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Titanium Ate Enolate Complexes: An NMR Study

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Reaction of lithium enolates with $Ti(OiPr)_4$ in THF at −40 °C is reported to give rise to the so-called titanium ate enolate complexes.[1] These complexes have been found to display a reactivity markedly different from that of the parent lithium enolates. Their use in stereoselective aldol condensations was described by Reetz and Thornton.[1,2] More recently we have shown that they add regio- and stereoselectively to unsaturated carbonyl compounds in a 1,4 fashion and offer various advantages over their lithium counterparts.[3] In particular, ketone enolate Ti complexes proved to be more regioselective than the parent Li enolates, allowing highly selective 1,4 addition even to unhindered α,β-enones. From a stereochemical point of view, the reaction outcome depends on the configuration of the starting materials: when adding to an *E* enone, *E* enolates give rise to *syn* compounds and *Z* enolates to the *anti* isomers (Scheme 1). The same trend is displayed by the parent lithium enolates, which, however, are less stereoselective.

Although the synthetic value of titanium ate enolate complexes has been demonstrated, very little is known about their structure. Most researchers agree that the reaction of lithium enolates with $Ti(OiPr)_4$ is not likely to result in the substitution of one of the alkoxy ligands by the enolate, but rather in the formation of a pentacoordinated titanium species. However, no structural data are available in the literature on the reaction product.

A second important question concerns the configuration of the enolates and whether it is conserved during the reaction with $Ti(OiPr)_4$. For the related case of $ClTi(OiPr)_3$, Thornton presented some evidence indicating that enolate isomerization during the titanation process is unlikely.[4] However, the very low reactivity of Ti ate enolates with chlorosilanes has precluded the usual determination of their stereostructure *via* the corresponding enolsilanes. This is obviously a point of major concern when trying to rationalize the stereochemical results obtained both in aldol condensation and Michael addition reactions. A better knowledge of the structure of these complexes would also be of help in designing efficient chiral modifications. Therefore, we have undertaken an NMR study of the Ti ate enolates themselves, with the aim of clarifying these issues.

Results and Discussion

Propiophenone Enolate. We began our investigation from the enolate of propiophenone because the solution behavior of the lithium enolate **1** in THF has been studied in some detail.[5] The enolate is formed as a 95% pure *Z*-isomer[6] by treating the ketone with LDA (Figure 1).

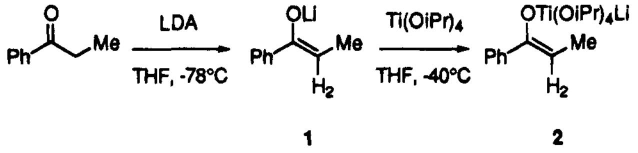

Figure 1. Propiophenone enolates.

The NMR spectra in THF-d_8 have revealed the presence in solution of at least two species that have been interpreted as an equilibrium mixture of dimers and tetramers. Mixed aggregates with LDA and complexes with diisopropylamine are also formed.[6] The ^{1}H-NMR spectrum of a 0.2 M solution of **1** in THF/hexane at −78 °C, and in the presence of 1 molar equiv of iPr_2NH, is shown in Figure 2a.

The signal for H_2 appears as two quartets at 4.24 and 4.38 ppm. The signals due to the aromatic protons also appear as a double set, as expected for a dimer−tetramer mixture. Particularly evident are the two doublets at 7.4 and 7.6 for the *ortho* protons. Upon treatment with 1 equiv of $Ti(OPr)_4$ at −78 °C, a new set of signals appears in the ^{1}H-NMR spectrum. Disappearance of **1** and $Ti(OiPr)_4$ is complete after 30 min at −40 °C. The spectrum of the reaction mixture at −48 °C is shown in Figure 2b. A single set of signals is now displayed by the enolate moiety. The aromatic protons appear as one doublet and two triplets at 7.6 (*ortho*), 7.0 (*meta*), and 6.9 ppm (*para*), respectively. The signal for H_2 appears as a single quartet at 4.85 ppm. The three very broad signals at 4.62, 4.5, and 4.4 ppm, in a ca. 2:1:1 ratio belong to the methines of the isopropoxy groups. There is no evidence of the formation of lithium isopropoxide as such (the signal of iPrOLi in THF at −50 °C resonates as a well-resolved septet at 3.8 ppm).

The broadening of the methine signals points to the existence of an exchange process with a low activation barrier that involves the alkoxide ligands. This process also affects the signal due to the isopropoxy methyl groups, which, at −48 °C, appear as a broad multiplet at 1.1 ppm. The fluxionality of the complex cannot be "frozen out" even at −90 °C (Figure 2c). At this temperature a lower energy exchange process is indicated by the broadening of all the lines due to the enolate moiety (H_2 quartet and aromatic proton signals, Figure 2c). The enolate solution is unstable when the temperature is raised above −20 °C, and this precluded further examinations of the time-averaged phenomena.[7]

Using ^{13}C-NMR as probe, the above picture is confirmed. In the Hetcor spectrum of the lithium enolate **1**, the vinyl quartets correlate to a ^{13}C signal at 84 ppm and to a much smaller one at ca. 90 ppm. After formation of **2**, the signal of C_2 shifts downfield by 10 ppm and resonates at 94 ppm. The broad alkoxide methine signals of the proton spectrum

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[1] Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691−94. Reetz, M. T.; Wenderoth, B. *Tetrahedron Lett.* **1982**, *23*, 5259−5262.

[2] Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722−5728.

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[5] See ref 141 in: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654.

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[7] ^{1}H-NMR spectra of **2** in toluene solution were also taken at −48 °C, in the presence of 1 equiv of $iPr\text{-}NH_2$. However, in this solvent the broadening of the signals was so extensive as to preclude the interpretation of the spectra. Addition of 10−20 equiv of THF improved the appearance of the signals but did not give any more information than the experiments in THF.

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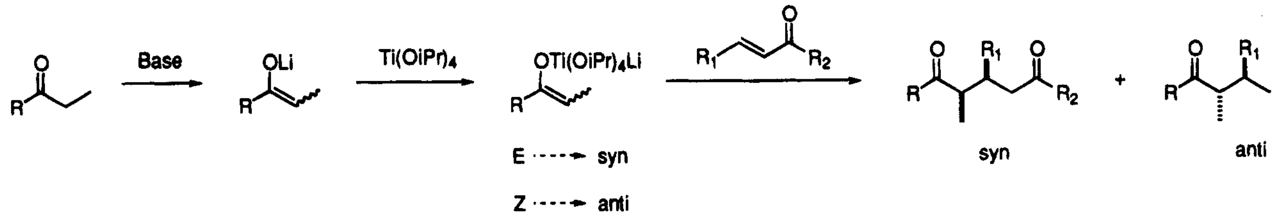
Scheme 1



correlate with a group of ^{13}C signals, also significantly broadened and centered at 75.7 and 74.5 ppm.

On the whole, these data can be interpreted within the hypothesis that the reaction between **1** and $Ti(OiPr)_4$ takes place through the formation of an O—Ti bond to give an ate complex of formula **2** with the ligands in rapid exchange. The formation of an O—Ti bond between the enolate and the metal center is supported by the downfield shift of the signals due to H_2 and C_2. The chemical shifts of these atoms are known to depend on the π electron density on the enolate oxygen and to increase as the latter decreases.[8] For comparison, the chemical shifts of C_1, C_2, and H_2 in **1**, **2**, and the corresponding silyl enol ether **3** are collected in Table 1.

The downfield shifts observed on going from **1** to **2** reflect the increased covalent character of the oxygen–metal bond on going from Li to Ti, which determines a decrease of π electron density at C_2. Thus, treatment of **1** with $Ti(OiPr)_4$ transforms this enolate into a softer nucleophile. This observation explains the improvement of regioselectivity in favor of the conjugate addition product observed when comparing the Ti ate enolates with the parent lithium enolates.[3] The reactivity of **2** ($C_2 = 94$ ppm) is expected to be intermediate between that of **1** ($C_2 = 84$ ppm) and that of the silyl enol ether **3** ($C_2 = 105$ ppm).

The fluxional behavior of the ligands observed in the spectrum of **2** seems to be in agreement with the formation of a pentacoordinate Ti complex. An intramolecular dynamic process is very likely to be the cause of the observed line broadening, based on the well-known stereochemical nonrigidity of five-coordinate metal centers. A similar dynamic behavior was recently observed in the ^1H-NMR spectra of the mixed alkoxide obtained by addition of iPrOLi to $Ti(OiPr)_4$.[10] In this case, the structure of the complex was determined by X-ray diffraction and shown to be a dimer of formula $[LiTi(OiPr)_5]_2$ that contains two pentacoordinated, roughly trigonal bipyramidal, Ti atoms connected by lithium bridges. In toluene solution the alkoxide ligands displayed fluxional behavior, with at least two processes, one with -20 °C $< T_c <$ rt, the other still rapid between -80 and -120 °C. It is likely that the addition of **1** to $Ti(OiPr)_4$ also gives rise to a pentacoordinate titanium species. This finding has straightforward implications on the possibility of designing an enantioselective enolate by using chiral alkoxide ligands for titanium.

Isopropyl Ethyl Ketone Enolate. The lithium enolate of isopropyl ethyl ketone (**4**) can be selectively generated in either the *E* or *Z* configuration by an appropriate choice of the base (Figure 3). Reaction of **4** with LHMDS gives rise to a 98% isomerically pure *Z* enolate **Z-5**.[6] The *E* enolate **E-5** can be obtained by treating **4** with LTMP·LiBr, as described by Collum.[11] The corresponding titanium ate enolates **Z-6** and **E-6** have been previously synthesized and shown to react with benzalpinacolone (**8**) with opposite stereochemical outcome (Figure 3).[3]

It appears that **4** would be an ideal substrate for investigating the issue of stereostructure conservation in the titanation process. Indeed, the formation of **Z-5** and **Z-6** could be followed in the usual manner by NMR spectroscopy, in 10:1 THF-d_8/hexane, and in the presence of 1 equiv of hexamethyldisilazane (HMDS) at -40 °C. The data are reported in Table 2. Also in this case, a simplification of the spectrum is observed on going from **Z-5** (Table 2, Entry 1) to **Z-6** (Table 2, Entry 2), *i.e.* the double set of signals of **Z-5** goes to a single set in **Z-6**. The vinyl proton H_2 appears as two quartets at 3.70 and 3.85 ppm in **Z-5** and shifts downfield to 3.95 ppm in **Z-6**. The septet due to $H_{2'}$ and the doublet due to the vinylic methyl group are visible in the proton spectrum of **Z-6** at 2.25 and 1.60 ppm, respectively, while they appear only as broad multiplets in the spectrum of **Z-5**. Fluxional behavior of the isopropoxide ligands in **Z-6** results in the collapse of their methine signals in one broad multiplet centered at ca. 4.7 ppm. Two broad singlets are also shown by the isopropoxide methine in the fully decoupled ^{13}C spectrum of **Z-6** at 72 and 76 ppm. The downfield shift of C_2, which moves from 84 ppm in **Z-5** to 92 ppm in **Z-6**, is in agreement with the observations made on propiophenone.

On the contrary, the ^1H and ^{13}C spectra of **E-5** generated *in situ* with LTMP·LiBr were of no practical use due to extensive broadening of all the relevant signals. Very likely, the presence of 1 equiv of LiBr in the solution gives rise to a complex equilibrium mixture of mixed aggregates. This phenomenon has been described before for THF solutions of **1** in the presence of LiCl,[5] and it is well known for lithium bases' solutions in THF.[12] Use of LTMP in the absence of LiBr is reported to give rise to a 2:1 mixture of **E-5** and **Z-5**, respectively.[11] Also in this case the ^1H-NMR spectrum in THF solution was too complex to be analyzed.

A solution to this problem was found in generating the lithium enolates in the absence of lithium salts by treating the corresponding enol silanes **E-7** and **Z-7** with 1 equiv of MeLi in THF-d_8/Et_2O solution.[13] Under these conditions, the ^1H- and ^{13}C-NMR spectra of the *Z* titanium enolate **Z-6** were identical to those previously recorded in

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[13] A 1 M solution of MeLi in Et_2O (halide content ca. 0.05 M) was used. The enol silanes were treated with 1 equiv of MeLi at room temperature for 1 h; then the solution was cooled to -40 °C and 1 equiv of $Ti(OiPr)_4$ was added. Reaction of **Z-6** (>95% *Z*) and **E-6** (from an 8:1 **E-7**:**Z-7** mixture) generated in this way with 0.5 equiv of benzalpinacolone (**8**) gave the 1,4-addition product in a ≥100:1 and 1:6 *anti-syn* ratio, respectively (as judged by GC analysis of the reaction crude).

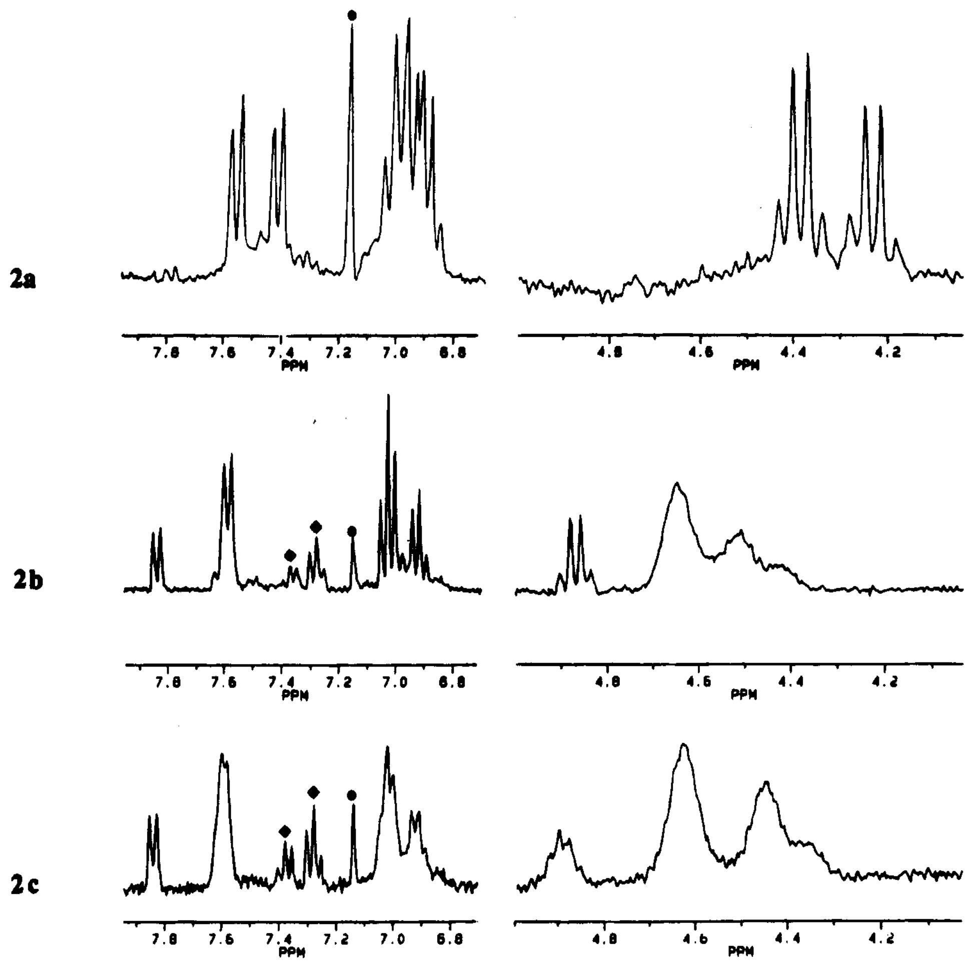
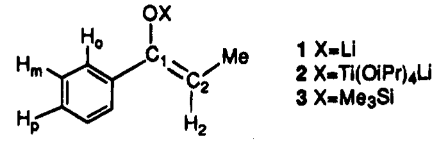


Figure 2. ^{1}H-NMR spectra of **1** and **2**. (**a**) Spectrum of **1** in 10:1 THF/hexane, at −78 °C. (**b**) Spectrum of **2** in 10:1 THF/hexane, at −48 °C. (**c**) Spectrum of **2** in 10:1 THF/hexane, −90 °C. ◆: residual ketone. ●: benzene.

Table 1. ^{1}H- and ^{13}C-NMR Data for 1−3[a]



compd	C_1	C_2	H_2	H_o	H_m	H_p
1[a]	160	84	4.24(q)	7.6	6.8−6.9 (m)	6.92 (t)
	159		4.38 (q)	7.4		6.97 (t)
2[a]	159	94.4	4.8 (q)	7.6	7.0	6.9
3[b]	149.9	105.2	5.33 (q)			

[a] Spectrum of a 0.2 M solution in 10:1 THF/hexane, with benzene-d_6 as internal standard and in the presence of 1 equiv of iPr$_2$NH. Chemical shifts expressed in ppm relative to TMS. Multiplicity of the ^{1}H signals in parentheses: q, quartet; d, doublet; t, triplet; m, multiplet. [b] Spectrum in CDCl$_3$, from ref 9.

the presence of HMDS (Table 2, cf entries 2 and 3). The data collected for **E-5** and **E-6** are reported in Table 2 (entries 4 and 5, respectively). The usual simplification of the spectrum and downfield shift of the signals due to H_2 (from 3.55 and 3.8 to 4.38) and C_2 (from 85 and 86 to 94.5) were observed after treatment of **E-5** with Ti(OiPr)$_4$.

It is apparent from the results of Table 2 that the two lithium isomers give rise to different Ti complexes (Table 2, compare entries 3 and 5). The collected data indicate that the difference lies in the stereochemistry of the enolate moiety, which appears to be conserved in the titanation process. The diagnostic signals are those due to $C_{2'}$ and $H_{2'}$. As a general rule, the ^{13}C chemical shift of the allylic carbon of an *E* enolate is ca. 6 ppm upfield from the corresponding *Z* isomer.[5] This allows the assignment of double-bond configuration for **E-6** ($C_{2'}$ = 30.4 ppm) and **Z-6** ($C_{2'}$ = 38.0 ppm). Additionally, the ^{1}H-NMR spectra of isopropyl ethyl ketone enolates are characterized by the chemical shift of the allylic proton $H_{2'}$, which in the *Z*-isomer resonates ca. 0.5 ppm upfield from the *E*-isomer both in the case of the enol silanes **7** (Table 2, entries 6 and 7; **E-7** $H_{2'}$ = 2.80 ppm, **Z-7** $H_{2'}$ = 2.24 ppm) and of the lithium enolates **5** (Table 2, entries 2 and 4; **E-5** $H_{2'}$ = 2.80 ppm, **Z-5** $H_{2'}$ = 2.00 ppm). This trend is confirmed in the titanium complexes. (**E-6** $H_{2'}$ = 2.75 ppm, **Z-7** H_2 = 2.25 ppm).

The configuration of **Z-6** was also confirmed by NOE difference experiments in THF-d_8 at −40 °C, which showed 4% NOE between H_2 and $H_{2'}$ (Figure 4). No Overhauser effect was observed between these two protons in the spectrum of **E-6**. Thus it was confirmed that the stereochemistry of the enolate is unchanged after reaction with Ti(OiPr)$_4$.

In conclusion, NMR spectroscopy of the reaction between the lithium enolates **1** and **5** and Ti(OiPr)$_4$ supports the hypothesis made in the literature that an oxygen−titanium bond is created in the reaction and a pentacoordinated Ti(IV) ate complex is formed. The stereochemistry of the enolates is conserved in the titanation process. Given the stereochemical nonrigidity of five-coordinate

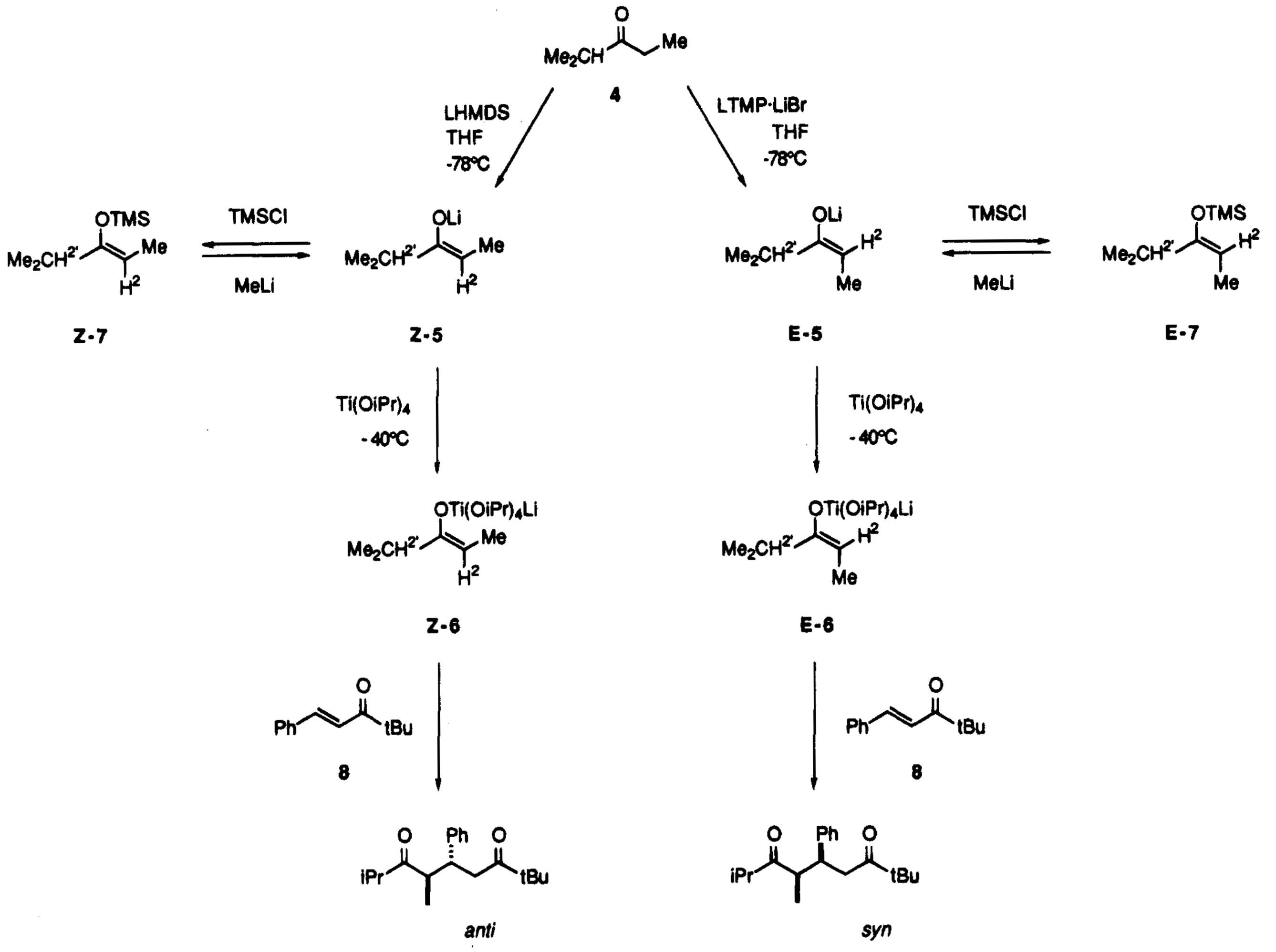
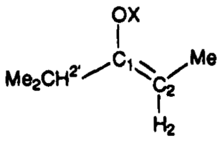


Figure 3. Isopropyl ethyl ketone enolates.

Table 2. ^{1}H- and ^{13}C-NMR Data for 5−7[a]

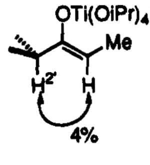


5 X=Li
6 X=Ti(OiPr)$_4$Li
7 X=Me$_3$Si

entry	compd	$C_{2'}$	C_1	C_2	H_2	$H_{2'}$
1	**Z-5**[b]		169	84	3.70 (bm) 3.85 (bm)	2.0 (bm)
2	**Z-6**[b]	38.2	167.3	92.1	4.05 (q)	2.25 (sp)
3	**Z-6**[c]	38.0	167.7	92.0	4.08 (q)	2.25 (sp)
4	**E-5**[c]	31.1 (b)	167.0	85.2 86.2	3.55 (bm) 3.80 (bm)	2.80 (bm)
5	**E-6**[c]	30.4	166.0	94.5	4.38 (q)	2.75 (sp)
6	**Z-7**[d]	36.4	157.7	100.4	4.58 (q)	2.24 (sp)
7	**E-7**[d]	30.0	158.3	99.2	4.52 (q)	2.80 (sp)

[a] Spectra were recorded in the indicated solvent, as 0.2 M solutions, at 300 MHz. Chemical shifts are in ppm from TMS. Multiplicity of the ^{1}H signals are in parentheses: q, quartet; m, multiplet; b, broad; sp, septet. [b] Lithium enolate generated with LHMDS from the ketone. Spectrum recorded at −40 °C in 10:1 THF-d_8/hexane, and in the presence of 1 equiv of HMDS. [c] Lithium enolate generated with MeLi from the enol silane. Spectrum recorded at −40 °C, in 7:1 THF-d_8/Et$_2$O. [d] Spectrum recorded at room temperature, in THF-d_8.

metal centers, these findings suggest that chiral modifications of the titanium enolates using simple chiral diols as ligands for the metal are not likely to be very effective.



Z-6

Figure 4. NOE of **Z-6**.

Experimental Section

All solutions were handled under nitrogen (from liquid nitrogen) and all the solvents were dried before use by distillation on sodium−benzophenone.

The lithium enolates **1** and **Z-5** were formed as a 0.2 M solution in 10:1 THF/hexane by adding the ketone to a 0.2 M solution of LDA or LHMDS, respectively (from the corresponding amine and 2.5 M BuLi in hexane), at −78 °C. The lithium enolates of isopropyl ethyl ketone **Z-5** and **E-5** were also generated in 8:1 THF-d_8/Et$_2$O solution by treating the corresponding enol silanes **Z-7** and **E-7** (0.2 M solution in THF-d_8) with 1 molar equiv of MeLi (1 M solution in Et$_2$O, halide content ca. 0.05 M, from Aldrich) for 1 h at room temperature.

The Ti ate complexes **2**, **E-6**, and **Z-6** were generated by treating the corresponding lithium enolates with 1 molar equiv of Ti(OiPr)$_4$ for 30 min at −40 °C.

The enolate solutions were transferred *via* cannula to the NMR tubes.

The NMR spectra were obtained on Bruker AC-300 and AC-200 instruments, using a 5-mm ^{1}H/^{13}C dual probe (^{1}H NMR 300 MHz and 200 MHz; ^{13}C NMR 75 MHz and 50 MHz). The spectra were recorded as solutions in THF/hexane (2% C$_6$D$_6$ internal standard, 7.15 ppm), THF-d_8/hexane, and THF-d_8/Et$_2$O (referenced to residual THF, 3.66 ppm) and at temperatures varying from −90 to 0 °C. Chemical shifts are reported in ppm relative to tetramethylsilane, coupling constants in hertz. When the solvent was THF/hexane, the ^{1}H-NMR spectra were recorded using Bruker microprograms to suppress the THF signals by presaturation.

Two-dimensional ^{1}H−^{13}C correlation (HETCOR) spectra were measured using standard microprograms optimized for one-bond coupling.

Titanium Enolate of Propiophenone (2). ^{1}H NMR (10:1 THF/hexane, −48 °C, 300 MHz, selected signals): 7.58 (2H, d, $J = 4.8$); 7.03 (2H, t, $J = 4.8$); 6.92 (1H, d, $J = 4.8$); 4.85 (1H, q, $J = 6.7$); 4.35−4.70 (4H, bm). ^{13}C NMR (10:1 THF/hexane, −48 °C, 75 MHz, selected signals): 159.3, 142.2, 94.36, 14.8.

Titanium Enolates of Isopropyl Ethyl Ketone (Z-6 and E-6). Z-6. ^{1}H NMR (8:1 THF-d_8/Et$_2$O, −40 °C, 300 MHz, selected signals): 1.05 (6H, d, $J = 6.0$); 1.62 (3H, d, $J = 6.5$); 2.28 (1H, sp, $J = 6.0$); 4.08 (1H, q, $J = 6.5$); 4.6−4.9 (4H, bm). ^{13}C NMR (8:1 THF-d_8/Et$_2$O, −40 °C, 300 MHz, selected signals): 12.8, 23.0, 28.3, 28.7, 38.1, 71.5, 75.0, 92.1, 167.7.

E-6. ^{1}H NMR (8:1 THF-d_8/Et$_2$O, −40 °C, 300 MHz, selected signals): 1.60 (3H, d, $J = 6.6$); 2.75 (1H, sp, $J = 6.0$); 4.38 (1H, q, $J = 6.6$), 4.5−4.7 (4H, bm). ^{13}C NMR (8:1 THF-d_8/Et$_2$O, −40 °C, 75 MHz, selected signals): 13.7, 22.1, 28.3, 28.7, 30.4, 71.2, 75.1, 94.5, 166.0.

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