First catalytic allyltitanation reactions

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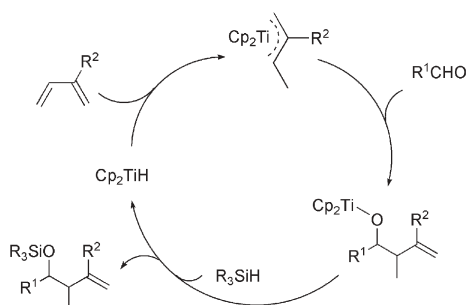
Catalytic allyltitanation reactions were accomplished from dienes and aldehydes with only 5% of titanocene complexes at the expense of employing stoichiometric amounts of PMHS.

π-Allyltitanium complexes can be readily prepared by hydro-titanation of conjugated dienes by [Cp$_2$TiH] generated *in situ* by the reaction of Cp$_2$TiCl$_2$ with Grignard reagent. They were first employed as effective allyl transfer reagents towards aldehydes and ketones to afford *anti* homoallylic alcohols with good regio- and diastereoselectivity.[1] Since then much effort has been devoted to extending the scope of this reaction using various dienes and electrophiles.[2] Since all the above mentioned studies required a stoichiometric amount of titanocene complex, the use of more sophisticated titanocene complexes (particularly precious optically active titanocene) is not reasonable. This report deals with the first catalytic version of this reaction with aldehydes as substrates.

In the original paper Sato reported that Cp$_2$TiCl$_2$ was recovered after the protic quench,[1a] therefore the development of a catalytic allyltitanation can be considered. A source of inspiration can be found in the catalytic epoxide opening.[3,4] Indeed this reaction, which also requires the *in situ* regeneration of Cp$_2$TiCl from Cp$_2$TiCl$_2$ after the protolytic cleavage of the Ti–O bond, has been achieved by the use of a stoichiometric amount of manganese dust. Nevertheless in the case of the catalytic allyltitanation, the *in situ* transformation of Cp$_2$TiCl into the allyltitanocene is required in addition.

Since the use of a Grignard reagent is not appropriate because of its high reactivity towards both HCl and carbonyl compounds, we decided to investigate a straightforward route consisting of the cleavage of the titanium alkoxide with a concomitant regeneration of titanocene(III) hydride species with the aid of silyl hydride (Scheme 1). Then the very sensitive and reactive complex [Cp$_2$TiH] would be trapped by diene to give π-allylic complex. Precedent for the σ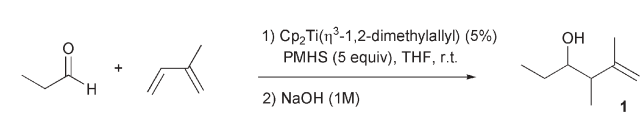-bond metathesis of the titanium–oxygen bond can be found in the catalytic hydrosilylation of organic carbonyl substrates.[5] Buchwald *et al.* have notably developed procedures for the hydrosilylation of esters, ketones and lactones with the safe and cheap poly(methylhydrosiloxane) (PMHS) as stoichiometric reductant and a catalytic amount of titanocene.[6]

These results prompted us to use silane for the catalytic allyltitanation to turnover. We reasoned that a slow addition of the aldehyde to the reaction mixture might allow the titanium hydride to react with diene rather than with aldehyde. With these conditions in mind, we decided to investigate the reaction of propanal with isoprene employing 5 equiv. of PMHS (relative to aldehyde) and 5% of π-allyltitanium complex generated *in situ* according to the stoichiometric reaction *i.e.* by using Cp$_2$TiCl$_2$ and 2 equiv. of ^{i}PrMgCl at 0 °C (entry 1 in Table 1). Once the purple π-allyltitanium complex was formed, the propanal was added at room temperature over 6 h by means of a syringe pump. The colour of the reaction mixture remained purple during almost 3 h and slowly passed from purple to orange-red. Then the reaction mixture was exposed to the air, diluted with 10 ml of THF and treated with 1 M NaOH (15 ml). Usual workup and flash chromatography afforded the homoallylic alcohol (1) in 42% yield as a mixture of two diastereoisomers (*anti* : *syn* = 60 : 40).[7]

Further experiments conducted with a longer addition time of the aldehyde didn't lead to significantly better yields. On the contrary, a rapid addition of the propanal to the reaction mixture a few minutes after the formation of the π-allyltitanium complex led immediately to a change of colour and to a dramatic decrease in yields (around 5%). In addition to 1, 10% of 6-methylhept-6-en-3-ol (2) [C$_2$H$_5$CH(OH)CH$_2$CH$_2$C(CH$_3$)=CH$_2$], which can be seen as the *anti*-Markovnikov product, was obtained after chromatographic purification of the crude mixture. Fortunately by revisiting the stoichiometric reaction we noticed that 2 can also be formed according to the purity of the π-allyltitanium complex used. Moreover, in a previous study relating to the synthesis of π-allyltitanium complexes, H. A. Martin has shown that the intermediate [Cp$_2$TiH] can be quickly deactivated by ^{i}PrMgCl if the concentration of diene is too low.[8] Therefore it can be assumed that such deactivation systematically occurred in our catalytic conditions leading to another titanium complex which catalysed the formation of 2.

We next examined the reaction of isoprene with propanal using other procedures to generate the π-allyltitanium complex. At first we simply replaced ^{i}PrMgCl by EtMgBr (entry 2 in Table 1) but it only led to 35% of the homoallylic alcohol (1) and 9% of 2. Then we reasoned that since [Cp$_2$TiH] is an intermediate in the formation of the π-allyltitanium complex, all the procedures described to synthesize titanium hydride could be envisioned. To test this hypothesis, we examined whether the procedure described

Scheme 1 Planned catalytic allyltitanation reactions.

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Table 1 Allyltitanation of propanal from isoprene[a]

1) Cp$_2$Ti(η^3-1,2-dimethylallyl) (5%)
PMHS (5 equiv), THF, r.t.

2) NaOH (1M)

Entry	Cp$_2$Ti(η^3-1,2-dimethylallyl) formation conditions	Yield of **1**[b] (%)
1	1. Cp$_2$TiCl$_2$, isoprene; 2. ^{i}PrMgCl (10%)/0 °C; 3. PMHS	42
2	1. Cp$_2$TiCl$_2$, isoprene; 2. EtMgBr (10%)/0 °C; 3. PMHS	35
3	1. Cp$_2$TiF$_2$; 2. PMHS/60 °C/2 min; 3. isoprene	55
4	1. Cp$_2$TiF$_2$, isoprene; 2. PhSiH$_3$ (10%); 3. PMHS	65
5	1. Cp$_2$TiCl$_2$, isoprene; 2. BuLi (10%)/−78 °C; 3. PMHS	90

[a] Conditions: catalyst (0.125 mmol), isoprene (10 mmol), PMHS (12 mmol). In all reactions the propanal (2.5 mmol) was added at room temperature over 6 h. [b] The ratio of the two diastereoisomers (*anti* : *syn*) is equal to 60 : 40 in all the cases.

Table 2 Catalytic allyltitanation of several aldehydes from various dienes[a]

			Homoallylic alcohol	
Entry	Diene	Aldehyde	Yield (%)	*anti* : *syn*[b]
1	isoprene	propanal	90	60 : 40
2	isoprene	hexanal	88	64 : 36
3	isoprene	citronellal	80	63 : 37
4	isoprene	isobutyraldehyde	48	70 : 30
5	isoprene	pivalaldehyde	24	> 95 : 5
6	isoprene	benzaldehyde	90	70 : 30
7	myrcene	propanal	86	60 : 40
8	butadiene	benzaldehyde	35	> 95 : 5

[a] Conditions: Cp$_2$TiCl$_2$ (0.125 mmol), BuLi (0.25 mmol), isoprene (10 mmol), PMHS (12 mmol). In all reactions the aldehyde (2.5 mmol) was added at room temperature over 6 h. [b] The ratio of the two diastereoisomers (*anti* : *syn*) was determinated by ^{1}H NMR analysis.

by Buchwald from Cp$_2$TiF$_2$ and PMHS could be used.[6c] Thus titanocene difluoride was briefly heated with PMHS at 60 °C (2 min) resulting in a colour change from yellow to dark blue. The flask was then cooled at 0 °C, and isoprene was added dropwise *via* syringe. The reaction mixture was stirred at room temperature until the colour passed from blue to dark purple (15 min). Then propanal was added to the *in situ* generated π-allyltitanium complex over 6 h to afford the homoallylic alcohols with 55% yield (entry 3). The use of phenylsilane as activating agent and of PMHS as stoichiometric reductant allowed us to increase the yield to 65% (entry 4). Although better yields were realised, more than 10% of the undesirable product (**2**) was still formed. According to the studies relating to the reaction of titanocenes with hydrosilanes it can be assumed that several titanium hydrides and silyl titanium hydrides are present in the reaction mixture.[6c,9] So we felt that among these species one catalyses the competitive formation of **2**. The fact that **2** is obtained whatever the catalytic conditions used (Cp$_2$TiCl$_2$–RMgX–PMHS or Cp$_2$TiF$_2$–PMHS) suggests that both systems have this species in common. Therefore we continued our efforts towards developing an improved protocol. Titanium hydride can also be formed by the reaction of titanocene dichloride with n-BuLi in the presence of PMHS.[10] The following reaction protocol employing lithium salt was then attempted. Two equiv. of n-BuLi were added to a THF solution of Cp$_2$TiCl$_2$ in the presence of isoprene at −78 °C. After 15 min, PMHS (5 equiv. per equiv. of aldehyde) was added and the reaction mixture was warmed to room temperature during which time the colour of the reaction mixture turned to dark purple. The propanal was then added at room temperature over 6 h and no colour change was observed. Usual treatment afforded the homoallylic alcohol (**1**) with 90% yield. It is important to point out that this new protocol eliminates the formation of the side product (**2**).

After optimizing our conditions using isoprene and propanal we explored the scope of this methodology (Table 2). Several trends are evident. The yield and the *anti* : *syn* ratio of the homoallylic alcohol are almost unaffected by increasing the length of the alkyl chain of the aliphatic primary aldehydes (entries 2,3). On the contrary, increasing the steric hindrance at the α-carbon of the aliphatic aldehyde led to increased *anti* diastereoselection but decreased yields (entries 4,5). Since it has been shown that the analog stoichiometric reactions gave satisfactory yields, we interpret these results as indicating that the size of the alkyl group of the aldehyde affects the key Ti–O cleavage step of the catalytic process rather than the C–C bond formation itself. By analogy, Buchwald has previously shown that the rate of hydrosilylation of bulky ketones is slow.[6a] This catalytic allyltitanation procedure tolerates aromatic aldehydes since the reaction of isoprene and benzaldehyde gave good yield and diastereoselectivity (entry 6). We also demonstrated the feasibility of the reaction with a more complicated diene such as myrcene (entry 7). Finally we have investigated one reaction with butadiene and benzaldehyde (entry 8). In order to use the butadiene as liquid, we conducted the reaction at −15 °C. At this temperature, the reaction proceeded but was considerably slowed down. The diastereoselectivity in favor of the *anti* product is excellent as reported by Collins in the stoichiometric case.[2a]

In summary, we have presented the first catalytic allyltitanation using PMHS as stoichiometric reductant. Further efforts to extend the scope of this reaction to other substrates such as ketones, imines or acetals are underway.

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Notes and references

1 (*a*) F. Sato, S. Ijima and M. Sato, *Tetrahedron Lett.*, 1981, **22**, 243; (*b*) B. Klei, J. H. Teuben and H. de Liefde Meijer, *J. Chem. Soc., Chem. Commun.*, 1981, 342.
2 (*a*) S. Collins, W. P. Dean and D. G. Ward, *Organometallics*, 1988, **7**, 2289; (*b*) J. Szymoniak, H. Lefranc, J. Besançon and C. Moïse, *Synthesis*, 1995, 815; (*c*) H. Urabe, K. Yoshikawa and F. Sato, *Tetrahedron Lett.*, 1995, **31**, 5595; (*d*) J. Szymoniak, D. Felix, J. Besançon and C. Moïse, *Tetrahedron*, 1996, **52**, 4377; (*e*) N. Thery, J. Szymoniak and C. Moïse, *Eur. J. Org. Chem.*, 2000, 1483.

3 (a) A. Gansäuer, M. Pierobon and H. Bluhm, *Angew. Chem., Int. Ed.*, 1998, **37**, 101; (b) A. Gansäuer and H. Bluhm, *Chem. Commun.*, 1998, 2143.

4 For a titanium-catalysed reaction with similar concept see: A. Fürstner and A. Hupperts, *J. Am. Chem. Soc.*, 1995, **117**, 4468.

5 (a) F. Sato, T. Jinbo and M. Sato, *Tetrahedron Lett.*, 1980, **21**, 2171; (b) R. Halterman, T. M. Ramsey and Z. L. Chen, *J. Org. Chem.*, 1994, **59**, 2642; (c) P. Beagley, P. J. Davies, A. J. Blacker and C. White, *Organometallics*, 2002, **21**, 5852; (d) R. Shu, J. F. Harrod and A. M. Lebuis, *Can. J. Chem.*, 2002, **80**, 489.

6 (a) M. B. Carter, B. Schiøtt, A. Gutiérrez and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 11667; (b) K. J. Barr, S. C. Berk and S. L. Buchwald, *J. Org. Chem.*, 1994, **59**, 4323; (c) X. Verdaguer, M. C. Hansen, S. C. Berk and S. L. Buchwald, *J. Org. Chem.*, 1997, **62**, 8522.

7 The catalytic system almost preserves the stereochemical control of the stoichiometric reaction. Indeed, the reaction of propanal with one equivalent of $Cp_2Ti(\eta^3$-1,2-dimethylallyl) at –20 °C led to the homoallylic alcohol **1** with a ratio of the two diastereoisomers (*anti : syn*) equal to 68 : 32.

8 H. A. Martin and F. Jellinek, *J. Organomet. Chem.*, 1968, **12**, 149.

9 (a) C. T. Aitken, J. F. Harrod and E. Samuel, *J. Am. Chem. Soc.*, 1986, **108**, 4059; (b) J. F. Harrod, Y. Mu and E. Samuel, *Can. J. Chem.*, 1992, **70**, 2980; (c) E. Spaltenstein, P. Pilar, K. A. Kreutzer, C. A. Willoughby, W. M. Davis and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 10308; (d) F. Lunzer, C. Marschner and S. Landgraf, *J. Organomet. Chem.*, 1998, **568**, 1998.

10 S. C. Berk, K. A. Kreutzer and S. L. Buchwald, *J. Am. Chem. Soc.*, 1991, **113**, 5093.