

Visible-Light-Promoted C–S Cross-Coupling via Intermolecular Charge Transfer

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The development of synthetic methods based on harnessing the power of visible light for promoting stereoselective reactions using photoredox catalysts is at the forefront of modern organic chemistry.

The group of Professor Garret Miyake at Colorado State University (Fort Collins, USA) and University of Colorado Boulder (USA) has been working toward developing strongly reducing organic photoredox catalysts that operate using visible light, in particular for organocatalyzed atom-transfer radical polymerization. “For example, we have shown that *N,N*-diaryl dihydrophenazines or *N*-arylphenoxazines are successful photoredox catalysts for the synthesis of polymers with controlled molecular weights and architectures,” explained Professor Miyake, continuing: “Additionally, these compounds have similar properties to precious metal ruthenium or iridium photoredox catalysts. We have also become interested in exploring if these organic molecules cannot only serve as sustainable alternatives to precious metal catalysts but potentially access even new reactivity, because these organic molecules can have even stronger reducing potentials, longer excited state lifetimes, while possessing high triplet quantum yields. In fact, these organic molecules can catalyze trifluoromethylation reactions or participate in dual photoredox coupling reactions that were previously only demonstrated with metal catalysts.”

Postdoctoral researcher Dr. Bin Liu started exploring the synthesis of aromatic thioethers because of their importance across a wide range of pharmaceuticals and natural products

(Figure 1). “In traditional approaches, aromatic thioethers are produced via the use of alkoxide bases, specific or air-sensitive ligands, high temperature, and transition-metal catalysts (Scheme 1),” confirmed Dr. Liu. “However, the high cost of typically employed precious transition metals (e.g. palladium) and limited functional group tolerance (e.g. due to the use of strong alkoxide bases) have imposed limitations on their use,” he said. Advances have been made in the production of aromatic thioethers via photoredox catalysis; however, these approaches either require UV irradiation or involve the use of nickel and iridium transition metals (Scheme 1).

Therefore, according to Professor Miyake, the continual development of environmentally friendly and atom-economical methods for constructing C–S bonds is of significant importance with broad impact across the areas of small-molecule synthesis and materials. “Liu’s investigation was performed using organic photoredox catalysts and he observed that C–S cross-coupled products could be obtained in high yields,” explained Professor Miyake. He continued: “However, his control experiments also revealed that the desired product was also isolated in high yield (97%) in the absence of the organic photoredox catalyst after one hour of white LED irradiation at room temperature. This result was clearly due to a novel reaction pathway leading to C–S bond formation.”

Another postdoctoral researcher, Dr. Chern-Hooi Lim, used density functional theory (DFT) calculations, in conjunction with UV–Vis spectroscopy, to support the formation of an EDA complex between the electron-rich thiolate anion and

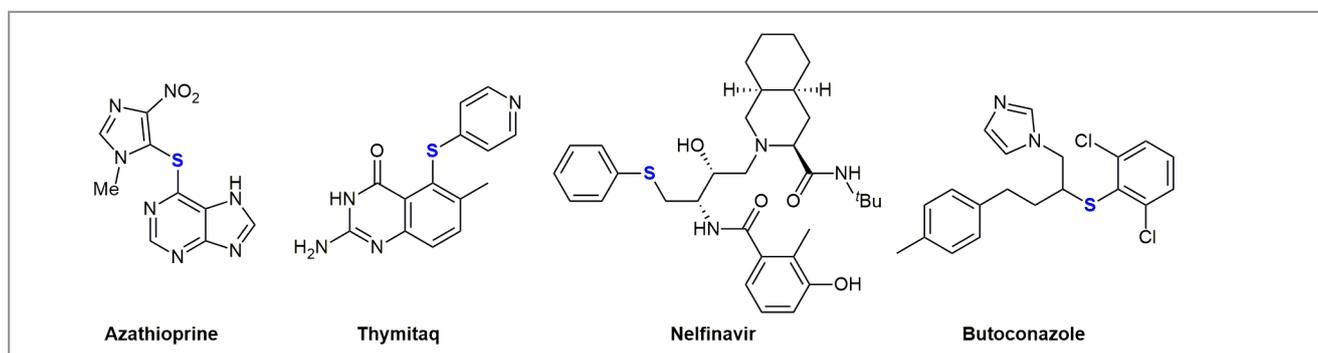
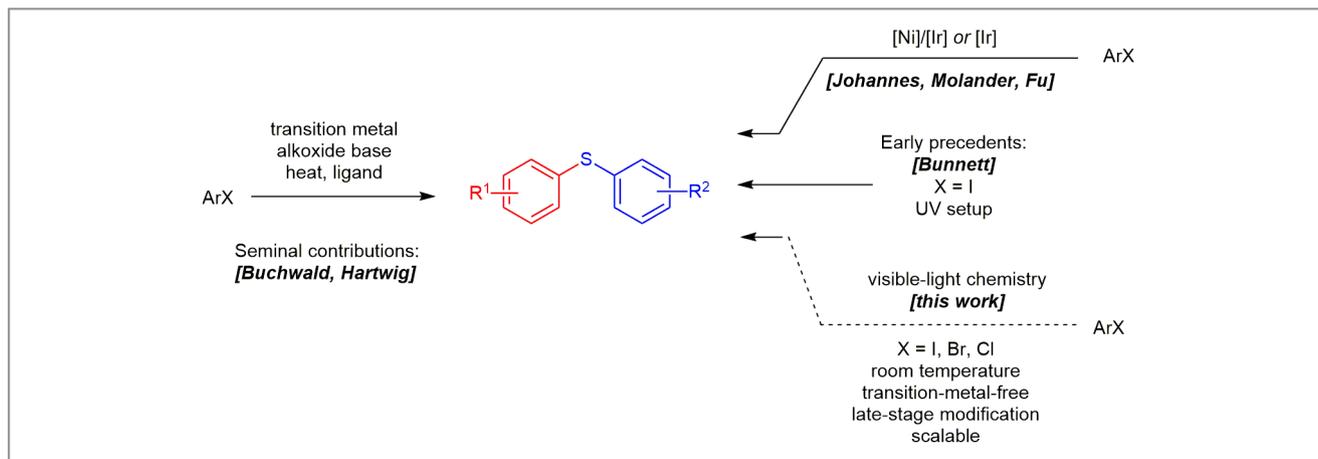


Figure 1 Thioether-containing medicinally relevant molecules



Scheme 1 Comparison of chemical methods to access aryl thioethers from aryl halides

the electron-poor aryl halide. “This EDA complex has UV-Vis absorption that extends into the visible region. Upon light absorption, an electron is transferred from the thiolate to the aryl halide species; this results in the formation of a thiyl radical and an aryl radical, which subsequently combine to form the C–S cross-coupled product,” explained Professor Miyake.

Expanding upon his original discovery, Dr. Liu developed this method consisting of a transition-metal-free cross-

coupling reaction between readily available aryl halides and aryl thiols to produce aromatic thioethers (>60 examples). Professor Miyake explained that the reaction is promoted by visible light via a proposed intermolecular charge-transfer mechanism. “This C–S cross-coupling methodology involves mild conditions: the reaction only requires the use of a mild base (e.g. Cs₂CO₃ and K₂CO₃) and the system is irradiated under visible light at room temperature,” remarked Professor

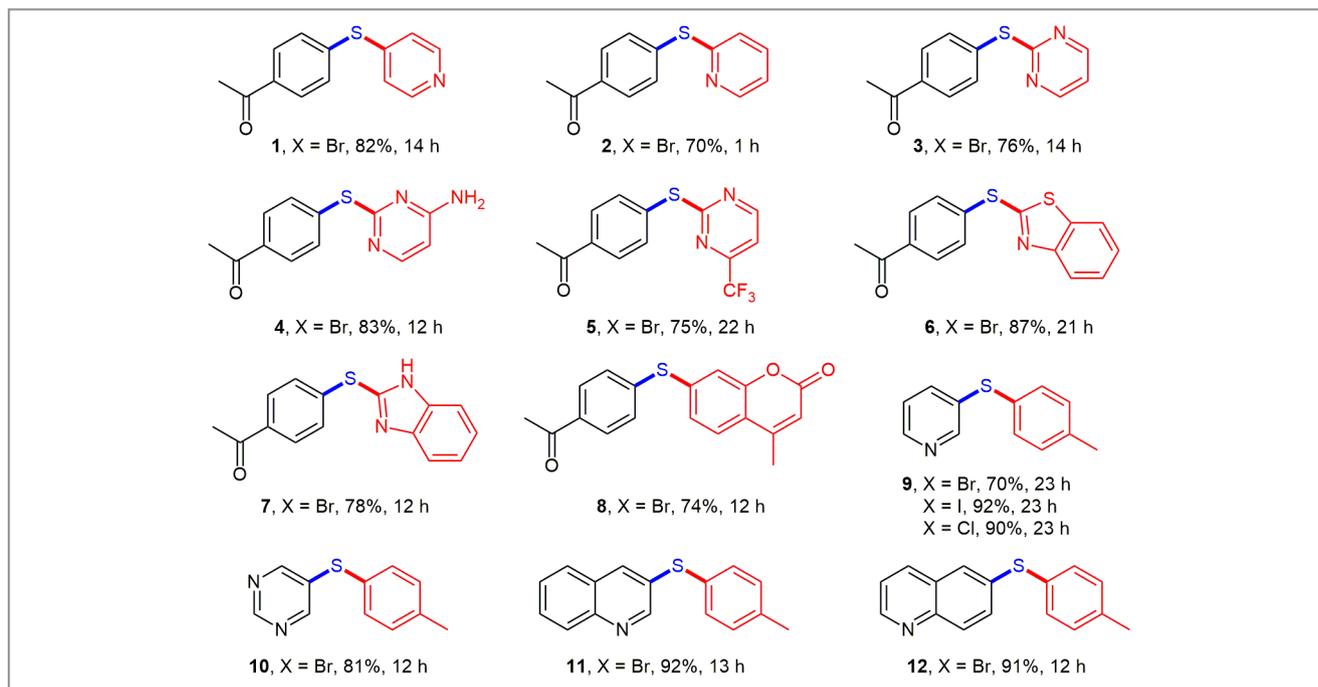


Figure 2 Scope of (hetero)arene coupling partners

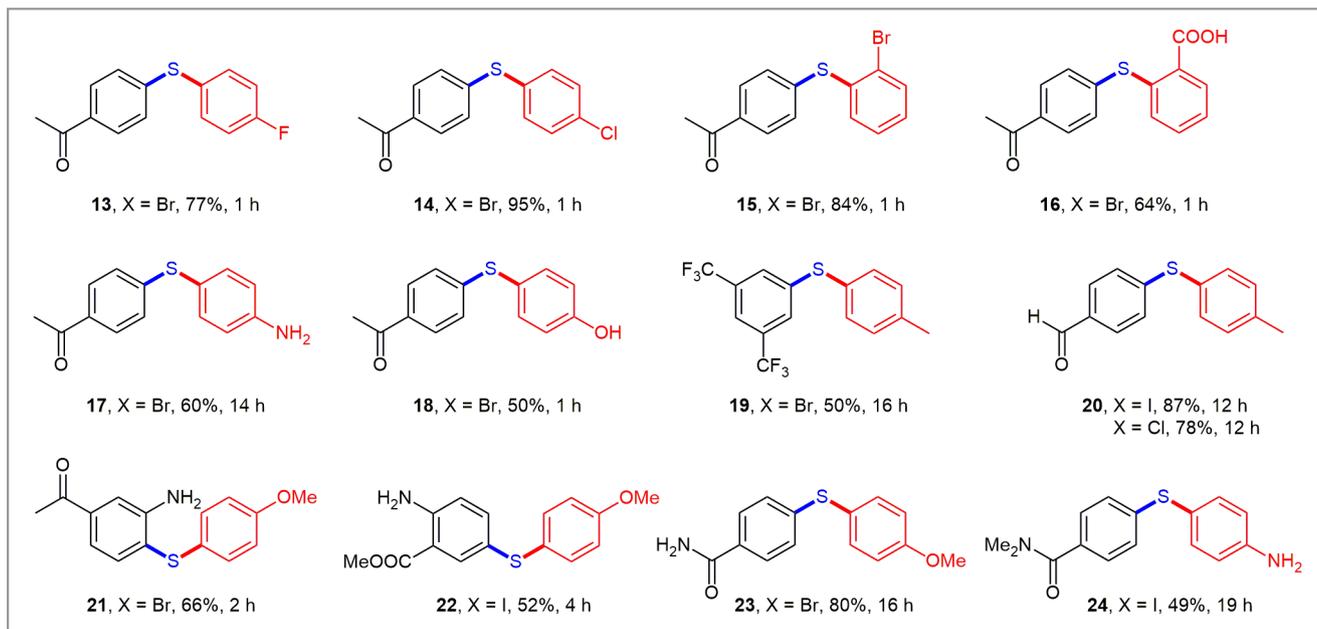


Figure 3 Selected examples of thiols and aryl halides

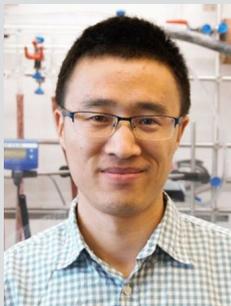
Miyake. “Furthermore, the use of mild and inorganic Cs_2CO_3 base has tolerated acidic functional groups such as amines, alcohols, and carboxylic acids.”

With the optimized conditions in hand, the substrate scope and functional group tolerance of the reaction was investigated extensively. “Gratifyingly, the scope of the reaction is very broad (with over 60 examples) and is summarized here by a number of representative examples described in Figures 2 and 3,” said Professor Miyake. He continued: “While this newly reported method represents a major advance in C–S cross-coupling methodology, limitations still exist in terms of alkyl thiols and electron-rich aryl halides that can be used.”

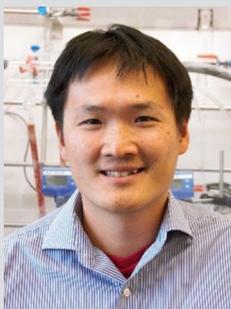
Professor Miyake concluded: “We believe this synthetic procedure may find broad applications facilitating the access to new thioether-containing compounds in pharmaceutical, agrochemical, and materials sciences.”

Mattes Fank

About the authors

*Dr. B. Liu*

Bin Liu received his B.S. degree from Nanchang University (P. R. of China) in 2009. He then joined Professor Bing-Feng Shi's group in Zhejiang University (P. R. of China) and obtained his Ph.D. in organic chemistry in 2014. In the same year, he worked as a postdoctoral fellow with Professor Bing-Feng Shi at the same university. Since 2016, he has worked in Professor Miyake's group as a research fellow at the University of Colorado, Boulder (USA) and Colorado State University (USA).

*Dr. C.-H. Lim*

Chern-Hooi Lim is an NIH Ruth L. Kirschstein postdoctoral fellow working in the group of Professor Miyake at Colorado State University (USA). He earned his Ph.D. with Professor Charles Musgrave in the Chemical and Biological Engineering Department at the University of Colorado, Boulder (USA) in 2015. His current research interests include small-molecule and polymer synthesis via visible-light photoredox catalysis using organic photoredox catalysts. He applies combined quantum mechanical modeling and organic synthesis approaches to organic photoredox catalyst design and elucidates mechanisms in catalysis and photochemistry.

*Prof. G. M. Miyake*

Garret M. Miyake earned his B.S. in Chemistry from Pacific University (USA). He completed his Ph.D. studies with Eugene Chen at Colorado State University (USA) before conducting postdoctoral research with Robert Grubbs at the California Institute of Technology (USA). He began his independent career at the University of Colorado, Boulder (USA) in 2014 and returned to Colorado State University in 2017. The Miyake group currently has research interests focusing on catalysis, organocatalyzed atom-transfer radical polymerization, and the synthesis of block copolymers that self-assemble to photonic crystals. He has been awarded a Sloan Research Fellowship as well as the 2017 American Chemical Society's Division of Polymer Chemistry Mark Young Scholar Award.