Acta Chemica Scandinavica B 34 (1980) 113 – 117

Reaction of Chiral Lithium Diorganocopper Reagents, LiRR*Cu, with α,β-Unsaturated Esters of Chiral Alcohols

BILL GUSTAFSSON, ANNA-TORA HANSSON and CHRISTINA ULLENIUS

Department of Organic Chemistry, Chalmers University of Technology and University of Göteborg, S-412 96 Göteborg, Sweden

Conjugate addition of organometallic reagents to chiral esters of *trans*-3-phenyl-2-propenoic or *trans*-2-butenoic acid has been studied. The reagents were PhMgBr, $LiPh_2Cu$, $LiMe_2Cu$, LiMeR*Cu, and LiPhR*Cu. The chiral ligand R* was the 2-(1-dimethylaminoethyl)phenyl group. The asymmetric induction varied between 0.3 and 49 % and was in some cases improved by the presence of the R* ligand. The influence of substituents on the β-carbon of the α,β-unsaturated esters on the stereochemical course of the reaction is related to their coordinating ability. The directing effects of the chiral ester functions are discussed.

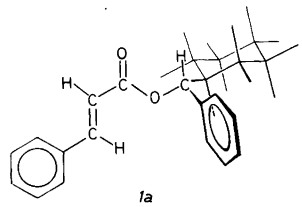
Lithium diorganocuprates are widely used as regioselective reagents in conjugate additions.[1-4] We have recently described the reaction of mixed, chiral cuprates, LiRR*Cu (R* = chiral group), with α,β-unsaturated carbonyl substrates (*cf.* Scheme 1), giving some asymmetric induction.[5-7] The results obtained from the reaction between lithium diorganocuprates and (−)-menthyl *trans*-3-(2-furanyl)propenoate suggested a favourable stereodifferentiating interaction between an *R* form of a cuprate and the menthyl group.[8]

Other authors have studied the addition of Grignard reagents to (−)-menthyl and "D-glucofuranosyl" esters of *trans*-2-butenoic acid.[9-11] The highest asymmetric induction obtained was 74 % enantiometric excess (e.e.).[10] The results were used as a basis for a discussion of the mechanism of Grignard additions to α,β-unsaturated carbonyl compounds. The directing effect of the alcohol moiety on the addition of Grignard reagents seems to be well established.

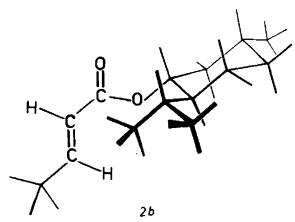
We now report a study of the addition of organic cuprates, particularly chiral cuprates, to α,β-unsaturated esters of these chiral alcohols. The D-glucofuranosyl group contains several oxygen atoms available for complexation with organometallic reagents. For comparison we also studied the reactions with esters of a simpler chiral alcohol, *S*-(−)- and *R*-(+)-cyclohexylphenylmethanol.[12,13]

The following chiral esters of *trans*-2-butenoic acid and *trans*-3-phenylpropenoic acid were prepared: *R*-(−)-cyclohexylphenylmethyl 3-phenylpropenoate *1a* (from *R*-(+)-cyclohexylphenylmethanol), *S*-(−) and *R*-(+)-cyclohexylphenylmethyl 2-butenoate *1b* (from *S*-(−)- and *R*-(+)-cyclohexylphenylmethanol), (−)-menthyl 3-phenylpropenoate *2a*, (−)-menthyl 2-butenoate *2b*, (−)-1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranosyl 3-phenylpropenoate *3a*, and (−)-1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranosyl 2-butenoate *3b*.

The 2-(1-dimethylaminoethyl)phenyl group was chosen as the chiral ligand in the mixed chiral cuprates, LiRR*Cu, *4*, assumed to be present as dimers in solution.[14]

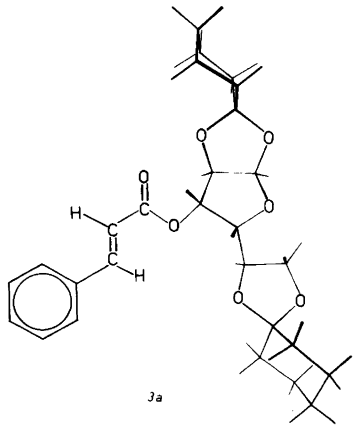


1a

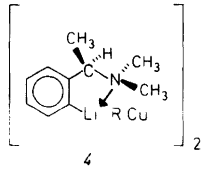


2b

0302-4369/80/020113-05$02.50

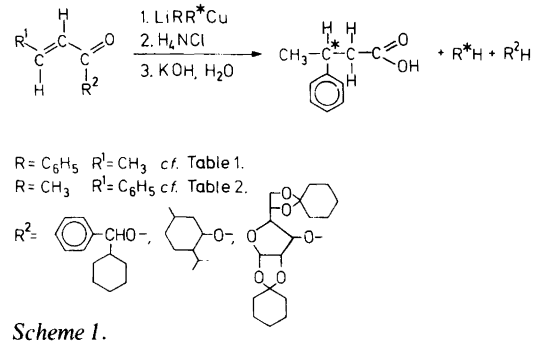


3a



4

R= CH_3, C_6H_5



Scheme 1.

RESULTS AND DISCUSSION

The conjugate additions studied all gave the same product, 3-phenylbutanoic acid, after hydrolysis. The product was formed in good or even high yields when a cuprate to substrate molar ratio of 4:1 was used. The results are summarized in Tables 1 and 2.

Large substituents on the substrate have been thought to lead to steric inhibition of the addition of cuprates to enones or enoates.[1] Our results clearly show that good chemical yields can be obtained and that chiral groups in the ester function or in the cuprate have an orienting effect on the reaction.

The asymmetric induction obtained on addition of cuprates to the esters varied from 0.3 % (substrate *3b*) to 37 % (substrate *1b*) enantiomeric excess. On the addition of a corresponding Grignard reagent to *1b*, the product was formed in 49 % e.e.

We could not reproduce the high enantiomeric excess obtained previously[10] by addition of Grignard reagents to the glucofuranosyl 2-butenoate *3b*, 33 % e.e. and 74 % e.e. in the presence of CuCl (*cf.* Table 2). These unsuccessful attempts are parallelled by the inability of Sawada and Inoye[11]

Table 1. Conjugate addition of $LiMe_2Cu$ and LiMeR*Cu [R* = 2-(1-dimethylaminoethyl)phenyl] reagents to the chiral *trans* esters (−)-cyclohexylphenylmethyl 3-phenyl-2-propenoate *1a* from (+)-alcohol, (−)-menthyl 3-phenyl-2-propenoate *2a*, and 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranosyl 3-phenyl-2-propenoate *3a* in diethyl ether at 0 °C to give after hydrolysis 3-phenylbutanoic acid. The reagent − substrate molar ratio was 4:1.

Substrate	Reagent	Reaction time/h	GLC yield/%	Isolated yield/%	$[\alpha]_{578}^{25}$ (°)	c/g ml^{-1} (benzene)	e.e./%	Conf.
R-1a	$LiMe_2Cu$	3 [a]	40	31	+19.5	0.089	32.5	S
2a	$LiMe_2Cu$	4.5	38	15	−3.9	0.085	6.5	R
2a	LiMe(*S*)-R*Cu	3	67	46	+1.8	0.110	3.0	S
2a	LiMe(*R*)-R*Cu	2	40	19	−6.2	0.095	10	R
2a	LiMe(*R,S*)-R*Cu	2	72	42	−1.1	0.090	1.8	R
3a	$LiMe_2Cu$	3	35	16	−0.3	0.050	0.6	R
3a	LiMe(*S*)-R*Cu	2	70	41	−4.3	0.095	7.2	R
3a	LiMe(*R*)-R*Cu	2	70	42	−3.0	0.136	5.0	R
3a	LiMe(*R,S*)-R*Cu	2	40	3 [b]	−3.8	0.011	6.3	R

[a] The reagent − substrate molar ratio was 12:1. [b] The 1,4-adduct was distilled before hydrolysis (compare experimental part).

Table 2. Conjugate addition of PhMgBr, $LiPh_2Cu$, and LiPhR*Cu [R* = 2-(1-dimethylaminoethyl)phenyl] reagents to the chiral *trans* esters *R*-(+)- and *S*-(−)-cyclohexylphenylmethyl 2-butenoate *1b*, (−)-menthyl 2-butenoate *2b*, and 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranosyl 2-butenoate *3b* in diethyl ether at 0 °C to give after hydrolysis 3-phenylbutanoic acid.

Substrate	Reagent	Reag − subst. molar ratio	Reaction time/h	GLC yield/%	Isolated yield/%	$[\alpha]_{578}^{25}$ (°)	c/g ml^{-1} (benzene)	e.e./%	Conf.
S-1b	PhMgBr[a]	1.4	0.2	90	52	+26.8	0.145	45	S
R-1b	PhMgBr	1.5	0.5		10	−29.5	0.105	49	R
S-1b	$LiPh_2Cu$	1.5	0.5	70	29	+22.3	0.138	37	S
S-1b	LiPh(*S*)-R*Cu	1.3	0.5	60	30	+18	0.070	30	S
S-1b	LiPh(*R*)-R*Cu	1.3	0.5	55	25	+16	0.038	27	S
2b	$LiPh_2Cu$	4.0	1	43	28	−7.6	0.230	13	R
2b	LiPh(*S*)-R*Cu	4.0	2	75	53	−2.8	0.290	4.7	R
2b	LiPh(*R*)-R*Cu	4.0	2	79	66	−6.2	0.050	10	R
2b	LiPh(*R,S*)-R*Cu	4.0	2	40	17	−5.2	0.200	9	R
3b	PhMgBr	2.5	2[b]		10	−1.5	0.085	2.5	R
3b	PhMgBr + CuI	2.5	2[b]		18	−5.4	0.099	9	R
3b	$LiPh_2Cu$	4.0	1.7	70	51	+4.4	0.080	7.3	S
3b	LiPh(*S*)-R*Cu	4.0	1	40	25	−1.6	0.340	2.7	R
3b	LiPh(*R*)-R*Cu	4.0	1	80	58	+1.6	0.400	2.7	S
3b	LiPh(*R,S*)-R*Cu	4.0	1	43	21	−0.2	0.177	0.3	R

[a] Reaction temp. −78 °C. [b] For experimental cond. *cf.* Ref. 10.

to add phenylcopper or $LiPh_2Cu$ to (−)-menthyl *trans*-2-butenoate. Their failure should be compared with our results with substrates *2a* and *2b*, 38 − 72 and 43 − 79 % yields, respectively.

The results of our experiments are compared below with predictions based on the assumption that RMgX and LiR_2Cu add to the least hindered side of an *s*-transoidal coplanar conformation of the substrates. Inspection of CPK space filling models then reveals (*cf.* conformations *1a*, *2b*, and *3a*): *1a* (ester group has *R* configuration) expected *S*, observed *S* configuration; *1b* (ester group has *S* configuration) expected *S*, observed *S*; *2a* ((−)-menthyl expected *S*, observed *R*; *2b* ((−)-menthyl) expected *R*, observed *R*; *3a* (D-glucofuranosyl) expected *R*, observed *R*; *3b* (D-glucofuranosyl) expected *S*, observed *S* with $LiPh_2Cu$, *R* with PhMgBr.

The introduction of the chiral ligand R*, 2-(1-dimethylaminoethyl)phenyl group, into the lithium diorganocuprates was expected to increase the enantiomeric excess due to the stereodifferentiating interaction between two chiral groups. It has been shown that the addition of a phenyl group from $LiPh_2Cu$ and LiPh(*R*)-R*Cu to (−)-menthyl *trans*-3-(2-furanyl)propenoate gives 2 % and 10 % e.e., respectively.[8] Such an increase in e.e. is also observed on addition of LiMe(*R*)−R*Cu to (−)-menthyl *trans*-phenylpropenoate *2a* (from 6.5 to 10.0 % e.e.). Both the *R*- and the *S*-form of LiMeR*Cu enhance the e.e. of the product obtained from the *trans*-3-phenylpropenoate *3a* from 0.5 % to 5.0 and 7.2 %, respectively. The ester *1a* did not react with the chiral cuprates (*cf.* Table 1). In contrast to the increase observed for *2a* and *3a*, the addition of chiral cuprates to *trans*-butenoates *1b*, *2b*, and *3b* gives a lower enantiomeric excess of the product compared to that observed on the addition of $LiPh_2Cu$ or PhMgBr (*cf.* Table 2).

The difference observed between the β-methyl and the β-arylsubstituted enoates is not sufficiently explained by the different steric requirements of the methyl group compared with the phenyl or furanyl group. Probably, complexation between the β-substituent and a metal has to be taken into account. If the reacting cuprate can be coordinated to two sites in the substrate, *i.e.* the carbonyl oxygen and the β-substituent, the stereodifferentiating effect of the chiral ester function and the chiral R* group in the cuprate would be more effective. The β-methyl group cannot coordinate to the cuprate metal atoms, while the furan oxygen most probably does so. Coordination between the benzene π-electrons and a metal atom is probably not as strong as the oxygen-metal coordination but should be taken into account. Posner *et al.* have demonstrated

the stereochemical effect of lithium-arene π-coordination in alkylations of lithium enolates.[15]

The asymmetric induction obtained on addition of $LiMe_2Cu$ and $LiPh_2Cu$ to the chiral esters demonstrates the stereodifferentiating abilities of the three chiral ester functions studied. The relatively high e.e. obtained with the cyclohexylphenylmethyl esters *1a* and *1b* could be related to the steric crowding here being closer to the reacting centre than in the other groups. There could also be an additional coordinative effect of the phenyl group in π-coordination to the cuprate. In the menthyl esters *2a* and *2b* the stereodifferentiating capacity is mainly due to the isopropyl group. It is one carbon atom further away from the reacting centre and relatively small. The 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranosyl group in *3a* and *3b* is sterically demanding. However, several oxygens are available for coordination, and there is also some mobility in the group. Thus the asymmetric induction effect is lost if several different conformations of the molecule can coordinate to the cuprate.

The asymmetric inductions obtained with substrates *1a* and *1b* show that the reaction between a cuprate and an unsaturated ester must follow a path without loss of configurational stability at the β-carbon. This is an important observation in relation to different mechanisms that have been proposed for cuprate reactions. Our results show that if an anion radical intermediate is formed in the initial step as proposed by House,[16] the *cis*–*trans* isomerisation of this species cannot be very fast. It was suggested that the isomerisation is fast but less than 10^8 s^{-1}.[16] The analogous rate of *cis*–*trans* isomerisation of *cis*-stilbene anion radicals to *trans*-stilbene anion radicals has been determined by Szwarc *et al.* to be 5×10^{-3} s^{-1}.[17]

Probably other mechanisms will better account for our results, *e.g.*, a nucleophilic attack of copper directly at the β-carbon, forming a short-lived Cu(III) intermediate, followed by carbon-carbon bond formation with retention of configuration (*cf.* Ref. 18). Another possible reaction sequence is the direct transfer of the organic group R from the cuprate to the β-carbon of an enone, possibly *via* insertion of the carbon–carbon bond into the copper–carbon bond in the cuprate, leading to the formation of an α-cuprioketone.[19-21] This reaction sequence would be analogous to the *cis*-addition of copper reagents to acetylenic compounds.[1]

EXPERIMENTAL

Reactions were performed and products analysed as described earlier.[5,7] Methyllithium and butyllithium were commercially supplied (Merck). Phenyllithium was prepared from bromobenzene and lithium.

Cyclohexylphenylmethanol was resolved using standard procedures,[12] $[\alpha]_{578}^{25}$ +38.9° (neat). ^1H NMR (270 MHz, $CDCl_3$) and a chiral shift reagent, Eu(III)[tris(3-trifluoromethylhydroxymethylene)-*d*-camphor] showed the enantiomeric purity to be better than 99 %. Lit. $[\alpha]_D^{20}$ 37.6° (neat).[12]

Preparation of substrates

Cyclohexylphenylmethyl 3-phenyl-2-propenoate, 1a. *R*-(+)-Cyclohexylphenylmethanol (10 mmol) was treated with butyllithium (10 mmol) in hexane. 3-Phenyl-2-propenoyl chloride (10 mmol) was added at 0 °C. The mixture was gently warmed for 30 min. After work-up and distillation, b.p. 180 °C/13 Pa, *1a* was isolated (2.5 g, 78 %), m.p. 117–117.5 °C, $[\alpha]_{578}^{25}$ −68.1° (*c* 0.118, C_6H_6). ^1H NMR (60 MHz, $CDCl_3$): δ 7.6 7.2 (10 H, m), 7.76 (1 H, d, *J* 16 Hz), 6.50 (1 H, d, *J* 16 Hz), 5.72 (1 H, d, *J* 7.5 Hz), 2.2–0.7 (11 H, m). MS: M^+ 320.182±0.005 ($C_{22}H_{24}O_2$ 320.178).

Cyclohexylphenylmethyl 2-butenoate, *1b*, was prepared in the same way as *1a* from *S*-(−)-cyclohexylphenylmethanol and 2-butenoyl chloride. Distillation at 110 °C/20 Pa afforded 72 % of *1b*, $[\alpha]_{578}^{25}$ −33.2° (*c* 0.141, C_6H_6). ^1H NMR (60 MHz, $CDCl_3$): δ 7.4–7.2 (5 H, m), 7.00 (1 H, qd, *J* 15.5 Hz, 6.8 Hz), 5.86 (1 H, qd, *J* 1.6 Hz, 15.5 Hz), 5.60 (1 H, d, *J* 7.2 Hz), 1.80 (3 H, dd, *J* 6.8 Hz, 1.6 Hz), 2.1–0.7 (11 H, m). The *R*-isomer was prepared in the same way.

(−)-Menthyl 3-phenylpropenoate, *2a*, was prepared from 3-phenyl-2-propenoyl chloride (100 mmol) and (−)-menthol (100 mmol) in the presence of pyridin in hexane. Distillation of the crude product gave 13 g (46 %) of *2a*, b.p. 168 °C/8 Pa.

(−)-Menthyl 2-butenoate, *2b* was prepared by the same method as *2a*. Distillation of the crude product gave 9.6 g (43 %) of *2b*, b.p. 182–185 °C/13 Pa.

1,2:5,6-Di-O-cyclohexylidene-D-glucofuranosyl 3-phenylpropenoate, *3a*, was prepared by the same method as *1a* above. The crude product was chromatographed on active alumina with chloroform and light petroleum (1:1) as eluent, *cf.* Ref. 10, yield 69 %, m.p. 130–131 °C.

1,2:5,6-Di-O-cyclohexylidene-D-glucofuranosyl 2-butenoate, *3b*, was prepared in the same way as *3a*. After chromatography 84 % of *3b* was isolated, m.p. 68–70 °C, *cf.* Ref. 10.

Reaction of cuprates

General procedure for the reaction of cuprates with α,β-unsaturated chiral esters. The unsaturated ester (10 mmol) was added under nitrogen to a cold solution (−5−0 °C) of the cuprate (40 mmol, counted as a monomer) in 80 ml of diethyl ether. The cuprate was prepared as described previously.[5,7,22] The reaction was followed by GLC (OV 17). The yield of the conjugate addition product was determined with *N,N*-dimethyl-1-phenylethylamine or biphenyl as internal standard. The mixture was stirred at −5−0 °C under nitrogen until all substrate was consumed, or for not more than 4.5 h. After the usual work-up the products from addition to *1a* and *1b* were distilled (150 °C/5 Pa) and hydrolysed (KOH in ethanol−water; 1 h). The optical rotations were measured at 578 nm and the enantiomeric excess calculated without corrections. The crude products from additions to substrates *2a*, *2b*, *3a*, and *3b* were hydrolysed (10 % KOH in ethanol−water 1:1, 16 h) before distillation, b.p. 100 °C/13 Pa. The optical rotation was then measured. For further details see Tables 1 and 2. The product from all reactions after hydrolysis was 3-phenylbutanoic acid, ^{1}H NMR (60 MHz, $CDCl_3$): δ 10.94 (1 H,s), 7.20 (5 H,s), 3.46 (1 H,m), 2.62 (1 H), 2.56 (1 H, d, *J* 2 Hz), 1.23 (3 H, d, *J* 7 Hz). IR (KBr) 1710 cm^{-1}.

Acknowledgements. We thank Professor Martin Nilsson for valuable discussions. We gratefully acknowledge the financial support from the Swedish Board of Technical Development and from the Swedish Natural Science Research Council.

REFERENCES

1. Posner, G. H. *Org. React. 19* (1972) 1.
2. Normant, J. F. *Synthesis* (1972) 63.
3. Jukes, A. E. *Adv. Organomet. Chem. 12* (1974) 215.
4. Normant, J. F. In Seyferth, D., Ed., *New Applications of Organometallic Reagents in Organic Synthesis*, Elsevier, New York 1976, p. 219.
5. Gustafsson, B., Nilsson, M. and Ullenius, C. *Acta Chem. Scand. B 31* (1977) 667.
6. Gustafsson, B. *Tetrahedron 34* (1978) 3023.
7. Hansson, A.-T., Rahman, M. T. and Ullenius, C. *Acta Chem. Scand. B 32* (1978) 483.
8. Gustafsson, B. and Ullenius, C. *Tetrahedron Lett.* (1977) 3171.
9. Inouye, Y. and Walborsky, H. M. *J. Org. Chem. 27* (1962) 2706.
10. Kawana, M. and Emoto, S. *Bull. Chem. Soc. Jpn. 39* (1966) 910.
11. Sawada, S. and Inouye, Y. *Bull. Kyoto Univ. Educ. Ser. B 51* (1977) 43.
12. MacLoed, R., Welch, F. J. and Mosher, H. S. *J. Am. Chem. Soc. 82* (1960) 876.
13. Cervinka, O. and Belovsky, O. *Collect. Czech. Chem. Commun. 32* (1967) 4149.
14. van Koten, G. and Noltes, J. G. *Chem. Commun.* (1972) 940.
15. Posner, G. H. and Lentz, C. M. *J. Am. Chem. Soc. 101* (1979) 934.
16. House, H. O. *Acc. Chem. Res. 9* (1976) 59.
17. Levin, G., Holloway, B. E., Mao, C. R. and Szwarc, M. *J. Am. Chem. Soc. 100* (1978) 5841.
18. Smith, R. A. J. and Hannah, D. J. *Tetrahedron 35* (1979) 1183.
19. Berlan, J., Battioni, J.-P. and Koosha, K. *Tetrahedron Lett.* (1976) 3355.
20. Berlan, J., Battioni, J.-P. and Koosha, K. *J. Organometal. Chem. 152* (1978) 359.
21. Olsson, T., Rahman, M. T. and Ullenius, C. *Tetrahedron Lett.* (1977) 75.
22. Nilsson, M., Rahman, M. T. and Ullenius, C. *Acta Chem. Scand. B 31* (1977) 514.

Received August 24, 1979.