



Reductive cyclization of enones by titanium(IV) aryloxyde and a Grignard reagent

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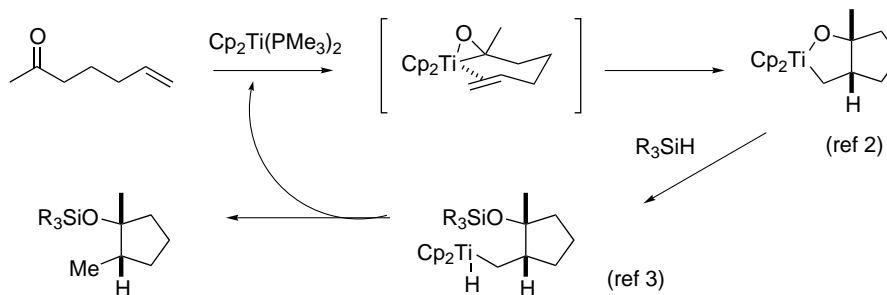
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Abstract—The titanium-mediated cyclization of δ,ϵ -enones by using dichlorotitanium diphenoxide–cyclohexylmagnesium chloride diastereoselectively afforded *cis*-substituted cyclopentanol and was thus found to parallel the stoichiometric and catalytic titanocene-mediated reactions. © 2001 Elsevier Science Ltd. All rights reserved.

Transition metal-promoted carbocyclizations between two unsaturated functionalities have been well documented to provide a convenient carbon–carbon bond formation via a metallacycle intermediate. The group 4 metal-mediated cyclizations of diynes, enynes, and dienes were first developed and have successfully been extended to those involving heteroatom-containing unsaturated functionalities.¹ For example, the titanocene-mediated, stoichiometric reductive cyclization of δ,ϵ -enones was shown by Whitby to afford oxatitanabicyclopentanes in good yields (Scheme 1).² The Buchwald and Crowe groups independently developed a useful catalytic variant by employing an in situ σ -bond metathesis with a silane [e.g. Ph_2SiH_2 or $(\text{EtO})_3\text{SiH}$].³ As part of our research program building upon the Kulinkovich cyclopropanation reactions,^{4,5} herein we report the comparison study of the titanium-mediated cyclizations of δ,ϵ -enones under the Kulinkovich reaction conditions [titanium(IV) alkoxide/phenoxide and a Grignard reagent].

Starting from **1**,⁶ several titanium alkoxides and phenoxides were first evaluated in THF by the addition of an excess of cyclopentylmagnesium chloride. As can be seen in Table 1, the nature of a titanium alkoxide or aryloxyde was found to exert an unexpectedly large influence on product yields. In general, titanium aryloxides (entries 5 and 6) were superior to titanium alkoxides (entries 1–3).⁷ More significantly, the introduction of a chloro group to the titanium afforded higher yields. Thus, use of dichlorotitanium diphenoxide (entry 5) gave *cis*-substituted cyclopentanol **2**, as a single diastereomer, in 63% yield. To our surprise, titanium(IV) phenoxide (entry 4) was ineffective, and the tertiary alcohol (structure not shown) derived from simple addition of the cyclopentyl Grignard (or titanium) reagent to the keto group was instead isolated in 56% yield.

With several enones, cyclopentyl- and cyclohexylmagnesium chlorides were next compared in the presence of



Scheme 1.

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Table 1.

1: R = Ph			
2: R = Ph			
Entry	Titanium reagent	Temp.	Yield (%)
1	Ti(O- <i>i</i> -Pr) ₄	rt	21
2	ClTi(O- <i>i</i> -Pr) ₃	rt	23
3	Cl ₂ Ti(O- <i>i</i> -Pr) ₂	rt	28
4	Ti(OPh) ₄	rt	0
5	Cl ₂ Ti(OPh) ₂	rt	63
6	Cl ₂ Ti(OPh) ₂	0°C	50

Table 2.

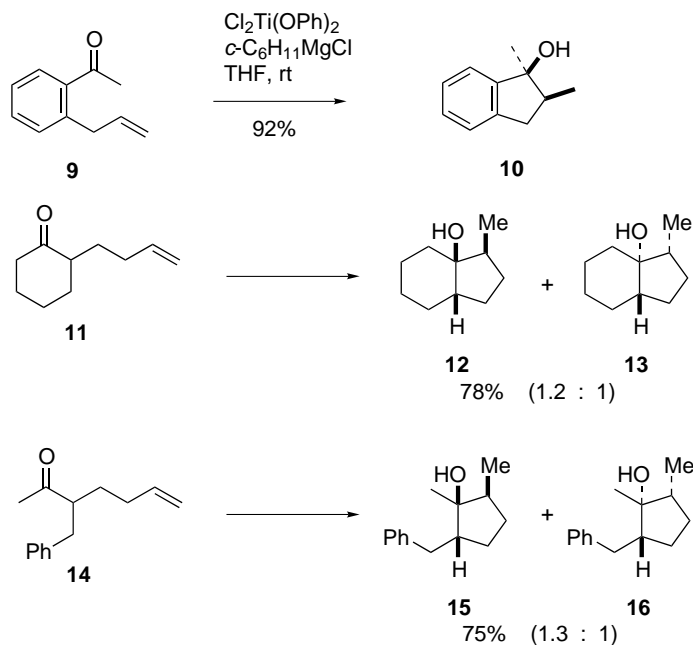
R		
1: Ph	2: 63%	75%
3: CH ₃	4: 68%	72%
5: <i>i</i> -Pr	6: 87%	86%
7: 1-cyclohexene	8: 30%	52%

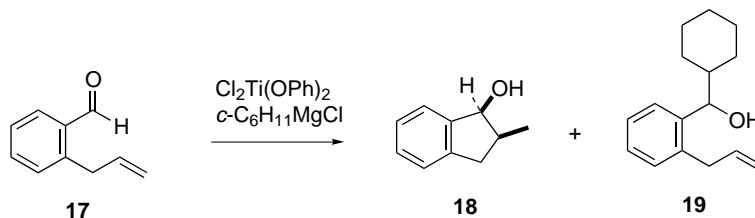
dichlorotitanium diphenoxide (Table 2). The cyclohexyl Grignard reagent proved to be more advantageous than the cyclopentyl Grignard. It is noteworthy that the cyclopentyl Grignard reagent has often been found to be the reagent of choice for the cyclopropanation reactions of carboxylic esters and derivatives.^{5b,c,8} For

example, cyclopropanone hemiacetals could be prepared by the titanium-mediated cyclopropanation of ethylene or propylene carbonate in moderate to good yields only by employing the cyclopentyl, not cyclohexyl, Grignard reagent.^{8a} The origin for subtle differences between cyclopentyl and cyclohexyl Grignard reagents in the titanium-mediated reactions is unknown and merits further investigation.

As additional examples, the bicyclic formation and the diastereoselectivity exerted by a resident stereocenter at the position α to the carbonyl were briefly examined (Scheme 2). Disappointingly, poor 1,2-diastereoselectivity was observed marginally in favor of the isomers which were derived from the presumed chair-like transition states having an α substituent at the pseudoequatorial position. The lack of diastereocontrol was in marked contrast to the good to excellent diastereoselectivity reported for the titanocene-mediated cyclizations.³ This discrepancy between these two closely related methods may be attributed primarily to higher reaction temperature conditions (i.e. room temperature) employed for the present work, compared to -20°C used for the titanocene procedures.^{3c}

Another conspicuous difference was found in the cyclization reactions of aldehydes, as illustrated with aldehyde **17** (Scheme 3). Whereas 5-hexenals and related aldehydes had been shown to be amenable to the titanocene-mediated cyclization,^{3b} the main pathway in the titanium phenoxide-based method was simple addition of the Grignard reagent to the aldehyde functionality, presumably as the corresponding titanium reagent. The altered reactivity of aldehydes was in accord with the well-known proclivity of organotitanium reagents for chemoselective addition to aldehydes in preference to ketones.⁹

**Scheme 2.**



solvent	temperature	yields	
THF	0 °C	-	85%
THF	rt	36%	55%
THF	50 °C	30%	50%
toluene	rt	15%	49%
ether	rt	26%	69%
dioxane	rt	-	74%

Scheme 3.

There are common limitations in the stoichiometric/catalytic titanocene-mediated cyclization of δ,ϵ -enones and the present procedure employing titanium(IV) phenoxide—a Grignard reagent: the formation of six-membered rings leading to the cyclohexanols failed in both methods. In addition, both procedures were intolerant of additional substitution on the mono-substituted olefins.

In summary, the dichlorotitanium diphenoxide–cyclohexylmagnesium chloride-mediated cyclization of δ,ϵ -enones was found to closely parallel the stoichiometric and catalytic titanocene-mediated processes for the formation of *cis*-substituted cyclopentanols, while a different pathway was predominant for δ,ϵ -enals. Additional comparison studies of the ‘titanocene’- and ‘dialkoxytitanium(II)’-mediated reactions would be of mechanistic and synthetic interest.¹⁰

Acknowledgements

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