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Phosphoryl-Related Directing Groups in Rhodium(III) Catalysis: A General Strategy to Diverse P-Containing Frameworks

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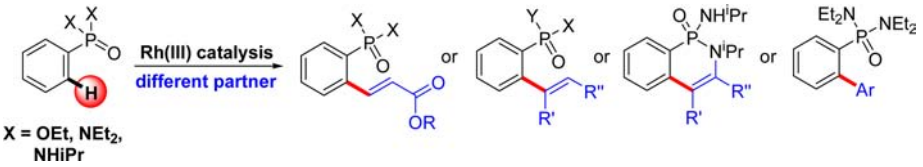
ABSTRACT



Herein, a rhodium(III)-catalyzed oxidative C−H activation of simple arylphosphonates and phosphonamides with subsequent coupling with alkenes (olefination), internal alkynes (hydroarylation and oxidative cyclization), or simple arenes to give access to diverse P-containing functional frameworks is reported.

Functionalized organophosphorus compounds are an important class of molecules due to their ubiquity in biological systems and their potential application in medicinal chemistry, materials chemistry, and catalysis.[1] However, accessible and efficient synthetic methods to modify these privileged organophosphorus structures are surprisingly underrepresented. Traditional strategies for the modification of organophosphorus compounds usually suffer from a limited substrate scope as well as nontrivial multistep reaction sequences.[2] Therefore, methods for the direct functionalizations of phosphonates and phosphonamides are desirable. This would give rise to the late stage functionalization of natural products and biologically active compounds. In recent years C−H bond activation has become a common technique to activate and functionalize aromatic C−H bonds *ortho* to coordinating functional (directing) groups. For this reason Cp*Rh(III)-catalyzed C_{sp^2} C−H activation with subsequent cross-coupling with alkenes (olefination), alkynes (hydroarylation and oxidative cyclization),[4,5] and/or simple arenes (C−H/C−H dehydrogenative coupling) is a rapidly evolving research field.[3] A wide range of carbonyl-derived directing groups have been used for this transformation.[4−6] Because there is a remarkable similarity in reactivity between these carbon species and their phosphorus counterparts, we anticipated that the phosphonate and phosphonamide analogues would have similar potential as directing groups (Scheme 1). It is also important to note that a variety of aryl phosphonate esters are commercially available or are

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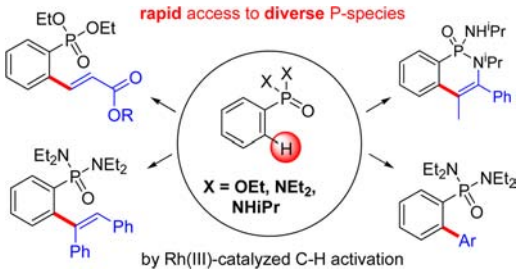
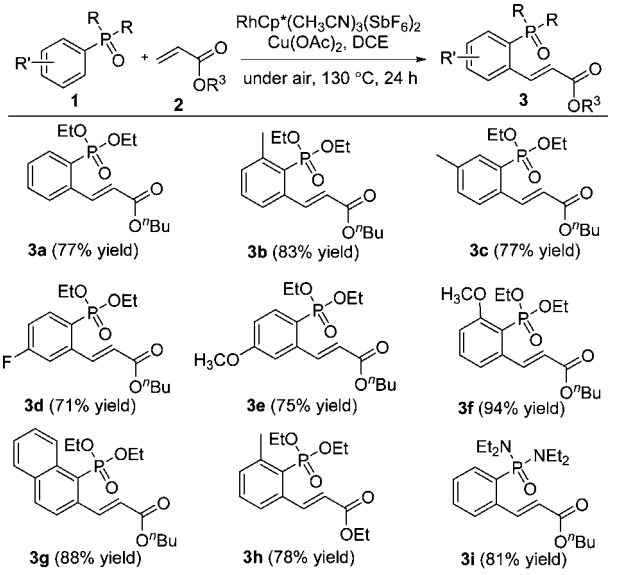
readily prepared by known procedures. While Kim and coworkers recently reported the use of benzyl- and phenoxyphosphonic *acids* as competent directing groups for palladium(II) and during the preparation of this manuscript, Lee and Miura reported the Rh(III)-catalyzed oxidative cyclization of alkynes and arylphosphonic acid; however, simple arylphosphonates and phosphonamides as directing groups in Rh(III) catalysis are still unknown and also until now no example exists for Rh(III)-catalyzed phosphoryl-related group directed hydroarylation and C−H/C−H coupling reaction.[7,8] Herein, we report a rhodium(III)-catalyzed oxidative C−H activation of simple arylphosphonate esters and phosphonamides and subsequent coupling with alkenes (Heck reaction), internal alkynes (hydroarylation and oxidative cyclization), or simple arenes (dehydrogenative coupling) to give access to diverse P-containing functional frameworks (Scheme 1).

Scheme 1. Arylphosphonates and Phosphonamides As Directing Groups in Rh(III) Catalysis



Our preliminary investigation focused on the oxidative Heck-type coupling of diethyl phenylphosphonate (**1a**) with *n*-butyl acrylate. After screening several parameters (Table S1 in the Supporting Information), the product **3a** was obtained in 77% isolated yield in the presence of the pregenerated cationic rhodium species $RhCp^*(CH_3CN)_3(SbF_6)_2$ (2.5 mol %), and $Cu(OAc)_2$ (1.0 equiv) in DCE under air at 130 °C for 24 h (Table S1, entry 14). Subsequently, we examined the scope of olefins as well as aryl phosphonates and phosphonamides in the oxidative Heck-type reaction. Overall, we were pleased with the generality of this method. As shown in Scheme 2,

Scheme 2. Scope of the Oxidative Heck Reaction with Diverse Aryl Phosphonates and Olefins



regardless of the electronic and steric effects, the phosphonates and phosphonamides were coupled smoothly with olefins to afford the desired 2-(1-alkenyl)phenylphosphonates and 2-(1-alkenyl)phenyl phosphonamides in satisfactory yields (Scheme 2, **3a**−**i**). The position of an additional substituent on substrates had little effect on the reaction efficiency as shown in the cases of diethyl phenylphosphonates bearing a methyl or methoxy substituent at the 2-, 3-, or 4-position (**3b**, **3c**, **3e**, and **3f**, respectively). As expected the reactions occurred preferentially at the more sterically accessible position when a *meta*-substituent is present in the phenyl ring of the aryl phosphonates (Scheme 2, **3c**). This method was remarkably compatible with a variety of important functional groups such as fluorine, and methoxy groups, which could be subjected

(4) For selected examples of the carbonyl-derived directing groups in the Rh(III)-catalyzed oxidative Heck reaction, see: (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (b) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 3024. (c) Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett.* **2011**, *13*, 2372. (d) Wang, F.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5430. (e) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (f) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064. (g) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (h) Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7167. (i) Willwacher, J.; Rakshit, S.; Glorius, F. *Org. Biomol. Chem.* **2011**, *9*, 4736. (j) Gong, T.-J.; Xiao, B.; Liu, Z.-J.; Wan, J.; Xu, J.; Luo, D.-F.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 3235. (k) Zhao, P.; Niu, R.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 4166.

(5) For selected examples of carbonyl-derived directing groups in the Rh(III)-catalyzed reaction with alkynes (hydroarylation and oxidative cyclization), see: (a) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (b) Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910. (c) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (d) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (e) Huestis, M.; Chan, P. L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338. (f) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (g) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2154. (h) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 4169. (i) Li, B.; Ma, J.; Liang, Y.; Wang, N.; Xu, S.; Song, H.; Wang, B. *Eur. J. Org. Chem.* **2013**, 1950. (j) Pham, M. V.; Ye, B.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 10610.

(6) Until now, only a few examples of carbonyl-derived directing groups in Rh(III)-catalyzed dehydrogenative cross-coupling, see: (a) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 2247. (b) Morimoto, K.; Ioh, M.; Hirano, K.; Satoh, T.; Shibata, Y.; Tanaka, K.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 5359. (c) Wencel-Delord, J.; Nimphius, C.; Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 13001.

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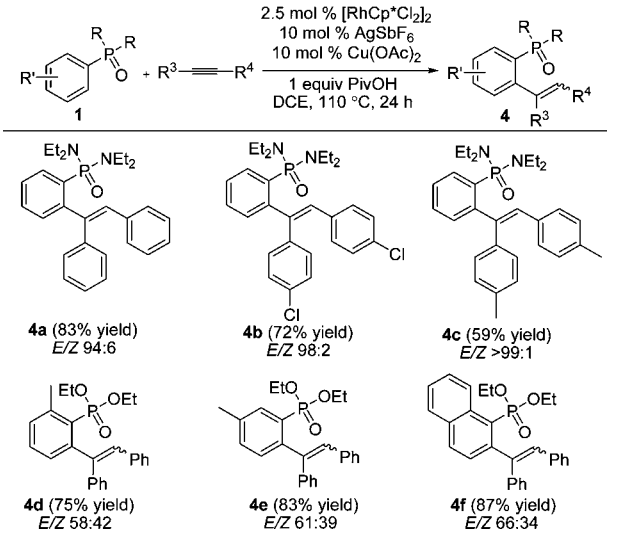
to further synthetic transformations (Scheme 2, **3d**–**f**). We ran two competition experiments to compare the directing group ability of the P=O ester with a carboxylic acid ester and an amide. For ethyl benzoate, we obtained a mixture of 2-(1-alkenyl)phenylphosphonate and 2-(1-alkenyl)-phenylbenzoate (approximately 1:1). For acetanilide, we only detected the product of 2-(1-alkenyl) acetanilide but no 2-(1-alkenyl)phenylphosphonate.

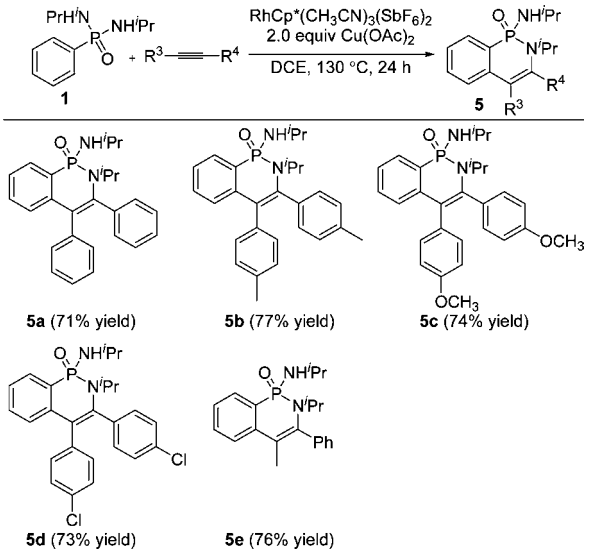
Scheme 3. Scope of the Rh(III)-Catalyzed Hydroarylation of Aryl Phosphonates and Phosphonamides



Having optimized the reaction of olefins with phosphonates and phosphonamides, we began studying the alkyne hydroarylation, an important method for the synthesis of highly substituted alkene derivatives. After optimization we found that $[RhCp^*Cl_2]_2$ with $AgSbF_6$ in combination with 10 mol % $Cu(OAc)_2$ and 1.0 equiv PivOH as an additive at 110 °C exhibited moderate catalytic activity in the hydroarylation reaction of diverse aryl phosphonates and phosphonamides (Scheme 3). The stereoselectivity of this reaction was found to be sensitive to the electronic property of the directing group. The use of phosphonate esters produced a mixture of olefinic *E*- and *Z*-isomers, while phosphonamides provided the corresponding *E*-alkene derivatives **4a**, **4b**, and **4c** stereoselectively in 83%, 72%, and 59% yields, respectively (Scheme 3).

The rhodium-catalyzed oxidative couplings of various aromatic substrates possessing a directing group with internal alkynes allows the straightforward synthesis of benzannulated heterocyclic compounds from readily available monofunctionalized aromatic substrates.[5] Recent studies have indicated that a number of heterocycle analogues containing phosphorus show similar bioactivity to their carbon counterparts. Phosphaisoquinolin-1-ones may have bioactivities similar to those of isoquinolin-1-ones, which have gained considerable pharmacological interest because of their diverse bioactivities. We hoped to apply the rhodium-catalyzed oxidative cyclization methodology between aromatic phosphonamides and internal

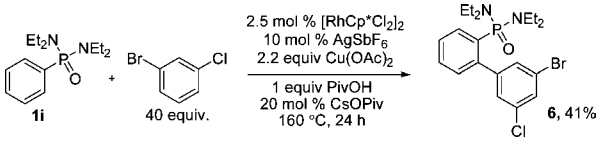
Scheme 4. Scope of the Rh(III)-Catalyzed Oxidative Cyclization of Aryl Phosphonates and Phosphonamides



alkynes to construct six-membered phosphaisoquinolin-1-one derivatives. After optimization, we found that, by treating phenylphosphonamide (**1a**) with diphenylacetylene, the oxidative cyclization product (**5a**) could be obtained in 71% yield. The scope of the reaction is outlined in Scheme 4. With respect to the scope of alkynes **3**, we found that the often reluctant diaryl alkynes work well (Scheme 4, **5a**–**d**) and that unsymmetrical alkynes display good regioselectivities (Scheme 4, **5e**). Unfortunately, our catalytic system does not tolerate terminal alkynes.

Furthermore, the preliminary result shows that the dehydrogenative cross-coupling of the aryl phosphonamide and simple arenes could also be achieved in moderate yield. When phosphonamide **1i** was treated with 40 equiv of 3-chlorobromobenzene as solvent under the previously reported reaction conditions,[6a] biaryl **6** was formed in 41% yield (Scheme 5). This cross-coupling represents a 2-fold C–H activation and allows rapid access to biaryl phosphorus derivates.

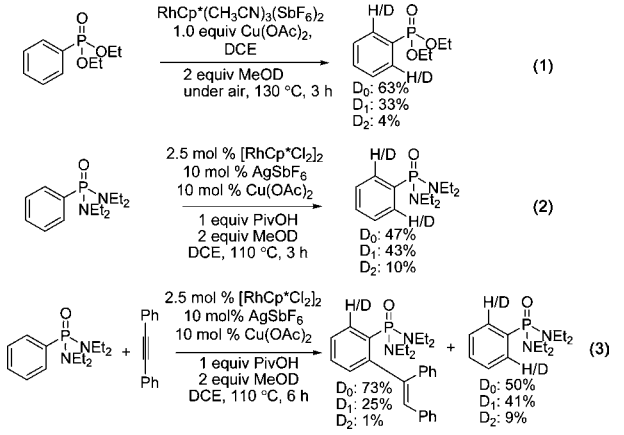
Scheme 5. Dehydrogenative Cross-Coupling of a Phosphonamide with a Simple Arene



To gain some insight into the mechanism, we conducted a series of deuteration experiments, looking for H/D scrambling to check the reversibility of the C–H activation step. Running the olefination and hydroarylation reaction without the acrylate or alkyne using methanol-d_4 under otherwise standard conditions, but with a decreased reaction time, showed a significant amount of H/D scrambling for the arylphosphonate (Scheme 6, eq 1) and phosphonamide

(Scheme 6, eq 2).[9] Running the hydroarylation reaction under standard conditions, but with a decreased reaction time and using methanol-d_4 as the deuterium source, resulted in significant H/D scrambling in the starting material, and the product of the hydroarylation (Scheme 6, eq 3) could be observed. These results support that the C−H activation is reversible.

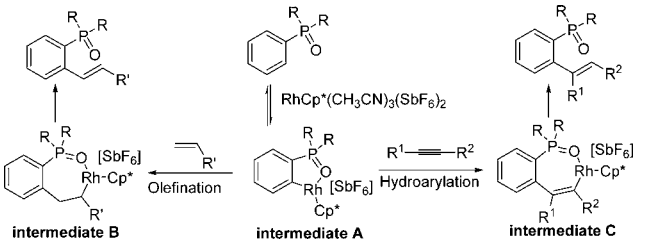
Scheme 6. Deuteration Experiments Probing the Reversibility of the C−H Activation Step



Although a more detailed investigation of the reaction mechanism is currently underway, from these preliminary mechanistic results we proposed a plausible catalytic mechanism as illustrated in Scheme 7.[4−6] The catalytic process is initiated by coordination with the phosphoryl-related directing group to generate the five-membered rhodacycle intermediate **A**. Subsequently, the seven-membered rhodacycle intermediate **B** or **C** is formed through insertion of alkene or alkyne into the rhodium−carbon bond of intermediate **A**. For oxidative cyclization we propose that P−NH acts as the directing group to form the five-membered intermediate, followed by insertion of the alkyne and oxidative annulation to obtain the product.

(9) Graczyk, K.; Ma, W.; Ackermann, L. *Org. Lett.* **2012**, *14*, 4110.

Scheme 7. Plausible Mechanism for the Rh(III)-Catalyzed Olefination and Hydroarylation of Aryl Phosphonates



In summary, we have demonstrated that simple arylphosphonates and phosphonamides can act as directing groups in Rh(III) catalysis. Using these phosphoryl-related directing groups, we developed the rhodium(III)-catalyzed oxidative C−H activation of simple arylphosphonates and phosphonamides and subsequent coupling with alkenes (olefination), internal alkynes (hydroarylation and oxidative cyclization), and simple arenes (C−H/C−H dehydrogenative cross-coupling) to give access to diverse P-containing frameworks including 2-(1-alkenyl)-phenylphosphonates, phosphaisoquinolin-1-ones, and biaryl phosphorus species.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.