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First Titanium-Catalyzed 1,4-Hydrophosphination of 1,3-Dienes

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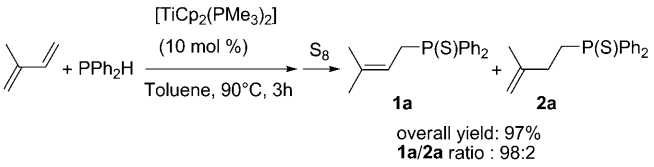
Tertiary phosphines are useful compounds widely employed as synthetic reagents in organic synthesis and as ligands for transition-metal complexes in organometallic catalysis. These compounds can be readily prepared by nucleophilic substitution using either phosphide anions or halogeno phoshines. A cleaner route to these compounds involves the addition of a P–H bond to an unsaturated C–C bond. This reaction, so-called hydrophosphination,[1] can be achieved under strong basic conditions[2] or radical activation.[3] Recently, metal-catalyzed hydrophosphination was revealed to be an attractive method that generally offers better control over regio- and stereoselectivity. In 1990, Pringle and Smith described the platinum-catalyzed hydrophosphination of acrylonitrile.[4] Ten years later, Marks and Douglass described the lanthanide-mediated intramolecular hydrophosphination of unactivated alkenes.[5] Since these pioneering works, the range of precatalysts for intra- and intermolecular hydrophosphination was extended to other metals such as nickel,[6] palladium,[7] rhodium,[8] cobalt,[9] or ruthenium.[10] Surprisingly, only one result using an early transition metal has been described,[11,12] although their use for the closely related hydroamination reaction has been known for a long time and clearly offers significant benefits.[13] Among these are the low cost of the metals, their low toxicity, and their eco-compatibility. Herein, we report the first regioselective 1,4-hydrophosphination of dienes using titanocene derivatives.

In 1998, Harrod et al. published an article dealing with the heterodehydrocoupling of phosphines and silanes catalyzed by titanium complexes.[14] He noticed that silanes and phosphines react in a similar way with titanocene. On the basis of this analogy and of our preliminary results on hydrosilylation,[15] we decided to examine the hydrophosphination of dienes using titanium-based catalysts. In an initial experiment, we carried out the reaction with isoprene and diphenylphosphine as substrates and $[TiCp_2(PMe_3)_2]$ as a precatalyst. The titanium species was first briefly heated at 90 °C with diphenylphosphine, resulting in a color change from brown to dark green. The flask was then cooled down to room temperature and isoprene was added dropwise. The reaction mixture was further stirred at 90 °C and monitored by GC analysis. To our delight, no remaining diphenylphosphine was detected after only three hours. NMR analysis of the products obtained after sulfidation confirmed that the hydrophosphination of isoprene occurred leading almost exclusively to the (3-methyl-but-2-enyl)diphenylthiophosphine (**1a**), which corresponds to the 1,4-tail-addition product (Scheme 1). Thus, for the first time, a titanium-based complex is revealed to be a remarkably efficient catalyst for the hydrophosphination of isoprene and outshines other catalysts in term of regioselectivity.[16,17]



Scheme 1. Titanium-catalyzed hydrophosphination of isoprene.

The difficulty in handling trimethylphosphine and the air-sensitive $[TiCp_2(PMe_3)_2]$ prompted us to scrutinize some other titanium(II) species to promote the reaction (Table 1). At first, we simply replaced $[TiCp_2(PMe_3)_2]$ by the unprotected titanocene "$[TiCp_2]$" generated in situ by adding two equivalents of *n*BuLi to a solution of titanocene dichloride in toluene. Using these conditions, the hydrophosphination of isoprene from PPh_2H proceeded as fast as the hydrophosphination catalyzed by $[TiCp_2(PMe_3)_2]$, but led to a mixture of 1,2- and 1,4-tail-addition products in a 1:1 ratio (Table 1,

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Supporting information for this article (experimental procedures, compounds characterisation data and EPR spectrum of the reaction mixture) is available on the WWW under http://dx.doi.org/10.1002/chem.200901863.

Table 1. Screening of titanium complexes for the catalytic hydrophosphination of isoprene from PPh_2H.[a]

Entry	Complex	Isolated yield [%]	**1a**/**2a** ratio
1	$[TiCp_2Cl_2]$[b]	94	50:50
2	[TiCp$_2$(BTMSA)]	92	51:49
3	$[TiCp_2(CO)_2]$	94	47:53
4	$[TiCp_2(PMe_3)_2]$	97	98:2
5	$[TiCpCl_2\{\eta^5\text{-}C_5H_4(CH_2)_2PPh_2\}]$[b]	96	97:3

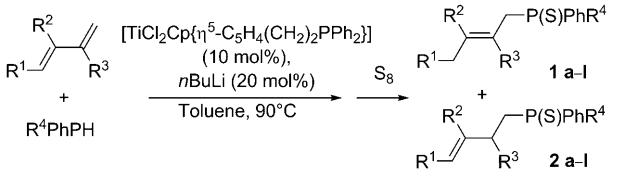
[a] Reaction conditions: Diphenylphosphine (0.21 mL, 1.25 mmol) and of isoprene (0.5 mL, 5 mmol) were added to a solution of complex (0.124 mmol) in toluene (2 mL). The reaction mixture was stirred 2 h at 90 °C (full consumption of Ph_2PH, followed by GC). S_8 (41.6 mg, 0.163 mmol) was added to allow easier purification on silica gel. The **1**/**2** ratio was determined by NMR spectroscopy. [b] *n*BuLi (2 equiv).

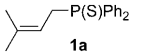
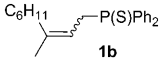
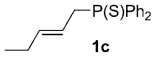
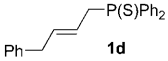
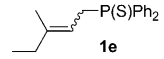
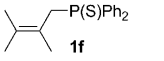
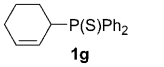
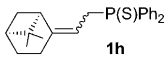
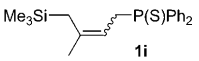
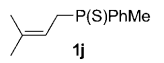
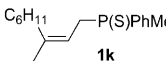
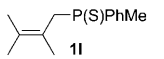
entry 1). Other titanocene complexes stabilized by CO or BTMSA (BTMSA = bis(trimethylsilyl)acetylene)[18] were used, but led in both cases to the same result (Table 1, entries 2 and 3). The reaction was then performed with [Ti(*i*PrO)$_2$(η^2-propene)], prepared in situ from $[Ti(OiPr)_4]$.[19] Surprisingly, the reaction under these conditions completely lost its regioselectivity leading to a mixture of 1,2- and 1,4-tail-addition products (**1a** and **2a**) accompanied by the two 1,4-head-addition products ((*Z*)- and (*E*)-2-methylbut-2-enyl)diphenylphosphine). We next envisaged the use of a phosphine-substituted titanocene as it is evident that the presence of the trimethylphosphine is a determining element for the regioselectivity of the reaction. Our group is indeed used to synthesize titanocene complexes bearing a pendant phosphine tether such as $[TiCl_2Cp\{\eta^5\text{-}C_5H_4(CH_2)_2PPh_2\}]$ (**3**)[20] for which previous studies have shown that the PPh_2 function is able to coordinate and so to stabilize the highly reactive titanium center obtained after reduction. Thus, the use of **3** as pre-catalyst and of two equivalents of *n*BuLi as reducing agent, under reaction conditions that were otherwise similar to those described above, led to the allylthiophoshine **1a** in 96 % yield with a regioselectivity comparable that obtained with $[TiCp_2(PMe_3)_2]$ (Table 1, entry 5 vs. 4).

The scope of the reaction was then explored using the in-situ-reduced form of $[TiCl_2Cp\{\eta^5\text{-}C_5H_4(CH_2)_2PPh_2\}]$ (**3**) instead of $[TiCp_2(PMe_3)_2]$. As highlighted in Table 2, the method proved to be successful for a wide range of dienes. Indeed, all the hydrophosphination products were obtained after sulfidation in high yields and excellent regioselectivities. Looking the results more in details, it appears that disubstituted 1,3-dienes or those substituted at the 1-position required longer reaction times than 1,3-dienes substituted at the 2-position to go to completion (Table 2, entries 3–6 vs. entries 1, 2 and 9). Cyclic dienes such as 1,3-cyclohexadiene underwent hydrophosphination to yield (cyclohex-2-enyl)diphenylthiophosphine (**1g**; Table 2, entry 7). The use of (1*R*)-nopadiene as substrate provided a straightforward route to the chiral allylthiophosphine **1h** in good yield (Table 2, entry 8). Interestingly, trimethylsilyl moiety did not interfere with the reaction and the addition of PPh_2H to 2-(trimethylsilylmethyl)-1,3-butadiene led to the allylthiophosphine **1i** with an $SiMe_3$ group in allylic position (Table 2, entry 9). Aware of the fact that most of the hydrophosphination reactions described to date are limited to PPh_2H,[1c] we attempted the titanium-catalyzed hydrophosphination with methylphenylphosphine. Although the reactions were slower to near completion, all the three dienes tested led to the 1,4-tail-addition products with very high yields, regio-, and diastereoselectivities (Table 2, entries 10, 11, and 12). In contrast to these results, the addition of the more basic phosphine PCy_2H to isoprene remained unsuccessful.

Regards to the diastereoselectivity of these reactions, changing from isoprene to other dienes involves the possibility to obtain either *E* or *Z* diastereoisomers for the 1,4-addi-

Table 2. Hydrophosphination of dienes using 10 mol % of $[TiCpCl_2\{\eta^5\text{-}C_5H_4(CH_2)_2PPh_2\}]$ (**3**) as precatalyst.[a]

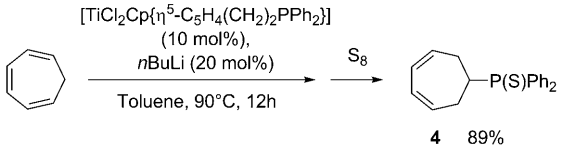


Entry	Diene	Product	*t* [h]	Isolated yield [%]	**1**/**2** ratio[b]
1	isoprene	 **1a**	3	96	97:3
2	myrcene	 **1b**	5	92	96:4[d]
3	1,3-pentadiene[c]	 **1c**	20	91	>98:2[e]
4	(*Z*)-1-phenyl-1,3-butadiene	 **1d**	24	88	>98:2[e]
5	3-methyl-1,3-pentadiene[c]	 **1e**	32	86	>98:2[f]
6	2,3-dimethyl-1,3-butadiene	 **1f**	12	97	>98:2
7	1,3-cyclohexadiene	 **1g**	22	89	>98:2
8	(1*R*)-nopadiene	 **1h**	16	86	>98:2[g]
9	2-(trimethylsilylmethyl)-1,3-butadiene	 **1i**	4	93	>98:2[h]
10	isoprene	 **1j**	16	97	98:2
11	myrcene	 **1k**	20	94	97:3[i]
12	2,3-dimethyl-1,3-butadiene	 **1l**	22	95	>98:2

[a] Reaction conditions: *n*BuLi (1.6 M in hexane, 0.155 mL, 0.248 mmol), phosphine (1.25 mmol) and diene (5 mmol) were successively added to a solution of **3** (58.6 mg, 0.124 mmol) in toluene (2 mL). The reaction mixture was stirred at 90 °C until full consumption of phosphine. [b] Determined by NMR spectroscopy. [c] A mixture of diastereoisomers was used. [d] *Z*/*E* ratio: 66:34. [e] Only the *E* isomer is formed. [f] *Z*/*E* ratio: 20:80. [g] *Z*/*E* ratio: 77:23. [h] *Z*/*E* ratio: 60:40. [i] Only the *Z* isomer is formed.

tion products **1**. The *Z*/*E* selectivity was unambiguously determined by NOESY NMR experiments and interestingly proved to be dependent upon the nature of the diene. For instance, whereas the hydrophosphination of myrcene led preferentially to the (*Z*)-allylthiophosphines (entries 2 and 11), other dienes such as 1,3-pentadiene and 1-phenyl-1,3-butadiene gave the (*E*)-allylthiophosphines (entries 3 and 4).

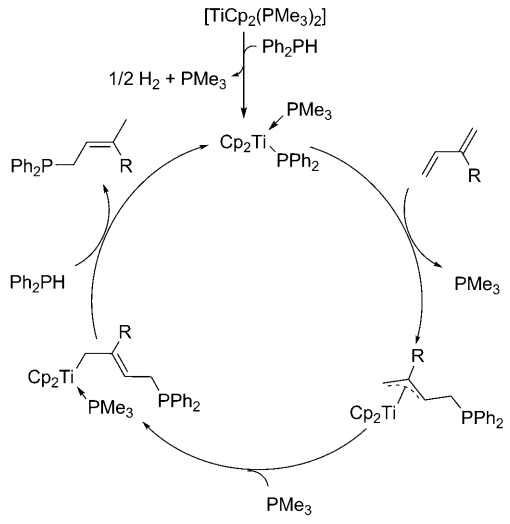
It is worth noting that the use of our titanium catalyst could be extended to the addition of PPh_2H to cyclic trienes and other C–C multiple bonds. Thus the addition of PPh_2H to 1,3,5-cycloheptatriene under similar conditions gave (3,5-cycloheptadienyl)diphenylthiophosphine (**4**) in 89% yield (Scheme 2). The hydrophosphination of styrene with diphenylphosphine could also be achieved. The reaction took 12 h at 90°C to near completion and led regioselectively to the *anti*-Markovnikov product ($Ph(CH_2)_2PPh_2$). Unfortunately, attempts to transpose this methodology to alkynes, such as phenylacetylene or diphenylacetylene, were ineffectual.



4 89%

Scheme 2. Hydrophosphination of 1,3,5-cycloheptatriene from PPh_2H catalyzed by $[TiCl_2Cp\{\eta^5\text{-}C_5H_4(CH_2)_2PPh_2\}]$ (**3**).

With regard to the mechanism of the hydrophosphination reaction, a proposed mechanism from $[TiCp_2(PMe_3)_2]$ and 2-substituted 1,3-dienes is reported in Scheme 3. This involves the formation of $[TiCp_2(PMe_3)(PPh_2)]$ generated from $[TiCp_2(PMe_3)_2]$ and diphenylphosphine.[14] Once this species formed, the labile PMe_3 is displaced by the less substituted double bond of the diene, which is then inserted into the titanium–phosphorous bond. At this stage, it is reasonable to assume that the *syn* π-allyl intermediate is formed as major isomer. Then, a π/σ rearrangement is initiated by the recoordination of PMe_3 (or of the PPh_2 function on the Cp ring in the case of **3**) to the titanium center. Finally protonolysis of the resulting η^1-allyl complex with the diphenylphosphine present in the reaction mixture leads to the 1,4-tail-addition product and regenerates $[TiCp_2(PMe_3)(PPh_2)]$ in the process.

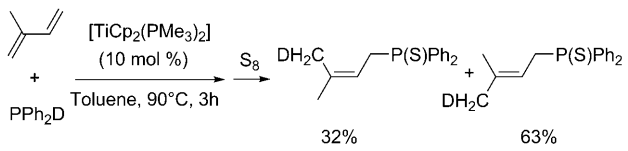


Scheme 3. Postulated mechanism of the $[TiCp_2(PMe_3)_2]$-catalyzed hydrophosphination of 2-substituted 1,3-dienes.

^{31}P NMR monitoring of the reaction of isoprene with PPh_2H using $[TiCp_2(PMe_3)_2]$ as catalyst was conducted. The spectra were recorded at room temperature from aliquots of the reaction mixture on running no-lock NMR sequences. Although the spectra clearly shows that the reaction did occur, no other signal than those due to PPh_2H, the allylphosphine, and the free PMe_3 could be observed. These data strongly suggest that the reaction produces NMR-silent paramagnetic titanium species. The presence of Ti^{III} species was indeed confirmed by the observation of unidentified signals in the EPR analysis of the reaction mixture. All the attempts to trap and to characterize these species using a stoichiometric amount of titanium complex led directly to the allylphosphine in moderate yields. Taking into account that the reaction is highly dependent on the concentration and pK_a of the phosphine, we presume that the protonolysis is the rate-determining step of the catalytic process and that the formation of the allyltitanium complex is reversible.

As mentioned above, the hydrophosphination of myrcene led preferentially to (*Z*)-allylphosphines, whereas other dienes led to (*E*)-allylphosphines. Although the opposite configurations of the double bond in these products is surprising at the first sight, it corresponds in fact to the same relative position of the (diphenylphosphino)methyl and R groups, which is consistent with the formation of the less congested *syn*-π-allyltitanium complex as the favored intermediate.

To confirm the ability of the intermediate $[TiCp_2(PMe_3)(PPh_2)]$ to catalyze the hydrophosphination reaction, we decided to generate this species using another procedure (i.e., addition of PPh_2H to $[TiCp_2(H)(PMe_3)]$ and to make use of the resulting complex for the catalytic addition of PPh_2H to isoprene. Using these conditions, the allylthiophosphine **1a** was obtained with 90% yield. Support of the mechanism outlined in Scheme 4 was also provided by a deuterium-labeling experiment. Thus, when the reaction of isoprene was conducted in the presence of PPh_2D and $[TiCp_2(PMe_3)_2]$ (10 mol%), the allylthiophoshine was obtained with 92% of



32% 63%

Scheme 4. 1,4-Addition of PPh_2D to isoprene catalyzed by $[TiCp_2(PMe_3)_2]$.

incorporation of deuterium at the methyl carbon atoms. The fact that the (*E*)-allylthiophosphine was predominant again gives evidence of the formation of the *syn*-π-allyltitanium complex as major intermediate.

In summary, we have described here the first titanium-catalyzed hydrophosphination of a wide range of dienes with excellent yields and the best regioselectivities ever encountered for this reaction. The importance of having a coordinating phosphine on the titanium toward the regioselectivity of the hydrophosphination has been demonstrated. We have also extended the scope of this reaction to cyclic dienes, trienes and activated olefins such as styrene. Preliminary results with methylphenylphosphine are presented and open the way of asymmetric titanium catalyzed hydrophosphination.

Experimental Section

Typical procedure for the titanium -catalyzed hydrophosphination of dienes: in a Schlenk tube, the titanium complex (e.g., **3**; 58.6 mg, 0.124 mmol) was introduced and suspended in freshly distilled toluene (2 mL). The mixture was cooled to −78 °C and then *n*BuLi was added (1.6 M in hexane, 0.155 mL, 0.248 mmol, 2 equiv). The brown solution was left for 1 h at −78 °C. Diphenylphosphine (0.21 mL, 1.25 mmol, 10 equiv) was added at room temperature and the solution was then warmed to 90 °C and slowly turned green. The solution was stirred for 10 min at 90 °C and cooled down to room temperature; isoprene (0.5 mL, 5 mmol, 40 equiv) was then added. The solution was then warmed again to 90 °C and stirred until full consumption of diphenylphosphine was observed (followed by GC). S_8 (41.6 mg, 0.163 mmol) was added to allow easy purification of the product by silica gel chromatography (Et_2O/pentane, 1:9), affording a colorless oil in 96 % yield (339.6 mg, 1.12 mmol).

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Keywords: dienes · homogeneous catalysis · hydrophosphination · phosphines · titanium

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