Organic LETTERS

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Palladium-Catalyzed Synthesis of Six-Membered Benzofuzed Phosphacycles via Carbon−Phosphorus Bond Cleavage

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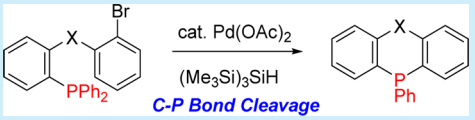
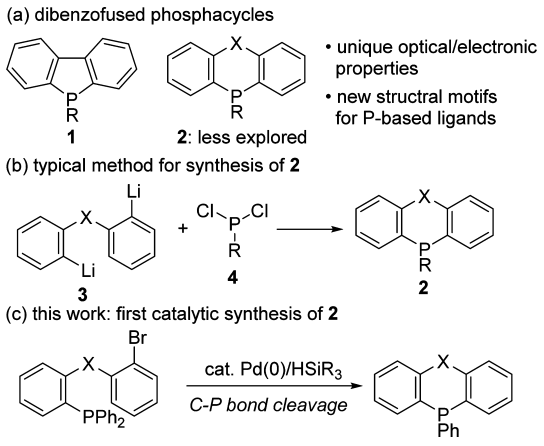
Supporting Information

ABSTRACT: The palladium-catalyzed synthesis of dibenzofused six-membered phosphacycles via carbon−phosphorus bond cleavage is developed. This method is compatible with a range of functional groups, such as esters, amides, and carbamates, which is in sharp contrast to the limitations of the classical method using organolithium reagents.



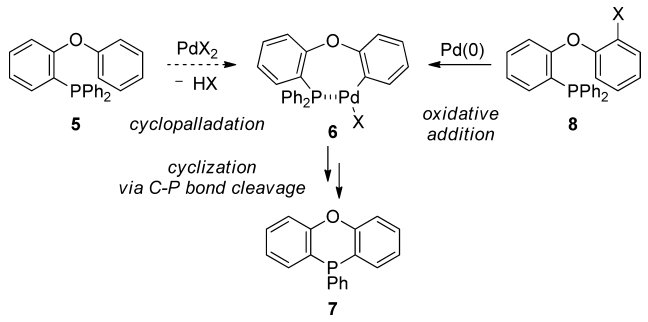
Phosphole and its benzo-fused derivatives have recently attracted significant attention as promising organic materials due to their unique optical and electronic properties.[1] For example, a dibenzo[*b*,*d*]phosphole skeleton **1** has frequently been employed as a structurally rigid and electronically tunable alternative of a biphenyl unit for incorporation into organic materials (Scheme 1a).[2] In contrast to the significant progress in the preparative methods and applications of phospholes, the chemistry of the corresponding six-membered phosphacycles is much less explored,[3] although they are expected to share many of their unique physical properties. One obvious reason that discourages the study of six-membered phosphacycles is the limited methods available for their syntheses. The six-membered phosphacycle **2** is typically assembled through a nucleophilic substitution reaction between a dilithium species **3** and dichlorophosphine **4** (Scheme 1b).[3a,g,k,m] However, the scope of this method is severely limited by low functional group compatibility and the air/moisture sensitivity of organolithium reagents. Therefore, more general methods that allow for access to elaborate derivatives are clearly needed. Herein, we describe a palladium-catalyzed method for the synthesis of phosphacyles **2** from triphenylphosphine derivative via the cleavage of the carbon−phosphorus (C−P) bond (Scheme 1c). To our knowledge, this reaction represents the first catalytic synthesis of **2**.[4]

Scheme 1. Six-Membered Phosphacycles: Utility and Synthesis



Recently, our group developed a palladium-catalyzed method for the synthesis of phospholes from triphenylphosphine derivatives through the cleavage of the C−P bond.[5] This catalytic method features (1) operational simplicity, (2) direct use of readily available tertiary phosphines as the phosphorus source, (3) excellent functional group compatibility, and (4) high modularity of the incorporated aromatic ring. Given these favorable attributes, we attempted to apply this C−P bond cleavage strategy to the synthesis of six-membered phosphacycle **2**. Thus, we envisioned that 2-phenoxytriphenylphosphine (**5**) would react with a palladium(II) catalyst to form palladacycle **6**, which would eventually lead to the formation of phosphacycle **7** via C−P bond cleavage similar to phosphole synthesis (Scheme 2).[5] However, the exposure of **5** to the conditions developed for the synthesis of phospholes (i.e., 5 mol % of $Pd(OAc)_2$, in toluene, 160 °C, 12 h) delivered none of the desired cyclized product **7**, and the starting phosphine **5** was recovered quantitatively. The unsuccessful result with **5** could be attributed

Scheme 2. Working Hypothesis



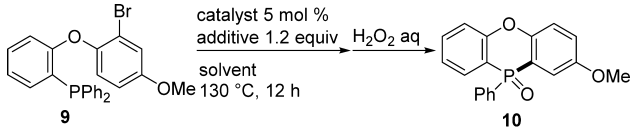
Received: November 9, 2014

   dx.doi.org/10.1021/ol503252t | *Org. Lett.* XXXX, XXX, XXX−XXX

to problems with the assembly of the seven-membered metallacyclic intermediate **6**, compared with the six-membered ring intermediate for phosphole synthesis during the cyclopalladation process. We surmised that the key intermediate **6** could also be generated by oxidative addition of halide **8** to palladium(0), which should occur relatively easily in view of the higher reactivity of the C−X bond compared with the C−H bond.

To verify the feasibility of our hypothesis, we initially examined the palladium-catalyzed reaction of phosphine **9** (Table 1).

Table 1. Optimization Studies



9 **10**

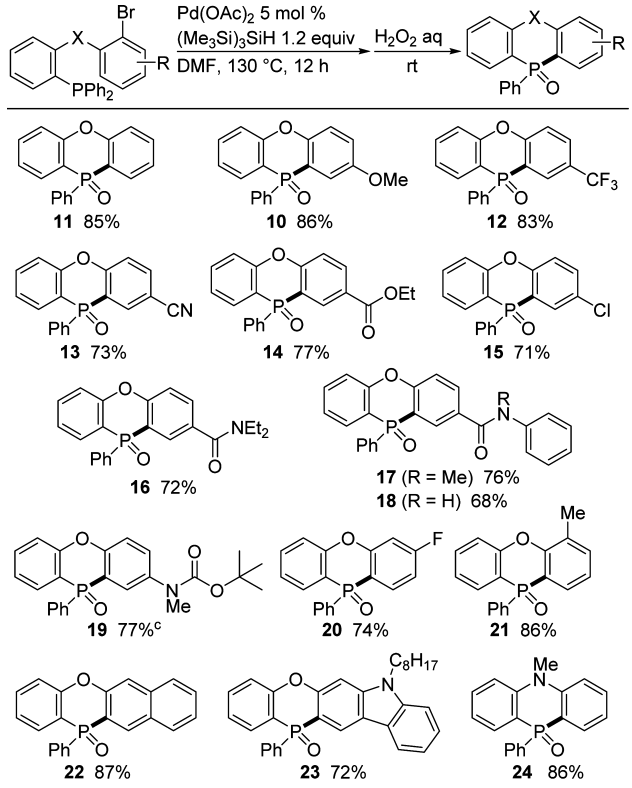
entry	catalyst	additive	solvent	NMR yield (%)
1	$Pd(OAc)_2$		DMF	19
2	$Pd(OAc)_2$	Zn	DMF	56
3	$Pd(OAc)_2$	$(EtO)_3SiH$	DMF	28
4	$Pd(OAc)_2$	Et_3SiH	DMF	36
5	$Pd(OAc)_2$	$^iPr_3SiH$	DMF	53
6	$Pd(OAc)_2$	$(Me_3Si)_3SiH$	DMF	83 (86)[b]
7	$Pd(OAc)_2$	$(Me_3Si)_3SiH$	toluene	81
8	$Pd(OAc)_2$	$(Me_3Si)_3SiH$	1,4-dioxane	76
9	$Pd_2(dba)_3{\cdot}CHCl_3$	$(Me_3Si)_3SiH$	DMF	70
10	$Pd(PPh_3)_4$	$(Me_3Si)_3SiH$	DMF	81

[a]Reaction conditions: **9** (0.20 mmol), catalyst (0.010 mmol), additive (0.24 mmol), solvent (0.40 mL), for 12 h. [b]Isolated yield.

Pleasingly, the expected cyclization occurred, when **9** in conjunction with 5 mol % of $Pd(OAc)_2$ was heated at 130 °C for 12 h in DMF (entry 1). Because the cyclic phosphane product was prone to oxidation upon workup, the yield of the product was quantified by conversion to the corresponding oxide **10** (19% yield based on NMR analysis). Consideration of the reaction mechanism led us to infer that the regeneration of an active Pd(0) species after formation of the product is inefficient under these conditions, and the catalyst turnover might be improved by addition of a suitable reducing agent (see Scheme 6 for our mechanistic proposal). Indeed, addition of metallic zinc was found to increase the yield of **10** to 56% (entry 2). Hydrosilanes were also found to be effective reductants for this cyclization reaction. Interestingly, the substituents on the silicon atom had a profound impact on the efficiency of the reaction (entries 3−6).[6] The addition of a bulkier hydrosilane such as $(Me_3Si)_3SiH$ improved the yield, providing 86% of **10** (entry 6). This catalytic cyclization could also be conducted in nonpolar solvents, such as toluene and dioxane, without significant decrease in yield (entries 8 and 9). In agreement with our mechanistic hypothesis, palladium(0) complexes also served as effective catalyst precursors (entries 9 and 10), which is in sharp contrast to the results from our previous Pd(II)-catalyzed phosphole synthesis.[5]

With optimized reaction conditions in hand, we next examined the scope of substrates for this catalytic cyclization reaction. As depicted in Scheme 3, a wide range of functional groups was tolerated. In particular, phosphacycles containing cyano, ester, amide and carbamate groups (i.e., **13**, **14**, **16**−**19**), which are inaccessible by the classical method using organlithium reagents, could be synthesized successfully. Our catalytic method also

Scheme 3. Palladium-Catalyzed Synthesis of Six-Membered Phosphacycles[a,b]

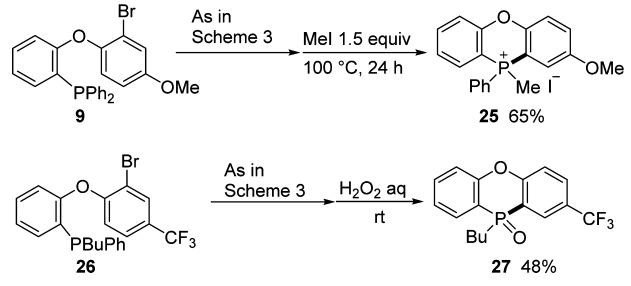


[a]Reaction conditions: bromide (0.30 mmol), $Pd(OAc)_2$ (0.015 mmol), $(Me_3Si)_3SiH$ (0.36 mmol), DMF (0.60 mL), at 130 °C for 12 h. [b]Isolated yield. [c]Substrate (0.30 mmol), $Pd(OAc)_2$ (0.015 mmol), $(Me_3Si)_3SiH$ (0.36 mmol), K_3PO_4 (0.36 mmol), DMF (0.60 mL), at 130 °C for 12 h.

enabled the incorporation of aromatic and heteroaromatic rings other than phenyl, allowing for the synthesis of π-extended phosphacycles, such as those containing naphthalene and carbazole (i.e., **22** and **23**). In addition to the phenoxaphosphinine scaffold, phenophosphazine derivative **24** could also be prepared by using a nitrogen-tethered substrate.

Although we routinely isolated the products as the oxides, the phosphorus center of the resulting phosphacycles can be differently modified through a suitable post-treatment. For example, treatment of phosphacycle **10** (prepared from **9**) with MeI produced the phosphonium salt **25** (Scheme 4). When the substrate bearing a PPhBu group, i.e., **26** was exposed to the catalytic conditions, a phenyl group, rather than a butyl group,

Scheme 4. Synthesis of Phosphonium Salt 25 and P-Alkyl Derivative 27

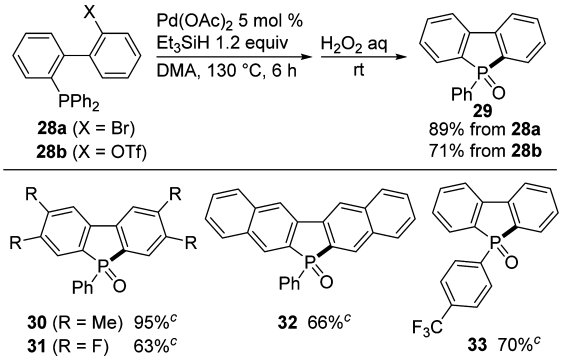


dx.doi.org/10.1021/ol503252t | Org. Lett. XXXX, XXX, XXX−XXX

was eliminated exclusively to deliver a P-alkyl-substituted phosphacycle **27**.[5]

Our catalytic cyclization reaction was also applicable for the synthesis of phosphole derivatives as shown in Scheme 5. In this case, the use of the less bulky Et_3SiH allowed for the formation of phospholes in an efficient manner, presumably because the formation of the six-membered metallacyclic intermediate occurs more easily than the corresponding seven-membered ring, as in **6**. Both bromides and triflates served as the appropriate precursors for the palladium-catalyzed cyclization via C−P bond cleavage. A brief survey of several biaryl substrates demonstrated that a series of fused phosphole derivatives could be synthesized in a similar manner. Unfortunately, the extension of this method to the synthesis of seven-membered phosphacycles was unsuccessful (see the Supporting Information for details).

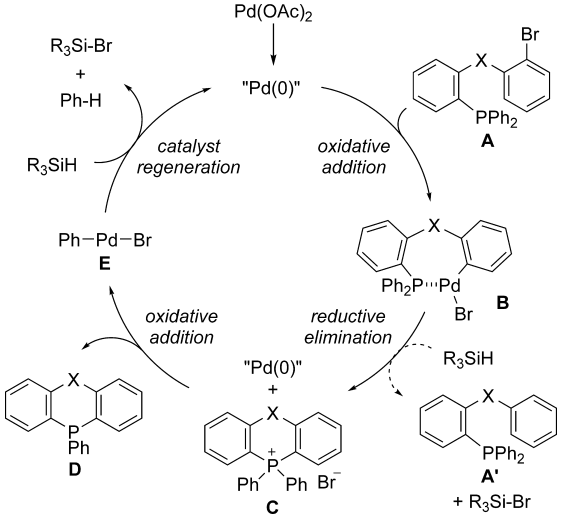
Scheme 5. Palladium-Catalyzed Synthesis of Phosphole Derivatives[a,b]



[a]Reaction conditions: substrate (0.30 mmol), $Pd(OAc)_2$ (0.015 mmol), Et_3SiH (0.36 mmol), DMA (0.60 mL), at 130 °C for 6 h. [b]Isolated yield. [c]Corresponding bromides were used as starting materials.

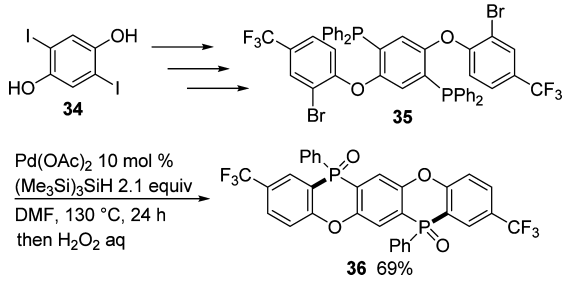
A possible mechanism for the reaction is depicted in Scheme 6. The oxidative addition of bromide **A** to the Pd(0) species initially forms a seven-membered palladacycle **B**. Subsequent C−P bond-forming reductive elimination from **B** generates a cyclic phosphonium salt **C**, along with a Pd(0) species.[7] The P−Ph bond in the phosphonium **C** can be cleaved through oxidative addition to the Pd(0) species,[8] releasing a phosphacycle product **D** and PhPdBr **E**. If intermediate **E** undergoes reductive elimination of PhBr, an active Pd(0) species can be regenerated. However, such a C−halogen bond-forming reductive elimination is known to be thermodynamically unfavorable.[9] Thus, the reaction only proceeded in low yield when the reaction was conducted in the absence of a reducing agent (entry 1, Table 1). Addition of hydrosilane can promote the regeneration of Pd(0) by reductively cleaving Pd(II) intermediate **E** to benzene and silyl bromide, similar to the process involved in the catalytic reductive dehalogenation of aryl halides.[10] When less bulky hydrosilanes were used, reductive debromination of **A** occurs competitively to form **A′**, thus resulting in a lower yield of the desired cyclized product **D**. Bulky $(Me_3Si)_3SiH$ effectively discriminates Pd(II) intermediates **B** and **E**, allowing for the exclusive formation of **D**.

Scheme 6. Possible Mechanism



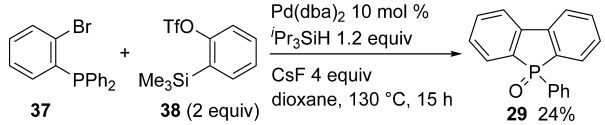
Our method could be useful for the construction of a π-extended ladder-type structure through double cyclization. Bisphosphine **35** prepared from **34** was readily converted to **36** via successive cleavage of C−P bonds (Scheme 7).

Scheme 7. Synthesis of π-Extended Phosphacycle 36



If the palladacycle intermediate that is capable of undergoing C−P bond cleavage, such as **B**, can be assembled in an intermolecular manner, the utility of the method would be further enhanced. One way to achieve such a goal involves a carbopalladation of bromide **37** across an alkyne, which should eventually lead to the formation of the benzophosphole derivative. A preliminary study revealed that our reaction design could be realized by using a benzyne as the alkyne component. Thus, the palladium-catalyzed reaction of bromide **37** with the benzyne precursor **38** in the presence of CsF and hydrosilane afforded the dibenzophosphole **29** in 24% yield (Scheme 8).[11]

Scheme 8. Intermolecular Assembly of Dibenzophosphole via Catalytic C−P Bond Cleavage



In summary, the first catalytic method for the synthesis of P,X-bridged biaryl derivatives was developed. The method features C−P bond cleavage, which allows for the use of tertiary phosphines as a stable and readily available phosphorus source. It proved to be highly compatible with several functional groups including esters, amides, and carbamates. This method overcomes the limitation encountered in the classical method that uses organolithium reagents. Applications of this method to the

dx.doi.org/10.1021/ol503252t | Org. Lett. XXXX, XXX, XXX−XXX

synthesis of other heterocycles through carbon−heteroatom bond cleavage are currently being investigated in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and details pertaining to the characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from The Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan, and ACT-C from JST, Japan. K.B. expresses his special thanks for a JSPS Research Fellowship for Young Scientists. We also thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance with the MS and HRMS.

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(11) The reaction of **37** with diphenylacetylene and 4-octyne produced no desired product under the standard conditions.

dx.doi.org/10.1021/ol503252t | *Org. Lett.* XXXX, XXX, XXX−XXX