

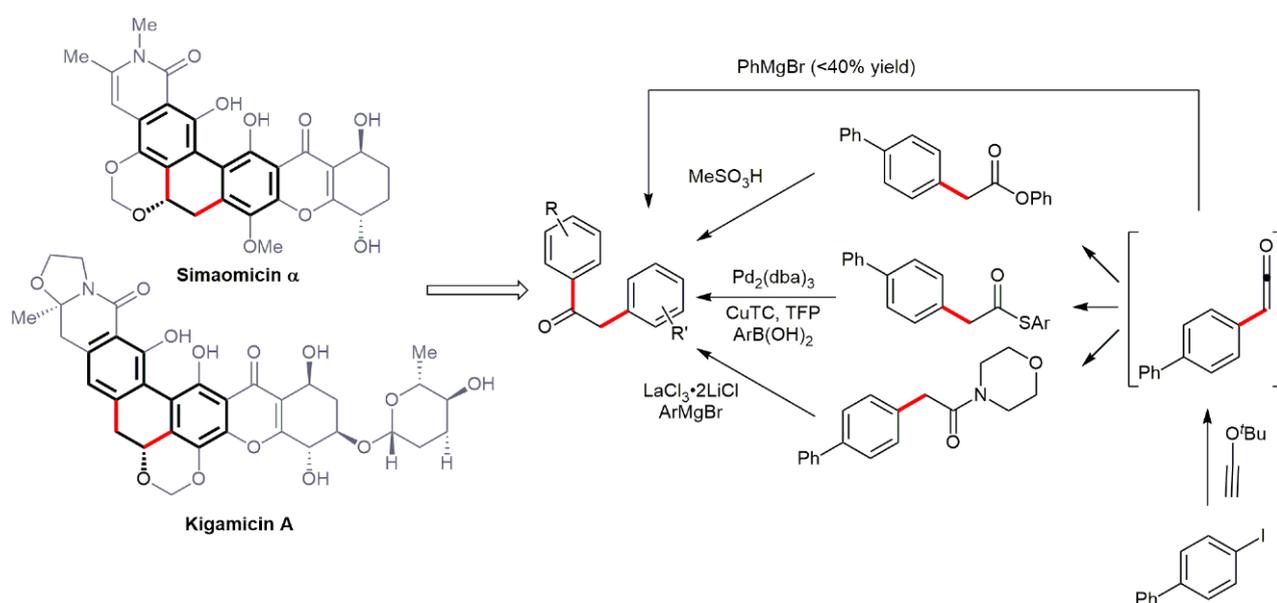
The Ketene-Surrogate Coupling: Catalytic Conversion of Aryl Iodides into Aryl Ketenes through Ynol Ethers

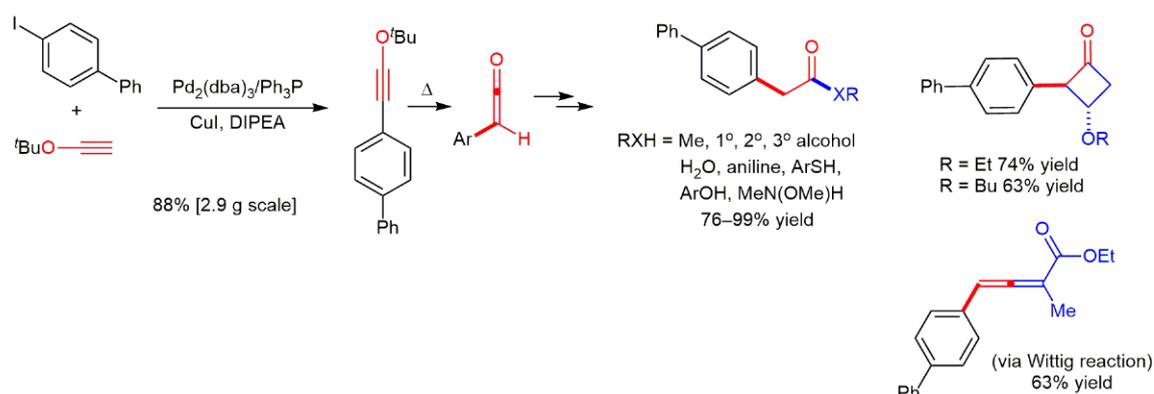
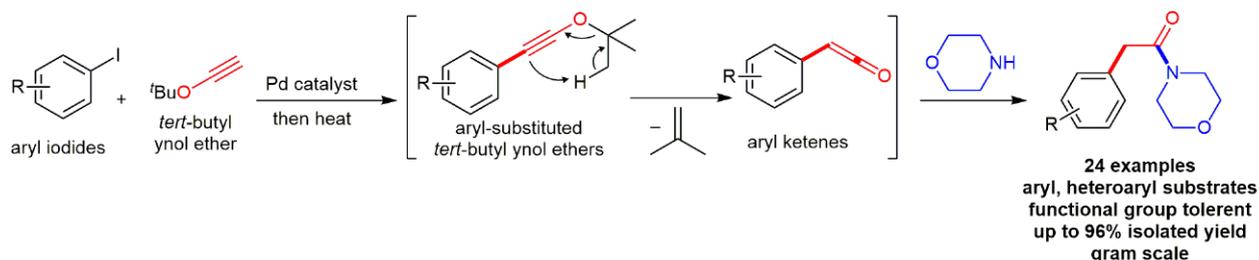
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■ The $\text{ArCH}_2(\text{CO})$ -fragment is present in a number of natural and bioactive molecules such as benzyl ketones and arylacetic acid esters or amides, and therefore represents an important target in organic synthesis. The ketene-surrogate coupling reaction that was developed by Professor Joseph Ready and Wenhan Zhang at the University of Texas Southwestern Medical Center (Dallas, USA) is a very useful method for the synthesis of these structural motifs. Professor Ready said: “The original driving force for developing the ketene-surrogate coupling reaction emerged from an interest in aryl benzyl ketones.” This substructure appears in several biologically active xanthone-type molecules, such as simaomicin α and kigamicin. A convergent approach to aryl benzyl ketones would involve two aryl fragments and a two-carbon conjunctive reagent. Professor Ready said: “For the two-carbon fragment, we selected ketene with the idea that coupling to an aryl group would yield an aryl ketene. If the aryl ketene could be trapped with an aryl carbanion, it would form the second carbon–carbon bond while keeping the carbon in the

ketone oxidation state.” He continued: “We found that *tert*-butoxyacetylene could couple with an aryl iodide to generate an aryl-substituted ynol ether, which underwent a [1,5]-hydride shift to yield the aryl ketene.” However, the direct Grignard addition to aryl ketenes proved challenging, generating a large amount of polymerized material. Accordingly, several alternative stepwise strategies were developed by the Dallas-based researchers to produce the desired ketones, including Fries rearrangement, the addition of Grignard to morpholine amides, and the Liebeskind coupling reaction.

According to Professor Ready, in addition to providing aryl benzyl ketones, this ketene-surrogate coupling shortens the synthesis of arylacetic acid derivatives. Specifically, various aryl iodides couple with *tert*-butoxyacetylene and yield the aryl ketenes. “In the course of evaluating the scope of the coupling reaction, the aryl ketenes were trapped with morpholine,” explained Professor Ready. “Thus, electron-rich or electron-deficient aryls, six- or five-membered heteroaryls, and substituted aryls all gave the morpholine amides in

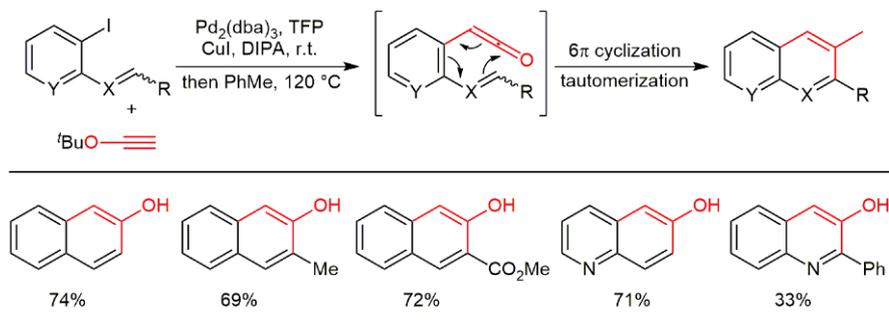




63–99% yield. Moreover, different nucleophiles could be used to trap the ketene intermediates.” Heteroatom-based nucleophiles, such as oxygen, nitrogen, and sulfur, can trap the aryl ketene intermediates yielding acids, esters, thioesters, and amides. Alternatively, enol ethers undergo [2+2] cycloadditions with the intermediate ketenes while Wittig reagents form allenes. The variability of both aryl iodides and nucleophiles provides the potential to build diverse libraries for drug discovery.

Professor Ready explained: “2-Vinyl iodobenzenes can form *ortho*-vinyl aryl ketenes under our protocol, and these

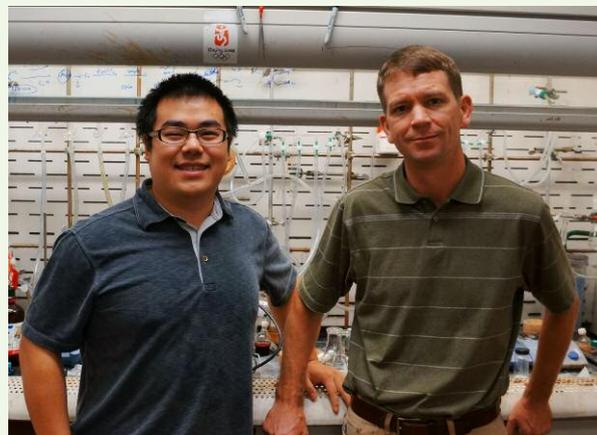
intermediates undergo a 6π -electrocyclic ring closure to produce naphthols, quinolinols, and isoquinolinols. Now, we are focusing on the annulation of those substrates containing heteroatoms, which will allow us to rapidly install the cores of some drug-like molecules. The cyclization of imines ($\text{X} = \text{N}$) to quinolines presently proceeds in moderate yield, but remains surprising nonetheless. The polarities of the imine and ketene appear mismatched for electrocyclization, as the reaction joins two electrophilic carbon atoms. Current efforts aim to optimize these transformations so they occur in preparatively useful yields.”



Professor Ready concluded: “As we consider the ketenes and ynol ethers available through this coupling, we are now interested in investigating their reactivity in a variety of contexts. For example, ynols can participate in cycloaddition reactions, but have not been explored as completely as olefin reagents. Likewise, we continue to search for protocols to effect the direct addition of carbon-based nucleophiles to ketenes. Finally, the couplings described here fail when attempted on the corresponding bromides or hindered aryl iodides. We are eager to expand the scope of the reaction to accommodate these important substrate classes.” ■

Matteo Zanda

About the authors



From left to right: W. Zhang, Prof. J. M. Ready

Joseph Ready obtained his undergraduate degree in chemistry from the University of North Carolina (USA). He received a PhD in chemistry at Harvard University (USA) in 2001 and then completed postdoctoral training at Yale University (USA). He joined the faculty at the University of Texas Southwestern Medical Center (USA) in 2003 where his research group is interested in synthetic and medicinal chemistry.

Wenhan Zhang received his B.Sc. degree from Sichuan University (P. R. of China) in 2011. His undergraduate research focused on the total synthesis of hirsutellones and the total synthesis of heliespirones A and C under the supervision of Professor Bo Liu. In 2012, he joined the group of Professor Joseph M. Ready at the University of Texas Southwestern Medical Center at Dallas as a graduate student. He is now working on developing new synthetic methodologies of aryl ynol ethers and their application in synthesis.