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# Radical Alkynylations with EthynylBenziodoXolones: From Photocatalysis to Direct Excitation

Stephanie G. E. Amos§ and Jerome Waser*

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*Abstract:* Ethynylbenziodoxolones (EBXs) have recently emerged as potent reagents for the alkynylation of radicals. Their combination with photocatalysis allows the synthesis of valuable alkynes at room temperature. Herein, we discuss two photomediated strategies for the synthesis of internal alkynes. The first transformation is a 1,2-oxyalkynylation of *N*- and *O*-alkenes using 4ClCzIPN as a photocatalyst. The second strategy makes use of EBXs as strong photooxidants allowing the oxidation of a variety of substrates with no need for a photocatalyst.

**Keywords**: Alkyne · Deoxygenation · Difunctionalization · Photochemistry

***Stephanie G. E. Amos*** was born in Exeter (UK) and moved to France aged 11. She has a BSc and MSc in chemistry from the University Claude Bernard Lyon 1 (UCBL, France). In 2016, she joined the CASYEN group (UCBL, France) with Prof. Bruno Andrioletti working on biomass valorization. She then joined the group of Prof. Jerome Waser at the Ecole Polytechnique Fédérale de Lausanne (EPFL, Switzerland) as an intern, developing a sulfenate alkynylation strategy. Stephanie is now studying photomediated alkynylations with hypervalent iodine reagents as a PhD student in the same group.

## 1. Introduction

### 1.1 *Alkynes and their Synthesis*

From the synthetic chemist's perspective, alkynes are versatile intermediates.[1] They can undergo selective Lewis acid or transition metal activation allowing the construction of complex (poly) cyclic scaffolds[2] or the conversion into diverse functional groups such as ketones[3] or allenes.[4] They can be reduced to *Z* and *E* alkenes and used in metathesis reactions.[5] Their intrinsic rigidity is valuable in medicinal chemistry and materials science.[1a,6] They can also be used in chemical biology for stapling and click reactions.[7] Traditionally, alkyne synthesis proceeds through the construction of an alkyne from aldehydes with the Ohira-Bestmann or the Corey-Fuchs reactions.[8] These reactions often require the presence of a strong base and can be limited by the presence of slightly acidic functional groups on the desired scaffold. In this regard, alkyne transfer appears as an attractive alternative. Internal alkynes can be accessed by the nucleophilic addition of acetylides to electrophilic centers.[9] Since the development of transition metal catalysis, the Sonogashira alkyne coupling reaction has enabled the coupling of C(*sp*)-C($sp^2$) centers.[10] More recently, the use of EthynylBenziodoXolones (EBXs) as an electrophilic alkyne source has allowed the alkynylation of nucleophilic centers.[11] Finally, alkyne transfer can also proceed through the alkynylation of free radicals using alkynyl radical traps such as alkynyl sulfones, free alkynes with a transition metal or EBXs.[12] The high energy associated to free radical intermediates helps to overcome the energy barriers associated to the construction of sterically demanding scaffolds, such as quaternary centers. In this regard, the development of radical alkynylation strategies is of utmost interest.

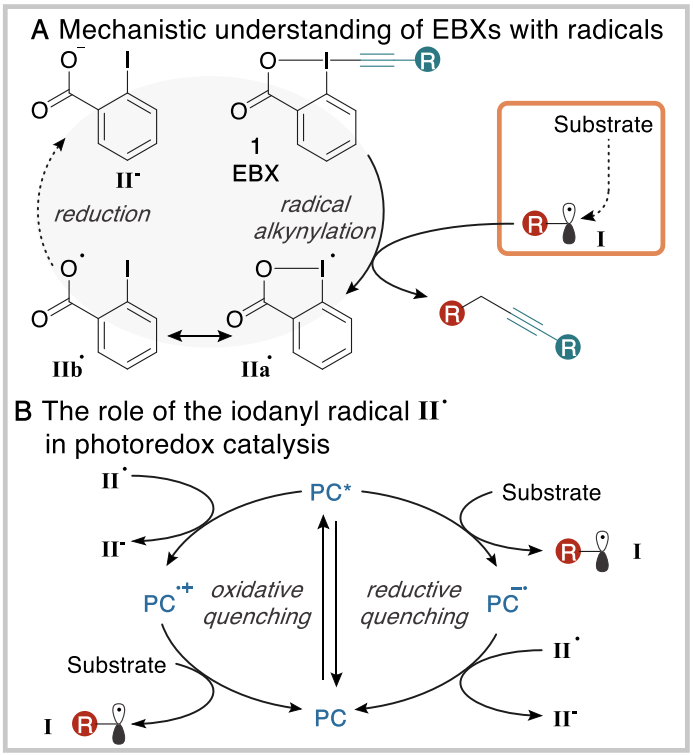
### 1.2 *Photomediated Alkynylations with EBXs*

Over the past decade, EBXs (**1**) have emerged as highly efficient radical traps, be it under thermal,[13] or photochemical activation.[14] Upon addition of radical **I** to the EBX reagent, the desired alkyne is formed releasing the iodanyl radical (**IIa**$^\bullet$ ↔**IIb**$^\bullet$, Scheme 1, **A**).[15] In photoredox catalyzed strategies, **II**$^\bullet$ will ultimately undergo reduction to the thermodynamically stable iodobenzoate **II**$^-$ ($E_{1/2}$(**II**$^\bullet$/**II**$^-$) = +0.25 V vs SCE). In a redox neutral photocatalytic cycle, the iodanyl radical **II**$^\bullet$ ensures the oxidation of the photocatalyst and the substrate the reduction (Scheme 1, **B**).[16] In a reductive quenching cycle the excited state photocatalyst (**PC***) can oxidize the substrate generating the radical **I** and the reduced **PC**$^{\bullet-}$. In turn, **PC**$^{\bullet-}$ would ensure the reduction of the iodanyl radical **II**$^\bullet$, turning over the photocatalytic cycle. In the oxidative quenching cycle, the iodanyl radical **II**$^\bullet$ could first oxidize **PC*** affording **PC**$^{\bullet+}$, which could then oxidize the substrate.[17] Invariably, the use of EBXs in a redox neutral photocatalytic cycle entails the exploitation of oxidizable substrates.

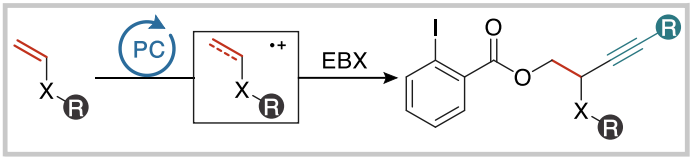
## 2. Photocatalyzed Enamide and Enol Ether Difunctionalization

The difunctionalization of *N*- and *O*-substituted alkenes is a highly efficient approach for the synthesis of complex aminated and oxygenated scaffolds in a single step.[18] In 2020, we published a photocatalytic *Umpolung* of enamides and enol ethers (Scheme 2). The method proceeds through the single electron oxidation of the alkene which can then be trapped by the 2-iodobenzoate. The ensuing radical was then alkynylated by the EBX reagent to afford the oxyalkynylated product.[19]

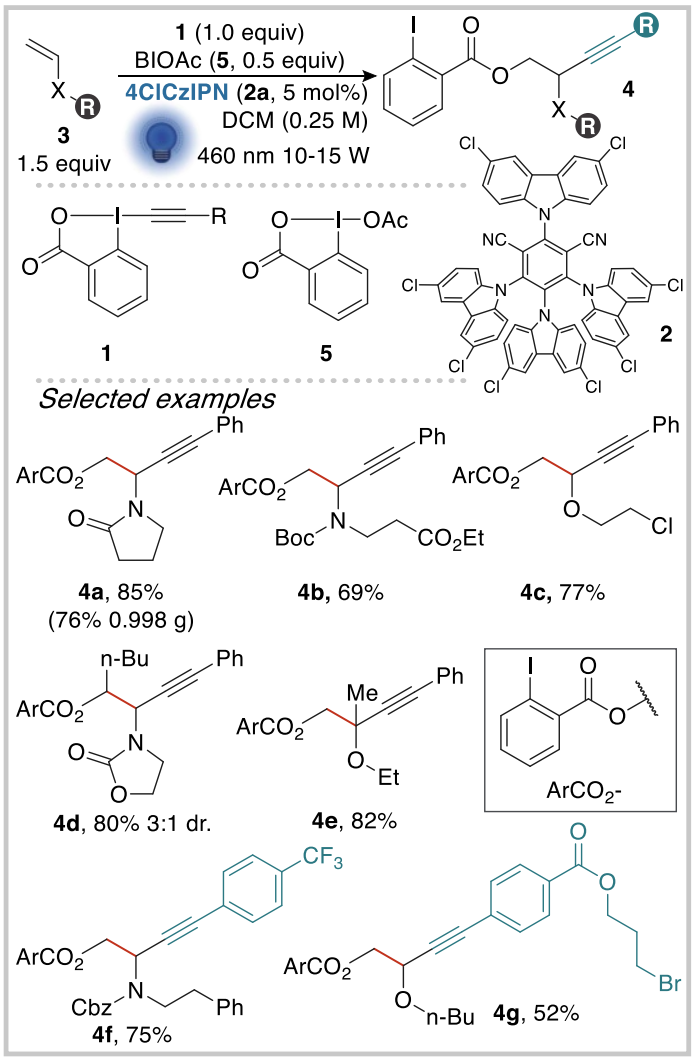
*Correspondence: Prof. Dr. J. Waser, E-mail: jerome.waser@epfl.ch, SB-ISIC LCSO, EPFL, Lausanne, CH-1015 Lausanne




Scheme 1. (**A**) Established mechanistic understanding of the reactivity of EBXs with radicals. (**B**) The role of the iodanyl radical **II•** in photoredox catalysis.




Scheme 2. Our approach to *N*- and *O*-substituted alkene difunctionalization.

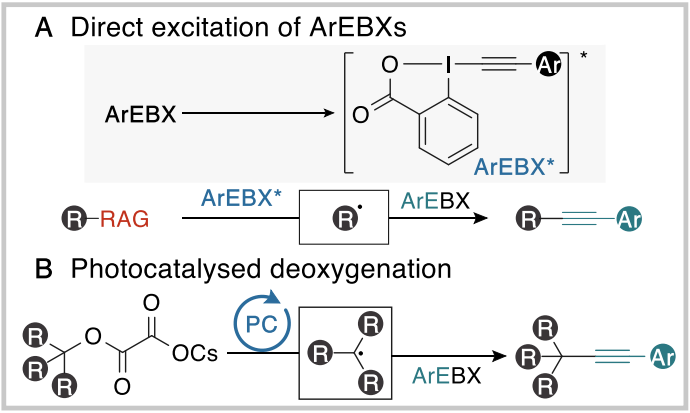



Scheme 3. Optimized conditions for the oxyalkynylation of enamides and enol ethers.

We found that 4ClCzIPN (**2a**) under blue LEDs irradiation could convert the alkene (**3**) to the desired product (**4**) Scheme 3). To ensure high yields, a substoichiometric quantity of BIOAc (**5**) was required. A variety of enamides, ene-carbamates and enol ethers could be difunctionalized affording a range of propargyl amine and alcohol derivatives in 37–85% yield (selected examples: **4a–g**). Furthermore, the reaction could be scaled up to access 1 g of **4a** (76% yield). Trisubstituted alkenes were also well tolerated, delivering scaffolds **4d** and **4e** in 58% to 82% yield. Finally, a variety of functionalized aryl alkynes could also be successfully transferred (**4f** and **4g**).

## 3. From Photoredox Catalysis to the Direct Excitation of ArEBXs: Deoxygenation and other Transformations

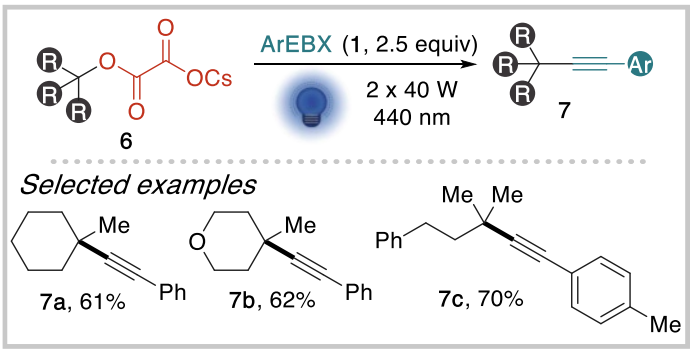
Refunctionalization strategies have gained importance over the past few decades. Indeed, the revalorization of biomass entails the transition from *poorly* functionalized to *highly* functionalized starting materials.[20] Earlier this year, we reported the direct photoexcitation of EBXs for the activation of a variety of redox active groups (RAGs) while developing a deoxyalkynylation of cesium oxalates (Scheme 4).[21] First, the direct excitation was explored and used to activate multiple redox active groups (RAGs) in absence of a photocatalyst (**A**). Second, we explored photocatalytic conditions to enable a broader scope for the deoxyalkynylation of tertiary alcohols (**B**).




Scheme 4. (**A**) Direct excitation of EBXs for radical alkynylations. (**B**) Photocatalytic deoxyalkynylation.

We found that blue LED irradiation (2 × 40 W, $\lambda_{max}$ = 440 nm) of the ArEBX (**1**) in presence of the cesium oxalate (**6**) provided the desired deoxyalkynylated products (**7**, Scheme 5). These conditions allowed us to access quaternary alkynes **7a–c** in up to 70% yield.

From a mechanistic standpoint, the absorption, fluorescence, and fluorescence excitation spectra of PhEBX (**1**)

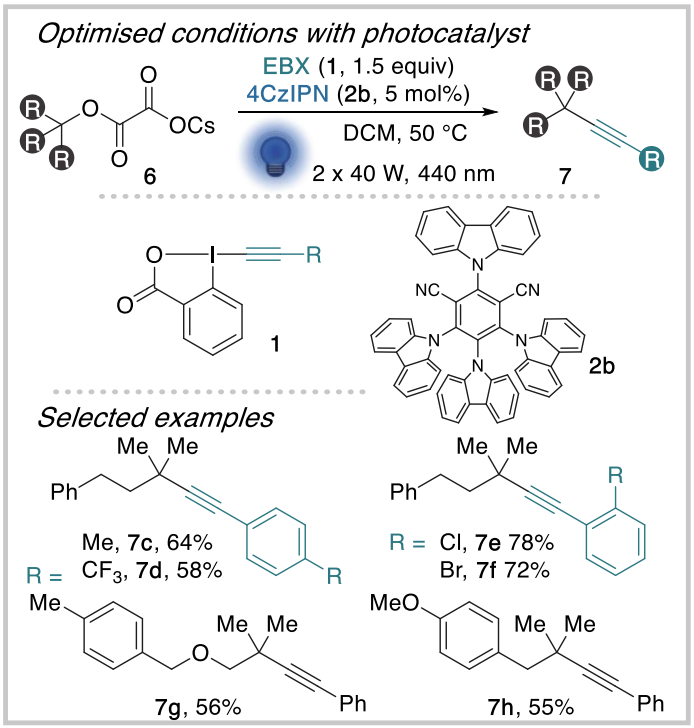



Scheme 5. Optimized conditions for the deoxyalkynylation of tertiary alcohols and selected examples.

all confirmed the possible excitation of **1** in the visible region (400–460 nm). Cyclic voltammetry experiments allowed the estimation of the redox potential $E_{1/2}$(**1***/**1**$^{\bullet-}$) to be approximately +1.8 V vs SCE, suggesting the strong oxidative character of **1***.

In addition to the deoxyalkynylation, it was also possible to activate other RAGs by simply using 2.5 equiv of PhEBX (**1**, Scheme 6, **A**). Decarboxylation afforded **9a** and **9b** (**B**, 81% and 41%) and enabled the fragmentation of oximes (**10**) to give alkynyl nitriles **11a** and **11b** (**C**, 74% and 69%). Deboronative alkynylation yielded **13a** and **13b** (**D**, 72% and 69%). THF could be readily alkynylated affording **15** in 81% yield (**E**) and enamide difunctionalization could also be achieved (**17**, 35% yield, **F**). Finally, an unprecedented deaminative alkynylation was performed *via* the formation of imine **18** delivering **19** in 57% (**G**).

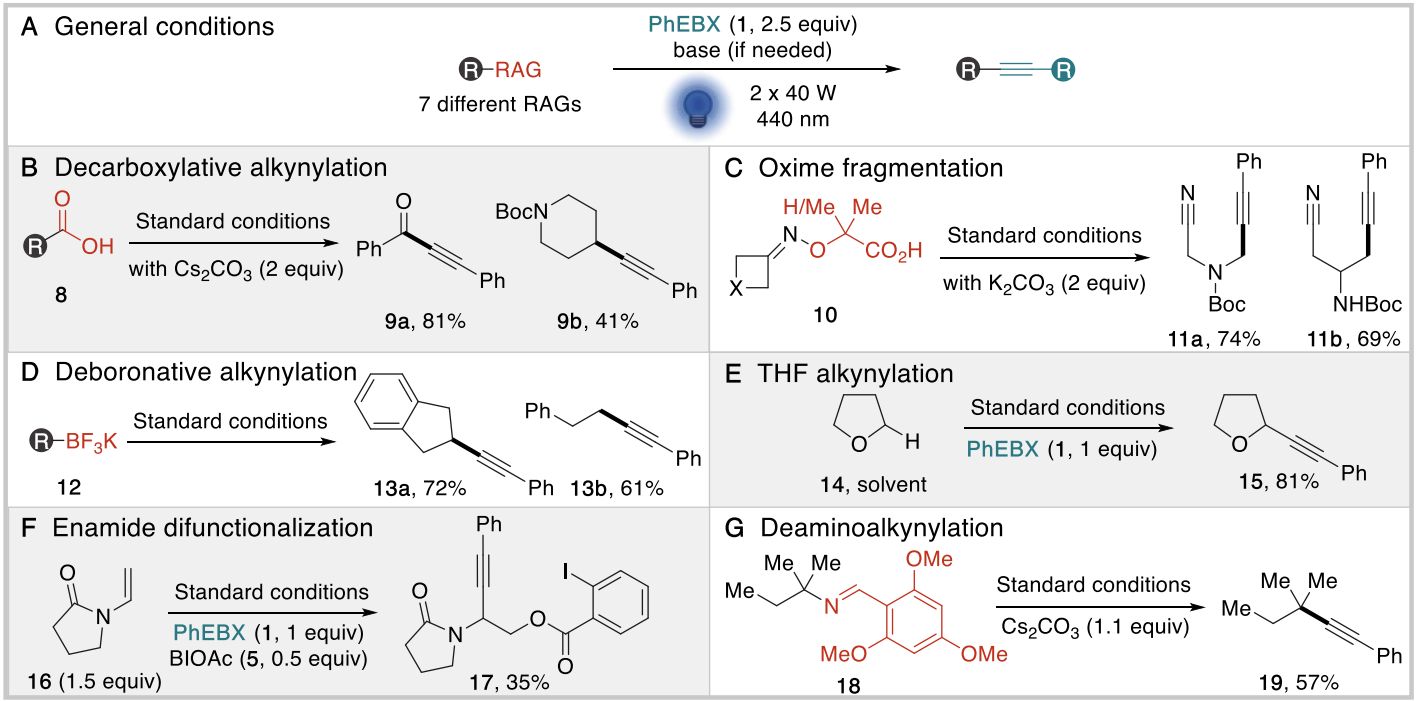
Although the scope of applications of the excited state PhEBX (**1**) was broad, the major drawback of this approach was that only Ph- and *p*Tol-EBXs afforded the desired deoxyalkynylated products in synthetically relevant yields (Scheme 5). To circumvent this limitation, we found that the deoxyalkynylation reaction could be performed with 4CzIPN (**2b**) as a photocatalyst with a lower loading of EBX reagent (1.5 equiv, Scheme 7). These photocatalytic conditions allowed us to access 21 different alkynylated quaternary centers in up to 82% yield allowing greater functional group tolerance either by varying the EBX or the alcohol **7c**–**7h** (55–78% yield).




Scheme 7. Deoxyalkynylation of oxalates with 4CzIPN.

## 4. Conclusions

When combined with radicals, EBXs are an attractive source of alkynes. Under photocatalytic conditions, their applications have been extended to atom economical difunctionalization and deoxyalkynylation. Under irradiation at 440 nm (2 × 40 W), they




Scheme 6. Scope of alkynylation reactions enabled by the direct photoexcitation of EBXs.

can undergo direct excitation to a highly oxidizing species unlocking the way to photocatalyst-free photomediated alkynylations. On the one hand, the fine tuning of a photocatalyst enables efficient alkynylations with greater tolerance. On the other hand, the direct excitation approach can enable facile reaction discovery and simplified reaction set-up. For the alkynylation of radicals with EBXs, both photocatalyzed and direct approaches appear as complementary and valuable and promise further developments in this field.

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