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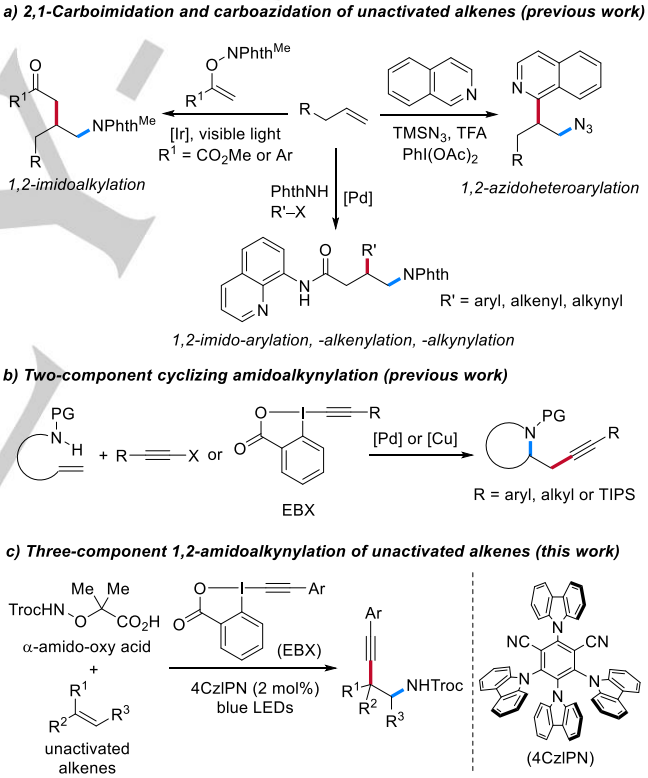
Transition-Metal-Free Three-Component Radical 1,2-Amidoalkynylation of Unactivated Alkenes

Heng Jiang and Armido Studer*

Abstract: A transition-metal-free radical 1,2-amidoalkynylation of unactivated alkenes is presented. α-Amido-oxy acids are used as amidyl radical precursors that are oxidized by an organic photoredox catalyst (4CzIPN). The electrophilic N-radicals chemoselectively react with various aliphatic alkenes and the adduct radicals are then trapped by ethynylbenziodoxolones (EBX) reagents to eventually provide the amidoalkynylation products. These transformations, which are conducted under practical and mild conditions, possess high functional group tolerance and show broad substrate scope. Mechanistic studies support the radical nature of these cascades.

1,2-Difunctionalization of alkenes by sequentially forming two novel vicinal σ-bonds increases complexity of a compound in a single operation. Such transformations have gained great interests in modern organic synthesis.[1] Along these lines, alkene carboamination is a valuable approach for the preparation of diverse amines. Transition-metal catalyzed or radical carboamination of activated alkenes including styrenes,[2] vinyl amides,[3] vinyl ethers[4] and acrylates[5] have been reported. Considering unactivated terminal alkenes as substrates, 1,2-carboamination generating a C–C σ-bond at the terminal position of the starting alkene has successfully been investigated in recent years by several groups. Thus, aminocarbonylation,[6] aminoalkylation,[7] azidofluoroalkylation[8] and aminoarylation[9] were achieved by applying radical chemistry or by using transition-metal catalysis. However, considering the reversed regioselectivity, only a few examples were reported for 2,1-carboamination of unactivated alkenes installing the C–N-bond at the terminal position of the alkene: In 2017, the Liu group disclosed a three-component Minisci-type reaction leading to 1,2-azidoheteroarylation of unactivated alkenes (Scheme 1a, right).[10] Very recently, the Feng group published a two-component, visible light initiated radical chain reaction for alkene 2,1-carboimidation by using an iridium complex as a photosensitizer and O-vinylhydroxylamine derivatives as both N-radical acceptors and N-radical precursors (Scheme 1a, left).[11] Engle disclosed elegant Pd-catalyzed 1,2-imidoarylation of specially designed terminal alkenes bearing a directing 8-aminoquinoline group (Scheme 1a, middle).[12]

The carbon carbon triple bond is a highly versatile reactive functionality in organic synthesis, which has found many applications as conjugating moiety also in biochemistry and in materials science.[13] Hence, alkene aminoalkynylation by sequentially introducing the highly valuable amino and alkynyl groups across a carbon carbon double bond would be an important synthetic transformation. To date, alkene aminoalkynylation is mainly restricted to two-component reactions comprising an intramolecular amidation with subsequent intermolecular alkynylation using transition-metal catalysis (Scheme 1b).[14] To our knowledge, transition-metal-free three-component 1,2-amidoalkynylation of unactivated alkenes is unprecedented.[15]



Scheme 1. Different strategies for 2,1-carboamination of unactivated alkenes.

Herein, we introduce a method for three-component radical alkene 1,2-difunctionalization by using α-amido-oxy acids as the amidyl radical precursors[16] and ethynylbenziodoxolones (EBX) as the alkynylating reagents (Scheme 1c).[17] We assumed that due to polar effects, an electrophilic amidyl radical will chemoselectively react with an unactivated alkene leaving the EBX-reagent untouched, since such I(III)-reagents are known to react efficiently with nucleophilic C-radicals.[18] Therefore, the nucleophilic radical adducts thus formed should then chemoselectively react with the EBX-reagent and telomerization

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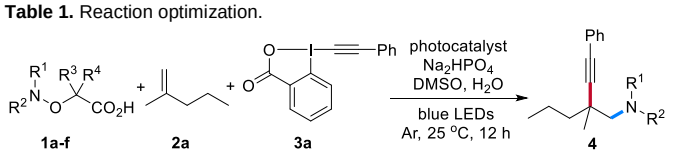
by renewed addition to the alkene acceptor should be suppressed.[19]

Table 1. Reaction optimization.



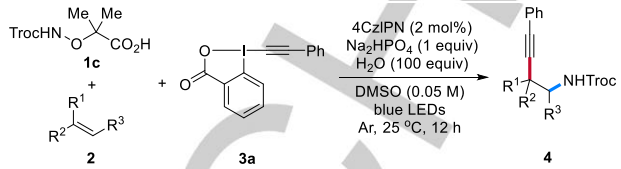
1a-f 2a 3a 4

Entry[a]	R^1, R^2	R^3, R^4	Photocatalyst	Yield%[b] (**4**)
1	H, Cbz (**1a**)	Me, Me	4CzIPN	29 (**4aa**)
2	H, Boc (**1b**)	Me, Me	4CzIPN	35 (**4ab**)
3	*H, Troc (**1c**)*	*Me, Me*	*4CzIPN*	*77, 70[c] (**4ac**)*
4	H, PhOCO (**1d**)	Me, Me	4CzIPN	n.d. (**4ad**)
5	H, Bz (**1e**)	Me, Me	4CzIPN	n.d. (**4ae**)
6	Phth (**1f**)	Me, Me	4CzIPN	n.d. (**4af**)
7	H, Troc (**1g**)	H, Me	4CzIPN	40 (**4ac**)
8	H, Troc (**1h**)	H, H	4CzIPN	11 (**4ac**)
9	H, Troc (**1c**)	Me, Me	Eosin Y	33 (**4ac**)
10	H, Troc (**1c**)	Me, Me	Rhodamine B	18 (**4ac**)
11	H, Troc (**1c**)	Me, Me	Fluorescein	15 (**4ac**)
12	H, Troc (**1c**)	Me, Me	Mes-Acr$^+$BF$_4^-$	7 (**4ac**)
13	H, Troc (**1c**)	Me, Me	–	n.d. (**4ac**)
14[d]	H, Troc (**1c**)	Me, Me	4CzIPN	n.d. (**4ac**)

[a] Reaction conditions: A mixture of **1** (0.2 mmol, 1 equiv), **2a** (0.6 mmol, 3 equiv), **3a** (0.3 mmol, 1.5 equiv), photocatalyst (0.004 mmol, 2 mol%), $NaHPO_4$ (0.2 mmol, 1 equiv) and H_2O (20 mmol, 100 equiv) in DMSO (4 mL) was irradiated by a 5 W blue LEDs at 25 ℃ for 12 h. [b] Isolated yields. [c] 1.0 mmol reaction scale. [d] Conducted in the dark.

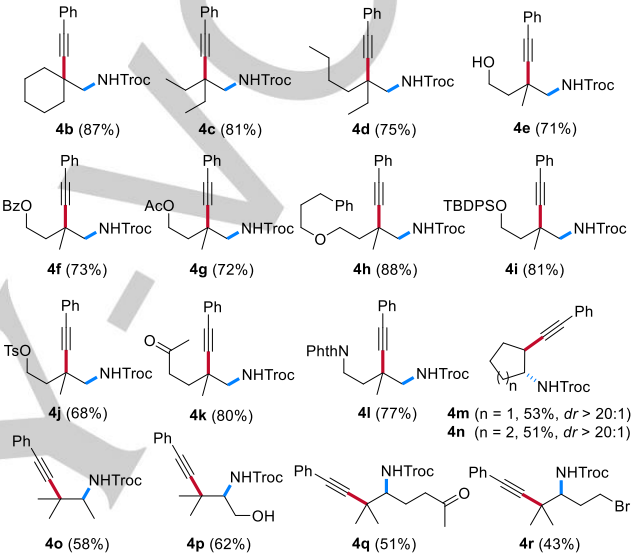
We chose 2-methylpent-1-ene (**2a**) as the amidyl radical acceptor and ethynylbenziodoxolone (EBX) reagent **3a** as the alkyl radical acceptor to examine the targeted amidoalkynylation cascade (Table 1). The organic photoredox catalyst 4CzIPN (see Scheme 1) was first tested, since it features oxidative ability in its excited state.[20],[21] We initially varied the N-protecting group of the starting α-aminooxy-2-propanoic acids **1** in combination with **2a**, **3a**, 4-CzIPN and Na_2HPO_4 in the mixed solvent system consisting of DMSO and H_2O. Reagents **1** and **3a** were readily prepared according to literature procedures (see SI).[16a],[18a] Cbz-protected amino-oxy-acid **1a** gave the desired 1,2-amidoalkynylated product **4aa** in encouraging 29% yield after irradiating the reaction mixture by 5W blue LEDs for 12 h (Table 1, entry 1). With the Boc-protected amino-oxy-acid **1b,** the targeted **4ab** was obtained in a slightly improved yield (35%, entry 2). To our delight, Troc-protected amino-oxy-acid **2c** provided **4ac** in 77% yield (entry 3, Troc = 2,2,2-trichloroethoxycarbonyl). Reagents **1d-f** bearing other common N-protecting groups such as the phenyloxycarbonyl (PhOCO), benzoyl (Bz) or phthaloyl (Phth) group turned out to be ineffective in this transformation (entries 4-6). Worse results were also noted by successively replacing the two methyl groups in reagent **1c** by H atoms (entries 7 and 8). Other frequently used organic photoredox catalysts such as Eosin Y, Rhodamine B, Fluorescein and Mes-Acr$^+$BF$_4^-$ provided significantly lower yields (entries 9-12).[22] In control experiments, product **4ac** was not formed in the absence of either photocatalyst or visible light irradiation (entries 13 and 14).

Table 2. 1,2-Amidoalkynylation of various alkenes.[a],[b]

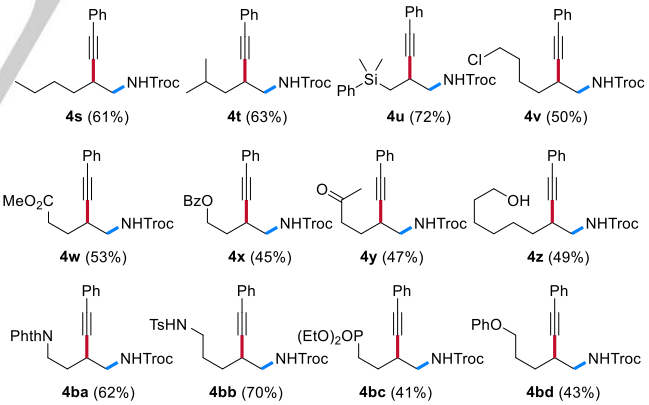


1c 2 3a 4

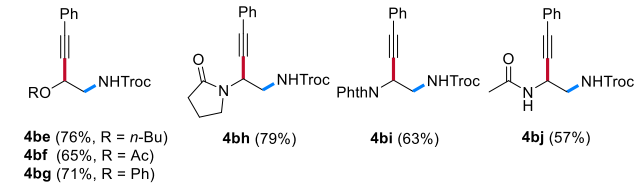
from disubstituted terminal alkenes and from internal alkenes:



from monosubstituted terminal alkenes:



from vinyl ethers and enamides:



[a] Reaction conditions: A mixture of **1c** (0.2 mmol, 1 equiv), **2** (0.6 mmol, 3 equiv), **3a** (0.3 mmol, 1.5 equiv), 4CzIPN (0.004 mmol, 2 mol%), $NaHPO_4$ (0.2 mmol, 1 equiv) and H_2O (20 mmol, 100 equiv) in DMSO (4 mL) was irradiated

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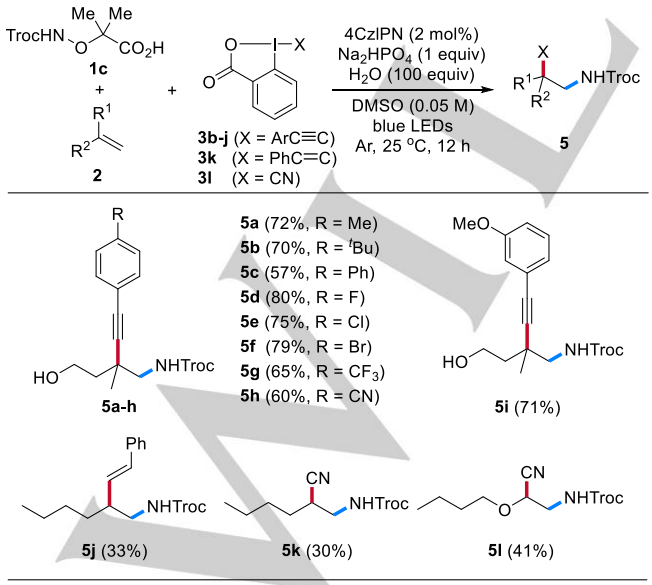
by a 5 W blue LEDs at 25 ℃ for 12 h. [b] Isolated yields are provided base on **1c**.

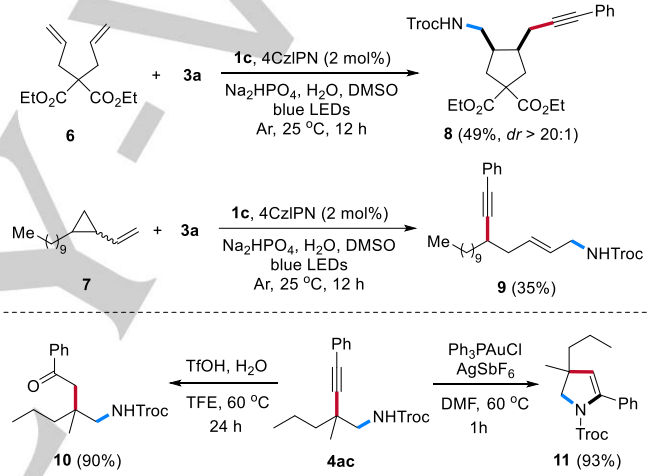
To explore reaction scope, various unactivated mono-, di- and tri-substituted alkenes were tested as substrates under optimized conditions using reagents **1c** and **3a** (Table 2). Non-functionalized 1,1-disubstituted alkenes engage in this transformation to give the desired Troc-protected amines bearing a newly formed all-carbon quaternary carbon center in high yields (**4b**-**d**, 75-87%). The amidoalkynylation features high functional group tolerance as various functionalities, such as alcohol (**4e**), ester (**4f**,**4g**), dialkyl ether (**4h**), silyl ether (**4i**), sulfonate (**4j**), ketone (**4k**) and imidyl (**4l**) groups are compatible with the reaction conditions. The corresponding products were isolated in good to excellent yields (68-87%). The internal symmetrical double bond of cyclopentene and cyclohexene could be amidoalkynylated to give the Troc-amides **4m** and **4n** in moderate yields and excellent *trans*-diastereoselectivity. We were pleased to find that sterically more hindered trisubstituted alkenes are eligible substrates providing the corresponding amides **4o**-**r** in 43-62% yields with complete regiocontrol. The slightly lower yields in these cases, as compared to the transformations with terminal disubstituted alkenes, can be understood considering steric effects, that lower the rate constant for amidyl radical addition to the alkene. Although monosubstituted alkenes are less nucleophilic than their 1,1-disubstituted congeners, reasonable yields were achieved for such systems. Hence, terminal non-functionalized alkyl alkenes (**4s** and **4t**) and derivatives bearing silyl (**4u**), chloro (**4v**), ester (**4w** and **4x**), keto (**4y**), alcohol (**4z**), amino (**4ba** and **4bb**), diethoxyphosphanyl (**4bc**) and ether (**4bd**) groups provided the corresponding Troc-amides in 43-72% yields. We also examined the reactivity of electron-rich alkenes such as vinyl ethers and enamides towards the radical 1,2-amidoalkynylation. As expected, such nucleophilic alkenes react efficiently and the β-amino alcohol derivatives **4be**-**4bg** and 1,2-diamino compounds **4bh**-**4bj** were obtained in moderate to good yields, further enlarging the scope of this method.

Table 3. Variation of the EBX reagent.[a],[b]



[a] Reaction conditions: A mixture of **1c** (0.2 mmol, 1 equiv), **2** (0.6 mmol, 3 equiv), **3** (0.3 mmol, 1.5 equiv), 4CzIPN (0.004 mmol, 2 mol%), $NaHPO_4$ (0.2 mmol, 1 equiv) and H_2O (20 mmol, 100 equiv) in DMSO (4 mL) was irradiated by a 5 W blue LEDs at 25 ℃ for 12 h. [b] Isolated yields are provided base on **1c**.

We next examined the scope with respect to the EBX trapping reagent (Table 3). Arylalkynyl-I(III) compounds bearing both electron-rich and electron-poor substituents at the aryl group such as *para*-substituted Me, *t*-Bu, Ph, F, Cl, Br, CF_3, CN and *meta*-substituted OMe were found to be efficient C-radical trapping reagents and the corresponding Troc-protected amines **5a**-**i** were isolated in good yields (57-80%). The use of β-styryl-benziodoxolone (**3k**) introduced by Olofsson and co-workers,[23] allowed the amidostyrenylation of 1-hexene (**5j**, 33%). In addition, amidocyanation of 1-hexene and vinyl butyl ether could also be accomplished by using cyanobenziodoxolone (**3l**) to provide **5k** and **5l**, albeit in lower yields.



Scheme 2. Mechanistic studies and synthetic applications.

Next, we conducted radical clock experiments to address the mechanism of the alkene amidoalkynylation. Product **8**, resulting from a typical 5-*exo* cyclization was obtained from 1,6-diene **6** in 49% yield and high diastereoselectivity, strongly supporting that radical intermediates are involved in this cascade. The radical nature of the process was further documented by the amidoalkynylation of vinylcyclopropane **7**, which gave exclusively the ring opening product **9** in 35% yield. Finally, to document the potential of the amidoalkynylation, two follow-up transformations were conducted. Hydrolysis of β-alkynyl-amide **4ac** gave the ketone **10** in 90% yield[24] and cyclization of **4ac** by using Au catalysis provided the 2-pyrroline **11** (93%).[25]

The proposed mechanism of the radical alkene 1,2-amidoalkynylation is presented in Scheme 3. The catalytic cycle starts by photo-excitation of 4CzIPN upon visible light irradiation to generate the excited 4CzIPN*, which oxidizes carboxylate **A**, formed by deprotonation of substrate **1**, to generate the carboxyl radical **B** along with the radical anion (4CzIPN)$^{\bullet-}$. Sequential fragmentation of CO_2 and acetone from **B** generates the amidyl radical **C**, which then adds to the carbon-carbon double bond in **2** to provide the adduct radical **D**. EBX reagent **3a** traps the C-

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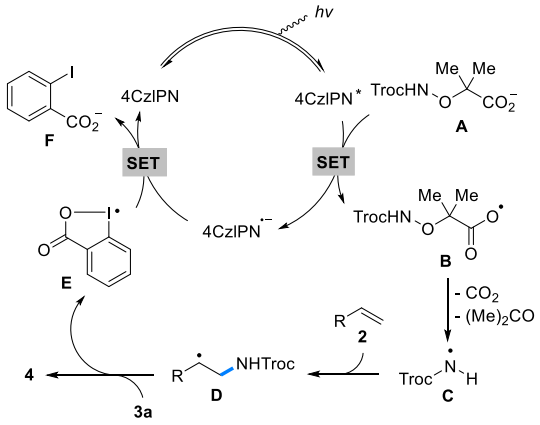
radical **D** to give product **4** with concomitant formation of iodanyl radical **E**. Transient radical **E** is then reduced by the longer lived radical anion (4CzIPN) $^{\bullet-}$ [26] to give *ortho*-iodobenzoate **F** and 4CzIPN, thereby closing the catalytic cycle. Two additional experiments were conducted to support the suggested mechanism (for details, see SI). Stern-Volmer quenching experiments of 4CzIPN with the sodium salt of **1c** supported formation of carboxyl radical **B** via SET oxidation of **A** with excited 4CzIPN. Moreover, cyclic voltammetry of **A** (tetrabutylammonium salt) revealed an oxidation peak at +1.30 V vs. SCE in acetonitrile, documenting the feasibility of the SET oxidation of **A** by photo-excited 4-CzIPN (+1.35 V vs. SCE in MeCN).



Scheme 3. Suggested mechanism.

In summary, we have established a practical method for 1,2-amidoalkynylation of various unactivated alkenes. By using a readily available Troc-protected α-aminoxy acid as the amidyl radical precursor and EBX-type reagents as the alkyl radical acceptors, various unactivated alkenes including mono-, di- and tri-substituted alkenes, vinyl ethers, vinyl esters and vinyl amides are efficiently 1,2-difunctionalized providing diverse β-alkynylated Troc-amides. The transition-metal-free process proceeds under mild conditions and a wide range of functional groups are tolerated. The ubiquity of amines and the importance of the alkynyl moiety in synthetic chemistry render this transformation highly valuable for medicinal and agrochemical research.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: alkene amidoalkynylation • radical cascades • amidyl radical • photoredox catalysis • transition-metal-free

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Layout 2:

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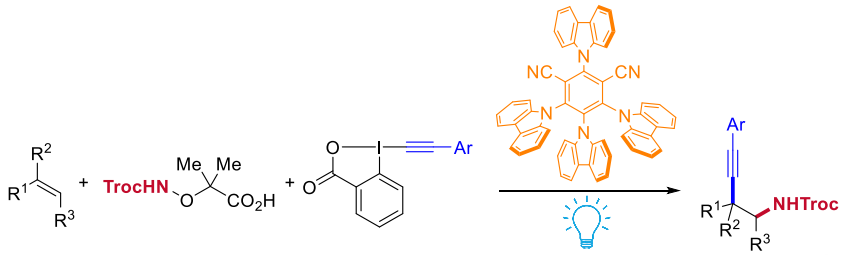

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Transition-Metal-Free Three-Component Radical 1,2-Amidoalkynylation of Unactivated Alkenes

Alkynylation and amidation shine up! Transition-metal-free 1,2-amidoalkynylation of unactivated alkenes has been achieved using a Troc-protected α-aminoxy acid as the amidyl radical precursor and EBX reagents as alkyl radical acceptors applying photoredox catalysis.