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Phosphinoyl Radical Initiated Vicinal Cyanophosphinoylation of Alkenes

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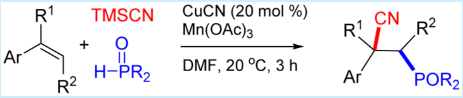
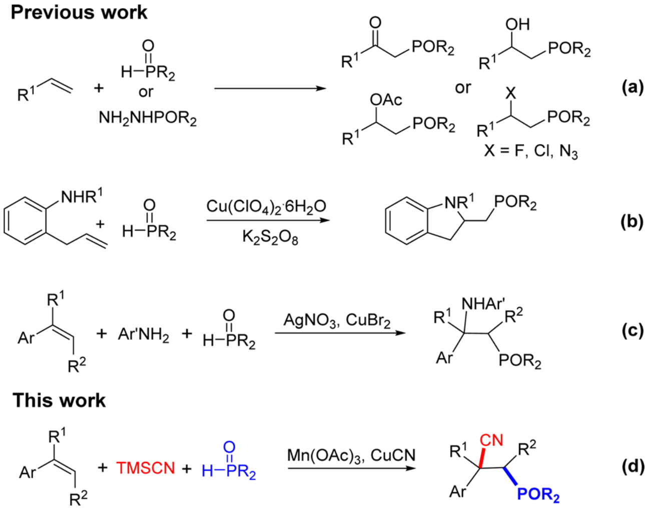
Supporting Information

ABSTRACT: A double-functionalization reaction of alkenes through Mn$(OAc)_3$-mediated phosphinoyl radical addition followed by CuCN-catalyzed cyanation is introduced. This one-pot reaction is performed under mild conditions to afford vicinal cyanophosphinoylation products.



Organophosphorus compounds have broad and desirable physical,[1] chemical,[2] and biological properties.[3] The development of ionic[4] and radical[5] phosphinoylation reactions has received much attention. Among them, radical-based vicinal bifunctionalization of alkenes is attractive due to high synthetic efficiency and structural diversity of products.[6] Bifunctionalization reactions such as oxyphosphinoylation,[7] hydroxyphosphinoylation, acetoxyphosphinoylation,[8] halophosphinoylation,[9] and aminophosphinoylation[10] have been reported in the literature (Scheme 1a−c).

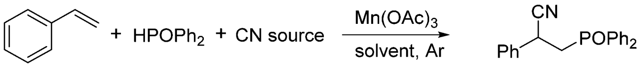
Scheme 1. Phosphorus Radical-Based Bifunctionalizations



Cyano is a versatile group which can be converted to amines, amides, acids, aldehydes, and heterocycles[11] for the synthesis of natural products and bioactive compounds.[12] Our groups are interested in exploring phosphorus radical reactions.[8c,10b,13] Presented in this paper is our effort on the development of cyanophosphinoylation as a new bifunctionalization reaction for alkenes (Scheme 1d). To the best of our knowledge, there is no such reaction in the literature.

The initial experiment was carried out using styrene **1a**, diphenylphosphine oxide ($HPOPh_2$) **2**, and trimethylsilylcyanide (TMSCN) as substrates, Mn$(OAc)_3$ as an oxidant, and *N*-methyl-2-pyrrolidinone (NMP) as a solvent. Only a trace amount of product **3a** was detected from a reaction at 55 °C for 3 h (Table 1, entry 1). Reactions using tetrabutylammonium cyanide (TBACN) or CuCN as a cyano source were conducted (Table 1, entries 2 and 3). No product was detected from the reaction with TBACN, while 25% of **3a** was obtained from the reaction using a stoichiometric amount of CuCN. Reactions with 20 mol % of CuCN in combination with 2 equiv of TMSCN or TBACN were conducted. Only a trace amount of

Table 1. Optimization of the Reaction Conditions[a]



1a **2** **3a**

entry	CN source	cat. (20 mol %)	solvent	temp (°C)	yield[b] (%)
1	TMSCN		NMP	55	trace
2	TBACN		NMP	55	ND[c]
3	CuCN		NMP	55	25
4	TBACN	CuCN	NMP	55	trace
5	TMSCN	CuCN	NMP	55	27
6	TMSCN	CuCN	NMP	40	33
7	TMSCN	CuCN	NMP	30	41
8	TMSCN	CuCN	NMP	20	47
9	TMSCN	CuCN	NMP	10	29
10	TMSCN	CuCN	DMF	20	70
11[d]	**TMSCN**	**CuCN**	**DMF**	**20**	**86**
12	TMSCN		DMF	20	trace

[a]Styrene (0.4 mmol), $HPOPh_2$ (0.6 mmol), CN source (0.8 mmol), $Mn(OAc)_3·2H_2O$ (1.0 mmol), CuCN (20 mol %), solvent (3 mL), 3 h under argon. [b]isolated yield. [c]ND means none detected. [d]$HPOPh_2$ (0.8 mmol) and $Mn(OAc)_3·2H_2O$ (1.2 mmol) were used.

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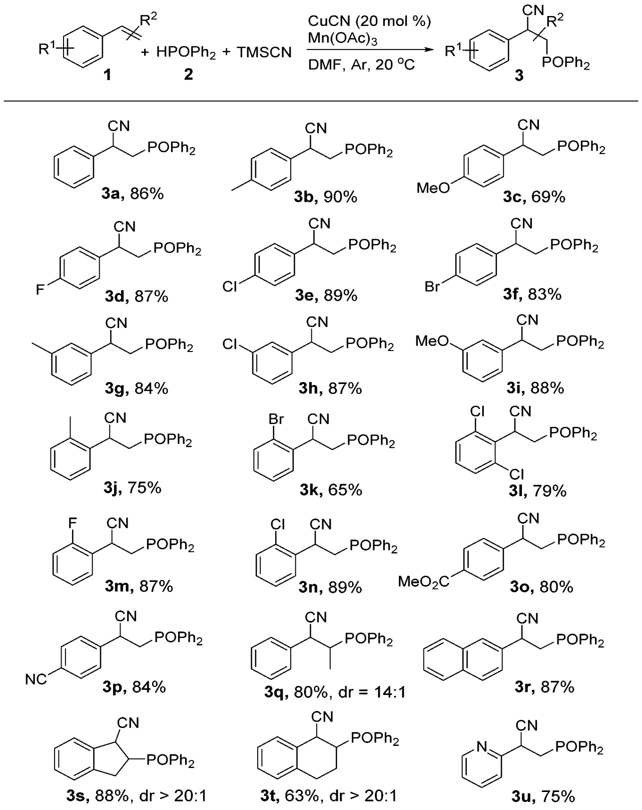
3a was observed from the reaction of TBACN/CuCN system, but 27% was obtained from the TMSCN/CuCN system (Table 1, entries 4 and 5). Replacing Mn(OAc)$_3$ with other oxidants, such as AgNO$_3$/K$_2$S$_2$O$_8$ and *tert*-butyl hydroperoxide (TBHP), or using other copper salts did not give better results (see Supporting Informtion, Tables S1 and S2). Reaction temperature was found to be crucial. Upon lowering the temperature from 55 to 20 °C, the yield of **3a** steadily increased from 27% to 47% but dropped to 29% at 10 °C (Table 1, entries 5−9). Screening of solvents (see SI, Table S3) revealed that DMF could give **3a** in 70% yield (Table 1, entry 10). The optimized conditions were found to be using 1:2:3 of alkene/HP(O)Ph$_2$/Mn(OAc)$_3$ in DMF at 20 °C for 3 h under argon, which gave **3a** in 86% yield (Table 1, entry 11). A control reaction without using CuCN only gave a trace amount of product (Table 1, entry 12).

The scope of this reaction with a number of substituted styrenes was examined under the optimized reaction conditions (Scheme 2). It was found that electron-donating groups (Me and MeO), halogen atoms (F, Cl, and Br), and electron-withdrawing groups (CN and CO$_2$Me) at different positions of benzene ring afforded products **3a−p** in 65−90% yields. A slightly lower yield (65%) of **3k** probably resulted from the steric hindrance of the *o*-bromo substituent. The reaction of *β*-methylstyrene occurred smoothly to afford **3q** in 80% yield. However, the reaction of *α*-methylstyrene did not give the desired product. The reaction of 2-vinylnaphthalene afforded **3r** in 87% yield. It was also found that reactions of cyclic alkenes processed well to give **3s** and **3t** in 88% and 63% yield, respectively. Furthermore, the reaction of 2-vinylpyridine afforded **3u** in 75% yield. But no product was observed from the reaction of 4-nitrostyrene due to the strong electron-withdrawing effect of the nitro group.

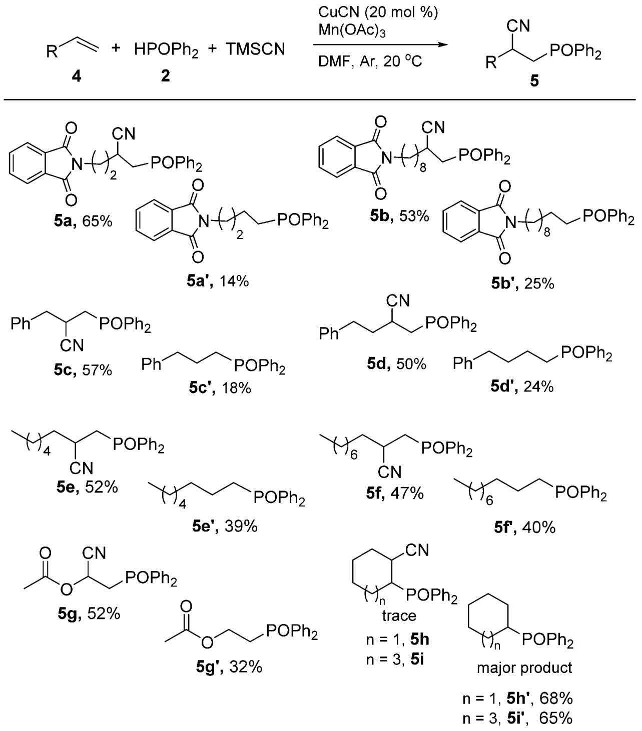
Scheme 2. Reactions of Substituted Styrenes 1[a]



[a]Alkene **1** (0.4 mmol), HPOPh$_2$ (0.8 mmol), TMSCN (0.8 mmol), CuCN (20 mol %), Mn(OAc)$_3$·2H$_2$O (1.2 mmol), DMF (3 mL) at 20 °C for 3 h under argon, isolated yield.

Results obtained from the reactions of aryl alkenes encouraged us to conduct reactions of aliphatic alkenes **4** (Scheme 3). In these cases, a mixture of desired bifunctional products **5a−g** (major) and phosphinoylation products **5a′−g′** (minor) were obtained due to competitive cyanation and hydrogen abstraction of the intermediate radical. The cyanation appears to be a predominant process except for the reactions of cyclic alkenes for **5h** and **5i**. In reactions of aliphatic alkenes without an aryl group, the amounts of phosphinoylation products **5e′** and **5f′** were slightly increased. It was interesting to find that reaction of vinyl acetate afforded **5g** and **5g′** in 52% and 32% yields, respectively. The reactions of other alkenes like 1,2-diphenylethylene, *α*-methylstyrene, 2-methylheptene, ethyl acrylate, and 2-vinylthiophene with dialkylphosphites were also performed, and no desired product was detected (see SI, Scheme S1).

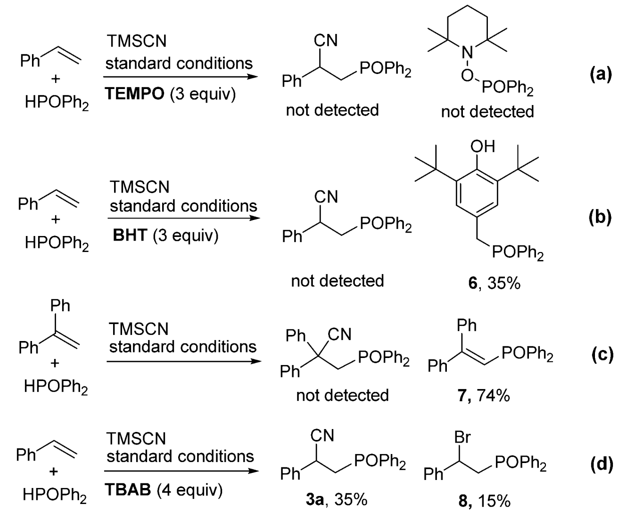
Scheme 3. Reactions of Aliphatic Alkenes 4[a]



[a]Alkene **5** (0.4 mmol), HPOPh$_2$ (0.8 mmol), TMSCN (0.8 mmol), CuCN (20 mol %), Mn(OAc)$_3$·2H$_2$O (1.2 mmol), DMF (3 mL), 3 h under argon, isolated yield.

Several control reactions were carried out in order to have a good understanding of the reaction mechanism. To confirm if the reaction process involved a phosphinoyl radical, reactions with radical trapping agents TEMPO and BHT were performed. It was found that the cyanophosphinoylation was suppressed and no expected product was detected, while radical coupling product **6** was isolated from the reaction with BHT and characterized by ^{1}H, ^{13}C, ^{31}P NMR and HRMS (Scheme 4a and 4b). No evidence indicates that CN radical was involved in the reaction process since no CN radical was trapped by 1,1-

Scheme 4. Control Reactions[a]

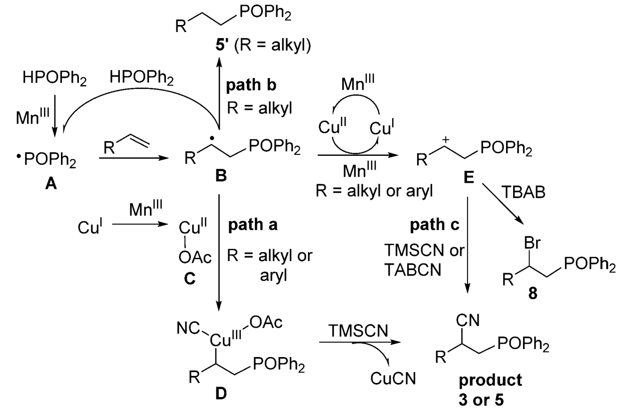


[a]Styrene (0.4 mmol), $HPOPh_2$ (0.8 mmol), TMSCN (0.8 mmol), CuCN (20 mol %), $Mn(OAc)_3 \cdot 2H_2O$ (1.2 mmol), DMF (3 mL) at 20 °C for 3 h under argon, isolated yield.

diphenylethylene and BHT (see SI, Scheme S2). In addition, the reaction of 1,1-diphenylethylene with $HPOPh_2$ and TMSCN only produced compound **7** in 35% yield (Scheme 4c). Furthermore, a reaction with 4.0 equiv of tetrabutylammonium bromide (TBAB) provided product **3a** and **8** in 35% and 15% yields, respectively. These results suggest that cyanation is a cationic reaction.

A mechanism for cyanophosphinoylation of alkenes is proposed on the basis of the results obtained from the control reactions (Scheme 5). Phosphinoyl radical **A**, generated from the oxidation of $HPOPh_2$ with $Mn(OAc)_3$, reacts with an alkene to form radical **B**[14,15] followed by the reaction of radical **B** with Cu^{II} complex to form complex **D**.[16] The reaction of **D** with TMSCN affords cyanophosphinoylation product **3** or **5** (Scheme 5, path a). Alternatively, radical **B** (R = alkyl) might abstract a proton from $HPOPh_2$ to give hydrophosphinoylation product **5′** (Scheme 5, path b).[14a,b] Intermediate radical **B** could also be converted to cationic intermediate **E** via a single-electron oxidation process, which reacts with CN^- from TMSCN and TBACN, or Br^- from TBAB to give product **3**, **5** and **8**, respectively (Scheme 5, path c).[14a,b]

Scheme 5. Proposed Mechanism for Cyanophosphinoylation



In summary, a new reaction for vicinal bifunctionalization of alkenes is developed using $Mn(OAc)_3$ as an oxidation agent to generate phosphinoyl radical for addition followed by CuCN-catalyzed cyanation. This one-pot reaction of readily available reagents and starting materials, including aromatic and aliphatic alkenes, is performed under mild conditions to afford vicinal cyanophosphinoylation products regioselectively. The cyano group in the cyanophosphinoylation products could be a valuable synthon to access other functional groups with synthetic or biological interests.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02621.

Experimental details and spectral data for compounds **3** and **5**−**8** (PDF)

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Notes

The authors declare no competing financial interest.

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