ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2019, **55**, 107

Received 18th October 2018,
Accepted 23rd November 2018

DOI: 10.1039/c8cc08362b

rsc.li/chemcomm

# Alkenylation of unactivated alkyl bromides through visible light photocatalysis†

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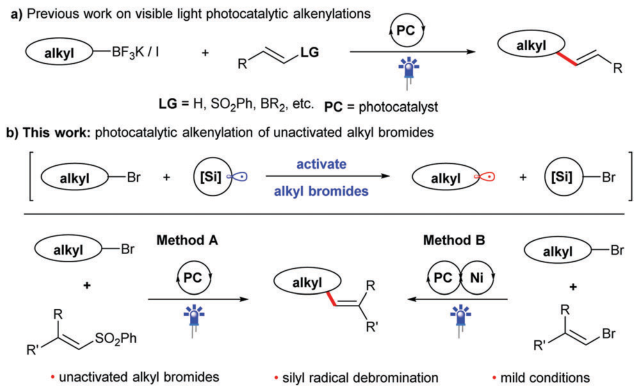
**Two visible-light driven alkenylation reactions of unactivated alkyl bromides, which were enabled by the use of Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ as the photocatalyst and (TMS)$_3$SiH as the atom transfer reagent to activate the alkyl bromides, were described for the first time. These protocols can be used to produce a variety of alkenes from easily available feedstock with good reaction efficiency and high chemo-selectivity under mild reaction conditions. To further demonstrate the applicability of the present strategy, the alkenylation of bioactive molecules and glycosyl bromides, as well as the alkynylation of unactivated alkyl bromides, was proven to be feasible.**

Alkenes are a class of fundamentally important compounds, as they are broadly applied in synthetic chemistry and materials science.[1] Tremendous research efforts have been devoted to the synthesis of alkenes, including the well-known Wittig-type reactions,[2] semi-reduction of alkynes,[3] Heck-type reactions[4] and many others.[5] Inherently, the cross coupling of an alkene moiety with the pre-functionalized alkane partner through transition metal catalysis has been considered as an ideal tool for this purpose with anticipated chemo- and regioselectivity.[4,5] Although being a great achievement, this valuable protocol still has some drawbacks. For example, organometallic reagents, which are widely used in these reactions, are usually sensitive to water and air.[6] In addition, the oxidative addition of alkyl halides to a metal catalyst is difficult and the generated transient species might undergo undesired β-hydride elimination.[4,5] Moreover, elevated temperatures are frequently required.

Visible light photocatalysis has attracted increasing interest from the synthetic community, because it enables the generation of reactive intermediates under mild conditions.[7] This strategy has been gradually applied in alkenylation reactions during the last decade.[8] In this context, alkyl fluoroborate salts, which have a photocatalytically addressable oxidation potential, have been widely used as potent radical precursors for many coupling reactions,[9] including alkenylation with alkenyl sulfones (Scheme 1a).[9a] However, the preparation of these reagents produces stoichiometric amounts of by-products and usually requires three consecutive steps, including the reaction using oxygen- and water-sensitive organometallic reagents under low temperatures, somewhat limiting its application. Thus, many other alkyl precursors have been developed to improve the photocatalytic alkenylation reaction.[8] Among them, easily available halides[10] have been proven to be an efficient feedstock for the alkenylation. Usually, activated alkyl halides, such as alkyl iodides or electron-deficient alkyl bromides, are required due to their higher reduction potential, which favors the generation of alkyl radicals *via* photocatalytic SET processes. Hence, the direct use of unactivated alkyl bromides in alkenylation reactions through visible light photocatalysis remains a challenge, despite their



Scheme 1 Reaction design: intermolecular alkyl–alkenyl coupling reactions *via* visible light photocatalysis.

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† Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data. CCDC 1879873. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc08362b

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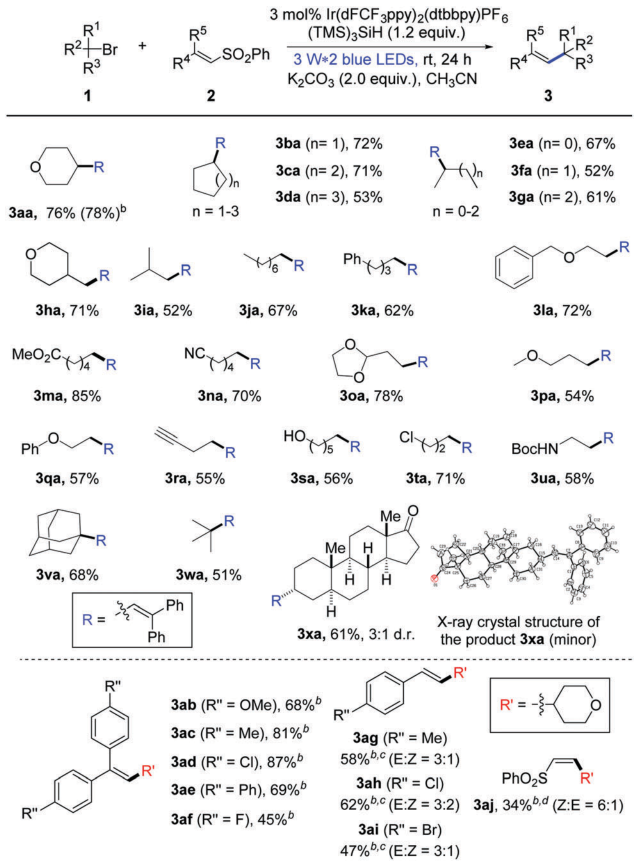
advantages of low price, bench stability and easy availability.[11] Inspired by the well-established process using organosilicon radicals to activate alkyl bromides,[12] we therefore envision that alkyl bromides can also be utilized as efficient alkyl radical precursors to participate in new alkenylation reactions through the combination of visible light photocatalysis and silicon radical debromination. In this work, we plan to develop two kinds of coupling reactions of non-activated alkyl bromides with phenyl vinyl sulfones (method A) or bromides (method B) as shown in Scheme 1b. If successful, these protocols will provide two competitive and alternative methods for the preparation of alkenes from easily available chemicals under mild conditions.

Initially, we began our investigations with the coupling of bromotetrahydropyran (**1a**) and diphenyl vinyl sulfone (**2a**) as the model reaction (please see the ESI,† Table S1).[13] In the presence of photocatalyst Ir(dF($CF_3$)ppy)$_2$(dtbbpy)$PF_6$, silicon radical precursor tris(trimethylsilyl)silane (TTMSS) and inorganic base $Na_2CO_3$, a high amount of the desired alkene product **3aa** was detected after blue light irradiation at room temperature (rt) for 24 hours (Table S1, entry 1: 83% NMR yield, ESI†). Then, routine optimization of the reaction parameters including bases, solvents, hydrosilanes and concentration (Tables S1–S4, ESI†) improved the result, in which the combination of $K_2CO_3$ and $CH_3CN$ (0.05 M) stood out as the best choice (for optimal conditions, see the footnote in Table 1).[13] Moreover, the reaction efficiency was not obviously affected by the air atmosphere (Table S1, entry 17, ESI†). Control experiments showed that visible light and a suitable photoredox catalyst were necessary for the transformation.[13]

Having established the optimal reaction conditions, we started to examine the generality of this photocatalytic alkenylation reaction. As highlighted in Table 1, the mild protocol enables the alkenylation of different unactivated bromides. The coupling with secondary cyclic alkyl bromides proceeded smoothly, providing the corresponding alkene products in good yields (**3aa–3da**: 53–78% yields). Acyclic secondary alkyl bromides can readily undergo this transformation too; the alkenylation products were obtained in 52–67% yields (**3ea–3ga**). In addition, primary and tertiary alkyl bromides were also converted into the desired products with satisfied results (**3ha–3xa**: 51–85% yields). To our delight, this protocol shows good functional group tolerance. Many alkyl bromides bearing ether, ester, alkyne, acetal and several other moieties can participate well in the photocatalytic alkenylation reaction (**1l–1r**). More importantly, the reaction with substrate **1s** containing a free hydroxyl group also proceeds smoothly with moderate yield. Besides, the reaction with dihalide **1t** showed excellent chemoselectivity between the bromide and the chloride. Moreover, this protocol allows the debrominative alkenylation of bioactive molecule **1x** under mild reaction conditions, delivering product **3xa** in good yield.[14]

Next, we probed the scope of phenyl vinyl sulfones under photocatalysis conditions. As summarized in Table 1, a variety of 2,2′-diaryl-substituted vinyl sulfones can be applied as efficient substrates and the electronic characteristic of aryls somewhat affect the reaction results. In the case of the chlorinated product **3ad**, a high yield of 87% was obtained and the phenyl chloride moieties were not affected by the silyl radical. In addition to 2,2′-diaryl-substituted vinyl sulfones, styrene-substituted sulfones can participate in this photochemical transformation as well. For example, when *para*-Me-, Cl-, or Br-substituted styrene sulfones were subjected to the standard reaction conditions, the desired alkenylation products **3ag–3ai** were obtained in good yields with modest *E*/*Z* ratios. Moreover, this protocol can be successfully extended to the alkenylation of alkyl-substituted vinyl sulfones (**3aj**, $Z:E = 6:1$), but in 34% yield.

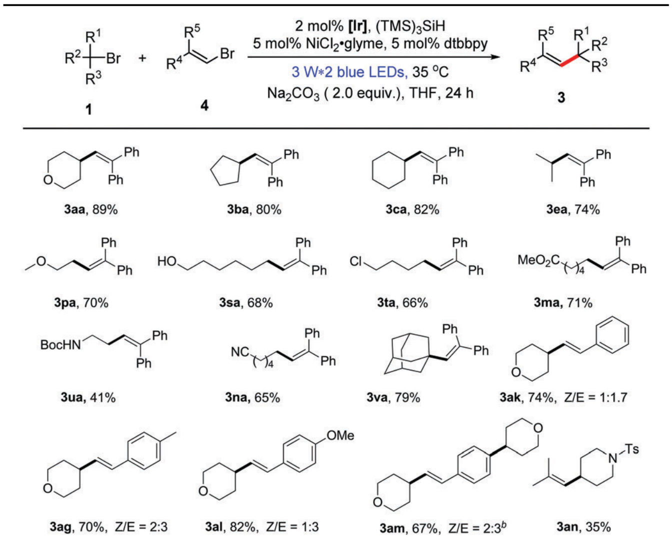
Table 1 Generality of the photocatalytic alkenylation of unactivated alkyl bromides with vinyl sulfones[a]



[a] Reaction conditions: **1** (0.6 mmol), **2** (0.2 mmol), TTMSS (0.24 mmol) Ir(dF($CF_3$)ppy)$_2$(dtbbpy)$PF_6$ (3 mol%), $K_2CO_3$ (2.0 equiv.) in $CH_3CN$ (4.0 mL) at rt under irradiation with 3 W × 2 blue LEDs for 24 h, isolated yield. [b] 1.5 equiv. of TTMSS. [c] (*E*)-Phenyl vinyl sulfone was used. [d] *cis*-1,2-Bis(phenylsulfonyl)ethane was used.

Recently, the use of nickel catalysis in combination with photoredox catalysis has been proven to be feasible for the coupling reaction of aryl halides.[15] However, examples for the dual catalytic coupling reactions of vinyl halides are rare.[16] In order to be more comprehensive, we present an additional method for the reaction of unactivated alkyl bromides with vinyl bromides through dual photoredox/nickel catalysis. With a slight alteration in the reaction conditions in the first alkenylation method, we established the optimal reaction conditions for the dual catalytic alkenylation of unactivated alkyl bromides with vinyl bromides.[13] As highlighted in Table 2, the transformation under the dual catalysis system generally provided the corresponding alkene

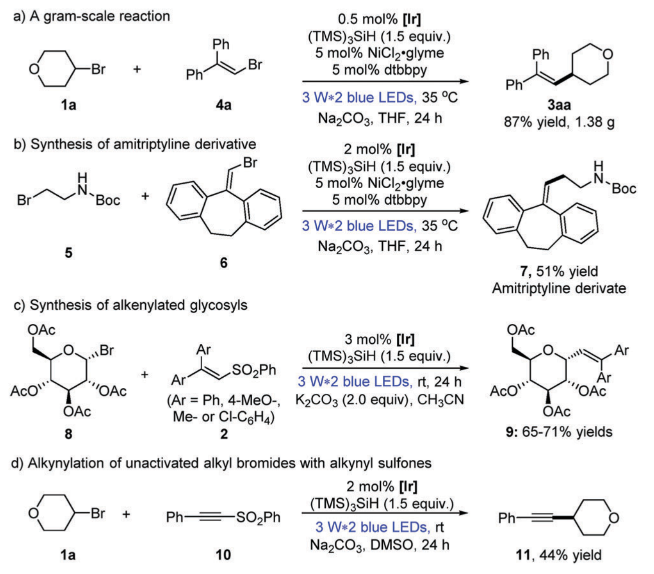
Table 2 Generality of the alkenylation of unactivated alkyl bromides with vinyl bromides *via* dual photoredox/nickel catalysis[a]



[a] Reaction conditions: alkyl bromides **1** (0.6 mmol), **6** (0.2 mmol), $Na_2CO_3$ (2.0 equiv.), $(TMS)_3SiH$ (0.24 mmol), [Ir] = $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (2 mol%), $NiCl_2$·glyme (5 mol%), dtbbpy (5 mol%), THF (2.0 mL), Ar atmosphere, 3 W × 2 blue LEDs, 35 °C for 24 h; isolated yields. [b] 6.0 equiv. of **1a** was used, DME as the solvent.

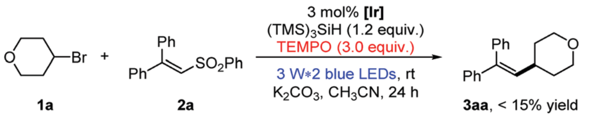
products in good yields (Table 2, 41–89% yields). In addition, it is general for alkyl bromides and shows good functional group compatibility. Furthermore, this protocol can also be extended to non-aromatic alkenes (**3an**, Table 2). Different from the formation of the mono-alkylated product **3ai** using method A, the double alkylated compound **3am** was obtained in good yield under the conditions of method B, demonstrating the different characteristics of the two presented methods.

To show the applicability of the dual photoredox/nickel catalysis systems, a gram-scale alkenylation reaction of alkyl bromide **1a** and vinyl bromide **4a** was conducted, for which the loading of the photocatalyst could be lowered to 0.5 mol% without affecting the reaction efficiency (Scheme 2a: 1.38 g, 87% yield).[13] Moreover, the pharmacophore amitriptyline derivative **7** was prepared from *tert*-butyl(2-bromoethyl)carbamate **5** in 51% yield, which could be easily transferred to the antidepressant drug, amitriptyline.[1d] Considering the significance of utilizing renewable starting materials from nature,[17] herein we realized the first photocatalytic alkenylation of glycosyl bromides with good efficiency and selectivity (Scheme 2c, **9aa–9ad**, 65–71% yields). Furthermore, this strategy of visible light photocatalysis and silicon radical debromination was successfully extended to the alkynylation of alkynyl phenyl sulfone **10**, albeit with a moderate yield (Scheme 2d: 44% yield).

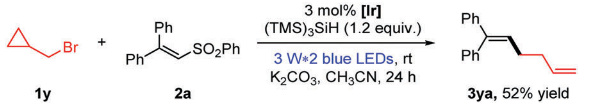


Scheme 2 Demonstration of the synthetic utility of the methodology.

As shown in eqn (1), the formation of **3aa** was nearly completely inhibited by the addition of the radical scavenger TEMPO. Yet, we were able to detect the trapping product of the free alkyl radical.[13] To further verify the presence of free alkyl radicals, a "radical-clock" experiment was performed with bromide **1y** (eqn (2)); as a result, an 1,5-diene product **3ya** was isolated in 52% yield *via* a radical-induced ring opening process.

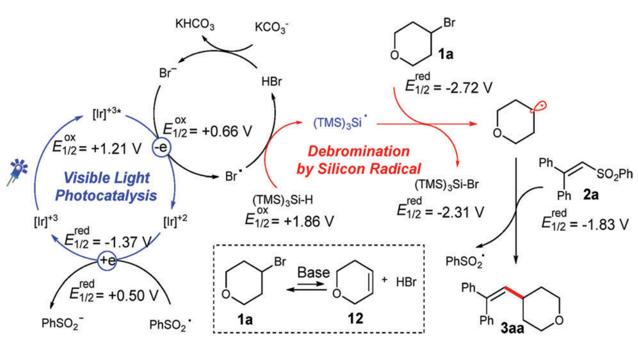


(1)



(2)

Based on these observation and related literature reports,[8b,12] we proposed a possible mechanism for the coupling of unactivated alkyl bromides and vinyl phenyl sulfones (Scheme 3).[18] Upon stirring a mixture of bromide **1a** with a carbonate base for 6 h, small amounts of the unsaturated compound **12** were detected.[18] The generated $Br^-$ can be oxidized by a photoredox catalyst, whereas the formed bromine radical can abstract a hydrogen atom from $(TMS)_3SiH$.[12e] The generated silyl radical will abstract a bromine atom from **1a**, and thereby the created alkyl radical is added to the double bond of **2a**. A consecutive cleavage of the C–S bond will release the desired product and an open shell phenyl sulfonyl radical. Finally, the phenyl sulfonyl radical then undergoes a SET with the reduced photo-catalyst to close the catalytic cycle. It has to be noted that only trace amounts of the product



Scheme 3 Proposed mechanism for the photocatalytic alkenylation of alkyl bromides with vinyl phenyl sulfones.

were formed without the addition of a base. However, product formation was observed when LiBr was added as a bromide source instead of the carbonate base. Moreover, the yield could be further increased a little by supplemental addition of LiBr, demonstrating the necessity for the presence of bromide species for the photocatalytic cycle.[18]

In summary, we developed two photocatalytic alkenylation reactions of unactivated alkyl bromides with vinyl phenyl sulfones or vinyl bromides. The combination of visible light photocatalysis and silicon radical debromination was the key of this success. Moreover, this strategy was proven to be feasible for the alkenylation of bioactive molecules and glycosyl bromides, as well as the alkynylation of unactivated alkyl bromides.

We are grateful to the National Science Foundation of China (No. 21822103, 21820102003, 21772052, 21772053, 21572074 and 21472057), the Foundation for the Author of National Excellent Doctoral Dissertation of PR China (No. 201422), the Natural Science Foundation of Hubei Province (2017AHB047) and the German Science Foundation (DFG, GRK 1626, Chemical Photocatalysis) for support of this research.

## Conflicts of interest

There are no conflicts to declare.

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18 See the ESI† for more details: proposed mechanistic cycle of method B, control experiments, the measurements of the quantum yield and the measurements of the potential of the compounds are shown in Scheme 3.