VIP Photochemistry Very Important Paper

DOI: 10.1002/anie.201406450

Photo-Organocatalysis of Atom-Transfer Radical Additions to Alkenes**

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In memory of Carlos F. Barbas III

***Abstract:** We have found that an organic molecule as simple as p-anisaldehyde efficiently catalyzes the intermolecular atom-transfer radical addition (ATRA) of a variety of haloalkanes onto olefins, one of the fundamental carbon–carbon bond-forming transformations in organic chemistry. The reaction requires exceptionally mild reaction conditions to proceed, as it occurs at ambient temperature and under illumination by a readily available fluorescent light bulb. Initial investigations support a mechanism whereby the aldehydic catalyst photochemically generates the reactive radical species by sensitization of the organic halides by an energy-transfer pathway.*

Atom-transfer radical addition (ATRA)[1] to alkenes provides a clear demonstration of the utility of radical reactivity in organic synthesis. The chemistry, pioneered by Kharasch almost 70 years ago,[2] has evolved to become an atom-economical and effective way to functionalize easily available olefinic substrates, mainly thanks to the contributions from the groups of Curran,[1b,3] Oshima,[4] and Renaud.[5] The addition of an organic halide across a carbon–carbon double bond generates a new C–C and C–X bond (X = halogen) in a single operation. This reactivity is also at the heart of atom-transfer radical polymerization (ATRP) processes.[1a,c] ATRA proceeds through a radical chain propagation mechanism (Figure 1 a), and the formation of the radicals from alkyl halides classically requires stoichiometric amounts of initiators, such as organotin reagents,[3] triethyl borane,[4] or potentially explosive oxidants,[2] and high reaction temperatures. Recently, metal-mediated catalysis,[6] including metal-based photoredox catalysis driven by visible light,[7] has further expanded the potential of the ATRA technology. However, we still need a suitable approach for generating radical intermediates under mild reaction conditions which avoids expensive transition-metal catalysts or toxic reagents.

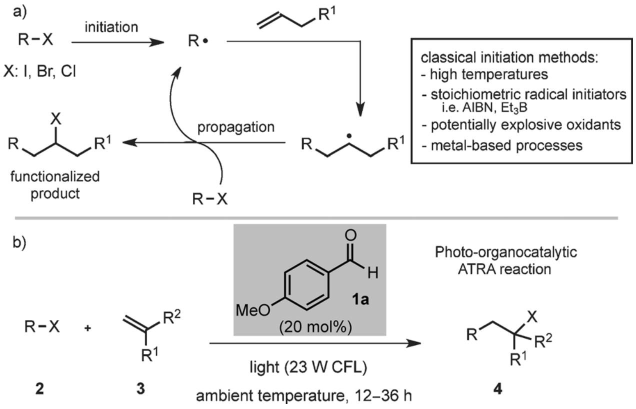

Figure 1. The atom-transfer radical addition (ATRA) technology. a) The classical radical chain mechanism of ATRA and the typical harsh reaction conditions required for radical generation. b) The discovered photochemical ATRA catalyzed by a simple organic molecule under exceptionally mild reaction conditions. AIBN = azobisisobutyronitrile.

Herein, we describe a strategy that addresses this gap in synthetic methodology. Motivated by our interest in devising metal-free photochemical processes,[8] we have found that an organic molecule as simple as *p*-anisaldehyde (**1a**) can efficiently catalyze the intermolecular ATRA of a variety of haloalkanes (**2**) onto olefins (**3**; Figure 1 b). The chemistry requires irradiation from a household 23 W compact fluorescent light (CFL) bulb to proceed, and ambient temperature is sufficient for achieving functionalized olefins (**4**) with synthetically useful results. Initial investigations support a mechanism whereby the aldehydic catalyst generates the reactive radical species by energy transfer[9] to the haloalkane substrates. Although the utility of UV-absorbing organic chromophores as triplet photosensitizers has been well-established for decades,[10] applications of triplet sensitization induced by readily available CFL light sources have found limited use in synthetic chemistry so far.[11]

Our initial explorations toward an ATRA protocol under mild reaction conditions focused on the reaction of diethyl 2-bromo-2-methylmalonate (**2a**) and 5-hexenol (**3a**; Table 1). All the experiments were conducted at ambient temperature in CH_3CN under 23 W CFL irradiation. We initially confirmed that the presence of *p*-anisaldehyde (**1a**; 20 mol %) was essential for reactivity (entries 1 and 2). In the absence of 2,6-lutidine, the reaction did not proceed at all (entry 3; the need for the base is rationalized in the mechanistic discussion). Other bases, including 2,4,6-collidine and *N*,*N*-dieth-

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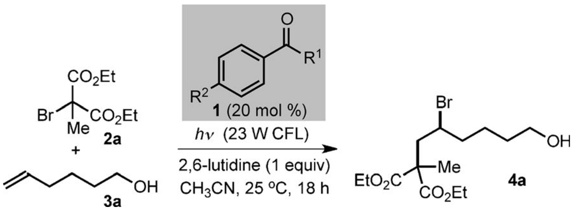
[**] This work was supported by the Institute of Chemical Research of Catalonia (ICIQ) Foundation and by the European Research Council (ERC) under the European Community's Seventh Framework Program (FP7 2007-2013)/ERC Grant agreement 278541 (ORGA-NAUT). E.M. is grateful to the Alma Mater Studiorum—Università di Bologna (Italy) for a Marco Polo fellowship.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201406450.

Table 1: Optimization studies.[a]



Entry	Catalyst	Light	Yield [%][b]
1	**1a** (R^1 = H, R^2 = OMe)	ON	95
2	none	ON	0
3	**1a** (no base)	ON	< 5
4	**1b** (R^1 = Ph, R^2 = H), 3 equiv	ON	42
5	**1c** (R^1 = H, R^2 = H)	ON	77
6	**1d** (R^1 = H, R^2 = Br)	ON	74
7	**1a** (R^1 = H, R^2 = OMe)	OFF	0
8	**1a** (R^1 = H, R^2 = OMe)	ON (in air)	0

[a] Unless otherwise noted, the reaction conditions were as follows: 2-bromo-2-methylmalonate **2a** (0.1 mmol), olefin **3a** (2 equiv), catalyst **1** (20 mol %), 25 °C, 18 h. [b] Determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

ylaniline, could be used as well. An aromatic ketone (benzophenone; **1b**) could promote the process only when used in super-stoichiometric amounts (entry 4), while the benzaldehyde derivatives **1c,d** were effective catalysts (entries 5 and 6). On the basis of its high activity and low cost, **1a** was selected for further optimizations.

The careful exclusion of light completely suppressed the ATRA process (Table 1, entry 7). To further verify the photochemical nature of the transformation, a possible thermal activation was tested by performing the reaction in the dark in DMF at 100 °C, and in toluene at reflux. Under these reaction conditions, the ATRA product **4a** could not be detected. The inhibition of the reactivity observed in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO; 2 equiv) and 2,6-di-*tert*-butyl-4-methylphenol or under an aerobic atmosphere (entry 8) was indicative of a radical mechanism.

The synthetic potential of the photochemical ATRA methodology catalyzed by 20 mol % of **1a** was then evaluated. As shown in Figure 2a, differently substituted organic halides (**2**) underwent the desired reaction with **3a** to provide

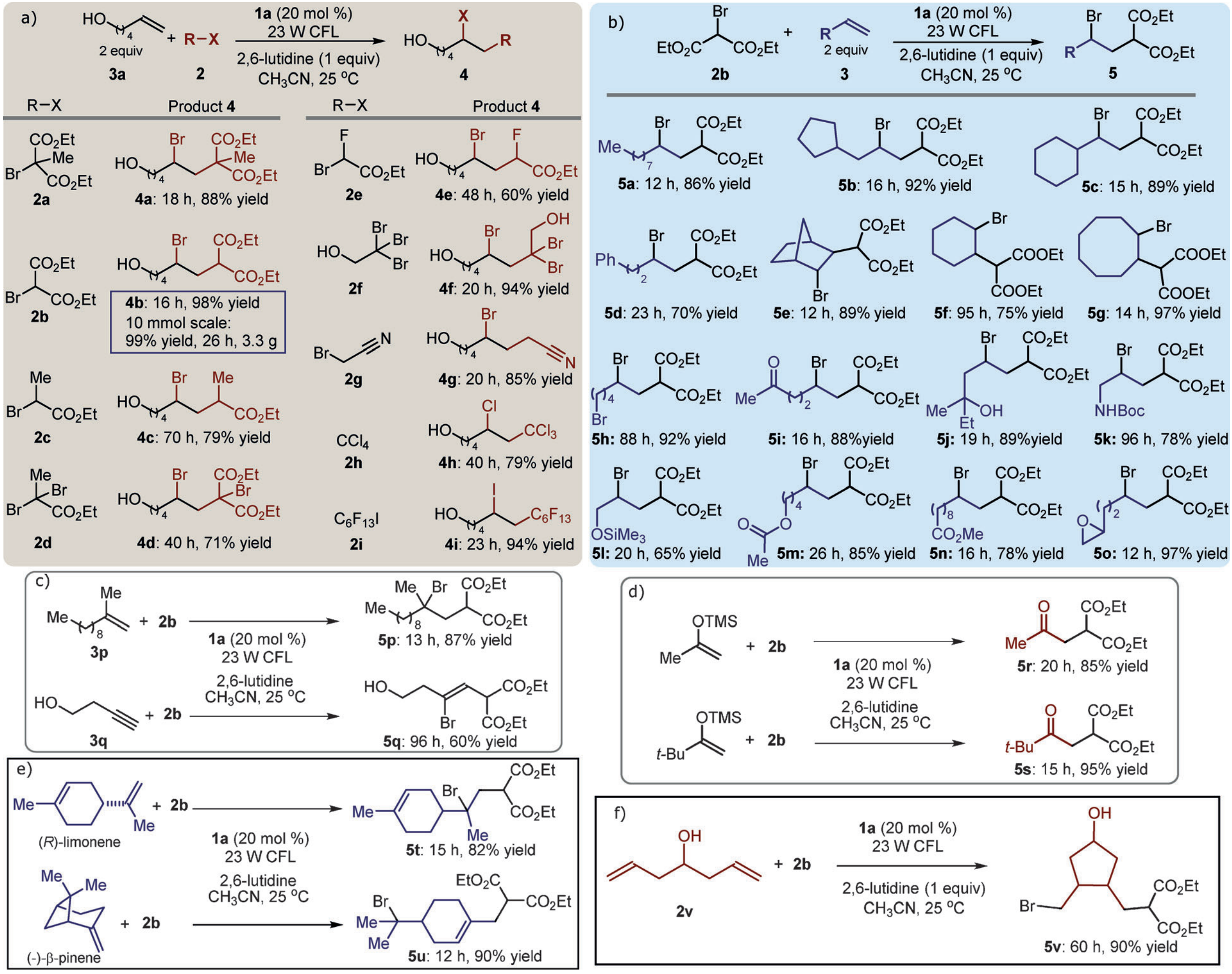


Figure 2. Evaluating the scope of the photochemical organocatalytic ATRA of olefins. Survey of the alkyl halides (a) and the olefins (b) which can participate in the process. c) Reaction of a disubstituted terminal olefin and of a terminal alkyne. Transformation of electron-rich olefins (d) and naturally occurring compounds (e). f) The 5-*exo*-trig radical cyclization. Products **4c**, **4e**, **5e–g**, **5j**, **5o**, and **5v** were formed with poor relative stereocontrol (diastereomeric ratios ranging from 1:1 to 2:1). TMS = trimethylsilyl.

the corresponding adducts **4** in excellent yields. The reaction of bromo malonate (**2b**) was successfully implemented on a gram scale, and the product **4b** was isolated in 99% yield (3.3 g) while the catalyst **1a** was not consumed and almost fully recovered (>90%). α-Bromo ester derivatives were smoothly converted into the corresponding products **4c**–**e**. The method allowed direct introduction of functional groups other than an ester, as the alcohol **4f** was isolated in excellent yield and the nitrile **4g** was prepared from bromoacetonitrile. In addition, the use of carbon tetrachloride and perfluorohexyl iodide granted access to the synthetically valuable polyhalogenated products **4h** and **4i**, respectively.

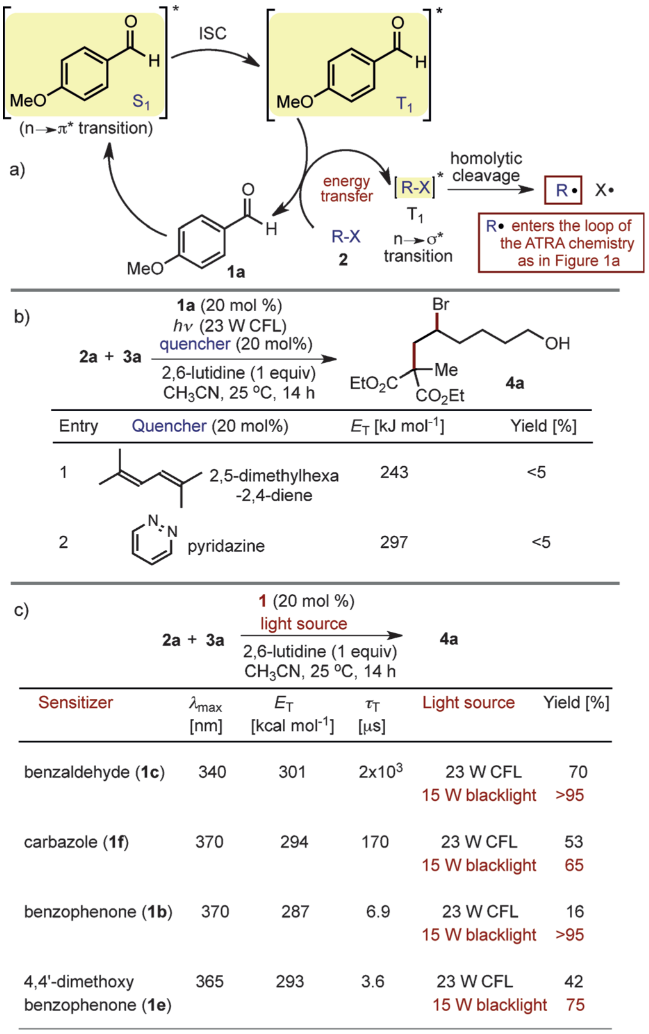
We next examined the reactivity of different olefins with **2b** (Figure 2b). Both terminal olefins and the inherently less reactive internal cyclic alkenes, including 2-norbornene, cyclohexene, and cyclooctene, were competent substrates, thus enabling the construction of complex frameworks **5a**–**g** from simple precursors. As a testament to the very mild nature of the protocol, terminal olefins adorned with a wide array of sensitive functionalities were efficiently transformed into the corresponding products **5h**–**o**. The ATRA process was also possible with a terminal disubstituted olefin and an alkyne (Figure 2c). Electron-rich silyl enol ethers allowed the preparation of functionalized carbonyl compounds (Figure 2d). In addition, the naturally occurring compounds (*R*)-limonene and (−)-β-pinene readily participated in the ATRA process to give **5t** and **5u**, respectively (Figure 2e). The opening of the cyclobutane ring leading to **5u** further highlighted the radical nature of the process. Similarly, the diene **2v** gave the product **5v** as a result of a 5-*exo*-trig radical cyclization (Figure 2f). The selectivity for all the ATRA reactions was excellent, since dimers or dehalogenated products were not detected. Control experiments, performed for all the reactions presented here, confirmed that the absence of the aldehyde **1a** or of light completely suppressed the process.

We then sought to elucidate the mode of catalysis of **1a**. We determined the light frequency required for an efficient ATRA process between **2a** and **3a** catalyzed by **1a** (the model reaction depicted in Table 1). The use of a 300 W Xenon lamp equipped with a cut-off filter at $\lambda = 385$ nm resulted in no reaction. Complete reactivity was restored when using a band-pass filter at $\lambda = 360$ nm. These experiments indicated that the near UV part of the CFL emission spectrum[12] was required to bring the catalyst **1a** to an excited state through the established symmetry forbidden $n \rightarrow \pi^*$ transition manifold ($\lambda_{max} = 344$ nm for **1a**).[13] In contrast, the organic halides **2**, the olefins **3**, and 2,6-lutidine do not absorb within this frequency region. We then performed investigations to correlate the photochemical activity of the catalyst **1a** with the substrates. We did not detect any ground-state association between the reaction components by spectroscopic and absorption measurements. The possibility for the olefins **3** to undergo a photochemical pathway when mixed with **1a** under irradiation was excluded, since Paternò–Büchi cycloadducts[13] were not detected. In contrast, illuminating a mixture of **1a** and halide **2a** provided trace amounts of the corresponding dehalogenated malonate derivative along with acidification of the medium, likely arising from HBr formation. We confirmed that trace amounts of acid were also generated during the ATRA reaction, which greatly affected the reactivity,[14] thus explaining the need for a base such as 2,6-lutidine[15] (entry 3 in Table 1). Detection of such photolysis products[16] suggests that **1a** can be capable of sensitizing the alkyl halides **2** to the excited triplet state upon illumination, thus inducing an $n \rightarrow \sigma^*$ transition which would result in a rapid homolytic dissociation of the C−X bond in **2**.[17] The photochemistry of **1a** is dominated by reactions of the lowest electronically excited triplet state,[13] which possesses a relatively long lifetime[18] along with a triplet energy (E_T) of 300 kJ mol^{-1}. This energetic value is in the range of the carbon–halogen bond dissociation energies of the alkyl halides used in this ATRA methodology (260–300 kJ mol^{-1}, see Table S1 in the Supporting Information), which is congruent with a homolytic cleavage of **2** induced by an energy-transfer mechanism. It is of note that the alkyl halides, by means of the external heavy atom effect,[19] can facilitate the intersystem crossing which drives the singlet–triplet state conversion of the excited **1a**.

Consistent with the triplet sensitization mechanism depicted in Figure 3a, the model photo-organocatalytic ATRA reaction was completely inhibited by the presence of oxygen, an efficient triplet state quencher. The process was largely insensitive to solvent polarity (e.g. DMSO, DMF, CH_2Cl_2, benzene, and *n*-hexane offered 83, 95, 85, 95, and 86% yield, respectively, of **4a** after 18 h). This observation further supports an energy-transfer pathway, since charged radical ion intermediates, possibly generated through electron-transfer manifolds, would be strongly destabilized in nonpolar media. In addition, the rate of the reaction was greatly increased when conducted in solvents with a high viscosity, such as cyclohexanol and benzyl alcohol (viscosity at 25 °C = 5.47 and 57.5 cP, respectively). We found that, in glycerol (934 cP), the model reaction reached completion (95% yield of **4a**) after 7 hours when using only 5 mol% of **1a**. This reactivity profile is consonant with the notion that the rate of exergonic triplet-energy transfers generally increases to the limit of diffusion control when conducted in viscous media.[20]

We also performed the model reaction in the presence of a triplet quencher (2,5-dimethylhexa-2,4-diene; entry 1 in Figure 3b) and an additive with a lower triplet-state energy than **1a** (entry 2), which effectively quenched the catalyst, thus ultimately lowering the reaction rate. Finally, we reasoned that, on the basis of the proposed mechanism, other organo-sensitizers could be as efficient as **1a** if provided with adequate excitation and triplet-state energies. When performing the ATRA reaction under 23 W CFL irradiation, the use of benzophenone (**1b**), 4,4′-dimethoxy benzophenone (**1e**), and carbazole (**1f**) inferred only a moderate reactivity (Figure 3c). However, much higher conversions were obtained using a 15 W black light CFL bulb ($\lambda_{max} = 360$), which showed a broader band in the near-UV region (for the emission spectra of the bulbs used in these experiments, see Figures S1 and S2 in the Supporting Information).

In summary, we have shown that the photochemical activity of a simple organic molecule[22] enables the intermolecular atom-transfer radical addition of haloalkanes onto



Entry	Quencher (20 mol%)	E_T [kJ mol^{-1}]	Yield [%]
1	2,5-dimethylhexa-2,4-diene	243	<5
2	pyridazine	297	<5

Sensitizer	λ_{max} [nm]	E_T [kcal mol^{-1}]	τ_T [μs]	Light source	Yield [%]
benzaldehyde (**1c**)	340	301	2x10^3	23 W CFL 15 W blacklight	70 >95
carbazole (**1f**)	370	294	170	23 W CFL 15 W blacklight	53 65
benzophenone (**1b**)	370	287	6.9	23 W CFL 15 W blacklight	16 >95
4,4'-dimethoxy benzophenone (**1e**)	365	293	3.6	23 W CFL 15 W blacklight	42 75

Figure 3. a) The proposed triplet sensitization mechanism which drives the photo-organocatalytic ATRA reaction. The generated radical enters the ATRA chain mechanism as depicted in Figure 1 a. b) Quenching experiments supporting the energy-transfer mechanism. c) Expanding the range of organo-sensitizers which can promote the ATRA reaction by choosing the appropriate light source. Triplet state energies (E_T) and triplet state lifetime (τ_T) taken from Ref. [21]. ISC = intersystem crossing.

olefins at ambient temperature and under illumination by a household light bulb. These findings are expected to open new avenues for reaction design in the field of radical processes. As an example, we are actively pursuing an enantioselective photo-organocatalytic version of the ATRA process.

Received: June 21, 2014
Revised: August 25, 2014

Keywords: energy transfer · organocatalysis · photochemistry · radicals · synthetic methods

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