A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
GDCh
International Edition
www.angewandte.org

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201705353
Angew. Chem. 10.1002/ange.201705353

Link to VoR: http://dx.doi.org/10.1002/anie.201705353
http://dx.doi.org/10.1002/ange.201705353

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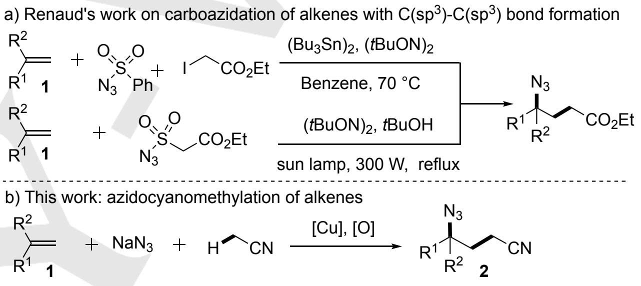
Copper-Catalyzed Three-Component Carboazidation of Alkenes with Acetonitrile and Sodium Azide

Ala Bunescu,+ Tu M. Ha,+ Qian Wang, and Jieping Zhu*

Abstract: A copper-catalyzed three-component reaction of alkenes, acetonitrile and sodium azide afforded γ-azido alkyl nitriles via formation of one C(sp^3)-C(sp^3) bond and one C(sp^3)-N bond. The transformation allows the concomitant introduction of two highly versatile groups (-CN and -N_3) across the double bond. A sequence involving a copper mediated generation of cyanomethyl radical followed by its addition to alkene and a C(sp^3)-N bond formation accounted for the reaction outcome. The resulting γ-azido alkyl nitrile can be easily converted to 1,4-diamine, γ-amino nitrile, γ-azido ester and γ-lactam of significant synthetic value.

Recent years have witnessed important progress in the field of difunctionalization of alkenes. However, the development of three-component carboamination reactions using simple starting materials remains a standing challenge.[1-2] Among various nitrogen sources, the azide is of particular interest as the resulting organoazides are valuable intermediates in synthesis.[3] Indeed, diazidation,[4] azidocyanation,[5] azidophosphonation,[6] oxyazidation,[7] and haloazidation of alkenes[8] have been reported recently. However, three-component carboazidation reaction with the formation of C(sp^3)-C(sp^3) bond is restricted only to few examples.[9-10] In this regard, Renaud and co-workers developed a carboazidation of alkenes **1** employing ethyl α-iodoacetate and phenylsulfonyl azide as the alkyl and the azide sources, respectively (Scheme 1a).[9a-9b] Subsequently, the same group developed an elegant, tin-free desulfonylative carboazidation reaction employing alkanesulfonyl azides as donors of both alkyl and azide groups.[9c] These methodologies have been applied to the syntheses of a series of alkaloids, demonstrating the utility of these azido carbonyl compounds.[9d] Alternatively, three-component azidotrifluoromethylation of alkenes has also been developed by the groups of Liu[10a] and Masson,[10b] respectively.

We have recently initiated a research program aimed at developing copper-catalyzed alkylative difunctionalization of alkenes using alkylnitrile as a key reactant.[11-12] The salient feature of this approach is that the C(sp^3)-H bond of alkyl nitriles was directly functionalized.[13-15] As a continuation of this project, we became interested in developing a three-component azidocyanomethylation of alkenes **1** for the synthesis of γ-azido alkylnitriles **2** (Scheme 1b). While conceptually simple, several challenges could impede the practical execution of the planned transformation. Indeed, azide anion is easily oxidized to azide radical which could subsequently initiate the radical process with the olefin leading to different azidation products. As a matter of fact, a majority of the reported examples of azidocyanation, oxyazidation and haloazidation were initiated by the addition of azide radical to the double bonds.[3] Therefore, to realize our planned transformation, we would have to inverse the established reactivity order and to generate selectively the cyanomethyl radical from acetonitrile in the presence of azide. We report herein a novel and efficient copper-catalyzed azidocyanomethylation of alkenes using acetonitrile and sodium azide as reaction partners (Scheme 1b). The protocol provides an easy access to γ-azido alkylnitriles, which are precursors of 1,4-diamine, γ-amino nitrile, γ-azido ester, γ-lactam and many other important motifs of high synthetic value.


a) Renaud's work on carboazidation of alkenes with C(sp^3)-C(sp^3) bond formation

b) This work: azidocyanomethylation of alkenes

Scheme 1. Carboazidation of Alkenes.

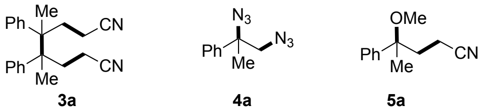


Figure 1. Side Products Isolated During Our Initial Studies.

The feasibility of the proposed transformation was assessed using α-methylstyrene (**1a**, R^1 = Ph, R^2 = Me, Scheme 1b) as a test substrate. Initial survey of the azide sources, the copper salts and the oxidants prompted us to focus on the following basic reaction parameters: NaN_3 (2.0 equiv), $Cu(OAc)_2$ (0.5 equiv) and di-*tert*-butyl peroxide (DTBP, 2.0 equiv), acetonitrile (*c* 0.1 M), 140 °C (see Supporting Information for details). Under these conditions, the desired 4-azido-4-phenylpentanenitrile (**2a**, R^1 = Ph, R^2 = Me) was formed in 26% yield together with 4,5-dimethyl-4,5-diphenyloctanedinitrile (**3a**, 21%) and vicinal diazide **4a** (9%, Figure 1).

The formation of diazide **4a** was indicative of the presence of the azide radical and we assumed that it was generated by oxidation of azide ion by Cu(II) salt. [16] Since ligands are known to modulate the redox potential of Cu(II)/Cu(I), a series of bidentate and tridentate ligands including bisoxazoline, bipyridine, terpyridine and phenanthroline derivatives were tested (see Supporting Information). Gratefully, addition of 1,10-phenanthroline (1,10-phen, 0.5 equiv) to the reaction mixture suppressed completely the formation of 1,2-diazide **4a**. Further

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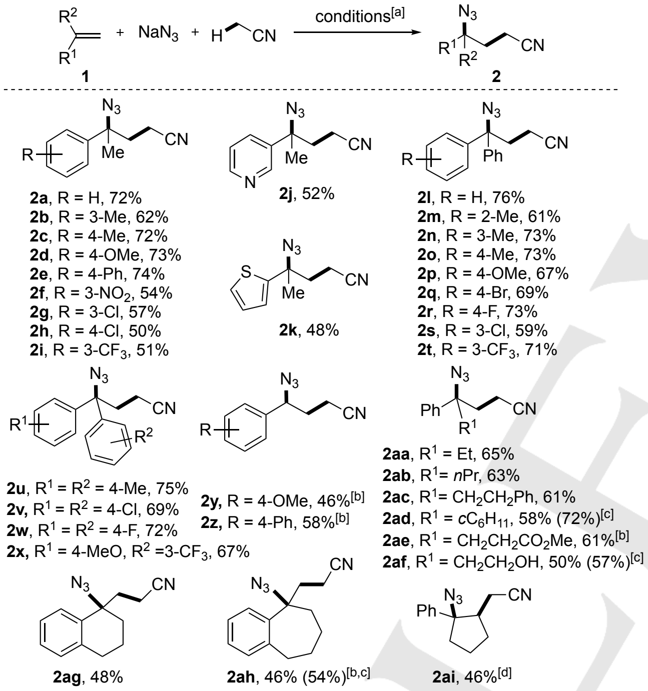
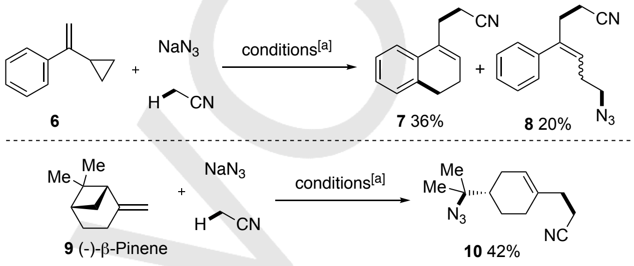
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) screening of reaction parameters showed that the yield of **2a** was increased significantly (63%) when methanol was used as co-solvent. Importantly, only a trace amount of γ-methoxy alkylnitrile **5a** (Figure 1) was detected under these conditions. Performing the reaction at 110 °C under otherwise identical conditions produced **2a** in 66% yield together with **5a** (4% yield). When the reaction was conducted with stoichiometric amount of $Cu(OAc)_2$, **2a** was formed in 88% yield as the only product. This result indicated that the active copper species might not be regenerated effectively under sub-stoichiometric conditions. Therefore, various co-oxidants were surveyed (see Supporting Information) and MnF_3 under air atmosphere turned out to be the most effective. Overall, the optimum conditions consisted of heating a solution of **1a** in MeCN/MeOH (v/v = 1/1, *c* 0.1 M) in the presence of $Cu(OAc)_2$ (0.2 equiv), MnF_3 (0.3 equiv), 1,10-phen (0.65 equiv) and DTBP (2.0 equiv) at 110 °C. Under these conditions, **2a** was isolated in 72% yield.



Scheme 2. Scope of Carboazidation Reaction. [a] $Cu(OAc)_2$ (0.2 equiv), 1,10-Phen (0.65 equiv), MnF_3 (0.3 equiv), DTBP (2.0 equiv), MeCN/MeOH (1:1, 0.1 M), 110 °C, air. [b] $Cu(OAc)_2$ (0.5 equiv), MnF_3 (0.15 equiv) were used. [c] yield in parenthesis was calculated based on conversion. [d] only one diastereoisomer was isolated.

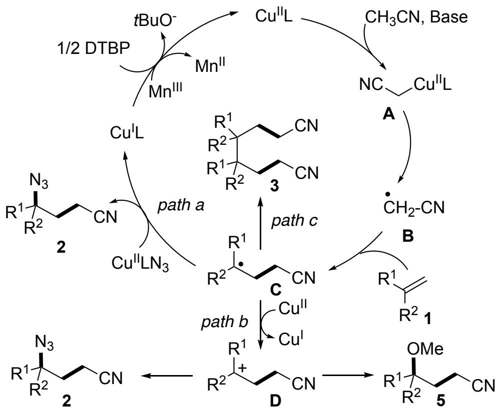
With the optimized conditions in hand, the generality of the carboazidation process was investigated (Scheme 2). Electron donating (Me, OMe) and withdrawing groups (NO_2, Cl, CF_3) on the phenyl ring of the α-methyl styrene derivatives were well tolerated leading to γ-azido alkylnitriles (**2b**-**2i**) in good yields. Heteroaromatics such as pyridine and thiofuran were compatible with the reaction conditions (**2j**, **2k**). The 1,1-diaryl ethylenes were similarly difunctionalized to afford the desired products (**2l**-**2x**) in good yields regardless of the electronic nature and the position of substituent on the aromatic ring (*p*-Cl, *p*-Br, *o*-F, *p*-CF_3, *p*-OMe, *o*-Me, *m*-Me, *p*-Me). Styrene derivatives such as 1-methoxy-4-vinylbenzene or *p*-phenylvinylbenzene were transformed into 4-azido-4-arylbutanenitriles **2y** and **2z** without event. Different alkyl groups including primary (Et, *n*Pr, CH_2CH_2Ph), secondary (cyclohexyl) and those bearing functional groups (ester, OH) at the α-position of styrene were compatible (**2aa**-**2af**). Exocyclic double bond and endocyclic trisubstituted alkene were also successfully difunctionalized, albeit with moderate yields (**2ag**-**2ai**). Unfortunately, propionitrile failed to react under our optimized conditions.



Scheme 3. Radical Clock Experiments. [a] $Cu(OAc)_2$ (0.2 equiv), 1,10-Phen (0.65 equiv), NaN_3 (2.0 equiv), MnF_3 (0.3 equiv), DTBP (2.5 equiv), MeCN/MeOH (1:1), 110 °C, air.

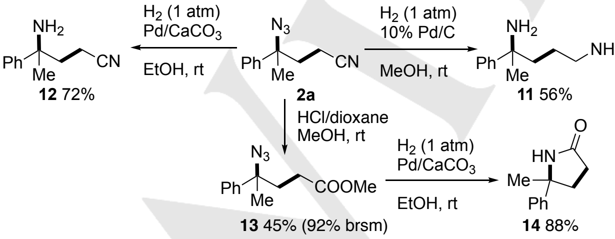
Control experiments were performed to gain insights on the reaction mechanism. The azidocyanomethylation of **1a** took place in the absence of DTBP albeit with low conversion. On the other hand, compound **2a** was not formed in the absence of $Cu(OAc)_2$, suggesting the essential role of copper to this reaction. Submitting 1-(1-cyclopropylvinyl)benzene (**6**) to our standard conditions afforded rearranged products **7** and **8** in yields of 36% and 20%, respectively (Scheme 3). Similarly, treatment of β-pinene (**9**) under our standard conditions afforded the ring-opened product **10** in 42% yield. The results of these two radical clock experiments are indicative of the radical intermediate in these reactions. By monitoring the reaction progress by ^1H NMR spectroscopy [$Cu(OAc)_2$ (0.5 equiv), 1,10-phen (0.5 equiv), DTBP (2.0 equiv), MeOH/MeCN = 1:1, 140 °C] we noticed that the yield of **2a** reached maximum (63%) after only 20 min and that only a trace amount of dimer **3a** was produced at this stage. Prolonging the reaction time (2 h) produced dimer **3a** in 7% yield without increasing the amount of **2a**. This observation indicated that active copper species, most probably Cu(II) salt, was required for the C-N_3 bond formation. In its absence, dimerization of benzyl radical would become competitive leading to dimer **3a**.

On the basis of the above experimental results, a possible reaction pathway for the azidocyanomethylation of alkenes is depicted in Scheme 4.[17] Coordination of acetonitrile to Cu(II) followed by deprotonation would afford cuprate **A**,[14d-g] which, upon homolytic cleavage, would afford cyanomethyl radical **B**.[18] Addition of **B** to alkenes **1** led to benzyl radical **C**, which upon reaction with $Cu(II)LN_3$ (ligand transfer or Cu(III) intermediate), would deliver γ-azido alkylnitrile **2** with the concurrent release of Cu(I) salt. Finally, oxidation of Cu^I by DTBP[19] or by MnF_3 would regenerate the catalytic Cu(II) species. The presence of intermediate **C** was clearly evidenced by our radical clock experiments (*cf* Scheme 3). The dimerization of **C** leading to dinitrile **3** (path c) was suppressed when the Cu(II) salt was efficiently regenerated or a stoichiometric amount of $Cu(OAc)_2$ was employed. The important role played by ligand could be explained by the fact that the coordination of 1,10-phen to copper acetate reduced effectively the redox potential of Cu(II)/Cu(I),[16] inhibiting thereby the generation of azide radical which would be responsible for the formation of 1,2-diazide **4**. It is worth noting that only a trace amount of **4** was generated despite the presence of Mn(III) salt that was known to oxidize azide ion to azide radical. [4d, 4e, 7b]



Scheme 4. Proposed Reaction Pathway for Carboazidation Reaction.

Alternatively, oxidation of radical **C** by Cu(II) followed by trapping of the resulting tertiary carbocation **D** by azide could also afford the carboazidation product **2** (path b).[20] Should this be the case, carbocation **D** would also be trapped by methanol in a $MeOH/CH_3CN$ solvent mixture leading to a competitive formation of γ-methoxy alkylnitrile **5**.[11c] However, this was not observed under our optimized conditions. Furthermore, the fact that azidocyanomethylation of methyl 4-phenylpent-4-enoate (**1ae**) produced **2ae** without competitive formation of γ-lactone was also against the carbenium intermediate.[11b] Consequently, we assumed that a copper-mediated azide transfer to radical **C** was more likely to occur (path a).



Scheme 5. Post Transformation of γ-Azido Alkylnitrile **2a**.

Conversion of γ-azido alkylnitrile **2a** to other useful structural motifs is depicted in Scheme 5. Hydrogenation of **2a** in the presence of Pd/C afforded diamine **11**. On the other hand, hydrogenation using Lindlar catalyst ($Pd/CaCO_3$) allowed the chemoselective reduction of azido function to provide γ-amino alkylnitrile **12**. Treatment of **2a** under acidic conditions (HCl in dioxane, MeOH) afforded γ-azido ester **13** which, upon hydrogenation of azide, was converted to pyrrolidinone **14**.

In conclusion, we reported the first examples of copper-catalyzed azidocyanomethylation of alkenes using acetonitrile and sodium azide as reaction partners. The reaction produced γ-azido alkylnitriles via formation of one $C(sp^3)$–$C(sp^3)$ bond and one $C(sp^3)$–N bond. The γ-azido alkylnitrile was readily converted to 1,4-diamine, γ-amino nitrile, γ-azido ester and γ-lactam, useful building blocks in organic synthesis and in medicinal chemistry.

Acknowledgements

We thank EPFL (Switzerland), Swiss National Science Foundation (SNSF) and Swiss National Centers of Competence in Research NCCR-Chemical Biology for financial supports.

Keywords: Homogeneous catalysis • multicomponent reaction • azide • alkenes • difunctionalization

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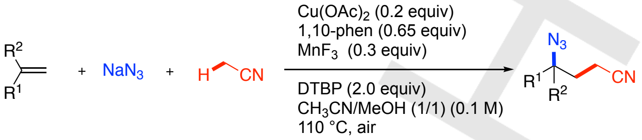
Entry for the Table of Contents (Please choose one layout)

Layout 1:

Synthetic Method

*Ala Bunescu, Tu Minh Ha, Qian Wang and Jieping Zhu**___________ ***Page – Page***

Copper-Catalyzed Three-Component Carboazidation of Alkenes with Acetonitrile and Sodium Azide



* Formation of one C(sp^3)-C(sp^3) bond and one C-N bond
* Introduction of two versatile functional groups (N_3, CN)
* Creation of a quaternary carbon
* High chemo- and regioselectivities

Be disciplined *Regioselective azidocyanomethylation of alkenes took place smoothly in the presence di-tert-butyl peroxide, a catalytic amount of Cu(OAc)$_2$ and MnF$_3$ to afford γ-azido alkylnitriles, highl valued synthetic building blocks.*