Novel Enantioselective Acylating Agents. The Reactions of Chiral Ortho Esters and Silylenol Ethers as a Route to Optically Active Monoprotected 1,3-Dicarbonyl Compounds

Tiziana Basile, Luigi Longobardo, Emilio Tagliavini,* Claudio Trombini, and Achille Umani-Ronchi*

Dipartimento di Chimica 'G. Ciamician,' Università di Bologna, Via Selmi, 2 I-40126 Bologna, Italy

A novel enantioselective route to monoprotected 2-substituted-1,3-dicarbonyl compounds has been developed *via* acylation of silylenol ethers with chiral ortho esters derived from diethyl or di-isopropyl (*R,R*)-tartrates; good yields and stereoselectivity can be achieved starting from cyclic enolsilanes.

In spite of the widespread use of ortho esters as protective groups or synthetic equivalents of carboxylic esters, the use of chiral ortho esters in the synthesis of optically active molecules has not been reported.[1] This is somewhat surprising considering the position assumed by the Lewis acid promoted reactions of chiral acetals as one of the main topics in asymmetric synthesis.[2] Since we have recently been engaged in this last field,[3] we decided to turn our attention to ortho esters containing a chiral dioxolane moiety as synthons for the enantioselective acylation of enolates.[4]

The required substrates were very easily obtained from the exchange reaction of diethyl or di-isopropyl (L)-tartrates (**2**) with a three- to five-fold excess of triethyl orthoacetate, orthopropanoate, or orthobenzoate (**1**) in very high yield, equation (1).

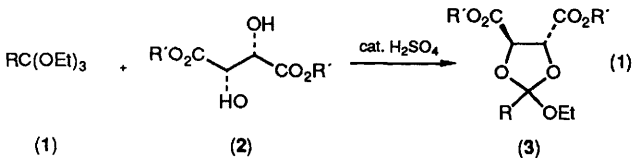
As the nucleophilic counterpart of the reaction we chose silylenol ethers, the most widely used enolate equivalents in the Mukaiyama reaction[5] and in its chiral version developed by Johnson.[6]

The results presented here have been obtained starting from cyclic derivatives in order to avoid any problem concerning the effect of the stereochemistry of the enolic double bond.† The reaction affords a monoprotected 1,3-dicarbonyl compound (**5**) containing a stereogenic centre in the 2-position (Scheme 1).

Table 1. Reactions of chiral ortho esters with silylenol ethers.[a]

R	*n*	Lewis acid	*T*/°C	*t*/h	Yield/%[b]	D.e./%[c]
Me	1	$TiCl_4$	−78	2	80	83
Me	1	$BF_3{\cdot}Et_2O$	−60	3	70	80
Me[d]	1	$BF_3{\cdot}Et_2O$	−60	3	70	80
Et	1	$BF_3{\cdot}Et_2O$	−50	8	75	73
Ph	1	$BF_3{\cdot}Et_2O$	−60	8	93	89
Me	0	$BF_3{\cdot}Et_2O$	−20	24	34	43
Me	2	$BF_3{\cdot}Et_2O$	−60	2	85	71

[a] All the reactions were performed using 1 mmol of (**3**), 2 mmol of (**4**), and 1.5 mmol of Lewis acid in 10 ml of CH_2Cl_2 under Ar and were quenched with sat. aq. $NaHCO_3$. [b] Yields were determined for the pure products obtained after silica gel chromatography. [c] Diastereoisomeric ratios were measured from the integration of the ^1H NMR signals corresponding to the hydrogens in positions 4 and 5 of the dioxolane ring. [d] Di-isopropyl tartrate was used.



† A deeper investigation of this effect is currently in progress.

As a general trend we observed that the ethoxy group of (**3**) is selectively replaced; side products resulting from dioxolane ring opening were not detected.‡

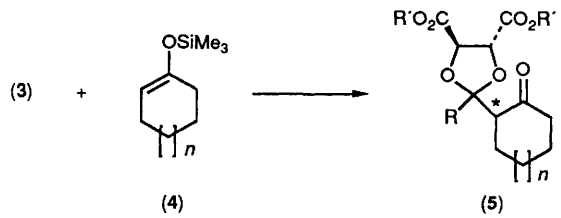
Chemical yields and diastereoisomeric excess (d.e.) values are reported in Table 1 for different Lewis acids, R groups, and ring sizes. In order to verify that the d.e. values are not due to thermodynamic equilibrium between diastereoisomeric products (**5**), promoted by acidic or basic media, two different mixtures of (**5**; R = Me, R′ = Et, *n* = 1) showing diastereoisomeric ratios of 9:1 and 6.3:1 respectively, were separately treated first with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −10 °C for 3 h then with sat. aq. $NaHCO_3$ at room temp. for 5 h. ^1H NMR analysis showed no change in the composition of either mixture. Yields are generally good, except in the case of cyclopentanone silylenol ether, which hardly reacts and does so with poor stereoselectivity.

In the case of the diethyl tartrate derivatives, the degree of asymmetric induction is good in the reactions with trimethylsiloxycyclohex-1-ene, ranging from 75% d.e. for the orthopropanoate to 89% for the orthobenzoate; both yield and stereoselectivity seem to be almost independent of the nature of the Lewis acid ($TiCl_4$ and $BF_3{\cdot}Et_2O$ have been tested) at least in the case of orthoacetate.

The cycloheptanone silylenol ether affords a fairly diastereoisomerically enriched product in high yield.

The substitution of the isopropyl group for the ethyl group in the ester functions of the dioxolane ring did not increase the extent of asymmetric induction, indicating that the preferred conformation of the carboxylic substituents is the one in which the alkoxy groups are directed in the opposite direction with respect to the incoming nucleophile; a similar trend has been observed previously in the reactions of enol boronates.[7]

The results obtained must be regarded in the light of the following considerations. (a) Chiral ortho esters appear to be general enantioselective acylating agents. Few other examples, if any, are known from the chemical literature. (b) The optically active starting material is commercially available in large quantities at a low price.



Scheme 1. *Reagents and conditions:* Lewis acid, CH_2Cl_2.

‡ Upon quenching the reaction mixture with bicarbonate solution, eventually unreacted (**3**) partially undergoes hydrolysis affording monoacyl tartrates.

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