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Tetrahedron Letters 48 (2007) 5491–5495

Tetrahedron Letters

The relative reactivities of various unsaturated compounds towards diisopropyloxy(η^2-cyclopentene)titanium

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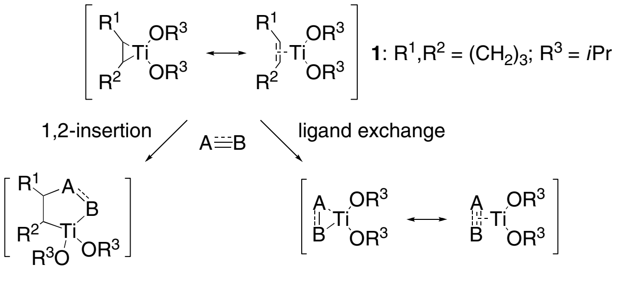
Received 26 April 2007; revised 28 May 2007; accepted 30 May 2007
Available online 6 June 2007

Abstract—Competition experiments were performed by adding pre-formed solutions of diisopropyloxy(η^2-cyclopentene)titanium in diethyl ether to various mixtures of unsaturated compounds at low temperature, establishing the following reactivity scale: aldehyde > nitrile > ketone > terminal alkyne > internal alkyne > terminal alkene > ester, carbonate.

The chemistry of dialkoxytitanacyclopropanes has undergone extensive development since the original publication by Kulinkovich et al. describing the titanium-mediated cyclopropanation of carboxylic esters, where they were proposed as intermediates.[1] Such organometallic species are usually generated from the reaction of tetraisopropyloxytitanium or chlorotriisopropyloxytitanium with a Grignard reagent, and can also be considered as dialkoxy(η^2-alkene)titanocene complexes. They may react with unsaturated compounds either according to a 1,2-insertion pathway (addition), as in the cases of esters (Kulinkovich reaction),[1,2] amides (Kulinkovich–de Meijere reaction),[3] and nitriles (Kulinkovich–Szymoniak reaction),[4] or by a ligand exchange process, as with alkenes,[5] alkynes,[6] aldehydes and ketones (Scheme 1).[7]



Scheme 1.

The relative reactivities of various acyl derivatives towards titanacyclopropanes were studied by Cha et al. 10 years ago.[8] The following general trend was disclosed: ester ≈ acyl chloride, anhydride ⩾ carbonate, thioester > formamide > carboxamide. More recently, the group of Bertus and Szymoniak demonstrated that nitriles react faster than esters and carbonates with titanacyclopropanes.[9] We reasoned that this known reactivity scale could be extended using the method we reported lately for the efficient and reproducible preparation of diethyl ether solutions of diisopropyloxy(η^2-cyclopentene)titanium **1** containing low amounts of unreacted Grignard reagent.[10]

Indeed, **1** can be pre-formed and then added at low temperature to the substrates to be studied. This is a great advantage for mechanistic studies, since possible unwanted side reactions caused by the isopropyloxytitanium(IV)/Grignard reagent combination before the formation of **1** are thus avoided. For instance, we found that no reaction occurred when pre-formed complex **1** was put in the presence of the reagent di*tert*butyldicarbonate (Boc_2O) at −50 °C for 30 min. In contrast, when cyclopentylmagnesium chloride was added at low temperature to a diethyl ether solution of Boc_2O and isopropyloxytitanium(IV), ester **2** was formed and isolated in 31% yield (Scheme 2). The fact that no iodinated ester was observed when the reaction was quenched with iodine rules out the intermediacy of **1** in the formation of **2**. The mechanism probably involves chelation of Boc_2O by the titanium complex and the addition of the Grignard reagent at one of the carbonyl groups, rather than at the metal centre.

Keywords: Titanium; Titanacyclopropanes; Ligand exchange; Pinacol coupling; Kulinkovich reaction.

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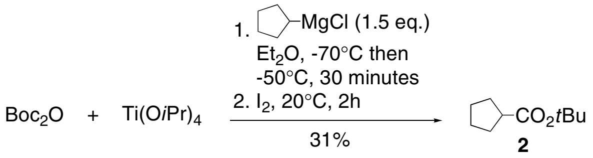
doi:10.1016/j.tetlet.2007.05.177



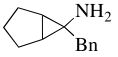
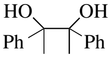
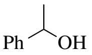
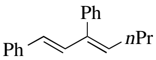
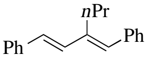
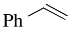
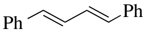
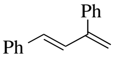
Scheme 2.

For the competition experiments, the following experimental protocol was applied: a solution of tetraisopropyloxytitanium (2.0 mmol) and cyclopentyl-magnesium chloride (3.0 mmol) in diethyl ether (5.0 mL) was allowed to warm from -70 °C to -50 °C in 5 min, and then maintained at that temperature for 8 min, resulting in the formation of about 1.0 mmol of **1**. The reaction medium was cooled down to -70 °C, and then added via a double-ended needle to a solution of an equimolar mixture of the two unsaturated compounds to be compared (5.0 mmol each) in diethyl ether (10 mL) at -70 °C. The temperature was then raised linearly to -30 °C in 30 min. 1 N aqueous HCl solution (20 mL) and diethyl ether (5.0 mL) were added at -30 °C. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2×20 mL). The combined organic phases were then dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the crude product, which was analysed by NMR spectroscopy. Pure products were isolated by flash chromatography over silica gel.

The results are presented in Tables 1 and 2. In spite of apparent complexity, they were generally easy to analyse, since most of the products observed were expected in light of the known chemistry of titanacyclopropane **1**.[10] For instance, cyclopentylketones **4** and **7** were formed by simple addition of complex **1** onto the corresponding nitriles (Scheme 1, 1,2-insertion) followed by hydrolysis, while the formation of benzaldehyde **3**, styrene **12** and alkene **21** results from ligand exchange of **1** with benzonitrile, phenylacetylene and 1-phenylpent-1-yne, followed by hydrolysis. Diol **8** arose from a pinacol-type coupling of acetophenone caused by ligand exchange followed by 1,2-insertion and hydrolysis. The formation of benzil **5** or diphenylbutadienes **13** and **14** can be explained by invoking similar homo ligand exchange/1,2-insertion sequences from benzonitrile or phenylacetylene. Aminocyclopropane **6** is a Kulinkovich–Szymoniak reaction product from benzyl cyanide.[4] In the general case, this reaction proceeds efficiently only when a Lewis acid such as BF$_3$·OEt$_2$ or TiCl$_4$ is added,[4] which accounts for the low yield of **6**.

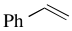
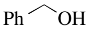
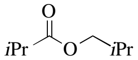
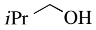
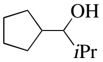
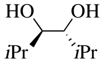
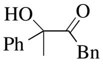
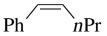
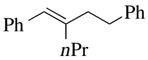
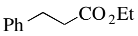
On some occasions, cross-coupling products were observed (**10**, **11**, **20**, **22** and **23**) that were formed by ligand exchange of **1** with one of the competing reagents followed by 1,2-insertion of the other, and then hydrolysis. Ligand exchange with acetophenone rather than the non-documented exchange with benzyl cyanide can reasonably be invoked to account for the formation of hydroxyketone **20** after subsequent 1,2-insertion of

Table 1. Competition experiments performed by adding complex **1** to diethyl ether solutions of equimolar mixtures of unsaturated compounds and phenylacetylene[a]

Entry	1	2	3	4	5	Products (origin)	
Compound A	PhCN	BnCN	PhC(O)Me	Ph—≡—*n*Pr	EtOCO$_2$Et		
Compound B			Ph—≡				
Yields (%)	24^{b}					PhCHO	**3** (A)
	12^{c}					cC$_5$H$_9$C(O)Ph	**4** (A)
	7^{c}					PhC(O)C(O)Ph	**5** (A)
		20^{b}					**6** (A)
		15^{b}				cC$_5$H$_9$C(O)Bn	**7** (A)
			$43^{c,d}$				**8** (A)
			13^{c}				**9** (A)
				10^{b}			**10** (A then B or B then A)
				5^{b}			**11** (A then B or B then A)
	7^{b}	6^{b}	8^{b}	11^{b}	7^{b}		**12** (B)
	1^{c}	3^{b}	7^{b}	42^{b}	47^{c}		**13** (B)
			8^{b}	17^{b}	20^{b}		**14** (B)
Reactivity ratio	5.4:1	3.9:1	2.4:1	1:4.7 or 1:>40	1:>40		

[a] Yields are calculated on the basis of 1.0 mmol of complex **1** expected to be formed from 2.0 mmol of Ti(O*i*Pr)$_4$ and 3.0 mmol of cC$_5$H$_9$MgCl.
[b] Yield estimated by ^{1}H NMR spectroscopy of the crude product.
[c] Isolated yield, in close agreement with the yield estimated by ^{1}H NMR spectroscopy of the crude product.
[d] *dl*/*meso* ≈ 77:23.

Table 2. Competition experiments performed by adding complex **1** to diethyl ether solutions of equimolar mixtures of two unsaturated compounds[a]

Entry	1	2	3	4	5	6	Products (origin)
Compound A	PhCHO	*i*PrCHO	PhCHO	PhC(O)Me[b]	Ph—≡—*n*Pr	$EtOCO_2Et$	
Compound B	PhCN		BnCN				
Yields (%)		31^{c}					**3** (B)
		13^{d}					**4** (B)
		7^{d}					**5** (B)
				11^{d}			**6** (B)
			2^{c}	14^{d}			**7** (B)
				$11^{d,e}$			**8** (A)
				5^{d}			**9** (A)
	117^{c}		125^{c}				 **15** (A)
		124^{c}					 **16** (A)
		18^{c}					 **17** (A)
		10^{c}					 **18** (A)
		4^{c}					 **19** (A)
				4^{d}			 **20** (A then B)
					63^{d}		 **21** (A)
					7^{d}		 **22** (A then B)
						21^{c}	 **23** (B then A)
Reactivity ratio	>40:1	3.1:1	62:1	1:1.2	>40:1	1:>40	

[a] Yields are calculated on the basis of 1.0 mmol of complex **1** expected to be formed from 2.0 mmol of $Ti(OiPr)_4$ and 3.0 mmol of cC_5H_9MgCl.

[b] The addition of complex **1** onto the solution of benzyl cyanide and acetophenone was performed at −30 °C because of solubility issues.

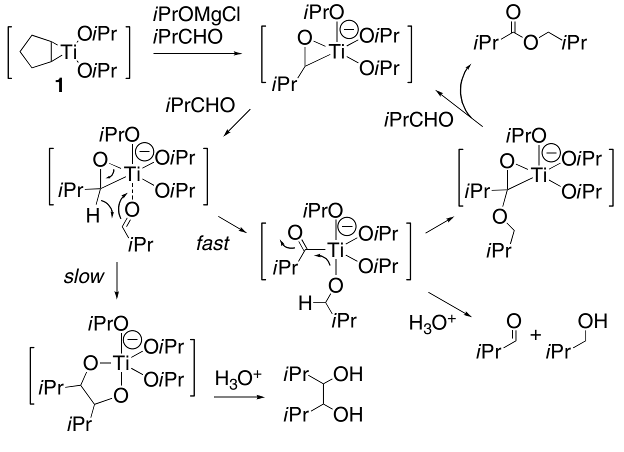
[c] Yield estimated by ^{1}H NMR spectroscopy of the crude product.

[d] Isolated yield, in close agreement with the yield estimated by ^{1}H NMR spectroscopy of the crude product.

[e] *dl*/*meso* ≈ 69:31.

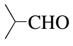
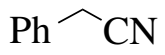
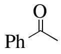
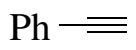
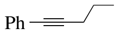
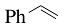
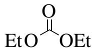
benzyl cyanide. Similarly, ethyl 3-phenylpropanoate **23** very probably arises from ligand exchange with styrene as the first elementary step,[11] and alkene **22** is most likely due to ligand exchange with the alkyne first. Indeed, had ligand exchange proceeded with styrene, the resulting titanacyclopropane would have reacted with 1-phenyl-pent-1-yne by ligand exchange rather than 1,2-insertion. In the cases of **10** and **11**, further experiments would be needed to get more insight on the mechanism of their formation and two conceivable reactivity ratios are proposed for the time being.

Amidst all the compounds evaluated, aldehydes proved to be the most reactive. Surprisingly, unlike ketones which reacted with **1** in a 2:1 molecular ratio to provide 1,2-diols after hydrolysis, aldehydes afforded primary alcohols and/or esters as the main reaction products. These processes resemble the Meerwein–Ponndorf–Verley (MPV)[12–14] and Tishchenko reactions,[15] which are typically mediated by aluminium alkoxide Lewis acids. In the present case, it is worthy of note that the products were formed in larger amounts than the initial quantity of complex **1**, and the latter was actually involved since the conversion of the competing nitriles was inhibited (Table 2, entries 1 and 3).[16] Moreover, when the experiments shown in entries 1 and 2 of Table 2 were repeated with deuterium oxide being added to quench the reactions, no deuterium incorporation at carbon was observed in the primary alcohol products. On the basis of these observations, a tentative, speculative mechanism may be proposed, but further experiments would be needed to support it (Scheme 3).



Scheme 3.

Table 3. Scale of reactivity of some unsaturated compounds with diisopropyloxy(η^2-cyclopentene)titanium **1** at low temperature ($\leqslant -30$ °C)

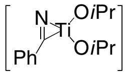
Unsaturated compound	Relative rate	Reactivity
PhCHO	240	MPV Reduction
	16.5	Tishchenko reaction, MPV reduction, 1,2-insertion and ligand exchange
Ph-CN	5.5	Ligand exchange and 1,2-insertion
	3.5	1,2-Insertion
	2.5	Ligand exchange
	1	Ligand exchange
	<0.2	Ligand exchange
	$<5 \times 10^{-3}$	Ligand exchange
	$<10^{-4}$	1,2-Insertion

Finally, it should be underlined that a part of the observed amounts of compounds **4**, **7**, **9**, **15**, **17** and **18** may also proceed from the reaction of residual amounts of cyclopentylmagnesium chloride with the nitriles, ketone or aldehydes put into play. The total yields of products resulting from such direct processes should normally not exceed 10%.[10]

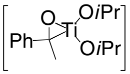
From all the results collected, a scale of reactivity of the unsaturated compounds under study can be proposed. Relative rates can be roughly estimated on the basis of the reactivity ratios found in the competition experiments, and are presented in Table 3, with phenylacetylene being chosen as a reference. Future work in the area should help refining these values and enrich the table. It should be pointed out that for the time being, these results can only be deemed valid in the special case of complex **1**, and differences in reactivity should be expected with other titanacyclopropanes. Indeed, very different results have been reported for some reactions, depending on the nature of the complex involved, either **1** or its [4.1.0] homologue diisopropyloxy(η^2-cyclohexene)titanium.[17] The behaviour of diisopropyloxy(η^2-trimethylsilylethylene)titanium may also be cited here. This complex was reported to add to aldehydes via a 1,2-insertion pathway in good yield,[18] in sharp contrast with our results obtained using **1**.

Importantly, besides establishing the reactivity scale mentioned above, the competition experiments also furnished some secondary information on the reactivity of diisopropyloxytitanocene complexes **24**, **25** and **26** resulting from ligand exchange of **1** with benzonitrile, acetophenone and phenylacetylene (Fig. 1).

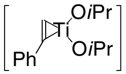
Namely, the results suggest that **24** reacts with benzonitrile in preference to phenylacetylene (Table 1, entry 1), and **26** reacts chemoselectively with phenylacetylene rather than ethyl carbonate (Table 1, entry 5). Similarly, **25** reacts exclusively with acetophenone rather than phenylacetylene (Table 1, entry 3), and about 3 times faster with acetophenone than with benzyl cyanide (Table 2, entry 4).



24



25



26

Figure 1.

In summary, through the means of competition experiments, a scale of reactivity has been established for the reaction of diisopropyloxy(η^2-cyclopentene)titanium **1** with several unsaturated compounds, including nitriles, carbonyl derivatives, alkynes and alkenes. Among the molecules tested, aldehydes reacted fastest, following an unusual mechanistic pathway. With the knowledge of the results presented herein, novel coupling reactions mediated by **1** can be envisioned, both in the inter- and intramolecular modes. We are currently developing such an application, which will be published in due time.

Acknowledgement

We are grateful to the Ministère délégué à l'Enseignement supérieur et à la Recherche for the funding granted to F.C.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.177.

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11. In a separate experiment carried out at 0 °C, a Kulinkovich reaction performed from styrene and ethyl carbonate, using $\mathrm{Ti(O}i\mathrm{Pr)_4}$ and $c\mathrm{C_5H_9MgCl}$, also afforded **23** and the

expected phenylcyclopropanone hemiacetal was not observed (see the Supplementary data).

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16. A control experiment was also carried out with isobutyraldehyde alone to check that the presence of a nitrile was not required for the reduction and esterification processes.
17. For a dramatic example, see: Laroche, C.; Bertus, P.; Szymoniak, J. *Tetrahedron Lett.* **2003**, *44*, 2485–2487.
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