutions), then dried. The ether solution (concentrated to 1 mL) was analyzed first by GC and HPLC, then by GC-MS. Mixtures of authentic standards were prepared from the uncomplexed starting arene and corresponding aryl nitrile product (dissolved in ether) and were also analyzed by GC-MS for direct comparison to the reaction products obtained above.

Comparison of the mass spectra obtained from the reaction products with those of the authentic standards confirmed the identity of the starting fluoroaromatics (2-fluoro-toluene, 4-fluorotoluene, 4-chlorofluorobenzene) and the resulting nitrile products (**15, 16, 17**). However, the reaction mixture containing 4-chlorofluorobenzene and **17** also contained a third minor product which was identified as benzonitrile **14** by its mass spectrum.

The formation of **14** as a side-product from the reaction of **6** with cyanide was due to the presence of a small quantity of **1** contaminating the starting complex **6**. Unfortunately, the chromatographic purification of **6**, during its original preparation, did not completely remove **1** as an impurity. As a consequence, **1** also underwent substitution with cyanide as a side-reaction, affording benzonitrile **14**.

In addition, the chemical yields for this set of reaction trials were estimated from the GC analyses using the standard mixtures for calibration. These results are shown in Table 2.9. The key feature of these results is that none of the yields surpassed the values reported earlier, which were determined without subjecting the reaction mixtures to oxidative decomplexation. This further establishes that all the aryl nitrile formed during the substitution reactions becomes decomplexed under the reaction conditions

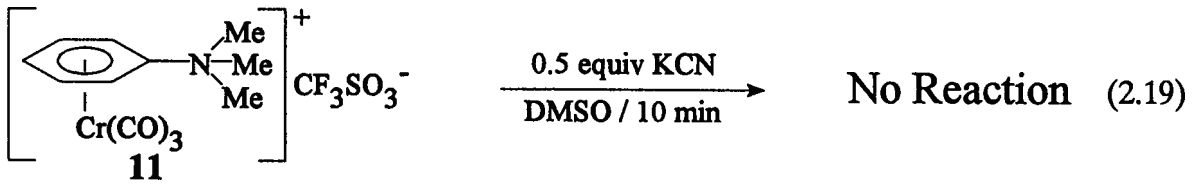
Table 2.9: Summary of Chemical Yields

Starting Complex	Nitrile Product	Temperature (°C)	Yield
4	**15**	120	~32%
5	**16**	135	~26%
6	**17**	115	~24%

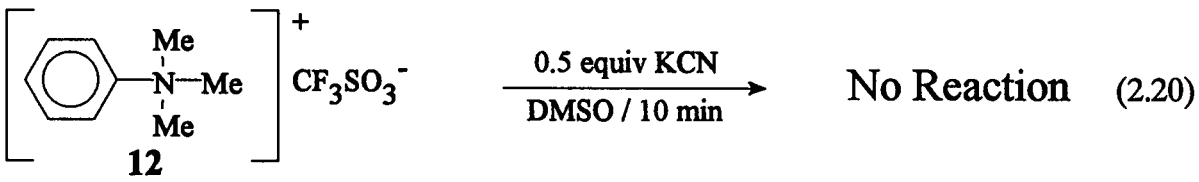
used.

Other leaving groups apart from halogen have been successfully used in classical aromatic nucleophilic substitution.[41] Hence, it was of additional interest to our study to examine other leaving groups that could possess greater mobility toward nucleophilic substitution for (η^6-arene)tricarbonylchromium systems. An obvious choice would be to examine nitro as a leaving group. Unfortunately, the attempts made to prepare (η^6-nitrobenzene)tricarbonylchromium were unsuccessful. Chromium tricarbonyl complexes with arene rings bearing a nitro substituent have been unknown until recently.*[42] However, prompted by radiolabelling studies using aromatics with dimethylsulfonium[24] and trimethylammonium[25,26] leaving groups for nucleophilic substitution reactions, we found that we were able to synthesize (η^6-*N,N,N*-trimethylanilinium)tricarbonylchromium trifluoromethanesulfonate **11**. Preliminary experiments were conducted in which complex **11** was allowed to react with cyanide as shown in equation 2.19. The same general procedure was used, as previously described for the earlier reactions (see page

*The successful synthesis of (η^6-2,4,6-trinitrotoluene)tricarbonylchromium, using $(CH_3CN)_3Cr(CO)_3$ as the precursor for complexing the arene, has been recently reported. This represents the first chromium tricarbonyl complex of a nitroaromatic.



38). The reactions were done at 100 and 120°C. Disappointingly, HPLC analysis showed the absence of the desired product **14**. The HPLC chromatograms of the reaction mixtures exhibited two new prominent peaks, a large peak and a much smaller peak with a longer retention time; these peaks could not be identified. Complex **11** was then heated in DMSO for 10 minutes at 100°C. After cooling, the HPLC chromatogram of this solution showed the presence of a single new peak. The retention time of this peak was very close to that of the large peak observed from the reactions above. These results seem to suggest that **11** is undergoing some kind of transformation or decomposition from the heating in solution. For comparison, a trial reaction was done with uncomplexed *N,N,N*-trimethylanilinium trifluoromethanesulfonate **12** and cyanide at 100°C (equation 2.20). No reaction was observed, as evidenced by HPLC analysis.



Unfortunately, the preliminary reactions conducted with **11** failed to produce any **14**. These results suggested some chemical breakdown of complex **11** while being heated. Additional time to study this problem, and the potential reactivity of **11**, was simply unavailable.

2.4 Labelling Studies with ^{11}C-Labelled Cyanide

In this section, the substitution reactions of complexes **1**, **4**, **5**, and **6** with radioactive [^{11}C]cyanide will be described. Due to the short half-life of ^{11}C (20.4 min), this radionuclide must be produced at or very close to the site where the radiolabelling chemistry is to be performed. Fortunately, ^{11}C is produced regularly at the TRIUMF facility for the ongoing PET program at U.B.C. The small TRIUMF/Nordion CP-42 cyclotron is used to generate positron emitting nuclides for PET, as well as other radioisotopes for commercial sale. Carbon-11 was produced as $^{11}CO_2$ by proton irradiation of N_2 gas via the nuclear reaction $^{14}N(p,\alpha)^{11}C$ at 15 MeV. The [^{11}C]cyanide was produced by sequential catalytic conversion of $^{11}CO_2$ according to equation 2.21.

$$^{11}CO_2 \xrightarrow[\text{2) Ni catalyst / 450°C}]{\text{1) } H_2} {}^{11}CH_4 \xrightarrow[\text{2) Pt / 1000°C}]{\text{1) } NH_3} H^{11}CN \qquad (2.21)$$

The H^{11}CN was trapped in an aqueous solution of NaOH (0.1 M) to generate Na^{11}CN for labelling use.

Although the maximum specific activity of ^{11}C is 9.22×10^6 Ci/mmol, the ubiquitous presence of ^{12}C in nature invariably dilutes the specific activity of any ^{11}C reagent to some value less than the maximum possible specific activity. The amount of dilution of ^{11}C by ^{12}C can vary widely depending on the production conditions used. Specific activity values for H^{11}CN that can be practically obtained are in the order of 2×10^3 Ci/mmol.[43] Unfortunately, the specific activity of the H^{11}CN produced at TRIUMF has not been determined, but the specific activity value is thought to be no lower than 0.5 Ci/mmol.[44] Therefore, the specific activity of the [^{11}C]cyanide used for this work

can possibly range somewhere between 0.5-2000 Ci/mmol (most likely in the lower values of this range). Since the quantity of actual ^{11}C-labelled product is so small,* standard chemical and spectroscopic methods of characterization, such as ^{1}H and ^{13}C NMR, cannot be used for direct product identification. Therefore, chromatographic methods (e.g., HPLC and GC), using non-radioactive analogues as standards, provides the best means of product identification available. The best suited chromatographic method for this purpose is HPLC.[43] For this work, product identification and analysis was performed with HPLC instrumentation that was equipped with both a UV detector and a radioactivity detector connected in series.

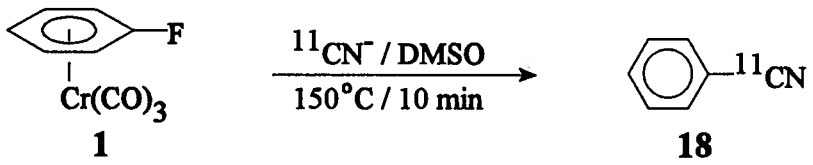
The radiolabelling studies began with investigating the reactivity of complex **1** with [^{11}C]cyanide using different amounts of added KCN (i.e., carrier). The general procedure used for the radiolabelling reactions with [^{11}C]cyanide is as follows. After the H^{11}CN was trapped in aqueous NaOH solution, a portion of this solution was removed and its radioactivity measured. The time at which this measurement was taken was recorded and designated as the *start of synthesis* (SOS). A known amount of KCN was added to the [^{11}C]cyanide solution, then this carrier-added (CA) solution of [^{11}C]cyanide was transferred to a reaction vessel and dried under a fast flow of inert gas. The (η^6-arene)tricarbonylchromium complex, dissolved in 1 mL of DMSO, was added to the dried [^{11}C]cyanide and the mixture was heated for 10 minutes. Upon cooling, 25-50 μL of the reaction mixture was subjected to radio-HPLC purification, and the peak

*As was discussed in Chapter 1, this applies only to ^{11}C and other short-lived radionuclides. For example, compounds labelled with ^{3}H can be analyzed by ^{3}H NMR.

corresponding to the [^{11}C]nitrile was collected and assayed for radioactivity. An equal volume of reaction mixture was also assayed at the same time, thereby determining the percentage of radioactivity in the reaction mixture contributed by the [^{11}C]nitrile product. The radiochemical yield was then calculated.

The radiochemical yields obtained have been decay corrected back to SOS to eliminate the variation of time taken for synthesis and chromatography. Therefore, the radiochemical yields can then be compared with one another, and any differences would reflect the relative efficacy of the reaction conditions used.

Complex **1** was treated with [^{11}C]cyanide as outlined in equation 2.22. The results



1 **18** (2.22)

obtained are summarized in Table 2.10. The first four entries (Table 2.10) represent CA

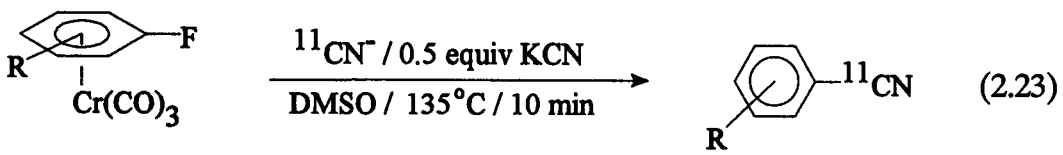
Table 2.10: Summary of Radiochemical Yields Obtained for Equation 2.22

Amount of **1** used (μmol)	Amount of KCN added	Radiochemical Yield
65	0.49 equiv	34%
41	0.37 equiv	36%
43	0.35 equiv	41%
65	0.11 equiv	21%
65	0	<1%[a]

[a]Trace product was observed, but its activity was too low to count in the Capintec well counter.

reactions, while the last entry represents a no carrier-added (NCA) reaction trial. These initial results demonstrated that some cyanide carrier must be present to achieve successful labelling with [^{11}C]cyanide, under the reaction conditions used. For the CA reactions, the addition of 0.35 equivalents of KCN afforded the highest radiochemical yield (41%). A representative radio-HPLC chromatogram of a CA reaction is shown in Figure 2.6. The chromatogram exhibits the presence of the product, [^{11}C-CN]benzonitrile **18** (peak B), and unreacted [^{11}C]cyanide (peak A). The radio-HPLC chromatogram of the NCA reaction trial is shown in Figure 2.7. This chromatogram shows the presence of **18** as only a small peak, indicating a very low radiochemical yield was obtained. The time taken for synthesis and chromatography—the synthesis time—was about 30-60 minutes (measured from SOS) depending on experimental circumstances. Most typically, the synthesis time was 40-45 minutes.

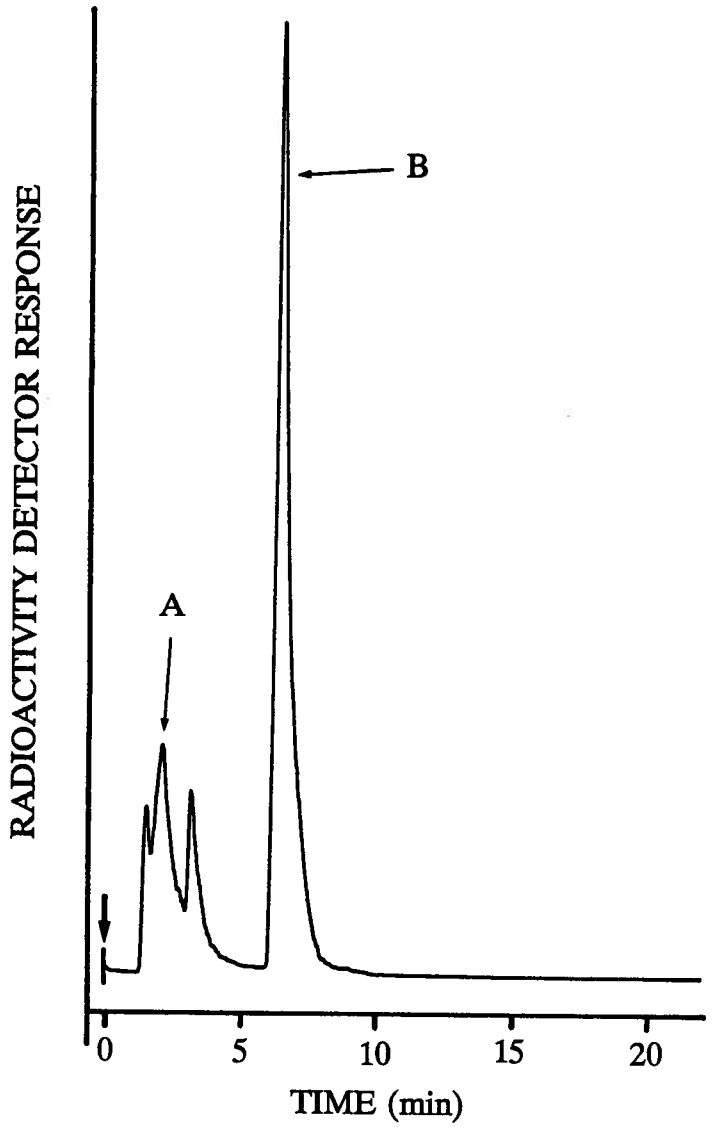
Additional CA [^{11}C]cyanide reactions were then performed with complexes **1**, **4**, **5**, and **6**. Each of these complexes were treated with [^{11}C]cyanide, using 0.5 equivalents of carrier, as shown in equation 2.23. The results obtained are summarized in Table 2.11.



(2.23)

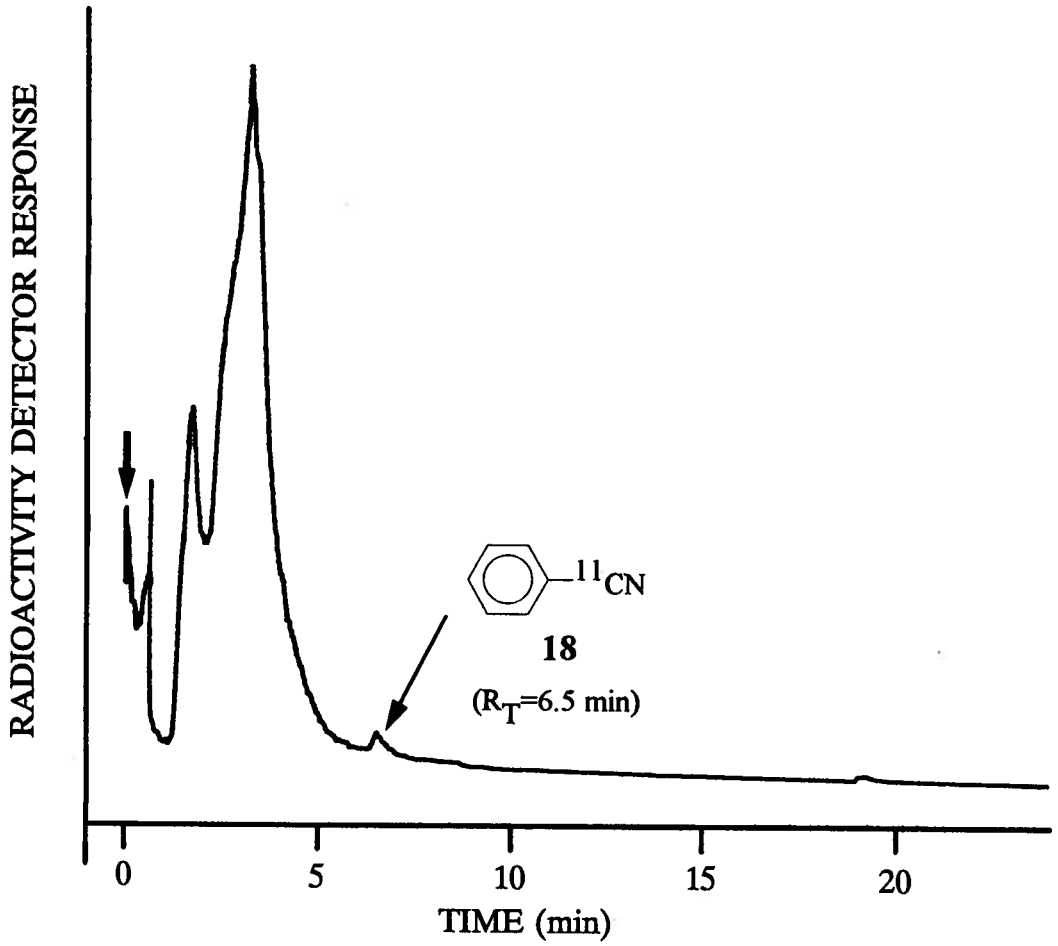
The radiochemical yields parallel fairly closely the chemical yields obtained with non-radioactive cyanide under similar reaction conditions (see Tables 2.3-2.6 for comparison).

Initially, H^{11}CN was trapped in aqueous 0.005 M NaOH solution for the first two reaction trials in order to minimize the amount of hydroxide present in the [^{11}C]cyanide



The compounds are: (A, 2.3 min), [^{11}C]cyanide; (B, 6.5 min), [^{11}C-CN]benzonitrile **18**. The radio-HPLC conditions are: C-18 reverse phase Whatman Partisil 10 ODS-3 column, 25 cm × 9 mm; eluent: isocratic methanol/water, 1:1; flow rate, 5.0 mL/min.

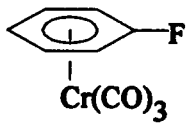
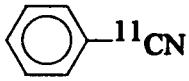
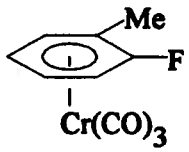
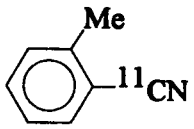
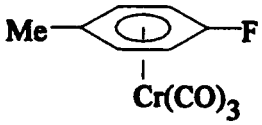
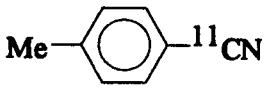
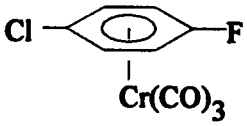
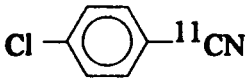
Figure 2.6: Radio-HPLC chromatogram obtained from the analysis of the reaction of complex **1** with [^{11}C]cyanide (with 0.37 equiv of carrier KCN added) at 150°C. The radiochemical yield of **18** was determined to be 36%.



The radio-HPLC conditions are: C-18 reverse phase Whatman Partisil 10 ODS-3 column, 25 cm × 9 mm; eluent: isocratic methanol/water, 1:1; flow rate, 5.0 mL/min.

Figure 2.7: Radio-HPLC chromatogram obtained from the analysis of the reaction of complex **1** with [^{11}C]cyanide (with no carrier KCN added) at 150°C. Only a trace of **18** was produced, for a radiochemical yield of <1%.

Table 2.11: Summary of Radiochemical Yields Obtained for Equation 2.23

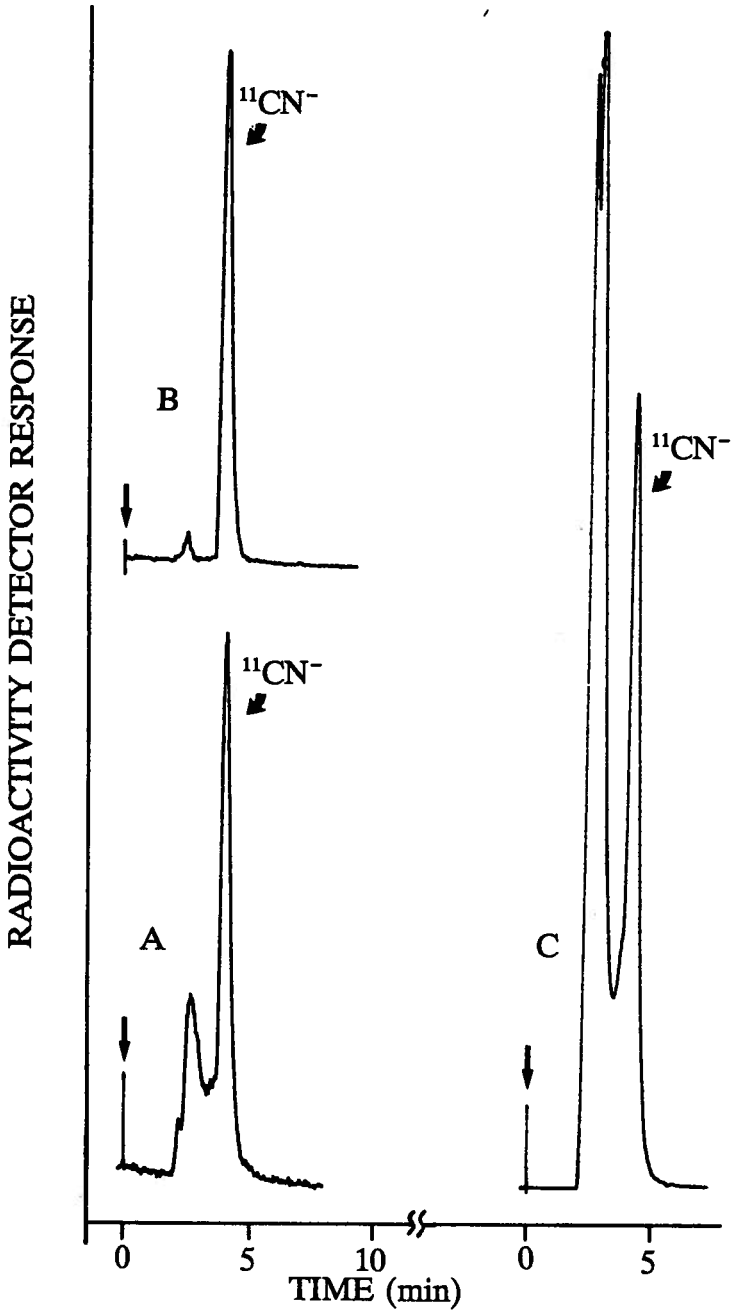
Starting Complex	^{11}C-Labelled Nitrile Product	Radiochemical Yield
 **1**	 **18**	35%
 **4**	 **19**	34%
 **5**	 **20**	31%
 **6**	 **21**	19%

reactions. After these early experiments, it was observed that the radioactivity of the trapped [^{11}C]cyanide was being lost during the drying procedure. In subsequent experiments, 0.1 M NaOH solution was used for trapping H^{11}CN.

However, examination of the radiolabelling results of **1** with NCA [^{11}C]cyanide and CA [^{11}C]cyanide (using 0.11 equiv of KCN) showed that in these cases the [^{11}C]cyanide

underwent nucleophilic substitution in low yield. It was thought that perhaps hydroxide was interfering with the reactivity of [^{11}C]cyanide when $^{11}CN^-$ is present in low concentration (little or no carrier used). Typically, a volume of 0.5 mL of 0.1 M NaOH (containing trapped $^{11}CN^-$) was used—this introduces 50 μmol of OH^- into the radiolabelling reaction. As a result, some experiments were done using different concentrations of NaOH solution to trap H^{11}CN, and 0.025 M NaOH was the least concentrated solution that efficiently trapped and retained the [^{11}C]cyanide upon drying.

Next, the behaviour of [^{11}C]cyanide alone in DMSO solution was examined by radio-HPLC. The chromatograms obtained are shown in Figure 2.8. Chromatogram A was obtained from the analysis of a solution of NCA [^{11}C]cyanide (originally trapped in 0.025 M NaOH, then dried as usual) in DMSO. Note the extra peaks, apart from the main peak (retention time, 4.1 min), that are present. With the addition of 25 μmol of KCN to this [^{11}C]cyanide solution, radio-HPLC analysis was repeated and chromatogram B was obtained. The extra peaks were significantly reduced in size, but not eliminated. A second batch of H^{11}CN was trapped in 0.05 M NaOH solution and dried, followed by the addition of 1 mL of DMSO. This solution of NCA [^{11}C]cyanide was heated at 150°C for 10 minutes. The colourless solution became amber in colour during heating. Radio-HPLC analysis of the NCA [^{11}C]cyanide solution, after cooling, exhibited chromatogram C. The effect of heating resulted in a dramatic change in the appearance of the radio-HPLC chromatogram relative to earlier results. When chromatogram A is compared with chromatogram C, the small extra peaks observed in A have become the dominant peaks observed in C. These results suggested that $^{11}CN^-$ (in low concentration) may be



The radio-HPLC chromatograms represent the following: (i) chromatogram A was obtained from a solution of NCA [^{11}C]cyanide in DMSO, (ii) chromatogram B resulted from the addition of carrier KCN (25 μmol) to the [^{11}C]cyanide solution used for chromatogram A, and (iii) chromatogram C was obtained from a second batch of NCA [^{11}C]cyanide that was heated at 150°C for 10 min in DMSO. The retention time for $^{11}CN^-$ was 4.1 min in each chromatogram.

Figure 2.8: Radio-HPLC chromatograms of [^{11}C]cyanide in DMSO.

changing into a different chemical form, in the presence of hydroxide, that cannot undergo nucleophilic substitution.

Two radiolabelling trials were done with **6**, in which hydroxide concentration was reduced. For the first trial, a batch of CA [^{11}C]cyanide was prepared using H^{11}CN that was trapped in 0.025 M NaOH, followed by the addition of 0.11 equivalents of KCN, and was dried as usual. Complex **6** was treated with the CA [^{11}C]cyanide at 150°C as described in the general procedure. [^{11}C-CN]-4-Chlorobenzonitrile **21** was obtained in a radiochemical yield of 21%. For the second trial, the H^{11}CN was trapped in a different manner to eliminate the presence of hydroxide from the [^{11}C]cyanide reagent. A second production run of H^{11}CN was trapped in a glass loop that was emersed in a CCl_4/CO_2 (-23°C) cooling bath. Any ammonia gas, from the conversion of $^{11}CH_4$ (equation 2.21), was swept through the glass loop with helium transfer gas. Then the glass loop was removed from the cooling bath and the H^{11}CN was slowly added to a reaction vessel containing a mixture of **6**, carrier KCN (ca. 0.4-0.8 equiv*), and 1 mL of DMSO. This mixture was heated for 10 minutes at 125-130°C. Radio-HPLC analysis of the cooled reaction mixture showed that **21** was obtained in 29% radiochemical yield. These two results suggested that some improvement of radiolabelling efficiency with [^{11}C]cyanide is possible by limiting the hydroxide quantity in the reaction mixture.

The identification of the [^{11}C]nitrile products, [^{11}C-CN]benzonitrile **18**, [^{11}C-CN]-2-tolunitrile **19**, [^{11}C-CN]-4-tolunitrile **20**, and [^{11}C-CN]-4-chlorobenzonitrile **21**, was

*Two small crystals of KCN were used, which were not weighed, thus the quantity indicated was estimated.

accomplished using radio-HPLC studies. The chromatographic behaviour of the [^{11}C]nitriles was consistent with that observed for the related non-radioactive aromatic nitriles (**14, 15, 16, 17**). For the reaction of complex **1** with CA [^{11}C]cyanide, additional product identification was performed with GC. The reaction mixture of a reaction trial was analyzed by GC (injection temperature, 250°C; oven temperature, 90°C; N_2 carrier gas flow, 2.0 mL/min) and found **18** to be present at a retention time (R_T) of 8.1 minutes. This was confirmed by the addition of standard (non-radioactive) benzonitrile **14** to an aliquot of reaction mixture and the assigned product peak (R_T=8.1 min) would correspondingly increase in size. Moreover, another portion of reaction mixture was subjected to radio-HPLC purification and the peak containing **18** was collected. The radio-HPLC fraction was analyzed by GC and the peak due to **18** exhibited the same retention time as standard **14**.

The radiolabelling results obtained in this study are still preliminary, but they demonstrated that aromatic nucleophilic substitution reactions with CA [^{11}C]cyanide can be successfully performed with (η^6-arene)tricarbonylchromium compounds. However, the use of high specific activity NCA [^{11}C]cyanide gave a disappointing result. The reasons for this are not clear, but this is not an uncommon problem when labelling with radionuclides; the general reasons for this phenomenon were discussed in Chapter 1. In this instance, it was thought that the presence of hydroxide, which was absent in the model labelling studies with non-radioactive cyanide, could be the problem. The hydroxide could affect the radiolabelling results in three different ways. The first possibility is that the hydroxide could be chemically changing the [^{11}C]cyanide into a

different form, thereby reducing the already low quantity of $^{11}CN^-$ available for reaction. Evidence for this possibility was suggested by the radio-HPLC studies of [^{11}C]cyanide alone in DMSO. It was observed that $^{11}CN^-$ underwent change to unidentified radio-products upon heating. This observation warrants additional study to determine what is actually happening to the $^{11}CN^-$. The second possibility is that the hydroxide is a competing nucleophile with $^{11}CN^-$. Since about 50 μmol of hydroxide is present, and the actual quantity of $^{11}CN^-$ is about one to three orders of magnitude less, the hydroxide is necessarily in significant excess. Therefore, reaction with hydroxide may become the dominant process, even if hydroxide is less reactive toward chromium tricarbonyl complexes than cyanide. The final possibility is that hydroxide could be hydrolysing the [^{11}C]nitrile product to the corresponding [^{11}C]amide and [^{11}C]carboxylic acid. Some water would need to be present in the reaction mixture for hydrolysis to occur. However, given the very small amount of [^{11}C]nitrile product formed, very little water would be necessary. It is quite possible that the drying of the trapped [^{11}C]cyanide solution is not totally complete, thereby leaving sufficient moisture to allow hydrolysis to proceed. Standards of the anticipated hydrolysis products, benzamide and benzoic acid, were subjected to HPLC analysis (using the same HPLC conditions as for the reaction mixtures) and exhibited retention times of 3.2 and 2.2 minutes, respectively. These retention times are consistent with those of the unidentified radio-peaks observed in the chromatograms presented in Figures 2.6 and 2.7.

2.5 Summary and Conclusions

The objective of this study was to explore the potential of (η^6-arene)tricarbonylchromium compounds as intermediates for the radiolabelling of arene structures. The results of this investigation have clearly demonstrated that chromium tricarbonyl complexes can be used to prepare aryl [^{11}C]nitriles in fair radiochemical yield. As a result, this study represents an important first step in the development of chromium tricarbonyl complexes for radiolabelling.

A range of simple (η^6-arene)tricarbonylchromium complexes were prepared in 12-89% yield from the reaction of free arene with $Cr(CO)_6$ in a refluxing mixture of di-*n*-butyl ether and THF. Arenes bearing electron-withdrawing groups gave much lower yields of chromium tricarbonyl product in comparison to arenes with electron-donating groups.

The reactivity of (η^6-halobenzene)tricarbonylchromium complexes **1**, **2**, and **3** with cyanide anion was investigated and only **1** was found to undergo aromatic nucleophilic substitution successfully. Hence, both chlorine and bromine were determined to be ineffective leaving groups for reactions with cyanide. Therefore, the reactivity of fluorine-substituted, chromium tricarbonyl complexes **1**, **4**, **5**, and **6** were studied in detail.

Complex **1** was allowed to react with cyanide (0.5 equiv) in DMSO over a temperature range of 105-150°C and gave benzonitrile **14** in 12-41% yield. The best yield (41%) was obtained at 135°C. Control experiments with uncomplexed fluorobenzene confirmed that no fluorine displacement by cyanide occurred with free fluorobenzene under the reaction conditions used for **1**.

Complex **4** was treated with cyanide (0.5 equiv) in DMSO over a temperature range of 95-135°C, which afforded **15** in yields of 26-43%; the best yields (41-43%) were produced at 105-115°C. Complex **5** was allowed to react with cyanide (0.5 equiv) in DMSO over a temperature range of 105-150°C and obtained yields of 11-29% of **16**. The best yields (26-29%) were exhibited at 115°C, while the next best results (22-26%) were observed at 135°C. The reaction of **6** with cyanide (0.5 equiv) in DMSO was studied at temperatures of 115 and 135°C only. The best yields of **17** (26-34%) were obtained at 115°C. The reaction time was kept to 10 minutes for these studies. When the reaction time was reduced to five minutes, the chemical yield was significantly reduced also.

The cyanide substitution reaction of **4** was also studied in the presence of 18-crown-6. These reactions were conducted over a temperature range of 95-135°C, and improvements in chemical yield, over earlier studies, were observed throughout the temperature range examined. The best yield of **15** (46%) was obtained at 105°C using three equivalents of 18-crown-6. Clearly, the use of crown ethers shows promise toward maximizing the yields obtained from the substitution reactions of cyanide with chromium tricarbonyl complexes.

Substitution reactions with **1**, **4**, **5**, and **6** were performed using [^{11}C]cyanide, and the corresponding aryl [^{11}C]nitriles **18**, **19**, **20**, and **21** were obtained. Some CA reactions were done (at 150°C) with **1** which indicated that 0.35 equivalents of carrier (KCN) was required to afford the best radiochemical yield (41%). Unfortunately, the NCA reaction trial with **1** gave only a trace of **18**. These initial results suggest that some carrier must

be present to achieve successful radiolabelling with [^{11}C]cyanide, however, continued development of this work could well enable NCA radiolabelling to be accomplished in the future. The aryl [^{11}C]nitriles **19**, **20**, and **21** were produced in 34%, 31%, and 19% radiochemical yields, respectively, using 0.5 equivalents of carrier at 135°C. The synthesis times, as measured from SOS, were typically 40-45 minutes in length, and are acceptable for radiolabelling with ^{11}C.

References

1. Fischer, E. O.; Ofele, K. *Angew. Chem.* **1957**, *69*, 715; *Chem. Ber.* **1957**, *90*, 2532-2535.

2. Zeiss, H.; Wheatley, P. J.; Winkler, H. J. S. *Benzenoid-Metal Complexes: Structural Determinations and Chemistry*; Ronald: New York, 1966.

3. Silverthorn, W. E. *Adv. Organomet. Chem.* **1975**, *13*, 47-137.

4. Collman, J. P.; Hegedus, L. S. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1980; Chapter 14.

5. Semmelhack, M. F. *J. Organomet. Chem. Libr.* **1976**, *1*, 361-395.

6. Jaouen, G. *Ann. N. Y. Acad. Sci.* **1977**, *295*, 59-78.

7. See reference 4; p 653.

8. Pearson, A. J. *Metallo-organic Chemistry*; Wiley Interscience: New York, 1985; pp 348-362.

9. McQuillin, F. J.; Parker, D. G.; Stephenson, G. R. *Transition Metal Organometallics for Organic Synthesis*; Cambridge University: Cambridge, 1991; pp 182-208.

10. Nicholls, B.; Whiting, M. C. *J. Chem. Soc.* **1959**, 551-556.

11. Rosca, S. I.; Rosca, S. *Rev. Chim.* **1974**, *25*, 461-465.

12. Alemagna, A.; Buttero, P. D.; Gorini, C.; Landini, D.; Licandro, E.; Maiorana, S. *J. Am. Chem. Soc.* **1983**, *48*, 605-607.

13. Mahaffy, C. A. L.; Pauson, P. L. *J. Chem. Res., Synop.* **1979**, 128.

14. Harrington, P. J. *Transition Metals in Total Synthesis*; Wiley Interscience: New York, 1990; pp 317-319.

15. Cary, F. A.; Sundberg, R. J. *Advanced Organic Chemistry—Part B: Reactions and Synthesis*; Plenum: New York, 1977; Chapter 7.

16. Kilbourn, M. R. *Fluorine-18 Labeling of Radiopharmaceuticals*; Nuclear Science Series, Monograph NAS-NS-3203; National Academy: Washington, DC, 1990.

17. *Radiopharmaceuticals for Positron Emission Tomography: Methodological Aspects*; Stöcklin, G., Pike, V. W., Eds.; Kluwer Academic: Boston, 1993.

18. *Radionuclides Production*; Helus, F., Ed.; CRC: Boca Raton, 1983; Vol. 2.

19. Davis, R.; Kane-Maguire, L. A. P. In *Comprehensive Organometallic Chemistry: The Synthesis, Reactions and Structures of Organometallic Compounds*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Toronto, 1982; Vol. 3, pp 1001-1021.

20. Mahaffy, C. A. L.; Pauson, P. L. *Inorg. Synth.* **1979**, *19*, 154-158.

21. Hudeček, M.; Toma, Š. *J. Organomet. Chem.* **1990**, *393*, 115-118.

22. See reference 19; p 1001.

23. Mahaffy, C. A. L.; Pauson, P. L. *J. Chem. Res., Miniprint* **1979**, 1776-1794.

24. Maeda, M.; Fukumura, T.; Kojima, M. *Chem. Pharm. Bull.* **1985**, *33*, 1301-1304; *J. Labelled Compd. Radiopharm.* **1986**, *23*, 1104-1105.

25. Angelini, G.; Speranza, M.; Wolf, A. P.; Shiue, C-Y. *J. Fluorine Chem.* **1985**, *27*, 177-191.

26. Haka, M. S.; Kilbourn, M. R.; Watkins, G. L.; Toorongian, S. A. *J. Labelled Compd. Radiopharm.* **1989**, *27*, 823-833.

27. Bunnet, J. F.; Hermann, H. *J. Org. Chem.* **1971**, *36*, 4081-4088.

28. Ofele, K. *Chem. Ber.* **1966**, *99*, 1732-1736.

29. Mahaffy, C. A. L. *J. Organomet. Chem.* **1984**, *262*, 33-37.

30. Gilbert, J. R.; Leach, W. P.; Miller, J. R. *J. Organomet. Chem.* **1973**, *49*, 219-225.

31. Müller, J.; Göser, P. *Recent Dev. Mass Spectrosc., Proc. Int. Conf. Mass Spectrosc.* **1969** (Pub **1970**), 1175-1180.

32. Carganico, G.; Buttero, P. D.; Maiorana, S.; Riccardi, G. *J. Chem. Soc., Chem. Commun.* **1978**, 989-990.

33. See reference 4; pp 653-661.

34. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 3rd ed.; Wiley Interscience: New York, 1985; Chapter 13.

35. See reference 34; pp 584-586.

36. See reference 34; pp 77-79, 321-322 and references contained therein.

37. Knipe, A. C. *J. Chem. Ed.* **1976**, *53*, 618-622.

38. Zubrick, J. W.; Dunbar, B. I.; Durst, H. D. *Tetrahedron Lett.* **1975**, 71-74.

39. Cook, F. L.; Bowers, C. W.; Liotta, C. L. *J. Org. Chem.* **1974**, *39*, 3416-3418.

40. Gokel, G. W.; Durst, H. D. *Synthesis* **1976**, 168-184.

41. Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier: New York, 1968; Chapter 5.

42. Azam, K. A.; Kabir, S. E.; Kazi, A. B.; Molla, A. H.; Ullah, S. S. *Chem. Abstr.* **1988**, *109*, 23086r.

43. Meyer, G.-J. *Radiochim. Acta* **1982**, *30*, 175-184.

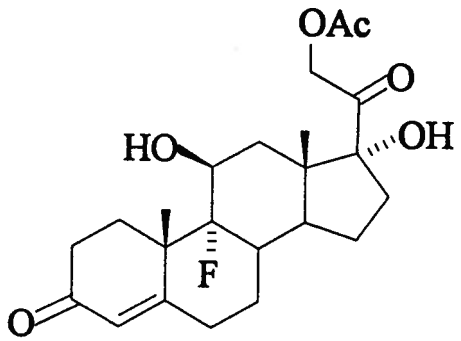
44. Ruth, T. J., TRIUMF, Vancouver, BC, personal communication.

Chapter 3

DEVELOPMENT OF METHODS FOR RAPID FLUORINE LABELLING

3.1 Introduction

In the early 1950s, the pioneering work of Fried and Sabo led to the first significant successful application of selective fluorination to modify the biological activity of an organic molecule.[1] The fluorosteroid, 9α-fluorohydrocortisone acetate **22**, that was



22

prepared by the Squibb Company researchers, showed approximately an 11-fold increase in glucocorticoid activity over that of cortisone acetate. This report stimulated much new research into developing ways of selectively introducing fluorine at specific sites in compounds of potential biological interest, in order to modify their biological activity.

Since the landmark work of Fried and Sabo, the study of selectively fluorinated

molecules has resulted in a variety of useful applications in biochemistry and medicine.[2,3] These applications include the use of fluorine-containing organic pharmaceuticals as anticancer and antiviral agents, antiinflammatory drugs, antibiotics, antifungal and antiparasitic agents, general anesthetics, and therapeutic drugs for mental illness. In addition, pharmaceuticals labelled with radioactive fluorine (^{18}F) play an important role in PET imaging. Perfluorinated hydrocarbons are no longer the major focus of study in fluorine chemistry. Currently, interest in selectively fluorinated compounds is continuing to increase, along with the recognition of the importance of selective fluorination methodology.[4,5]

The attractiveness and utility of fluorine as a substituent in biologically active molecules are due to the unique properties of fluorine that can induce profound and unexpected effects on biological activity. Firstly, fluorine is the most electronegative of all elements, with an electronegativity (Pauling scale) of 3.98 as compared to 3.44 for oxygen, 3.16 for chlorine, or 2.96 for bromine. It is this property which produces pronounced electronic effects in a molecule after the introduction of a fluorine substituent. Secondly, fluorine, with its small van der Waals radius (1.35 Å), closely resembles hydrogen (van der Waals radius 1.20 Å) in size. As a result, the fluorinated analogue will usually closely resemble the non-fluorinated molecule in size when a fluorine is substituted for hydrogen. This allows, for instance, fluorinated analogues to still meet steric requirements at enzyme receptor sites. Thirdly, fluorine forms a stronger bond with carbon than does hydrogen—the carbon-fluorine bond energy is 456-486 kJ/mol, while carbon-hydrogen bond energy varies from 356 to 435 kJ/mol.

Therefore, carbon-fluorine bonds exhibit increased thermal and oxidative stability over that of carbon-hydrogen bonds. Lastly, fluorine, when replacing hydrogen in a molecule, usually enhances lipophilicity which increases the rate of absorption and transport of the fluorine-containing compound in vivo. In many cases, this characteristic may be the most important in improving pharmacological activity.[6,7]

An additional feature of fluorine is the availability of the artificially prepared radionuclide, ^{18}F, which decays by positron emission. Fluorine-18 (half-life, 109.7 min) is one of the four key radionuclides used in PET. The other commonly used positron emitting nuclides (^{11}C, ^{13}N, ^{15}O) possess very short half-lives (~2-20 min) in comparison to ^{18}F. The longer half-life of ^{18}F allows for more complex or multistep radio-pharmaceutical syntheses to be conducted, and the resulting compounds can be transported over moderate distances for use at different locations. In addition, the study of relatively slow biological processes can be performed with ^{18}F-labelled agents, which would not be feasible with agents using nuclides with shorter half-lives. Furthermore, ^{18}F-labelled compounds have the potential to produce PET images of superior resolution due to the relatively low energy positron (maximum 0.635 MeV) emitted by ^{18}F (see Table 1.2 for comparison)—this factor will be of increasing importance as PET instrumentation improves.[8,9]

The utilization of ^{18}F-labelled pharmaceuticals with PET imaging has enabled a number of human biochemical and physiological processes to be investigated in vivo, as was presented in Chapter 1. More recently, however, the application of PET is being extended beyond the study and diagnosis of disease to the area of drug discovery,

development, and approval of new pharmaceuticals. Drug candidates can be labelled with positron emitting nuclides, such as ^{11}C and ^{18}F, to provide information regarding drug absorption, distribution, metabolism, and elimination in vivo (human or animal subjects) using PET imaging. These studies can complement information obtained using ^{3}H- and ^{14}C-labelled analogues in animals. Alternatively, established PET imaging protocols can be used to monitor the biological behaviour of drug candidates in vivo to determine the therapeutic potential or efficacy of such compounds. For disease states where no animal models exist, PET becomes a unique tool that still enables drug assessment to be carried out. Also, given the interest in fluorine-containing biologically active molecules, it would be possible—in principle, at least—to study the in vivo biochemistry of the ^{18}F-labelled analogues via PET.[10]

Underlying the continued development and application of fluorinated compounds is the ongoing need for new and improved methods to selectively introduce fluorine into polyfunctional molecules at specific sites. However, the mild and selective introduction of fluorine into organic molecules has been and continues to be of considerable challenge to organic chemistry. Although elemental fluorine was first prepared by Moissan in 1886,[11] the organic chemistry of fluorine developed slowly in comparison to the other halogens. It was quickly discovered that the reaction of fluorine with organic compounds was highly exothermic, and often resulted in explosions. These observations understandably discouraged further research with fluorine for decades after Moissan's time. In the 1930s, Bockemüller demonstrated that fluorine, when diluted with inert gas (usually nitrogen), could be used for selective fluorination of organic substrates under

controlled conditions.[12] Since that time, new fluorinating agents and reactions have been developed making possible the synthesis of the many organofluorine compounds available today.[13,14]

Currently, the range of methods for introducing fluorine into organic compounds is based on the use of either elemental fluorine, hydrogen fluoride, inorganic fluorides, or various organofluorine reagents. These fluorinating agents can be broadly characterized as sources of either nucleophilic or electrophilic fluorine. With these fluorinating agents, many methods have been developed to effect the transformation of different organic functional groups to organofluorine derivatives, and are catalogued in multiple books[15,16] and reviews.[4,13,17,18] However, many of these methods, though successful in conventional synthetic chemistry, are not compatible with the requirements of radiolabelling with ^{18}F.[8,9]

A primary limitation of radiofluorination methodology is the limited range of useful synthetic precursors that can be produced in ^{18}F-labelled form. The only reagent available for nucleophilic fluorination is [^{18}F]fluoride anion.[19] However, [^{18}F]fluoride has seen increasing application because of continuing investigations performed studying the different variables involved in optimizing the reaction conditions for its use with structurally diverse substrate molecules. Investigators have studied the influence of reaction solvent, source of $^{18}F^-$, fluoride counterion, catalyst (e.g., crown ethers), ^{19}F carrier levels, reaction vessel material, substrate concentration, leaving group, and temperature on the radiochemical yields obtained with [^{18}F]fluoride.[9,19] Reaction conditions have been developed such that a number of aliphatic and aromatic

compounds have now been successfully radiolabelled with $^{18}F^-$.[9,20] As a result, [^{18}F]fluoride has gained increased importance for radiofluorination work.

In contrast to nucleophilic fluorination, a number of electrophilic fluorinating agents have been produced in ^{18}F-labelled form, using [^{18}F]F_2 as the source of ^{18}F in each case. A list of the various fluorinating agents prepared with ^{18}F is presented below. However,

Fluorinating Agents Labelled with ^{18}F[9,20]

fluorine (F_2)	chlorine monofluoride (ClF)
perchloryl fluoride (ClO_3F)	trifluoromethyl hypofluorite (CF_3OF)
xenon difluoride (XeF_2)	trifluoroacetyl hypofluorite (CF_3COOF)
nitrosyl fluoride (NOF)	acetyl hypofluorite (CH_3COOF)
N-fluoro-2-pyridone	*N*-fluoropyridinium triflates

N-fluoro-*N*-alkylsulfonamides (RSO_2NFR')

N-fluoro-bis(trifluoromethylsulfonyl)imide ($(CF_3SO_2)_2NF$)

most of these reagents have not actually been evaluated as to their scope and utility for radiolabelling with ^{18}F.[9] In practical experience, the vast majority of electrophilic fluorinations are performed with [^{18}F]F_2 and $CH_3COO^{18}F$.[21,22] Acetyl hypofluorite is a relatively new reagent that was originally developed by Rozen and co-workers in 1981,[23] and then was prepared in ^{18}F-labelled form in 1982.[24] Acetyl hypofluorite has been found to be a milder and more selective electrophilic fluorinating agent, in comparison to elemental fluorine, for a variety of substrate molecules.[25,26] Moreover, the development of a simple on-line gas-solid phase synthesis of acetyl hypofluorite[27] has significantly increased its utility for radiofluorinations. The other ^{18}F-labelled fluorinating agents listed previously are not trivial to produce on a routine basis, and as

a result, have not engendered serious interest by PET research groups as yet.[21] Clearly, much additional research needs to be done in order to develop the full potential of electrophilic fluorination methodology for radiolabelling.

The requirement to develop methods to prepare ^{18}F-labelled aromatic compounds for the PET program at U.B.C. prompted Adam and co-workers[28,29] to examine the reactivity of main group organometallic derivatives with electrophilic fluorinating agents. It was essential that the fluorination reaction be rapid, the fluorinating agent be readily available in ^{18}F-labelled form for routine use, and be efficient in the incorporation of radiofluorine. Also, it was desired that the reaction conditions be mild and the experimental manipulations be as simple as possible to perform to accommodate future automation. It was known that the electrophilic halogenation of organometallic derivatives such as those of tin[30] and mercury[31] was well established. However, very little study had been done regarding the reactivity of carbon-metal bonds with electrophilic fluorinating agents. As a result, the reactivity of aryl-tin, (then later) aryl-silicon, -germanium, -lead, -mercury, and -thallium bonds, with elemental fluorine was investigated.[28,29] Fluorobenzene was successfully produced from phenyltri-*n*-butyltin (48-70% yield), tetraphenyltin (15-56% yield), tetraphenyllead (48% yield), and diphenyl-mercury (26-36% yield). The other organometallic derivatives studied gave only poor yields (2.4-12%), or no detectable product in the case of the organothallium derivative. These studies represent the first reports of the cleavage of aryl-metal bonds by electrophilic fluorination.

Since the reports of Adam et al.,[28,29] the fluorination of organometallic compounds has

been under study by other researchers as well. As a result, various simple aromatic compounds have been radiolabelled with ^{18}F utilizing organotin,[29,32,33] organosilicon,[33,34,35] organogermanium,[33] and organomercury[36,37] derivatives. In addition, aryllithium[38,39] and Grignard[39,40] reagents have also been successfully radiofluorinated. More significantly, the strategy of electrophilic fluorination of organometallic derivatives have been applied to the preparation of ^{18}F-labelled pharmaceuticals for PET. Aryl-tin precursors were used to prepare both 3-*O*-methyl-6-[^{18}F]fluorodopa[41] and 6-[^{18}F]fluorodopa[42] by reaction with $CH_3COO^{18}F$ (20% radiochemical yield) and $[^{18}F]F_2$ (25% radiochemical yield), respectively. 6-[^{18}F]Fluorodopa has also been prepared from an aryl-silicon derivative using $[^{18}F]F_2$ (5-10% radiochemical yield)[43] and an aryl-mercury derivative using $CH_3COO^{18}F$ (~40% radiochemical yield).[44] 6-[^{18}F]Fluorometaraminol[45] and 4-[^{18}F]fluoro-*m*-tyrosine[46] were successfully prepared from organomercury substrates by reaction with $CH_3COO^{18}F$ in approximately 30% and 25-30% radiochemical yields, respectively. 6-[^{18}F]fluoroveraldehyde was readily prepared in 30% radiochemical yield from an organotin precursor using $[^{18}F]F_2$, but interestingly could not be obtained from the corresponding organomercury derivative.[47] This case reaffirms the need for various synthetic options to be available to successfully synthesize a desired ^{18}F-labelled compound.

The application of electrophilic fluorination via organometallic intermediates has been almost exclusively focussed on introducing fluorine onto aromatic rings. This is understandable because of the many organic compounds of biological interest that contain aromatic rings in their structures. Nonetheless, other potential applications also

exist. Some alkyl fluorides have been prepared via organometallic derivatives, such as cyclohexyl fluoride[48] and *n*-tetradecyl fluoride[49] from the corresponding Grignard reagents, in low yield. Benzyl [^{18}F]fluoride was prepared from potassium benzylpentafluorosilicate in 6% radiochemical yield.[35] Generally, however, primary and secondary alkyl fluorides have been readily obtained using nucleophilic substitution with fluoride anion. Alternatively, a number of biologically interesting molecules exist which contain a vinyl function in their structures.[50,51,52] The vinyl functionality provides a potential site for labelling with fluorine. Moreover, some important biomolecules specifically contain the fluorovinyl grouping,[7,53,54] and may be of interest for ^{18}F-labelling. These potential applications prompted interest in extending the strategy of electrophilic fluorination of organometallic derivatives as a general methodology to prepare fluorovinyl compounds, and is suitable for radiofluorinations with ^{18}F.

Upon review of the fluorination studies of aryl-metal systems, it seemed that the organotin reagents gave the highest chemical and radiochemical yields, although organomercury and -silicon derivatives gave good results also. The electrophilic fluorination reactions of aryl-tin reagents are rapid. Previous work[55] with vinyl-tin compounds have demonstrated that they are sufficiently stable to be prepared in bulk, and then stored for use as needed. Vinyl-tin compounds can be readily prepared by reduction of the corresponding acetylenic compounds with tin hydride reducing agents.[56,57] In addition, other methods of preparation of vinyl-tin derivatives are also available.[58] These factors suggested to us that vinyl-tin substrates offered the best potential as reagents for fluorination studies.

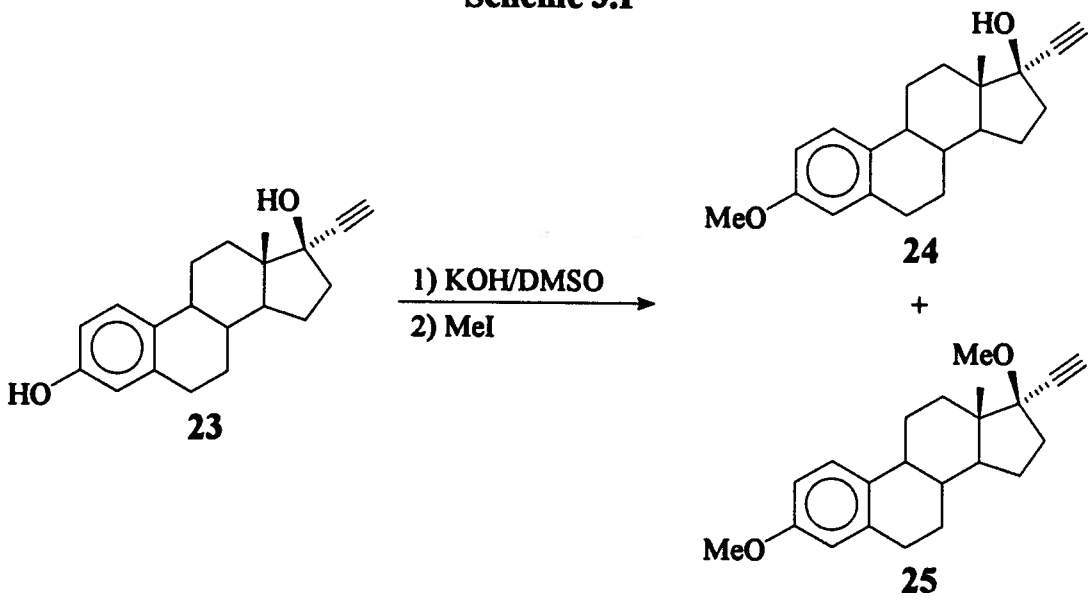
In this chapter, the preparation of the vinyl-tin derivatives employed for this work will be described. This will be followed by fluorination studies of the vinyl-tin substrates with elemental fluorine and acetyl hypofluorite. Lastly, the successful radiofluorination of a vinyl-tin derivative of a steroid will be presented.

3.2 Synthesis of Vinyl-Tin Precursors

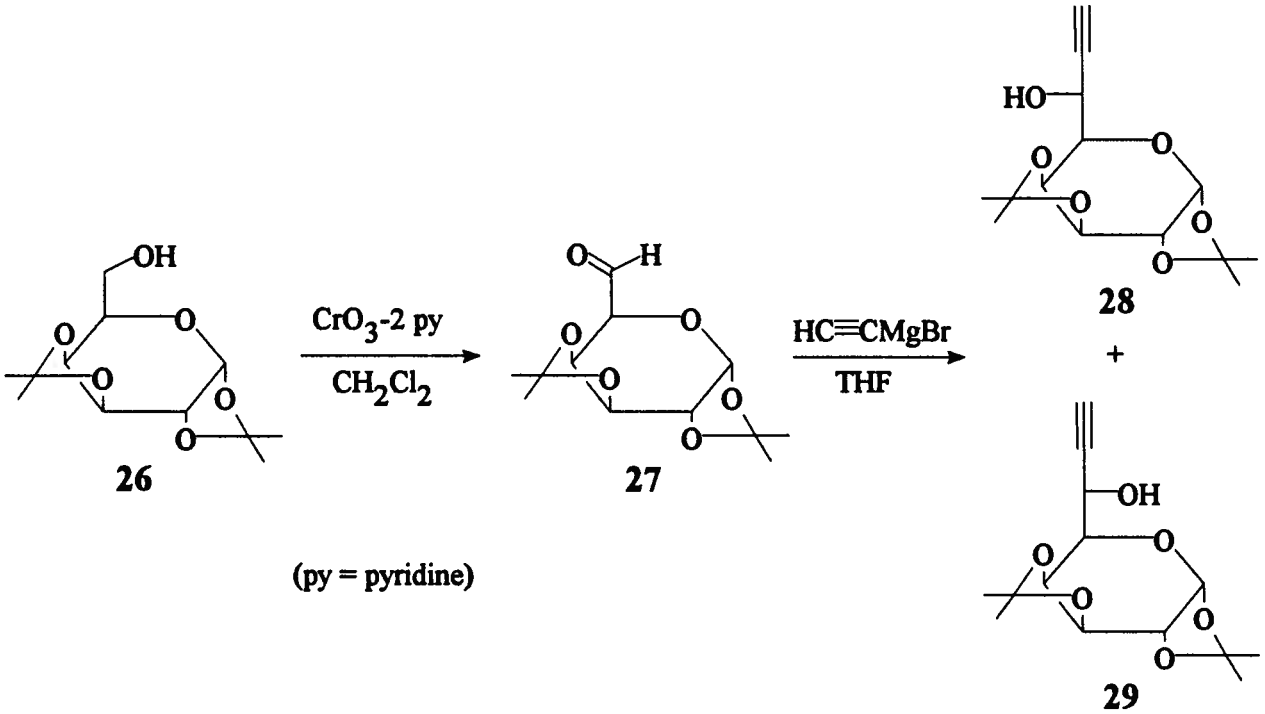
The vinyl-tin derivatives were prepared by hydrostannylation of the corresponding acetylenic precursors, and most of the results obtained have been described previously in the author's M.Sc. Thesis.[55] The acetylenic starting materials were either obtained commercially or prepared using literature methods, as summarized in Schemes 3.I and 3.II.

The acetylenic compounds, 17α-ethynyl-1,3,5(10)-estratriene-3,17β-diol **23**, 3-methoxy-17α-ethynyl-1,3,5(10)-estratriene-17β-ol **24**, 3,17β-dimethoxy-17α-ethynyl-1,3,5(10)-estratriene **25**, 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-oct-7-ynopyranose **28**, and 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-ynopyranose **29**, were hydrostannylated (see Schemes 3.III and 3.IV) by an adaptation of literature procedures.[57] The acetylenic precursors were treated with approximately two equivalents of tri-*n*-butyltin hydride and a catalytic amount of AIBN (2,2´-azobis(2-methylpropionitrile)), followed by heating the mixture at 95°C overnight. The (*E*)-vinylstannylated products were isolated by chromatographic workup of the reaction mixtures, and the chemical yields are summarized in Table 3.1. Each of the (*E*)-vinylstannanes was characterized by their physical properties (optical rotation values,

Scheme 3.I

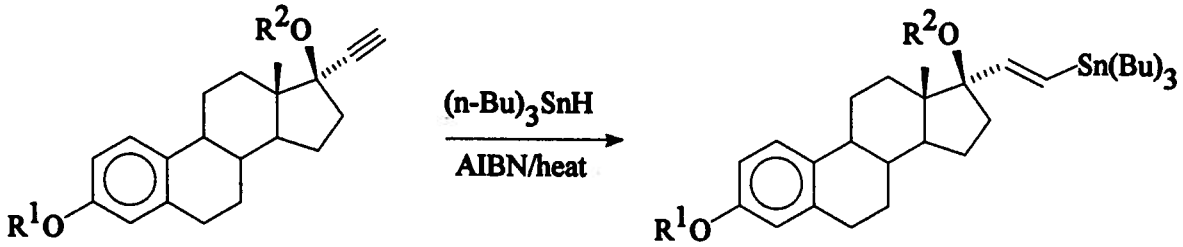


Scheme 3.II



(py = pyridine)

Scheme 3.III



23 $R^1 = R^2 = H$

24 $R^1 = Me, R^2 = H$

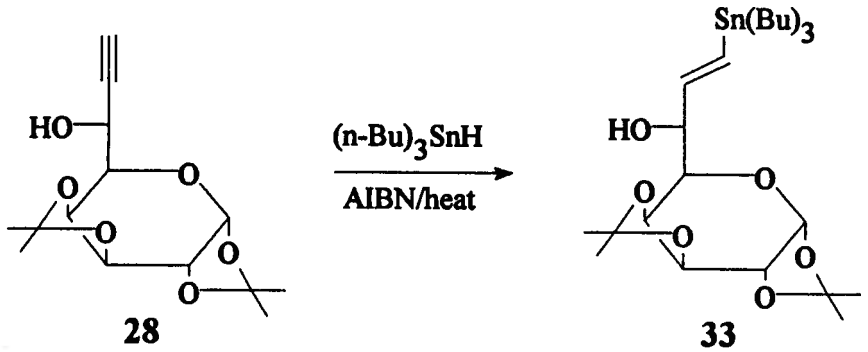
25 $R^1 = R^2 = Me$

30 $R^1 = R^2 = H$

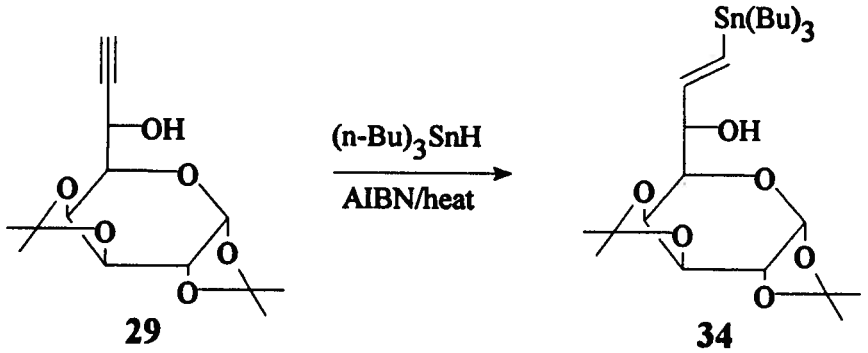
31 $R^1 = Me, R^2 = H$

32 $R^1 = R^2 = Me$

Scheme 3.IV



28 **33**



29 **34**

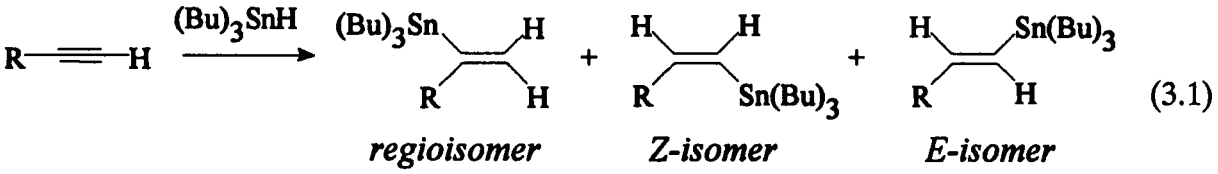
melting points of crystalline products), elemental analysis, and spectral data (^{1}H NMR, mass spectrometry).

The AIBN catalyzed hydrostannylation reaction was found to be quite successful for all the acetylenic precursors used. However, higher yields of (*E*)-vinylstannylated

Table 3.1: Yields of (*E*)-Vinylstannanes

Starting Material	Product	Chemical Yield
23	**30**	59%
24	**31**	90%
25	**32**	94%
28	**33**	61%
29	**34**	59%

product were obtained from the steroidal acetylenic compounds, **24** and **25**, in comparison with the carbohydrate acetylenic substrates (**28, 29**). It is known that the hydrostannylation reaction can produce three different isomers when using terminal acetylenes,[59] as shown in equation 3.1. As a consequence, the chemical yield of (*E*)-vinylstannane will

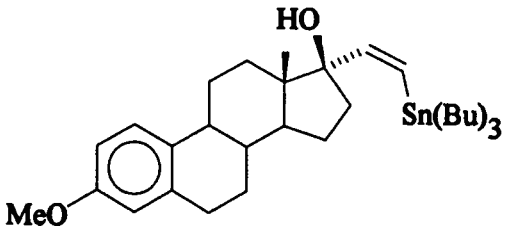


(3.1)

vary depending on the proportion of (*Z*)-vinylstannane and "regioisomer" which are produced. It was observed that the hydrostannylation reactions of **28** and **29** produced greater proportions of alternative isomeric products, thus giving consistently lower yields of (*E*)-vinylstannanes. The lower hydrostannylation yield of 17α-(*E*)-tributylstannylvinyl-

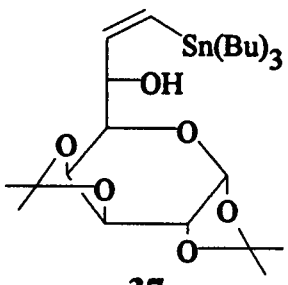
1,3,5(10)-estratriene-3,17β-diol **30** from **23** was due to significant protonolysis of vinyl-tin product formed during the reaction;* this was most probably due to the presence of the unprotected phenolic hydroxyl group.

During a more recent preparation of 3-methoxy-17α-(*E*)-tributylstannylvinyl-1,3,5(10)-estratriene-17β-ol **31**, the isomeric product, 3-methoxy-17α-(*Z*)-tributylstannylvinyl-1,3,5(10)-estratriene-17β-ol **36**, was also isolated (~10% yield). Compound **36** has not

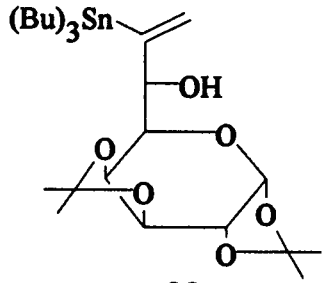


36

been fully characterized as yet. However, in the preparation of (*E*)-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-*C*-tributylstannyl-L-*glycero*-α-D-*galacto*-oct-7-enopyranose **34**, both alternative isomeric products, (*Z*)-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-*C*-tributyl-



37



38

stannyl-L-*glycero*-α-D-*galacto*-oct-7-enopyranose **37** and 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-*C*-tributylstannyl-L-*glycero*-α-D-*galacto*-oct-7-enopyranose **38**, were isolated as

*A significant amount of 17α-vinyl-1,3,5(10)-estratriene-3,17β-diol **35** was recovered from the hydrostannylation of **30**; see Experimental for details.

a 3:2 mixture. The chemical yields of **37** and **38** were estimated to be 15% and 10%, respectively. Compounds **37** and **38** were identified by their ^{1}H NMR spectral data.

3.3 Labelling Studies with Non-Radioactive Fluorine

Prior to this study, there were some reports of vinylmetallated compounds having been used for the synthesis of fluorovinyl compounds. There was an early report in which the direct fluorination of a vinyl-tin compound (1,2,3,4,7,7-hexafluoro-5,6-bis(trimethylstannyl)bicyclo[2.2.1]hepta-2,5-diene) with F_2 was studied, but the desired product was afforded in <5% yield.[60] Since then, Di Raddo and Diksic[61] prepared 4-[^{18}F]fluoroantipyrine using [^{18}F]F_2 in 18% radiochemical yield from 4-(trimethylsilyl)antipyrine. Lee and Schwartz[62] prepared various simple vinyl fluorides in 71-88% yield using vinyllithium reagents and *N-tert*-butyl-*N*-fluorobenzenesulfonamide as the source for electrophilic fluorine. Interestingly, Flanagan et al.[51] attempted to fluorinate 6-chloromercuricholest-5-en-3β-ol with elemental fluorine, acetyl hypofluorite, and xenon difluoride under various conditions, but without success.

Our study examined the reactivity of the (*E*)-vinylstannanes, **30**, **31**, 3,17β-dimethoxy-17α-(*E*)-tributylstannylvinyl-1,3,5(10)-estratriene **32**, (*E*)-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-*C*-tributylstannyl-D-*glycero*-α-D-*galacto*-oct-7-enopyranose **33**, and **34**, with elemental fluorine and acetyl hypofluorite.

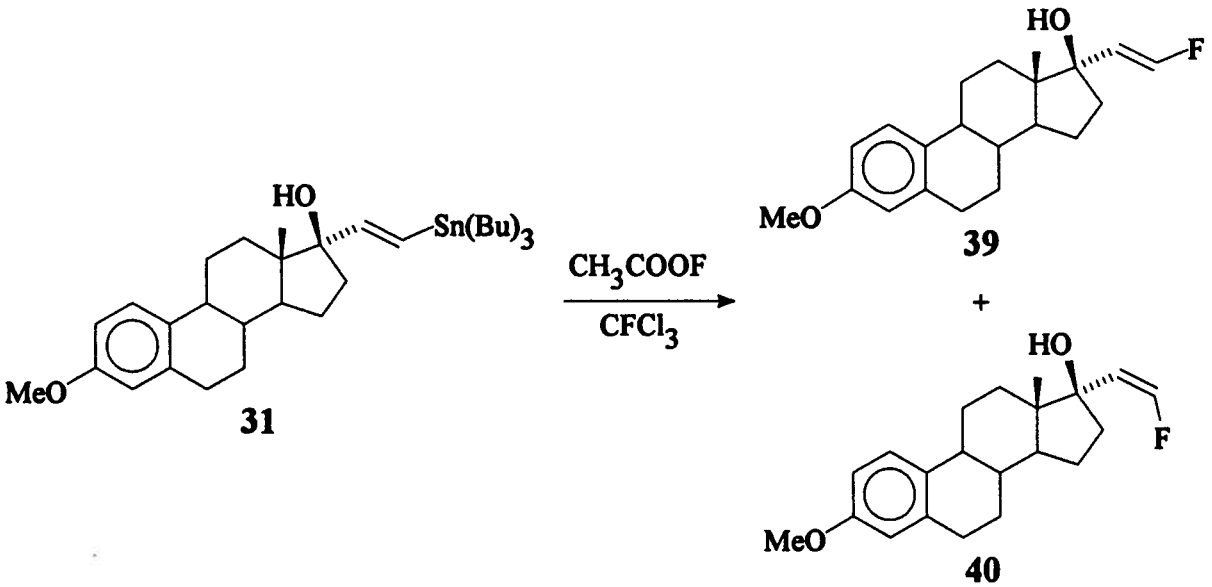
The fluorination of **31** was initially studied in small scale experiments using excess F_2 or gaseous CH_3COOF, and the resulting crude reaction mixtures were analyzed by TLC and ^{19}F NMR. It was evident from TLC analysis that both fluorinating agents produced

multiple products, but the ^{19}F NMR spectra indicated that the reaction of **31** with CH_3COOF produced significantly more fluorovinyl product than with F_2. It was also observed that neither fluorinating agent consumed all of the starting material.

As a result, **31** was fluorinated with CH_3COOF (Scheme 3.V) on a larger scale in the following manner. Compound **31** was treated with approximately 1.3 equivalents of gaseous CH_3COOF in $CFCl_3$ at room temperature. This procedure was conducted with six portions of **31** in order to employ a sufficient amount of starting material for fluorination. The crude reaction mixtures were combined and subjected to column chromatography. The fractions containing 3-methoxy-17α-(*E*)-fluorovinyl-1,3,5(10)-estratriene-17β-ol **39** and 3-methoxy-17α-(*Z*)-fluorovinyl-1,3,5(10)-estratriene-17β-ol **40** were subjected to additional purification by HPLC, whereby **39** and **40** were isolated in 29.5% and 3.8% yield, respectively.

Compounds **39** and **40** were readily characterized by ^1H and ^{19}F NMR.

Scheme 3.V



Having successfully isolated the fluorovinyl products **39** and **40**, the opportunity emerged to quantitatively study the fluorination reactions of **31** under different conditions. A number of small scale reactions with **31** were conducted using the following general procedure. A solution of **31** (in a chosen solvent) was treated with a small excess (ca. 1.2-1.4 equiv) of fluorinating agent (F_2 or CH_3COOF). The solvent was evaporated and the reaction mixture was dissolved in a known volume of chloroform. This solution was analyzed by HPLC to determine the combined yield of both fluorovinyl products **39** and **40**. (A solution of **39** was used as an external standard.)

Firstly, **31** was allowed to react with gaseous CH_3COOF (Scheme 3.V) at both -78°C and room temperature. The results are summarized in Table 3.2. The best yields of fluorinated product were obtained at room temperature, although fewer side-products were observed (by HPLC) when the reaction was performed at -78°C. Secondly, **31** was

Table 3.2: Summary of Yields Obtained for the Reaction of **31** with Acetyl Hypofluorite

Solvent	Temperature[a]	Yield[b]	no. of runs	Average Yield[b]
$CFCl_3$	-78°C	26-31%	2	29%
$CFCl_3$	r.t.	41-42%	2	41%
CH_3OH	r.t.	14%	1	14%
CH_3CN	r.t.	24%	1	24%
THF	r.t.	9.3%	1	9.3%

[a]r.t. = room temperature.
[b]Refers to the combined yield of **39** and **40**.

treated with CH_3COOF in alternative solvents, namely dried methanol, acetonitrile, and

tetrahydrofuran, at room temperature. The yields are summarized in Table 3.2. None of these solvents provided improved yields of fluorinated product. Clearly, $CFCl_3$ proved to be the best solvent tested for the fluorination reaction of **31**. Finally, the reaction of **31** with elemental fluorine (Scheme 3.VI) was studied at both -78°C and room temperature. The results are summarized in Table 3.3. It was evident by both analytical

Scheme 3.VI

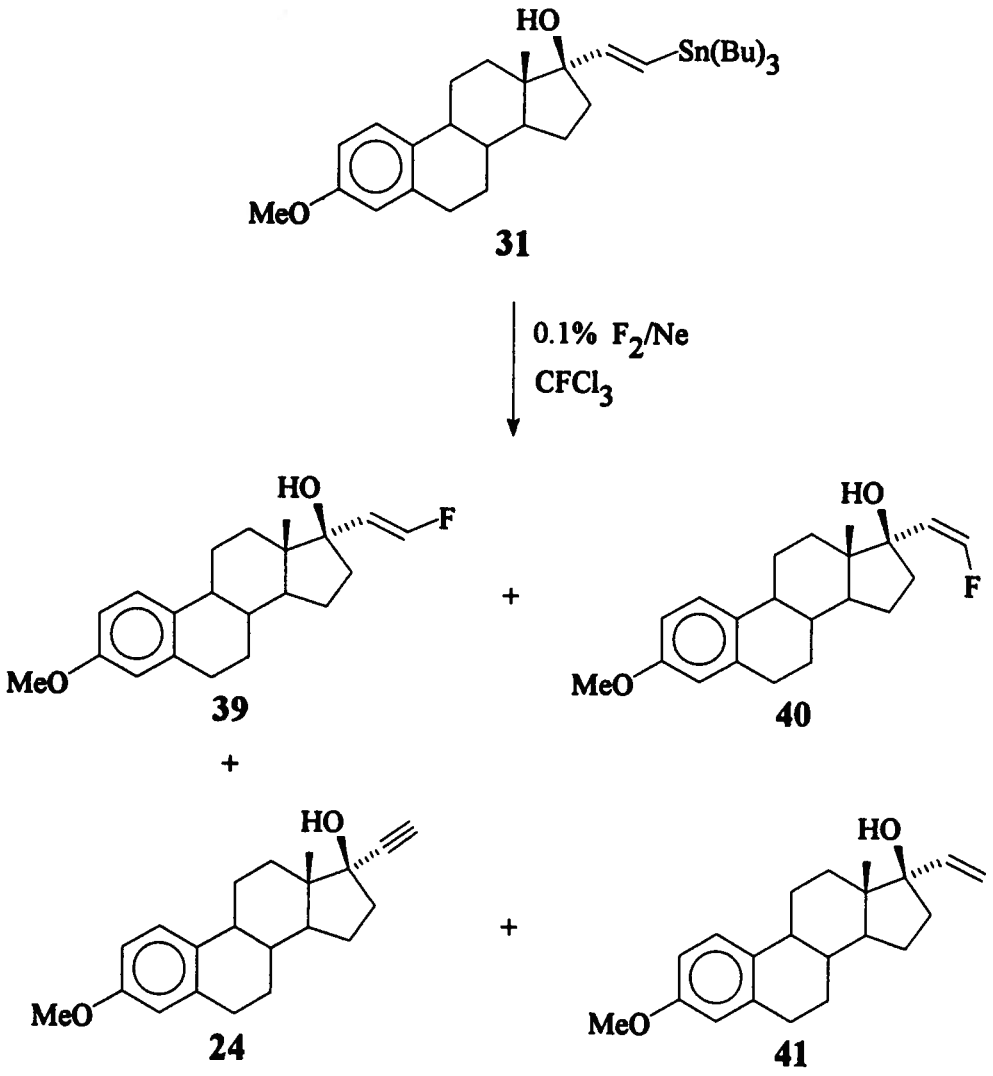
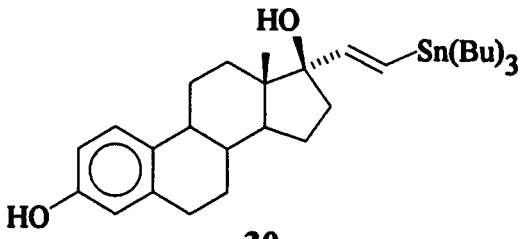


Table 3.3: Summary of Yields Obtained for the Reaction of **31** with Fluorine

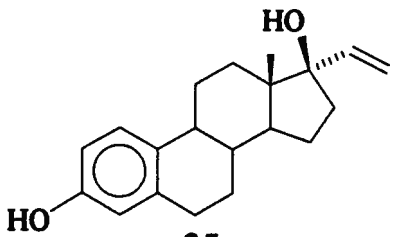
Temperature[a]	Yield of **39** and **40**	Yield of **24**	Yield of **41**
-78°C	4.2%	2.2%	14.5%
r.t.	9.0%	5.4%	7.2%
[a]r.t. = room temperature.			

TLC and HPLC that **31** is less reactive toward F_2 than CH_3COOF as less starting material is consumed by F_2. However, reaction with F_2 does result in the formation of two identified non-fluorinated side-products, **24** and 3-methoxy-17α-vinyl-1,3,5(10)-estratriene-17β-ol **41**. The identity of these compounds was established via HPLC; by comparison of their respective retention times with those of authentic standards. The identity of **41** was further confirmed by ^1H NMR spectroscopy of a preliminary reaction trial done with F_2 at -78°C. The reaction of **31** with F_2 clearly gave the lowest yields of fluorovinyl product (**39** and **40**) in comparison to the reactions performed with CH_3COOF.

The reactivity of **30** with fluorine and acetyl hypofluorite was investigated. Compound **30** was treated with approximately 0.8 equivalents of dilute (0.1%) F_2 in Ne gas mixture in $CFCl_3$ at -78°C. The TLC chromatogram of the reaction mixture exhibited the formation of a new, more polar component, along with other minor components. This dominant new component, as observed by TLC, was isolated by column chromatography for identification by NMR. The 270 MHz ^1H NMR spectrum revealed that the isolated material was 17α-vinyl-1,3,5(10)-estratriene-3,17β-diol **35**. No trace of fluorovinyl product was observed in the NMR spectrum. Alternatively, **30** was treated with



30

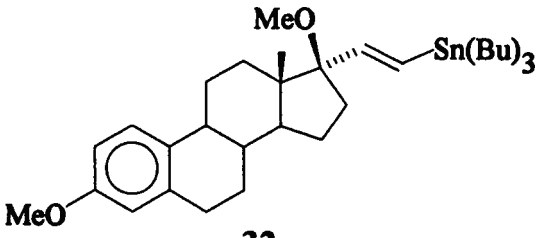


35

approximately 1.2 equivalents of gaseous CH_3COOF in $CFCl_3$ at -78°C. TLC analysis of the crude reaction mixture indicated the total consumption of starting material and the formation of an extremely complex mixture. The ^{19}F NMR spectrum of the reaction mixture exhibited several weak signals of fluorinated products which could not be assigned. The corresponding ^1H NMR spectrum could not provide any useful information due to its extremely complex pattern.

Unfortunately, no fluorovinyl product could be obtained from **30** using either F_2 or CH_3COOF as fluorinating agents. Since the 3-*O*-methylated (*E*)-vinylstannane **31** was successfully fluorinated as described earlier, the difficulty in fluorinating **30** is most likely due to the presence of the unprotected phenolic hydroxyl group. Therefore, this functionality must be protected with an easily removed protecting group, such as *tert*-butyldimethylsilyl, in order to develop a synthetic route to 17α-(*E*)-fluorovinyl-1,3,5(10)-estratriene-3,17β-diol.

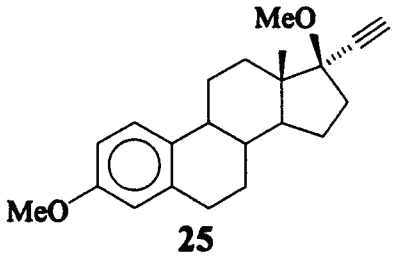
The reactivity of **32** was also studied with fluorine and acetyl hypofluorite. The use of elemental fluorine was investigated first. Four small scale reaction trials were performed in which **32** was allowed to react with approximately 0.9 equivalents of dilute fluorine at -78°C (2 trials), 0°C (1 trial), and room temperature (1 trial), in $CFCl_3$. The



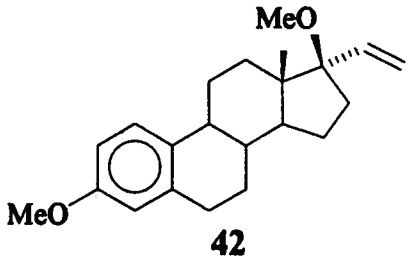
32

TLC analysis of each reaction trial exhibited similar results; the TLC chromatograms showed the consumption of some starting material and the formation of a dominant, slower migrating component amongst several other minor components. In order to isolate the dominant new component observed by TLC, the reaction mixtures were combined and subjected to column chromatography on silica gel. Half of the original amount of **32** used for all four trials was recovered in one portion; then the dominant new component was isolated with continued elution. The 270 MHz ^{1}H NMR spectrum of this isolated material revealed that a mixture of several compounds were present. The compounds were identified as **25**, 3,17β-dimethoxy-17α-vinyl-1,3,5(10)-estratriene **42**, and 3,17β-dimethoxy-17α-(*E*)-fluorovinyl-1,3,5(10)-estratriene **43** in an approximate ratio of 71:18:11, plus another component that could not be identified was present.

The use of acetyl hypofluorite, prepared in two different forms, was investigated next. Compound **32** was added to a slight excess of CH_3COOF prepared in a solution of glacial acetic acid and ammonium acetate by the method of Rozen et al.[23] at room temperature. The reaction proceeded for about 15 minutes before the acetic acid was removed. The crude reaction mixture was analyzed by TLC, which revealed the consumption of some starting material and the formation of a new, more polar component



25



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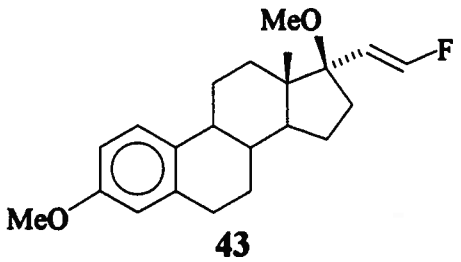


43

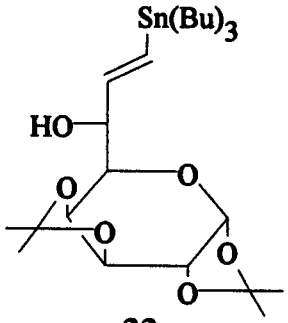
plus some other minor components. The reaction mixture was further analyzed by ^{1}H and ^{19}F NMR spectroscopy. The ^{19}F NMR spectrum exhibited a few weak signals due to unidentified products, whereas the ^{1}H NMR spectrum indicated the presence of **25**, **32**, and **42**, but not fluorovinyl product **43**.

Compound **32** was then treated with excess gaseous CH_3COOF in $CFCl_3$ at -78°C. The TLC chromatogram of the reaction mixture exhibited only a small degree of conversion of starting material to a new, slower migrating component, along with other minor components. The 270 MHz ^{1}H NMR spectrum of the reaction mixture revealed largely unreacted starting material and a very small amount of **25** present. However, the ^{19}F NMR spectrum showed the presence of **43**.

These studies of the reactivity of **32** indicate that this derivative is relatively unreactive toward CH_3COOF in comparison to **31**. No fluorovinyl product **43** could be obtained

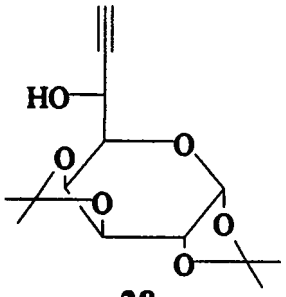
with the use of CH_3COOF in acetic acid, whereas only a minute amount of **43** could be produced with gaseous CH_3COOF. The reaction of **32** with elemental fluorine produced some **43** which could be identified in a mixture of products. These results suggested that fluorine was the most effective fluorinating agent used with **32**. However, a larger scale fluorination of **32** utilizing F_2 was not pursued due to the low potential yield and anticipated separation problems.

Next, the reactivity of **33** toward fluorine and acetyl hypofluorite was examined in several small scale experiments. In the first experiment, **33** was allowed to react with approximately 0.9 equivalents of dilute fluorine in $CFCl_3$ at -78°C. The TLC chromato-



33

gram of the reaction mixture revealed the formation of a new, more polar component in addition to a few minor components. The dominant new component, as observed by TLC, was isolated by column chromatography and subjected to ^1H NMR spectroscopy. This material consisted of four different compounds that were identified as **28**, 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-oct-7-enopyranose **44**, (*E*)-8-*C*-fluoro-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-oct-7-enopyranose **45**, and (*Z*)-8-*C*-fluoro-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-oct-7-enopyranose **46**, in which **44** was the dominant component.



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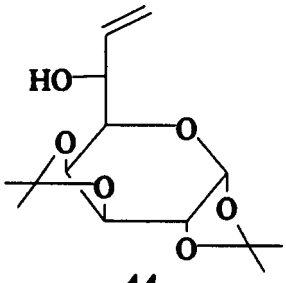

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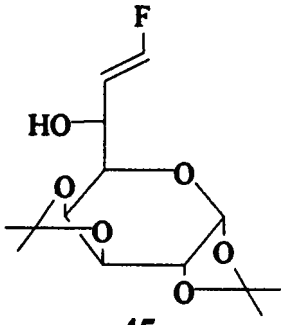

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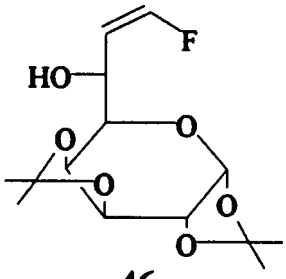


46

For the second experiment, **33** was added to approximately 0.8 equivalents of CH_3COOF prepared in a solution of glacial acetic acid and ammonium acetate at room temperature. The reaction was allowed to proceed for about 10 minutes, then the acetic acid was removed. The crude reaction mixture was analyzed by TLC, which showed the formation of a dominant, slower migrating component plus a few minor components. Column chromatography of the reaction mixture resulted in the isolation of the dominant new component observed by TLC. This material was examined by ^1H NMR spectroscopy, which revealed that a mixture of **44**, **45**, and **46** was present and **44** was the major component.

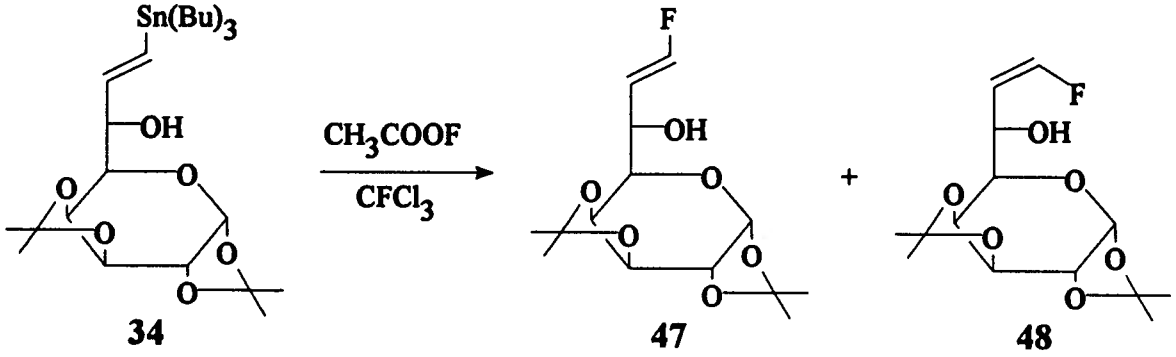
In the third experiment, **33** was treated with approximately 1.2 equivalents of gaseous CH_3COOF in $CFCl_3$ at -78°C. Analytical TLC of the reaction mixture revealed the

formation of a dominant, more polar component and a few minor components. The dominant new component, as observed by TLC, was isolated via preparative TLC (silica gel), and analyzed by ^{1}H and ^{19}F NMR spectroscopy. This material was found to be largely a mixture of **45** and **46**, with some unidentified impurities present.

The fluorination studies of **33**, though qualitative in nature, showed that gaseous CH_3COOF was the most effective fluorinating agent used. This agent gave the highest degree of conversion of **33** to fluorovinyl product (**45** and **46**). The use of F_2 or CH_3COOF in acetic acid solution produced **44** as the main product. Unfortunately, the supply of **33**—as starting material—was virtually all consumed so that further larger scale fluorination work could not be conducted. Therefore, fluorination studies were continued using the L-*glycero*-α-D-*galacto* epimer **34** instead.

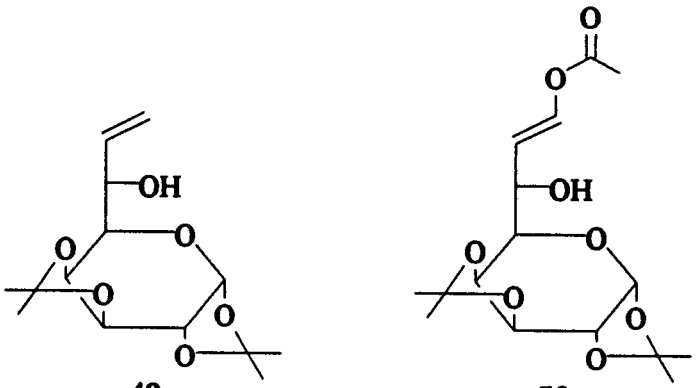
Compound **34** was fluorinated with CH_3COOF (Scheme 3.VII) in the following

Scheme 3.VII



manner. Compound **34** was treated with approximately 1.3 equivalents of gaseous CH_3COOF in $CFCl_3$ at room temperature. This procedure was performed with two portions of **34** to increase the reaction scale. The crude reaction mixtures were

combined and subjected to column chromatography. (*E*)-8-*C*-Fluoro-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-enopyranose **47** was isolated in the first chromatography fraction, and then two fractions were collected that contained mixtures of **47**, (*Z*)-8-*C*-fluoro-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-enopyranose **48**, and 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-enopyranose **49**. The ratio of components in each chromatography fraction was



49 **50**

measured by ^{1}H NMR spectroscopy. The isolated yields of **47** and **48** were determined to be 36% and 10%, respectively. Furthermore, an additional fraction was subsequently collected which was found to contain a single compound, identified as (*E*)-8-*C*-acetoxy-7-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-enopyranose **50** by ^{1}H NMR.

Compound **47** was readily characterized by ^{1}H and ^{19}F NMR.

3.4 Radiofluorination Work

In this section, the radiofluorination of (*E*)-vinylstannane **31** using acetyl [^{18}F]hypofluorite will be presented. The production of ^{18}F, like ^{11}C, is also routinely performed at the TRIUMF facility. Fluorine-18 can be produced either using the TRIUMF 500 MeV

cyclotron, or more efficiently with the smaller TRIUMF/Nordion CP-42 cyclotron via the $^{20}Ne(p,2pn)^{18}F$ nuclear reaction. For this work, circumstances required that the TRIUMF 500 MeV cyclotron be utilized. Radiofluorine was produced by proton irradiation of a gas mixture of natural Ne* with approximately 0.1% F_2 present using the $^{20}Ne(p,Spall)^{18}F$ reaction at 500 MeV. The radiofluorine is obtained in the form of ^{18}F-labelled F_2.

Unfortunately, the production of $[^{18}F]F_2$ is necessarily carrier-added. Since the cyclotron target is constructed from nickel-based alloy, it must be passivated with F_2. This process creates a thin layer of nickel fluoride within the interior surface of the cyclotron target, and provides a source of carrier fluorine to be present. Moreover, a small percentage (0.1-2.0%) of molecular fluorine must be present in the neon target gas for $[^{18}F]F_2$ production. However, if the amount of carrier F_2 is reduced too much in the target gas mixture in order to significantly increase specific activity, low yields and poor recoveries of $[^{18}F]F_2$ are obtained.[9] As a result, the practical upper limit on the specific activity of $[^{18}F]F_2$ that can be achieved is reported to be around 12 Ci/mmol.[63]

Therefore, all electrophilic fluorinations performed with ^{18}F-labelled F_2, and reagents derived from $[^{18}F]F_2$, result in products of low specific activity.[64] Whenever a radiofluorinated product must be produced in high specific activity, the only available labelling reagent is [^{18}F]fluoride anion.[65] Nonetheless, there has been discussion in the literature about producing high specific activity $[^{18}F]F_2$. The key idea is to exploit the stability of the negative fluorine ion in the gas phase and attract the gaseous anionic $^{18}F^-$

*Natural neon consists of 90.92% of ^{20}Ne, 0.26% of ^{21}Ne, and 8.82% of ^{22}Ne.

to an electrode, then perform an electrochemical oxidation to generate $[^{18}F]F_2$.[19] To date, there are no reports of anyone exploiting this approach, but such a development would represent a true breakthrough for high specific activity radiofluorinations.

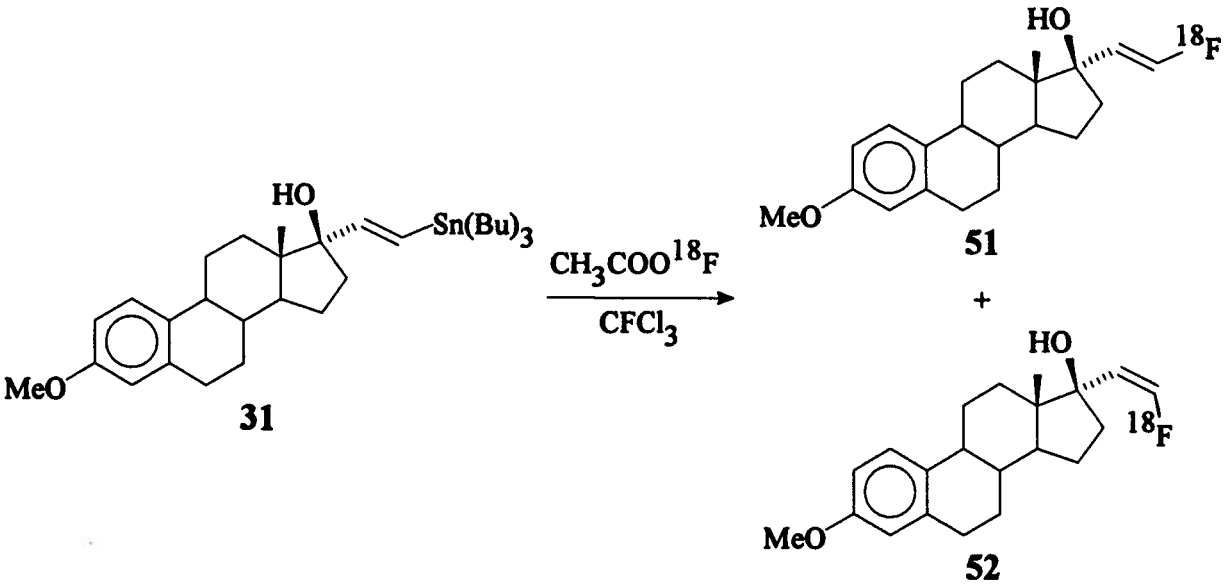
Another aspect regarding the use of ^{18}F-labelled F_2 is that the maximum radiochemical yield possible is 50%. Due to the need of carrier F_2 to be present in the neon cyclotron target, it would be a statistical improbability that both fluorine atoms in the $[^{18}F]F_2$ produced would be fluorine-18 (i.e., $^{18}F—^{18}F$). Therefore, only one fluorine-18 atom is expected to be present in a ^{18}F-labelled F_2 molecule (i.e., $^{18}F—^{19}F$). As a result, if an electrophilic fluorination reaction proceeded in 100% maximum chemical yield, the corresponding radiofluorination procedure would be expected to give 50% radiochemical yield at best, since there is only a 50% probability of the fluorine-18 atom becoming incorporated rather than the fluorine-19 atom. For reactions using fluorination reagents such as $CH_3COO^{18}F$, which contain only one fluorine atom, the maximum radiochemical yield continues to be 50% because all these reagents are prepared from $[^{18}F]F_2$. This is an unfortunate disadvantage of all radiofluorination methods that utilize $[^{18}F]F_2$ as the source of fluorine-18.[9]

The general procedure used for the radiofluorination reactions of **31** is as follows. The 500 MeV cyclotron gas target was filled with the desired amount of 1% F_2/Ne gas mixture, then pure Ne was added to dilute the F_2 gas content to approximately 0.1% F_2 in Ne. The target gas mixture was irradiated with the 500 MeV proton beam. (Typical ^{18}F production parameters were 10 min of target irradiation at 69 μA of beam current.) When irradiation of the cyclotron target was stopped, the time was noted and designated

as the *end of bombardment* (EOB). After target irradiation was completed, the contents of the target were passed through a potassium acetate/acetic acid column to produce gaseous acetyl [^{18}F]hypofluorite and was added to a solution of **31** (110-120 μmol) in $CFCl_3$ (20 mL). The reaction mixture was assayed for radioactivity (before and after evaporation of $CFCl_3$), along with the ammonium acetate/acetic acid column. After dissolution in some chloroform, a small aliquot of reaction mixture was subjected to radio-HPLC purification and the peak corresponding to ^{18}F-labelled fluorovinyl product was collected, then assayed for activity. An equal volume of reaction mixture was also assayed at the same time in order to determine the percentage of product that was present in the reaction mixture. Based on the total activity of ^{18}F produced at EOB, the radiochemical yield was then determined. The resulting radiochemical yields were decay corrected back to EOB.

Compound **31** was radiofluorinated with $CH_3COO^{18}F$, as outlined in Scheme 3.VIII.

Scheme 3.VIII



The results obtained are summarized in Table 3.4. Compound **31** was kept in excess relative to fluorinating agent in order to minimize side-reactions and to maximize the efficiency of incorporation of radiofluorine. Using excess fluorinating agent would help maximize the chemical yield, but could produce lower radiochemical yields. The radiofluorination reaction of **31** gave the highest radiochemical yields (19%) when conducted at room temperature. The radiolabelled product that was isolated for yield determinations was a mixture of 3-methoxy-17-α-(*E*)-[^{18}F]fluorovinyl-1,3,5(10)-estra-

Table 3.4: Summary of Radiochemical Yields Obtained for the Reaction of **31** with Acetyl [^{18}F]Hypofluorite

Amount of $CH_3COO^{18}F$ used	Temperature[a]	Radiochemical Yield[b]
~0.74 equiv	r.t.	19%
~0.50 equiv	r.t.	19%
~0.77 equiv	-78°C	9.7%
~0.50 equiv	-78°C	5.0%

[a]r.t. = room temperature.
[b]Refers to the combined yield of **51** and **52**; the radiochemical yield was determined from the initial activity of $[^{18}F]F_2$ produced at EOB.

triene-17β-ol **51** and 3-methoxy-17α-(*Z*)-[^{18}F]fluorovinyl-1,3,5(10)-estratriene-17β-ol **52**. The specific activity of this product mixture was not determined. However, in a separate experiment, the specific activity of $CH_3COO^{18}F$ generated using ^{18}F production parameters described earlier was determined to be about 190 mCi/mmol. Therefore, the isolated product mixture would be of quite low specific activity, as expected.

The identification of the [^{18}F]fluorovinyl products **51** and **52** was accomplished using

radio-HPLC studies. The chromatographic behaviour of **51** and **52** was consistent with that observed for the related non-radioactive fluorovinyl compounds (**39** and **40**). In addition, the leftover reaction mixtures (after radio-HPLC analysis), obtained from the radiofluorinations done at room temperature (first two entries of Table 3.4), were allowed to decay to zero activity. These mixtures were then analyzed by ^{19}F NMR spectroscopy. The ^{19}F NMR spectra readily confirmed the presence of **39** and **40**, thereby confirming the successful radiofluorination of **31**.

In this study, the fluorination reaction of **31** with gaseous acetyl hypofluorite was successfully extended to accomplish the ^{18}F-labelling of **31**. The radiofluorination reaction is essentially instantaneous upon addition of fluorinating agent. The time taken from EOB to the isolation of crude reaction mixture was in the order of 15-17 minutes. The additional time required thereafter was for the radio-HPLC purification work. Clearly, the synthesis time is quite short and well suited for radiolabelling with ^{18}F.

3.5 Summary and Conclusions

The purpose of this study was to develop a general methodology to directly prepare fluorovinyl compounds from vinyl-tin intermediates, and to utilize this synthetic approach for radiofluorinations with ^{18}F. This objective was indeed fulfilled to a large degree, as most of the vinyl-tin substrates studied were successfully fluorinated using gaseous acetyl hypofluorite. In addition, one of the vinyl-tin derivatives was radiofluorinated with acetyl [^{18}F]hypofluorite in respectable radiochemical yield.

The vinyl-tin substrates were readily obtained from the AIBN catalyzed hydrostannyl-

ation of the corresponding acetylenic precursors, with tri-*n*-butyltin hydride, in 59-94% yield. The reactivities of (*E*)-vinylstannanes **30**, **31**, **32**, **33**, and **34** were studied with elemental fluorine and acetyl hypofluorite under varied conditions.

The most effective fluorinating agent used to fluorinate **31** was gaseous acetyl hypofluorite, at room temperature, which afforded yields of 41-42% of **39** and **40** as an isomeric mixture (yields determined via HPLC analysis). In contrast, fluorination of **31** with elemental fluorine gave 9.0% yield at best. Furthermore, (*E*)-fluorovinyl **39** and (*Z*)-fluorovinyl **40** were prepared and isolated in 29.5% and 3.8% yields, respectively, from the reaction of **31** with CH_3COOF.

Compound **30** could not be directly fluorinated using either F_2 or CH_3COOF. This result is most likely due to the presence of the unprotected phenol function of **30**. By protecting this group, it would be anticipated that **30** can be successfully fluorinated in an analogous manner to **31**. Alternatively, **32** was found to be relatively unreactive toward fluorination as compared to **31**. Reaction of **32** with gaseous CH_3COOF produced only a trace of (*E*)-fluorovinyl product **43**. Better results were observed employing elemental F_2 as some **43** could be obtained as a minor component in a mixture of products.

Compound **33** was readily fluorinated using gaseous CH_3COOF. Treatment of **33** with CH_3COOF (prepared in acetic acid solution) or with F_2 also generated fluorinated product, but gave **44** as the main product. However, the stock of **33** had been virtually all consumed, so that further larger scale reactions with gaseous CH_3COOF could not be performed. Therefore, fluorination studies were continued with L-*glycero*-α-D-*galacto*

epimer **34** instead. Compound **34** was allowed to react with gaseous CH_3COOF (at room temperature) and (*E*)-fluorovinyl **47** and (*Z*)-fluorovinyl **48** were obtained in 36% and 10% yield, respectively.

Compound **31** was radiofluorinated using gaseous acetyl [^{18}F]hypofluorite in 19% radiochemical yield. The radiolabelled product consists of a mixture of (*E*)-[^{18}F]fluorovinyl **51** and (*Z*)-[^{18}F]fluorovinyl **52** of low specific activity. The reaction times were of the order of 15-17 minutes (measured from EOB) which is well suited for radiolabelling with ^{18}F.

References

1. Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, *76*, 1455-1456.

2. *Ciba Foundation Symposium in Carbon-Fluorine Compounds: Chemistry, Biochemistry and Biological Activities*; Elsevier: New York, 1972.

3. *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha Ltd.: Tokyo, 1982.

4. Furin, G. G. *Sov. Sci. Rev., Sect. B:* **1991**, *16*, 1-140.

5. *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991.

6. Filler, R.; Naqvi, S. M. In *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha Ltd.: Tokyo, 1982; Chapter 1.

7. Welch, J. T. In *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991; Chapter 1.

8. Fowler, J. S.; Wolf, A. P. *The Synthesis of Carbon-11, Fluorine-18, and Nitrogen-13 Labeled Radiotracers for Biomedical Applications*; Nuclear Science Series, Monograph NAS-NS-3201; Technical Information Center, U.S. Department of Energy: Springfield, VA, 1982.

9. Kilbourn, M. R. *Fluorine-18 Labeling of Radiopharmaceuticals*; Nuclear Science Series, Monograph NAS-NS-3203; National Academy: Washington, DC, 1990.

10. *Nuclear Imaging in Drug Discovery, Development, and Approval*; Burns, H. D., Gibson, R. E., Dannals, R. F., Siegl, P. K. S., Eds.; Birkhäuser: Boston, 1993.

11. Moissan, H. *Compt. Rend.* **1886**, *102*, 1543-1544; *103*, 202-205.

12. Bockmüller, W. *Liebigs Ann. Chem.* **1933**, *506*, 20-59.

13. Purrington, S. T.; Kagen, B. S.; Patrick, T. B. *Chem. Rev.* **1986**, *86*, 977-1018.

14. Banks, R. E.; Tatlow, J. C. In *Fluorine: The First Hundred Years (1886-1986)*; Banks, R. E., Sharp, D. W. A., Tatlow, J. C., Eds.; Elsevier Science: New York, 1986; Chapter 4.

15. Hudlický, M. *Chemistry of Organic Fluorine Compounds: A Laboratory Manual with Comprehensive Literature Coverage*, 2nd ed.; John Wiley and Sons: New York, 1976.

16. *New Fluorinating Agents in Organic Synthesis*; German, L., Zemskov, S., Eds.; Springer-Verlag: Berlin, 1989.

17. Sharts, C. M.; Sheppard, W. A. *Org. React. (N. Y.)* **1974**, *21*, 125-406.

18. Gerstenberger, M. R. C.; Haas, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 647-667.

19. Nickles, R. J.; Gatley, S. J.; Votaw, J. R.; Kornguth, M. L. *Int. J. Appl. Radiat. Isot.* **1986**, *37*, 649-661.

20. Berridge, M. S.; Tewson, T. J. *Int. J. Appl. Radiat. Isot.* **1986**, *37*, 685-693.

21. Adam, M. J., TRIUMF, Vancouver, BC, personal communication.

22. See reference 9; pp 70-90.

23. Rozen, S.; Lerman, O.; Kel, M. *J. Chem. Soc., Chem. Commun.* **1981**, 443-444.

24. Fowler, J. S.; Shiue, C.-Y.; Wolf, A. P.; Salvador, P. A.; MacGregor, R. R. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 1634-1636.

25. Rozen, S.; Lerman, O.; Kol, M.; Hebel, D. *J. Org. Chem.* **1985**, *50*, 4753-4758.

26. Adam, M. J. *J. Chem. Soc., Chem. Commun.* **1982**, 730-731; Adam, M. J.; Pate, B. D.; Nesser, J.-R.; Hall, L. D. *Carbohydr. Res.* **1983**, *124*, 215-224.

27. Jewett, D. M.; Potocki, J. F.; Ehrenkaufer, R. E. *J. Fluorine Chem.* **1984**, *24*, 477-484.

28. Adam, M. J.; Pate, B. D.; Ruth, T. J.; Berry, J. M.; Hall, L. D. *J. Chem. Soc., Chem. Commun.* **1981**, 733.

29. Adam, M. J.; Berry, J. M.; Hall, L. D.; Pate, B. D.; Ruth, T. J. *Can. J. Chem.* **1983**, *61*, 658-660.

30. Ingham, R. K.; Rosenberg, S. D.; Gilman, H. *Chem. Rev.* **1960**, *60*, 459-539.

31. Larock, R. C. *Tetrahedron* **1982**, *38*, 1713-1754.

32. Adam, M. J.; Ruth, T. J.; Jivan, S.; Pate, B. D. *J. Fluorine Chem.* **1984**, *25*, 329-337.

33. Coenen, H. H.; Moerlein, S. M. *J. Fluorine Chem.* **1987**, *36*, 63-75.

34. Di Raddo, P.; Diksic, M.; Jolly, D. *J. Chem. Soc., Chem. Commun.* **1984**, 159-160.

35. Speranza, M.; Shiue, C.-Y.; Wolf, A. P.; Wilbur, D. S.; Angelini, G. *J. Chem. Soc., Chem. Commun.* **1984**, 1448-1449.

36. Visser, G. W. M.; Halteren, B. W. v.; Herscheid, J. D. M.; Brinkman, G. A.; Hoekstra, A. *J. Chem. Soc., Chem. Commun.* **1984**, 655-656.

37. Visser, G. W. M.; Bakker, C. N. M.; Halteren, B. W. v.; Herscheid, J. D. M.; Brinkman, G. A.; Hoekstra, A. *J. Org. Chem.* **1986**, *51*, 1886-1889.

38. Ehrenkaufer, R. E.; MacGregor, R. R. *Int. J. Appl. Radiat. Isot.* **1983**, *34*, 613-615.

39. Satyamurthy, N.; Bida, G. T.; Barrio, J. R.; Phelps, M. E. *J. Nucl. Med.* **1984**, *25*, P23.

40. Oberdorfer, F.; Hofman, E.; Maier-Borst, W. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 999-1005.

41. Adam, M. J.; Lu, J.; Jivan, S. *J. Labelled Compd. Radiopharm.* **1994**, *34*, 565-570.

42. Namavari, M.; Bishop, A.; Satyamurthy, N.; Bida, G.; Barrio, J. R. *Int. J. Appl. Radiat. Isot.* **1992**, *43*, 989-996.

43. Diksic, M.; Farrokhzad, S. *J. Nucl. Med.* **1985**, *26*, 1314-1318.

44. Luxen, A.; Barrio, J. R.; Bida, G. T.; Satyamurthy, N. *J. Labelled Compd. Radiopharm.* **1986**, *23*, 1066-1067.

45. Mislankar, S. G.; Gildersleeve, D. L.; Mulholland, G. K.; Massin, C. C.; Toorongian, S. A.; Wieland, D. M. *J. Nucl. Med.* **1987**, *28*, 624.

46. Barrio, J. R.; Perlmutter, M. M.; Luxen, A.; Melega, W. P.; Grafton, S. T.; Huang, S. C.; Hoffman, J. M.; Van Moffaert, G.; Mazziotta, J. C.; Phelps, M. E. *J. Nucl. Med.* **1989**, *30*, 752; Gildersleeve, D. L.; Van Dort, M. E.; Rosenspire, K. C.; Toorongian, S.; Wieland, D. M. *J. Nucl. Med.* **1989**, *30*, 752.

47. Luxen, A.; Perlmutter, M. M.; Barrio, J. R. *J. Labelled Compd. Radiopharm.* **1989**, *26*, 1-2.

48. Purrington, S. T.; Jones, W. A. *J. Fluorine Chem.* **1984**, *26*, 43-46.

49. Barnette, W. E. *J. Am. Chem. Soc.* **1984**, *106*, 452-454.

50. Knapp, F. F., Jr.; Goodman, M. M.; Kabalka, G. W.; Sastry, K. A. R. *J. Med. Chem.* **1984**, *27*, 94-97; Perlman, M. E.; Watanabe, K. A.; Schinazi, R. F.; Fox, J. J. *J. Med. Chem.* **1985**, *28*, 741-748.

51. Flanagan, R. J.; Charleson, F. P.; Synnes, E. I.; Wiebe, L. I.; Theriault, Y. X.; Nakashima, T. T. *Can. J. Chem.* **1985**, *63*, 2853-2860.

52. Franke, L. A.; Hanson, R. N. *J. Nucl. Med.* **1984**, *25*, 1116-1121.

53. Bey, P.; McCarthy, J. R.; McDonald, I. A. In *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991; Chapter 8.

54. Allmendinger, T.; Felder, E.; Hungerbuehler, E. In *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991; Chapter 13.

55. Balatoni, J. A., M.Sc. Thesis, The University of British Columbia, Dec. 1985.

56. van der Kerk, G. J. M.; Noltes, J. C. *J. Appl. Chem.* **1959**, *9*, 106-113.

57. Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851-3854; Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404-408.

58. Omae, I. *J. Organomet. Chem. Libr.* **1989**, *21*, 1-341.

59. Poller, R. C. *The Chemistry of Organotin Compounds*; Academic: New York, 1970; pp 112-113.

60. Banks, R. E.; Haszeldine, R. N.; Prodgers, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 596-598.

61. Di Raddo, P.; Diksic, M. *Int. J. Appl. Radiat. Isot.* **1985**, *36*, 953-956.

62. Lee, S. H.; Schwartz, J. *J. Am. Chem. Soc.* **1986**, *108*, 2445-2447.

63. See reference 9; p 5.

64. See reference 9; pp 22-24.

65. See reference 9; p 37 and 43.

Chapter 4

GENERAL CONCLUSIONS

The investigation presented in Chapter 2 demonstrated that (η^6-arene)tricarbonyl-chromium complexes can be used as synthetic intermediates for the radiolabelling of the attached arene ring with ^{11}C via nucleophilic substitution with [^{11}C]cyanide. This result represents the first application of chromium tricarbonyl complexes for radiolabelling with short-lived nuclides. From a broader perspective, however, this accomplishment could be the first step to a range of new radiolabelling methods based on the utilization of organotransition metal complexes. A number of transition metal systems facilitate the addition of various nucleophiles onto unsaturated organic molecules while complexed to the metal centre.[1] This pattern of reactivity needs to be explored further with nucleophilic forms of medically useful radioisotopes,[2] such as ^{18}F, ^{75}Br, ^{77}Br, and ^{123}I.

The application of chromium tricarbonyl complexes could be significantly advanced with additional studies. A further exploration of reaction conditions should be conducted to improve radiochemical yields, particularly with NCA [^{11}C]cyanide. This could include an investigation of various crown ether and other catalysts, employment of microwave drying of the [^{11}C]cyanide solution and microwave heating of the radiolabelling reaction, and the use of smaller volumes of reaction solvent to concentrate the reactants. Also, a study of alternative ways of trapping H^{11}CN in the absence of hydroxide may result in

significantly improved labelling yields. Furthermore, other potentially effective leaving groups should be explored to complement or supersede fluorine. Lastly, the substitution reactions of F^-, Br^-, and I^- with chromium tricarbonyl complexes warrant study because of the importance of radiohalogens in nuclear medicine.[2]

The investigation described in Chapter 3 revealed that vinyl-tin derivatives can be directly fluorinated with gaseous acetyl hypofluorite, in most cases, to produce stable and ^{18}F-labelled vinyl fluorides. This result represents another extension of the use of organotin compounds for electrophilic fluorinations, including radiofluorinations with ^{18}F. Very recently, other researchers have reported using vinyl-tin compounds to prepare vinyl fluorides. Tius and Kawakami[3] fluorinated a number of simple vinyl-tin derivatives with XeF_2 (in the presence of $AgPF_6$) in 24-52% yield, however, reaction times ranged from 3-18 hours. Hodson and co-workers[4] used cesium fluoroxysulfate to fluorinate some vinyl-tin compounds which produced vinyl fluorides in 25-56% yield, and in some cases, α-fluoroketones were unexpectedly made in 47-75% yield (reactions were run overnight). Matthews et al.[5] reported the electrophilic fluorination of several (fluorovinyl)stannanes with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) affording difluoro olefins in 35-74% yield (30 min reaction time at 80°C). Each of these reports provides new methods for fluorinating vinyl-tin compounds which is very positive, however, each of these methods, for various reasons, would appear to be incompatible for radiolabelling with ^{18}F. What is gratifying is that several years after choosing vinyl-tin intermediates for our fluorination studies, other research groups are also selecting tin reagents for the preparation of vinyl fluorides.

Undoubtedly, the application of organotin compounds will continue to be extended as interest in selectively fluorinated organic molecules remains.

Nonetheless, the following suggestions for future work can be made. The exploration of alternative fluorinating agents for use with vinyl-tin substrates would be very prudent. Also, the reactivity of fluorine and acetyl hypofluorite should be further examined with a wider range of structurally diverse vinylstannylated derivatives. Moreover, the fluorination of vinyl-silicon and -mercury derivatives warrant some additional study.

In retrospect, it is pleasing to see that although a few years have unfortunately elapsed since the experimental work was performed and the writing of this thesis completed, the results obtained are still new and currently relevant, and have not been duplicated in the literature. Even though various aspects of the specific experimental studies could have been done differently, the studies pursued for this thesis were well worthwhile and exhibit significant future potential. The application of organometallic compounds as synthetic intermediates for radiolabelling is only in the early stages of development still, but will continue to expand with future research.

References

1. Davies, S. G. *Organotransition Metal Chemistry: Applications to Organic Synthesis*; Pergamon: Toronto, 1982; Chapter 4.

2. Nozaki, T. In *Radionuclides Production*; Helus, F., Ed.; CRC: Boca Raton, 1983; Vol. 2, Chapter 3.

3. Tius, M. A.; Kawakami, J. K. *Synth. Commun.* **1992**, *22*, 1461-1471.

4. Hodson, H. F.; Madge, D. J.; Widdowson, D. A. *Synlett* **1992**, 831-832.

5. Matthews, D. P.; Miller, S. C.; Jarvi, E. T.; Sabol, J. S.; McCarthy, J. R. *Tetrahedron Lett.* **1993**, *34*, 3057-3060.

Chapter 5

EXPERIMENTAL

5.1 General Methods

Solutions were concentrated under reduced pressure with a Büchi rotary evaporator, except for solutions of organochromium complexes, which were concentrated in vacuo using a high vacuum, rotary vacuum pump assembly. Melting points were taken in capillaries (in air) using a Büchi 510 oil bath melting point apparatus, or were obtained on a Fisher-Johns melting point apparatus, and are uncorrected. Optical rotations were determined using a Perkin-Elmer model 141 polarimeter.

Tetrahydrofuran (THF) and diethyl ether were distilled from calcium hydride or sodium benzophenone ketyl.[1] Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from calcium hydride, then carefully stored under nitrogen. Di-*n*-butyl ether was distilled from sodium under nitrogen, while hexane, dichloromethane, and acetonitrile were distilled from calcium hydride. Methanol was distilled from magnesium methoxide prepared in situ by reaction of methanol with magnesium turnings. For high pressure liquid chromatography (HPLC) work, singly distilled water, HPLC grade acetonitrile and methanol, and reagent grade hexanes and diethyl ether were used, which were filtered (0.45 μm Millipore brand Durapore membrane) before use. All other solvents used were of spectro or reagent grade, and were used without further treatment.

Thin-layer chromatography (TLC) was performed on pre-coated silica gel plates (Baker-flex Silica gel 1B2-F or E. Merck Silica gel 60, No. 5534). Visualization was effected either by (a) spraying with 30% sulfuric acid in ethanol, then heating, (b) with short-wavelength UV light, or (c) by visual inspection (for coloured, organochromium compounds). The TLC solvent systems used were very similar to those listed for the column chromatography of the individual compounds. Column chromatography was performed using Silica gel 60 (E. Merck, 70-230 mesh). Flash chromatography was performed using Silica gel 60 (E. Merck, 230-400 mesh) by the method of Still et al.[2]

HPLC was done with a system consisting of a Spectro-Physics SP 8700 solvent delivery system, a Rheodyne 7126 injector, an ISCO (model V[4]) variable wavelength UV detector operated at 254-280 nm, and a Spectro-Physics SP 4270 integrator recorder, using one of the following columns, either (a) a Waters 10 μm C-18 reverse phase RCM column (column A), (b) two Waters 10 μm C-18 reverse phase RCM columns connected in series (column B), (c) a C-18 reverse phase Whatman Partisil 10 ODS-3 column, 25 cm $\times$ 9 mm, equipped with a Waters C-18 guard column (column C), or (d) normal phase Phenomenex Ultremex 5 Silica column, 25 cm $\times$ 10 mm (column D). The following solvent mixtures were used for HPLC: (i) methanol/water, 1:1 (solvent A), (ii) water/acetonitrile, 1:1 (solvent B), (iii) water/acetonitrile, 3:2 (solvent C), and (iv) hexanes/diethyl ether, 4:1 (solvent D). The following gradient solvent programs were also used for HPLC: (i) from 0 to 10 min, an isocratic mixture of methanol/water (85:15) was used, followed by a systematic increase to 100% methanol during 10 to 12 min, and a constant composition of 100% methanol was maintained from 12 to 20 min

(solvent program A), and (ii) from 0 to 18 min, an isocratic mixture of methanol/water (75:25) was used, followed by a systematic increase to 100% methanol during 18 to 21 min, and a constant composition of 100% of methanol was maintained from 21 to 30 min (solvent program B). Radio-HPLC analysis and purification was performed with the same HPLC system fitted with a NaI(Tl) scintillation detector system and a dual channel strip chart recorder. Radioactive samples were assayed with either a Capintec well counter (model CRC-543X) or a Beckman 8000 scintillation counter.

Analytical gas chromatography (GC) was performed with a Hewlett-Packard model 5840A GC, equipped with an FID detector, using a 30 m $\times$ 0.75 mm i.d. wide bore (Supelco SPB-1) capillary column. Unless otherwise stated, GC analyses were performed isothermally using the following conditions: injection temperature, 200°C; oven temperature, 120°C; N_2 carrier gas flow, 2.0 mL/min.

Low resolution electron impact mass spectra were recorded with either a Kratos/AEI MS902 or a Kratos/AEI MS50 mass spectrometer. An ionization potential of 70 eV was used for the mass spectra obtained. Spectra are quoted as m/z values, while selected ion fragmentations are reported as percentages of the base peak. High resolution mass measurements were determined using the Kratos/AEI MS50 mass spectrometer. Gas chromatography-mass spectrometry (GC-MS) was performed using a Delsi Nermag R10-10C quadruple mass spectrometer interfaced with a Varian 6000 GC or a Kratos MS80 coupled to a Carlo Erba 4160 GC.

All microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

5.2 NMR Methods and Instrumentation

^{1}H NMR spectra were measured at room temperature at 270 and 400 MHz. The 270 MHz spectra were obtained with a home-built spectrometer based on a Bruker WP-60 console, a Nicolet 1180 computer (32K), a Nicolet 293B pulse programmer, a one Megabyte Diablo disk drive (model 31), and an Oxford Instruments Superconducting solenoid magnet. In addition to this spectrometer, a separate data processing system, consisting of another Nicolet 1180 computer (32K), one Megabyte Diablo disk drive (model 31) and a digital plotter, was available for processing and plotting of NMR data. Standard NTCFTB software was used on the spectrometer and data station. Furthermore, some of the 270 MHz data was transferred from the Nicolet 1180 data station to a newer Nicolet 1280 computer, for processing with increased computer memory and digital plotting.

The 400 MHz spectra were obtained with a Bruker WH-400 high-resolution spectrometer equipped with an Aspect 3000 computer. Along with this spectrometer, a separate Bruker data processing system, comprised of an Aspect 3000 computer, digital plotter and dot matrix printer, was available for data processing and plotting. Factory Bruker software was used on the spectrometer and data station.

^{19}F NMR spectra were measured at 188 and 254 MHz, also at room temperature. The 188 MHz spectra were obtained with a Bruker AC-200E spectrometer. The NMR data from this spectrometer was transferred to and processed on the Bruker data station, described above. The 254 MHz spectra were obtained using the previously described home-built spectrometer (controlled by the Nicolet 1180 computer) with a home-built,

^{19}F-tuned probe.*

5.3 Experimental for Chapter 2

5.3.1 Sources of Materials

Chemicals and reagents were purchased from suppliers as follows. Chromium hexacarbonyl was obtained from Pressure Chemical Co. Fluorobenzene, 2- and 4-fluorotoluene, 4-chlorofluorobenzene, 4-chlorobenzonitrile, methyltrifluoromethane-sulfonate, and 18-crown-6 were purchased from Aldrich Chemical Co. Eastman Kodak Co. supplied the benzonitrile and 4-tolunitrile, and ICN Pharmaceuticals Inc. supplied the 2-tolunitrile. HPLC grade methanol and acetonitrile were obtained from Fisher Scientific Ltd., or BDH Chemicals.

5.3.2 General

All manipulations for the preparation and purification of the (η^6-arene)tricarbonyl-chromium complexes were performed so as to maintain all chemicals under an atmosphere of nitrogen or argon using conventional bench-top techniques for the manipulation of air-sensitive compounds.[3]

The (η^6-arene)tricarbonylchromium complexes, that were synthesized from $Cr(CO)_6$, were prepared either using a 200-mL, round-bottom, three-neck flask fitted with a nitrogen inlet, a magnetic stir bar, and a condenser equipped with a mineral oil-bubbler

*The probe construction and electronics was done by Tom Markus (Electronics shop, Chemistry Department, U.B.C.).

(glassware A), or a specially constructed reaction apparatus (glassware B) that consists of a 250-mL, round-bottom flask fused to a 3 in. long condenser which is joined to an additional 3 in. long glass tube (1 in. o.d.) equipped with a central ST* 24 ground glass joint and two angled ST 19 ground glass joints. This glassware is fitted with a glass rod that is placed through the central ST 24 joint and reaches to a dimple at the bottom of the flask and has a small paddle near the bottom of the flask (to stir the reaction mixture) plus a 3 in. long screw paddle which closely fits the interior wall of the condenser region (to scrap and return sublimed $Cr(CO)_6$ to the reaction mixture). The glass rod is rotated by a variable speed, overhead stirrer motor. The assembled glassware is also equipped with a nitrogen inlet and mineral oil bubbler. With either set-up, the glassware was wrapped with aluminum foil to protect the reaction from light.

Silica gel 60 (E. Merck, 70-230 mesh) was used for the filtration of organochromium solutions to remove any decomposition.

All substitution reactions were carried out in oven-dried Pierce Reacti-vials® (Rockford, IL) equipped with magnetic stir bars and screw caps that were fitted with Teflon-lined, silicone septa.†

$H^{11}CN$ was produced via the catalytic conversion of $^{11}CO_2$. The $^{11}CO_2$ was produced on the TRIUMF/Nordion CP-42 cyclotron using the $^{14}N(p,\alpha)^{11}C$ reaction at 15 MeV. The $^{11}CO_2$ in the N_2 target gas was converted to $^{11}CH_4$ by mixing the target gas with

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*ST denotes standard taper.

†These septa provided an excellent seal to maintain the exclusion of air and moisture, and to prevent the loss of volatile components.

H_2(g) then passing the mixture over a Ni catalyst at 450°C. Thereafter, the $^{11}CH_4$ was combined with NH_3(g) and passed over Pt at 1000°C, thus obtaining $H^{11}CN$.[4] The $H^{11}CN$ was trapped in an aqueous solution of NaOH (1 mL, 0.1 M) to produce $Na^{11}CN$.

5.3.3 Preparation of (η^6-Arene)tricarbonylchromium Complexes

Preparation of (η^6-fluorobenzene)tricarbonylchromium 1.

Chromium hexacarbonyl (1.0 g, 4.54 mmol) and fluorobenzene (5.0 mL, 53 mmol) were dissolved in a mixture of (n-Bu)$_2$O/THF (80 mL/10 mL) in glassware A. The reaction mixture was degassed by performing three freeze-pump-thaw cycles. Upon reintroducing a nitrogen atmosphere into the reaction vessel, the stirred reaction mixture was heated to reflux for 48 h. The reaction mixture was cooled to room temperature and filtered through a short pad of silica gel to remove any greyish-green decomposition. The bright yellow filtrate was evaporated to dryness in vacuo. The residue was dissolved in diethyl ether, and the resulting solution was transferred by canula filtration into a Schlenk tube. The undissolved residue was then washed with some hexane and these washings were likewise added to the ether solution. Solvent was slowly removed under reduced pressure until yellow crystals began to appear. The ether/hexane mixture was warmed gently until all crystals redissolved, then was placed in the freezer for crystallization. Bright yellow crystals were isolated and dried under a flow of N_2, initially, then under a high vacuum overnight. Two additional crops of crystals were obtained from the mother liquor, affording a total yield of 0.84 g (80%) of **1**, mp 117°C {lit.[5] mp 116-117°C}. Mass spectrum, m/z: 232 (M^+, 38), 204 (M^+-CO, 3), 176 (M^+-

2(CO), 9), 148 (M^+-3(CO), 54), 96 (M^+-$Cr(CO)_3$, 21), 71 (33), 52 (100).

Preparation of (η^6-chlorobenzene)tricarbonylchromium 2.

Chromium hexacarbonyl (1.86 g, 8.45 mmol) and chlorobenzene (25 mL, 0.25 mol) were added to diglyme (30 mL) in glassware B. The stirred reaction mixture was heated to reflux for 16.5 h. The reaction mixture was cooled to room temperature, then filtered through a short pad of Celite using some diethyl ether to rinse and facilitate the transfer of the reaction vessel contents. The yellow filtrate was concentrated via distillation under reduced pressure, then some petroleum ether was added to induce crystallization. Even with cooling, no crystals had formed. Therefore, some ethyl acetate was added to this solution and was then evaporated in vacuo. This process was repeated several times and the volume of diglyme was successfully reduced. Once again, petroleum ether was added to the concentrated solution till a small amount of precipitation occurred, then was placed in a fridge for cooling. A single large, yellow crystal was obtained, which was removed and washed with cold petroleum ether, then dried under a flow of argon. The filtrate was heated and filtered hot, to remove some greenish decomposition, then was placed back in the fridge for crystallization. Yellow crystals (400 mg) were isolated and dried in vacuo. The large single crystal, obtained initially, was recrystallized from hot petroleum ether. This afforded 265 mg of additional yellow crystals, which gave a total yield of 47% (665 mg) of **2** (based on $Cr(CO)_6$ consumed*), mp 100-101°C {lit.[6] mp

*Unreacted $Cr(CO)_6$ remaining in the reaction vessel was recovered by sublimation under high vacuum; this gave 0.60 g of recovered $Cr(CO)_6$.

101-102°C}.

Preparation of (η^6-bromobenzene)tricarbonylchromium 3.

Chromium hexacarbonyl (4.00 g, 18.2 mmol) and bromobenzene (10.0 mL, 95.2 mmol) were added to a mixture of (n-Bu)$_2$O/THF (100 mL/10 mL) in glassware B. The reaction mixture was degassed by performing a single freeze-pump-thaw cycle. Upon reintroducing an N_2 atmosphere over the reaction mixture, it was heated, with stirring, to reflux for 44 h. The cooled reaction mixture was filtered through a short pad of silica gel and the yellow filtrate was reduced to dryness in vacuo. Compound **3** was obtained as dark yellow crystals, in a yield of 992 mg (19%), mp 101-105°C {lit.[7] mp 120°C}. Mass spectrum, m/z: 294 (^{81}Br: M^+, 31), 292 (^{79}Br: M^+, 34), 266 (^{81}Br: M^+-CO, 3), 264 (^{79}Br: M^+-CO, 3), 238 (^{81}Br: M^+-2(CO), 6), 236 (^{79}Br: M^+-2(CO), 6), 210 (^{81}Br: M^+-3(CO), 26), 208 (^{79}Br: M^+-3(CO), 28), 158 (^{81}Br: M^+-$Cr(CO)_3$, 5), 156 (^{79}Br: M^+-$Cr(CO)_3$, 4), 133 (^{81}Br: 5), 131 (^{79}Br: 7), 52 (100).

Preparation of (η^6-2-fluorotoluene)tricarbonylchromium 4.

Chromium hexacarbonyl (1.0 g, 4.54 mmol) and 2-fluorotoluene (5.8 mL, 53 mmol) were dissolved in a mixture of (n-Bu)$_2$O/THF (80 mL/10 mL) in glassware A. All subsequent steps were essentially identical to the preparation of compound **1**. Compound **4** was obtained as yellow crystals, in a total yield of 0.99 g (89%), mp 71-72°C {lit.[8] mp 73-74°C}. Mass spectrum, m/z: 246 (M^+, 15), 218 (M^+-CO, 1), 190 (M^+-2(CO), 4), 162 (M^+-3(CO), 25), 110 (M^+-$Cr(CO)_3$, 26), 109 (44), 71 (12), 52 (100).

Preparation of (η^6-4-fluorotoluene)tricarbonylchromium 5.

Chromium hexacarbonyl (4.00 g, 18.2 mmol) and 4-fluorotoluene (10.0 mL, 91 mmol) were added to a mixture of (n-Bu)$_2$O/THF (100 mL/10 mL) in glassware B. The reaction mixture was degassed by performing a single freeze-pump-thaw cycle. Upon reintroducing an N_2 atmosphere over the reaction mixture, it was heated, with stirring, to reflux for 16.5 h. The cooled reaction mixture was filtered through a short pad of silica gel and the yellow filtrate was reduced to dryness under reduced pressure. After further drying in vacuo, compound **5** was obtained as bright yellow crystals, in a yield of 3.79 g (85%), mp 59-60°C {lit.[8] mp 61-62°C}. Mass spectrum, m/z: 246 (M^+, 11), 218 (M^+-CO, 1), 190 (M^+-2(CO), 3), 162 (M^+-3(CO), 23), 110 (M^+-Cr(CO)$_3$, 17), 109 (31), 71 (16), 52 (100).

Preparation of (η^6-4-chlorofluorobenzene)tricarbonylchromium 6.

Chromium hexacarbonyl (4.00 g, 18.2 mmol) and 4-chlorofluorobenzene (10.0 mL, 93.9 mmol) were added to a mixture of (n-Bu)$_2$O/THF (100 mL/10 mL) in glassware A. The stirred reaction mixture was heated to reflux for 23 h. Upon cooling to room temperature, the reaction mixture was concentrated to about 10 mL under reduced pressure and a plug of sublimed Cr(CO)$_6$ (1.1 g) was recovered from the condenser. The concentrated reaction mixture was chromatographed on neutral alumina (Fisher, 80-200 mesh) with hexane as the eluent. A single yellow band was collected and the solvent was removed in vacuo. TLC analysis, on alumina (eluent: hexane), of the yellow residue showed the presence of two components. Column chromatography was repeated on the

two-component mixture using silica gel with hexane/ether (5:1). The first fraction, after solvent removal, afforded 0.42 g of **6** as yellow crystals, mp 61-62°C {lit. mp: none found}. TLC analysis on silica gel (eluent: hexane/ether, 1:1), indicated the presence of only one component. Mass spectrum, *m/z*: 268 (^{37}Cl: M^+, 6), 266 (^{35}Cl: M^+, 17), 240 (^{37}Cl: M^+-CO, 2), 238 (^{35}Cl: M^+-CO, 3), 212 (^{37}Cl: M^+-2(CO), 2), 210 (^{35}Cl: M^+-2(CO), 5), 184 (^{37}Cl: M^+-3(CO), 9), 182 (^{35}Cl: M^+-3(CO), 25), 132 (^{37}Cl: M^+-$Cr(CO)_3$, 10), 130 (^{35}Cl: M^+-$Cr(CO)_3$, 29), 95 (22), 89 (^{37}Cl: 3), 87 (^{35}Cl: 9), 71 (14), 52 (100).

A second fraction (0.12 g) was collected, which contained a mixture of **1** and **6**, with **6** being the dominant component as determined by TLC analysis (silica gel; eluent: hexane/ether, 1:1). This material unfortunately underwent partial decomposition and was discarded.

A final fraction was collected, and after the eluate was evaporated to dryness in vacuo, 0.11 g of yellow crystals were isolated, mp 97-100°C. TLC analysis (silica gel; eluent: hexane/ether, 1:1) showed this material to be a mixture of **1** and **6**, with **1** being the major component present. Mass spectrometric analysis of this mixture gave the following results; mass spectrum, *m/z*: compound **1**, 232 (M^+, 22), 204 (M^+-CO, 3), 176 (M^+-2(CO), 5), 148 (M^+-3(CO), 27), 96 (M^+-$Cr(CO)_3$, 40); compound **6**, 268 (^{37}Cl: M^+, 0.6), 266 (^{35}Cl: M^+, 2.0), 240 (^{37}Cl: M^+-CO, 0.1), 238 (^{35}Cl: M^+-CO, 0.3), 212 (^{37}Cl: M^+-2(CO), 0.2), 210 (^{35}Cl: M^+-2(CO), 0.4), 184 (^{37}Cl: M^+-3(CO), 1.1), 182 (^{35}Cl: M^+-3(CO), 3.7), 132 (^{37}Cl: M^+-$Cr(CO)_3$, 1.8), 130 (^{35}Cl: M^+-$Cr(CO)_3$, 6.9).

The isolated yield of **6** (obtained from the first fraction) was 12%, based on the amount of $Cr(CO)_6$ consumed.

Preparation of (η^6-*N*,*N*-dimethylaniline)tricarbonylchromium 7.

Chromium hexacarbonyl (4.00 g, 18.2 mmol) and *N*,*N*-dimethylaniline (20 mL, 0.16 mol) were dissolved in a mixture of (n-Bu)$_2$O/THF (60 mL/5 mL) in glassware A. The stirred reaction mixture was heated to reflux for 21 h. After cooling to room temperature, the volume of the reaction mixture was concentrated under reduced pressure and a large crop of yellow crystals deposited. The remaining supernatant was then canula transferred to another flask. The crystals were collected on a glass frit and washed repeatedly with cold hexane, then dried in vacuo. Compound **7** was isolated as yellow crystals, for a yield of 3.30 g (70%), mp 137-138°C {lit.[6] mp 144°C}.

Preparation of (η^6-benzonitrile)tricarbonylchromium 10.

DMSO (2 mL) was added to compound **1** (44.8 mg, 0.193 mmol) and NaCN (21.4 mg, 0.437 mmol) contained in a 5-mL Reacti-vial® under argon. The reaction mixture was stirred for 23 h at ambient temperature. The reaction mixture was then added to water (20 mL) and subsequently extracted with diethyl ether (3 × 15 mL). The ether extracts were washed with aqueous, saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The dried ether extracts were filtered through a short pad of silica gel and the solvent was taken to dryness under reduced pressure. Compound **10** was isolated as yellow crystals, in a yield of 32 mg (69%).

Preparation of (η^6-*N,N,N*-trimethylanilinium)tricarbonylchromium trifluoromethanesulfonate 11.

Compound **7** (1.00 g, 3.89 mmol) was added to CH_2Cl_2 (25 mL) and stirred at room temperature until dissolved. Methyltrifluoromethanesulfonate (1.1 mL, 9.7 mmol) was added by syringe and the mixture was stirred overnight. Yellow crystals had deposited and the supernatant was canula transferred to another flask. This solution was stirred overnight. The yellow crystals were dried in vacuo, then dissolved in acetonitrile. The resulting solution was transferred by canula filtration into a Schlenk tube. The volume of CH_3CN was reduced by a third under reduced pressure, then diethyl ether was added until the solution became slightly cloudy. This mixture was placed in the freezer overnight.

The previous solution, in which the reaction was allowed to continue, afforded another crop of yellow crystals. These were isolated and recrystallized as described for the first batch of crystals. Both batches of crystals were isolated, and dried under a flow of N_2 initially, then under high vacuum. Compound **11** was obtained as yellow crystals, in a total yield of 0.97 g (59%). An analytical sample was obtained by performing two sequential recrystallizations of a portion of **11** from acetonitrile/diethyl ether, mp 120-121°C (dec.).* Anal. calcd. for $C_{13}H_{14}CrF_3NO_6S$: C 37.06, H 3.35, N 3.32, S 7.61; found: C 37.40, H 3.53, N 3.49, S 7.44. ^{1}H NMR (270 MHz, DMSO-d_6) δ: 3.56 (s, 9H, $N(CH_3)_3$), 5.77 (t, 2H, H-3,5), 6.07 (t, 1H, H-4), 6.69 (d, 2H, H-2,6).

*Performed in capillaries that were packed and sealed under nitrogen.

Preparation of *N,N,N*-trimethylanilinium trifluoromethanesulfonate 12.

N,N-Dimethylaniline (1.00 mL, 7.89 mmol) and methyltrifluoromethanesulfonate (1.1 mL, 9.7 mmol) were added sequentially by syringe to CH_2Cl_2 (25 mL) while under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature. After 30 min, TLC analysis indicated that all the *N,N*-dimethylaniline present was consumed. The copious quantities of white crystals that deposited, were collected and dried in vacuo. These crystals were recrystallized from dichloromethane/diethyl ether, which afforded a total yield of 1.87 g (83%) of **12**, mp 82-83°C {lit. mp: none found}. ^{1}H NMR (270 MHz, DMSO-d_6) δ: 3.61 (s, 9H, N(CH_3)$_3$), 7.58-7.67 (m, 3H, H-3,4,5), 7.97 (d, 2H, H-2,6).

Preparation of *N,N,N*-trimethylanilinium iodide 13.

N,N-Dimethylaniline (1.00 mL, 7.89 mmol) and iodomethane (0.54 mL, 8.67 mmol) were added to CH_2Cl_2 (25 mL) under a nitrogen atmosphere. The reaction mixture was allowed to stir overnight at room temperature. The resulting white crystals which had deposited were collected, washed with diethyl ether and dried under reduced pressure. Compound **13** was obtained in a yield of 1.16 g (56%). ^{1}H NMR (270 MHz, DMSO-d_6) δ: 3.61 (s, 9H, N(CH_3)$_3$), 7.58-7.68 (m, 3H, H-3,4,5), 7.97 (d, 2H, H-2,6).

5.3.4 Substitution Reactions of Organochromium Complexes

Substitution reactions with stable cyanide.

General Procedure: An aliquot (200 μL, 10 mg/mL) of aqueous KCN (32 μmol) was

injected into a 5-mL Reacti-vial® under inert atmosphere. The water was evaporated to dryness, using a block heater, under a rapid flow of nitrogen or argon. The (η^6-arene)tricarbonylchromium complex (65 μmol) was taken up in DMSO (1 mL), then added by syringe to the Reacti-vial®. The stirred mixture was heated at the desired temperature in a thermostated silicone oil bath for 10 minutes. After cooling (ice/water bath) to room temperature, the reaction mixture was quantitatively transferred to a volumetric flask and diluted to a known volume with DMSO. This solution was analyzed by HPLC, which was standardized with known solutions of expected aryl nitrile product, to determine the extent of product formation. The chemical yields were calculated using KCN as the limiting reagent.

A separate set of reactions were performed to isolate the organic products and identify these by GC-MS, therefore, the workup of these reaction mixtures, after cooling, was conducted as follows. The reaction mixture was diluted with water or saturated NaCl solution (3 mL), and extracted with diethyl ether (1 × 6 mL, 2 × 3 mL). The combined ether extracts were washed with water or saturated NaCl solution (2 × 3 mL). The stirred ether solution was treated with iodine (146 μmol) at 0°C for 2 hours to ensure complete decomplexation. The treatment was quenched with the addition of aqueous sodium thiosulfate solution (5 mL, 0.1M) and the ether layer was washed further with sodium thiosulfate solution (4 mL, 0.1M), then with saturated NaCl solution (2 × 4 mL) and was dried over anhydrous magnesium sulfate. The dried ether layer was filtered and concentrated under reduced pressure to 1 mL. The concentrated ether solution was analyzed initially by GC and HPLC, then by GC-MS.

Reaction of 1 with cyanide.

A typical reaction trial was performed as follows. Compound **1** (15.6 mg, 67.2 μmol) was allowed to react with KCN (2.10 mg, 32.2 μmol), at 135°C, as described in the general procedure above. The final DMSO mixture was analyzed by HPLC (column A; eluent: solvent A; flow rate, 2.5 mL/min; UV detection, 280 nm) and it was determined that 1.34 mg of benzonitrile **14** (R_T*=5.4 min) was present, for a yield of 40%.

Other reaction trials were conducted at 105, 115, 120, and 150°C, which gave yields† of 12, 32, 31, and 33%, respectively.

Reaction of 4 with cyanide.

A typical reaction trial was performed as follows. Compound **4** (16.2 mg, 65.8 μmol) was allowed to react with KCN (2.10 mg, 32.2 μmol), at 105°C, as described in the general procedure. The final DMSO mixture was analyzed by HPLC (column B; eluent: solvent C; flow rate, 2.5 mL/min; UV detection, 270 nm) and it was determined that 1.62 mg of 2-tolunitrile **15** (R_T=12.1 min) was present, for a yield of 43%.

Other reaction trials were conducted at 95, 115, 125, and 135°C, which gave yields† of 26, 41, 29, and 36%, respectively.

Two reaction trials were performed using 1.5 mg (6.1 μmol) of **4** with KCN (2.00 mg, 30.7 μmol), at 135 and 143°C, using the general procedure. In each case, 0.41 mg of **15**

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*R_T denotes retention time.

†These results represent the best chemical yields obtained where more than one reaction trial was performed.

was obtained, for a yield of 58% based on **4** as the limiting reagent.

A separate reaction trial was done to identify the organic products by GC-MS. Compound **4** (16.2 mg, 65.8 μmol) was allowed to react with cyanide, at 120°C, as described in the general procedure. The concentrated ether solution was analyzed by GC and only two significant peaks were observed, which were identified as 2-fluorotoluene (R_T=3.2 min) and 2-tolunitrile **15** (R_T=5.7 min). This sample was further analyzed by HPLC (column A; eluent: solvent C; flow rate, 2.5 mL/min; UV detection, 270 nm) and found that **15** eluted first (R_T=7.3 min), followed by 2-fluorotoluene (R_T=16.2 min). Identification of the above products was accomplished by the comparison of the GC and HPLC retention times with those of authentic samples. The identity of the products was further confirmed by GC-MS, using for comparison the mass spectra (acquired under very similar instrumental conditions) obtained from a premade solution of authentic samples. Mass spectra, *m/z*: 2-fluorotoluene, 110 (M^+, 48), 109 (M^+-H, 100), 108 (M^+-2H, 15), 89 (3), 83 (15), 74 (12), 59 (15), 57 (6); compound **15**, 117 (M^+, 100), 116 (M^+-H, 85), 115 (M^+-2H, 13), 90 (44), 89 (47), 63 (16).

Reaction of 5 with cyanide.

A typical reaction trial was performed as follows. Compound **5** (16.1 mg, 65.4 μmol) was allowed to react with KCN (2.10 mg, 32.2 μmol), at 115°C, as described in the general procedure. The final DMSO mixture was analyzed by HPLC (column B; eluent: solvent C; flow rate, 2.5 mL/min; UV detection, 270 nm) and it was determined that 1.11 mg of 4-tolunitrile **16** (R_T=12.2 min) was present, for a yield of 29%.

Other reaction trials were conducted at 105, 125, 135, and 150°C, which gave yields* of 11, 21, 26, and 21%, respectively.

A separate reaction trial was done to identify the organic products by GC-MS. Compound **5** (16.5 mg, 67.0 μmol) was allowed to react with cyanide, at 135°C, as described in the general procedure. The concentrated ether solution was analyzed by GC and only two prominent peaks were observed, which were identified as 4-fluorotoluene (R_T=3.2 min) and 4-tolunitrile **16** (R_T=6.3 min). This sample was further analyzed by HPLC (column A; eluent: solvent C; flow rate, 2.5 mL/min; UV detection, 270 nm) and found that **16** eluted first (R_T=7.7 min), followed by 4-fluorotoluene (R_T=15.9 min). Identification of the above products was performed by the comparison of the GC and HPLC retention times with those of authentic samples. The identity of the products was further confirmed by GC-MS, using for comparison the mass spectra (acquired under very similar instrumental conditions) obtained from a premade solution of authentic samples. Mass spectra, *m/z*: 4-fluorotoluene, 110 (M^+, 66), 109 (M^+-H, 100), 89 (2), 83 (21), 57 (3); compound **16**, 117 (M^+, 100), 116 (M^+-H, 52), 90 (38), 89 (30), 63 (7).

Reaction of 6 with cyanide.

A typical reaction trial was performed as follows. Compound **6** (18.2 mg, 68.3 μmol) was allowed to react with KCN (2.10 mg, 32.2 μmol), at 115°C, as described in the

*These results represent the best chemical yields obtained where more than one reaction trial was performed.

general procedure. The final DMSO mixture was analyzed by HPLC (column B; eluent: solvent C; flow rate, 2.5 mL/min; UV detection, 270 nm) and it was determined that 1.53 mg of 4-chlorobenzonitrile **17** (R_T=12.5 min) was present, for a yield of 34%.

A reaction trial was also conducted at 135°C, which gave a yield of 21%.

An additional reaction trial was performed at 115°C that was heated only for 5 min (instead of 10 min) and gave a chemical yield of 17%.

A separate reaction trial was done to identify the organic products by GC-MS. Compound **6** (17.7 mg, 66.3 μmol) was allowed to react with cyanide, at 115°C, as described in the general procedure. The concentrated ether solution was analyzed by GC and two major peaks were observed, which were identified as 4-chlorofluorobenzene (R_T=3.5 min) and 4-chlorobenzonitrile **17** (R_T=7.1 min), and also a smaller unknown peak was observed that was identified eventually (by GC-MS) as benzonitrile **14** (R_T=4.5 min). This sample was further analyzed by HPLC (column A; eluent: solvent A; flow rate, 2.5 mL/min; UV detection, 270 nm) and found that **14** eluted first (R_T=4.6 min), followed by **17** (R_T=7.6 min) and an unidentified peak (R_T=10.1 min), then finally 4-chlorofluorobenzene (R_T=18.3 min) appeared last. Identification of the principal products was performed by the comparison of the GC and HPLC retention times with those of authentic samples. The identification of the products was completed by GC-MS, using for comparison the mass spectra (acquired under very similar instrumental conditions) obtained from a premade solution of authentic samples in the case of the principal products, and by inspection of the mass spectrum obtained for **14**. Mass spectra, *m/z*: 4-chlorofluorobenzene, 132 (^{37}Cl: M^+, 32), 130 (^{35}Cl: M^+, 100), 95 (M^+-Cl,

58), 94 (M^+-HCl, 11), 69 (13), 68 (13), 65 (8), 51 (11), 50 (36); compound **17**, 139 (^{37}Cl: M^+, 31), 137 (^{35}Cl: M^+, 100), 112 (^{37}Cl: M^+-HCN, 1), 110 (^{35}Cl: M^+-HCN, 3), 102 (M^+-Cl, 36), 76 (14), 75 (25), 74 (11), 68 (4), 51 (19), 50 (35); compound **14**, 103 (M^+, 100), 102 (M^+-H, 2), 77 (M^+-CN, 8), 76 (M^+-HCN, 40), 63 (4), 52 (9), 51 (21), 50 (26).

Reaction of 4 with cyanide in the presence of 18-crown-6 and DMSO.

A typical reaction trial was performed as follows. Compound **4** (16.0 mg, 65.0 μmol) was allowed to react with KCN (2.10 mg, 32.2 μmol), at 105°C, as described in the general procedure except that about 1.2 equivalents of 18-crown-6 (9.8 mg, 37 μmol) was added to the reaction mixture before heating. The final DMSO mixture was analyzed by HPLC (column B; eluent: solvent C; flow rate, 2.5 mL/min; UV detection, 270 nm) and it was determined that 1.65 mg of 2-tolunitrile **15** (R_T=14.3 min) was present, for a yield of 44%.

Other reaction trials were conducted at 95, 115, 125, and 135°C, which gave yields of 35, 40, 42, and 41%, respectively.

An additional reaction trial was performed using 16.2 mg (65.8 μmol) of **4** with KCN (2.10 mg, 32.2 μmol), at 105°C, which used approximately 3 equivalents of 18-crown-6 (26 mg, 98 μmol) and afforded a chemical yield of 46%.

Reaction of 4 with cyanide in the presence of 18-crown-6 and CH_3CN.

Two reaction trials were performed as follows. In the first trial, **4** (16.2 mg, 65.8 μmol) was allowed to react with KCN (2.10 mg, 32.2 μmol), at 80°C, as described in the

general procedure except that 1 equivalent of 18-crown-6 (8.5 mg, 32 μmol) was added to the reaction mixture and CH_3CN was used as the reaction solvent. The final CH_3CN mixture was analyzed by HPLC (column B; eluent: solvent C; flow rate, 2.5 mL/min; UV detection, 270 nm) and it was determined that 0.094 mg of 2-tolunitrile **15** (R_T=13.8 min) was present, for a yield of 3%. This mixture was stored and reanalyzed approximately 18 hours later by HPLC; it was found that 0.81 mg of **15** was now present, which represents a yield of 21%. The mixture was stored again, then reanalyzed 13.5 days after the initial HPLC analysis. At this time, 1.90 mg of **15** was determined to be present, for a final yield of 50%.

The second reaction trial was performed in the same way as the first, except that an oil bath temperature of 95°C was used (it was noted that the reaction mixture was refluxing). A chemical yield of 4% was obtained, as determined by HPLC. The mixture was stored, and upon reanalysis about 16 hours later, the yield was found to be increased to 21%. This mixture was stored again, then reanalyzed 13.5 days after the initial HPLC analysis. The final yield of **15** was found to be 46%.

Attempted reaction of 11 with cyanide.

Two reaction trials were performed as follows. In the first trial, **11** (27 mg, 64 μmol) was allowed to react with KCN (2.10 mg, 32.2 μmol), at 100°C, as described in the general procedure. The final DMSO mixture was analyzed by HPLC (column A; eluent: solvent C; flow rate, 2.5 mL/min; UV detection, 270 nm) and the chromatogram exhibited a large peak (R_T=7.9 min) and a much smaller peak (R_T=18.2 min), but

neither peak could be identified. Under these HPLC conditions, benzonitrile **14** was exhibiting a retention time of 4.4 min. Therefore, HPLC analysis confirmed the absence of any desired **14** in the product mixture.

The second reaction trial was performed in the same way as the first, except the reaction temperature used was 120°C. The same essential results were obtained as reported in the first trial above.

Heating of 11 in DMSO without cyanide present.

Compound **11** (27 mg, 64 μmol) was heated in DMSO (1 mL) for 10 min at 100°C, in the same fashion as described in the general procedure; the addition of aqueous KCN and its associated drying was not done. The resulting DMSO solution was analyzed by HPLC (column A; eluent: solvent C; flow rate, 2.5 mL/min; UV detection, 270 nm) and the chromatogram exhibited a single large peak (R_T=8.1 min) which could not be identified.

Attempted reaction of fluorobenzene with cyanide.

Fluorobenzene (5.7 μL, 60 μmol) was allowed to react with KCN (2.00 mg, 30.7 μmol), at 135°C, as described in the general procedure. The final DMSO mixture was analyzed by HPLC (column A; eluent: solvent B; flow rate, 2.5 mL/min; UV detection, 270 nm) and the chromatogram exhibited a single peak (R_T=4.2 min) which was identified as fluorobenzene. Under these HPLC conditions, benzonitrile **14** had a retention time of 2.8 min, thereby confirming the absence of **14** in the product mixture.

Attempted reaction of 2-fluorotoluene with cyanide.

2-Fluorotoluene (6.6 μL, 60 μmol) was allowed to react with KCN (2.00 mg, 30.7 μmol), at 135°C, as described in the general procedure. The final DMSO mixture was analyzed by HPLC (column A; eluent: solvent B; flow rate, 2.5 mL/min; UV detection, 270 nm) and the chromatogram exhibited a single peak (R_T=7.2 min) which was identified as 2-fluorotoluene. Under these HPLC conditions, 2-tolunitrile **15** had a retention time of 3.9 min, thereby confirming the absence of **15** in the product mixture.

Attempted reaction of 4-fluorotoluene with cyanide.

4-Fluorotoluene (6.6 μL, 60 μmol) was allowed to react with KCN (2.00 mg, 30.7 μmol), at 135°C, as described in the general procedure. The final DMSO mixture was analyzed by HPLC (column A; eluent: solvent B; flow rate, 2.5 mL/min; UV detection, 270 nm) and the chromatogram exhibited a single peak (R_T=7.3 min) which was identified as 4-fluorotoluene. Under these HPLC conditions, 4-tolunitrile **16** had a retention time of 4.1 min, thereby confirming the absence of **16** in the product mixture.

Attempted reaction of 4-chlorofluorobenzene with cyanide.

4-Chlorofluorobenzene (6.4 μL, 60 μmol) was allowed to react with KCN (2.00 mg, 30.7 μmol), at 135°C, as described in the general procedure. The final DMSO mixture was analyzed by HPLC (column A; eluent: solvent B; flow rate, 2.5 mL/min; UV detection, 270 nm) and the chromatogram exhibited a single peak (R_T=7.6 min) which was identified as 4-chlorofluorobenzene. Under these HPLC conditions, 4-

chlorobenzonitrile **17** had a retention time of 4.6 min, thereby confirming the absence of **17** in the product mixture.

Attempted reaction of 12 with cyanide.

Compound **12** (18 mg, 63 μmol) was allowed to react with KCN (2.10 mg, 32.2 μmol), at 100°C, as described in the general procedure. The final DMSO mixture was analyzed by HPLC (column A; eluent: solvent C; flow rate, 2.5 mL/min; UV detection, 270 nm) and no product peaks were observed in the chromatogram (**12** is not observable by UV detection at 270 nm). Under these HPLC conditions, benzonitrile **14** had a retention time of 4.1 min, thereby confirming the absence of **14** in the product mixture.

5.3.5 Labelling Work with [^{11}C]Cyanide

Substitution reactions with [^{11}C]cyanide.

General Procedure: After the H^{11}CN was generated and trapped in aqueous NaOH solution (1 mL, 0.1 M), 0.5-1.0 mL of this radioactive stock solution was taken (the solution was counted at this stage and the time was noted*) and a known amount of non-radioactive KCN (carrier) was added, then this mixture was added to a 5-mL Reacti-vial® (which contained an inert atmosphere). The [^{11}C]cyanide solution was rapidly evaporated to dryness (using a block heater) under a fast flow of nitrogen or argon. A solution of (η^6-arene)tricarbonylchromium (40-65 μmol) in DMSO (1 mL) was added by syringe to the Reacti-vial®. The stirred mixture was heated at the desired temperature

*This point in time was designated as the *start of synthesis* (SOS).

in a thermostated silicone oil bath for 10 minutes. Upon cooling (ice/water bath) to ambient temperature, a small portion of the reaction mixture was subjected to radio-HPLC purification and the peak corresponding to the [^{11}C]nitrile product was collected and counted to determine the decay corrected radiochemical yield.

Reaction of 1 with [^{11}C]cyanide.

A representative reaction trial was performed as follows. Compound **1** (9.5 mg, 41 μmol) was treated with a mixture of 27.8 mCi (SOS) of [^{11}C]cyanide and 0.37 equivalents of carrier KCN (0.98 mg, 15 μmol), then heated at 150°C, as described in the general procedure. HPLC analysis (column C; eluent: solvent A; flow rate, 5.0 mL/min; UV detection, 254 nm) of the reaction mixture determined that 9.93 mCi (decay corrected to SOS) of [^{11}C-CN]benzonitrile **18** (R_T=6.5 min) was produced for a radiochemical yield of 36%.

Other reaction trials were conducted at 150°C which used varying amounts of carrier KCN (0.11, 0.35, 0.49 equiv) and gave 21%, 41%, and 34% radiochemical yields, respectively.

An additional reaction trial was performed at 135°C, which used 0.51 equivalents of carrier KCN, and afforded a radiochemical yield of 35%.

Reaction of 1 with no carrier-added [^{11}C]cyanide.

Compound **1** (15 mg, 65 μmol) was treated with 22.8 mCi (SOS) of [^{11}C]cyanide (with no carrier KCN added), then heated at 150°C, as described in the general procedure.

HPLC analysis (column C; eluent: solvent A; flow rate, 5.0 mL/min; UV detection, 254 nm) of the reaction mixture determined that only a trace of [^{11}C-CN]benzonitrile **18** (R_T=6.5 min) was present—the activity of the collected product fraction was too low to be counted with the Capintec well counter.

Reaction of 4 with [^{11}C]cyanide.

Compound **4** (14.8 mg, 60.1 μmol) was treated with a mixture of 8.50 mCi (SOS) of [^{11}C]cyanide and 0.51 equivalents of carrier KCN (2.00 mg, 30.7 μmol), then heated at 135°C, as described in the general procedure. HPLC analysis (column A; eluent: solvent B; flow rate, 2.5 mL/min; UV detection, 270 nm) of the reaction mixture determined that 2.93 mCi (decay corrected to SOS) of [^{11}C-CN]-2-tolunitrile **19** (R_T=4.0 min) was produced for a radiochemical yield of 34%.

Reaction of 5 with [^{11}C]cyanide.

Compound **5** (14.8 mg, 60.1 μmol) was treated with a mixture of 7.84 mCi (SOS) of [^{11}C]cyanide and 0.51 equivalents of carrier KCN (2.00 mg, 30.7 μmol), then heated at 135°C, as described in the general procedure. HPLC analysis (column A; eluent: solvent B; flow rate, 2.5 mL/min; UV detection, 270 nm) of the reaction mixture determined that 2.39 mCi (decay corrected to SOS) of [^{11}C-CN]-4-tolunitrile **20** (R_T=4.1 min) was produced for a radiochemical yield of 31%.

Reaction of 6 with [^{11}C]cyanide.

Compound **6** (12.3 mg, 46.1 μmol) was treated with a mixture of 16.73 mCi (SOS) of [^{11}C]cyanide (in this case the H^{11}CN was trapped in 0.025 M NaOH solution) and 0.11 equivalents of carrier KCN (0.33 mg, 5.0 μmol), then heated at 150°C, as described in the general procedure. HPLC analysis (column C; eluent: solvent A; flow rate, 3.0 mL/min; UV detection, 254 nm) of the reaction mixture determined that 3.54 mCi (decay corrected to SOS) of [^{11}C-CN]-4-chlorobenzonitrile **21** (R_T=12.0 min) was produced for a radiochemical yield of 21%.

Another reaction trial was performed at 135°C, which used 0.51 equivalents of carrier KCN, and afforded a radiochemical yield of 19%.

Reaction of 6 with [^{11}C]cyanide in the absence of base.

An experiment was done to eliminate the presence of base (both ammonia and hydroxide) from the labelling [^{11}C]cyanide reagent. The H^{11}CN/NH_3 gas stream was passed through a glass loop, which was emersed in a CCl_4/CO_2 (-23°C) cooling bath, and trapped out the H^{11}CN, while sweeping away the NH_3 with helium gas flow. The glass loop was removed from the cooling bath and H^{11}CN was slowly purged into a Reacti-vial® which contained a mixture of **6** (10.0 mg, 37.5 μmol), carrier KCN (1-2 mg, 15-31 μmol*), and DMSO (1 mL) under N_2 atmosphere. When the H^{11}CN transfer was complete, the radioactive mixture was counted (3.87 mCi, SOS). This mixture was

*Two small crystals of KCN were used, which were not weighed, thus the quantity indicated was estimated.

heated for 10 minutes at 125-130°C. After cooling, HPLC analysis (column C; eluent: solvent A; flow rate, 3.0 mL/min; UV detection, 254 nm) of the reaction mixture determined that 1.11 mCi (decay corrected to SOS) of [^{11}C-CN]-4-chlorobenzonitrile **21** (R_T = 14.9 min) was produced for a radiochemical yield of 29%.

5.4 Experimental for Chapter 3

5.4.1 Sources of Materials

17α-Ethynylestradiol **23** was obtained from Sigma Chemical Co. Tri-*n*-butyltin hydride was purchased from the Aldrich Chemical Co. and Alfa Products, and 2,2´-azobis- (2-methylpropionitrile), commonly referred to as AIBN, was supplied by Aldrich Chemical Co.

The *O*-methylated estradiols, 3-methoxy-17α-ethynyl-1,3,5(10)-estratriene-17β-ol **24** and 3,17β-dimethoxy-17α-ethynyl-1,3,5(10)-estratriene **25**, were prepared by adapting the method of Johnstone and Rose.[9] Compound **23** was treated with powdered potassium hydroxide in DMSO, followed by the addition of iodomethane. Flash chromatography of the crude product mixture on silica gel with hexanes/diethyl ether (2:1) afforded **24** and **25** in 67% and 31% yields, respectively. 3-Methoxy-17α-vinyl-1,3,5(10)-estratriene-17β-ol **41** was also prepared by an adaptation of the procedure of Johnstone and Rose.[9] A mixture of **23** and 17α-vinyl-1,3,5(10)-estratriene-3,17β-diol **35**, obtained from the hydrostannylation of **23** (see Subsection 5.4.3), was treated with potassium hydroxide in DMSO, and then with iodomethane. Flash chromatography on silica gel with hexanes/ diethyl ether (1:1) gave pure **41** in 52% yield (based on the amount of **35** used).

The acetylenic sugars, 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-oct-7-ynopyranose **28** and its L-*glycero*-α-D-*galacto* epimer **29**, were prepared according to published procedures in two steps. First, 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose **27** was prepared by oxidation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **26** (Koch-Light Laboratories Ltd.) using either chromium trioxide-dipyridine complex (in 52% yield) as described by Arrick and co-workers,[10] or the chromium trioxide-pyridine complex in the presence of acetic anhydride (in 68% yield) according to Garegg and Samuelsson.[11] Then **27** was treated with ethynylmagnesium bromide according to the procedure of Hems et al.[12] and a mixture of **28** and **29** was obtained (85% yield) in a ratio of 62:38 (determined by ^{1}H NMR), respectively. This mixture was separated using column chromatography on silica gel with dichloromethane/ hexanes/diethyl ether (6:2:1).

Research grade Ne and 1% F_2 in Ne gas mixture were specially prepared in ultra-high purity (suitable for ^{18}F production) by either Matheson Gas Products (Edmonton, AB) or Canadian Liquid Air Ltd. (Vancouver, BC).

Freon-11 ($CFCl_3$) was purchased from Matheson Gas Products.

5.4.2 General

Fluorine gas is toxic, highly corrosive, and generally dangerous, and therefore requires handling with great care.[13,14] Hence, a specialized fluorine gas handling system was used to perform all studies involving elemental fluorine and acetyl hypofluorite, and is shown in Figure 5.1. This gas handling system was constructed from components, such

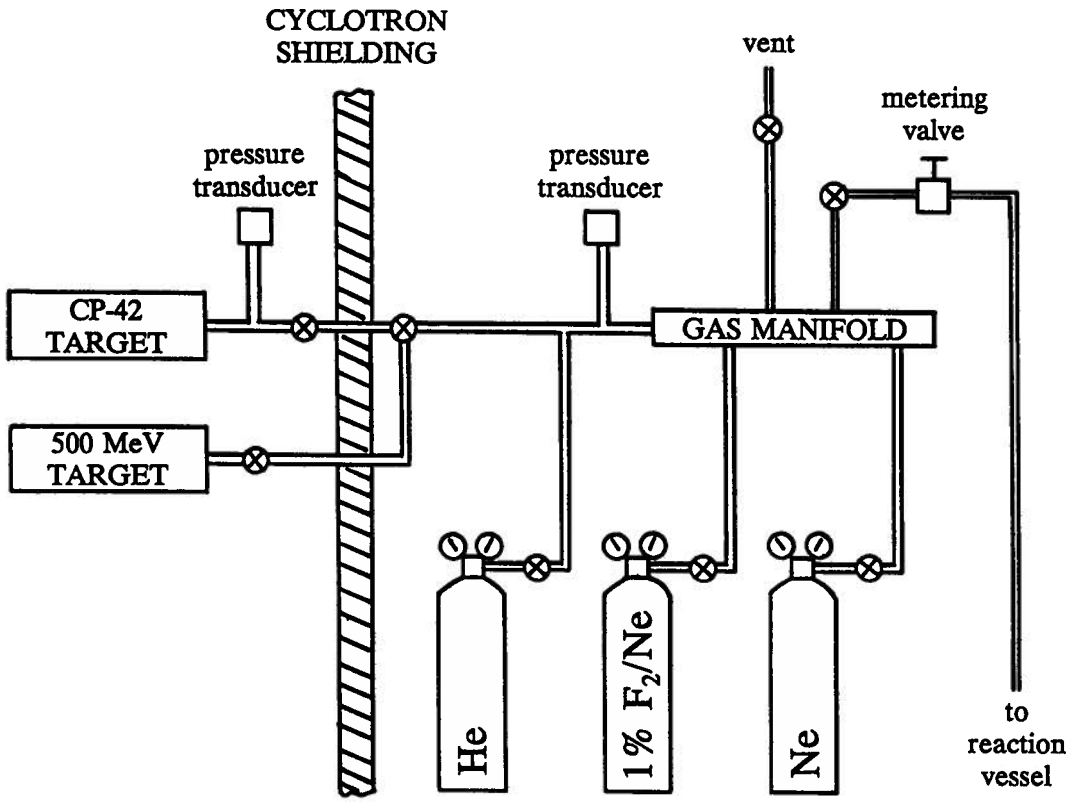

Figure 5.1: Schematic of the fluorine gas handling system used to perform the fluorination reactions.

as stainless steel and Teflon, that are compatible with reactive fluorine gas. The fluorine tank and gas handling system are stationed in a fume hood specifically designed for use with radionuclides. The gas handling system is connected via 1/8 in. o.d. stainless steel tubes to the gas targets used on the TRIUMF/Nordion CP-42 cyclotron and the larger TRIUMF 500 MeV cyclotron. The cyclotron gas targets are essentially gas-tight cylinders, fabricated from nickel (for the CP-42 cyclotron)[15] or Inconel 600, a nickel-based alloy (for the 500 MeV cyclotron).[16] The gas handling system was connected to the reaction vessel with Teflon tubing (1/16 or 1/8 in. o.d.) using Swagelok fittings

(Crawford Fitting Co., Salon, OH) and Teflon ferrules.

Gaseous CH_3COOF was produced by passing a dilute mixture of F_2 (~0.1%) in Ne through a column containing a solid mixture of potassium acetate/acetic acid in a molar ratio of 2:3. The CH_3COOK/CH_3COOH mixture was prepared according to the method of Jewett et al.[17]

The quantification of the amount of F_2 or CH_3COOF used for fluorination experiments was accomplished by iodometric titration.[18,19] Prior to performing actual fluorination reactions with vinyl-tin substrates, one or two "dummy" trials would be done in which the fluorinating agent was added to an aqueous solution of excess KI, and the liberated I_2 was then titrated with standardized 0.1 M sodium thiosulfate solution.

$[^{18}F]F_2$ was produced by the $^{20}Ne(p,Spall)^{18}F$ reaction with a target gas mixture of 0.1% F_2 in natural neon that was irradiated with 500 MeV protons from the TRIUMF cyclotron.[16]

Gaseous $CH_3COO^{18}F$ was prepared by venting the $[^{18}F]F_2$ produced after target irradiation through the solid CH_3COOK/CH_3COOH column[17] that was described earlier.

5.4.3 Preparation of Vinyl-Tin Substrates

General procedures for hydrostannylation of acetylenic compounds.

Procedure A: Under an N_2 atmosphere, a solution of acetylenic compound in 1,4-dioxane was prepared. To this stirred solution, five equivalents of tri-*n*-butyltin hydride was added by syringe, then the mixture was refluxed overnight. The solvent was removed and the crude mixture was chromatographed on a silica gel column to obtain

the stannylated product.

Procedure B: Under an N_2 atmosphere, a mixture of acetylenic compound, a catalytic amount of AIBN, and two equivalents of tri-*n*-butyltin hydride were combined, and the stirred mixture was heated overnight (thermostated silicone oil bath, 95°C). After cooling, the entire reaction mixture was chromatographed on a silica gel column to isolate the stannylated product.

General: In all cases, the vinyl-tin products after chromatographic isolation were thoroughly dried under high vacuum, then stored in vacuo over sodium hydroxide pellets. Vinyl-tin compounds are sufficiently air-stable so that they can be easily handled in the open under normal conditions, however, prolonged exposure to the atmosphere will result in gradual decomposition. Proper storage, therefore, is very important.

Preparation of 17α-(*E*)-tributylstannylvinyl-1,3,5(10)-estratriene-3,17β-diol 30 and 17α-vinyl-1,3,5(10)-estratriene-3,17β-diol 35.

Method A: Compound **23** (1986 mg, 6.70 mmol) in 1,4-dioxane (10 mL) was hydrostannylated as described in procedure A. Flash chromatography of the crude mixture was performed on silica gel (3.5 cm × 15 cm) with dichloromethane/hexanes/diethyl ether (6:2:1). The first fraction contained **30** as the dominant product plus two unidentified byproducts, while further elution isolated a mixture of **23** and **35** (1090 mg) in a ratio of 29:71 as determined by ^{1}H NMR. Therefore, 774 mg of **35** was estimated to be present in the second fraction for a yield of 38%. The first fraction was further purified by column chromatography on silica gel (150 mg) with dichloromethane/

hexanes /ether (6:4:1) which afforded 780 mg of **30** (20% overall isolated yield) as a very viscous syrup, and upon drying overnight in vacuo, crystallized as an off-white solid. An analytical sample was obtained by flash chromatography on silica gel with dichloromethane/hexanes/ether (6:4:1), mp 86-87.5°C, $[\alpha]_D^{24}$ +19.0° (*c* 1.7, 1,4-dioxane). Anal. calcd. for $C_{32}H_{52}O_2Sn$: C 65.43, H 8.92; found: C 65.60, H 8.78. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.81-0.97 (m, 18H, 18-C*H*$_3$ and Sn(C*H*$_2$CH$_2$CH$_2$C*H*$_3$)$_3$), 1.20-2.37 (several m, 26H, 17-O*H*, Sn(CH$_2$C*H*$_2$C*H*$_2$CH$_3$)$_3$, C*H* and C*H*$_2$ of steroid nucleus), 2.80 (m, 2H, C*H*$_2$ of steroid nucleus), 5.30 (s, 1H, 3-O*H*), 6.07 (d, $J_{20,21}$ = 19.4 Hz, $^2J_{Sn,H}$ = 70 Hz, 1H, H-21), 6.20 (d, $^3J_{Sn,H}$ = 66 Hz, 1H, H-20), 6.57 (d, $J_{2,4}$ = 2.9 Hz, 1H, H-4), 6.62 (dd, $J_{1,2}$ = 8.8 Hz, 1H, H-2), 7.13 (d, 1H, H-1). Mass spectrum, *m/z*: 531 (^{120}Sn: M^+-C_4H_9, 100).

In an attempt to separate **35** from **23** for characterization, column chromatography of a portion of the mixture of **23** and **35** was performed on silica gel with dichloromethane/ hexanes/ether (6:4:1). Unfortunately, complete separation was not achieved as **23** co-eluted with all fractions containing **35**, with the largest percentage of **23** being present in the early fractions. Therefore, a sample was obtained by combining several of the late fractions that contained the lowest percentage of **23**. This sample was recrystallized from benzene/hexanes, then analyzed by HPLC (column C; eluent: methanol/water, 3:1; flow rate, 6.0 mL/min; UV detection, 280 nm) and found that a ratio of **23** (R_T=3.6 min) to **35** (R_T=5.0 min) of 19:81 was present. As a result, to effectively isolate **35** an HPLC separation was carried out by injecting this sample (dissolved in THF) in several portions onto column C and eluting **35** using the same conditions (flow rate was changed to 3.0 mL/min) employed for HPLC analysis. The peaks corresponding to **35** were collected,

but due to a minute amount of **23** still present, the isolated material was subjected to additional HPLC purification. The material obtained from the second HPLC purification was recrystallized from benzene/hexanes, which afforded **35** as white crystals, mp 169.5-170°C, $[\alpha]_D^{25}$ +58.5° (*c* 1, 1,4-dioxane). Anal. calcd. for $C_{20}H_{26}O_2$: C 80.50, H 8.78; found: C 80.54, H 8.72. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.95 (s, 3H, 18-C*H*$_3$), 1.24-2.37 (several m, 14H, 17-O*H*, C*H* and C*H*$_2$ of steroid nucleus), 2.80 (m, 2H, C*H*$_2$ of steroid nucleus), 4.68 (br s, 1H, 3-O*H*), 5.15 (dd, $J_{20,21a}$ = 10.8 Hz, $J_{21a,21b}$ = 1.2 Hz, 1H, H-21a), 5.20 (dd, $J_{20,21b}$ = 17.3 Hz, 1H, H-21b), 6.11 (dd, 1H, H-20), 6.56 (d, $J_{2,4}$ = 2.8 Hz, 1H, H-4), 6.62 (dd, $J_{1,2}$ = 8.2 Hz, 1H, H-2), 7.14 (d, 1H, H-1). Mass spectrum, *m/z*: 298 (M^+, 51), 280 (M^+-H_2O, 15). Exact mass calcd. for $C_{20}H_{26}O_2$: 298.1934; found: 298.1934.

Method B: Compound **23** (1.00 g, 3.37 mmol) was hydrostannylated as described in procedure B. Column chromatography on silica gel (100 g) with dichloromethane/ hexanes/diethyl ether (6:4:1) afforded in one portion 1.17 g (59%) of **30**. Physical and spectral (^{1}H NMR) properties of this material were identical with those reported earlier. TLC analysis of the reaction mixture confirmed the presence of **35**, but the compound was not eluted off the column.

Preparation of 3-methoxy-17α-(*E*)-tributylstannylvinyl-1,3,5(10)-estratriene-17β-ol 31.

Compound **24** (492 mg, 1.59 mmol) was hydrostannylated as described in procedure B. Column chromatography on silica gel (100 g) with hexanes/diethyl ether (5:1) yielded in the first fraction 114 mg of crude 3-methoxy-17α-(*Z*)-tributylstannylvinyl-1,3,5(10)-

estratriene-17β-ol **36**, and in the following two fractions, 860 mg of **31**. Compound **31** was isolated as a colourless oil in 90% yield, $[\alpha]_D^{24}$ +17.1° (*c* 1.2, 1,4-dioxane). Anal. calcd. for $C_{33}H_{54}O_2Sn$: C 65.90, H 9.05, O 5.32; found: C 65.83, H 9.00, O 5.28. Mass spectrum, *m/z*: 602 (^{120}Sn: M^+, 0.2), 545 (^{120}Sn: M^+-C_4H_9, 100).

Preparation of 3,17β-dimethoxy-17α-(*E*)-tributylstannylvinyl-1,3,5(10)-estratriene 32.

Compound **25** (1.00 g, 3.08 mmol) was hydrostannylated as described in procedure B. Column chromatography on silica gel (200 g) with hexanes/diethyl ether (20:1) yielded in the first fraction 0.23 g of **32** plus a minute amount of unidentified byproduct, and in the second fraction 1.56 g of pure **32**. Compound **32** was isolated in an overall yield of 94% as an oil, and after drying in vacuo for 15-30 minutes, crystallized as a white solid. The material from the second fraction exhibited mp 50-52.5°C, $[\alpha]_D^{24}$ +44.1° (*c* 1.2, $CHCl_3$). Anal. calcd. for $C_{34}H_{56}O_2Sn$: C 66.35, H 9.17, O 5.20; found: C 66.37, H 9.18, O 5.35. ^{1}H NMR (270 MHz, C_6D_6) δ: 0.93 (t, J = 7.3 Hz, 9H, $Sn(CH_2CH_2CH_2CH_3)_3$), 1.01 (m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$), 1.12 (s, 3H, 18-CH_3), 1.21-2.29 (several m, 25H, $Sn(CH_2CH_2CH_2CH_3)_3$, CH and CH_2 of steroid nucleus), 2.63-2.86 (m, 2H, CH_2 of steroid nucleus), 3.23 (s, 3H, 17-OCH_3), 3.39 (s, 3H, 3-OCH_3), 6.23 (d, $J_{20,21}$ = 19.7 Hz, $^2J_{Sn,H}$ = 75 Hz, 1H, H-21), 6.37 (d, $^3J_{Sn,H}$ = 69 Hz, 1H, H-20), 6.68 (d, $J_{2,4}$ = 2.6 Hz, 1H, H-4), 6.75 (dd, $J_{1,2}$ = 8.6 Hz, 1H, H-2), ~7.16 (d, 1H, H-1). Mass spectrum, *m/z*: 616 (^{120}Sn: M^+, 1), 601 (^{120}Sn: M^+-CH_3, 5), 559 (^{120}Sn: M^+-C_4H_9, 66).

Preparation of (*E*)-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-*C*-tributylstannyl-D-*glycero*-α-D-*galacto*-oct-7-enopyranose 33.

Compound **28** (884 mg, 3.11 mmol) was hydrostannylated as described in procedure B. Column chromatography on silica gel (200 g) with dichloromethane/hexanes/diethyl ether (6:6:1) afforded in one fraction 1093 mg (61%) of **33**. Compound **33** was isolated as a colourless syrup, $[\alpha]_D^{23}$ -36.1° (*c* 1, $CHCl_3$). Anal. calcd. for $C_{26}H_{48}O_6Sn$: C 54.28, H 8.41; found: C 54.21, H 8.52. ^1H NMR (270 MHz, $CDCl_3$) δ: 0.81-0.97 (m, 15H, $Sn(CH_2CH_2CH_2CH_3)_3$), 1.21-1.55 (2 m, 24H, 2 × $C(CH_3)_2$ and $Sn(CH_2CH_2CH_2CH_3)_3$), 2.81 (d, $J_{6,OH}$ = 7.0 Hz, 1H, 6-O*H*), 3.68 (dd, $J_{5,6}$ = 6.5 Hz, $J_{4,5}$ = 1.7 Hz, 1H, H-5), 4.32 (dd, $J_{1,2}$ = 5.0 Hz, $J_{2,3}$ = 2.3 Hz, 1H, H-2), 4.34 (m, $J_{6,7}$ = 4.4 Hz, $J_{6,8}$ = 1.4 Hz, 1H, H-6), 4.45 (dd, $J_{3,4}$ = 8.0 Hz, 1H, H-4), 4.61 (dd, 1H, H-3), 5.59 (d, 1H, H-1), 6.18 (dd, $J_{7,8}$ = 19.2 Hz, $^3J_{Sn,H}$ = 64 Hz, 1H, H-7), 6.38 (dd, $^2J_{Sn,H}$ = 70 Hz, 1H, H-8). Mass spectrum, *m/z*: 561 (^{120}Sn: M^+-CH_3, 3), 519 (^{120}Sn: M^+-C_4H_9, 100).

Preparation of (*E*)-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-*C*-tributylstannyl-L-*glycero*-α-D-*galacto*-oct-7-enopyranose 34.

Compound **29** (898 mg, 3.16 mmol) was hydrostannylated as described in procedure B except that after 19 hours of heating, 0.50 mL of tri-*n*-butyltin hydride (0.54 g, 1.86 mmol) was added and heating was continued for another three hours. Column chromatography on silica gel (200 g) with hexanes/diethyl ether (4:1) yielded in the first fraction 444 mg of a mixture of (*Z*)-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-*C*-tributylstannyl-L-*glycero*-α-D-*galacto*-oct-7-enopyranose **37** and 7,8-dideoxy-1,2:3,4-di-*O*-

isopropylidene-7-*C*-tributylstannyl-L-*glycero*-α-D-*galacto*-oct-7-enopyranose **38** in a ratio of 3:2 as determined by ^{1}H NMR. As a result, 266 mg of **37** and 178 mg of **38** was estimated to be present in the mixture, for chemical yields of 15% and 10%, respectively.

Further elution afforded 1076 mg of **34** in a second fraction, for a 59% yield. Compound **34** was isolated as a colourless syrup, $[\alpha]_D^{24}$ -37.0° (*c* 1.3, $CHCl_3$). Anal. calcd. for $C_{26}H_{48}O_6Sn$: C 54.28, H 8.41, O 16.68; found: C 54.57, H 8.47, O 16.55. Mass spectrum, *m/z*: 561 (^{120}Sn: M^+-CH_3, 2), 519 (^{120}Sn: M^+-C_4H_9, 100).

5.4.4 Fluorination Reactions of Vinyl-Tin Compounds

Fluorination of vinyl-tin substrates with elemental F_2 or gaseous CH_3COOF.

General Procedure: A solution of vinyl-tin compound (60-200 μmol) was prepared (different solvents were employed) and placed in a glass reaction vessel (oven dried) under inert atmosphere. A stream of inert gas was passed through the vinyl-tin solution via a 1/16 in. o.d. Teflon tube, positioned at the bottom of the solution, which was controlled by the fluorine gas handling system (see Figure 5.1). To conduct fluorinations at 0 or -78°C, the vinyl-tin solution was cooled with either an ice/water (0°C) bath or a CO_2/2-propanol (-78°C) cooling bath.

The desired quantity of 1% F_2/Ne gas mixture (60-230 μmol F_2) was loaded into either the CP-42 or 500 MeV gas target using the fluorine gas handling system, and then pure Ne was added to dilute the F_2 concentration to approximately 0.1% in Ne. To perform fluorinations with F_2, the diluted F_2/Ne gas mixture was then added directly to the vinyl-tin solution after the inert gas flow was turned off. However, to perform

fluorinations with gaseous CH_3COOF, the diluted F_2/Ne gas mixture was instead passed through a solid CH_3COOK/CH_3COOH column and the effluent added to the vinyl-tin solution. Both fluorinating agents (F_2 or CH_3COOF) were added at a flow rate of ~50 mL/min to the vinyl-tin solution. After the addition of fluorinating agent was completed, the reaction mixture was transferred to a round-bottom flask and the solvent was removed in vacuo. The residue was analyzed by TLC, then worked up as considered appropriate.

Preparation of 3-methoxy-17α-(*E*)-fluorovinyl-1,3,5(10)-estratriene-17β-ol 39 and 3-methoxy-17α-(*Z*)-fluorovinyl-1,3,5(10)-estratriene-17β-ol 40.

Compound **31** (92.7 mg, 154 μmol) was dissolved in $CFCl_3$ (20 mL) and added to a glass reaction vessel (2.0 cm o.d. × 10 cm length). This solution was treated with approximately 1.3 equivalents of CH_3COOF, at room temperature, as described in the general procedure. Five additional fluorinations of compound **31** were conducted in the same manner, employing a total of 554.6 mg of **31** (922 μmol).

The reaction mixtures obtained were combined, then subjected to column chromatography on silica gel (100 g) with hexanes/diethyl ether (4:1) as the eluent. The first fraction (55 mg) collected contained **39** in 96% purity as indicated by HPLC analysis (column D; eluent: solvent D; flow rate, 3.5 mL/min; UV detection, 280 nm). With continued elution, a second fraction (66 mg) was obtained which contained a mixture of **39** (R_T=17.8 min) and **40** (R_T=26.2 min) in a ratio of 79:21 by HPLC analysis. Both of the isolated chromatography fractions were subjected to further purification via HPLC.

Each fraction was dissolved in a minimum of ether, and then was injected in several portions onto the HPLC silica gel column and eluted using the same conditions employed for HPLC analysis. The peaks corresponding to **39** and **40** were collected, whereby all of **39** was isolated in one batch (90.0 mg) and all of **40** was isolated in another batch (11.5 mg). The isolated yields of **39** and **40** were 29.5% and 3.8%, respectively.

Quantification of yields for the reaction of 31 with gaseous CH_3COOF.

Compound **31** (76.4 mg, 127 μmol) was dissolved in $CFCl_3$ (20 mL) and added to a glass reaction vessel (2.0 cm o.d. $\times$ 10 cm length). This solution was treated with approximately 1.3 equivalents of CH_3COOF, at room temperature, as described in the general procedure. After solvent removal, the residue was dissolved in a known volume of $CHCl_3$. The product mixture was analyzed by HPLC (column C; solvent program A; flow rate, 6.0 mL/min; UV detection, 280 nm) using a standard solution of **39** as an external standard. It was determined that 17.0 mg of **39** and **40** (both co-elute, R_T=5.0 min) was present, for a yield of 41% based on the amount of **31** used.

Additional fluorination trials were conducted using alternative reaction solvents. Compound **31** (74.1 mg, 123 μmol) was dissolved in dried CH_3OH (20 mL) and treated with approximately 1.3 equivalents of CH_3COOF as described above. It was determined by HPLC analysis that 5.59 mg of **39** and **40** was obtained, for a yield of 14%.

Compound **31** (80.7 mg, 134 μmol) was dissolved in dried CH_3CN (20 mL), which required about 0.5 mL of $CHCl_3$ to help solubilize **31**, and was treated with

approximately 1.2 equivalents of CH_3COOF as described above. It was determined by HPLC analysis that 10.4 mg of **39** and **40** was obtained, for a yield of 24%.

Compound **31** (71 mg, 118 μmol) was dissolved in dried THF (20 mL) and treated with approximately 1.4 equivalents of CH_3COOF as described above. It was determined by HPLC analysis that 3.62 mg of **39** and **40** was obtained, for a yield of 9.3%.

Quantification of yields for the reaction of 31 with elemental F_2.

Compound **31** (103.2 mg, 172 μmol) was dissolved in $CFCl_3$ (20 mL) and added to a glass reaction vessel (2.0 cm o.d. $\times$ 10 cm length). This solution was treated with approximately 1.25 equivalents of F_2, at room temperature, as described in the general procedure. After solvent removal, the residue was dissolved in a known volume of $CHCl_3$. The product mixture was analyzed by HPLC (column C; solvent program A; flow rate, 6.0 mL/min; UV detection, 280 nm) using a standard solution of **39** as an external standard. It was determined that 5.10 mg of **39** and **40** (both co-elute, R_T=4.97 min) was present, for a yield of 9.0% based on the amount of **31** used. In addition, two side-products that were present in significant amounts were identified as 3-methoxy-17α-ethynyl-1,3,5(10)-estratriene-17β-ol **24** (R_T=4.39 min) and 3-methoxy-17α-vinyl-1,3,5(10)-estratriene-17β-ol **41** (R_T=5.70 min). Standard solutions of **24** and **41** were prepared for use as external standards. HPLC analysis indicated that 2.89 mg of **24** and 3.85 mg of **41** were present, for yields of 5.4% and 7.2%, respectively.

An additional fluorination experiment was done using 95.9 mg (159 μmol) of **31** in $CFCl_3$ (20 mL), which was treated with approximately 1.35 equivalents of F_2 at -78°C,

as described above. It was determined by HPLC analysis that 2.23 mg of **39** and **40** was obtained, for a yield of 4.2%. Furthermore, the side-products **24** and **41** were obtained in 2.2% (1.11 mg) and 14.5% (7.23 mg) yields, respectively.

Preparation of (*E*)-8-*C*-fluoro-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-enopyranose 47 and (*Z*)-8-*C*-fluoro-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-enopyranose 48.

Compound **34** (83.6 mg, 145 μmol) was dissolved in $CFCl_3$ (20 mL) and added to a glass reaction vessel (2.0 cm o.d. × 10 cm length). This solution was treated with approximately 1.3 equivalents of CH_3COOF, at room temperature, as described in the general procedure. A second fluorination of compound **34** (80.9 mg, 141 μmol) was performed as outlined above. The reaction mixtures obtained were combined, then subjected to column chromatography on silica gel (60 g) with dichloromethane/hexanes/diethyl ether (6:2:1) as the eluent.

The first fraction (29.5 mg) collected contained **47** in ~98% purity as indicated by ^{1}H NMR. The second fraction (4.0 mg) contained a mixture of **47**, **48**, and 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-enopyranose **49** in a ratio of 43:36:21 as determined by ^{1}H NMR. The third fraction (9.0 mg) contained a mixture of **47**, **48**, and **49** in a ratio of 6:83:11. The final fraction (5.4 mg) contained a single compound that was identified as (*E*)-8-*C*-acetoxy-7-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-enopyranose **50**.

The chemical yield of **47**, as contained in the first three chromatography fractions, was

determined to be 36% (32 mg). The yield of **48**, as contained in the second and third fractions, was determined to be 10% (9 mg).

A larger scale synthesis of **47** and **48** was carried out as follows. Compound **34** (81.9 mg, 142 μmol) was dissolved in $CFCl_3$ (20 mL) and added to a glass reaction vessel (2.0 cm o.d. $\times$ 10 cm length). This solution was treated with approximately 1.35 equivalents of CH_3COOF, at room temperature, as described in the general procedure. Three additional fluorinations of compound **34** were performed in the same manner, employing a total of 326.5 mg of **34** (567 μmol). The reaction mixtures were combined, then subjected to column chromatography on silica gel (140 g) with dichloromethane/hexanes /diethyl ether (6:2:1) as the eluent.

5.4.5 Radiofluorinations with Acetyl [^{18}F]Hypofluorite

General procedure for radiofluorination with gaseous $CH_3COO^{18}F$.

A solution of vinyl-tin compound (110-120 μmol) in $CFCl_3$ (20 mL) was prepared in a glass reaction vessel (2.0 cm o.d. $\times$ 12.5 cm length) under inert atmosphere. The 500 MeV gas target was filled with 4 or 6 psi (0.27 or 0.41 atm) of 1% F_2/Ne gas mixture, then pure Ne was added until 100 psi (6.8 atm) was reached. For a typical ^{18}F production run, the target gas mixture was irradiated for 10 minutes at 69 μA. When the irradiation of the target gas was stopped, this time was noted and designated as the *end of bombardment* (EOB). After irradiation, the radioactive gas mixture was passed through a solid CH_3COOK/CH_3COOH column and into the reaction vessel at a flow rate of ~50 mL/min. With the addition of $CH_3COO^{18}F$ completed, the reaction mixture

was transferred to a round-bottom flask, then assayed for radioactivity. The CH_3COOK/ CH_3COOH column was also assayed for activity. The reaction mixture was evaporated to dryness in vacuo and reassayed for activity, then dissolved in a small amount of $CHCl_3$. An aliquot of this mixture was subjected to radio-HPLC purification and the peak corresponding to the ^{18}F-labelled product was collected, then counted to determine the percentage of product present in the reaction mixture. The decay corrected radiochemical yield was calculated by dividing the total activity due to product (in the reaction mixture) with the total activity of ^{18}F produced in the cyclotron target at EOB.

Reaction of 31 with $CH_3COO^{18}F$ at room temperature.

Compound **31** (72.1 mg, 120 μmol) was radiofluorinated using approximately 0.74 equivalents of $CH_3COO^{18}F$ (produced with 6 psi of 1%F_2/Ne), at room temperature, as described in the general procedure. HPLC analysis (column C; solvent program A; flow rate, 6.0 mL/min; UV detection, 254 nm) of the reaction mixture determined that 3.68 mCi (decay corrected to EOB) of 3-methoxy-17α-(*E*)-[^{18}F]fluorovinyl-1,3,5(10)-estratriene-17β-ol **51** and 3-methoxy-17α-(*Z*)-[^{18}F]fluorovinyl-1,3,5(10)-estratriene-17β-ol **52** (both co-elute, R_T=5.5 min) was produced for a radiochemical yield of 19%.

An additional radiofluorination trial was conducted using a greater excess of vinyl-tin **31**. Compound **31** (71.0 mg, 118 μmol) was radiofluorinated using approximately 0.5 equivalents of $CH_3COO^{18}F$ (produced with 4 psi of 1% F_2/Ne), at room temperature, as described in the general procedure. HPLC analysis (column C; solvent program B; flow rate, 6.0 mL/min; UV detection, 254 nm) of the reaction mixture determined that

3.79 mCi (decay corrected to EOB) of **51** and **52** (both co-elute, R_T=11.0 min) was produced for a radiochemical yield of 19%.

Reaction of 31 with $CH_3COO^{18}F$ at -78°C.

Compound **31** (69.0 mg, 115 μmol) was radiofluorinated using approximately 0.77 equivalents of $CH_3COO^{18}F$ (produced with 6 psi of 1% F_2/Ne), at -78°C, as described in the general procedure. HPLC analysis (column C; solvent program A; flow rate, 6.0 mL/min; UV detection, 254 nm) of the reaction mixture determined that 1.72 mCi (decay corrected to EOB) of **51** and **52** (both co-elute, R_T=5.4 min) was produced for a radiochemical yield of 9.7%.

An additional radiofluorination trial was conducted using a greater excess of vinyl-tin **31**. Compound **31** (71.7 mg, 119 μmol) was radiofluorinated using approximately 0.5 equivalents of $CH_3COO^{18}F$ (produced with 4 psi of 1% F_2/Ne), at -78°C, as described in the general procedure. HPLC analysis (column C; solvent program B; flow rate, 6.0 mL/min; UV detection, 254 nm) of the reaction mixture determined that 1.65 mCi (decay corrected to EOB) of **51** and **52** (both co-elute, R_T=10.7 min) was produced for a radiochemical yield of 5.0%.

References

1. Gordon, A. J.; Ford, R. A. *The Chemist's Companion: A Handbook of Practical Data, Techniques and References*; Wiley Interscience: New York, 1972; p 439.

2. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

3. Shriver, D. F.; Drezdzon, M. A. *The Manipulation of Air-sensitive Compounds*, 2nd ed.; Wiley Interscience: Toronto, 1986.

4. Adam, M. J.; Grierson, J. R.; Ruth, T. J.; Pedersen, K.; Pate, P. D. *J. Nucl. Med.* **1987**, *28*, 1599-1603.

5. Bunnet, J. F.; Hermann, H. *J. Org. Chem.* **1971**, *36*, 4081-4088.

6. Mahaffy, C. A. L.; Pauson, P. L. *Inorg. Synth.* **1979**, *19*, 154-158.

7. Ofele, K. *Chem. Ber.* **1966**, *99*, 1732-1736.

8. Mahaffy, C. A. L. *J. Organomet. Chem.* **1984**, *262*, 33-37.

9. Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169-2173.

10. Arrick, R. E.; Baker, D. C.; Horton, D. *Carbohydr. Res.* **1973**, *26*, 441-447.

11. Garegg, P. J.; Samuelsson, B. *Carbohydr. Res.* **1978**, *67*, 267-270.

12. Hems, R.; Horton, D.; Nakadate, M. *Carbohydr. Res.* **1972**, *25*, 205-216.

13. Hudlický, M. *Chemistry of Organic Fluorine Compounds: A Laboratory Manual with Comprehensive Literature Coverage*, 2nd ed.; John Wiley and Sons: New York, 1976; pp 13-14.

14. *Matheson Gas Data Book*, 5th ed.; Matheson Gas Prducts: East Rutherford, NJ, 1971; pp 261-265.

15. Ruth, T. J. *Int. J. Appl. Radiat. Isot.* **1985**, *36*, 107-110.

16. Ruth, T. J.; Adam, M. J.; Burgenjon, J. J.; Lenz, J.; Pate, B. D. *Int. J. Appl. Radiat. Isot.* **1985**, *36*, 931-933.

17. Jewett, D. M.; Potocki, J. F.; Ehrenkaufer, R. E. *J. Fluorine Chem.* **1984**, *24*, 477-484.

18. Skoog, D. A.; West, D. M. *Fundamentals of Analytical Chemistry*; Holt, Rhinehart and Winston: New York, 1965; pp 462 and 485-490.

19. Casella, V.; Ido, T.; Wolf, A. P.; Fowler, J. S.; MacGregor, R. R.; Ruth, T. J. *J. Nucl. Med.* **1980**, *21*, 750-757.