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Palladium-Catalyzed Hydrophosphorylation and Hydrophosphinylation of Cyclopropenes

Bassam K. Alnasleh, William M. Sherrill, and Michael Rubin*

Department of Chemistry, Univeristy of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045-75832

mrubin@ku.edu

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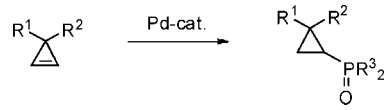
ABSTRACT



Novel transition-metal-catalyzed addition of P−H entities across the cyclopropene double bond has been developed. This transformation allows for mild and efficient preparation of phosphorus-containing cyclopropanes in good yields and high degrees of diastereoselectivity.

Phosphorus-containing cyclopropanes are an important class of compounds with great potential for both medicinal chemistry and organic synthesis. Thus, derivatives of cyclopropylphosphonic acid make attractive targets for drug discovery, as they are omnipresent among biologically active compounds including antiproliferative,[1] antiviral,[2] and antimalarial[3] agents. Phosphorylated cyclopropanes also hold great promise as potential selective herbicides.[4] Furthermore, cyclopropylphosphines have been shown to serve as efficient ligands in several transition-metal-catalyzed transformations.[5] The existing approaches to cyclopropylphosphorus compounds span various modes of [2 + 1] cycloaddition,[6] MIRC,[7] and related 1,3-cyclizations.[8] They can also be obtained by derivatization of the pre-existing cyclopropane moiety, including reactions of P-nucleophiles with cyclopropanone equivalents[9] or P-electrophiles with cyclopropylmetals.[5,10] The efficiency of these methods, however, dramatically decreases with the increase of steric demand at the cyclopropyl core. Recently, we[11] and Marek[12] developed an alternative approach to cyclopropylphosphorus compounds via a formal [2,3]-rearrangement of cyclopropenylmethylphosphinites, which permits synthesis of densely substituted methylenecyclopropylphosphine oxides (Scheme 1, eq 1).

In light of this finding, we wondered whether addition of a phosphorus entity to the double bond of cyclopropene could also be achieved in an intermolecular fashion via a direct hydrophosphorylation (Scheme 1, eq 2).[13] It should be

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(2) See, for example: (a) Zhou, S.; Brietenbach, J. M.; Borysko, K. Z.; Drach, J. C.; Kern, E. R.; Gullen, E.; Cheng, Y.-C.; Zemlicka, J. *J. Med. Chem.* **2004**, *47*, 566. (b) Yan, Z.; Zhou, S.; Kern, E. R.; Zemlicka, J. *Tetrahedron* **2006**, *62*, 2608.

(3) Devreux, V.; Wiesner, J.; Goeman, J. L.; van der Eycken, J.; Jomaa, H.; van Calenbergh, S. *J. Med. Chem.* **2006**, *49*, 2656.

(4) (a) Asada, T.; Aoki, T.; Masui, M.; Nakaida, Y.; Yasushi, Y.; Yamamoto, I. JP 02001460. (b) Hayakawa, K.; Mori, I.; Iwasaki, G.; Matsunaga, S. EP 528760. (c) Cox, J. M.; Bellini, P.; Barret, R.; Ellis, R. M.; Hawkes, T. R. WO9315610.

(5) Molander, G. A.; Burke, J. P.; Carroll, P. J. *J. Org. Chem.* **2004**, *69*, 8062.

(6) (a) Barluenga, J.; Fernandez-Rodriguez, M. A.; Garcia-Garcia, P.; Aguilar, E.; Merino, I. *Chem.−Eur. J.* **2005**, *12*, 303. (b) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437. (c) Slootweg, J. C.; de Kanter, F. J. J.; Schakel, M.; Lutz, M.; Spek, A. L.; Kozhushkov, S. I.; de Meijere, A.; Lammertsma, K. *Chem.−Eur. J.* **2005**, *11*, 6982. (d) Charette, A. B.; Bouchard, J.-E. *Can. J. Chem.* **2005**, *83*, 533. (e) Ferrand, Y.; Le Maux, P.; Simonneaux, G. *Org. Lett.* **2004**, *6*, 3211. (f) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 2117. (g) Krysiak, J.; Lyon, C.; Baceiredo, A.; Gornitzka, H.; Mikolajczyk, M.; Bertrand, G. *Chem.−Eur. J.* **2004**, *10*, 1982. (h) Slootweg, J. C.; Schakel, M.; de Kanter, F. J. J.; Ehlers, A. W.; Kozhushkov, S. I.; de Meijere, A.; Lutz, M.; Spek, A. L.; Lammertsma, K. *J. Am. Chem. Soc.* **2004**, *126*, 3050. (i) Despagnet, E.; Gornitzka, H.; Rozhenko, A. B.; Schoeller, W. W.; Bourissou, D.; Bertrand, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 2835. (j) Moore, J. D.; Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2002**, *67*, 8123. (k) Midura, W. H.; Mikolajczyk, M. *Tetrahedron Lett.* **2002**, *43*, 3061.

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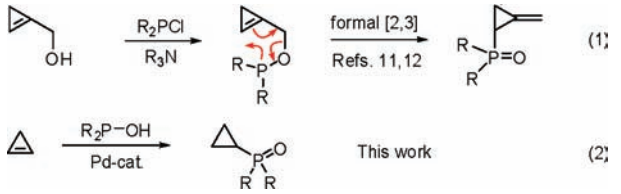
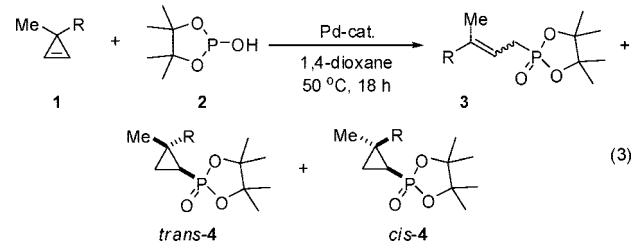
Scheme 1



mentioned that, while a plethora of different additions of various metallic species across the C=C bond of cyclopropene have been developed, additions of nonmetallic entities with preservation of the three-membered carbocycle have represented a significant challenge.[14] Thus, Yamamoto demonstrated that palladium-catalyzed additions of C- and N-pronucleophiles to dialkylcyclopropene proceed with ring opening, affording allylmalonates and allylamine derivatives.[15] A single example of transition-metal-catalyzed addition of a carbon pronucleophile to cyclopropene proceeding with preservation of a three-membered ring was recently shown by Chisholm.[16] Herein, we report an efficient and atom-economic approach to cyclopropylphosphonates and cyclopropylphosphine oxides via the diastereoselective palladium-catalyzed hydrophosphorylation and hydrophosphinylation of cyclopropenes.[17]

We began our optimization by testing the reaction between 3-methyl-3-phenylcyclopropane (**1a**) and 4,4,5,5-tetramethyl-2-oxo-1,3,2-dioxaphospholane (**2**) (eq 3). It was found that thermal and radically initiated reactions did not proceed at all; however, formation of hydrophosphorylation products was observed in the presence of several Pd catalysts (Table 1). Yet, most catalytic systems tested provided very sluggish reactions with moderate facial selectivity. Furthermore, the

Table 1. Optimization of the Reaction Conditions[a]



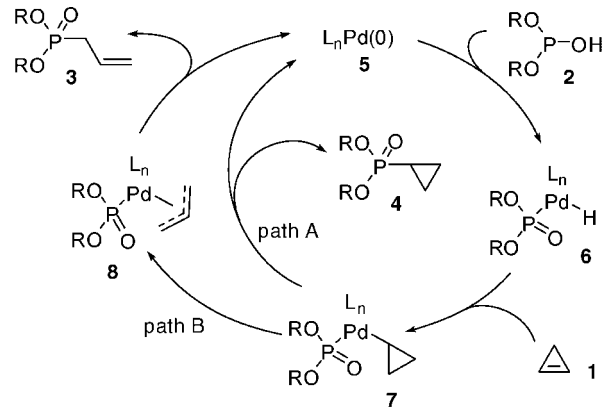
no.	R	catalyst	**4**, % (trans/cis)[b]	**3**, %[b]
1	Ph	(π-allylPdCl)$_2$/TTMPP[c]	60 (2.5:1)	10
2	Ph	(π-allylPdCl)$_2$/PPh_3	7 (N/D)	–
3	Ph	$Pd(OAc)_2$/TTMPP	45 (15:1)	40
4	Ph	$Pd(OAc)_2$/PPh_3	30 (4.5:1)	34
5	Ph	Pd_2dba_3·$CHCl_3$/TTMPP	13 (N/D)	–
6	Ph	Pd_2dba_3·$CHCl_3$/dppe	NR	–
7	Ph	Pd_2dba_3·$CHCl_3$/dppf	98 (4:1)	–
8	Ph	$Pd(PPh_3)_4$	89 (19:1)	6
9	CO_2Me	$Pd(PPh_3)_4$	100 (3:1)	–
10	CO_2Me	Pd_2dba_3·$CHCl_3$/dppf	97 (9:1)	–

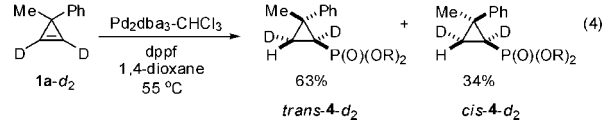
[a] Reactions performed on a 0.1 mmol scale. [b] GC conversion, *n*-octane was used as an internal standard. [c] TTMPP: tris(2,4,6-trimethoxyphenyl)phosphine.

reaction was complicated by the formation of a side product, allylphosphonate **3** (Table 1). Our attempts to accelerate the addition by increasing the reaction temperature resulted in a marked shift toward formation of the ring opening product **3**. Gratifyingly, employment of $Pd(PPh_3)_4$ allowed the desired phosphonate **4a** with very high diastereo- and chemoselectivity to be accessed (entry 8).

A putative mechanism for this transformation is shown in Scheme 2. First, oxidative addition of palladium into the

Scheme 2. Mechanistic Rationale for the Pd-Catalyzed Hydrophosphorylation of Cyclopropenes





(7) MIRC − Michael-Initiated Ring Closure. See, for example: (a) Swamy, K. C. K.; Kumar, K. V. P. P.; Suresh, R. R.; Kumar, N. S. *Synthesis* **2007**, 1485. (b) Waszkuc, W.; Janecki, T. *Org. Biomol. Chem.* **2003**, *1*, 2966. (c) Stevens, C. V.; Van Heecke, G.; Barbero, C.; Patora, K.; De Kimpe, N.; Verhe, R. *Synlett* **2002**, 1089.

(8) (a) Zeuner, F.; Angermann, J.; Moszner, N. *Synth. Commun.* **2006**, *36*, 3679. (b) Odinets, I. L.; Vinogradova, N. M.; Lyssenko, K. A.; Petrovskii, P. V.; Mastryukova, T. A.; Roschenthaler, G.-V. *Heteroatom Chem.* **2006**, *17*, 13.

(9) Tesson, N.; Dorigneux, B.; Fadel, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2267.

(10) Buron, C.; Tippmann, E. M.; Platz, M. S. *J. Phys. Chem. A* **2004**, *108*, 1033.

(11) Rubina, M.; Woodward, E. W.; Rubin, M. *Org. Lett.* **2007**, *9*, 5501.

(12) Masarwa, A.; Stanger, A.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 8093.

(13) For Pd-catalyzed hydrophosphorylation of olefins, see, for example: (a) Xu, Q.; Han, L.-B. *Org. Lett.* **2006**, *8*, 2099. (b) Han, L.-B.; Mirzaei, F.; Zhao, C.-Q.; Tanaka, M. *J. Am. Chem. Soc.* **2000**, *122*, 5407.

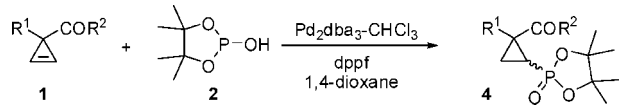
(14) For recent reviews see, for example: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221. (c) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719.

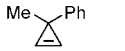
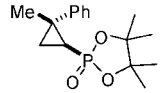
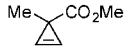
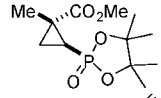
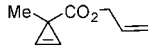
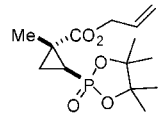
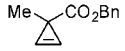
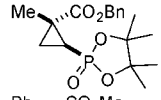
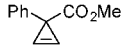
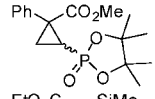
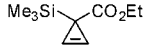
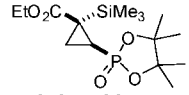
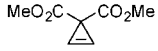
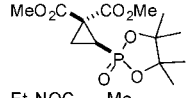
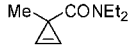
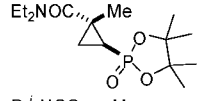
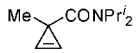
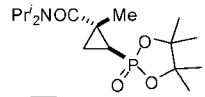
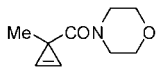
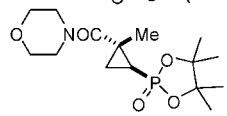
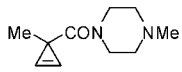
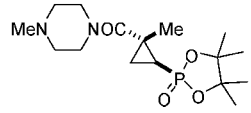
(15) Nakamura, I.; Bajracharya, G. B.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 2297.

(16) Yin, J.; Chisholm, J. D. *Chem. Commun.* **2006**, 632.

(17) For noncatalyzed additions of phosphorus species to 1,2-dichlorocyclopropenes, see: (a) Svara, J.; Fluck, E. *Chem.-Zeit.* **1985**, *109*, 11. For Diels−Alder reaction of cyclopropene with 1,3,5-triphosphabenzene, see: (b) Peters, C.; Disteldorf, H.; Fuchs, E.; Werner, S.; Stutzmann, S.; Bruckmann, J.; Kruger, C.; Binger, P.; Heydt, H.; Regitz, M. *Eur. J. Org. Chem.* **2001**, 3425.

Table 2. Palladium-Catalyzed Hydrophosphorylation of 3,3-Disubstituted Cyclopropenes



no.	cyclopropene **1**		temperature and time	product[a]		facial selectivity	yield, %[b]
1		**1a**	1 h at 25 °C		**4a**	95:5	86
2		**1b**	2.5 h at 30 °C		**4b**	90:10	80
3		**1c**	1 h at 25 °C		**4c**	100:0	75
4		**1d**	1 h at 25 °C		**4d**	90:10	94[c]
5		**1e**	1 h at 25 °C		**4e**	71:29	99[c]
6		**1f**	1.5 h at 25 °C[d]		**4f**	100:0	99
7		**1g**	1 h at 25 °C		**4g**	N/A	100
8		**1h**	18 h at 55 °C		**4h**	96:4	97[c]
9		**1i**	6 h at 50 °C		**4i**	92:8	80
10		**1j**	24 h at 55 °C		**4j**	91:9	86
11		**1k**	7 h at 50 °C		**4k**	100:0	99

[a] Relative configuration of a major diastereomer is shown. [b] Isolated yields of a major diastereomer. [c] Isolated yield of two diastereomers. [d] THF was used as a solvent.

P−H bond produces palladium hydride species **6**. Subsequent migratory insertion of cyclopropene **1** affords cyclopropylpalladium complex **7** (Scheme 2).[18] The latter, upon reductive elimination (path A), produces cyclopropylphosphonate **4**. This reaction is *syn*-specific, as demonstrated by the hydrophosphorylation of deuterium-labeled cyclopropene **1a**-d_2 (eq 4).[19]

Alternatively, at higher temperatures, species **7** would undergo ring cleavage via β-carbon elimination (path B).[14a] The resulting $^3\eta$-allylpalladium species **8** would afford, after reductive elimination, allylphosphonate **3**.

With the optimized conditions in hand, we moved on to investigate the scope of the new hydrophosphorylation reaction. It was disappointing to discover that methyl ester **1b** provided only marginal diastereoselectivity in the presence of $Pd(PPh_3)_4$ (Table 1, entry 9). Further optimization revealed that the $Pd_2(dba)_3$•$CHCl_3$−dppf combination, which appeared to be an inferior catalyst for the 3-methyl-3-phenylcyclopropene **1a** (Table 1, entry 7), provided a much better *trans*/*cis* ratio with the ester-substituted substrate **1b** (Table 1, entry 10). Other ester-containing cyclopropenes **1c**,**d** afforded the corresponding products with equally high diastereoselectivities (Table 2, entries 3 and 4). In contrast to the phenyl-substituted analog **1a**, all esters reacted

(18) It was demonstrated that the diastereoselectivity of this process is temperature-dependent. See Supporting Information for details.

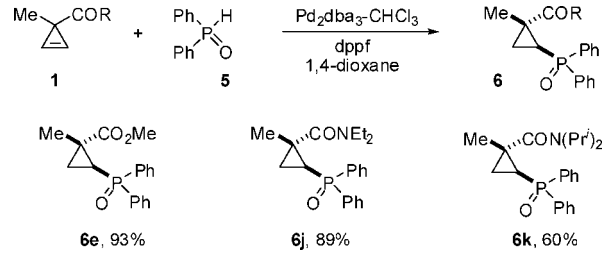
(19) See Supporting Information for details.

smoothly at ambient temperature, providing complete conversion within 1−2 h (Table 2, entries 2−7). Diastereoselectivity of hydrophosphorylation was mainly controlled by sterics, as evident from the comparison of the results obtained using 1-methyl-substituted cyclopropenylcarboxylates **1b**−**d** (entries 2−4) with those of the 1-phenyl- (entry 5) and 1-TMS-substituted analogs (entry 6). Indeed, while the reactions of cyclopropenes **1a**−**d** predominantly provided products **4a**−**d** in a *trans*-configuration, introduction of the bulky phenyl substituent in the structure (**1e**) led to a significant deterioration of the diastereoselectivity (entry 5). Finally, installation of an even larger TMS group (**1f**) resulted in reversal of diastereoselectivity, affording cyclopropyl phosphonate **4f** with the phosphorus moiety oriented *cis* with respect to the ester function.

We further examined the hydrophosphorylation reaction on a series of 3-carboxamidocyclopropenes **1h**−**k** (Table 2, entries 8−11). It was found that, in contrast to cyclopropenylcarboxylates, amides **1h**−**k** reacted more sluggishly and required prolonged heating at 50−55 °C. Nonetheless, the corresponding products **4h**−**k** were obtained in good yields with high to excellent diastereoselectivities (Table 2, entries 7−10).

Inspired by the success in the catalytic hydrophosphorylation, we explored the possibility of addition of diorganylphosphine oxides to cyclopropenes.[20] Gratifyingly, the conditions optimized for hydrophosphorylation also proved efficient for the hydrophosphinylation reaction (Scheme 3). The reactivity pattern was similar to that observed in the hydrophosphorylation reaction. Thus, ester **1e** underwent the transformation quickly at room temperature, while reaction of amides **1j** and **1k** required extended heating at 50−55 °C for complete conversion. Importantly, in all three cases, the corresponding cyclopropylphosphine oxides **6e**,**j**,**k** were obtained in excellent yield as single diastereomers (Scheme 3).

Scheme 3. Palladium-Catalyzed Hydrophosphinylation of Cyclopropenes[a]



[a] Reaction conditions. **6e**: 1 h at 25 °C; **6j**: 48 h at 55 °C; **6k**: 78 h at 50 °C.

In conclusion, a novel, efficient transition-metal-catalyzed method for diastereoselective addition of cyclic phosphites and phosphine oxides across the strained double bond of cyclopropene was developed. This transformation is applicable to a wide range of 3,3-disubstituted cyclopropenes and is general with respect to the electronic nature of the P−H entity. The discovered method has great potential for providing expeditious access to a series of novel functionalized cyclopropylphosphonic acids and cyclopropylphosphines. Studies on the possibility of carrying out this reaction in an asymmetric fashion is currently underway in our laboratories.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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