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Rhodium(III)-catalyzed Oxidative Coupling through C–H Bond Cleavage Directed by Phosphinoxy Groups

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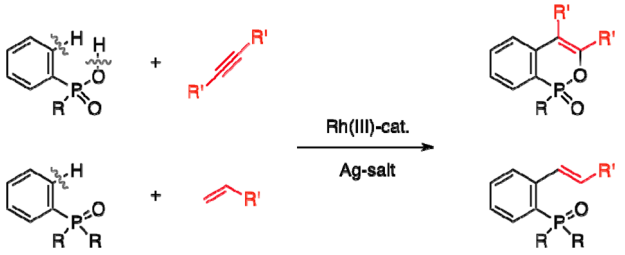
ABSTRACT

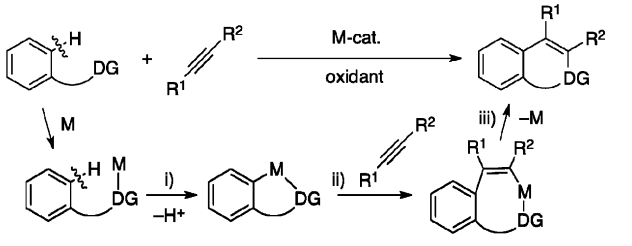


A straightforward synthesis of phosphaisocoumarins is achieved by the rhodium-catalyzed oxidative coupling of diarylphosphinic and phenylphosphonic acid derivatives with alkynes. The P–OH groups effectively act as the key function for the regioselective C–H bond cleavage. Related oxidative coupling of phenylphosphine oxides with alkenes can also be conducted smoothly under similar conditions.

Transition-metal-catalyzed regioselective C–H functionalizations with the aid of directing groups (–DG) have been recognized as important and environmentally benign synthetic tools, because these procedures provide atom- and step-economical routes to complex target molecules from simple starting materials.[1] Particularly, the oxidative coupling reactions of aromatic substrates possessing a directing group with internal alkynes through (i) chelation-directed C–H bond cleavage, (ii) alkyne insertion, and (iii) annulation allow the straightforward syntheses of benzannulated heterocycles from readily available monofunctionalized aromatic substrates (Scheme 1).[1m]

As an early example, we reported the rhodium-catalyzed oxidative coupling of benzoic acids with alkynes to produce isocoumarin derivatives (DG = COO(H) in Scheme 1).[2] After the discovery, similar annulations of various aromatic substrates have also been developed by us[3] and other groups.[4] Produced benzannulated heterocycles are usually of interest because of their optical, electrochemical, and biological properties. Phosphaisocoumarins have also gained much attention as a new class of inhibitors for pancreatic cholesterol esterase.[5] Ding and co-workers reported their multistep syntheses via Sonogashira coupling and subsequent copper-catalyzed cyclization of resulting *ortho*-alkynylphenylphosphonic acids.[6] A more simple and flexible approach toward phosphaisocoumarins is the oxidative coupling of phenylphosphonic acids with alkynes via P–OH directed C–H functionalization. However, the utilization of P–OH groups as directing

Scheme 1



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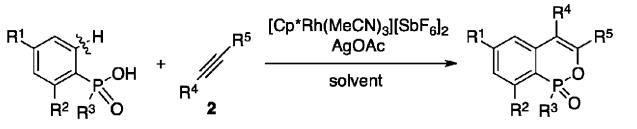
groups has been scarcely explored.[7] In the context of our studies on rhodium-catalyzed oxidative annulation,[1m,3] we succeded in finding that a series of phenylphosphinic acids undergoes oxidative coupling with internal alkynes under rhodium catalysis to achieve the single-step syntheses of phosphaisocoumarin derivatives. A related oxidative coupling between phosphine oxides and alkenes using a similar catalyst system is also disclosed herein.

In an initial attempt, diphenylphosphinic acid (**1a**) (0.25 mmol) was treated with 1 equiv of diphenylacetylene (**2a**) (0.25 mmol) in the presence of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (0.01 mmol) and AgOAc (1 mmol) as catalyst and oxidant, respectively, in diglyme (3 mL) at 120 °C for 2 h under N_2.

Table 1. Reaction of Phenylphosphinic Acids **1** with Alkynes **2**[a]



1 **2** **3**

entry	1	2	solvent	product, % yield[b]
1[c,d]	**1a**	**2a**	diglyme	**3a**, (79)
2[c,d]			dioxane	**3a**, (71)
3[c,d]			DMF	**3a**, (34)
4[c,d]			*o*-xylene	**3a**, (tr)
5[c]			diglyme	**3a**, (94)
6[c,e]			diglyme	**3a**, (68)
7			diglyme	**3a**, 95 (99)
8[f]			diglyme	**3a**, (78)
9	**1b**: R = Me	**2a**	diglyme	**3b**: R = Me, 69
10	**1c**: R = OMe		diglyme	**3c**: R = OMe, 45
11	**1d**	**2a**	diglyme	**3d**, 86
12	**1e**	**2a**	diglyme	**3e**, 78
13	**1a**	**2b**: R = OMe	diglyme	**3f**: R = OMe, 61
14		**2c**: R = Cl	diglyme	**3g**: R = Cl, 79
15	**1a**	**2d**	diglyme	**3h**, 66[g]

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.38 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (0.01 mmol), AgOAc (0.75 mmol), in solvent (3 mL) at 120 °C under N_2 for 2 h. [b] Isolated yield based on the amount of **1** used. Value in parentheses indicates GC yield. [c] With AgOAc (1 mmol). [d] With **2a** (0.25 mmol). [e] $[Cp^*RhCl_2]_2$ was used as a catalyst. [f] With AgOAc (0.5 mmol). [g] **3h**/isomer = 93:7.

(1) Selected recent reviews for C−H functionalization: (a) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (b) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (c) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2012**, *18*, 10092. (d) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (e) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (f) Kuninobu, Y.; Takai, K. *Chem. Rev.* **2011**, *111*, 1938. (g) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (h) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (i) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (j) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (k) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (l) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (m) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (n) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395. (o) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (p) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (q) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (r) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (s) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (t) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987. (u) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (v) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (w) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (x) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (y) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (z) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698.

(2) (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (b) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 5362.

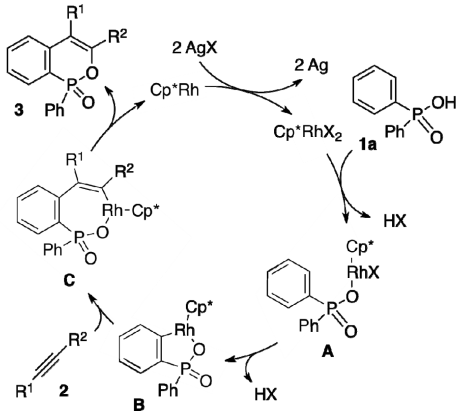
(3) Selected recent reports: (a) Unoh, Y.; Hirano, K.; Satoh, T.; Miura, M. *Tetrahedron* **2013**, *69*, 4454. (b) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 9548. (c) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 600. (d) Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 2867. (e) Umeda, N.; Hirano, K.; Satoh, T.; Shibata, N.; Sato, H.; Miura, M. *J. Org. Chem.* **2011**, *76*, 13. (f) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744. (g) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068. (h) Mochida, S.; Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Asian J.* **2010**, *5*, 847. (i) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (j) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6295. (k) Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 3478.

(4) Selected examples: (a) Kim, D.-S.; Park, J.-W.; Jun, C.-H. *Chem. Commun.* **2012**, *48*, 11334. (b) He, T.; Too, P. C.; Chen, R.; Chiba, S.; Sun, H. *Chem. Asian J.* **2012**, *7*, 2090. (c) Li, B.-J.; Wang, H.-Y.; Zhu, Q.-L.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3948. (d) Jayakumar, J.; Parthasawathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 197. (e) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846. (f) Wei, X.; Zhao, M.; Du, Z.; Li, X. *Org. Lett.* **2011**, *13*, 4636. (g) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (h) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2154. (i) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (j) Song, G.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487. (k) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (l) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (m) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. (n) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050. (o) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (p) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. See also reviews: (q) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichim. Acta* **2012**, *45*, 31. (r) Chiba, S. *Chem. Lett.* **2013**, *41*, 1554.

As a result, the oxidative annulation effectively proceeded to afford 1,3,4-triphenyl-1*H*-2,1-benzoxaphosphorin-1-oxide (**3a**) in 79% yield (entry 1 in Table 1). In other solvents such as dioxane, DMF, and *o*-xylene, the product yield decreased (entries 2−4). Increasing the amount of **2a** (0.38 mmol) led to enhancement of the product yield to 94% (entry 5). The use of $[Cp^*RhCl_2]_2$ (0.005 mmol) as catalyst in place of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ reduced the reaction efficiency (entry 6). With a slightly decreased amount of AgOAc (0.75 mmol), **3a** was obtained almost quantitatively (entry 7). However, further decrease in the amount of AgOAc reduced the product yield (entry 8). Under the optimized conditions, the reactions of various phenylphosphinic acids **1** with alkynes **2** were next examined. Bis(*para*-substituted phenyl)phosphinic acids **1b** and **1c** underwent coupling with **2a** to afford the corresponding phosphaisocoumarins **3b** and **3c** (entries 9 and 10). In these cases, 1:2 coupling products were also detected by GC-MS. Therefore, the yields of desired 1:1 coupling product **3** seem to somewhat decrease for the overreaction. As expected, the use of sterically hindered bis(*ortho*-methylphenyl)phosphinic acid (**1d**) was found to suppress the overreaction to give **3d** selectively in 86% yield (entry 11). The reaction of phenylphosphonic acid monoethyl ester (**1e**) with **2a** proceeded smoothly to produce **3e** in 78% yield (entry 12). It should be noted that this compound is an important intermediate and their hydrolysis and alcoholysis with or without ring-opening have been established.[8] *para*-Methoxy- and chloro-substituted diphenylacetylenes **2b** and **2c** also coupled with **1a** to produce the corresponding phosphaisocoumarins **3f** and **3g** (entries 13 and 14). The reaction of unsymmetrical 1-phenyl-1-propyne (**2d**) gave **3h** predominantly, along with minor amounts of an isomer and a separable 1:2 coupling product (entry 15).

A plausible mechanism for the reaction of diphenylphosphinic acid (**1a**) with alkyne **2** is illustrated in Scheme 2, in which neutral ligands are omitted. Coordination of **1a** to a Rh^{III} center and subsequent cyclorhodation on one of the phenyl groups of a resulting intermediate **A** take place to form a five-membered rhodacycle intermediate **B**. Then, alkyne insertion to form **C** and reductive elimination may occur to release **3**. The Rh^{I} species seems to be oxidized by Ag^{I} to regenerate Rh^{III}.

Scheme 2



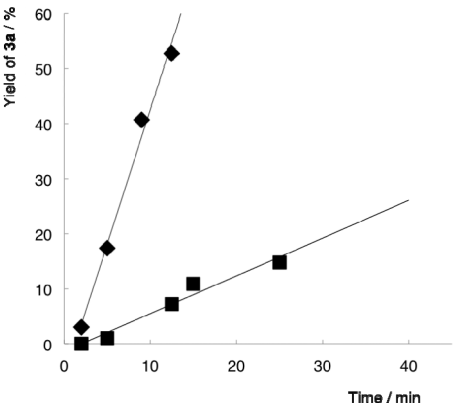
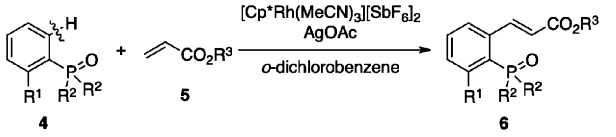
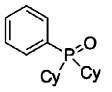
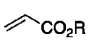
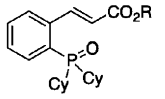
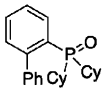
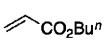
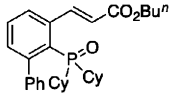
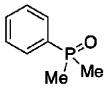
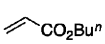
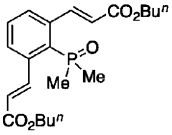


Figure 1. Time course of the yields of formed **3a**-d_0 (diamonds) and **3a**-d_9 (squares) during the early stages of the reactions of **1a**-d_0 and **1a**-d_{10} with **2a**.

Table 2. Reaction of Phenylphosphine Oxides **4** with Acrylates **5**[a]



entry	4	5	product, % yield[b]
			
1[c,d]	**4a**	**5a**: R = Bu^n	**6a**: R = Bu^n, 15
2[c]		**5a**: R = Bu^n	**6a**: R = Bu^n, 46
3		**5a**: R = Bu^n	**6a**: R = Bu^n, 64
4		**5b**: R = Et	**6b**: R = Et, 67
5		**5c**: R = Cy	**6c**: R = Cy, 60
6		**5d**: R = Bu^i	**6d**: R = Bu^i, 63
7		**5e**: R = Bu^t	**6e**: R = Bu^t, 42
			
8	**4b**	**5a**	**6f**, 57
			
9	**4c**	**5a**	**7**, 71

[a] Reaction conditions: **4** (0.25 mmol), **5** (2 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (0.02 mmol), AgOAc (1 mmol), in *o*-dichlorobenzene (3 mL) at 120 °C under N_2 for 6 h. [b] Isolated yield based on the amount of **4** used. [c] With **5a** (0.75 mmol) and $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (0.01 mmol). [d] In diglyme.

For providing additional mechanistic information, deuterated diphenylphosphinic acid (**1a**-d_{10}) was treated with **2a** under standard reaction conditions. During the early stage (~13 min), the reaction of **1a**-d_{10} (squares in Figure 1) proceeded significantly more slowly than that of **1a**-d_0 (diamonds). The observed kinetic isotope effect (KIE) was 6.8. This fact suggests that the rate-determining step involves C−H(D) bond cleavage (**A** to **B** in Scheme 2).

Next, we examined the oxidative coupling using alkenes in place of alkynes as coupling partners. Treatment of **1a** with 2 equiv of butyl acrylate (**5a**) in the presence of a $[Cp^*Rh(MeCN)_3][SbF_6]_2$/AgOAc system and subsequent methylation with MeI and K_2CO_3 gave a trace amount of alkenylated product along with a significant amount of methyl ester of recovered **1a**. Interestingly, phenylphosphine oxides **4** were found to react with alkenes **5**. Thus, dicyclohexyl(phenyl)phosphine oxide (**4a**) (0.25 mmol) reacted with **5a** (0.75 mmol) in the presence of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (0.01 mmol) and AgOAc (1 mmol) in diglyme at 120 °C to afford *ortho*-alkenylated product **6a** in 15% yield (entry 1 in Table 2). This reaction was found to proceed more smoothly in *o*-dichlorobenzene (entry 2). With the increased amounts of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (0.02 mmol) and **5a** (2 mmol), the product yield was improved up to 64% (entry 3). Under similar condtions, related acrylates, such as ethyl (**5b**), cyclohexyl (**5c**), *iso*-butyl (**5d**), and *tert*-butyl (**5e**) acrylates also underwent the coupling with **4a** to produce **6b**−**e** in 42−67% yields (entries 4−7). The reaction of dicyclohexyl(biphenyl-2-yl)-phosphine oxide (**4b**), which is readily available by simple oxidation of Cy-JohnPhos, similarly proceeded to produce **6f** (entry 8). In the case with sterically less hindered dimethyl(phenyl)phosphine oxide (**4c**), dialkenylation took place to selectively produce **7** in 71% yield (entry 9).

In summary, we have demonstrated that the rhodium-catalyzed oxidative coupling of phenylphosphinic acids with alkynes proceeds efficiently to give phosphaisocoumarin derivatives selectively. Under similar rhodium catalysis, phenylphosphine oxides couple with alkenes to form the corresponding *ortho*-alkenylated products. These represent rare but effective examples involving C−H bond cleavage directed by phosphinoxy groups.

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Supporting Information Available. Standard experimental procedure and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(5) Li, B.; Zhou, B.; Lu, H.; Ma, L.; Peng, A.-Y. *Eur. J. Med. Chem.* **2010**, *45*, 1955.

(6) (a) Wei, P.; Ding, Y.-X. *Synthesis* **2005**, 599. (b) Peng, A.-Y.; Ding, Y.-X. *Org. Lett.* **2004**, *6*, 1119. (c) Peng, A.-Y.; Ding, Y.-X. *J. Am. Chem. Soc.* **2003**, *125*, 15006.

(7) During the preparation of this manuscript, Kim and co-workers reported the palladium-catalyzed oxidative coupling of benzyl- and phenoxyphosphonic acids with alkenes: (a) Meng, X.; Kim, S. *Org. Lett.* **2013**, *15*, 1910. (b) Chan, L. Y.; Kim, S.; Ryu, T.; Lee, P. H. *Chem. Commun.* **2013**, *49*, 4682.

(8) (a) Peng, A.-Y.; Guo, Y.-J.; Ke, Z.-H.; Zhu, S. *Eur. J. Org. Chem.* **2008**, 5277. (b) Peng, A.-Y.; Li, B.; Yang, X.; Lin, J. *Synthesis* **2008**, 2412.