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ACCELERATION OF THE CONJUGATE ADDITION OF Ti "ATE" ENOLATES *VIA* LEWIS ACID CATALYSIS.

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Abstract. *The conjugate addition of Ti "ate" complexes of ketone enolates to α,β-unsaturated ketones can be accelerated by activating the substrate via complexation with t-BuMe$_2$SiCl or trityl triflate.*

INTRODUCTION.

The conjugate addition of enolates to α,β-unsaturated ketones and esters gives rise to 1,5-dicarbonyl compounds and has the potential of generating two new stereocenters (**Figure**). Over the last few years, the stereochemical control of this reaction has become the focus of much attention.[1] We recently reported that the Ti "ate" complexes of ketone and ester enolates, obtained by treating the corresponding lithium enolates with Ti(OiPr)$_4$, add to unsaturated carbonyl compounds in a conjugate fashion (1,4 addition) with high regio- and stereoselectivity and offer various advantages over their lithium counterparts.[2] The Ti enolate of *t*-butyl propionate adds to E-configurated esters and ketones to give *anti* adducts with selectivities up to 95%. The corresponding lithium enolate gives rise to the *syn* isomers, unless HMPA is used as solvent.[1a] As for ketone enolate Ti complexes, they were found to be more regioselective than the parent Li enolates, and to give highly selective 1,4 addition even to unhindered α,β–unsaturated ketones. From a stereochemical point of view, the reaction outcome was shown to depend on the configuration of the starting materials:[3] when adding to an E enone, E enolates afford *syn* compounds, and Z enolates the *anti* isomers. The same trend is displayed by the parent lithium enolates, which, however, are less stereoselective.[1a]

The titanium enolates of ketones appeared to be less reactive than their lithium counterparts. Reactions with unsaturated ketones are somewhat sluggish, typically requiring 2 mol equiv of enolate and reaction times of *ca.* 20 h at -50°C.[2] We now report that these reactions can be accelerated by Lewis acid activation of the electrophilic partner, with no loss of stereoselectivity. In the new conditions only a stoichiometric amount of the enolate is

required to achieve comparable yields with respect to the uncatalyzed reaction.

RESULTS AND DISCUSSION.

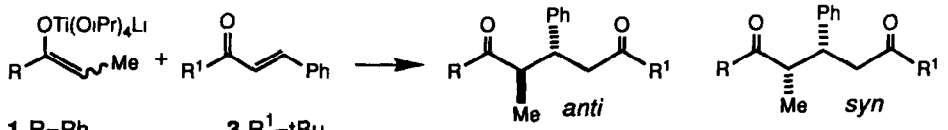
Silyl halides are known to accelerate conjugate addition of cuprate reagents to a variety of unsaturated carbonyl substrates.[4] The observation that titanium enolates react very slowly, if at all, with *t*-BuMe_2SiCl (TBDMSCl) prompted us to examine this reagent as a likely activator for the conjugate addition reaction.

The addition of propiophenone enolate **1** to benzalpinacolone **3** was chosen as a model (**Figure**; **Table**). In our original conditions,[2] *i.e.* 2 mol equiv of enolate, 21h at -50°C, this reaction gives very good yields (85%) of >92% isomerically pure diketone **5a** (Entry 1). Yields are reduced to 56% if the reaction is run with 2 mol equiv of enolate for 2h at -40°C (Entry 2), and drop to 20% if only 1 mol equiv of enolate is used at this temperature for the same time (Entry 3). However, when 1 mol equiv of **1** was added to a 1:1 mixture of **3** and TBDMSCl, 67% of conjugate addition product was isolated as a single *anti* isomer after 2h at -40° (Entry 4). The same sort of acceleration could be obtained by using other Lewis acids known to catalyze the Mukaiyama-Michael reaction,[5] such as trityl triflate (TrOTf; 0.5 mol equiv, Entry 5) or $MgBr_2$ (Entry 6). Use of enantiomerically pure di-isopinocampheylchloroborane (iPc_2BCl) resulted in a low yield (*ca.* 20%) of racemic **5a**, as determined by ^{1}H-NMR in the presence of Eu(hfc)$_3$.

Conjugate addition of **1** to benzalacetone **4** in the presence of TBDMSCl occurred with no loss of regioselectivity compared to the uncatalyzed reaction (Entry 7 and 8). However, electrophilic activation does enhance 1,2 carbonyl reactivity as well as 1,4: for example, when the Ti enolate of diethylketone (**Figure**, R=Et) was added to **4** in the presence of TrOTf, a small amount (*ca.* 20% of the total yield) of the aldol addition products was observed in the crude reaction mixture by ^{1}H-NMR, beside the expected 1,5 diketone. This side reaction, which is not observed in the uncatalyzed case, could not be suppressed even by using very bulky Lewis acids, such as MAD.[6]

We had previously shown[2] that the stereochemical outcome of the Michael addition of i-propyl ethyl ketone Ti enolate **2** to **3** depends on the configuration of the starting lithium enolate.[3] The Z enolate can be generated with lithium hexamethyldisilazide (LHMDS) and, after treatment with Ti(OiPr)$_4$, reacts with **3** to give the *anti* adduct with high diastereoselectivity (Entry 9). The E enolate is generated with lithium tetramethylpiperidide·LiBr (LTMP·LiBr) according to Collum,[7] and, after treatment with Ti(OiPr)$_4$, gives a mixture of products, with the *syn* isomer predominating (Entry 12). In the presence of TBDMSCl the reaction appears to be *anti* selective, regardless of the ketone enolate geometry (Entry 10 and 13). It should be noted that the addition of TBDMSCl to the E enolate, while influencing the stereoselectivity of the process, does not appear to accelerate the addition to **3** (Entry 10 and 11). These observations may point to a change in the reaction mechanism brought about by the presence of the Lewis acid activator. Work is in progress to clarify the mechanistic aspects of this reaction.

Figure.



5a R=Ph, R^1=tBu **5s**

6a R=Ph, R^1=Me **6s**

7a R=iPr, R^1=tBu **7s**

Table. Acid-catalyzed conjugate addition of Ti enolates 1 and 2 to 3 and 4.[a]

Entry	Enolate	Substr.	Product	Catalyst (eq)	t (h), T (°C)	Y (%)	*anti/syn* [b]
1	1	3	5	*none* [c]	21, -50	85	92:8
2	1	3	5	*none* [c]	2, -40	56	92:8
3	1	3	5	*none*	2, -40	20	92:8
4	1	3	5	TBDMSCl (1)	2, -40	67	≥96:4
5	1	3	5	TrOTf (0.5)	0.8, -40	50	≥96:4
6	1	3	5	$MgBr_2$ (1)	2, -40	53	≥93:7
7	1	4	6	*none* [c]	20, -50	70	≥97:3
8	1	4	6	TBDMSCl (1)	0.8, -50	45[d]	≥97:3
9	2[e]	3	7	*none* [c]	20, -50	65	>97:3
10	2[e]	3	7	TBDMSCl (1)	4, -50	57	96:4
11	2[e]	3	7	TrOTf (0.5)	4, -50	55	>97:3
12	2[f]	3	7	*none* [c]	20, -50	91	17:83
13	2[f]	3	7	TBDMSCl (1)	20, -50	45	60:40

a. Reactions performed in THF using 1 mol equiv of the Ti complex. Unless otherwise noted, the starting lithium enolates were generated with LDA. **b.** Determined by GC. **c.** Reactions performed with 2 mol equiv of Ti complex. **d.** Ca. 20% of aldol addition product present in crude NMR. **e.** Z enolate generated with LHMDS. **f.** E enolate generated with LTMP·LiBr (see *ref. 7*).

EXPERIMENTAL

General Methods.

Tetrahydrofuran (THF) was distilled from sodium / benzophenone and diisopropylamine and hexamethyldisilazane from CaH_2 immediately before use. LTMP-LiBr was prepared according to *ref.* 7. All reactions were run under a nitrogen atmosphere. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 200 MHz and 50.3 MHz, respectively. Chemical shifts are expressed in ppm downfield from tetramethylsilane.

General procedure for the acid catalyzed Titanium enolate conjugate addition.
To a 0.15M THF solution of the lithium base indicated in the **Table** (0.12 mmol) the ketone (0.1 mmol) is added at -78°C and the solution stirred for 20 min before adding $Ti(OiPr)_4$ (0.1 mmol). The solution is warmed up to -40°C, stirred for an additional 30 min at this temperature, then a 1:1 mixture of TBDMSCl and the enone (0.1 mmol in 0.5 ml of dry THF) is added by syringe. The solution is stirred for the time and at the temperature indicated in the **Table** before quenching with a saturated NH_4F aqueous solution and working-up as usual.

(2RS,3RS)-1,3-Diphenyl-2,6,6-Trimethyl-1,5-heptanedione (5a).
^{1}H-NMR: 1.01 (s, 9H); 1.24 (d, 3H, J=7.0Hz); 2.85 (dd, 1H, J=4.0Hz, 17.5Hz); 3.08 (dd, 1H, J=8.7Hz, 17.5Hz); 3.77 (m, 1H, J=4.0Hz, 7.0Hz, 8.7Hz); 3.92 (quint., 3H, J=7.0Hz); 7.18 (m, 5H); 7.48 (m, 3H); 7.85 (m, 2H). ^{13}C-NMR, selected data: 14.3, 26.1, 38.1, 42.3, 45.2. Anal. Calcd. for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: (**5a**) C, 82.08; H, 7.96.

(2RS,3SR)-1,3-Diphenyl-2,6,6-Trimethyl-1,5-heptanedione (5s). ^{13}C-NMR, selected data: 16.4, 26.0, 41.1, 43.3, 44.9.

(2RS,3RS)-1,3-Diphenyl-2-Methyl-1,5-hexanedione (6a). ^{1}H-NMR: 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, selected data: 14.1, 30.3, 42.7, 45.0, 45.7. Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: (**6a**) C, 81.28; H, 7.32.

(5RS,6RS)-5-Phenyl-2,2,6,8-Tetramethyl-3,7-nonanedione (7a). ^{1}H-NMR: 0.72 (d, 3H, J=6.0Hz); 0.93 (d, 3H, J=7.0Hz); 1.0 (s, 9H); 1.1 (d, 3H, J=7.0Hz); 2.41 (sett., 1H, J=7.0Hz); 2.78 (dd, 1H, J=4.0Hz, 18.0Hz); 3.02 (m, 1H); 3.57 (m, 1H); 7.15 (m, 5H). ^{13}C-NMR, selected data: 14.5, 17.3, 18.2, 26.0, 38.5, 40.6, 42.5, 49.8. Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: (**7a**) C, 79.25; H, 9.64.

(5RS,6SR)-5-Phenyl-2,2,6,8-Tetramethyl-3,7-nonanedione (7s). ^{1}H-NMR: 0.88 (d, 3H, J=7.1Hz); 0.93 (s, 9H); 1.08 (d, 3H, J=5.7Hz); 1.1 (d, 3H, J=5.7Hz); 2.60 (dd, 1H, J=4.3Hz, 17.1Hz); 2.74 (sett., 1H, J=5.7Hz); 3.03 (m, 2H); 3.48 (m, 1H); 7.15 (m, 5H). ^{13}C-NMR, selected data: 16.1, 18.1, 25.9, 40.1, 40.6, 42.5, 49.4. Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: (**7s**) C, 79.31; H, 9.85.

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