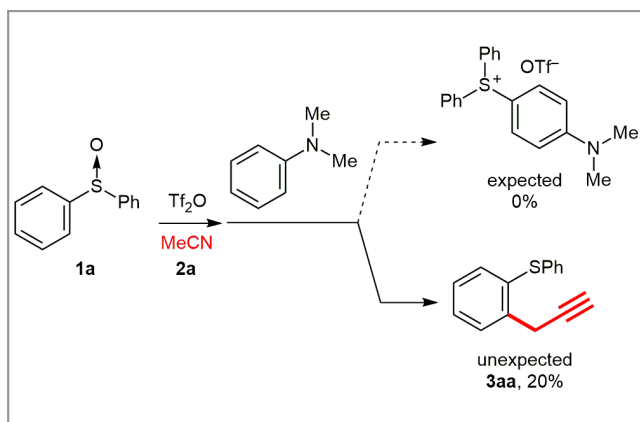


# Redox-Neutral $\alpha$ -Arylation of Alkyl Nitriles with Aryl Sulfoxides: A Rapid Electrophilic Rearrangement

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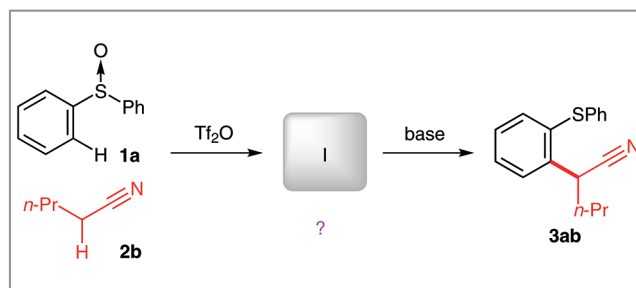
$\alpha$ -Aryl nitriles are structural frameworks frequently encountered in drugs and bioactive compounds. These compounds are also versatile synthetic building blocks that can be used to synthesize  $\alpha$ -aryl amides, carboxylic acids, ketones and  $\beta$ -aryl amines by simple hydrolysis or reduction. Although various approaches can produce  $\alpha$ -aryl nitriles, the use of impractical substrates, expensive and toxic transition-metal catalysts and limited functional group tolerance have been obstacles towards their synthetic applications.



**Scheme 1** Serendipitous discovery of the method

Recently, Professor Bo Peng from Zhejiang Normal University (P. R. of China) disclosed a metal-free cross-coupling reaction between readily available aryl sulfoxides and alkyl nitriles, achieving an unprecedented  $\alpha$ -arylation of nitriles. Professor Peng said: “Like other fascinating reactions found by accident, our method also came from a serendipitous discovery (Scheme 1). Initially, a Master’s student – Li Shang – unexpectedly obtained *ortho*-cyanomethylated product **3aa** in his attempts to prepare a triaryl sulfonium salt. Eventually, a molecule of the solvent – acetonitrile – was unambiguously anchored on the *ortho*-position of the aryl sulfoxide.” He continued: “We soon realized that this preliminary result was clearly due to a novel reaction pathway leading to  $\alpha$ -arylation of nitriles. Therefore, we decided to study the reaction further.”

Professor Peng explained: “The transformation actually consisted of two steps including the triflic anhydride ( $\text{TiF}_2\text{O}$ )



**Scheme 2** Optimization of reaction conditions

treatment and subsequent base neutralization (Scheme 2). Neither step is well understood at the moment. Also, a mysterious intermediate **I**, arising as a black box, retarded optimization of the first step. However, the overall transformation could still be evaluated according to its efficiency in producing final product **3ab**. This one-pot, two-step reaction would act as a probe, eventually allowing us to identify the elusive intermediate **I**.”

He continued: “Although without proper understanding of the reaction, we were fortunate to get the optimum conditions that allowed us to study the reaction mechanism further. Subsequent low-temperature NMR studies not only identified the structure of the imine sulfonium **I** but also witnessed its robust formation and its extreme instability (Scheme 3). We further investigated the reaction by using DFT calculations and found that the reaction could be divided into three essential steps, including electrophilic assembling, deprotonation, and [3,3]-sigmatropic rearrangement.”

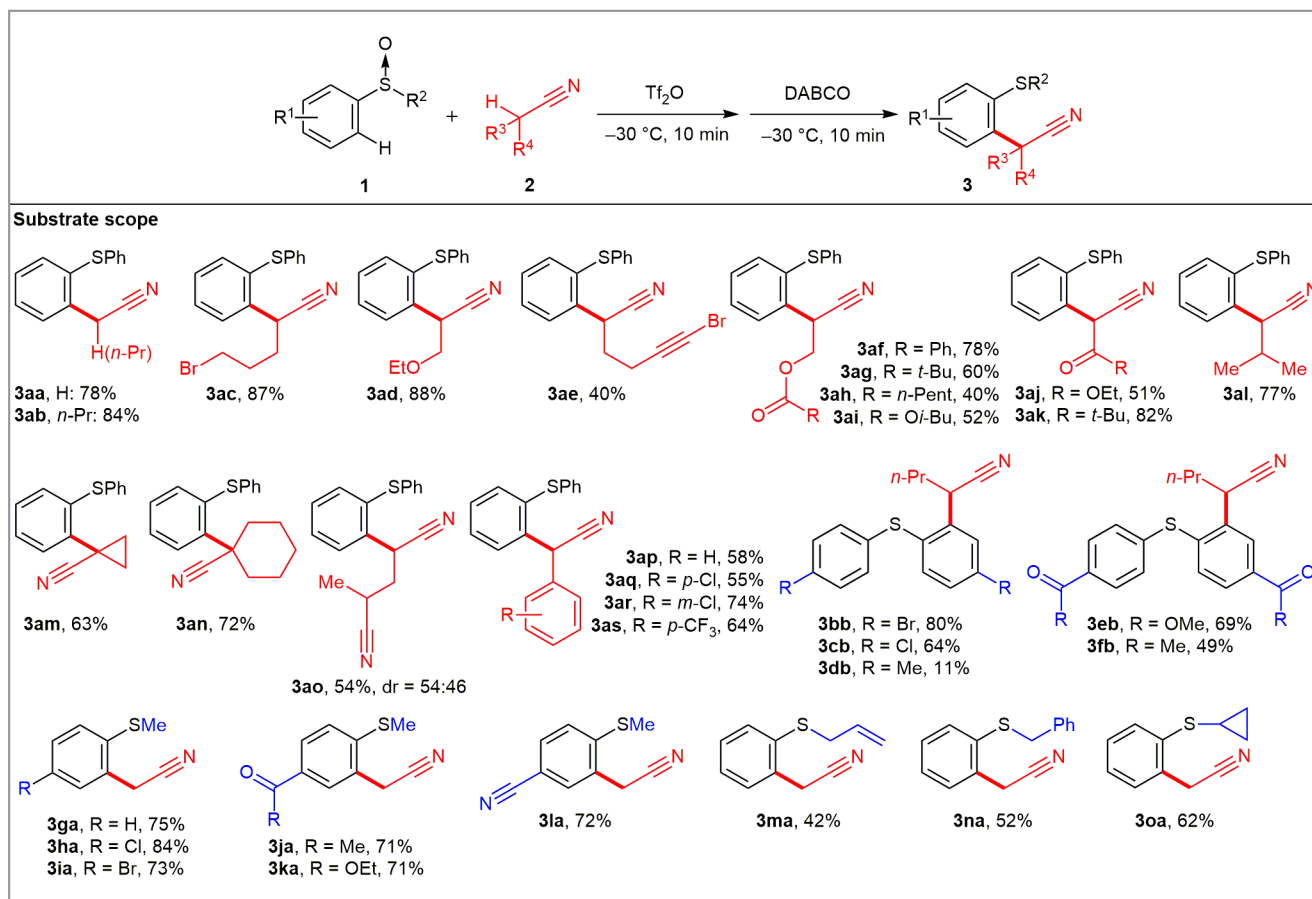
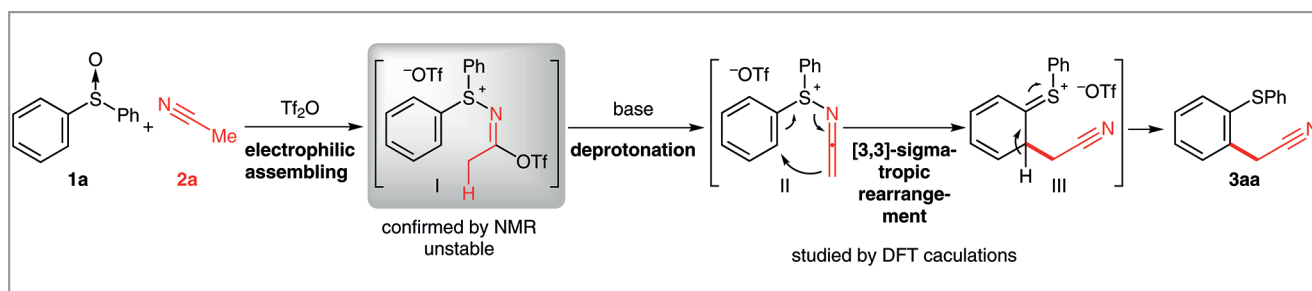
Professor Peng added: “The reaction also proved to be applicable to a wide range of aryl sulfoxides and alkyl nitriles (Scheme 4). It’s remarkable that the reaction tolerated various functionalities including alkyl halide, alkynyl bromide, ether, ester, carbonate, ketone, and nitrile to produce  $\alpha$ -aryl nitriles **3** in modest to very good yields (Scheme 4).”

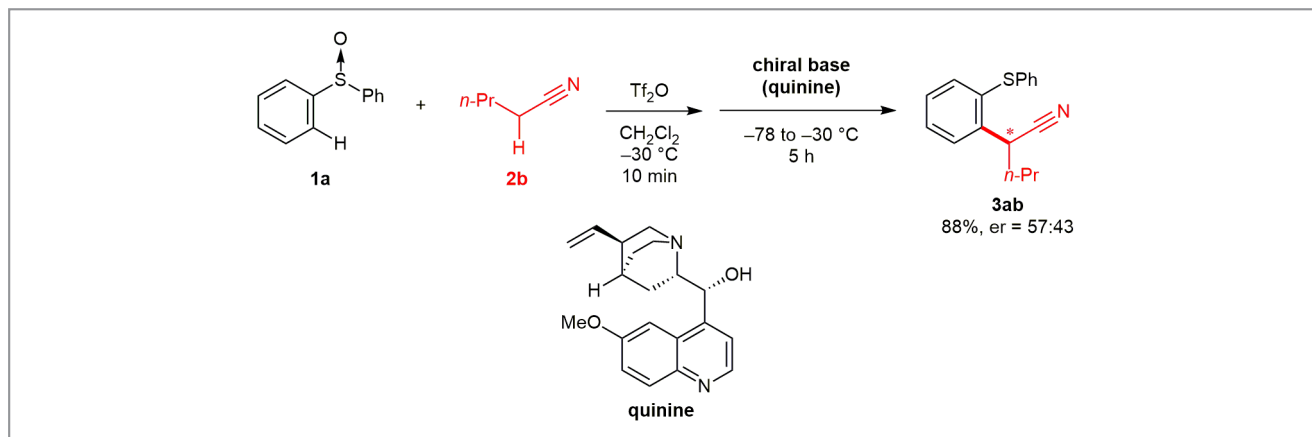
Professor Peng remarked: “The transformability of products and the scalability of this reaction were demonstrated by our further efforts. But the most exciting aspect to us is the attempt to use a chiral base to induce asymmetric  $\alpha$ -arylation of nitrile **2b** (Scheme 5). We found that the use of quinine as a chiral base indeed influenced the stereoselectivity of the

reaction. Although a low enantiomeric ratio (er = 57:43) was observed, this preliminary result still confirmed the feasibility of developing  $Tf_2O$ /chiral-base-mediated asymmetric  $\alpha$ -arylation of alkyl nitriles.”

Professor Peng concluded: “We were very lucky. An accidental discovery led us to a robust arylation transformation (Scheme 1). The advent of the reaction not only provides a new

method to access  $\alpha$ -aryl nitriles but also promotes the development of other ‘S–N’ bond breaking induced [3,3]-sigmatropic rearrangements. We envision that the electrophilic rearrangement protocol would become a unique type of Claisen rearrangement in the future.”



Scheme 5 Attempts of chiral-base-induced asymmetric  $\alpha$ -arylation of nitriles

*Matthew Fenske*

### About the authors



L. Shang

**Li Shang** obtained his B.Sc. degree from Anyang Normal University (P. R. of China) in 2014. He then studied as a Master's student at Zhejiang Normal University (P. R. of China). In 2015, he joined the research group of Professor Bo Peng. His research focuses on the study of unprecedented sulfur(IV) species.



Prof. B. Peng

**Bo Peng** graduated from Nanjing University of Science and Technology (P. R. of China) with his B.Sc. degree, and then obtained his Ph.D. from Dalian University of Technology (P. R. of China) in 2010. After postdoctoral research at the Max-Planck-Institut für Kohlenforschung (Germany) and the University of Illinois at Urbana-Champaign (USA), he started his independent career as a principle investigator at Zhejiang Normal University (P. R. of

China) in 2015. In the same year, he was named as a Qianjiang Scholar. His current interests focus on the formation and transformation of highly reactive but unstable organic species.



Prof. Y. Chang

**Yonghui Chang** was born in Henan province (P. R. of China) in 1975. He studied chemical engineering technology at Hunan University (P. R. of China), receiving his B.E. in 1998 and his Ph.D. in biochemistry technology under the guidance of Professor Hanjie Ying at Nanjing Technology University (P. R. of China) in 2009. After working as a lecturer at Hainan Normal University (P. R. of China) for two years, he became an Associate

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