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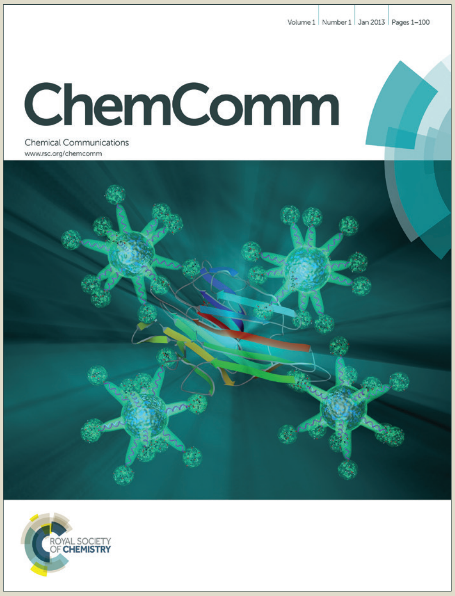

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No Photocatalyst Required – Versatile, Visible Light Mediated Transformations with Polyhalomethanes

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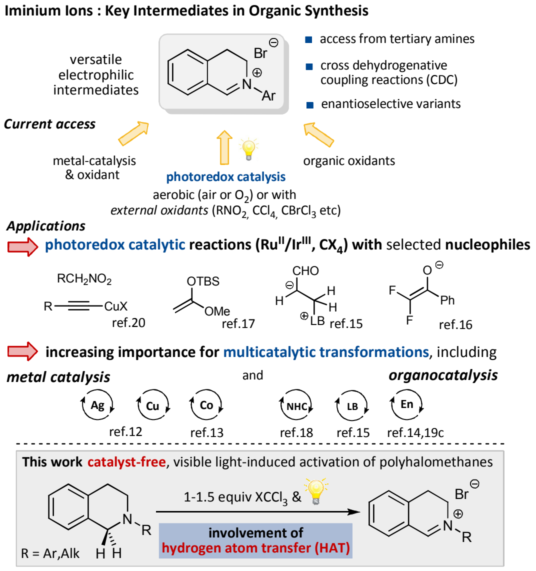
A visible light mediated, but photocatalyst-free method for the oxidative α-CH functionalization of tertiary amines with a broad scope of carbon- and heteroatom nucleophiles using polyhalomethanes has been developed. In addition, the pivotal visible light triggered activation of polyhalomethanes offers mild conditions for efficient Kharasch-type additions onto non-activated olefins. Preliminary mechanistic studies are reported.

Visible light photocatalysis has recently emerged as a versatile strategy for challenging C-H activation reactions of sp^3-hybridized carbon atoms allowing for the direct and selective construction of C-X and C-C bonds without the need of substrate pre-activation.[1] The use of photoredox catalysis for the facile generation of reactive intermediates, such as iminium ions[2] or α-amino radicals[3] from tertiary amines[4] is highly attractive due to the mild conditions and hence its potential compatibility for multicatalytic processes.[5] As an alternative to cross dehydrogenative coupling reactions (CDC),[6] which are generally either metal-catalyzed or mediated by organic oxidants, a multitude of novel methods employing different photocatalysts have been established.[7] Using the CDC activation of tetrahydroisoquinolines (THIQ) as a benchmark reaction typical photocatalysts range from organometallic complexes[8] (mostly Ru^{2+} and Ir^{3+} based) and simple organic dyes[9] to MOFs, graphene oxides as well as organic and inorganic semiconductors.[10] Dual catalysis involving photocatalysis,[11] which allows access to unprecedented transformations by a beneficial combination of the concurrent catalytic generation of both electrophile and nucleophile, has been developed for metal and organocatalytic activation modes. In the context of THIQ iminium derivatives as electrophiles the nucleophilic catalytic intermediates have been formed *via* metal catalysis[12,13] as well as *via* covalent[14,15,16] and non-covalent organocatalysis including highly enantioselective approaches to β-amino acid esters[17] and α-acylated tertiary amines[18] or propargylic amines.[12b]

In the context of our own interest in novel synergistic and cooperative catalytic activation modes combining organocatalysis with photoredox catalysis,[19] we also investigated the photocatalytic approach to iminium ion precursors from tertiary amines, namely THIQs. Apart from the great number of metal and organocatalyzed oxidative processes, two major groups of photocatalytic methods have been described: aerobic techniques in the presence of air or O_2 and procedures which rely on the addition of external oxidants, such as alkyl halogenides (bromomalonate, $BrCCl_3$ etc.)[20] or nitro compounds[2,18] to regenerate the photocatalyst. With respect to the above mentioned required compatibility to potentially unstable nucleophilic catalytic intermediates we decided to focus on methods with external oxidants to avoid detrimental interactions of reactive oxygen intermediates such as superoxide radical anions or peroxides.[21]

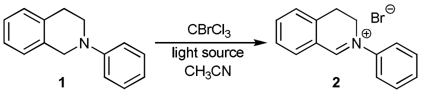


Scheme 1 Iminium ions: access strategies and applications.

Based on the well-documented weak C–Hal bonds in polyhalomethanes (low bond dissociation energies (BDEs), e. g. Br–CCl_3: 55.3 kcal/mol),[22] being in the energy range accessible by visible light together with the established ability of CCl_3• radicals to serve as acceptors in hydrogen atom transfer reactions (HAT), we questioned whether these prerequisites would allow a direct, *photocatalyst-free*, visible light mediated access to iminium intermediates from tertiary amines.[23] With respect to BDEs the trichloromethyl radical (H–CCl_3 BDE ≈ 95 kcal/mol) should readily abstract a hydrogen atom from amine substrates (α-C–H BDE ≈ 84-90 kcal/mol)[22] to generate α-amino radicals and subsequently the crucial iminium ions upon either an electron or atom transfer pathway. We hoped to provide an alternative to the oxidation-potential-gated methods and hence to introduce a highly practical general pathway to a C-H functionalization using visible light as sole driving force for substrate partners with weak C–H bonds. Moreover, we anticipated that such a strategy would be ideally suited for multicatalytic transformations and the implementation of substrates that might form detrimental by-products *via* undesired photocatalytic processes.[24] Herein we describe the successful realization of this proposal and present preliminary studies providing insights to the mechanism.

As outlined in Table 1 we started our search for the best conditions with the direct transformation of *N*-phenyl THIQ **1** to its corresponding iminium salt **2**. An initial evaluation of the reagent $CBrCl_3$ revealed that stochiometric amounts seemed to be sufficient, however a small excess (Table 1, entry 4) ensured a cleaner reaction within a shorter time frame. Similar results could be obtained by irradiation with a household compact fluorescent light bulb or sunlight (entries 5, 6). For the successful transformation to the iminium salt the presence of light proved to be essential; lower energy light sources, such as green light were not sufficient (entries 7,8). The thermal reaction[25] in acetonitrile at 70 °C or 100 °C using toluene as solvent (decomposition) was not competitive.[26] Employment of less activated CCl_4 ($Cl–CCl_3$ BDE = 70.9 kcal/mol;[22] $\lambda_{corr} \approx 404$ nm) still allows completion of the reaction using our standard conditions, however with a strongly increased reaction time.[26]

Table 1 Transformation of THIQ **1** to its iminium salt – initial studies and reaction optimization.[a]



Entry	Equiv of $CBrCl_3$	Light Source	Temperature	Reaction Time[b]	Yield (%)[c]
1	3.0	blue LEDs	rt	30	91
2	1.0	blue LEDs	rt	30	97
3	1.0	blue LEDs	rt	60	99
4	1.5	blue LEDs	rt	30	quant.
5	1.5	22 W CWF bulb	rt	30	quant.
6	1.5	sunlight	rt	30	91
7	1.5	**No** light	70 °C	30	23
8	1.5	green LEDs	rt	30	14
9[d]	1.5	blue LEDs	rt	30	95

[a] 0.25 mmol of THIQ in 0.5 mL acetonitrile, x mmol of $CBrCl_3$ as noted. [b] in min. [c] Determined by ^1H NMR spectroscopy using bromoform (1 equiv) as internal standard. [d] Large scale experiment using 2.5 mmol of THIQ.

An additional comprehensive survey on solvent effects[26] demonstrated the robustness of this transformation. The reaction could be successfully conducted in organic solvents ranging from less polar ethers, halogenated solvents and alkanes to more polar alcohols, but also in water. Having established our best conditions we examined the scope of different THIQs in this transformation: both electron-poor and electron-rich substrates allowed for an efficient generation of their corresponding iminium ions (figure 1).[27] Notably, our protocol also allows transformations of *N*-alkyl THIQs to their corresponding iminium salts **6** and **7**, which have only scarcely been applied[28] in visible light photoredox catalyses due to their higher oxidation potential.[29] Employment of *N*-acyl THIQ substrates with further increased oxidation potential[29c] leads to highly reactive *N*-acyliminium salts[30] which cannot be isolated. However, C-H activation of these substrates (for a further example, see transformation of dimethylformamide (DMF) in figure 3) was proven by isolation of their corresponding by-products, such as a cyclized derivative stemming from the corresponding Boc-protected THIQ.[26]

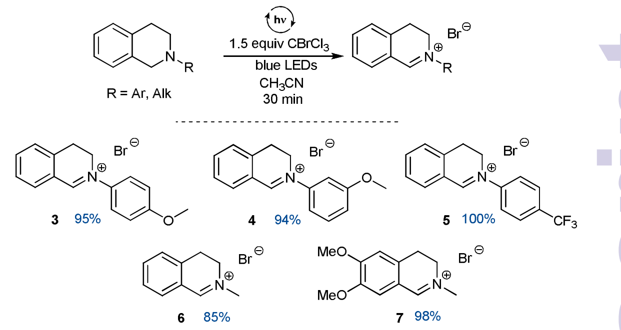


Fig. 1 Visible light assisted generation of iminium ions from *N*-aryl and *N*-alkyl THIQs (yields determined by NMR using CH_2Br_2 or $CHBr_3$ as internal standard).

Next we checked the applicability of our conditions for subsequent C–C and C–X cross coupling reactions. We examined literature known nucleophiles which were directly added to the reaction mixture after irradiation with blue light.[9a,12,15,20] Both phosphorous and carbon nucleophiles reacted smoothly with the pregenerated iminium salt in a sequential one-pot fashion and without further manipulation of the reaction conditions required (figure 2A). Apart from C-H-acidic nitromethane (aza-Henry reaction) and malonate providing excellent yields, electron-rich indole proved to be a competent substrate for the corresponding arylation reaction. Next we focused on expanding the method to multicatalytic processes. As outlined in figure 2B our method is applicable to both metal and organocatalytic *in situ* generation of nucleophiles. Cu-catalyzed alkynylation[12,20] proceeds in excellent yield and Lewis-base catalyzed Morita-Baylis-Hillman[15] reaction affords the acroleinated THIQ **12** in good yield. All reactions are easily handled and provide similar yields to the related transformations using an additional photocatalyst.

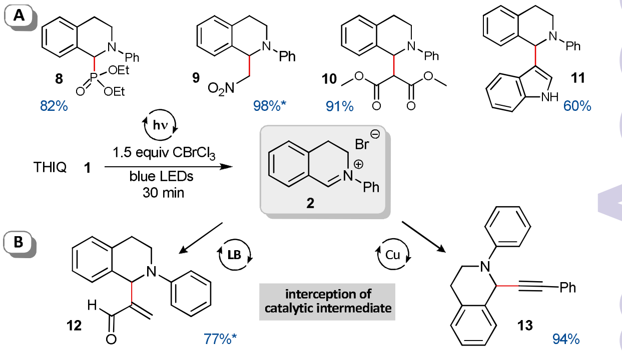


Fig. 2 Cross coupling reactions of iminium bromide salts with carbon and heteroatom nucleophiles (yields determined by NMR using CH_2Br_2 as internal standard, isolated yields*).

In addition, we could extend the scope of C-nucleophiles to trifluoroborate salts which are also competent reaction partners. This is perhaps most remarkable as photo*catalytic* pathways either using aerobic conditions (e. g. with Ru or xanthene dyes as photocatalysts where occuring oxygen species[21] may contribute to the decomposition of trifluoroborate **14**)[31] or with external oxidants were not equally successful for providing the corresponding vinylation product in a sequential one-pot fashion (best yield: 58%). This is most probably connected with a detrimental interaction of the substrate with remaining catalyst-derived species. Interestingly, as noticed in a control reaction to prove potential side reactions, DMF can also undergo styrenylation under similar conditions, albeit in low yield only (not optimized[26]).

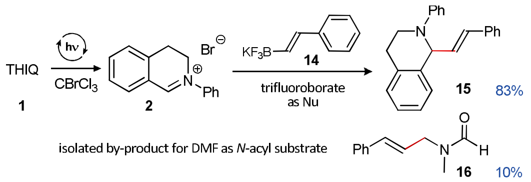


Fig. 3 Cross coupling with potassium styryl trifluoroborate (yields determined by NMR using CH_2Br_2 as internal standard).

At this stage we undertook an *in situ* IR tracing of the standard THIQ reaction to gain further mechanistic insights (figure 4). This experiment clearly reveals the fast and clean transformation of the THIQ starting material **1** to its corresponding iminium salt **2** in approx. 8 min according to the indicative vibrational bands at 1604 cm^{-1} (THIQ **1**) and 1640 cm^{-1} for developing iminium salt **2**.

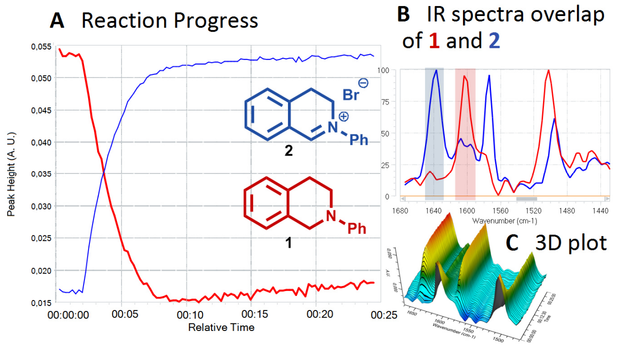


Fig.4 *In situ* IR-reaction monitoring of visible light-assisted generation of THIQ iminium ion **2** from THIQ **1** with $CBrCl_3$.

Further control experiments with short periods of irradiation and subsequent dark periods resulted in interruption of the reaction progress in the absence of light and recovery of the former reactivity upon further illumination, hence demonstrating the light dependence of the reactions. This suggests that, if a radical chain mechanism is operative, the corresponding chain might only be very short as only during irradiation periods significant reaction progress is observed.[26] To additionally exclude a possible involvement of UV light we irradiated the sample through a UV filter (75% w/v $NaNO_2$ solution, cut-off: λ = 400 nm).[26] No differences in yield and performance for the formation of the iminium bromide **2** were observed. Based on the observation of a short-lived, intense blue coloration of the THIQ solution containing $CBrCl_3$ upon irradiation,[26] the participation of a redox pathway *via* the known formation of amine polyhalomethane electron donor acceptor (EDA) complexes[32] might be operative. However, due to the aforementioned low BDE of C–Br bonds and the observed positive results in transforming of substrates with higher oxidation potentials, we questioned whether this reaction is solely promoted by the formation of an EDA complex. Based on both cyclovoltammetric measurements and a series of KI/starch tests[26] we can exclude a direct oxidation or the presence of an oxidant before irradiation; in addition, blue light irradition of $CBrCl_3$ alone showed a positive KI/starch test. Hence, we additionally suggest an initial homolytic bond fission to yield a bromine and a trichloromethyl radical (see scheme 2A) as a second, alternative pathway. To validate our preliminary mechanistic picture, we performed a Kharasch reaction (figure 5), i. e. the ATRA reaction of a polyhalomethane t non-activated alkenes.[33,34] Typical ATRA initiations such as radical starters, Lewis acids or by high temperature or UV ligh have recently been supplemented by a number of photoredox catalytic transformations (using Ru, Ir and Cu based catalysts).[35,36] Using a similar set-up as optimized for the THIQ transformations we could access the addition product **18** of the ω-hydroxy alkene **17** in excellent yield and selectivit comparable to catalyst mediated processes, however under remarkably mild conditions.

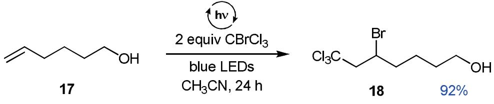
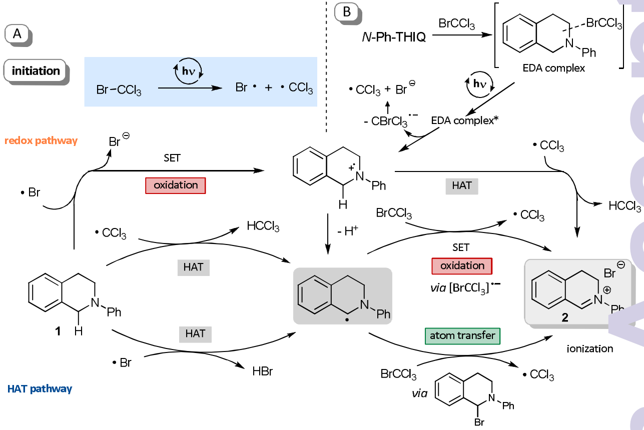


Fig. 5 Kharasch addition of $CBrCl_3$ with visible light.

Scheme 2 summarizes our preliminary mechanistic picture Besides an involvement of EDA complexes in terms of amin substrates (scheme 2B), whose excitation facilitates charge transfer to generate both the amino radical cation and an insta $CBrCl_3$ radical anion, a number of different mechanistic pathw are conceivable upon light-mediated fission of $CBrCl_3$, namely both a redox pathway where the bromine radical generates the common amino radical cation, while the other routes builds or hydrogen atom transfers as crucial steps. The fact that we could also observe the formation of chloroform,[26] also points to the important involvement of CCl_3• radicals in HAT steps as hydrogen acceptor.



Scheme 2 Mechanistic considerations.

With respect to the BDEs the trichloromethyl radical (H–CCl BDE ≈ 95 kcal/mol) should readily abstract a hydrogen atom from amine substrates (α-C–H BDE ≈ 84-90 kcal/mol),[22] but similaril a bromine radical (H–Br BDE ≈ 88 kcal/mol) could still be able t trigger the formation of the central α-amino radical which migh undergo numerous pathways towards the iminium ion **2**.

In conclusion, we have demonstrated the applicability o visible (blue) light for the activation of polyhalomethanes in a broad range of different reactions. CDC coupling of THIQs as well as Kharasch-type addition reactions to olefins we achieved in good to excellent yields. As the light-assisted α-C–H activation of amines does not only rely on redox properties, but rather on suitably low BDEs of th corresponding C–H bonds, we expect this mild, metal-free and operational simple method to not only provide a valuable alternative to established catalyst-promoted procedures especially in the context of dual or multicatalytic reactions.

but also to be broader applicable for currently unattainable transformations. More detailed mechanistic studies are currently in progress.

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