OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

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Proton-Coupled Electron Transfer Enables Tandem Radical Relay for Asymmetric Copper-Catalyzed Phosphinoylcyanation of Styrenes

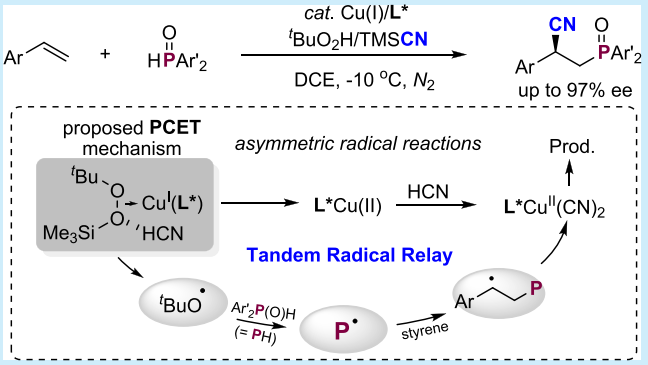
Guoyu Zhang,[†] Liang Fu,[‡] Pinhong Chen,[‡] Jianping Zou,*[,†] and Guosheng Liu*[,‡,§]

[†]Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Soochow University, Suzhou, Jiangsu 215123, China

[‡]State Key Laboratory of Organometallic Chemistry, and [§]Shanghai Hongkong Joint Laboratory in Chemical Synthesis, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: A tandem radical relay strategy was realized for the first Cu(I)-catalyzed enantioselective phosphinocyanation of styrenes. In this reaction, ^{t}BuOOSiMe$_3$ generated *in situ* from ^{t}BuOOH serves as a radical initiator to trigger *t*-butoxy radical production upon oxidization of L*Cu(I) species via proton-coupled-electron transfer (PCET) pathway, which leads to sequential phosphinoyl radical and benzyl radical formations. The resultant *β*-cyanodiarylphosphine oxides could be easily converted to a series of chiral *γ*-amino phosphine ligands.



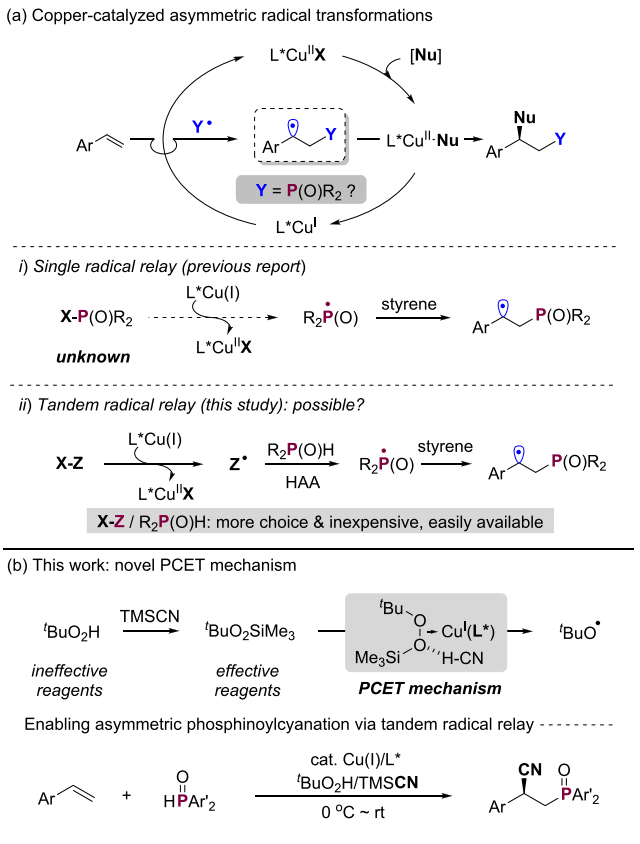
Organophosphorus compounds can be frequently found in medicinal chemistry, agrochemistry, and material science;[1] in addition, optically pure organophosphines bearing a chiral *β*-functional group are widely used as organocatalysts and ligands in asymmetric catalysis.[2] Therefore, considerable efforts have been made toward their synthesis. Among them, radical phosphinoylation reactions serve as an efficient and powerful tool,[3] and a series of phosphinoylation-based difunctionalizations of alkenes have been developed.[4] Despite these advances, the involvement of highly reactive carbon-centered radical intermediates makes an asymmetric version extremely difficult to accomplish. To the best of our knowledge, no such asymmetric reactions have been documented to date.

In our continuing efforts to develop asymmetric radical transformations (ARTs),[5] we have recently developed a copper-catalyzed radical relay process for the enantioselective cyanation,[6] arylation,[7] and alkynylation[8] of styrenes (Scheme 1a). Critical to the success is that a key benzylic radical intermediate is enantioselectively trapped by chiral (L*)-Cu^{II}(Nu) species. Moreover, the benzylic radical was generated by radical (Y) addition to styrenes, and the Y radical was directly derived from electrophiles X-Y (e.g., NFSI and NFAS for the generation of nitrogen-centered radicals, Togni [CF$_3$]$^+$ reagent for producing a CF$_3$ radical) through a single electron transfer (SET) process. We thus hypothesized that, if a phosphinoyl radical could be generated for the similar asymmetric radical reaction, it would provide an efficient and straightforward approach to gain access to valuable chiral organophosphine oxides. However, to the best of our knowledge, the lack of P-based electrophiles for the generation of phosphinoyl radicals impedes the development of the asymmetric phosphinoyl radical-initiated reactions (Scheme 1a, *i*).[9] Therefore, we envisaged that *tandem radical relay processes,* namely, two sequential radical relay steps, by introducing an additional radical relay step, in which phosphinoyl radicals could be generated from R$_2$P(O)H through a hydrogen atom abstraction (HAA) process by Z radical (e.g., *tert*-butoxy radical) generated from easily available electrophiles X-Z (e.g., ^{t}BuOOH or ^{t}BuOOBu^t) and L*Cu(I) catalysts, would be a reasonable strategy to solve the aforementioned problem and greatly expand copper-catalyzed asymmetric radical transformations (Scheme 1a, *ii*). Notably, in this tandem radical relay process, the resulting Z radical should react favorably with R$_2$P(O)H rather than undergo radical addition to styrenes. In addition, the rate for hydrogen atom abstraction (HAA) should be much faster than that of a combination of the Z radical with Cu(I) species, avoiding the termination of the copper catalyst.[10] Herein, we disclose a novel proton-coupled-electron transfer (PCET) mechanism to generate *tert*-butoxy radical from unusual *tert*-butyl peroxide silane (TNPS) reagent, which allows generation of phosphinoyl radical from the seqential HAA of R$_2$P(O)H. This tandem radcal relay is compatible with the sequential asymmetric

Received: May 7, 2019

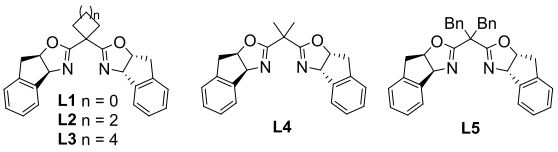
DOI: 10.1021/acs.orglett.9b01607
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Asymmetric Radical Phosphinoylation of Alkenes



Scheme 2. Optimization of the Reaction Conditions[a]

entry	ligand	oxidant	3a yield (%)[b,c]	3a' yield (%)[b,d]
1[e]	L1	tBuOOH (2 equiv)	15 (71% ee)	**85**
2	L1	tBuOOH (2 equiv)	**70** (71% ee)	15
3	L2	tBuOOH (2 equiv)	55 (58% ee)	16
4	L3	tBuOOH (2 equiv)	70 (73% ee)	5
5	L4	tBuOOH (2 equiv)	53 (49% ee)	17
6	L5	tBuOOH (2 equiv)	77 (92% ee)	14
7[f]	L5	tBuOOH (2 equiv)	80 (92% ee)	9
8	L5	tBuOOH (4 equiv)	11 (92% ee)	**78**
9[g]	L5	tBuOOH (2 equiv)	**82 (96% ee)**	0
10	L5	tBuOOBut or tBuOOBz	0	0



[a]The reaction was run on a 0.1 mmol scale, $Cu(CH_3CN)_4PF_6$ (5 mol %), ligand (6 mol %), **1a** (0.1 mmol), **2a** (0.2 mmol), TMSCN (0.2 mmol), and oxidant (0.2 mmol) in DCE (1 mL) at room temperature under N_2. [b]^{1}H NMR yield using CH_2Br_2 as an internal standard. [c]Enantiomeric excess (ee) value was determined by HPLC on a chiral stationary phase. [d]**3a′** as racemate. [e]tBuOOH in water was used. [f]TMSCN (3.0 equiv). [g]At −10 °C.

cyanation, which enables highly chemo- and enantioselective phosphinoylcyanation of alkenes (Scheme 1b).

Stoichiometric amounts of metal salts (e.g., $Mn(OAc)_3$, $AgNO_3$, etc.) are often used as oxidants to generate phosphinoyl radicals by oxidizng $R_2P(O)H$;[4] as we expected, they proved to be incompatible to the asymmetric reaction to give racemic product. Alternatively, tBuOOH is also considered as an efficient oxidant to react with $R_2P(O)H$ to generate the phosphinoyl radicals under metal or metal-free conditions.[11] Owing to its inexpensive and easily available properties, tBuOOH was selected to examine the asymmetric phosphinoylcyanation reaction via *tandem radial relay*. However, a *tert*-butyl peroxyl radical was likely to be generated, and underwent cross coupling with carbon-centered radicals to give ether peroxides as reported in difunctionalizations of alkenes.[12] In fact, tBuOOH in water or decane was respectively employed for the reaction of 4- bromostyrene **1a** with diphenylphosphine oxide **2a** using $Cu(CH_3CN)_4PF_6$ and bisoxazoline (Box) ligand **L1** as catalyst; it was surprising that the opposite results were obtained. The ether peroxide product **3a′** was indeed obtained as the predominant product using tBuOOH in water as the oxidant, along with a small amount of the desired phosphinoylcyanation product **3a** with 71% ee (Scheme 2, entry 1). Fortunately, the desired asymmetric phosphinoylcyanation became a major pathway when using tBuOOH in decane, which gave the desired product **3a** with the same enantioselectivity (entry 2). Further ligand screening revealed that *gem*-disubstituted Box ligands played a significant role in enhancing both reactivities and enantioselectivities (entries 3−6), and **L5** with sterically bulky *gem*-dibenzylic groups gave **3a** with 92% ee (entry 6). In addition, the ratio of tBuOOH to TMSCN was also essential for the reaction, employing an equimolar or more TMSCN than tBuOOH led to the desired product **3a** as a major product in 92% ee (entries 6−7), while using more tBuOOH than TMSCN resulted in the predominant ether peroxide product **3a′** in 78% yield (entry 8), which was similar to the reaction using tBuOOH in water (entry 1). Notably, the ether peroxide product **3a′** obtained as racemate in these reactions (entries 1−8) was completely inhibited at −10 °C (entry 9). Compared to tBuOOH, both tBuOOBut and tBuOOBz were ineffective (entry 10); in addition, NFSI and $PhI(OAc)_2$ used in our previous studies were also ineffective.[5]

With the optimal reaction conditions in hand, the substrate scope of this enantioselective copper-catalyzed phosphinocyanation of styrenes was then investigated. As shown in Scheme 3, styrenes bearing electron-donating and withdrawing groups on the benzene ring were suitable for the reaction, giving the desired products **3a−3q** in good yields with excellent enantioselectivities (60−96% yields and 76−97% ee). Notably, various functional groups, such as halide, ester, ether, and CF_3, could be well tolerated under our current mild conditions. In addition, reactions of naphthalene-derived substrates also worked well to give the desired products **3r−3t** in good yields with excellent enantioselectivities. Furthermore, vinyl heteroarene **1u** and estrone-derived styrene **1v** could also be employed as substrates to afford the corresponding products **3u** and **3v** in good yields with excellent enantioselectivities. Notably, the model reaction could be performed on a 10 mmol scale without loss of reaction efficiency and enantioselectivity. The absolute structure of (*S*)-**3a** was unambiguously determined by the X-ray crystallography.

The phosphorus substrate scope was also investigated, as shown in Scheme 4. Diarylphosphorous oxides bearing

DOI: 10.1021/acs.orglett.9b01607
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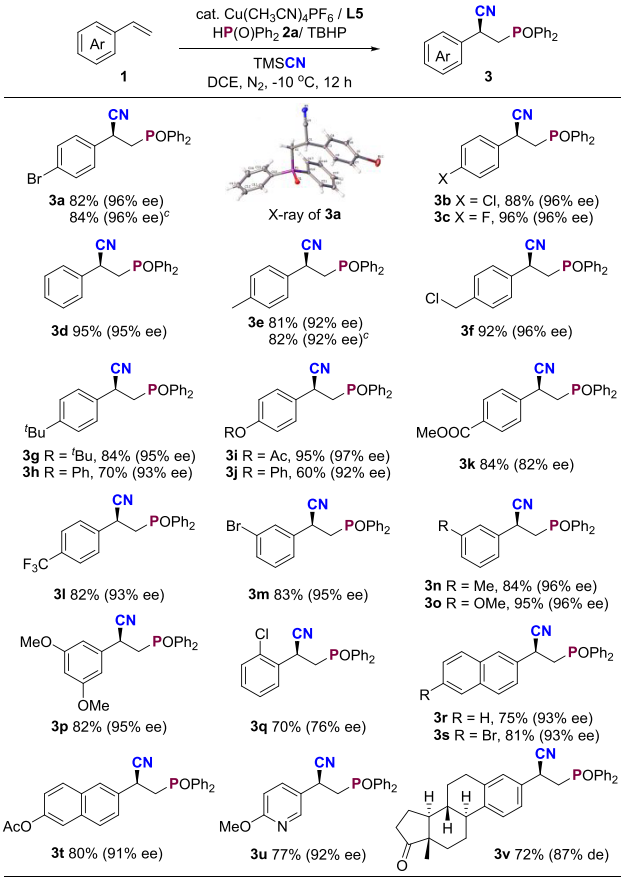
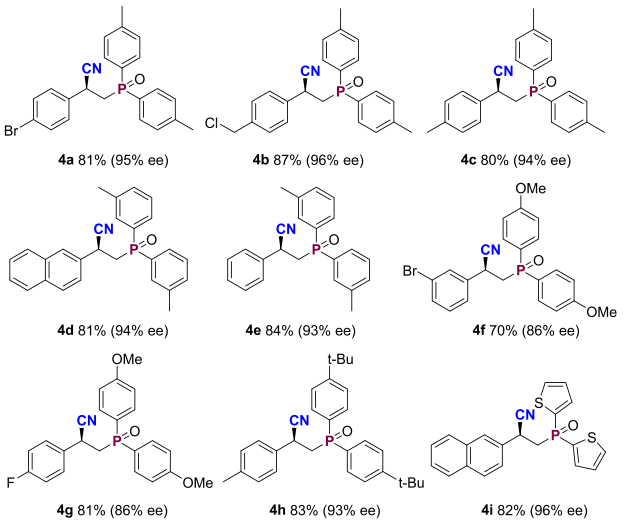
Scheme 3. Scope of Alkenes[a,b,c]



[a]Reaction conditions: **1** (0.2 mmol), $Cu(CH_3CN)_4PF_6$ (5 mol %), **L5** (6 mol %), **2a** (0.4 mmol), TMSCN (0.4 mmol), ^{t}BuOOH in decane (0.4 mmol) in DCE (2 mL) at −10 °C under N_2. [b]Isolated yield and ee value was determined by HPLC on a chiral stationary phase. [c]On a 10 mmol scale.

Scheme 4. Scope of Phosphorous Substrates[a,b]

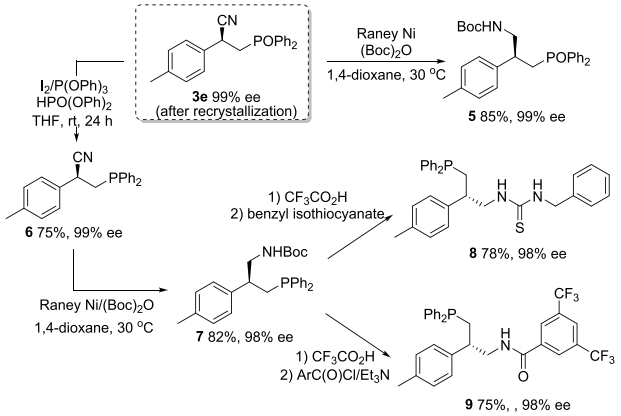


[a]Reaction conditions: **1** (0.2 mmol), $Cu(CH_3CN)_4PF_6$ (5 mol %), **L5** (6 mol %), **2** (0.4 mmol), TMSCN (0.4 mmol), ^{t}BuOOH in decane (0.4 mmol) in DCE (2 mL) at −10 °C under N_2. [b]Isolated yield and ee value was determined by HPLC on a chiral stationary phase.

electron-rich groups at the *para* or *meta* position of the aromatic ring reacted smoothly with styrenes to deliver the desired products **4a**−**4h** in good yields (70−87%) with excellent enantioselectivities (86−96% ee). In addition, di(thiophen-2-yl)phosphine oxide was also suitable for the reaction to afford the product **4i** in 82% yield with 96% ee.

To showcase the synthetic utility of the method, the optically pure phosphinocyanated product **3e** after recrystallization could be converted into the Boc-protected amine **5** in 85% yield with 99% ee in a one-pot fashion (Scheme 5). In addition, the phosphine oxide **3e** could also be selectively reduced to afford the chiral phosphine **6** bearing *β*-cyano group in 75% yield with 99% ee,[13] which could be further reduced to give the chiral amine-based phosphine **7** in 82% yield with 98% ee. Importantly, compound **7** was easily converted to the corresponding chiral phosphine ligands **8** and **9** in moderate yields, which are a new class of potential chiral organocatalysts in asymmetric catalysis.[2b,d,14]

Scheme 5. Synthetic Transformations



As mentioned above, ^{t}BuOOH to TMSCN ratio was essential for the phosphinoylcyanation reaction, and using more ^{t}BuOOH than TMSCN resulted in the predominant phosphinoyl-oxygenation product **3a′** (Scheme 2, entries 6 vs 8). To elucidate this outcome, a series of control experiments were conducted. The reaction of ^{t}BuOOH in decane with TMSCN gave ^{t}BuO$_2$SiMe$_3$ and HCN in quantitative yields immediately, while no reaction occurred in the case of ^{t}BuO$_2$SiMe$_3$ and HCN (Scheme 6a). In addition, a reaction using a premixed solution of ^{t}BuOOH in decane and TMSCN gave similar results as the standard reaction furnishing the phosphinoylcyanation product **3a** (Scheme 6b). However, when ^{t}BuO$_2$SiMe$_3$ was synthesized[15] and tested for the reaction of **1a** and **2a** with TMSCN, no reaction occurred at all, and ^{t}BuOOSiMe$_3$ and $Ph_2P(O)H$ **2a** were almost quantitatively recovered (>95%, Scheme 6c, left), whereas upon treatment of TMSCN with water,[16] the resultant HCN reacted with ^{t}BuO$_2$SiMe$_3$ under the same reaction conditions to give the desired product **3a** in good yield and excellent enantioselectivity (Scheme 6c, right). These results revealed that HCN rather than TMSCN acted as a real cyanide source to participate in the cyanation of benzylic radicals and excessive amounts of HCN did not poison copper catalysts presumably due to a small dissociation constant of HCN (HCN in H_2O, pK_a = 9.2), which were distinctly different from our previous studies of the cyanide effect.[6b]

DOI: 10.1021/acs.orglett.9b01607
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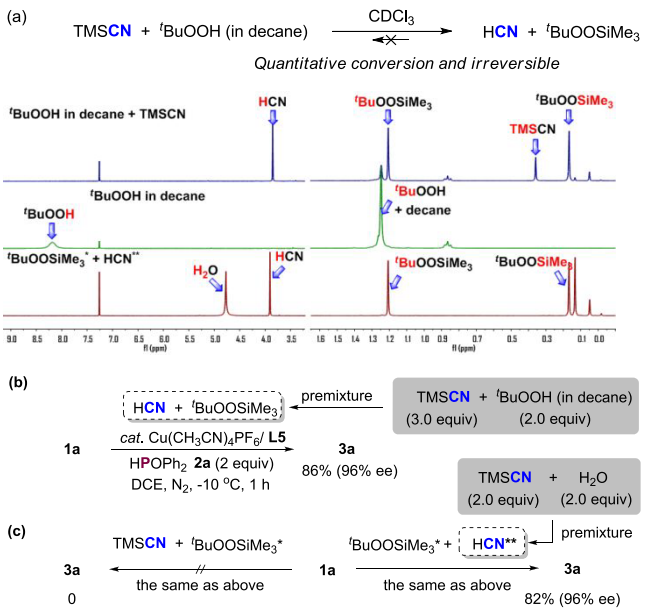
Scheme 6. Control experiments[a]



[a] *^{t}BuOOSiMe$_3$ was synthesized; HCN** was generated from TMSCN and H_2O.

To provide more insight into the possible mechanism, additional experiments were carried out. A colorless solution of (**L5**)Cu(I) in CH_2Cl_2 turned blue immediately after ^{t}BuOOSiMe$_3$ was added (Figure 1a), and a mixture of ^{t}BuOOSiMe$_3$ and (**L5**)Cu(I) was then analyzed by UV spectrum. As shown in Figure 1a, when 0−1.0 equiv of ^{t}BuOOSiMe$_3$[17] was individually added to the solution of (**L5**)Cu(I) in CH_2Cl_2, an absorption band of the colorless mixture (**L5**)Cu(I) at 235 nm decayed and a new absorption band at 295 nm emerged, but no significant change to the spectrum was observed when more than 1 equiv of ^{t}BuOOSiMe$_3$ was added. Meanwhile, the absorption band at 590 nm significantly increased after adding ^{t}BuOOSiMe$_3$. These observations suggested that a remarkable interaction between ^{t}BuOOSiMe$_3$ and (**L5**)Cu(I) indeed occurred, and the titration experiment revealed that there was only a ^{t}BuOOSiMe$_3$ molecule connecting to a copper center (Figure 1a). Furthermore, the interaction of ^{t}BuOOSiMe$_3$ with (**L5**)Cu(I) was monitored by EPR spectroscopy. To our surprise, the single electron transfer between ^{t}BuOOSiMe$_3$ and (**L5**)Cu(I) did not occur (Figure 1b, red line); however, a Cu(II) signal was immediately detected by EPR spectroscopy after adding HCN (Figure 1b, purple line), but no Cu(II) signals were detected using TMSCN (blue line). This, along with the reaction outcomes in Scheme 3c, prompted us to conclude that the single electron oxidation of (**L5**)Cu(I) with ^{t}BuOOSiMe$_3$ only occurred through a possible PCET process in the presence of HCN (Scheme 4c, right), rather than TMSCN, to deliver *tert*-butoxy radical and (**L5**)Cu(II) species which were key intermediates for the asymmetric phosphinoylcyanation.

Although the interaction between ^{t}BuOO^{t}Bu and (**L5**)Cu(I) was also observed with a small reaction constant (see Figure.S4), the single electron oxidation of ^{t}BuOOBu^t with (**L5**)Cu(I) did not occur in the presence of TMSCN or HCN (see Figure 1c), which agreed with the ineffective ^{t}BuOO^{t}Bu in the catalytic reaction. Thus, ^{t}BuOOSiMe$_3$ exhibited a unique reactivity toward the (**L5**)Cu(I) oxidation.

Based on these experiments and our previous studies,[6] a plausible radical mechanism is described in Scheme 7. At the beginning, TBHP reacted with TMSCN to generate the real reactive oxidant ^{t}BuOOSiMe$_3$ (TBPS) and HCN (Scheme 7a, eq 1). Then, the resulting ^{t}BuOOSiMe$_3$ initially coordinated to (**L5**)Cu^I(CN) to form **int-I** which underwent PCET to give

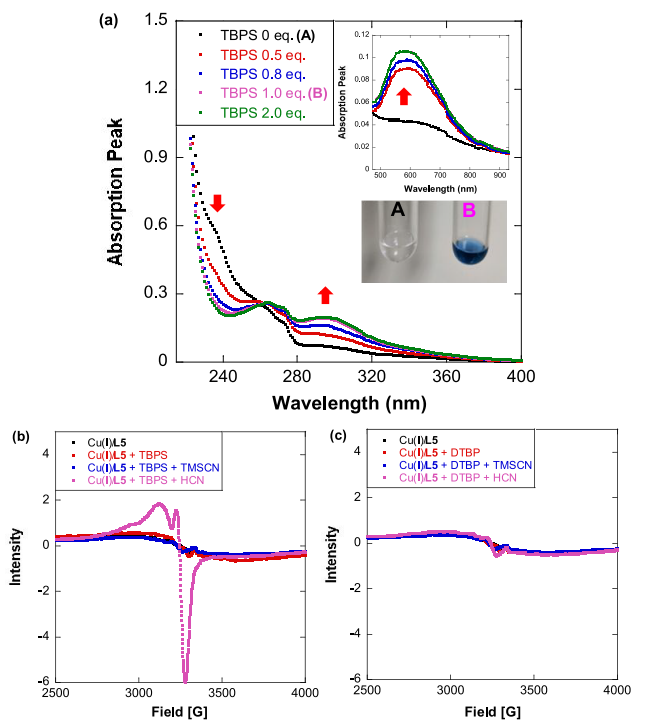
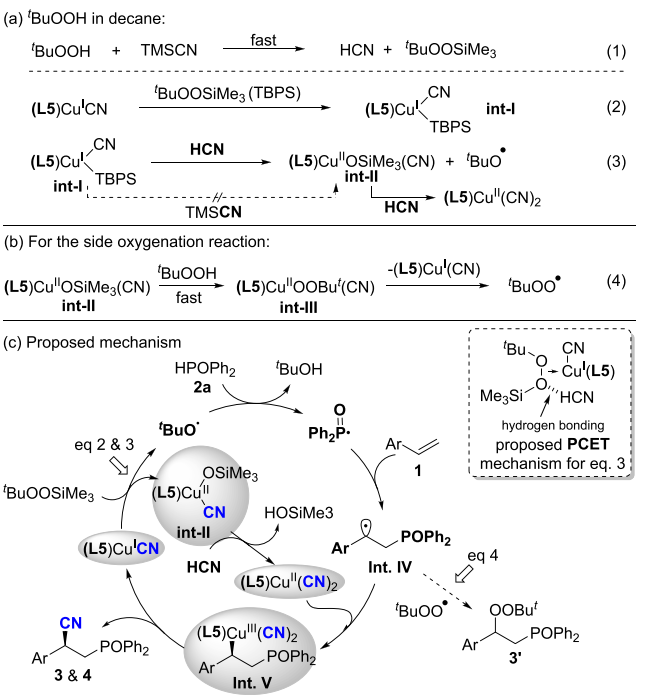


Figure 1. Studies on the single electron oxidation of Cu(I)/**L5** with ^{t}BuOOSiMe$_3$ (TBPS) by UV (a) and EPR spectrum (b); and with ^{t}BuOOBu^t (DTBP) by EPR spectrum (c).

Scheme 7. Proposed Mechanism



DOI: 10.1021/acs.orglett.9b01607
Org. Lett. XXXX, XXX, XXX−XXX

Cu(II) species **int-II** and *tert*-butoxy radical in the presence of HCN (eqs 2−3), possibly triggered by a hydrogen bonding effect (Scheme 7c, right). Subsequently, the Cu(II) species **int-II** reacted with HCN to yield active (**L5**)$Cu^{II}(CN)_2$ species. Meanwhile, the *tert*-butoxy radical could abstract the hydrogen of $Ph_2P(O)H$ to give phosphinoyl radicals,[11b,c] which sequentially added to styrenes. Eventually, the resultant benzylic radical **int-IV** was enantioselectively trapped by (**L5**)$Cu^{II}(CN)_2$ to give the enantiomerically enriched phosphinoylcyanation products.

In addition, when an excessive amount of ^{t}BuOOH was used for the reaction, the reaction of **1a** with **2a** gave the major product **3a′** (Scheme 2, entry 8). Previous studies demonstrated that an alkylperoxo Cu(II) complex (Cu^{II}−OOR) could be converted into peroxyl radicals.[18] Therefore, we reasoned that ^{t}BuOOH could react quickly with Cu(II) species **int-II** to provide **int-III** which released the peroxyl radical to couple with benzylic radicals to give racemic product **3′** (Scheme 7b).[12,19]

In summary, we have developed the first copper-catalyzed enantioselective phosphinocyanation of alkenes via a tandem radical relay, which allows for the straightforward and efficient synthesis of various phosphine-containing alkylnitriles in good yields with excellent enantioselectivities under very mild conditions. Preliminary mechanistic studies reveal that the *in situ* generated *tert*-$BuOOSiMe_3$ acts as an oxidant and HCN is the real cyanide source, which provides a potential protocol for introducing ^{11}CN into molecules by using ^{11}C-labeled HCN. Further applications of this method are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01607.

Synthetic procedures, characterization, and X-ray data (PDF)

NMR spectra and HPLC analysis (PDF)

Accession Codes

CCDC 1915903 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jpzou@suda.edu.cn.

*E-mail: gliu@mail.sioc.ac.cn.

ORCID

Jianping Zou: 0000-0002-8092-9527

Guosheng Liu: 0000-0003-0572-9370

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Basic Research Program of China (973-2015CB856600), the National Nature Science Foundation of China (Nos. 21532009, 21790330, and 21821002 for GL, 21472133 for JZ), the Science and Technology Commission of Shanghai Municipality (Nos. 17XD1404500, 17QA1405200, and 17JC1401200), and the strategic Priority Research Program (No. XDB20000000) and the Key Research Program of Frontier Science (QYZDJSSWSLH055) of the Chinese Academy of Sciences. JZ thanks the support from the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD). GL thanks Prof. Liang Deng @ SIOC, and Prof. Hairong Guan @ University of Cincinnati for the helpful discussion.

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DOI: 10.1021/acs.orglett.9b01607
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