FINAL REPORT

Title: *Development of Solid State Reagents for Preparing Radiolabeled Imaging Agents*

Project ID: 0014595

Program Manager: Srivastava; Phone: 301-903-4071 Division: SC-23.2

PI: Kabalka

Award Register#: ER64698

Performance Period: September 15, 2008 – September 14, 2011

1) Research Overview:

The goal of this research was on the development of new, rapid, and efficient synthetic methods for incorporating short-lived radionuclides into agents of use in measuring dynamic processes. The initial project period (Year 1) was focused on the preparation of stable, solid state precursors that could be used to efficiently incorporate short-lived radioisotopes into small molecules of use in biological applications (environmental, plant, and animal). The investigation included development and evaluation of new methods for preparing carbon-carbon and carbon-halogen bonds for use in constructing the substrates to be radiolabeled. The second phase (Year 2) was focused on developing isotope incorporation techniques using the stable, boronated polymeric precursors. The final phase (Year 3), was focused on the preparation of specific radiolabeled agents and evaluation of their biodistribution using micro-PET and micro-SPECT. In addition, we began the development of a new series of polymeric borane reagents based on polyethylene glycol backbones.

I am pleased to report that the project met nearly all of the goals outlined in the original proposal. We successfully developed appropriate new carbon-carbon bond forming reactions that can be used to prepare substrates containing reactive functional groups for eventual radioisotope incorporation. We synthesized and fully characterized a series of air and water stable polymeric boronated precursors. These polymer based reagents were utilized to carry out radioisotope incorporations in which the desired products were easily separated from the solid-state reagents.

2) **Accomplishments/deliverables for the project period:**

a. Journal Articles

1. Yao, Min-Liang; Reddy, Marepally Srinivasa; Zeng, Wenbin; Hall, Kelly; Walfish, Ingrid; Kabalka, George W. “Identification of a Boron-Containing Intermediate in the Boron Tribromide Mediated Aryl

Propargyl Ether Cleavage Reaction." *J.Org. Chem.* **2009**, *74*, 1385-1387.

2. Yao, M.-L.; Quick, T. R.; Wu, Z.; Quinn, M. P.; Kabalka, G. W. "Titanium(IV) Halide Mediated Coupling of Alkoxides and Alkynes: An Efficient and Stereoselective Route to Trisubstituted (E)-Alkenyl Halides." *Org. Lett.* **2009**, *11*, 2647-2649.

3. Kabalka, G. W.; Yao, M.-L. "No-carrier-added radiohalogenations utilizing organoboranes: The Synthesis of Iodine-123 Labeled Curcumin." *J. Organometal. Chem.* **2009**, *694*, 1638-1641.

4. Kabalka, G. W.; Coltuclu, Vitali, "Thermal and Microwave Hydrolysis of Organotrifluoroborates Mediated by Alumina." *Tetrahedron Lett.* **2009**, *50*, 6271-6272.

5. Akula, Murthy R.; Yao, Min-Liang; Kabalka, George W. "Triolborates: Water-soluble Complexes of Arylboronic Acids as Precursors to Iodoarenes." *Tetrahedron Lett.* **2010**, *51*, 1170-1171.

6. Kabalka, G. W.; Yao, M.-L. "No-carrier-added radiohalogenations utilizing organoboranes: The Synthesis of Iodine-123 Labeled Curcumin." *J. Organometal. Chem.* **2009**, *694*, 1638-1641.

7. Yao, M.-L.; Quinn, Michael; Kabalka, G. W. "Boron Trichloride Mediated Alkyne-Aldehyde Coupling Reactions." *Heterocycles* **2010**, *80*, 779-785.

8. Akula, Murthy R.; Yao, Min-Liang; Kabalka, George W. "Triolborates: Water-soluble Complexes of Arylboronic Acids as Precursors to Iodoarenes." *Tetrahedron Lett.* **2010**, *51*, 1170-1171.

9. Yong, L., Yao, M. L., Green, J. F., Hall, K., Kabalka, G. W. "Syntheses and Characterization of Polymer-Supported Organotrifluoroborates: Applications in Radioiodination Reactions." *Chem. Commun.* **2010**, *46*, 2623-2625.

10. Akula, M. R.; Yao, M.-L.; Kabalka, G. W. "No-carrier-added Radioiodination of Triolborates, Water-Soluble Complexes of Boronic Acids." *J. Labelled Compds. Radiopharm,* **2011,** *54*, 132-134.

11. Yong, L.; Yao, M.-L.; Hall, K.; Green, J. F.; Kabalka, G. W. "Radioiodination of Polymer-Supported Organotrifluoroborates." *J. Labelled Compds. Radiopharm,* **2011**, *54*, 173-174.

b. Presentations at Meetings (published abstracts)

1. "Trioborates: Water-Soluble Compexes of Organoboranic Acids as Precursors for No-Carrier-Added Radiohalogenations." M. Akula, M. L. Yao, D. Townsend, G. W. Kabalka, 18th International Symposium on Radiopharmaceutical Sciences, Edmonton, Alberta, Canada (July 2009).

2. "New Approaches to Radiohalogentaion Using Solid State Reagents." L. Yong, M. L.; Yao, J. F. Green, K. Hall, G. W. Kabalka, 18th International Symposium on Radiopharmaceutical Sciences, Edmonton, Alberta, Canada (July 2009).

3. "Chemoselective Bromodeboronation of Organotrifluoriborates using Tetrabutylammonium Tribromide (TBATB)." M. L. Yao, S. Marepally, A. Pippin, G. W. Kabalka, The 61st ACS Southeast Regional Meeting, San Juan, Puerto Rico (October 2009).

4. "New Approaches to Halogenation using Solid-State Boronated Reagents." K. Hall, L. Yong, M. L. Yao, J. F. Green, A. Shaikh, G. W. Kabakla, The 61st ACS Southeast Regional Meeting, San Juan, Puerto Rico (October 2009).

5. "A Convenient Synthesis of Aryl Iodides via Cyclic Triolborates." M.L. Yao, M. Akula, G. W. Kabakla, The 61st ACS Southeast Regional Meeting, San Juan, Puerto Rico (October 2009). "Trioborates: Water-Soluble Compexes of Organoboranic Acids as Precursors for No-Carrier-Added Radiohalogenations." M. Akula, M. L. Yao, D. Townsend, G. W. Kabalka, 18th International Symposium on Radiopharmaceutical Sciences, Edmonton, Alberta, Canada (July 2009).

6. "New Approaches to Radiohalogentaion Using Solid State Reagents." L. Yong, M. L.; Yao, J. F. Green, K. Hall, G. W. Kabalka, 18th International Symposium on Radiopharmaceutical Sciences, Edmonton, Alberta, Canada (July 2009).

7. "Chemoselective Bromodeboronation of Organotrifluoriborates using Tetrabutylammonium Tribromide (TBATB)." M. L. Yao, S. Marepally, A. Pippin, G. W. Kabalka, The 61st ACS Southeast Regional Meeting, San Juan, Puerto Rico (October 2009).

8. "New Approaches to Halogenation using Solid-State Boronated Reagents." K. Hall, L. Yong, M. L. Yao, J. F. Green, A. Shaikh, G. W. Kabakla, The 61st ACS Southeast Regional Meeting, San Juan, Puerto Rico (October 2009).

9. "A Convenient Synthesis of Aryl Iodides via Cyclic Triolborates." M.L. Yao, M. Akula, G. W. Kabakla, The 61st ACS Southeast Regional Meeting, San Juan, Puerto Rico (October 2009).

10. "New Directions in Isotope Production and Radiochemistry at the DOE." M. L. Yao, L. Yong, G. W. Kabalka, ACS National Meeting, Boston, MA (August 2010).
11. "Synthesis, Characterization of PEG-Supported Organotrifluoroborates and Their Application in Radio-iodination." Li Yong, Min-Liang Yao, Kelly Hall, George W. Kabalka, SE/SW Regional Mtg ACS, New Orleans, LA (December, 2010)
12. "Synthesis of 2-acetamido-2,4-dideoxy-4-[18F]fluoro-□-D-hexopyranoses". Murthy Akula, Srinivasa Marepally, Lee Collier, George W. Kabalka, 19th ISRS, Amsterdam, Netherlands (August 2011)
13. "A rapid microfluidic synthesis of [^{18}F]fluoroarenes from nitroarenes". Thomas Moore, Murthy Akula, Lee Collier, George W. Kabalka, 19th ISRS, Amsterdam, Netherlands (August 2011)
14. "Microfluidic synthesis of N-[6-(4-[^{18}F]fluorobenzylidene)aminooxyhexyl]maleimide [^{18}F]FBAM". Murthy Akula, Srinivasa Marepally, Lee Collier, George W. Kabalka, 19th ISRS, Amsterdam, Netherlands (August 2011)
15. "Room Temperature Palladium-Catalyzed Homo-Coupling of PEG-Supported Organotrifluoroborates". L. Yong, M.-L. Yao, G. W. Kabalka, IME BORON XIV, Niagara Falls, Canada (September 2011)
16. "Isotope Incorporation Using Organoboranes". G. W. Kabalka, M. Akula, L. Yong, M.-L. Yao, IME BORON XIV, Niagara Falls, Canada (September 2011)

c. Invited Lectures

1. "The Use of Boron in Medical Imaging of Cancer" International Workshop on PET in Boron Neutron Capture Therapy." Pisa, Italy (November 2008)
2. "Isotope Incorporation via Organoboranes" BASF Boron Conference, New Brunswick, NJ (November 2008)
3. "The Design and Synthesis of Medical Imaging Agents" South East Regional ACS Meeting Nashville, TN (November 2008)
4. "Boron in Medicine and Agricultrue" 5th BASF Boron Conference, Hyderabad, India (March 2009)

5. "The Synthesis of Medical Imaging Agents using Organoboranes" The University of Hyderabad, Hyderabad, India (March 2009)

6. "Short Lived Isotope Incorporation Based on Solid State Boron Reagents" The University of Delhi, Delhi India (March 2009)

7. "Organoboranes for Use in Isotope Incorporation" International Isotope Society Meeting, Bad Soden, Germany (October 2009)

8. "Synthesis of Neutron Capture Therapy Agents:, 14th International Congress on Neutron Capture Therapy, Buenos Aires, Argentina (October 2010)

9. "Isotope Incorporation Using Borane Precursors:, The Negishi-Brown Nobel Lectures, Purdue University, October 2010

10. "Modern Approaches to Isotope Incorporation". Tennessee State University (January 2011)

11. "The Synthesis of PET Radiotracers". TennesseeTechnical University, Cookeville, TN (February 2011)

12. "Isotope Incorporation Using Organoborane Chemistry". Northeastern University, Boston, MA (March 2011)

13. "Isotope Incorporation Using Organoboranes". G. W. Kabalka, M. Akula, L. Yong, M.-L. Yao, IME BORON XIV, Niagara Falls, Canada (September 2011)

The preparation of the solid state reagents is so straightforward that we anticipate the reagents will be used by other laboratories for radiolabeling protocols. One postdoctoral Fellow, one graduate student, and two undergraduate students were supported by this US Department of Energy grant.

3) Potential benefits/applications of DOE funded research for DOE and other agency or industry:

With the advent of micro-PET and micro-SPECT techniques for analyzing the dynamic function of living systems (plants and animals), the need for simple and rapid isotope incorporation chemistry has increased dramatically. Isotopically labeled compounds are used for real-time, high-resolution imaging of dynamic biological processes that are relevant to energy and environmental studies. These include elucidation of aspects of plant metabolism relevant to bio-fuel production as well as insights into microbial metabolism. The results of this study are also fundamentally important in the area of nuclear medicine diagnostic and/or therapeutic research. The new chemistry provides the components for simple radiolabeling "kits" (reagents that can

be utilized by moderately skilled technicians for generating radiolabeled agents with little or no additional manipulation). These “kits” can be used to prepare a wide variety of radiopharmaceuticals that for use in solving problems of clinical significance.