Pure Appl. Chem., Vol. 84, No. 11, pp. 2309–2315, 2012.
http://dx.doi.org/10.1351/PAC-CON-12-01-13

Isotope incorporation using organoboranes*

George W. Kabalka‡, Min-Liang Yao, Murthy Akula, and Li Yong

Departments of Chemistry and Radiology, University of Tennessee, Knoxville, TN 37920, USA

Abstract: Isotopes have played an important role in chemistry, biology, and medicine. For the last three decades, we have focused on the use of organoboron compounds as precursors to isotopically labeled physiologically active reagents. During that period, we have successfully developed methods for incorporating short- and long-lived isotopes of carbon, nitrogen, oxygen, and the halogens using a variety of reactive organoboron precursors. In addition, labeling strategies employing polymer-supported organoboron derivatives were developed. In this report, we present a short overview focused on the evolution of radiolabeling techniques based on boron chemistry.

Keywords: boron; isotopes; radiolabeling; radiotracers; synthesis.

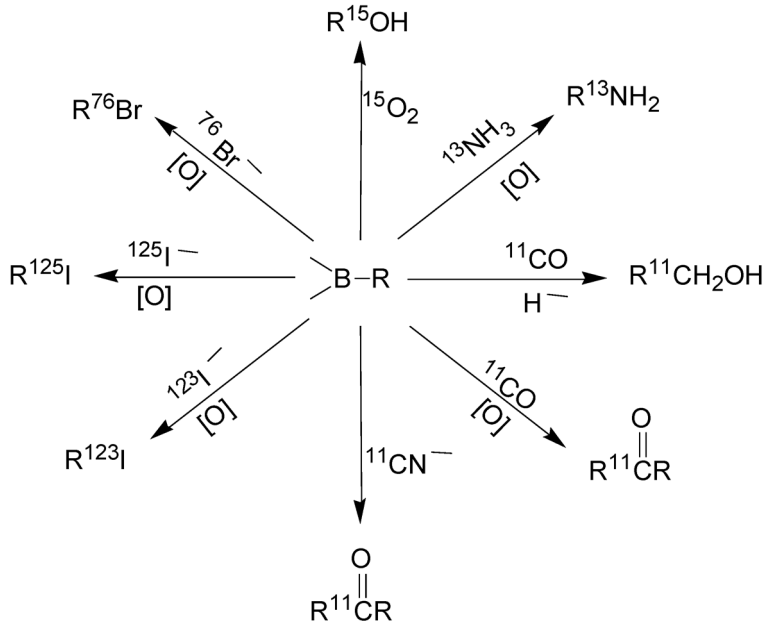
Isotopes have played an important role in chemistry, biology, and medicine since they were first used as tracers by Hevesey [1,2]. Both stable [3–5] and radioactive [6,7] isotopes have been used extensively in the synthesis of isotopically labeled compounds. The use of radioisotopes has increased significantly because of advances in radiation detection techniques such as single photon emission computerized tomography (SPECT) and positron emission tomography (PET). These newer systems permit noninvasive, in vivo, three-dimensional imaging of living systems after administration of appropriate radiolabeled molecules. The use of stable isotopes for labeling organic molecules has also increased because of rapid advances in analytical instrumentation such as multinuclear magnetic resonance spectroscopy (and imaging) as well as gas chromatography-mass spectrometry techniques.

The preparation of isotopically labeled compounds generally begins with a few basic building blocks such as carbon dioxide, carbonate salts, nitric oxide, water, and halide salts [8–10]. These are the species that are generated in cyclotrons and nuclear reactors or that are the most amenable to cryogenic distillation (the most common method for separating stable isotopes). The availability of these building blocks has traditionally been a significant barrier to the synthesis of complex isotopically labeled agents (radiotracers) [11–13]. In addition, the chemical stability of these reagents preclude many classic organic synthetic methods. For example, methodologies based on powerful fluorinating reagents such as Selectfluor^{TM} are not applicable to radiolabeling chemistry because the desired radioactive fluorine-18 labeled analogue cannot be prepared. Generally speaking, incorporation of radioisotopes at a late stage of a multistep synthesis is important to minimize reagent loss due to radioactive decay. The incorporation of isotopes at a late stage is critical in the syntheses of molecules 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). Although not particularly efficient, the early installation of a radioactive carbon fragment was often required because of the stringent reaction conditions required by the available chemistry (Grignard reactions and various solvolytic approaches).

Pure Appl. Chem.* **84, 2183–2498 (2012). A collection of invited papers based on presentations at the 14th International Meeting on Boron Chemistry (IMEBORON-XIV), Niagara Falls, Canada, 11–15 September 2011.
‡Corresponding author: E-mail: kabalka@utk.edu

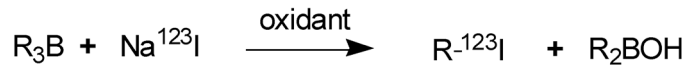
The application of organoboron to the synthesis of isotopically labeled compounds began in the 1970s [14,15]. Initially, only the hydrogen isotopes (tritium and deuterium) had been investigated, and the major purpose of the deuteration study was to determine the stereochemistry and regiochemistry of organoboron reactions [16,17]. Later, studies centered on the incorporation of stable and radioisotopes of elements other than hydrogen were initiated. The new radiolabeling chemistry-based organoboranes was attractive because of the fact that a wide variety of functionally substituted organoboranes could be prepared using the simple techniques developed by Nobel Laureate Herbert C. Brown and his research associates [18–20]. At that time, organoboranes were unique among the reactive organometallic and organometalloidal reagents available because they could be prepared with a variety of functional groups while maintaining high chemical reactivity.

The use of organoboranes as precursors to isotopically labeled reagents has been of continuous interest in our laboratory for over 30 years [15,21]. In that time, we have investigated the feasibility of using a variety of reactive organoboron precursors for isotope labeling purposes. Precursors investigated include the organoboranes, organoboronic acids, organoboronate esters, organotrifluoroborates, and organotriolborates. To date, we have successfully developed methods for incorporating numerous short- and long-lived isotopes of carbon, nitrogen, oxygen, and the halogens (Scheme 1). In addition, labeling strategies employing polymer-supported organoboron derivatives were also developed. These new radiolabeling technologies dramatically facilitated the incorporation of short-lived isotopes. In this report, we present a short overview focused on the evolution of radiolabeling techniques based on boron chemistry.



Scheme 1 Isotope incorporation based on organoborane precursors.

In 1981, we discovered that the iodination of organoborane intermediates occurred readily using sodium iodide in the presence of mild oxidants [22], Scheme 2. Unlike the traditional nucleophilic substitution methods [23], the iodination of organoboranes proceeds via electrophilic substitution. A significant aspect of the new iododeboronation reactions is that they can be carried out utilizing "no-carrier-added" radioiodine, which simply means that the radiolabeled product is not diluted by the corresponding non-radioactive isotope (important when the quantity of radiolabeled agent is to be kept



Scheme 2 Incorporation of radioiodine via organoborane precursors.

below a pharmacological dosage). Owing to their ready availability and lack of toxicity, organoboron compounds have found wide application in the synthesis of a plethora of isotopically labeled agents of use in medicine and biology [23,24].

Later we discovered that this combinative system (sodium iodide and mild oxidants) was effective for radioiodinating vinylborane derivatives to generate stereodefined iodoalkenes. The oxidative iodination sequence was used successfully in the preparation of 17-α-iodovinylestradiol, the first use of a terminal iodovinyl group as a method for increasing the in vivo retention of a radioiodine [25], Fig. 1. The report of the preparation of radioiodinated vinyl iodides via vinylborane chemistry quickly led to the discovery of radiohalogenations using other vinyl and aromatic organometallic reagents, such as tin, mercury, and silane. Those halodemetallation reactions have become valuable methods for obtaining aryl halides or alkenyl halides that are otherwise inaccessible using other methods [26].

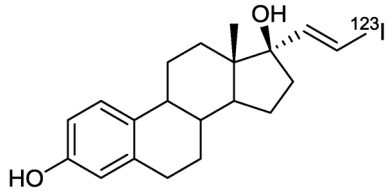


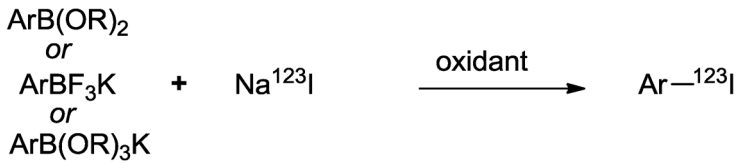
Fig. 1 The first radioiodinated iodovinylestradiol.

It should be noted that organoboranes were also used to incorporate isotopes of oxygen [27,28], nitrogen [29], and carbon [30,31]. [^{15}O]-Butanol, [^{13}N]-putrescine, and a wide variety of [^{11}C]-fatty acids were prepared.

Although the radiolabeling of trialkylboranes, alkenylboranes, and arylborane derivatives is very efficient (high radiolabeling yield and short reaction time), we and others realized the preparation of the prerequisite organoborane reagents could be difficult. The preparation of arylborane derivatives was more problematic since transmetallation reactions were generally required. The air-sensitivity of many organoboranes was also a drawback. Thus, organoborane routes to isotopically labeled compounds were supplanted by routes involving more easily synthesized reagents, such as organotin and organomercury reagents, even though they necessitated the use of heavy metals.

The situation changed dramatically due to the development of Suzuki/Miyaura chemistry (transmetallation), which has made a wide variety of aryl-, vinyl-, and alkylboronic esters readily available in the laboratory (and commercially) [32]. Direct boration of arenas (via C–H activation) developed in recent years made the preparation of functionalized organoboron esters even more straightforward [33]. Recent advances in potassium organotrifluoroborate chemistry [34] provided an alternative route (after the boron incorporation) to functionalized organoboron derivatives. The trifluoroborates are remarkably stable when compared to the corresponding boronic acids, exhibiting shelf lives on the order of years under atmospheric conditions.

The newly developed radiohalogenation chemistry works efficiently at the no-carrier-added level for boronic acids [35], boronic esters [36,37], trifluoroborates [38–40], and triolborates [41]. Although these boron derivatives display varying efficiencies, the facile interconversion [42–44] between boronic acids, boronic esters, and trifluoroborates allow us to choose whichever precursor is most effective for the task at hand, Scheme 3.



Scheme 3 Radioiodination of organoborane derivatives.

We used the newly developed radioiodination chemistry to synthesize reagents for use in medical imaging. We have, for example, synthesized iodine-123 labeled *N*-isopropyl p-iodoamphetamine (IMP) using arylboronic acid precursor [45], refecoxib [46], and iodocurcumin [47] using organotrifluoroborate precursors, Fig. 2.

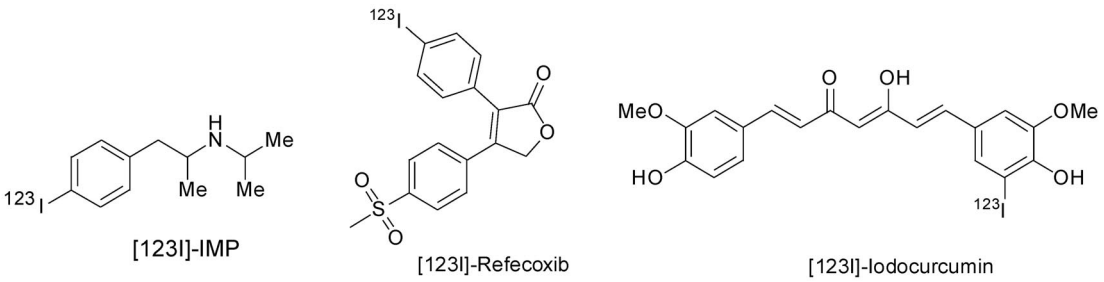


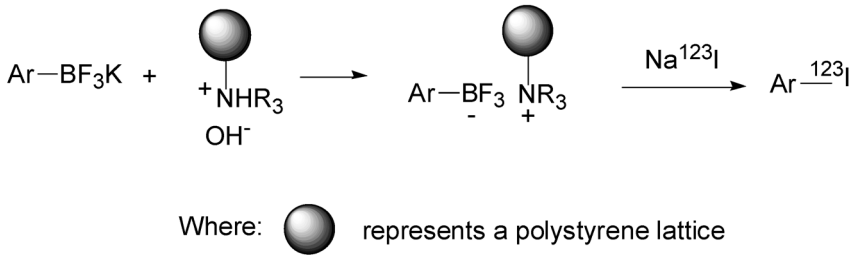
Fig. 2 Radioiodinated agents of use in nuclear medicine imaging research.

Recently, in collaboration with G. J. Meyer's group in Hannover, Germany, the new chemistry has also been used for incorporation of astatine-211 [48].

The palladium-catalyzed Suzuki cross-coupling reaction also provided new strategies to incorporate carbon-isotopes into molecules. Coupling of organoboron reagents with organic halides in the presence of carbon-11 labeled carbon monoxide provides a new route to carbon-11 labeled benzophenone derivatives [49]. The coupling of aryl boronic esters and aryl boronic acids with carbon-11 labeled CH_3I has been successfully used in [^{11}C]-MTEB synthesis [50]. Interestingly, an approach based on aryltrifluoroborate synthesis [42] was utilized to prepare carrier-added F-18 labeled organotrifluoroborate [51]. Using this methodology, a number of potential radiopharmaceutical trifluoroborates have been produced [52].

The removal of excess starting reagents from radiolabeling reactions is important in obtaining pure radiotracers for in vivo applications. Although preparative high-performance liquid chromatography (HPLC) can be used for this purpose, it is time-consuming, which can be problematic when working with short-lived isotopes. To address this issue, we evaluated the feasibility of using polymeric reagents for radiolabeling chemistry [53,54]. The principle of this approach is that, upon reaction with a radionuclide, the desired radiolabeled product will be released into solution from the polymeric precursor. By simple filtration, the excess polymeric precursor can be easily removed. As proof of principle, we successfully prepared nitrogen-13 labeled γ-aminobutyric acid and putrescine using polystyrene-supported organoborane reagents [55]. This methodology found few practical applications because the polymeric organoboron precursors were unstable under atmospheric conditions. However, the concept of applying solid-supported precursors in radiolabeling chemistry has continued to be of interest to a number of research groups [56–60], including our own [61].

To combine the advantages of both polymer and organotrifluoroborate chemistry in the preparation of radiotracers, we synthesized and performed quantitative analyses on resin-supported organotrifluoroborates [62]. We then used them in radioiodination reactions [63], Scheme 4. The advantage of



Scheme 4 The use of polymeric organotrifluoroborates for radioiodinations.

the new polymer-supported reagents over previously reported polymer-supported materials is that libraries of air-stable, polymer-supported organotrifluoroborates can be easily prepared.

We are currently investigating the use of the newly developed polymeric trifluoroborate reagents in the preparation of radiolabeled reagents. The growing need for structurally complex compounds labeled with stable and radioisotopes will continue to challenge organic chemists. It is clear that organoborane reagents will play an ever-increasing role in the area of research.

ACKNOWLEDGMENT

Financial support from the U.S. Department of Energy and the Robert H. Cole Foundation is acknowledged.

REFERENCES

1. G. Hevesy, F. Z. Paneth. *Z. Anorg. Chem.* **82**, 323 (1913).
2. G. Hevesy, E. Hofer. *Nature (London)* **134**, 879 (1934).
3. G. N. Lewis. *J. Am. Chem. Soc.* **55**, 3503 (1933).
4. R. Schoenheimer, D. Rittenburg, M. Fox, A. S. Keston, S. Ratner. *J. Am. Chem. Soc.* **59**, 1768 (1937).
5. H. G. Wood, C. H. Werkman, A. Hemingway, A. O. Nier. *J. Biol. Chem.* **143**, 133 (1942).
6. G. Hevesy, R. Hobbie. *Nature (London)* **128**, 1038 (1931).
7. H. L. Blumgart, O. C. Yens. *Am. J. Physiol.* **72**, 216 (1925).
8. T. A. Baillie. *Stable Isotopes*, University Park Press, Baltimore (1977).
9. M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert, P. M. Yankwich. *Isotopic Carbon*, John Wiley, New York (1949).
10. V. F. Raaen. *Carbon-14*, McGraw Hill, New York (1968).
11. D. G. Ott. *Synthesis with Stable Isotopes*, Wiley-Interscience, New York (1981).
12. A. Murray, D. L. Williams. *Organic Synthesis with Isotopes*, Interscience, New York (1958).
13. M. Allard, E. Fouquet, D. James, M. Szlosek-Pinaud. *Curr. Med. Chem.* **15**, 235 (2008).
14. G. W. Kabalka. *Aspects of Mechanism and Organometallic Chemistry*, J. H. Brewster (Ed.), Plenum Press, New York (1978).
15. G. W. Kabalka. *Acc. Chem. Res.* **17**, 215 (1984).
16. H. C. Brown, K. J. Murray. *J. Org. Chem.* **26**, 631 (1961).
17. H. C. Brown, B. C. S. Rao. *J. Org. Chem.* **22**, 1136 (1957).
18. H. C. Brown. *Organic Synthesis via Boranes*, John Wiley, New York (1975).
19. H. C. Brown. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY (1972).
20. H. C. Brown, M. Zaidlewicz, E. Negishi. *Comprehensive Organometallic Chemistry*, G. Wilkinson, F. G. A. Stone (Eds.), Pergamon Press, Oxford (1982).
21. G. W. Kabalka. *J. Labelled Compd. Radiopharm.* **50**, 888 (2007).

22. G. W. Kabalka, E. E. Gooch. *J. Chem., Chem. Commun.* 1011 (1981).
23. R. H. Seevers, R. E. Counsell. *Chem. Rev.* **82**, 575 (1982).
24. G. Grampa, F. Marinoni. *Farm. Soc. Chim. Ital.* **7**, 569 (1952).
25. G. W. Kabalka, E. E. Gooch, K. A. R. Sastry. *J. Nucl. Med*. **22**, 908 (1981).
26. M.-L. Yao, S. R. Marepally, L. Yong, I. Walfish, D. W. Blevins, G. W. Kabalka. *Org. Lett.* **12**, 700 (2010).
27. G. W. Kabalka, T. J. Reed, K. A. Sastry. *Synth. Commun.* **13**, 737 (1983).
28. G. W. Kabalka, G. W. McCollum, A. *S.* Fabirkiewicz, R. M. Lambrecht, J. S. Fowler, M. Sajjad, A. P. Wolf. *J. Labelled Compd. Radiopharm.* **21**, 1247 (1984).
29. G. W. Kabalka, K. A. R. Sastry, G. W. McCollum, C. A. Lane. *J. Chem. Soc., Chem. Commun.* 62 (1982).
30. G. W. Kabalka, E. E. Gooch, C. J. Collins, V. F. Raaen. *J. Chem. Soc., Chem. Commun.* 607 (1979).
31. G. W. Kabalka, M. C. Delgado, U. S. Kunda, S. A. Kunda. *J. Org. Chem.* **49**, 174 (1984).
32. T. Ishiyama, M. Murata, N. Miyaura. *J. Org. Chem.* **60**, 7508 (1995).
33. S. Kawamorita, H. Ohmiya, K. Hara, A. Fukuoka, M. Sawamura. *J. Am. Chem. Soc.* **131**, 5058 (2009).
34. G. A. Molander, N. Ellis. *Acc. Chem. Res.* **40**, 275 (2007).
35. G. W. Kabalka, T. M. Shoup, G. B. Daniel, M. K. Goodman. *Nucl. Med. Biol.* **27**, 279 (2000).
36. G. W. Kabalka, M. R. Akula, J. H. Zhang. *Nucl. Med. Biol.* **29**, 841 (2002).
37. G. W. Kabalka, M. R. Akula, J. H. Zhang. *Nucl. Med. Biol.* **30**, 369 (2003).
38. G. W. Kabalka, A. R. Mereddy. *Nucl. Med. Biol*. **31**, 935 (2004).
39. G. W. Kabalka, A. R. Mereddy. *J. Labelled Compd. Radiopharm.* **48**, 359 (2005).
40. G. W. Kabalka, A. R. Mereddy, J. F. Green. *J. Labelled Compd. Radiopharm.* **49**, 11 (2006).
41. M. R. Akula, M.-L. Yao, G. W. Kabalka. *J. Labelled Compd. Radiopharm.* **54**, 132 (2011).
42. E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf. *J. Org. Chem.* **60**, 3020 (1995).
43. A. K. L. Yuen, C. A. Hutton. *Tetrahedron Lett.* **46**, 7899 (2005).
44. D. W. Blevins, M.-L. Yao, L. Yong, G. W. Kabalka. *Tetrahedron Lett.* **52**, 6534 (2011).
45. G. W. Kabalka, R. S. Varma, Y.-Z. Gai, R. M. Baldwin. *Tetrahedron Lett.* **27**, 3843 (1986).
46. H. M. Schuller, G. W. Kabalka. U.S. Patent Appl. Pub. US 2006067879 (2006).
47. G. W. Kabalka, M.-L. Yao. *J. Organomet. Chem.* **694**, 1638 (2009).
48. G.-J. Meyer, D. Krull, M. Grote, F. M. Bengel, M.-L. Yao, G. W. Kabalka. *J. Labelled Compd. Radiopharm.* **54**, S576 (2011).
49. N. W. Nader, F. Oberdorfer. *Appl. Radiat. Isot*. **57**, 681 (2002).
50. J. Madsen, P. Merachtsaki, P. Davoodpour, M. Bergstrom, B. Langstrom, K. Andersen, C. Thomsen, L. Martiny, G. M. Knudsen. *Bioorg. Med. Chem.* **11**, 3447 (2003).
51. R. Ting, M. J. Adam, T. J. Ruth, D. M. Perrin. *J. Am. Chem. Soc.* **127**, 13094 (2005).
52. G. E. Smith, H. L. Sladen, S. C. G. Biagini, P. J. Blower. *J. Chem. Soc., Dalton Trans.* **40**, 6196 (2008).
53. G. W. Kabalka, M. M. Goodman, J. F. Green, R. Marks, D. Longord. *J. Labelled Compd. Radiopharm.* **32**, 165 (1993).
54. G. W. Kabalka, J. F. Green, M. M. Goodman, J. T. Maddox, S. J. Lambert. *Current Topics in the Chemistry of Boron*, G. W. Kabalka (Ed.), Royal Society of Chemistry, Cambridge, UK (1994).
55. (a) G. W. Kabalka, Z. Wang, J. F. Green, M. M. Goodman. *Appl. Radiat. Isot.* **43**, 389 (1992); (b) G. W. Kabalka, J. F. Green, M. M. Goodman, J. T. Maddox, S. J. Lambert. "Radiopharmaceutical synthesis via boronated polymers", in: *Current Topics in the Chemistry of Boron*, G. W. Kabalka (Ed.), p. 199, The Royal Society of Chemistry, Cambridge, UK (1994).
56. P. A. Culbert, D. H. Hunter. *React. Polym.* **19**, 247 (1993).
57. K. Kowai, H. Ohta, M. A. Channing, A. Kubodera, W. C. Eckelman. *Appl. Radiat. Isot.* **47**, 37 (1996).

58. A. Pollak, D. G. Roe, C. M. Pollock, L. F. L. Lu, J. R. Thornback. *J. Am. Chem. Soc.* **121**, 11593 (1999).
59. R. Dunn-Dufault, A. Pollak, J. Fitzgerald, J. R. Thornback, J. R. Ballinger. *Nucl. Med. Biol*. **27**, 803 (2000).
60. A. Donovan, J. Forbes, P. Dorff, P. Schaffer, J. Babich, J. F. Valliant. *J. Am. Chem. Soc.* **128**, 3536 (2006).
61. G. W. Kabalka, V. Namboodiri, R. Akula. *J. Labelled Compd. Radiopharm.* **44**, 921 (2001).
62. L. Yong, M.-L. Yao, J. F. Green, K. Hall. G. W. Kabalka. *Chem. Commun.* **46**, 2623 (2010).
63. L. Yong, M.-L. Yao, H. Kelly, J. F. Green, G. W. Kabalka. *J. Labelled. Compd. Radiopharm.* **54**, 173 (2011).

