Diastereoselectivity in the Preparation of β-Silylesters from αβ-Unsaturated Esters and Amides Attached to Chiral Auxiliaries†

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The conjugate addition of the phenyldimethylsilyl-cuprate reagent to cinnamate and crotonate esters and amides of various known chiral auxiliaries is diastereoselective, making available β-silylesters of high enantiomeric excess; the sense of the diastereoselectivity is anomalously different from established precedent in the case of silyl-cuprate addition to the cinnamate ester (**1**, R = Ph, R* = **d**).

We have established that the alkylation of β-silylenolates is highly diastereoselective[1] and that the products can be used in the synthesis of aldols[2] and of allylsilanes.[3] To extend this work to the synthesis of optically active compounds, we needed to induce specific chirality into the conjugate addition that established the chiral centre carrying the silyl group (**1**) → (**2**). A potentially general and versatile way to do this is to attach a resolved chiral auxiliary R* at the carbonyl group, since this group, when it is an ester or amide, can be detached later with ease and, in principle, recycled. Several ester and amide groups have already been recommended for stereocontrol of conjugate additions in general;[4—10] our need to see if they worked with our silyl-cuprate reagent has given us this

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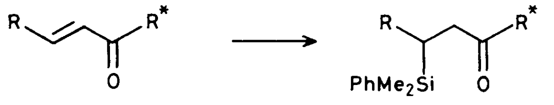
† No reprints available.

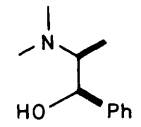
Table 1. Diastereoselectivity in conjugate additions (**1**) → (**2**).

(**1**) R	R*	Reagents and conditions	Yield/ %	(**2**) d.e.[a]/ %	Configuration of major diastereoisomer at C-3[b]
Ph	**a**	i, Bu^nLi, THF; ii, $TiCl_4$; iii, $(PhMe_2Si)_2CuLi_2CN$, −78 °C	60	76	*S*
	b	$(PhMe_2Si)_2CuLi_2CN$, Et_2O, THF, −78 °C	82	20	*R*
	c	$(PhMe_2Si)_2CuLi_2CN$, THF, −78 °C	74	8	*R*
	d	,, ,, ,,	77[c]	88[c]	*R*
Me	**d**	,, ,, ,,	74	10	*S*[d]
Pr^i	**d**	,, ,, ,,	74	56	*R*
Ph	**e**	$PhMe_2SiLi + MgBr_2 + CuBr{\cdot}Me_2S$, THF, −78 °C[e]	84	78	*R*
Me	**e**	,, ,, ,, ,, ,,	83	78	*S*[d]
$PhMe_2Si$	**d**	$PhMgBr + CuCN$, THF, Et_2O, −78 °C	71	74	*R*
	d	$MeMgI + Cu(OAc)_2{\cdot}H_2O$,[f]THF, Et_2O, −15 °C	76	54	*S*[d]
	e	$PhMgBr + CuBr{\cdot}Me_2S$,[g]THF, Et_2O, Me_2S, −55 °C	92	92	*S*
	e	$MeMgBr + MgBr_2$,, ,, ,, ,, −65 °C[h]	82	52	*R*[d]

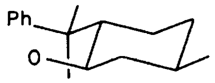
[a] Measured by integration of appropriately resolved signals in the ^1H n.m.r. spectra. [b] Proved by preparing the carboxylic acid (**2**, R* = OH), and converting the silyl into a hydroxy group (ref. 2, and by a new, one-pot method to be reported), giving β-hydroxy acids or esters of known absolute configuration. [c] After recrystallisation (3 × from hexane) the yield was 67% and the diastereoisomeric excess (d.e.) 95%. [d] This is not a change in diastereoselectivity, merely a change in group priorities in the CIP nomenclature. [e] The silyl-lithium reagent (49 mmol) in THF (200 ml) and $MgBr_2$ (10.3 g) were mixed at 0 °C; after 20 min, this solution was added to $CuBr{\cdot}Me_2S$ (5 g) in THF (100 ml) at −50 °C. After 30 min, the solution was cooled to −78 °C, and the imide (**1e**) (5 g) and $MgBr_2$ (2.76 g), premixed in dry THF (35 ml), added over 50 min. The mixture was kept at −78 °C for 2 h, brought to room temperature, and worked up using diethyl ether and ammonium chloride solution, and chromatography on silica gel, eluting with EtOAc : hexane (1 : 6). [f] A. J. Birch and M. Smith, *Proc. Chem. Soc.*, 1962, 356; J. A. Marshall, W. I. Fanta, and H. Roebke, *J. Org. Chem.*, 1966, **31**, 1016. [g] Ref. 8. [h] 1 h at −65 °C, warmed to 0 °C over 3 h.



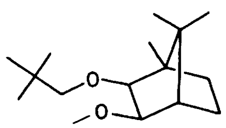
(**1**) (**2**)



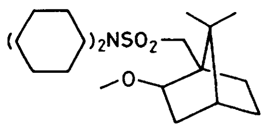
(**a**)



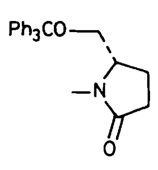
(**b**)



(**c**)

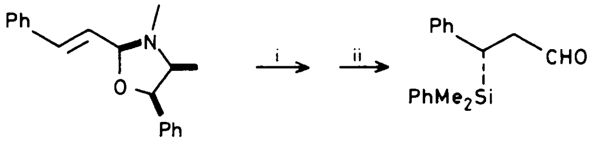


(**d**)



(**e**)

opportunity to produce a report on their relative effectiveness. In the meantime, Oppolzer has reported[11] that another chiral auxiliary, his camphor-derived sultam, not tested by us, is also effective in controlling the diastereoselectivity of the conjugate addition of our silyl-cuprate reagent.



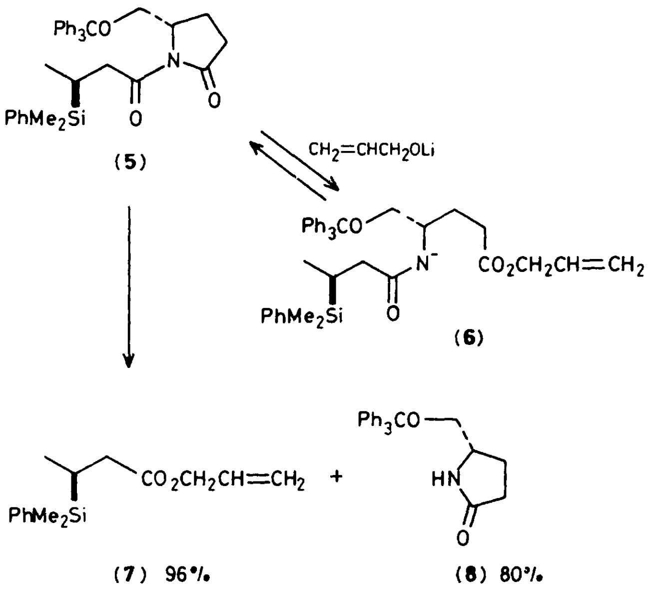
(**3**) (**4**)

79%, 60% e.e.

Reagents: i, $(PhMe_2Si)_2CuLi_2CN$; ii, NH_4Cl, NH_4OH.

The groups we have tested are Mukaiyama's ephedrine-derived group (**a**),[4] Corey's phenmenthyl group (**b**) (first used in conjugate additions by Oppolzer[5]), Oppolzer's camphor-derived groups (**c**)[6] and (**d**),[7] and Koga's glutamic acid-derived group (**e**).[8] We also tested Normant's ephedrine-derived oxazolidine (**3**).[9] Our best results with each system are summarised in Table 1 and on the structure (**4**).

In each case, the sense of the diastereoselectivity is the same as that observed by the people who introduced the various groups, except for the reaction of the silyl-cuprate reagent with the esters (**1b**), (**1c**), and (**1d**). Oppolzer found that conjugate additions of alkyl-cuprates to these esters took place when the enone was in the s-*trans* conformation. Our results with the copper(I)-mediated attack of Grignard reagents on the β-silylenone (**1**, R = $PhMe_2Si$, R* = **d**) are typical, giving the diastereoisomer expected from Oppolzer's work. In contrast, the reaction of the silyl-cuprate on the esters (**1**, R = Ph, Me, or Pr^i, R* = **d**) gave the diastereoisomer opposite to that expected from Oppolzer's work, but consistent with our earlier observation that the silyl-cuprate shows a strong preference for reacting with enones in the s-*cis* conformation (**1**).[1] We presume that a balance of forces between attack in the s-*trans* conformation, inherently preferred by the system, and attack in the s-*cis* conformation, preferred by the silyl-cuprate reagent, explains the variable degree of selectivity, high for cinnamate and low for crotonate, that detracts from the use of this chiral auxiliary. In any event, the high but opposite diastereoselectivity in the two



ways of forming (**2**, R = Ph, R* = **d**) is remarkable, given that one gets the same major diastereoisomer regardless of whether the silyl group is added to the cinnamate or the phenyl group is added to the β-silylenoate.

This variability led us to Koga's group (**e**), where we get opposite diastereoisomers with the two routes, thus making either enantiomer of the β-silylester available with acceptably high enantiomeric excesses (e.e.s) from the one chiral auxiliary. Furthermore, this group is easily removed. Koga used acid-catalysed ester exchange, which had the unfortunate effect of removing the trityl group from the chiral auxiliary. We find that, although alkoxide treatment initially opens the ring (**5**) → (**6**), leaving the mixture for a longer time [CH_2=$CHCH_2OLi$, 1.5 equiv., tetrahydrofuran (THF), room temperature, 24 h; $PhCH_2OLi$ works equally well] releases the β-silyl ester (**7**), presumably because the ring-opening is reversible. In these conditions the trityl group is retained, and the chiral auxiliary (**8**) is ready for recycling. We recommend this group, which appears to be the equal of Oppolzer's sultam.[11]

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