

Copper-Catalyzed Synthesis of 1,3-Butadienylphosphine Oxides and Chemoselective Phosphoryl Reduction to Stereodefined 1,3-Butadienylphosphines

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Abstract: Copper-catalyzed C–P cross-coupling reactions between diphenylphosphine oxide and various 1-bromo-1,3-butadienes readily provided a set of functionalized 1,3-butadienyldiphenylphosphine oxides. Application of the latter to the synthesis of stereodefined 1,3-butadienyldiphenylphosphines was successfully achieved *via* chemoselective reduction of their phosphoryl moiety.

Keywords: butadienylphosphine oxides; butadienylphosphines; copper catalysis; C–P coupling

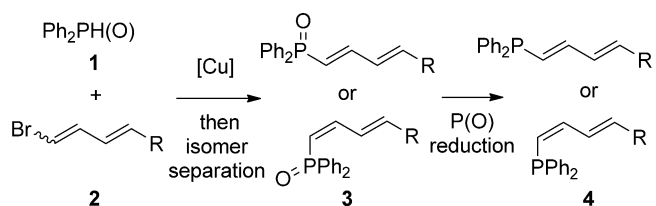
Copper-catalyzed *carbon-heteroatom* bond forming reactions have recently emerged as a useful and cheaper alternative to the analogous palladium-catalyzed transformations, but studies so far have mostly targeted the N, O, and S series.^[1] In comparison C–P bond forming reactions have received only little attention, and with a main focus on arylphosphorus compounds.^[2–5] Regarding the vinyl series, most described procedures involve H-phosphonates as coupling partners,^[3b,4a,6] while phosphines (2 reported examples of alkenylphosphines)^[4a,5] or phosphine oxides (1 reported procedure towards alkenylphosphine oxides),^[6a] are scarce and recent. No example with dieny derivatives was described in the literature.

As part of our research program related to the development of catalytic C–P bond forming reactions,^[7] we report here a new and straightforward entry to variously substituted 1,3-butadienyldiphenylphosphine oxides **3** (Scheme 1) *via* copper(I)-catalyzed cross-coupling reactions between 1-bromo-1,3-butadienes **2**

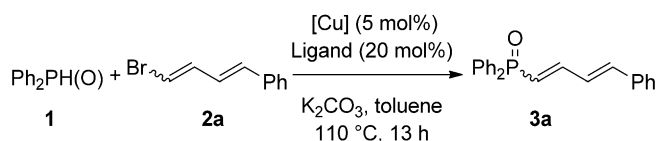
and diphenylphosphine oxide (**1**). The targeted products are relevant molecules for applications in organic synthesis,^[8] as well as homogeneous catalysis.^[9] They could also be seen as potential precursors of the challenging butadienylphosphines if the chemoselective reduction of the phosphoryl moiety was accessible. Worthy of note is that the few reported syntheses of 1,3-butadienyldiphenylphosphine oxides are limited in scope or poor-yielding.^[10]

Thus our goal was to develop a general and efficient catalytic access to these promising versatile molecules and to apply them to the preparation of 1,3-butadienyldiphenylphosphines **4** (Scheme 1), valuable new ligands in homogeneous catalysis,^[11] through developing a chemoselective reduction of the phosphoryl moiety.

In a preliminary set of experiments, we examined the cross-coupling reaction between the commercially available diphenylphosphine oxide (**1**) and readily available 1-bromo-4-phenyl-1,3-butadiene (**2a**) (*E,E*/*Z,E* = 66:34),^[12] under various catalytic conditions. The reactions were performed in toluene – a non-chelating solvent – at 110  C in the presence of K₂CO₃ (1.5 equiv.) as the base. A small excess (1.5 equiv.) of



Scheme 1. Proposed strategy towards stereodefined 1,3-butadienylphosphines and their oxides.

Table 1. Influence of the nature of the copper source and the structure of the ligand on the cross coupling reaction of **1** with bromodiene **2a**.^[a]

Entry	Cu Source	Ligand	Yield ^[b] [%]
1	CuI	DMEDA	88 (88)
2	CuI	proline	58
3	CuI	ethyl 2-cyclohexanone-carboxylate	36
4	CuI	–	46
5	–	DMEDA	0
6	CuTC ^[c]	DMEDA	86 (72)
7	CuBr	DMEDA	68
8	CuBr ₂	DMEDA	48

^[a] Reaction conditions: **1** (303 mg, 1.5 mmol, 1.5 equiv.), **2a** (1 mmol, 1 equiv., *E,E/Z,E* = 66:34), CuI (5 mol%), ligand (20 mol%), K₂CO₃ (1.5 equiv.), toluene (4 mL), 110°C, 13 h.

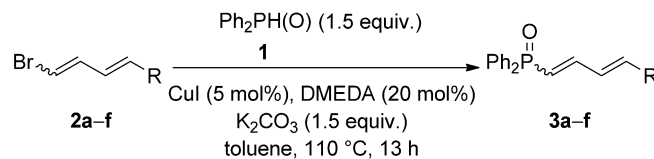
^[b] Calculated from the crude product ¹H NMR spectrum, value in parentheses is isolated yield.

^[c] CuTC = copper thiophenecarboxylate.

1 was used to ensure a full conversion of **2a**. Copper iodide (5 mol%) was first selected as the copper source and a set of well-established ligands in copper-catalyzed reactions was screened with a 1:4 metal/ligand ratio (Table 1).

A poor or modest reactivity of the catalytic systems involving proline, or ethyl 2-cyclohexanonecarboxylate was observed (Table 1, entries 2 and 3). By contrast DMEDA (*N,N'*-dimethylethylenediamine) proved to be a very efficient ligand for this transformation, and provided the targeted dienylphosphine oxide **3a**^[13] in 88% yield as a mixture of stereoisomers (Table 1, entry 1).

In the absence of ligand the yield was much lower (entry 4) and no reaction was observed if the copper catalyst was omitted (entry 5). Various combinations of the best ligand DMEDA with copper sources other than CuI were next evaluated but none of them was superior to the CuI/DMEDA catalytic system (Table 1, entry 1 versus entries 6–8). After screening various catalyst loadings and metal/ligand ratios, the catalytic conditions with CuI (5 mol%) and DMEDA (20 mol%) were found to be optimal for the formation of butadienylphosphine oxide **3a**. The reaction conditions being optimized, we evaluated the scope and limitations of this reaction. For this purpose variously substituted 1-bromo-1,3-butadienes **2b–f** were readily prepared,^[12] and tested as cross-coupling partners of diphenylphosphine oxide (**1**). The results are collected in Table 2.

Table 2. Scope of the copper-catalyzed cross coupling reaction of diphenylphosphine oxide (**1**) with 1-bromo-1,3-butadienes **2**.^[a]

Entry	2 ^[b] <i>EE/ZE</i>	DienylP(O)	3 ^[b] <i>EE/ZE</i>	Yield [%] ^[c]
1	2a 66:34		3a 75:25	88
2	2a 2:98		3a 10:90	85
3	2b 67:33		3b 70:30	73
4	2c 65:35		3c 75:25	87
5	2d 64:36		3d 75:25	75
6	2e 78:22		3e 85:15	66
7	2f 64:36		3f 79:21	78

^[a] Reaction conditions: **2a–f** (1 mmol, 1 equiv.), **1** (303 mg, 1.5 mmol, 1.5 equiv.), CuI (5 mol%), DMEDA (20 mol%), K₂CO₃ (1.5 equiv.), toluene (4 mL), 110°C, 13 h.

^[b] Isomer ratio determined by ¹H NMR.

^[c] Isolated yield.

Electron-rich aryl-substituted bromodienes **2b** and **2c** bearing an *ortho*- and *para*-anisyl group respectively, were readily coupled with **1** in good to high yields (73 to 87%) (Table 2, entries 3 and 4). Similarly electron-poor aryl-substituted bromodienes **2d** and **2e** bearing a *para*-chlorophenyl and an *ortho*-nitrophenyl group respectively underwent efficient C–P bond formation. The corresponding 1,3-butadienylphosphine oxides **3d** and **3e** were isolated in 75 and 66% yields, respectively (Table 2, entries 5 and 6). Not only aryl- but also an alkyl-substituted bromodiene proved to be a suitable coupling partner of **1** under the defined reaction conditions. Indeed bromodiene **2f** was readily converted into butadienylphosphine oxide **3f**, which was isolated in 78% yield (Table 2, entry 7).

Regarding the stereoselectivity of the reaction, only a slight isomerization of the double bond in favour of the *E*-isomer was observed during the coupling reaction (see Table 2). The use of stereochemically enriched (*Z,E*)-bromodiene **2a** (2:98 isomer ratio) as substrate,^[14] provided the corresponding butadienylphosphine oxide **3a** with a (*E,E*)/(*Z,E*) ratio of 10:90 (Table 2, entry 2).

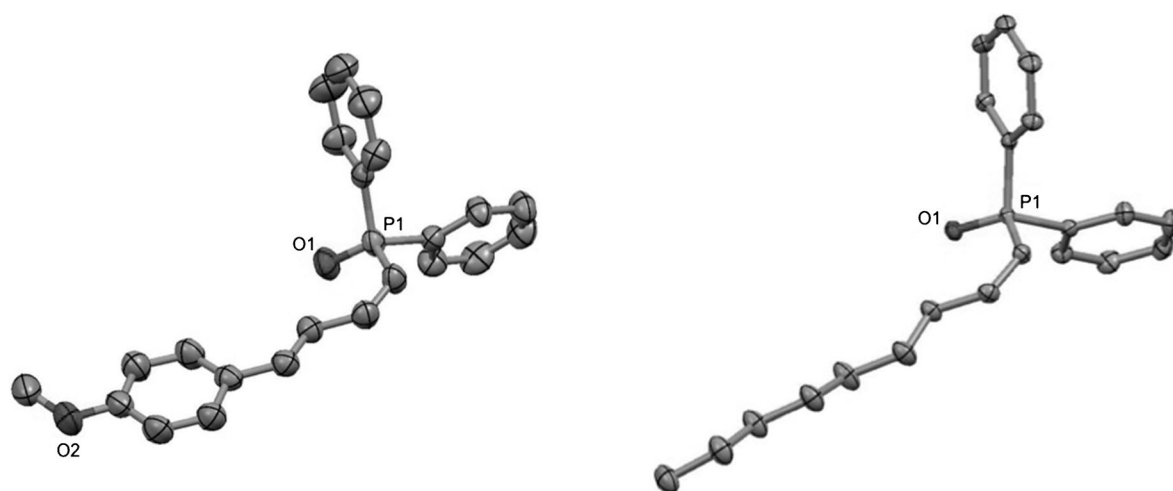


Figure 1. X-ray structures of (*Z,E*)-1,3-butadienylphosphine oxides **3c** (left) and **3f** (right).

Worthy of note is that the (*E,E*) and (*Z,E*) isomers of all butadienylphosphine oxides **3** could be separated by column chromatography on silica gel. Single crystals of the (*Z,E*) isomers of **3c** and **3f** were obtained by slow evaporation of solvent and their structures were unambiguously confirmed by X-ray diffraction analysis (Figure 1).

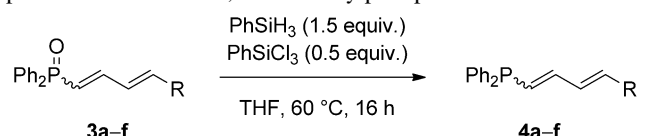
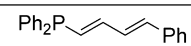
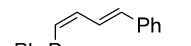
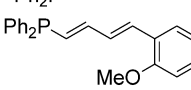
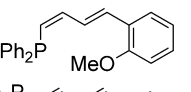
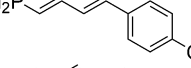
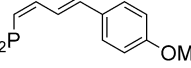
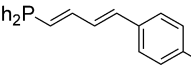
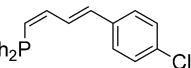
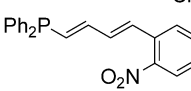
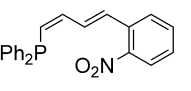
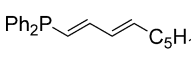
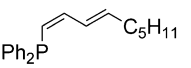
With a set of variously functionalized and isomerically pure 1,3-butadienyldiphenylphosphine oxides in hand, we next investigated the reduction of their phosphoryl moiety. This would give access to 1,3-butadienylphosphines, a relevant class of ligands for homogeneous catalysis.^[11,15,16] With the exception of the reduction product of **3a** (R = Ph),^[11,17] all other targeted dienylphosphines are unprecedented.

Phosphoryl reduction is usually achieved under rather harsh conditions involving hydride or silane reagents.^[18] Thus the chemoselective reduction of phosphine oxides into phosphines in the presence of other reducible functions is highly challenging.^[19] The difficulty is even greater when the phosphorus atom is directly linked to the unsaturation like in alkenyl derivatives because the presence of the P=O function will enhance the double bond reactivity towards reduction. No successful example of selective reduction of butadienylphosphine oxides into butadienylphosphines could be found in the literature. For example, it was reported that the reduction of 1,3-butadienyldiphenylphosphine oxide with phenylsilane led to double bond hydrogenation.^[10a] Other reducing agents (LiAlH₄, HSiCl₃, Si₂Cl₆) also proved to be unsuitable for the chemoselective conversion into butadienylphosphines.^[16] Previous work in our laboratories demonstrated that the use of a 3:1 mixture of phenylsilane and trichlorophenylsilane in THF at 30 °C was optimal for the phosphoryl reduction of alkynylphosphine oxides, another challenging substrate type.^[20] The *in situ* generated active reducing agent is believed to be PhSiHCl₂. The presence of chlorine atoms on silicon,

by increasing the oxophilic properties of the silane reagent, probably accounts for its higher reactivity. These mild reduction conditions were tested on (*E,E*)-dienylphosphine oxide **3a** using 1.5 equiv. of PhSiH₃ and 0.5 equiv. of PhSiCl₃. The reaction proved to be sluggish at 30 °C, but when the reaction temperature was raised to 60 °C, a conversion superior to 98% could be reached after 16 h, and no side-product was formed. The resulting (*E,E*)-dienylphosphine **4a** was isolated in 92% yield after filtration on alumina (Table 3, entry 1).^[21] The defined reaction conditions were applied to isomerically pure dienylphosphine oxides **3a–f** and proved to be general and chemoselective. Indeed whatever the substitution pattern of substrates **3**, the phosphoryl reduction was successfully achieved without affecting the conjugated diene moiety. The targeted stereopure aryl- or alkyl-dienyl-diphenylphosphines **4a–f** were delivered in high yields ranging from 67 to 93% yield (Table 3) whatever the substituents. This two-step procedure – copper(I)-catalyzed C–P cross-coupling followed by chemoselective reduction of the phosphoryl moiety – thus offers an efficient and general access to stereodefined 1,3-butadienylphosphines.

In conclusion, we have developed a new and straightforward catalytic synthesis of a variety of 1,3-butadienylphosphine oxides. It relies on the copper(I)-catalyzed cross-coupling reaction between diphenylphosphine oxide and readily available 1-bromo-1,3-butadienes. Separation of the (*E,E*) and (*Z,E*) stereoisomers was readily achieved through silica gel column chromatography. The reduction of the phosphoryl moiety could be chemoselectively accomplished for the first time and afforded a set of stereopure 1,3-butadienylphosphines. Further exploration of the potential of the 1,3-butadienylphosphine oxides as building blocks through chemical modification of the diene moiety *via* Michael addition or Diels–Alder reactions will be the next goal of this

Table 3. Chemoselective reduction of 1,3-butadienylphosphine oxides **3** into 1,3-butadienylphosphines **4**.^[a]

				
Entry	3 EE/ZE	DierylP	4 EE/ZE	Yield [%] ^[b]
1	3a 100:0		4a 100:0	92
2	3a 0:100		4a 0:100	92
3	3b 100:0		4b 100:0	93
4	3b 0:100		4b 0:100	83
5	3c 100:0		4c 100:0	88
6	3c 0:100		4c 0:100	75
7	3d 100:0		4d 100:0	68
8	3d 0:100		4d 0:100	72
9	3e 100:0		4e 100:0	81
10	3e 0:100		4e 0:100	67
11	3f 100:0		4f 100:0	85
12	3f 0:100		4f 0:100	73

^[a] Reaction conditions: **3a–f** (0.5 mmol, 1 equiv.), PhSiH₃ (92 μL, 0.75 mmol, 1.5 equiv.), PhSiCl₃ (40 μL, 0.25 mmol, 0.5 equiv.), THF (1 mL), 60 °C, 16 h.

^[b] Isolated yield.

work together with the use of the obtained new family of butadienylphosphine ligands in catalysis.

Experimental Section

Typical Procedure for the Cross-Coupling Reaction of Diphenylphosphine Oxide (**1**) with 1-Bromo-1,3-butadienes **2** (Synthesis of **3a** as an Example, Table 2, entry 1)

An oven-dried Schlenk tube was evacuated and refilled with nitrogen 3 times and then charged with CuI (9.5 mg, 5 mol%) and K₂CO₃ (207 mg, 1.5 equiv.) followed by anhy-

drous, degassed toluene (2 mL) and DMEDA (22 μL, 20 mol%). The solution was stirred for 5 min. Then 1-bromo-4-phenyl-1,3-butadiene (**2a**) (209 mg, 1 mmol, 1 equiv.) and diphenylphosphine oxide (303 mg, 1.5 equiv.) were added at once followed by anhydrous, degassed toluene (2 mL) to rinse the tube walls. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 110 °C for 13 h. After cooling the crude product was purified by filtration on silica gel with ethyl acetate as eluent to provide the desired product **3a**; yield: 291 mg (0.88 mmol, 88%); see the Supporting Information.

Typical Procedure for Phosphoryl Reduction of 1,3-Butadienylphosphine Oxides **3** into 1,3-Butadienylphosphines **4** (Synthesis of **4a** as an Example, Table 3, entry 1)

An oven-dried Schlenk tube was evacuated and refilled with nitrogen three times and then charged with 4-phenyl-1,3-butadienylphosphine oxide (**3a**) (165 mg, 0.5 mmol, 1 equiv.) followed by anhydrous, degassed THF (1 mL), phenylsilane (92 μL, 1.5 equiv.) and phenyltrichlorosilane (40 μL, 0.5 equiv.). The solution was stirred at 60 °C for 16 h. The reaction mixture was allowed to cool to room temperature then degassed H₂O was added. The organic layer was dried on MgSO₄ and after filtration and solvent evaporation, the crude product was purified by filtration on alumina with pentane as eluate to provide the desired product **4a**; yield: 145 mg (0.46 mmol, 92%); see the Supporting Information.

CCDC 924259 and CCDC 924258 contain the supplementary crystallographic data for the (*Z,E*)-isomers of **3c** and **3f** respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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