Charge-Transfer-Directed Radical Substitution Enables *para*-Selective C–H Functionalization

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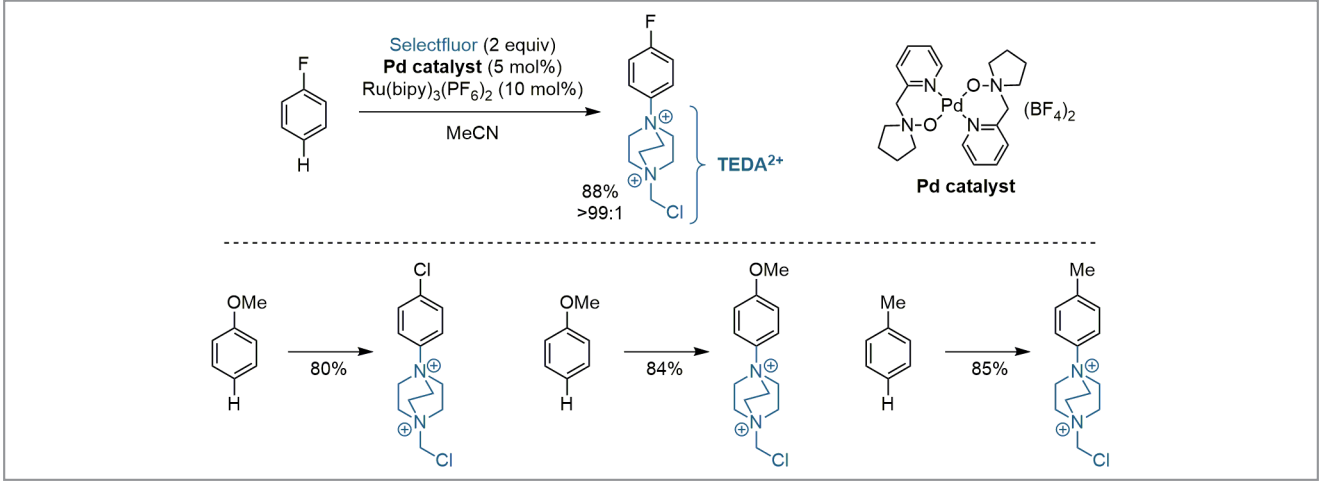
C–H bond functionalization continues to attract enormous interest from the synthetic organic chemistry community, as a response to the need for more atom-economical, environmentally benign and economically efficient chemical processes. The chelation-assisted approach for C–H functionalization is very successful and useful, and now a wide variety of Lewis basic functional groups can be made to provide chelation assistance through an appropriate choice of catalyst and conditions. However, the requirement for a specific group to promote a reaction in a specific position limits the potential substrate scope of such reactions. Unfortunately, when a coordinating directing group is not utilized, positional selectivity is nearly always lost, and multiple constitutional isomers are obtained as products. This selectivity issue hampers the utility of C–H functionalization significantly, because product mixtures imply a lower yield of the desired isomer, and waste in the form of the undesired ones. Therefore, C–H functionalization reactions that can afford high and predictable positional selectivity without the requirement for a particular directing group have the potential to be very powerful. Therefore, when the group of Professor Tobias Ritter from Harvard University (USA) and Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr (Germany) entered the field of C–H functionalization, they did so with the goal of developing useful C–H functionalization reactions that would not require the use of coordinating directing groups to provide chelation assistance.

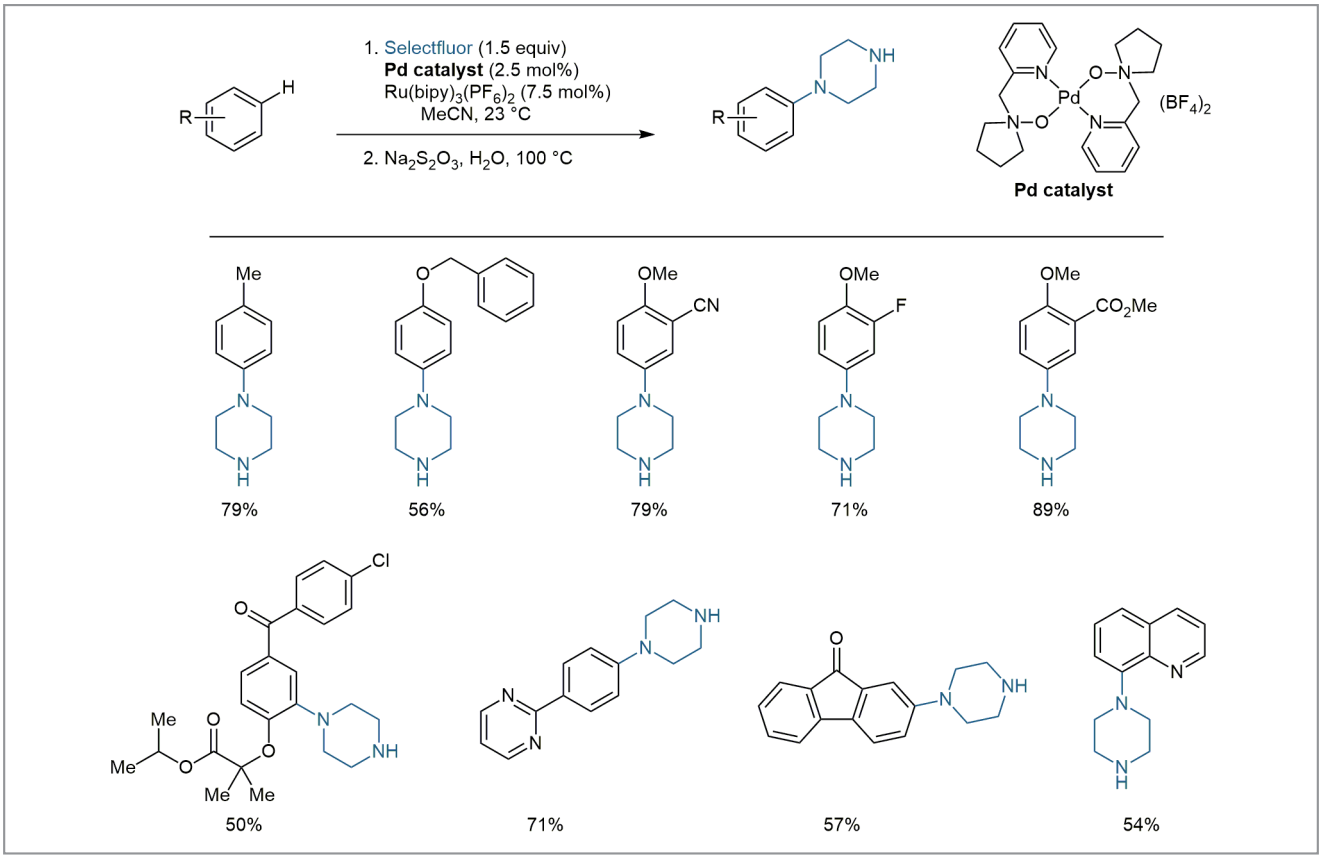
Professor Ritter explained: "We discovered the aromatic TEDAylation reaction quite by accident while attempting an oxidative C–H functionalization reaction with the electrophilic fluorinating reagent Selectfluor as oxidant. With fluorobenzene as substrate, we observed by 19F NMR full conversion of the arene to a single product, but not the expected product, or any other product that we could readily imagine would arise from the reaction conditions. It took days for us to realize that the product was what we affectionately came to term an aryl–TEDA compound, arising from incorporation of the non-fluorine component of F–TEDA into the arene. That it took us so long to solve the mystery can be attributed partly to the unprecedented nature of such a reaction (direct cross-coupling of an aromatic compound to form a quaternary ammonium salt), and partly to the fact that Ar–TEDA compounds, because of their two positive charges, are difficult to observe with standard analytical tools of organic chemistry, such as thin-layer chromatography and GC/MS. These facts perhaps also explain why Ar–TEDA formation has not been discovered before, despite the fact that other groups have published other reactions with conditions that we have found to produce Ar–TEDA compounds."



Scheme 1 Aryl–TEDA formation reaction exhibits high *para* selectivity for a variety of arenes

The group was delighted to find that nearly every simple arene they subjected to the same conditions led to a single product in high yield, which for monosubstituted arenes corresponded to the *para*-substituted isomer (Scheme 1). "Such a result is unprecedented in non-chelation-assisted C–H functionalization. However, Ar–TEDA products were a new class of compounds with no known application; thus, it was up to us to establish some utility for these strange new compounds," said Professor Ritter. He continued: "Fortunately, through much experimentation, we discovered that treatment of Ar–TEDA salts with sodium thiosulfate at elevated temperature affords aryl piperazines, which unlike Ar–TEDAs, are a very useful class of compounds, being a common motif in pharmaceuticals. We optimized a two-step, one-pot procedure that affords aryl piperazines in high selectivity directly from the corresponding C–H compound (Scheme 2). This method has the advantage over traditional syntheses of aryl piperazines in that it does not require a prefunctionalized starting material, such as an aryl bromide; crucially, this advantage relies on the high and predictable selectivity of the Ar–TEDA formation step. Thus, our new reaction went from a curiosity of fundamental reactivity to a potentially useful synthetic method."

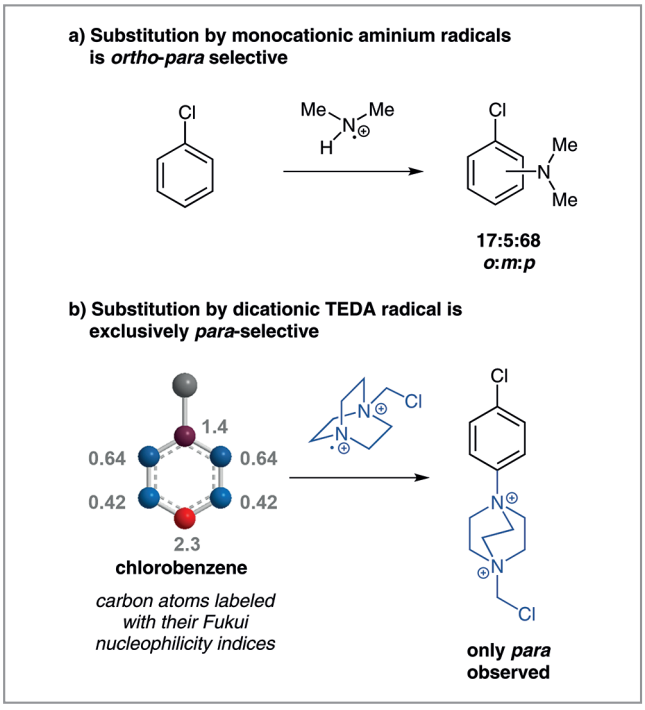
After months of reaction development, Professor Ritter and co-workers had yet to arrive at a convincing explanation for the remarkable *para* selectivity of the reaction. "We had already realized that the C–N bond formation likely occurred through radical aromatic substitution between the $TEDA^{2+\bullet}$ radical and arenes, which is similar in kind to reactivity reported by Italian chemist Francesco Minisci in the 1960s," remarked Professor Ritter. Minisci noted that in contrast to aromatic substitution by neutral carbon-based radicals, which occur with very poor positional selectivity, substitutions by cationic aminium radicals exhibit higher selectivity, with electron-donating substituents directing substitution predominantly *ortho* and *para* to themselves. Professor Ritter commented: "This result is intuitive, as one would expect such electrophilic radicals to have selectivity similar to electrophilic aromatic substitution. What is harder to explain is why $TEDA^{2+\bullet}$, with one more positive charge, exhibits such a high propensity to attack *para* to substituents, even at the expense of the



Scheme 2 Aryl–TEDA formation enables two-step, one-pot synthesis of aryl piperazines

ortho positions, which according to the basic model of electrophilic aromatic substitution are just as activated towards electrophilic attack as the *para* position."

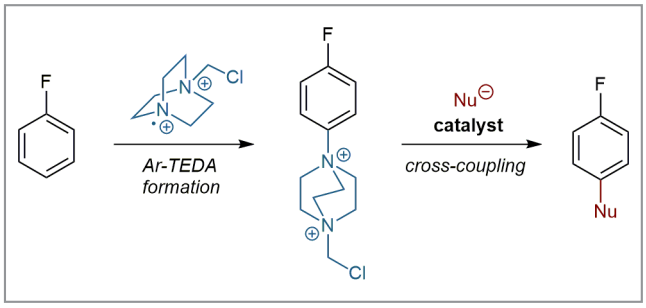
The breakthrough came with the realization that the *ortho* and the *para* positions differ significantly in their ability to donate electron density to incoming electrophilic species in the transition state of addition, as measured by Fukui nucleophilicity indices. "The realization that the *ortho* and *para* positions are thus electronically differentiated allowed us to argue that the selectivity of the reaction is controlled by arene-to-radical charge-transfer contribution to the transition state of addition; the contribution of such charge-transfer forms becomes more important with increasing electrophilicity of the radical, which is why adding an extra positive charge to a cationic aminium radical, as in the case of TEDA, leads to exclusive selectivity for the *para* position (Scheme 3)," explained Dr. Boursalian, a former graduate student with Ritter and first co-author of the paper.



Scheme 3 The additional positive charge on $TEDA^{2+\bullet}$ leads to increased para selectivity over substitution by monocationic aminium radicals. The para selectivity is predictable by Fukui nucleophilicity indices.

"One corollary to our proposal is that highly *para*-selective radical additions are not in principle limited to the $TEDA^{2+\bullet}$ radical," said Professor Ritter. He continued: "Potentially any radical of sufficiently high electron affinity can afford very high *para* selectivity, and incorporation of multiple positive charges is the best way to increase the electron affinity of a radical. The challenge then becomes designing stable precursors that can reliably generate such highly electrophilic radicals under conditions relevant to organic synthesis. Work in our group is underway to identify such precursors, which can act as convenient reagents for *para*-selective functionalization of arenes to useful products."

"Another direction we are exploring is to find applications for the unusual and unprecedented class of Ar–TEDA compounds beyond the synthesis of aryl piperazines. One enticing possibility that we are currently investigating is the use of Ar–TEDA compounds as cross-coupling electrophiles, with the TEDA moiety acting as a pseudohalide," said Professor Ritter. He concluded: "If a catalyst can be found that can cleave the Ar–TEDA bond, then in principle cross-coupling should be possible with an arbitrary nucleophile, opening the way to a general, two-step sequence for *para*-selective C–H functionalization (Scheme 4)."



Scheme 4 Potential application of Ar–TEDA compounds as cross-coupling electrophiles

About the authors

Prof. T. Ritter

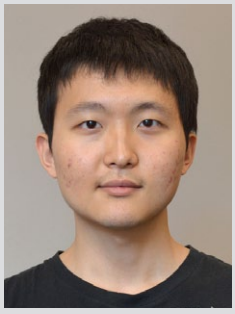
Tobias Ritter was born in 1975 in Lübeck (Germany) and studied in Braunschweig (Germany), Bordeaux (France), Lausanne (Switzerland), and Stanford (USA). After research with Professor Barry M. Trost at Stanford, he obtained his Ph.D. working with Professor Erick M. Carreira at ETH Zurich (Switzerland) in 2004. He then carried out postdoctoral research with Professor Robert H. Grubbs at Caltech (USA). In 2006, he was appointed as Assistant Professor in the Department of Chemistry and Chemical Biology at Harvard University (USA), promoted to Associate Professor in 2010, and to Professor of Chemistry and Chemical Biology in 2012. He is also a faculty member at the Massachusetts General Hospital (USA) in the Department of Radiology. In 2015, Tobias Ritter became a Director at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (Germany). He currently maintains groups in Mülheim and in Cambridge (USA).

Dr. G. Boursalian

Greg Boursalian started his higher education at Moorpark College in Moorpark, CA (USA), before transferring to UC Berkeley (USA) to complete his Bachelor's in chemistry in 2009. At Berkeley, he performed undergraduate research in the lab of Professor Peter Vollhardt. After a half-year stint at the Nano-science Center at the University of Copenhagen (Denmark), Greg started his graduate studies at Harvard University (USA) in 2010 as an NSF Predoctoral Fellow, and joined the group of Professor Tobias Ritter shortly thereafter. He graduated in May 2016, having spent the final year of his graduate studies at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (Germany), where Professor Ritter has moved his group. His doctoral thesis is entitled 'Reactivity and Selectivity in C–H Functionalization by Electrophilic Radicals.'

Dr. A. R. Mazzotti

Anthony R. Mazzotti was born in Taylorville, IL (USA) in 1988 and received his B.S. degree in chemistry in 2010. He obtained his Ph.D. in 2016 from Harvard University (USA), where he worked on the fluorination of arylboronic acid derivatives and selective arene C–H functionalization with Tobias Ritter. During his studies, he was awarded both the Barry M. Goldwater Scholarship and the National Science Foundation Graduate Research Fellowship.



W. S. Ham

Won Seok Ham was born in Anyang, Gyeonggi-do (South Korea) in 1991. He received his B.A. degree in biochemistry at Columbia University in New York City (USA). In 2013, he joined the group of Professor Tobias Ritter as a Ph.D. student at Harvard University (USA). Won Seok is a recipient of the Doctorate Scholarship from Kwanjeong Educational Foundation. A major focus of his research is the development of practical, selective aromatic C–H functionalization.