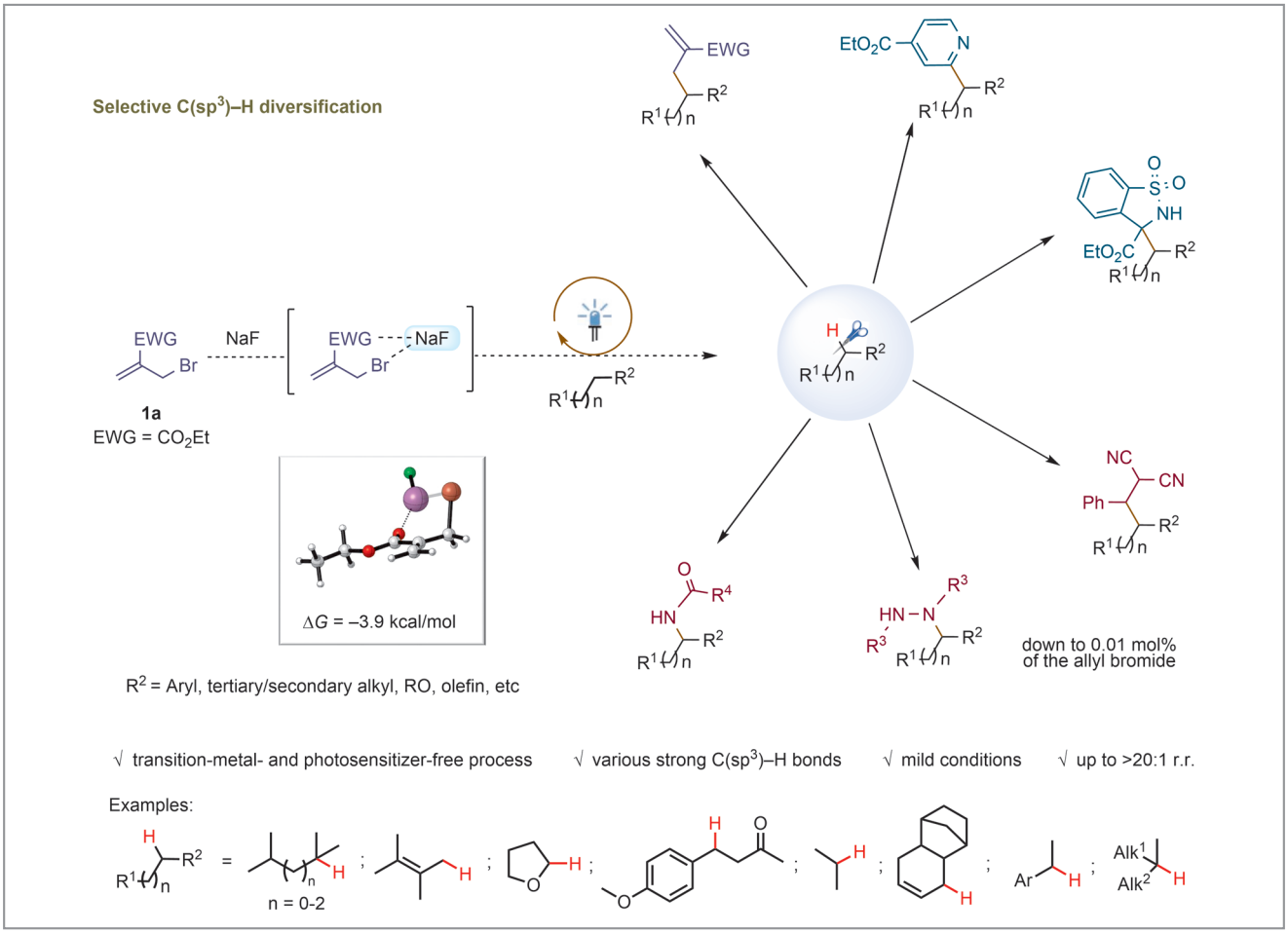
Photochemical Diversification of Strong C(sp³)–H Bonds Enabled by Allyl Bromide and Sodium Fluoride

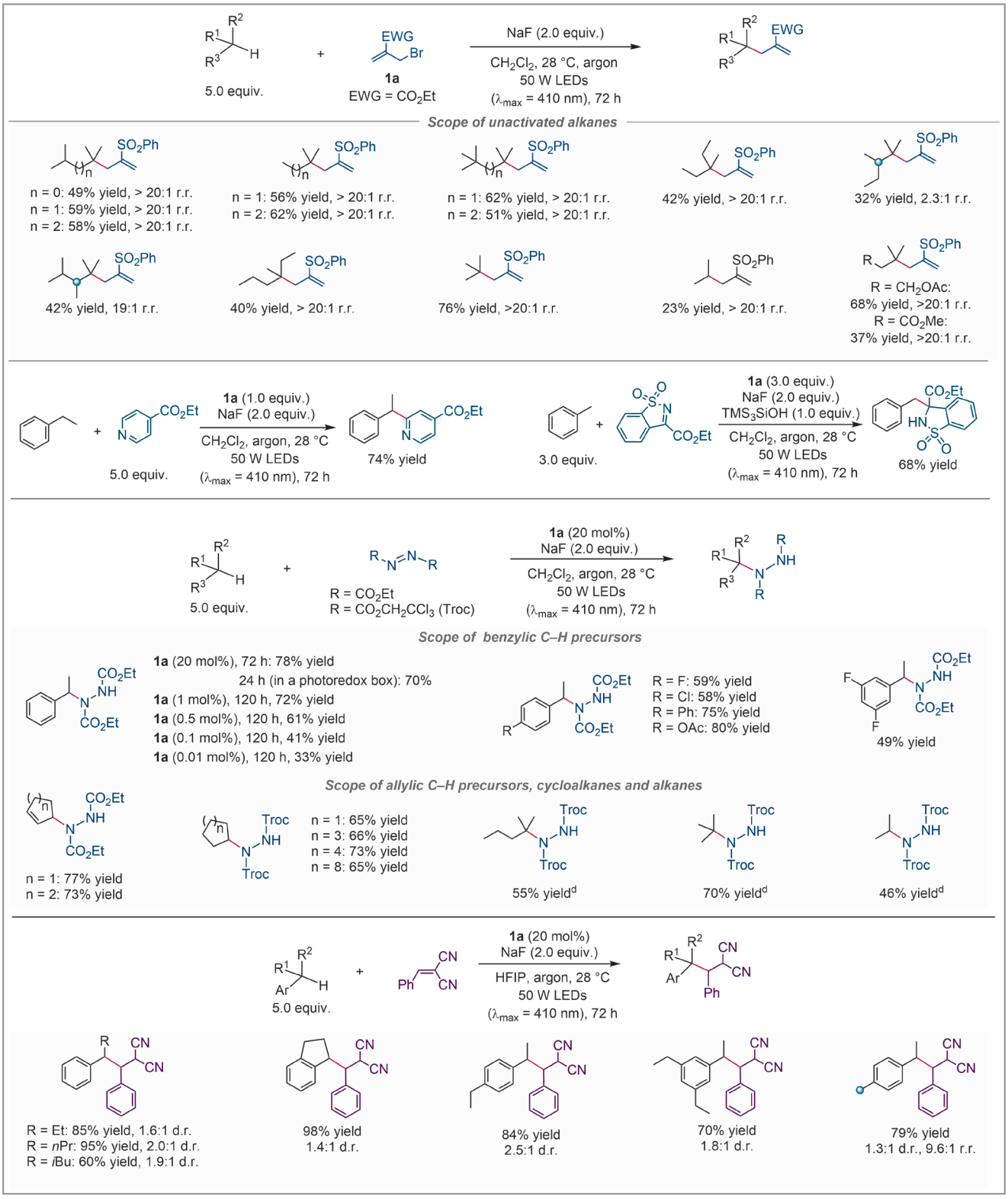
Nat. Synth. **2023**, in press; DOI: 10.1038/s44160-023-00291-w

The direct functionalization of C(sp³)–H bonds has become a hot research topic and has been recognized as one of the most convenient approaches to increase the value of cheap raw chemical materials in synthetic chemistry due to its atom- and step-economy. "The high bond-dissociation energies (96–105 kcal/mol), low polarity and similar chemical environments for alkane C(sp³)–H bonds mean that the available methods often rely on harsh reaction conditions with strong redox systems, or expensive and sophisticated catalysts, which limits the industrial applications. Therefore, the exploration of convenient methods to realize the cost-effective and mild C–H bond functionalization of alkanes is highly desired," said Professor Lei Gong from Xiamen University (P. R. of China), who has been investigating this topic.

In a study recently published in *Nature Synthesis*, a team led by Professor Gong developed a new strategy for the diversification of strong C(sp³)–H bonds enabled by allyl bromide and sodium fluoride under visible-light irradiation (Scheme 1). "In this work, we have successfully developed a C(sp³)–H functionalization strategy through the interaction of sodium



Scheme 1 Overview of this work



Scheme 2 Scope of selected substrates

 Synform **2023/09**, A151–A154 • Published online: August 16, 2023 • DOI: 10.1055/s-0040-1720606

fluoride and an allyl bromide. Binary NaF–allyl bromide adducts generated *in situ* appear to play essential roles in the reaction as light-active species, initiators for radical-mediated C–H cleavage and potential functionalization reagents. This new strategy does not rely on expensive and complex metal catalysts and organic catalysts," explained Professor Gong. He continued: "This would provide a new opportunity for the C–H diversification of hydrocarbon feedstocks and the late-stage modification of bioactive molecules."

The key to success for the transformation was the homolytic cleavage of C–Br bonds and the consequent formation of bromine radicals through the weak interaction between sodium fluoride and ethyl 2-(bromomethyl)acrylate induced by visible light. The generated bromine radicals can effectively activate C(sp^3)–H bonds of alkanes by hydrogen atom transfer to produce alkyl radicals, which undergo radical cross-coupling with allyl radicals to provide allylated products. "The C(sp^3)–H functionalization can also be achieved by adding competitive reagents," said Professor Gong. In a further development of the research project, the alkyl radical produced could be effectively captured by adding heteroaromatics and sulfimide. "At the same time, we were surprised to find that the hydrazination and alkylation of C(sp^3)–H bonds can be successfully realized even with a catalytic amount of allyl bromide as initiator," said Professor Gong. Diverse C(sp^3)–H functionalizations of alkanes, cycloalkanes and other relatively unreactive substances were enabled by this catalytic system, which furnished various allylated, heteroarylated, alkylated, hydrazinated and aminated products in good yields, with high chemoselectivity and site selectivity (Scheme 2).

"Experimental and DFT studies support the interaction between sodium fluoride and allyl bromide. The sodium fluoride plays an essential role in stabilizing radicals and regulating their electrical properties. DFT calculations show that the low energy barrier for the activation and transfer of hydrogen bromide by *N*-centered radicals is the key to the

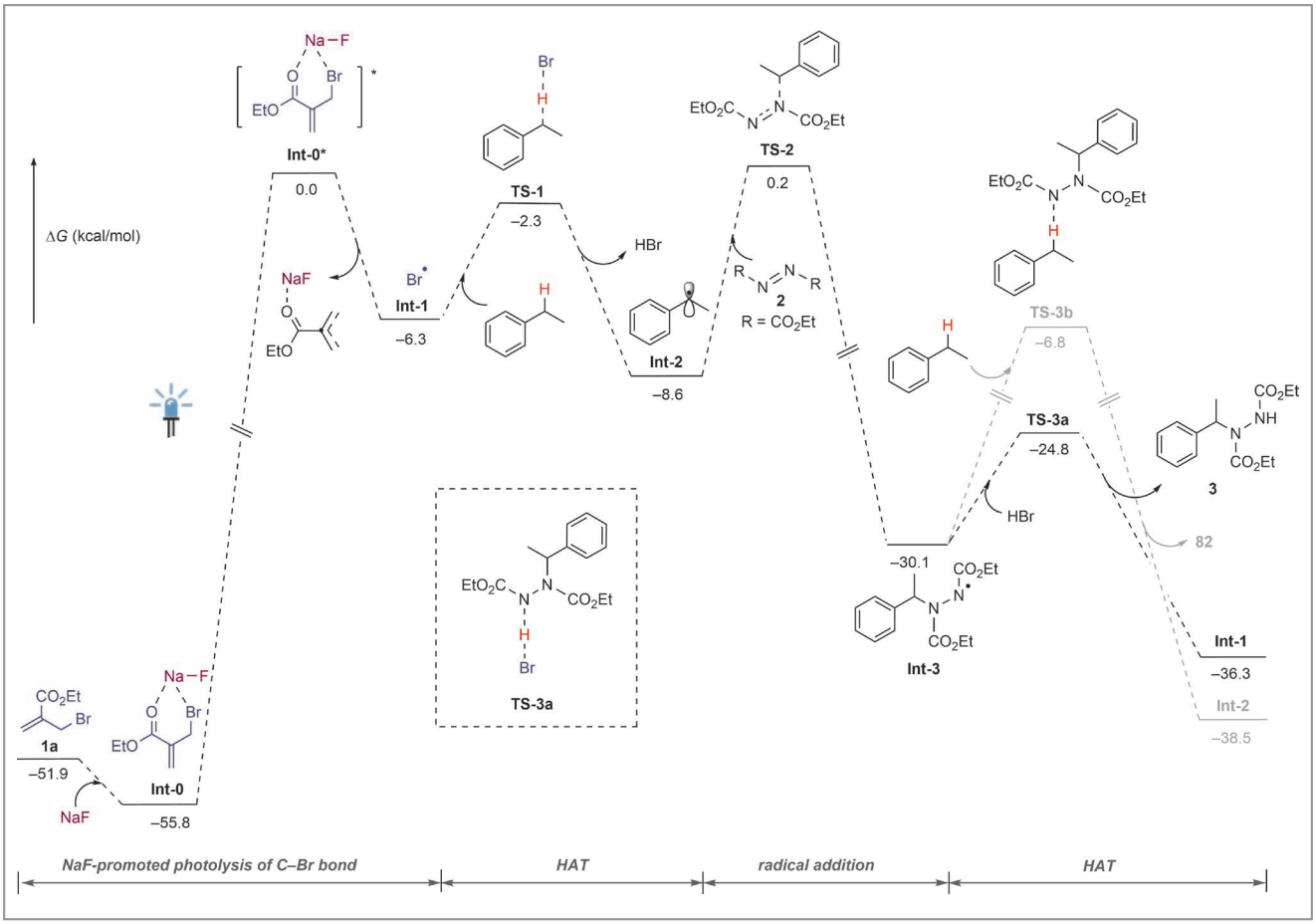


Figure 1 The barrier of the hydrazination reaction

reaction through the use of catalytic amounts of allyl bromide (Figure 1)," said Professor Gong.

Professor Gong concluded: "In summary, this study provides a new strategy for the conversion of inert C(sp^3)–H bond without photocatalysts and transition metals. It also reveals the regulatory role of main-group elements in the photochemical process, and provides a new green modification method for pharmaceutical chemists."

About the authors

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Ziqi Ye was born in Fujian, P. R. of China, in 1996. He received his B.Sc. degree from Fuzhou University, P. R. of China (2018) and then became a postgraduate student under the guidance of Professor Lei Gong at Xiamen University. His current research interest is the development of new photochemical methods for selective C–H functionalization.

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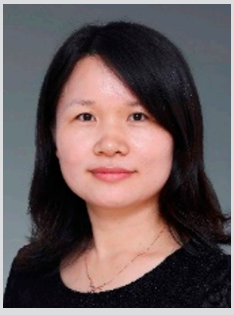
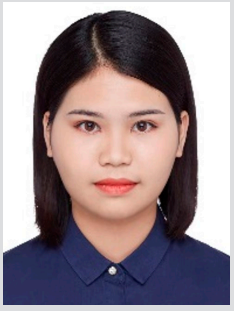


Prof. Y-M. Lin

Yu-Mei Lin received her Ph.D. degree from Xiamen University (P. R. of China) in 2010, directed by Prof. Haiping Xia. Then, she worked with Prof. Stefanie Dehnen at Philipps-Universität Marburg (Germany) as a Alexander Humboldt fellow. She joined Xiamen University as an Associate Professor in 2013. Her current research interests involve the synthesis, reactivity and properties of metalla-aromatics, and the design of new catalysts based on organometallic scaffolds.



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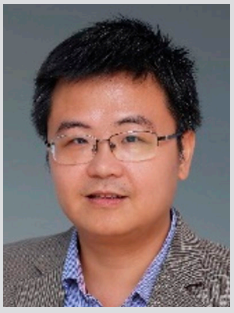

Prof. L. Gong

Lei Gong received his BSc (2002) and PhD degrees (2008) from Xiamen University (P. R. of China) under the guidance of Professor Haiping Xia. Thereafter he moved to Philipps-Universität Marburg, Germany, where he worked as a postdoctoral fellow with Professor Eric Meggers. In 2011, he was appointed as an associate professor at the College of Chemistry and Chemical Engineering at Xiamen University. Since 2019, he has been a full professor at Xiamen University. He received the Thieme Chemistry Journals Award in 2021. His current research interests are the development of economic and environmentally friendly photochemical synthesis, as well as selective C–H functionalization.

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