Incorporation of Stable and Radioactive Isotopes via Organoborane Chemistry

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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 quickly from chemistry to medicine.[4] From that time, the applications of radioactive isotopes far exceeded those of their stable counterparts.

In recent years the medical use of radioisotopes has increased significantly due to advances in radiation detection techniques.[5] The development of single-photon emission computerized tomography (SPECT)[6] and positron emission tomography (PET)[7] has revolutionized diagnostic medical imaging. These computerized systems permit noninvasive, in vivo, three-dimensional imaging of organs after administration of appropriate agents labeled with short-lived nuclides.[8] The techniques are used for in vivo pharmokinetics, organ imaging, evaluation of organ function, and physiological mapping. They complement the traditional X-ray CAT scan and are partially responsible for the tremendous upsurge in the use of radiopharmaceuticals in hospitals today. (According to current estimates, between 25% and 30% of all hospital admissions in the U.S. recieve a radiopharmaceutical of some type.)

Until 1970, there was little increase in the use of stable isotopes for labeling organic molecules. Prior to that time, development was hampered by the lack of availability of both the isotopes and efficient analytical techniques. In 1969, the Division of Biology and Medicine of U.S. Atomic Energy Commission established a program to make increased quantities of stable isotopes of carbon, oxygen, and nitrogen available at significantly reduced costs.[9] At about the same time, rapid advances in instrumentation were occurring. Fourier transform nuclear magnetic resonance and gas chromatography–mass spectrometry could now be applied to isotopically labeled materials, and the identity and position of the stable isotope in a given molecule could be readily identified. Not surprisingly, the use of stable isotopes has increased steadily since 1970.[10] On the medical front, the recent development of whole-body NMR scanners promises to increase the need for compounds labeled with NMR-active, stable isotopes such as carbon-13, nitrogen-15, and oxygen-17.[11]

The problems peculiar to the syntheses of isotopically labeled compounds became apparent to me while I was collaborating with C. J. Collins at Oak Ridge National Laboratory on studies concerning the structure of coal.[12] My interests were heightened by a later collaboration with the Medical and Health Sciences Division of Oak Ridge Associated Universities which focused on the synthesis of carbon-11-labeled amino acids.[13]

Syntheses of isotopically labeled compounds start from a few basic building blocks such as carbon dioxide,

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(9) Stable isotopes produced by the separation facility at Los Alamos Scientific Laboratory in excess of requirements of the Department of Energy are transferred to the Stable Isotope Sales outlet at the Mound Facility, Miamisburg, OH, for distribution (at cost).

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carbonate salts, nitric oxide, water, and halide salts. These are the species that are generated in the cyclotrons and reactors or that are the most amenable to cyrogenic distillation (the most common method for separating stable isotopes). The chemical stability of these building blocks has traditionally been a significant barrier to the synthesis of complex isotopically labeled agents.[14] The problem is most apparent in synthetic schemes for radiopharmaceuticals containing short-lived isotopes such as carbon-11 ($t_{1/2}$ = 20.4 min), nitrogen-13 ($t_{1/2}$ = 10 min), oxygen-15 ($t_{1/2}$ = 2 min), and fluorine-18 ($t_{1/2}$ = 110 min). However, these are the isotopes of greatest interest for studies involving humans due to their ideal decay characteristics[15] and the fact that they can be prepared with very high specific activities (>1000 Ci/mmol, "no carrier added"[16]). From the chemist's perspective the short half-lives and low concentrations of these radionuclides provide formidable challenges. As a general rule, the total time for delivery of the labeled product to the patient can be no more than 3 half-lives. Thus, the time allotted for delivery (injection into the patient) of a ^{11}C-glucose derivative which must be synthesized from a carbon oxide is 60 min (3 × $t_{1/2}$). The problem is even more acute for the synthesis of oxygen-15-labeled alcohols which might be used for blood flow studies (3 × 2 min). (These studies can only be carried out in medical institutions in which cyclotrons, laboratories, and patient facilities are located in close proximity). To compound the problem, the lower concentration of many "no-carrier-added" reagents (<10^{-9} M) often renders classic (e.g., S_N2) reaction pathways ineffective.

In 1976 I initiated a research program which was focused on designing rapid syntheses for physiologically active materials labeled with short-lived isotopes. To date, we have successfully developed methods which can be used for incorporating carbon-11, nitrogen-13, oxygen-15, iodine-123, and bromine-77 (isotopes useful for human studies). The syntheses are designed to rapidly incorporate the isotope in the final synthetic step so that the radiochemical yields are maximized. A significant aspect of this new methodology is that it can also be used for the preparation of materials labeled with stable isotopes.

These new syntheses generally involve the organoboranes rather than traditional substitution reactions and Grignard reagents.[17] Brown and others have already demonstrated the versatility of the organoboranes in organic synthesis.[18] The early studies also demonstrated an important aspect of the organoboranes: they could be prepared from molecules containing a wide variety of functional groups.[19] (This is important from the medical viewpoint since functionality generally is responsible for physiological activity). More importantly, the early research demonstrated that a variety of elements would replace boron under appropriate reaction conditions, and these elements possess radioactive isotopes that are of interest in current radiopharmaceutical research. The reported reaction conditions were, however, too harsh and the reaction times too lengthy for utilization in radiopharmaceutical syntheses. In addition, little information was available concerning the mechanism and kinetics of many of the organoborane reactions known at that time.

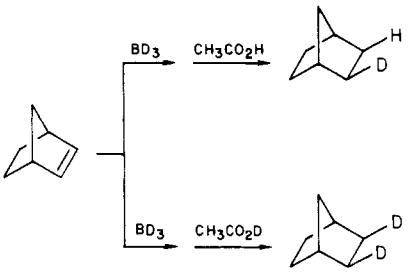
$$R_3B \xrightarrow[NaOMe]{I_2} RI$$

$$R_3B \xrightarrow[2.\ KOH]{1.\ CO/\Delta} R_3COH$$

$$R_3B \xrightarrow{NH_2OSO_3H} RNH_2$$

$$R_3B \xrightarrow[NaOH]{H_2O_2} ROH$$

When we initiated our program[20] only the hydrogen isotopes, tritium and deuterium, had been incorporated into organic molecules via organoborane chemistry. The deuteration reactions were carried out in order to determine the stereochemistry and regiochemistry of the hydroboration reaction and the related solvolysis reactions of organoboranes.[21] Tritiated alkenes were prepared via a hydroboration–dehydroboration sequence involving tritiated BH_3.[22]



On the basis of the unique versatility of the organoboranes, we felt that they could be utilized for the incorporation of other isotopes.

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(15) These nuclides decay by positron emission resulting in the emission of two 511-keV γ annihilation photons which can be readily detected outside the body. In addition, they possess short half-lives ($t_{1/2}$ < 1 h) which minimizes the radiation dose to the patient. (Rocha, A. F. G.; Harbert, J. C. "Textbook of Nuclear Medicine: Basic Science"; Lea and Fekigur: Philadelphia, 1978.)

(16) The availability of very high specific activity pharmaceuticals is important because the quantity of material which is necessary for a patient study is kept below pharmacological dosage which prevents physiological effects in the patient. It has been customary to refer to radioactive preparations to which no isotopic (stable) carrier has been intentionally added as "carrier-free." The increasing use of very high specific activity, short-lived isotopes of elements widely available in the environment (e.g., carbon-11) has focused attention on the problem of accidently introducing carrier atoms. The suggestion has been made that the term "carrier-free" be reserved for those instances where evidence is provided which demonstrates that the element is, in fact, carrier-free. The term "no-carrier-added" would then be utilized for the instances in which the specific activity, although very high, has not actually been measured. (Wolf, A. P. *J. Nucl. Med.* **1981**, *22*, 392. Tewson, T. J.; Welch, J. M. *Ibid.* **1981**, *22*, 392.)

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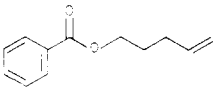
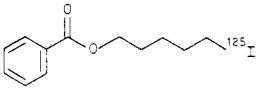
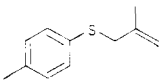
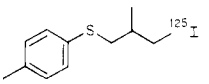
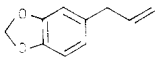
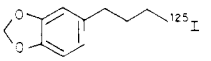
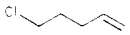
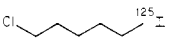
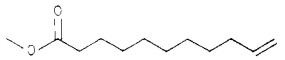
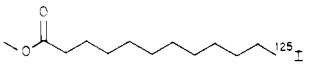
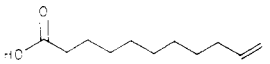
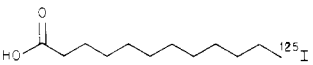
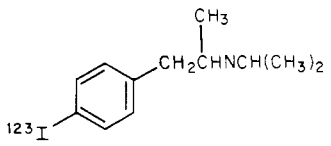
Table I
Synthesis of Iodine-125-Labeled Alkyl Iodides

substrate	product	radiochemical yield (isolated), %
		82
		94
		74
		78
		85
		89

Iodine

Radioiodine has a long history in tracer studies and was the first isotope used routinely in therapeutic nuclear medicine.[23] Its popularity has increased in recent years due to the availability of iodine-123 which has a half-life of 13.3 h and possesses nearly ideal decay characteristics.[24] Radiolabeled agents such as *N*-isopropyl-*p*-[^{123}I]iodoamphetamine (I),[25] ω-[^{123}I]iodoheptadecanoic acid (II),[26] and *m*-[^{131}I]iodobenzylquanadine (III),[27] have proven to be extremely effective in brain, heart, and adrenal studies.[28]



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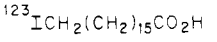
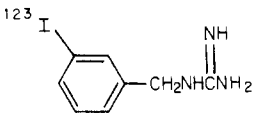


II



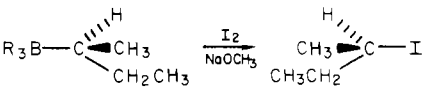
III

At first glance the iodination reaction developed by Brown appeared ideal for radioiodine incorporation.[29]

$$3I_2 + R_3B \xrightarrow[NaOMe]{I_2} 3R\text{-}I + 3NaI + B(OMe_3)$$

On closer examination, the reaction was not appropriate for incorporating iodine-123 into many functionally substituted molecules. The problem centered on the fact that the reaction required the use of molecular iodine whereas radioiodine is obtained (and most safely handled) in the reduced (iodide) form. The labeled iodide could, of course, be oxidized to molecular iodine, but one-half of the expensive isotope would then be lost as sodium iodide. In addition, the necessity of using a strong base precluded the use of many important functional groups in the organoborane.

We embarked on a mechanistic study of the iodination reaction and found that it proceeded via an electrophilic attack by the iodine molecule on the electron-rich borate complex.[30] Simultaneously, Brown's



group found that *exo*-trinorbornylborane yielded *endo*-2-iodonorbornane. The findings were significant because they demonstrated that molecular iodine was not the only reagent which could be utilized. The iodination reagent need simply contain an electropositive iodine moiety. A number of such reagents are available, including iodine-monochloride.

$$Cl_2 + Na^+I^- \rightarrow NaCl + I^{\delta+}\text{–}Cl^{\delta-}$$

We found that iodine monochloride readily reacted with trialkylboranes to generate a variety of functionally substituted iodinated and radioiodinated reagents (Table I).[31] In addition, the reaction did not require the presence of a strong base and was complete in less than sixty seconds!

$$R_3B + ICl \xrightarrow{NaOAc} RI + R_2BOAc$$

Even though iodine-123- and iodine-125-labeled iodine monochlorides are readily available, they are not stable over long periods of time. Consequently, we

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(28) Radioiodinations are often carried out utilizing isotope exchange reactions (radioiodine for iodine-127) and, consequently, contain carrier atoms. Nucleophilic substitution and electrophilic addition reactions have also been utilized. An excellent review of radioiodinating procedures was recently published by Seevers and Counsell: Seevers, R. H.; Counsell, R. E. *Chem. Rev.* **1982**, *82*, 575.
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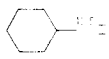
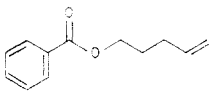
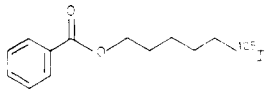
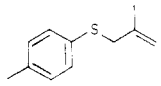
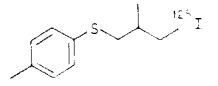
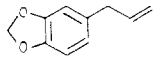
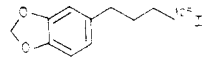
Table II
Synthesis of I-125-Labeled Compounds via the Reaction of Organoboranes with Sodium Iodide (I-125)

alkene	product	radiochemical yield, %
$H_2C{=}CH(CH_2)_3CH_3$	$^{125}ICH_2(CH_2)_4CH_3$	97
		97
		94
		99
		78
$H_2C{=}CH(CH_2)_8CO_2CH_3$	$^{125}ICH_2(CH_2)_9CO_2CH_3$	94
$H_2C{=}CH(CH_2)_{16}CO_2H$	$^{125}ICH_2(CH_2)_{17}CO_2H$	89
$H_2C{=}CH(CH_2)_{19}CO_2H$	$^{125}ICH_2(CH_2)_{20}CO_2H$	91

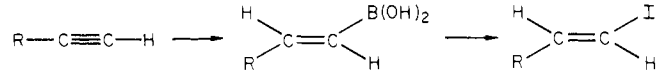
developed a simple, one-pot procedure for radioiodinations which utilizes mild oxidizing agents such as chloramine-T or *N*-chlorosuccinimide.[32] The new

$$R_3B + Na^{123}I \xrightarrow[H_2O]{[O]} R^{123}I + R_2BOH$$

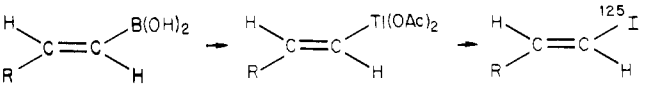
method is straightforward: radiolabeled sodium iodide is added to a trialkylborane in THF and then chloramine-T is added; after a minute, the product is isolated via column chromatography or HPLC. Excellent yields of the radioiodinated agents are obtained (Table II).[33] Of particular interest are the ω-iodo fatty acids which have been examined as myocardial visualization agents.[34]

A significant aspect of these new reactions is that they can be carried out utilizing "no-carrier-added" radioiodine.[35] This is important because it insures that the quantity of labeled agent is kept well below the pharmacological dosage. [Most traditional routes for iodine labeling involve substitution reactions which often lead to dilution of the radiolabeled agent by the nonlabeled starting material.] Not surprisingly, the isolated yields of the "no-carrier-added" materials are generally lower than those obtained in tracer-level studies due to losses on the surface of reaction vessels.

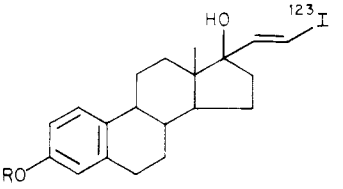
We then turned our attention to other borane reagents. Brown had demonstrated that vinylboranes can be readily prepared and converted into the corresponding vinyl iodides.[36]



We applied our new iodination methodology to a series of vinylborane reagents and obtained the corresponding vinyl iodides in excellent yields (Table III).[37]



We also utilized the vinylboranes to synthesize labeled vinyl iodides via transmetalation reactions. These reactions are useful because they often do not require an oxidant. Significantly, the vinyl iodide agents proved to be more stable to deiodination in vivo than the corresponding alkyl iodides and they hold promise as a method for stabilizing radioiodine in a number of pharmaceuticals.[38] We have, for example, synthesized the first iodovinyl steroids which are potential agents for classifying breast tumors.[39] Related iodovinyl steroids labeled with a variety of radioiodines have been developed in other laboratories and are being evaluated for pharmaceutical use.[40]

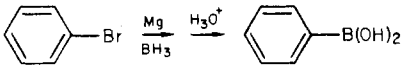


We also synthesized a series of radioiodinated (*E*)-iodovinyl, tellurium-substituted, fatty acids in collaboration with Knapp. These agents exhibit good myocardial uptake and extended in vivo retention time.[41,42]

$$ICH{=}CH(CH_2)_xTe(CH_2)_yCO_2H$$

Another method of increasing the in vivo retention time of radioiodine is to incorporate the iodine on a phenyl substituent.[43] Numerous research groups are developing methods for attachment of iodine to aromatic rings.[28] We have found that arylboronic acids are rapidly iodinated using the new reaction (Table IV).[44]

At present, it is difficult to prepare the arylboronic acids that would be precursors to useful pharmaceuticals. We have approached the problem from two directions. We have developed new methodology for preparing boronic acids directly from aryl halides; we found that arylboronic acids can be synthesized by preparing the magnesium arylborohydrides in a one-pot reaction and then hydrolyzing them to the corresponding arylboronic acids.[45]



(32) Kabalka, G. W.; Gooch, E. E. *J. Org. Chem.* **1981**, *46*, 2582. Kabalka, G. W.; Gooch, E. E. *J. Chem. Soc., Chem. Commun.* **1981**, 1011.
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(41) Knapp, F. F.; Goodman, M. M.; Kabalka, G. W.; Sastry, K. A. R. *J. Med. Chem.* **1984**, *27*, 94.
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(43) Machulla, H.-J.; Marsmann, M.; Dutschka, K. *J. Radioanal. Chem.* **1980**, *56*, 253. Dudczak, R.; Angelberger, P.; Wagner-Loffler, M.; Kletter, K.; Schmoliner, R.; Frischauf, H. *J. Nucl. Med.* **1981**, *22*, P81. Kline, R. C.; Swanson, D. P.; Wieland, D. M.; Thrall, J. H.; Gross, M. D.; Pitt, B.; Beierwaltes, W. H. *Ibid.* **1981**, *22*, 129. Winchell, H. S.; Baldwin, R. M.; Lin, T. H. *Ibid.* **1980**, *21*, 940.
(44) Kabalka, G. W.; Sastry, K. A. R.; Sastry, U.; Somayaji, V. *Org. Prep. Proc. Int.* **1982**, *14*, 359. Kabalka, G. W.; Sastry, K. A. R.; Muralidhar, K. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 795.

Table III
Synthesis of Iodine-125-Labeled Vinyl Iodides

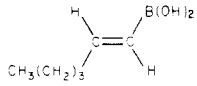
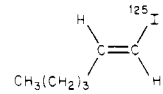
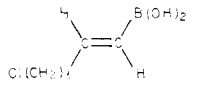
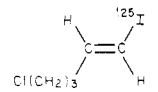
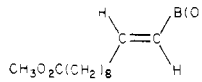
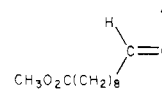
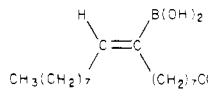
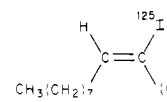
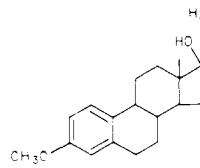
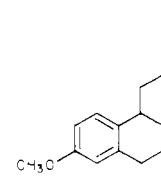
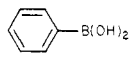
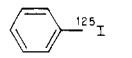
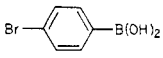
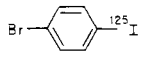
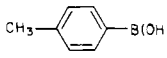
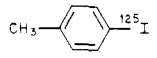
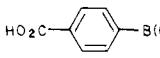
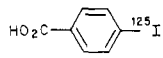
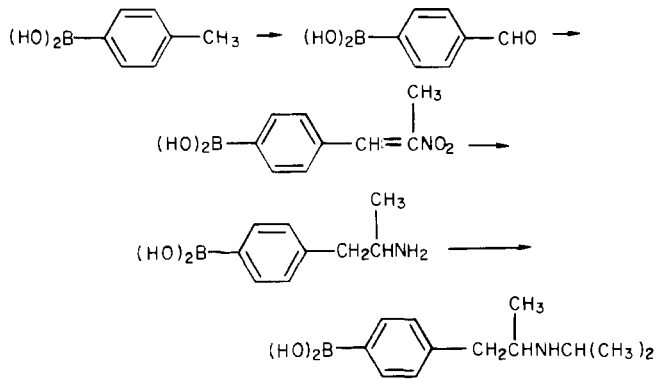
vinylboronic acid	product	radiochemical yield, %
		77
		87
		56
		42
		55

Table IV
Synthesis of Iodine-125-Labeled Aryl Iodides

arylboronic acid	product	radiochemical yield, %
		91
		78
		86
		74

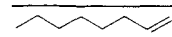
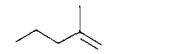
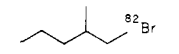
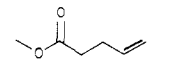
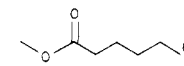
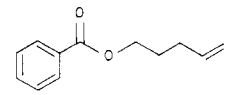
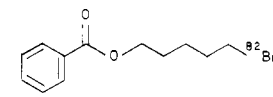
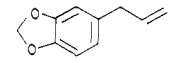
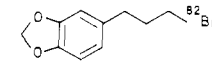
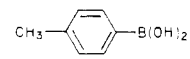
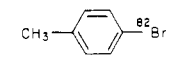
The other approach involves synthesizing important arylboronic acids from simple arylboronic acids.



Other Halogens

Our interest in halogen labeling is not limited to radioiodine. Bromine-77 can be prepared[46,47] and is a potentially useful isotope because bromide does not accumulate in the thyroid. A one-pot radiobromination

Table V
Synthesis of Bromine-82-Labeled Reagents

alkene	alkylbromide	% yield
		90
		64
		79
		71
		50
		56

was developed and has been used to synthesize a variety of radiobromine-labeled materials (Table V).[48] The reaction is complete in a matter of seconds.

$$R_3B \xrightarrow[[O]]{Na^*Br} RBr$$

We have investigated the fluorination of organoboranes because of the ideal physical properties of fluorine-18 for medical imaging.[49] Limited successes have been achieved by utilizing electrophilic fluorinating agents such as acetyl hypofluorite on organoboranes.

Oxygen

We have developed a method for incorporating isotopically labeled oxygen.[50] The reaction is based on the well-known, direct reaction of molecular oxygen

(45) Kabalka, G. W.; Sastry, U.; Sastry, K. A. R.; Knapp, F. F.; Srivastava, P. C. *J. Organomet. Chem.* **1983**, *259*, 269.
(46) Knight, L.; Krohn, K. A.; Welch, M. J.; Spomer, B.; Hager, L. P., ref 8, pp 149–154.
(47) Scholl, H.; Kloster, G.; Stöcklin, G. *J. Nucl. Med.* **1983**, *24*, 417.
(48) Kabalka, G. W.; Sastry, K. A. R.; Hsu, H. C.; Hylarides, M. D. *J. Org. Chem.* **1981**, *46*, 3113. Kabalka, G. W.; Sastry, K. A. R.; Pagni, P. *J. Radional. Chem.* **1982**, *74*, 315.
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(50) Kabalka, G. W.; Reed, T. J.; Sastry, K. A. R. *Synth. Commun.* **1983**, *737*, 13.

Table VI
Synthesis of Oxygen-17-Labeled Alcohols

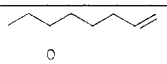
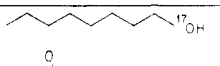
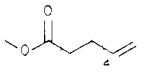
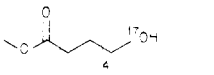
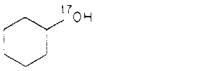
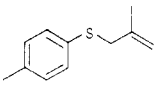
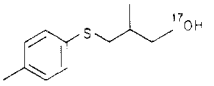
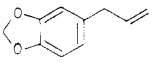
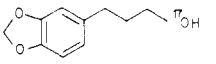
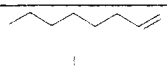
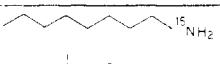
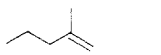
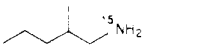
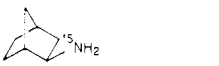
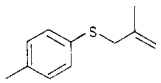
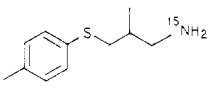
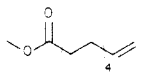
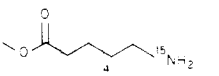
alkene	product	% yield
		93
		94
		90
		92
		76

Table VII
Synthesis of Nitrogen-15-Labeled Amines

alkene	product	% yield
		85
		71
		66
		75
		79

with organoboranes.[51] A variety of oxygen-17-labeled alcohols have been synthesized (Table VI).

$$R_3B \xrightarrow[2.\ H_2O]{1.\ ^{17}O_2} 2ROH + RB(OH)_2$$

We have synthesized oxygen-15-labeled butanol for potential use as a blood tracer in collaboration with Wolf.[52] The product alcohol can be isolated in less than 8 min by utilizing HPLC techniques.

Nitrogen

There is a great deal of interest in nitrogen isotopes (nitrogen-13 for positron emission tomography and nitrogen-15 for NMR investigations). We developed a simple, one-pot, high-yield synthesis of nitrogen-labeled amines via organoborane chemistry (Table VII).[53] The reaction involves the in situ formation of chloramine.[54]

$$R_3B \xrightarrow[NaOCl]{^{15}NH_3} R^{15}NH_2$$

The labeled chloramine is generated in the presence of the organoborane and an instantaneous reaction ensues. The reaction can also be used to synthesize dialkylamines.[55] We are currently synthesizing nitrogen-13-labeled amines in collaboration with Finn and Wolf.[63]

(51) Brown, H. C.; Midland, M. M.; Kabalka, G. W. *J. Am. Chem. Soc.* **1971**, *93*, 1024.
(52) Kabalka, G. W.; McCollum, G. W.; Fabirkiewicz, A. S.; Lambrecht, R. M.; Fowler, J. S.; Sajjad, M.; Wolf, A. P. *J. Labelled Compd. Radiopharm.*, in press.
(53) Kabalka, G. W.; Sastry, K. A. R.; McCollum, G. W.; Yoshioka, H. *J. Org. Chem.* **1981**, *46*, 4296. Kabalka, G. W.; Sastry, K. A. R.; McCollum, G. W.; Lane, C. A. *J. Chem. Soc., Chem. Commun.* **1982**, 62.
(54) Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565.
(55) Kabalka, G. W.; McCollum, G. W.; Kunda, S. A. R. *J. Org. Chem.* **1984**, *49*, 1656.

Carbon

Carbon isotopes have long played an important role in both radiopharmaceutical and chemical research. Ironically, the first radioactive isotope of carbon to be used in research was carbon-11,[3] but because of its short half-life (20 min), it was soon displaced by carbon-14 in tracer studies. In recent years there has been a resurgence of interest in carbon-11 because it is a positron emitter. This fact and its short half-life make it ideal for medical use but a challenge for the chemists involved in producing carbon-11-labeled pharmaceuticals.

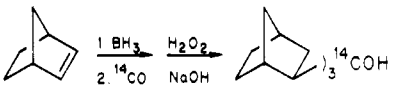
The reaction of organoboranes with carbon monoxide appeared to be an ideal method for incorporating carbon isotopes.[56] However, the reported reaction times

$$R_3B \xrightarrow{CO/H^-} \xrightarrow{KOH} RCH_2OH$$

$$R_3B \xrightarrow{CO/H_2O} \xrightarrow{KOH} R_2CHOH$$

$$R_3B \xrightarrow{CO} \xrightarrow[H_2O_2]{NaOH} R_3COH$$

for the carbonylation reaction were far too long for incorporation of carbon-11. Consequently, we initiated a study of the carbonylation reaction and found that only the hydride-moderated reaction was fast enough for use in carbon-11 reactions (the reaction requires <15 min). Even though the remaining carbonylation reactions required longer reaction times, they are ideal for the incorporation of carbon-14 and carbon-13.[57]



In a separate study at Brookhaven National Laboratory, Wolf found that simple carbon-11-labeled aldehydes could be prepared via the organoborane-carbonylation sequence.[58] In a later study we synthesized carbon-11-labeled butanol in collaboration with Mt. Sinai Hospital, Miami Beach.[59]

$$CH_3(CH_2)_4CH{=}CH_2 \xrightarrow{BH_3} \xrightarrow{^{11}CO/H^-} \xrightarrow[H_2O_2]{KH_2PO_4} CH_3(CH_2)_7{}^{11}CHO$$

We also synthesized a variety of carbon-13-labeled alcohols, aldehydes, and acids using the carbonylation reactions (Table VIII).[60] The carbon-13-labeling methodology is being utilized for preparing precursors for use in NMR imaging studies.

Pelter's cyanidation reaction can be used to construct larger carbon-labeled molecules.[61] For example, in our

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(57) Kabalka, G. W.; Gooch, E. E.; Collins, C. J.; Raaen, V. F. *J. Chem. Soc., Chem. Commun.* **1979**, 607.
(58) Tang, D. Y.; Lipman, A.; Meyer, G.-J.; Wan, C.-N.; Wolf, A. P. *J. Labelled Compd. Radiopharm.* **1979**, *16*, 435.
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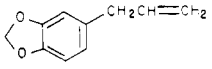
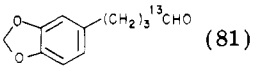
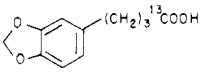
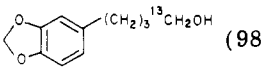
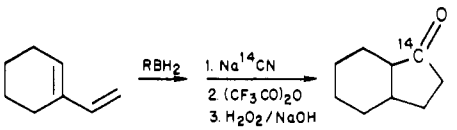
Table VIII
Synthesis of Carbon-13-Labeled Aldehydes, Acids, and Alcohols

alkene	aldehyde (% yield)	acid (% yield)	alcohol (% yield)
$H_3C(CH_2)_6CH=CH_2$	$H_3C(CH_2)_8{}^{13}CHO$ (86)	$H_3C(CH_2)_8{}^{13}COOH$ (94)	$H_3C(CH_2)_8{}^{13}CH_2OH$ (91)
	 (84)	 (93)	 (89)
	 (81)	 (84)	 (98)
p-$MeC_6H_4SCH_2C(CH_3)=CH_2$	p-$MeC_6H_4SCH_2$-$CH(CH_3)CH_2{}^{13}CHO$ (83)	p-$MeC_6H_4SCH_2$-$CH(CH_3)CH_2{}^{13}COOH$ (89)	p-$MeC_6H_4SCH_2$-$CH(CH_3)CH_2{}^{13}CH_2OH$ (90)
$HO(CH_2)_9CH=CH_2$	$HO(CH_2)_{11}{}^{13}CHO$ (85)	$HO(CH_2)_{11}{}^{13}COOH$ (98)	$HO(CH_2)_{11}{}^{13}CH_2OH$ (93)

preliminary studies we used the reaction to incorporate carbon-13 and carbon-14.[62]



We are investigating the use of the cyanidation reaction to synthesize carbon-11 labeled estrone as a potential breast-tumor imaging agent.

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Conclusions

Although we have succeeded in developing new routes for isotope incorporation via organoborane reactions, much remains to be done. The growing need for labeled compounds of increased complexity will continue to challenge organic chemists. It is clear that organoboranes and other organometallic reagents will play an ever increasing role in this area of research.

I gratefully acknowledge financial support from the U.S. Department of Energy, National Institutes of Health, and Research Corporation. I also thank my students and research associates for their contributions to our research efforts.

cis-Alkyl- and *cis*-Acylrhodium and -iridium Hydrides: Model Intermediates in Homogeneous Catalysis

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Although homogeneous catalysis by transition-metal complexes has made significant contributions to industrial and laboratory processes,[1] the mechanistic detail of some of these processes still remains to be resolved. Much of our current mechanistic understanding is based on studies of model compounds, such as *cis*-alkyl- and *cis*-acylmetal hydrides, which are thought to be involved in some very useful transition-metal-catalyzed processes. These reactions, which form or break C–H bonds, include olefin hydrogenation, olefin hydroformylation, and aldehyde decarbonylation, all catalyzed by Rh(I) (Scheme I).

Relatively little is known about the reactivity of *cis*-alkyl- and *cis*-acylmetal hydrides. For example, intramolecular reductive elimination of an aldehyde from a metal complex, which has been proposed as the product-forming step in the cobalt-catalyzed[2] and rhodium-catalyzed[3] olefin hydroformylation reactions, has not been directly observed until very recently[4] for any well-characterized metal system. This lack of studies is perhaps a result of the relative rarity of *cis*-alkyl- and *cis*-acylmetal hydride complexes, which may be attributed to instability. Indeed, *cis*-hydridoalkyl complexes have been observed to decompose at low temperatures.[5] On the other hand, very stable *cis*-hydridoalkyliridium complexes have been recently isolated, raising the question whether this stability is thermodynamic or kinetic in nature.[6-10]

David Milstein was born in Ulm, Germany, and received his Ph.D. (Summa cum Laude) with J. Blum at the Hebrew University of Jerusalem in 1976, while concurrently serving as a Research Chemist at the Nuclear Research Center in Negev, Israel. Following postdoctoral work with J. K. Stille at Colorado State University, he joined the Central Research and Development Department of the Du Pont Co., where he is presently a Group Leader. His research interests are mostly in the areas of synthetic and mechanistic organometallic chemistry and homogeneous catalysis.

(1) G. W. Parshall, "Homogeneous Catalysis", Wiley, New York, 1980.
(2) R. F. Heck and D. S. Breslow, *J. Am. Chem. Soc.*, **83**, 4023 (1961).
(3) (a) G. Yagupsky, C. K. Brown, and G. Wilkinson, *J. Chem. Soc. A*, 2753 (1970); (b) C. K. Brown and G. Wilkinson, *J. Chem. Soc. A*, 2753 (1970).
(4) D. Milstein, *Organometallics*, 1, 1549 (1982).
(5) J. Halpern, *Acc. Chem. Res.*, **15**, 332 (1982).
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(7) T. H. Tulip and D. L. Thorn, *J. Am. Chem. Soc.*, **103**, 2448 (1981).
(8) A. H. Janowicz and R. G. Bergman, *J. Am. Chem. Soc.*, **104**, 352 (1982).
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