

Asymmetric α -Photoalkylation of β -Ketocarboxyls by Primary Amine Catalysis: Facile Access to Acyclic All-Carbon Quaternary Stereocenters

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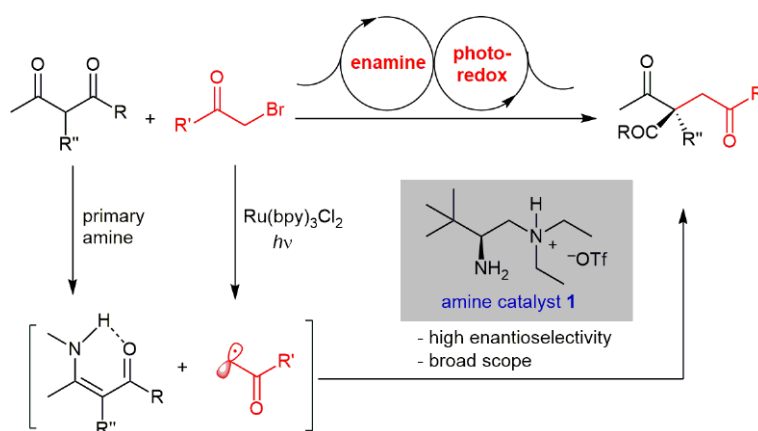
■ Asymmetric α -alkylation of carbonyl compounds is one of the fundamental C–C bond-forming reactions in forging a carbon stereogenic center, particularly for constructing acyclic all-carbon quaternary stereogenic centers, which remains a significant challenge in asymmetric catalysis and synthesis in spite of the tremendous advances in this field (see refs. 2–7 of the original manuscript). Recently, Professor Sanzhong Luo and co-workers from the Institute of Chemistry, Chinese Academy of Sciences (ICCAS) in Beijing (P. R. of China) reported the construction of acyclic all-carbon quaternary stereocenters using an open-shell radical substitution strategy by invoking the synergy of photoredox catalysis and primary amine catalysis (Scheme 1).

Professor Luo said: “For this transformation, besides the issue of stereocontrol of β -ketocarboxyls, another easily conceived pitfall is the stability and compatibility of diamine catalyst **1** under photoredox conditions. To our delight, the reaction enables the creation of all-carbon stereocenters with excellent enantioselectivities and a broad range of substrates (Scheme 2).” More intriguingly, as explained by Professor Luo, *N*-benzyl β -ketoamide reacted to furnish the expected C-alkylation adduct in 90% yield with 96% ee (**4j**). Intra-

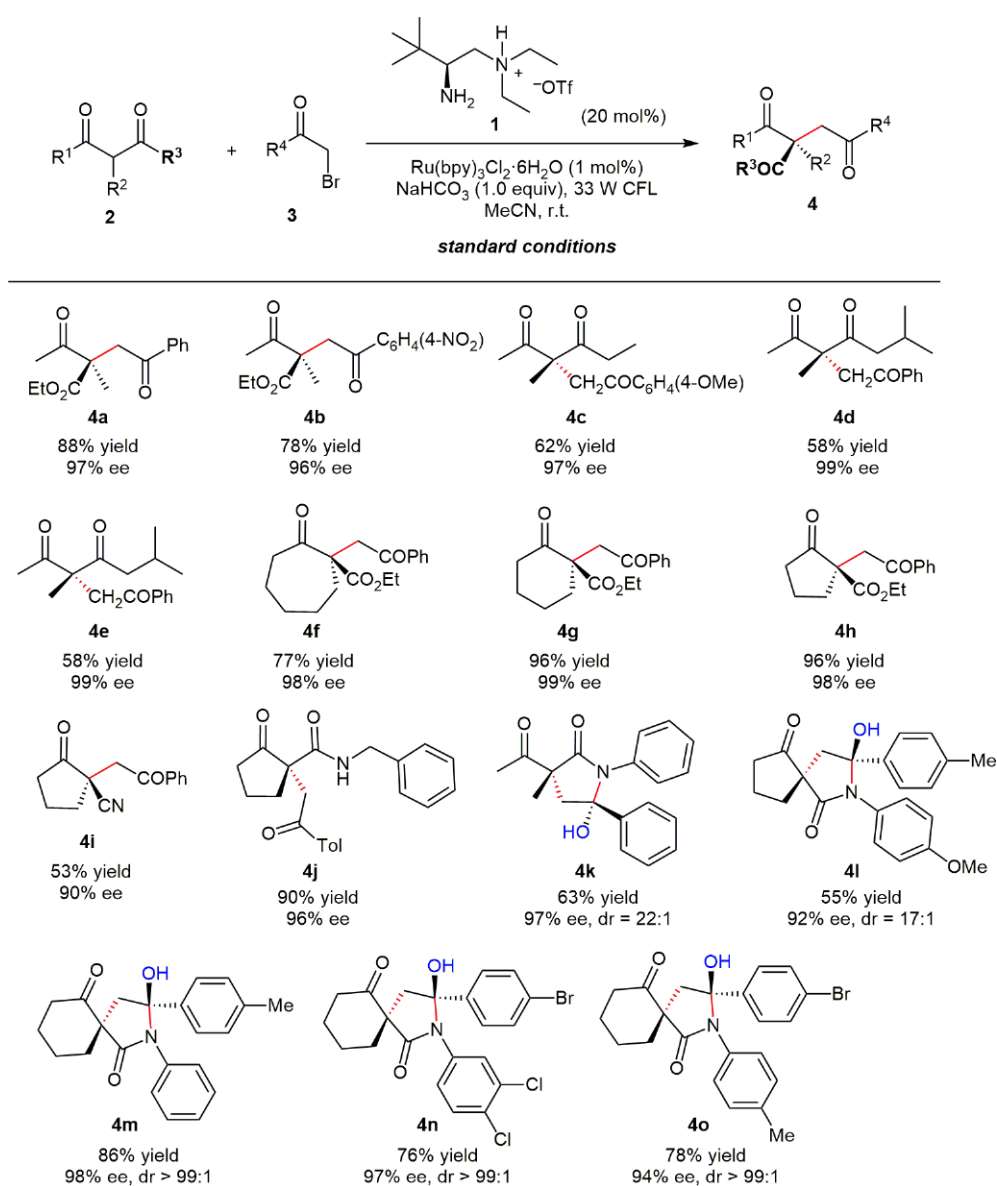
molecular ketalization occurs spontaneously in the reactions involving *N*-aryl amides (**4k–o**). “The reason for high chiral induction in the ketalization step may originate from H-bonding to hydroxy-carbonyl as well as π – π interaction between the two aromatic rings,” suggested Professor Luo, who added that this class of spiro- γ -lactams has recently been found to have promising pharmaceutical profiles and their asymmetric synthesis has not been achieved so far.

“Based on the known precedence as well as our own experimental observations, we believe the current reaction proceeds via a photoredox catalysis productive pathway (Scheme 3),” continued Professor Luo. “Accordingly, a transition state **TS-6** was proposed to account for the stereo-induction, wherein H-bonding between the protonated tertiary amine and the keto moiety of radical **5** would guide the approach of the radical species. This study provides an unprecedented H-bonding strategy in dictating the reactions of radical intermediates, neutral species in nature.”

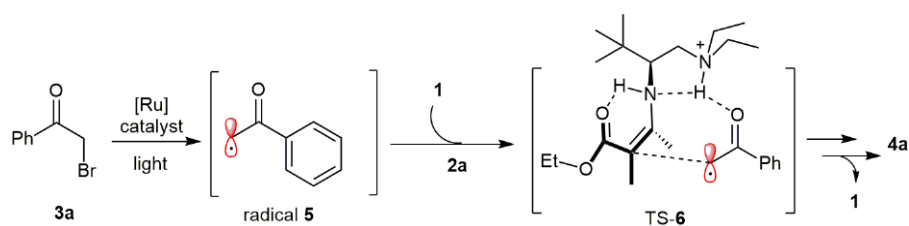
The synthetic utility of the obtained 1,4-dicarbonyl compounds was also demonstrated by the authors: when treated with phenylhydrazine, adduct **4g** underwent cyclocondensation to form indole derivative **7** or dihydropyridazine **8** under



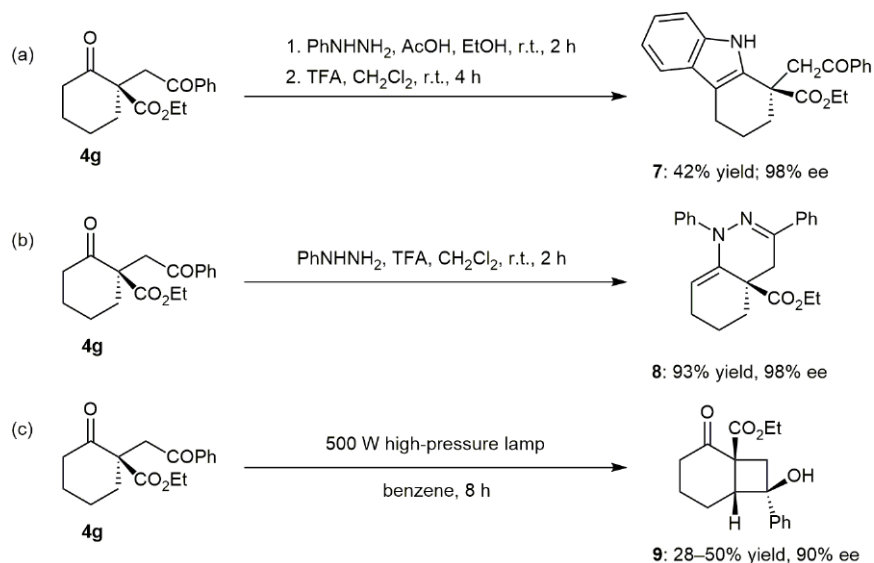
Scheme 1 The design: α -photoalkylation of β -ketocarboxyls



Scheme 2 Reaction scope



Scheme 3 Photoredox pathway



Scheme 4 Synthetic utility of the new method

different acidic conditions. “Both of these compounds are privileged structural motifs in pharmaceuticals,” said Professor Luo, who explained that the Norrish type II photoreaction of **4g** can also proceed to furnish cyclobutane **9** bearing two non-consecutive quaternary centers with high diastereoselectivity and enantioselectivity.

Professor Luo concluded: “In summary, we have developed an enantioselective α -photoalkylation of β -ketocarboxyls by merging photoredox catalysis with chiral primary amine catalysis. The reactions enable the creation of all-carbon stereocenters with excellent enantioselectivities and a broad range of substrates including the elusive 1,3-diketones and β -ketoamides for the first time in an asymmetric alkylation reaction.”

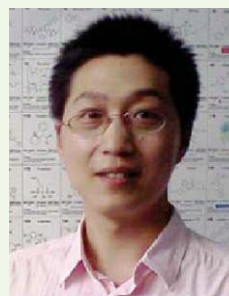
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About the authors



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Yunbo Zhu was born in 1987 in Shanxi province (P. R. of China). He obtained his BSc in chemistry from Northwest University (P. R. of China) in 2010. He began to pursue a PhD degree at the Institute of Chemistry, Chinese Academy of Sciences (ICCAS) under the supervision of Professor Sanzhong Luo in 2012.



Dr. L. Zhang

Long Zhang was born in 1980 in Hebei (P. R. of China). He graduated from Nankai University (P. R. of China) in 2005 with a major in chemistry. He then spent five years pursuing a PhD degree in a joint project between Nankai University and the Institute of Chemistry, Chinese Academy of Sciences (ICCAS) under the supervision of Professors Jin-Pei Cheng and Sanzhong Luo. After obtaining his PhD, he joined Professor Luo's group as an assistant professor in July 2010. His work focuses on the development of new asymmetric aminocatalysts as well as on DFT studies of mechanisms.

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Sanzhong Luo was born in 1977 in Henan (P. R. of China). He graduated from Zhengzhou University (P. R. of China) in 1999, and then spent his graduate studies successively at Nankai University, the Chinese Academy of Sciences and the Ohio State University (USA) and received his PhD under the supervision of Professor Jin-Pei Cheng in 2005. He started his independent career in July 2005 at the Institute of Chemistry, Chinese

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Academy of Sciences (ICCAS) and became a full professor there in 2011. He was a visiting scholar at Stanford University (USA, with Professor B. M. Trost) in 2009. His research focuses on bio-inspired asymmetric catalysis and synthesis.