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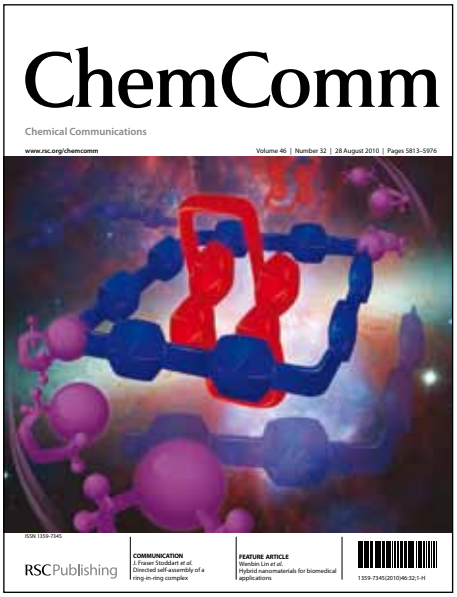

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ARTICLE TYPE

Rhodium-Catalyzed Oxidative Coupling through C□H Activation and Annulation Directed by Phosphonamide and Phosphinamide Group‡,†

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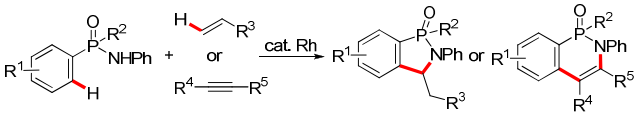
Rhodium-catalyzed oxidative couplings *via* C□H activation and annulation directed by phosphonamide and phophinamide group were developed under aerobic conditions, which produced benzazaphosphole 1-oxides and phosphaisoquinolin-1-oxides with high selectivity, a wide substrate scope and an excellent functional group tolerance.

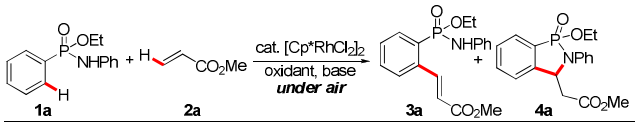
Transition-metal-catalyzed C□H bond activations have been established to be a very efficient process for the formation of C□C and C□heteroatom bonds.[1] In general, *ortho* C□H bond activation can be achieved by the application of a multitude of directing groups with the assitance of coordination of transition metals. In a variety of directing groups for C□H bond activations,[2] carboxyl and hydroxyl compounds[3] and nitrogen-containing ones[4,5] have been extensively explored. We have recently interested in development of new phosphoryl-related directing groups[6] in the C□H bond activations and its application to synthesis of phosphorus heterocyclic compounds.[6a,7] Although the oragnophosphorus compounds have been recognized as crucial compounds in the area of pharmaceutical and agricultural chemistry,[8] their employment in transition-metal-catalyzed C□H bond activations has been barely studied.[9] Therefore, development of efficient C–H activation using phosphorus-related directing group is stimulating. Herein, we report Rh-catalyzed annulation reaction through C□H activation of phosphonamides and phosphinamides under aerobic conditions, thus producing benzazaphosphole 1-oxides and phosphaisoquinolin-1-oxides (Scheme 1).[10]



Scheme 1 Rh-catalyzed C-H activation and annulations.

To search the usefulness of the phosphonamide-based directing groups in the C–H activation, we embarked on our studies with ethyl *N*-phenyl phenylphosphonamidate (**1a**) as shown in Table 1. First, when $[Cp^*RhCl_2]_2$ (4 mol %) and Ag_2CO_3 (2 equiv) in acetonitrile (110 °C, 20 h) under air[11] were applied to cyclization of **1a**, the reaction did not proceed (entry 1). Use of *t*-BuOH and toluene gave *ortho*-alkenylated product **3a** and *ortho*-alkenylation followed by *aza*-Michael reaction product **4a** in trace (entries 2 and 3). Among the solvents tested, xylene gave **4a** in 23% yield (entry 6). After surveying a wide array of bases (See the SI), we observed CsOPiv gave the best reactivity (entries 7-9). Next, a variety of oxidants were examined in the presence of CsOPiv in xylene. The reaction was relatively sensitive to the choice of oxidants used, and AgOAc and $Na_2S_2O_8$were not effective (entries 11 and 12). The oxidants, Ag_2O and TEMPO, gave moderate conversion of the starting **1a** (entries 10 and 13). To our delight, TEMPO (2 equiv) and CsOPiv (0.75 equiv) in xylene turned out to be the most effective and resulted in the complete consumption of **1a** to produce selectively benzazaphosphole 1-oxide **4a** in 88% yield (entry 14). When CsOPiv was not used (entry 15), the reaction did not proceed because deprotonation of **1a** could occur to give the corresponding salt which trigger C−H activation in a similar manner to that of benzoic acid substrates.[12]

Table 1 Reaction optimization[a]



Entry	Oxidant (equiv)	Base (equiv)	Solvent	Yield[b] (%) 3a	4a
1	Ag_2CO_3 (2)	none	MeCN	0	0
2	Ag_2CO_3 (2)	none	*t*-BuOH	2	2
3	Ag_2CO_3 (2)	none	toluene	4	2
4	Ag_2CO_3 (2)	none	PhCl	0	8
5	Ag_2CO_3 (2)	none	dioxane	18	13
6	Ag_2CO_3 (2)	none	xylene	0	23
7	Ag_2CO_3 (2)	NaOAC (0.5)	xylene	8	39
8	Ag_2CO_3 (2)	Na_2CO_3 (0.5)	xylene	8	17
9	Ag_2CO_3 (2)	CsOPiv (0.5)	xylene	0	42
10	Ag_2O (2)	CsOPiv (0.5)	xylene	0	43
11	AgOAc (2)	CsOPiv (0.5)	xylene	0	14
12	$Na_2S_2O_8$ (2)	CsOPiv (0.5)	xylene	0	6
13	TEMPO (2)	CsOPiv (0.5)	xylene	0	59 (60)
14	TEMPO (2)	CsOPiv (0.75)	xylene	0	84 (88)[c]
15	TEMPO (2)	none	xylene	0	0

[a] **1a** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), solvent (0.8 mL) at 110 °C for 20 h. [b] Yield were determined by ^1H NMR intergration methods with CH_2Br_2 as an internal standard. [c] Isolated yield.

With these results in hand, various phosphonamides (**1**) were investigated under the standard conditions using methyl acrylate (Scheme 2). Substrate having 2-methyl group on the *P*-phenyl ring underwent *ortho*-alkenylation followed by *aza*-Michael reaction, thus providing benzazaphosphole 1-oxide

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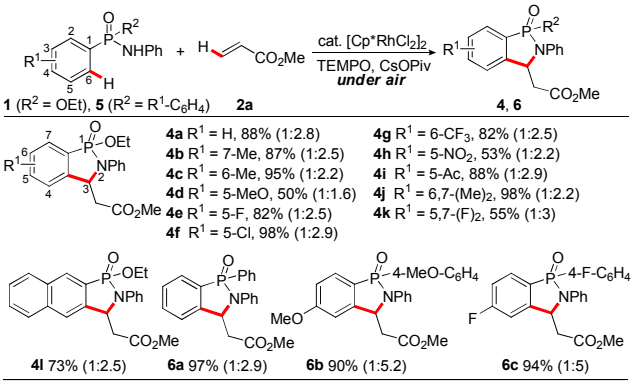
4b in 87% yield (*dr* = 1:2.5). Rh-catalyzed oxidative cyclization of 3-methyl substrate with **2a** took place regioselectively at the sterically less hindered position to provide **4c** (95%) possessing methyl group on 6-position. Phosphonamide bearing electron donating 4-methoxy group gave the cyclic compound **4d** in 50% yield. Functional groups commonly used in organic synthesis were tolerated. When 4-fluoro and 3-trifluoromethyl substituted phosphonamides were used, the corresponding cyclized products (**4e** and **4g**) were obtained in 82% yield, respectively. Substrates having 4-chloro and 4-acetyl group was oxidatively cyclized to give **4f** and **4i** in high yields. The tolerance of fluoro and ketone group on the phenyl ring is especially valuable, affording an opportunity for further functionalization. The cyclized product **4h** was obtained in 53% yield albeit the presence of strong electron-withdrawing nitro group. When substrate possessing 2,3-dimethyl group was subjected to the standard conditions, the desired tandem product **4j** was isolated in 98% yield. However, 2,4-difluoro substituted phosphonamide was less reactive due to electronic effect, thus providing the cyclized product **4k** in 55% yield. 2-Naphthalenylphosphonamide worked well too. When *N*,*P*,*P*-triphenylphosphinamide (**5a**) was treated with rhodium catalyst, the cyclized product **6a** was obtained in 97% yield (*dr* = 1:2.9). Also, substrates having 4-methoxy and 4-fluoro group were smoothly converted to benzazaphosphole 1-oxides **6b** and **6c** in 90% and 94% yields, respectively.

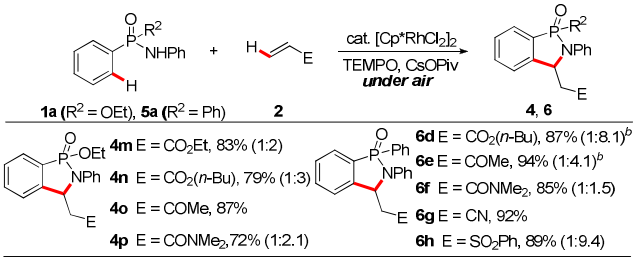


[a] **1** or **5** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), TEMPO (0.4 mmol), CsOPiv (0.15 mmol), xylene (0.8 mL) at 110 °C for 20 h. Ratios in parentheses indicate diastereomeric ratios by ^{1}H NMR.

Scheme 2 Arylphosphonamides and arylphosphinamides scope.[a]

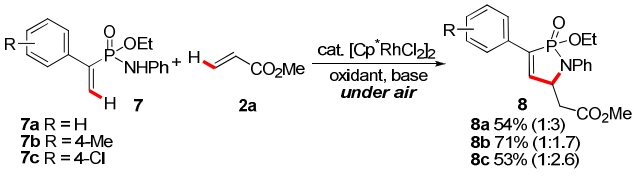
As shown in Scheme 3, the scope of the oxidative cyclization is extensive and various electron-deficient alkenes could be successfully employed in the tandem *ortho*-alkenylation and *aza*-Michael reaction. Methyl vinyl ketone and *N*,*N*-dimethylacrylamide reacted with **1a** to furnish the corresponding benzazaphosphole 1-oxide **4o** and **4p** in 87% and 72% yields, respectively. Similarly, acrylonitrile and vinyl sulfone also worked well with **5a** producing **6g** and **6h** in excellent yields.

We also examined Rh-catalyzed oxidative cyclization of alkenylphosphonamides **7** with methyl acrylate (Scheme 4). The use of DCE as the solvent was necessary to obtain acceptable yields with substrates **7**. When α-styrylphosphonamide (**7a**) was treated with **2a** under the optimum conditions, the corresponding product **8a** was obtained in 54% yield through tandem *ortho*-alkenylation and *aza*-Michael reaction. Electronic variation of substituents on the arene moiety of **7** had a little affected on the reaction efficiency. Although **7c** having electron-withdrawing chloro group on the phenyl ring was cyclized to provide **8c** in 53% yield, substrate **7b** bearing electron-donating methyl group underwent the cyclization with **2a**, producing azaphosphole 1-oxide **8b** in 71% yield.



[a] **1a** or **5a** (0.2 mmol), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), TEMPO (0.4 mmol), CsOPiv (0.15 mmol), xylene (0.8 mL) at 110 °C for 20 h. Ratios in parentheses indicate diastereomeic ratios by ^{1}H NMR. [b] Diastereomeric ratio after isolation.

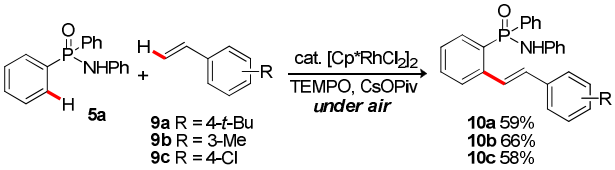
Scheme 3 Activated alkenes scope.[a]



[a] **7** (0.2 mmol), **2a** (0.8 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $Cu(OAc)_2$ (0.2 mmol), Cs_2CO_3 (0.4 mmol), DCE (0.8 mL) at 80 °C for 30 h. Ratios in parentheses indicate diastereomeric ratios by ^{1}H NMR.

Scheme 4 Alkenylphosphonamides scope.[a]

In contrast to activated alkenes, when non-activated alkenes were employed in Rh-catalyzed C□H activation, only *ortho*-alkenylation occurred to give the corresponding products **10** (Scheme 5). For example, exposure of **5a** to 4-*t*-butylstyrene **9a** in the presence of Rh catalyst, TEMPO and CsOPiv in toluene under aerobic conditions provided **10a** in 59% yield. Likewise, the use of 3-methyl- and 4-chlorostyrene furnished the *ortho*-alkenylated products (**10b** and **10c**) in good yields.



[a] **5a** (0.2 mmol), **9** (1.8 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), TEMPO (0.4 mmol), CsOPiv (0.15 mmol), toluene (0.8 mL) at 110 °C for 20 h.

Scheme 5. Non-activated alkenes scope.[a]

Next, Rh-catalyzed oxidative couplings *via* C□H activation and annulation from **5a** and various alkynes were investigated (Scheme 6). When **5a** was treated with various alkynes **11** under the optimum conditions, the phosphaisoquinolin-1-ones **12** were obtained in good to excellent yields through Rh-catalyzed cyclization. Dialkylacetylenes such as hex-3-yne and dec-5-yne

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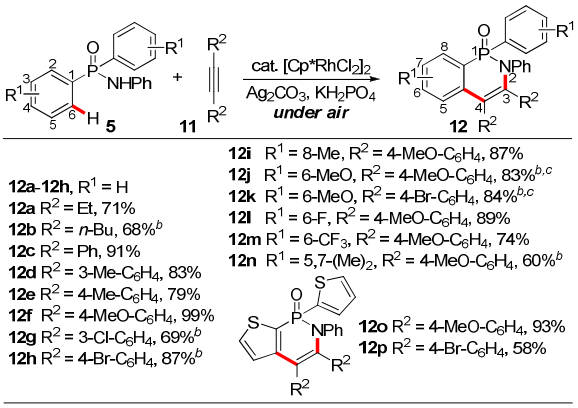
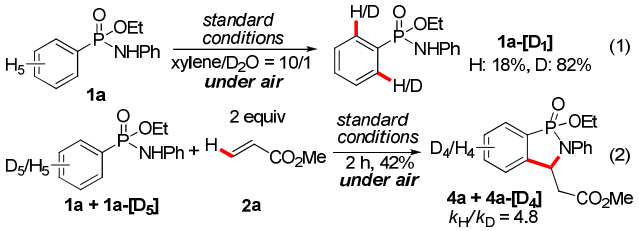
turned out to be compatible with the reaction conditions. We were please to observe that **5a** was readily reacted with electron-rich and electron-deficient diarylacetylenes as well. The tolerance of chloro and bromo group is especially important, as following catalytic cross-couplings are promising. Electron-rich arylphosphinamide **5** having methyl, methoxy, fluoro and trifluoromethyl group on the *P*-phenyl ring were cyclized to afford the corresponding phosphaisoquinolin-1-ones in good to excellent yields. Substrate having 3,5-dimethyl group was smoothly activated and annulated to furnish **12n** in 60% yield. Phosphinamide bearing 1-thiophenyl group underwent the oxidative cyclization in reasonable yield.



[a] **5** (0.15 mmol), **11** (0.3 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), Ag_2CO_3 (0.3 mmol), KH_2PO_4 (0.15 mmol), *t*-BuOH (1.5 mL) at 110 °C for 16 h. [b] Reaction time: 30 h. [c] Reaction temperature: 130 °C.

Scheme 6 Scope of arylphosphinamides and alkynes. [a]

To obtain insight into the reaction mechanism, a catalytic C□H bond transformation in the presence of D_2O performed, thereby affording a remarkable D/H exchange in the *ortho*-position of the recovered starting material **1a-[D$_1$]** (eq 1, Scheme 7). A significant kinetic isotope effect (KIE) was detected (k_H/k_D = 4.8), suggesting that the C□H bond cleavage at the *ortho*-position of phosphonamide is most likely involved in the rate-determining step (eq 2).



Scheme 7 Studies with isotopically labeled compounds.

In summary, we have developed an efficient rhodium-catalyzed oxidative couplings *via* C□H activation and annulation using arylphosphonamides and arylphosphinamides under aerobic conditions, which produced benzazaphosphole 1-oxides and phosphaisoquinolin-1-oxides with high selectivity, a wide substrate scope and an excellent functional group tolerance.

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Notes and references

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‡ This paper is dedicated to Professor Nakcheol Jeong on the occasion of his 60th birthday.

§ Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds.]. See DOI: 10.1039/b000000x/

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