Synthetic Methods

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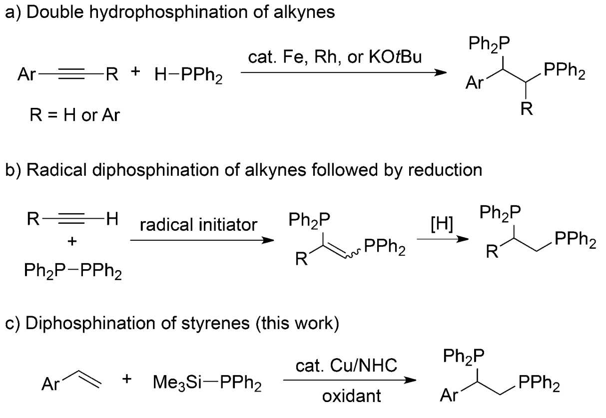
Copper-Catalyzed Vicinal Diphosphination of Styrenes: Access to 1,2-Bis(diphenylphosphino)ethane-Type Bidentate Ligands from Olefins

Yuto Okugawa, Koji Hirano, and Masahiro Miura**

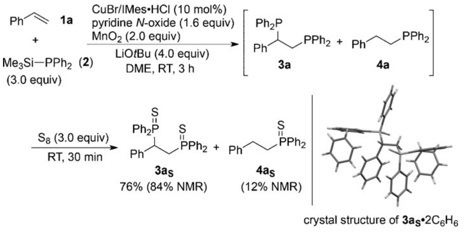
Abstract: *A copper/N-heterocyclic carbene (NHC) catalyzed oxidative vicinal diphosphination of styrenes with diphenyl(trimethylsilyl)phosphine proceeds in the presence of LiOtBu and a pyridine N-oxide/MnO_2 combined oxidant to deliver the corresponding 1,2-bis(diphenylphosphino)ethanes (DPPEs) in good yields. The present copper catalysis can provide access to the DPPE-type ligands directly from the relatively simple alkenes.*

Organophosphorus compounds are ubiquitous in modern organic chemistry because they are indispensable synthetic reagents,[1] key elements in material science,[2] and supported ligands for many transition-metal catalysts.[3] Particularly, the family of 1,2-bis(diphenylphosphino)ethanes (DPPEs) is now one of the representative bidentate ligands and frequently employed for various transition metal catalyzed reactions owing to their uniquely rigid chelating nature. Among numerous synthetic routes to the DPPE-type ligands, an addition reaction of phosphino groups to C–C multiple bonds has received significant attention since relatively simple starting materials can be used as a platform for the construction of the DPPE-type framework. Nakazawa reported an iron-catalyzed double hydrophosphination approach to the target structure from terminal arylacetylenes (Scheme 1 a).[4a] The diphosphination product is conceivably poisonous to the metal catalyst,[5] but good catalyst turnover was achieved. Very recently, Giuseppe, Castarlenas, Oro, and co-workers also developed a rhodium-based catalyst system for the same double hydrophosphination.[4b] While somewhat limited in scope, KO*t*Bu is also known to promote a similar transformation.[6] Additionally, a radical-mediated vicinal diphosphination (vic-diphosphination) of terminal alkynes with the diphosphane compounds $R_2P{-}PR_2$ and subsequent reduction of the double bond can be a good alternative (Scheme 1 b).[7,8] However, the direct preparation of the DPPE-type ligands from alkenes of ready availability still remains largely elusive. Given the relatively robust nature and ready accessibility of the alkenes, as well as versatile and important roles of DPPE-type ligands in synthetic organic chemistry, development of new catalysis which enables the direct vic-diphosphination of alkenes is appealing. Herein, we report a copper/N-heterocyclic carbene (NHC) catalyzed oxidative vic-diphosphination of styrenes: diphenyl(trimethylsilyl)phosphine works as an efficient phosphorous source, and the corresponding doubly phosphinated products, namely DPPEs, are formed in synthetically useful yields (Scheme 1 c). The copper catalysis is the first successful example of the catalytic synthesis of DPPE-type ligands directly from relatively simple alkenes, to the best of our knowledge.[9] We note that during the preparation of this manuscript, Ogawa and co-workers reported a relevant radical phosphinylphosphination of aliphatic alkenes with $Ph_2(O)P{-}PPh_2$.[10]



Scheme 1. Phosphine addition approaches to DPPE-type ligands.

We selected styrene (**1a**) and diphenyl(trimethylsilyl)phosphine ($Me_3Si{-}PPh_2$; **2**) as model substrates and started optimization studies (Scheme 2). The expected phosphination products **3a** and/or **4a** could be air-sensitive and easily oxidized to the phosphine oxides. Thus, for the ease of the handling, we added elemental sulfur (S_8) as a quencher upon workup and analyzed the corresponding more-stable phosphine sulfides **3a**$_S$ and **4a**$_S$ by ^1H and ^{31}P NMR spectroscopy. After the extensive screening of various reaction parameters, we were pleased to find that a CuBr/IMes·HCl [IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene] catalyst, in conjunction with a pyridine *N*-oxide/MnO_2combined oxidant



Scheme 2. Copper-catalyzed vic-diphosphination of styrene (**1a**) with diphenyl(trimethylsilyl)phosphine (**2**): Optimal reaction conditions. DME = dimethoxyethane.

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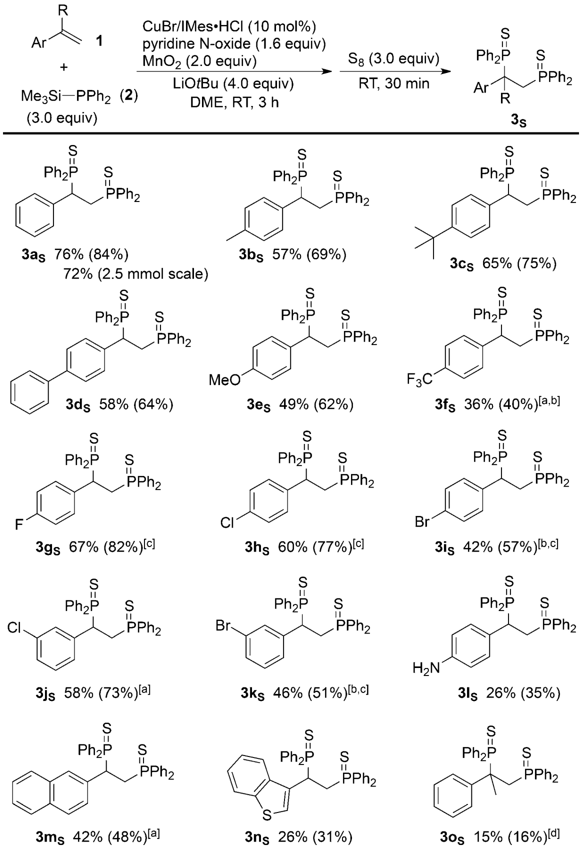
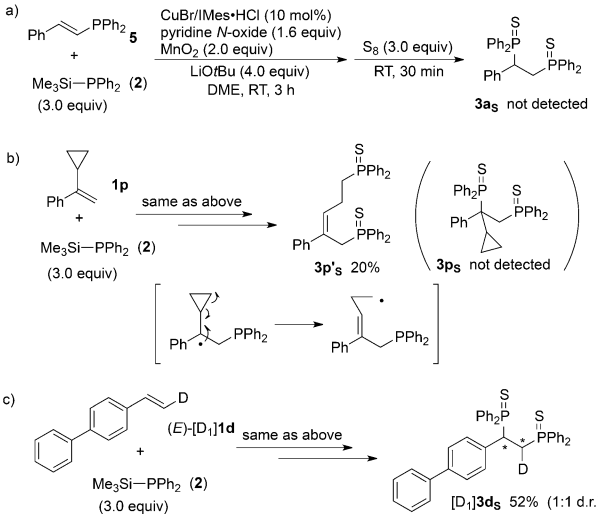
and a LiO*t*Bu base, promoted the desired vic-diphosphination of **1a** in DME at room temperature to form **3a**$_\mathrm{S}$ in 84 % yield as determined by NMR spectroscopy (76 % yield upon isolation). The structure of **3a**$_\mathrm{S}$ was unambiguously confirmed by NMR, HRMS, and X-ray analysis.[11] The simple hydrophosphination byproduct **4a**$_\mathrm{S}$ was also detected (12 % ^{1}H NMR yield), but it could be readily separated by column chromatography. Several observations during the optimization studies are to be noted: the use of the corresponding diphenylphosphine (H−PPh$_2$) gave a larger amount of the undesired **4a**$_\mathrm{S}$; the choice of the oxidant was critical, and other common oxidants, as well as either pyridine *N*-oxide or MnO$_2$ alone dramatically decreased the reaction efficiency. Among the NHCs examined, only IMes and SIMes [SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene] showed catalytic activity. Nitrogen- and phosphine-based ancillary ligands were ineffective, probably because the competitive coordination of the initially formed diphosphination products **3a** and/or **4a** to the copper center inhibited the catalyst turnover, as proposed in the literature.[5] Other transition-metal catalysts such as iron, cobalt, and manganese did not produce **3a**$_\mathrm{S}$ at all. And even in the absence of CuBr, MnO$_2$ somewhat promoted the reaction, and a small amount of **3a**$_\mathrm{S}$ (9–15 % by NMR) was detected.[12]

Under the reaction conditions shown in Scheme 2, we implemented the catalytic diphosphination reaction of an array of styrene derivatives (**1**; Scheme 3). In some cases, the SIMes ligand was used to simplify the purification step.[13] The substrates bearing electron-neutral (**3b**$_\mathrm{S}$–**d**$_\mathrm{S}$) and electron-donating (**3e**$_\mathrm{S}$) substituents at the *para* position underwent the reaction smoothly to furnish the corresponding DPPE derivatives in synthetically acceptable yields. An electron-withdrawing trifluoromethyl group (**3f**$_\mathrm{S}$) gave somewhat lower yield because of the competitive simple hydrophosphination. The copper catalysis was also compatible with *para*-halogenated styrenes, and the desired **3g**$_\mathrm{S}$–**i**$_\mathrm{S}$ were formed in good yields. Notably, the resultant chloro and bromo moieties should be useful synthetic handles for further manipulations. The introduction of Cl and Br at the *meta* position was also tolerated (**3j**$_\mathrm{S}$ and **3k**$_\mathrm{S}$). The free amino group interfered with the reaction, but the corresponding **3l**$_\mathrm{S}$ could be isolated in pure form. The condensed 2-vinylnaphthalene (**3m**$_\mathrm{S}$) and 3-vinylbenzothiophene (**3n**$_\mathrm{S}$) could also be employed for this transformation. However, the reaction with α-substituted styrenes was sluggish, and **3o**$_\mathrm{S}$ was obtained in only 15 % yield, even with a 20 mol % catalyst loading. Additionally notable is that the diphosphination could be easily carried out at a tenfold scale, thus indicating the good reproducibility and scalability of this process (**3a**$_\mathrm{S}$).

To gain some mechanistic insight, the following experiments were conducted (Scheme 4). When the independently prepared styrylphosphine **5** was subjected to the standard reaction conditions, **3a**$_\mathrm{S}$ was not detected at all (Scheme 4 a). The result suggests that **5** is not an intermediate in the catalytic diphosphination reaction and that an oxidative phosphination/hydrophosphination sequence is not operative. In contrast, a well-known radical clock, α-cyclopropylstyrene (**1p**),[14] afforded the corresponding ring-opening diphosphinated product **3p′**$_\mathrm{S}$ without any contamination of the usual **3p**$_\mathrm{S}$, although the conversion was not so high (Scheme 4 b). Thus, a benzylic radical species is involved in the catalytic cycle. Additionally, even with the stereodefined (*E*)-[D$_1$]**1d**, no stereospecific reaction occurred, and the corresponding



Scheme 3. Copper-catalyzed vic-diphosphination of various styrenes (**1**) with **2**. Reaction conditions: see Scheme 2. Yields of isolated products are given. Yields determined by ^{1}H NMR spectroscopy are given within parentheses. [a] With SIMes·HCl instead of IMes·HCl. [b] At 0 °C for 12 h. [c] Contaminated with 3–4 % of protodebrominated product **3a**$_\mathrm{S}$. [d] With 20 mol % of CuBr/IMes·HCl.



Scheme 4. Experiments for mechanistic insight.

diphosphinated product [D$_1$]**3d$_S$** was obtained as a 1:1 diastereomeric mixture (Scheme 4c). The outcome also supports the intermediacy of a benzylic radical.

Additional studies were performed by ^{31}P NMR spectroscopic analysis in [D$_8$]THF (Figure 1). We initially checked the stability of $Me_3Si{-}PPh_2$ (**2**)[15] toward the oxidants, namely pyridine *N*-oxide and MnO_2. While no major change was observed by the addition of pyridine *N*-oxide, MnO_2 not only

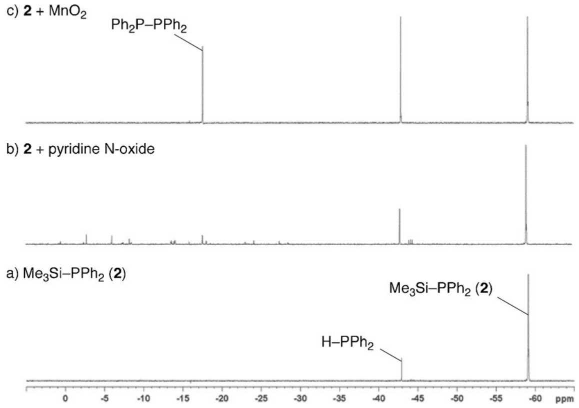
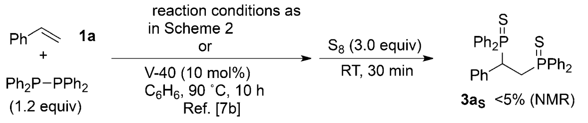


Figure 1. ^{31}P NMR spectra (162 MHz) of a) $Me_3Si{-}PPh_2$ (**2**), b) **2**/pyridine *N*-oxide, and c) **2**/MnO_2 (filtration was performed to remove insoluble MnO_2 before NMR analysis) in [D$_8$]THF at room temperature.

increased the amount of $H{-}PPh_2$ but also formed the corresponding diphosphane $Ph_2P{-}PPh_2$.[7d,16] However, control experiments of **1a** with the isolated diphosphane under otherwise identical copper-catalyzed conditions, as well as, the reported radical conditions (Scheme 1b)[7b] furnished **3a$_S$** in only less than 5% yield (Scheme 5), and thus $Ph_2P{-}PPh_2$ can be just a dead end species. In contrast, upon treatment of $Me_3Si{-}PPh_2$ (**2**) with stoichiometric IMesCuBr and LiO*t*Bu, a new signal at $\delta = -17$ ppm appeared, and was assigned to $IMesCuPPh_2$ (Figure 2).[17] At the same time, a small amount of $Ph_2P{-}PPh_2$ and a broad signal around $\delta = -33$ ppm were also detected. The latter could correspond to $Li{-}PPh_2$.[18] Although subsequent addition of **1a** resulted in no change in either the ^{31}P or ^{1}H NMR spectra, additional **2** and 1.0 equivalent of pyridine *N*-oxide generated two signals, $\delta = -23.7$ and 0.6 ppm, which are assigned to the diphosphinated product **3a**.[4]

On the basis of the above findings, we propose the reaction mechanism of **1a** with **2** as follows (Scheme 6). A CuBr salt is initially converted into IMesCuO*t*Bu (**6**) by salt metathesis of LiO*t*Bu and coordination of the IMes generated in situ. Subsequent ligand exchange between **6** and **2**, driven by formation of an O–Si bond forms $IMesCuPPh_2$ (**7**). While the direct insertion of **1a** into the Cu–P bond of **7** does not occur, pyridine *N*-oxide and additional **2** promotes the reaction, probably through a copper phosphide species of higher oxidation states, for example **8**, to form the desired **3a** along with the copper(I) species **9**. The catalytic cycle is closed by the final metathesis of **9** with LiO*t*Bu. Although the details of the **7**→**3a** transformation remains to be elucidated, a homolysis of the Cu–P in copper phosphides of higher oxidation state might be involved as a key step, and the benzyl radical **10** is a plausible intermediate.[19] Further studies, including the role of MnO_2, are essential for clarification of the detailed mechanism.[20]



Scheme 5. Control experiments with diphosphane $Ph_2P{-}PPh_2$.

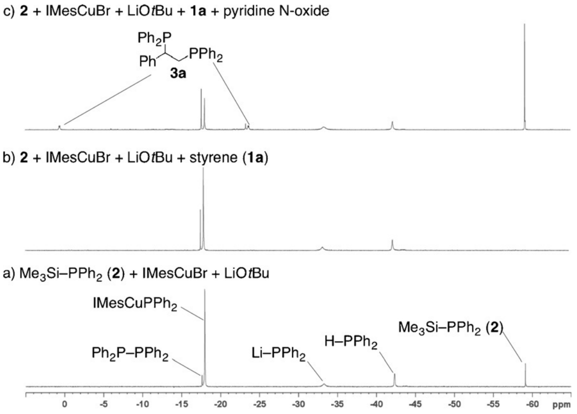
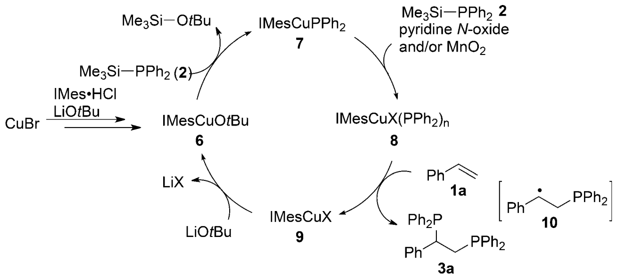


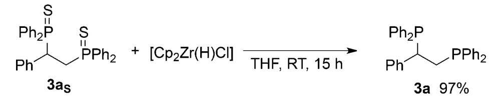
Figure 2. ^{31}P NMR spectra (162 MHz) measured during the stoichiometric reaction in [D$_8$]THF at room temperature. a) $Me_3Si{-}PPh_2$ (**2**)/IMesCuBr/LiO*t*Bu (1:1:1). b) **2**/IMesCuBr/LiO*t*Bu/styrene (**1a**) (1:1:1:1). c) **2**/IMesCuBr/LiO*t*Bu/**1a**/pyridine *N*-oxide (2:1:1:1:1).



Scheme 6. Plausible mechanism. X = Br, Cl, or $OSiMe_3$.

Finally, we attempted the desulfidation of **3a$_S$** to the free P^{III} form **3a**. After a survey of several representative reported conditions, a simple mixing with the Schwartz reagent [$Cp_2Zr(H)Cl$][8,21] was found to be optimal, and **3a** was isolated in 97% yield (Scheme 7).

In conclusion, we have developed a copper/NHC-catalyzed oxidative vic-diphosphination of styrenes with $Me_3Si{-}PPh_2$ in the presence of a pyridine *N*-oxide/MnO_2 combined oxidant and a LiO*t*Bu base. The reaction proceeds smoothly at room temperature, and the corresponding disphosphinated products are formed directly from the alkene. The copper catalysis can provide a unique and potentially more effective approach to DPPE-type bidentate ligands, which are of high



Scheme 7. Desulfidation of **3a$_S$** into **3a**. Cp = cyclopentadiene.

value in the research field of transition metal catalysis. Ongoing efforts to uncover a detailed mechanism, expand the substrate scope,[22] and develop asymmetric catalysis are in progress.

Acknowledgements

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Angew. Chem. **2016**, *128*, 13756–13759

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[2] For Selected examples, see: a) T. Baumgartner, R. Réau, *Chem. Rev.* **2006**, *106*, 4681; b) T. Baumgartner, *Acc. Chem. Res.* **2014**, *47*, 1613.

[3] a) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; b) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998; *Angew. Chem.* **2002**, *114*, 2096; c) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008; *Angew. Chem.* **2002**, *114*, 2108.

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[5] Actually, in the palladium-catalyzed phosphination of terminal alkynes with diphosphanes, the initially formed (*Z*)-1,2-diphosphinoethenes works as a catalyst poison to inhibit the catalytic cycle: S.-i Kawaguchi, A. Ogawa, *Synlett* **2013**, 2199.

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[8] Yorimitsu and Oshima also reported a copper-catalyzed *anti*-hydrophosphination of 1-alkynylphosphines, leading to (*Z*)-1,2-diphosphinoethenes. Subsequent reduction of the double bond formed the corresponding DPPE-type ligands: A. Kondoh, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2007**, *129*, 4099.

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[10] Y. Sato, S.-i. Kawaguchi, A. Nomoto, A. Ogawa, *Angew. Chem. Int. Ed.* **2016**, *55*, 9700–9703; *Angew. Chem.* **2016**, *128*, 9852–9855.

[11] CCDC 1483892 ($\mathbf{3a_S}\cdot 2\,C_6H_6$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[12] MnO_2 can mainly work as an oxidant to the copper but concurrently promote a minor radical diphosphination reaction. See Figure 1 and the Supporting Information for more detailed optimization studies. Although MnO_2 is reported to oxidize PPh_3 into $O{=}PPh_3$ in a benzene or acetonitrile, the corresponding oxides of the hydrophosphinated and diphosphinated products were not detected in our system. See: A. Alberti, P. Astolfi, P. Carloni, L. Greci, C. Rizzoli, P. Stipa, *New J. Chem.* **2015**, *39*, 8964.

[13] Some diphosphination products $\mathbf{3_S}$ and 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazole-2-thione (IMes=S) were difficult to separate from each other by column chromatography.

[14] a) V. W. Bowry, J. Lusztyk, K. U. Ingold, *J. Am. Chem. Soc.* **1991**, *113*, 5687; b) V. W. Bowry, K. U. Ingold, *J. Am. Chem. Soc.* **1991**, *113*, 5699; c) A. Ogawa, I. Ogawa, N. Sonoda, *J. Org. Chem.* **2000**, *65*, 7682; d) E. Shirakawa, X. Zhang, T. Hayashi, *Angew. Chem. Int. Ed.* **2011**, *50*, 4671; *Angew. Chem.* **2011**, *123*, 4767.

[15] As shown in Figure 1 a, $Me_3Si{-}PPh_2$ (**2**) was sensitive to adventitious water and readily hydrolyzed into $H{-}PPh_2$. However, the addition of hydrating reagents such as 4 Å M.S., Na_2SO_4, and $MgSO_4$ did not improve the yield of the diphosphination product (see the Supporting Information).

[16] MnO_2 probably provided $Ph_2P{-}PPh_2$ by a Ph_2P radical species. Indeed, the reaction of $Me_3Si{-}PPh_2$ (**2**) with MnO_2 in the presence of a radical inhibitor, TEMPO, decreased the amount of $Ph_2P{-}PPh_2$ formed, although the trapped product, TEMPO$-$$PPh_2$, was not clearly detected.

[17] The ^{31}P NMR chemical shift of the related $IPrCuPPh_2$ in C_6D_6 was reported to be $\delta = -27.8$ ppm: G. C. Fortman, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2010**, *29*, 3966. Additionally, when IPrCuBr was subjected to our reaction conditions (**2** and LiO*t*Bu in [D$_8$]THF), a similar signal at $\delta = -25.7$ ppm was observed (see the Supporting Information).

[18] V. A. Stepanova, V. V. Dunina, I. P. Smoliakova, *Organometallics* **2009**, *28*, 6546.

[19] For a related copper-catalyzed oxyboration of alkenes involving radical intermediates, see: T. Itoh, T. Matsueda, Y. Shimizu, M. Kanai, *Chem. Eur. J.* **2015**, *21*, 15955.

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[21] a) M. Zablocka, B. Delest, A. Igau, A. Skowronska, J.-P. Majoral, *Tetrahedron Lett.* **1997**, *38*, 5997; b) M. Saito, Y. Nishibayashi, S. Uemura, *Organometallics* **2004**, *23*, 4012.

[22] At present, attempts to apply other alkenes including 1,3-dienes, allenes, and aliphatic alkenes remain unsuccessful. The use of $Me_3Si{-}PCy_2$ also formed a trace amount of the corresponding diphosphinated product.

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