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STEREOSELECTIVE MICHAEL ADDITIONS OF TITANIUM "ATE" COMPLEXES OF KETONE AND ESTER ENOLATES.*

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Abstract: *The conjugate addition of Ti "ate"complexes of ketone and ester enolates to α,β-unsaturated carbonyl compounds was studied. The reaction was found to be highly regio- and stereoselective. Compared to the lithium enolates, ketone enolate Ti complexes showed an improved 1,4-regioselectivity. t-Butyl propionate enolate Ti complex gave the opposite stereochemical results compared to the parent lithium enolate.*

Introduction.

The stereoselective Michael addition of enolates to α,β-unsaturated carbonyl compounds has recently attracted a great deal of attention.[1] This does not come as a surprise, in view of the remarkable success encountered in developing stereoselective enolate reagents for the aldol addition reaction.[2] The scope of such reagents could be significantly expanded if they were also found to be effective in the vinylogous 1,4-addition reaction. The task, however, is not as straightforward as it may look. In fact, low reactivity of the α,β-unsaturated substrates, or competing 1,2-addition processes often impair the desired Michael addition.[3]

Recently, it has been reported by Evans that titanium enolates of phenylalanine derived propionyloxazolidinone add in a highly stereoselective fashion to terminal activated double bonds.[4] With β-substituted substrates, control of the relative stereochemistry of the newly generated stereocenters ("internal" stereoselectivity[5]) cannot be achieved.

In contrast, the lithium enolates of ketones and esters (**Figure 1**) exhibit good levels of internal selectivity in the addition to activated double bonds.[1,6,7] Although some exceptions have been found,[7] in most cases a correlation has been observed between enolate configuration and product stereostructure. With E-acceptors, E- (Z-) enolates tend to give the *syn* (*anti*) diastereomer (**Figure 1**). With Z-acceptors the opposite is true, *i.e.* E- (Z-) enolates tend to give the *anti* (*syn*) diastereomer, generally with lower selectivity. These trends are usually reinforced by the presence of bulky substituents on the enolate and the acceptor. The experimental data[1a] and MNDO calculations[8] concurr to suggest that the foregoing stereochemical trends can be qualitatively rationalized assuming that the reaction takes place through cyclic eight-membered transition state structures, whose conformational properties dictate the overall

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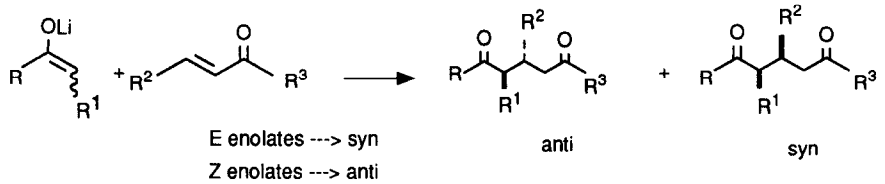
* *This paper is dedicated to Prof. Cesare Cardani on his 70th birthday.*

stereochemical outcome. Versions of this reaction employing chiral reagents have appeared, and moderate to excellent enantiomeric excesses have been obtained.[9]

Figure 1.



From a synthetic point of view, however, many problems are still to be solved in order to achieve full regio- and stereocontrol of the conjugate addition reactions of ketone and ester enolates:

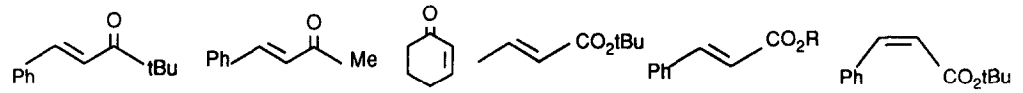
- regioselectivity. 1,2-addition can be a significant side reaction depending on the substitution pattern of substrate and Li enolate. The most general way of avoiding aldol addition relies upon the use of HMPA as cosolvent;[6a]
- good stereoselectivity depends on the stereochemistry of the enolate, which is not always easy to control;
- cyclic enones, such as cyclohexenone, do not react with lithium enolates of esters and ketones.[6a]
- General methods of coupling internal diastereoselection in the formation of the new bond with enantioface differentiation of substrates are still wanting.

Part of the foregoing problems have been addressed and solved to some extent by exploiting enamines and enolethers as the nucleophilic partner.[10]

A different approach could make use of metal enolates other than the alkali ones. In this respect, Ti appears to be a likely candidate. Although various reports point to the propensity of Ti reagents toward 1,2- rather than 1,4- addition,[11] titanium based reagents are often involved in conjugate addition processes.[4,11b,12] In particular, titanium "ate" complexes, prepared by reacting Li-enolates with $Ti(OiPr)_4$, have been shown to afford good 1,4-regiocontrol in the addition to 1-acyl-pyridinium salts[13] and to chalcone.[14] Another attractive feature of titanium-based reagents is that their chiral modification appears to be easier than that of the lithium analogues.[11a,b] Indeed, chiral titanium "ate" enolates have been succesfully used in carbonyl addition reactions.[15] We therefore undertook an investigation of the addition of Ti "ate" enolates of ketones and esters to α,β-unsaturated carbonyl compounds in an effort to establish the regioselectivity and the internal diastereoselectivity of such a process. Our initial results are reported in this paper.

RESULTS AND DISCUSSION.

Enones **1-3** and enoates **4-7** were used in the present study. The addition of the Ti "ate" enolates of diethylketone **8**, propiophenone **9**, *i*-propylethylketone **10**, *t*-butyl and ethyl propionate **11** and **12**, and *t*-butyl phenylacetate **13** were examined.

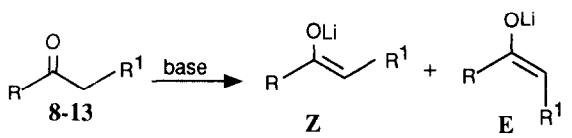


1 **2** **3** **4** **5** R=tBu **7**

6 R=Et

The starting lithium enolates were prepared by standard literature procedures with the isomeric ratios reported in **Scheme 1**.

Scheme 1. Lithium enolates and their stereoisomeric ratios.



8-13 **Z** **E**

8 R=Et, R^1=Me
9 R=Ph, R^1=Me
10 R=iPr,R^1=Me
11 R=OtBu, R^1=Me
12 R=OEt, R^1=Me
13 R=OtBu, R^1=Ph

	base	Z : E	ref.
8	LDA	30 : 70	16
8	LHMDS	70 : 30	17
9	LDA	100 : 0	17
9	LHMDS	70 : 30	17
10	LHMDS	92 : 8	18
10	LTMP·LiBr	4 : 96	19
11	LDA	5 : 95	18
12	LDA	6 : 94	20
13	LDA	71 : 29	21

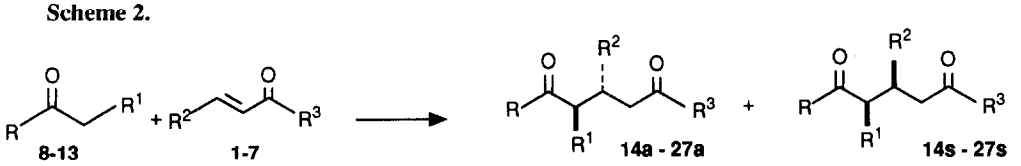
LDA= iPr_2NLi; LHMDS= $(Me_3Si)_2NLi$; LTMP= Lithium 2,2,6,6-Tetramethylpiperidide

The corresponding Ti "ate" complexes were generated by titanation with 1 mol equiv of $Ti(OiPr)_4$ for 30 min at -40°C in a 0.1M THF solution.[11b, 15, 22] Ethyl propionate (**12**) enolate partially decomposes under these conditions, therefore lithium-titanium exchange at -78°C was sought. However, the "ate" complex formation is extremely slow at this temperature, and still incomplete after 3h, as shown by the Michael addition results (*vide infra*). Use of excess $Ti(OiPr)_4$[15] was found to dramatically reduce reaction rates in the 1,4-nucleophilic addition.

The actual nature of the postulated Ti "ate" complexes is not known. In particular, it is not clear whether the stereostructure of the double bond in the Li enolates is altered upon titanation. Our attempts to trap the titanium enolate of **11** with *t*-butyldimethylsilyltriflate, *t*-butyldimethylsilylchloride / HMPA or Ac_2O were unsuccessful, but data from Thornton's work[15] indicate that enolate isomerization during the titanation process is unlikely.

The Michael additions were performed by adding the acceptor, neat or in THF solution, to 2 mol equiv of enolate. The condensation adducts **14-27** (**Scheme 2**) were isolated and their stereostructures determined as described in the Experimental. The results were compared to those obtained with the parent lithium enolates in terms of reactivity, regioselectivity and stereoselectivity.

Scheme 2.



	R	R^1	R^2	R^3		R	R^1	R^2	R^3
14 a/s	Et	Me	Ph	tBu	**21 a/s**	OtBu	Me	Ph	OtBu
15 a/s	Ph	Me	Ph	tBu	**22 a/s**	OtBu	Me	Ph	OEt
16 a/s	iPr	Me	Ph	tBu	**23 a/s**	OEt	Me	Ph	OtBu
17 a/s	Et	Me	Ph	Me	**24 a/s**	OtBu	Me	Me	OtBu
18 a/s	Ph	Me	Ph	Me	**25 a/s**	OtBu	Ph	Ph	OtBu
19 a/s	Ph	Me	$-(CH_2)_3-$		**26 a/s**	OEt	Ph	Ph	OtBu
20 a/s	OtBu	Me	Ph	tBu	**27 a/s**	OtBu	Ph	Me	OtBu

Ketone Enolates.

The Michael additions of ketone enolates were examined first. The results obtained with the titanium complexes are reported in **Table 1**. For comparison, the results of the addition of diethylketone lithium enolate to **1** are collected in **Table 2**.

Table 1. Michael addition of ketone enolate - $Ti(OiPr)_4$ "ate" complexes to α,β-unsaturated ketones.[a]

	Ket.	R	R^1	Sub.	R^2	R^3	base[b]	T(°C)	t(h)	Prod. (y,%)	*anti/syn*[c]
1	**8**	Et	Me	**1**	Ph	tBu	LDA	-78	21	**14**(50)	75:25
2	**8**	Et	Me	**1**	Ph	tBu	LDA[d]	-78	40	**14**(41)	80:20[d]
3	**8**	Et	Me	**1**	Ph	tBu	LHMDS	-78	40	**14**(69)	95:5
4	**8**	Et	Me	**1**	Ph	tBu	LHMDS	-50	20	**14**(81)	89:11
5	**8**	Et	Me	**1**	Ph	tBu	LHMDS[e]	-50	20	**14**(11)	75:25[e]
6	**9**	Ph	Me	**1**	Ph	tBu	LHMDS	-50	21	**15**(85)	>92:8
7	**10**	iPr	Me	**1**	Ph	tBu	LHMDS	-50	20	**16**(65)	>97:3[f]
8	**10**	iPr	Me	**1**	Ph	tBu	LTMP·LiBr	-50	20	**16**(91)	17:83[f]
9	**8**	Et	Me	**2**	Ph	Me	LHMDS	-78	16	**17**(50)[g]	>91:9
10	**9**	Ph	Me	**2**	Ph	Me	LHMDS	-50	19	**18**(70)	>97:3
11	**9**	Ph	Me	**3**	$-(CH_2)_3-$		LHMDS	-40	17	**19**(32)	67:33[f]

a. Reactions performed by adding the enones to 2 mol equiv of the Ti complexes generated from the corresponding Li enolate by titanation with $Ti(OiPr)_2$. Unless otherwise stated, all reactions were performed in THF. **b.** See Scheme 1 for the isomeric ratios of the starting lithium enolates. **c.** Determined by ^{1}H-NMR or GC. **d.** Reaction run in Et_2O **e.** Reaction run in toluene. **f.** Determined by ^{13}C-NMR. **g.** 10% of cyclized material was formed. See note 23.

The titanium enolates of ketones appear to be less reactive than their lithium counterparts (Compare **Table 1**, Entries 1-8 and **Table 2**). Reaction with unsaturated ketones is somewhat sluggish, requiring several hours at -78°C. Unsaturated esters are altogether inert. As an exception, addition to cyclohexenone **3** to give the Michael addition product does take place, albeit with low yield and selectivity (Entry 11, **Table 1**). We have already pointed out that this reaction does not occur with lithium enolates.

On the other hand, use of the titanium reagents largely improved the 1,4-regioselectivity of the addition reactions. No aldol adducts were isolated from reactions of α,β-unsaturated ketones with Ti

complexes, even when the substrate carbonyl was very unhindered as in benzalacetone **2** (**Table 1**, Entries 9 and 10).[23] For comparison, the lithium enolate of **8** generated with LDA reacted with **2** to give 58% of 1,2-addition products and 9% of 1,4 adducts in a 56:44 *anti:syn* ratio.

The regioselectivity of Ti complex additions was not affected by a change of solvent from THF to Et_2O or toluene (**Table 1**, Entries 1, 2 and 5). In contrast, a marked solvent effect was observed in the reaction of diethylketone lithium enolate. Use of Et_2O instead of THF was found to increase the amount of 1,2-addition product and to promote stereorandom 1,4-addition. For instance, with benzalpinacolone **1**, 20% of 1,2-addition product was revealed by ^{1}H-NMR inspection of the crude reaction mixture (**Table 2**, Entry 3). This value is to be compared with less than 3% of 1,2-addition observed in THF solution (**Table 2**, Entry 1). Since the *t*-butyl substituent should effectively shield the carbonyl group from nucleophilic attack, the behavior of the lithium enolate in Et_2O solution appeared to suggest the intervention of single electron transfer processes in this solvent. In fact, when the reaction was run in Et_2O, but in the presence of 3 mol equiv of p-dinitrobenzene, a strong electron acceptor,[24] the same results were obtained as in THF solution (**Table 2**, Entry 4).

Table 2. Addition of the lithium enolate of diethylketone **8** to benzalpinacolone **1**.[a]

	Ket.	Enoliz. Conditn.	E/Z	t(h)	1,2:1,4[b] Addition	1,4[c] *a/s*	Conv.%[b]
1	**8**	LDA	70:30	1.5	<3:97	60:40	85
2	**8**	LHMDS	30:70	3.5	0:100	80:20	50
3	**8**	LDA[d]	n.d.	3.5	20:80	50:50	90
4	**8**	LDA[d]	n.d.	1.5	<3:97[e]	60:40	95
5	**8**	-[f]	81:19	12	<3:97	61:39	78
6	**8**	-[f]	15:85	72	<3:97	85:15	77

a. Reactions performed by adding the enone to 2 mol equiv of the lithium enolate. Unless otherwise stated, all reactions were performed at -78°C in THF solution. **b**. As determined by ^{1}H-NMR of the crude reaction mixtures. **c**. Determined by ^{1}H-NMR or GC. **d**. Reaction run in Et_2O. **e**. 3 mol equiv of p-dinitrobenzene added to the reaction mixture before **1**. **f**. Enolate generated by treating the corresponding trimethylsilylenolethers with MeLi. From Ref. 6a.

The major stereoisomer formed in the reactions of diethylketone "ate" complexes with **1** was found to be **14a**, independent of the configuration of the starting enolate. However, starting from the Z-enolate generated with LHMDS (**Table 1**, Entry 3) the reaction appeared to be more *anti* selective than starting from the E-isomer generated with LDA (**Table 1**, Entry 1). *Anti:syn* ratios up to 95:5 were obtained. The use of LHMDS was also observed to improve the *anti* selectivity in the conjugate addition to **1** of diethylketone lithium enolate (**Table 2**, Entries 1 and 2), but in this case the **14a/14s** ratio did not exceed 80:20. At this stage, direct involvement of the base in the titanium complex which undergoes the addition reaction cannot be ruled out. For the lithium enolates, it is worth noting that the stereochemical results observed for diethylketone **8** with LDA or LHMDS do not differ significantly from those obtained in an amine-free solution by Heathcock and Oare[6a] (**Table 2**, compare Entries 1 and 5, and 2 and 6).

The Ti complexes arising from the Z-configurated enolates of propiophenone **9** and *i*-propylethylketone **10** also displayed synthetically useful *anti* selectivity with both **1** and **2** (**Table 1**, Entries 6, 7, 10). On the contrary, starting with the E-enolate of *i*-propylethylketone reaction with

benzalpinacolone **1** gave preferentially the *syn* isomer **17s** (**Table 1**, Entry 8).

It appears, therefore, that the stereochemical behavior of the Ti "ate" complexes of ketone enolates in the addition to E- configurated α,β-unsaturated ketones parallels that of the parent lithium enolates: *anti* adducts are obtained from Z-enolates and *syn* adducts from E-enolates (with the exception of diethylketone enolates, which are always *anti* selective). The main advantages in the use of Ti rather than lithium are:

- an increased 1,4-regioselectivity, which allows Michael addition to unhindered conjugated carbonyls;[25]
- higher *anti* selectivity with "small" nucleophiles, such as diethylketone;
- *anti* selective conjugate addition to cyclic ketones.[25]

Ester Enolates.

Table 3. Michael addition of ester enolates to α,β-unsaturated carbonyl compounds.[a]

	Est.	R	R^1	Metal	Sub.	R^2	R^3	T(°C)	t(h)	Prod. (y,%)	*anti/syn*
1	**11**	OtBu	Me	Li	**1**	Ph	tBu	RT	3	**20**(90)	6:94[b]
2	**11**	OtBu	Me	Ti	**1**	Ph	tBu	-78	2	**20**(41)	88:12[c]
3	**11**	OtBu	Me	Li	**5**	Ph	OtBu	-78	1	**21**(61)	6:94[c]
4	**11**	OtBu	Me	Ti	**5**	Ph	OtBu	-40	0.5	**21**(68)	91:9[c]
5	**11**	OtBu	Me	Ti	**7**	Ph	OtBu	-40	0.5	**21**(50)[i]	20:80
6	**12**	OEt	Me	Ti[f]	**5**	Ph	OtBu	-40	0.5	**23**(22)	>95:5[b]
7	**12**	OEt	Me	Ti[e]	**5**	Ph	OtBu	-78	1.5	**23**(70)	80:20[b]
8	**11**	OtBu	Me	Ti	**6**	Ph	OEt	-40	0.5	**22**(51)[d]	90:10[c]
9	**11**	OtBu	Me	Li	**4**	Me	OtBu	-78	1.5	**24**(85)	5:95[g]
10	**11**	OtBu	Me	Ti	**4**	Me	OtBu	-78	0.5	**24**(90)	78:22[g]
11	**13**	OtBu	Ph	Li	**5**	Ph	OtBu	-78	1	**25**(60)	8:92[b,h]
12	**13**	OtBu	Ph	Ti	**5**	Ph	OtBu	-40	2	**25**(50)[i]	33:67[b]
13	**13**	OtBu	Ph	Li[j]	**5**	Ph	OtBu	-78	1	**25**(85)	<2:98[b]
14	**13**	OtBu	Ph	Ti[j,k]	**5**	Ph	OtBu	-78	5	**25**(70)[i]	20:80[b]
15	**13**	OtBu	Ph	Li[j]	**4**	Me	OtBu	-78	1	**27**(55)	<5:95
16	**13**	OtBu	Ph	Ti[j,k]	**4**	Me	OtBu	-78	2	**27**(70)	<5:95

a. Unless otherwise stated, all Li enolates were generated by using LDA as a base, in THF solution. All Ti complexes were generated by titanation of the corresponding lithium enolate with $Ti(OiPr)_4$ at -40°C for 30 min. **b**. Determined by ^{1}H-NMR **c**. Determined by ^{13}C-NMR. **d**.10% of products arising from 1,2-addition was also isolated. **e**.Titanation conditions: 3 h at -78°C. **f**.Titanation conditions: 3 h at -78°C , followed by 15 min at -40°C. **g**. Determined by GC. **h**. See ref. 7a. **i**.As determined via ^{1}H-NMR of the crude reaction mixtures. **j**.The lithium enolate was generated with LHMDS in THF for 45 min at -78°C. **k**.Titanation conditions: 1h at -40°C.

Ester enolate complexes present a rather different scenario. First of all, their nucleophilicity being higher than that of ketone enolates, addition to α,β-unsaturated esters can be achieved. By the same token, a strong tendency for 1,2-addition sets in. Reaction of *t*-butyl propionate titanium enolate with benzalacetone **2** gave rise exclusively to carbonyl addition products, and Claisen addition to E-ethyl cinnamate occurred, although as a minor reaction pathway. However, when the substrate carbonyl was suitably hindered, conjugate addition to unsaturated esters and ketones took place smoothly. The reactions of propionates and phenylacetates were examined as representatives of E-configurated and Z-configurated enolates, respectively (see **Scheme 1**). The results are reported in **Table 3**, which also contains the relevant comparison with the lithium reagents.

Propionate derived "ate" complexes gave rise selectively to *anti* adducts, both with benzalpinacolone

1 and E-configurated α,β-unsaturated esters **4-6** (**Table 3**, Entries 2, 4, 6-8, 10). The stereochemical outcome of propionate titanium complex reactions was neatly reversed compared to that displayed by the corresponding lithium enolates (Compare Entries 1 and 2, 3 and 4, and 9 and 10 in **Table 3**). The *anti* selectivity does not depend strongly on the size of the R and R^3 groups (**Table 3**, Entries 4 and 6, and 4 and 8). However, the use of ethyl propionate instead of *t*-butyl propionate resulted in low yield due to decomposition of the enolate during titanation at -40°C (Entry 6). When the titanation was performed for 3h at -78°C the yield increased but low selectivity was observed indicating incomplete "ate" complex formation (Entry 7). Addition to Z-*t*-butyl cinnamate (Entry 5) gave rise to prevalent formation of the *syn* isomer in moderate yield.

As an example of a Z-configurated ester enolate, *t*-butyl phenylacetate was examined. The lithium enolate is reported to deviate from Heathcock's rule, since it gives rise to *syn*-2,3-diphenylglutarates upon addition to E-cinnamates.[7] We found that this trend was reinforced when LHMDS was used as the enolizing base (Compare Entries 11 and 13 in **Table 3**) and that *syn* selectivity was displayed in the addition to *t*-butyl crotonate too (**Table 3**, Entry 15). Titanium complexes were also found to be *syn* selective when adding to E-crotonate and E-cinnamate (Entries 12, 14, 16). Addition to Z-*t*-butyl cinnamate did not occur at -40°C.

It can therefore be concluded that for ester enolate Ti "ate" complexes the outcome of the Michael additions depends on the configuration of both the donor and the acceptor. Use of *t*-butyl propionate Ti complex in the addition to E-configurated esters and ketones gave *anti* adducts with levels of selectivity previously achieved only by the use of HMPA.[1, 10]

It would be difficult to rationalize the behavior of the present Ti enolate complexes in term of a transition state model. We feel, however, that the potential of these reagents in obtaining regio- and stereoselective Michael addition to unsaturated carbonyl compounds is now well established. Work is in progress to develop enantioselective versions of this reaction.

EXPERIMENTAL.

All new compounds gave satisfactory elemental analysis (C±0.3%; H±0.2%). ^{1}H- and ^{13}C-NMR spectra were recorded at 200 MHz and at 50.3 MHz, respectively.

Determination of Product Stereostructures.

The products of addition to benzalpinacolone **14-16** and **20** have been described by Heathcock, who showed how ^{1}H-NMR spectroscopy can be used to assign their stereostructures.[6a] These rules were also used to assign the benzalacetone addition products **17**[26] and **18**.

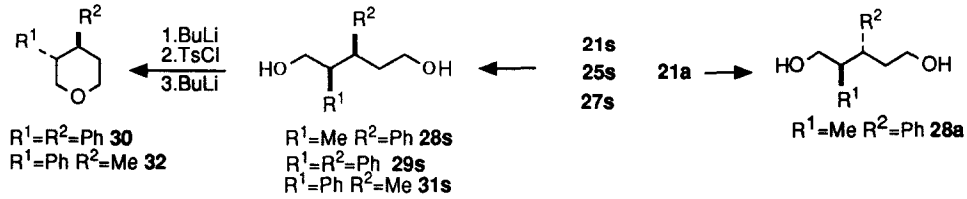
As reported by Yamaguchi,[27] the relative stereochemistry of 2,3-dimethylglutarates such as **24** can also be assigned by NMR spectroscopy. The ^{13}C signal due to the 3-methyl group is observed at 17 ± 0.2 ppm for the *anti* isomer, and at 16 ± 0.1 ppm for the *syn* isomer in $CDCl_3$.

Diketone **19** formed by addition of propiophenone **9** to cyclohexenone **3** was compared to an authentic 77:23 **19a:19s** sample, made by $TryPF_6$ catalyzed addition of propiophenone silylenolether to **5**.[28]

In order to determine the stereostructures of the condensation products of propionates and cinnamates **21-23**, a pure sample of **21s** was synthesized using *t*-butylpropionate lithium enolate.[6b] The corresponding Ti "ate" complex gave rise to a different stereoisomer, which was therefore assigned the *anti* configuration. Pure samples of **21a** and **21s** were transformed into the corresponding diols **28a** and **28s** by LAH reduction (**Scheme 3**). The stereostructures of **22** and **23** were then determined by LAH reduction.

The 2,3-diphenylglutarates **25** have been previously described.[7a] The stereochemistry of **25s** was confirmed by transforming it into the corresponding tetrahydropyran derivative **30** *via* diol **29s**, following Yamaguchi's protocol[6b] (**Scheme 3**). The same procedure allowed us to establish the stereostructure of **27s** which, upon reduction to **31s** and cyclization, gave the tetrahydropyran **32**.

Scheme 3.



28a: ^{1}H-NMR ($CDCl_3/D_2O$): 1.03 (d, 3H, J=7.0Hz); 1.85 (m, 2H); 2.07 (m, 1H); 2.73 (ddd, 1H, J=3.6Hz, 7.6Hz, 12Hz); 3.20-3.55 (m, 4H); 7.25 (m, 5H).
^{13}C-NMR ($CDCl_3$, selected peaks): 14.5, 34.2, 41.2, 44.1, 61.1, 66.1.

28s: ^{1}H-NMR ($CDCl_3/D_2O$): 0.79 (d, 3H, J=7Hz); 1.85-2.20 (m, 3H); 2.88 (ddd, 1H, J=5Hz, 7Hz, 12Hz); 3.38-3.62 (m, 4H); 7.25 (m, 5H).

29s: ^{1}H-NMR ($CDCl_3/D_2O$): 1.90 (m, 2H); 2.15 (m, 2H); 3.10 (m, 1H); 3.25 (m, 1H); 3.35-3.60 (m, 2H); 3.93 (m, 2H); 6.95 (m, 5H); 7.15 (m, 5H).
^{13}C-NMR ($CDCl_3$, selected peaks): 36.1, 43.6, 53.4, 60.8, 64.5.

30: ^{1}H-NMR (C_6D_6): 1.60 (m, 1H); 1.92 (m, 1H), 2.82 (ddd, 1H, J=4.Hz, 12Hz, 12Hz); 3.07 (ddd, 1H, J=4Hz, 12Hz, 12Hz); 3.45 (m, 2H); 4.13 (m, 2H); 6.95 (m, 10H).

31s: ^{1}H-NMR ($CDCl_3/D_2O$): 0.78 (d, 3H, J=7.1Hz); 1.38 (m, 1H); 1.82 (m, 1H); 2.08 (m, 1H); 2.51 (dt, 1H, J=6.8Hz, 7.0Hz); 3.74 (m, 2H); 3.93 (d, 2H, J=7Hz); 7.25 (m, 5H).

32: ^{1}H-NMR ($CDCl_3$): 0.8 (d, 3H, J=6.7Hz); 1.50 (m, 1H); 1.75 (m, 1H); 1.90 (dddq, 1H, J=4Hz, 6.7Hz, 11Hz, 11Hz); 2.43 (ddd, 1H, J=4Hz, 11Hz, 11Hz); 3.35 (dd, 1H, J=11Hz, 11Hz); 3.55 (m, 1H); 3.90 (m, 1H); 4.70 (m, 1H); 7.30 (m, 5H).

General Procedure for the Titanium Enolate Condensations.

A. Ketone Enolates.

To a 0.15M THF solution of the base indicated in **Table 1** (0.23 mmol) the ketone (0.2 mmol) is added at -78°C and the solution stirred for 20 min before adding $Ti(OiPr)_4$ (0.2 mmol). The solution is warmed up to -40°C, stirred for an additional 30 min at this temperature, then cooled to -78°C and the α,β-unsaturated substrate is added (0.1 mmol in 0.5 ml of dry THF). The reaction is run for the time and at the temperature indicated in **Table 1** before quenching with a saturated NH_4F solution.

17a: ^{1}H-NMR ($CDCl_3$): 0.82 (t, 3H, J=7.4Hz); 1.12 (d, 3H, J=7.4Hz); 2.03 (s, 3H); 2.31 (dq; 2H, J=7.4Hz, 21.2Hz); 2.83 (m, 3H); 3.52 (ddd, 1H, J=8.4Hz, 8.4Hz, 5.3Hz); 7.25 (m, 5H).
^{13}C-NMR ($CDCl_3$, selected peaks): 7.3, 13.9, 30.3, 33.5, 43.0, 45.7, 51.3.

17s: ^{1}H-NMR ($CDCl_3$): 0.88 (d, 3H, J=6.3Hz); 1.05 (t, 3H, J=7.4Hz); 2.00 (s, 3H); 2.49 (dq, 2H, J=7.4Hz, 17.9Hz); 2.78 (m, 3H); 3.43 (dt, 1H, J=5.3Hz, 9.5Hz); 7.30 (m, 5H).

18a: ^{1}H-NMR ($CDCl_3$): 1.23 (d, 3H, J=6.6Hz); 2.02 (s, 3H); 2.90 (d, 2H, J=6.6Hz); 3.73 (dt, 1H, J=6.6Hz, 6.6Hz); 3.84 (dq, 1H, J=6.6Hz, 6.6Hz); 7.18 (m, 5H); 7.48 (m, 3H); 7.85 (m, 2H).
^{13}C-NMR ($CDCl_3$, selected peaks): 14.1, 30.3, 42.7, 45.0, 45.7.

19a: ^{1}H-NMR ($CDCl_3$): 1.2 (d, 3H, J=6.8Hz); 1.5-2.5 (m, 9H); 3.48 (quint, 1H, J=6.8Hz); 7.55 (m, 2H); 7.95 (m, 3H).
^{13}C-NMR ($CDCl_3$, selected peaks): 14.3, 24.9, 29.8, 41.1, 41.2, 44.5, 45.1.

33: ^{1}H-NMR ($CDCl_3$): 0.81 (d, 3H, J=7Hz); 0.97 (t, 3H, J=7Hz); 1.65 (m, 2H); 2.07 (m, 2H); 2.6 (m, 4H); 3.93 (dt, 1H, J=4Hz, 14Hz); 7.30 (m, 5H).

34: ^{1}H-NMR ($CDCl_3$): 0.88 (d, 3H, J=7.5Hz); 1.18 (t, 3H, J=7.5Hz); 2.35 (m, 2H); 2.55 (m, 2H); 2.89 (dd, 1H, J=14Hz, 16Hz); 3.53 (dt, 1H, J=4Hz, 14Hz); 5.95 (s, 1H); 7.30 (m, 5H).

B. Ester Enolates. Procedure A.

To a 0.15M THF solution of LDA (0.23 mmol) *t*-butyl propionate (0.2 mmol) is added at -78°C, and the solution stirred for 20 min before adding $Ti(OiPr)_4$ (0.2 mmol). Stirring is continued for 30 min at -40°C, then the α,β-unsaturated substrate is added (0.1 mmol in 0.5 ml of dry THF). The reaction is run for the time and at the temperature indicated in **Table 3**, before quenching with a saturated NH_4F solution.

21a: ^{1}H-NMR ($CDCl_3$): 1.19 (d, 3H, J=7Hz); 1.20 (s, 18H); 2.45 (dd, 1H, J=10,5Hz, 15Hz); 2.60 (m, 1H); 2.72 (dd, 1H, J=5.0Hz,15.0Hz); 3.27 (m, 1H); 7.25 (m, 5H).
^{13}C-NMR ($CDCl_3$, selected peaks): 15.1, 27.6, 27.7, 39.2, 45.3, 46.3.
21s: ^{1}H-NMR ($CDCl_3$): 0.92 (d, 3H, J=6.9Hz); 1.20 (s, 9H); 1.48 (s, 9H); 2.5 (m, 1H); 2.60 (m, 2H); 3.23 (m, 1H); 7.25 (m, 5H).
^{13}C-NMR ($CDCl_3$, selected peaks): 15.9, 27.6, 28.0, 40.5, 45.5, 46.2.
22a: ^{1}H-NMR ($CDCl_3$): 1.08 (t, 3H, J=6.8Hz); 1.20 (m, 12H); 2.58 (dd, 1H, J=10Hz, 15Hz); 2.70 (m; 1H); 2.80 (dd, 1H, J=5Hz, 15Hz); 3.35 (m, 1H); 3.98 (q, 2H, J=6.8Hz); 7.25 (m, 5H).
^{13}C-NMR ($CDCl_3$, selected peaks): 13.9, 15.1, 27.6, 38.0, 45.1, 46.0, 60.2.
23a: ^{1}H-NMR ($CDCl_3$): 1.05 (t, 3H, J=6.8Hz); 1.19 (d, 3H, J=7Hz); 1.21 (s, 9H); 2.55 (dd, 1H, J=10Hz, 15Hz); 2.65-2.82 (m, 2H); 3.38 (m, 1H); 3.95 (q, 2H, J=6.8Hz).
^{13}C-NMR ($CDCl_3$, selected peaks): 13.8, 14.7, 27.7, 38.6, 60.0.
23s: ^{1}H-NMR ($CDCl_3$): 0.95 (d, 3H, J=6.8Hz); 1.20 (s, 9H); 1.30 (t, 3H, J=6.8Hz); 2.55-2.70 (m, 3H); 3.30 (m, 1H); 4.18 (q, 2H, J=6.8Hz); 7.25 (m, 5H).
^{13}C-NMR ($CDCl_3$, selected peaks): 14.1, 15.6, 27.6, 40.4, 45.3, 60.4.
24a: ^{13}C-NMR ($CDCl_3$, selected peaks): 12.5, 16.9, 33.2, 39.8, 44.8.
24s: ^{13}C-NMR ($CDCl_3$, selected peaks): 12.4, 15.8, 32.7, 40.5, 44.4.

B. Phenylacetate Enolates. Procedure B.

Phenylacetate **13** (0.2 mmol) is added to a 0.15M THF solution of LHMDS (0.23 mmol) the at -78°C, and the solution is stirred for 45 min before adding $Ti(OiPr)_4$ (0.2 mmol). Stirring is continued for 1 h at -40°C, then the α,β-unsaturated substrate is added (0.1 mmol in 0.5 ml of dry THF). The reaction is run for the time and at the temperature indicated in **Table 3** before quenching with a saturated NH_4F solution.

25s: ^{13}C-NMR ($CDCl_3$, selected peaks): 40.3, 46.0, 58.6.
26s: ^{1}H-NMR ($CDCl_3$): 1.18 (s, 9H); 1.28 (d, 3H, J=6.8Hz); 2.75 (m, 2H); 3.78 (m, 2H); 4.18 (m, 2H); 7.05 (m, 10H).
27s: ^{1}H-NMR ($CDCl_3$): 0.78 (d, 3H, J=6.5Hz); 1.38 (s, 9H); 1.45 (s, 9H); 2.15 (dd, 1H, J=10Hz, 15Hz); 2.45 (dd, 1H, J=6Hz, 15Hz); 2.62 (m, 1H); 3.30 (d, 1H, J=10Hz); 7.3 (m, 5H).
^{13}C-NMR ($CDCl_3$, selected peaks): 16.9, 33.6, 40.8, 58.3.

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3. For example, dialkylboron enolates, which are among the most useful stereoselective nucleophiles in aldol condensations, cannot be used as Michael donors since they only react with strongly activated olefins: the dibutylboron enolate of diethylketone (generated with Bu_2BOTf and DIPEA in dichloromethane) did not add to chalcone, *t*-butyl acrylate, crotonate, 2-cyano crotonate, 2-cyano benzalpinacolone, dimethyl fumarate. Reaction with ethylidene malonate occurred at -78°C to give a 1:1 diastereomeric mixture of 1,4 addition products in 45% yield.
Cavicchioli, M. unpublished results from this laboratory.
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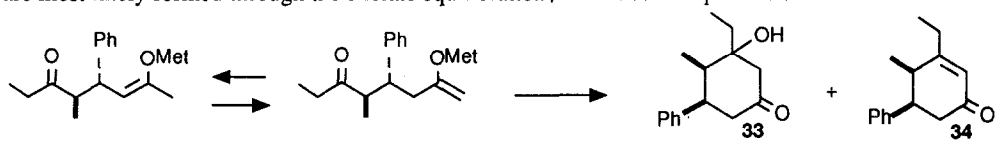
23. When the titanium enolate of diethyl ketone is added to **2** (**Table 1**, Entry 8) small amounts of the cyclohexanone derivatives **33** and **34** are also isolated after flash chromatography. These compounds are most likely formed through the enolate equilibration / aldol addition process shown below.



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25. These reactions could be obtained *via* acid catalyzed silylenolether addition, but the *anti* selectivity is generally higher with the present Ti enolates: see, for instance, *ref.* 10, 26, and 28.
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