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Photo-induced Dearomatizing Three-component Coupling of Arylphosphines, Alkenes, and Water

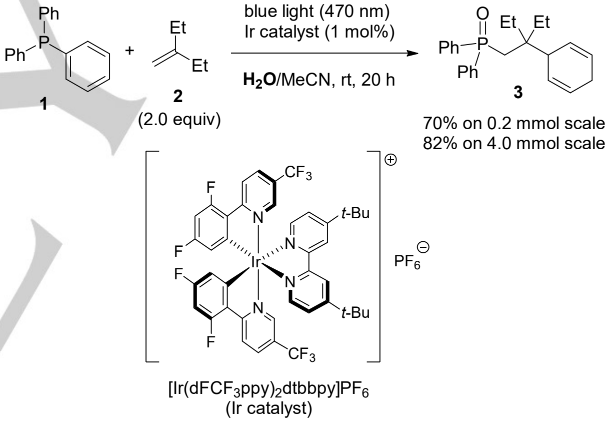
Yusuke Masuda, Hiromu Tsuda, and Masahiro Murakami* [a]

Abstract: Herein reported is a unique photo-induced reaction which couples a triarylphosphine, an alkene, and water to produce 2-(cyclohexa-2,5-dienyl)ethylphosphine oxide. An alkene inserts into a C(aryl)–P bond of the arylphosphine, the aryl ring is dearomatized into the cyclohexadienyl ring, and the phosphorus is oxidized. The three components are all readily available, and their intermolecular coupling significantly increases molecular complexity. The products are applicable to the Wittig olefination.

Photoredox catalysis has brought about a renaissance in radical chemistry to renew interests in the use or co-use of water as the solvent, since a polar environment that water creates is innocuous for electronically neutral intermediates.[1] We have recently developed the photo-catalyzed reactions of unprotected sugars in aqueous media. They follow a radical pathway directly leading to products without any protection/deprotection procedure.[2] Water was employed as the solvent or co-solvent for the sake of solubility of sugars. During our continuing investigation on related radical-mediated reactions in aqueous media, we encountered an unexpected reaction which incorporated a water molecule in a product as an essential component. Herein reported is a unique three-component coupling reaction of triarylphosphines, alkenes, and water.

A solution of triphenylphosphine (**1**, 0.20 mmol) and alkene **2** (2 equiv) in water/acetonitrile (1/2 v/v) was irradiated with blue light (470 nm) in the presence of [Ir(dFCF$_3$ppy)$_2$dtbbpy]PF$_6$ (Ir catalyst, 1 mol%) for 20 h (Scheme 1). It was our true surprise that 1,4-cyclohexadiene-phosphine oxide **3** was isolated from the crude reaction mixture by chromatographic purification (70% yield based on **1**). The reaction was marked by dramatic skeletal changes; the alkene **2** was inserted into a C(phenyl)–P bond of triphenylphosphine (**1**), the phenyl ring was dearomatized into the cyclohexadiene ring, and the phosphorus atom was oxidized. Water split into an oxygen atom and two hydrogen atoms, being separately incorporated in the produced molecule (vide infra). The reaction turned out to be scalable to a gram scale. When 1.0 g of triphenylphosphine (4.0 mmol) was subjected to the coupling reaction with lower catalyst loading (0.25 mol%), the product **3** was obtained in an even better isolated yield (82%, 1.2 g, 3.3 mmol).

The Birch reaction arguably represents one of the most authentic examples of a dearomatization reaction. It employs strongly reductive metallic lithium or sodium in ammonia to reduce benzene rings into 1,4-cyclohexadiene rings.[3] Transition-metal catalysis also provides a variety of synthetic reactions involving dearomatization of aromatic rings, especially π-extended arenes.[4] Recently, photoredox-catalyzed dearomatization reactions have been explored.[5] For example, Jui[5e] and Stephenson[5f] demonstrated that the well-designed arene substrates were dearomatized through intramolecular carbocyclization. König[5c] and Miyake[5h] reported photoredox-catalyzed Birch-type reduction of arenes, which necessitated sacrificial reductants. The present dearomatizing coupling reaction is unique in that all three components are readily available compounds of simple structures and couple together in a highly atom-economical manner with significant increase of molecular complexities. No sacrificial reductants are required.



Scheme 1. Dearomatizing coupling of triphenylphosphine, alkene, and water.

The results of the following experiments provided valuable insights into the mechanism of the unexpected reaction. First, fluorescence quenching experiments were carried out. The obtained results confirmed that the excited Ir catalyst was quenched by triphenylphosphine.[6] When the reaction was performed in anhydrous acetonitrile, no reaction occurred and both the phosphine **1** and the alkene **2** remained intact (Scheme 2a). Therefore, water is likely to participate in the early stage of the reaction pathway. Next, D$_2$O and H$_2$O^{18} were employed in place of H$_2$O. The product **3-*d*** obtained with D$_2$O incorporated two deuterium atoms selectively at the 1- and 3-positions of the cyclohexadiene ring, as shown in Scheme 2b, with high D/H ratios. On the other hand, the phosphine oxide **3-O^{18}** obtained with H$_2$O^{18} incorporated an O^{18} isotope, which was identified by high-resolution mass spectrometry (Figure 2c). When tri(*p*-tolyl)phosphine (**4**) was subjected to the reaction with the alkene **2**, the geminally disubstituted sp^2 carbon of **2** was bound to the ortho carbon of the original *p*-tolyl group (Scheme 2d). Finally, a

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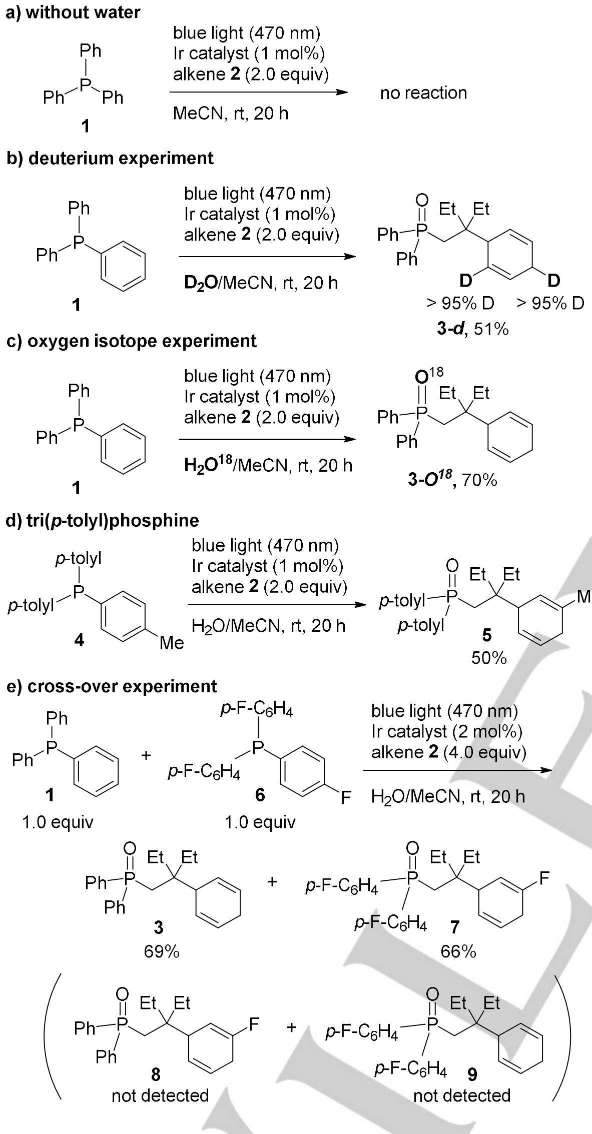
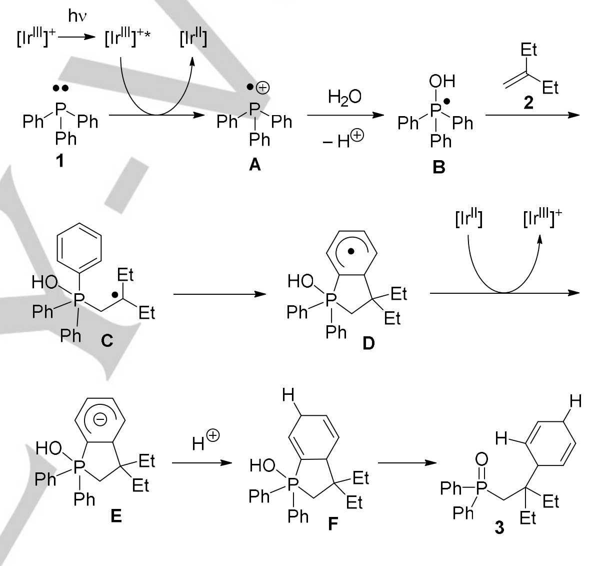
cross-over experiment was conducted (Scheme 2e). A mixture of triphenylphosphine (**1**) and tri(*p*-fluorophenyl)phosphine (**6**) was used as the arylphosphine component. No cross-over product **8** nor **9** was observed, which confirmed that the aryl ring once detached from phosphorus was still tied up with the parent phosphorus through an ethylene linker after dearomatization.



Scheme 2. Mechanistic experiments.

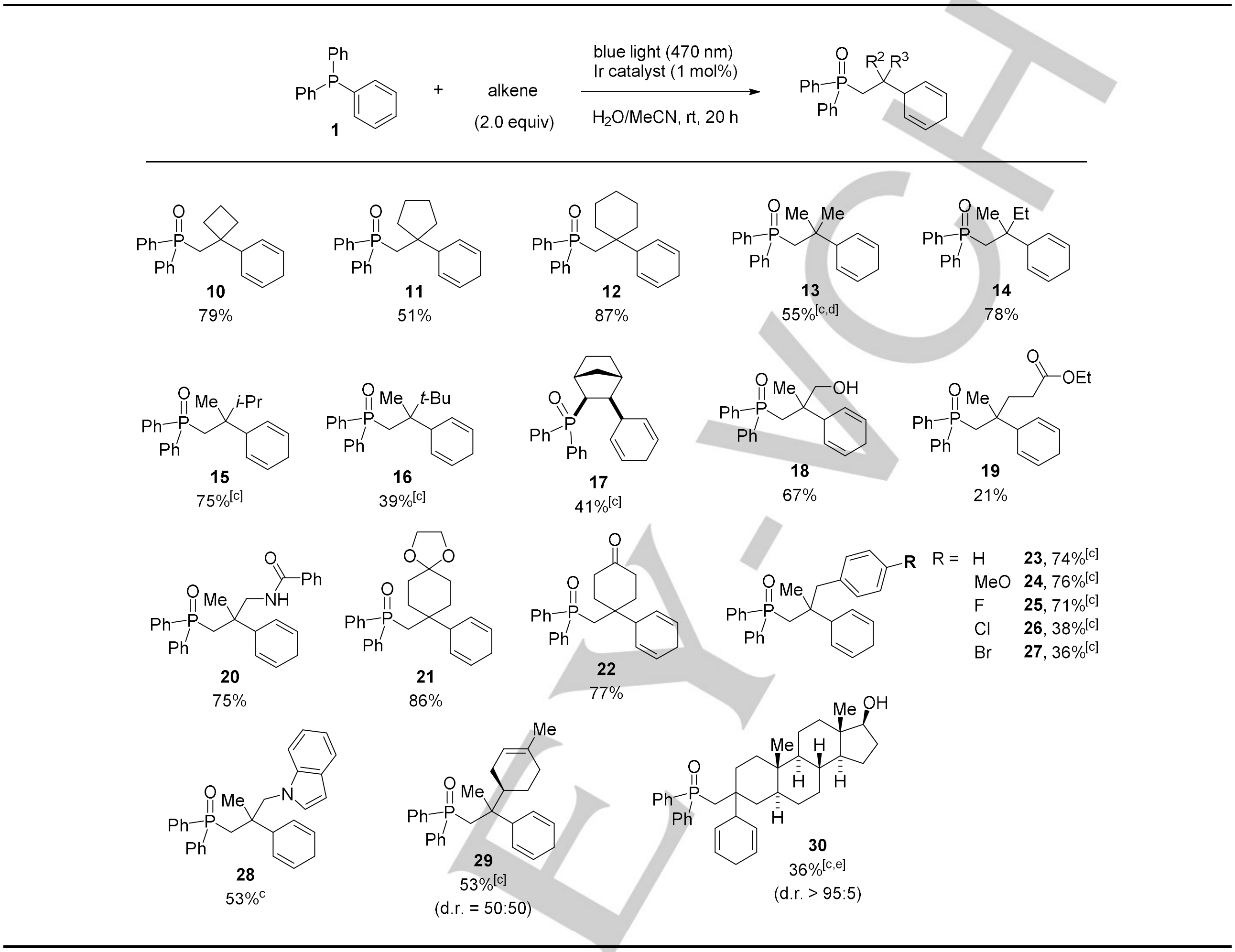
The results mentioned above led us to propose a reaction pathway shown in Scheme 3 for the present dearomatizing coupling reaction. An iridium(III) catalyst is initially excited upon photoirradiation ($E_{1/2}^{red}$[Ir(III)*/Ir(II)] = +1.21 V vs SCE in CH_3CN).[7] Triphenylphosphine (**1**) ($E_{1/2}^{ox}$ = +0.98 V vs SCE in CH_3CN)[8] transfers a single electron to the excited iridium(III) catalyst to generate triphenylphosphine radical cation **A** and an iridium(II) complex. A water molecule adds onto the radical cation **A**, and the following deprotonation generates phosphoranyl radical **B**.[8,9] Although the radical center of **B** is sterically hindered, it adds to the geminally disubstituted alkene **2** at the less-hindered side, forming thermodynamically stable tertiary alkyl radical **C**. It undergoes 5-trig cyclization onto the phenyl group to generate even more stable cyclohexadienyl radical **D** at the expense of aromaticity. The iridium(II) complex transfers a single electron back to **D** to regenerate iridium(III). The resulting anion **E** is protonated by water with a site-selectivity which is analogous to that of the Birch reduction to form hydroxyphosphorane **F**.[10] Finally, **F** rearranges to the product **3** through protonative cleavage of the C(alkenyl)–P bond. An analogous decomposition of hydroxyphosphoranes had been observed in hydrolysis of phosphonium salts.[11] The last two protonation events are in accord with the result of the deuterium experiment shown in Scheme 2b.



Scheme 3. Proposed reaction pathway.

Various alkenes were examined for the coupling reaction with triphenylphosphine (**1**) (Table 1). Methylenecycloalkanes ranging from 4- to 6-membered rings furnished the corresponding products **10-12** in yields ranging from 51% to 87%. Gaseous 2-methylpropene at an atmospheric pressure successfully participated in the reaction to afford **13** in 55% yield. Even the alkene having a tertiary butyl group underwent the coupling reaction to give the product **16** possessing two quaternary carbons in juxtaposition. Whereas vicinally disubstituted alkenes such as cyclohexene hardly coupled with **1** and water, 2-norbornene was reactive enough to afford the coupling product **17** as a single diastereomer, which was unambiguously confirmed by an X-ray crystallographic analysis. This result is consistent with the proposed mechanism involving a 5-trig cyclization step onto a phenyl ring. On the other hand, mono-, tri- and tetra-substituted alkenes failed to give the coupling product, probably due to the instability of the radical species corresponding to **C** or steric reasons.

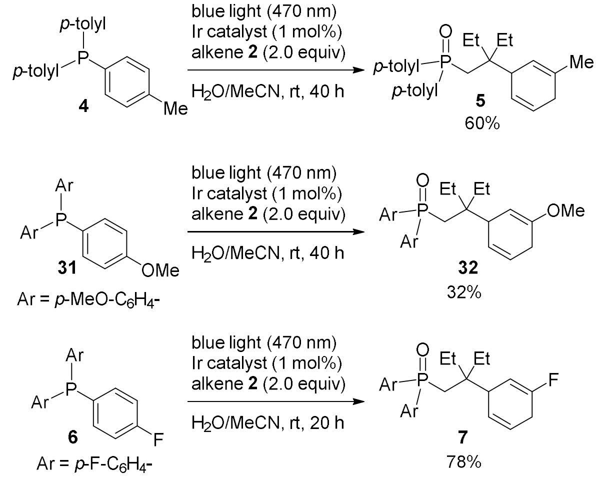
Table 1. Scope with respect to alkenes. [a,b]



[a] Reaction conditions: triphenylphosphine (0.20 mmol), alkene (0.40 mmol, 2 equiv), Ir catalyst (0.002 mmol, 1 mol%), H_2O (1 mL), MeCN (2 mL), blue LEDs (470 nm), rt, 20 h. [b] Isolated yield. [c] Reaction time of 48 h. [d] 1 atm of 2-methylpropene (balloon). [e] Acetone instead of MeCN.

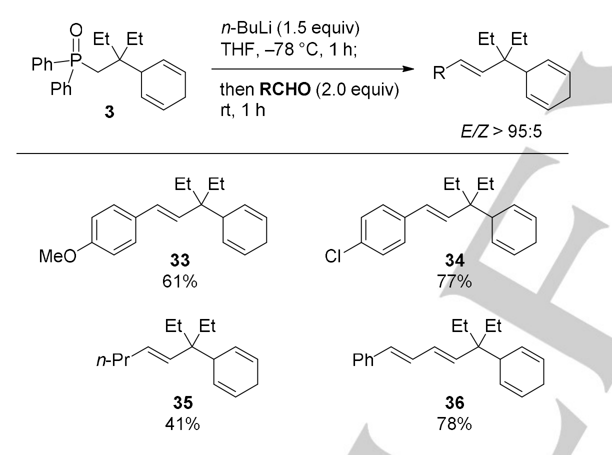
Next examined were a range of geminally disubstituted alkenes possessing various functionalities. Free hydroxy, ester, amide, and acetal groups were all tolerated under the reaction conditions (**18**-**21**). Notably, the alkene bearing a ketonic carbonyl group participated in the reaction to furnish the 1,4-cyclohexadiene **22** in 77% yield keeping the carbonyl group intact. Methallylbenzene derivatives were also suitable substrates. Functional groups such as methoxy (**24**) and fluoro (**25**) groups on the phenyl ring were compatible with the reaction conditions. The coupling reaction of chloro- and bromo-substituted methallylbenzenes was accompanied by polymerization to afford the products **26** and **27** in lower yields of 36% and 38%, respectively. 1-Allylindole afforded the coupling product **28** in 53% yield. Limonene has two alkenyl groups, and the propenyl moiety selectively reacted with **1** to form the product **29** in 53% yield as a mixture of diastereomers. Testosterone-derived alkene also underwent the coupling reaction, and the desired product **30** was obtained in 36% yield.[12]

We investigated the substrate scope also with respect to triarylphosphines (Scheme 4). Tri(*p*-methoxyphenyl)phosphine gave the product **32** in 32% yield along with tri(*p*-methoxyphenyl)phosphine oxide (ca. 42% yield). A fluoro group was tolerated, and the fluoro-1,4-cyclohexadiene **7** was obtained in 78% yield. Trialkylphosphines were not suitable substrates due to a lack of an aryl group.



Scheme 4. Synthesis of disubstituted 1,4-cyclohexadienes.

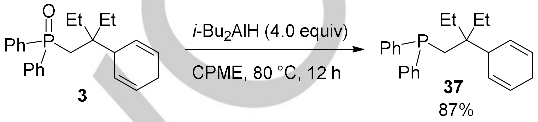
Table 2. Olefination with phosphine oxide 3. [a,b]



[a] Reaction conditions: **3** (0.20 mmol), *n*-BuLi (0.30 mmol, 1.5 equiv), THF (3 mL), –78 °C, 1 h; then aldehyde (0.40 mmol, 2.0 equiv), rt, 1 h. [b] Isolated yield.

The produced phosphine oxides having an α-methylene group were eligible to the Horner-Wittig olefination reaction.[13] An α-anion was readily generated from **3** by treatment with butyllithium (1.5 equiv, THF, –78 °C, 1 h). Then, an aldehyde (2.0 equiv) was added to the reaction mixture, which was allowed to warm to room temperature over 1 h. The corresponding alkene was obtained in moderate to good isolated yields. Of note was that *E*-isomers were produced almost exclusively, which was attributable to the steric bulkiness of the tertiary alkyl substituent (Table 2).[14] Methoxy- and chloro-substituted styrene derivatives **33** and **34** were synthesized in 61% and 77% yield, respectively. In addition to aromatic aldehydes, an aliphatic aldehyde also participated in the olefination reaction to afford alkene **35** in 41% yield. Even tetraene product **36** was successfully obtained when cinnamyl aldehyde was employed.

We next carried out a reduction reaction of the phosphine oxide **3** (Scheme 5).[15] When it was treated with diisobutylaluminium hydride in cyclopentyl methyl ether (CPME), alkyldiphenylphosphine **37** was produced in 87% yield. Thus, the present coupling reaction offers a facile access to a new class of alkyldiarylphosphine(III) compounds starting from triarylphosphines.



Scheme 5. Reduction of phosphine oxide **3**.

In conclusion, we have developed the unique photo-induced three-component coupling reaction of arylphosphines, alkenes, and water. As a result of dearomatization, the products acquire a 1,4-cyclohexadiene moiety. The phosphine oxide moiety is utilized for olefination of aldehydes. Possibilities such as the usage of the produced phosphines as a bidentate ligand for transition metals is under investigation.

Acknowledgements

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Keywords: Dearomatization • Photocatalysis • Phosphine • Alkene • Water

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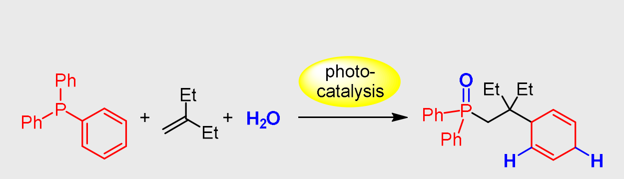

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