DOI: 10.1002/anie.201406633

C–H Functionalization: Collaborative Methods to Redefine Chemical Logic

Huw M. L. Davies and Daniel Morton**

Daniel Morton
Managing Director,
Center for Selective
C–H Functionalization

Huw M. L. Davies
Asa Griggs Candler
Professor and Director,
Center for Selective
C–H Functionalization

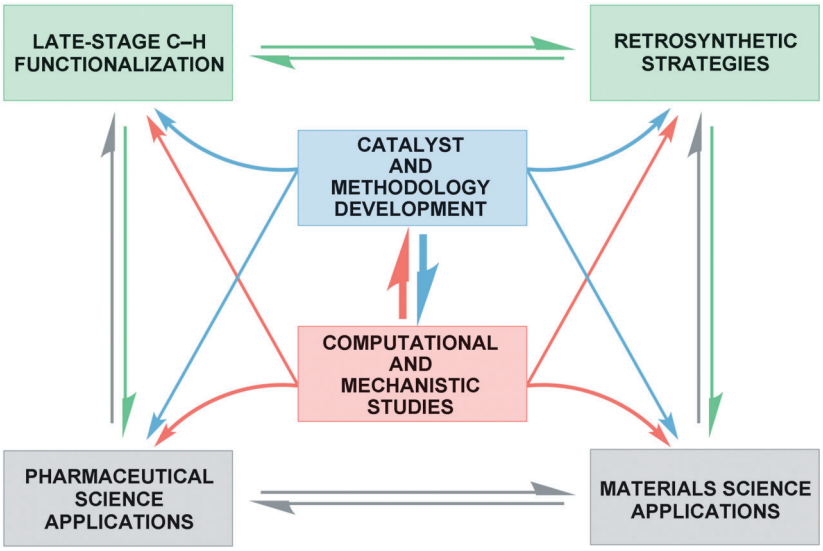
In many fields of academic scientific research, collaborations come about quite naturally. One discipline, however, that has tended not to follow this pattern is organic synthesis. That is not to say that organic chemists don't collaborate, but synthetic organic chemistry is primarily considered an enabling science. Advances in synthesis empower research in many other fields, and synthetic organic chemists are often actively engaged in interdisciplinary collaboration. However, it is rare to find synthetic organic chemists collaborating with each other toward a goal within their own discipline. Many arguments could be put forth for this lack of cooperation, but perhaps the most convincing is that organic chemistry, compared to many other fields, when most effective, is readily accessible. It does not rely upon highly sophisticated instrumentation or facilities that are available only to a few. A fantastic new synthetic method would ideally be extremely easy to perform from readily available materials. So, what really distinguishes a research program in organic synthesis are the ideas behind the work. As a consequence, sharing one's most exciting research ideas and insights with other organic chemists is risky, because, in principle, it would not require too much effort for an organic chemist to take advantage of an open exchange of ideas with another. Hence, synthetic organic chemists need to establish a high level of trust before they can effectively collaborate within their own discipline.

An area of intense interest at the heart of modern organic synthesis is C–H functionalization. The development of techniques that can predictably modify C–H bonds selectively would fundamentally change the logic of organic synthesis; the C–H bonds would become the favored reaction partners and the "functional groups" would be relegated to structural adornments. Of course, in order to achieve such a scenario many massive challenges must be met. Certainly, free radical reactions have taught us that the selective functionalization of the least stable C–H bond is possible, but the ability to precisely control product selectivity in functional-group-containing molecules possessing multiple, disparate C–H bonds is the defining challenge for this field.

In recent years, several significant advances have been made in the field of C–H functionalization. New reagents and various transition-metal catalysts, originating from the organometallic community, have revealed the possibility of achieving truly selective C–H functionalization methods. Many of the early studies focused on simple organic substrates. However, in order for this field to develop, it was necessary to move beyond simple substrates to be challenged in more complex molecular scaffolds. To make this leap and develop this transformation from a novelty into a practical synthetic process, the fundamentals of the reaction mechanism would need to be thoroughly understood. This would require advanced theoretical, mechanistic, and experimental analysis as these organometallic systems are often complex with subtle controlling factors. New catalysts, new reagents, and improved reaction engineering would be required to ensure that the methodology is robust, cost-effective, and sustainable. For C–H functionalizations, predictive rules need to be developed to define what C–H bonds are likely to react in a complex molecular setting; these results must be taken into account in synthesis design (retrosynthesis). Ideally these academic explorations would be conducted in partnership with industry to ensure that the developing methodologies are rapidly applied to "real world" synthetic problems (see schematic overview).

The challenges faced when introducing a whole new way of thinking about constructing organic molecules are exponentially greater than those for developing a single new reaction and certainly beyond the grasp of a single investigator. To meet the challenges associated with bringing C–H functionalization into the mainstream of synthetic chemistry, a multifaceted approach is required. Therefore, in 2009 we responded to a solicitation from the National Science Foundation for a Phase I Center in Chemical Innovation. The founding team of the Center for Selective C–H Functionalization (CCHF; see http://www.nsf-cchf.com/), consisted of one computational chemist (Jamal Musaev) and five synthetic chemists with expertise in not only designing new catalysts and synthetic methods in C–H functionalization, but also under-

[*] Prof. H. M. L. Davies, Dr. D. Morton
Department of Chemistry, Emory University
1515 Dickey Drive, Atlanta, GA 30322 (USA)
E-mail: hmdavie@emory.edu
daniel.morton@emory.edu



standing the logic of the synthesis of complex molecules (Simon Blakey, Huw Davies, Justin Du Bois, Christina White, and Jin-Quan Yu). When we started, none of us had collaborated together, and even though our research programs were complementary, many in the field would have considered us as potential competitors rather than collaborators. Our first meeting was a very exciting affair, devoting a one-day symposium to sharing our established research programs and then a second day of brainstorming in which we had to let go of our usual scientific reservations, so that we could find some common ground, which eventually became the foundation of our Center.

Phase I funding lasted three years and was considered to be a pilot project for preparing the group to apply to become a much larger Phase II Center. For us the Phase I period was crucial because we needed to build trust and to explore whether the concept of conducting one's research within a collaborative team was advantageous. During this time, we also needed to expand the team from the central core of methodology developers. The growth was carefully planned, focusing on the addition of people who were not only excellent scientists, but also likely to embrace the collaborative dynamic we were building. The current members of the Center, as well as their areas of expertise and institutions are given in Table 1. Early on, the team developed a very close partnership with Novartis Institutes for BioMedical Research, facilitated by Larry Hamann, so that results can be quickly tested for their utility in the synthesis of pharmaceuticals. During the first phase of funding this team began working together and making the connections that were compelling in the justification of a Phase II Center that was awarded in 2012.

So, how do 23 research groups, located over 15 universities, many of which could easily be in direct competition with each other, manage to collaborate? Effective, open, and stimulating communication is essential. Every week we meet over our videoconference system for technical–scientific discussions, logistical issues, and Center updates. When Phase II funding was awarded, we arranged a Center-wide symposium at Emory University to move the ideas we had on paper into real collaborations in a face-to-face setting. This was a crucial meeting because the whole group needed to gain confidence with letting down their scientific guards so that we could share ideas. This behavior is so unusual within the organic chemistry community that we spent half a day discussing our expectations and what would be best practices for engagement (look for collaborations first, avoid competition with/within the Center, be a doer not a listener, etc.). The meeting provided an excellent environment for open scientific exchanges with the experts in one's field, without fear of competition, something that can be difficult to find. We have organized the Center into six thematic areas and every week we discuss technical details around a specific theme. Even though only about six groups would be nominally connected to each theme we typically have about 20 groups joining each meeting because we encourage continuous

Table 1: Members of the Center, their areas of expertise, and institutions.

Member	Area	Institution
John Berry	Inorganic	University of Wisconsin
Donna Blackmond	Kinetics	The Scripps Research Institute, La Jolla
Simon Blakey	Methodology	Emory University
Andy Borovik	Inorganic	University of California, Irvine
Huw Davies	Methodology	Emory University
Justin Du Bois	Methodology	Stanford University
Stefan France	Methodology	Georgia Institute of Technology
Ken Houk	Theory	University of California, Los Angeles
Chris Jones	Chemical engineering	Georgia Institute of Technology
Jared Lewis	Bioinorganic	University of Chicago
Christine Luscombe	Organic materials	University of Washington
Cora MacBeth	Inorganic	Emory University
Seth Marder	Organic materials	Georgia Institute of Technology
John Montgomery	Methodology	University of Michigan
Mo Movassaghi	Total synthesis	Massachusetts Institute of Technology
Jamal Musaev	Theory	Emory University
Richmond Sarpong	Methodology	University of California, Berkeley
David Sherman	Bioinorganic	University of Michigan
Matt Sigman	Physical organic	University of Utah
Eric Sorensen	Total synthesis	Princeton University
Brian Stoltz	Total synthesis	California Institute of Technology
Jin-Quan Yu	Methodology	The Scripps Research Institute, La Jolla
Richard Zare	Mechanistic studies	Stanford University

exploration of new collaborative opportunities. The enthusiasm level of the faculty and students has been incredibly high because everyone feels that their research programs are greatly enriched from the collaborative atmosphere. This is one of the key strengths of the Center community network, ongoing research projects are presented to a large and diverse audience of faculty and student peers and the discussion and feedback generated are very helpful.

Organization and engagement is also essential for such a geographically dispersed collective to operate effectively. Members have demonstrated an exceptional level of commitment to the collaborative network, not simply in terms of the scientific engagement, but also involvement in the integrative activities of the Center. This has been facilitated by a management team based at Emory University consisting of a Director (Huw Davies), Managing Director (Daniel Morton), and Education, Outreach, and Diversity Director (Monya Ruffin). A Governance Committee, a Scientific Advisory Board, and a Student Advisory Board help guide Center activities.

How is this approach affecting the research? Since its inception, the Center has published over 70 papers, over half of which have multiple faculty members as co-authors. Through a combination of computational and experimental studies, we have gained not only a greater understanding of the chemistry, but also begun to develop predictive systems to lead our studies. Some excellent examples include the first characterization of a dirhodium carbenoid, the analysis, understanding and predication of site-selectivity in C–H amination, and the modelling and prediction of remote C–H activation templates. Collaborations between the methodology and total-synthesis groups have led to streamlined synthesis of complex targets and the design of more robust C–H functionalization methods for skeletal construction and late-stage C–H functionalization. The Center has also found traction with some of the "real-world" challenges brought to the community, preparing novel electron-transport polymer building blocks inaccessible through known methods and developing techniques to expand substrate scopes to more pharmaceutically applicable systems.

How is this approach affecting the researchers? Cultivating a research community has revealed benefits, for faculty and students alike, beyond what we imagined. The open and free exchange of ideas and feedback provide a research environment and experience unlike that possible in an individual group setting. We hope this enables and empowers our members to be better communicators and collaborators in the future.

Collaboration does not stop at the door. The Center has collaborative projects beyond its membership, with projects, either active or completed, that have included over ten different research groups from across the USA. We are currently making global connections to partners in Asia and Europe. The Center is also developing a new mechanism to facilitate engagement with industrial partners. We have benefited from an extremely fruitful partnership with Novartis that has challenged the way we think about our chemistry and while we are strengthening this relationship we are exploring ways to engage with other industries from across the chemical sciences. Ultimately through our scientific work and educational activities we aim to not only bring C–H functionalization to the mainstream attention of the chemical community, but also to train chemists who can take advantage of the benefits a collaborative network creates.