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Rhodium-Catalyzed Oxidative Cyclization of Arylphosphonic Acid Monoethyl Esters with Alkenes: Efficient Synthesis of Benzoxaphosphole 1-Oxides

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ABSTRACT

Rhodium-catalyzed tandem oxidative alkenylation and an intramolecular *oxy*-Michael reaction were developed using arylphosphonic acid monoethyl esters and alkenes under aerobic conditions, which produced benzoxaphosphole 1-oxides in good to excellent yields.

C−H bond functionalizations catalyzed by transition metals have been demonstrated to be a very streamlined method for the formation of C−C and C−heteroatom bonds.[1] In particular, *ortho* C−H bond functionalizations can be accomplished by the employment of a variety of directing groups with the aid of coordination of transition metals. In a number of directing groups for C−H bond functionalizations,[2] nitrogen-containing compounds,[3−5] carboxyl and hydroxyl ones[6,7] have been broadly investigated.

Recently, our attention in the C−H bond functionalizations catalyzed by transition metals has been concentrated

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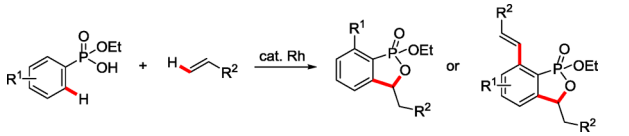
on phosphoryl-related directing groups.[8] Although the phosphonic acid and its derivatives have been used as essential compounds in the field of organic, bioorganic, and medicinal chemistry,[9] their application in C−H bond functionalizations catalyzed by transition metals has been scarcely investigated.[10,11] Furthermore, the structural variation of phosphonic acid derivatives would be more flexible than that of carboxylic acid derivatives by introduction of different groups to the pentavalent phosphorus atom. In this regard, we have been interested in developing an efficient synthetic method for a wide range of organophosphorus compounds with the purpose of making focused chemical libraries effective for chemical biology study and drug discovery.[8,12]

Previously, Miura reported that benzoic acid reacted with acrylate, acrylamide, and acrylonitrile in the presence of rhodium catalyst to afford 7-vinylphthalide along with its dehydrogenated derivative.[13] Also, Ackermann have disclosed ruthenium-catalyzed oxidative C−H bond alkenylations.[14] Herein, we report for the first time rhodium-catalyzed tandem oxidative alkenylation and intramolecular *oxy*-Michael reaction using arylphosphonic acid monoethyl esters and alkenes under aerobic conditions, thus producing benzoxaphosphole 1-oxides which have been barely studied (Scheme 1).[15] Furthermore, tandem dialkenylation and *oxy*-Michael reaction are described.

Scheme 1. Rhodium-Catalyzed Oxidative Cyclization Using Arylphosphonic Acid Monoethyl Esters



We began by screening the reaction between *ortho*-tolylphosphonic acid monoethyl ester **1a** and methyl acrylate **2a** in the presence of $[Cp^*RhCl_2]_2$ as a catalyst and AgOAc as an oxidant with a variety of bases and solvents (Table 1). Reactions with a base gave a mixture of the cyclized product **3a** and alkenylated product **4a** (entries 1−8). Following alkenylation of phosphonic acid, alkenylated product **4a** undergoes *oxy*-Michael reaction to give the corresponding **3a** product. Among the intensive bases tested, Na_2HPO_4 was found to enhance the selectivity of the product ratio (entry 4). However, the tandem reaction was not completed still and thus, intermediate **4a** was produced in 28% yield. Accordingly, a number of solvents such as *t*-AmOH, 1,4-dioxane, DMF, xylene, toluene, and CH_3CN were examined in the presence of Na_2HPO_4. Although xylene and toluene provided **3a** in good yields, **4a** did not entirely disappear during the tandem reaction (entries 12 and 13). Further screening of the solvent revealed that the use of CH_3CN as a solvent improved the yield of **3a** to 89% (85% isolated yield, *dr* = 1:1.1) (entry 14). Notably, *ortho*-alkenylated product **4a** was not detected. When Na_2HPO_4 was not used (entry 15), 19% of **3a** was only observed because deprotonation of the phosphonic acid monoethyl ester to give the corresponding salt which triggers C−H activation in a similar manner to that of benzoic acid substrates did not occur effectively.[16]

Reactions of **1a** with various electron-deficient alkenes **2** were carried out under the optimized conditions to determine the scope and limitations of the present method (Scheme 2). The scope of the tandem *ortho*-alkenylation and *oxy*-Michael reaction is broad, and various electron-deficient alkenes could be successfully employed. *n*-Butyl acrylate reacted with **1a** to furnish **3b** in 87% yield. Methyl vinyl ketone and ethyl vinyl ketone worked well too (**3c** and **3d**). When **1a** was subjected to acrylonitrile, the cyclized product **3e** was isolated in 90% yield. We were pleased to obtain benzoxaphosphole 1-oxide **3f** (71%) from **1a** and *N*, *N*-dimethyl acrylamide. Vinyl phosphate and vinyl sulfone (3 equiv) reacted with **1a** to afford **3g** and **3h** in 61% and 71% yields, respectively. However, styrene, 4-phenyl-1-butene, cyclohexene, vinyltriethoxysilane, and vinyltrimethylsilane failed to give benzoxaphosphole 1-oxide.

With these results in hand, diverse arylphosphonic acid monoethyl esters were examined under the standard conditions using methyl acrylate (Scheme 3). A substrate

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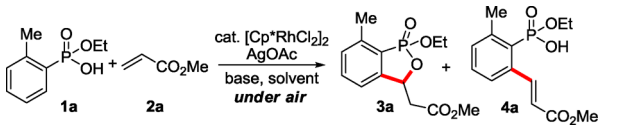
Table 1. Reaction Optimization[a]



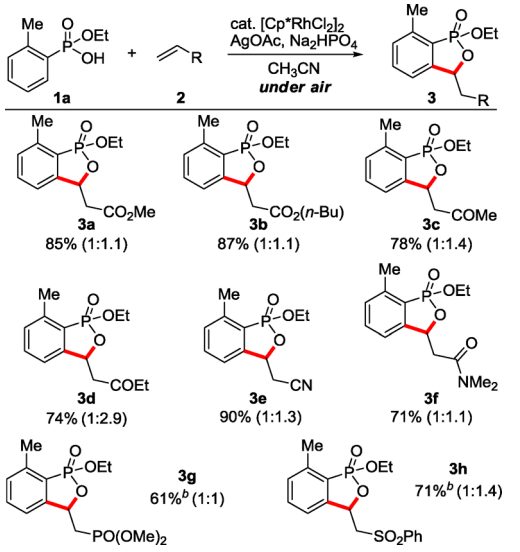
entry	base	solvent	yield (%)[b,c]
1	LiOAc	*t*-BuOH	42 (57)
2	Li_2CO_3	*t*-BuOH	47 (50)
3	$NaHCO_3$	*t*-BuOH	16(77)
4	Na_2HPO_4	*t*-BuOH	63 (28)
5	KH_2PO_4	*t*-BuOH	31 (69)
6	K_2HPO_4	*t*-BuOH	55 (45)
7	K_2CO_3	*t*-BuOH	26 (58)
8	CsF	*t*-BuOH	25 (49)
9	Na_2HPO_4	*t*-AmOH	35 (57)
10	Na_2HPO_4	1,4-dioxane	39 (53)
11	Na_2HPO_4	DMF	55(17)
12	Na_2HPO_4	xylene	65(12)
13	Na_2HPO_4	toluene	66(13)
14	Na_2HPO_4	CH_3CN	89 (1<, 1:1.1[d])
15	none	CH_3CN	19 (23, 56[e])

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2 equiv), $[Cp^*RhCl_2]_2$ (4 mol %), AgOAc (2 equiv) in solvent (2 mL) at 110 °C for 16 h. [b] ^1H NMR yields of **3a** using CH_2Br_2 as an internal standard. [c] Numbers in parentheses are ^1H NMR yield of **4a**. [d] Diastereomeric ratio. [e] Yield of **1a**.

having a 2-ethyl and 2-methoxy group on the phenyl ring promoted alkenylation followed by *oxy*-Michael reaction, thus producing the benzoxaphosphole 1-oxides **3i** and **3j** in 89% and 85% yields, respectively. Reaction with 2-phenylated phosphonic acid monoethyl ester **1k** also produced the cyclized product **3k** in quantitative yield (98%). Substrate **1l** possessing an electron-withdrawing chloro group was all smoothly cyclized to provide **3l** in 80% yield. The tolerance of the chloro group is particularly important, as the following catalytic cross-couplings are hopeful. When substrate **1m** bearing a 2,3-dimethyl group was subjected to the standard conditions, the desired tandem product **3m** was isolated in 90% yield. However, 2,5-dimethyl substituted substrate **1n** was less reactive due to the steric effect and the cyclized product **3n** was isolated in 35% yield along with the starting material (65%). Arylphosphonic acid monoethyl ester **1o** having both a 2-methyl and 4-methoxy group was cyclized to **3o** in 86% yield. Substrate **1p** bearing a 1-naphthalenyl group worked well too, resulting in the formation of **3p** in 82% yield.

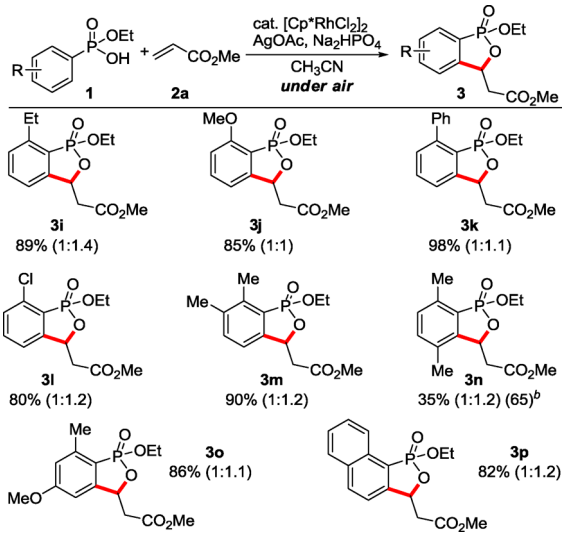
Next, when phenylphosphonic acid monoethyl ester was treated with methyl acrylate under the standard conditions, 7-alkenylated benzoxaphosphole 1-oxide **5a** was obtained selectively in 76% yield through tandem dialkenylation and an *oxy*-Michael reaction (Scheme 4). Surprisingly, 7-alkenylated benzoxaphosphole 1-oxide having an *exo*-methylene group at the 3-position was not contaminated.[13] Subjecting substrates having a methyl and methoxy group at the *para*-position to **2a** furnished **5b** and **5c** in 75% and 77% yields, respectively. Functional groups

Scheme 2. Rh-Catalyzed Oxidative Cyclization of **1a**[a]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (2 equiv), $[Cp^*RhCl_2]_2$ (4 mol %), AgOAc (2 equiv), Na_2HPO_4 (1 equiv), and CH_3CN (2 mL) at 110 °C for 16 h. Isolated yields. Numbers in parentheses indicate diastereomeric ratio. [b] Alkene (3 equiv) and CH_3CN (1 mL) were used.

Scheme 3. Rh-Catalyzed Oxidative Cyclization[a]

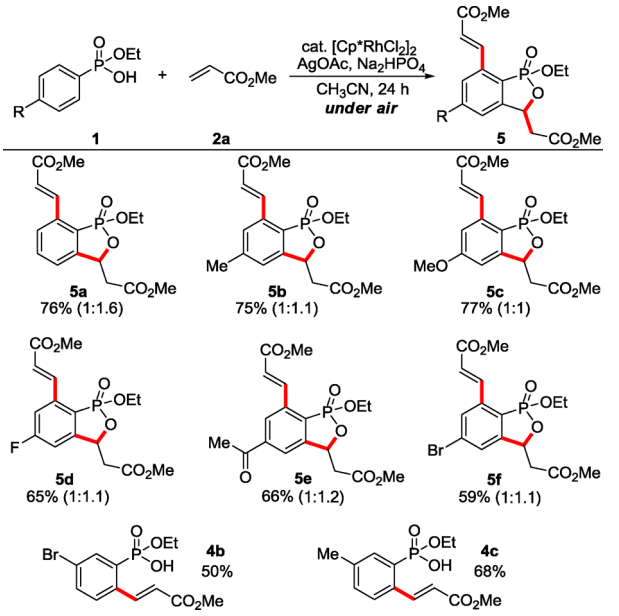


[a] Numbers in parentheses indicate diastereomeric ratio. [b] Recovery yield of starting material.

commonly used in organic synthesis were tolerated. When electron-withdrawing 4-fluoro and 4-acetyl substituted phosphonic acids were used, the corresponding cyclized products **5d** and **5e** were obtained in good yields. The tolerance of the fluoro and ketone group on the phenyl ring is especially useful, providing an opportunity for further functionalization. A substrate bearing a 4-bromo group was smoothly cyclized to provide **5f** in 59% yield. However, when substrates having a 3-bromo and 3-methyl group were subjected to the Rh-catalyst, *ortho*-alkenylation

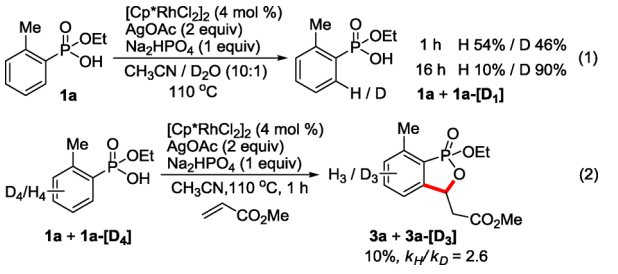
only occurred and then, 2-alkenylated products **4b** and **4c** were obtained in 50% and 68% yields, respectively. It seems that a subtle balance between the steric and electronic properties of the substituent on the phenyl ring is needed for the tandem reaction.

Scheme 4. Rh-Catalyzed Cyclization[a]



[a] Numbers in parentheses indicate diastereomeric ratio.

To obtain insight into the reaction mechanism, a catalytic C−H bond transformation in the presence of D_2O was carried out, thus providing a significant D/H exchange in the *ortho*-position of the recovered starting material **1a-[D$_1$]** (eq 1). We also performed kinetic



isotope effect (KIE) studies (eq 2). A remarkable kinetic isotope effect (KIE) was observed (k_H/k_D = 2.6),[17] indicating that the C−H bond cleavage at the *ortho*-position of phosphonic acid monoethyl ester is most likely involved in the rate-determining step.

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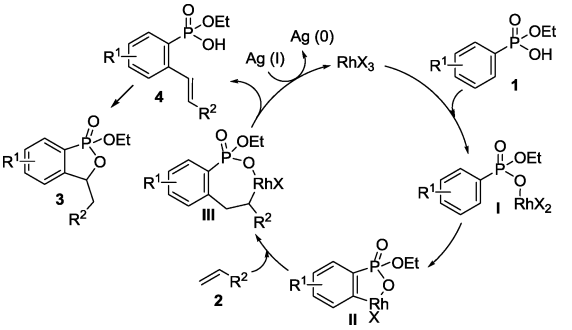
As shown in Scheme 5, a plausible reaction mechanism for the reaction of arylphosphonic acid monoethyl esters **1** with alkenes **2** is described. A proposed catalytic cycle was initiated by coordination of **1** to Cp*RhX_2(III) to provide a rhodium(III) phosphonate **I**. Sequential *ortho*-rhodation to provide a rhodacycle intermediate **II**, alkene insertion, and β-hydride elimination took place to give *ortho*-alkenylated arylphosphonic acid monoethyl esters **4**, and then, an *oxy*-Michael reaction gave rise to benzoxaphosphole 1-oxides **3**.

Scheme 5. A Plausible Mechanism



In summary, we have developed an efficient rhodium-catalyzed tandem oxidative alkenylation and intramolecular *oxy*-Michael reaction from arylphosphonic acid monoethyl esters and alkenes under aerobic conditions, which produced benzoxaphosphole 1-oxides in good to excellent yields. Moreover, arylphosphonic acid monoethyl esters having a substituent at the *para*-position underwent tandem dialkenylation and an *oxy*-Michael reaction to afford 7-alkenylated benzoxaphosphole 1-oxides. Current efforts are directed toward the development of an efficient reaction using a phosphoryl functional group and its application.

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Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.