

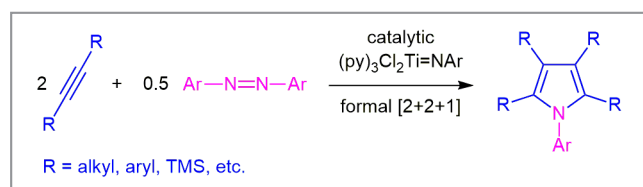
Catalytic Formal [2+2+1] Synthesis of Pyrroles from Alkynes and Diazenes via Ti^{II}/Ti^{IV} Redox Catalysis

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Polysubstituted pyrroles are very common and important structural motifs in many biologically active compounds, drugs and materials, but the synthesis of these compounds is often very challenging. Recently, the group of Professor Ian A. Tonks at the University of Minnesota – Twin Cities (USA) has reported a groundbreaking and efficient method for accessing pyrroles having up to five substituents on the ring through a formal [2+2+1] cyclization of alkynes and diazenes promoted by a Ti^{II}/Ti^{IV} redox catalytic cycle.

“Our research in Ti-catalyzed [2+2+1] reactions,” said Professor Tonks, “has been motivated by two factors: first, by the growing interest in using ‘earth-abundant’ metals to carry out catalytic transformations; and second, from the fundamental question of whether early transition metals – which typically do not undergo facile two-electron redox processes – can be used in *practical* redox catalytic reactions. In general,” he continued, “the organic community has focused heavily on Fe/Co/Ni/Cu catalysts as earth-abundant replacements for many classic organometallic reactions, but Ti has several advantages over these metals: Ti is the 2nd most abundant transition metal in Earth’s crust (after Fe) and common Ti waste products (TiO₂) are typically nontoxic.”

Professor Tonks explained: “The work in our *Nature Chemistry* paper is the coalescence of several observations. We first envisioned a potential Ti^{II}/Ti^{IV} catalytic cycle in 2013 while I was finishing my thesis with John Bercaw at Caltech. During this time a visiting student from TU Munich, Josef Meier, discovered that pyrroles and an unidentified Ti^{II} byproduct could form when reacted with a pyridine (bis)phenolate Ti imido complex, albeit in extremely low yield.¹ This initial observation came about while Josef and I were characterizing the byproducts of an otherwise unremarkable alkyne hydroamination reaction – and I think highlights an important teaching moment: always characterize your byproducts; they may be more interesting than your desired reaction!”



Professor Tonks revealed that the inspiration to use azobenzene to reoxidize Ti^{II} back to a Ti^{IV} imido and close the catalytic cycle was instigated by work from Ian Rothwell in the early 1990s, who first showed that Ti^{II} aryl oxide complexes could cleave azobenzene to form Ti imidos.² “For the Ti-catalyzed [2+2+1] reaction, this reagent proved critical,” said Professor Tonks. “‘Standard’ nitrene sources such as azides failed to yield productive reactivity, most likely because they are strong nucleophiles and effectively outcompete alkynes as ligands for Ti.”

For such a simple precatalyst, the ability for TiCl₂(py)₃NR to facilely change between Ti^{II} and Ti^{IV} is quite remarkable. Professor Tonks explained: “We hypothesize that diazenes (or potentially alkynes) serve a dual role in this reaction: not only are they used as the nitrene source for pyrrole synthesis, but they also may be serving as redox ‘non-innocent’ ligands – accepting electron density into the N–N π* to prevent the formation of high-energy naked Ti^{II} species.”

From the perspective of organic synthesis, the Ti-catalyzed [2+2+1] reaction also represents a new retrosynthetic disconnection for pyrrole syntheses. “The deceptively simple core of the pyrrole heterocycle belies the challenges of constructing polysubstituted (in particular tetra- and pentasubstituted) and/or electron-rich pyrroles,” said Professor Tonks. “Speaking of these challenges, Gevorgyan recently published a review article³ in which over 60 different multicomponent routes to pyrroles are presented; and a review article⁴ on the synthesis of Lipitor highlights the pitfalls of multicomponent strategies for pyrrole synthesis. While our [2+2+1] synthetic methodology is still in its infancy,” he continued, “the fact that we can synthesize (for the first time, in many cases) a variety of highly substituted, *electron-rich* pyrroles highlights it as a potentially generalizable method for pyrrole synthesis.”

According to Professor Tonks, one of the appealing characteristics of this reaction is the simplicity of the precatalyst: TiCl₂(py)₃NR complexes can be synthesized in one pot from TiCl₄, and new undergraduate researchers in Professor Tonks’ lab synthesize it as one of their first reactions. “Ease of synthesis is an incredibly important factor when developing catalysts: it is difficult for researchers to adopt an early transition metal catalyzed protocol that involves significant inorganic synthesis. In this regard, I’ve been influenced heavily by

Laurel Schafer's (UBC) hydroamination catalysis that utilizes elegantly simple ligand architectures," remarked Professor Tonks.

He continued: "Our current limitations in [2+2+1] synthesis arise mostly from issues related to regioselectivity and functional group tolerance. We are currently developing new catalyst frameworks to address these challenges. Remarkably, every Ti imido complex we have synthesized has shown at least some degree of pyrrole formation – because of this, we have high hopes that we will be able to rationally design catalysts that can exert greater regiocontrol and are more functional group tolerant than the simple system reported in our paper."

"Extending the chemistry of the azatitanacycle intermediates towards further multicomponent reactions has been the goal for a number of researchers in this field. Aaron Odom, Philip Mountford, Tom Livinghouse and Lutz Gade have all demonstrated quite unique chemistry from these reactive intermediates," added Professor Tonks, concluding: "With this precedent in place, we hypothesize that utilizing diazene oxidants with Ti imido catalysts will ultimately lead to broad classes of useful and practical oxidation reactions."

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About the authors



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Zach Gilbert was born in Fort Knox, Kentucky (USA) in 1990. He received his BS degree in chemistry from Appalachian State University in Boone, N.C. (USA) in 2012. He is currently a PhD student at the UMN (USA) studying under the guidance of Professor Ian A. Tonks. His work focuses on the development of titanium redox catalysis toward multicomponent reactions.



Dr. R. Hue

Ryan Hue was born in Latrobe, PA (USA) in 1984. He received his BS in chemistry from the University of Pittsburgh (USA) in 2007, and then moved to the University of Minnesota (USA) to pursue his PhD in inorganic chemistry with Wayne Gladfelter. He received his PhD in 2013 before joining the laboratory of Ian Tonks to study chain transfer polymerization reactions and titanium redox catalysis.



Prof. I. A. Tonks

Ian Tonks was born in Knoxville, Tennessee (USA), in 1983. He received his BA in chemistry from Columbia University (USA) in 2006 while working on zinc thiophenolates with Gerard Parkin. During his undergraduate education, he spent three summers as an NSF-REU fellow working with John Margrave (Rice University, USA), George Whitesides (Harvard University, USA) and Craig Jensen (University of Hawaii–Manoa, USA).

Upon graduation, Ian joined the laboratory of John Bercaw at the California Institute of Technology (USA) working in the areas of early transition metal catalyzed olefin polymerization and metal hydrazido chemistry. He received his PhD in December 2011 and moved to the University of Wisconsin–Madison (USA) to work as a postdoctoral scholar under Clark Landis from 2012–2013. He was appointed as an Assistant Professor of Chemistry at the University of Minnesota–Twin Cities (USA) in 2013, where his work has focused on early transition metal redox catalysis and metal-catalyzed multicomponent polymerization reactions.