

Dual Catalysis for Enantioselective Convergent Synthesis of Enantiopure Vicinal Amino Alcohols

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Enantiopure vicinal amino alcohols and derivatives are essential structural motifs in natural products and pharmaceutically active molecules and serve as main stereogenic sources in asymmetric synthesis (Figure 1). Despite numerous efforts devoted to synthesizing these highly valuable compounds, general catalytic enantioselective methods featuring high efficiency and selectivity and, most importantly, broad substrates scopes are still rare, thus representing a challenging endeavor to organic chemists.

Recently, based on a visible-light-induced dual catalytic strategy, a highly effective cross-coupling of nitrones with aromatic aldehydes to give enantiopure vicinal amino alcohols has been demonstrated by Professor Pei-Qiang Huang's group in collaboration with the theoretical group led by Pro-

fessor Xin Lu, both at Xiamen University (P. R. of China). "Our group has long focused on the umpolung construction of carbon-carbon bonds at the *N*- α -carbon and has previously explored two asymmetric methods for preparing enantiopure vicinal amino alcohols from chiral substrates," said Associate Professor Xiao Zheng, who continued: "In these previous works, we developed a SmI_2 -mediated Barbier-type reaction of chiral *N*-Boc *N,S*-acetals with aldehydes/ketones (*Org. Lett.* **2005**, *7*, 553), and a radical cross-coupling of chiral nitrones with aldehydes/ketones (*Org. Biomol. Chem.* **2009**, *7*, 2967) to give the desired enantiopure products (Scheme 1)."

Based on these efficient coupling mechanisms between amine and alcohol moieties, the group further envisioned the exploration of this transformation in a catalytic enantio-

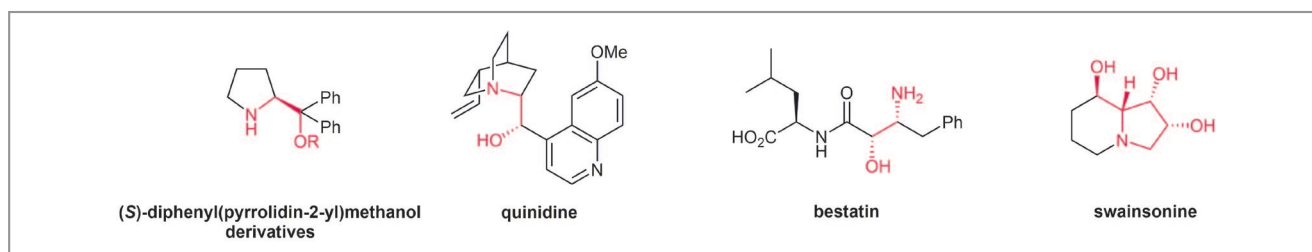
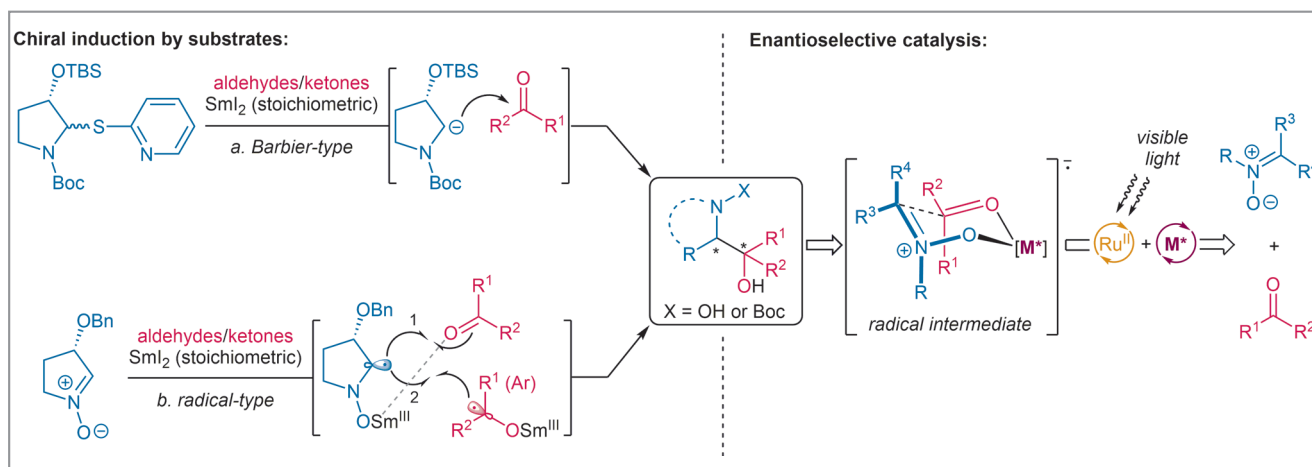


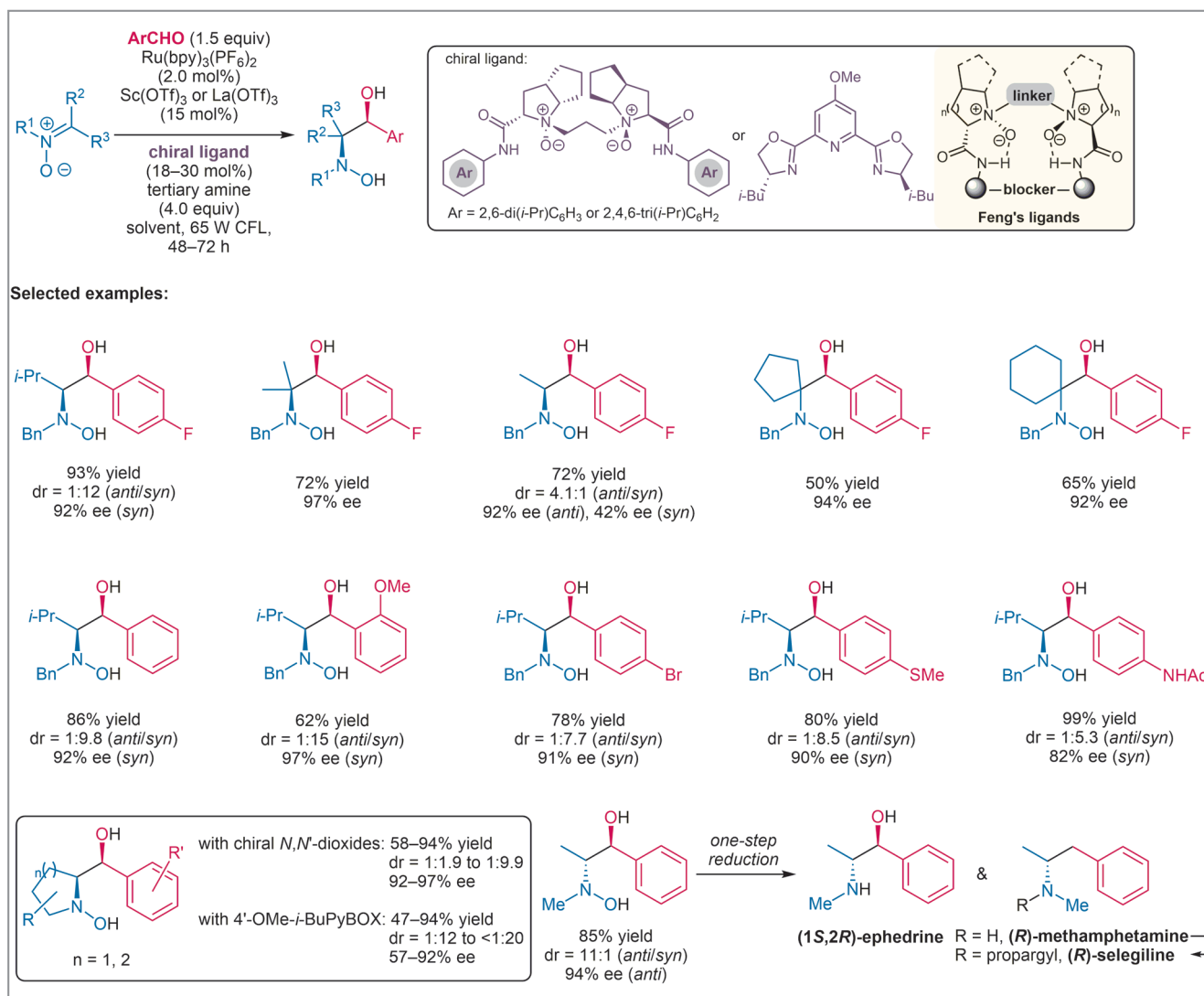
Figure 1 Examples of valuable enantiopure vicinal amino alcohols



Scheme 1 SmI_2 -mediated and catalytic enantioselective design for enantiopure vicinal amino alcohols

selective manner. They decided to prove two interrelated hypotheses: firstly, if an oxophilic chiral Lewis acid could be used to coordinate with nucleophilic oxygen present in the nitrogen-containing substrates and aldehydes/ketones, an enantioselective cross-coupling could be achieved. Secondly, if a catalyzed single-electron transfer (SET) with a low loading of metal could be used to generate α -aminoalkyl radicals or ketyl radicals at low concentration, homocoupling could be inhibited and chiral Lewis acid induced enantioselective cross-coupling would then predominate. If that was the case, a visible-light-induced photocatalytic SET reduction should be the preferred technology, especially considering that the synergistic catalysis of Lewis acid and photocatalyst current-

ly stays at the forefront of modern organic synthesis. "Since samarium ions are Lewis acidic, traditional SmI_2 -promoted radical transformations are obviously unsuitable for enantioselective synthesis, unless stoichiometric amounts of chiral ligands are used," explained Chen-Xi Ye, the graduate student who realized the chemistry. He further commented: "We hypothesized that by using coordinatively saturated photocatalysts in a dual catalytic system, it should be possible to separate Lewis acidity from reducing character, thus enabling flexible stereo-induction via Lewis acid coordinated chiral ligands." With this concept in mind, Chen-Xi Ye began to screen a series of hemiaminals and nitrones, which had been used as substrates to generate α -aminoalkyl radicals in the

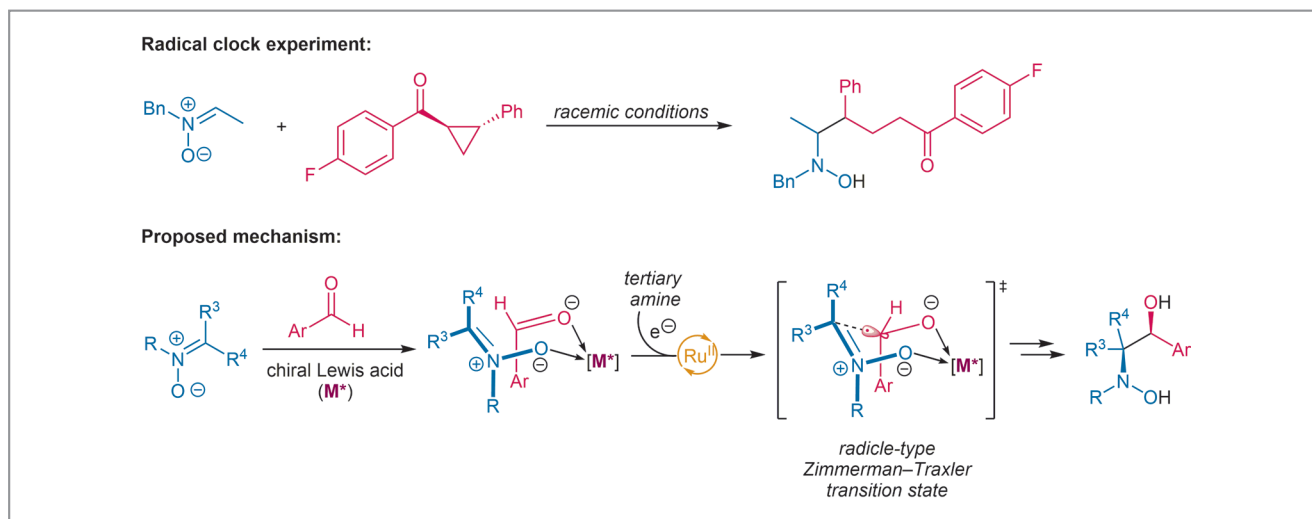


Scheme 2 Selected examples for enantioselective coupling of nitrones and aromatic aldehydes

group's previous works. He subsequently examined a series of photocatalysts/Lewis acids in a novel photocatalytic enantioselective cross-coupling reaction of nitrones and aromatic aldehydes. The optimization of the reaction conditions turned out to be a laborious process, during which $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ with rare-earth ion trifluoromethanesulfonate proved to be an excellent catalytic combination. Even more gratifyingly, chiral ligands such as N,N' -dioxides and PyBOXs were both very effective for chiral induction. Professor Pei-Qiang Huang remarked: "This work represents an important advance in utilizing versatile chiral N,N' -dioxides, which are also known as Feng's ligands (*Acc. Chem. Res.* **2011**, *44*, 574). In fact, this is the first time that Feng's ligands have given a high level of stereoselectivity in a catalytic radical reaction. This should definitely promote the application of such privileged chiral ligands." A number of structurally varied substrates were examined in the dual catalytic system and, for the most part, good to excellent yields and stereoselectivities were obtained. "Although the N,N' -dioxides were potentially reduced under neat reductive photocatalysis conditions, especially in the presence of a Lewis acid, I found that $\text{Sc}(\text{OTf})_3$ -coordinated N,N' -dioxides were stable complexes, which can be used synergistically with $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ to catalyze the enantioselective cross-coupling of many acyclic and cyclic nitrones with aromatic aldehydes efficiently, with high levels of diastereo- and enantioselectivities (Scheme 2)," remarked Chen-Xi Ye. This proved to be a robust technology for the synthesis of enantiopure vicinal N -hydroxyamino alcohols, which could be easily transformed into vicinal amino alcohols or amphetamine derivatives via one-step reduction. Professor Huang

remarked: "Importantly, two pharmaceutically valuable compounds, namely (1*S*,2*R*)-ephedrine and (*R*)-selegiline, were concisely prepared by using our strategy (Scheme 2)."

Professor Xin Lu and his student Yared Yohannes Melcamu conducted in-depth theoretical studies to decipher the reaction mechanism. "With detailed density functional theory (DFT) computational calculations, the starting point and the diastereoselectivity of the reaction could be perfectly unraveled," said Professor Xin Lu, who added: "DFT calculations explained the reason why aliphatic aldehydes were incompatible in this reaction. More importantly, we established a reliable model for predicting the diastereoselectivity of the products by comparing the energies of six-membered-ring transition states." The DFT calculations confirmed that the stereoselectivity of the cross-coupling was induced through a radical-type Zimmerman–Traxler transition state. "Meanwhile, a complex of nitron, aldehyde and Lewis acid was formed favorably at the starting point of the reaction, which led to a more efficient SET reduction by the $\text{Ru}(\text{II})$ photocatalyst, concomitantly inhibiting the homocoupling of both substrates," said Professor Xin Lu. Additionally, an analogous 6-*endo*-trig radical annulation led to a nitroxyl radical-containing intermediate, followed by hydrogen abstraction from $[i\text{-Pr}_2(\text{Et})\text{N}]^+$ to give the chain termination product, which is the desired vicinal hydroxyamino alcohol. "Thus, the role of Hünig's base in this reaction is that of a co-reductant, as well as of an efficient donor for hydrogen and protons. All these results were coherent with experimental studies, thus leading to a convincing mechanistic proposal (Scheme 3)," remarked Professor Lu.



Scheme 3 Mechanistic investigations on the process

Associate Professor Xiao Zheng concluded: "This novel photocatalyst-merged dual-catalytic method features mild conditions, easy operation, broad substrate scope, high yield and stereoselectivity, and has enormous potential for practical use. Based on a deep insight into this reaction, we can accurately predict and understand its stereoselectivity, which will benefit further research and applications of this method. In summary, a concise strategy – which exhibits a high efficiency rivalling those of industrial biosynthetic procedures – has been established to obtain vicinal amino alcohols and amphetamine derivatives. Notably, higher stereoselectivity can be obtained when the temperature of the cross-coupling process is lowered. The synthetic application of this protocol and a significant exploration of photocatalytic generation of α -aminoalkyl radicals from nitrones are still in progress. The latter is expected to lead to more breakthroughs in organic synthesis."

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About the authors



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interests cover catalytic radical reaction methods and asymmetric catalysis.

Chen-Xi Ye obtained both his B.Sc. degree (in 2013) and M.Sc. degree (in 2016) from Xiamen University (P. R. of China), where he carried out his research under the supervision of Associate Professor Xiao Zheng and Professor Pei-Qiang Huang. He made up his mind to study abroad, so he is looking for a Ph.D. supervisor. Currently, he works as a research assistant to keep abreast of the advances in chemical synthesis. His research



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Yared Yohannes Melcamu graduated from the University of Asmara (Eritrea) in 2001 and received his MChem from NENU (Changchun, P. R. of China). He then joined Professor Xin Lu's research group at Xiamen University (P. R. of China) as a Ph.D. student, where he has been working on theoretical investigations of transition-metal catalysis in collaboration with Xiao Zheng's group.



Prof. X. Zheng

Xiamen University as an Associate Professor in 2005. He served as a research staff in the group of Teck-Peng Loh at the School of Physical and Mathematical Sciences of Nanyang Technological University (Singapore) from 2008–2009. He returned to Xiamen University and joined the faculty of the Department of Chemistry in 2009. His research interests include radical reaction methods and their application for natural product and pharmaceutical relevant molecule synthesis.

Xiao Zheng grew up in Xianyou, Fujian Province (P. R. of China). He received his chemistry education at Xiamen University (P. R. of China). After his Ph.D. work with Professor Pei-Qiang Huang, he served as a post-doctoral fellow in the group of Professor Wen-Ge Li of College of Oceanography and Environmental Science of Xiamen University (2003–2005). He joined the faculty of the Department of Pharmaceutical Science of

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Prof. X. Lu

Xin Lu grew up in Changning, Hunan Province (P. R. of China). He received his chemistry education at Xiamen University (P. R. of China). After his Ph.D. work with Professor Qianer Zhang and Nanqin Wang, he joined the faculty at Xiamen University and the State Key Laboratory of Physical Chemistry of Solid Surfaces in 1996, and became Professor of Physical Chemistry in 2002. He visited the

Cherry L. Emerson Center for Scientific Computation, Emory University (USA) during 1999–2000, and the Department of Chemistry, UC Berkeley (USA) as Berkeley Scholar during 2007–2008. He received the Young Chemist's Award of Chinese Chemical Society (2000), the Fok Ying-Tung Fund from the Fok Ying-Tung Education Foundation (2002), and the National Science Fund for Distinguished Young Scholars (2005–2008). His research interests include theoretical simulations of chemical processes on solid surfaces and the chemistry of carbon nanotubes and fullerenes.



Prof. P.-Q. Huang

Pei-Qiang Huang was born and grew up in Fujian Province (P. R. of China). He obtained his B.Sc. (1982) from Xiamen University (P. R. of China) and D.E.A. (1984) from the Université de Montpellier II (France) under the direction of Professor B. Castro (INSERM-CNRS). After accomplishing the research work at the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette, France) under the supervision of Professor H.-P. Husson,

he received his Ph.D. from the Université de Paris-Sud (Orsay, France) in 1987. He served as a postdoctoral fellow in the group of Professor W.-S. Zhou at Shanghai Institute of Organic Chemistry (P. R. of China) from 1988–1990. He was appointed as an Associate Professor at Xiamen University in 1990, and was promoted to Full Professor in 1993. Professor Huang's research team is interested in new synthetic methodologies, total synthesis of natural products, and chemical biology.