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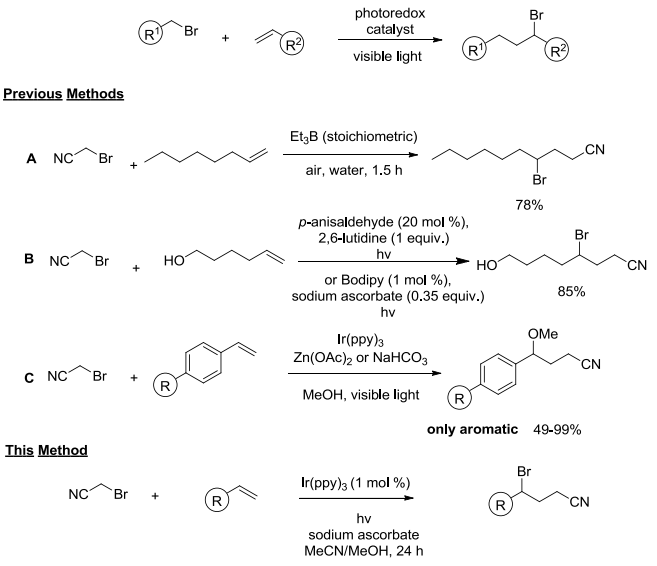
Expanding the Scope of Photocatalysis: Atom Transfer Radical Addition of Bromoacetonitrile to Aliphatic Olefins

Errika Voutyritsa,[a] Ierasia Triandafillidi,[a] and Christoforos G. Kokotos*[a]

Abstract: An efficient photocatalyzed bromocyanomethylation of alkenes is reported. Among a range of organocatalysts and metal complexes, $Ir(ppy)_3$ proved to be the best photocatalyst in promoting the addition of $BrCH_2CN$ to olefins. This photocatalytic atom transfer protocol can be expanded into a wide substrate scope of aliphatic olefins bearing various functional groups, leading to the corresponding products in good to excellent yields. In addition, linchpin catalysis was developed, since the bromo-group can undergo further transformation into useful functional groups, like the synthesis of amino acids.

Introduction

Radical generation from alkyl halides via homolytic cleavage of the C-X bond leads to the incorporation of alkyl moieties in carbon chains, providing useful intermediates, in Organic Synthesis.[1] Photocatalysis allows the generation of these radicals under mild conditions, following various mechanisms, including hydrogen abstraction from alkanes or halide abstraction from alkyl halides. These alkyl radicals are versatile as reactive intermediates, in particular for C-C bond formation events making this method appealing. Atom transfer radical addition (ATRA) or atom transfer radical cyclization (ATRC) of haloalkanes and halocarbonyls to unsaturated compounds, forming C−C and C−X bonds, is reported with a range of metal catalysts, such as ruthenium,[2] iron,[3] nickel,[4] palladium,[5] iridium[6] and copper.[7] Photoredox catalysis has provided a revolution in the field, since MacMillan,[8] Yoon[9] and Stephenson[10] have proved the ability of Photoredox catalysts to introduce novel organic transformations.[11] Around the same time, Bach,[12] Nicewicz[13] and Melchiorre[14] through their seminal work have developed photochemical reactions as useful tools in Organic Chemistry. Bromonitriles are potentially useful scaffolds for the synthesis of biologically active compounds and have demonstrated important synthetic utilities.[15,16] The last few years, photochemical atom transfer radical addition (ATRA) of bromoacetonitrile to olefins starts to play a dominant role among the methods reported for their synthesis. Although there are various examples of the addition of haloalkanes to olefins (Scheme 1, top), knowledge on the addition of bromoacetonitrile to olefins is rather limited (Scheme 1, **A-C**). More specifically, in 2001, Oshima and coworkers treated bromo-compounds and olefins with triethylborane in water to provide the corresponding products in good yields. Only one example, utilizing bromoacetonitrile, was demonstrated and the reaction employed stoichiometric amount of the promoter (Scheme 1, **A**).[17] In 2014, the group of Melchiorre developed a photoorganocatalytic method for the atom transfer radical addition of haloalkanes onto olefins (Scheme 1, **B**). In this case, only one example using bromoacetonitrile was reported.[18a] A very recent photoorganocatalytic example, demonstrating a single example with bromoacetonitrile was also reported by Cozzi and coworkers.[18b] Also, two methods were developed for the addition of bromoacetonitrile to styrene derivatives under Photoredox catalysis (Scheme 1, **C**).[19,20] In both instances, the olefin was only limited to styrene derivatives and the intermediate radical was trapped by the alcoholic solvent, evidence that this method proceeds via a carbocation intermediate and that the more versatile bromide intermediates could not be isolated. We have recently turned our attention to Photocatalysis, both in Photoorganocatalysis[21a-e] and Photoredox catalysis.[21f] Herein, we describe an expansion of current knowledge into a synthetic protocol for the ATRA addition of bromoacetonitrile utilizing tris[2-phenylpyridinato-C^2,*N*]iridium(III) as the photocatalyst onto a wide substrate scope of aliphatic olefins bearing various functional groups (Scheme 1, bottom).



Scheme 1. Photocatalytic methodologies for the bromocyanomethylation of olefins.

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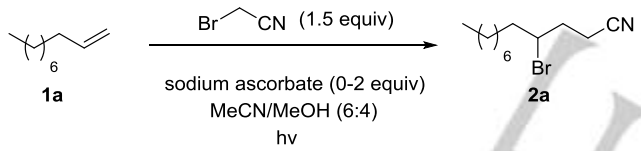
Results and Discussion

We began our investigations with the reaction between 1-decene (**1a**) and bromoacetonitrile with a number of catalysts. This reaction was chosen in order to overcome the current literature limitation with the employment of styrene derivatives. Utilizing metal complexes, as the photocatalyst, high yields were obtained, with $Ir(ppy)_3$ proving to be the best photocatalyst (Table 1, entries 1-3). A range of organic photocalalysts were also tested in the reaction, providing the desirable products in lower yields (Table 1, entries 7-9). After identifying $Ir(ppy)_3$ as the optimum photocatalyst, we proceeded with the optimization of the reaction conditions, studying the reaction's performance with and without the catalyst or sodium ascorbate and under dark conditions (Table 1, entries 4-6). In the absence of the photocatalyst, no reaction took place (Table 1, entry 4). When no sodium ascorbate was employed, no product could be identified (Table 1, entry 5). This is in complete agreement with literature,[19,20] that aliphatic olefins do not lead to product formation, when sodium ascorbate is absent. Moreover, when the reaction was kept in the dark, 1-decene did not convert to the corresponding product (Table 1, entry 6). Then, a variety of solvents was tested. Acetonitrile combined with methanol proved to be the best solvent system, leading to the higher yield (Table 1, entry 3). Others solvents led to lower yields (Table 1, entries 10-12). Unlike previous literature precedent, no alcoholic addition was observed. We believe that the nature of the substituent on the double bond (aryl vs aliphatic), that can stabilize the intermediate radical formed, is crucial for the reaction outcome. Also, the use of sodium ascorbate can alter the reaction mechanism.

The next step was to explore the scope of the olefin partner (Scheme 2). All tested double bonds were converted to the corresponding products in excellent yields. Initially, the atom transfer radical addition was performed with aliphatic olefins, leading to the corresponding products in high yields (**2a**, **2b**, **2e**, **2f**). Less reactive internal cyclic alkenes for ATRA reactions, including 2-norbornene (**1d**) and cyclooctene (**1c**), were competent substrates, leading to the desirable products in high yields (**2c** and **2d**). Allyl ethers proved to be very efficient substrates, since the products were obtained in high yields (**2i** and **2j**). Terminal olefins bearing a wide array of functionalities were efficiently transformed into the corresponding products in good yields (**2g**, **2h** and **2k**-**2o**). Finally, in the case of **1p** (a 1,1-disubstituted double bond), after ATRA addition, an elimination occurs leading to **2p**.

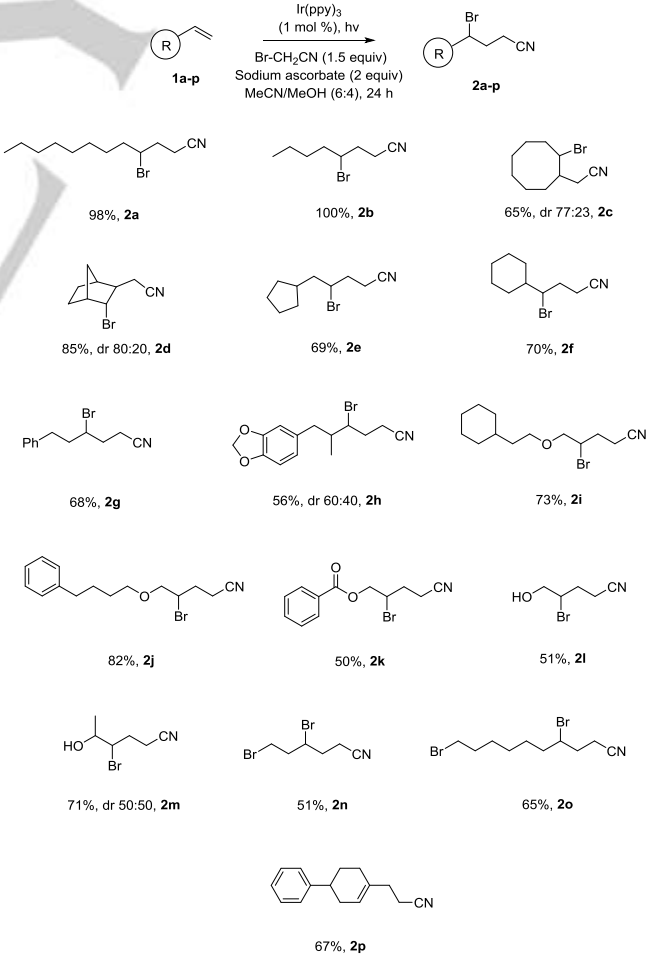
In a recent study, Cismesia and Yoon challenged the ability of a light-dark experiment as the sole evidence for photocatalytic closed cycle mechanism versus a chain propagation cycle.[22] If a closed catalytic cycle is involved, a maximum theoretical quantum yield (Φ) of 1 is expected (every photon absorbed by the photocatalyst produces a molecule of the product, although if

Table 1. Optimization of the reaction conditions for the photocatalytic atom transfer radical addition of bromoacetonitrile to olefins.



Entry	Catalyst (mol%)	Sodium Ascorbate (equiv.)	Yield[a] (%)
1	$Ru(bpy)_3Cl_2·6H_2O$ (1)	2	78
2	$Ru(phen)Cl_2$ (1)	2	62
3	$Ir(ppy)_3$ (1)	2	98
4	$Ir(ppy)_3$ (1)	-	0
5	-	2	0
6[b]	$Ir(ppy)_3$ (1)	2	0
7	Eosin Y (10)	2	32
8	Benzophenone (10)	2	0
9	Benzoin (10)	2	26
10[c]	$Ir(ppy)_3$ (1)	2	66
11[d]	$Ir(ppy)_3$ (1)	2	48
12[e]	$Ir(ppy)_3$ (1)	2	28

[a] Isolated yield. [b] Reaction was kept in the dark. [c] CH_2Cl_2 was used instead of MeCN/MeOH. [d] MeCN was used instead of MeCN/MeOH. [e] MeOH was used instead of MeCN/MeOH.

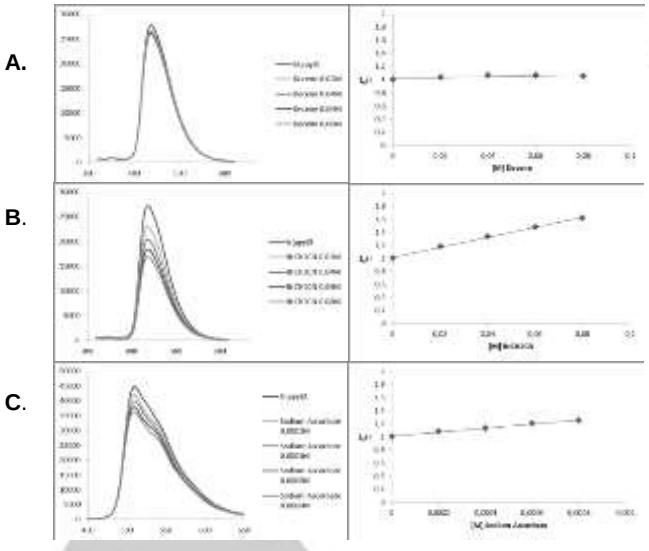


Scheme 2. Substrate scope of the reaction.

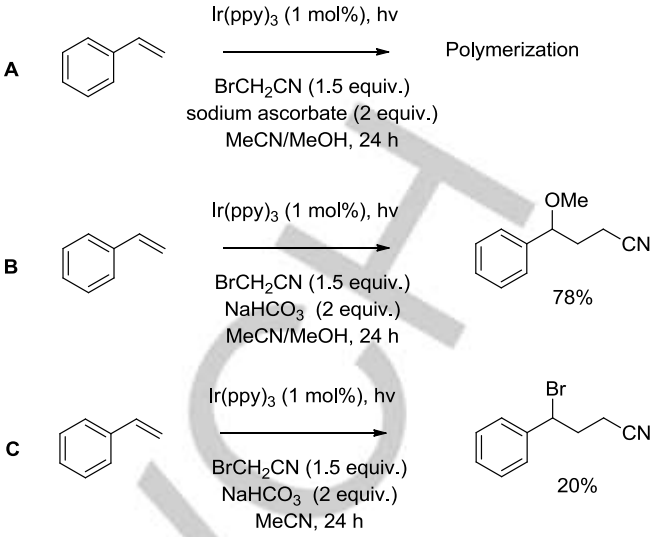
non-productive pathways or other phenomena are involved, the quantum yield will decrease). Although a quantum yield lower than 1 does not exclude the possibility of a short chain propagation. On the contrary, a quantum yield of Φ >> 1 would mean a chain propagation process, since one-photon induced initiation would lead to multiple molecules of the product. We have calculated the quantum yield of the reaction was calculated by dividing the moles of the product formed by the einsteins of photons consumed, leading to a quantum yield of 2.49 under identical reaction conditions that reaction was performed, hinting that a chain propagation is followed.

Fluorescence quenching studies were then carried out in order to understand the reaction mechanism. After irradiation of $Ir(ppy)_3$ at 372 nm, its fluorescence was measured at 518 nm. Increasing the amount of the added 1-decene, no changes in the fluorescence were observed (Scheme 3, **A**). Increasing the amount of the added bromoacetonitrile, a constant decrease in the fluorescence was observed (Scheme 3, **B**). Increasing, also, the amount of the added sodium ascorbate, a constant decrease in the fluorescence was also observed (Scheme 3, **C**). Comparing the slopes of the two diagrammes, ascorbate is a better quencher than bromoacetonitrile.

When we attempted to employ styrene as the olefin partner, in the exact same conditions, we could only observe polymerization events to occur (Scheme 4, **A**). This is in accordance with our previous postulation and findings that a different mechanism is in place, when aryl vs alkyl substituent on the olefin are employed and whether sodium ascorbate is added or not.[21g] In order to verify this, we performed the reaction as desribed in literature,[19] and indeed, the product bearing the ether was obtained in 78% yield (Scheme 4, **B**). When sodium bicarbonate was used, instead of sodium ascorbate, and acetonitrile was employed as the solvent, the desired ATRA product was obtained in low yield (Scheme 4, **C**). Thus, when styrene derivatives are employed (aryl substituent on the olefin), sodium ascorbate is not required for product formation. It seems that in that case, once the intermediate radical **B** is formed, it is



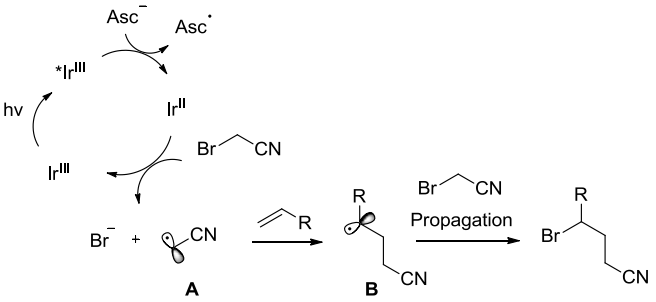
Scheme 3. Fluorescence studies. A) Fluorescence quenching of $Ir(ppy)_3$ with progressive addition of 1-decene. **B)** Fluorescence quenching of $Ir(ppy)_3$ with progressive addition of bromoacetonitrile. **C)** Fluorescence quenching of $Ir(ppy)_3$ with progressive addition of sodium ascorbate.



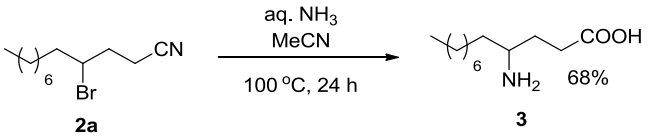
Scheme 4. Test reactions with styrene.

oxidized to the corresponding carbocation, which is stabilized by the adjacent aryl moiety (benzylic cation), closing the Photoredox catalytic cycle, regenerating the iridium catalyst. The carbocation formed reacts quickly with the nucleophilic alcoholic solvent to yield the ether (Scheme 4, **B**). If the alcoholic solvent is omitted, a low yield of the ATRA product is obtained (Scheme 4, **C**). On the other hand, the addition of sodium ascorbate completely alters the reaction mechanism, and now styrene derivatives lead to polymerization. However, this opens the door for the successful employment of olefins bearing alkyl substituents that could not be employed before. Additional mechanistic experiments (employing TEMPO or BHT in the reaction conditions led to no product formation) verifying the radical nature of the process.

On the basis of these data, we propose the mechanism outlined in Scheme 5. Upon irradiation, Ir^{III} is excited and the excited photocatalyst is reduced by sodium ascorbate, which reacts with bromoacetonitrile forming electrophilic radical **A** and regenerates the photocatalyst. The formed radical **A** reacts with the olefin leading to new radical **B**. Then, propagation with bromoacetonitrile leads to the desired products (Scheme 5). Radical **B** cannot be oxidized to the corresponding carbocation, since the R group is aliphatic and cannot stabilize it. We attribute the fact that no product derived from nucleophilic attack of the alcoholic solvent is observed to this event. Thus, the presence of sodium ascorbate alters the reaction mechanism of the metal photocatalyst making it prone to react with aliphatic olefins. The



Scheme 5. Proposed reaction mechanism.



2a **3**

Scheme 6. Synthesis of 4-aminododecanoic acid (**3**).

nature of the aliphatic substituent does not permit oxidation of the intermediate radical **B** to a carbocation and its trapping from the nucleophilic solvent is avoided. So, the only pathway which can be followed is propagation.

As already mentioned, bromonitriles obtained from the photocatalyzed bromocyanomethylation of alkenes can be easily converted to a variety of organic compounds through SN_2 substitution reaction. The bromo group can easily be converted to a hydroxy[23] or an azide[24] group. With this considered, reaction with ammonia led to amino acid 3 in 68% yield (Scheme 6). Thus, 4-bromododecanenitrile (**2a**) was successfully transformed into the corresponding amino acid **3** in high yield (Scheme 6).

Conclusions

In conclusion, an efficient atom transfer radical addition of bromoacetonitrile to olefins was developed. The reaction takes place under mild conditions including a low catalyst loading. A variety of aliphatic and cyclic aliphatic olefins were tested successfully, leading to products in high to excellent yields. Mechanistic studies were carried out in order to understand the reaction mechanism. A linchpin to the corresponding amino acid was also demonstrated.

Experimental Section

In a glass vial with a screw cap containing tris[2-phenylpyridinato-C^2,*N*]iridium(III) (1.5 mg, 0.0025 mmol) in acetonitrile (2 mL) and methanol (1.5 mL), alkene (0.25 mmol), $BrCH_2CN$ (45 mg, 0.375 mmol) and sodium ascorbate (100 mg, 0.50 mmol) were added consecutively. The vial was sealed with a screw cap and left stirring under household bulb irradiation (2 x 80W household lamps) for 24 hours. The desired product was isolated after purification by column chromatography.

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Keywords: photocatalysis • radical addition • olefin • bromoacetonitrile • amino acids

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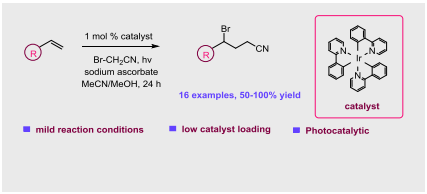
Photocatalysis. A photocatalytic method for the bromocyanomethylation of alkenes is described.



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