Heterocycle Synthesis Hot Paper

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Palladium-Catalyzed Direct Synthesis of Phosphole Derivatives from Triarylphosphines through Cleavage of Carbon–Hydrogen and Carbon–Phosphorus Bonds**

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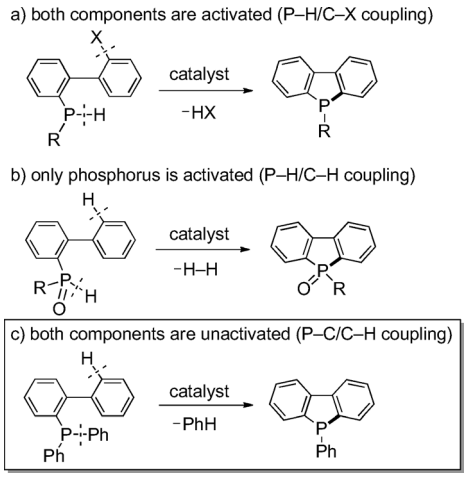
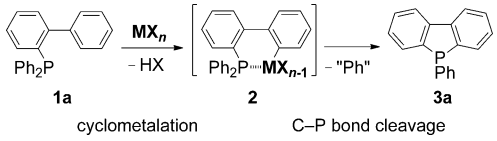
Phospholes have recently received much attention as promising organic materials because of their characteristic optical and electronic properties, which are derived from the phosphorus-bridged 1,3-dienic π system.[1] The method most frequently used for the synthesis of phospholes involves the nucleophilic substitution of a P–X bond with a stoichiometric amount of an organometallic species such as organolithium or organomagnesium reagents.[2] The issue of functional group compatibility associated with this classical method has been addressed to some extent by using transition metal catalysis. Catalytic [2+2+2] cycloaddition of dialkynylphosphines with polyynes has been used for the synthesis of helicene analogues of phospholes.[3] More versatile synthesis is enabled by catalytic C–P bond formation reactions. The intramolecular cross-coupling of aryl halides or their equivalents with hydrophosphines has been successfully used in the synthesis of a phosphole skeleton (Scheme 1a).[1h] However, this method still needs considerable improvement in terms of the degree of functionalization of the starting material and the instability of a hydrophosphine group. In this context, Takai and Kuninobu et al. made notable progress by developing a palladium-catalyzed synthesis of dibenzophosphole oxides by dehydrogenative cyclization of hydrophosphine oxides (Scheme 1b).[4] In view of the widespread availability and stability of triarylphosphines, a more synthetically valuable approach would involve intramolecular cross-coupling between triarylphosphine and an arene through simultaneous cleavage of C–P and C–H bonds (Scheme 1c). Herein, we report the realization of a catalytic reaction of this type.



Scheme 1. Catalytic synthesis of phospholes through C–P bond formation.

We expected that the reaction of biphenylphosphine **1a** with a suitable transition metal complex would afford metallacycle **2** through a common cyclometalation process (Scheme 2).[5] If one of the phenyl groups on the phosphorus center in **2** is eliminated, the desired phosphole **3a** would be formed. Although such metal-mediated C–P bond cleavage of a simple triarylphosphine is apparently a challenge,[6–9] reports by us and Xi and co-workers on C–Si and C–Ge bond cleavage in the catalytic syntheses of siloles[10] and germoles[11] via intermediates analogous to **2** encouraged us to pursue the development of this new mode of phosphole synthesis.



Scheme 2. Working hypothesis.

Not surprisingly, a simple extension of the methods for Si and Ge did not work with phosphorus-based substrate **1a**

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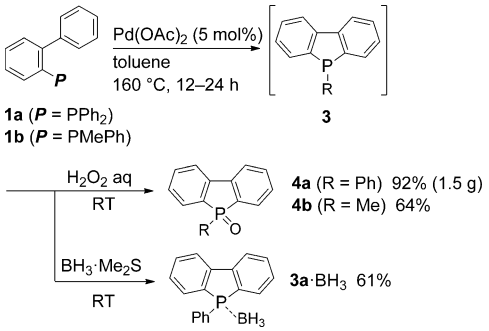
because of the difference in fundamental properties between groups 14 (Si and Ge) and 15 (P). After several experiments, the expected reaction was found to occur by mixing **1a** with a catalytic quantity of $Pd(OAc)_2$ at 160 °C (Scheme 3).[12]

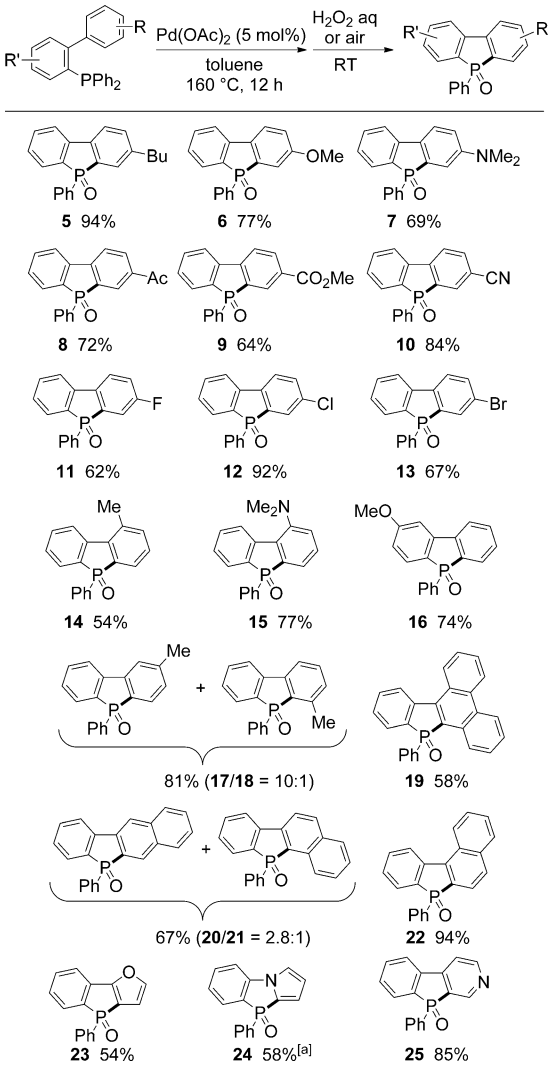


Scheme 3. Palladium-catalyzed synthesis of phosphole.

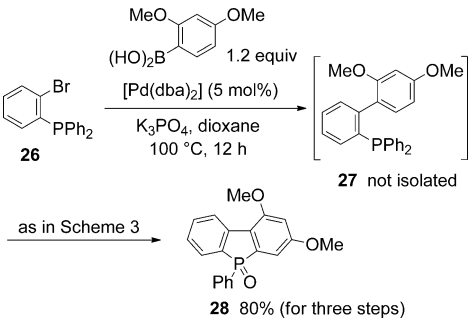
Since the generated phosphole **3a** is susceptible to oxidation upon workup, the product was isolated as oxide **4a** by treatment with aqueous H_2O_2. Alternatively, complexation with BH_3 afforded **3a**·BH_3 as a stable and crystalline solid. Notably, this synthesis can be conducted on the gram scale without any modification (1.5 g of **4a** were synthesized successfully). A biphenyl bearing a PMePh group, as in **1b**, underwent palladium-catalyzed cyclization to deliver P-alkyl phosphole oxide **4b** through exclusive cleavage of the P–Ar bond rather than the P–Me bond.[13]

This operationally trivial method was successfully applied to the synthesis of a diverse array of phospholes (Scheme 4). The high functional group tolerance allows access to a range of electronically different phospholes bearing ether (**6** and **16**), amine (**7** and **15**), ketone (**8**), ester (**9**), nitrile (**10**), and fluoride (**11**) groups. The compatibility of chlorides and bromides (as in **12** and **13**), which can serve as handles for further structural modification of the phosphole skeleton, is particularly useful (see Scheme 8). C–P bond formation can occur smoothly with substrates bearing an *ortho* substituent to deliver 1-substituted dibenzophospholes, as in **14** and **15**. Substrates bearing a *meta* substituent underwent regioselective cyclization at the less hindered site to form **17** as the major product. Unlike the substrates required for the reported methods for the synthesis of phospholes (Scheme 1 a, b), the starting biarylphosphines used in this study are readily accessible. Some of them are commercially available ligands (for example, **15** is derived from a ligand known as PhDavePhos[14]). Others can be rapidly prepared from the commercially available (2-bromophenyl)diphenylphosphine (**26**) through a cross-coupling reaction, and the subsequent phosphole formation can be performed without isolation of the biarylphosphine intermediate **27** (Scheme 5). The modularity of this synthesis enables various π systems, including naphthalenes (**20–22**), phenanthrenes (**19**), furans (**23**), pyrroles (**24**), and pyridines (**25**), to be incorporated into the phosphole framework.

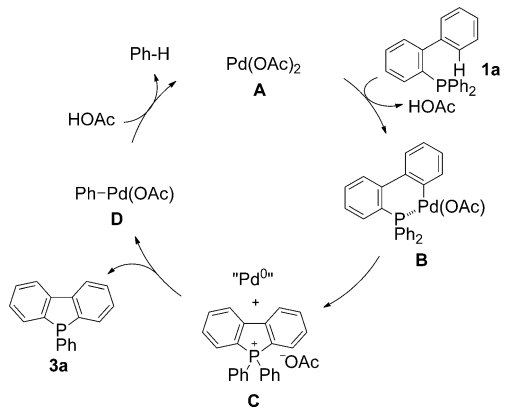
A possible mechanism is depicted in Scheme 6. The reaction is initiated by the reaction of Pd^{II} with **1a** to form the cyclopalladated complex **B**.[15] Subsequent reductive elimination from **B** leads to the formation of phosphonium **C** along



Scheme 4. Reaction scope. Reaction conditions: biarylphosphine (0.30 mmol), $Pd(OAc)_2$ (0.015 mmol), and toluene (1.0 mL) in a sealed tube at 160 °C, for 12 h. Yields of isolated products are shown. [a] The reaction was set up in a glovebox because of the sensitivity of the starting phosphine to oxygen.



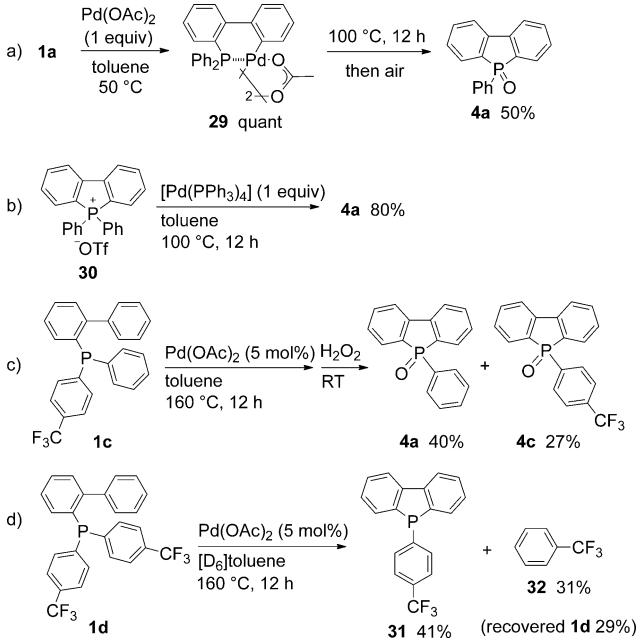
Scheme 5. Synthesis of phosphole **28** from **26**. dba = dibenzylideneacetone.



Scheme 6. A possible mechanism.

with Pd^0.[6a–c,16] The phosphonium **C** immediately undergoes oxidative addition to Pd^0, which is in close proximity, to provide phosphole **3a** and {PhPd(OAc)} (**D**) through cleavage of a C–P bond.[8a,b,17] Finally, **D** is protonated by AcOH, which is released in the initial cyclometalation step, to regenerate $Pd(OAc)_2$ (**A**).[18]

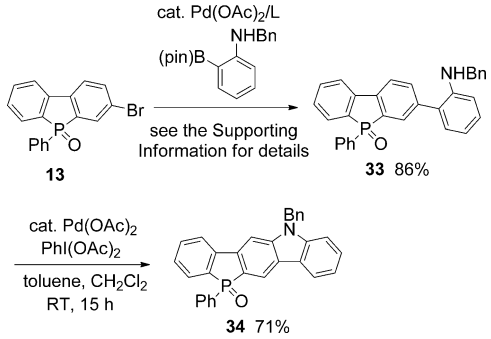
Several experimental results that support our proposed mechanism were obtained (Scheme 7). First, cyclopalladated complex **B** could indeed be synthesized by the reaction of **1a** with $Pd(OAc)_2$ (1 equiv) at 50 °C. X-ray crystallographic analysis revealed that the complex was formed as a dimer (**29**, Scheme 7a). Heating a solution of **29** in toluene at 100 °C afforded phosphole **4a**, thus suggesting that the metallacycle **29** is a plausible intermediate for the catalytic cycle.[19] Second, the potential intermediacy of phosphonium salt **C** in the C–P bond cleavage process was confirmed. The reaction of independently synthesized **30** with $[Pd(PPh_3)_4]$ at



Scheme 7. Mechanistic studies. Tf = trifluoromethanesulfonyl.

100 °C led to the formation of phosphole **4a** (Scheme 7b). This mechanistic scenario is also consistent with the observation of cyclization of **1c**, in which the more electron-deficient aryl group on the phosphorus was eliminated preferentially over the phenyl group (Scheme 7c).[20] Third, by examining the reaction of **1d** (Scheme 7d), the fate of the cleaved aryl group was determined to be the corresponding arene, as is proposed in Scheme 6 .

The functionalized phospholes obtained in the present study are amenable to further elaboration. For example, the Suzuki–Miyaura reaction of bromophosphole **13** followed by catalytic C–H amination[21] enables rapid assembly of the extended π-conjugated molecule **34** (Scheme 8).



Scheme 8. Synthetic elaboration of **13**. Bn = benzyl.

In summary, a palladium-catalyzed method for the synthesis of phospholes from triarylphosphines has been developed. Synthetic advantages over reported methods include 1) operational simplicity, 2) direct use of simple starting materials, 3) excellent functional group compatibility, and 4) high modularity of the aromatic component to be incorporated. These features enable rapid access to a structurally diverse array of phosphorus-based π systems, the physical properties of which are of significant interest.[22] The application of this method to the synthesis of elaborated phosphole derivatives and other heterocyclic compounds is being actively investigated by us.

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Keywords: carbon-hydrogen bond cleavage · carbon-phosphorus bond cleavage · homogeneous catalysis · palladium · phosphole

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[19] Although the stoichiometric reactions shown in Scheme 7a proceeded to completion at 100°C, the catalytic reaction at 100°C gave **4a** in only 29% yield. This may suggest that excess **1a** present in the catalytic setting inhibits some of the steps in the catalytic cycle and/or that catalyst regeneration is turnover-limiting.

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[22] We have observed that several phospholes synthesized in this study exhibited intense solid-state fluorescence. See the Supporting Information for details.

Communications

Heterocycle Synthesis

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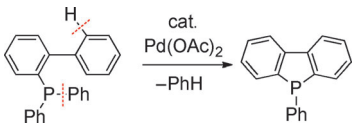
N. Chatani* _____ ■■■■–■■■■

Palladium-Catalyzed Direct Synthesis of Phosphole Derivatives from Triarylphosphines through Cleavage of Carbon–Hydrogen and Carbon–Phosphorus Bonds



(Phosp)hole in one: A palladium-catalyzed synthesis for directly assembling phosphole skeletons from triarylphosphines through C—H and C—P bond cleavage was developed. This approach overcomes several of the limitations of the so far reported methods. Phospholes bearing a range of functionalities (including Br, F, CO_2Me, Ac, and CN) and an array of fused rings (naphthalenes, anthracenes, furans, and pyrroles) can be easily synthesized.