Diastereoselectivity of the Conjugate Addition of Organocopper Reagents to (E)-γ-Hydroxy-α,β-unsaturated Sulfones

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Key Words: vinyl sulfones, organocopper reagents, stereoselective conjugate additions, acyclic stereocontrol.

Abstract: The conjugate addition of organocopper reagents, mainly the higher order cuprates R_3CuLi_2 , to (E)y-hydroxy- $\alpha_1\beta$ -unsaturated phenyl sulfones takes place with excellent yields and high anti-selectivity.

The conjugate additions of organocopper reagents to γ -alkoxy- α , β -unsaturated esters and ketones and their applications to acyclic stereocontrol have drawn the attention of several groups¹. The diastereoselectivity observed in these reactions is puzzling, being strongly dependent upon the redox potential of the organocopper reagent and the Michael acceptor, the geometry of the double bond and the nature of the γ -oxygenated functionality. A thorough rationalization of the stereochemical results of these conjugate additions has been recently reported by Yamamoto and col.^{1a} On the other hand, we have previously described that the conjugate addition of alkyllithium reagents to (E)- γ -alkoxy- α -trimethylsilyl- α , β -unsaturated sulfones is highly *syn*diastereoselective². These Michael acceptors are prepared in two steps from the readily available racemic³ or enantiomerically pure⁴ γ -hydroxy- α , β -unsaturated sulfones 1. As a complementary stereochemical method of acyclic stereocontrol, we hereby report that the conjugate addition of some organocopper reagents to vinyl sulfones 1⁵ takes place with excellent yields and high *anti*-diastereoselectivity.

In the first instance we studied the reaction of an excess of Me₂CuLi (4 equiv.) with γ -oxygenated vinyl sulfones **2** which have protective groups at γ -position, such as Ac, MOM and TBDMS (scheme 1). A fast reaction was observed in Et₂O, even at low temperature (-30°C, 30 min.). However, instead of the conjugate addition products, a E/Z mixture of allylic sulfones **3**, resulting from the reductive elimination of the γ -oxygenated functionality, was formed as predominant or exclusive products. These results contrast with the previously reported reactivity of γ -alkoxy or γ -silyloxy- α , β -unsaturated esters and ketones, which usually react with Me₂CuLi in a clean conjugate manner.^{1,6}



Fortunately, the conjugate addition of organocuprates took place cleanly when unprotected γ -hydroxy vinyl sulfones 1 were used as Michael acceptors. In table 1 are summarized the results obtained in the reaction of several methyl copper reagents with the vinyl sulfone 1b. In all cases the reactions were performed with an excess of organocopper reagent (4 equiv.) in Et₂O at rt for 5 h.

PhS		MeLi + CuX Et ₂ O, rt	PhSO ₂	ŎH <u>–</u> Me nti- 4b	PhSO ₂ Me syn-4b	
Entry	Methyl copper reagent	CuX (1 equiv.)	MeLi:CuX	Additive (1 equiv.)	Ratio <i>anti/syn</i> (% de) ^a	% Yield
1	MeCu	Cul	1:1		*	
2	Me ₂ CuLi	Cul	2:1		2:1 (33)	85 ^b
3	Me ₂ Cu(CN)Li ₂	CuCN	2:1		3:2 (20)	50 ^b
4	Me ₂ CuLi.BF ₃	Cul	2:1	BF ₃ .OEt ₂	6:1 (71)	15 ^C
5	Me ₂ Cu(CN)Li ₂ .BF ₃	CuCN	2:1	BF ₃ .OEt ₂	9:1 (80)	10 ^C
6	Me ₃ CuLi ₂	Cul	3:1		11:1 (84)	90 ^b

Table 1: Conjugate addition of methyl copper reagents to vinyl sulfone 1b.

a) Determined by ¹H-NMR. b) Yield in pure adduct **4b** (*syn+anti*) after chromatography. c) Calculated by ¹H-NMR on the crude mixture; the major product was starting material.

Whereas the reaction between 1b and MeCu, prepared from equal molar ratios of MeLi and CuI, did not proceed at all, recovering the starting material (entry 1), a smooth and clean conjugate addition occurred in the reaction with Me₂CuLi affording a 2:1 mixture of *anti:syn* adducts $4b^7$ in 85% yield after chromatography (entry 2). A similar diastereoselectivity, but lower chemical yield (50%), was obtained in the addition of the higher order cyanocuprate Me₂Cu(CN)Li₂ (entry 3). It should be noted that the addition of 1 equiv. of BF₃.OEt₂ (entries 4 and 5) remarkably enhances the *anti-selectivity*. However, the conversions were very low regardless the reaction time (10-15% yield), presumably owing to the low stability of these organocopper.BF₃ reagents at rt⁸. By far, the best chemical and stereochemical result was obtained with the higher order cuprate⁹ Me₃CuLi₂, which gave a 11:1 mixture of *anti:syn* adducts in 90% yield (entry 6).

In order to evaluate the generality of the *anti*-stereoselectivity in the conjugate addition of the higher order cuprates⁹ R₃CuLi₂, we studied the reaction of three γ -hydroxy vinyl sulfones (**1a-c**) and two organocopper reagents (Me₃CuLi₂ and *n*-Bu₃CuLi₂) in Et₂O at rt¹⁰. The results are collected in table 2.

Table 2: Conjugate addition of higher order cuprates R_3^1 CuLi₂ to vinyl sulfones 1.

PhSO2~	OH	R	R ₃ CuLi ₂ Et ₂ O, rt	- Ph	$SO_2 \xrightarrow{I}_{R^1}$ anti	R ₊ PhSO ₂	$ \overset{OH}{\underset{R^1}{\overset{R^1}}} R $		
	Substrate					Product			
Entry		R	R ¹	t (h)		anti/syn (% de) ^a	% Yield ^b		
1	1a	Me	Me	2	4a	8:1 (78)	92		
2	1b	<i>n</i> -Bu	Ме	5	4b	11:1 (84)	90		
3	1c	∔Pr	Me	4	4c	15:1 (88)	89		
4	1a	Me	n-Bu	16	5a	3:1 (50)	85		
5	1b	<i>n</i> −Bu	<i>n</i> -Bu	16	5b	4:1 (60)	88		
6	1c	i⊦Pr	<i>n</i> -Bu	16	5c	10:1 (82)	91		

a) Determined by ¹H-NMR. b) In pure adduct after chromatography.

Some important facts are deduced from the data of table 2. First, all conjugate additions took place with excellent yield (85-92% after chromatography) producing predominantly the *anti*-isomers (de= 50-88%). Secondly, the *anti*-diastereoselectivity increases with the size of the R substituent (compare entries 1-3 and 4-6). Thirdly, for every Michael acceptor the reaction with Me₃CuLi₂ always proceeded with higher *anti*-selectivity than that observed with *n*-Bu₃CuLi₂ (compare entries 1/4, 2/5 and 3/6).

The *anti*-selectivity of these conjugate additions may be interpreted taking into account the Felkin-Anh model for chiral Michael acceptors¹¹ (conformation A, scheme 2). This model displays the R group at a diedral angle of 90° in relation to the double bond and the hydroxyl group in the inside position. Hence, the attack of the organocuprate opposite to the sterically demanding R group could explain the observed *anti*-selectivity and its increase with the steric bulkiness of R. Accordingly with this model, the low value of $J_{\beta\gamma}$ observed in the ¹H-NMR spectra of substrates 1 ($J_{\beta\gamma}$ = 3.6-4.0 Hz) indicates that the conformation A is the most populated in the conformational equilibrium around C_B-C_Y bond¹².





In summary the good yields and *anti*-selectivity observed in the conjugate addition of R_3CuLi_2 to the readily available vinyl sulfones 1 complements the previously reported *syn*-stereoselective methodology based on the addition of organolithiums to their α -trimethylsilyl derivatives. The application of both methods of acyclic stereocontrol to the enantioselective synthesis of polypropionate chains from enantiomerically pure vinyl sulfones 1 is underway.

Acknowledgements: We thank the Dirección General de Investigación Científica y Técnica (DGICYT) for financial support (Grant PB90-0178).

References and Notes

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- 7. Concerning the stereochemical assignment of *syn* and *anti* adducts **4** and **5**, the adducts of *syn*stereochemistry had been previously prepared by *syn*-stereoselective conjugate addition of organolithiums to α -trimethylsilyl- γ -oxygenated vinyl sulfones (see ref. 2). Moreover, *syn* and *anti* **4a** had been prepared unequivocally by stereoespecific opening of the epoxides of *trans* and *cis*-2-butene with the carbanion of phenyl methyl sulfone, respectively (see ref. 2b).
- 8. No reaction was observed at lower temperatures (-30°C or 0°C).
- 9. It should be clearly noted that the higher order cuprates notation R₃CuLi₂ is written merely to indicate that the stoichiometry of R (from RLi) and Cu (from CuI) is 3:1.
- 10. <u>General procedure:</u> The higher order cuprates R₃CuLi₂ were prepared as follows: methyllithium or n-butyllithium (1.56 mmol, 12 equiv.) was added to an ether (2 mL) suspension of CuI (100 mg, 0.52 mmol, 4 equiv.) cooled at 0°C and the resulting black suspension was stirred at 0°C for 30 min under argon atmosphere. To this suspension was slowly added an ether (1 mL) solution of vinyl sulfones 1 (0.13 mmol, 1 equiv.) and the mixture was allowed to warm to rt and stirring was continued during the time indicated in table 2. The reaction was quenched by adding a 1:1 mixture (5 mL) of sat. NH₄Cl aqueous solution and aqueous ammonia solution. The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were dried (Na₂SO₄) and evaporated. The residue was analyzed by ¹H-NMR and purified by flash chromatography (hexane-ethyl acetate, 3:1). Adducts **4** and **5** were obtained in 85-92% yield.
- 11. This model has also been used to explain the stereoselectivity of the addition of some organocopper reagents to γ -alkoxy and γ -silyloxy- α , β -unsaturated esters (see for instance refs. 1a and 6).
- For a recent publication about values of J_{βγ} and conformational equilibrium in allylic alcohols, see: Guns, B.W.; Wolf, M.A.; Ohm, K.; Peat, A.J. *Tetrahedron Lett.* **1993**, *34*, 1417.

(Received in UK 8 June 1993; accepted 16 July 1993)