American Chemical Society

National Awards Nomination Packet

Herbert C. Brown Award for Creative Research in Synthetic Methods:2018
for: Martin Burke

Received: 10/27/2015 *Cycle Year: 2*

"For the development of powerfully simple methods that harness the inherent modularity of complex natural products to enable their more generalized and automated synthesis."

NOMINATOR:

Paul Wender

Stanford University
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Stanford, CA 94305-4401
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- Have you discussed this award nomination with the nominee? *Yes*

NOMINEE:

Martin Burke

Univ Illinois Urbana Champaign
600 S Mathews Ave
Urbana, IL 61801-3602
UNITED STATES

Tel: (217)244-8726
Fax: (217)244-8024
Email: mdburke@illinois.eduXXX

ACS Current Member: Yes
Years of Service: 17
Date of birth: 01/01/1976
Present Position: Professor of Chemistry
Industry: Academia

- Does the nominee employ and require good safety protocols and practices in his/her laboratory? *Yes*
- What is the nominee's present position? *Professor of Chemistry*
- What professional discipline does the nominee work in? *Academia*
- Prior Recipient ? *Yes*
- Reason? Nominee has won at least one award in the past 5 years. Last award won: Nobel Laureate Signature Award for Graduate Education in Chemistry:2017 in 2017
- Work Differs: The EJ Corey Award in 2013 honored early work in Marty's lab on the initial development of MIDA boronates for iterative cross-coupling. This nomination alternatively cites new breakthroughs described in more recent publications that build on these early studies but constitute a distinct and major step forward. These advances could not have been anticipated by earlier studies and represent a major breakthrough in the research.

SUPPORTER 1

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Confidential

October 19, 2015

ACS Brown Award

Dear Colleagues:

I enthusiastically nominate Martin Burke for the ACS Brown Award. I have only the highest praise for Marty and his research. He has produced towering contributions marked by exceptional creativity, vision, depth and fearlessness. He is a unique candidate for this special honor.

Marty has made major, differentiating contributions to synthesis. He pioneered the MIDA boronate platform for small molecule synthesis, which is seeing *global* utilization in both the pharmaceutical and academic communities. He has produced a long list of commercially available synthetic building blocks. He has advanced this technology to a platform approach for robotic synthesis. His recent Science manuscript (2015) on this subject is extraordinary, showing not only an ability to decipher global synthetic approaches to whole families of natural targets and analogs but providing the first generation of machines to automate such fine chemical syntheses. His vision opens the field of fine chemical synthesis to those not skilled in the science in the same way that Merrifield's contributions opened up the use of peptides to those not skilled in peptide synthesis. Marty has developed impressive synthetic approaches to deciphering the mechanism of action of the clinically important antifungal agent amphotericin-B. His ability to integrate synthesis with design to learn about function is a powerful example of function-oriented synthesis (*Accounts*2015). Marty's multiple advances establish him as a thought leader in synthesis. Marty aims to design small molecules to replicate protein function, a visionary program called "molecular prosthetics".

In creating the MIDA boronate platform, Marty recognized that "synthesis still represents the rate-limiting step in small molecule science." To address this problem, he invented a novel strategy for making small molecules, dubbed *iterative cross-coupling*. In this approach, conceptually analogous to peptide coupling, a palladium-mediated cross-coupling reaction is employed recursively to assemble bifunctional "haloboronic acid" building blocks with all the required functional groups, oxidation states, and stereochemistry pre-installed. Making this approach possible, Marty discovered a new concept (*JACS*2007) for reversibly attenuating the reactivity of a boronic acid, thereby avoiding oligomerization of bifunctional haloboronic acids. The concept involves rehybridization of the reactive Bsp^2 center in a boronic acid into its Bsp^3 hybridized counterpart via complexation with a trivalent heteroatomic ligand such as *N*-methyliminodiacetic acid (MIDA). Lacking a boron p orbital, these "MIDA boronates" are unreactive under anhydrous cross-coupling conditions. These reagents are generally air-stable, highly crystalline, and fully compatible with chromatography, collectively rendering them outstanding building blocks for synthesis.

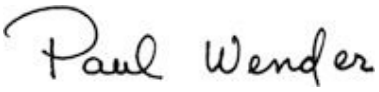
Marty's group has completed the total syntheses of a remarkable range of natural products and pharmaceuticals using his iterative cross-coupling strategy, including ratanhine, crocacin-C, retinal, parinaric acid, ratanhiaphenol-III, peridinin, synechoxanthin, renierapurpurin, a glucagon receptor inhibitor under investigation by Merck, as well as the polyene cores of amphotericin-B and vacidin-A. These achievements buttress the case that MIDA boronates as a general platform for small molecule synthesis. His recent *Science* manuscript further exemplifies the power of his approach, r*eporting automated syntheses of 14 classes of small molecules*. While some seek to make a target, and others to create a general strategy, Marty has shown the strategic synthetic insight, mechanistic understanding and vision to boldly approach the synthesis multiple families of natural products and their analogs.

Marty's impact on synthesis is enormous. Sigma-Aldrich now offers ~100 of Marty's MIDA boronates as commercial reagents. These reagents have appeared in many recent papers from leading academic groups worldwide. MIDA boronates are also being used by many pharmaceutical companies in drug discovery, and there is already one multi-kilogram scale process in the pharmaceutical industry based on MIDA boronates. Few achieve in a lifetime what Marty has in his early career.

Equally impressive have been Marty's achievements in using synthesis to understand small molecule biological function, such as the antifungal activity of amphotericin. Harnessing the power of synthesis and his MIDA boronate platform, Marty has provided new insights on the mechanism of action of amphotericin as described in breakthrough papers in *JACS* and *PNAS*. In stark contrast to the widely accepted "channel model" in which amphotericin is thought to kill yeast via membrane permeabilization, Marty's experiments indicate that amphotericin possibly kills yeast by simply binding ergosterol, a finding that holds special promise for developing resistance-refractory antimicrobial agents.

In conclusion, Marty has demonstrated the innovative capacity to make broad major advances in both synthesis and mechanistic chemistry. This rare but powerful combination has enabled him to lay the foundation for potentially transformational approaches to organic synthesis and to studies on the mode of action of biologically active small molecules. Marty is a truly exceptional candidate for the Brown Award.

Best,



Paul A. Wender
Bergstrom Professor of Chemistry
Professor of Chemical and Systems Biology

Martin D. Burke – *Curriculum Vitae*

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University of Illinois at Urbana-Champaign
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Education

1998-2005	Harvard Medical School & Massachusetts Institute of Technology Division of Health Sciences and Technology National Institutes of Health Fellow in the Medical Scientist Training Program Boston, Massachusetts, Degree awarded: M.D.
1999-2003	Harvard University, Department of Chemistry and Chemical Biology Howard Hughes Medical Institutes Predoctoral Fellow Thesis advisor: Professor Stuart L. Schreiber Cambridge, Massachusetts, Degree Awarded: Ph.D.
1994-1998	Johns Hopkins University Howard Hughes Medical Institute Undergraduate Research Fellow Research advisors: Professors Henry Brem and Gary H. Posner Baltimore, Maryland, Degree Awarded: B.A. Chemistry

Appointments

2014	Professor of Chemistry, University of Illinois at Urbana-Champaign
2011	Associate Professor of Chemistry, University of Illinois at Urbana-Champaign
2009	Early Career Scientist, Howard Hughes Medical Institute
2009	Affiliate Faculty, Dept. of Biochemistry, University of Illinois at Urbana-Champaign
2005	Assistant Professor of Chemistry, University of Illinois at Urbana-Champaign

Awards and honors

2016	Aldrich Lectureship, McGill University and University of Montreal, Canada
2016	Burkett Lectureship, Depauw University
2015	University of Bristol Chemical Synthesis CDT-Syngenta Award, UK
2014	Thieme-International Union of Pure and Applied Chemistry (IUPAC) Prize in Synthetic Organic Chemistry
2014	American Asthma Foundation Scholars Award
2014	Hirata Gold Medal, Japan
2014	International Organic Chemistry Foundation Lectureship Award, Japan
2013	Kavli Foundation Emerging Leader in Chemistry Award, American Chemical Society
2013	Elias J. Corey Award for Outstanding Original Contribution in Organic Synthesis by a Young Investigator, American Chemical Society
2013	University of Illinois Innovation Discovery Award
2012	Novartis Chemistry Lectureship: Basel, Horsham, Shanghai, Singapore, and Cambridge
2011	Arthur C. Cope Scholar Award, American Chemical Society
2011	Teacher Ranked as Excellent, UIUC Center for Teaching Excellence
2010	Bristol-Myers Squibb Lectureship at Harvard University
2010	Frontiers in Chemistry Lectureship at The Scripps Research Institute
2010	Novartis Lectureship at The University of California Berkeley
2009	Howard Hughes Medical Institute Early Career Scientist
2009	Alfred P. Sloan Foundation Research Fellowship
2009	Bristol-Myers Squibb Unrestricted Grant in Synthetic Organic Chemistry Award

2009	Eli Lilly Grantee Award
2009	AstraZeneca Excellence in Chemistry Award
2009	Amgen Young Investigator Award
2009	Bristol-Myers Squibb Lectureship at Princeton University
2009	Thieme Chemistry Journals Award
2008	Teacher Ranked as Excellent, UIUC Center for Teaching Excellence
2008	Arnold and Mabel Beckman Foundation Young Investigator Award
2008	"World's 35 Top Innovators Under 35" *Technology Review* Magazine
2008	National Science Foundation CAREER Award
2008	"Scientist to Watch" *The Scientist* Magazine
2007	Teacher Ranked as Outstanding, UIUC Center for Teaching Excellence
2006	Teacher Ranked as Excellent, UIUC Center for Teaching Excellence
2005	ACS Petroleum Research Foundation Type G Award
2005	Camille and Henry Dreyfus New Faculty Award
2005	Henry Asbury Christian Award, Harvard Medical School
2003	National Institutes of Health Medical Scientist Training Program Fellowship
2000	Howard Hughes Medical Institute Predoctoral Fellowship
1998	Hunterian Research Award - Johns Hopkins Department of Neurosurgery
1997	Phi Beta Kappa - Junior Year, Johns Hopkins University
1997	Howard Hughes Undergraduate Research Fellowship - Johns Hopkins University
1997	Provost's Undergraduate Research Award - Johns Hopkins University
1994-1998	Dean's List - Johns Hopkins University
1994-1998	Beneficial Hodson Scholar - Johns Hopkins University
1994-1998	Maryland Distinguished Scholar

Martin D. Burke – *20 Selected Publications and Patents*

20. J. Li, S.G. Ballmer, E.P. Gillis, S. Fujii, M.J. Schmidt, A.M.E. Palazzolo, J.W. Lehmann, G.F. Morehouse, M.D. Burke, "Synthesis of Many Different Types of Organic Small Molecules Using One Automated Process" *Science* **2015**, *347*, 1221-1226.

19. E.M. Woerly, J. Roy, M.D. Burke, "Synthesis of Most Polyene Natural Products Using Just Twelve Building Blocks and One Coupling Reaction" *Nature Chem.* **2014**, *6*, 484-491.

18. 27. G.R. Dick, E.M. Woerly, M.D. Burke, "A General Solution to the 2-Pyridyl Problem" *Angew. Chem. Int. Ed.* **2012**, *51*, 2667-2672.

17. B. C. Wilcock, B.E. Uno, G.L. Bromann, M.J. Clark, T.M. Anderson, M.D. Burke, "Electronic Tuning of Site-Selectivity" *Nature Chem.* **2012**, *4*, 996-1003.

16. K.C. Gray, D.S. Palacios, I. Dailey, M. Endo, B.E. Uno, B.C. Wilcock, M.D. Burke, "Amphotericin Primarily Kills Yeast by Simply Binding Ergosterol." *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 2234-2239.

15. J. Li, M.D. Burke, "Pinene-Derived Iminodiacetic Acid (PIDA): A Powerful Ligand for Stereoselective Synthesis and Iterative Cross-Coupling of C(sp^3) Boronate Building Blocks" *J. Am. Chem. Soc.* **2011**, *131*, 13774-13777.

14. S. Fujii, S.Y. Chang, M.D. Burke, "Total Synthesis of Synechoxanthin through Iterative Cross-Coupling" *Angew. Chem. Int. Ed.* **2011**, *50*, 7862-7864.

13. E.M. Woerly, A.H. Cherney, E.K. Davis, M.D. Burke, "Stereoretentive Suzuki-Miyaura Coupling of Haloallenes Enables Fully Stereocontrolled Access to (-)-Peridinin" *J. Am. Chem. Soc.* **2010**, *132*, 6941-6943.

12. S.J. Lee, T.M. Anderson, M.D. Burke, "A Simple and General Platform for Generating Stereochemically Complex Polyene Frameworks via Iterative Cross-Coupling." *Angew. Chem. Int. Ed.* **2010**, *47*, 8860-8863.

11. D.M. Knapp, E.P. Gillis, M.D. Burke. "A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable MIDA Boronates" *J. Am. Chem. Soc.* **2009**, *131*, 6961-6963.

10. E.P. Gillis, M.D. Burke. "Multistep Synthesis of Complex Boronic Acids from Simple MIDA Boronates" *J. Am. Chem. Soc.* **2008**, *130*, 14084-14085.

9. S.J. Lee, K.C. Gray, J.S. Paek, M.D. Burke. "Simple, Efficient, and Modular Syntheses of Polyene Natural Products via Iterative Cross-Coupling" *J. Am. Chem. Soc.* **2008**, *130*, 466-468.

8. E.P. Gillis and M.D. Burke. "A Simple and Modular Strategy for Small Molecule Synthesis: Iterative Suzuki-Miyaura Coupling of B-Protected Haloboronic Acid Building Blocks." *J. Am. Chem. Soc.* **2007**, *129*, 6716-6717.

7. M.D. Burke et al, "Protected Organoboronic Acids with Tunable Reactivity, and Methods of Use Thereof. US \Patent Application 62/202,437.

6. M.D. Burke, J.Q. Li, E.P. Gillis, PCT/US**2012**/035247 "Automated Synthesis of Small Molecules Using Chiral Nonracemic Boronates"

5. Burke et al PCT/US**2011**/045064 "Apparatus and Methods for the Automated Synthesis of Small Molecules"

4. M.D. Burke, et al "Cross-Coupling of Unactivated Secondary Boronic Acids." US Application 61/899,296

3. M.D. Burke, G.R. Dick, E.P. Gillis, J.A. Klubnick, D.M. Knapp, B.E. Uno, "Methods for Forming Protected OrganoBoronic Acids" U.S. Utilility Patent Application No.: 13/030,83. Claims Granted 7/23/2013.

2. M.D. Burke, D.M. Knapp, E.P. Gillis, "Slow-Release of Unstable Boronic Acids from Air-Stable MIDA Boronates" U.S. Patent # 9,006,463 Issued April 14, 2015..

1. M.D. Burke, E.P. Gillis, S.J. Lee, D.M. Knapp, K.C. Gray, "System for Controlling the Reactivity of Boronic Acids" U.S. Patent # 8,013,203 Issued Sept. 6, 2011.

HHMI
HOWARD HUGHES MEDICAL INSTITUTE

October 18, 2015

Dear Award Selection Committee,

I am delighted to support Marty Burke's nomination for the H. C. Brown Award. Marty has created a powerfully simple and automated process for making complex natural products, drugs, and materials. His overall goal is to enable making most small molecules the same way, and thereby bring the power of small-molecule synthesis to non-specialists. Marty's MIDA boronate-based synthetic methods have already had a major impact in both academia and industry, and illuminated an actionable roadmap toward this long-term aspiration. Marty is thus a truly exceptional candidate for the H.C. Brown award.

Marty's approach involves iterative assembly of bifunctional "haloboronic acid" building blocks with all the required functional groups, oxidation states, and stereochemistry are pre-installed. This essentially reduces the complex problem of small molecule synthesis to simply making and coupling building blocks. He has developed a suite of powerful methods for making and coupling N-methyliminidoacetic acid (MIDA) boronates. In 2007 he reported that MIDA boronates are unreactive toward cross-coupling, and yet readily hydrolyzed under mild orthogonal conditions. This discovery first enabled the total synthesis of complex natural products using just one reaction iteratively. In 2008, Marty described a "slow-release cross-coupling" method that enables couplings with even highly unstable boronic acids. He has also discovered the first method for cross-coupling unactivated chiral Csp^3 boronic acids with stereoretention. These advances expand the range of targets that are amenable to iterative synthesis.

Marty also developed many new methods for making MIDA boronates, which have expanded access to many challenging building blocks. Finally, he recently reported in *Nature Chemistry* that most polyene natural product motifs can be made from just 12 building blocks and one coupling reaction. He also laid out a vision for how the inherent redundancy of natural products should enable most of them to be made from a bounded collection of building blocks. This year, in *Science* Marty reported a transformative breakthrough – a machine that makes many different types of small molecules using the same fully automated building block assembly process. In this work, he used a powerful "linear-to-cyclized" strategy to expand the scope of this platform to even include highly complex and Csp^3-rich macrocyclic and polycyclic natural products.

For two centuries, chemists have made different target molecules using customized strategies and methods. Marty's work has advanced organic synthesis towards a more generalized, automated approach. He is an outstanding candidate for this award.

Sincerely yours,

David Liu
Professor of Chemistry and Chemical Biology
Investigator, Howard Hughes Medical Institute

David R. Liu, Ph.D.
Investigator

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Potsdam-Golm, October 19, 2015

Support of the nomination of Marty Burke for the ACS Herbert C. Brown Award for Creative Research in Synthetic Methods

Dear Members of the Selection Committee,

I herein express my strongest possible support for Marty Burke's nomination for the ACS Herbert C. Brown Award for his pioneering work in automated synthesis with MIDA boronates. I have followed this work closely since his breakthrough JACS communication in 2007, which first demonstrated the synthesis of a complex natural product using just one reaction iteratively. This was achieved with the brilliantly simple strategy of reversibly blocking the reactivity of bifunctional haloboronic acid building blocks with the "MIDA" ligand. Marty has since created an entire platform of MIDA boronate-based methods and building blocks, which collectively comprise an increasingly general approach for making small molecules. Challenging more than a century of history in the field of synthetic organic chemistry, which largely focused on customized approaches to making each target, Marty boldly proposed—and has now increasingly demonstrated—that many (and possibly most!) natural products may be accessible from a limited number of MIDA boronate building blocks and the same coupling chemistry. For example, in a paper published in Nature Chemistry in 2014, he showed that the biosynthetically grounded inherent redundancy of polyene natural products enables more than 75% coverage of polyene natural product space using just 12 MIDA boronate building blocks. Marty's new methods are already having major impact in both academia and industry. Hundreds of his building blocks are now commercially available and widely used, with industrial applications on both the discovery and process scale.

In a highly impactful paper in Science in 2015, Marty's group disclosed a molecule-making machine, analogous to a peptide synthesizer that automatically assembles MIDA boronate building blocks into a wide range of pharmaceuticals, materials, and natural products, including even some highly complex and Csp3-rich macro- and polycyclic targets. This paper sparked a vigorous debate worldwide about the future of organic synthesis. Marty is also the scientific founder of a new biotechnology company, called REVOLUTION Medicines, which is industrializing and harnessing his automated synthesis platform to systematically transform natural products into new powerful new drugs.

The company was just recently recognized as one of the top 15 private biotech companies in the world by FierceBiotech. Perhaps most excitingly, Marty has articulated a powerful vision and defined an actionable roadmap for achieving generalized and automated on-demand small molecule synthesis. This could ultimately bring the power of making small molecules to non-specialists and unleash the tremendous and still largely untapped functional potential that small molecules possess.

Best personal regards

Prof. Peter H. Seeberger