deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-156951. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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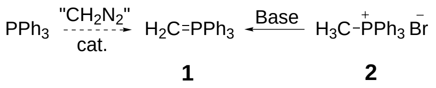
Methylenation of Aldehydes: Transition Metal Catalyzed Formation of Salt-Free Phosphorus Ylides**

Hélène Lebel,* Valérie Paquet, and Caroline Proulx

Among the olefination processes,[1] the methylenation of carbonyl derivatives is a very important transformation in synthesis.[2] Recently even more attention has been devoted to this reaction since terminal alkenes are ideal precursors for ring-closing metathesis reactions.[3] Although the Wittig reaction has been quite reliable for performing this transformation, several drawbacks are still associated with it. The most important problems include the low reactivity of the reagent with sterically hindered carbonyl derivatives as well as the possible epimerization of base-sensitive substrates.[4] Several systems employing stoichiometric amounts of organometallic reagents have been developed to overcome these problems. For example, organometallic compounds based on titanium (Tebbe/Petasis) and zinc (Oshima/Lombardo) provide efficient methylenation of numerous carbonyl substrates.[5] However, the use of stoichiometric amounts of expensive and in some cases pyrophoric compounds, as well as the competitive reductive coupling of aldehydes observed with these reagents,[6] are undesired factors and indicate that there is still a significant need to develop new reagents to carry out this transformation. Few approaches to transition metal catalyzed olefinations have been disclosed, but they are all limited to the synthesis of α,β-unsaturated esters.[7, 8]

Numerous methods for the preparation of phosphorus ylides by deprotonation of phosphonium salts with a base have been reported.[9] Conversely, sulfur, oxonium, nitrogen, carbonyl, and thiocarbonyl ylides have been successfully prepared from diazo compounds with the use of transition metal catalysts.[10] However, with the exception of one report by Fujimura and Honma on the use of diazoacetate precursors,[11] such a strategy has never been applied to the preparation of phosphorus ylides. Here we disclose the first transition metal catalyzed methylenation of aldehydes, based on the synthesis of salt-free phosphorus ylides from diazo reagents.

In principle, the generation of $Ph_3P{=}CH_2$ (**1**) requires the use of CH_2N_2 as the diazo precursor (Scheme 1). Our first attempts at the methylenation of cinnamaldehyde (**3**) with CH_2N_2 using $[RuCl(NO)(PPh_3)_2]$ as the catalyst were very disappointing (Table 1, entries 1, 2). No alkene product was observed, although $[RuCl(NO)(PPh_3)_2]$ is known to produce stable carbene species in the presence of CH_2N_2.[12] We also investigated $TMSCHN_2$ (TMS = trimethylsilyl) as a safer alternative to CH_2N_2, since $Ph_3P{=}CHTMS$ can be rapidly desilylated in the presence of an alcohol to generate the corresponding salt-free phosphorus methylide.[13, 14] The methylenation of **3** proceeded smoothly with $TMSCHN_2$ in the presence of PPh_3 and $[RuCl(NO)(PPh_3)_2]$. In the absence of an alcohol, diene **4** was produced quantitatively in 16 h (entry 3). In contrast, conversion was quantitative after 2 h when one equivalent of 2-propanol was added (entry 4). For comparison, only 45 % conversion was observed for the formation of α,β-unsaturated ester **5** under similar conditions with ethyl diazoacetate (EDA, entry 5). We then surveyed various catalysts for the methylenation of **3** with $TMSCHN_2$, PPh_3, and 2-propanol. Many ruthenium and rhodium complexes effectively catalyzed the methylenation with $TMSCHN_2$ and 2-propanol, whereas low activity was often observed with EDA. The best catalytic activity was observed with Wilkinson's catalyst, $[RhCl(PPh_3)_3]$, which allowed the quantitative conversion of **3** into diene **4** within 30 min at 25 °C with $TMSCHN_2$ (entry 14). Again, the combination of $TMSCHN_2$ and 2-propanol proved to be superior to CH_2N_2 and EDA (entries 12, 13). Under similar conditions, $[\{Rh(OAc)_2\}_2]$ was inefficient at catalyzing the olefination of **3** (entries 23, 24).



$$PPh_3 \xrightarrow[\text{cat.}]{\text{"}CH_2N_2\text{"}} \underset{\mathbf{1}}{H_2C{=}PPh_3} \xleftarrow{\text{Base}} \underset{\mathbf{2}}{H_3C{-}\overset{+}{P}Ph_3\ \overset{-}{Br}}$$

Scheme 1. Generation of **1**.

The catalyst loading could be lowered to 2.5 mol % with no detrimental effect on the activity when $[RhCl(PPh_3)_3]$ was

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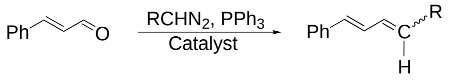
Table 1. The effect of the catalyst on the olefination of **3**.



3

R = H (**4**), CO_2Et (**5**)

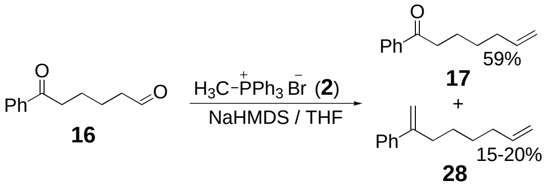
Entry	Catalyst[a]	Diazo compound	Conditions	Conv. [%][b] (product)
1	$[RuCl(NO)(PPh_3)_2]$	CH_2N_2	THF, 50 °C, 16 h	≤ 5
2	$[RuCl(NO)(PPh_3)_2]$	CH_2N_2	benzene, 50 °C, 16 h	≤ 5
3	$[RuCl(NO)(PPh_3)_2]$	$TMSCHN_2$	THF, 50 °C, 16 h	≥ 98 (**4**)
4	$[RuCl(NO)(PPh_3)_2]$	$TMSCHN_2$	THF/*i*PrOH, 50 °C, 2 h	≥ 98 (**4**)
5	$[RuCl(NO)(PPh_3)_2]$	EDA	THF, 50 °C, 16 h	45 (**5**)
6	$[RuCl_2(PPh_3)_3]$	$TMSCHN_2$	THF/*i*PrOH, 50 °C, 16 h	≥ 98 (**4**)
7	$[RuCl_2(PPh_3)_3]$	EDA	THF, 50 °C, 8 h	92 (**5**)[c]
8	$[Ru(NO)_2(PPh_3)_2]$	$TMSCHN_2$	THF/*i*PrOH, 50 °C, 16 h	90 (**4**)
9	$[Ru(NO)_2(PPh_3)_2]$	EDA	THF, 50 °C, 16 h	≤ 5
10	$[RuClCp(PPh_3)_2]$	$TMSCHN_2$	THF/*i*PrOH, 50 °C, 16 h	90 (**4**)
11	$[RuClCp(PPh_3)_2]$	EDA	THF, 50 °C, 16 h	40 (**5**)
12	$[RhCl(PPh_3)_3]$	CH_2N_2	THF, 25 °C, 16 h	60 (**4**)
13	$[RhCl(PPh_3)_3]$	EDA	THF, 25 °C, 16 h	60 (**5**)
14	$[RhCl(PPh_3)_3]$	$TMSCHN_2$	THF/*i*PrOH, 25 °C, 0.5 h	≥ 98 (**4**)
15	$[RhCl(PPh_3)_3]$[d]	$TMSCHN_2$	THF/*i*PrOH, 25 °C, 0.5 h	≥ 98 (**4**)
16	$[RhCl(PPh_3)_3]$	$TMSCHN_2$	THF/*i*PrOH, 0 °C, 16 h	31 (**4**)
17	$[RhCl(PPh_3)_3]$	$TMSCHN_2$	THF/MeOH, 25 °C, 0.5 h	78 (**4**)
18	$[RhCl(PPh_3)_3]$	$TMSCHN_2$	THF/EtOH, 25 °C, 0.5 h	87 (**4**)
19	$[RhCl(PPh_3)_3]$	$TMSCHN_2$	THF/*t*BuOH, 25 °C, 0.5 h	16 (**4**)
20	$[RhCl(PPh_3)_3]$	$TMSCHN_2$	CH_2Cl_2/*i*PrOH, 25 °C, 1 h	≥ 98 (**4**)
21	$[RhCl(PPh_3)_3]$	$TMSCHN_2$	Et_2O/*i*PrOH, 25 °C, 5 h	≥ 98 (**4**)
22	$[RhCl(PPh_3)_3]$	$TMSCHN_2$	toluene/*i*PrOH, 25 °C, 16 h	≥ 98 (**4**)
23	$[\{Rh(OAc)_2\}_2]$	EDA	THF, 25 °C, 16 h	≤ 5
24	$[\{Rh(OAc)_2\}_2]$	$TMSCHN_2$	THF/*i*PrOH, 25 °C, 16 h	≤ 5

[a] Catalyst: 5 mol%. [b] Determined by gas chromatography (GC). [c] Yield of isolated product, see reference [11]. [d] Catalyst: 2.5 mol%. EDA = ethyl

used with $TMSCHN_2$ and 2-propanol (Table 1, entry 15). Below this concentration, the reaction did not go to completion. Only 31% conversion was observed when the reaction was carried out at 0 °C, (entry 16). 2-Propanol was the best alcohol surveyed (entries 14 vs 17–19). Although THF was the most effective solvent, equally high conversions were obtained in dichloromethane, diethyl ether, and toluene, but longer reaction times were required (entries 20–22).

The reaction conditions used were quite general (Table 2). In all cases, terminal alkenes were isolated in excellent yields. Methylenation of the aromatic aldehyde **12** produced the styrene derivative **13** in 60% yield (entry 5). This result is impressive since the highest yield reported so far for the synthesis of **13** was only 33% using Lombardo's reagent.[4f] The sterically hindered aldehyde **14** reacted smoothly to produce alkene **15** in 79% yield (entry 6). In contrast, **15** was isolated in only 40% and 50% yield when **1** was generated from **2** upon reaction with PhLi or sodium 1,1,1,3,3,3-hexamethyldisilazane (NaHMDS), respectively (see Scheme 1).[15]

The reaction can be performed in the presence of secondary amides (Table 2, entry 5), enolizable ketones (entry 7), or epoxides (entry 8), and a wide variety of protecting groups are compatible (silyl and benzyl ethers, acetonides, carbamates). The reaction with aldehyde **16** was highly chemoselective and resulted in the exclusive formation of **17** in 87% yield (entry 7). For comparison, alkene **17** was isolated in only 59% yield, along with product **28** in 15–20% yield, when **16** was treated with **1** generated by deprotonation of **2** with NaHMDS [Eq. (1)]. The new reaction conditions are mild and nonbasic, thus chiral nonracemic α-substituted aldehydes react without epimerization. The Garner's aldehyde **24** (93% *ee*) was converted into **25** in 86% yield and with 93% *ee* (entry 11). Finally, aldehyde **26** afforded the terminal alkene **27** in 89% yield while maintaining the stereochemical integrity of the adjacent chiral center (entry 12). These observations are in sharp contrast to the results obtained with non-lithium-free phosphorus ylides.[4]



16

17

28

(1)

In contrast to the reported methods of olefination based on decomposition of transition metal diazo compounds, it seems unlikely that the current reaction proceeds through a metal carbene intermediate. No reaction was observed when **3** was treated with the preformed metal carbene $[CH_2{=}RuCl(NO)(PPh_3)_2]$ obtained from CH_2N_2 and $[RuCl(NO)(PPh_3)_2]$.[12] In addition, no carbene was detected by spectroscopic methods when $TMSCHN_2$ and 2-propanol were added to $[RuCl(NO)(PPh_3)_2]$. Rhodium(II) acetate, known for producing metal carbenes with diazo compounds, was inefficient at catalyzing the olefination reaction at room temperature. Finally, it is known that diazo compounds react with Rh^I

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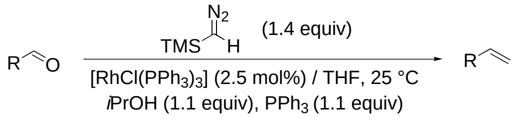
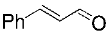
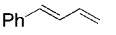
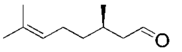
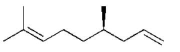
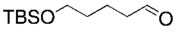
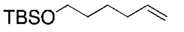
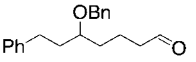
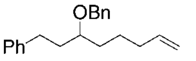
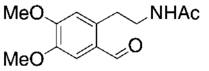
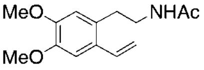
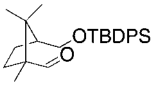
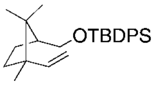
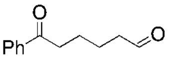
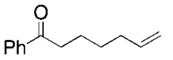
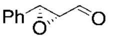
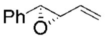
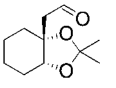
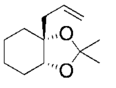
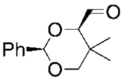
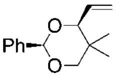
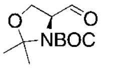
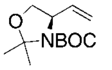
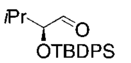
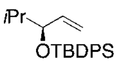
Table 2. The Rh-catalyzed methylenation of aldehydes.



Entry	Substrate	Product	t [h]	Yield [%][a]
1	 **3**	 **4**	0.5	88
2	 **6**	 **7**	7	84
3	 **8**	 **9**	8	91
4	 **10**	 **11**	1	98
5	 **12**	 **13**	0.5	60
6	 **14**	 **15**	7	79
7	 **16**	 **17**	0.5	87
8	 **18**	 **19**	1	86
9	 **20**	 **21**	1.5	79
10	 **22**	 **23**	5	74
11	 **24**	 **25**	4	86
12	 **26**	 **27**	3	89

[a] Yield of isolated product.

through nitrogen complexation and the adduct does not produce carbene species.[16] The proposed catalytic cycle involves the activation of the TMSCHN$_2$ by [RhCl(PPh$_3$)$_3$] through nitrogen complexation. Nucleophilic attack by PPh$_3$ followed by desilylation (mediated by 2-propanol) and nitrogen extrusion leads to the formation of Ph$_3$P=CH$_2$ (**1**) and regeneration of the catalyst. The formation of **1** was confirmed by ^{31}P NMR spectroscopy when TMSCHN$_2$ (1.0 equiv) was mixed with PPh$_3$ (1.0 equiv), 2-propanol (1.0 equiv), and [RhCl(PPh$_3$)$_3$] (2.5 mol%).

In conclusion, we have developed the first Rh^{I}-catalyzed methylenation of aldehydes using readily available reagents. The conditions are mild enough to be compatible with sensitive and enolizable substrates, thus highlighting the nonbasic character of phosphorus ylides in the absence of an inorganic component.

Experimental Section

Representative procedure: To a solution of [RhCl(PPh$_3$)$_3$] (0.023 g, 0.025 mmol) and PPh$_3$ (0.577 g, 2.20 mmol) in THF (10 mL) was added 2-propanol (0.15 mL, 2.00 mmol) followed by the substrate (2.00 mmol). TMSCHN$_2$ (1.75 mL, 2.80 mmol) was added to the resulting red mixture. Immediate gas evolution was observed, and the mixture was stirred at room temperature. Extraction and subsequent purification by flash chromatography provide the desired alkene.

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Carbanions Substituted by Transition Metals: Synthesis, Structure, and Configurational Restrictions of a Lithium Titanium Phosphonate

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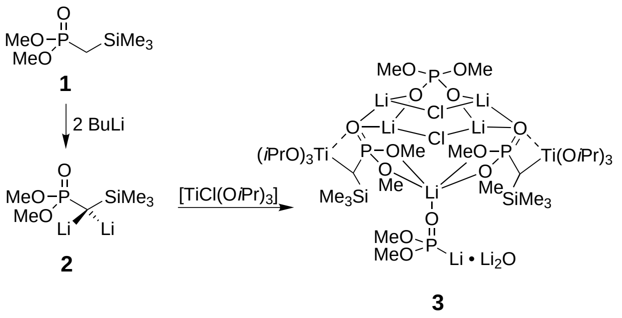
Lithium “carbanions” that are stabilized by transition metals represent a new class of organodimetallic reagents in which an acceptor-substituted anionic C atom is directly connected to a transition metal.[1] Such compounds are expected to possess properties that differ from those of ordinary acceptor-stabilized lithium compounds. In principle, multiple C–C bond-forming reactions are possible by the subsequent addition of various electrophiles, while the reactivity of the anionic C atom and its configurational stability could be directed by the steric and electronic impact of the transition metal.[2] Our main goal is the design and development of chirally modified organodimetallic reagents that facilitate highly stereoselective asymmetric transformations. Recently, we reported on the structure determination of a lithiated titanium sulfone, an intermediate that occurs in the *E*-selective olefination of aldehydes.[1, 3] As part of our program for the exploration and structure determination of new chiral organodimetallic compounds, we have synthesized a lithiated titanium phosphonate, determined its solid-state structure by X-ray analysis, and compared the experimental data with the results of density functional theory (DFT) calculations on a model system.[4, 5]

Dilithiation of dimethyl (trimethylsilylmethyl)phosphonate **1** with 2.2 equivalents of *n*BuLi in diethyl ether in the presence of a trace of water, followed by addition of [TiCl(O*i*Pr)$_3$] and removal of LiCl by filtration gave the lithium titanium phosphonate **3** as green crystals in 48% yield.[6] Figure 1 depicts a C3D plot of the aggregate **3**.



Compound **3** contains two monolithiated titanium phosphonate units together with two LiCl, Li$_2$O, lithiated

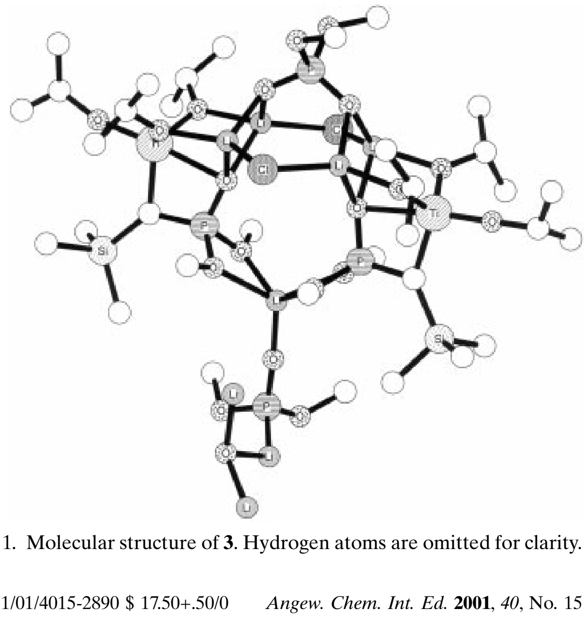


Figure 1. Molecular structure of **3**. Hydrogen atoms are omitted for clarity.

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