JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b11499 • Publication Date (Web): 04 Dec 2018

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Copper-Catalyzed Radical 1,4-Difunctionalization of 1,3-Enynes with Alkyl Diacyl Peroxides and *N*-fluorobenzenesulfonimide

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KEYWORDS. allenes, 1,4-carbocyanation, 1,4-sulfimidocyanation, 1,3-enynes, allenyl radical, radical relay, copper catalysis

ABSTRACT: Many reactions involving allenyl ion species have been studied but reactions involving allenyl radicals are less well understood, perhaps because of the inconvenience associated with the generation of short-lived allenyl radicals. We describe here a versatile method for the generation of allenyl radicals and their previously unreported applications in the intermolecular 1,4-carbocyanation and 1,4-sulfimidocyanation of 1,3-enynes. With the assistance of the trifunctional reagents, alkyl diacyl peroxides or *N*-fluorobenzenesulfonimide, a range of synthetically challenging multi-substituted allenes can be prepared with high regioselectivity. These multisubstituted allenes can be easily transformed into synthetically useful structures such as fluorinated vinyl cyanides, lactones, functionalized allenyl amides, 1-aminonaphthalenes and pyridin-2(1*H*)-ones, and several novel transformations are reported. The results of radical scavenger and radical clock experiments are consistent with the proposed allenyl radical pathway. Density functional theory (DFT) and IR spectroscopy studies suggest the formation of an isocyanocopper(II) species in the ligand exchange step. Based on the results of IR, DFT and diastereoselectivity studies, an isocyanocopper(II)/copper(I) catalytic cycle is proposed, which differs from the previously considered Cu(III) mechanism in cyanation reactions.

INTRODUCTION

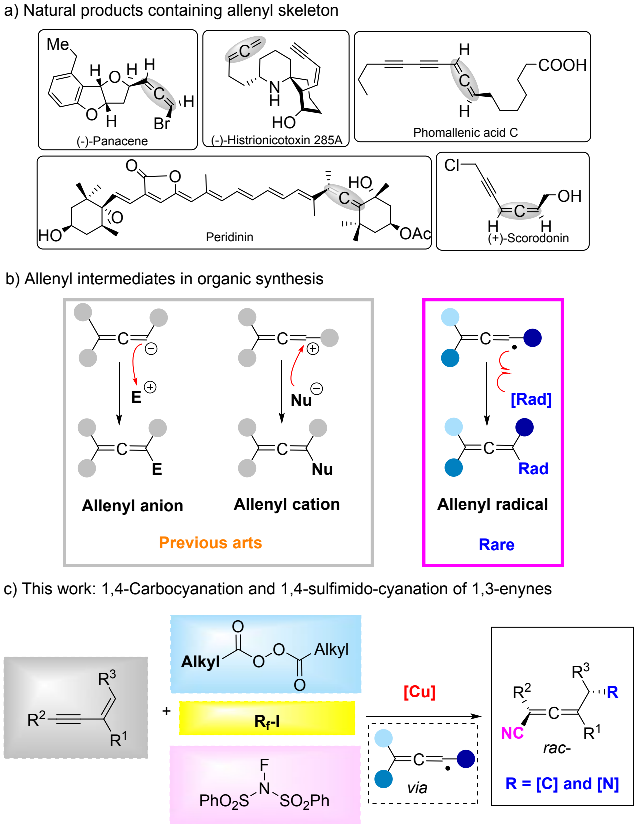
Allenes are important structural motifs found in natural products and are key intermediates in the synthesis of complex molecules (Scheme 1a).[1,2] Classical methods for the synthesis of allenes include prototropic re-arrangements,[3] sigmatropic rearrangements,[4] nucleophilic substitutions,[5] 1,4-additions to enynes[6-8] and other methods.[9,10] While most of these methods usually introduce only one functional group, 1,4-addition to 1,3-enynes introduces two functional groups simultaneously and has attracted increasing attention in recent years. Groups led by Ma, Kambe, Yoshida and Kimura have developed efficient 1,4-difunctionalization reactions of 1,3-enynes using organometallic reagents, affording allenes *via* allenyl anion intermediates (Scheme 1b).[6] Compared to the allenyl ionic intermediates, allenyl radicals have been less utilized in organic synthesis.

1,4-Difunctionalization of 1,3-enynes[11] *via* a radical pathway is unusual, as is intermolecular 1,4-difunctionalization.[12] This is probably due to the generation of short-lived allenyl radicals.[13] 1,4-Di-functionalization of 1,3-enynes that proceeds *via* an allenyl radical pathway could be very useful. The allenyl radical is very reactive and is susceptible to oxidation to an allenyl cation, as an effective electrophile, or reduction, forming a carbon-metal bond,[12] to the allenyl anion, as a nucleophile. Consequently, reactions which cannot proceed by an allenyl anion pathway may take advantage of a feasible allenyl radical pathway.

Nitriles are versatile building blocks useful in the synthesis of carboxylic acids, amines, amides, and ketones,[14] and are also an important class of organic compounds, frequently found in pharmaceuticals and other important chemicals.[15] Due to the unique role of the cyano group, its introduction into organic molecules is important in synthetic chemistry. Difunctionalizations of alkenes with a cyanation reaction have been well developed.[16] In these difunctionalization cyanation reactions, copper salts are frequently utilized either as catalysts or as stoichiometric reagents. The copper(III)/-

copper(I) catalytic cycles proposed in other C-C bond and C-N bond formation reactions,[17] have also been frequently proposed in cyanation reactions.[16a-d,16g,16i] Notwithstanding these significant breakthroughs in difunctionalization cyanation reactions, the 1,4-difunctionalization cyanation of 1,3-enynes has been only reported once by Liu et al.[18] in work that uses Togni's reagent. On the basis of our previous work,[19] we envisioned that the allenyl radical pathway could offer a solution to this type of reaction. In view of the fact that the structure and reactivity of allenyl radicals differ from those of the conventional alkene counterpart, the difunctionalization cyanation of 1,3-enynes could proceed through some unique reaction pathway (Scheme 1c). We report in this paper our recent discovery of copper-catalyzed intermolecular 1,4-carbocyanation and 1,4-sulfimidocyanation of 1,3-enynes, reactions that proceed *via* allenyl radical intermediates through a radical or radical relay pathway.

Scheme 1. Allenyl intermediates and this work.

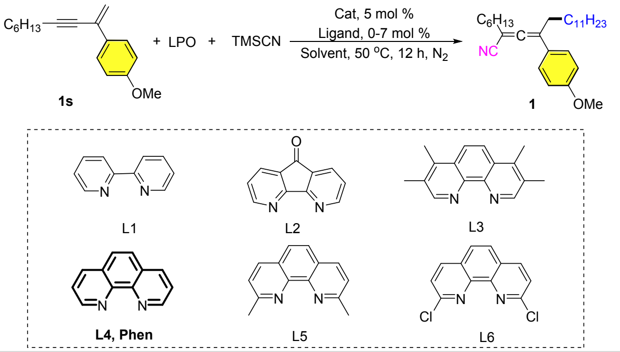


RESULTS AND DISCUSSION

1,4-Alkylcyanation of 1,3-enynes

Carboxylic acids are inexpensive, stable and non-toxic feedstock chemicals. An alkyl diacyl peroxide, readily prepared from carboxylic acids, is a type of activated carboxylic acid. Such peroxides usually serve as oxidants and recently have been systematically studied by our group[19] as alkylating reagents and internal oxidants, acting simultaneously. In addition to behaving as alkylating reagents and internal oxidants, alkyl diacyl peroxides can serve as a reagent that could safely release the cyano group from trimethylsilyl cyanide (TMSCN) or generate a new radical through a radical relay process.

Table 1. Optimization of conditions for 1,4-alkylcyanation with lauroyl peroxide (LPO).[a]

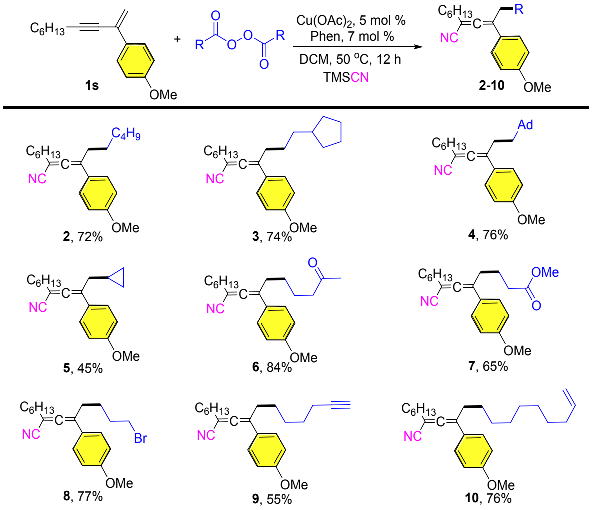


entry	cat.	solvent	ligand	yield (%)
1	$Fe(OTf)_3$	CH_3CN	-	trace
2	$Ni(acac)_2$	CH_3CN	-	trace
3	$Pd(OAc)_2$	CH_3CN	-	trace
4	$CoCl_2$	CH_3CN	-	trace
5	CuTc	CH_3CN	-	15%
6	CuTc	CH_3CN	L1	40%
7	CuTc	CH_3CN	L2	38%
8	CuTc	CH_3CN	L3	45%
9	CuTc	CH_3CN	L4	57%
10	CuTc	CH_3CN	L5	52%
11	CuTc	CH_3CN	L6	48%
12	CuI	CH_3CN	L4	50%
13	$Cu(OAc)_2$	CH_3CN	L4	65%
14	$Cu(OTf)_2$	CH_3CN	L4	60%
15	$CuBr_2$	CH_3CN	L4	62%
16	$Cu(OAc)_2$	THF	L4	46%
17	$Cu(OAc)_2$	DCM	L4	75%(73%[b])
18	$Cu(OAc)_2$	Toluene	L4	38%
19[c]	$Cu(OAc)_2$	DCM	L4	20%
20[d]	$Cu(OAc)_2$	DCM	L4	55%
21[e]	$Cu(OAc)_2$	DCM	L4	50%

[a] Reaction conditions: 1,3-Enyne (**1s**), (0.2 mmol), LPO (3 equiv), TMSCN (3 equiv), catalyst (5 mol %), and ligand (0 or 7.0 mol %), solvent (1 mL), 50 °C, 12 h under N_2. [b] Yield of isolated product. [c] room temperature. [d] 70 °C. [e] LPO (1.5 equiv), TMSCN (1.5 equiv).

Our investigation began with the reaction of a 1-(dec-1-en-3-yn-2-yl)-4-methoxybenzene (**1s**) with the commercially available LPO and TMSCN. Details of the optimization of the conditions are provided in Table 1. The iron, nickel, palladium and cobalt catalysts that were examined were not active in this reaction (Table 1, entries 1-4). The reaction with 5 mol% of copper(I)-thiophene-2-carboxylate (CuTc) forms the product in 15% yield (entry 5). Studies of ligands (entries 6-11) revealed that phenanthroline (L4) improved the yield significantly, the product being obtained in 57% yield (entry 9). Optimization of copper catalysts and solvents showed that $Cu(OAc)_2$ is the optimal metal catalyst and DCM is the optimal solvent (entry 17). No 1,2-alkylcyanation product was observed, the sole product being the 1,4-alkylcyanation product, a tetrasubstituted allene (**1**) which is produced exclusively in 73% yield.

Table 2. Substrate scope of alkyl diacyl peroxides for 1,4-alkylcyanations.[a]



[a] Reaction conditions: 1,3-Enyne (**1s**, 0.2 mmol), alkyl diacyl peroxide (3 equiv), TMSCN (3 equiv), in DCM (1 mL), 50 °C, yields of isolated products.

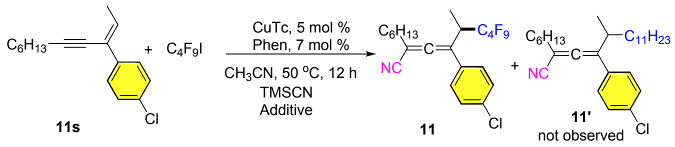
The scope of diacyl peroxides as the alkylating reagent was studied under the optimized reaction conditions and the results are shown in Table 2. Simple alkyl diacyl peroxides afford the desired products (**2-5**) in good (45-76%) yields. Alkyl diacyl peroxides with additional functionality such as bromo, alkenyl or ester groups are well tolerated in this reaction, delivering the corresponding products (**6-10**) in 55-84% yield.

1,4-Fluoroalkylcyanation of 1,3-enynes

Introduction of fluoroalkyl moieties into commonly used building blocks has recently been attracting increasing attention.[20] Notwithstanding the recent significant progress in the fluoroalkylation of unsaturated hydrocarbons,[21] efficient methods for the production of fluoroalkylated allenes from 1,3-enynes are not known. We questioned if fluoroalkylated iodides could serve as a reagent with which to generate fluoroalkylated allenes.

Unfortunately, under the previously defined standard conditions, no product was observed (Table 3, entry 1) and in view of the oxidative nature of this reaction, oxidative additives were studied. *t*-Butyl hydroperoxide (TBHP) and *t*-butyl peroxybenzoate (TBPB) enabled the reactions, which give the desired products in 10-27% yield (Table 3, entries 2-4). It was surmised that alkyl diacyl peroxides could promote this reaction as trifunctional reagents *via* a radical relay pathway only if the radical relay step is faster than alkyl radical addition to 1,3-enynes. Surprisingly, with 1.5 equivalents of LPO (entry 5), the reaction reached essentially full conversion and the 1,4-perfluoroalkylcyanation product (**11**) was isolated in 89% yield. No 1,4-alkylcyanation product (**11'**) was observed in this reaction.

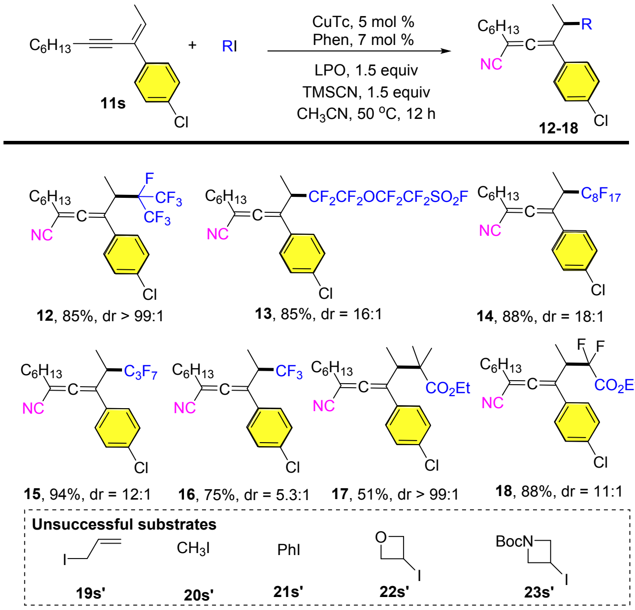
Table 3. Optimization of conditions for 1,4-alkylcyanation with *n*-C_4F_9I.[a]



entry	additive	**11**, yield (%)[b]
1	/	/
2	TBHP(in H_2O)	27
3	TBHP(in decane)	15
4	TBPB	10
5	LPO	90 (89, dr=13.5:1) [c]
6	LPO (1.0 equiv)	80

[a]Reaction conditions: 1,3-Enyne (**11s**, 0.2 mmol), *n*-C_4F_9I (1.5 equiv), additive (1.5 equiv), TMSCN (1.5 equiv), in CH_3CN (1 mL), 50 °C. [b] yields are determined by ^1H NMR. [c] Yield of isolated product in parentheses.

Table 4. Substrate scope of alkyl iodides in 1,4-alkylcyanations.[a,b]

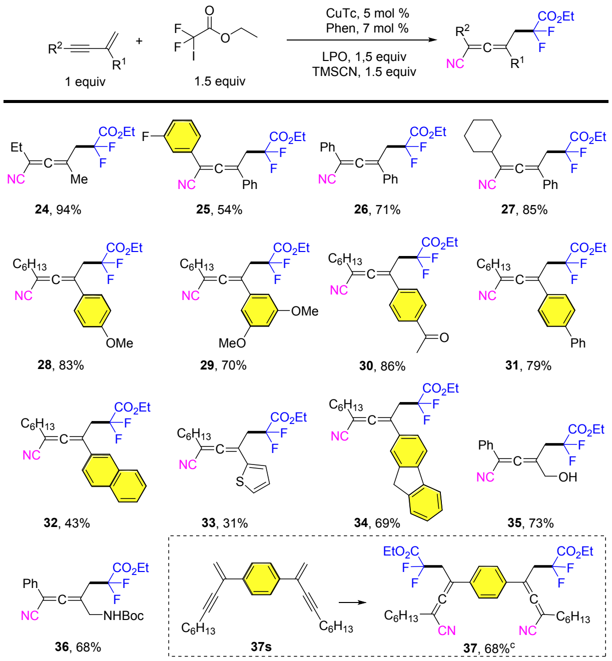


[a] Reaction conditions: 1,3-Enyne (**11s**, 0.2 mmol), RI (1.5 equiv), LPO (1.5 equiv) in CH_3CN (1 mL), 50 °C, 12 h under nitrogen atmosphere. [b] Yield of isolated product.

The scope of fluoroalkylated iodides under the optimized reaction conditions was studied and the results are shown in Table 4. Perfluoroalkyl iodides afford products **12-15** in 85-94% yield with diastereoisomeric ratios ranging from 12:1 to 99:1. Interestingly, trifluoromethyl iodide (CF_3I) can be used to introduce a CF_3 group into the 1,3-enyne and the product (**16**) can be isolated in 75% yield with a dr value of 5.3:1. Iodoacetates can also participate in this reaction, giving products **17** and **18** in 51% and 86% yield, respectively. Other alkyl iodides (**19s'-23s'**) are not reactive under these conditions.

With these conditions in hand, we investigated the scope of 1,3-enynes and the results are shown in Table 5. The substrate scope of the reactants is broad, producing the corresponding products **24-36** in up to 94% yield. Many functional groups, including -OH and -NHBoc are tolerated, giving products **35-36**. Double 1,4-fluoroalkylcyanation of **37s** occurred and the product (**37**) was isolated in 68% yield as a single isomer.

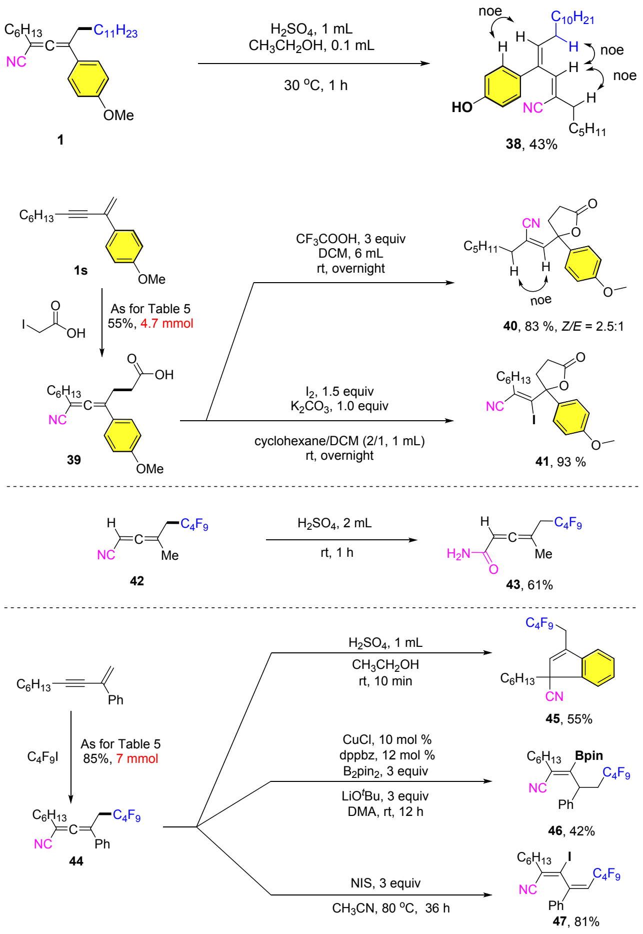
Table 5. Substrate scope of 1,3-enynes for 1,4-fluoroalkylcyanation.[a,b]



[a] Reaction conditions: 1,3-Enyne (0.2 mmol), RI (1.5 equiv), LPO (1.5 equiv) in CH_3CN (1 mL), 50 °C, 12 h under N_2. [b] Yield of isolated product. [c] 6 equiv of LPO and 6 equiv of TMSCN were used.

Synthetic applications of this methodology for carbocyanation of 1,3-enynes have been demonstrated and are shown in Scheme 2. Under acidic conditions, the allene (**1**) was isomerized to the diene (**38**) in 43% yield. Lactones **40** and **41**[22] were prepared in high yields from allene **39** which is generated from the 1,3-enyne (**1s**) in one step with iodoacetic acid. Interestingly, the allene (**42**) with a perfluoroalkyl group selectively produced the allenyl amide (**43**) in 61% yield under similar acidic conditions, while phenyl allene (**44**) delivered a fused ring compound (**45**). The allene (**44**) could also be easily transformed into vinyl-Bpin (**46**) and conjugated vinyl iodide (**47**) in 42% and 81% yield, respectively.

Scheme 2. Synthetic applications for carbocyanation products.

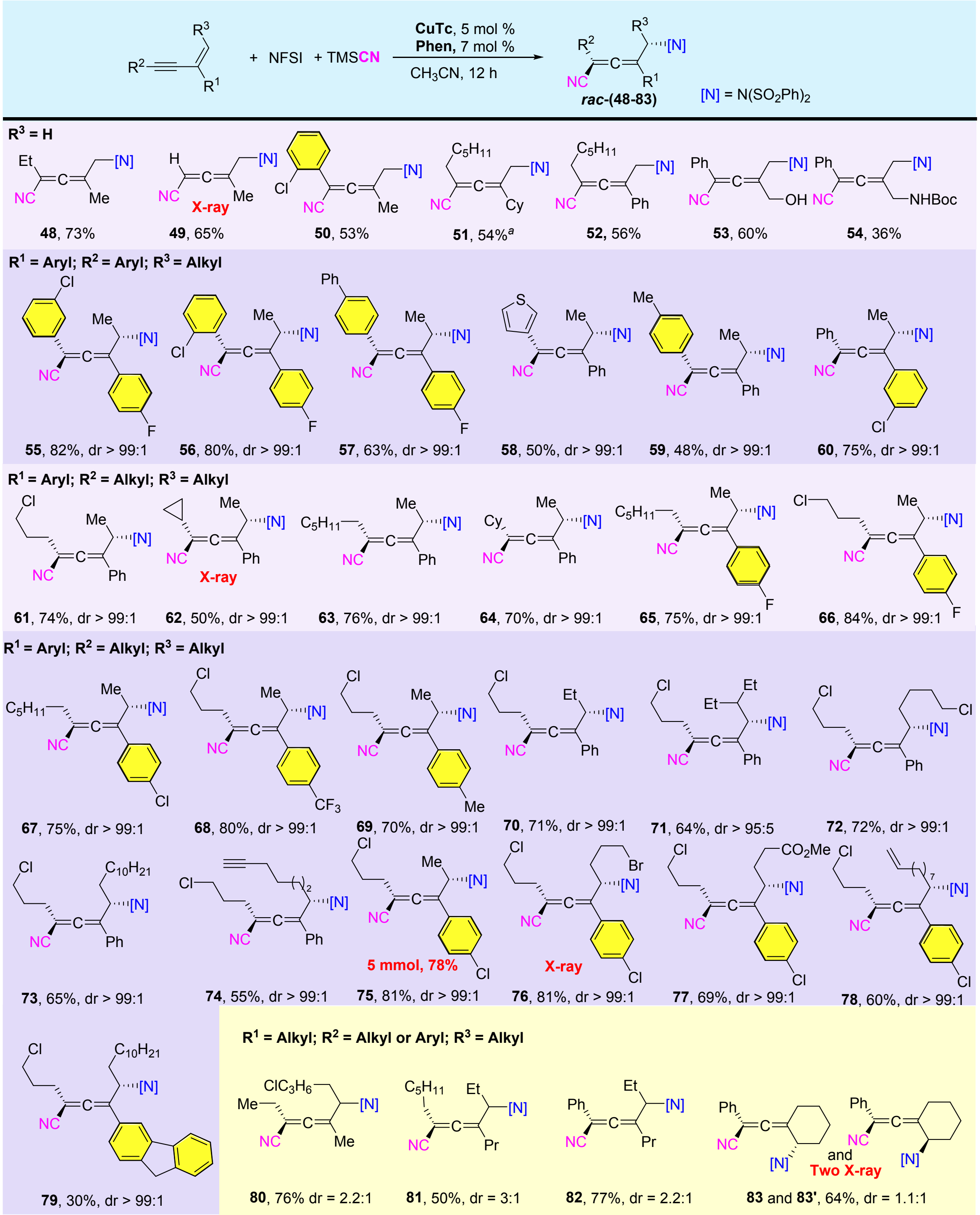


1,4-Sulfimidocyanation of 1,3-enynes

C-C and C–N bonds are two of the most ubiquitous natural chemical bonds.[23,24] The introduction of both carbon and nitrogen functionalities into 1,3-enynes, generating allenes is unprecedented. We envisioned that the allenyl radical pathway could lead to amine-containing allene motifs. *N*-fluorobenzenesulfonimide (NFSI) has been shown by Zhang and others[16a,25] to be a very useful amination reagent. Accordingly, we studied the 1,4-sulfimido-cyanation of 1,3-enynes with NFSI and TMSCN.

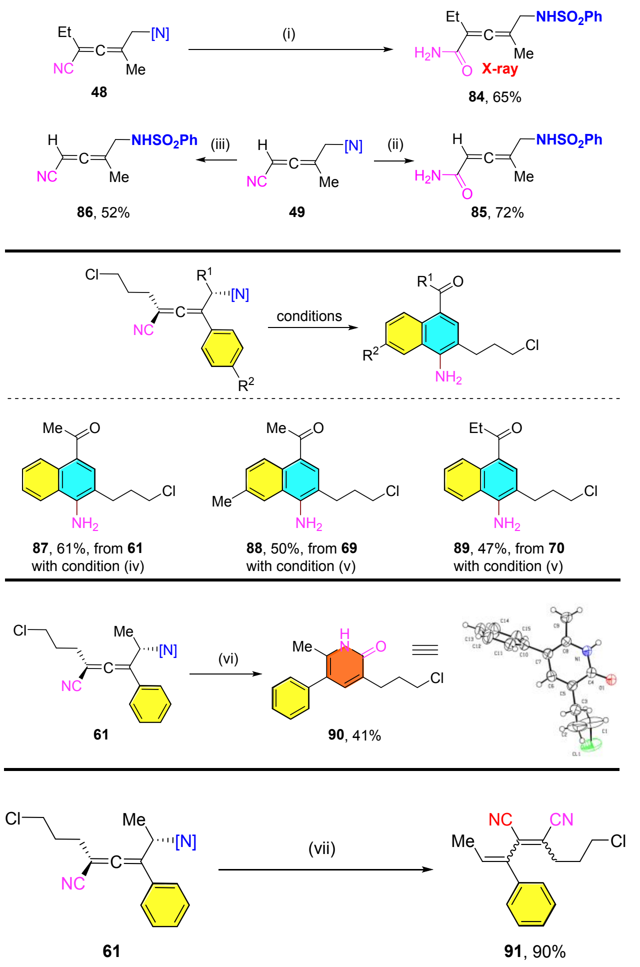
After comprehensive optimization of conditions, the optimal reaction conditions were confirmed and the 1,4-sulfimidocyanation product (**48**) was obtained in 73% yield in presence of CuTc (for details, see Table S1 in Supporting Information - SI). With these conditions in hand, we investigated the scope of 1,3-enynes (Table 6). Reactions of disubstituted 1,3-enynes afford tri- and tetra-substituted allenes (**48-54**) in moderate yields. Both R¹ and R² can be alkyl or aryl groups. Hydroxyl and amino groups are tolerated (**53** and **54**). Reactions of trisubstituted 1,3-enynes can deliver tetrasubstituted allenes (**55-83**), whose synthesis otherwise could be challenging. When both R¹ and R² are aryl groups and R³ is an alkyl group, the corresponding products (**55-60**) are obtained in moderate to high yields. Heteroaromatic compounds such as thiophene can be used in the reaction (**58**). Reactions of electron-deficient 1,3-enynes tend to give the desired products in better yields (**55**, **56** vs. **57-63**). All the reactions deliver the corresponding products with high diastereoisomeric selectivity, single diastereoisomers being obtained in most cases. Subsequently, we investigated the cases in which R^1 is an aryl group, and R^2 and R^3 are alkyl groups. Additional functionalities such as chloro (**61**, **66-79**), cyclopropyl (**62**), alkynyl (**74**), bromo (**76**), ester (**77**), or alkenyl (**78**) are well tolerated in the reaction. The diastereoselectivity of these reactions is excellent and products are isolated in most cases as a single diastereoisomer. Interestingly, when R^1 of the trisubstituted 1,3-enynes is an alkyl group (**80-83**) the dr values drop dramatically. The structures of products **49**, **62**, **76**, **83**, and **83'** were confirmed by X-ray crystallographic analysis.

Table 6. Substrate scope of 1,3-enynes for 1,4-sulfimido-cyanations.



Reaction conditions: 1,3-Enyne (0.5 mmol), NFSI (1.5 equiv), TMSCN (1.5 equiv), in CH_3CN (2 mL), rt-50 °C, 12 h under N_2. Yield of isolated product. [a] Reaction was performed at 80 °C.

Scheme 3. Synthetic applications of nitrogen-containing allenes.

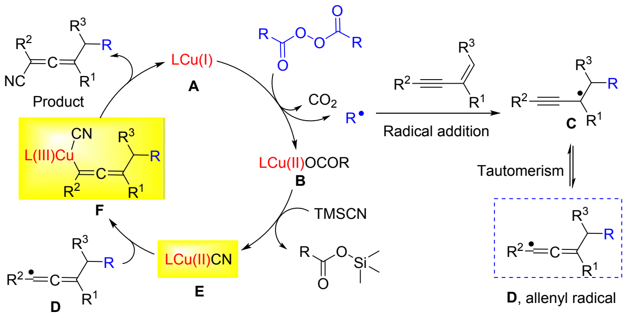


Reaction conditions: (i) 1 mL of conc. H_2SO_4, rt, 2 h. (ii) 1 mL of conc. H_2SO_4, 10 °C, 2 h.(iii) 0.5 mmol, 2 mL conc. H_2SO_4, -10 °C, 8 h. (iv) 1 mL of conc. H_2SO_4, -16 °C, 12 h. (v) 1 mL of conc. H_2SO_4, 0 °C, 12 h. (vi) 1 mL of conc. H_2SO_4, 0.5 mL of H_2O, 90 °C, 12 h. (vii) 5 mol % of $Pd(PPh_3)_4$, 1.5 equiv of TMSCN, THF, 80 °C, 5 h.

Synthetic applications of nitrogen-containing tri- or tetra-substituted allenes have been demonstrated and are shown in Scheme 3. A tetrasubstituted allene (**48**) and a trisubstituted allene (**49**) can be successfully converted into the corresponding amides (**84**, **85**) in the presence of H_2SO_4. One of the sulfonyl groups of $N(SO_2Ph)_2$ is simultaneously deprotected. When the temperature was decreased to -10 °C, the cyano group remained untouched, affording the cyano allene **86** in 52% yield. Under similar reaction conditions, substrates **61**, **69**, and **70** with a phenyl group attached to the allene molecule, produces 1-naphthylamines (**87-89**) in moderate yields. This type of transformation has not been published previously. When the reaction is performed in aqueous H_2SO_4, the tetrasubstituted allene (**61**) produces a pyridin-2(1*H*)-one (**90**) in 41% yield. With palladium as the catalyst, the allene (**61**) produces compound **91** in 90% yield.[26] The structures of products **84** and **90** were confirmed by X-ray crystallographic analysis.

Mechanism studies

Scheme 4. Plausible catalytic cycle for the 1,4-alkylcyanation of 1,3-enynes.



Based on previous findings in cyanation reactions,[16] a plausible mechanism for this reaction is proposed in Scheme 4. The reaction is initiated by a single electron transfer from the copper(I) catalyst (**A**) to an alkyl diacyl peroxide generating an alkyl radical (R•) and a copper(II) complex (**B**). The alkyl radical (R•) generated in this way adds to the 1,3-enyne, giving the allenyl radical (**D**). Similar to previous reported cyanation reactions,[16f,16g] the copper complex **B** can exchange the ligand with TMSCN to generate the Cu(II)CN complex (**E**). **E** subsequently couples with the allenyl radical (**D**) to generate the copper(III) intermediate (**F**), which readily undergoes reductive elimination. Finally, the product is released and the copper (I) catalyst is regenerated. This mechanism is straightforward, but the observed high diastereo-selectivity raises the question as to how a remote chiral center at allenyl group of **D** or **F** can control the stereoselectivity of the C-C coupling in these cyanation reactions. Mechanistic studies were undertaken to obtain an answer to this question.

First, radical scavenger and radical clock studies were conducted in an effort to find evidence of allenyl radicals. As shown in Scheme 5, the 1,4-carbocyanation reaction was chosen as the example. Upon addition of three equivalents of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) into a standard reaction, no reaction ensues and no desired product is observed (Scheme 5a), indicating involvement of a radical pathway in the reaction. Further verification of the existence of the radical **C** using a radical clock experiment was initiated with an 1,3-enyne (**92**) in which R^1 is a cyclopropyl group (Scheme 5b). Under the standard conditions, no ring-opening product (**93'**) is observed and the cyclic product (**93**) was isolated in 40% yield. We suspected that the ring-opening of this specialized cyclopropane is not fast because the neighboring phenyl group (R^2) may stabilize the allenyl radical **D** by resonance. We then prepared substrate **94** and examined it in the ring-closing reaction which was expected to be faster.[27] With a catalytic amount of $Cu(OAc)_2$, products **95** and **96** were isolated in

50% and 25% yield, respectively (Table 7, entry 1). This suggests that allenyl radicals are indeed generated *in situ*. The reaction rate of the coupling of allenyl radical with Cu(II) complex is comparable to that of the radical cyclization. To assess the presence of the copper cyanide complex (**E**), CuCN was utilized as the source of both the copper and the cyano source. Interestingly, the uncyclized product (**96**) was isolated or observed as the only or the dominant product in most cases when a stoichiometric quantity of CuCN was added (Table 7, entries 2, 4 and 6). Control experiments with Cu(OAc)$_2$/TMSCN were also conducted (Table 7, entries 3 and 5). Different product ratios are observed for the two copper complexes. On the basis of the results in Table 7, it is probable that the catalytic reaction with Cu(OAc)$_2$/TMSCN proceeds through a different pathway compared with the reaction that starts with CuCN. To further confirm that this reaction goes through an allenyl radical rather than an allenyl cation, ten allenyl cation trapping experiments were done with two different 1,3-enyne substrates **1s** and **48s**. No water or CH_3OH adduct, which could prove the formation of the allenyl cation was ever observed (Tables 8, 9 and SI). Considering all of these results together, the allenyl radical pathway is preferred over the allenyl cation pathway.

Scheme 5. Radical trapping and ring-opening experiments

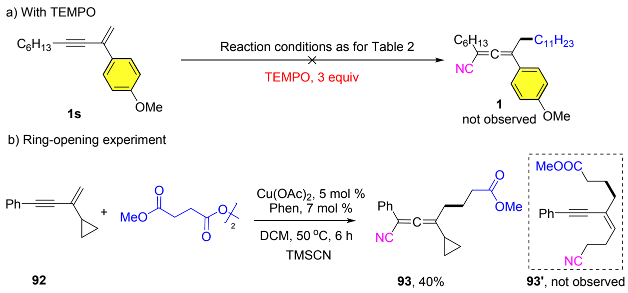
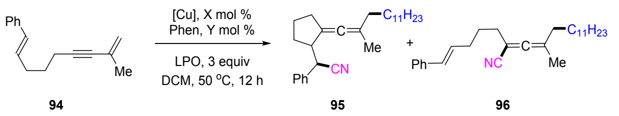
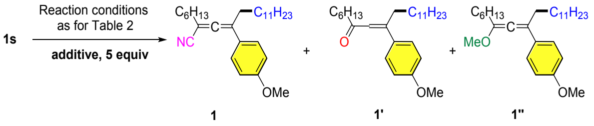


Table 7. Ring-closing experiments



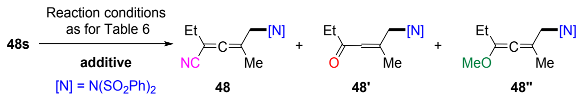
entry	[Cu]	Phen (mol %)	TMSCN	95	96
1	Cu(OAc)$_2$, 5 mol %	7	3 equiv	50%	25%
2	CuCN, 3 equiv	420	/	0	33%
3	Cu(OAc)$_2$, 3 equiv	420	3 equiv	0	0
4	CuCN, 100 mol %	140	/	0	23%
5	Cu(OAc)$_2$, 30 mol %	42	3 equiv	28%	36%
6	CuCN, 30 mol %	42	/	1%	4%

Table 8. Probe experiments for the allenyl cation with LPO



entry	additive	1	1'	1''
1	none	73%	/	/
2	H_2O	71%	0	/
3	MeOH	69%	/	0

Table 9. Probe experiments for the allenyl cation with NFSI



entry	additive	48	48'	48''
1	none	73%	/	/
2	H_2O, 10 equiv	71%	0	/
3	H_2O, 0.5 mL	71%	0	/
4	MeOH, 10 equiv	69%	/	0
5	MeOH, 0.5 mL	64%	/	0

Density functional theory (DFT) calculations on the 1,4-alkylcyanation of 1,3-enynes were performed in an effort to understand the mechanism at the atomic level. Figure 1 depicts the overall potential energy surface of the Cu-catalyzed reaction.[28] The copper catalyst, **Cu-1**, a complex of CuTc with a ligand, 1,10-phenanthroline (**L**), is considered to be the active catalyst, since 30 min pre-coordination was conducted in the experiment. Initially, oxidation of **Cu-1** with hexanoic peroxyanhydride (**HPO**), results in a hexanoyloxyl radical (**INT1**) and a Cu(II) complex (**INT2**) appended to a hexanoate. A high exergonicity (23.7 kcal/mol) indicates that the oxidation process is thermodynamically favorable. The transformation of radical **INT1** to an allenyl radical **INT5** is shown in the SI (Figure S9). The generated hexanoyloxyl radical (**INT1**) undergoes decarboxylation (**TS5**), leading to an alkyl radical (**INT7**) with a quite low barrier (3.4 kcal/mol). Subsequently the alkyl radical reacts with a 1,3-enyne to form an allenyl radical, **INT5**, in a step which is exergonic by 24.4 kcal/mol and has a free energy barrier of 11.0 kcal/mol. The potential energy surface for the formation of the allenyl radical is similar to that reported in our previous publication.[19a] On the basis of the calculation concerning the oxidation process, the presence of **A**, **B**, **C** and **D** in the proposed mechanism (Scheme 4) are reasonable.

Next, we focused on the cyanide exchange step. Complexation of TMSCN with **INT2** to form intermediate **INT3**, was calculated to be endergonic (5.1 kcal/mol uphill), suggesting that the approach of TMSCN may be hindered due to the bulk of the trimethylsilyl group of TMSCN. Interestingly, a cyanide exchange transition state, **TS1**, is located with a free energy barrier of 26.6 kcal/mol leading to an isocyanocopper complex **INT4**.[29] The linearity of Si-C-N and the bulk of TMS forces the exchange to occur *via* a seven-membered ring transition state **TS1**, in which ring strain is relaxed (Figure S10). Moreover, transition state **TS1-F**, is also identified, further confirming the generation of isocyanocopper complex **INT4** as well as the generation from **TS1**. It is noteworthy that an isocyanocopper complex is still delivered *via* the cyanide exchange transition state, **TS1-F**, when the other radical initiator, NFSI, is employed (See Figure S10 and Figure S11 in SI for more details).

The reaction pathway in which the allenyl radical couples directly with the terminal carbon atom of isocyanide in **INT4** was then considered. A triplet transition state **TS2** is found for the cyanation of the allenyl radical with a 22.0 kcal/mol barrier. Unlike the Cu(III) mechanism proposed in the literature,[16a-d,16f,16i] the linear allenyl radical in **TS2** couples directly with the terminal carbon of the isocyanocopper(II) complex.[30] In this manner, Cu(II) accepts one electron from isocyanide, forming Cu(I)[31] via an outer-sphere pathway.[32] As an alternative, the other cyanation processes originating from an accepted cyanocopper complex should also be considered. A transition state **TS3** corresponding to the CN flipping is also located with an 11.4 kcal/mol barrier leading to formation of **INT6** in which the exergonicity of **INT6** is 5.7 kcal/mol relative to **INT4**. Although the cyanocopper complex (**INT6**) is more thermodynamically favored than the isocyanocopper complex (**INT4**), **TS4** faces a much higher barrier (35.5 kcal/mol) to access the cyano-substituted allene.

On the basis of DFT studies, an alternative reaction mechanism, involving isocyanocopper, for the 1,4-alkylcyanation of 1,3-enynes is revealed.

To support the results from DFT studies, further control experiments were conducted. First, in order to verify the ligand exchange step between the copper(II) species (**INT2**) and TMSCN, the reaction solution was examined by GC-MS. As predicted by the DFT calculation in Figure 1, the trimethylsilyl carboxylate ($C_{11}H_{23}COOSiMe_3$) was observed in GC-MS when LPO was used, supporting the hypothesis that the cyanide arises from TMSCN exchange with the carboxylate. Second, because the DFT studies predict the formation of the isocyanocopper species, a series of infrared spectroscopy studies were carried out to examine the existence of an isocyanocopper species. A regular solution in DCM, with the same concentration in the reaction conditions, and a 10 times more concentrated solution of 1,10-Phen ligand and Cu(OAc)$_2$ treated with 10 equivalents of TMSCN was examined by IR spectroscopy

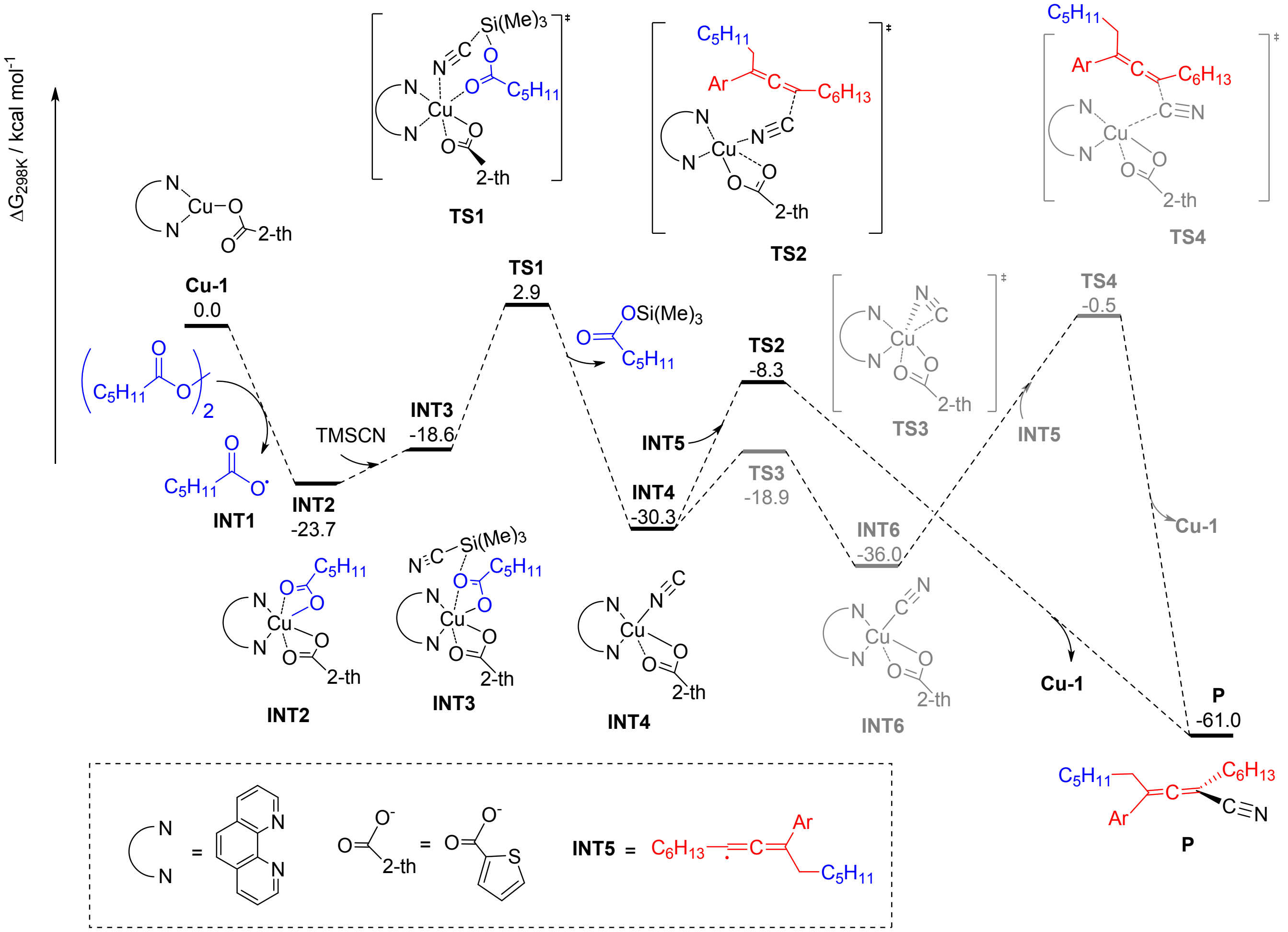


Figure 1. The Gibbs free energy profile for the Cu-catalyzed alkylcyanation. A simplified hexanoic peroxyanhydride is employed in place of LPO to reduce the computational demand and the complexity of the conformational space. Relative free energies are in kcal/mol.

(Figure 2). Two peaks at 2154 and 2132 cm^{-1} were observed in the solution and remained unchanged for 60 min. However, in the 10 times more concentrated solution, a new peak at 2088 cm^{-1} was observed in the first few minutes, and then subsequently decreased to a much smaller peak. According to reported works,[33] we tentatively assigned the peak of 2088 cm^{-1} to an isocyanocopper species,[29c,34] and those at 2154/2132 cm^{-1} to a cyanocopper species, which arise from tautomerization of the isocyanocopper species. More details of the computational predictions for CN stretching frequencies are discussed in the Computational Method and Details section in the SI.

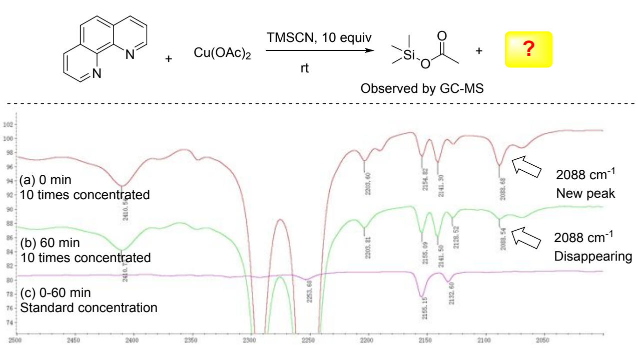


Figure 2. IR studies for the ligand exchange step.

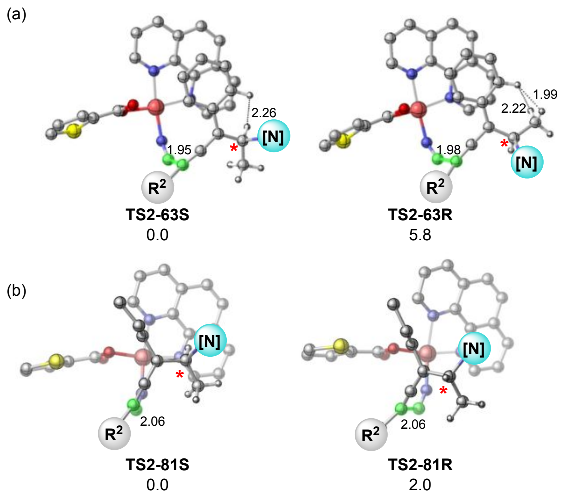
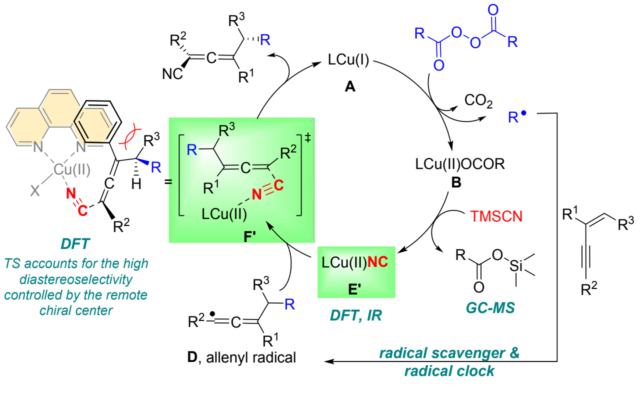


Figure 3. Optimized structures of (a) **TS2-63S** and **TS2-63R** and (b) **TS2-81S** and **TS2-81R** with relative free energies in kcal/mol. For clarity, the majority of the hydrogen atoms are omitted. $N(SO_2Ph)_2$ and *n*-pentyl groups are simply depicted as a blue ball with symbol [N] or a gray ball with symbol R^2, respectively. Distances shown in Figure are in Å.

With these encouraging results from the IR spectroscopy studies that suggest the presence of the isocyanocopper, we next investigated whether this isocyanocopper mechanism can account for the observed diastereoselectivity of the reactions. Substrates **63** and **81,** in which R^1 is a phenyl or propyl group, respectively, were selected as the models with which to study the diastereoselectivity, because of their dramatically different dr selectivity.[35] Figure 3(a) and (b) shows the four transition states **TS2-nS** and **TS2-nR** (n = 63 and 81), which determine the diastereoselectivity. The free energy difference between **TS2-63S** and **TS2-63R** is 5.8 kcal/mol, and between **TS2-81S** and **TS2-81R** is 2.0 kcal/mol. The trend is consistent with the experimental observation that much higher dr selectivity is achieved when R^1 is an aryl group. Interestingly, in **TS2-63S** and **TS2-63R**, an apparent π-π stacking interaction was found between the phenyl group and the 1,10-phenanthroline ligand. Such stacking forces the linear allenyl radical to adopt a pose in which the remote chiral center is close to the ligand. The energy of **TS2-63R** is therefore greater because of the repulsion between the substituents, R^1 and R^3. Distortion/interaction analysis (Figure S12) was also investigated to determine the contributive factor of the energy difference. The examination reveals that the repulsion between R^1 and R^3 causes the distortion of radical and reduces the π-π interaction between the ligand and the phenyl group (R^1). On the other hand, when R^1 is an alkyl group, the allenyl group may adopt more orientations in **TS2-81** due to the absence of the π-π stacking interaction. The lowest energy transition states for S and R are shown in Figure 3(b). The flexibility of the allenyl radical may orient the remote chiral center away from the copper complex and consequently decrease the discriminatory effect. So far, the pathway through isocyanocopper intermediate without a chiral ligand explains the diastereoselectivity well while the substituent R^1 is an aryl group and the initial radical is bulky. Calculation of the 1,4-fluoroalkylcyanation of **16** and **17** based on the π-π stacking model is also consistent with the experimental observations (Figure S13).

Scheme 6. Revised plausible catalytic cycle for the 1,4-alkylcyanation of 1,3-enynes.



Based on these mechanistic studies, a revised mechanism is proposed in Scheme 6.[31-32] The isocyanocopper species (**E'**) was predicted and observed. More interestingly, a novel cyanation transition state (**F'**), in which the linear allenyl radical couples with the terminal carbon of isocyanocopper, was revealed. This transition state accounts for the high diastereoselectivity controlled by the remote chiral center.

CONCLUSION

Copper-catalyzed 1,4-alkylcyanation, 1,4-fluoroalkylcyanation and 1,4-sulfimidocyanation of 1,3-enynes leading to multi-substituted allenes *via* allenyl radical intermediates has been demonstrated. Alkyl diacyl peroxides serve as trifunctional reagents which are the key to the 1,4-carbocyanation while *N*-fluorobenzenesulfonimide is the key to the 1,4-sulfimidocyanation. Broad substrate scope and excellent functional group tolerance are observed in this reaction. Many synthetically challenging allenes are readily available from these methods and diverse transformations of allene products are being pursued for the synthesis of a variety of complex molecules. Distinct from the previous proposed Cu(III) mechanism in cyanation reactions, our mechanism studies suggest the formation of an isocyano-copper(II) species which is responsible for the next diastereoselective cyanation step. This study should shed some light on the study of copper catalyzed cyanation reactions.

ASSOCIATED CONTENT

Supporting Information

Data for the crystal structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC). **49** (CIF, CCDC 1588172), **62** (CIF CCDC 1587985), **76** (CIF, CCDC 1588594), **83** (CIF, CCDC 1588011), **83**' (CIF, CCDC 1588174), **84** (CIF, CCDC 1588171), and **90** (CIF, CCDC 1588173). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. All other data are available within the paper and its Supplementary Information files, or from the corresponding authors upon request.

Supplementary information and chemical compound information are available free of charge on the ACS Publications website. Correspondence and requests for materials should be addressed to H. B.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank the National Key R&D Program of China (Grant No. 2017YFA0700103), the NSFC (Grant Nos. 21502191, 21672213, and 21871258), the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB20000000), the Haixi Institute of CAS (CXZX-2017-P01), the Shenzhen Basic Research Program (JCYJ20170412150343516) for financial support. We thank Professor Weiping Su, Daqiang Yuan and Gang Xu from our institute for X-ray structural analysis. We thank Dr. G. W. A. Milne for his writing suggestions.

REFERENCES

(1) For selected books on allenes: (a) *The Chemistry of the Allenes*; Landor, S. R. Ed.; Academic Press: London, **1982**. (b) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, **1984**. (c) *Modern Allene Chemistry*, Vol. 1 and 2 (Eds.: Krause, N.; Hashmi, A. S. K.), Wiley-VCH: Weinheim, Germany, **2004**.

(2) For selected reviews on allenes: (a) Hoffmann-Röder, A.; Krause, N. Synthesis and Properties of Allenic Natural Products and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2004**, *43*, 1196; (b) Ma, S. Some Typical Advances in the Synthetic Applications of Allenes. *Chem. Rev.* **2005**, *105*, 2829; (c) Brummond, K. M.; DeForrest, J. E. Synthesizing Allenes Today (1982-2006). *Synthesis* **2007**, *2007*, 795; (d) Ma, S. Electrophilic Addition and Cyclization Reactions of Allenes. *Acc. Chem. Res.* **2009**, *42*, 1679; (e) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. Transition Metal Catalyzed Cycloisomerizations of 1,n-Allenynes and -Allenenes. *Chem. Rev.* **2011**, *111*, 1954; (f) Yu, S.; Ma, S. How Easy Are the Syntheses of Allenes? *Chem. Commun.* **2011**, *47*, 5384; (g) Yu, S.; Ma, S. Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses. *Angew. Chem. Int. Ed.* **2012**, *51*, 3074; (h) Ye, J.; Ma, S. Conquering Three-Carbon Axial Chirality of Allenes. *Org. Chem. Front.* **2014**, *1*, 1210.

(3) For selected examples on the synthesis of allenes based on prototropic rearrangements, see: (a) Marshall, J. A.; Wang, X. J. Synthesis of Macrocyclic Homopropargylic Alcohols through Intramolecular S_E' Addition of Allenylstannanes and Their Subsequent Conversion to 2,5-Furanocycles. *J. Org. Chem.* **1991**, *56*, 6264; (b) Doye, S.; Hotopp, T.; Wartchow, R.; Winterfeldt, E. The Enantioselective Total Synthesis of (–)-Myltaylenol. *Chem. Eur. J.* **1998**, *4*, 1480; (c) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. Enantioselective Synthesis of Chiral Allenoates by Guanidine-Catalyzed Isomerization of 3-Alkynoates. *J. Am. Chem. Soc.* **2009**, *131*, 7212.

(4) For selected examples on the synthesis of allenes based on sigmatropic rearrangements, see: (a) Sherry, B. D.; Toste, F. D. Gold(I)-Catalyzed Propargyl Claisen Rearrangement. *J. Am. Chem. Soc.* **2004**, *126*, 15978; (b) Li, Z.; Boyarskikh, V.; Hansen, J. H.; Autschbach, J.; Musaev, D. G.; Davies, H. M. L. Scope and Mechanistic Analysis of the Enantioselective Synthesis of Allenes by Rhodium-Catalyzed Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement between Donor/Acceptor Carbenoids and Propargylic Alcohols. *J. Am. Chem. Soc.* **2012**, *134*, 15497; (c) Mundal, D. A.; Lutz, K. E.; Thomson, R. J. A Direct Synthesis of Allenes by a Traceless Petasis Reaction. *J. Am. Chem. Soc.* **2012**, *134*, 5782; (d) Jiang, Y.; Diagne, A. B.; Thomson, R. J.; Schaus, S. E. Enantioselective Synthesis of Allenes by Catalytic Traceless Petasis Reactions. *J. Am. Chem. Soc.* **2017**, *139*, 1998.

(5) For selected examples on the synthesis of allenes based on substitution of propargylic compounds, see: (a) Ishikawa, T.; Manabe, S.; Aikawa, T.; Kudo, T.; Saito, S. Intramolecular Catalytic Friedel–Crafts Reactions with Allenyl Cations for the Synthesis of Quinolines and Their Analogues. *Org. Lett.* **2004**, *6*, 2361; (b) Ito, H.; Sasaki, Y.; Sawamura, M. Copper(I)-Catalyzed Substitution of Propargylic Carbonates with Diboron: Selective Synthesis of Multisubstituted Allenylboronates. *J. Am. Chem. Soc.* **2008**, *130*, 15774; (c) Xu, B.; Hammond, G. B. Thermodynamically Favored Aldol Reaction of Propargyl or Allenyl Esters: Regioselective Synthesis of Carbinol Allenoates.

Angew. Chem. Int. Ed. **2008**, *47*, 689; (d) Yang, Z.; Hao, W.-J.; Wang, S.-L.; Zhang, J.-P.; Jiang, B.; Li, G.; Tu, S.-J. Synthesis of Allenyl Sulfones Via a TBHP/TBAI-Mediated Reaction of Propargyl Alcohols with Sulfonyl Hydrazides. *J. Org. Chem.* **2015**, *80*, 9224; (e) Kessler, S. N.; Bäckvall, J.-E. Iron-Catalyzed Cross-Coupling of Propargyl Carboxylates and Grignard Reagents: Synthesis of Substituted Allenes. *Angew. Chem. Int. Ed.* **2016**, 55, 3734; (f) Zhao, J.; Szabó, K. J. Catalytic Borylative Opening of Propargyl Cyclopropane, Epoxide, Aziridine, and Oxetane Substrates: Ligand Controlled Synthesis of Allenyl Boronates and Alkenyl Diboronates. *Angew. Chem. Int. Ed.* **2016**, 55, 1502; (g) Qian, D.; Wu, L.; Lin, Z.; Sun, J. Organocatalytic Synthesis of Chiral Tetrasubstituted Allenes from Racemic Propargylic Alcohols. *Nat. Commun.* **2017**, *8*, 567.

(6) For selected examples on the synthesis of allenes from 1,3-enynes with organometallic reagents, see: (a) Ma, S.; Zhang, J.; Lu, L. Pdo-Catalyzed Coupling Cyclization Reaction of Aryl or 1alkenyl Halides with 1,2-Allenyl Ketones: Scope and Mechanism. An Efficient Assembly of 2,3,4-, 2,3,5-Tri- and 2,3,4,5-Tetrasubstituted Furans. *Chem. Eur. J.* **2003**, *9*, 2447; (b) Todo, H.; Terao, J.; Watanabe, H.; Kuniyasu, H.; Kambe, N. Cu-Catalyzed Regioselective Carbomagnesiation of Dienes and Enynes with Sec- and Tert-Alkyl Grignard Reagents. *Chem. Commun.* **2008**, 1332; (c) Zhao, J.; Liu, Y.; He, Q.; Li, Y.; Ma, S. Experimental and Theoretical Study of Tunable 1,3-Lithium Shift of Propargylic/Allenylic Species, Transmetallation, and Pd-Catalyzed Cross-Coupling Reactions. *Chem. Eur. J.* **2009**, *15*, 11361; (d) Tomida, Y.; Nagaki, A.; Yoshida, J.-i. Asymmetric Carbolithiation of Conjugated Enynes: A Flow Microreactor Enables the Use of Configurationally Unstable Intermediates before They Epimerize. *J. Am. Chem. Soc.* **2011**, *133*, 3744; (e) Mori, Y.; Kawabata, T.; Onodera, G.; Kimura, M. Remarkably Selective Formation of Allenyl and Dienyl Alcohols Via Ni-Catalyzed Coupling Reaction of Conjugated Enyne, Aldehyde, and Organozinc Reagents. *Synthesis* **2016**, *48*, 2385.

(7) Nishimura, A.; Tamai, E.; Ohashi, M.; Ogoshi, S. Synthesis of Cyclobutenes and Allenes by Cobalt-Catalyzed Cross-Dimerization of Simple Alkenes with 1,3-Enynes. *Chem. Eur. J.* **2014**, *20*, 6613.

(8) (a) Zhang, W.; Xu, H.; Xu, H.; Tang, W. DABCO-Catalyzed 1,4-Bromolactonization of Conjugated Enynes: Highly Stereoselective Formation of a Stereogenic Center and an Axially Chiral Allene. *J. Am. Chem. Soc.* **2009**, *131*, 3832; (b) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. Enantioselective Bromolactonization of Conjugated (*Z*)-Enynes. *J. Am. Chem. Soc.* **2010**, *132*, 3664; (c) Wang, H.-Y.; Zhang, W.; Schienebeck, C. M.; Bennett, S. R.; Tang, W. Intermolecular Bromoesterification of Conjugated Enynes: An Efficient Synthesis of Bromoallenes. *Org. Chem. Front.* **2014**, *1*, 386.

(9) (a) Mainetti, E.; Fensterbank, L.; Malacria, M. New Elements in the Reactivity of A-Cyclopropyl Vinyl Radicals. *Synlett* **2002**, *2002*, 0923; (b) Qian, H.; Yu, X.; Zhang, J.; Sun, J. Organocatalytic Enantioselective Synthesis of 2,3-Allenoates by Intermolecular Addition of Nitroalkanes to Activated Enynes. *J. Am. Chem. Soc.* **2013**, *135*, 18020; (c) Wang, Z.; Li, X.; Huang, Y. Direct A-Vinylidenation of Aldehydes and Subsequent Cascade: Gold and Amine Catalysts Work Synergistically. *Angew. Chem. Int. Ed.* **2013**, *52*, 14219; (d) Wang, M.; Liu, Z.-L.; Zhang, X.; Tian, P.-P.; Xu, Y.-H.; Loh, T.-P. Synthesis of Highly Substituted Racemic and Enantioenriched Allenylsilanes Via Copper-Catalyzed Hydrosilylation of (*Z*)-2-Alken-4-Ynoates with Silylboronate. *J. Am. Chem. Soc.* **2015**, *137*, 14830; (e) Chu, W.-D.; Zhang, L.; Zhang, Z.; Zhou, Q.; Mo, F.; Zhang, Y.; Wang, J. Enantioselective Synthesis of Trisubstituted Allenes Via Cu(I)-Catalyzed Coupling of Diazoalkanes with Terminal Alkynes. *J. Am. Chem. Soc.* **2016**, *138*, 14558.

(10) (a) Huang, Y.; del Pozo, J.; Torker, S.; Hoveyda, A. H. Enantioselective Synthesis of Trisubstituted Allenyl–B(Pin) Compounds by Phosphine–Cu-Catalyzed 1,3-Enyne Hydroboration. Insights Regarding Stereochemical Integrity of Cu–Allenyl Intermediates. *J. Am. Chem. Soc.* **2018**, *140*, 2643; (b) Sang, H. L.; Yu, S.; Ge, S. Copper-Catalyzed Asymmetric Hydroboration of 1,3-Enynes with Pinacolborane to Access Chiral Allenylboronates. *Org. Chem. Front.* **2018**, *5*, 1284.

(11) (a) Mouriès, V.; Delouvrié, B.; Lacôte, E.; Fensterbank, L.; Malacria, M. Radical Β-Elimination of a Sulfinyl Group to Afford Allenes. *Eur. J. Org. Chem.* **2002**, *2002*, 1776; (b) Alameda-Angulo, C.; Quiclet-Sire, B.; Zard, S. Z. An Expedient Approach to Allenes and Polycyclic Structures Using Propargyl Radicals. *Tetrahedron Lett.* **2006**, *47*, 913.

(12) Terao, J.; Bando, F.; Kambe, N. Ni-Catalyzed Regioselective Three-Component Coupling of Alkyl Halides, Arylalkynes, or Enynes with R-M (M = MgX', ZnX'). *Chem. Commun.* **2009**, 7336.

(13) (a) Volman, D. H.; Maas, K. A.; Wolstenholme, J. Photochemical Formation of Free Radicals from Olefinic and Acetylenic Compounds in the Frozen State as Studied by Electron Spin Resonance1. *J. Am. Chem. Soc.* **1965**, *87*, 3041; (b) Adam, W.; Ortega-Schulte, C. M. Spin Delocalization by Triple-Bonded Functionalities in Propargyl and Heteropropargyl Radicals, Assessed from the EPR-Spectral D Parameter of 1,3-Cyclopentanediyl Triplet Diradicals. *J. Org. Chem.* **2003**, *68*, 1007; (c) Maury, J.; Jammi, S.; Vibert, F.; Marque, S. R.; Siri, D.; Feray, L.; Bertrand, M. EPR Investigation of Zinc/Iodine Exchange between Propargyl Iodides and Diethylzinc: Detection of Propargyl Radical by Spin Trapping. *J. Org. Chem.* **2012**, *77*, 9081.

(14) (a) Fatiadi, A. J. In *Preparation and Synthetic Applications of Cyano Compounds*; Patai, S., Rappaport, Z., Ed.; Wiley: New York, **1983**. (b) Larock, R. C. In *Comprehensive Organic Transformations*; Wiley-VCH: New York, **1989**; p 819. c) Wang, T.; Jiao, N. Direct Approaches to Nitriles Via Highly Efficient Nitrogenation Strategy through C-H or C-C Bond Cleavage. *Acc. Chem. Res.* **2014**, *47*, 1137.

(15) (a) Maden, A. J.; Hayward, M. J. Sheet Materials for Use as Membranes in Membrane Introduction Mass Spectrometry. *Anal. Chem.* **1996**, *68*, 1805; (b) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *J. Med. Chem.* **2010**, *53*, 7902; (c) Bacosca, I.; Hamciuc, E.; Bruma, M.; Ignat, M. Poly(Amide Imide)s Containing Functional Nitrile Groups for High Performance Materials. *React. Funct. Polym.* **2011**, *71*, 905; (d) Wu, S.; Liu, Y.; Yu, G.; Guan, J.; Pan, C.; Du, Y.; Xiong, X.; Wang, Z. Facile Preparation of Dibenzoheterocycle-Functional Nanoporous Polymeric Networks with High Gas Uptake Capacities. *Macromolecules* **2014**, *47*, 2875.

(16) (a) Zhang, H.; Pu, W.; Xiong, T.; Li, Y.; Zhou, X.; Sun, K.; Liu, Q.; Zhang, Q. Copper-Catalyzed Intermolecular Aminocyanation and Diamination of Alkenes. *Angew. Chem. Int. Ed.* **2013**, *52*, 2529; (b) Ilchenko, N. O.; Janson, P. G.; Szabo, K. J. Copper-Mediated Cyanotrifluoromethylation of Styrenes Using the Togni Reagent. *J. Org. Chem.* **2013**, *78*, 11087; (c) He, Y. T.; Li, L. H.; Yang, Y. F.; Zhou, Z. Z.; Hua, H. L.; Liu, X. Y.; Liang, Y. M. Copper-Catalyzed Intermolecular Cyanotrifluoromethylation of Alkenes. *Org. Lett.* **2014**, *16*, 270; (d) He, Y. T.; Li, L. H.; Zhou, Z. Z.; Hua, H. L.; Qiu, Y. F.; Liu, X. Y.; Liang, Y. M. Copper-Catalyzed Three-Component Cyanotrifluoromethylation/Azidotrifluoromethylation and Carbocyclization of 1,6-Enynes. *Org. Lett.* **2014**, *16*, 3896; (e) Zhao, W.; Montgomery, J. Functionalization of Styrenes by Copper-Catalyzed Borylation/ Ortho-Cyanation and Silver-Catalyzed Annulation Processes. *Angew. Chem. Int. Ed.* **2015**, *54*, 12683; (f) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. Enantioselective Cyanation of Benzylic C-H Bonds Via Copper-Catalyzed Radical Relay. *Science* **2016**, *353*,

1014; (g) Wang, D.; Wang, F.; Chen, P.; Lin, Z.; Liu, G. Enantioselective Copper-Catalyzed Intermolecular Amino- and Azidocyanation of Alkenes in a Radical Process. *Angew. Chem. Int. Ed.* **2017**, *56*, 2054; (h) Wang, D.; Zhu, N.; Chen, P.; Lin, Z.; Liu, G. Enantioselective Decarboxylative Cyanation Employing Cooperative Photoredox Catalysis and Copper Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 15632; (i) Meng, F.; Zhang, H.; Guo, K.; Dong, J.; Lu, A. M.; Zhu, Y. Access to Cyano-Containing Isoxazolines Via Copper-Catalyzed Domino Cyclization/Cyanation of Alkenyl Oximes. *J. Org. Chem.* **2017**, *82*, 10742; (j) Wang, F.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* **2018**, *51*, 2036.

(17) (a) Yamanaka, M.; Kato, S.; Nakamura, E. Mechanism and Regioselectivity of Reductive Elimination of Pi-Allylcopper (III) Intermediates. *J. Am. Chem. Soc.* **2004**, *126*, 6287; (b) Hickman, A. J.; Sanford, M. S. High-Valent Organometallic Copper and Palladium in Catalysis. *Nature* **2012**, *484*, 177; (c) Yoshikai, N.; Nakamura, E. Mechanisms of Nucleophilic Organocopper(I) Reactions. *Chem. Rev.* **2012**, *112*, 2339; (d) Casitas, A.; Ribas, X. The Role of Organometallic Copper(III) Complexes in Homogeneous Catalysis. *Chem. Sci.* **2013**, *4*, 2301.

(18) Wang, F.; Wang, D.; Zhou, Y.; Liang, L.; Lu, R.; Chen, P.; Lin, Z.; Liu, G. Divergent Synthesis of CF_3 -Substituted Allenyl Nitriles by Ligand-Controlled Radical 1,2- and 1,4-Addition to 1,3-Enynes. *Angew. Chem. Int. Ed.* **2018**, 57, 7140.

(19) (a) Qian, B.; Chen, S.; Wang, T.; Zhang, X.; Bao, H. Iron-Catalyzed Carboamination of Olefins: Synthesis of Amines and Disubstituted Beta-Amino Acids. *J. Am. Chem. Soc.* **2017**, *139*, 13076; (b) Jian, W.; Ge, L.; Jiao, Y.; Qian, B.; Bao, H. Iron-Catalyzed Decarboxylative Alkyl Etherification of Vinylarenes with Aliphatic Acids as the Alkyl Source. *Angew. Chem. Int. Ed.* **2017**, *56*, 3650; (c) Li, Y.; Han, Y.; Xiong, H.; Zhu, N.; Qian, B.; Ye, C.; Kantchev, E. A.; Bao, H. Copper-Catalyzed Regioselective 1,2-Alkylesterification of Dienes to Allylic Esters. *Org. Lett.* **2016**, *18*, 392; (d) Zhu, N.; Zhao, J.; Bao, H. Iron Catalyzed Methylation and Ethylation of Vinyl Arenes. *Chem. Sci.* **2017**, *8*, 2081.

(20) (a) Prakash, G. K. S.; Yudin, A. K. Perfluoroalkylation with Organosilicon Reagents. *Chem. Rev.* **1997**, *97*, 757; (b) Ma, J. A.; Cahard, D. Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions. *Chem. Rev.* **2004**, *104*, 6119; (c) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of Fluorine and Fluorine-Containing Functional Groups. *Angew. Chem. Int. Ed.* **2013**, 52, 8214.

(21) (a) Li, Z.; Garcia-Dominguez, A.; Nevado, C. Pd-Catalyzed Stereoselective Carboperfluoroalkylation of Alkynes. *J. Am. Chem. Soc.* **2015**, *137*, 11610; (b) Domański, S.; Chaładaj, W. A Broadly Applicable Method for Pd-Catalyzed Carboperfluoro-Alkylation of Terminal and Internal Alkynes: A Convenient Route to Tri- and Tetrasubstituted Olefins. *ACS Catal.* **2016**, *6*, 3452; (c) Kawamura, S.; Sodeoka, M. Perfluoroalkylation of Unactivated Alkenes with Acid Anhydrides as the Perfluoroalkyl Source. *Angew. Chem. Int. Ed.* **2016**, 55, 8740; (d) Lin, J. S.; Wang, F. L.; Dong, X. Y.; He, W. W.; Yuan, Y.; Chen, S.; Liu, X. Y. Catalytic Asymmetric Radical Aminoperfluoroalkylation and Aminodifluoromethylation of Alkenes to Versatile Enantioenriched-Fluoroalkyl Amines. *Nat. Commun.* **2017**, *8*, 14841.

(22) Jiang, X.; Fu, C.; Ma, S. Highly Stereoselective Iodolactonization of 4,5-Allenoic Acids--an Efficient Synthesis of 5-(1'-Iodo-1'(Z)-Alkenyl)-4,5-Dihydro-2(3h)-Furanones. *Chemistry* **2008**, *14*, 9656.

(23) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. Asymmetric Synthesis of Active Pharmaceutical Ingredients. *Chem. Rev.* **2006**, *106*, 2734.

(24) Bao, H.; Tambar, U. K. Catalytic Enantioselective Allylic Amination of Unactivated Terminal Olefins Via an Ene Reaction/[2,3]-Rearrangement. *J. Am. Chem. Soc.* **2012**, *134*, 18495.

(25) (a) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. Palladium-Catalyzed C-H Aminations of Anilides with N-Fluorobenzenesulfonimide. *J. Am. Chem. Soc.* **2011**, *133*, 1694; (b) Ni, Z.; Zhang, Q.; Xiong, T.; Zheng, Y.; Li, Y.; Zhang, H.; Zhang, J.; Liu, Q. Highly Regioselective Copper-Catalyzed Benzylic C-H Amination by *N*-Fluorobenzenesulfonimide. *Angew. Chem. Int. Ed.* **2012**, *51*, 1244; (c) Zhang, H.; Song, Y.; Zhao, J.; Zhang, J.; Zhang, Q. Regioselective Radical Aminofluorination of Styrenes. *Angew. Chem. Int. Ed.* **2014**, 53, 11079; (d) Zhang, G.; Xiong, T.; Wang, Z.; Xu, G.; Wang, X.; Zhang, Q. Highly Regioselective Radical Amination of Allenes: Direct Synthesis of Allenamides and Tetrasubstituted Alkenes. *Angew. Chem. Int. Ed.* **2015**, *54*, 12649; (e) Zheng, G.; Li, Y.; Han, J.; Xiong, T.; Zhang, Q. Radical Cascade Reaction of Alkynes with *N*-Fluoroarylsulfonimides and Alcohols. *Nat. Commun.* **2015**, *6*, 7011.

(26) Tsuji, Y.; Taniguchi, M.; Yasuda, T.; Kawamura, T.; Obora, Y. Palladium-Catalyzed Cyanation of Propargylic Carbonates with Trimethylsilyl Cyanide. *Org. Lett.* **2000**, *2*, 2635.

(27) Newcomb, M. Radical Kinetics and Clocks in Encyclopedia of Radicals in Chemistry, Biology and Materials. Chatgilialoglu, C., A., S., Eds.; Wiley: Chichester, 2012; Vol. 1, p 107.

(28) The Overall potential energy surface including Cu(III) mechanism are shown in Figure S7 and discussed in the Si. For the sake of clarity, only the most relevant part is shown in Figure 1.

(29) (a) Toma, L. M.; Delgado, F. S.; Ruiz-Perez, C.; Carrasco, R.; Cano, J.; Lloret, F.; Julve, M. Synthesis, Crystal Structures and Magnetic Properties of Single and Double Cyanide-Bridged Bimetallic Fe2(III)Cu(II) Zigzag Chains. *Dalton Trans.* **2004**, 2836; (b) Xu, F.; Huang, W.; You, X. Z. Novel Cyano-Bridged Mixed-Valent Copper Complexes Formed by Completely in Situ Synthetic Method Via the Cleavage of C-C Bond in Acetonitrile. *Dalton Trans.* **2010**, *39*, 10652; (c) Dietz, O.; Rayon, V. M.; Frenking, G. Molecular Structures, Bond Energies, and Bonding Analysis of Group 11 Cyanides TM(CN) and Isocyanides TM(NC) (TM = Cu, Ag, Au). *Inorg. Chem.* **2003**, *42*, 4977.

(30) Ratani, T. S.; Bachman, S.; Fu, G. C.; Peters, J. C. Photoinduced, Copper-Catalyzed Carbon-Carbon Bond Formation with Alkyl Electrophiles: Cyanation of Unactivated Secondary Alkyl Chlorides at Room Temperature. *J. Am. Chem. Soc.* **2015**, *137*, 13902.

(31) (a) Shen, H.; Liu, Z.; Zhang, P.; Tan, X.; Zhang, Z.; Li, C. Trifluoromethylation of Alkyl Radicals in Aqueous Solution. *J. Am. Chem. Soc.* **2017**, *139*, 9843; (b) Tan, X.; Liu, Z.; Shen, H.; Zhang, P.; Zhang, Z.; Li, C. Silver-Catalyzed Decarboxylative Trifluoromethylation of Aliphatic Carboxylic Acids. *J. Am. Chem. Soc.* **2017**, *139*, 12430.

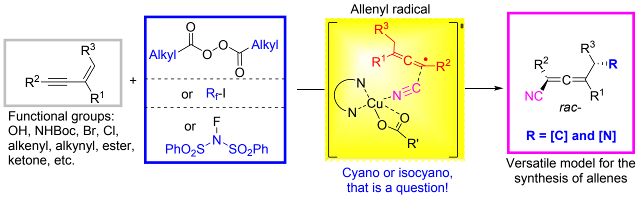
(32) (a) Chen, B.; Fang, C.; Liu, P.; Ready, J. M. Rhodium-Catalyzed Enantioselective Radical Addition of CX_4 Reagents to Olefins. *Angew. Chem. Int. Ed.* **2017**, *56*, 8780; (b) Liu, Z.; Chen, H.; Lv, Y.; Tan, X.; Shen, H.; Yu, H. Z.; Li, C. Radical Carbofluorination of Unactivated Alkenes with Fluoride Ions. *J. Am. Chem. Soc.* **2018**, *140*, 6169.

(33) (a) Emokpae, T. A.; Ukwueze, A. C. Reactions of Copper(I) and Zinc(II) Halides with Phenylacetylene. *Inorg. Chim. Acta* **1986**, *112*, L17; (b) Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. “Higher Order” Cyanocuprates $R_2Cu(CN)Li_2$: Discrete Reagents or Lower Order Lithium Cyanide (LiCN) Modified Gilman Cuprates? *J. Am. Chem. Soc.* **1990**, *112*, 4032; (c) Singh, R.; Dikshit, S. K. Cyano-Bridged Copper(I)-Ruthenium(II) Complexes: Syntheses, Characterization and Spectroscopic Studies. *Polyhedron* **1993**, *12*, 1697; (d) Rodríguez-Fortea, A.; Alemany, P.; Alvarez, S.; Ruiz, E.; Scuiller, A.; Decroix, C.; Marvaud, V.; Vaissermann, J.; Verdaguer, M.; Rosenman, I.; Julve, M. Exchange Coupling in Cyano-Bridged Homodinuclear

Cu(II) and Ni(II) Complexes: Synthesis, Structure, Magnetism, and Density Functional Theoretical Study. *Inorg. Chem.* **2001**, *40*, 5868; (e) Lin, Y. Y.; Lai, S. W.; Che, C. M.; Fu, W. F.; Zhou, Z. Y.; Zhu, N. Structural Variations and Spectroscopic Properties of Luminescent Mono- and Multinuclear Silver(I) and Copper(I) Complexes Bearing Phosphine and Cyanide Ligands. *Inorg. Chem.* **2005**, *44*, 1511; (f) Petrovic, D.; Bannenberg, T.; Randoll, S.; Jones, P. G.; Tamm, M. Synthesis and Reactivity of Copper(I) Complexes Containing a Bis(Imidazolin-2-Imine) Pincer Ligand. *Dalton Trans.* **2007**, 2812.

(34) (a) Ismail, Z. K.; Hauge, R. H.; Margrave, J. L. Infrared Study of Matrix-Isolated Lithium Isocyanide. *J. Chem. Phys.* **1972**, *57*, 5137; (b) Chen, X.; Li, Q.; Andrews, L.; Gong, Y. Infrared Spectroscopic and Theoretical Studies of Group 3 Metal Isocyanide Molecules. *J. Phys. Chem. A* **2018**, *122*, 7099.

(35) For comparison, methyl group is taken as the substituent R^3 instead of ethyl to mimic the product **81**.


Functional groups:
OH, NHBoc, Br, Cl,
alkenyl, alkynyl, ester,
ketone, etc.
Alkyl
Alkyl
or R$_f$-I
or
PhO$_2$S
SO$_2$Ph
Allenyl radical
Cu
Cyano or isocyano,
that is a question!
rac-
R = [C] and [N]
Versatile model for the
synthesis of allenes