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Diastereoselectivity in Conjugate Addition of Alkylcuprates to Vinylogous Ester of N,O-Diprotected Serinal.

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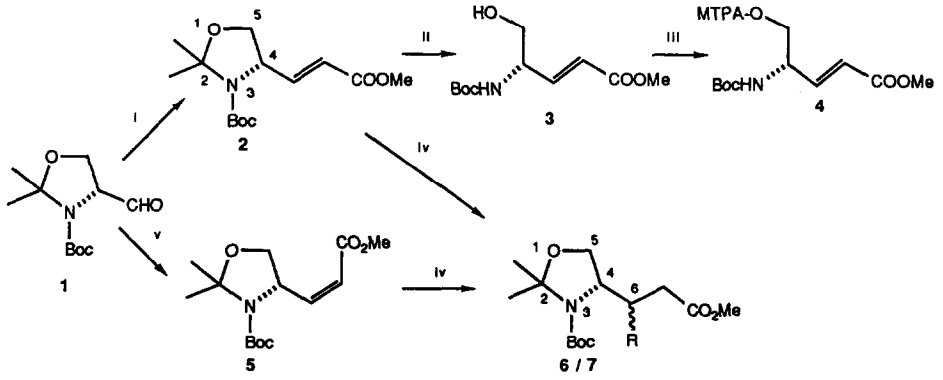
Summary. Various alkylcuprates were added to the Z and E vinylogous esters of N,O-diprotected (D) or (L) serinal **1**. Good to excellent yields and asymmetric inductions were observed.

In the chiral pool, N-protected α-amino aldehydes are of increasing interest as building blocks for the synthesis of amino sugars, peptides, natural or non-natural polyfunctional amino acids.[1] But generally configurational lability is observed at the stage of the aldehyde or/and low diastereoselectivity is achieved in Grignard or aldol type additions.[2] Recently the use of N,N-dibenzylamino aldehydes has been reported as an alternative solution.[3] Furthermore the N,O-diprotected serinal **1** was reported to be configurationally stable and was used



I. $(C_2H_5O)_2POCH_2CO_2Me$, K_2CO_3; II. PPTS, MeOH; III. Mosher's reagent; iv. R_2CuLi, v. $(CF_3CH_2O)_2POCH_2CO_2Me$, $KN(TMS)_2$, 18-crown -6,THF (see ref. 14).

Scheme

in Diels-Alder or aldol reactions with high diastereoselectivity.[4] These results prompted us to investigate the 1,4-addition of dialkylcuprates to the vinylogous ester **2** of the protected serinal **1**.

Oxazolidine **1** is readily available in the two antipodal series from the corresponding (D) and (L) serines.[5] Submitted to a Wittig-Horner reaction under protic conditions,[6] compound **1** afforded the unsaturated ester **2** [18] (yield 85%; E/Z : 98/2). The optical integrity of C-4 in ester **2** was proven using partial hydrolysis (**2**→**3**) and esterification with the Mosher's acid chloride (**3**→**4**).[7,18] When **2** was obtained from (D) serine[8] the enantiomeric purity of **2** was greather than 98% (^{19}F-NMR and ^{1}H-NMR). The conjugate addition of various cuprates to the ester **2** in presence of trimethylsilyl chloride took place smoothly .[9] After purification through column chromatography , both diastereomers **6/7** were obtained in good yield, but as an inseparable mixture (see scheme and table). The sharp signals observed for the methyl groups in the **6/7** mixture allowed a direct determination of their respective ratio by ^{1}H-NMR.[10] As the major isomer in the **6/7** mixture had always its methyl signal more downfield that the minor one, we assumed that the cuprate addition followed the same course irrespective of the nature of the cuprates. Roughly the diastereomeric excess is increasing with the size of the alkylcuprates and the asymetric inductions are good to excellent compared to similar cases for oxazolidines[11] or imidazolines[12] used as chiral auxiliaries and to the Michaël version of Schöllkopf's bislactim ethers .[13] In the hope to reverse the **6/7** ratio during the conjugate addition, we prepared ester **5**,[18] the Z isomer of compound **2**.[14] But as it appears on table (entry 2 and 9) virtually the same composition of the **6/7** mixture was obtained during the addition of methyl- or benzylcuprates to **5**. If a mono electronic transfer is involved before the nucleophilic substitution occurs, the cis-trans isomerisation may explain these results.[15] In fact examination of molecular models revealed that there is no steric hindrance between the oxazolidine and the carboxylate in either **2** or **5**. Therefore it can be assumed that the 1,4 addition on ester **2** is in line with the Felkin-Anh model as it has been proposed for the 1,2 addition on aldehyde **1** under non chelation control.[4] Starting from (D) serinal **1** the alkyl groups are transfered from the Re side and the S and R configurations respectively can be

expected at C-4 and C-6 of the major isomer. Interestingly compounds **6/7** are good candidates to prepare β-branched glutamic acid derivatives,[16] the oxazolidine being an amino-acid equivalent. Work is in progress to confirm the stereochemical outcome of the reaction and will be reported in due course.

Entry	R	Yield%[b]	Conditions	6/7[c]
1	Me	55	(CuI, MeLi (2 eq)) 5 eq, Et_2O, -20°C	70/30
2[a]	Me	53	(CuI, MeLi (2 eq)) 5 eq, Et_2O, -20°C	81/19
3	Vinyl	65	($(CH_2=CH)_4Sn$, PhLi (4eq)) 0.5 eq, CuBr-Me_2S) 3 eq, Et_2O, Me_2S, -70°C [d]	83/17
4	Pr	98	(C_3H_7MgBr (2 eq), CuBr-Me_2S, LiBr (2 eq)) 3 eq, Et_2O, -50°C	>97/3
5	Bu	56	(BuLi (2 eq), CuI) 3 eq, Et_2O, -40°C	>97/3
6	Methallyl	78	($(CH_2=CH(CH_3)CH_2MgCl$ (2 eq), Ph_3SnCl (2 eq), PhLi (2 eq), CuI) 3 eq, Bu_2S, Et_2O, -70°C [e]	89/11
7	Ph	42	(PhLi (2 eq), CuI) 3 eq, Et_2O, -40°C	
8	Bz	86	($PhCH_2MgBr$ (2 eq), CuBr-Me_2S, LiBr (2 eq)) 3 eq, Et_2O, -45°C	92/8 83/17
9[a]	Bz	58	($PhCH_2MgBr$ (2 eq), CuBr-Me_2S, LiBr (2 eq)) 3 eq, Et_2O -45°C	79/11

Table : 1,4-additions of various cuprates to compounds **2** or **5**.

a) reactions performed on the Z isomer **5**. b) isolated but not optimized yields. c) determinated by ^1H-NMR (200 MHz) with $CDCl_3$ as solvent. d) for preparation see ref.11. e) for preparation see ref. 17.

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18.Selected ^{1}H-NMR data : **2** (200 MHz, $CDCl_3$) : δ 1.43 (s, 9H, *tert*-Bu), 1.49 (s, 3H, Me), 1.61 (s, 3H, Me), 3.76 (s, 3H, COOMe), 3.80 (dd,J 9.1 and 2.3 Hz, 1H, CH_AH_BO), 4.10 (dd, J 9.1 and 6.4 Hz, 1H, CH_AH_BO), 4.36-4.63 (m, 1H, NH), 5.95(t large, J 15.0 Hz, 1H, vinylic), 6.88 (dd, J 15.0 and 7.5 Hz, 1H, vinylic)
3 (80 MHz, $CDCl_3$) : δ 1.4 (s, 9H, *tert*-Bu), 3.1 (s large, 1H, OH), 3.5-3.8 (m, 2H, CH_2-OH), 3.7 (s, 3H, COOMe), 4.0-4.4 (m, 1H, CH-N), 5.3 (d, J 8 Hz, 1H, NH), 5.9 (dd, J 2 and 16 Hz, 1H, vinylic), 6.9 (dd, J 5 and 15 Hz, 1H, vinylic)
4 (200 MHz, $CDCl_3$) : δ 1.42 (s, 9H, *tert*-Bu), 3.50 (s, 3H, OMe), 3.77 (s, 3H, COOMe), 4.19 (dd, J 4.6 and 10.8 Hz, 1H, CH_AH_BO), 4.35 (dd, J 5.2 and 11.1 Hz, 1H, CH_AH_BO), 4.59-4.78 (m, 1H, CH-N), 4.87 (d, J 8.8 Hz, 1H, NH), 5.93(dd, J 1.7 and 15.7 Hz, 1H, vinylic), 6.79 (dd, J 4.9 and 15.7 Hz, 1H, vinylic), 7.35-7.50 (m, 5H, aromatics)
5 (80 MHz, $CDCl_3$) : δ 1.4 (s, 9H, *tert*-Bu), 1.5 (s, 3H, Me), 1.6 (s, 3H, Me), 3.7 (s, 3H, COOMe), 3.6-3.9 (m, 1H, CH_AH_BO), 4.2 (dd, J 8 and 7 Hz, 1H, CH_AH_BO), 5.4 (dt, J 8 and 3 Hz, 1H, CH-N), 5.8 (d, J 12 Hz, 1H, vinylic), 6.3 (dd, J 12 and 8 Hz, 1H, vinylic)
Typical experimental procedure: To a solution of benzylcuprate (1 mmol, 3 eq.) were added at -40 °C, trimethylchlorosilane (0.14 ml, 1 mmol, 3 eq.) and a solution of compound **2** in dry ether (2 ml). The mixture was stirred 30mn at -40 °C and allowed to reach the room temperature. Saturated ammonium chloride is added (3 ml) and the organic phase is separated, dried, filtered and concentrated *in vacuo*.The obtained oil was purified by column chromatography using silica gel (8 g) eluting with hexane/ether: 8/2 to yield 128 mg (86%) of an oil. ^{1}H NMR($CDCl_3$): δ 1.45 (s, 9H,*tert*-Bu), 1.53 (s, 3H, Me), 1.65 (s, 3H, Me), 2.25-3.18 (m, 5H, CH-CH_2-CO_2Me,CH_2Ar), 3.59 (s,3H, CO_2Me), 3.73-4.13 (m, 3H, OCH_2CHN), 6.96-7.48 (m, 5H, ArH). Minor isomer δ 3.51 (s,3H, CO_2Me).

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