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Editorial

Photocatalytic Minisci-type multicomponent reaction for the synthesis of 1-(halo)alkyl-3-heteroaryl bicyclo[1.1.1]pentanes

Bioisosteres play an important role in pharmaceutical and agricultural compound design that has been developed to enhance the properties of molecules. As a sp^3-rich small ring cage hydrocarbons, bicyclo[1.1.1]pentanes (BCPs) were commonly considered as a bioisostere of the *para*-substituted arenes, internal alkynes, and *tert*–butyl groups, and its introduction can significantly improve pharmacokinetic properties, including passive permeability, aqueous solubility, metabolic stability [1]. Over the past decades, numerous pharmaceutically relevant molecules with biaryl frameworks were improved by the approach of bioisosteric replacement. Conventional strategies for the synthesis of such BCP-aryls derivatives mostly depend on the stepwise C–C formation *via* the direct addition to bridgehead C–C bond of [1.1.1]propellane to provide active BCP-intermediates and followed by a second transition-metal cross-coupling sequence. However, these pioneer works were limited by the low step economy, the use of unstable reagents, and harsh conditions in industrial productions. Recently, radical-mediated one-step, multi-component reactions [2-6] for synthesizing various BCP-aryl derivatives have made progress, although these strategies were limited to the prefunctionalized (het)arenes and tertiary alkyl radicals [7]. Therefore, it is of great significance to develop a method for diverse BCP-aryls that can be compatible with primary, secondary, tertiary radicals and direct C–H functionalization of (het)arenes.

Li and Xu from College of Material, Chemistry and Chemical Engineering at Hangzhou Normal University have been committed to research in radical coupling, and have developed a series of green and efficient methodologies for direct C–H modification of heteroarenes. Based on the previous work of photocatalytic functionalization of C–H bond, they recently developed a series of efficient one-pot multicomponent reactions for the difunctionalization of bicyclo[1.1.1]pentane (BCP).

In 2023, they disclosed a novel and green strategy to directly synthesize perfluoroalkyl/heteroaryl disubstituted BCP derivatives enabled by EDA complex process, of which photoinduced system no need any photocatalysts and transition-metal catalysts (Scheme 1a) [8]. The substrates investigation shows that a wide range of bioactive heteroarenes such as pyrazinones, quinoxalinones, azauracils and various perfluoroalkyl iodine are well compatible. Furthermore, numerous pharmaceutically relevant molecule moieties, such as ibuprofen, loxoprofen, indomethacin, dehydrocholic and other acids, were also successfully installed into BCPs scaffold, which demonstrates its potential of various utilities in synthetic chemistry.

As ubiquitous feedstocks, organic halides are widely used as significant materials in organic synthesis and industrial production. In the laboratory, organohalides are generally converted into the corresponding alkyl radicals through the photoinduced single electron transfer (SET) process, which is well received in laboratory synthesis as a mild and efficient path. However, this photoinduced SET strategy may be hindered by the relatively high reduction potential of particular C-halo bonds, which may require a strong reducing platform. In view of this situation, they developed a novel method for the synthesis of (halo)alkyl/aryls disubstituted BCPs enabled by α-aminoalkyl radical-mediated halogen-atom transfer (XAT) (Scheme 2a) [9]. Diverse commercially available organic halide radical precursors are successfully converted to primary, secondary, tertiary, and polyhalides radicals through XAT process enabled by α-aminoalkyl radical. A wide range of heteroarenes and complex compounds containing bioactive molecules are also well compatible as radical acceptors in this multi-component transformation, which significantly expands the range of BCP-aryls derivatives and shows its application value in drug discovery.

Very recently, another strategy for activation of alkyl halides with relatively high reduction potentials was disclosed by this group, where diverse organic halides precursors converted into various alkyl radicals enabled by consecutive photoinduced electron transfer (ConPET) sequence (Scheme 2) [10]. Various unfunctionalized heteroarenes and all kinds of carbon radicals, including primary, secondary, tertiary and polyhalides radicals are well compatible in this photocatalytic Minisci-type multicomponent reaction with [1.1.1]propellane, providing corresponding (halo)alkyl BCP-aryls in moderate-to-good yields. In addition to a series of complex compounds mentioned above, numerous alkyl halides containing bioactive molecules and pharmaceutical frameworks are also converted into radicals and involved in the strain-release addition onto central C–C bond of [1.1.1]propellane smoothly without affection of steric hindrance (Scheme 2a). The Minisci-type substrate examples are plenty and diversified, which demonstrates its practicality and potential in drug development.

A plausible mechanism for this Minisci-type multicomponent reaction was proposed as shown in Scheme 2b. First, the photocatalyst Mes-Acr$^+$BF$_4^-$ absorbs a photon to reach the excited state, which could occur SET process with azauracil to produce a Mes-Acr$^\bullet$ and heteroarene cation radicals. Then, the Mes-Acr$^\bullet$ continues to absorb a photon to access the desired *Mes-Acr$^\bullet$, which provides a strong reduction platform to undergo electron transfer with diverse alkyl halides, affording corresponding alkyl radicals. The pho-

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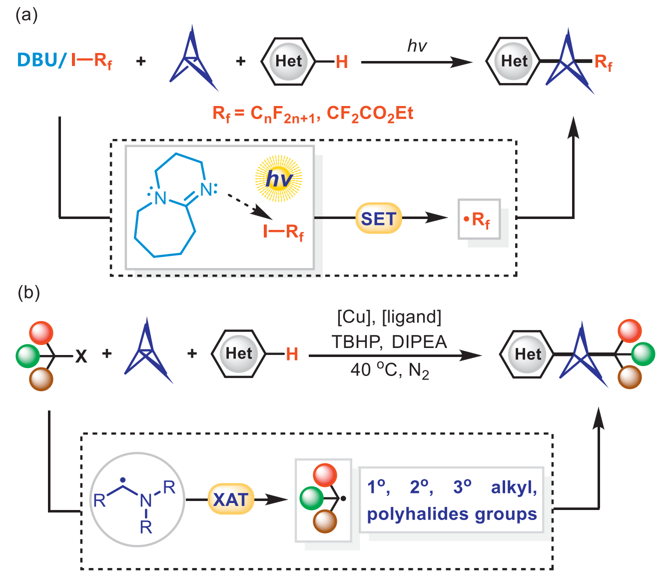


Scheme 1. Previous strategies for the difunctionalization of [1.1.1]propellane. (a) Electron donor-acceptor (EDA) complex-meditated multicomponent reaction. (b) Multicomponent reaction enabled by α-aminoalkyl radical-mediated halogen-atom transfer.

tocatalyst $\text{Mes-Acr}^{+}\text{BF}_4^{-}$ is regenerated after the completion of reduction process. The alkyl radicals directly undergo radical addition with the central C–C bond of [1.1.1]propellane to produce an active BCP-alkyl radical intermediate. Next, BCP-alkyl radical intermediate attacks heteroarene cation radicals, then experiences a deprotonation process to generate the desired product.

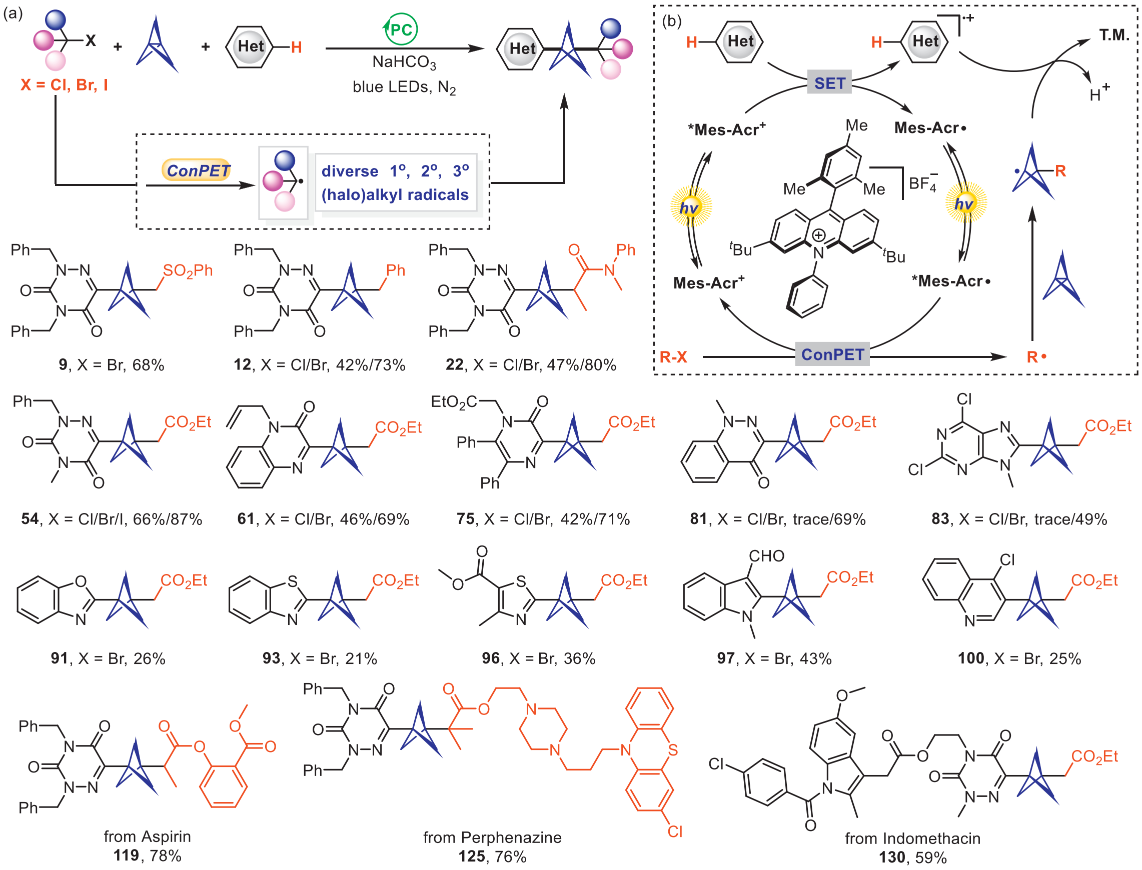
In conclusion, Li and Xu have developed a visible-light-induced strategy and photocatalytic Minisci-type reaction respectively for the synthesis of all kinds of (halo)alkyl BCP-aryls derivatives. These multicomponent reactions are compatible with primary, secondary, tertiary alkyl radicals and numerous pharmaceutically relevant molecules, which displays great practicality in synthetic chemistry and drug development.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Rong-Nan Yi: Writing – original draft. **Wei-Min He:** Writing – review & editing.



Scheme 2. Photocatalytic Minisci-type multicomponent reaction for the synthesis of (halo)alkyl BCP-aryls. (a) Representative examples of the synthetic scope. (b) Proposed mechanism.

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References

[1] J. Xu, P. Zhang, W. Li, Chem Catal. 3 (2023) 100618.
[2] T. Zeng, J. Yang, K. Yan, W. Wei, J. Wen, Green Synth. Catal. 4 (2023) 35–40.
[3] W.T. Ouyang, H.T. Ji, J. Jiang, et al., Chem. Commun. 59 (2023) 14029–14032.
[4] L. Dai, G. Zhong, Chin. J. Org. Chem. 43 (2023) 2589–2590.
[5] C.H. Ma, Y. Ji, J. Zhao, et al., Chin. J. Catal. 43 (2022) 571–583.
[6] H.C. Li, K.Y. Zhao, Y. Tan, et al., Org. Lett. 25 (2023) 8067–8071.
[7] S. Cuadros, J. Paut, E. Anselmi, et al., Angew. Chem. Int. Ed. 63 (2024) e202317333.
[8] J. Zhu, Y. Guo, Y. Zhang, et al., Green Chem. 25 (2023) 986–992.
[9] Y. Guo, J. Zhu, Y. Wang, et al., ACS Catal. 14 (2024) 619–627.
[10] J. Zhu, Y. Hong, Y. Wang, et al., ACS Catal. 14 (2024) 6247–6258.