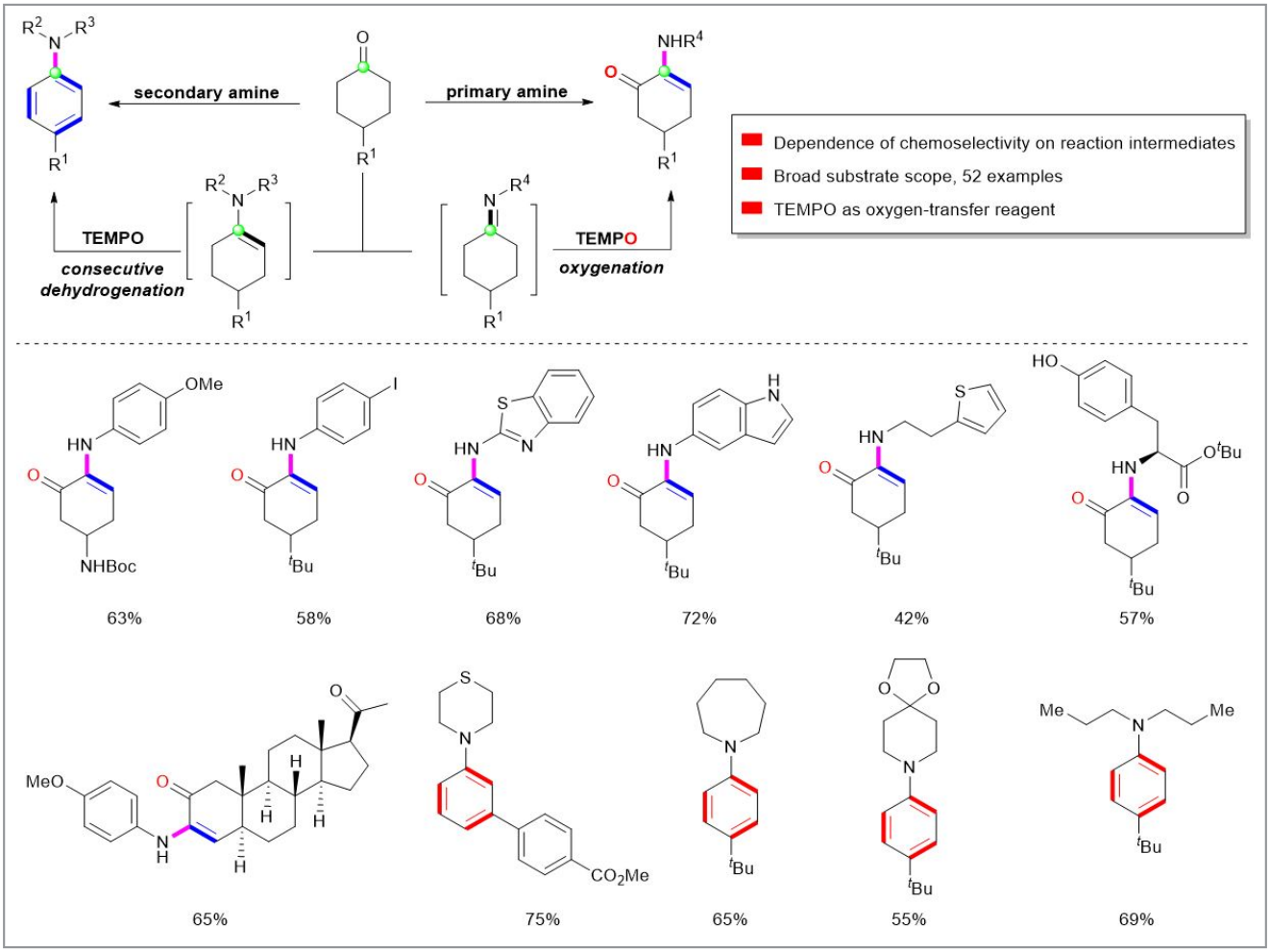
Differentiation between Enamines and Tautomerizable Imines in the Oxidation Reaction with TEMPO

Nat. Commun. **2018**, *9*, 5002

Imines and enamines are ubiquitously encountered intermediates in organic synthesis, especially in recently developed aminocatalysis reactions for the efficient and selective functionalization of aldehydes and ketones. Imines featuring α-hydrogens are in equilibrium with their enamine tautomers. This imine–enamine tautomerism is the nitrogen analogue of keto–enol tautomerism, but with higher reactivity. This feature makes the tautomerizable imine resemble the reactivity of the corresponding enamine in organic transformations. Although several examples have been reported on the utilization of this tautomerizable character of imines for organic synthesis, the exact difference in reactivity between the imine-derived enamine tautomer and the real enamine remains underdeveloped. In light of this, the research groups of Professor Weiping Su and Wei Zhuang at Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences (P. R. of China) collaborated to develop a unique model reaction pattern that could discriminate this subtle



Scheme 1 The dissimilarity in reactivity between enamine and α-hydrogen-containing imine, with selected examples

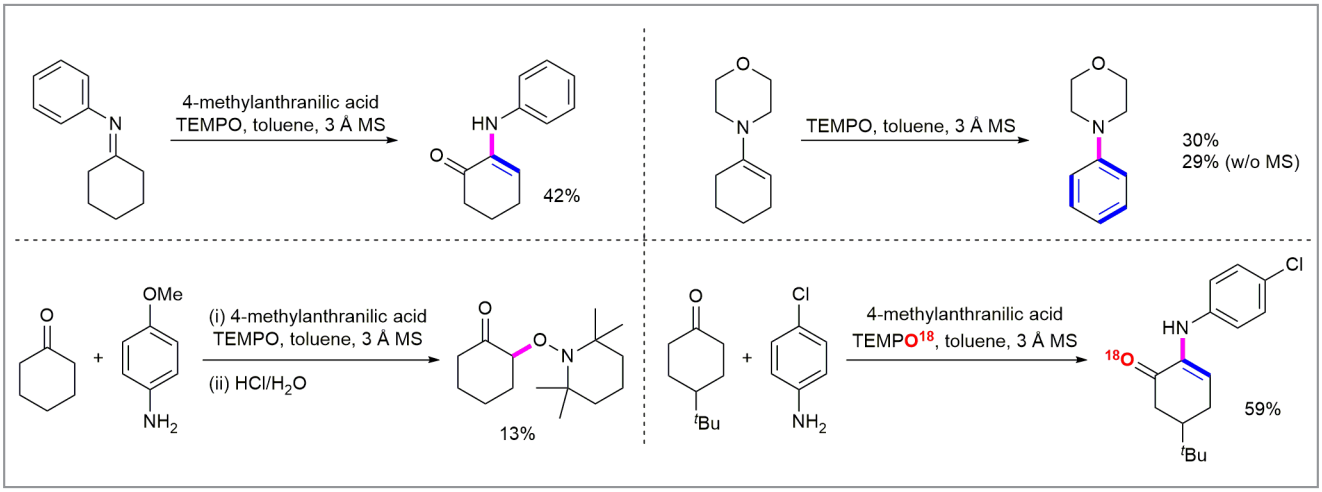
discrepancy, affording molecular diversity depending on the chemistry of imine and enamine tautomers and offering an insight into their structure–reactivity relationship.

As a continuing interest in the oxidative transformations with TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) as oxidant in Professor Su's group, Dr. Xiaoming Jie initiated the investigation with reactions of amines, cyclohexanones and TEMPO. He explained: "It has been established that the outcome of the reaction is exclusively dependent on the amine species, in which a distinct difference could be exhibited between enamines and tautomerizable imines: i) when primary amines were used, the *in situ* generated tautomerizable imines gave rise to the formation of α-amino enones, which are versatile synthetic intermediates for heterocycle synthesis; ii) conversely, when secondary amines were used, the *in situ* generated enamines led to the production of arylamines; the latter is orthogonal to the established strategy making use of transition-metal catalysts (Scheme 1)."

Dr. Yaping Shang made a contribution to the substrate scope development as well as experimental mechanism studies (Scheme 2). She explained: "I examined the reaction of presynthesized imine and enamine with TEMPO under standard reaction conditions, and obtained α-amino enone and aryl amine, respectively, indicating that imine and enamine are indeed reaction intermediates. Moreover, both the isolated α-aminoxylated ketone intermediate and the ^{18}O-labeling experiment revealed that the oxygen atom in the α-amino enone originated from TEMPO." In order to make further confirmations about the product structure, Dr. Xiaofeng Zhang characterized the structures of four representative compounds.

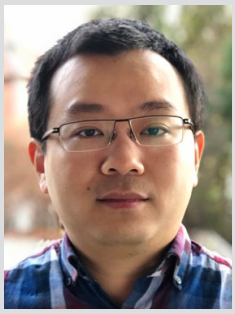
Dr. Zhe-Ning Chen and Prof. Wei Zhuang helped to conduct computational studies to give an in-depth understanding about the differences between imines and enamines in this transformation at a molecular level. They said: "The results demonstrate that the NH-containing enamine kinetically favors α-radical formation by TEMPO-mediated hydrogen atom abstraction from the NH moiety and then 1,4-elemination to generate α-amino enones. Whereas the NH-lacking enamine – derived from a secondary amine – prefers β-radical formation and subsequent consecutive β-elimination of H/TEMPO to deliver arylamines. Therefore, due to imine–enamine tautomerization, the α-hydrogen-containing imine displays distinctly different reactivity in terms of regioselectivity and chemoselectivity relative to the enamine that lacks the NH moiety."

Prof. Su concluded: "This protocol offers a simple platform to combine the chemistry of imine and enamine together and to show their reactivity differences through distinctive product distribution under nearly identical reaction conditions. The underlying mechanism is interesting and we anticipate that our findings will provide valuable clues to enlighten more diverse reaction patterns based on the reactivity difference of tautomerizable imines and enamines. We will continue to investigate in this direction and are curious to see what we will discover in the future."



Scheme 2 Experimental mechanistic studies

About the authors

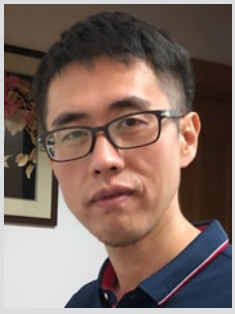


Dr. X. Jie

Xiaoming Jie was born and grew up in Hebei (P. R. of China). He earned a B.Sc. from Nanjing Agricultural University (P. R. of China). He completed his Ph.D. at Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences (P. R. of China) under the supervision of Prof. Weiping Su in 2013. He then continued to work in Prof. Su's group as a research assistant and was promoted to a research associate in 2016. At the end of 2017, he moved to Westfälische Wilhelms-Universität Münster (Germany) to carry out postdoctoral research with Prof. Gerhard Erker where he has focused on the synthesis and reactivity investigation of cyclic frustrated Lewis pairs.

Dr. Y. Shang

Yaping Shang was born and grew up in Inner Mongolia (P. R. of China). She received her B.Sc. from Inner Mongolia University for the Nationalities (P. R. of China) and her Ph.D. under the supervision of Prof. Weiping Su at Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences (P. R. of China) in 2013. She then worked as a research assistant in Prof. Su's group and was promoted to a research associate in 2018. Her research interests are radical-based dehydrogenation reactions and C–H activation reactions in pharmaceutical synthesis.



Prof. Z.-N. Chen

Zhe-Ning Chen received his Ph.D. from Xiamen University (P. R. of China) in 2012 under the supervision of Prof. Xin Xu and Prof. Gang Fu. In 2013, he moved as a postdoctoral fellow to the University of Hong Kong (HK) to work in Prof. Hao Hu's group. In August 2016, he joined Prof. Wei Zhuang's group as an associate professor at the Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences. His research interests lie in computational organic chemistry, and the development of extended hybrid models and sampling strategies for the accurate description of chemical reactions.

Prof. W. Zhuang

Wei Zhuang graduated from the University of Science and Technology of China in 2000. He received his Ph.D. in 2007 from the University of California at Irvine under the supervision of Prof. Shaul Mukamel. From 2007 to 2009, he carried out postdoctoral research in the group of Prof. David Chandler at the University of California Berkeley. He started his independent career in 2010 at Dalian Institute of Chemical Physics, Chinese Academy of Sciences. In 2016, he moved to Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences. His research interests lie in computational organic chemistry, and theoretical studies of ion effect, water dynamics at molecular interfaces as well as ultrafast spectroscopy.

Prof. W. Su

Weiping Su graduated from Anhui Education Institute in 1987 and earned his Ph.D. at Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences in 1999 under the supervision of Prof. Maochun Hong. After one year of working as an assistant professor at the same institute, he moved to the United States to do postdoctoral studies with Prof. Richard H. Holm at Harvard University (2000–2001), Prof. Jin Li at Rutgers University (2001–2002), and Prof. John G. Verkade at Iowa State University (2002–2005). Then, he joined the faculty at Fujian Institute of Research on the Structure of Matter in 2006. His research interests include synthetic methodology, discoveries of metal-complex-based homogeneous catalysts and nanoparticle-based recyclable catalysts, and the structure-property relationships of catalysts.

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