Enantioselective Photochemistry through Lewis Acid Catalyzed Triplet Energy Transfer

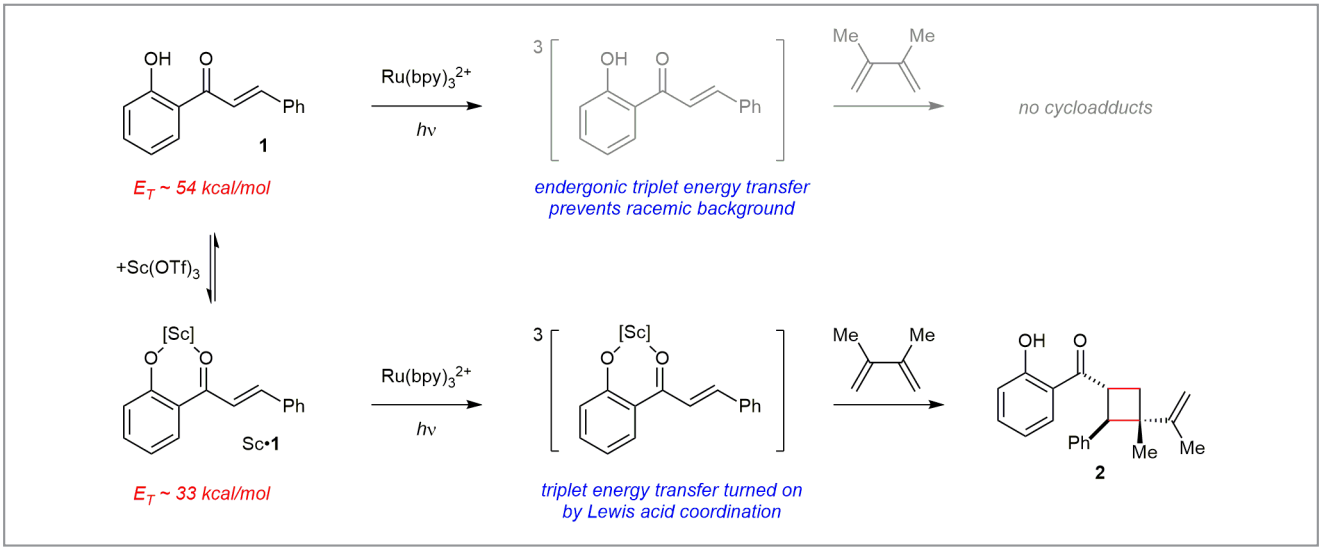
Science **2016**, *354*, 1391–1395

Carbonyl photochemistry is prominent in many of the most important reactions in photochemical synthesis. It has been known for many decades that the photochemical properties of carbonyl compounds can be modulated by Lewis acid catalysts. Professor Tehshik P. Yoon of the University of Wisconsin–Madison (USA) explained: "In the 1980s, Fred Lewis showed that the coordination of enones to oxophilic Lewis acids such as BF_3 and $EtAlCl_2$ could completely change the energetics of their singlet excited states.[1] This phenomenon can result in changes to the UV absorption spectra of coordinated enones and in an increased efficiency of subsequent photocycloaddition reactions. Recently, Thorsten Bach's laboratory has exploited these effects to design highly enantioselective photocycloaddition reactions using chiral Lewis acids".[2]

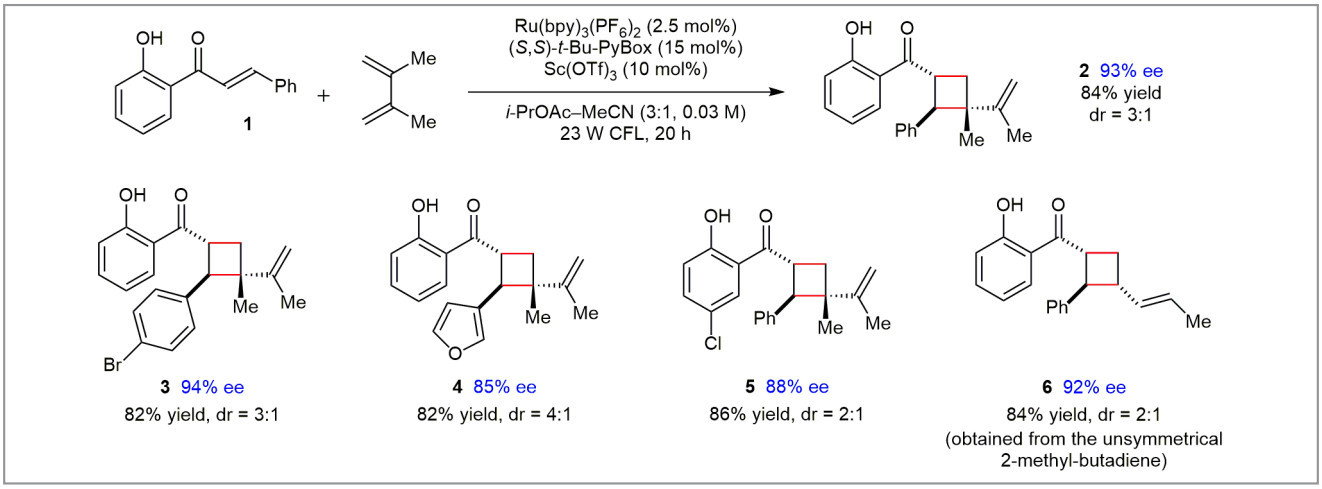
The group of Professor Yoon has also been working in this area and the central discovery reported in their recent *Science* paper is that Lewis acids can have a similarly large impact on the triplet excited states of enones. Professor Yoon said: "We found that the coordination of $Sc(OTf)_3$ to 2′-hydroxychalcone **1** results in a surprisingly large decrease in the energy of its first excited triplet state. When **1** is irradiated in the presence of $Sc(OTf)_3$ and $Ru(bpy)_3^{2+}$, triplet energy transfer is thermodynamically feasible from photoexcited $Ru^*(bpy)_3^{2+}$ only to the Lewis acid coordinated assembly, and not to the free chalcone (Scheme 1)."

This result opens up the possibility of chiral Lewis acid catalysis of triplet sensitization. "When a chiral pybox $Sc(OTf)_3$ complex is used in combination with $Ru(bpy)_3^{2+}$, we are able to synthesize highly enantioenriched cyclobutanes using relatively low concentrations of both co-catalysts," said Professor Yoon (Scheme 2). He continued: "A large part of this investigation involved the optimization of this system and an exploration of the variety of chalcones and dienes that participate in the reaction."

Professor Yoon explained: "We think that this strategy for asymmetric catalysis is important for a few different reasons. First, this is another example of highly enantioselective photochemistry using tandem photocatalysis, a topic that my laboratory has been interested in for several years.[3] We think that one of the major benefits of using a separate enantiocontrolling catalyst, that is chemically distinct from the photochemically active moiety, is that the structure of the chiral controller can be optimized extensively without significantly altering the photochemical behavior of the photocatalyst." He continued: "In addition, the transformation we have discovered is an example of a triplet photosensitization reac-



Scheme 1 Conceptual scheme for Lewis acid catalyzed triplet energy transfer



Scheme 2 Enantioselective catalytic triplet sensitization reactions

tion. One advantage of photosensitized reactions over direct photochemical reactions is that the reactive triplet state can be accessed without first passing through a singlet excited state. The reactivity of enones in their singlet excited states can be substantially different from those in their triplet states – for instance, the regiochemical outcomes can differ, and the quantum yields of singlet and triplet photoreactions can be quite different, particularly in intermolecular reactions where the shorter lifetimes of singlet states can be especially problematic. By bypassing the singlet state and directly accessing the organic triplet, we were able to focus on optimizing the chemistry of the triplet state photoreaction without having to worry about any negative impacts on the singlet photochemistry."

Professor Yoon revealed that their initial observation of this reactivity was accidental. "We were investigating whether photoredox activation of the hydroxychalcone substrates might lead to Diels–Alder cycloaddition reactions, along the lines of what Porco had reported a few years ago using chemical redox catalysts,[4]" explained Professor Yoon. He continued: "In our first few experiments, although we did observe some formation of the [4+2] cycloadducts that Porco described, the main products of these reactions were these unexpected cyclobutanes described in our *Science* paper. I was, frankly, a little irritated at first. I had planned to apply the Diels–Alder reaction to a total synthesis project, for which the [2+2] products were not at all useful. Moreover, I really did not understand how these cyclobutanes were forming. I kept proposing possible trivial explanations, and Travis (i.e. Dr. Travis R. Blum, first author of the article, then Ph.D. student) kept running control experiments to disprove my hypotheses."

Professor Yoon remarked: "There have only been a few other times in my career to date when a morass of confusing empirical data has suddenly resolved into a clear and coherent picture. It's a delightful feeling, especially when the conclusion is more interesting than the problem we were originally attempting to solve. After making multiple observations that seemed inconsistent with photoredox activation, the ultimate inescapable conclusion that emerged was that we were observing Lewis acid catalyzed triplet energy transfer. We were excited by this realization because this mechanism seemed to really represent a fundamentally new physical effect that had not previously been characterized. As much work as it was to complete the synthesis and characterization work for this paper, we spent just as much effort convincing ourselves that the mechanistic picture we were proposing was reasonable. We ended up needing to collaborate with Desiree Bates, a computational chemist in our department, to learn to estimate the energies of organic excited states using DFT computations. We also had to go outside of our department to find a spectrometer capable of detecting the weak, low-energy emission that we think is arising from the low-energy triplet states that we are accessing."

From a different perspective, Professor Yoon pointed out that the control of stereochemistry in photochemical reactions has long been recognized as a difficult problem. He said: "Some of the earliest attempts to control the enantioselectivity of photochemical reactions date back to the1930s,[5] but for a long time, there was a persistent belief that the reactivity of highly photoexcited molecules was simply too uncontrollable to ever be amenable to asymmetric catalysis in any general way. This belief has only been disproven within the last de-

cade or so.[6] Therefore we think any new strategy for enantioselective catalysis of photochemical reactions remains interesting, particularly when they involve excited state organic intermediates."

"I'm proud of this paper, and I'm even more proud of the way that the story came together. This was a project that we might have missed entirely had Travis not been curious about a set of anomalous results. We learned a lot about characterizing and investigating the properties of excited states," said Professor Yoon. He concluded: "The next steps will be to develop applications for this reactivity, which is something we are actively pursuing at the moment. We are also curious to know how general this phenomenon is. If we can show that the triplet-lowering effect of Lewis acids on carbonyl compounds is general and not in some way specific to this class of 2-hydroxychalcone substrates, I think we might have a really robust way to control the stereochemistry of excited-state organic photoreactions."

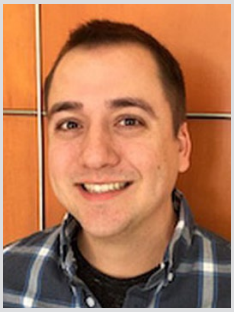
REFERENCES

(1) (a) F. D. Lewis, D. K. Howard, J. D. Oxman *J. Am. Chem. Soc.* **1983**, *105*, 3344; (b) F. D. Lewis, S. V. Barancyk *J. Am. Chem. Soc.* **1989**, *111*, 8653.
(2) (a) H. Guo, E. Herdtweck, T. Bach *Angew. Chem. Int. Ed.* **2010**, *49*, 7782. (b) R. Brimioulle, T. Bach *Science* **2013**, *342*, 840.
(3) (a) Y. P. Yoon *Acc. Chem. Rev.* **2016**, *49*, 2307; (b) J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon *Science* **2014**, *344*, 392.
(4) (a) H. Cong, D. Ledbetter, G. T. Rowe, J. P. Caradonna, J. A. Porco Jr. *J. Am. Chem. Soc.* **2008**, *130*, 9214; (b) H. Cong, C. F. Becker, S. J. Elliott, M. W. Grinstaff, J. P. Porco Jr. *J. Am. Chem. Soc.* **2010**, *132*, 7514.
(5) W. Kuhn, E. Knopf *Naturwissenschaften* **1930**, *18*, 183.
(6) R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach *Angew. Chem. Int. Ed.* **2015**, *54*, 3872.

About the authors

Dr. T. Blum

Travis Blum attended Hobart and William Smith Colleges (USA), and obtained his Bachelor's degree in 2010 after studying the total synthesis of bioactive marine depsipeptides. He then moved to the University of Wisconsin–Madison (USA), where he was awarded an NIH Chemical Biology Interface Training Grant and studied both electron-transfer and energy-transfer photocatalysis during his doctoral work under Professor Tehshik P. Yoon. He received his Ph.D. in 2016, and is currently a postdoctoral fellow at Harvard University (USA) in the laboratory of Professor David Liu.



Dr. Z. Miller

Zach Miller completed his undergraduate studies in chemistry at Wittenberg University (USA), during which time he was awarded an NSF REU that was carried out at Syracuse University (USA) under the direction of Professor Donald Dittmer. In 2015, he completed his Ph.D. studies at the University of Michigan (USA) under the guidance of Professor John Montgomery where he focused on organometallic catalysis.

Dr. D. Bates

Desiree Bates received her B.S. from Winona State University (USA) in 2006 and her Ph.D. in theoretical and computational chemistry from Mississippi State (USA) with Professor Gregory Tschumper in 2011. As the computational chemistry leader in the chemistry department's computer center at UW–Madison (USA), where she has served since 2011, she collaborates with students and research groups at a variety of levels on how to employ computational approaches to aid their research.

Dr. I. Guzei

Ilia Guzei obtained his Ph.D. in chemistry at Wayne State University (USA) in 1996 based on his work with pyrazolato complexes of transition metals and crystallographic studies. After a postdoctoral stay at University of Delaware (USA) and a brief appointment at Iowa State University (USA), Ilia became Director of Crystallography at the Chemistry Department of University of Wisconsin (USA) in 2000. At UW–Madison he received an Excellence Early Career Award in 2009, Chancellor's Award for Excellence in Research in 2013, and was promoted to Distinguished Scientist in 2015.

Prof. T. P. Yoon

Tehshik Yoon was born in 1975 in Montreal (Canada) and was raised in Blacksburg, VA (USA). He received his A.B. from Harvard University (USA), where he performed undergraduate research with Professor David Evans, and his M.S. from Caltech (USA), where he studied with Professor Erick Carreira. He was the first Ph.D. student of Professor David MacMillan, first at Berkeley (USA) and then Caltech (USA), and completed postdoctoral studies with Professor Eric Jacobsen at Harvard University (USA). Since 2005, Tehshik has served on the faculty at the University of Wisconsin–Madison (USA). He was promoted to Associate Professor in 2011 and to Professor in 2013.