

Photomediated Ring Contraction of Saturated Heterocycles

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Skeletal editing, the precise manipulation of a molecule's core scaffold, especially at the single atom level, is an emerging concept of importance in organic chemistry.¹ Recent reports in this area have included nitrogen deletion,² single-atom insertion,³ and ring contractions.⁴ Through a collaboration involving researchers at the University of California-Berkeley in Prof. Richmond Sarpong's laboratory and at the research labs of Merck & Co., Inc., Kenilworth, NJ, USA – known as MSD outside of the US and Canada – a light-mediated ring contraction of saturated six-membered heterocycles to five-membered rings that relocates the heteroatom from an endocyclic to exocyclic position has been achieved. This academia/industry partnership started as part of the “Disruptive Chemistry” initiative at MSD – an effort focused on developing enabling chemical reactions of importance for industrial applications, including novel scaffold changes to precisely edit molecules. “Disruptive Chemistry is an initiative within MSD where we took action in addressing unmet synthetic needs through academic partnerships. The collaboration between MSD and Berkeley was one key pillar of that strategy, and together with Richmond's lab, we were able to make major inroads in the area of bicyclic amine synthesis and molecular editing,” said Dr. Charles Yeung. As part of this collaboration, the Sarpong group (graduate students Justin Jurczyk and Sojung Kim) and scientists at MSD (Dr. Charles Yeung, Dr. Michaelyn Lux, Dr. Colin Lam, and Dr. Donovan Adpressa) worked productively on several projects, including the synthesis of bicyclic amines^{5,6} and piperidine peripheral functionalization.⁷ Building on insights from their Pd-catalyzed piperidine functionalization research, they reasoned that α -benzoylated piperidine scaffolds could undergo further diversification using the photoactive benzoyl group. Indeed, initial reactions on these acylated frameworks (see **I**, Scheme 1B) were anticipated to yield Norrish–Yang type azetidinol products (e.g., **III**). However, upon irradiation, *cis*-cyclopentyl amine **II**, whose initial structure was elucidated by Dr. Adpressa, was observed as the major product. “We recognized the importance of this transformation, as – in the context of piperidines – this single-step reaction transforms the core structure of the saturated aza-cycle in an unconventional manner, affording a cyclopentyl amine in the process,” said Professor Sarpong. He continued: “It also represented a form of skeletal editing, much like the earlier accounts from Seebach and Suárez (Scheme 1A),^{8,9} on using ring-opening and subsequent ring-closure to effect the relocation of a hetero-

atom to the periphery of a ring (Scheme 1B). The optimization and extension of the transformation to other aliphatic heterocyclic structural motifs were therefore pursued.”

Justin Jurczyk and Dr. Lux undertook an extensive screening of solvent, wavelength, and concentration to optimize the transformation. In addition, they examined different protecting groups on the piperidine substrates and observed that sulfonyl groups (e.g. **IV**, Scheme 1C) worked well, whereas other common groups on nitrogen resulted in lower yields and diminished reactivity under the optimized conditions. Dr. Lux explained: “To overcome this issue, we employed the high-throughput experimentation (HTE) capabilities at MSD to identify an additive that improved the yield of the ring-contraction products for non-sulfonamide substrates (e.g., **V**). 3-Cyanoumbelliferone was identified as a suitable additive that led to improved efficiency in the conversion of several non-sulfonyl piperidines.”

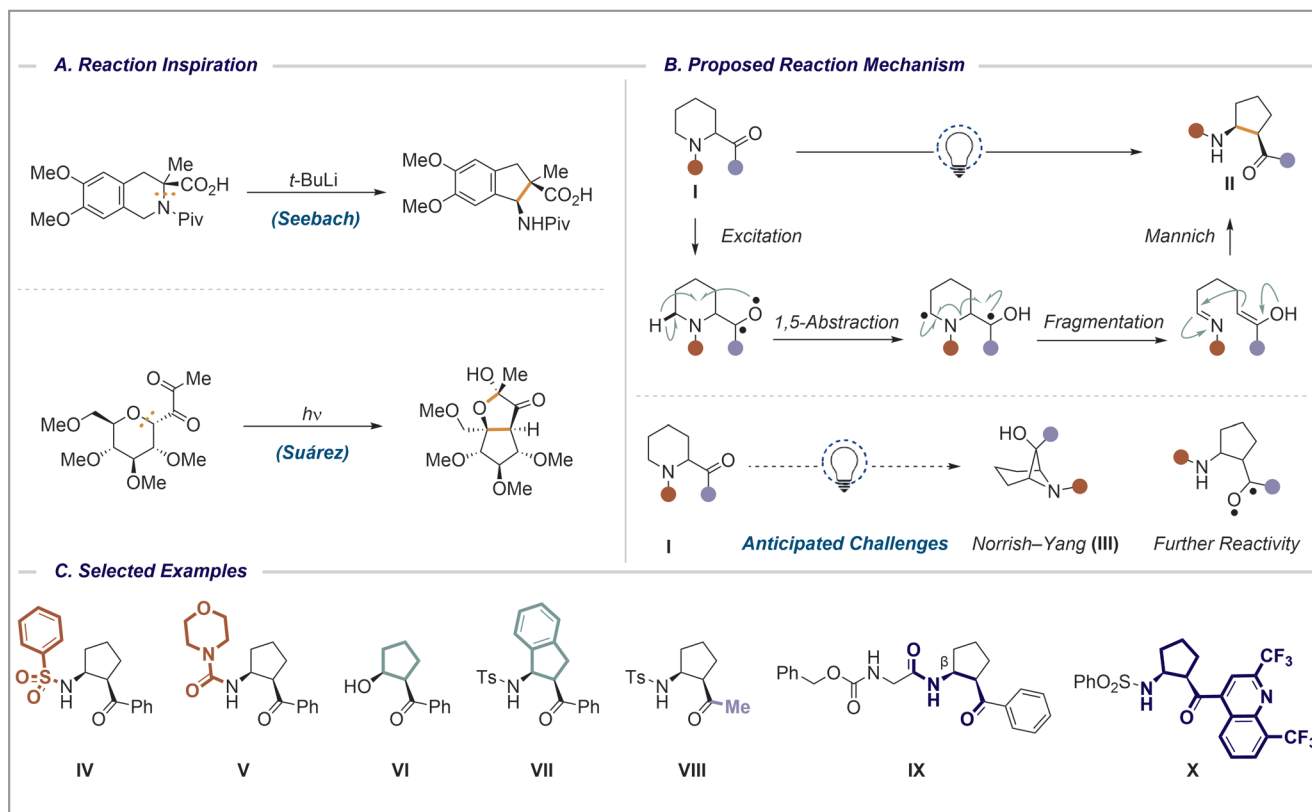
Next, the team embarked on expanding the reaction beyond piperidine frameworks and explored a diverse set of alternative photoactive ketone auxiliaries. “Overall, the optimized reaction conditions were found to be general for a broad range of substrates, including cyclic ethers (e.g. **VI**) and thioethers, and benzannulated aliphatic cyclic heterocycles (**VII**),” explained Dr. Yeung. He continued: “Additionally, in the exploration of ketone auxiliaries, it was observed that a range of aromatic ketones worked well in this capacity. To expand the scope beyond aromatic ketones, Justin Jurczyk and Dr. Lux examined aliphatic ketones (e.g. **VIII**), which required UV light rather than 400 nm light sources and extended the scope to alkenyl and alkynyl ketones – ultimately showing that non-aryl ketones were effective auxiliaries albeit less efficient.” More complex, biologically relevant, molecules were then examined. Several scaffolds, including a peptide residue (**IX**) and a mefloquine derivative (**X**) also participated in this transformation. “Given the complexity of the products that were obtained, comprehensive structural elucidation, performed by Dr. Adpressa, was conducted,” added Dr. Yeung.

Early in the collaboration, in parallel with the experimental work, the team also leveraged the computational chemistry capabilities at MSD to accelerate reaction development through an in-depth investigation of reaction mechanism and stereoselectivity. “One of the most interesting results from the calculations was that the transition state energies for the intramolecular Mannich step correlated with the *cis/trans*

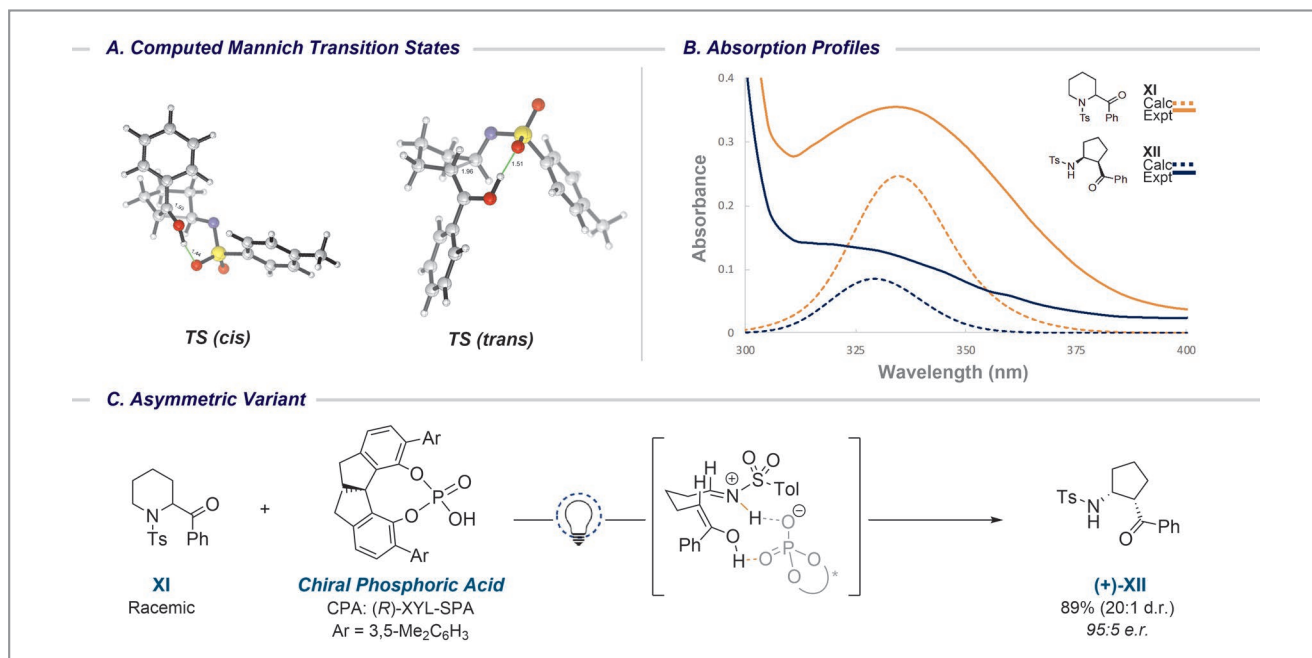
ratios observed experimentally ($\Delta\Delta G^\ddagger$ on the order of 1 kcal/mol),” remarked Professor Sarpong. He continued: “The energy differences could be rationalized by a shorter and stronger hydrogen bond as well as a more staggered arrangement of substituents about the forming C–C bond in the *cis*-product-yielding transition state (Scheme 2A).” The more pronounced photoreactivity of the starting material compared to the product was also supported by experimentally measured and DFT calculated absorption profiles ($n \rightarrow \pi^*$ transition) (Scheme 2B). “Here, selective irradiation of the starting material could be achieved because of the hypsochromic shift of absorbance for the product relative to the starting material, as well as a decrease in molar absorptivity for the product,” said Dr. Lam, who added: “This collaboration is a very nice illustration of how DFT calculations can impact organic reaction development in an industrial setting. They are not only important academically, but also increasingly often applied, in real-time collaboration with chemists, to support a wide range of investigations in both drug discovery and pharmaceutical development, including route planning, drug/catalyst design, mechanistic studies, structural elucidation, and other areas.”

Given the insights into the observed diastereoselectivity of the ring contraction (stemming from a highly organized transition state from an achiral imine-enol intermediate), Justin Jurczyk, Sojung Kim, and Dr. Lux investigated an enantioselective variant of the ring contraction reaction. BINOL-derived chiral phosphoric acids were identified as effective catalysts that led to the formation of ring contraction products in up to 90% *ee* (conversion of **XI** into **XII**, Scheme 2C).

Reflecting on the collaboration, Professor Sarpong said: “This is an exciting example of an academic–industry collaboration that highlighted a key need for diversifying chemical space, especially of saturated heterocycles. The current work came about as the result of a productive and sustained collaboration between the groups at Berkeley and at MSD over several years. The groundwork was set with our earlier work,⁷ which then evolved to a broader interest in the Norrish–Yang reaction. The work in the *Science* paper is a combination of a deep command of what had been reported in the literature and serendipity. Careful experimentation, computational analysis, and structural elucidation led to the identification of the optimal conditions that we report. There is still a lot to



Scheme 1 Highlights of the *Science* paper



Scheme 2 Computational insight and development of an asymmetric contraction variant

be done in this area.” He concluded: “We are optimistic about the application of this method not only to diversification of the core structures of pharmaceutically and agrochemically relevant compounds, but also to complex molecule synthesis and the preparation of light-responsive materials.”

Mattias Fomale

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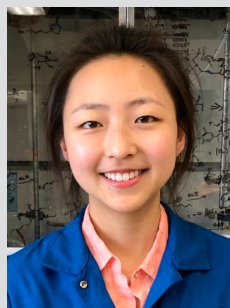
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About the authors



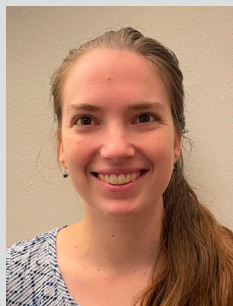
J. Jurczyk

Justin Jurczyk was born in New Jersey (USA) and completed his B.S. in chemistry at Allegheny College, Pennsylvania (USA) under the direction of Prof. Ryan Van Horn. He then moved to the San Francisco Bay Area (USA) and is currently working toward his Ph.D. in chemistry at the University of California, Berkeley (USA) under the supervision of Prof. Richmond Sarpong. Here, his studies focus on the development of strategies aimed at saturated cyclic amine diversification.



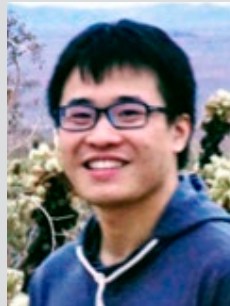
S. F. Kim

Sojung F. Kim was born in California (USA) and completed her B.S. in chemistry at The Pennsylvania State University (USA) under the direction of Professor Thomas E. Mallouk and Professor Xin Zhang. She is currently living in the San Francisco Bay Area (USA) and working toward her Ph.D. in chemistry at the University of California, Berkeley (USA) under the supervision of Professor Richmond Sarpong. Her studies currently focus on skeletal editing strategies of saturated cyclic amines and enantioselective transformations of iminium ions.



Dr. M. C. Lux

Michaelyn C. Lux was born in Michigan (USA) and completed her B.Sc. in chemistry at Michigan State University (USA); she continued to Ph.D. studies as part of the Tri-Institutional PhD Program in chemical biology under the supervision of Prof. Derek Tan where she worked on Pd-catalyzed domino reactions to form bicyclic ethers. She continued to postdoctoral studies as part of the MRL postdoctoral program under the mentorship of Dr. Charles Yeung and worked on the synthesis of bridged bicyclic amines and skeletal editing of piperidines. She is currently a Senior Scientist in Discovery Chemistry at Merck & Co., Inc., Kenilworth, NJ, USA.



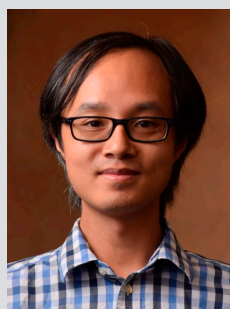
Dr. Y.-h. Lam

Yu-hong (Colin) Lam received his undergraduate and doctoral training in organic synthesis (with Prof. Véronique Gouverneur) at Oxford University (UK) and conducted postdoctoral studies in computational chemistry (with Prof. Ken Houk) at UCLA (USA). He is an Associate Principal Scientist at Merck & Co., Inc., Kenilworth, NJ, USA. and co-chair of the Computational Chemistry Working Group of the International Consortium for Innovation and Quality in Pharmaceutical Development. He specializes in the practical applications of quantum chemical calculations to support both drug discovery and process development.



Dr. D. Adpressa

Donovan Adpressa was born in California (USA) and completed his Ph.D. in chemistry at Oregon State University (USA) with a focus on the discovery and structure elucidation of novel natural products, under the mentorship of Prof. Sandra Loesgen. Donovan has continued to pursue his passion for structure elucidation as a Senior Scientist in Analytical Research & Development at Merck & Co., Inc., Kenilworth, NJ, USA.



Dr. C. S. Yeung

Charles S. Yeung completed his B.Sc. (Honours) at the University of British Columbia (Canada), Ph.D. at the University of Toronto (Canada) under the guidance of Prof. Vy Dong, specializing in using transition-metal catalysis to activate CO₂ and C–H bonds, and postdoctoral fellowship at Harvard University (USA) with Prof. Eric Jacobsen, innovating in asymmetric reactions catalyzed by hydrogen bonding catalysts. Charles is currently an Associate Principal Scientist in Discovery Chemistry at Merck & Co., Inc., Kenilworth, NJ, USA, and was one of three Disruptive Chemistry Fellows involved in a long-term academia–industry partnership tackling bicyclic amine synthesis and molecular editing. Charles' interests include neuroscience, oncology, targeted protein degradation, catalysis, and HTE.

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Prof. R. Sarpong

Richmond Sarpong is a Professor of Chemistry at the University of California, Berkeley (USA) where he and his group specialize in synthetic organic chemistry. Richmond became interested in chemistry after seeing, firsthand, the effectiveness of the drug ivermectin in combating river blindness during his childhood in Ghana, West Africa. Richmond described his influences and inspirations in a TEDxBerkeley talk in 2015 (Face of

Disease in Sub-Saharan Africa – <https://www.youtube.com/watch?v=nlsY87-zkXA>). Richmond completed his undergraduate studies at Macalester College in St. Paul, MN (USA) with Prof. Rebecca C. Hoyer and his graduate work was carried out with Prof. Martin F. Semmelhack at Princeton University (USA). He conducted postdoctoral studies at Caltech (USA) with Prof. Brian M. Stoltz and began at Berkeley in 2004.