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Aims and Scope

The series Topics in Current Chemistry presents critical reviews of the present and future trends in modern chemical research. The scope includes all areas of chemical science, including the interfaces with related disciplines such as biology, medicine, and materials science.

The objective of each thematic volume is to give the non-specialist reader, whether at the university or in industry, a comprehensive overview of an area where new insights of interest to a larger scientific audience are emerging.
Thus each review within the volume critically surveys one aspect of that topic and places it within the context of the volume as a whole. The most significant developments of the last 5–10 years are presented, using selected examples to illustrate the principles discussed. A description of the laboratory procedures involved is often useful to the reader. The coverage is not exhaustive in data, but rather conceptual, concentrating on the methodological thinking that will allow the non-specialist reader to understand the information presented.

Discussion of possible future research directions in the area is welcome.

Review articles for the individual volumes are invited by the volume editors.

In references *Topics in Current Chemistry* is abbreviated *Top Curr Chem* and is cited as a journal.

Impact Factor 2008: 5.270; Section “Chemistry, Multidisciplinary”: Rank 14 of 125
Authors and editors wish to dedicate this volume to the memory of Keith Fagnou
During the past several decades, extensive investigations into transition metal-catalyzed carbon–hydrogen (C–H) bond activation processes have greatly improved our understanding of how to cleave and functionalize inert C–H bonds effectively. In addition to enriching the discipline of organometallic chemistry in a general sense, researchers in this field have made tremendous strides toward harnessing this knowledge to develop novel chemical technologies that will benefit humankind in practical ways. For example, the selective oxidation of methane and related petroleum components is recognized as a significant challenge with wide-ranging commercial implications. In particular, the refinement of this technology would change how bulk chemicals are produced industrially and would enable alternative strategies for utilizing natural energy resources in an economical fashion.

In more recent years, it has become evident that the direct formation of carbon–carbon and carbon–heteroatom bonds from unactivated C–H bonds via C–H activation has enormous potential for advancing the field of chemical synthesis. In accordance with the basic principles of retrosynthetic analysis, C–H activation reactions can drastically shorten possible routes to a given natural product by providing unprecedented disconnections in both the early and late stages. This volume contains valuable and insightful contributions from several leading experts in this area. Collectively, these chapters focus on relevant progress during the past 5 years toward the development of increasingly versatile and efficient C–H activation reactions that have the potential to be broadly applicable in the realm of organic chemistry.

Though the recognition that C–H activation could potentially be a uniquely powerful synthetic tool dates back several decades, there has nevertheless been a marked increase in the depth and breadth of research in recent years, including both the development of a diverse array of catalytic C–H activation reactions and the implementation of the novel transformations as key steps in campaigns toward natural products. Although this volume focuses on more recent progress, the authors of each section have attempted to situate these contemporary investigations within the context of previous work by presenting a historical view of the subject that they are discussing. In spite of these efforts, unfortunately not all of the important contributions could be included in this short volume.
The volume begins with a chapter by M. Lautens on a novel class of synthetic transformations built upon the logic of the Catellani reaction, a Pd(0)-catalyzed, norbornene-mediated arene alkylation/olefination. Within this broad theme, this section focuses on recent innovative advances in improving the versatility and overall synthetic usefulness of this reaction. The following chapter by K. Fagnou features insightful discussion of another prominent catalytic system (Pd(0)/ligand and Ar–X) for C–H arylation. This transformation has a relatively long history; however, Fagnou has made numerous new contributions toward better understanding this reaction mechanistically and expanding its synthetic scope. In this chapter, a particular emphasis is placed on the arylation of heterocycles, which may be of special interest to medicinal chemists. In the next chapter, O. Daugulis highlights recent discoveries in the area of C–H arylation using Pd(II) and Cu(II) catalysts. The author is a leading expert on this topic and is responsible for many of the advances in arylation chemistry with ArI during the past 5 years. Subsequently, M.J. Gaunt comprehensively reviews the development of C–H arylation and olefination of indoles and pyrroles. In this section, the discussion of the recent, exciting developments from the Gaunt laboratory demonstrating regiochemical control through careful tuning of protecting groups is especially enjoyable to read. Describing a slightly different strategy for C–H arylation, R.C. Larock relates an interesting story on the development of remote C–H arylation through spatial migration of a preformed aryl–metal bond, many of the examples of which are based on contributions from his own group.

This section is followed by discussion of recent developments in arene/arene coupling, a somewhat ambitious research endeavor to forge biaryl carbon–carbon bonds with high selectivity in the absence of any prefunctionalized substrates. S.L. You, one of the major contributors in this area, provides an exceptionally thorough account on this matter. Although arene/arene homocoupling catalyzed by both Pd and Cu catalysts is well documented, recent advances show promise for coupling two different arene partners to one another. The discussion of Pd-catalyzed C–H functionalization is then closed by a beautiful chapter by G.S. Liu on allylic C–H functionalization, which includes almost every major advancement in the past 5 years, especially some highlights from M.C. White’s laboratory.

The volume then shifts direction slightly to discuss C–H functionalization reactions by other transition metal catalysts. L. Ackermann covers many of the most important developments in Ru-catalyzed C–H arylation. Although Ru-catalyzed C–H activation reactions reported by Murai and Kakiuchi are among the earliest catalytic C–H activation reactions for carbon–carbon bond formation, Ackermann focuses on an exciting new development in Ru-catalyzed C–H arylation with the assistance of various ligands reported from his own laboratory and others. Next, K. Itami introduces recent work in catalyst design and highlights synthetic applications of Rh(I)-catalyzed C–H arylation reactions. Seminal work from R.G. Bergman and J.A. Ellman is highlighted. In this chapter, the use of C–H activation in material science speaks to the emerging opportunity for this technology in that research area. In the next chapter, C.J. Li describes an oxidative cross-dehydrogenative coupling (CDC), a process mainly developed in his own
laboratory. In this context, the ability to use substrates containing allylic C–H bonds could potentially render this reaction a powerful tool in synthesis.

Finally, this volume closes by covering the most advanced field of C–H functionalization chemistry in terms of synthetic applications in complex settings, namely Rh(II)-catalyzed carbene and nitrene insertion processes. First, H.M.L. Davies gives a comprehensive outlook of the state of the art in carbene insertion chemistry, while providing insights into his trademark donor–acceptor concept and the remarkably efficient Davies catalyst. Early contributions from M.P. Doyle and others are also discussed. Next, J. Du Bois presents a beautiful story concerning the development of stereoselective nitrene insertion and recent advances therein. Highly complex natural products, including landmarks such as (-)-tetrodotoxin, have been made using Du Bois’s C–H amination reactions.

As editors of the volume, we hope that 12 chapters herein from leading experts in the field provide an overview of the cutting edge in contemporary C–H functionalization. At the same time, many of the authors have also generously offered their views on future research trends, which we hope will be useful for our colleagues in the field. We are grateful to H. Yamamoto for encouraging us to take on this task. Additionally, we would like to thank graduate student K.M. Engle for his diligent editing efforts. We are deeply indebted to all contributors for providing such incredibly organized and insightful articles. J.-Q. Yu also wishes to thank colleagues in the NSF Center on Stereoselective C–H Functionalization for all of their inspiration and support.

Authors and editors wish to dedicate this volume to the memory of Keith Fagnou.

Spring 2010

Jin-Quan Yu
Zhangjie Shi
Keith Fagnou was a man of diverse and exceptional abilities. He was born in Saskatoon, Saskatchewan on June 27, 1971 and attended the University of Saskatchewan where he graduated with a degree in Education. He taught secondary school but realized his true passion lay in research. Keith moved to Toronto and took third and fourth year courses in Chemistry to be accepted into the graduate program. It was in just such a course that I first met Keith.

Keith approached me about working in my laboratory for the summer and as he already had an undergraduate degree, he was not eligible for any summer scholarships. I looked over his transcript and noticed that he was a terrific student and had done particularly well in my course. His alternative was to go back to the Navy where he would be on the high seas navigating huge boats. In spite of some concerns about my finances, I offered him a fully funded position and for both of the rest was, as they, history.

Keith had no research experience so I teamed him up with Tomislav Rovis, now Stille Professor at Colorado State University. Tom was a senior student in my group at that time and about to head off to Harvard and work with Dave Evans. Tom suggested Keith investigated a long-standing problem in our group, namely adding heteroatoms to strained heterobicyclic systems. Tom had come across a paper suggesting rhodium might be a suitable metal and Keith dutifully set out to find out if this was the answer. After a few months, the first results trickled in and not only was rhodium a suitable catalyst, but also the stereochemistry of the addition was opposite to what would have been predicted based on the earlier work. Keith had a project and was on a mission to get results. Coincidently, I had lectured at an OMCOS meeting in Göttingen and met a scientist from Ciba Speciality Chemicals who asked me if we might be interested in trying the Josiphos family of ligands. He sent some for Tom to try: While they failed to improve his reaction, they were available to Keith who showed that they gave excellent selectivity.

Keith was admitted to our graduate program and was keen to stay in Toronto since his wife was a student in the medical school. Her busy schedule gave Keith the maximum time available to undertake his masters and doctoral studies, and he made the most of this time. His first paper, published in JACS in 2000 with Tom Rovis,
described the enantioselective ring opening of oxabicycles using alcohols as nucleophiles. He followed this up with a paper coauthored by an undergraduate, Mark Taylor, now my colleague at the University of Toronto, on the ring opening with phenols as nucleophiles. Ultimately, Keith published 18 papers while a member of my group – certainly a record. Among the more notable were widely cited reviews on “Rhodium-Catalyzed Carbon–Carbon Bond Forming Reactions with Organometallic Compounds” which appeared in Chemical Reviews, “Halide Effects in Transition Metal Catalysis” in Angewandte Chemie, and “Transition Metal-Catalyzed Enantioselective Ring-Opening Reactions of Oxabicyclic Alkenes” coauthored with Sheldon Hiebert that appeared in Accounts of Chemical Research. In addition to his time in Toronto, Keith spent time at AstraZeneca in Montreal where he got his first taste of life in the pharmaceutical industry and the wonder of Montreal bagels which were his main source of nutrition during this period. Edward Roberts, now at Scripps, and Christopher Walpole were important influences during this stay.

Keith left the group and took up a position at the University of Ottawa, but not before winning many awards in recognition of his success during his PhD. Among the most notable were the NSERC PGS, Boehringer Ingelheim Prize, Governor General’s Gold Medal, John Charles Polanyi Prize, and an NSERC PDF to work with Robert Grubbs. A confluence of circumstances led him to seek an academic job immediately following graduation rather than following through on the postdoc, and I had no trouble offering my strongest support. In fact given his interest in C–H activation, it was probably vital that he took an academic job right away: many others were entering this field and Keith might have found himself a bit behind the pack had his start been delayed by 2 years. In any case, Keith certainly made the most of his time in Ottawa.

Over the next 5 years, Keith made a remarkable impact on the field of direct arylation chemistry. The systematic manner in which his group approached one of the “holy grails” of organic synthesis (namely, carbon–carbon bond formation by functionalization of inert C–H bonds) is a testament to the extraordinary “vision” of this young scientist. His group’s first paper, published in JACS in 2004, describes palladium-catalyzed intramolecular direct arylations under mild conditions. Over the next 5 years, the Fagnou group built upon this result to develop an arsenal of synthetic methods than enable the effective, regioselective construction of C–C bonds from unactivated precursors. One of his most influential papers appeared in Science in 2007 and reported on the direct, oxidative cross-coupling of arenes without functionalization of either partner. I remember the day Keith called to share the news that this paper was accepted and the happiness in his voice.

Understanding the mechanistic details of the C–H activation step was a major thrust of Keith’s research, and information from these studies played a key role in the methods developed by his coworkers. The Fagnou group’s mechanistic studies of C–H arylation reactions are among their most highly cited work, and represent a contribution whose impact will likely be felt for years to come. In total, some 40 papers have or will appear in many of the best journals and will serve to summarize his independent career. His research program was on a rapid upward trajectory: in 2008, his group published five papers in JACS. He remained a modest
and self-effacing individual even as his international profile rose. He was invited to be a Visiting Professor in Paris in 2008 and we exchanged messages reminiscing on our experiences in the City of Light. One comment stands out as he reported that he felt he should have been born a wealthy Parisian rather than a kid from Saskatoon. I could do nothing but smile and agree having grown up in Hamilton.

Keith managed to make the job of being a professor look easy. He was beloved by his students and began attracting the best students in the country to his group. The “Fagnou Factory” as they called themselves worked hard and enjoyed the environment Keith created and sustained. His first PhD managed a job at Merck Frosst without a postdoc, a remarkable feat attesting to the educational rigor of Keith’s labs. Keith was also a superb lecturer (in both English and French); in fact, when I was away I always asked him to fill in for me in spite of knowing the students might have wished I was away more often after hearing him give clear and well-planned lectures. He was equally skilled at research presentations and on one occasion, he lectured for me at Pacificchem in Hawaii and I received a flurry of emails the next day, indicating that his lecture was much appreciated and the symposium organizers were glad he had come in my place! Apparently, I was told he was careful to avoid looking too suntanned on his return but he and Sheldon Hiebert were very grateful I had sent them to Hawaii in December.

Keith was selected for many awards in recent years, including an A.P. Sloan Fellowship, an Eli Lilly Granteeship, Amgen Young Investigator Award, AstraZeneca Award, Merck Process Research Award, University of Ottawa Researcher of the Year, and most recently the OMCOS Award. He was the only Canadian to be so honored and the list of prior winners (Kobayashi, Carriera, Fu, Ma, Hartwig, and Nozaki) is a Who’s Who of the field of catalysis. At the time of his death, he held the position “University of Ottawa Research Chair in Novel Catalytic Transformations.”

Keith began to enjoy the fruits of his labors and everywhere I went I heard Keith had just visited or was coming soon. People who visited our department always mentioned a rising young star in Ottawa who they met at Gordon Conference or international conference. He began to travel regularly and to take his family when he could. The past summer he took his young son Zachary back to Paris for a father–son trip. His wife Danielle Gervais-Fagnou, now an MD in Ottawa, his daughter Clara, and his youngest Samuel were never far from his thoughts and he regularly spoke about coaching his son’s hockey team or heading out on an outdoor adventure. Keith paid attention to the needs of his family and still had a life outside the lab and home. He played hockey, jogged, and generally took good care of himself. His unexpected death on November 11, 2009 was a shock to all who knew and cared about this gentle, kind, funny man with an irreverent sense of humor. The reaction of the community speaks to the high regard held for Keith and the number of lives he touched. The world has lost a great person, a warm and loving husband and father, and a scientist whose accomplishments had already put him front and center of an active and important field. Sadly, we will not have the chance to see the full measure of his contributions to science.

December 15, 2009

Mark Lautens and Mark Taylor
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