

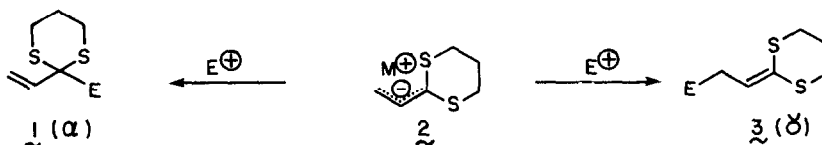
REGIOSELECTIVE CONTROL OF ALLYL ANIONS WITH CADMIUM CHLORIDE:
 α vs. γ CONDENSATION WITH ALDEHYDES

Lei Bo and Alex G. Fallis*

Department of Chemistry, Memorial University of Newfoundland,
St. John's, Newfoundland, Canada, A1B 3X7

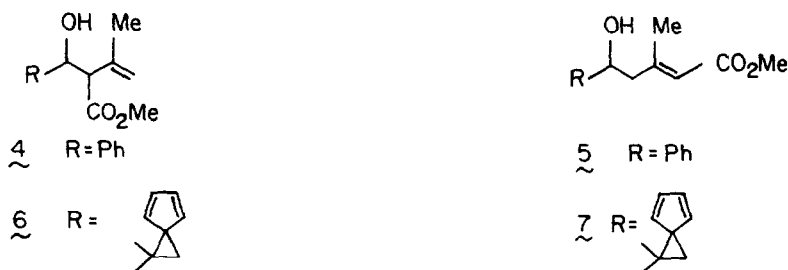
Summary: A general method for directing the condensation of allyl anions such as **1** with aldehydes preferentially to the γ position of the unsaturated nucleophile is described. The procedure employs cadmium chloride to control the regioselectivity and will facilitate the extended use of vinylogous anions in synthesis.

There is considerable current interest in the synthetic application of allylic carbanions such as those employed in the vinylogous Reformatsky reaction, and related species derived from ketene dithioacetals.¹⁻³ The control of α vs. γ substitution in heteroatom-stabilized allylic anions and resonance-stabilized enolates depends upon the complex interplay between the nature of the heteroatom(s), charge delocalization, steric effects, solvation, the type of electrophile, and the counterion. These difficulties are compounded by the observation that halides and carbonyl systems often exhibit opposite regioselectivities.³ We wish to report that organocadmium reagents generated *in situ* from the corresponding alkyl lithium derivatives condense preferentially with aldehydes at the γ position of the allylic anion. This is in contrast to the reported behaviour of the "crotyl-cadmium" reagent prepared from crotyl magnesium bromide, which afforded exclusively the methylallyl adducts.^{4,5}



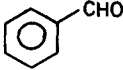
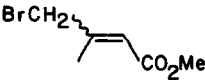
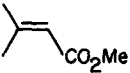
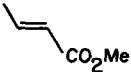
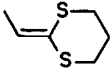
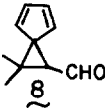
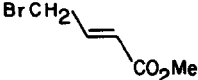

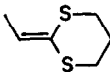
As part of a larger synthetic project we required a reliable procedure for the direct introduction of a conjugated allyl unit. Modified Reformatsky conditions (dry Zn, THF)⁶ worked well when either methyl 4-bromocrotonate or methyl 3-bromomethyl-2-butenate (Table, entry 1) were reacted with benzaldehyde and gave the γ product 5 exclusively. Unfortunately 60:40 and 40:60 α/γ mixtures (6:7) were obtained with the spiro-cyclopentadiene aldehyde 8⁷ (entries 5 and 6), presumably as a consequence of the hindered environment of the carbonyl group. Thus various lithium anion-salt combinations derived from 2-ethylidene-1,3-dithiane were examined. Zielger and Tam established earlier that allylation of the lithium anion derived from 2-ethylidene-1,3-dithiane (2, M = Li) afforded the α product 1 preferentially (cf., entry 7), while the corresponding copper derivative gave the γ allylation product 3 exclusively.² However, even in the case of the cuprate derivative a significant quantity of the undesired α product was produced with aldehyde 8 (entry 9) and this became the dominant product in the presence of zinc chloride (entry 8).

Except for the reaction of organocadmium reagents with acid chlorides, organocadmium species have received relatively little attention.⁸ Pure, salt free alkyl cadmiums do not react with carbonyl compounds but this reactivity can be altered significantly by the addition of magnesium or lithium salts.^{9,10} As summarized in the Table treatment of the lithium anions with cadmium chloride in THF at -78°C resulted in the γ condensation product predominating (entries 4 and 10). The tendency for methyl crotonate to react with lithium amides except in the presence of HMPA¹¹ required the addition of HMPA and reduced the influence of the cadmium (entry 3). However, the case of methyl 3,3-dimethylacrylate (entry 2) is noteworthy as this permits one to reverse the normal regiochemical behaviour encountered with these lithium enolates.



The method is straightforward and can be readily conducted as follows (entry 4); 2-Ethylidene-1,3-dithiane (0.321 g, 2.2 mmol) in THF (5 ml) was added dropwise to a magnetically stirred LDA solution (diisopropylamine 0.232 g, 2.3 mmol; n-butyllithium in hexane 2.5M, 0.8 mL, 2.2 mmol) in THF (20 mL) at -40°C . Stirring was continued at -40°C for 0.5 h after addition was complete. The reaction was then cooled to -78°C , CdCl_2 (0.210 g, 1.2 mmol, fine powder, previously dried at $110^\circ\text{C}/0.5$ Torr for 12 h) added in one

TABLE

Entry	Aldehyde	Substrate	Metal/Salt	$\alpha:\gamma$	Isolated Yield
1			Zn(THF)	0:100	85%
2	"		LDA/CdCl ₂	15:85	75%
3	"		LiNCy ₂ /CdCl ₂ HMPA	50:50	90%
4	"		LDA/CdCl ₂	10:90	95%
5			Zn(THF)	60:40	60%
6	"		Zn(THF)	40:60	63%
7	"		LDA	90:10	96%
8	"	"	LDA/ZnCl ₂	60:40	70%
9	"	"	LDA/CuI.P(OMe) ₃	35:65	61%
10	"	"	LDA/CdCl ₂	10:90	90%

portion and after stirring the resulting yellow-white suspension for 2 h at -78°C benzaldehyde (0.106 g, 1.0 mmol) in THF (5 mL) was added. After 0.5 h, the reaction mixture was warmed to -10°C , quenched with saturated aqueous NH_4Cl , filtered, the filtrate extracted with ether (3 x 30 mL), dried, filtered, concentrated, and the product purified by flash chromatography (15% ethyl acetate/n-hexane) to give 0.220 g (87%) of the γ -product, δ 5.97 (1H, t, $J = 7$ Hz, vinyl H), 4.74, 4.77 (1H, t, $J = 6.5$ Hz, H-C-OH) and 0.041 g (8%) of the α -isomer, δ 5.3-6.0 (3H, m, vinyl H's), 4.88, 4.92 (1H, s, H-C-OH).

Further work will be required to determine the exact nature of the reactive cadmium reagent although yields were less if the ratio of the lithium to cadmium species was not 2:1. Solvation effects are also important as the γ selectivity diminished in the presence of more soluble salts such as cadmium iodide and polar additives such as HMPA. Our research into cadmium reagents including 'ate complexes' is continuing. These procedures to influence the regioselectivity of carbonyl condensations will facilitate the extended use of vinylogous anions in synthesis.

Acknowledgements: We are grateful to Memorial University of Newfoundland and the Natural Science and Engineering Research Council of Canada for financial support of this research and B. Gregory for high resolution mass spectra.

REFERENCES AND NOTES

1. Hudlicky, T.; Natchus, M.G.; Kwart, L.D.; Colwell, B.L. *J. Org. Chem.*, 1985, 50, 4300.
2. Ziegler, F.E.; Tam, C.C. *J. Org. Chem.*, 1979, 44, 3428.
3. Biellmann, J.; Ducep, J. *Org. Reactions*, 1982, 27, 1.
4. Abenhaim, D.; Henry-Basch, E. *C.R. Acad. Sci., Ser. C*, 1968, 267, 87.
5. Abenhaim, D.; Henry-Basch, E.; Freon, P. *Bull. Soc. Chim. Fr.*, 1969, 4043.
6. Rice, L.E.; Boston, M.C.; Finklea, H.O.; Suder, B.J.; Frazier, J.O.; Hudlicky, T. *J. Org. Chem.*, 1984, 49, 1845.
7. Antczak, K.; Kingston, J.F.; Fallis, A.G. *Can. J. Chem.*, 1984, 62, 2451; oxidation of the corresponding alcohol with active MnO_2 afforded the aldehyde 8 (81%).
8. Jones, P.R.; Desio, P.J. *Chem. Rev.*, 1978, 78, 491.
9. Kollonitsch, J. *J. Chem. Soc. [A]*, 1966, 453.
10. Kollonitsch, J. *J. Chem. Soc. [A]*, 1966, 456.
11. Herrmann, J.L.; Kieczkowski, G.R.; Schlessinger, R.H. *Tetrahedron Lett.*, 1973, 2433.

(Received in USA 22 July 1986)