

Photocatalytic C–H Activation and the Subtle Role of Chlorine Radical Complexation in Reactivity

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The transformation of small molecules, such as methane and ethane, into value-added chemicals is extremely attractive given their abundance in natural gas. The catalytic C–H functionalization of methane remains a major challenge in the chemical industry and an active area of research. The groups of Professors Patrick J. Walsh and Eric J. Schelter at the University of Pennsylvania (Philadelphia, USA) have been actively investigating this important topic over the last few years.

“While many common catalysts for C–H activation employ low-abundance transition metals, a recent thrust in the field of catalysis has been to develop catalysts based on earth-abundant elements, including certain lanthanides,” explained Professors Walsh and Schelter. “Within lanthanides, cerium stands out for its accessible Ce(III)/Ce(IV) redox couple that, together with its characteristic electronic structure, make it attractive for photoredox applications.” Prior efforts to develop cerium photoredox catalysts by the Costanzo labs and the Schelter labs demonstrated activation of benzylic C–H bonds of toluene. “In a recent breakthrough, Prof. Zhiwei Zuo (now at Shanghai Institute of Organic Chemistry, P. R. of China) reported a cerium photocatalyst capable of functionalizing methane, ethane, and higher alkanes (*Science* **2018**, *361*, 668–672). This discovery highlighted the broad utility of cerium photocatalysts and their potential applications to cleave unactivated C–H bonds,” said Professor Schelter. He continued: “To rationalize the observed reactivity and explain a perceived beneficial impact of certain alcohols on the reactivity of the Ce-photoredox catalyst, Zuo’s team proposed the intermediacy of a key cerium alkoxide, $[\text{Bu}_4\text{N}]_2[\text{Ce}^{\text{IV}}\text{Cl}_5(\text{OR})]$, $\text{R} = -\text{CH}_2\text{CCl}_3, -\text{CH}_3, -\text{CH}_2\text{CF}_3$. This species was believed to generate Ce^{III} and alkoxy radicals ($\bullet\text{OR}$) upon photolysis. Based on the proposed $\text{Ce}^{\text{IV}}\text{–OR}$ photochemistry, Zuo has expanded Ce-photoredox catalysis to a wide range of alcohols and ketones, observing reactions attributed to alkoxy radicals, including beta-scission, intermolecular HAT to alkoxy radicals, and intramolecular 1,5-HAT to alkoxy radicals. From the perspective of inorganic chemistry, Zuo’s proposed alkoxides raised questions in our minds about catalyst speciation and the spectroscopic similarity between the proposed ‘cerium alkoxide’ and $[\text{NEt}_4]_2[\text{CeCl}_6]$. Zuo’s original paper was an impressive achievement in photocatalytic methane activation, but some of the details of the spectroscopy and mechanism

piqued our interest, based on our work with a related catalyst. This observation, combined with our interests in lanthanide photochemistry, inspired us to investigate the proposed mechanism of the Ce-catalyzed functionalization of alkanes.”

The hunt for the proposed cerium alkoxide was initiated with a three-pronged approach: independent synthesis, spectroscopic studies, and kinetics experiments. Professor Schelter explained: “Qiaomu Yang, the lead student author on the manuscript, first independently synthesized Zuo’s proposed alkoxide intermediate. Metathesis of $\text{NaOCH}_2\text{CCl}_3$ with CeCl_6^{2-} led to the isolation of $[\text{CeCl}_5(\text{OCH}_2\text{CCl}_3)]^{2-}$, which was characterized spectroscopically and by X-ray diffraction. The UV-vis spectrum of this compound was different than that of CeCl_6^{2-} and different from the spectrum reported by Zuo, fueling our suspicions that cerium alkoxides were not involved in the chemistry.” With an authentic sample of the proposed key intermediate as a reference, spectroscopic studies of stoichiometric and catalytic reactions were undertaken. Zuo’s proposed catalyst, $[\text{CeCl}_5(\text{OCH}_2\text{CCl}_3)]^{2-}$, was found to be unstable to the reaction conditions, rapidly decomposing to CeCl_6^{2-} upon irradiation. Moreover, the Philadelphia-based researchers found that addition of $\text{HOCH}_2\text{CCl}_3$ (up to 600 equiv) to CeCl_6^{2-} in the absence of light or under irradiation under the conditions of the C–H functionalization induced no changes in the UV-vis spectrum from CeCl_6^{2-} , indicating that $[\text{CeCl}_5(\text{OCH}_2\text{CCl}_3)]^{2-}$ was not formed under these conditions.

“We next examined the kinetics of the C–H functionalization under catalytic conditions,” said Professor Schelter. He remarked: “Comparison of rates with CeCl_6^{2-} in the presence and absence of varying equivalents of $\text{HOCH}_2\text{CCl}_3$ indicated that alcohol had *no impact* on the rates of the photoredox C–H functionalization, supporting the hypothesis that it was not involved in the functionalization (Figure 1A, 1B). Kinetic isotope effect experiments using cyclohexane and cyclohexane- d_{12} with CeCl_6^{2-} in the presence and absence of $\text{HOCH}_2\text{CCl}_3$ were identical ($k_H/k_D = 2.0\text{--}2.1$), suggesting that both reactions proceeded through a common intermediate. Furthermore, positional selectivity experiments with *n*-hexane with and without alcohol demonstrated that the catalyst in both reactions gave identical selectivity of C1:C2:C3 of 1.0:1.8:1.8, again pointing to the identity of the catalyst in these two reactions as being the same: CeCl_6^{2-} (Figure 1C).”

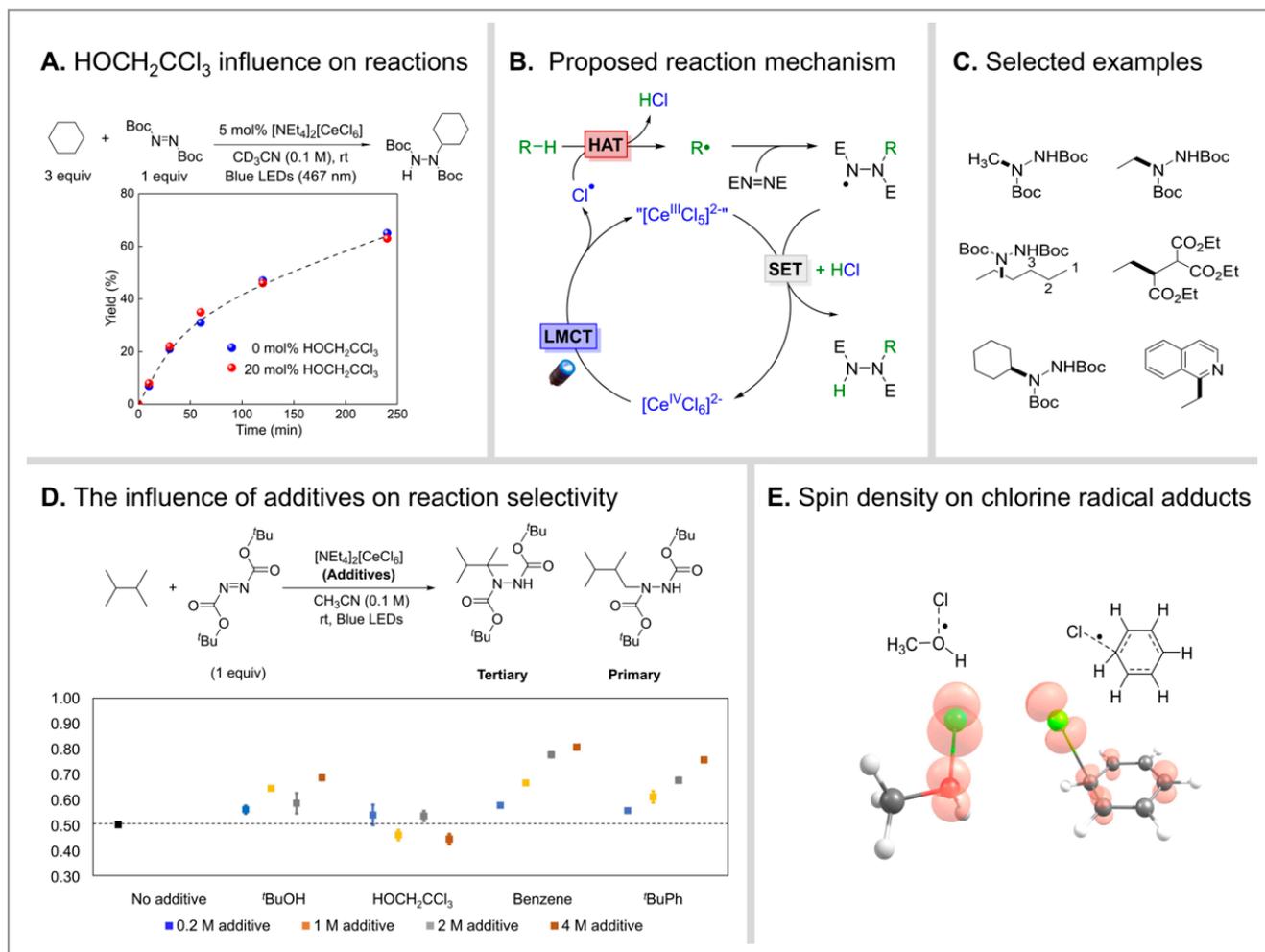


Figure 1 Highlights of the paper

Based on these studies, the authors of this *Science* paper proposed a revised mechanism (Figure 1B). “Photo-excitation of CeCl_6^{2-} results in ligand-to-metal charge transfer (LMCT), leading to dissociation of $\cdot\text{Cl}$ and formation of the reduced Ce^{III} complex,” said Professor Schelter, who continued: “The chlorine radical undergoes HAT with the alkane to generate the radical intermediate $\text{R}\cdot$ and HCl . $\text{R}\cdot$ is trapped by the diazo complex to give an N -centered radical. This intermediate undergoes reduction by Ce^{III} and protonation to generate the product hydrazine and close the catalytic cycle with formation of CeCl_6^{2-} .”

Extensive studies in the presence and absence of alcohol revealed one instance where either methanol or $\text{HOCH}_2\text{CCl}_3$ had a beneficial impact on the C–H functionalization and that was with methane. “In this case, rather than the formation of alkoxy radicals, it is postulated that hydrogen-bonding of the

alcohols to the methyl radical stabilizes this reactive intermediate,” explained Professor Schelter.

One of the pillars of Zuo’s alkoxy radical mechanism was the ‘alkoxy radical-like’ chemistry that was observed, which included what appeared to be alkoxy radical trapping products. The team envisioned that understanding this behavior would have implications beyond applications of the Ce photoredox chemistry and be of value to the larger chemistry community. “The missing piece of the puzzle was if alkoxy radicals were not involved, what was responsible for the alkoxy radical-like reactivity?” said co-corresponding author Professor Patrick Walsh.

Based on prior observations in the literature, it was known that chlorine radicals can interact with Lewis basic sites on molecules, and that this interaction can delocalize the chlorine radical character to proximal atoms. Computational and

experimental studies were undertaken by Qiaomu Yang to measure the impact of alcohols and arenes on C–H cleavage selectivity. “Experimentally, 2,3-dimethylbutane, which has two types of C–H bonds, was used as a selectivity probe,” said Professor Schelter. He continued: “With catalytic CeCl_6^{2-} , $\text{HOCH}_2\text{CCl}_3$ had no impact on the selectivity, whereas increasing concentrations of *t*-BuOH resulted in improved selectivity for the weaker methyne C–H bond. This change in selectivity toward the more reactive C–H bond could also be engendered by arenes, including benzene and *t*-BuPh (Figure 1D). As shown in Figure 1E, the chlorine radical interacts with the pi-cloud of the arenes, as established in the DFT study outlined in the manuscript. Taken together, these results indicate that adducts with the chlorine radical and methanol result in radical character delocalization on the oxygen of the alcohol. It is proposed that this behavior is responsible for the alkoxy radical-like reactivity observed by the Zuo team.”

“The identification of species on the catalytic cycle and the mapping of reaction mechanisms is important for understanding the chemistry and to position the research community to design the next generation of catalysts,” said Professor Schelter, who concluded: “We anticipate that the high reactivity of chlorine, and the ability to generate $\text{Cl}\cdot$ through LMCT of M–Cl bonds will continue to be important in the conversion of light hydrocarbons such as methane into value-added chemicals and fuels.”

Mattis Fenske

About the authors



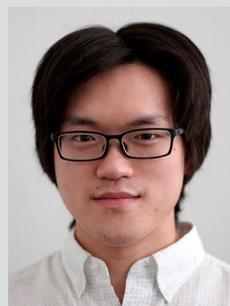
Prof. E. J. Schelter

Professor Eric J. Schelter was born in Pontiac, MI, USA. He earned a B.S. at Michigan Technological University (USA, 1999) where he worked with Rudy Luck. He earned a PhD at Texas A&M University (USA) where he worked with Kim R. Dunbar (2004) and was a post-doc at Los Alamos National Laboratory (USA, 2004–2009) with Drs. Jaqueline Kiplinger, Joe Thompson, and Kevin John. In 2009 he was appointed as an Assistant Professor at the University of Pennsylvania (USA). He was promoted to Associate Professor in 2015 and Professor in 2018. His research group studies separations chemistry, photochemistry, electronic structure, bio-inorganic modeling, and molecular materials chemistry especially of the lanthanide and actinide elements.



Prof. P. J. Walsh

Professor Patrick J. Walsh completed his B.A. at the University of California San Diego (USA) where he performed research with Prof. Charles Perrin. He obtained his Ph.D. at UC Berkeley (USA) with Prof. Robert G. Bergman (Ph.D., 1991) and was a postdoc with Prof. K. B. Sharpless at Scripps Research Institute (USA). From 1994–1999 he was an assistant professor at San Diego State University (USA) and professor at Centro de Graduados e Investigación, Instituto Tecnológico de Tijuana (Mexico, 1996–1999). In 1999 he moved to the University of Pennsylvania (USA).



Q. Yang

Qiaomu Yang was born and raised in Zhengzhou, Henan, China. He received his B.S. in chemistry from Tsinghua University (P. R. of China) in 2016 under the supervision of Prof. Zhongqiang Yang and Prof. Guifang Dong. He is currently a PhD candidate at the University of Pennsylvania (USA) under the supervision of Prof. Eric J. Schelter. His research interests include photochemical reactions, photophysical

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Yusen Qiao was born in Beijing, P. R. of China. He holds a B.S. in chemistry from Peking University (P. R. of China) and Ph.D. in inorganic chemistry from University of Pennsylvania (USA). Yusen was a postdoctoral researcher at Lawrence Berkeley National Laboratory (USA) from 2019 to 2020. In his Ph.D. and postdoc, he studied the synthesis, electronic structures, magnetism, photophysics and photocatalysis of lanthanide and actinide organometallics. He is currently a Senior Research Specialist at the Dow Chemical Company (USA) and develops new surfactant and alkoxylation technology.