

Metal-Free Radical Vicinal Dihalogenation of Olefins Enabled by Synergetic Photocatalytic Energy Transfer and Halogen-Atom Transfer

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ABSTRACT:

Vicinal dihaloalkane is extremely important structural unit, and dihalogenation of alkene provides a prospective way access to such moiety. Despite more than a century of development, it is still challenging and necessary to avoid the use of toxic and harmful halogenating reagents and to develop more efficient, sustainable, and broader functional group tolerant and skeleton-compatible strategies. We report herein the first metal-free protocol for radical vicinal dichlorination and dibromination by a photocatalytic energy transfer strategy using *N*-halo-benzophenimine (NXB) as the readily accessible halogenating reagents. This approach undergoes the radical addition of a halogen atom derived from the N-X bond photolysis of NXB onto olefins, followed by a halogen-atom transfer process. This approach features facile operation, mild reaction conditions, a wide of functional group tolerance, and is compatible with a large of complex scaffolds such as unsaturated fatty acid, terpenes steroid, alkaloid, sugar, amino acid, and peptide.

Vicinal dihaloalkane structural units, such as dichloro and dibromo moieties, are useful building blocks in molecular architecture which can be found in marine nature products, flame-resistant materials, polymers, as well as pharmaceuticals (Fig. 1A) [1-4]. In addition, due to the inherent high reactivity of carbon-halogen bond, such structures also serve as versatile synthons in organic transformations [5-8]. The dihalogenation of naturally abundant alkenes provides a simple and efficient way to obtain this structure, which is often regarded as the seminal work of olefin

difunctionalization [9-11], and has been a long-standing concern in chemistry for the past century [12-14]. To date, there have been two main reaction processes to achieve this goal, one is the canonical electrophilic addition of halogen elements or halonium ions onto alkenes to form halonium ion intermediates, and the other is the radical process, in which the carbon-centered radical intermediate would be involved by the addition of halogen radicals onto olefins (Fig. 1B). The former as the dominant way can be dated back to 1862 in the bromination of benzene using elemental Br₂ by Fittig [15]. Soon afterwards, the vicinal dichlorination of alkenes was firstly realized by Widman in 1877 [16]. Despite powerful effects, the extremely corrosive and toxic nature of elemental Cl₂ and Br₂ renders it experimentally uninviting. Consequently, NCS (N-chlorosuccinimide), NBS (N-bromosuccinimide), R₄NCl₃, and PhICl₂ etc. as somewhat safer and milder nucleophilic surrogates have been developed and applied in dihalogenation [17-23], and some of which are also used in enantioselective variants [24-26]. In addition, the in situ oxidative generation of halogen or its equivalent from halide with strong oxidants such as oxone and MnO₄⁻ has been proved to be an alternative too [27-29]. A paradigm of this improvement is to combine it with the selenium-catalysis to achieve the conversion of inherent anti-selectivity to stereospecific *syn*-selectivity in the olefin dichlorination by a dual S_N2 attacking of C-Se bond of seleniranium ion intermediate [30]. However, the functional group compatibility due to the strong oxidation and electrophilic properties of these reagents also limits their application in REDOX-sensitive substrates. Furthermore, the introduction of stoichiometric even excess amounts of oxidants runs counter to the philosophy and development of sustainable chemistry today. In order to overcome these shortcomings, Morandi recently reported a particularly elegant electrophilic olefin dihalogenation tactic by merging shuttle reactions with paired electrolysis (e-shuttle), realizing the halogen transfer from the common solvent dichloroethane (DCE) and dibromoethane (DBE) even the hazardous waste haloalkanes to alkenes [31].

On the other hand, with the renaissance of radical chemistry, the latter, viz the radical dihalogenation, has received increasing attention from chemists because it can provide a complementary strategy relying on the unique reaction properties of radical. One

attractive way is to employ the ground state or the excited state of certain transition metal halides as the chlorinating reagents as well as the key intermediates for the generation of halogen radical. The former is represented by the Mn^{III}-catalyzed electrochemical oxidation of halide ion by Lin [32] and the direct use of stoichiometric pre-synthesized MnCl₃(OPPh₃)₂ by Lacy [33]; while the latter is represented by the CuCl₂ or FeCl₃-mediated LMCT (ligand-to-metal charge transfer) process under visible light irradiation by Wan and West successively [34,35]. Very recently, an Iridium-photocatalyzed radical-ionic cross approach for alkene dihalogenation has also been reported by using halosulfoxime ester as halogenating reagents by Oestreich [36]. Unfortunately, the widespread functional group tolerance has not been proved probably due to the low compatibility of sulfinyl chloride moiety. Moreover, a photocatalytic radical version of reversible shuttle reactions (p-shuttle) using lead halide perovskite quantum dot has also been developed for olefin vicinal dihalogenation [37]. Despite great success, these radical processes still face the transition metal pollution and/or the unsatisfactory functional group tolerance. Thus, it is still urgent and necessary to develop more efficient, sustainable, and functional-group tolerant radical olefin dihalogenation tactic under metal free conditions.

Visible light facilitated photocatalytic energy transfer (EnT) strategy has boomed recently as it provides a completely new reaction mode totally different from photoredox process, which involve the radical pairs derived from the excited state rather than single electron transfer dependent on REDOX potentials, resulting in potentially good compatibility with substrate bearing REDOX sensitive functionalities [38-40]. The advantages of this strategy have also been well demonstrated in difunctionalization of olefins, especially in benzophenoxime(imine)-mediated olefin amino-functionalization reported by Glorius and others [41-47], which employs the excellent trap character for carbon radicals of the in situ formed persistent benzophenoniminyl (BPI) radical. Recently, we have also reported a unique ketoxime carbonate-tuned anti-Markovnikov hydroxyoxygenation and aminoxyoxygenation of olefins by photocatalytic EnT homolysis of N-O bond of ketoxime carbonates [48]. This switchable method employs the stability difference of the formed iminyl radicals not only to achieve the

normal trap ability of BPI radical but also to realize the inhibition of the trap ability of iminyl radical by introducing β -scission to decrease its stability. Although EnT strategy shows good olefin difunctionalization potential, as far as we know, the olefin dihalogenation facilitated by such a strategy has not been realized yet, probably due to the lack of suitable halogenating reagents.

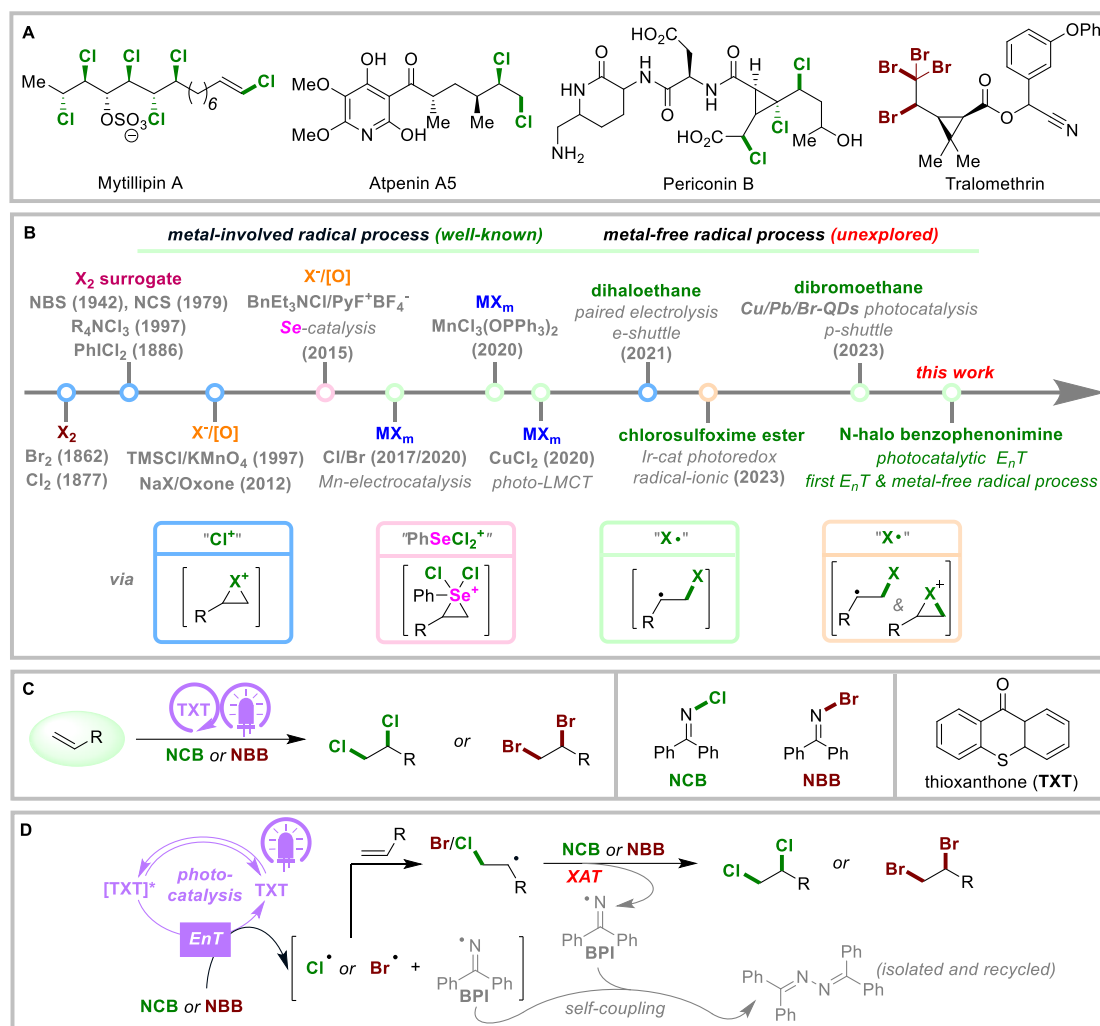


Fig. 1 Strategies for alkene dihalogenation. **A.** Representative natural products containing vicinal dihalogen unit. **B.** Survey of dihalogenation of alkenes. **C.** Metal-free radical dihalogenation of alkenes enabled by a photocatalytic energy transfer strategy. **D.** Supposed mechanism.

Based on our continuous interesting in olefin difunctionalization [49-55] and inspired by the previous studies, we sought to identify a metal-free and functional group tolerant radical dihalogenation by photocatalytic EnT process (Fig. 1C). Since N-Cl and N-Br bonds are weak bonds with low BDEs (bond dissociation energy), *N*-halo-benzophenimine (NXB) were undoubtedly chosen as the potential dihalogenating

reagents for olefin under visible light-driven EnT process. We hypothesized that NXB could be sensitized to a triplet state by photosensitizer under visible light irradiation, and then N-X bond homolysis occurs to generate halogen radicals and iminyl radical. The addition of a halogen radical onto olefin would form a carbon radical that probably inclines to undergo a much easier halogen-atom-transfer (XAT) process from another NXB to realize the dihalogenation, bypassing the trap of the persistent BPI radical and forcing its self-coupling. Herein, we demonstrate the realization of this goal by employing readily accessible NXB as the halogenating reagents and thioxanthone (TXT) as the photocatalyst under visible light irradiation. To the best of our knowledge, this work not only represents the first successful example of dihalogenation of olefins employing an EnT strategy as well as the first protocol under metal-free radical conditions, but also broadens the new application mode of benzophenimine-based reagents by suppressing the intrinsic cross-coupling property of BPI radical.

At the beginning of this study, two halogenating reagents *N*-chloro-benzophenimine (NCB) and *N*-bromo-benzophenimines (NBB) were conveniently prepared by the reaction of commercially available benzophenimine with *tert*-BuOCl and NBS, respectively. The properties characterization of the prepared NCB and NBB were then conducted by density functional theory (DFT) calculations, cyclic voltammetry and UV-Vis absorption experiments. The calculated BDEs of N-Cl and N-Br bonds are 55.1 kcal/mol and 44.3 kcal/mol, respectively. Such low BDEs of N-X bonds indicates that the hypothesized EnT-promoted N-X bond homolysis and subsequent XAT are really feasible for the realization the vicinal olefin dihalogenation. The measured reduction peak potentials of two reagents by cyclic voltammetry are -1.17 V and -1.57 V vs. SCE, and the obtained λ_{longest} by UV-Vis absorption are 330 nm and 335 nm, respectively (Fig. 2B). On the other hand, three available organic photosensitizers such as xanthone (XT), TXT, and benzophenone (BP) were chosen as the catalysts to promote the reaction.[56] The reaction optimization was commenced by photoirradiation of a mixture of 4-phenyl-but-1-ene, NCB, and photocatalyst in ethyl acetate (3 mL) under Ar at room temperature for 6 h (Fig. 2C). The optimal conditions were obtained by using TXT (5 mol %) as the photosensitizer catalyst and 6 W blue

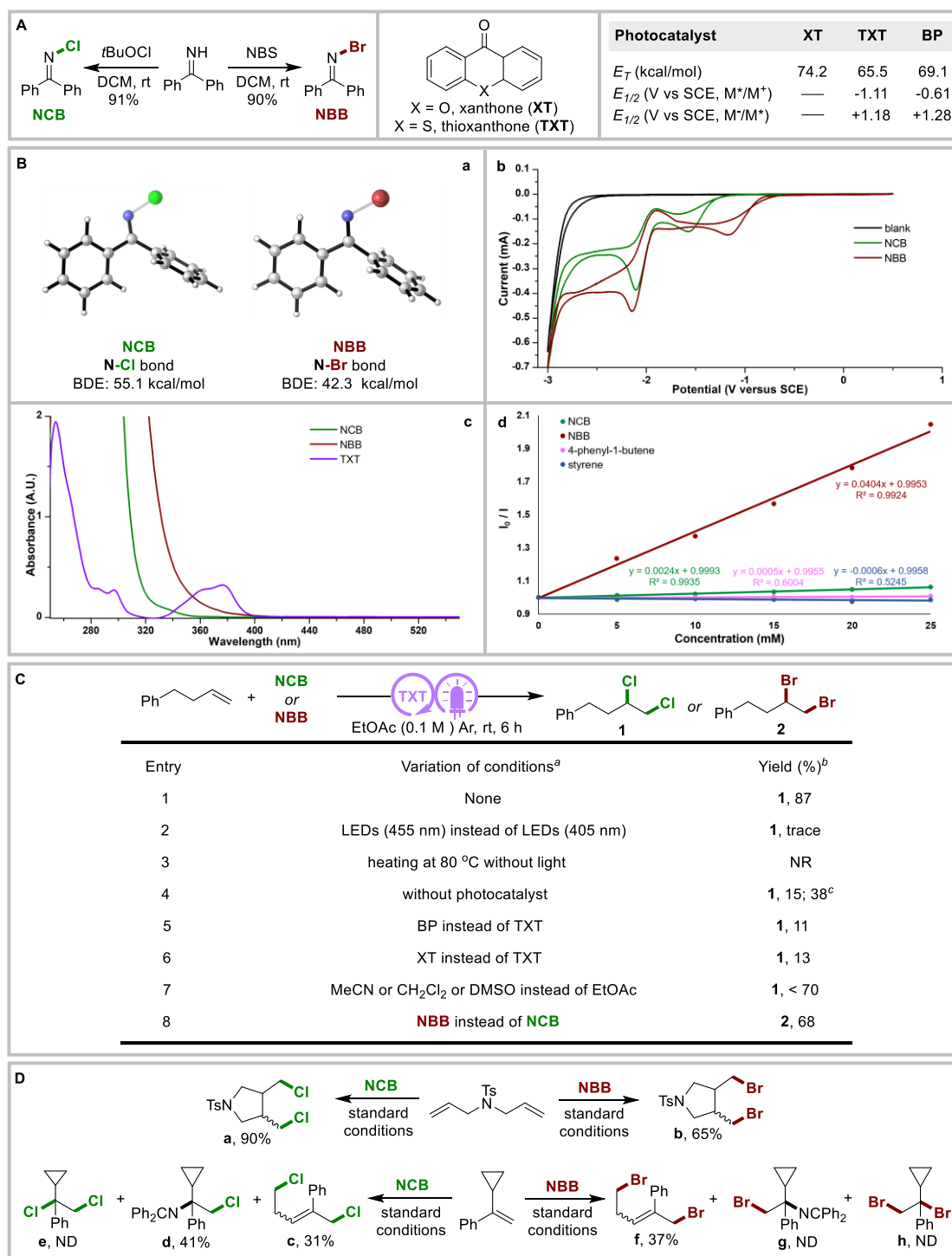


Fig. 2 Development of metal-free radical dihalogenation of olefin by photocatalytic energy transfer. A. Preparation of halogenating reagents NCB and NBB and investigation of photosensitizer. **B.** Characterization of NCB and NBB by a) DFT calculations of BDEs (Gaussian 09, optimized at the B3LYP/6-31 + G(d, p) level, sum of electronic and thermal enthalpies refinements were conducted at the M062X/def2TZVP); b) cyclic voltammetry; c) UV-Vis absorption; and d) Stern-Volmer quenching experiments. **C.** Optimal conditions: olefin (0.3 mmol, 1.0 equiv), NCB (0.75 mmol, 2.5 equiv), and TXT (5 mol %) in EtOAc (3 mL) was stirred at room temperature (rt, 20 °C) under argon atmosphere with irradiation of blue LEDs (405 nm, 6 W) for 6 h. ^b Isolated yield. ^c After 24 h. **D.** Radical clock experiments.

LEDs (405 nm) as the visible light source by giving the desired dichlorinated product **1** in 87% yield without the detection of the chloroaminated product (Fig. 2C, Entry 1). Blue light irradiation was essential for an efficient reaction, and no product was produced using blue LEDs (455 nm) as light source or heating the reaction system at 80 °C under dark (Fig. 2C, Entries 2 and 3). Photocatalyst could significantly accelerate the reaction rate as product **1** was only obtained in 38% yield after 24 h irradiation without photocatalyst (Fig. 2C, Entry 4). Other photocatalysts BP and XT had no effect on the reaction, neither accelerated the reaction rate nor increased the yield of product **1** (Fig. 2C, Entries 5 and 6). Ethyl acetate was proved to be the best among the solvents screening (Fig. 2C, Entry 7). When NBB was used as brominating reagent to react with 4-phenyl-but-1-ene under the optimal reaction conditions, the vicinal dibromination was also realized, affording the desired product **2** in 68% yield (Fig. 2C, Entry 8).

With the establishment of the optimal conditions, the reaction mechanism was then studied. The fluoresce quenching experiments revealed that the quenching of the excited photocatalyst TXT by the prepared halogenating reagents NCB and NBB is significant, whereas by the alkenes such as 4-phenyl-but-1-ene and styrene is almost no effective (Fig. 2B). By comparison of the measured oxidation potentials of NCB and NBB with the reduction potential of the excited TXT, the quenching of the excited TXT by the former is unlikely to follow an electron-transfer process and more likely abided by an EnT process because the REDOX potentials between them are apparently unmatched.

To further confirm that a radical process was involved in the reaction, the typical radical probing experiments (also known as radical clock experiments) of 5-exo-trig cyclization and 3-membered ring opening were carried out as shown in Fig. 2D. When diallyl sulfonamide was treated with halogenating reagents NCB and NBB under optimal conditions, only cascade cyclized dichlorination and dibromination products **a** and **b** were obtained in 90 % and 65% yields, respectively, without the detection of the direct alkene dihalogenated product. These results not only clearly indicated that a radical process is involved in the reaction but also revealed that the reaction rate of the XAT process between the formed carbon radical and NHBPI is slower than that of the

5-exo-trig cyclization process but faster than that of the cross coupling with BPI radical. When α -cyclopropyl styrene was employed in dichlorination, both ring opening dichlorination product **c** and cyclopropyl retained chloroamination product **d** were obtained in 31% and 41% yield, respectively, while the olefin direct dichlorination product **e** was not observed. These phenomena revealed that the generated benzyl radical is preferred to couple with BPI radical rather than undergoes Cl-atom transfer and the coupling rate is almost as fast as the ring-opening rate of cyclopropyl and much faster than the chlorination rate of benzyl radical. On the other hand, when α -cyclopropyl styrene was treated with NBB, only the ring-opening dibromination product **f** was obtained in 37% yield, and the cyclopropyl retained olefin bromoamination and dibromination products **g** and **h** were undetected, indicating that NBB is a more efficient XAT reagent and Br-atom transfer is much faster than Cl-atom transfer for a carbon radical.

To explore the scope and availability of the established metal-free photocatalytic EnT strategy, dichlorination of a variety of structurally different olefins such as unactivated and activated alkenes was tested under the optimal conditions, and the results are illustrated in Table 1. Unactivated alkenes were explored first. Linear mono-/di-substituted terminal alkenes such as dodec-1-ene and 6-methyleneundecane were both transformed smoothly in the reaction, affording the desired vicinal dichlorinated products **3** and **4** in 91% and 95% yields, respectively. Linear internal alkene (*E*)-oct-4-ene was also converted to the corresponding product **5** in 62% yield as a mixture of 1.2:1 diastereomers. Cyclic alkenes with different ring size such as cyclohexene and cycloheptene were transformed smoothly in the reaction, affording the desired products **6** and **7** in moderate yields with excellent diastereoselectivity of > 20:1. Besides unfunctionalized simple olefins, the protocol also exhibited excellent compatibility for substituted olefins with a variety of functionalities. Functional groups such as bromo, azido, and cyano were tolerated very well in the conversion, as demonstrated in the cases **8-10**. Derivatives from unsaturated primary alcohol, including ester and ether such as benzoate, furoate, thiophenate, tosylate and phosphonate and phenoxy ether, were all tolerated and converted very well with the protocol, delivering the

corresponding products **11-16** in excellent yield. Notably, unsaturated free alcohol, aldehyde and ketone containing REDOX sensitive hydroxyl, formyl, and carbonyl groups, respectively, were good candidates for the reaction as well and afforded the dichlorinated products **17-19** in good yields, exhibiting the advantage of photocatalytic EnT strategy. In addition, unsaturated free acid and its amide derivative were proved to be suitable to dichlorination, giving rise to the desired products **20** and **21** in 61% and 46% yields, respectively. When sulphonyl and phosphoryl substituted olefins were participated in the reaction, the desired dichlorination took place very well and provide products **22** and **23** in 72% and 85% yields, respectively. Significantly, structurally diverse linear and cyclic unsaturated primary and secondary amines dichlorinated very well to form the corresponding products **24-27** in 63%-98% yields. Notably, the practicability of this protocol was demonstrated by a successful gram-scale generating 1.06g of product **3** in 89% yield, accompanied by the recovery of 1,2-bis(diphenylmethylene)hydrazine and benzophenone in 74% (1.67 g) and 13% (0.29 g) yields, respectively. As bis(diphenylmethylene) hydrazine can be easily hydrolyzed to ketone with dilute muriatic acid, the sustainability of the method was also well proved by the regeneration of the starting material benzophenonimine by the reaction of the recycled ketone with ammonia in 99% yield.

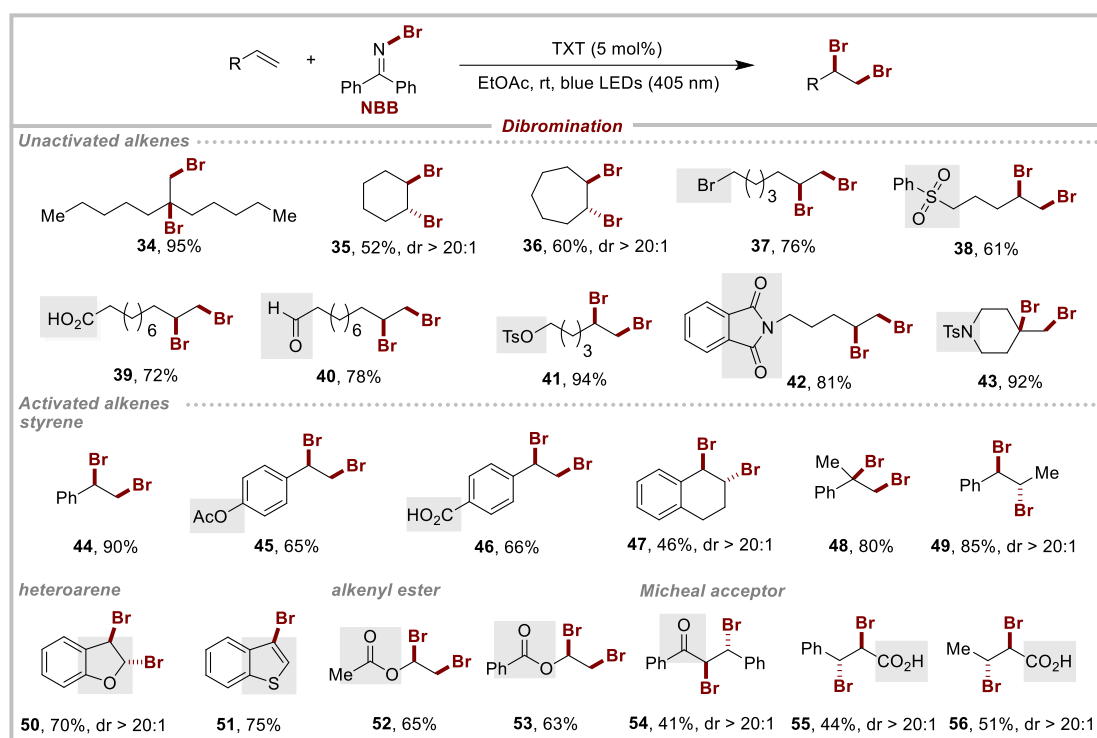
Next, we explored the applicability of this approach by employing both electron-rich and electron-deficient activated alkenes as the reaction partner. Unfortunately, when styrene was treated with NCB, the chloramination product **28'** was obtained in 87% as the sole product without the observation of dichlorination product **28** [57]. This phenomenon can be attributed to the fact that the metastable benzyl radical is more easily trapped by BPI radical than to undergo Cl-atom transfer with NCB. This view has also confirmed by the radical clock reaction as illustrated in Fig. 2D. In order to suppress the chloramination to facilitate the dichlorination process, we hypothesized that it is possible to reduce the trapping ability of BPI radical for carbon radical by acting on the nitrogen atom of BPI via halogen bonding (XB) effect. Delightedly, when stoichiometric 1,3,5-trifluoro-2,4,6-triiodobenzene (TFTIB), a typical halogen bonding promoter, was added to the standard reaction conditions using DCM as the solvent, the

styrenes bearing either electron-donating or withdrawing groups such as 4-acetoxy, 4-Me and 4-Cl on phenyl ring were all converted to the corresponding dichlorination products **29-31** in moderate yields. In addition, electron-rich heteroaromatic benzofuran and electron deficient trans-Chalcone were also suitable for this variant dichlorination, affording the desired products **32** and **33** in 31% and 35% yields, respectively. To confirm that the XB-tuned vicinal dichlorination initiated by EnT process also experiences a radical process, some control experiments was conducted as shown in Table 1. The reaction was almost inhibited and no products were observed when radical scavenger TEMPO (2,2,6,6-tetramethyl-piperidine-*N*-oxyl) was added in the reaction system. In addition, the addition of water or *n*BuOH in the reaction system had no effect on the reaction, the desired dichlorination was proceeded smoothly and no water or *n*BuOH trapped products were detected. These results clearly verified that the variant dichlorination tuned by XB effect undoubtedly undergoes a radical process as well. The XB of N \cdots I between BPI radical and TFTIB is also confirmed by DFT calculation and the calculated interaction energy is about 4.2 kcal/mol. Such the bonding effect causes a steric hindrance on BPI radical, which may reduce its trapping ability for carbon radicals, thus favoring the Cl-atom transfer process.

Having successful achieved dichlorination, we then turned our attention to the vicinal dibromination. As shown in Table 2, with the exception of benzothiophene, dibromination of the representative unactivated and activated alkenes with NBB were both successful by affording the desired dibromination products **34-50** and **52-56** in good to excellent yields. When benzothiophene was involved in the conversion, due to the normal dibrominated product was unstable under the reaction conditions, it was further converted to monobromated product **51** by the eliminating HBr, with a yield of 75%. The excellent diastereoselectivity was demonstrated by the cases **35**, **36**, **47**, **49**, **50**, and **54-56**. Functionality tolerance was also proved by the cases **37-43**, **45**, **46**, and **52-56** in which tosylate, sulphonyl, carboxyl and formyl groups as selected challenging functional groups were well tolerated and retained in the products. It is noteworthy that unlike the dichlorination of the activated olefins, its dibromination is quite easy and neither produces the bromoamination product nor requires the BX reagent to promote

an efficient reaction. Obviously, this result is closely related to the fact that the BDE of N-Br bond is much lower than that of N-Cl bond, which enables the Br-atom transfer between the relatively stable benzyl radicals and NBB to proceed smoothly even in the face of competition from the extremely fast cross-coupling of BPI radical. In fact, this conclusion is also strongly supported by the radical clock ring-opening experiment as illustrated in Fig. 2D.

Table 2 | Scope of simple alkenes in dibromination

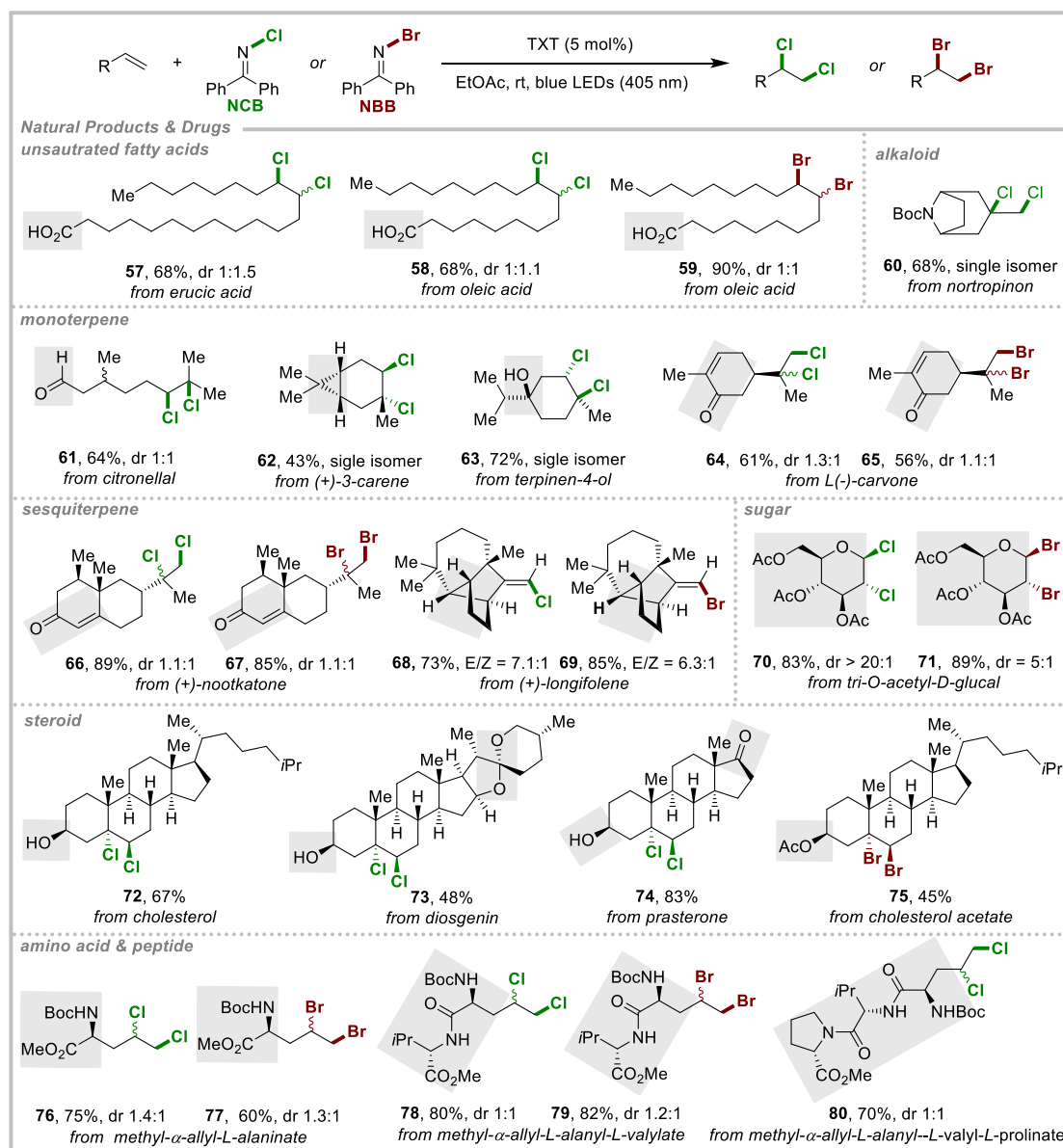


Reaction conditions: Alkene (0.3 mmol, 1.0 equiv), NBB (0.75-0.90 mmol, 2.5-3.0 equiv), and thioxanthone (TXT, 5 mol %) in EtOAc (3 mL) were stirred at room temperature (rt, 20 °C) under argon atmosphere with irradiation of blue LEDs (405 nm, 6 W) for 6-18 h. Isolated yields are given. Diastereoisomer ratio (dr) value was determined by ¹H NMR spectroscopy analysis.

To further demonstrate the advantage of this protocol, the late-stage dichlorination and dibromination of natural products and pharmaceutical molecules were conducted. As shown in Table 3, the excellent complex scaffold compatibility and the aforementioned REDOX sensitive functional group tolerance were also fully demonstrated. Natural linear unsaturated fatty acids such as free erucic acid and oleic acid converted smoothly in the protocol and produced the corresponding dichlorinated products **57** and **58** in 68% and 68% yields as diastereoisomers with 1:1.5 and 1:1.1

ratios, respectively. Dibromination of free oleic acid proceeded very well to provide product **59** in 90% yield with a similar diastereoselectivity. Alkaloid represented by nortropinone derivative was also highly compatible with this approach, providing dichlorinated product **60** in 68% yield as a sole stereoisomer. As terpenes are a wide source of structurally complex alkenes, we then investigated the applicability of this protocol for a series of monoterpenes as well as sesquiterpenes. Linear monoterpene citronellal containing a highly sensitive functional group aldehyde converted very well in the reaction and produced the corresponding olefin dichlorinated product **61** in 64% yield as diastereoisomers with a ratio of 1:1. In addition, cyclic monoterpenes such as (+)-3-carene and terpene-4-ol containing functional moieties of cyclopropane and hydroxyl, respectively, were both well tolerated in the transformation, affording the corresponding dichlorinated products **62** and **63** in moderate to good yields as a single isomer. Notably, when cyclic monoterpene *L*-(-)-carvone bearing two different olefins, viz electron-deficient enone on the ring and the unactivated terminal alkene, was participated in the reaction, it was converted smoothly in the form of the highly chemo- and regio-selective dichlorination and dibromination of the latter, producing **64** and **65** in 61% and 56% yields as a mixture of diastereoisomer, respectively. Sesquiterpenes such as (+)-nootkatone and (+)-longifolene were also investigated then. Dichlorination and dibromination of the former were succeeded too, as demonstrated in the case of **66** and **67** with excellent yields; whereas the latter suffered monohalogenation rather than dihalogenation of alkene moiety to provide the corresponding vinyl chloride **68** and vinyl bromide **69** in excellent yields as a mixture of stereoisomers with *Z/E* ratios of 7.1:1 and 6.3:1, respectively. The reason for monohalogenation can be attributed to the existence of a large steric hindrance effect around the olefin, resulting in the failure of introduction of the second halogen atom. Sugar represented by acyl *O*-triacyl *D*-glucal was well compatible in the conversion, producing the dichlorinated and dibrominated products **70** and **71** in 83% and 89% yields, respectively. The former was generated as a single diastereomer and the latter was obtained as a mixture of diastereomers with 5:1 ratio. Steroids such as cholesterol, diosgenin, and prasterone were also good candidates in this tactic, as demonstrated in the dichlorinated cases **72-74** as well as in the

Table 3 | Late-stage dichlorination and dibromination of natural products



Reaction conditions: Alkene (0.3 mmol, 1.0 equiv), NCB or NBB (0.75-0.90 mmol, 2.5-3.0 equiv), and thioxanthone (TXT, 5 mol %) in EtOAc (3 mL) were stirred at room temperature (rt, 20 °C) under argon atmosphere with irradiation of blue LEDs (405 nm, 6 W) for 6-18 h. Isolated yields are given. E/Z and diastereoisomer ratio (dr) values were determined by ¹H NMR spectroscopy analysis.

dibrominated case **75**. In these cases, functional groups such as hydroxyl, carbonyl, ether, and ester were all well tolerated. Notably, this approach can be applied the late-stage modification of unsaturated amino acids and its dipeptide and tripeptide as well. For instance, methyl α -allyl-L-glycinate converted smoothly in the reaction, affording the corresponding dichlorinated and dibrominated products **76** and **77** in 75% and 60% yields, respectively. Its dipeptide with L-valine and tripeptide with L-valine and L-

proline were also good partners for the reaction, delivering the dichlorinated dipeptide **78** and tripeptide **79** as well as the dibrominated peptide **80** in 80%, 82%, and 70% yields, respectively.

In conclusion, we have developed an efficient and sustainable metal-free radical olefin dichlorination and dibromination strategy by using *N*-chloro-benzophenonimine and *N*-bromo-benzophenonimine as the halogenating reagents and TXT as the photosensitizer under photocatalytic EnT conditions, respectively. The reaction initiates by N-X bond homolysis to halogen radical and BPI radical, followed by a cascade halogen radical addition and XAT process. This protocol represents the first successful example of metal-free and EnT tactic for radical dihalogenation of olefin. This approach features facile operation, mild reaction conditions, and a wide of functional group tolerance, and is compatible with a large of complex scaffolds such as unsaturated fatty acid, alkaloid, terpene, steroid, sugar, amino acid, as well as peptide. We anticipate that this tactic will not only promote the late-stage modification of natural products and drug containing olefins to obtain the previously inaccessible dihalogenated structures, but also guide the future design and application of benzophenonimine-based functionalization reagents in photoenergy organic synthesis.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 22171118, 21873041, and 21632001) for financial support.

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