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Stereoselective Aldol Reactions. Reaction of Chiral Ester Titanium Enolate with Aldehydes

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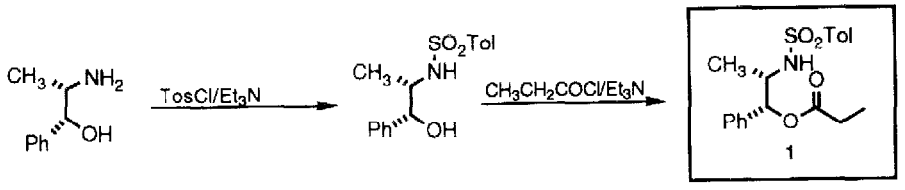
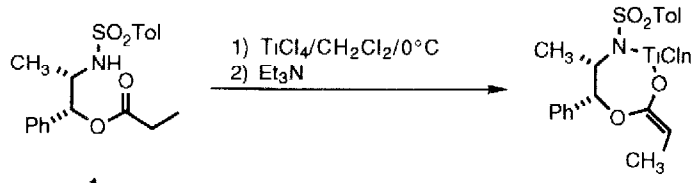
Abstract *The chiral ester **1** was enolized under $TiCl_4/Et_3N$ conditions and reacted with aldehydes to give moderate to good stereoselectivities The chiral auxiliary group can be removed by simple saponification and recovered*

Stereoselective aldol reactions has been one of the most actively studied subjects in organic chemistry during the last decade [1] Among the numerous methodologies now available, the most successful process is probably utilizing the chiral boron enolate,[1a d] which often gives a high level of stereoselection More recently, D A Evans and his co-workers have generated chiral chlorotitanium enolates by applying $TiCl_4/Et_3N$ conditions,[2] which provides a much simpler experimental operation and a high level of stereoselection upon reaction with electrophiles Unfortunately this methodology is so far limited to ketones and activated carboxyl derivatives We now wish to report work which demonstrates that the ester **1** can also be enolized under $TiCl_4/Et_3N$ conditions This enolate reacts with aldehydes to give aldols with moderate to good diastereoselectivity

Since simple alkyl esters had been reported not to enolize in the $TiCl_4/Et_3N$ system,[2] we prepared the ester **1**, considering that the sulfonamido group in the molecule should react readily with titanium chloride to form a new Lewis acid,[1e f] which lies very close to the carbonyl group of the ester This internal Lewis acid complexation may then promote enolization



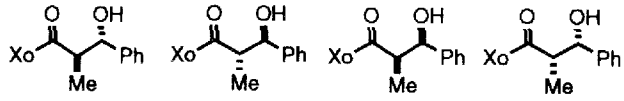
The ester **1** was prepared from (1R,2S)-norephedrine in two simple steps (1) sulfonation with 1 05 eq of *p*-toluenesulfonyl chloride and 1 3 eq of triethylamine in CH_2Cl_2 at 20°C for 10 h (92%), (2) acylation with 1 5 eq of propionyl chloride and 2 eq of triethylamine in CH_2Cl_2 at 20°C to give, after flash chromatography, crystalline ester **1** [m p 82°C, $[a]_D$ = -20° (c 1 1, $CHCl_3$)] in 80% yield



1 2

Successive treatment of the ester **1** with 1 05 eq of $TiCl_4$ in CH_2Cl_2 at 0°C for 15 min and then with 2 1 eq of triethylamine at 0°C resulted a dark brown solution The dark brown color appeared only when the second eq of triethylamine was added to the reaction mixture This appears to indicate that the sulfonamido group reacted with $TiCl_4$ prior to enolization A ^{1}H-NMR spectroscopic study showed that under these conditions the ester **1** was completely transformed into a single enolate, presumably **2** [3]

Scheme



2 + PhCHO $\xrightarrow{CH_2Cl_2/-40°C}$ A_1 + A_2 + S_1 + S_2

ratio 70 0 8 3 18 3 3 0

total yield 94%

2 + PhCHO/$TiCl_4$ $\xrightarrow{CH_2Cl_2/-78°C}$ A_1 + A_2 + S_1 + S_2

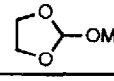
ratio 2 8 3 1 4 6 89 5

total yield 96%

The titanium enolate **2** reacted with benzaldehyde at -40°C in 2 h and gave aldol adduct with a moderate diastereoselectivity, the major diastereomer being the *anti* aldol A_1 as indicated in the Scheme [4] On the other hand, when the enolate **2** was reacted with the pre-formed 1 1 complex of benzaldehyde and $TiCl_4$, the reaction was complete at -78°C in a few minutes and gave the *syn* aldol S_2 as the major isomer with good diastereoselectivity (see Scheme)

We examined the influence of the amount and type of the Lewis acid used in the pre-mixing with the aldehydes on the diastereoselectivity of the reactions Various Lewis acids such as BCl_3, $AlCl_3$, $SnCl_4$ and $TiCl_4$ were tested The best diastereoselectivity was obtained when equal amounts of $TiCl_4$ and aldehyde were mixed prior to the reaction with the enolate **2** Further experiments were conducted to examine the scope of this reaction Several aldehydes and ketals were reacted with enolate **2** As summarized in the Table, reactions of aromatic aldehydes and ketals with enolate **2** gave good diastereoselectivities, while reaction of aliphatic aldehydes gave moderate diastereoselectivities

Table $TiCl_4$ Promoted Aldol Reaction of Enolate **2** with Representative Aldehydes[a]

ALDEHYDE[b]	YIELD[c] (%)	PERCENTAGE OF DIASTEREOMERS[e] A_1	A_2	S_1	S_2	$[\alpha]_D$[f]
PhCHO	98 (85)[d]	2 8	3 1	4 6	89 5	-20 5° (c 0 8, $CHCl_3$)
$pCH_3OPhCHO$	93	7 7	7 3	8 7	76 3	
CH_3CH_2CHO	82(70)[d]	2 9	8 3	4 0	84 8	-15 0° (c 1 1, THF)
$(CH_3)_2CHCHO$	99(50)[d]	21 3	16 8	2 1	59 8	-22 7° (c 0 9, THF)
1,3,5-Trioxane	92(76)[d]	6 5			93 5	+4 3° (c 1 0, $CHCl_3$)
	80 (58)[d]	15 3			84 7	+32 3° (c 1 0, $CHCl_3$)

[a]General procedure for the aldol reaction To a solution of ester **1**(1 mmol) in 10 mL of dry CH_2Cl_2 was added 1 05 mmol of neat $TiCl_4$ dropwise via syringe under argon at 0°C After stirring for 15 min, freshly distilled triethylamine (2 1 mmol) was added dropwise resulting in a brown solution [4] After stirring at 0° for 1 h, this brown solution was transfered very slowly into a mixture of aldehyde (2 mmol) and $TiCl_4$ (2 1 mmol) in 5 ml of CH_2Cl_2 at -78°C After stirring at -78°C for 15 min, the reaction was quenched by addition of aq NH_4Cl with vigorous stirring After workup (CH_2Cl_2/aq NH_4Cl), the ratio of diasteromers was determined by HPLC and the major isomer was purified by flash chromatography [b]Two equivalents were used in all the reactions [c]Total yields of the four diastereomers were determined by HPLC [d]Isolated yield of the major diastereomer(S_2) [e]The stereochemistry of diastereomers A_1, A_2, S_1 and S_2 are shown in the scheme[6], the percentage of diastereomers was determined by HPLC [f]Optical rotation of the major diastereomers (S_2)

The major diastereomer of all the above reactions were easily purified by flash chromatography and freed from auxiliary group by mild hydrolysis conditions (LiOH/THF-MeOH) with no loss of chirality The auxiliary group is recoverable and reusable These results show that titanium ester enolate could be an attractive approach for the preparation of chiral aldols Work towards further improvement of the diastereoselectivities by using different chiral sulfonamido-alcohols as the auxiliary group is now underway

References and Notes

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2 Evans, D A , Urpi, F , Somers, T , Clar, J S , Bilodeau, M T *J Am Chem Soc* **1990,** *112,* 8215

3 The ^{1}H-NMR sample of **2** was prepared following the same procedure (see text) in CD_2Cl_2 and the spectrum was recorded at 20°C ^{1}H-NMR (300MHz, CD_2Cl_2) d 7 78 (dd, J = 1 0, 8 0, 2H), 7 40-7 22 (m, 5H), 7 16 (dd, J = 1 0, 8 0, 2H), 4 79 (q, J = 7 3, 1H, $=CHCH_3$), 4 48 (d, J = 6 4, 1H *OCH*), 4 40 (quintet, J = 6 4, 1H, NCH), 2 41 (s, 3H), 1 69 (d, J = 7 3, $=CHCH_3$), 0 87 (d, J = 6 4, 3H)

4 The major isomers of the reactions shown in the Scheme and in Table (see text) were isolated by flash chromatography and had satisfactory ^{1}H-NMR, IR and mass spectra The purity of the isolated aldol products were >97% as determined by HPLC The absolute stereochemistry of the aldols were determined by first removing the auxiliary group by mild hydrolysis (LiOH/THF-MeOH/20°C) and then transforming the free acid into its methyl ester (CH_2N_2/ether/0°C), the optical rotation of the methyl ester was measured and compared with the literature

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