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# Nickel Catalysed 1,4-Addition of Organotitanium Ate Complexes to Sterically Hindered Enones

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***Abstract:*** *The 1,4-addition of organotitanium ate complexes to enones by nickel catalysis is reported. With a methyltitanium ate complex good yields of conjugate addition to sterically hindered enones are achieved. Phenyltitanium ate complexes react with less sterically encumbered enones to the 1,4-addition products in moderate to high yields.*

In the field of 1,4-additions of organometallic compounds to enones the organocopper chemistry has many applications in a catalytic or stoichiometric manner. However, there are limitations in the catalytic copper chemistry when the enone moiety of the substrate is sterically hindered [1]. Therefore, conjugate addition of an alkyl group to the sterically encumbered C-5 position of a 3-keto-$\Delta^4$-steroid in a catalytic reaction is difficult to achieve [1a]. In these sterically demanding cases nickel catalysed 1,4-additions of organometallics are advantageous [2].

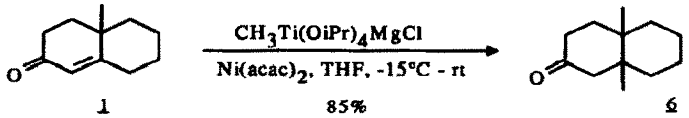
We were searching for a method which allows us to use organomagnesium or organolithium compounds for the desired 1,4-addition reactions. To moderate the high nucleophilicity of these reagents towards carbonyl groups [3] we converted them to organotitanium ate complexes and tested these titanated species with altered properties and less nucleophilic nature in conjugate addition reactions.

Organotitanium compounds are predominantly used for selective 1,2-additions to a carbonyl moiety [4]. There are few examples reported in the literature where titanium reagents gave 1,4-addition without any catalyst [5].

Lipshutz and Nakamura reported the conjugate addition of organotitanium ate complexes catalysed by copper-(I)[6]. This method is important for selective $S_N2'$ reactions; however, it appears to have some limitations in the addition to sterically demanding enones [7].

We hereby report that the 1,4-addition of organotitanium ate compounds $RTi(OiPr)_4M$ (R= $CH_3$, Ph; M= MgX, Li) to enones is catalysed by nickel acetylacetonate [$Ni(acac)_2$]. The conversion of 10-methyl-$\Delta^{1,9}$-octalone (1) to the ketone 6 gave a yield of 85 % (scheme 1).

**Scheme 1.**



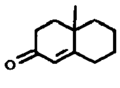
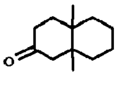
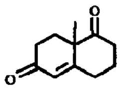
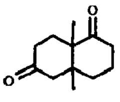
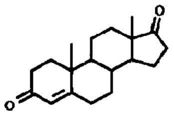
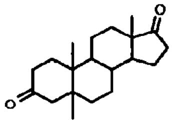
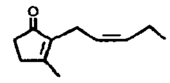
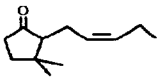
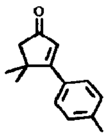
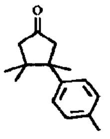
1 6

In comparison, the copper catalysed 1,4-addition of methylmagnesium bromide to 1 gave 40% conjugate addition and 60% of 1,2 product [1h].

The titanium ate complexes $RTi(OiPr)_4MgX$ ($X=Cl$, Br) are prepared in situ from $Ti(OiPr)_4$ and the Grignard reagent RMgX [8]. The formation of the titanate complex from alkyllithium is possible in the same way.

With this type of reagent we checked the 1,4-addition-method on other sterically hindered enones. As shown in table 1, the enones 1 to 5 were ß-alkylated in high yields.

**Table 1.** 1,4-Addition of $CH_3Ti(OiPr)_4MgCl$ to enones by $Ni(acac)_2$ catalysis

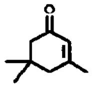
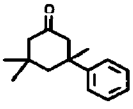
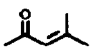
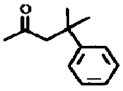
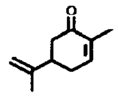
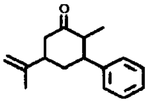
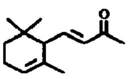
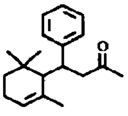
| Enone | Product [a] | Yield (%) [b] | Conditions [h] [c] |
|---|---|---|---|
|  1 |  6 | 85 | 21 |
|  2 |  7 | 83 | 21 |
|  3 |  8 | 73 [d] | 24 |
|  4 |  9 | 87 | 21 |
|  5 |  10 | 78 [e] | 24 |

[a] For a general procedure see ref. [9]. All experiments were performed on a 10 mmmol scale. [b] Isolated yields obtained after purification by column chromatography on silica gel. [c] Reaction temperature -15°C - r.t.. [d] No 5α-product of 8 was detected. [e] A 2.5 equivalent excess of $CH_3Ti(OiPr)_4MgCl$ was used.

The reaction appears to be one of wide generality, accommodating a wide variety of α,ß-unsaturated ketone to yield the corresponding ß-substituted ketones in good yield. Isophorone (11) was 1,4-methylated in 91% yield. However, the conjugate methylation of less hindered enones is easily achieved by a Cu(I)-catalysed trimethylaluminium reaction developed in our laboratory [3].

When phenylmagnesium bromide is transmetallated to titanium, we observed a transfer of the aryl group to some enones with varying yields (table 2). The loss of regioselectivity is probably due to steric influences. The hindered enones 1 to 5 only gave 1,2-addition products.

**Table 2.** 1,4-Addition of $PhTi(OiPr)_4MgCl$ to enones by $Ni(acac)_2$ catalysis

| Enone | Product $^a$ | Yield (%) $^b$ | Conditions [h] $^c$ |
|---|---|---|---|
|  11 |  15 | 82 | 3 |
|  12 |  16 | 92 | 6 |
|  13 |  17 | 68 | 22 |
|  14 |  18 | 42 | 24 |

$^a$ For a general procedure see ref. [9]. All experiments were performed on a 10 mmol scale. $^b$ Isolated yields obtained after vacuum distillation. $^c$ Reaction temperature -15°C - r.t.

Reaction of Grignard reagent PhMgBr with the enone 11 in the presence of nickel catalyst yielded predominantly the 1,2-addition product. This indicates that the titanium intermediate has different (softer or less nucleophilic) properties from the Grignard reagent.

For $MeTi(OiPr)_4MgCl$ used without a catalyst we found only small amounts of 1,4-addition product. The catalyst is essential for 1,4-regioselectivity. The nature of the reactive species is presently unknown.

The reaction of $Me_2Ti(OiPr)_3MgCl$ with enone 1 in the presence of nickel acetylacetonate proceeds faster than $MeTi(OiPr)_4MgCl$ and with good regioselectivity (84% of isolated 1,4-addition product). To achieve a complete conversion a 1:1 mixture of $Me_2Ti(OiPr)_3MgCl$ reagent and enone is used. Only one alkyl group was transferred under the given conditions.

$MeTi(OiPr)_3$ shows less reactivity than the methyltitanium ate complexes in the nickel catalysed conjugate addition.

$Ph_2Ti(OiPr)_3Li$ reacts faster and more regioselectively than the mono aryl reagent $PhTi(OiPr)_4MgCl$ under the same conditions. With α-ionone (14) 68% yield of 18 was achieved.

In the presence of TMSCl as an additive we did not observe any acceleration of the reaction. This underlines the different nature of the nickel catalysis compared to copper catalysed reactions.

The method described, with Ni(acac)$_2$ as catalyst, seems to be limited to alkyl groups without a ß-hydrogen. A reaction of n-BuTi(OiPr)$_4$M gave a product mixture.

In conclusion, we have developed a convenient method for the conjugate addition of methyl groups to enones. The addition of phenyl groups suffers from some restrictions. A Grignard reagent is transformed to a titanium-ate species which achieves good regioselectivity by nickel catalysis. This new process is a good alternative to other catalytic reactions for 1,4-additions to sterically hindered enones.

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7. In our hands, the methylation of 10-methyl-$\Delta^{1,9}$-octalone **1** by the previous described method in ref.[6] gave poor yield of the 1,4-addition product **6**.
8. The ate type of representation is, however, only a formalism, since the aggregation state and coordination number are currently unknown. With a Grignard reagent in the absence of Ti(OiPr)$_4$ we found mainly 1,2-addition product.
9. ***Preparation of the titanium ate complex :***
   3,85 ml (13mmol) titanium(IV)isopropoxide in 5 ml tetrahydrofuran (THF) are cooled to -30°C and 4,33 ml (13mmol) methylmagnesium chloride (3M, THF) are added. The yellow mixture is allowed to warm to 0°C over a period of 1 h.
   The procedure is representative for other organocompounds.
   ***General procedure for the alkylation of enones :***
   The green solution of 128 mg (0.5mmol) nickel acetylacetonate and 10 mmol enone in 15 ml THF is treated with 13 mmol of the methyltitanium ate complex at -15°C. The reaction mixture turns black. The mixture is allowed to warm to room temperature slowly. After the reaction has finished (6 to 24 h), the mixture is diluted with 20 ml ether and quenched with 2 ml water. After stirring for 1 to 2 h the precipitate is filtered off and the solution is concentrated. Distillation or column chromatography yielded the 1,4-addition compounds.

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