

Ruthenium(II)-Catalyzed Olefination via Carbonyl Reductive Cross-Coupling

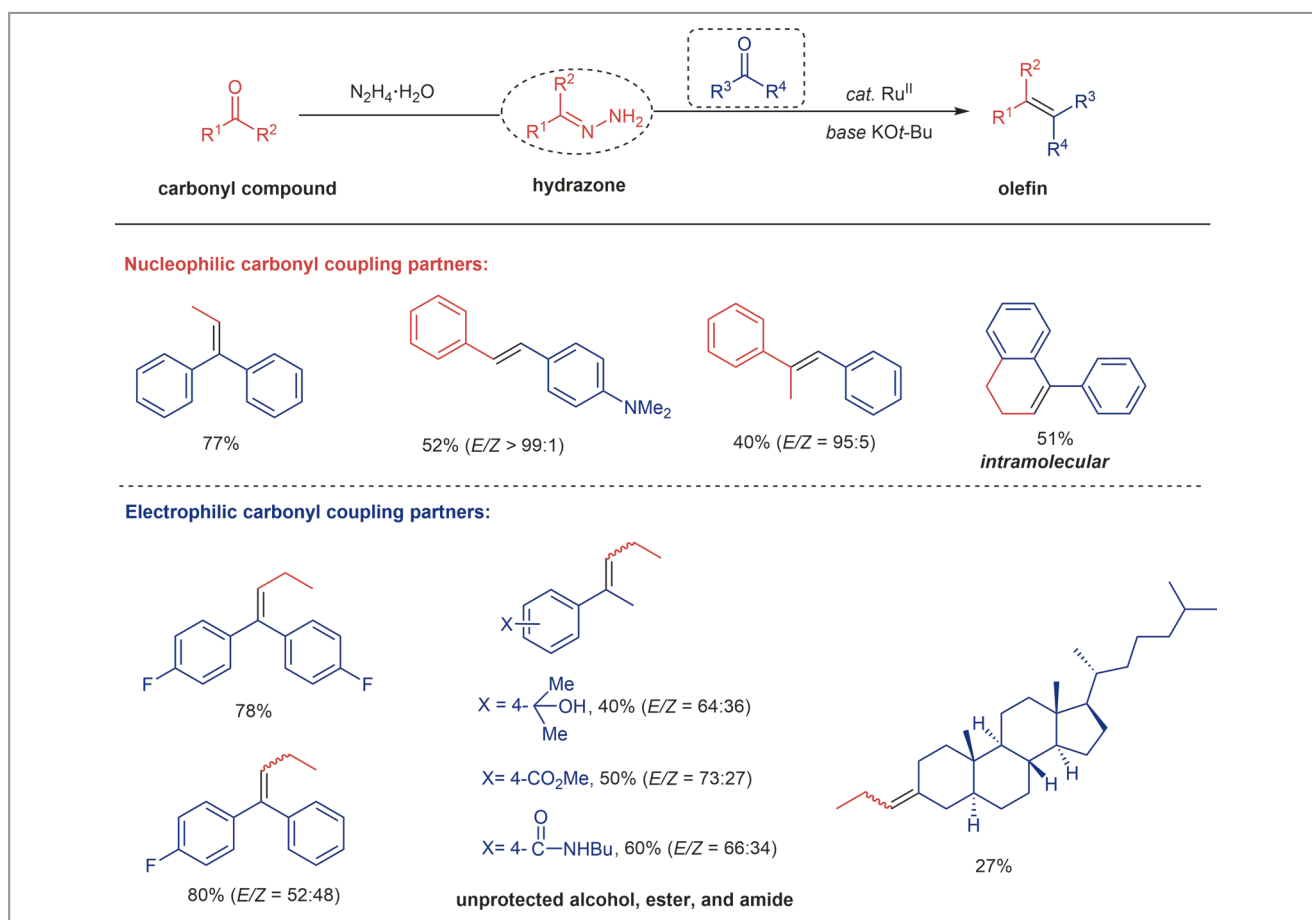
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Efficient construction of carbon–carbon double bonds is a central subject in synthetic chemistry. The direct reductive coupling of naturally ubiquitous carbonyl compounds offers a tremendous synthetic potential for the synthesis of olefins, yet the catalytic carbonyl cross-coupling reaction remains largely elusive.

Recently, a new paper describing an innovative ruthenium(II)-catalyzed, hydrazine-mediated olefination reaction via direct carbonyl reductive cross-coupling was published by the group of Professor Chao-Jun Li at McGill University (Montreal, Canada). Professor Li explained: “From

the sustainability point of view, carbonyl cross-coupling represents an ideal strategy to access olefins because naturally widespread carbonyl functional groups are generally regarded as renewable feedstocks. As a proof of principle, we have developed a new and efficient catalytic method for olefin synthesis, which possesses a distinct mechanistic profile and highlights the use of abundant carbonyl functional groups.”

“Considering the state-of-the-art in this field, the well-known McMurry reaction enables direct reductive homo-couplings of carbonyl compounds to access olefins by employing stoichiometric amounts of low-valent titanium reagents



Scheme 1 Ruthenium(II)-catalyzed olefination via carbonyl reductive cross-coupling

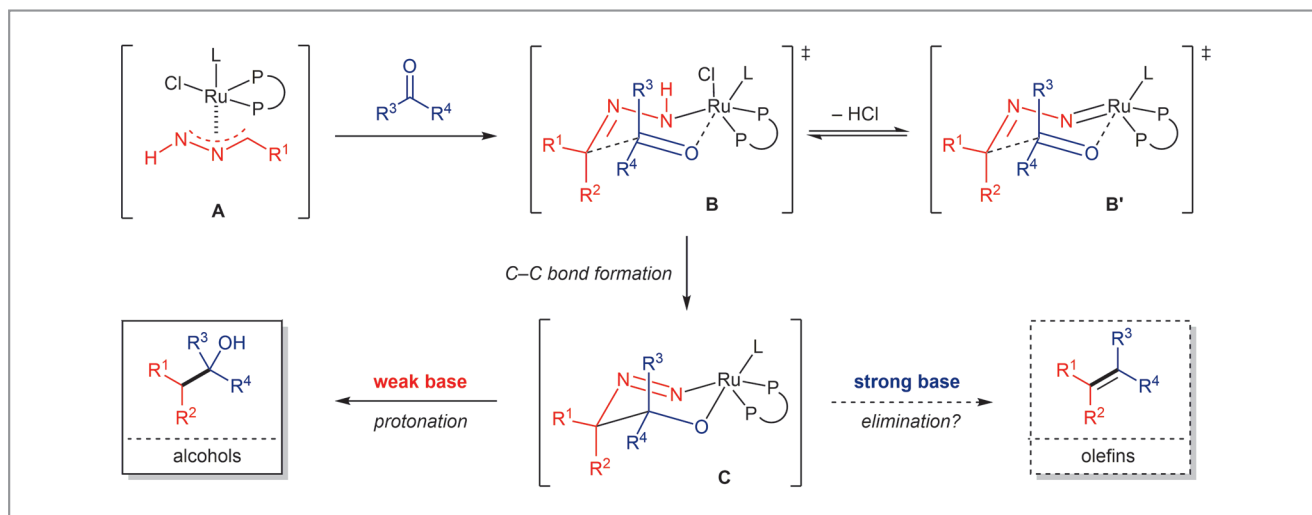
and strong metal reductants (e.g. LiAlH_4 and alkali metals),” said Professor Li (for references, see the original *Chem. Sci.* article). He added: “Although the issue of selective cross-couplings of two unsymmetrical carbonyl compounds has been addressed, three challenges still remain: (1) the use of stoichiometric quantities of metal wastes accompanied by excessive amounts of metal-based reagents, (2) poor chemoselectivity and (3) unsatisfactory functional group tolerance.”

“Our catalytic method not only enables facile and selective cross-couplings of two unsymmetrical carbonyl compounds in either an intermolecular or intramolecular fashion but also features good functional group tolerance. Furthermore, the reaction generates nitrogen and water as the only environmentally benign stoichiometric by-products,” explained Professor Li. He continued: “This new ruthenium(II)-catalyzed chemistry accommodates a variety of substrates and proceeds under mild reaction conditions. Specifically, this chemistry covers a broad spectrum of nucleophilic or electrophilic carbonyl coupling partners, regardless of their electronic nature. The intramolecular olefination also proceeds smoothly in the present reaction system. Notably, functional groups that are commonly incompatible with traditional carbonyl olefination approaches, such as unprotected alcohols, esters, and amides, are well tolerated in this chemistry and potentially amenable to further functionalization.”

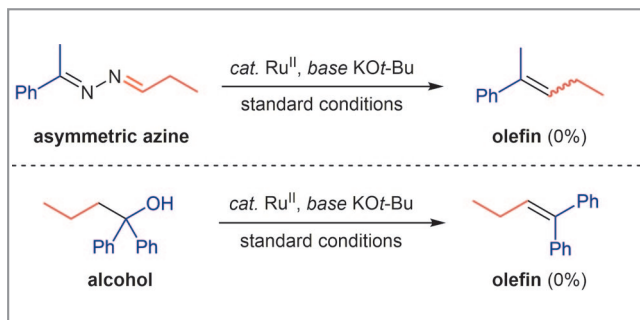
“Very recently, we have disclosed a novel ruthenium-catalyzed deoxygenation chemistry for the highly selective and efficient cleavage of aliphatic primary C–O bonds in complex organic molecules (*J. Am. Chem. Soc.* **2016**, *138*, 5433; also Ir-catalyzed, see: *Eur. J. Org. Chem.* **2013**, 6496). Capitalizing on

the proposed intermediate **A**, its coupling with another carbonyl molecule was conceived for C–C bond formation via a six-membered chair-like cyclic transition state **B** (alternatively, **B'** with the loss of HCl). Upon its further rearrangement, a wide range of *sec*- and *tert*-alcohols were readily obtained by the protonation of **C** (*Nat. Chem.* **2016**, *9*, 374). Diverging from **C**, we conjectured that the olefin production might also be feasible through an elimination pathway. In fact, this hypothesis gained further support from a few literature precedents of metalloazines in the late 80's. In these papers, Schwartz and co-workers reported the use of metalloazines as stoichiometric reagents for carbon–carbon double bond formation (for references, see the original *Chem. Sci.* article),” said Professor Li. He continued: “The base plays an important role in a series of hydrazone-based processes developed recently in our lab. While a weak base (e.g. K_3PO_4) generally works better for carbonyl addition, imine addition and Michael reactions employing aromatic carbonyl substrates (for references, see the original *Chem. Sci.* article), a strong base (e.g. KOt-Bu) is required to trigger olefination reactions when aliphatic carbonyl counterparts are involved as hydrazone precursors.”

The group performed further experiments to shed light on the mechanistic details of this reaction, which turned out to be an E1cB-type process. “Our control experiments indicated that metal-assisted decomposition of the corresponding asymmetric azine and base-mediated elimination of the corresponding alcohol should not be involved in the present reaction system, because none of the olefin products was detected in either case,” said Professor Li.



Scheme 2 Design principle for olefination via catalytic carbonyl reductive cross-coupling



Scheme 3 Control experiments for the olefin formation

He concluded: "Olefins are ubiquitous chemicals in areas such as materials science, as well as vitally important substrates for the chemical and pharmaceutical industry; therefore, we hope that both academia and industry will take advantage of this new catalytic approach to synthesize olefins directly from simple and naturally abundant carbonyl compounds. This chemistry possesses a distinct mechanistic profile and has the advantages of cross-coupling capability, mild reaction conditions, good functional group tolerance and stoichiometric benign by-products. Taken together, our findings are expected to spur more interest in developing catalytic methods in this field."

Matthew Farnish

About the authors



Dr. W. Wei

Wei Wei earned his B.Sc. with honors (2005) and M.Sc. (2008) in Chemistry at Liaocheng University and Sichuan University (P. R. of China), respectively. He pursued his Ph.D. at Chengdu Institute of Biology, Chinese Academy of Sciences (P. R. of China). His Ph.D. research mainly focused on the development of efficient synthetic methodologies based on aerobic oxidation and dioxygen activation. Then, he moved to Qufu Normal University (P. R. of China) as an Associate Professor in 2012. During 2016–2017, he worked as a postdoctoral researcher at McGill University (Canada) where he studied the carbonyl reductive olefination reaction with Professor Chao-Jun Li. His recent research focuses on the development of green approaches to construct sulfur- or phosphorus-containing compounds.



Dr. X.-J. Dai

Xi-Jie Dai was born and raised in the Southeastern coast of China, where he earned his B.Sc. with honors (2009) and M.Sc. (2012) in Chemistry at Donghua University and Xiamen University (P. R. of China), respectively. He then travelled to the Western hemisphere, pursuing his Ph.D. with Professor Chao-Jun Li at McGill University (Canada). His Ph.D. studies were initially focused on the development of direct and selective alcohol deoxygenation strategies using late transition metals. Later, he and other colleagues pioneered new synthetic routes to forge carbon–carbon single and double bonds between unsubstituted hydrazones and various electrophiles (e.g. aldehydes, ketones, imines, activated alkenes) with a catalytic amount of metal. After graduating from McGill this year, he decided to cross the Canada–USA border to work with Professor Stephen L. Buchwald at Massachusetts Institute of Technology (USA) as a NSERC Postdoctoral Fellow. He is currently working on the copper-hydride project at MIT. He strongly advocates making new benchtop synthetic discovery more practical and approachable for a wide spectrum of audiences. His interests also include in-depth exploration of a larger chemical space and beyond by leveraging the advancement of robotic technology in the pharmaceutical industry.



Dr. H. Wang

Haining Wang received his B.S. degree in July 2005 from Hefei University of Technology (HFUT, P. R. of China) and earned his Ph.D. degree in organic chemistry from the Institute of Chemistry, Chinese Academy of Sciences (ICCAS, P. R. of China) in 2011. In 2011, he moved to Nanjing University (P. R. of China) as an associate researcher, working with Professor Yian Shi. During 2014–2017, he worked as a postdoctoral researcher at the McGill University (Canada) where he studied umpolung Grignard-type reactions with Professor Chao-Jun Li. Since 2017 he has held the position of R&D Scientist in 1-Material Inc. (Canada). His recent research focuses on the design, synthesis, and application of organic photovoltaic materials.



Prof. C.-J. Li

Chao-Jun Li received his Ph.D. (with honor) with Professors T. H. Chan and D. N. Harpp at McGill University (Canada) in 1992 and spent 1992–1994 as a NSERC Postdoctoral Fellow with Professor Barry M. Trost at Stanford University (USA). He was an Assistant (1994), Associate (1998) and Full Professor (2000) at Tulane University (USA). Since 2003, he has been a Canada Research Chair (Tier I) and E. B. Eddy Chair Professor (since 2009) at McGill University (Canada). Currently, he serves as the Co-Director of the FQRNT Center for Green Chemistry and Catalysis and the Associate Editor for *Green Chemistry* (RSC) (since 2005). He received a number of prestigious awards including the US NSF's CAREER Award (1997), a US Presidential Green Chemistry Challenge Award (2001), the Canadian Green Chemistry and Engineering Award (2010), and the R. U. Lemieux Award of the Canadian Society for Chemistry (2015). Professor Li was elected as a Fellow of the RSC (UK, 2007), the Royal Society of Canada (2012), the AAAS (2012), the CIC (2013), the ACS (2015), and TWAS (2016). His current research efforts are to develop green chemistry for organic synthesis. Representative well-known researches include Grignard-type reactions in water, alkyne–aldehyde–amine coupling (A^3 -coupling), and cross-dehydrogenative-coupling (CDC) reactions among others. He was listed among the World's Most Cited Scientists by Thomson Reuters/Clarivate Analytics (2014, 2015, 2016, and 2017).