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COMMUNICATION

# A Bench-Stable Copper Photocatalyst for the Rapid Hydrophosphination of Activated and Unactivated Alkenes

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**Cu(acac)$_2$ (1) is a highly active catalyst for the hydrophosphination of alkenes. Photocatalytic conditions are critical, which provide high conversions with unactivated substrates that have never before been reported with an air-stable catalyst or at ambient temperature. The commercial availability, ease of use, and broad substrate scope of compound 1 makes hydrophosphination more availalble to synthetic chemists.**

Metal-catalyzed hydrophosphination is a powerful tool in still-challenging P–C bond formation because of the ubiquity of alkene substrates[1] and potential for perfect atom economy of the transformation.[2] Indeed, phosphines are integral molecules in organic synthesis, catalysis and are of importance in materials science and biologically active molecules.[3] However, one of the limitations to more widespread use of hydrophosphination is that many catalysts are air- and/or water-sensitive, complicated to prepare, or suffer from limited substrate scope or modest activity.[4-7] Catalysts that are not readily available and easy to use do not augment the synthetic chemist's toolbox.[8]

A broadly applicable catalyst is one that also addresses some of the outstanding challenges of hydrophosphination.[4] For example, unactivated alkene substrates remain underutilized in hydrophosphination. Attempts to use these substrates have shown limited success,[9-10, 11] with few previous reports of greater than 50% conversion. These have required air-sensitive catalysts, and elevated temperatures[9, 11] or high intensity irradiation (Chart 1).[10]

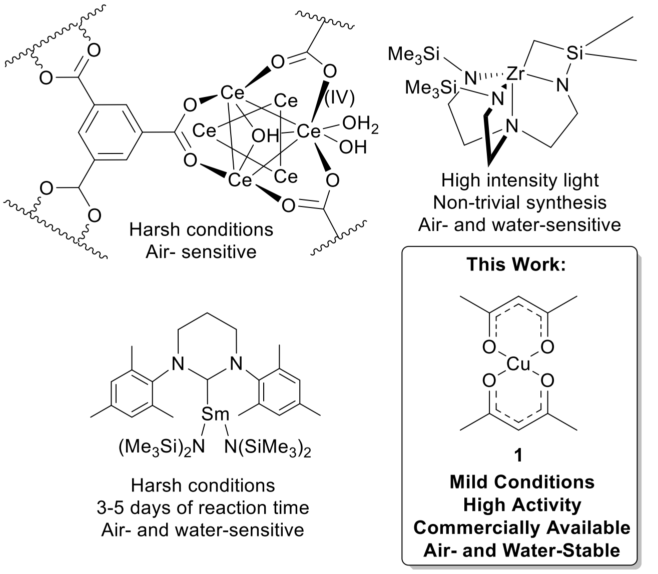
Despite advances in activity,[12] catalysts for hydrophosphination in routine synthesis require readily available, inexpensive catalysts that have established reactivity with a wide range of substrates. Therefore, we set out to search for a highly active, commercially available, air-stable, and base metal hydrophosphination catalyst.

Copper is a desirable metal due to its recyclability, relative abundance, low toxicity, and the air- and water-stability of many precursors.[13] Additionally, copper has a rich photochemistry.[14, 15] Our group has observed improved hydrophosphination reactivity upon irradiation with Zr,[10, 16, 17] Fe,[18, 19] and Ru[20] catalysts.

Based on the literature, we identified Cu(acac)$_2$ (**1**) as an ideal candidate for study. Hydrophosphination with copper has been performed with a range of copper salts[21, 22, 23] and by copper coordinated by N-heterocyclic carbene (NHC)[24, 25] and phosphine[26] ligands. Additionally, Beletskaya demonstrated compound **1** to be effective for the addition of phosphorus(V) substrates to alkynes.[27] Indeed, several groups have found **1** to be more effective at C–H amination reactions than other copper salts.[28, 29]

This analysis led to the general hypothesis that highly successful hydrophosphination reactivity can be achieved by employing **1** as a pre-catalyst. This hypothesis has borne out, and herein is reported the substantial activity of **1** under low

**Chart 1**: Examples of intermolecular hydrophosphination catalysts that are reported to have greater than 50% conversion with unactivated alkenes



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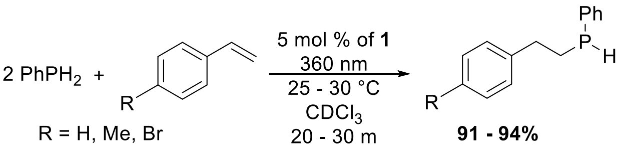
Electronic Supplementary Information (ESI) available: [Experimental procedures, compound characterization data, Supplementary figures and tables, and photographs and description of the photocatalysis reactor]. See DOI: 10.1039/x0xx00000x intensity 360 nm irradiation at ambient temperature. This overall high activity is accompanied by a significant substrate scope of alkenes and alkynes. The hydrophosphination activity of **1** rivals or surpasses the activity of reports with *any* catalyst, under any reaction conditions. In this regard, **1** achieves the aim of an easy-to-use, highly active, and readily available hydrophosphination catalyst.

Hydrophosphination of styrene was examined first due to its common use in recent studies.[23, 30, 31, 32, 33] A chloroform-$d_1$ solution of styrene was treated with 2 equiv. of phenylphosphine in the presence of 5 mol % of **1** (Eqn (1), see SI for optimization).† The mixture was irradiated with a broad wavelength 9-W UV/A lamp (commercial germicidal lamp: see SI for details) at ambient temperature for 20 min, resulting in complete conversion of styrene as measured by $^1$H NMR spectroscopy and 91% selectivity for the anti-Markovnikov, single activation product $PhPHCH_2CH_2Ph$ as determined by $^{31}P\{^1H\}$ NMR spectroscopy. Reactions with primary phosphines are often run with excess phosphine to minimize the double activation product, and indeed, small amounts of the tertiary phosphine with similarly limited amounts of 1,2-diphenyldiphosphine were observed. These byproducts and catalyst were readily separated by chromatography, in a glovebox, to afford isolated product in 66% yield. Isolation of pure phosphine products from these reactions is well established[23, 34, 35] and not the subject of this investigation. The use of a glovebox for the handling of primary phosphine starting materials and isolation of P(III) products remains a limitation to still more general use of hydrophosphination.

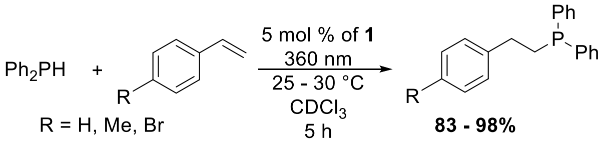


(1)

Continuous irradiation throughout the reaction is necessary for accelerated catalysis (see SI for details). However, the reaction does proceed under ambient light. Reactions with 2 equiv. of phenylphosphine and styrene and 5 mol % of **1** under ambient light and temperature proceeded to completion over the course of 7 h and to 90% conversion over 75 min at 60 °C.

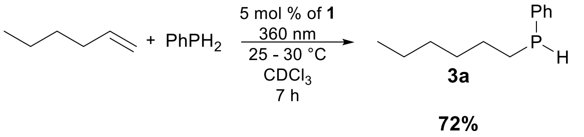
*Para*-substituted styrenes bearing electron withdrawing groups or donating substituents were also amenable to these conditions and converted to the respective secondary phosphine product in >90% in 25 min when treated with 2 equiv. of phenylphosphine under 360 nm (Eqn (1)).

Initial screening also demonstrated that secondary phosphines are also viable substrates. Treatment of styrene and 1 equiv. of diphenylphosphine with 5 mol % of **1** resulted in 85% conversion to $Ph_2PCH_2CH_2Ph$ (**2**) after 5 h of 360 nm irradiation and 95% conversion was observed after 24 h of irradiation (Eqn (2)). When para-substituted styrene substrates were treated with 1 equiv. of diphenylphosphine, the tertiary phosphine products were formed in good to excellent yields in under 5 h. Under these conditions, it was not empirically obvious that either electron donating or withdrawing substituents promote the reaction for either phenyl- or diphenylphosphine.



(2)

Unactivated alkenes, a significant challenge,[4] were screened next and found to be good substrates for this system. Treatment of 1-hexene with 2 equiv. of phenylphosphine and 5 mol % of **1** gave greater than 70% conversion to the single activation, secondary phosphine product when monitored by $^{31}P\{^1H\}$ and $^1$H NMR over 7 h (Eqn (3)) and 80% after 20 h (Table 1, **3a**). A control reaction under identical photocatalytic conditions but in the absence of **1** exhibited less than 3% conversion over 24 h and demonstrates the importance of **1**.



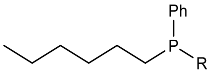
(3)

To date, this is the fastest report of hydrophosphination of an unactivated alkene substrate with a primary phosphine.[10, 36] The only other report with a comparable activity is with zirconium under photolysis from a higher intensity 253.7 nm Hg arc lamp for 24 h operating at 400 W (vs. 9 W for this reaction).[10]

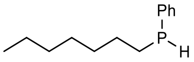
Treatment of 1-hexene with diphenylphosphine and 5 mol % of **1** under irradiation at 360 nm in chloroform-$d_1$ gave 25% conversion of phosphine to a mixture of products after 24 h. However, irradiation of a neat mixture of 1-hexene, and increasing to 3 equiv. of diphenylphosphine, and 5 mol % of **1** for 24 h resulted in 64% conversion to product **3b** as determined by $^1$H and $^{31}P\{^1H\}$ NMR spectroscopy. Improved hydrophosphination under neat conditions has also been observed in other studies.[18, 36, 37] Yet more optimization is possible.

Despite the more modest reactivity of 1-hexene with $Ph_2PH$, there remains only one catalyst that can rival its speed.[9] However, **1** is desirable because it is air stable, commercially available, and is active at ambient temperatures. Additionally, **1** is the only catalyst able to demonstrate greater than 50% conversion with both $PhPH_2$ and $Ph_2PH$.

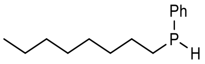
**TABLE 1.** Hydrophosphination of unactivated alkenes with **1**



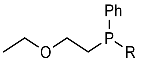
**3a**, R = H, 80%[a], 20 h
**3b**, R = Ph, 64%[b], 24 h



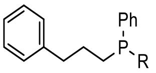
**3c**, 73%[a],16 h



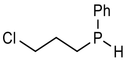
**3d**, 88%[a], 16 h



**3e**, R = H, 82%[a], 6 h
**3f**, R = Ph, 55%[c], 24 h



**3g**, R = H, 74%[a], 16 h
**3h**, R = Ph, 70%[c], 24 h



**3i**, 63%[a], 18 h

Conversions determined by integration of $^1$H and $^{31}P\{^1H\}$ NMR spectra. All runs with 5 mol % of **1.** [a] 0.38 mmol unsaturated substrate and 0.76 mmol $PhPH_2$ in 0.6 ml $CDCl_3$ [b] neat; 0.114 mmol 1-hexene and 3 equiv. of $Ph_2PH$ [c] neat; 0.38 mmol unsaturated substrate and 3 equiv. of $Ph_2PH$.

Additional aliphatic alkenes were then explored. Treatment of terminal alkenes such as 1–heptene, and 1–octene with 2 equiv. of phenylphosphine and 5 mol % of **1** both gave greater than 70% conversion to the single activation, secondary phosphine product when monitored by $^{31}$P{$^{1}$H} and $^{1}$H NMR over 16 h at 360 nm (products **3c-d**). Reaction of ethoxy ethene with phenylphosphine gave 82% conversion to product **3e** in 6 h, the fastest and highest conversion observed to date.[10] When 1 equiv. of diphenylphosphine was used with ethoxy ethane under the same conditions, 32% conversion to product **3f** was achieved after 24 h. This could be improved under neat conditions with 3 equivalents of diphenylphosphine, in which in 70% conversion to product **3f** occurred after 24 h of irradiation**.** Similarly, allyl benzene was converted in 74% to product **3g** after 16 h with 2 equiv. of phenylphosphine and 55% with diphenylphosphine to product **3h** under the neat conditions described above. Allyl chloride is an uncommon hydrophosphination substrate, and this reaction proceeds to 63% conversion to **3i**, which illustrates the functional group tolerance of this catalyst.

More sterically encumbered substrates are accessible in this system as well (Table 2). A cis/trans mixture of β-methylstyrene treated with phenylphosphine and **1** under irradiation resulted in 99% conversion and 82% isolated yield in 20 h to previously unreported **4a**. Treatment of α-methyl styrene and phenylphosphine with **1** under irradiation resulted in 92% conversion to **4b** in just over 2 h. When α-methyl styrene was treated with 1.5 eq. of diphenylphosphine the result was 83% conversion after 20 h of irradiation (**4c**)**.**

Several other unsaturated substrates were also tested. Reaction of 2,3-dimethyl,1-3-butadiene afforded the 1,4-addition product within 80 min with phenylphosphine (**4d**) and 8 h with 1 equiv. diphenylphosphine (**4e**) under photocatalytic conditions with 5 mol % of **1**. A strained internal alkene, norbornene, gave 96% conversion with 2 equiv. of phenylphosphine (**4f**). All Michael acceptors tested reacted rapidly with both phenyl- and diphenylphosphine (**4g–j**). Initial NMR spectra obtained before irradiation indicated that full conversion methyl acrylate and acrylonitrile had occurred, even when kept in the dark.

**TABLE 2.** Hydrophosphination of disubstituted and activated alkenes

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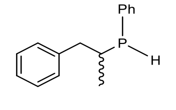
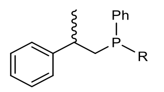
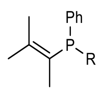
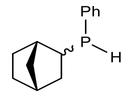
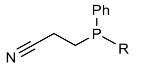
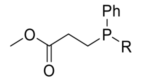
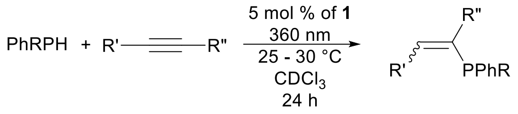
|  |  |  |
| **4a**, 99%$^{a}$ (82%)$^{b}$, 20 h | **4b**, R = H, 92%$^{a}$, 2.25 h<br>**4c**, R = Ph, 83%$^{b}$, 20 h | **4d**, R = H, 99%$^{a}$, 80 m<br>**4e**, R = Ph, 93%$^{d}$, 8 h |
|  |  |  |
| **4f**, 96%$^{a}$, 50 m | **4g**, R = H, 98%$^{d,e}$, 20 m<br>**4h**, R = Ph, 90%$^{d,e}$, 25 m | **4i**, R = H, 99%$^{d,e}$, 15 m<br>**4j**, R = Ph, 99%$^{d,e}$,10m |

Conversions determined by integration of $^{1}$H and $^{31}$P{$^{1}$H} NMR spectra. Reactions conducted in 0.6 ml CDCl$_3$, with 5 mol % of **1** and 0.38 mmol of alkene [a] 2 equiv. PhPH$_2$ [b] isolated yield, [c] 1.5 equiv. Ph$_2$PH and 0.25 mmol alkene [d] 1 equiv. Ph$_2$PH [e] ambient light



**5a:** R = H, R' = Ph, R" = Et, 80%, 3:1 *Z:E*
**5b:** R = Ph, R' = Ph, R" = Et, 75%, 1:1.1 *Z:E*
**5c:** R = R' = Ph, R" = H, 41%, 32:1 *Z:E*

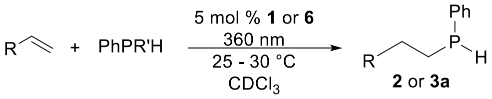
(4)

Treatment of internal and terminal alkynes under irradiation with either phenyl- or diphenylphosphine provided access to vinyl phosphine products **5a–c** (Eqn (4), see SI for additional alkyne substrates and conditions). Reaction of 1-phenyl-1-butyne with 1 equiv. of phenylphosphine and 5 mol % of **1** under 360 nm irradiation for 24 h afforded the vinyl phosphine product in 81% conversion with 100% selectivity for P–C bond formation at the alkyl substituted position and a 3:1 preference for the Z-isomer. Reaction with 2 equiv. of phenylphosphine under the same conditions afforded the vinyl phosphine product in nearly quantitative conversion and 2.45:1 selectivity but led to only trace conversion to the double hydrophosphination product after 72 h and this reaction was not pursued further.

The mechanism of catalysis is still under consideration and questions remain about the role of light and the importance of open shell intermediates. Further experimentation is underway. However, preliminary data suggests a Cu(I) phosphido intermediate is an active intermediate in this catalysis based on several observations and experiments.

Acetylacetone is visible in the $^{1}$H NMR spectrum and 1,2-tetraphenyldiphosphine is observed in the $^{31}$P NMR spectrum of catalytic reaction mixtures with **1**. Treatment of 5 mol % of **1** with Ph$_2$PH in the absence of alkene results in the formation of gradual formation of 2 equiv. of acetylacetone and one half an equivalent (per Cu) of 1,2-tetraphenyldiphosphine. The solution behavior of this reaction is consistent with [(Ph$_2$PH)CuPPh$_2$]$_n$ previously reported by Caulton[38] and other Cu phosphido compounds in the literature (see SI for details).[39, 40]

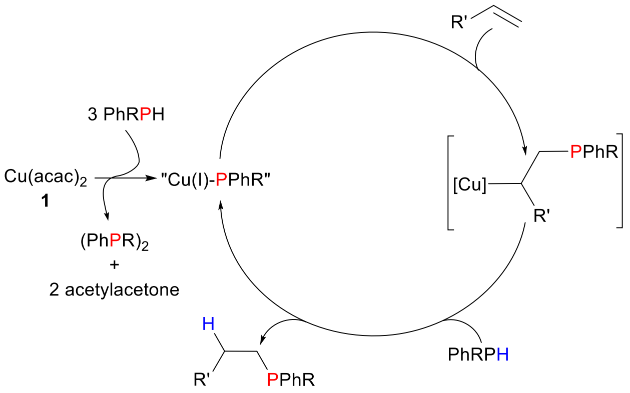
As a proxy for Cu(I), we tested the activity of [(PPh$_3$)CuH]$_6$ (**6**) in these reactions (Eqn (5)), knowing that stoichiometric reaction of **6** with Ph$_2$Ph affords (PPh$_3$)CuPPh$_2$.[38] The activities of **1** and **6** are very similar, suggesting that a Cu(I)-phosphido may be active in the catalysis. Although a radical mechanism cannot be ruled out, the formation of Cu(I) indicates that a two-electron process is a viable, if not the predominant reaction pathway. With this insight, and because nucleophilic attack on an unactivated alkene can be dismissed, a catalytic cycle is proposed in Scheme 1.



**2** or **3a**

**1**, R = Ph, R' = Ph, **2**, 5 h, 83%
**1**, R = C$_6$H$_{13}$, R' = H, **3a** 20 h, 80%
**6**, R = Ph, R' = Ph, **2**, 5 h, 78%
**6**, R = C$_6$H$_{13}$, R' = H, **3a**, 24 h, 70%

(5)



**Scheme 1**: Plausible catalytic cycle

In summary, commercially available Cu(acac)$_2$ (**1**) has been demonstrated to be a rapid and efficient hydrophosphination pre-catalyst for primary and secondary phosphines with a diverse collection of substrates under low intensity UV-A irradiation. Thermal activation of this bench-stable precursor is also possible, and preliminary mechanistic work suggests involvement of copper(I). This is the first report of an air- and water-stable catalyst that is active with these substrates. Additional study of this and related systems is underway.

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## Conflicts of interest

There are no conflicts to declare.

## Notes and references

†In an N$_2$ filled dry box, phosphine, unsaturated substrate, and **1** were mixed in 0.6 mL of CDCl$_3$ (where applicable) and transferred to an NMR tube. For neat reactions, **1** and substrates were added directly to a J-Young NMR tube. After an initial $^1$H and $^{31}$P{$^1$H} NMR spectra, the NMR tube was irradiated and monitored by $^1$H and $^{31}$P{$^1$H} NMR spectroscopy. The photoreactor temperature was 25–30 °C. See SI for further details.

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TOC graphic

$Cu(acac)_2$ is a highly active, bench-stable catalyst precursor for hydrophosphination of a wide range of alkenes and alkynes.