Visible Light-Promoted Three-Component Carboazidation of Unactivate Alkenes with TMSN₃ and Acrylonitrile



Bo Yang,^{*a*} Xiang Ren,^{*a*} Xuzhong Shen,^{*a*} Tongtong Li,^{*a*} Zhan Lu^{*,*a*}

ABSTRACT A novel difunctionalization of unactivated alkenes has been reported via visible light-promoted three-component carboazidation using TMSN₃ and acrylonitrile as partners without any stoichiometric oxidants. This protocol is operationally simple for straightforward access to azido derivatives with good functional group tolerance from readily available starting materials. A facile azido radical-catalyzed [3+2] cycloaddition reaction of vinylcyclopropane with acrylonitrile was also observed to deliver a multi-substituted cyclopentane.

KEYWORDS alkene difunctionalization, visible light photocatalysis, three-component reaction, redox-neutral, organoazide

Introduction

Alkene difunctionalizations have been continuously attractive for efficient construction of various useful synthetic intermediates and targets.^[1] Organoazides have been used as efficient synthetic intermediates due to their diversity of further transformations. $^{rac{1}{2}}$ The combination of the formations of carbon-azide bond and carbon-X (halogen, P, O, N) bonds have been successfully reported.^[3] The carboazidation of alkenes used to form carbon-(sp or sp²) carbon bonds or fluorinated carbon bonds.^[4] However, to the best of our knowledge, the three-component carboazidation reaction with the formation of non-fluorinated carbon (sp³)-carbon (sp³) is still limited (Scheme 1). Renaud and co-workers reported two types of carboazidation of alkenes with α -iodoacetate and phenylsulfonyl azide, or using alkylsulfonyl azides as both alkyl and azido sources.^[5] Recently, Zhu^[6] group and Yang^[7] group, respectively, reported carboazidation of terminal styrenes or cyclic styrene with acetonitrile or aldehydes as carbon sources using peroxides as oxidants. Li and co-workers reported an azidomethylation of active alkenes with dimethyl sulfoxide as a methyl source using H_2O_2 as an oxidant.^[8] So far, over

Scheme 1 The Carboazidation of Alkenes



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stoichiometric peroxides have to be used and aliphatic alkene is a still challenging substrate. Here, we reported a three-component carboazidation of unactivated alkenes with $TMSN_3$ and acrylonitrile via visible light photocatalysis without any stoichiometric oxidants.

Our group is quite interested in visible light-promoted alkene difunctionalizations.^[9] In our previous studies, the azido radical^[10] could react with alkene to form carbon radical^[11] which could be trapped by dioxygen.^[9e] Based on these result, we hypothesized that the Michael acceptor, such as acrylonitrile, was an alternative trapper which leads to the formation of carbon (sp³)-carbon (sp³) bond to afford the carboazidation product (Scheme 1b).

The proposed mechanism was presented in Scheme 1c. The azidotrimethylsilane could be oxidized by iridium photocatalyst (EIr*/Ir-= +0.66 V)^[12] to azido radical based on the oxidation potential of the azidotrimethylsilane (measured 0.66 V vs SCE in MeCN and 0.600 V vs SCE in acetone) or azido anion (0.655 V vs SCE in MeCN)^[13]

The azido radical could be trapped by alkene to generate benzyl radical species I which could undergo radical Michael addition to form carbon center radical II. This carbon radical II could be reduced by low valent photocatalyst to regenerate the ground state of photocatalyst, and afford the corresponding product **3a** in the presence of proton source.

Results and Discussion

Based on the above hypothesis, we extensively investigated the reaction conditions for the carboazidotion of α -methyl styrene with various photocatalyst at room temperature under the irradiation of 8 W blue LEDs for 9 h using water as proton donor and acetonitrile as a solvent. The various visible light photocatalysts were screened using TMSN₃ as an azido source and acrylonitrile as a Michael acceptor, and $Ir(ppy)_2(dtbbpy)PF_6$ was found to catalyze the reaction to afford three-component carboazidation product in 67% yield (entry 1, Table 1 and also in Table S1). It should be noted that the generated azido radical could react much rapider with α -methyl styrene than electron-deficient acrylonitrile. Various solvents were tested and no better results were observed (entries 2-7). The reaction with 2 equiv. of TMSN₃ in a solvent of MeCN (0.2 M) afforded the desired product in 80% yield (entry 8 as the standard conditions A). No desired products were obtained in the absence of photocatalyst or light (entries 10 and 11). Additionally, the reaction took place by using MeOH (3 equiv.) instead of H₂O (10 equiv.) to give 3a in 71% yield (entry 12 as the standard conditions B).

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Table 1 Optimization of Conditions of Carboazidation of Alkenes^a



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	Entry	Changes to	Yield ^b (%)
	1	-	67
	2	THF	57
	3	MeOH	0
	4	DCM	21
	5	Acetone	61
	6	MeNO ₂	17
	7	dioxane	61
	8	TMSN ₃ (2 equiv.), 0.2 M	80 (75)
+	9	$TMSN_3$ (2 equiv.), 0.2 M without water	67
	10	entry 8 without photocatalyst	0
	11	entry 8 without light	0
	12	$TMSN_3$ (2 equiv.), acetone (0.2 M),	71 (70)
		MeOH (3 equiv.) was used instead of $\rm H_2O$	

Conditions: α -methyl styrene (0.3 mmol), TMSN₃ (3 equiv.), acrylonitrile (6 equiv.), water (10 equiv.), Ir(ppy)₂(dtbbpy)PF₆ (2 mol%), solvent (0.1 M), at room temperature under the irradiation of 8 W blue LEDs for 9 h. ^b rields were determined by ¹H NMR analysis using mesitylene as an internal standard. Isolated yield in the parentheses.

With optimized conditions in hands, the scope of substrate was explored (Table 2). The α -methyl styrenes with various substituents, such as ether, halides, amine, amide, at para- or meta- position on aryl ring were suitable for this transformation. However, the sterically hindered substrates with ortho-substitution could not afford the desired product. The α -1°-alkyl substituent could be tolerated (**3k-l**), however, the $\alpha - 2^{\circ}$ alkyl substituent was not suitable (3m). The simple styrenes with electron-rich or electron-deficient substitutions could be transferred to the corresponding carboazidation products in 58-79% yields. The aliphatic alkenes could participate in reactions to afford **3u** and **3v** in 62% and 47% yield, respectively. The acyl protected cinnamyl alcohol could be delivered to 3w in 37% yield with poor diastereoselectivity. The trisubstituted alkene could also involve in the reaction to give 3x in 45% yield with 3.9/1 dr. The alkene containing estrone-derivative could be transformed nto the corresponding product. The intramolecular reaction of 1,6-diene 4 could undergo smoothly to afford cyclization product 5 in 62% yield with 3.2/1 dr (Table 2 eq. 1). The other Michael acceptors have been tested. The reaction of styrene with diethyl fumarate afforded 3aa in 21% yield with 2/1 dr. The reaction of styrene with cyclohex-2-enone afforded **3ab** in 34% yield with 1/1 While the reaction of styrene with diethyl 2-methylenemalonate did not afford desired product 3ac.

To demonstrate the synthetic utility, the further derivatizations have been carried out (Scheme 2). The click reaction of **3a** afforded **6** in 67% yield. The reduction reaction of **3a** could afford **7** in 97% yield. The nitrile group could be hydrolyzed to give **8** in 66% yield, with the recovery of **3a** for 25%. The lactam **9** could be obtained via reduction and cyclization of **8** using 10 mol% Pd/C under one atmosphere of hydrogen in 56% yield.

Table 2 Substrate Scope



^{*a*} Conditions A: Ir(ppy)₂(dtbbpy)PF₆ (2 mol%), MeCN (0.2 M), alkene (0.3 mmol), Michael acceptor (6.0 equiv), TMSN₃ (2 equiv), H₂O (10 equiv), r.t., 8 W blue LEDs. ^{*b*} Conditions B: Ir(ppy)₂(dtbbpy)PF₆ (2 mol%), acetone (0.2 M), alkene (0.3 mmol), Michael acceptor (6.0 equiv), TMSN₃ (2 equiv), MeOH (3 equiv), r.t., 8 W blue LEDs.

The reactions were inhibited in the presence of TEMPO or air which demonstrated the possibility of radical process (eq. 2 and 3). The reaction of **1a** using D_2O afforded **D-3a** in 68% yield with 45% D-incooperation, which indicated that the H_2O was the hydrogen donor (eq. 4). We also carried out the fluorescence quenching study, and found that the fluorescence of photocatalyst could be quenched by TMSN₃, which was consistent with our hypothesis (See SI Figure S3.). The reaction of radical-clock substrate **10** under the standard conditions did not afford any carboazidation or ring-opening carboazidation products (eq. 4). Unexpected, a facile azido radical initiated [3+2] cycloaddition reaction of **10** with acrylonitrile was observed to deliver a substituted cyclopentane **11** in 92% yield (major isomer/ other minor isomers 1.5/1). The reaction of **10** without TMSN₃ did not occur. To the best of our knowledge, it is a first case of

nitrogen radical-promoted [3+2] cycloaddition of vinylcyclopropane with alkene. These results also strongly supported the radical pathway. We proposed that the generated azido radical could attack carbon-carbon double bond on the VCP to afford the benzyl radical species (**B**), which could lead to a radical ring opening pathway and generate carbon center radical (**C**). The radical **C** could be trapped by acrylonitrile to afford radical species **D** which underwent the intramolecular cyclization to afford **E**. The deazidination reaction of **E** could occur to afford **11** and regenerate the azido radical. The control experiments have been added in SI.

Scheme 2 Further Derivatizations.



Scheme 3 Possible Mechanism of The Formation of Compound 11



Conclusions

In summary, we reported the first example of visible light-promoted three-component carboazidation of unactivated alkenes using TMSN₃ and acrylonitrile as reaction partners without any stoichiometric peroxides. The intramolecular reaction of 1,6-diene could also undergo smoothly to afford the cyclization product. The reaction afforded δ -azido alkylnitriles, which could be readily converted into valuable building blocks for medicinal chemistry and organic synthesis. A facile azido radical initiated [3+2] cycloaddition reaction of vinylcyclopropane with acrylonitrile was observed to deliver a substituted cyclopentane. The asymmetric alkene difunctionalization is undergoing in our laboratory.

Supporting Information

The supporting information for this article is available on the WWW under <u>https://doi.org/10.1002/cjoc.2018xxxxx</u>.

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