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Stereoselective Conjugate Addition of Propionate Ti Ate Enolate to Unsaturated Chiral Ketones: a New Insight in the Reaction Mechanism

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Abstract: *The reactions of the Ti ate enolate 1 and the Li enolate 2 with the chiral enone 3 were studied. Both reactions are moderately stereoselective, leading to the synthesis of the 2,3-anti-3,4-anti and the 2,3syn-3,4anti isomers with 78% and 82% selectivity, respectively. The addition of 1 appears to take place via an inverse demand Diels-Alder reaction, rather than a conjugate addition. This finding can explain the different stereochemical behavior of lithium and titanium enolates in the addition to enones.*

We recently reported that Ti "ate" complexes of ketone and ester enolates, obtained by treating the corresponding Li enolates with 1 mol equiv of $Ti(OiPr)_4$, add to unsaturated carbonyl compounds in a 1,4-fashion with high regio- and stereoselectivity and offer various advantages in comparison with their Li counterparts.[1] For ketone enolates, the use of the Ti complexes improves both the regioselectivity and the stereoselectivity of the conjugate addition. The sense of selectivity is the same as for Li (*i.e.* when adding to E enones, E enolates afford *syn* compounds, and Z enolates the *anti* isomers).[2] On the contrary, for ester enolates the stereochemical outcome of the addition is reversed on going from Li to Ti. For instance, the Ti enolate of t-butylpropionate **1** adds to E-configurated esters and ketones to give *anti* ketoesters with stereoselectivities up to 95%, while the addition of the parent Li enolate **2** is 90-95% *syn* selective (**Figure 1**).[3]

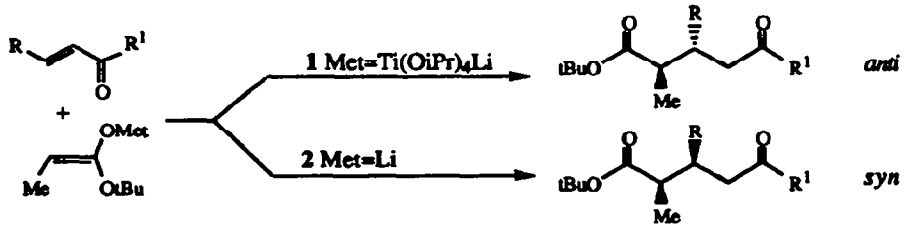

Figure 1. Addition of ester enolates **1** and **2** to unsaturated ketones.

In this paper we report on the reaction of ester enolates **1** and **2** with the chiral substrate **3**, which led to a deeper understanding of the stereodivergent behavior of the two enolates.

Enone **3** was synthesized from 2-phenylpropanal, as previously reported.[4] Addition of the lithium enolate **2** (**Figure 2**) at 0 °C afforded a mixture of ketoesters, with the *2,3-syn-3,4-anti* isomer **4** constituting ca. the 80% of the product mixture.[5] The same isomer was obtained by Heathcock and Uehling in the $TiCl_4$ catalyzed reaction of **3** with the t-butyldimethyl silylketeneacetal of t-butylpropionate.[6]

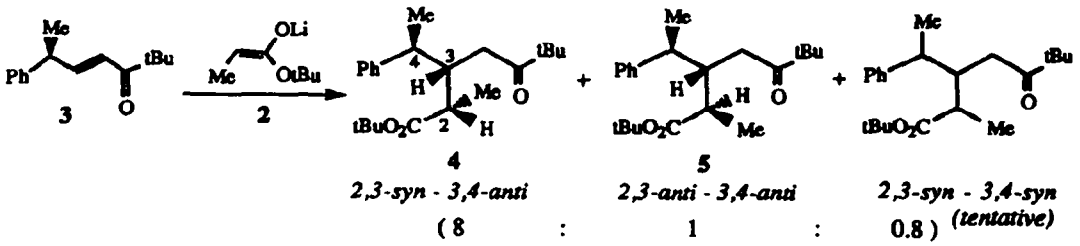

Figure 2. Addition of the lithium enolate **2** to **3**.

On the contrary, reaction between **3** and the Ti enolate **1** at -30 °C (**Figure 3**), followed by NH_4F quenching, resulted in the formation of a ca. 5:1 mixture[7] of the two enols **6** and **7**, in quantitative yield. These enols were characterized by ^1H- and ^{13}C-NMR of the crude reaction mixture.[8] They appear to be stabilized by H-bonding between the enol and the ester carboxy group (see Figure 3), which is revealed in the IR spectrum by the low frequency of the carbonyl stretching (1715 cm^{-1}), and in the ^1H-NMR spectrum by the presence of a D_2O exchangeable proton as a sharp singlet at 6.6 ppm. Transformation in a 5:1 mixture of ketoesters **5** and **4**[9] takes place spontaneously in a few hours. However, the enols could be trapped by treating the reaction crude with tosylisocyanate.[10] The resulting N-sulfonylamides **8** (**Figure 3**) could be chromatographed on silica gel, and were fully characterized.[11]

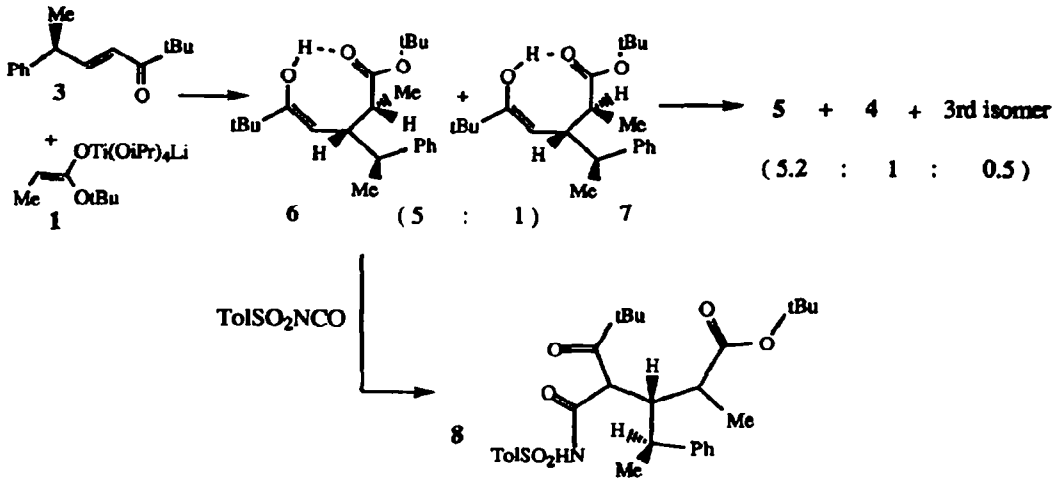

Figure 3. Addition of the titanium enolate **1** to **3**.

The *2,3-anti-3,4-anti* configuration of the major ketoester **5** was established by X-ray analysis of the corresponding acid **9** obtained in isomerically pure form by removal of the t-butylester with CF_3CO_2H, and crystallization from pentane (**Figure 4**).[12]

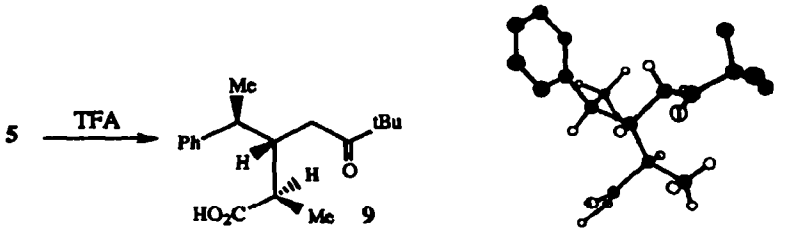

Figure 4. Synthesis and X-ray structure of ketoacid **9**.

The formation of the enols **6** and **7** in the Ti mediated reaction, as opposed to the direct formation of ketoesters in the Li mediated reaction, can be explained if the reaction between **3** and the Ti enolate **1** takes place through a cycloadditive mechanism, rather than a nucleophilic addition to the activated double bond. [4+2] Hetero-cycloadditions are known to occur between enones and electronrich dienophiles such as enolethers and keteneacetals.[13] These cycloadditions (the so-called inverse demand Diels-Alder reactions) take place thermally or under Lewis acid catalysis and, starting from ketene acetals, give rise to 2,2-dialkoxy-dihydropyranes.[13f,14] Thus, cycloaddition of **1** and **3** followed by water quenching should afford the hemiorthoesters **10** and **11** (**Figure 5**). Breakdown of these intermediates is expected to occur mainly by opening of the ring and release of the enol form.[13f, 15] At present we do not know whether the mechanism that leads to the formation of **6** and **7** is concerted as for enolethers,[13] or stepwise as for enamines.[13a,c] From a stereochemical point of view, we can observe that, assuming a concerted mechanism and that the stereochemistry of **1** is E,[2] the selective formation of **5** over **4** can be explained with the models of **Figure 5**.

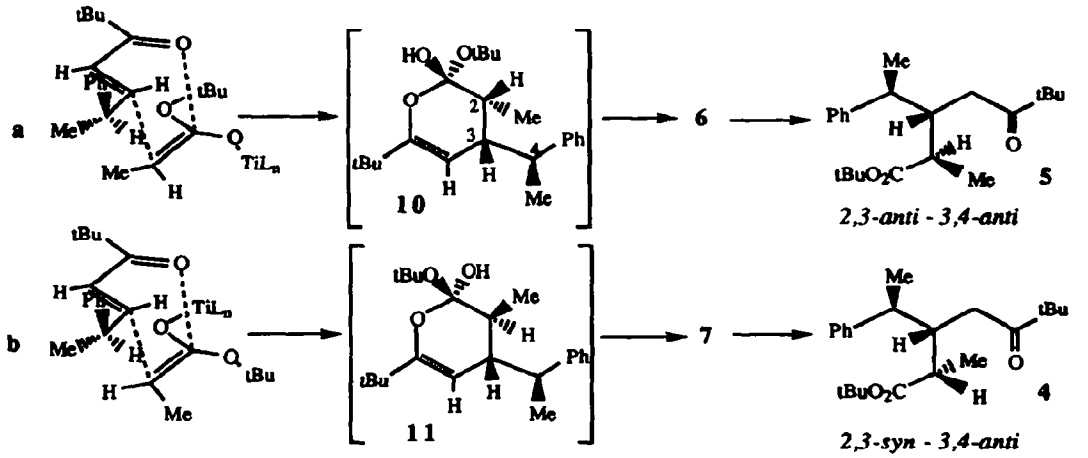

Figure 5. Proposed mechanism for the addition of **1** to **3**.

Structures **a** and **b** show the approach of the enolate to the face of **3** predicted by the Felkin model.[16] Both **a** and **b** allow the favorable interaction between the enolate oxygen and the carbonyl carbon which generally leads to *endo* selectivity in these type of cycloadditions.[13a] Structure **b** should be disfavored by the steric hindrance created by the metal ligands in the *endo* orientation.[14]

More generally, the isolation of **6** and **7** sheds some light on the stereochemical divergence of lithium and titanium ester enolates. The reaction of lithium enolates is a real nucleophilic addition to the activated double bond and takes place through eight-membered cyclic transition structures, which dictate the sterochemical outcome.[3, 17] On the contrary, the addition of the titanium enolate **1** is an inverse-demand [4+2] cycloaddition, proceeding with *endo* selectivity.

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5. The stereochemistry of **4** was determined by treatment with CF_3CO_2H to give the free acid, whose NMR spectra were identical to those reported by Heathcock in *ref. 6*.
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7. The exact determination of this ratio is impaired by the instability of the enols(see text) and the presence in the reaction crude of variable quantities of the ketoesters **4** and **5**. Analysis of the crude NMR at different times within the first 24 h, shows that **4** is formed from the enol more rapidly than **5**.
8. **6**: ^{1}H-NMR ($CDCl_3$): 1.0 (d, 3H, J=7 Hz); 1.1 (s, 9H); 1.22 (d, 3H, J=6.5 Hz); 1.38 (s, 9H); 2.2 (dq, 1H, J=7 Hz, J=4.5 Hz); 2.62 (m, 1H); 3.05 (ddd, 1H, J=J=10 Hz, J=4.5 Hz); 4.12 (d, 1H, J=10Hz); 6.6 (1H, s). ^{13}C-NMR ($CDCl_3$, selected): 10.8, 16.3, 35.5, 42.0, 42.2, 42.8, 81.0, 95.5, 146.0, 161.0, 177.5. IR ($CHCl_3$): 1715, 1690, 1620. **7**: ^{1}H-NMR ($CDCl_3$, selected): 4.23 (d, 1H, J=10Hz). ^{13}C-NMR ($CDCl_3$, selected): 43.8, 44.4, 94.5.
9. A third isomer (ca. 7% of the mixture of the ketoesters) could also be detected in the ^{13}C-NMR spectrum. Its structure was not fully characterized and is tentatively attributed as *2,3-anti-3,4-syn*.
10. Acylation by TosNCO appears to be stereospecific, since starting from a 5:1 mixture of **6** and **7**, **8** is obtained as a 5:1 mixture of isomers.
11. The stereostructure of **8** was not determined. However, the transformation of a 5:1 mixture of the enols in a 5:1 mixture of **5** and **4** supports the configuration of **6** and **7** depicted in **Figure 3**.
12. $C_{18}H_{26}O_3$, Monoclinic, $P2_1/c$, M_r=290.40, a=14.933(2), b=6.306(1), c=19.128(3) Å, β=105.20(1)°, V=1738.2(5) Å^3, Z=4, d_{calc}=1.110 g.cm^{-3}, μ (Mo Kα)=0.069 mm^{-1}; *Enraf-Nonius* CAD4 diffractometer, Mo Kα radiation, λ=0.71069 Å; cell parameters from 25 reflections in the range 8.75< ϑ <15.65; 3402 collected reflections, 1935 observed reflections [I > 2σ (I)]; range: 0<ϑ<26°, h -18 -> 18, κ 0 -> 7, *l* 0 ->23; structure solved by MULTAN82 and refined by full-matrix least-squares. Heavy atoms anisotropic, H atoms isotropic; H atoms of tBu groups fixed in calculated positions. Final R=0.048, R_w=0.048, $\Delta\rho_{max}$=0.015 eÅ^{-3}.
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