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THE SYNTHESIS OF RADIOLABELED COMPOUNDS VIA ORGANOMETALLIC INTERMEDIATES

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INTRODUCTION

Isotopically labeled compounds have played an important role in chemistry, biology and medicine since Hevesey pioneered their use as tracers.[1] Both stable[2] and radioactive[3] isotopes were utilized in early investigations but the situation changed dramatically with the discovery of the cyclotron by Lawrence in 1930 and the construction of the nuclear reactor by Fermi in 1942. These pioneering advances made significant quantities of radioisotopes available to the research community and experimentation progressed rapidly from chemistry to medicine.[4,5] In recent years, the development of new routes to radiolabeled agents has become important due to the availability of relatively inexpensive cyclotrons which are capable of producing a selection of useful isotopes. For example, these cyclotrons make it possible to routinely generate short-lived radionuclides such as ^{11}C and ^{13}N with half-lives of 20 min and 10 min, respectively. These short half-lives increase the constraints

within which the synthetic organic chemist must operate while designing and implementing synthetic strategies.

Advances in radiation detection techniques have also increased the medical uses of radioisotopes.[6] The development of single-photon emission computerized tomography (SPECT)[7] and positron emission tomography (PET)[8] has revolutionized diagnostic medical imaging. These computerized systems permit noninvasive, *in-vivo*, three-dimensional imaging of internal organs after administration of appropriate agents labeled with short-lived nuclides.[9] The techniques are used for *in-vivo* pharmokinetics, organ imaging, evaluation of organ function, and physiological mapping.

The development of new approaches to labeling molecules with radionuclides via organometallic intermediates is the focus of this article. Several reviews are available which emphasize the pharmaceutical aspects of radiolabeled compounds.[10–15] Radiohalogenations of proteins,[16–23] nucleic acids[20] and cell surfaces[23] have also been reviewed. These areas are referred to in this article only when organometallic intermediates are involved.

Tracer molecules for investigating biochemical processes occurring in living organisms have traditionally been labeled with ^{14}C and tritium because of their long half-lives and because they can be substituted for stable carbon and hydrogen in organic molecules without changing biological properties. Currently, short-lived nuclides such as ^{11}C, ^{13}N and ^{15}O are also being used to label organic molecules. Although radioisotopes of iodine have been the traditional choices for preparing analogs of naturally occurring biomolecules, ^{18}F has recently become popular in medical applications because fluorine forms stable carbon–fluorine bonds and the fluorine atom is nearly isosteric with hydrogen. Some of the more commonly used radioisotopes are listed in the Table I along with information on their half-life and mode of decay.

The use of organometallic reagents for incorporating radionuclides has not been extensively developed because their reactivity often precludes their use in the synthesis of molecules containing

Table I

Properties of Some Important Isotopes

Nuclide	Half-Life[a]	Decay Mode[b]
Tritium	12.35 y	β^-
Carbon-11	0.34 h	β^+
Carbon-14	5730 y	β^-
Nitrogen-13	0.16 h	β^+
Oxygen-15	0.03 h	β^+
Fluorine-18	1.83 h	β^+, EC
Bromine-75	1.62 h	β^+, EC
Bromine-76	16.2 h	β^+, EC
Bromine-77	2.38 d	EC
Bromine-82	35.3 h	β^-
Iodine-123	13.2 h	EC
Iodine-125	60.14 d	EC
Iodine-131	8.03 d	β^-

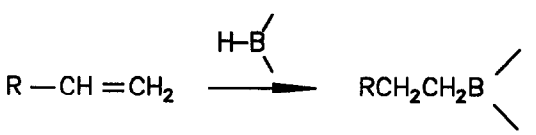
[a]Times are: year = y; day = d, hour = h; [b]Decays are: β = beta; β^+ = positron; EC = electron capture.

reactive functional groups.[25] This is a serious limitation since the most efficient isotope incorporation reactions are designed so that the radionuclide is introduced late in the synthetic sequence to maximize the radiochemical yield. (Radioisotopes are generally very expensive.)

In the following sections, successful organometallic sequences are characterized according to the metal or metalloid involved. The radioisotopes utilized are summarized in subsections. In general, radiohalogens are the most widely used radioisotopes because of their ready availability.[26-29] The current popularity of ^{18}F is based on the fact that the stability of the alkyl halide, *in vivo*, follows the order RI > RBr > RCl > RF. The ideal radionuclides from a medical and biological point of view are the short-lived isotopes of carbon, nitrogen, and oxygen. Until the recent development of small relatively inexpensive cyclotrons, these agents were not widely available. Consequently, few synthetic methodologies exist but, by analogy to reactions involving their stable and long-lived counterparts, future development should be rapid.

BORANES

In spite of the demonstrated versatility of the organoboranes in organic synthesis,[30] boranes were virtually ignored as potential precursors to radiolabeled compounds. With the exception of hydrogen isotopes, the first report of the use of organoboranes in the synthesis of labeled compounds appeared in 1978.[31] The development of organoborane-isotope incorporation methodology has been rapid since the initial report. The early studies demonstrated an important aspect of the organoboranes: they could be prepared from molecules containing a wide variety of functional groups.[32a] (This is important since functionality is generally responsible for physiological activity.) Under the proper conditions, functionally substituted organoboranes are obtained via the simple addition of a suitable boron hydride reagent to an appropriately substituted alkene. More importantly, the early research demonstrated that a

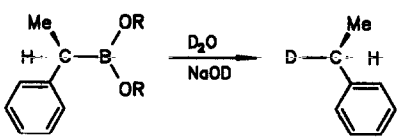


(where R can contain: $-NO_2$, $-CN$, $-CO_2H$, $-CO_2R$, $-X$ etc.)

variety of elements would replace boron under appropriate reaction conditions, and these elements possess radioactive isotopes that are of interest in current radiopharmaceutical research.[32b]

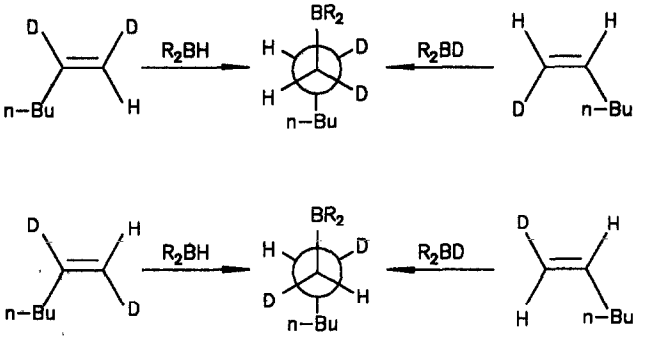
Hydrogen isotopes

As noted, hydrogen isotopes had been utilized in early borane research. Reports of deuterium[33] and tritium-labeled[34] boranes began to appear shortly after the first convenient preparation of diborane was reported by Schlesinger and Brown.[35] The early studies focused on the mechanism of the hydrolysis,[36] oxidation,[37] and substitution reactions[38] of boranes rather than on the synthesis of labeled organic molecules. If labeled compounds were synthesized, they were generally by-products. For example, Davies *et al.* synthesized optically active α-deuteroethylbenzene to demonstrate that the basic hydrolysis of alkylboronic acids proceeds with inversion of configuration at carbon.[39]



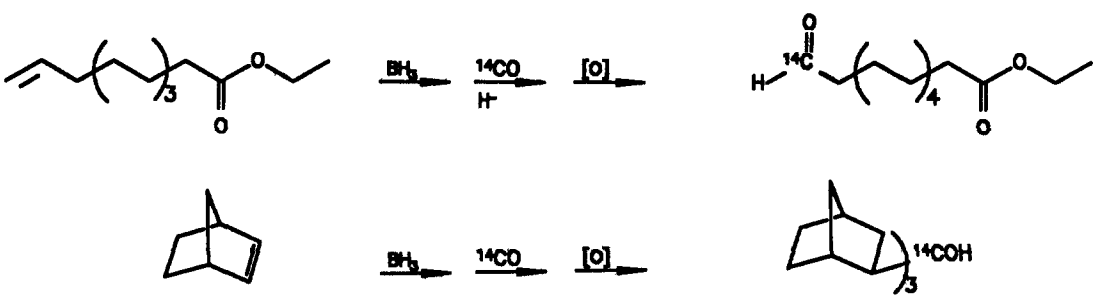
Deuterated boranes have also been used to elucidate the regiochemistry and stereochemistry of

a variety of organoborane transformations including the regiochemistry of the hydroboration–protonolysis sequence[40,41] and the hydroboration–oxidation sequence;[42] and the stereochemistry of the hydroboration reaction itself.[43] Deuteroboration has also been utilized to confirm the stereo- and regiochemistry of the hydroboration of alkynes[44] and the reduction of carbonyl compounds.[45-47] The deuteration studies are important because they clearly delineate the stereochemistry and regiochemistry to be expected from the corresponding tritiation reactions. The availability of stereodefined tritiated agents can have a significant impact in biochemical research.

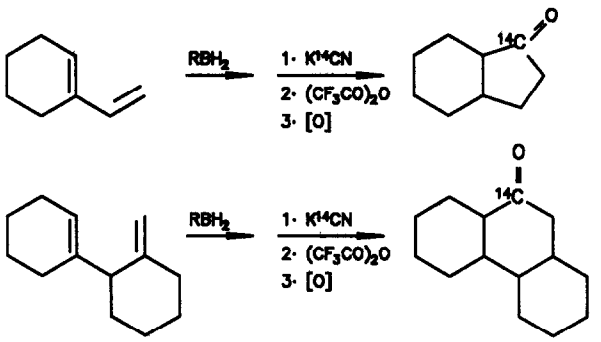


Carbon isotopes

Isotopes of carbon have played a significant role in chemical and medical research studies since Ruben *et al.* first used ^{11}C as a tracer.[48] ^{14}C soon replaced ^{11}C in research due to its significantly longer half-life ($t_{1/2}$ = 5740 years). The ready reaction of organoboranes with simple carbon precursors such as carbon monoxide[49] and cyanide salts[50] make these reactions ideal routes for carbon isotope incorporation. As noted earlier, the first use of organoborane chemistry for the incorporation of isotopic carbon was reported in 1978.[31] The carbonylation reaction has since been used to incorporate ^{14}C,[51] ^{13}C,[52] and ^{11}C.[53]

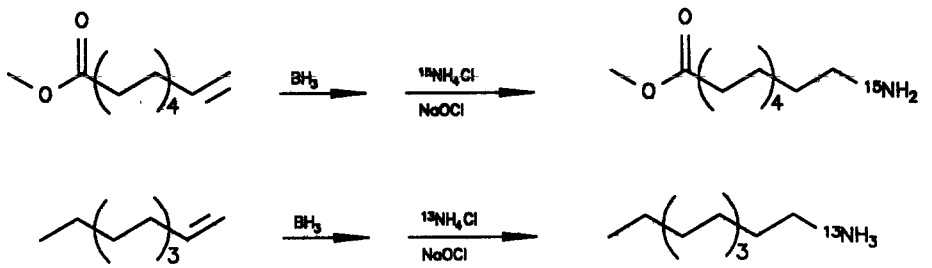


The hydroboration–carbonylation sequence can be accomplished in the presence of a variety of functional groups, which makes it particularly valuable in the radiopharmaceutical area. A further advantage is that the isotope is incorporated into the molecule in the final stages of the synthesis. Unfortunately, only the hydride-induced carbonylation sequence is sufficiently rapid (~15 min) for use in ^{11}C syntheses; the procedure produces terminally labeled aldehydes as well as the corresponding alcohols. The desire to prepare more complex molecules led to the development of the cyanidation procedure as a method for incorporating carbon isotopes. It was found that the cyanidation procedure could be utilized to successfully incorporate ^{14}C,[54] ^{13}C,[55] and ^{11}C.[56] The syntheses of ^{14}C labeled indanone and phenanthrone[54] are part of an extended investigation focused on the syntheses of estradiol and related hormones labeled with short-lived isotopes for use in evaluation of breast tumors.

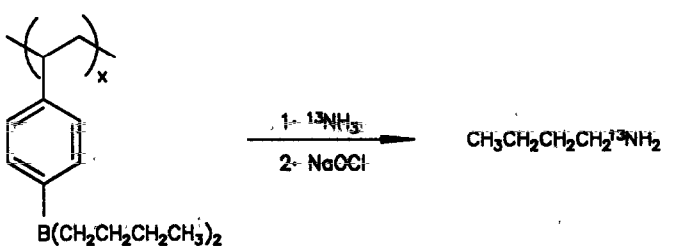


Nitrogen isotopes

The utility of ^{15}N in agricultural chemistry is well documented but the recent availability of ^{13}N has lead to development of new isotope incorporation methodology. Organoboranes are known to react with chloramine and hydroxylamine-O-sulfonic acid[57] and this makes them ideal candidates for use in the syntheses of nitrogen labeled compounds. The development of a rapid, one-pot amination sequence which tolerated a wide variety of functional groups was the key to the success

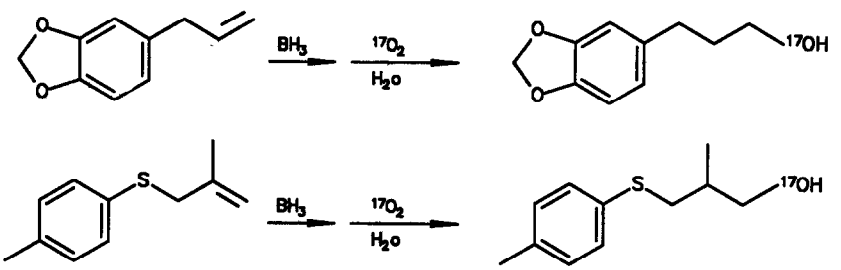


of this approach.[58] The synthesis employs labeled ammonia, one of the most convenient sources of isotopically labeled nitrogen. The sequence has been utilized to prepare ^{15}N[59] and ^{13}N[60] labeled amines. Recent developments include the successful synthesis of a ^{13}N labeled amine using a polymeric organoborane.[61]

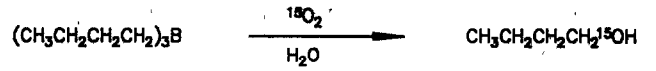


Oxygen isotopes

Organoboranes react readily with a variety of oxidizing agents to produce alcohols, peroxides, acids and various carbonyl compounds. The direct reaction of oxygen with organoboranes, first reported in 1862 and then later developed into a useful synthetic procedure,[62] appeared to be a most promising isotope-incorporation route since all oxygen isotopes are readily available as molecular oxygen. The reaction has been utilized to prepare a number of ^{17}O-labeled alcohols in excellent yields.[63]

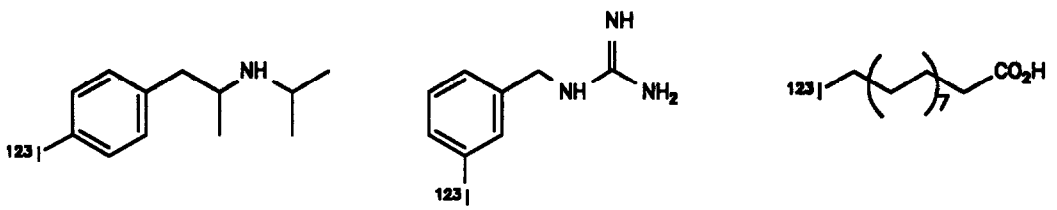


More recently, the direct reaction of ^{15}O-labeled oxygen gas has been utilized to prepare the first ^{15}O-labeled organic compound, ^{15}O-labeled butanol.[64] The synthesis of this material was particularly difficult because ^{15}O has a half-life of only 2.0 min! The value of ^{15}O-labeled butanol lies in the fact that it can be used to measure blood flow employing modern nuclear medicine detection methodology (PET scanning). The need for a rapid synthetic protocol has led to the development of a procedure in which $[^{15}O]$-O_2 is passed over an alkylborane polymer.[65]



Halogen isotopes

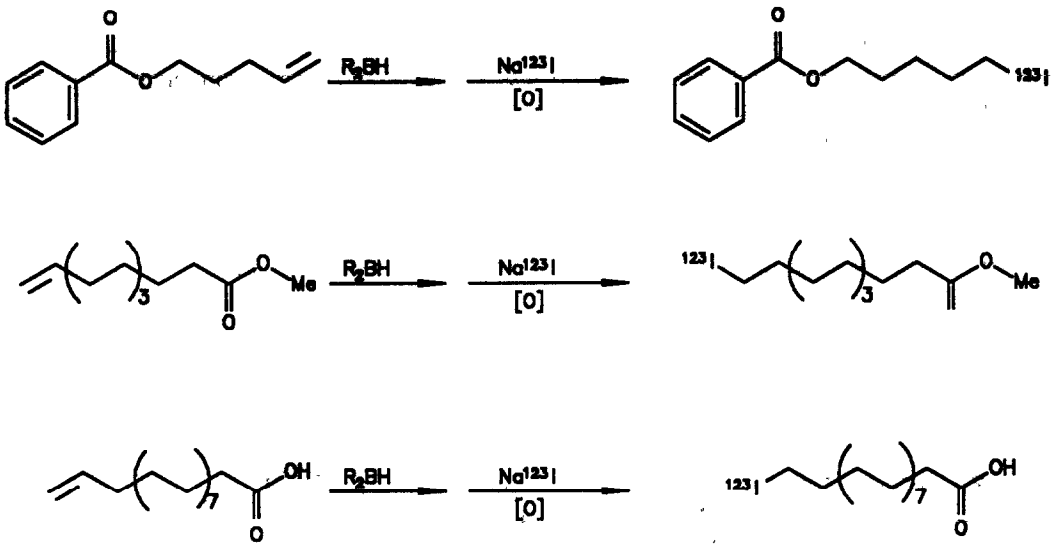
The radiohalogens have a long history in nuclear medicine.[66] Not surprisingly, radioiodination techniques have been extensively developed due to the availability of a variety of useful iodine isotopes. ^{123}I, a single-photon-emitting isotope with a half-life of 13.3 h, has recently become commercially available and is gaining in popularity because of its nearly ideal decay characteristics. A number of ^{123}I-labeled agents such as N-isopropyl-*p*-iodoamphetamine (**1**),[67] *m*-iodobenzylguanidine (**2**)[68] and iodoheptadecanoic acid (**3**)[69] have proven to be quite effective in clinical investigations.



1 2 3

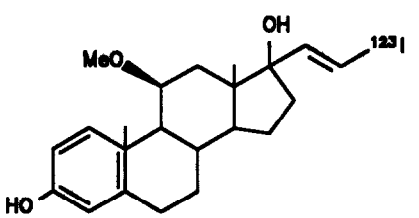
The reaction of organoboranes with molecular iodine in the presence of base was effectively developed by Brown *et al.*[70] The method was not suitable as a radioiodination technique due to the necessity of using sodium methoxide, which could be deleterious to desired functionality, and the requirement for molecular iodine, which is a particularly dangerous and expensive chemical form for iodine radioisotopes (radioiodine is available in the halide form).

The iodination reaction was investigated in an effort to develop a methodology more suitable to radioiodination sequences. It was discovered that the iodination of organoboranes involved the electrophilic attack of iodine on an electron-rich organoborane complex which was significant because it meant that any electrophilic form of iodine could be utilized.[71] A new iodine methodology was developed in which radiolabeled sodium iodide was oxidized *in situ* to an electrophilic species which then reacted with the organoborate complex.[72] The most convenient procedure involves the *in-situ* oxidation of sodium iodide by mild oxidants such as chloramine-T in the presence of an organoborane.[73,74]



A significant aspect of the *in-situ* iodination methodology is that the radioiodinations can be carried out on a 'no-carrier-added' basis.[75] In fact, it has been reported that iodinations can be achieved on TLC plates using atmospheric oxygen as the oxidizing agent![76] No-carrier-added syntheses are important because they ensure that the quantity of labeled agent is kept well below pharmacological dosages during nuclear medicine procedures. Traditional routes to iodine-labeled materials often involve substitution reactions which can lead to dilution of the desired product by non-labeled starting materials.

The radioiodination of vinylboranes has made a significant impact in the radiopharmaceutical arena. Prior to a report in 1982,[77,78] it had been assumed that vinyl halides would be metabolically labile and thus unsuitable for radiopharmaceutical studies. It has since been demonstrated that radioiodinated iodovinyl derivatives have a remarkably long half-life *in vivo* and a number of materials have been developed, including iodovinyl steroids (**4**),[78] fatty acids (**5**) of varying types,[79] barbiturates (**6**)[80] and phosphonium halides (**7**).[81]



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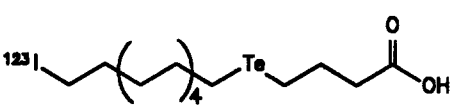

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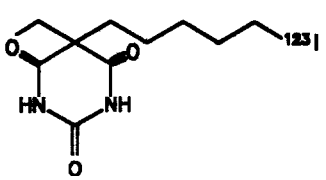

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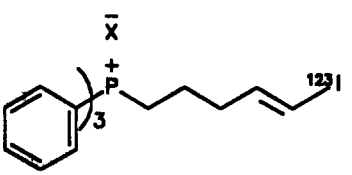

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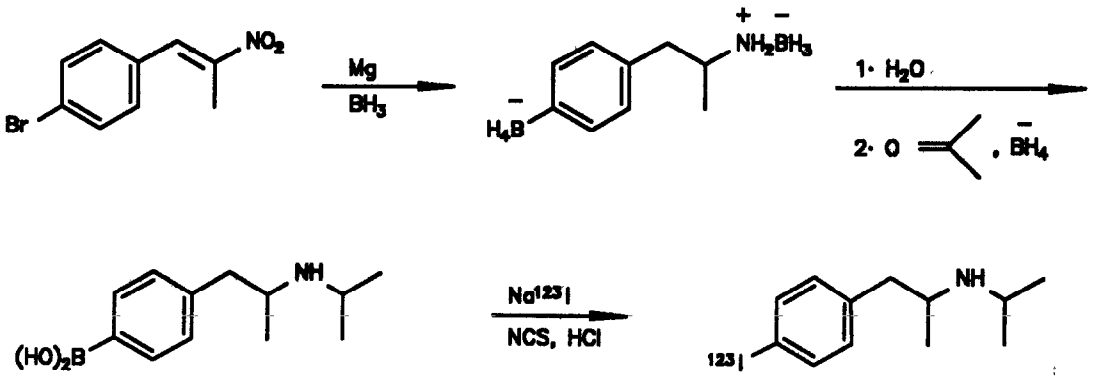
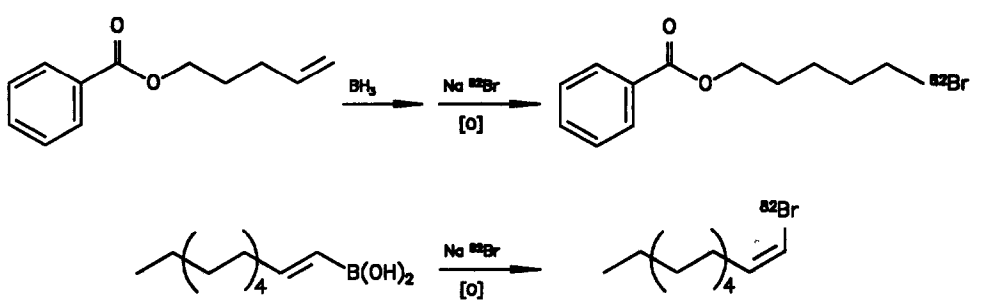
The first syntheses of the radioiodinated vinyl iodides involved the *in-situ* oxidation of sodium iodide in the presence of a vinylboronic acid[82] and were based on earlier iodination reactions involving molecular iodine.[83] The reactions possess an advantage over a number of more recently developed synthetic routes due to the inherent stability of the prerequisite vinylboronic acids, normally crystalline, air-stable solids.

Aromatic iodides are under renewed investigation in the radiopharmaceutical literature because they are also more stable toward metabolic decomposition than the corresponding alkyl iodide derivatives.[84] The iodination of aromatic rings can be achieved via the direct reaction of arylboronic acids with labeled sodium iodide in the presence of a mild oxidizing agent.[77,85] The reaction is effective but is somewhat limited due to the modest variety of arylboronic acids which can be readily prepared. The situation has improved with the recent development of transmetallation reactions which will make arylboronic acids more readily available.[86] The synthesis of 'no-carrier-added' ^{123}I-labeled, N-isopropyl *p*-iodoamphetamine is representative of the versatility of these new reactions.[87]



^{18}F, ^{77}Br and ^{34m}Cl are isotopes of interest in the nuclear medicine field. Only modest yields of fluorinated materials have been obtained to date via the reaction of reagents such as acetyl hypofluorite, xenon difluoride and cesium fluoroxysulfate with trialkylborane reagents. However, a number of chlorination reactions involving organoboranes have been reported.[88] A few of the reactions appear suitable for use in radiochlorination sequences[89] but no radiolabeling methods have been reported.

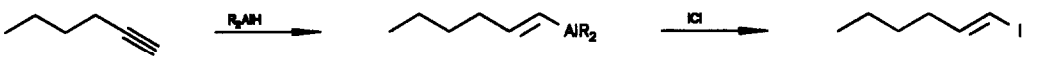
An *in-situ* synthesis for preparing radiobrominated derivatives of alkyl, vinyl and aryl bromides has been reported.[90]



Although the role of organoboranes in the syntheses of isotopically labeled compounds is relatively new, it is clear that these reagents will be utilized with ever-increasing frequency because of the ease with which functionally substituted organoboranes can be prepared and because they react with a wide variety of isotopically labeled precursors.

ALANES

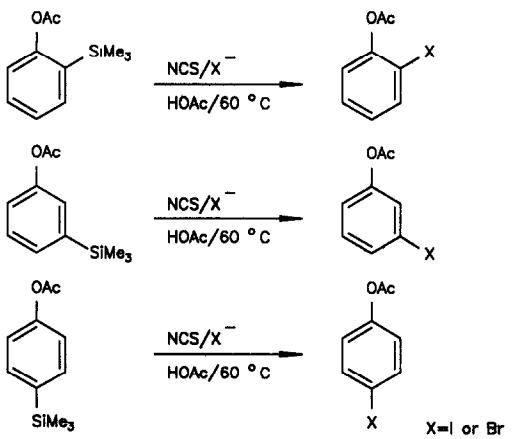
The vinylalanes, prepared via the *in situ* hydroalumination of alkynes can also be readily iodinated or brominated.[91] The highly reactive nature of hydroaluminating reagent and the alane intermediate formed *in situ* have limited their use in organic syntheses. To date, no radiolabeling sequences based on alanes have appeared in the literature.



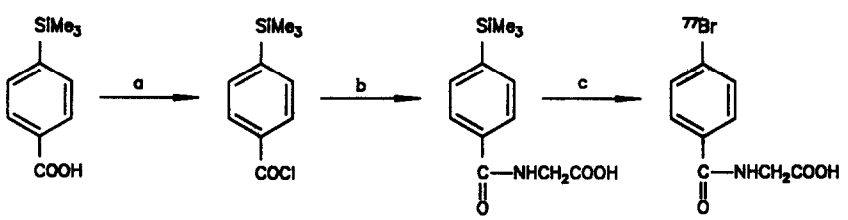
SILANES

Organosilanes have been used extensively as intermediates in radiohalogenations. Organosilanes are readily available from inexpensive starting materials and they are non-toxic. Unfortunately, organic derivatives of silicon, and the remaining Group IVb elements, have not been successfully used to incorporate elements other than the halogens. Nevertheless the organosilanes have proven to be valuable precursors for radiohalogenation because they are quite stable and do not require storage under anhydrous or inert atmospheres.[92]

Arylsilanes offer an effective route to a variety of halogenated aromatic derivatives.[93] The ease of accessibility of aryltrimethylsilyl intermediates[94] and the high reactivity of even highly deactivated (e.g. nitrosubstituted[95]) aromatic ring systems towards electrophilic halogenating agents makes this an attractive radiohalogenation route.[96,97] [Although the direct introduction of radiohalogens on to highly activated aromatic rings (e.g. phenols and anilines) is well established,[98] only a few methods are available for radiohalogenating less activated aromatic systems.[99]] The reagents are also useful

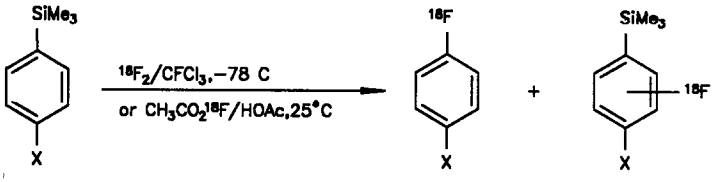


for incorporating radioisotopes of bromine and fluorine. Initial radiobromination studies were carried out using *p*-trimethylsilylbenzoic acid.[100] The reaction was then extended to the preparation



a) $SOCl_2$; b) $H_2nCH_2COOH/NaOH$; c) Na ^{77}Br, t-butylhypochlorite, 50°C.

of ^{18}F labeled aryl fluorides using two reagents: $[^{18}F]F_2$ and $[^{18}F]CH_3COOF$.[101,102] Moderately high specific activities were achieved using these protocols. The highest yield was obtained with trialkylsubstituted arylsilanes.[103,104] This approach is an attractive route to ^{18}F labeled radiopharmaceuticals for use in positron emission tomography.



Coordinatively saturated, hexavalent silicon compounds, such as the organopentafluorosilicates, have also found application in radiolabelling.[105] Organopentafluorosilicates are air and moisture stable and are readily cleaved by halogens.[106,107] This makes them ideal intermediates for site specific incorporation of 'no-carrier-added' radioiodine and radiobromine into organic molecules

$$\text{R-SiF}_5\text{K}_2 \xrightarrow[\text{R = alkyl or aryl}]{\text{oxid/*X}^{\ominus}} \text{R-*X.}$$

Although good radiochemical yields were achieved, there are limitations to the use of organopentafluorosilicates. In contrast to the trimethylsilyl group which can be easily carried through on an entirely synthetic scheme, organopentafluorosilicates must be introduced late in the syntheses because they are insoluble in most organic solvents and because their immediate precursors, organotrichlorosilanes, are extremely reactive. However, the insolubility of the organopentafluorosilicates may be an advantage in the purification process; the organopentafluorosilicates can often be purified by filtering the reaction mixture through a Millipore filter. Additional purification may be readily achieved by ion chromatography.

Radiofluorination of potassium arylpentafluorosilicates, $K_2[RSiF_2]$, was accomplished using ^{18}F-labeled acetyl hypofluorite in acetic acid.[108] The high reactivity of the arylpentafluorosilicate

$$\text{R-SiF}_5\text{K}_2 \xrightarrow[\text{CH}_3\text{CO}_2\text{H}]{\text{CH}_3\text{CO}_2{}^{18}\text{F}} \text{R-}^{18}\text{F}$$

and its insoluble character was exploited in this study.[109]

GERMANES

Halogen-demetallation reactions have been successfully applied to germanium reagents.[110] Although the electronegativity[111] of germanium is the same as that for silicon and tin, its bond energy,[112] covalent radius[113] and lability to proton displacement[114] are intermediate. Based on these favorable chemical properties, a series of *p*-substituted aryltrimethylgermanium compounds have been used as model compounds in radiohalogenations with ^{77}Br and ^{131}I in an effort to assess the utility of 'no-carrier-added' radiohalogenations.[115] High radiochemical yields were rapidly obtained in both activated and deactivated ring systems using 'no-carrier-added' ^{131}I in a variety of solvents using dichloramine-T as the oxidant

$$p\text{-X-C}_6\text{H}_4\text{Ge(CH}_3)_3 \xrightarrow[\text{Dichloramine-T}]{^{131}\text{I}^-} p\text{-X-C}_6\text{H}_4\text{-}^{131}\text{I.}$$

(X = H, F, Br, CH_3, CF_3, CH_3NO_2 etc.)

Aromatic radiobromination yields are generally lower than those for radioiodinations. This may be due to the relative instability of the BrCl intermediates and the relatively high oxidation potential

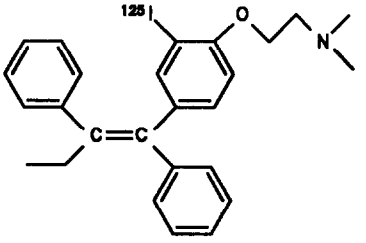
of the bromine chloride. The use of aryltrimethylgermanium compounds as precursors in radiohalogenation reactions is complementary to the use of the corresponding organosilicon and organotin substrates. Unlike the silicon analogs, aryltrimethylgermanium can be used for rapid radiobromination and radioiodination of nearly all types of aromatic systems. In a study of the reactivity of aryltrimethyl derivatives of IVB organometallics, the halogenation yields were found to increase in the order Si < Ge < Sn.[116] The chemical stability[114] and low toxicity[117] of organogermanium compounds are advantageous. In spite of these advantages, organogermanium compounds have not been used as widely as the corresponding organosilicon and organotin compounds.

STANNANES

Organostannanes are among the most useful of the organometallic reagents for isotope incorporation. Unlike the organoboranes, the stannanes are currently limited to incorporation of radiohalogens. As a general rule, the boranes and stannanes produce the same radiohalogenated products. The choice is often based on the ease of preparation and handling of the starting material. Halodestannylation[118–120] sparked the current interest in the radiohalogenation of group IV organometallics; the attractive features being their ease of preparation and their chemical stability. The availability of a variety of organotin reagents and the large body of literature on organotin chemistry helped maintain interest in the area. However, the strength of the carbon–tin bond and the high toxicity[121] are potential drawbacks.

Organotin compounds are readily prepared via transmetallation reactions using lithium and magnesium metallated aromatics[122] or via nucleophilic displacements using the trialkyltin anion.[123] They are excellent radiohalogenation intermediates. Palladium catalyzed routes are also available which utilize hexalkyldistannanes[124,125] and they may prove useful for the preparation of functionally substituted organotin compounds.

The hydrostannylation reaction (which involves the addition of tri-*n*-butyltin hydride, $(n\text{-}Bu_3)SnH$, to an alkyne to afford the corresponding *trans*-vinyl-tri-*n*-butyltin compounds) has been utilized in a number of radioiodination schemes. The tri-*n*-butyltin compounds, upon treatment with labeled iodine monochloride or sodium iodide and chloramine-T, produce the corresponding radioiodinated derivatives. Iododestannylation reactions have been used to radiolabel tamoxifen (**8**),[118,126,127] and iodovinylestradiol (**9**).[128] The approach has also been successfully applied to



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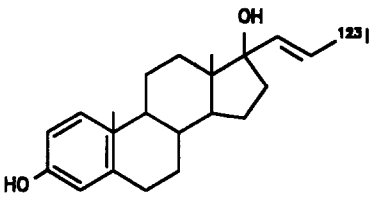

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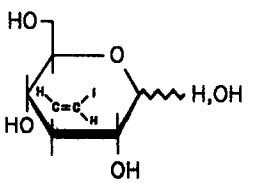
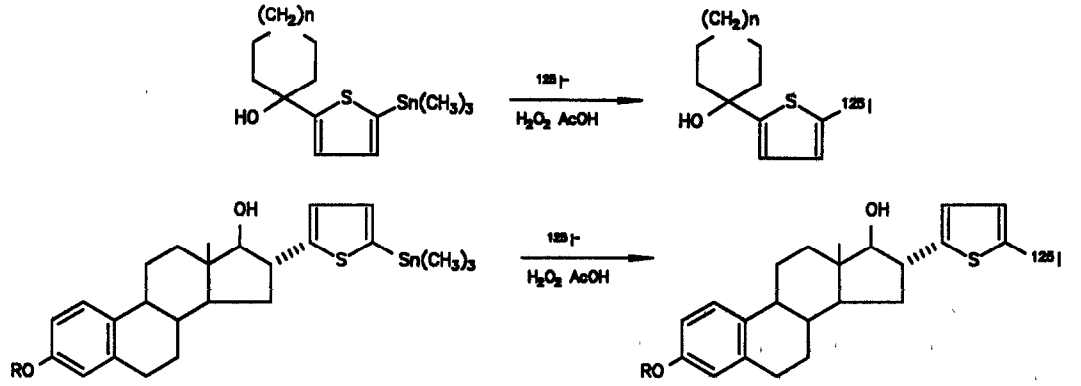
the radioiodination of steroids and fatty acids, functionalized as *trans*-vinyl-(*tri-n*-butyl)tin substrates.[129] The reaction has also found application in the synthesis of (E)-C-3[^{125}I]iodovinyl-D-allose.[130]



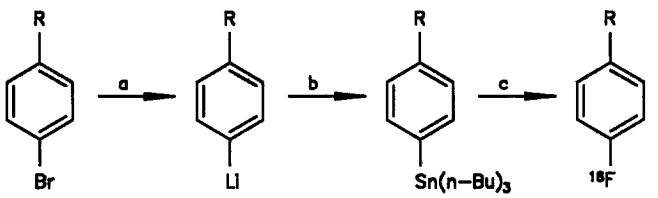
Recently, radioiododestannylations were used to prepare a series of four specifically labeled thienyl alcohols.[131]



A variety of arylstannanes were synthesized and used to radioiodinate para-iodophenyl (PIP) compounds which have found application as labels for monoclonal antibodies.[132] Such small non-phenolic radioiodinated intermediates are used to conjugate to monoclonal antibodies and their fragments; they resist *in vivo* enzymatic deiodination.[133–136]

Aromatic radiobromination via the cleavage of carbon–tin bonds was reported by Adam *et al.*[120] A series of substituted arylstannanes were reacted with ^{82}Br; nearly quantitative radiochemical yields were obtained under mild conditions.[137] Similarly, radiobromodestannylation is a useful method for preparation of aryl bromides labeled with bromine isotopes at the 'no-carrier-added' level.[138]

Fluorination reactions using ^{18}F have been extensively investigated in model systems.[139–141] Aryltin derivatives, upon treatment with ^{18}F labeled elemental fluorine[142] acetyl hypofluorite[143] afforded good radiochemical yields of labeled aryl fluorides.[144]



where R=H, Cl, F, CH_3, OCH_3, 3,4–$(OCH_3)_2$ etc

a) n–BuLi; b) $Cl,Sn(n–Bu)_3$; c) $[^{18}F]–F_2$,–78 C or $CH_3CO^{18}F$,R·T·

Although fluorination with ^{18}F has been investigated in model systems, the fluorination of more complex organic molecules has met with only limited success.[145] Poor radiochemical yields are obtained and products are often contaminated with the non-halogenated, non-metallated organic molecules which form via a proto-destannylation side-reaction.

Among the group IV organometallics, it appears that the organostannanes provide the highest yields of fluorinated, brominated and iodinated products. The rather harsh stannylation procedures, the ready proto-destannylation reactions, and the fact that they can be used to prepare only aromatic and vinyl derivatives limit their utility.

MERCURIALS

Organomercury compounds offer a number of advantages over other organometallic intermediates. These include stability, easy accessibility, and high reactivity towards halogenation

reagents. Aliphatic, vinylic and aromatic mercury reagents can be readily radiohalogenated in high yields.[146]

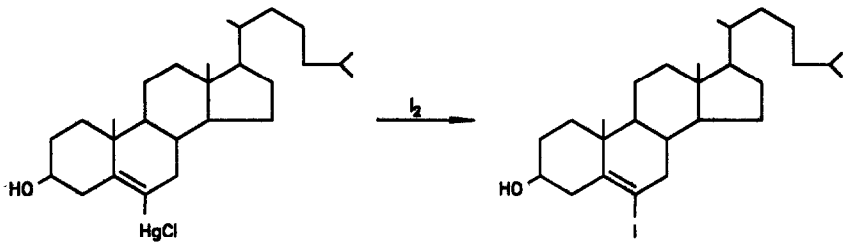
Organomercurials are generally obtained either by transmetallation, direct electrophilic substitution on aromatic systems, or by mercuration of alkenes.[146]

$$RCH{=}CH_2 \xrightarrow{a,b,c} RCH_2CH_2HgCl$$

$$RC{\equiv}CH \xrightarrow{a,b,c} RCH{=}CHHgCl$$

(a) HBR'_2; (b) $Hg(OCOCH_3)_2$; (c) NaCl

6-Chloromercuricholest-5-en-3β-ol (**10**) has been used in the preparation of 6-iodocholest-5-en-3β-ol, (**11**),[147,148] which is the precursor for an adrenal imaging agent.[149,150,151] The successful use



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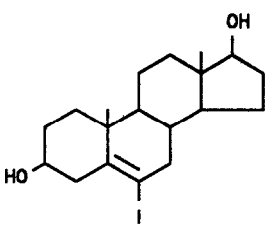
of organomercurcials for incorporating isotopes of both bromine and iodine promoted extension of this approach to the Δ-5 steroids. The synthesis of [^{131}I]6-iodoandrost-5-en-3β,17β-diol, (**12**), [^{131}I]6-iodoandrost-5-en-3β-ol,17-one, (**13**), [^{131}I]6-iodopregn-5-en-3β-ol-20-one, (**14**), and [^{131}I]6-iodopregn-5-en-3β,20-diol, (**15**), has been carried out via the corresponding 6-chloromercury derivatives which were prepared by direct mercuration of the parent steroids.[152] The chloromercury compounds provide a simple high yield protocol for labelling with radioiodine.



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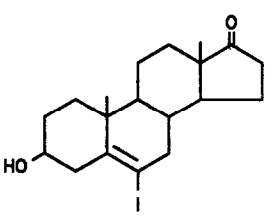

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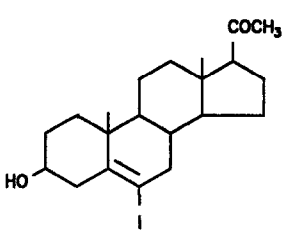

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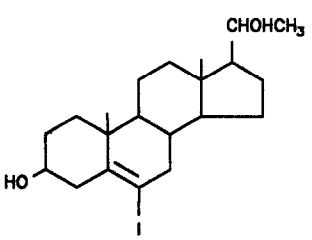

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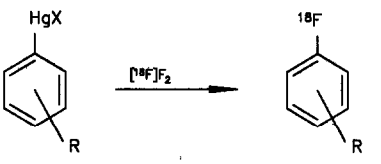
Similarly, high yield radiobrominations[153,154] and radiofluorinations[140,155] have been reported using organomercurial precursors. High specific activity radiobrominations of a number of complex organic molecules has been reported.[156]

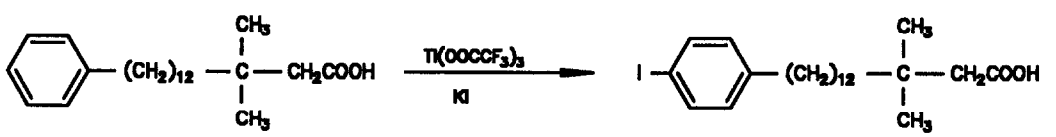
The reaction of vinylboronic acids with mercuric acetate in tetrahydrofuran affords crystalline organomercuric acetates.[157] Such *in situ* generated vinylmercuric acetates upon treatment with a halide such as sodium iodide or sodium bromide provide the corresponding vinylmercuric halides in high yield. These crystalline mercury halide intermediates undergo a radioiodination reaction similar to that reported for boronic acids. Iodo-demercuration of *p*-aminophenylmercuric acetate has proved to be a facile method for the synthesis of *p*-[^{125}I]iodoaniline.[158] The reaction of radiobromine gives the corresponding vinyl-radiobromide as a mixture of *cis* and *trans* isomers. The method has been applied to the synthesis of a potential myocardial perfusion agent, triphenyl-(-1-[^{82}Br]-bromo-1-penten-5-yl)phosphonium iodide. The fluorination of organomercurials has

received very little attention although attempts have been made to radiofluorinate mercury compounds with dilute F_2[140] and acetylhypofluorite.[159]

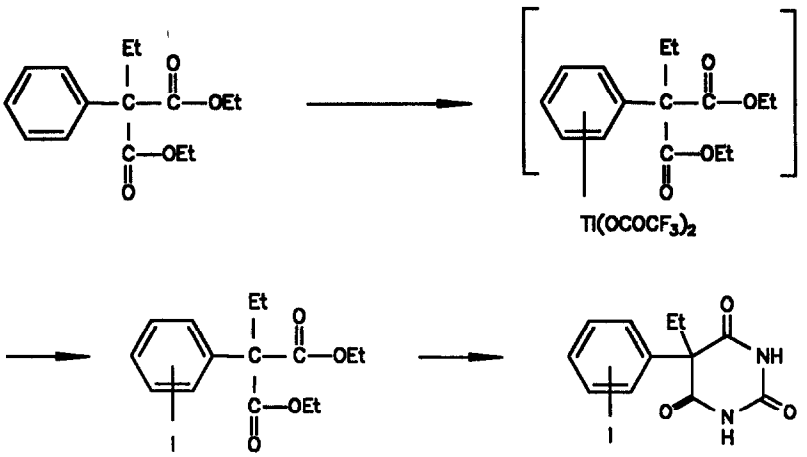


THALLATES

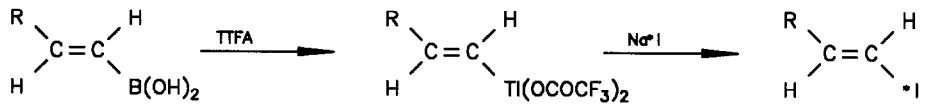
Thallium(III) trifluoroacetate can be used to thallate aromatic rings and the resulting arylthallium bis-trifluoroacetates yield aromatic iodides upon treatment with inorganic iodide.[160,161] The substitution pattern is predominantly *para* except in the case of aromatic rings containing strongly electron withdrawing groups, in which case the *meta* predominates.[160] In benzoic acid derivatives, *ortho* isomers predominate.[161] Organothallium chemistry has found application in radioiodination procedures; aromatic derivatives of cellulose,[162] phenyl fatty acid analogs,[163,164] and thienyl[166] fatty acids have all been radioiodinated using thallation. Recently, a new β,β-dimethyl-branched fatty acid, 15-*p*-[^{125}I]iodophenyl-3,3-dimethylpentadecanoic acid was obtained using a thallation–iodination sequence.[167]



Direct thallation of molecules bearing NH and OH has been found to be difficult. To circumvent problems, alternate indirect approaches have been developed.[168,169] A procedure that involves similar chemistry has been used to radioiodinate cytosine and deoxycytosine residues.[170–172] The nucleoside is treated with thallium(III) chloride in the presence of radioactive iodide ion. The reaction produces radioiodine labeled 5-iodocytosine.



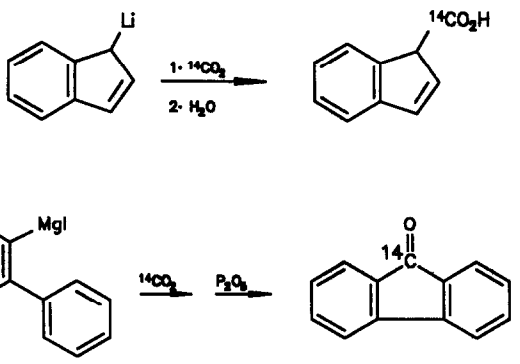
Alkylvinylthallium trifluoroacetate intermediates are readily accessible *in situ* from the corresponding vinylboronic acids and TTFA. They undergo facile radioiodination with radioiodide to yield vinyl iodides. This reaction sequence may find application for radioiodination of substrates sensitive to acidic media and oxidizing agents.



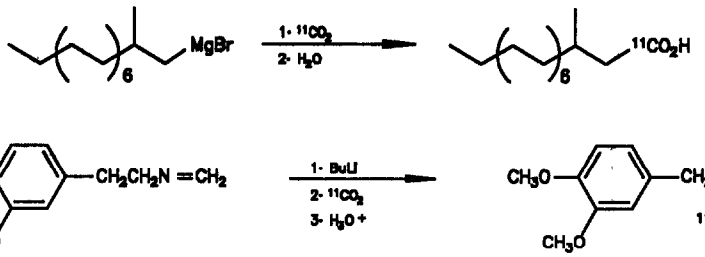
Although thallium has proved to be very useful for radioiodine labelling, it has not yet been successfully employed for introducing radioisotopes of bromine and fluorine. However, it has been shown that arylthallium difluorides will decompose to aryl fluorides in the presence of boron trifluoride[173] and this method may one day be applied to ^{18}F-labelling.[173]

ORGANOLITHIUM AND GRIGNARD REAGENTS

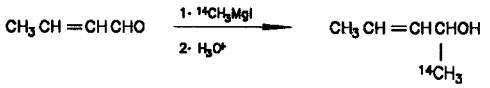
Main group organometallic reagents such as the lithium and magnesium reagents were among the first to be used for incorporating radioisotopes of carbon. The facile reaction carboxylation reactions of these agents are well known.[4,174,175]



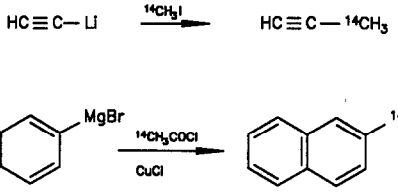
Not surprisingly, the carboxylation reaction has also been utilized for incorporating ^{11}C into a variety of compounds.[176,177,178]



The use of carbon-labeled Grignard and lithium reagents is essentially limited to the long-lived isotopes of carbon due to the short half-life of ^{11}C[179] (although ^{11}C labeled methyl iodide is



available[178]). Of course it is also possible to generate carbon-labeled products via the reaction of Grignard and lithium agents with radiolabeled precursors other than carbon dioxide.[180]



SUMMARY

Organometallic reagents have proved to be valuable intermediates for preparing radiolabeled materials. Virtually all organometallic materials can be used in radiohalogenation reactions. The choice of the starting reagent often depends on its ease of preparation and the simplicity of product purification.

Organoborane and organostannane reactions have been developed most extensively. Currently, organoboranes are the reagent of choice for incorporating non-halogen radioisotopes. Rapid synthetic routes for incorporating radioisotopes of carbon, oxygen, and nitrogen have all been developed. The procedures are efficient and the products easily isolated. The non-toxicity and stability of the boranes can be a significant advantage but the organostannanes are more reactive in fluorination reactions. Organomercurials hold significant promise in radiohalogenated reactions since they are often the easiest to prepare. Organogermanes and organosilanes have not been developed extensively but there is no doubt that they will soon play a significant role in the radiopharmaceutical area. The alanes also offer promise since they are reactive reagents and it would appear that they offer ready access to carbon and oxygen labeled agents. Organomagnesium and organolithium agents are potentially valuable. They have been used to incorporate carbon and oxygen isotopes but the limited availability of starting materials may hamper their utility.

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