Article

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Rhodium(III)-Catalyzed Direct Coupling of Arylphosphine Derivatives with Heterobicyclic Alkenes: A Concise Route to Biarylphosphines and Dibenzophosphole Derivatives

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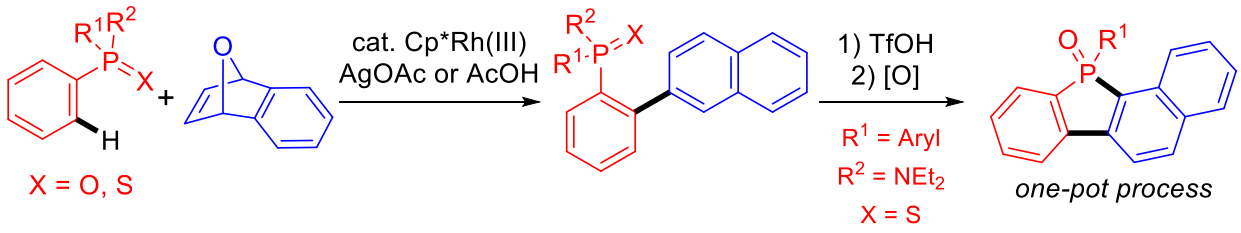


ABSTRACT

The redox-neutral direct coupling of arylphosphine oxides with heterobicyclic alkenes proceeds smoothly under rhodium(III) catalysis involving hydroarylation followed by dehydrative aromatization to form biarylphosphine oxides. Related phenylphosphinic- and phenylphosphonic esters as well as phenylphosphine sulfides also undergo ortho-arylative coupling. Furthermore, phenylphosphinothioic amides can be transformed to fused dibenzophosphole derivatives through the rhodium-catalyzed coupling with heterobicyclic alkenes and successive intramolecular phospha-Friedel-Crafts reaction in one-pot manner.

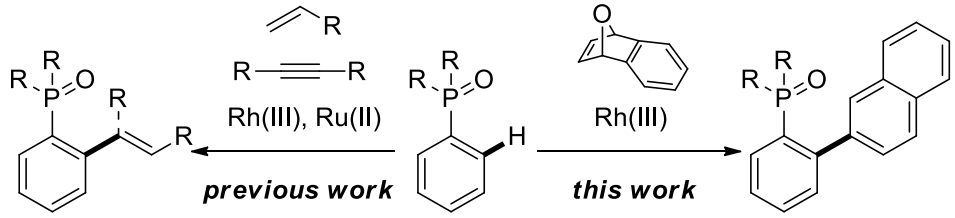
KEYWORDS

rhodium, phosphine, phosphole, heterobicyclic alkene, C-H bond functionalization, arylation

INTRODUCTION

Various organophosphorus molecules have been utilized in pharmaceutical, agrochemical, and organic materials fields.[1] Besides, arylphosphine derivatives are versatile ligands for transition-metal complexes in organometallic chemistry.[2] Therefore, convenient methods for the precious preparation and modification of arylphosphines and their synthetic intermediates including arylphosphine oxides and sulfides have been continuously needed to be developed.

Meanwhile, transition-metal-catalyzed direct C–H bond functionalization reactions with the assistance of a coordinating-functional group (directing group) are now regarded as atom- and step-economical synthetic tools, because they allow the regioselective direct modification of given substrates without prefunctionalization.[3,4] We[5] and other groups[6-9] have recently reported that the P=O and P=S groups in arylphosphine oxides and sulfides act as good directing groups to lead to their catalytic ortho-alkenylation (Scheme 1, left). Compared to such ortho-alkenylations, the ortho-arylation of arylphosphine derivatives has been less explored,[6m, 6o, 7c] in spite of their importance as a straightforward route to biarylphosphines. Various biarylphosphines are known as Buchwald-type phosphine ligands, which are widely employed as ligands for transition-metal catalysts in numerous C–C, C–N, and C–O bond forming cross-coupling reactions.[10] In the context of our studies on the direct functionalization of arylphosphine derivatives, we succeeded in finding that arylphosphine oxides undergo direct coupling with 1,4-epoxydihydronaphthalenes under rhodium catalysis to produce biarylphosphine oxides via the insertion of 1,4-epoxydihydronaphthalenes into the ortho-C–H bond (hydroarylation) and subsequent dehydrative aromatization (Scheme 1, right).[11] It was confirmed that thus obtained biarylphosphine oxides can be readily reduced to the corresponding biarylphosphines. Furthermore, a one-pot synthesis of dibenzophosphole derivatives has also been achieved by the sequence of direct coupling of phenylphosphinothioic amides with 1,4-epoxydihydronaphthalenes and successive TfOH-mediated phospha-Friedel-Crafts reaction. These new findings are described herein.

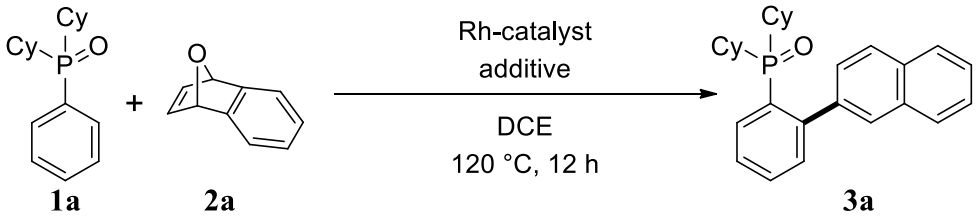


Scheme 1. Transition-Metal-Catalyzed Direct Functionalization of Arylphosphine Oxides

RESULTS AND DISCUSSION

First, we carried out optimization studies using dicyclohexylphenylphosphine oxide (**1a**) and 1,4-epoxydihydronaphthalene (**2a**) as model substrates (Table 1). Thus, **1a** (0.25 mmol) was treated with **2a** (0.25 mmol) in the presence of $[Cp^*Rh(MeCN)_3(SbF_6)_2]$ (0.01 mmol, 4 mol %) and AgOAc (0.05 mmol, 20 mol %) in DCE at 120 °C under N_2 for 12 h. As a result, the desired ortho-arylated product **3a** was formed in 60% GC yield (entry 1). As additive, $Cu(OAc)_2 \bullet H_2O$ and Ag_2CO_3 in place of AgOAc were not suitable (entries 2 and 3). A neutral rhodium complex, $[Cp^*RhCl_2]_2$, did not show any catalytic activity (entry 4). A combination of $[Cp^*RhCl_2]_2$ and $AgSbF_6$, which appears to form a cationic rhodium species in situ, was less effective than $[Cp^*Rh(MeCN)_3(SbF_6)_2]$ (entry 5). Increasing the amount of **2a** (1.5 equiv) improved the product yield up to 69% (entry 6). Addition of 3 equiv of acetic acid or pivalic acid in place of AgOAc was found to be comparably effective (entries 7 and 8). Finally, **3a** was obtained in 78% isolated yield by using 1.2 equiv of **2a** at 130 °C (entry 9).

Table 1. Optimization Studies for the Rh-Catalyzed Direct Naphthylation of Dicyclohexylphenylphosphine Oxide (1a)[a]



1a **2a** **3a**

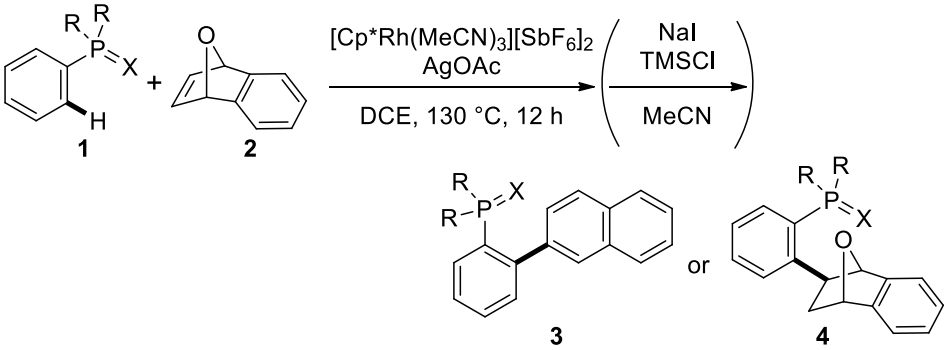
entry	Rh-catalyst (mol %)	**2a** (equiv)	additive (mol %)	yield (%)[b]
1	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4)	1.0	AgOAc (20)	60
2	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4)	1.0	$Cu(OAc)_2 \cdot H_2O$ (20)	trace
3	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4)	1.0	Ag_2CO_3 (10)	trace
4	$[Cp^*RhCl_2]_2$ (2)	1.0	AgOAc (20)	0
5	$[Cp^*RhCl_2]_2$ (2)	1.0	AgOAc (20) $AgSbF_6$ (8)	38
6	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4)	1.5	AgOAc (20)	69
7	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4)	1.5	AcOH (300)	68
8	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4)	1.5	PivOH (300)	67
9[c]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4)	1.2	AgOAc (20)	80 (78)

[a] Reaction conditions: **1a** (0.25 mmol) in DCE (2 mL) under N_2 for 12 h. [b] GC yield. Yield after purification is given in parentheses. [c] At 130 °C.

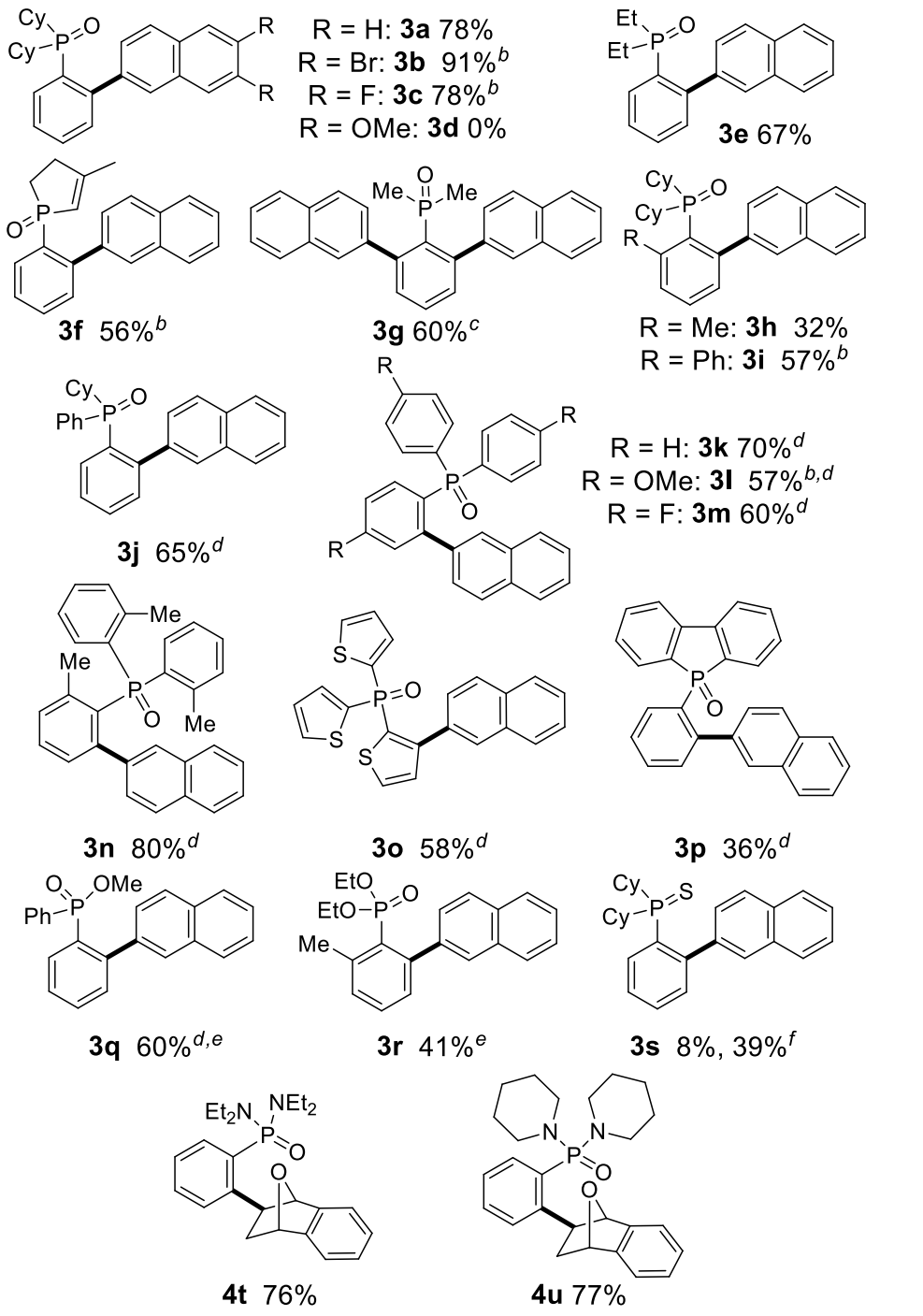
With the optimized conditions in hand (entry 9 in Table 1), we investigated the substrate scope of this reaction (Table 2). Halogen-substituted alkenes **2b** and **2c** smoothly coupled with **1a** to give **3b** and **3c** in good yields. In these cases, as well as in some other reactions described below, mixtures of naphthylated **3** and oxabicyle retained **4** were formed. Therefore, the crude products were treated with trimethylsilyl chloride/NaI in MeCN to convert partially formed **4** to **3**. In contrast, methoxy-substituted **2d** underwent fast ring-opening isomerization to fail to form expected **3d** in any amount. While diethylphenylphosphine oxide (**1e**) and 2,3-dihydro-4-methyl-1-phenyl-1*H*-phosphole oxide (**1f**) reacted with **2a** in a similar manner to give **3e** and **3f**, the sterically less hindered dimethylphenylphosphine

oxide (**1g**) underwent 1:2 coupling under conditions with 2.4 equiv of **2a** to produce **3g** in 60% yield. The reactions of ortho-methyl- and ortho-phenyl-substituted dicyclohexylphenylphophine oxides **1h** and **1i** were somewhat sluggish, probably due to steric reasons. In the latter case, 6-arylated product **3i** was exclusively obtained, no 2'-arylation being observed. It should be noted that the direct arylation of the same substrate **1i** is known to take place at the 2'-position under palladium catalysis.[6m] The reactions of di- and triarylphosphine oxides with **2a** were carried out using them in a 2:1 ratio to suppress the formation of multi-arylated products. Thus, cyclohexyldiphenylphosphine oxide (**1j**), para- (**1k**-**m**) and ortho- (**1n**) substituted triphenylphosphine oxides, and tris(2-thienyl)phosphine oxide (**1o**) underwent monoarylation to afford the corresponding products **3j**-**o** selectively. The arylation of 5-phenyl-5*H*-dibenzophosphole oxide (**1p**) occurred not on the dibenzophosphole ring but on the phenyl moiety, probably because of favorable geometry of the phenyl C–H bond toward the metal center. In addition to phosphine oxides, methyl diphenylphosphinate (**1q**) and diethyl *o*-tolylphosphonate (**1r**) also underwent arylation. However, these substrates were less reactive and required the addition of a stoichiometric amount of AgOAc. Dicyclohexylphenylphosphine sulfide (**1s**) coupled with **2a** under standard conditions to give arylated product **3s** in only 8% yield. The use of 3 equiv of AcOH in place of AgOAc improved the yield of **3s** to 39%. The silver salt additive does not seem to be suitable for the reaction because of its strong thiophilicity.[5c, 12a] Interestingly, the reactions of phenylphosphonamides **1t** and **1u** with **2a** gave bicyclic scaffold-retained products **4t** and **4u** selectively in good yields.

Table 2. Reaction of Arylphosphine Derivatives 1 with 1,4-Epoxydihydronaphthalene 2[a]


[Cp*Rh(MeCN)3][SbF6]2
AgOAc
DCE, 130 °C, 12 h
NaI
TMSCl
MeCN
or

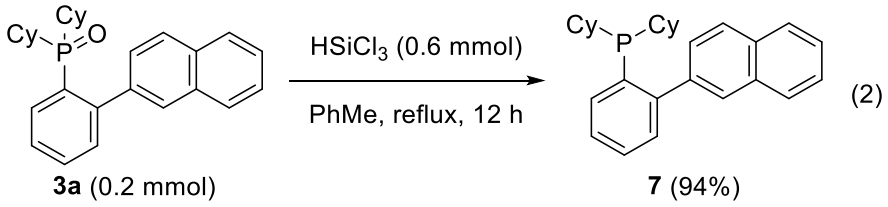
1 2 3 4


R = H: 3a 78%
R = Br: 3b 91%b
R = F: 3c 78%b
R = OMe: 3d 0%
3e 67%
3f 56%b
3g 60%c
R = Me: 3h 32%
R = Ph: 3i 57%b
3j 65%d
R = H: 3k 70%d
R = OMe: 3l 57%b,d
R = F: 3m 60%d
3n 80%d
3o 58%d
3p 36%d
3q 60%d,e
3r 41%e
3s 8%, 39%f
4t 76%
4u 77%

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.3 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (0.01 mmol), AgOAc (0.05 mmol), in DCE (2 mL) at 130 °C under N_2 for 12 h. Isolated yields are shown. [b] The resulting crude mixture was treated with TMSCl (0.5 mmol) and NaI (0.5 mmol) in MeCN (3 mL) at 80 °C for 12 h. [c] **2** (0.5 mmol) was used. [d] **1** (0.5 mmol) and **2** (0.25 mmol) were used. [e] AgOAc (0.5 mmol) was used. [f] AcOH (0.75 mmol) was used in place of AgOAc.

Phenylphosphonamide **1t** also reacted with *N*-Boc-bridged alkene **5** to produce azabicycle-retained compound **6** in 61% yield (eq 1).

Next, we examined the reduction of product **3a** to transform to the corresponding biarylphosphine. Thus, **3a** was treated with $HSiCl_3$ in refluxing toluene to afford Buchwald-type dialkylbiarylphosphine **7** (eq 2). This sequence is effective for the synthesis of biarylphoshine derivatives from simple arylphosphine oxides.



To demonstrate further utility of this Rh catalysis, we next attempted to combine the present arylation of **3** with a phospha-Friedel-Crafts type cyclization to produce dibenzophosphole derivatives. It is worth noting that benzo-fused phospholes have recently attracted much attention in the field of organic materials because of their unique optoelectronic properties, and the straightforward synthesis of these molecules has become an important challenge.[12, 13] It is known that phosphinothioic amides undergo Friedel-Crafts type P-arylation with simple arenes in the presence of an appropriate Lewis acid.[14]

Therefore, we envisaged that if phenylphosphinothioic amides couple with **2** to form ortho-naphthylated products, they may undergo Friedel-Crafts type cyclization. Consequently, we treated *N*,*N*-diethyldiphenylphosphinothionic amide (**8a**) (0.5 mmol) with alkene **2a** (0.25 mmol) under the conditions used for the reaction of phosphine sulfide **3s** in Table 2. Then, TfOH (0.5 mL) was added and heated at 100 ^{o}C for 12 h to complete the cyclization. Finally, the resulting mixture was treated with mCPBA for oxygenation on the phosphorus atom to provide 11-phenyldibenzo[*b*,*g*]phosphindole 11-oxide (**9a**) in 62% yield (Table 3). The same one-pot procedure could be applied to the reactions using a number of phosphinothioic amides and alkenes to produce a series of dibenzophosphole oxides **9b-f**. A related diphenylphosphinamide (**1v**) also underwent phaspha-Friedel-Crafts reaction, albeit with a poor yield (eq 3). It should be noted that the reaction starting from **8a** under previously reported $AlCl_3$-mediated Friedel-Crafts conditions[14] gave a mixture of products cyclized at the α- and β-naphthyl positions. In contrast, our TfOH-mediated conditions gave exclusively the α-cyclized product.[15] In a recently reported naphthalene-fused benzophosphole synthesis by means of Pd-catalyzed direct coupling,[13d, 13g] the α/β-selectivity has been found to be sterically controlled. Thus, our methodology is complimentary to the previous report.

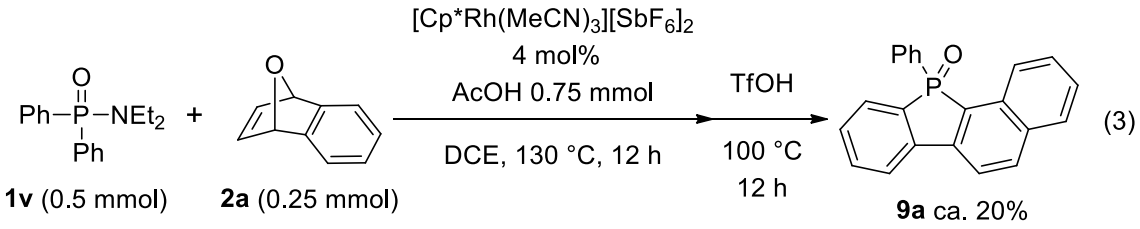
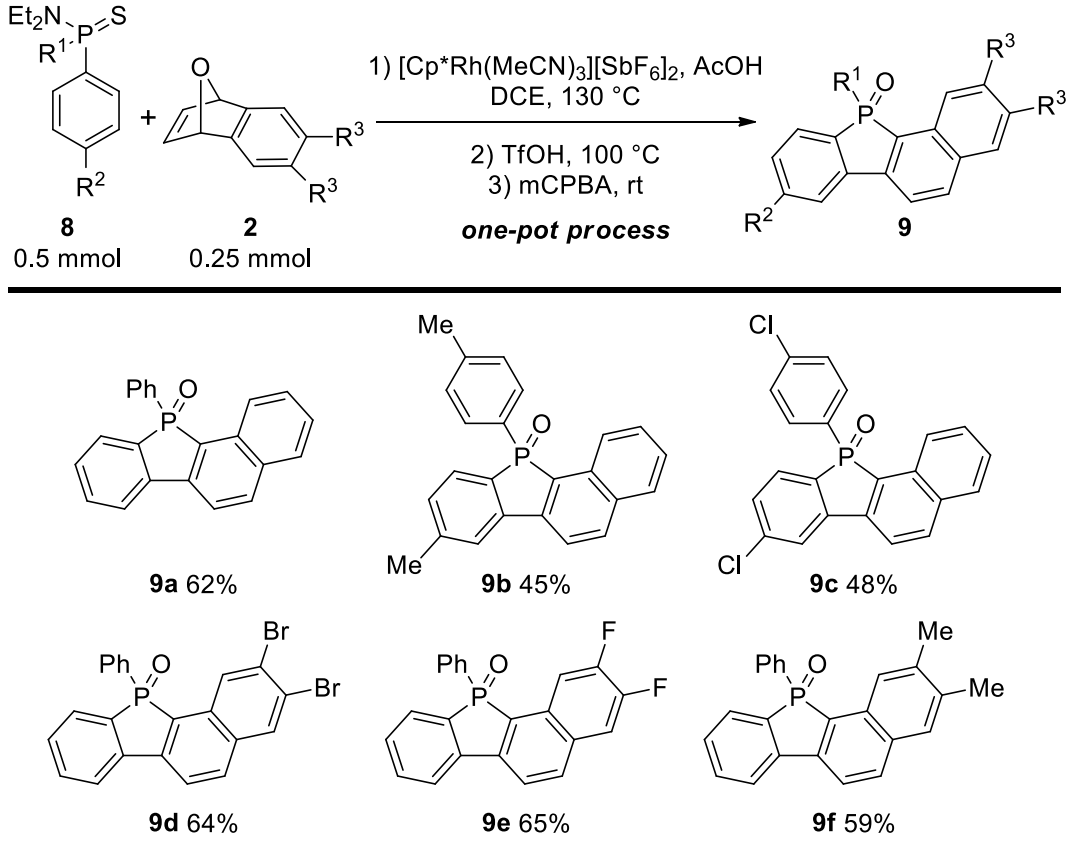


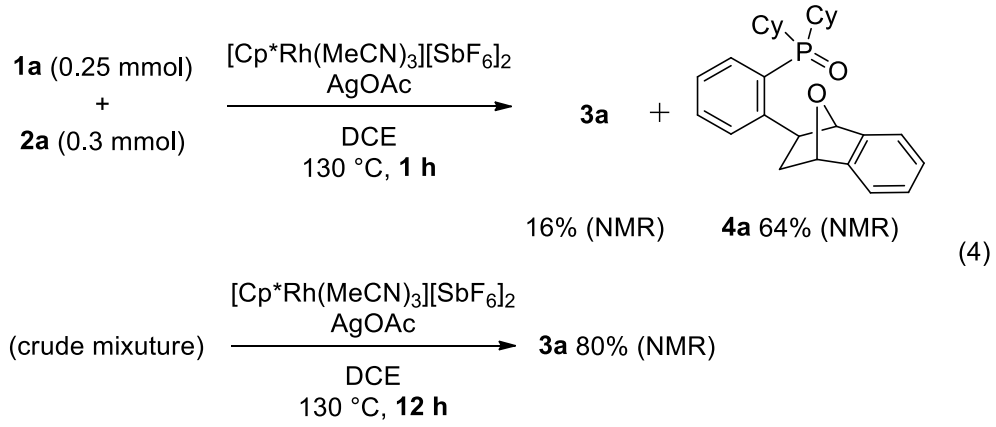
Table 3. One-pot Synthesis of Dibenzophophole oxides 9 by Rh(III)-catalyzed Direct Naphthylation–Intramoleculer Phospha-Friedel-Crafts Reaction of Arylphosphinothioic Amide 8[a]

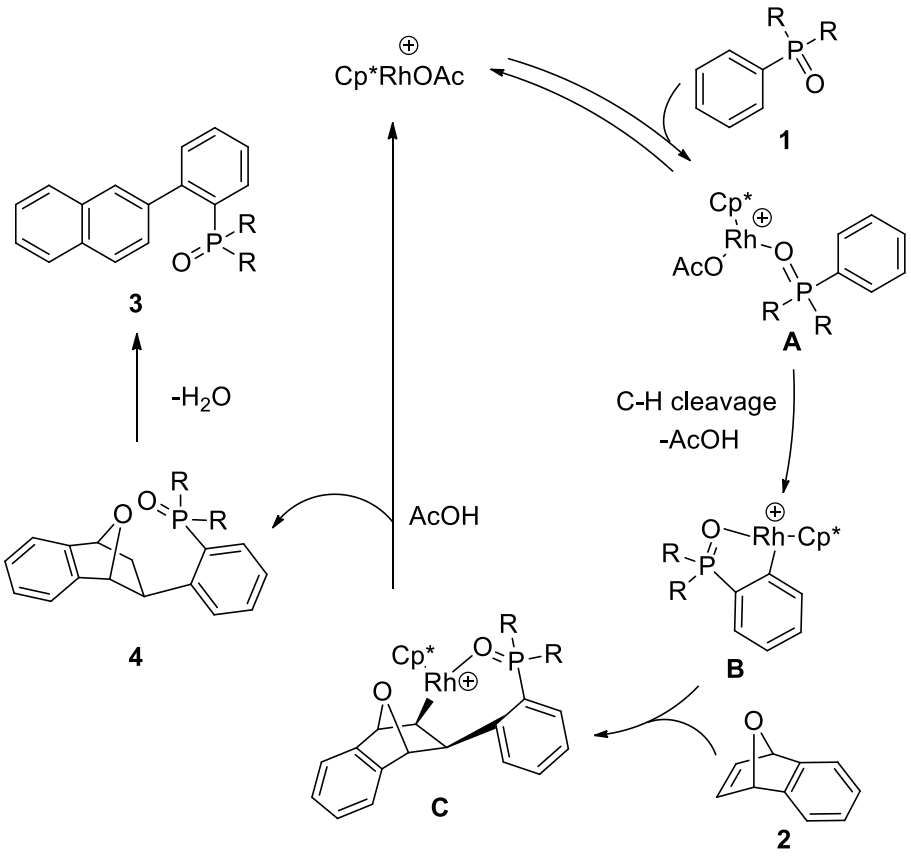


[a] Reaction conditions: 1) **8** (0.5 mmol), **2** (0.25 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (0.01 mmol), AcOH (0.75 mmol), in DCE (2 mL) at 130 °C under N_2 for 12 h; 2) TfOH (0.5 mL) at 100 °C under N_2 for 12 h; 3) mCPBA, rt. Isolated yields are shown.

To obtain mechanistic insight, a number of additional experiments were performed. At the early stage of the reaction of **1a** with **2a** under standard conditions, a significant amount of **4a** (64%) was formed together with **3a** (16%) (eq 4). Further treatment of the mixture led to the complete disapperance of once formed **4a** and selective formation of **3a**. Thus, **4a** is considered to be the initial principal product. A plausible mechanism for the formation of **4** from phenylphosphine oxide **1** with oxabicyclic alkene **2** is illustrated in Scheme 2. Coordination of the P=O directing group of **1** to the metal center of catalyst forms a cationic Rh(III) intermediate **A** followed by C-H bond cleavage at the ortho-position of **A** takes place to yield a five-membered rhodacycle intermediate **B**. Then, the alkene insertion and subsequent protonolysis of a resulting intermediate **C** may occur to produce oxabicycle-retained product **4**. Further heating may induce dehydrative aromatization to afford biarylphosphine oxide **3**. β-Oxygen elimination

in the intermediate **C** leading to the ring-opening could occur, if any, only to a minor extent.[11a]

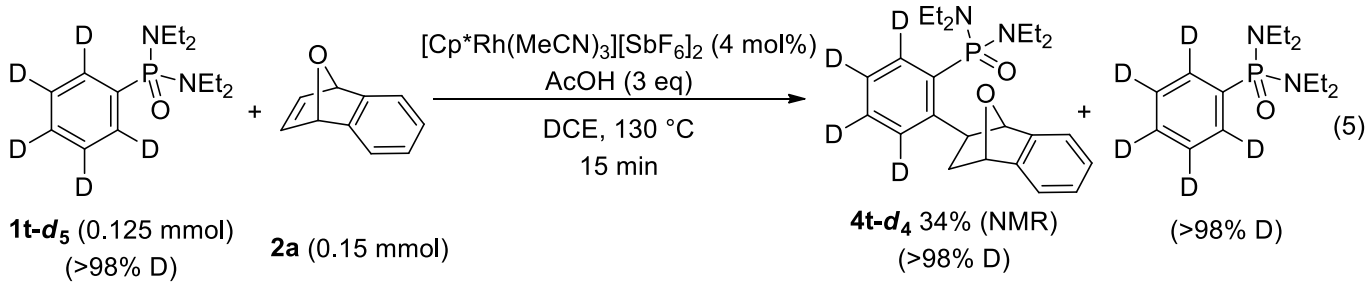


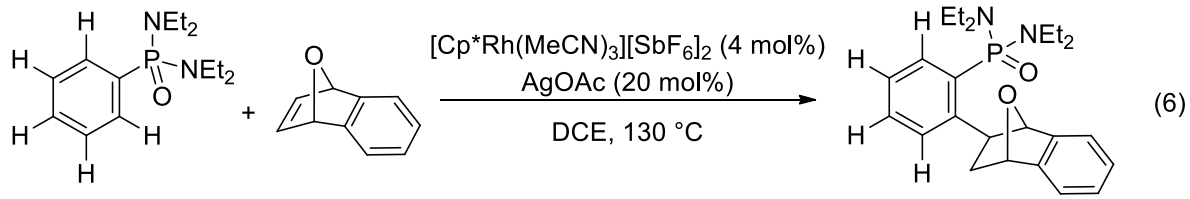


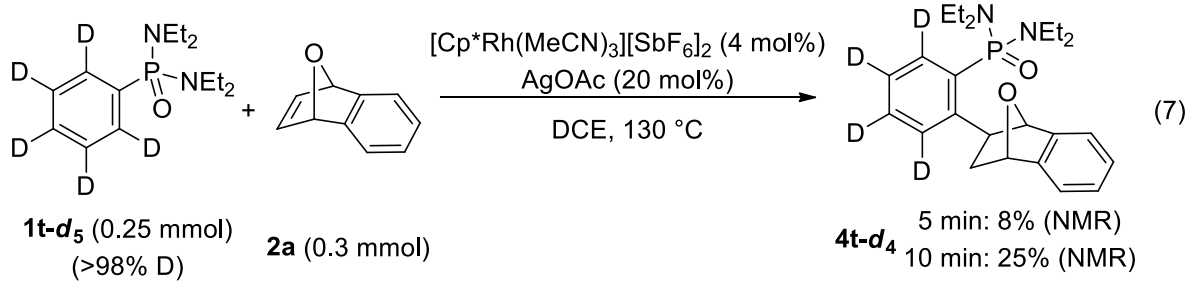
Scheme 2. Plausible Reaction Mechanism

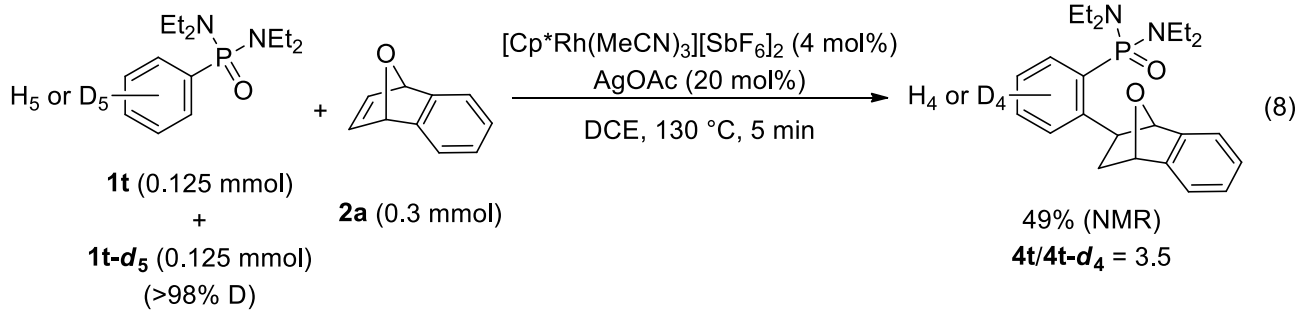
Next, some deuterium labeling studies were also conducted. As shown in eq 4, the reaction of **1a** with

2a gave a mixture of **3a** and **4a** at the early stage. Therefore, we chose **1t** as a model substrate for simplification, because the reaction of **1t** with **2a** gave only **4t** (Table 2). When **1t-d_5** was treated in the presence of 3 equiv of acetic acid for 15 min, no D/H scrambling was observed in recovered **1t-d_5** as well as formed **4t-d_4** (eq 5). Furthermore, significant kinetic isotope effects (KIE) were observed in parallel and competitive reactions of **1t** and **1t-d_5** (eqs 6/7 and 8). These results suggest the C–H bond cleavage step is most likely irreversible and rate-limiting.

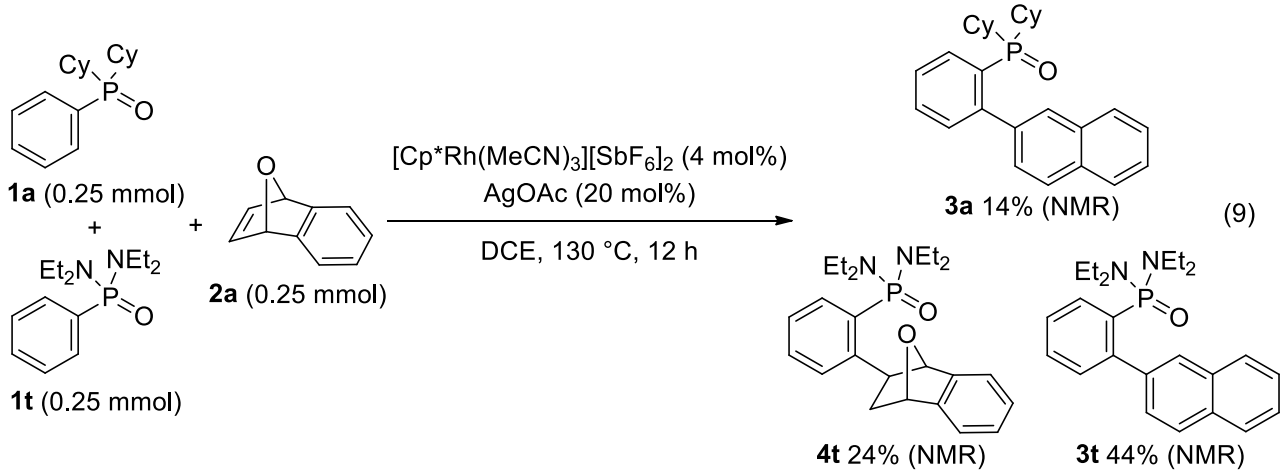






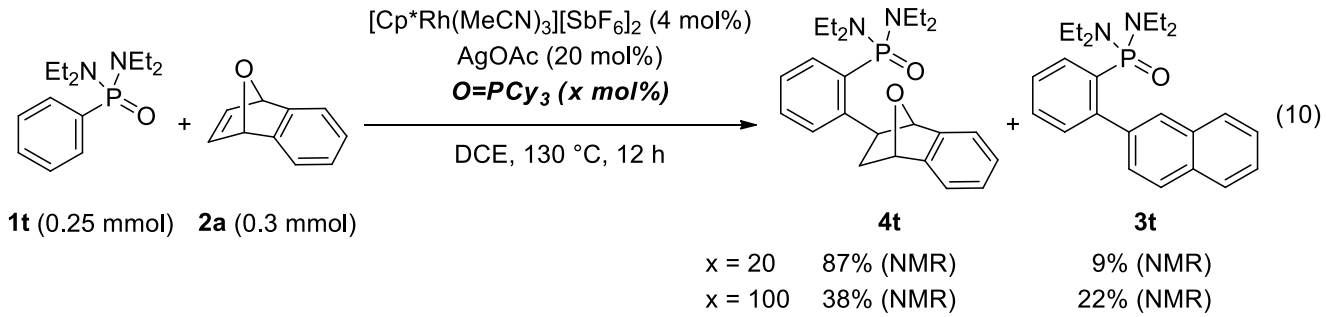


In addition, we investigated relative reactivity between phosphine oxide **1a** and phosphinamide **1t** (eq 9). In a competitive experiment with **2a**, **1t** reacted more smoothly than **1a**. Furthermore, a significant amount of aromatized **3t** was also formed, in contrast to the independent reaction in which only a trace amount of **3t** was observed as described above.



(9)

Based on the result of eq 9, we examined the effect of a phosphine oxide additive. When 20 mol% of $O{=}PCy_3$ was added to the reaction of **1t** with **2a** under standard conditions, **4t** and **3t** were formed in 87% and 9% yields, respectively (eq 10). Increasing the amount of $O{=}PCy_3$ to 1 equiv enhanced the yield of **3t** to 22%, while the total yield of **3t** and **4t** was somewhat lower. Although the exact role of the added phosphine oxide is unclear at this stage, these results indicate that a phosphine oxide can promote the dehydrative aromatization of **4t**.



(10)

CONCLUSION

We have demonstrated that the rhodium-catalyzed redox-neutral direct ortho-arylation of arylphosphine derivatives with heterobicyclic alkenes can be conducted efficiently. A number of biaryl phosphine derivatives could be obtained from simple aryl phosphine oxides. Furthermore, the combination of rhodium-catalyzed ortho-arylation and acid-mediated intramolecular phospha-Friedel-Crafts reaction enables the concise synthesis of dibenzophosphole derivatives from readily available diarylphosphinothionic amides in one-pot mammer. Further development of the direct functionalization of organophosphorus compounds is now in progress in our laboratory.

EXPERIMENTAL SECTION

General Procedures for Rh(III)-catalyzed Coupling of Phosphine Derivatives with Heterobicyclic Alkenes. In a 10 mL sealable tube, the indicated amounts of **1** and **2a** in Table 2, [Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$] (8.3 mg, 0.01 mmol), and AgOAc (8.4 mg, 0.05 mmol) were placed with a magnetic stir bar under N_2 atmosphere. Then, DCE (2 mL) was added by a syringe. The reaction mixture was heated at 130 °C in an oil bath for 12 h. After cooling, the reaction was quenched with 10 mL of water and extracted three times with DCM (20 mL x 3). The combined organic layer was dried over Na_2SO_4 and volatiles were removed in vacuo. [If necessary, the resulting residue was treated with NaI (74.9 mg, 0.5 mmol) and TMSCl (54.3 mg, 0.5 mmol) in MeCN (3 mL) at 80 °C under N_2 atmosphere for overnight. After cooling, the reaction was quenched with sat. $NaHCO_3$ and sat. $Na_2S_2O_3$ and extracted three times with DCM (20 mL x 3). The combined organic layer was dried over Na_2SO_4 and volatiles were removed in vacuo.] The residue was purified by column chromatography on silica gel to give product.

Synthesis of Benzo[*b*]phosphole Derivatives by One-Pot Rh-catalyzed Coupling and phospha-Friedel-Crafts Reaction. In a 10 mL sealable tube, **8** (0.5 mmol), **2** (0.25 mmol), and [Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$] (8.3 mg, 0.01 mmol) were placed with a magnetic stir bar under N_2 atmosphere. Then DCE (2 mL) and AcOH (43 μl, 0.75 mmol) were added by a syringe. The reaction

mixture was heated at 130 °C in an oil bath for 12 h. After cooling, TfOH (0.5 mL) was added by a syringe. The resulting mixture was heated up again to 100 °C for 12 h. After cooling, the reaction mixture was poured into sat. $NaHCO_3$, and extracted three times with DCM (20 mL x 3). The combined organic layer was dried over Na_2SO_4 and volatiles were removed under reduced pressure. The obtained mixture was dissolved in DCM (5 mL) again, and mCPBA (~70 wt%, 130 mg, ~0.5 mmol) was slowly added and stirred for a few minutes. After checking the full conversion of phosphole sulfide on TLC, the reaction was quenched by sat. $NaHCO_3$ and sat. $Na_2S_2O_3$. Subsequently the crude material was extracted three times with DCM (20 mL x 3). The combined organic layer was dried over Na_2SO_4 and volatiles were removed under reduced pressure. The desired product was obtained after purification by column chromatography on silica gel.

ASSOCIATE CONTENT

Supporting Information

Supporting Information Available: Detailed experimental procedures, additional data, analytical data, and ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra. 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.

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