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Rhodium-Catalyzed Regioselective Olefin Hydrophosphorylation

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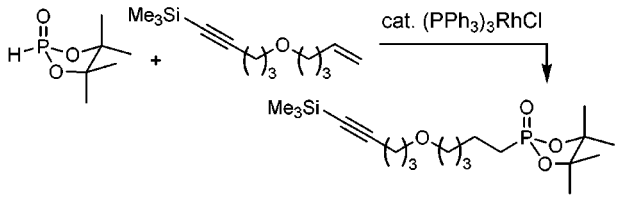
ABSTRACT



Parameters influencing the selectivity of the $(PPh_3)_3RhCl$-catalyzed hydrophosphorylation of olefins and enynes are described. The reaction between differentiated dienes was shown to be highly responsive to olefin substitution. The trimethylsilyl group effectively reversed the normal preference for hydrophosphorylation of an alkyne over an alkene.

New methods for phosphonate synthesis continue to attract attention because phosphonates display biologically important properties as natural products,[1] analogues of phosphates[2] (including RNA/DNA),[3] phosphonopeptides,[4] amino acid analogues,[5] and pro-drugs.[6] The number of methods for the preparation of organophosphonates is limited, and traditionally phosphonates are prepared by Arbuzov reaction of phosphites with organic halides.[7] Given the indispensable utility of phosphonates as bioactive molecules and synthetic tools (e.g., Wadsworth−Emmons and related reactions), research into the synthesis of phosphonates and associated reactions is important. In this regard, Tanaka recently reported the palladium(II)-catalyzed hydrophosphorylation of terminal and strained cyclic olefins with the pinacol-derived phosphonite **1** (Scheme 1).[8−0]

A significant advantage of transition metal catalyzed olefin hydrophosphorylations over traditional phosphonate synthesis is the mild reaction conditions. However, to successfully predict the effectiveness of the reaction in the context of a complex synthetic target with multiple sites of unsaturation, information regarding the selectivity of the olefin hydrophosphorylation is required. In addition to defining the parameters that influence the selectivity between differentiated olefins, the effect and compatibility with other functionalities such as amides and vinyl ethers need to be addressed. Currently, the major drawback of the hydrophosphorylation reaction shown in Scheme 1 is its dependence upon *cis*-$PdMe_2(PPh_2(CH_2)_4PPh_2)$ as catalyst, which is air-

(1) For a review, see: Fields, S. C. *Tetrahedron* **1999**, *55*, 12237−12273.
(2) For a review, see: Blackburn, M. G. *Chem. Ind. (London)* **1981**, 134−144.
(3) For reviews, see: (a) Eckstein, F.; Thomson, J. B. *Methods Enzymol.* **1995**, *262*, 189−202. (b) Egli, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1894−1909. (c) De Clercq, E. *Biomed. Pharmacother.* **1996**, *50*, 207−215.
(4) For a review, see: Failla, S.; Finocchiaro, P.; Consiglio, G. A. *Heteroat. Chem.* **2000**, *11*, 493−504. For a recent report: Rushing, S. D.; Hammer, R. P. *J. Am. Chem. Soc.* **2001**, *123*, 4861−4862.
(5) Kafarski P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Prod.* **1991**, *63*, 193−215.
(6) For a review, see: Krise, J. P.; Stella, V. J. *Adv. Drug Delivery Rev.* **1996**, *19*, 287−310.
(7) (a) *Organic Phosphorus Compounds*; Kosolapoff, G. M., Maier, L., Eds.; Wiley-Interscience: New York, 1972. (b) *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992. (c) Corbridge, D. E. C. *Phosphorus: An Outline of Its Chemistry, Biochemistry and Uses*, 5th ed.; Elsevier: Amsterdam, 1995.
(8) Han, L.-B.; Mirzaei, F.; Zhao, C.-Q.; Tanaka, M. *J. Am. Chem. Soc.* **2000**, *122*, 5407−5408.
(9) Radical olefin hydrophosphorylation is known: Stiles, A. R.; Vaughan, W. E.; Rust, F. F. *J. Am. Chem. Soc.* **1958**, *80*, 714−716.
(10) Alkyne hydrophosphorylation was reported previously, see: (a) Han, L.-B.; Zhao, C.-Q.; Tanaka, M. *J. Org. Chem.* **2001**, *66*, 5929−5932. (b) Han, L.-B.; Hua, R.; Tanaka, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 94−96. (c) Han, L.-B.; Choi, N. R.; Tanaka, M. *Organometallics* **1996**, *15*, 3259−3261. (d) Zhao, C.-Q.; Han, L.-B.; Goto, M.; Tanaka, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1929−1932.

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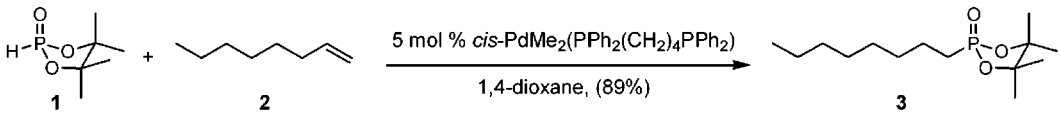
Scheme 1



sensitive and not commercially available.[11] A better catalyst would be commercially available, more robust and relatively air-stable. In this communication we disclose that Wilkinson's catalyst, $(PPh_3)_3RhCl$, efficiently catalyzes olefin hydrophosphorylation and describe the effect of alkene and alkyne substitution on the selectivity of the reaction.

A preliminary screening of various metal species in dioxane at 100 °C, including $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and $(PPh_3)_3RhCl$, revealed that each catalyzed the hydrophosphorylation of 1-octene **2** in the presence of hydrogen phosphite **1**,[12] albeit in moderate yields (Table 1).[13] However,

Table 1. Effect of Metal Catalyst and Additives on the Hydrophosphorylation Reaction **1** + **2** → **3**[a]

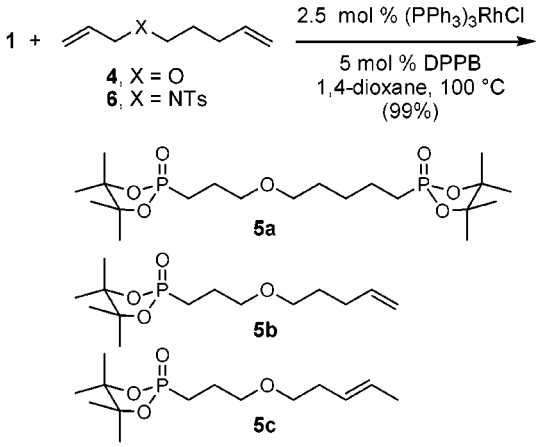
entry	catalyst	mol %	additive	yield[d] (%)
1[b]	$(PPh_3)_3RhCl$	5		57
2[c]	$(PPh_3)_3RhCl$	5	5% DPPB	95
3[c]	$(PPh_3)_3RhCl$	2.5	2.5% DPPB	91
4[b]	$(PPh_3)_3RhCl$	1.25	1.25% DPPB	85 (99)[e]
5[c]	$(PPh_3)_3RhCl$	1.25	5% DPPB	99
6[b]	$(PPh_3)_3RhCl$	5	10% Ph_3P	42
7[b]	$(PPh_3)_3RhCl$	5	10% $^nBu_3P$	nr[f]
8[b]	$(PPh_3)_3RhCl$	5	5% DPPB, 150% DMF	96
9[b]	$Pd(PPh_3)_4$	5		37
10[b]	$Pd_2(dba)_3$	2.5	5% DPPB	25

[a] Reactions were performed at 100 °C in 1,4-dioxane under an atmosphere of Ar. [b] One milimole scale. [c] Ten milimole scale. [d] Isolated yields. [e] After additional DPPB.[15] [f] No reaction.

in the presence of $Ph_2P(CH_2)_4PPh_2$ (DPPB), Wilkinson's catalyst gave excellent yields (entry 2, 95%).[14] The formation of DPPB oxides during the course of the reaction suggested that DPPB might serve to reduce a catalytically inactive oxidized rhodium species. In entry 4 the reaction failed to go to completion, but the stalled reaction resumed upon addition of additional DPPB.[15] In this regard, the addition of more than 1 equiv of DPPB per rhodium allowed efficient and reproducible hydrophosphorylation with low catalyst loading (1.25 mol % rhodium, entry 5). Substituting DPPB with more economical phosphines either had no effect on turnover versus Wilkinson's catalyst alone (Ph_3P, entry 6) or fully attenuated catalyst activity ($^nBu_3P$, entry 7).

With an active and convenient rhodium catalyst in hand, an investigation into its ability to differentiate between two dissimilar olefins was initiated. To determine whether subtle electronic effects could direct the hydrophosphorylation, diene **4** was treated with 0.9 equiv of **1** under the new catalysis conditions (Scheme 2).[16] The products **5a**, **5b**, and

Scheme 2



5c were obtained in a 1.3:1:1 ratio, and therefore only a small 3:1 preference existed for reaction at the allylic position. Additionally, isomerization of the bis-homoallylic olefin to an internal position occurred in **5c**. Similar yield and product distributions were observed with tosamide **6**.

While substrates **4** and **6** showed that a subtle electronic difference between olefins was insufficient to significantly control the regioselectivity of the hydrophosphorylation,[17] the catalyst was adept at distinguishing between disubstituted and monosubstituted olefins, as summarized in Table 2. In the competition between a terminal olefin and a stereochemically pure trans olefin (entry 1), reaction occurred only at the sterically more accessible position, and the stereochemical integrity of the trans olefin remained intact. In entry 2 complete regiocontrol was also observed, but in this instance

(11) de Graaf, W.; Boersma, J.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *Organometallics* **1989**, *8*, 2907−2917.

(12) The use of $HP(O)Ph_2$ and $HP(O)(OEt)_2$ failed in the reaction. Details will be described elsewhere.

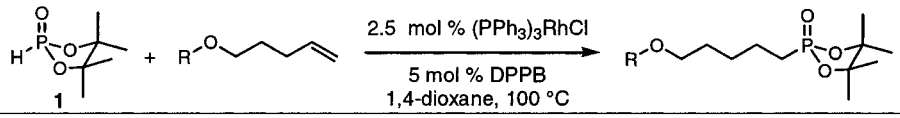
(13) Similar results have been observed; see ref 8.

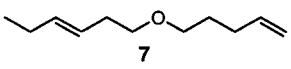
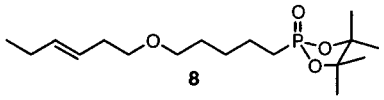
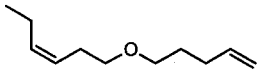
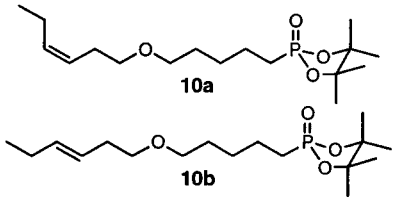
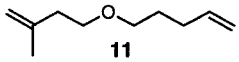
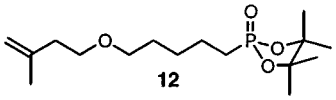
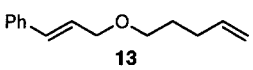
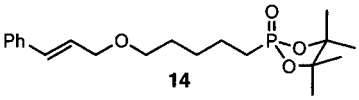
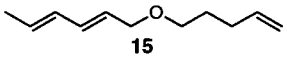
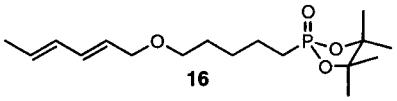
(14) Although reactions were typically assembled in an inert atmosphere glovebox, the use of Wilkinson's catalyst that had been stored exposed to air for weeks performed equally well provided 2 equiv of DPPB per Rh was added to the reaction.

(15) The reaction mixture was yellow throughout the initial period of the reaction but turned orange/brown before complete consumption of phosphonate **1** (85% yield from one-half of the reaction). After 2 mol % additional DPPB was added to the reaction, the yellow color returned and the reaction proceeded to completion.

(16) **General Experimental Procedure.** A round-bottomed flask was charged with the olefin (1.1 equiv), hydrogen phosphonate **1** (1.0 equiv), 2.5 mol % $(PPh_3)_3RhCl$, 5 mol % DPPB, and dioxane (0.25 M). The reaction mixture was heated at 100 °C for 20 h and then concentrated in vacuo. The phosphonates were purified by flash chromatography on silica gel.

Table 2. Selective Hydrophosphorylation

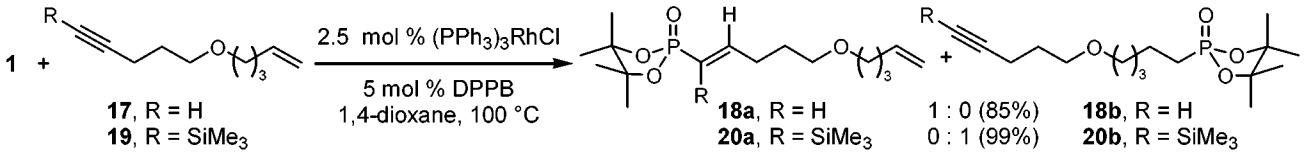


Entry	Substrate	Product(s)	Isolated Yield (ratio)
1			91%
2			81% (1:1)
3			95%
4			90%
5			56%

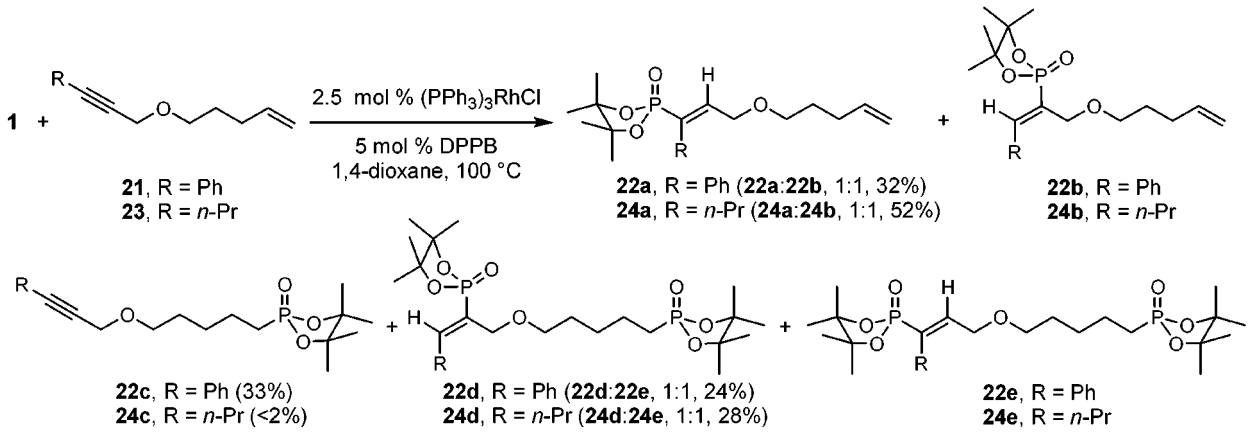
stereochemical scrambling to the trans olefin **10b** occurred in half of the product. Isomerization of the cis olefin suggests a close interaction with the rhodium catalyst, but no internal hydrophosphorylation was detected. In entry 3, preference for the terminal olefin over the 2,2-disubstituted alkene was observed. Attempts to achieve hydrophosphorylation at the remaining site of unsaturation in **12** by employing an excess of hydrogen phosphonate **1** were unsuccessful. In entry 4, the internal olefin is in conjugation with a phenyl ring, and this had no impact on the selectivity or yield of the reaction. In entry 5, only hydrophosphorylation was observed at the terminal olefin, and the low 56% yield was accredited to the instability of the product that decomposed on standing.[18]

While alkyne hydrophosphorylation is well documented,[10] no reports have appeared on the selectivity of hydrophosphorylation of alkynes versus monosubstituted olefins. To address this deficiency, treatment of enyne **17** under the standard reaction conditions[16] gave the *E* vinyl phosphonate **18a** as a single regio- and stereoisomer from hydrophosphorylation exclusively at the triple bond (Scheme 3). Importantly, substitution of the terminal alkyne with a trimethylsilyl protecting group (*n*-BuLi, THF, −78 °C; Me_3SiCl, 96%) resulted in a reversal of reactivity and only the olefin underwent hydrophosphorylation (**19** → **20b**). The TMS protecting group allows access to the terminal alkyne for further functionalization, as it can be easily removed with methanolic K_2CO_3 or Bu_4NF. In contrast to the impressive regioselectivity observed in the above experiments, competitive hydrophosphorylation with enynes **21** and **23** gave complex mixtures of regio- and stereoisomers (Scheme 4).

Scheme 3



Scheme 4



In summary, we have reported that $(PPh_3)_3RhCl$ in the presence of DPPB is an efficient catalyst for the hydrophosphorylation of olefins.[19] The reaction is highly sensitive to olefin substitution, and monosubstituted olefins can be reliably converted to their aliphatic phosphonates in the presence of other olefins. Additionally, a trimethylsilyl group is an effective acetylene protecting functionality that reverses the normal preference for alkyne hydrophosphorylation over a terminal olefin.

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Supporting Information Available: Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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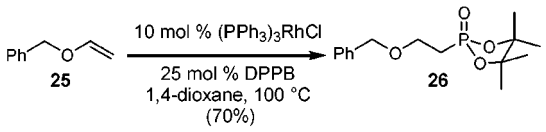
(17) To explore whether more significant electronic effects would influence the hydrophosphorylation of a monosubstituted olefin, the vinyl ether **25**, a substrate that offers an attractive synthetic handle for further synthetic modifications, was exposed to our standard reaction conditions.[16] This gave rather disappointing results, but by increasing both the catalyst loading and the reaction time (2 d) a 70% yield of the β-benzyloxy phosphonate **26** was obtained.



(18) Palladium-catalyzed hydrophosphorylation of dienes has been reported: Miraei, F.; Han, L.-B.; Tanaka, M. *Tetrahedron Lett.* **2001**, *42*, 297−299.

(19) The use of pinacol-derived phosphonates in Horner-like coupling reactions will be described elsewhere.