Cyclometallated Ruthenium Catalyst Enables Late-Stage Directed Arylation of Pharmaceuticals

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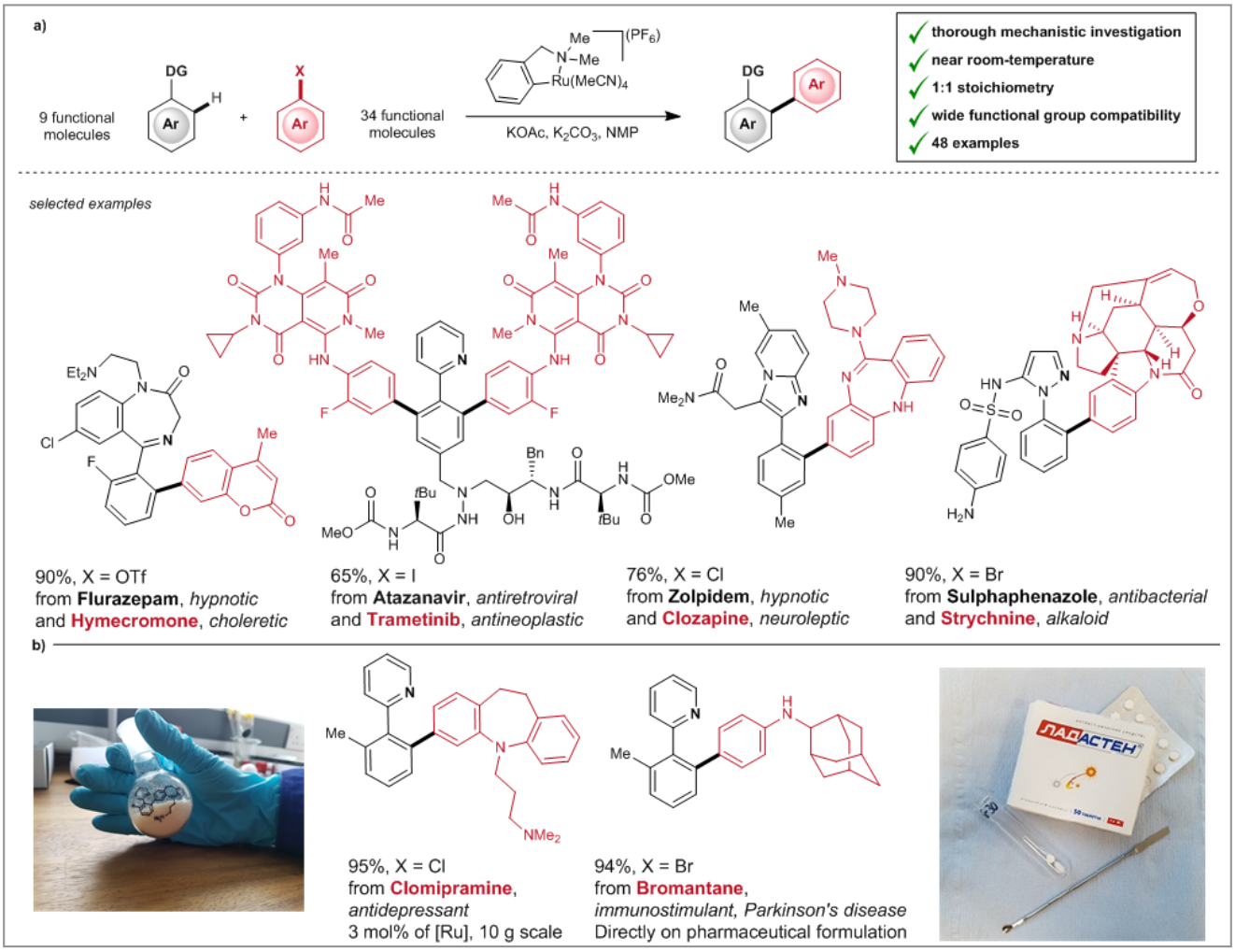
While the C–H activation field has moved forward dramatically over the last two decades, a recurrent problem lies in the difficulty of activating C–H bonds in the presence of potentially much more reactive functional groups, and to do so under conditions where delicate functionalities can survive. Often, new methodologies developed will be applicable to only a small range of simple substrates and fail when facing 'real world' molecules bearing a range of functional groups. This is particularly the case for many drug-like molecules, which often contain several polar functionalities, and are therefore not only delicate, but also able to coordinate and poison catalysts. However, being able to directly functionalize C–H bonds of complex molecules (i.e., late-stage functionalization) is one of the major targets in the field. Late-stage functionalization allows fast access to new molecules and the exploration of new chemical space while avoiding costly *de novo* syntheses.



Scheme 1 The new methodology and its scope

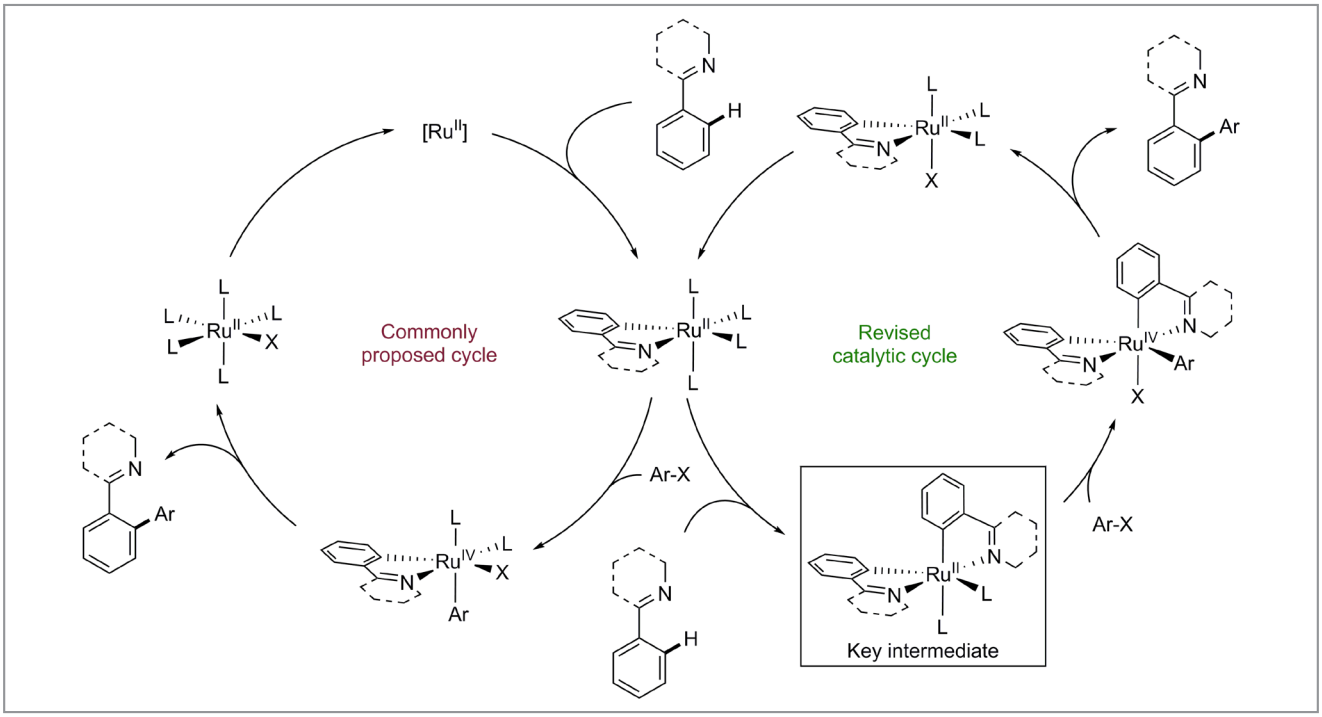
Developing milder and more functional-group-tolerant C–H arylation methodologies, such as that shown in Scheme 1, has been a target of Professor Igor Larrosa's group at the University of Manchester (UK) from day one.

"While investigating the use of ruthenium catalysts on the C–H arylation of electron-deficient aromatics, we made a few observations that did not seem to fit with accepted mechanisms on how ruthenium catalysts are operating (Scheme 2)," said Professor Larrosa. He continued: "That led us into a fully fledged mechanistic investigation on the arylations of phenylpyridines with aryl halides, by means of kinetic analysis, stoichiometric reactions, and isolation of organometallic intermediates. We were very excited when we discovered that a key catalytic intermediate had been missed out until now in these processes: the usually proposed cyclometallated intermediate is not able to undergo oxidative addition with the aryl halide. Instead, a second cyclometallation takes place to form a bis-cyclometallated intermediate, which is the real species capable of oxidative addition. More importantly, we found that the generally employed catalysts were not catalytic intermediates but off-cycle species."

These mechanistic insights led the group to the design of a new class of ruthenium catalysts: species that already contain a cyclometallating unit. "In particular, we found that a benzylamine cyclometallating unit was able to impart greatly enhanced reactivity to the ruthenium catalyst, when compared to previous catalysts, so that high reactivity was achieved at close to room temperature," explained Professor Larrosa.

"The most important feature of this new catalyst is that, due to its extremely high reactivity, it is able to carry out late-stage arylation on a broad spectrum of highly functionalized molecules, presenting superb compatibility with delicate functional groups and with the presence of several of those functional groups in the same molecule," remarked Professor Larrosa. He continued: "Furthermore, because of the high reactivity, only stoichiometric amounts of the coupling partner are needed, instead of the typical need for an excess (sometimes even 2- or 3-fold excess) of one of them."

Professor Larrosa concluded: "We believe this class of catalysts will become very useful not only for late-stage arylation but also for other types of late-stage functionalization."



Scheme 2 The commonly proposed and revised mechanisms

About the authors

Dr. M. Simonetti

Marco Simonetti received his MSc in 2010 from the University of Insubria (Italy) under the supervision of Prof. Andrea Penoni. In 2011, he joined the group of Prof. Antonio Papagni at the University of Milano-Bicocca (Italy). Later, he joined Prof. Igor Larrosa's group at Queen Mary University of London (UK) where he obtained his PhD in 2015. He continued working with Prof. Larrosa at the University of Manchester (UK) on the development of Ru-catalyzed C–H functionalization reactions, until January 2018. In March 2018, he joined Dr Daniele Leonori's group at the University of Manchester (UK) where is currently developing photocatalytic transformations.

D. M. Cannas

Diego M. Cannas graduated in medicinal chemistry and technology at The University of Urbino "Carlo Bo" (Italy) in 2015 under the supervision of Prof. Giovanni Piersanti. In the same year, he moved to the UK to join the group of Prof. Igor Larrosa at The University of Manchester as a PhD student. His research interests focus on transition-metal-catalyzed C–H functionalization and reaction mechanism elucidation.

Professor I. Larrosa

Igor Larrosa graduated in chemistry from the University of Barcelona (Spain) in 1999, where he also completed MChem (2000) and PhD (2004) degrees with Profs. Felix Urpi and Pere Romea. After a research period in Prof. Erick M. Carreira's laboratories at ETH (Zurich), Igor moved as a postdoctoral researcher to Imperial College London (UK) to work in Prof. Anthony G. M. Barrett's group. In September 2007 he started his independent career as a Lecturer at Queen Mary University of London (UK). In 2011, Igor was awarded a European Research Council starting grant. Since 2014, Igor has held a Chair in Organic Chemistry at the University of Manchester. Igor's research interests lie in transition-metal catalysis, with particular emphasis on the development of novel methodologies for C–H and C–C activation.