

Phosphinoyl Radical-Initiated α,β -Aminophosphinoylation of Alkenes

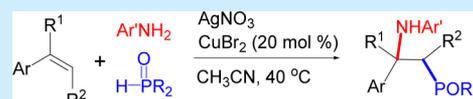
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S Supporting Information

ABSTRACT: A new double functionalization reaction of alkenes through AgNO₃-mediated phosphinoyl radical addition followed by Cu(II)-catalyzed amination is introduced. This one-pot, three-component reaction is performed under mild conditions to afford α,β -aminophosphinoylation products.



Unique chemical, biological, and physical properties associated with organophosphorus compounds have found broad applications as agricultural chemicals,¹ drug and drug candidates for HIV,² chronic inflammation,³ type 2 diabetes mellitus,⁴ glucocorticoid receptor antagonists,⁵ ligands and organocatalysts,⁶ essential synthetic building blocks,^{7,8} drug release nanomaterials,⁹ degradable polymers,¹⁰ and fire retardant materials.¹¹ Bifunctional α,β -aminophosphinoyl compounds also possess special biological activities.^{2–4} Synthetic methods for α,β -aminophosphinoylated compounds are limited to the reactions of cyanobenzene or β -carbonylphosphinoyl compounds which are not readily available, and the reaction processes could be tedious.^{4a,7a–c} Phosphorus radical-based reactions have been developed as a powerful method¹² for oxyphosphinoylation,¹³ hydroxyphosphinoylation, acetoxyphosphinoylation,¹⁴ halophosphinoylation,¹⁵ and other bifunctionalization reactions of alkenes (Scheme 1a–d).¹⁶ Our recent success in the development of oxyphosphinoylation reac-

tions^{13c,14c} encouraged us to explore aminophosphinoyl reactions. Introduced in this paper is a AgNO₃-mediated phosphinoyl radical addition followed by Cu(II)-catalyzed amination for bifunctionalization of alkenes (Scheme 1f). The intramolecular aminophosphinoylation reaction is reported (Scheme 1e).¹⁷ To the best of our knowledge, there is no intermolecular aminophosphinoylation reaction in the literature.

Substrates styrene **1a**, Ph₂P(O)H **2a**, and aniline **3a** were used for the development of reaction conditions. The phosphinoyl radical could be readily generated from the oxidation of HP(O)Ph₂ with AgNO₃,¹² but a catalyst for sequential amination is key for aminophosphinoylation. Reactions with CuBr as a catalyst in different solvents revealed that CH₃CN is a good choice which gave product **4a** in 51% yield (Table 1, entries 1–3). Screening of different copper salts

Scheme 1. Phosphorus Radical-Initiated Bifunctionalization

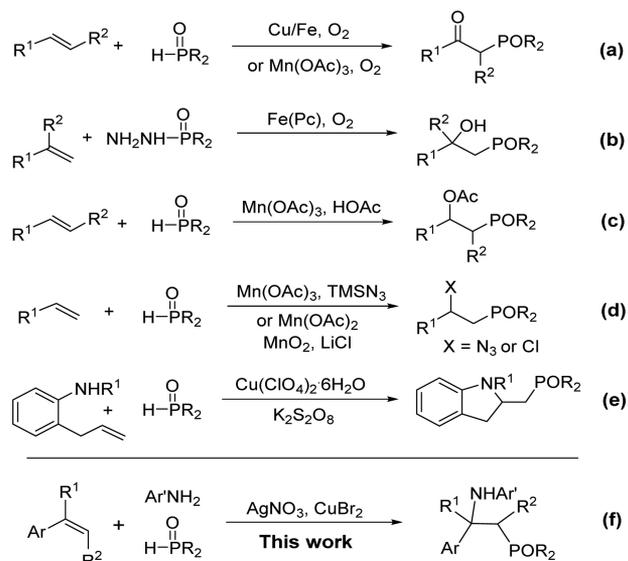


Table 1. Optimization of Reaction Conditions^a

entry	solvent	temp (°C)	Cu cat. (mol %)	yield ^b (%)
1	CH ₃ CN	40	CuBr (40)	51
2	DMF	40	CuBr (40)	37
3	DMSO	40	CuBr (40)	19
4	CH ₃ CN	40	CuI (40)	43
5	CH ₃ CN	40	CuCl (40)	37
6	CH ₃ CN	40	CuO (40)	36
7	CH ₃ CN	40	Cu(OAc) ₂ (40)	45
8	CH ₃ CN	40	CuBr ₂ (40)	68
9	CH ₃ CN	60	CuBr ₂ (20)	53
10	CH ₃ CN	40	–	ND ^c
11	CH ₃ CN	40	CuBr ₂ (20)	68
12 ^d	CH ₃ CN	40	CuBr ₂ (20)	47

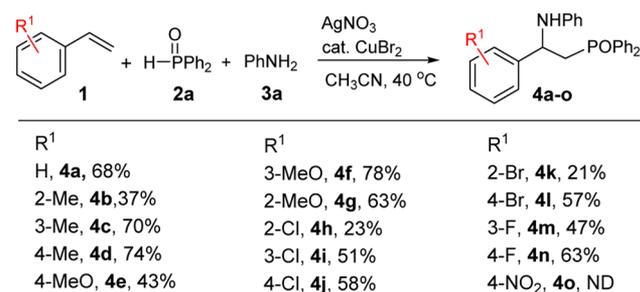
^aConditions: **1a** (1.0 mmol), **2a** (1.5 mmol), **3a** (3.0 mmol), AgNO₃ (2.0 mmol), CuBr₂ (20 mol %) in CH₃CN (5 mL) at 40 °C, 5 h under Ar. ^bIsolated yield. ^cND means none detected. ^dUnder air.

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indicated that CuBr₂ afforded an increased yield of 68% (Table 1, entries 4–8), whereas a control reaction without a Cu-catalyst gave no product (Table 1, entry 10). Further exploring the reaction conditions by changing the loading of CuBr₂ (10–40 mol %), the amount of aniline (2–4 equiv), and reaction temperature (25–60 °C) and time (3–8 h) gave the optimized conditions which include using 1:1.5:3 of 1a:2a:3a with 2.0 equiv of AgNO₃ and 20 mol % of CuBr₂ (see Supporting Information (SI)). The reaction in CH₃CN at 40 °C for 5 h under argon gave 4a in 68% yield (Table 1, entry 11). It was confirmed that AgNO₃ is a good oxidant (see SI) and the reaction has to be performed under air-free conditions (Table 1, entry 12).

Reactions with different styrenes 1 were conducted under the optimized conditions (Scheme 2). Small alkyl and alkoxy

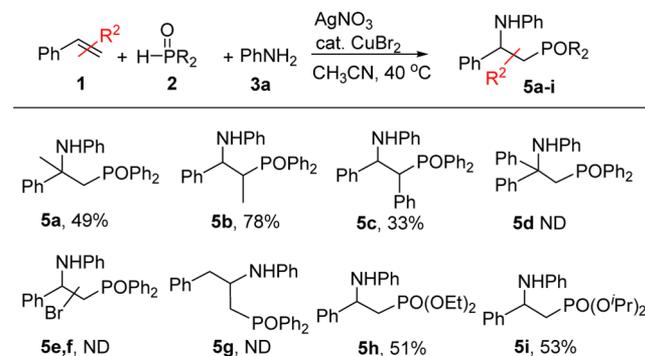
Scheme 2. Reactions of Different Styrenes 1 with 2a and 3a^{a,b}



^aReaction conditions: 1 (1.0 mmol), 2a (1.5 mmol), 3a (3.0 mmol), AgNO₃ (2.0 mmol), CuBr₂ (20 mol %) in CH₃CN (5 mL), 40 °C, Ar, 5 h. ^bIsolated yield.

groups as well and halogen groups on the benzene gave corresponding products 4 in satisfactory yields except for the groups at the *ortho*-position (**4b**, **4g**, **4h**, **4k**) due to steric effects. No product **4o** was detected from the reaction of 4-nitrostyrene. Reactions of α - or β -substituted styrenes could afford products 5a–c in 33–78% yields depending on the steric effect of the R² group (Scheme 3). However, no products were obtained for **5d–e** due to the presence of phenyl and bromo groups as the R² group at the 1- or 2-position of the styrenes. The reaction of nonconjugated allylbenzene failed to give product **5g** probably due to the intermediate carbon radical without phenyl group conjugation being too unstable to react

Scheme 3. Reactions of Alkenes 1 with 2 and 3a^{a,b}

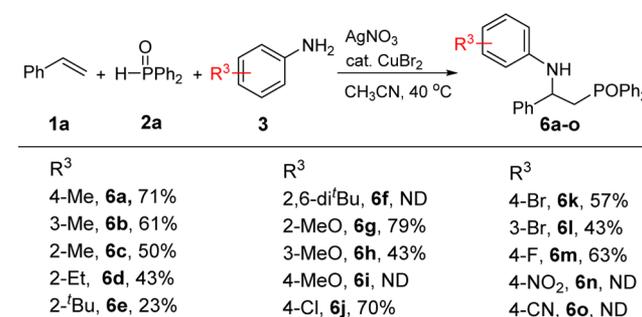


^aThe reaction conditions are similar to those shown in Scheme 2. ^bIsolated yield.

with aniline. It is worth noting that dialkylphosphites (R = OEt or OⁱPr) were amenable to this reaction to give α,β -aminophosphonated products **5h** and **5i** in synthetically useful yields.

Reactions of different anilines were also performed (Scheme 4). Products **6a–e** bearing Me, Et, and ^tBu as the R³ group

Scheme 4. Reactions of 1a, 2a with Different Anilines 3^{a,b}

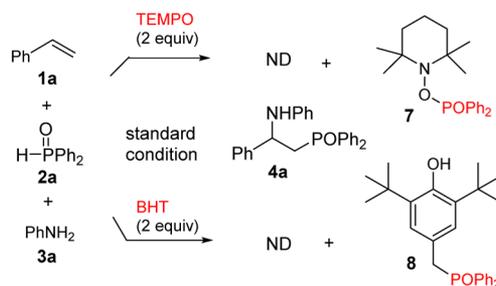


^aThe reaction condition is similar to that shown in Scheme 2. ^bIsolated yield.

were obtained in 23–71% yields. No product **6f** was obtained from the 2,6-di^tBu-substituted aniline. Reactions of 2- or 3-methoxyanilines afforded **6g** and **6h** in 79% and 43% yields, respectively. The reaction 4-methoxyaniline gave no product **6i**, but rather the oxidation product of 4-methoxyaniline. Halogen-substituted anilines at the 3- or 4-position gave corresponding products **6j–m** in 43–70% yields. Anilines with 4-nitro and 4-cyano groups failed to give products **6n** and **6o**.

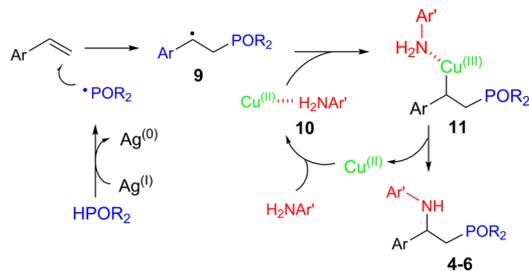
To understand if the α,β -aminophosphinoylation process involved radicals, two control reactions using TEMPO or BHT as the radical tracking agent were carried out under the standard conditions described in Scheme 5. In both cases, the

Scheme 5. Control Reactions with Radical Tracking Agents



formation of **4a** was completely suppressed, and only radical coupling products **7** and **8** were obtained. Based on these results, a mechanism was proposed for the α,β -aminophosphinoylation reaction (Scheme 6). The phosphinoyl radical generated from the oxidation of **2a** with AgNO₃ adds to styrene to form radical **9** which coordinates with Cu(II)-aniline complex **10** to form Cu(III) complex **11**.¹⁸ Reductive elimination of **11** affords α,β -aminophosphinoylation products **4–6**.

In summary, we have developed a new alkene bifunctionalization reaction using AgNO₃ to generate a phosphinoyl radical from diarylphosphine oxides followed by CuBr₂-catalyzed amination with anilines to afford α,β -aminophosphinoylation products. This three-component, one-pot reaction is performed under mild conditions. The reaction scope for different

Scheme 6. Mechanism for α,β -Aminophosphinoylation

substrates has been explored. In addition to diarylphosphine oxides, dialkylphosphites could also be used for the synthesis of α,β -aminophosphonated compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02183.

Experimental details and spectral data for compounds 4–8 (PDF)

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Notes

The authors declare no competing financial interest.

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