Catalytic Photochemical Enantioselective α-Alkylation with Pyridinium Salts

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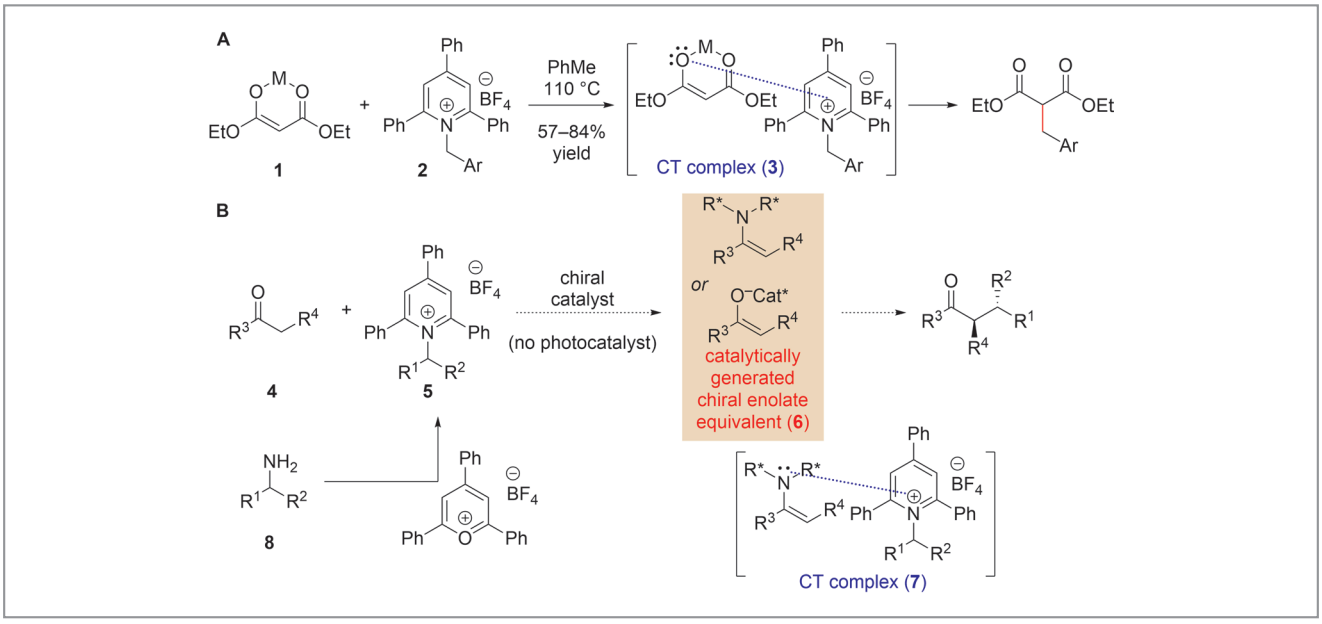
The research group of Professor Uttam Tambar at the UT Southwestern Medical Center in Dallas (USA) has a long-standing interest in asymmetric catalysis, with a burgeoning interest in photochemistry. "During 2020, while many labs around the world were grappling with the challenges of COVID-19, we found comfort in meeting virtually every day to talk about new research directions for our group once we could return to lab," said Professor Tambar. He continued: "Through these discussions, we started to think of ways to merge our interests in asymmetric catalysis and photochemistry. The growth of stereoselective photochemistry in recent years has been largely motivated by the significance of discovering new catalytic reactions that are environmentally benign, utilize sustainable sources of energy (such as low-energy visible light), and provide access to medicinally relevant chiral enantioenriched molecules that are not easily synthesized by other methods." [1]

As the group was contemplating its own ideas for stereoselective photochemistry, Santhi Yetra became enamored by the activation of Katritzky salts via photoinduced electron transfer. Professor Tambar explained: "We were drawn to an early paper by Professor Alan Katritzky in which he proposed a non-obvious mechanism for the alkylation of simple malonate anions by pyridinium salts (Scheme 1A).[2] While initial examination of this α-alkylation reaction would suggest a simple S_N2 mechanism, Katritzky's kinetic studies supported a non-chain radical substitution process that is initiated by a charge-transfer (CT) complex **3** between the malonate anion **1** and the Katritzky salt **2**. And then, on April 26, 2020, we asked the question that would serve as the basis for a new research direction in our lab: can we take advantage of CT complexes **7** between pyridinium salts **5** and catalytically generated electron-rich chiral enolate equivalents **6** to establish a general platform for photochemical enantioselective α-alkylations of carbonyl compounds **4** (Scheme 1B)?"

Given the prevalence of carbonyl compounds with α-stereocenters in biologically active molecules,[3] new strategies for their stereoselective synthesis have represented some of the most important developments in the group's field. "In our own graduate school curriculum at UT Southwestern, asymmetric α-alkylations are one of the first stereoselective



Scheme 1 Catalytic enantioselective α-alkylation of carbonyl compounds with pyridinium salts via charge-transfer complexes

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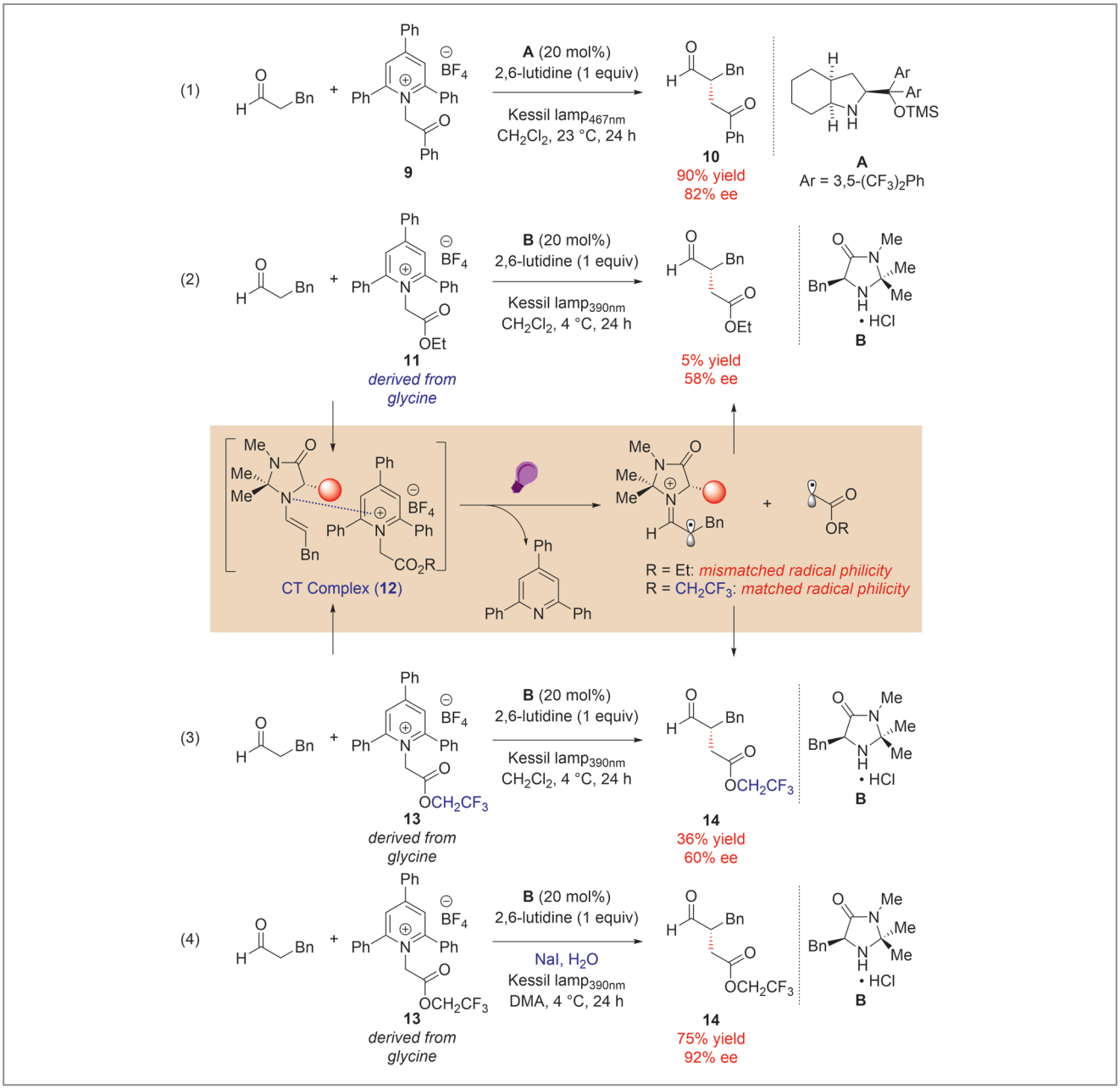
carbon–carbon bond forming reactions we teach in the advanced organic chemistry course," said Professor Tambar. He continued: "These reactions are usually categorized by the mode of catalysis and the enolate precursor, with alkyl halides and sulfonates typically utilized as the electrophiles. But the use of different classes of alkylating agents is underexplored. Our idea to couple pyridinium salts **5** with catalytically generated chiral enolate equivalents **6** would allow us to employ alkylating reagents that are ultimately derived from primary amines **8**, which have inherent advantages over traditionally used alkyl halides. For example, due to the abundance of primary amines in compound libraries and natural products, the ability to utilize them as alternatives to alkyl halides will present new opportunities in complex molecule synthesis.



Scheme 2 Development of chiral amine catalyzed photochemical enantioselective α-alkylation of aldehydes with pyridinium salts

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In addition, pyridinium salts **5** are synthesized from primary amines **8** in one step and are air- and moisture-stable solids that can be easily purified and stored for long periods of time, unlike the more reactive alkyl halides."

To develop their proposed reaction, the group had to define two important parameters: the choice of catalyst and the choice of pyridinium substrate. For the catalyst, Prof. Tambar and co-workers chose to activate aldehydes with chiral amine catalysts popularized by Professors David MacMillan and Benjamin List.[4] "We were heavily influenced by early physical chemistry papers on CT complexes by Mulliken, Marcus, and Kochi,[5] as well as recent reviews on the use of CT complexation in reaction design,[6]" explained Professor Tambar. He continued: "The most influential organic chemist in this field is Professor Paolo Melchiorre, who pioneered the use of α-bromoketones and benzylic bromides as alkylating agents via light-activated CT complexation with chiral enamines formed from the *in situ* condensation of aldehydes and chiral amine catalysts.[7]"

Professor Tambar told us that their initial choice of pyridinium substrate focused on Katritzky salts derived from α-aminoketones (**9**, Scheme 2, equation 1). He explained: "The carbonyl group next to the primary amine was necessary for both formation of the CT complex with the catalytically generated chiral enamine and subsequent carbon–carbon bond formation. We quickly optimized the formation of α-alkylation products **10** from simple aldehydes and α-aminoketone-based pyridinium salts to 90% yield and 82% ee."

At this point, the group recognized the unique opportunity to use pyridinium salts derived from α-amino acids, which represent renewable and sustainable sources of alkylating reagents. In addition, the use of enantiopure natural amino acids in a reaction that proceeds through a radical intermediate would allow for catalyst-controlled stereoconvergency. "Unfortunately, with α-amino acid derived substrate **11**, we were plagued by low yields and enantioselectivities for several weeks (Scheme 2, equation 2)," said Professor Tambar. He went on: "We were confident that we were forming CT complexes **12** with catalytically generated chiral enamines, as we observed the liberation of 2,4,6-triphenylpyridine under the reaction conditions. But the desired carbon–carbon bond formation was inefficient. These experiments taught us an important lesson in the development of radical-mediated reactions: the formation of reactive radical intermediates is not sufficient for the formation of new bonds via radical intermediates. Through Dr. Eric Welin's recent review on radical philicity, we learned of the importance of matching the reactivity of radical intermediates.[8] Our first major breakthrough was the use of the electron-deficient pyridinium salt derived from the 2,2,2-trifluoroethyl ester (**13**), which resulted in an enhanced yield (Scheme 2, equation 3)."

Although the Tambar lab had experience in developing enantioselective reactions, this was their first attempt to develop a photochemical enantioselective process, which presents unique experimental challenges. Most importantly, precise control of low temperatures for long times becomes challenging when a lamp is used to irradiate a reaction mix-

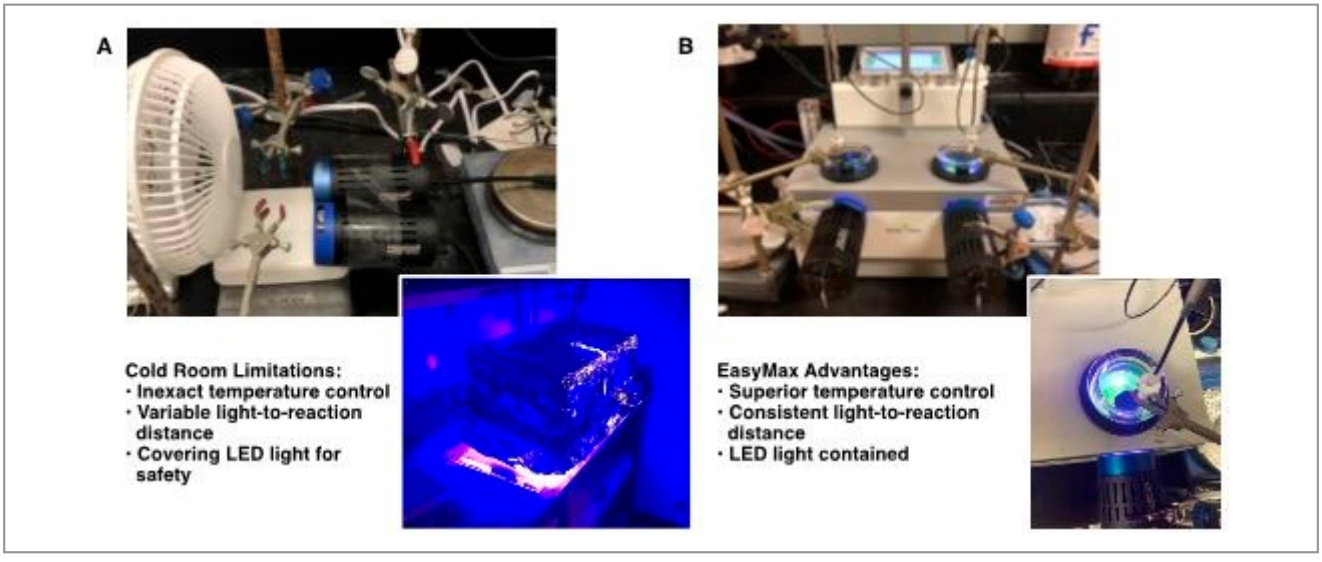
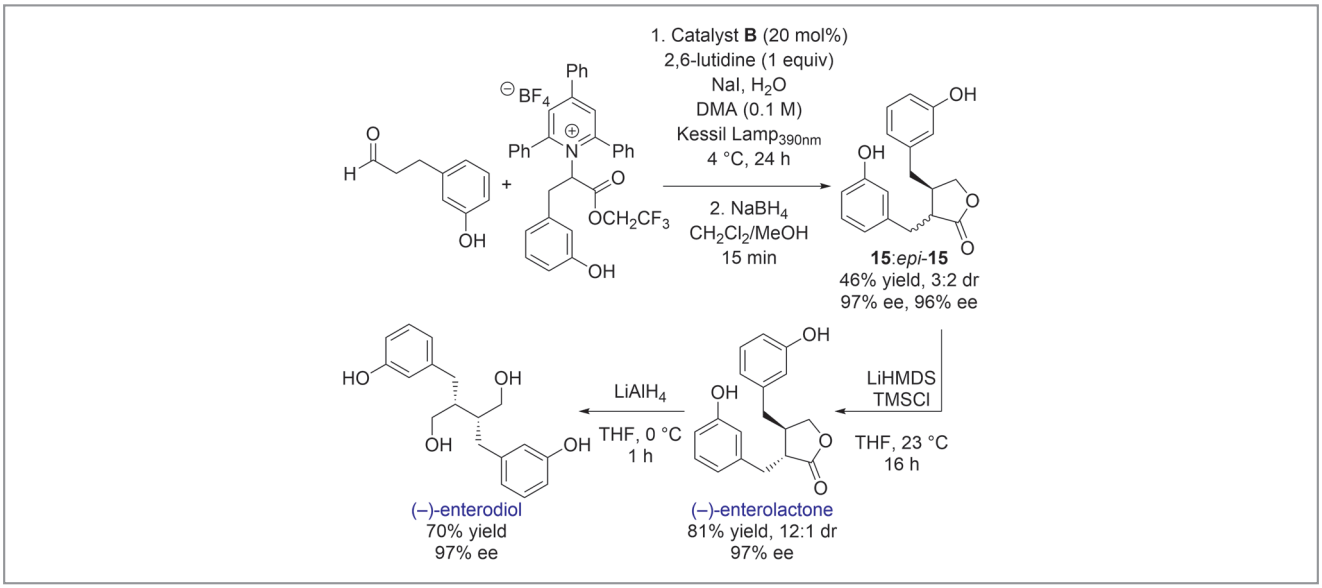


Figure 1 Control of low temperatures for long times in stereoselective photochemical reactions

ture from a close distance. Professor Tambar remarked: "For months we were plagued with inconsistencies in ee, which we attributed to the difficulty of maintaining the reaction temperatures. Initially we ran the reactions in a 4 °C cold room utilized by biochemists (Figure 1A). Santhi Yetra and Nathan Schmitt could be seen shivering late at night through the little window of the cold room. We also used an elaborate web of clamps to maintain a constant distance between the lamp, the reaction vials, and the fan that was used for additional cooling of the mixture. As inconsistencies persisted, we finally purchased the EasyMax 102 Advanced Thermostat system from Mettler-Toledo AutoChem, Inc. (Figure 1B). This turned out to be the most important purchase for the success of the project. Although the EasyMax had never been used for photochemical reactions, we identified two key features of this instrument. First, it enables the maintenance of a constant low reaction temperature for long times. Second, the instrument has a clear window into the reaction chamber, which is typically used to view into the reaction, but we identified this as an opportunity to shine light from a lamp at a controlled distance without impacting the reaction temperature. To our delight, the EasyMax provided a new level of consistency in our results."

Professor Tambar revealed that as this was the lab's first foray into charge-transfer complexes, they had to learn a whole new set of concepts and experimental techniques. UV-Vis absorption turned out to be an essential tool for reaction optimization, but none of the synthetic chemistry labs at UT Southwestern had a UV-Vis spectrometer. "Fortunately, this is an essential instrument for biochemists in our medical center," said Professor Tambar. He continued: "Through UV-Vis studies, we quickly learned of the subtle effect of reaction components on the formation of CT complexes. For example, distinct classes of chiral amine catalysts and reaction solvents displayed different λ_{max} values for the characteristic CT band. In the presence of MacMillan's amine catalyst **B** and with DMA as the reaction medium, we formed the desired product **14** in greater than 90% ee, but the yield was still low. The next breakthrough in optimization came from Nathan Schmitt's observation in the literature of the effect of iodide salts on CT complexation.[9] We added NaI and a small amount of water to solubilize the inorganic salt, which resulted in the optimized reaction conditions (Scheme 2, equation 4)."

Once the reaction was developed, the group was motivated to apply the method to synthesize complex target molecules. "During Nathan Schmitt's yearly thesis committee meeting, Professor Myles Smith suggested that we examine the lignan natural products as possible targets," said Professor Tambar. He went on: "Unfortunately, our method inherently displayed low diastereoselectivity with pyridinium salts derived from substituted α-amino acids. Although the diastereomeric products **15** were obtained in high ee and poor dr, we recognized the potential to epimerize the mixture in the presence of base for the synthesis of the desired products with high diastereoselectivity. We utilized this approach to synthesize the lignan natural products (–)-enterolactone and (–)-entero-



Scheme 3 Synthesis of lignan natural products

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diol in high diastereoselectivity and enantioselectivity (Scheme 3)."

The group is now thinking about future directions for this project. Professor Tambar said: "We think back to our initial thoughts in April 2020 to take advantage of CT complexes between pyridinium salts and catalytically generated electron-rich chiral enolate equivalents to establish a general platform for enantioselective α-alkylations of carbonyl compounds. We plan to examine other modes of activation besides organocatalysis to forge new carbon–carbon bonds via this mechanistically interesting photochemical activation of pyridinium salts." He concluded: "We also believe CT complexes may find broader use in other areas of synthetic chemistry beyond asymmetric catalysis."

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Santhivardhana Reddy Yetra received his BSc in chemistry at the Acharya Nagarjuna University, Guntur (India), in 2008 and his MSc from Andhra University (India) in 2010. He completed his PhD at the CSIR-National Chemical Laboratory, Pune (India), under the supervision of Professor A. T. Biju. Subsequently, he was a postdoctoral fellow with Professor Lutz Ackermann at Georg-August-Universität Göttingen, Germany. Currently, he is a postdoctoral researcher in the lab of Professor Uttam Tambar at University of Texas Southwestern Medical Center (USA). His research interests include asymmetric catalysis, transition-metal catalysis and photochemistry.

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Prof. U. K. Tambar

Uttam K. Tambar moved from India to New York City (USA) in 1982. He received his A.B. degree from Harvard University (USA) in 2000, where he conducted research with Professors Cynthia Friend and Stuart Schreiber. He obtained his Ph.D. from the California Institute of Technology (USA) in 2006 under the guidance of Professor Brian Stoltz. After he completed his NIH Postdoctoral Fellowship at Columbia University (USA) with Professor James Leighton in 2009, Uttam began his independent research career at UT Southwestern Medical Center in Dallas (USA). The Tambar lab is interested in asymmetric catalysis, natural product synthesis, chemical biology, and medicinal chemistry. Uttam is currently the Bonnie Bell Harding Professor in Biochemistry, Director of Diversity for Biochemistry, Director of the Organic Chemistry Graduate Program, and Co-Leader of the Simmons Cancer Center's Chemistry and Cancer Program.

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