

α -Amino Radical-Mediated Diverse Difunctionalization of Alkenes: Construction of C–C, C–N, and C–S Bonds

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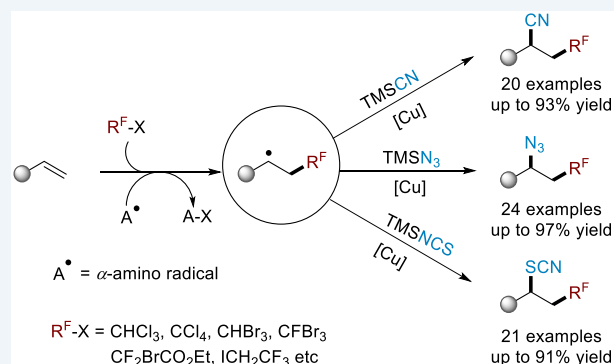
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ABSTRACT: A general catalytic methodology for 1,2- R^F/Y -difunctionalization of conjugated alkenes is reported. Diverse functionalized carbon radicals ($R^F\bullet$), which are generated through copper(I)-initiated selective halogen atom abstraction via a *tert*-butyl hydroperoxide-induced α -amino radical process, undergo regiocontrolled addition to carbon–carbon double bonds. The newly formed carbon radicals combine with $Y = \text{CN}, \text{N}_3$, or NCS from TMSY in a copper(I)-promoted process to form a broad spectrum of α -cyano-, α -azido-, and α -thiocyano- β -substituted products with additional functionalities in R^F in high yields. Conversion of the reaction products to functionalized cyclopropane, amide, amine, triazole, thiol, and tetrazole highlights the potential utility of this method.

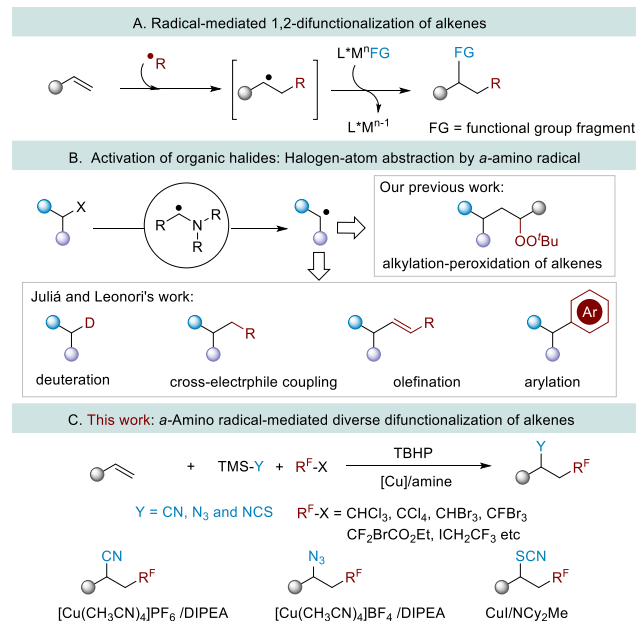
KEYWORDS: α -amino radical, dichloromethyl radical, cyanation reactions, azidation reactions, thiocyanation reactions



Radical-mediated difunctionalization of alkenes provides powerful and attractive strategies to increase molecular and functional complexity.¹ As with their oxidative ionic counterparts, bromination and dihydroxylation, these reactions add two new functional groups to the reactant alkene (Scheme 1A). Organic halides are important and versatile compounds whose addition to alkenes provides wide applications in synthetic organic chemistry. Different reaction modes involving organic halides have been developed, such as classical nucleophilic substitution and metal-catalyzed cross-coupling reactions. Their activation through halogen-atom transfer (XAT), generating various carbon radicals, represents another powerful method to construct target molecules. In one of the most notable examples of these reactions, Kharasch et al. reported the addition of carbon tetrachloride and chloroform to olefins in the presence of acetyl peroxide.² In addition, tin and silicon reagents combining with initiators are also often utilized to convert organic halides into their corresponding carbon radicals.³ In particular, silyl radicals have been used in the activation of halides in metallaphotoredox catalysis as reported by MacMillan.⁴

Apart from these powerful halogen-abstracting reagents, our group and Leonori and Juliá's group demonstrated that α -amino radicals are another type of powerful and alternative XAT reagents based on their strong nucleophilicity similar to tin and silyl radicals.⁵ Previously we reported the TBHP-induced formation of an α -amino radical that abstracted a halide atom ($\text{I} > \text{Br} > \text{Cl}$), producing the carbon radical which selectively underwent addition to carbon–carbon double bonds and terminated in the formation of α -peroxy- β -substituted ethylbenzene products (Scheme 1B, right).^{5a} Leonori, Juliá, and co-

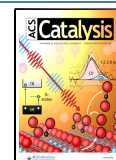
Scheme 1. Radical-Mediated 1,2-Difunctionalization of Alkenes and Activation of Alkyl Halides by α -Amino Radical



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workers presented the deuteration, cross-electrophile coupling, Heck-type olefination, and aromatic C–H alkylation reactions of the alkyl radicals, generating from the XAT of halides. (Scheme 1B, down).^{5b} Both methodologies provided efficient XAT with the TBHP-induced transformation allowing difunctionalization. Considering the strong affinity between silane and oxygen, we questioned whether other functional groups could be introduced instead of the *tert*-butyl peroxy group by adding the TMSY (Y = CN, N₃, or NCS) reagents.

Though TMSY reagents (Y = CN, N₃, or NCS), especially TMSCN, have been used to trap the radical intermediate generated from the addition of •CF₃ or a nitrogen radical to C=C bonds,⁶ methodologies in which two Y functionalities are introduced have been rare, and a general methodology for 1,2-R^F/Y difunctionalization with three Y functional groups has not been reported. Inspired by these reports and our previous work, we sought a broad catalytic methodology for 1,2-difunctionalization and focused on the formation of C–C, C–N, C–S bonds, instead of the C–O bond of a mixed peroxide to provide a greater diversity of compounds.

The dichloromethyl group widely exists in a variety of biologically active compounds including antibiotics, antineoplastics, and analgesics.⁷ In addition, C–Cl bonds are easily cleaved to facilitate the synthesis of amines,⁸ alcohols,⁹ carbonyl compounds,¹⁰ heterocycles,¹¹ cyclopropanes, and other valuable compounds.¹² In this investigation of 1,2-difunctionalization, we begin our report with three dichloromethyl/Y difunctionalizations of alkenes to synthesize α -cyano-, α -azido-, and α -thiocyano- β,β -dichloropropylarene products in high yields (Scheme 1C). After the selective addition of the CHCl₂ radical to the carbon–carbon double bond, C–C, C–N, and C–S bonds are formed instead of the C–O bond from TBHP by combining appropriate Cu(I) catalysts with amine and TMSY (Y = CN, N₃, or NCS), utilizing the strong affinity between silane and oxygen. Expansion of this study to fragments beyond dichloromethyl demonstrates that this is a broad methodology for the addition of diverse functional groups to alkenes.

The cyano group is a unique functional group that is not only found abundantly in bioactive natural products and pharmaceuticals, but is also a versatile precursor to many other functional groups.¹³ We began our studies by examining the 1,2-dichloromethylcyanation of *p*-methylstyrene (**1a**) with TMSCN as the cyanation reagent. Our concern was whether cyano group transfer could compete with the known trapping by •BuOO•. We added TMSCN under our previous reaction conditions,^{5a} and cyanide product **2a** was obtained in 30% yield along with 5% of peroxide byproduct **2a'** (Table 1, entry 1). The number of equivalents of TMCN and TBHP had a great influence on the ratio of desired product **2a** and byproduct **2a'**, and the best equivalent ratio was recognized as 5.0/2.0 after careful investigation of the feed ratio (Table S1, entries 1–8). Optimization of the reactants and determination that the most effective catalyst was [Cu(CH₃CN)₄]PF₆ increased the yield of **2a** to 93% (Table 1, entries 2–5). Further optimization of the reaction conditions found that byproduct **2a'** could be completely avoided by decreasing the reaction temperature from 50 °C to room temperature (99% isolated yield of **2a**, Table 1, entries 6–7). A photocatalytic system to generate the α -amino radical produced only a trace amount of product (for more details, see Supplementary Table S1).

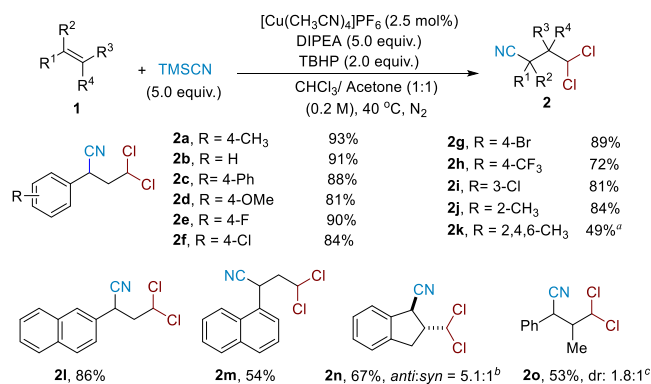
Considering the balance of yield and reaction time, we examined the scope of alkenes **1** under the conditions of Table 1, entry 6 (Scheme 2). Styrenes bearing electron-rich and electron-

Table 1. Optimization of Reaction Conditions for Dichloromethylcyanation^a

entry	[Cu]	x (mol %)	y/z (equiv)	yield (%) ^b	2a/2a'
1	CuI	1.0	3.0/1.0	30/5	
2	CuI	1.0	5.0/2.0	61/9	
3	CuI	2.5	5.0/2.0	72/8	
4	[Cu(CH ₃ CN) ₄]BF ₄	2.5	5.0/2.0	83/6	
5	[Cu(CH ₃ CN) ₄]PF ₆	2.5	5.0/2.0	93 (90) ^c /5	
6 ^d	[Cu(CH ₃ CN) ₄]PF ₆	2.5	5.0/2.0	97 (93) ^c /0	
7 ^e	[Cu(CH ₃ CN) ₄]PF ₆	2.5	5.0/2.0	99 (99) ^c /0	

^aReaction conditions: unless indicated otherwise, **1a** (0.4 mmol), [Cu] (x mol %), TMSCN (y equiv), DIPEA (5.0 equiv), TBHP (70% in H₂O, z equiv) in CHCl₃/acetone (1:1, 2.0 mL) at 50 °C for 12 h under N₂ atmosphere. ^bThe yields of **2a**/**2a'** were determined by ¹H NMR spectroscopic analyses of the reaction mixture using CHBr₃ as the internal standard. ^cIsolated yield in parentheses. ^dAt 40 °C, for 24 h. ^eAt rt, for 5 d.

Scheme 2. Substrate Scope of Alkenes for Dichloromethylcyanation



^aGeneral conditions: **1** (0.4 mmol), TMSCN (2.0 mmol), [Cu(CH₃CN)₄]PF₆ (2.5 mol %), DIPEA (2.0 mmol), TBHP (70% in H₂O, 0.8 mmol), CHCl₃/acetone (1:1, 2.0 mL), N₂, 40 °C, 24 h. ^b20% starting material was recovered. ^cThe *anti:syn* ratio was determined by ¹H NMR spectroscopy. ^dThe *dr* value was determined by ¹H NMR spectroscopy.

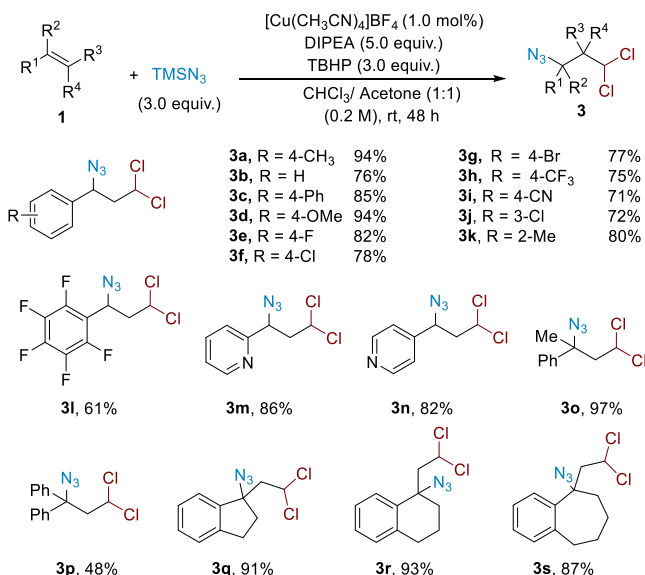
deficient substituents at the *para*-, *meta*-, and *ortho* positions of the phenyl moiety provided products in good to excellent yields (**2a**–**2j**), although 2,4,6-trimethylstyrene gave a lower yield with 20% of the starting material recovered (**2k**). In addition, 1-vinylnaphthalene and 2-vinylnaphthalene were also compatible with this methodology (**2l**–**2m**). Reactions with vicinal disubstituted alkenes were also investigated, and they afforded products in good yields (**2n**–**2o**), albeit only a 1.8:1 *dr* value was obtained with *trans*- β -methylstyrene.

Organic compounds that contain nitrogen are of great importance in natural products and pharmaceuticals,¹⁴ and azido transfer is an efficient method to construct the C–N bond.¹⁵ Based on our success in the use of TMSN₃ in radical-mediated functionalization of alkenes with diazo compounds,¹⁶ we next sought to develop reaction conditions for the dichloromethylazidation of *p*-methylstyrene **1a**. This reaction was found to be sensitive to air, which may due to the undesired oxidation of styrene as we elaborated before.¹⁷ Using the

optimized conditions from dichloromethylcyanation with $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{BF}_4$ as the catalyst, product **3a** was obtained in 94% isolated yield (for more details, see [Supplementary Table S2](#)).

The scope of applicable alkenes was then evaluated for this dichloromethylazidation process ([Scheme 3](#)). Both electron-

Scheme 3. Substrate Scope of Alkenes for Dichloromethylazidation^a

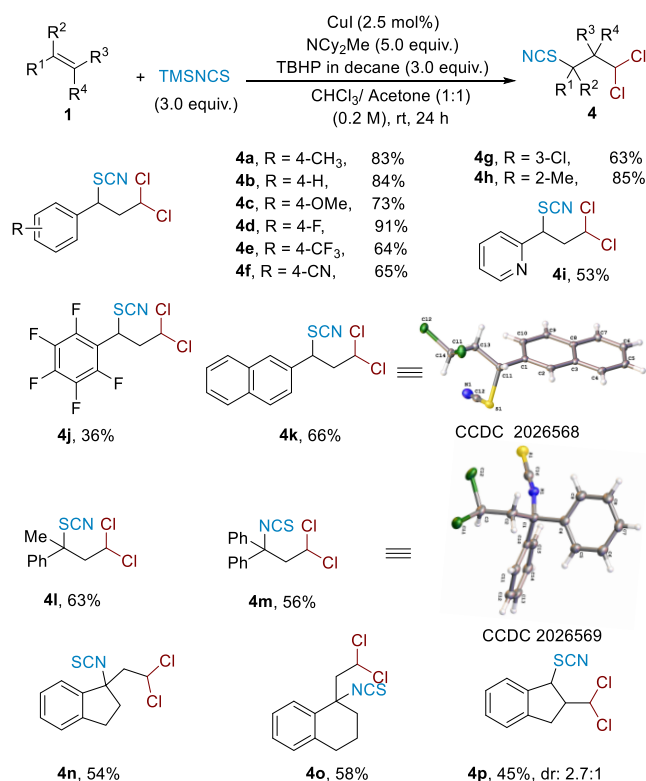


^aGeneral conditions: **1** (0.4 mmol), TMSN₃ (1.2 mmol), $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{BF}_4$ (1.0 mol %), DIPEA (2.0 mmol), TBHP (70% in H₂O, 1.2 mmol), CHCl₃/acetone (1:1, 2.0 mL), N₂, rt, 48 h.

donating (**3a**, **3c**, **3d**, and **3k**) as well as electron-withdrawing (**3e–3j**) substituents on the aromatic ring of styrene offered the products in good to excellent yields. Pentafluorostyrene and heteroaromatic alkenes, 2-vinylpyridine and 4-vinylpyridine styrene, were also compatible with this reaction and provided dichloromethylazidation products in moderate to high yields (**3l–3n**). Substitution at the α -position was also examined. While α -methylstyrene delivered the product in excellent yield (**3o**), the reaction of 1,1-diphenylethylene offered the desired product **3p** along with α -peroxy- β,β -dichloropropylarene **3p'** in 1:1 ratio. Furthermore, substrates containing exocyclic C=C bonds delivered the corresponding products in excellent yields (**3q–3s**).

Inspired by the present results, we explored the dichloromethylthiocyanation reaction using TMSNCS as the source of thiocyanide. The desired dichloromethylthiocyanation product **4a** was obtained in 29% yield when TMSNCS was used instead of TMSN₃. After extensive screening of reaction parameters, the highest yield (83%) was obtained in reactions with anhydrous TBHP in decane using NCy₂Me with catalytic amounts of CuI (for details, see [Supplementary Table S3](#)). The structure of the amine has proven to be important in this process ([Table S3](#), entries 6 and 9–13). This may be due to the rate matching effect between the halide abstraction by the α -amino radical and the terminating step of the benzyl radical. The substrate scope of this protocol was then investigated ([Scheme 4](#)). Diverse alkenes were reacted with TMSNCS according to this methodology, affording the corresponding products in moderate to excellent yields (**4a–4h**) with higher yields obtained when the aryl substituent was electron-donating. Pentafluorostyrene and 2-

Scheme 4. Substrate Scope of Alkenes for Dichloromethylthiocyanation^a

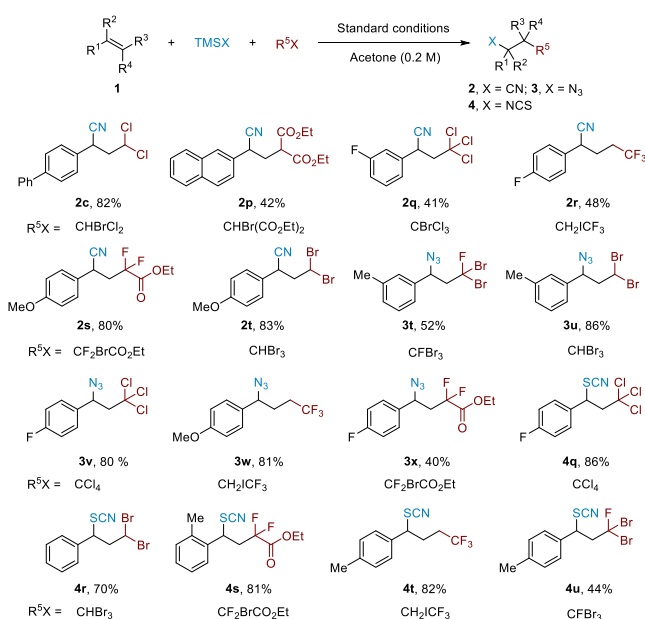


^aGeneral conditions: **1** (0.4 mmol), TMSNCS (1.2 mmol), CuI (2.5 mol %), NCy₂Me (2.0 mmol), TBHP in decane (1.2 mmol), CHCl₃/acetone (1:1, 2.0 mL), N₂, rt, 24 h.

vinylpyridine were also compatible, although their yields were lower (**4i–4j**). Additionally, reaction with 2-vinylnaphthalene smoothly delivered product **4k**, and its X-ray structure was obtained for full characterization. To our surprise, the isothiocyanate products of three α,α -disubstituted alkenes (1,1-diphenylethylene and substrates containing exocyclic C=C bonds) **4m–4o** were obtained instead of the expected thiocyanates. The X-ray structure of product **4m** was also obtained for full characterization. Though isomerization between thiocyanates and isothiocyanates had been reported,¹⁸ we did not detect initial thiocyanate products when the reactions were monitored by NMR spectroscopy. The formation of the isothiocyanate products may be due to steric effects in the capture of SCN at sulfur versus nitrogen.¹⁹ In addition to **4n** and **4o**, we also obtained alkene byproducts **4n'** and **4o'** (18% and 14%, respectively) which suggest the involvement of benzylic carbocations. 1-Indene underwent dichloromethylthiocyanation with moderate yield but low diastereoselectivity (**4p**).

To further examine the generality of this protocol, we investigated reactions with other halogenated compounds and diverse alkylcyanation, alkylazidation and alkylthiocyanation of alkenes were achieved ([Scheme 5](#)). When mixed halogenated compounds were used, selectivity for Br > Cl > F removal was observed ([Scheme 5](#), **2c**, **2q**, **3t**, and **4u**). α -Halogenated esters were also competent and provided the corresponding carboxylate products in moderate to good yields ([Scheme 5](#), **2p**, **2s**, **3x**, and **4s**). Furthermore, iodine could also be efficiently removed from ICH₂CF₃ to produce products **2r**, **3w**, and **4t** in moderate to high yields ([Scheme 5](#)). Finally, carbon tetrachloride and bromoform were also compatible and

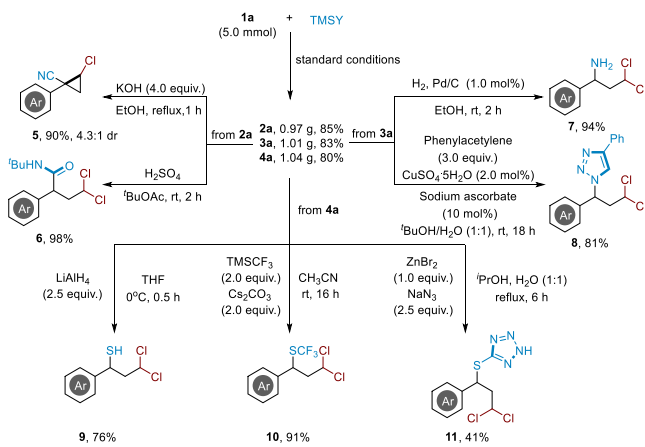
Scheme 5. Substrate Scope of Alkyl Halide for Difunctionalization of Alkenes^a



furnished the corresponding products in good yields (**2t**, **3u**, **3v**, **4q**, and **4r**).

The synthetic utility of this difunctionalization methodology was then investigated (Scheme 6). Three gram-scale reactions

Scheme 6. Gram-scale Reactions and Synthetic Transformations



were performed to obtain starting materials, and all of them furnished their corresponding products in satisfying yields. Functionalized cyclopropane derivative **5** was obtained when **2a** was simply treated with base. Owing to the versatility of the nitrile group, **2a** could also be easily transformed to *N*-*tert*-butyl amide **6** in excellent yield under modified Ritter reaction conditions.²⁰ Furthermore, the azide group was reduced to amine **7** in high yield under standard hydrogenation conditions, and 1,2,3-triazole **8** was produced through classical Click reaction with phenylacetylene.²¹ Moreover, the thiocyanate group was smoothly reduced to thio **9** with LiAlH₄, and it could

also be converted to thiotrifluoromethyl group when treated with TMSCF₃ with base Cs₂CO₃, which further suggests the utility of this methodology. Finally, tetrazole **11**, which can act as a bioisostere for carboxylate groups because of their similar pK_a values, was produced in the presence of NaN₃ and ZnBr₂.²²

Radical trapping experiments were performed with TEMPO, and the reactions were terminated leaving only unreacted starting materials, which suggest the radical nature of these transformations. The discovery that isothiocyanates **4m**–**4o** were obtained instead of their corresponding thiocyanates suggests a different pathway for these substrates that would also have to be consistent with elimination products **4n'** and **4o'**. On the basis of these results and previous reports,^{5a,6,23} a possible mechanism is proposed in Figure 1. The reaction is initiated by

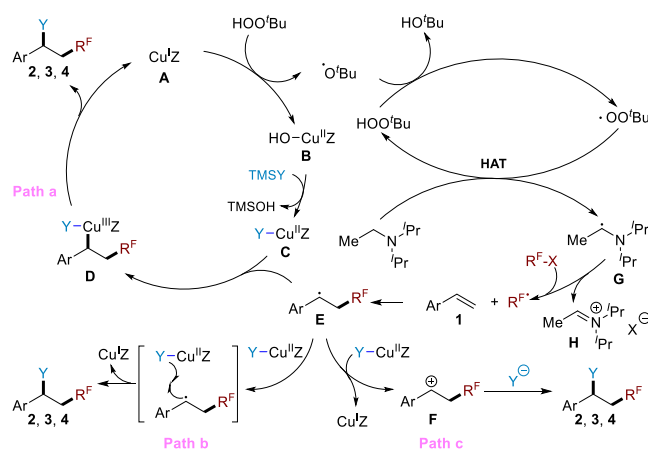


Figure 1. Plausible mechanism for α -amino radical-mediated diverse difunctionalization of alkenes.

the Cu(I) catalyzed decomposition of TBHP, delivering the Cu(II) species **B** and the *tert*-butoxy radical. The Cu(II) species **B** undergoes ligand transfer with TMSY (Y = N₃, CN, and NCS) forming the Cu(II)-Y species **C**. The *tert*-butoxy radical reacts with another molecule of TBHP to provide the *tert*-butylperoxy radical, which further undergoes the HAT process with the amine affording the key α -amino radical **G** intermediate. α -Amino radical **G** selectively abstracts a halogen atom from R^FX generating the R^F radical and iminium salt **H** which was identified in our earlier study.^{5a} Addition of R^F• to the C=C produces benzyl radical **E**. There are three possible pathways for the formation of the final products. In Path a, the benzyl radical **E** reacts with Cu(II)-Y **C** to form Cu(III) species **D** that, followed by reductive elimination, regenerates the Cu(I) catalyst and produces product **2**, **3**, or **4**. Alternatively, product could be formed through the outer-sphere ligand transfer between Cu(II)-Y and radical **E** (Path b). Finally, radical **E** could be oxidized by Cu(II) through a single electron transfer (SET) process providing carbocation **F** that is trapped by azide, cyanide, or thiocyanate. Experimental data provides support for the radical-polar crossover²³ Path c from the isothiocyanation of 1-methylene-2,3-dihydro-1*H*-indene and 1-methylene-1,2,3,4-tetrahydronaphthalene, accompanied by alkene byproducts **4n'** and **4o'**, that indicate carbocation involvement in these cases. However, the other two pathways for the formation of other products could not be excluded.

In conclusion, we have developed copper catalyzed carbocyanation, carboazidation and carbothiocyanation of alkenes utilizing the selective abstraction of a halogen atom

(X) by α -aminoalkyl radicals. A diverse set of β,β -dichloronitriles, β,β -dichloroazides, and β,β -dichlorothiocyanates using CHCl_3 as the precursor of $\bullet\text{CHCl}_2$, as well as corresponding products from alkyl halides, were obtained in good to excellent yields. The incorporation of dichloromethyl group and other functionalities with nitrile, azide, or thiocyanate into alkenes expands possibilities for further transformations, and some of these have been demonstrated by the synthesis of chlorocyclopropanenitrile, amide, amine, triazole, thiol, and tetrazole products. Further applications utilizing α -aminoalkyl radicals to activate alkyl halides for radical addition reactions are ongoing in our laboratory.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.0c04243>.

Experimental procedure and spectroscopic data for all new compounds (PDF)

X-ray crystallographic data for **4k** (CIF)

X-ray crystallographic data for **4m** (CIF)

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Notes

The authors declare no competing financial interest.

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