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Flow photochemical Giese reaction via silane-mediated activation of alkyl bromides

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ABSTRACT

Organic halides play a key role as building blocks in synthesis because of their low cost and wide availability. In recent years, halogen-atom transfer (XAT) has emerged as a reliable approach to exploit these substrates in radical processes. Herein, we report a hydroalkylation of electron-poor olefins using alkyl bromides based on a UVA-induced silane-mediated XAT reaction. Our protocol is operationally simple, displays a broad scope and does not require a photocatalyst. Flow technology was used to reduce the reaction times and scale the process. Notably, a two-step protocol, combining the XAT protocol with a subsequent Horner-Wadsworth-Emmons reaction, has been developed to enable the allylation of C(sp^3)–Br bonds.

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Introduction

The functionalization of olefins is a crucial transformation within the organic chemistry realm. Specifically, the hydroalkylation of carbon–carbon double bonds permits the installment of both a hydrogen atom and an alkyl fragment across the π-system of the unsaturated substrate. In parallel to polar processes [1–3], recent endeavors have been focused on the development of radical alternatives due to the complementarity, and often unique selectivity, with respect to ionic strategies [4]. For example, the venerable Giese reaction is a well-established method to selectively hydroalkylate olefins bearing an electron-withdrawing group (EWG) through the intermediacy of a C(sp^3)-centered radical (Fig. 1a) [5–8]. This process was first developed using toxic tin-based compounds in combination with a harmful initiator and high temperatures to activate the alkyl halide that served as the radical precursor (Fig. 1b).

In the past decade, the advent of photoredox catalysis has expanded the synthetic chemist's toolbox [9] for producing open-shell intermediates under much milder and safer conditions, and has spurred new interest in the radical domain [10–14]. For instance, photocatalytic halogen atom abstraction (XAT) [15] protocols have been extensively used to produce alkyl radicals starting from the corresponding alkyl iodide/bromide/chloride simply using a photocatalyst (PC) and stoichiometric quantities of a silane [16–17], an alkylamine [18–19] or a borane [20] under light illumination (Fig. 1c). These processes rely on the use of light and a photocatalyst to generate, through either single electron transfer (SET) or hydrogen atom abstraction (HAT) [21], silicon-centered, α-amino or boryl radicals. Such radical species are known to be able to abstract the halide atom to ultimately afford the coveted open-shell intermediate.

While working on a protocol that exploited photocatalytic HAT and silicon-centered radical-promoted XAT to afford a cross-electrophile coupling [22], we observed that while the use of the PC was essential to obtain the desired product, non-negligible amounts of silyl bromide were observed when the light-absorbing catalyst was excluded. We reasoned that such a compound could

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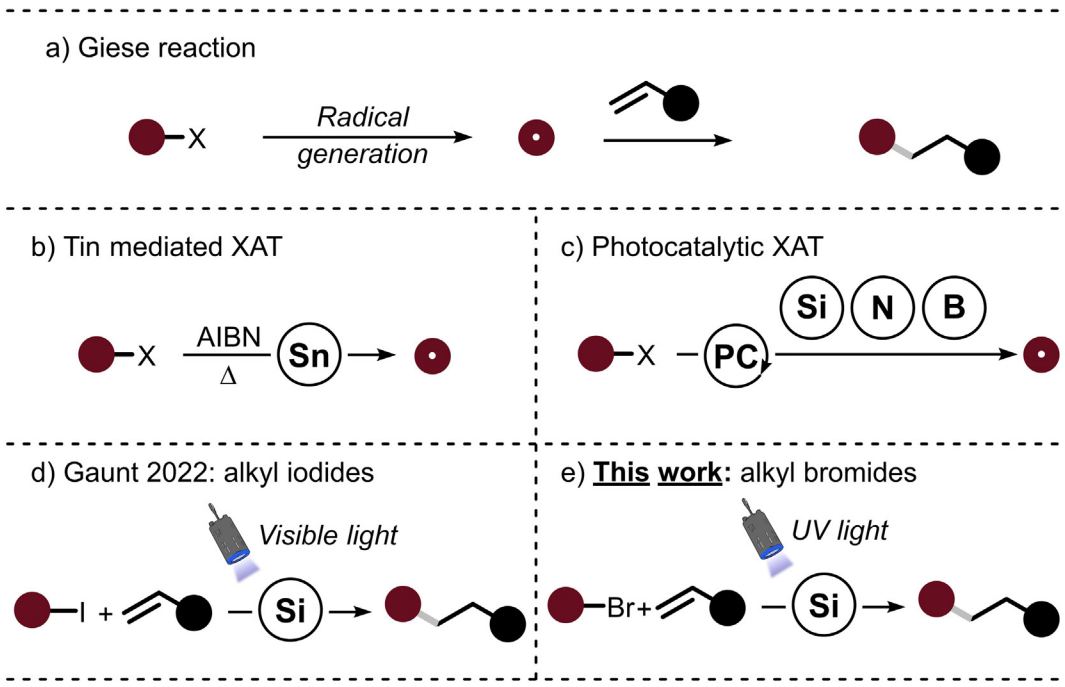


Fig. 1. (a) Giese reaction general scheme. General strategies for radical generation: (b) Tin mediated halogen atom transfer (XAT); (c) activation by single electron transfer (SET) or by hydrogen atom transfer (HAT); (d) photoinduced XAT from alkyl iodides; (e) photoinduced XAT from alkyl bromides. Sn = organotin, PC = photocatalyst, Si = Silanes, N = alkylamines, B = borane.

have been formed by the direct photolysis of one of the reaction components, ultimately affording a silicon-centered radical that is responsible to cleave the alkyl-bromine bond [23].

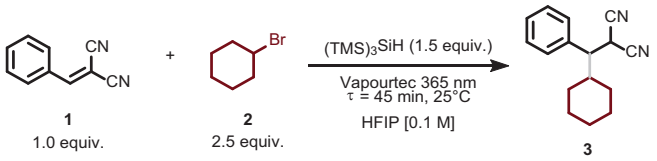
Tantalized by this observation, we wondered whether we could capitalize on this photolysis event as the initiation step for a self-sustaining radical-chain process [24], such as Giese-type additions. We also reasoned that performing this process under microfluidic conditions could lead to shortened reaction times due to an intensified irradiation of the reaction mixture and, in general, a safer and easier-to-scale protocol [25–27]. In parallel to our research endeavors, it should be mentioned that the group of Gaunt independently disclosed a similar strategy that uses commercial tris (trimethylsilyl)silane ($(TMS)_3SiH$) and visible light to effectively combine a range of alkyl iodides with activated alkenes to form the targeted $C(sp^3)$–$C(sp^3)$ bonds (Fig. 1d) [28].

Herein, we report the development of a remarkably straightforward method that enables the coupling of alkyl bromides and electron-poor olefins in a Giese-type process using only non-toxic $(TMS)_3SiH$ and UV-light illumination in flow (Fig. 1e). This method enables the coupling of primary, secondary, and tertiary alkyl bromides with different electron-poor olefins. Moreover, due to the continuous-flow conditions, the synthetic value of this method was further extended through a telescoped approach that resulted in the installment of allyl fragments.

Results and discussion

Our initial investigation focused on the reaction between 2-benzylidenemalonitrile **1**, cyclohexyl bromide **2** in the presence of $(TMS)_3SiH$ under 365 nm irradiation in a Vapourtec UV-150 flow reactor (PFA, ID: 1.3, V: 10 mL). When performing the reaction in acetonitrile (entry 1, Table 1), we observed the formation of the desired product **3**, albeit in very low yield. While, the replacement of acetonitrile with hexafluoroisopropanol (HFIP, entry 2) increased the yield to 21 %, a series of optimization experiments showed that the reaction could be improved to 73 % yield by

Table 1
Reaction condition: 2-benzylidenemalonitrile **1** (0.3 mmol), cyclohexyl bromide **2** (0.75 mmol), tris(trimethylsilyl)silane (0.45 mmol), HFIP (3 mL), Vapourtec Reactor 16 W (λ = 365 nm and reactor volume = 10 mL), 25 °C, 45 min. [a] Yields of **3** are calculated by ^1H NMR using 1,1,2,2 tetrachloroethylene as external standard. [b] Yield of the isolated compound. TTMS: trimethylsilyl; HFIP: hexafluoroisopropanol.



Entry	Deviation from the reaction condition	[a] Conversion % **1**	[a] Yield % **3**
1	CH_3CN	15 %	7
2	–	32 %	21
3	40 °C	78 %	70
4	120 min	100 %	62
5	120 min, 40 °C	100 %	73
6	Dark, 50 °C	16 %	trace
7	405 nm, 40 °C	32 %	27
8	60 min, 40 °C, 1.1 equiv. $(TMS)_3SiH$	86 %	73
9	60 min, 40 °C, 1.1 equiv. $(TMS)_3SiH$, 1.5 alkyl bromide	47 %	47
10	**120 min, 40 °C, 1.1 equiv. $(TMS)_3SiH$**	**100 %**	**[b] 72**

increasing the temperature to 40 °C and extending the residence time to 120 min (entries 3–5). Control experiments revealed that light is essential for the observed reactivity while with a different wavelength the reaction proceeds slowly (entries 6 and 7). Reducing the amount of $(TMS)_3SiH$ did not affect the yield of **3** (entry 8), however reducing the equivalents of alkyl bromide led to lower yields (entry 9). The optimized conditions were found to be a combination of 2.5. equiv. of alkylbromide **2**, 1.1 equiv. of $(TMS)_3SiH$, 120 min of residence time and 40 °C as the reaction temperature (entry 10).

With these conditions in our hands, we investigated the scope of the reaction by using several primary, secondary and tertiary

alkyl bromides (Fig. 2a). First, malononitrile olefin **1** was combined with a diverse set of secondary heterocyclic alkyl bromides, such as *N*-Cbz-azetidine and *N*-Cbz-piperidine bromide derivatives, affording the corresponding products in good yields (**4** and **5**, 51 % and 61 % yield, respectively). This method is also amenable to introduce secondary heterocycles bearing an oxygen atom: 3 bromooxetane could be readily activated and delivered product **6** in good yield when lutidine was used as base (48 %). Moreover, the process is not limited to cyclic derivatives as 2 bromooctane was smoothly converted into the desired product **7** in 68 % yield (d.r. 1:1). Unfortunately, when evaluating the scope of primary alkyl bromides, we obtained very poor results when using HFIP as solvent. However, this could be readily remediated when acetonitrile was used as solvent. In particular, aliphatic primary bromides worked well regardless of the chain length (**8** and **9**, 62 % and 50 % yield). Also, the process is not sensitive to benzylic positions as a bromide bearing a phenyl group proved to be a good coupling partner (**10**, 63 % yield). Similarly to the secondary analogue, oxygen-containing primary alkyl bromides required the addition of lutidine to obtain the corresponding product **11** in good yield. Notably, bromopropyl boronic pinacol ester served as an adequate reaction partner, leading to compound **12** in synthetically useful yields. Next, we focused on the scope of tertiary alkyl bromides. Also in this case, we observed that acetonitrile outcompeted HFIP as reaction solvent, as in the latter case we observed mostly reduction of **1** and only traces of the desired product. Under these conditions, we were able to functionalize various acyclic tertiary derivatives, leading to compounds **13**–**17** in good yields. Moreover, also cyclic tertiary bromides, such as 1-bromo-1 methylcyclohexane and 1-bromoadamantane, were swiftly converted into the corresponding products **15** and **16** (45 % and 54 % yield, respectively). Finally, we selected the reaction between 2-bromo-2 methylpropane and

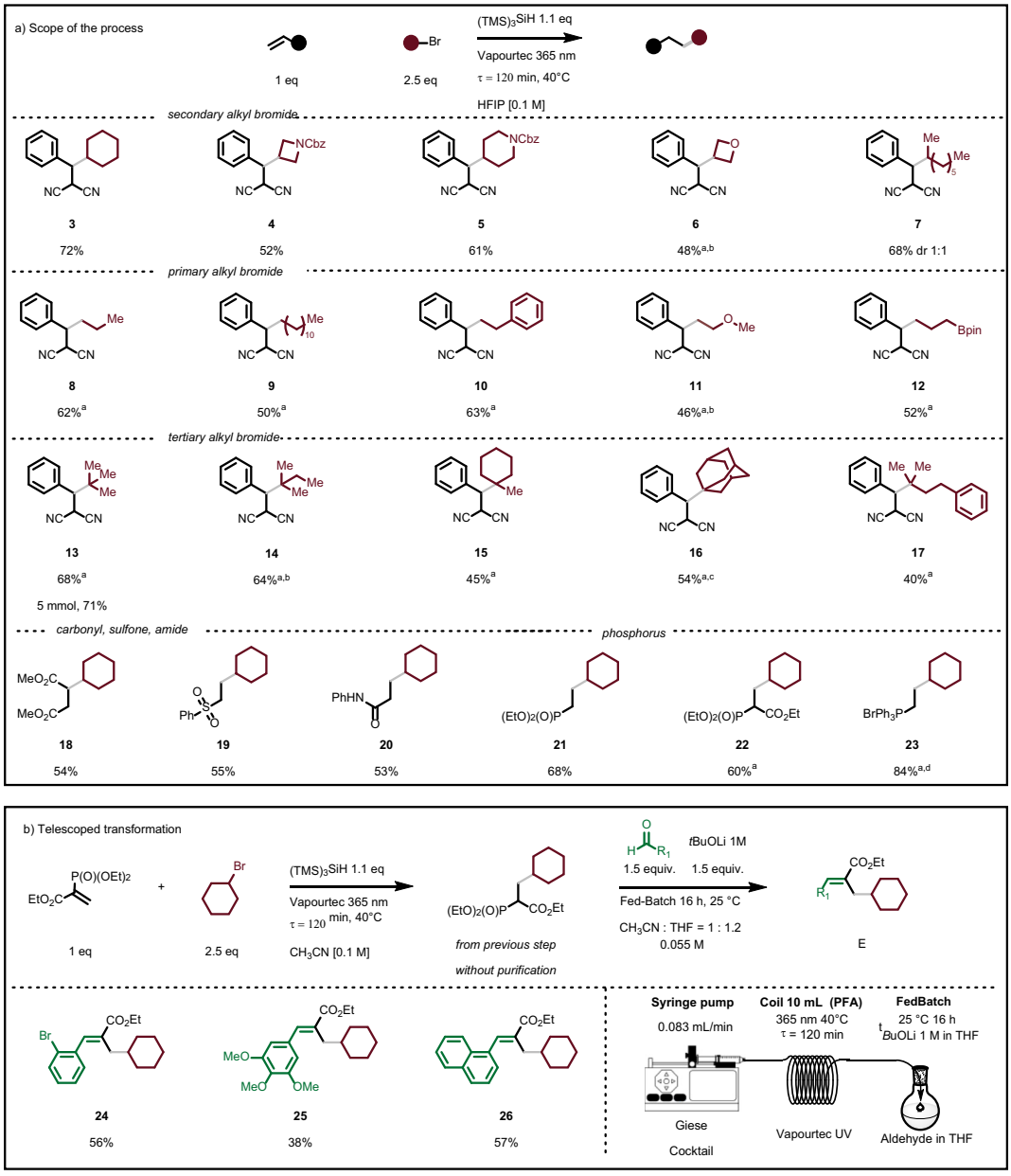


Fig. 2. A) alkyl bromide and olefin scope. reaction condition: olefin (0.5 mmol), alkyl bromide (1.25 mmol), tris(trimethylsilyl)silane (0.55 mmol), solvent (5 mL), Vapourtec Reactor 16 W (λ = 365 nm, reactor volume = 10 mL), 40 °C, 120 min. Yield referred to isolated product. [a] CH_3CN in place of HFIP; [b] 2,6-lutidine (2 equiv.); [c] 180 min;[d] In batch, purified by crystallization. b) Scope of the Giese addition-HWE olefination. Reaction conditions for the first step as for entry **22**. Reaction conditions for the second step: aldehyde (1.5 mmol), *t*BuOLi (1.5 mmol) in THF, 25 °C, 16 h. Yield referred to isolated product over two steps.

1 to perform a scale up. Gratifyingly, by simply extending the total collection time under continuous-flow conditions, we were able to perform a 10-fold scale up (5 mmol scale) and obtain the desired compound **13** in slightly higher yield with respect to the model reaction (0.5 mmol scale), further highlighting the crucial role of flow technology when scaling up photochemical processes (see Supporting Information for further details) [29].

Subsequently, we subjected to our reaction protocol various electron-poor olefins as potential reaction partners. We observed that cyclohexyl bromide **2** could be readily reacted with olefins bearing esters (**18**, 54 % yield), sulphones (**19**, 55 % yield) and amides (**20**, 53 % yield). Furthermore, this protocol also enables the functionalization of triphenylvinylphosphonium bromide, which was recently used in a conjunctive photocatalytic olefination procedure [30], to yield compound **23** in excellent yield (84 %). Moreover, other phosphorus-based reagents, such as phosphonate derivatives, were successfully reacted to furnish the corresponding products in good yields (**21** and **22**, 68 % and 60 % yield respectively).

The generation of compound **22** led us wonder whether we could perform a telescoped process where, after the photochemical Giese-type functionalization, the ensuing phosphonate product could be reacted in a classical Horner–Wadsworth–Emmons (HWE) olefination [31]. Previous work from our group already highlighted how such a strategy could be implemented in the HAT domain, enabling a modular and regioselective allylation of C(sp^3)–H bonds [32]. If successful, this method would expand this type of processes to the allylation of C(sp^3)–Br bonds [33–35]. For this purpose, a telescoped flow/fed-batch approach was developed (Fig. 2b), in which the reaction mixture was pumped into the photochemical reactor and subsequently exited into a round-bottom flask containing a solution of aldehyde and lithium *tert*-butoxide in tetrahydrofuran. Under these conditions, three different aromatic aldehydes were efficiently reacted to yield trisubstituted olefins **24**–**26** with moderate to good overall yields (38–57 %) and perfect selectivity to the *E* isomer, without requiring any intermediate purification.

Finally, we performed some experiments to elucidate the nature of the reaction mechanism (Fig. 3). When the silicon-based reagent was excluded from the model reaction under the optimized conditions, both starting materials were left untouched, highlighting the key role of this reagent in the photochemical protocol. Furthermore, the same model reaction, performed in the presence of $(TMS)_3SiD$ revealed the incorporation of deuterium at the α-position of the cyano group (compound **27**), suggesting that the electrophilic radical, formed after the radical addition over **1,** reacts with the silane to generate the radical chain propagator. Finally, when performing the model reaction in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), no product was observed. Instead, by analysis of the crude by GC–MS, we observed the formation of product **28**, in agreement with the radical capture of the cyclohexyl radical by TEMPO. Taken together, these results suggests that indeed a photochemical and radical pathway is operative [36].

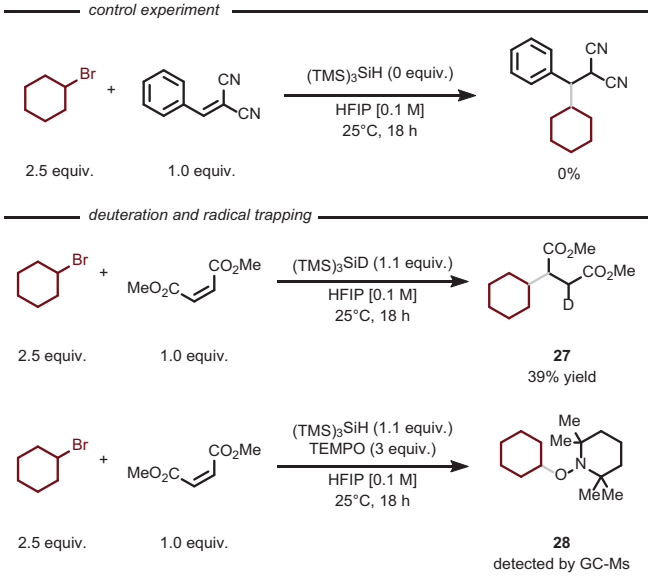


Fig. 3. Evidence of the essential role of $(TMS)_3SiH$ in this transformation; labelling experiment suggesting that HAT happens from the $(TMS)_3SiH$ and radical trap experiment to confirm that formation of radicals is involved.

Conclusion

In conclusion, we reported a direct and operationally simple procedure for the hydroalkylation of electron-poor olefins using alkyl bromides. This halogen atom transfer procedure does not utilize a photocatalyst and requires only the use of $(TMS)_3SiH$ and UV-A light illumination in flow. The process has been smoothly scaled without the need for reoptimization of the reaction conditions. Additionally, the simplicity of this process renders it amenable to be coupled with subsequent transformations in a telescoped fashion, as proved by its coupling with a HWE olefination to enable a net allylation of C(sp^3)–Br bonds.

Data availability

No data was used for the research described in the article.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2023.154380.

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