

# The Reaction between Mixed Chiral Homocuprates Containing the 2-(1-Dimethylaminoethyl)phenyl Group and $\alpha$ -Ethylenic Carbonyl Compounds

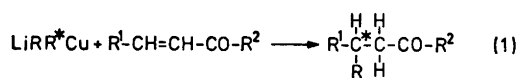
ANNA-TORA HANSSON, MOHAMMED T. RAHMAN\* and CHRISTINA ULLENIUS

Department of Organic Chemistry, Chalmers University of Technology and University of Göteborg, S-402 20 Göteborg, Sweden

Good yields of 1,4-addition products are obtained from the addition of chiral lithium methyl-, butyl-, and phenyl-[2-(1-dimethylaminoethyl)phenyl]cuprate reagents to methyl crotonate, methyl cinnamate, 3-phenylpropenal and 4'-substituted 4-phenylbutenones in diethyl ether. The asymmetric induction, however, is less than 1 % (e.e.).

The 1,4-addition of lithium diorganocuprates, Gilman reagents, to  $\alpha$ -ethylenic carbonyl compounds as a versatile method for the formation of carbon-carbon bonds has been amply demonstrated during the last ten years.<sup>1-4</sup>

When the carbonyl compound carries a substituent on its  $\beta$ -carbon, an asymmetric centre can be formed in the reaction (1).

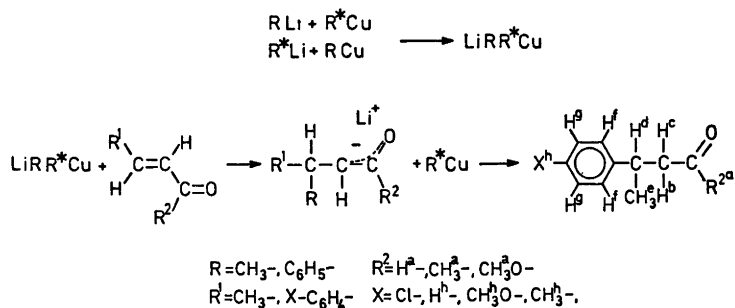


\* Present address: Department of Chemistry, Dacca University, Dacca-2, Bangladesh.

Asymmetric surroundings for the reaction should favour the formation of one of the enantiomers. Chiral surroundings could be established in different ways, for example by using a chiral solvent or a chiral complexing agent. Chiral phosphines have successfully been used in the rhodium-catalysed asymmetric hydrogenation of some acetaminoacrylic acids.<sup>5,6</sup>

Some attempts have been made to achieve asymmetric induction in 1,4-additions to acid derivatives. Copper catalyzed additions of Grignard reagents to optically active  $\alpha$ -ethylenic esters have been studied.<sup>7,8</sup> High enantiomeric excess has been reported from the addition of lithium compounds to chiral oxazoline derivatives of  $\alpha,\beta$ -unsaturated acids.<sup>9</sup>

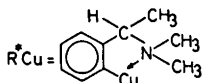
We are studying the effect of a chiral group as a part of a mixed lithium diorganocuprate on its ability to cause asymmetric induction to  $\alpha,\beta$ -unsaturated aldehydes and ketones as well as to acid derivatives. The reaction could also be designed to allow the use of the chiral group in less than stoichiometric amounts (cf. Scheme 1).



Scheme 1.

We have previously investigated the formation of racemic mixed homocuprates from alkyl- and phenyllithium and 2-(1-dimethylaminoethyl)phenylcopper ( $R^*Cu$ ) and their reactions with methyl cinnamate and methyl crotonate.<sup>10</sup> The racemic mixed cuprates selectively transfer the R group (Scheme 1) to methyl cinnamate, and 2-(1-dimethylaminoethyl)phenylcopper could be recovered from the reaction.<sup>10</sup>

In the formulas below the cuprates are shown as monomers although they are probably present as dimers<sup>11</sup> or even larger clusters.



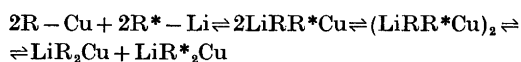
We now report the results of the reactions of chiral mixed homocuprates with  $\alpha$ -ethylenic ketones, esters, and an aldehyde.

## RESULTS AND DISCUSSION

The experimental conditions together with chemical yields and enantiomeric excess obtained in the 1,4-addition of chiral, mixed cuprates to  $\alpha, \beta$ -unsaturated ketones, esters and an aldehyde are summarized in Tables 1 and 2.

Several experimental variables have been varied so that their effects on the chemical yield as well as the enantiomeric excess could be studied. The chemical yields are usually good and even comparable to those obtained from the addition of the corresponding unmixed cuprate. It should be noted that the mixed cuprate contains only one equivalent of the group to be added. The other group,  $R^*$ , is recovered as  $R^*H$  or could be recycled (as  $R^*Cu$ ).

The enantiomeric excess is consistently low but reproducible (exps. 1, 2; 3, 4; 5 and 6 in Table 1). The low asymmetric induction in these reactions may question the presence of a mixed cuprate. The possible formation of equilibrium mixtures of different cuprates must be taken into account:



Addition of organolithium reagents to these unsaturated substrates typically results in 1,2-

Table 1. 1,4-Addition of chiral lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate,  $LiMeR^*Cu$ , to  $\alpha, \beta$ -unsaturated aldehyde and ketones. Reactions were run in diethyl ether at  $-5$  to  $0^\circ C$  with a cuprate:substrate molar ratio 1.1:1.

Exp. No.	$LiMeR^*Cu$	Substrate	1,4-Addition product	Isolated yield/%	$[\alpha]_{D}^{25}$ (°)	Enantiomeric excess/%
1	(+)	$C_6H_5-CH=CH-CHO$	$C_6H_5-CH(CH_3)-CH_2-CHO$	37	-1.8	0.1 <sup>a</sup>
2	(-)	$C_6H_5-CH=CH-CHO$	$C_6H_5-CH(CH_3)-CH_2-CHO$	13	+1.5	<0.1
3	(-)	$C_6H_5-CH=CH-CO-CH_3$	$C_6H_5-CH(CH_3)-CH_2-CO-CH_3$	52	+0.01	<0.1
4	(+)	$C_6H_5-CH=CH-CO-CH_3$	$C_6H_5-CH(CH_3)-CH_2-CO-CH_3$	78	-0.01	<0.1
5	(-)	$4-CH_3-C_6H_4-CH=CH-COCH_3$	$4-CH_3-C_6H_4-CH(CH_3)-CH_2-COCH_3$	60	+0.06	0.1
6	(+)	$4-CH_3-C_6H_4-CH=CH-COCH_3$	$4-CH_3-C_6H_4-CH(CH_3)-CH_2-COCH_3$	60	+0.05	<0.1
7	(-)	$4-CH_3O-C_6H_4-CH=CH-COCH_3$	$4-CH_3O-C_6H_4-CH(CH_3)-CH_2-COCH_3$	75	-0.01	<0.1
8	(-)	$4-Cl-C_6H_4-CH=CH-COCH_3$	$4-Cl-C_6H_4-CH(CH_3)-CH_2-COCH_3$	80	-0.40	<0.1
9	(+)	$4-Cl-C_6H_4-CH=CH-COCH_3$	$4-Cl-C_6H_4-CH(CH_3)-CH_2-COCH_3$	80	+2.30	<0.1

<sup>a</sup> Measured after oxidation to the corresponding acid, see Experimental. <sup>b</sup> Estimated from NMR using a chiral shift reagent.

Table 2. 1,4-Addition of chiral mixed lithium diorganocuprates, LiRR\*Cu, to  $\alpha,\beta$ -unsaturated esters. The cuprate:substrate molar ratio was 4:1. R\* = (-)-2-(1-dimethylaminoethyl)phenyl. Substrates: 1 = methyl *trans*-cinnamate, 2 = methyl *trans*-crotonate. Products: 3 = methyl 3-phenylbutanoate, 4 = methyl 3-phenylheptanoate.

Exp. No.	Mixed cuprate	Substrate	Solvent	Temp./°C	1,4-Addition product	Isolated yield/%	$[\alpha]_{578}^{25}$ (°)	c/g ml <sup>-1</sup> (ethanol)	Enantiomeric excess/%
10	LiMeR*Cu	1	ether	-5 to 0	3	46	+0.17	0.150	0.4
11	LiPhR*Cu	2	ether	-5 to 0	3	70	-0.21	0.250	0.5
12	MgBrPhR*Cu	2	ether	0 to +5	3	26	-0.16	0.105	0.4
13	LiPhR*Cu	2	ether	-20 to -15	3	76	-0.19	0.320	0.4
14	LiPhR*Cu	2	ether	+35	3	65	-0.11	0.270	0.2
15	LiPhR*Cu	2	toluene	+23	3	49 <sup>a</sup>	-0.02	0.220	0.04
16	LiPhR*Cu	2	THF	0 to +5	3	3 <sup>b</sup>	+0.4	0.001	0.9
17	LiBuR*Cu	1	ether	-20	4	68	+0.09	0.250	-

<sup>a</sup> After 3 h. <sup>b</sup> The main product is a derivative of dimethyl cyclohexanonedicarboxylate.<sup>15</sup>

additions (*cf.* Ref. 12). This reaction has not been observed with the mixed cuprates. Thus any fast equilibrium resulting in lithium compounds can be ruled out. The formation of an unmixed cuprate, LiR<sub>2</sub>Cu, has to be considered more seriously. The oxidation of a mixed cuprate should result in some formation of the cross-coupling product R-R\*. When lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate was exposed to oxygen, 2% of *N,N*-dimethyl-1-(2-methylphenyl)ethylamine was isolated together with *N,N*-dimethyl-1-phenylethylamine (46%) and 2,2'-bis-(1-*N,N*-dimethylaminoethyl)biphenyl (19%). There are, however, other indications that a substantial amount of a mixed, chiral cuprate is present in the reaction mixture and takes part in the reaction. In the reaction of the mixed, chiral lithium phenyl[2-(1-dimethylaminoethyl)phenyl]cuprate with menthyl 3-(2-furyl)acrylate<sup>13</sup> and menthyl cinnamate<sup>14</sup> the configuration of the chiral group R\* has an influence on the enantiomeric excess, which shows that the chiral groups of the cuprate and the substrate interact.

The formation of opposite enantiomers in the reactions of methyl cinnamate and methyl crotonate (Table 2, expts. 10 and 11) indicates that the chiral cuprate reacts preferentially from one side of the substrates.

Changes in the reaction temperature from -20°C to +35°C or of solvents seem to effect the enantiomeric excess to some extent, but the effects have to be verified in a system giving higher asymmetric induction.

The 1,4-addition of lithium methyl-, butyl-,

and phenyl[2-(1-dimethylaminoethyl)phenyl]cuprates to aldehydes, ketones and esters is fast in diethyl ether and gives high yields of products. According to GLC analyses most of the unsaturated compound has reacted within a few minutes at 0°C. Comparison of experiments 11, 13 and 14 in Table 2 indicates that the formation of byproducts can be suppressed at lower temperatures.

When tetrahydrofuran or toluene are used as solvents, the reaction is considerably slower. The 1,4-addition product can be obtained in toluene after extended reaction time at elevated temperature (exp. 15, Table 2). However, in THF the 1,4-addition product is formed in a very low yield (exp. 16, Table 2). Most of the crotonate reacted, forming a derivative of dimethyl cyclohexanonedicarboxylate.<sup>15</sup>

The stronger complexing ability of THF compared to diethyl ether obviously increases the nucleophilicity of the initially formed enolate (see Scheme 1). The enolate can compete with the cuprate as a nucleophile by attacking another molecule of methyl crotonate. This sequence is repeated and then followed by a ring closure to the observed product. The same type of competing reaction seems to operate in the reaction of lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate with 4-(4-methoxyphenyl)-3-buten-2-one and in the reaction of lithium dimethylcuprate with 4-(4-methylphenyl)-3-buten-2-one (*cf.* EXPERIMENTAL).

A substantial difference in yield of methyl 3-phenylbutanoate was obtained depending on the reacting species (Table 2, expts. 10 and 11).

Besides electronic and steric factors there is a possible salt effect. In exp. 10 the cuprate was prepared from commercial methyllithium. The phenyllithium in exp. 11 contained stoichiometric amounts of lithium halides from its preparation. We have previously noted that 1,4-additions proceed faster and in higher yields when the cuprate reagent contains stoichiometric amounts of lithium salts.<sup>16</sup>

3-Phenylpropenal reacted with  $\text{LiMe}_2\text{Cu}$  to give equal amounts of 1,2- and 1,4-addition products, while the less reactive mixed cuprate,  $\text{LiMeR}^*\text{Cu}$ , selectively produced the 1,4-addition product.

Thus we conclude that at least a substantial part of the 1,4-addition products are formed from the attack of a mixed chiral cuprate. The steric requirements of the (dimethylaminoethyl)phenyl group do not seem to be sufficient to induce a high degree of enantiomeric purity in the product. Work on other chiral groups is in progress.

## EXPERIMENTAL

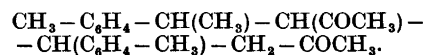
Organometallic reactions were carried out under dry, oxygen-free nitrogen. Dry diethyl ether was distilled from sodium benzophenone ketyl and toluene from  $\text{LiAlH}_4$ . Commercial butyllithium in hexane and methyllithium in ether were standardized.<sup>17</sup> Phenyllithium was prepared from bromobenzene and lithium and its concentration determined by titration with  $\text{HCl}$ .<sup>18</sup>  $\text{CH}_3$ -,  $\text{CH}_3\text{O}$ - and  $\text{Cl}$ -substituted benzalacetones were prepared by standard methods.<sup>19</sup>

*General procedure for the reaction of lithium dimethylcuprate with enones.* To a cold ( $-5$  to  $0^\circ\text{C}$ ) solution of  $\text{LiMe}_2\text{Cu}$  (from 40 mmol of  $\text{MeLi}$  and 20 mmol of  $\text{CuI}$ ) in 50 ml of ether was added the neat ketone or aldehyde (20 mmol). The resulting mixture was stirred for 30 min at  $-5^\circ\text{C}$ . Yellow  $\text{MeCu}$  was precipitated. The mixture was partitioned between ether and an aqueous solution of  $\text{NH}_3/\text{NH}_4\text{Cl}$  (pH 8). The ether solution was washed with aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ , dried and concentrated.<sup>20</sup> The mixture was analyzed by GLC (OV 17 or SE 30) and the products were isolated after distillation or column chromatography (silica gel) followed by distillation. The latter procedure resulted in large losses of material.

*Reaction of trans-3-phenylpropenal with  $\text{LiMe}_2\text{Cu}$ .* GLC (OV 17) analyses indicated a 1:1 mixture of 1,4- and 1,2-addition products. Distillation of the crude product gave 3-phenylbutanal (0.85 g, 29%) b.p.  $80^\circ\text{C}/130$  Pa, lit.<sup>21</sup> b.p.  $92-93^\circ\text{C}/1.9$  kPa, IR  $1725\text{ cm}^{-1}$ ,  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.70 (1 H, t,  $J_{ab}$ ,  $J_{ac}$  2.2

Hz)  $\text{H}_a$ , 7.31 (5 H, m)  $\text{H}_f$ ,  $\text{H}_g$ ,  $\text{H}_h$ , 3.35 (1 H, qdd,  $J_{de}$  7.0 Hz)  $\text{H}_d$ , 2.74 (1 H, ddd,  $J_{bc}$  16.5 Hz,  $J_{bd}$  7.6 Hz)  $\text{H}_b$ , 2.65 (1 H, ddd,  $J_{cd}$  7.1 Hz)  $\text{H}_c$ , 1.32 (3 H, d)  $\text{H}_e$ , and 4-phenyl-3-buten-2-ol (0.6 g, 37%) b.p.  $100^\circ\text{C}/13$  Pa, m.p.  $30-32^\circ\text{C}$ , lit.<sup>22</sup> b.p.  $139^\circ\text{C}/21$  kPa m.p.  $30-32^\circ\text{C}$ ,  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.23 (5 H, m), 6.57 (1 H, d,  $J$  15.2 Hz), 6.26 (1 H, dd,  $J$  15.2 Hz, 6.3 Hz), 4.49 (1 H, qd,  $J$  6.3 Hz), 1.60 (1 H, broad s) -OH, 1.37 (3 H, d,  $J$  6.3 Hz).

*Reaction of trans-4-(4-methylphenyl)-3-buten-2-one with  $\text{LiMe}_2\text{Cu}$ .* Distillation of the crude product (2.9 g) gave 4-(4-methylphenyl)-2-pentanone (0.63 g, 18%), b.p.  $100^\circ\text{C}/30$  Pa, lit.<sup>23</sup> b.p.  $115-117^\circ\text{C}/1.3$  kPa, IR  $1715\text{ cm}^{-1}$ ,  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.09 (4 H, s)  $\text{H}_f$ ,  $\text{H}_g$ , 3.25 (1 H, qdd,  $J_{de}$  7.0 Hz)  $\text{H}_d$ , 2.70 (1 H, dd,  $J_{bd}$  10.4 Hz)  $\text{H}_b$ , 2.62 (1 H, dd,  $J_{bc}$  16.0 Hz,  $J_{cd}$  4.0 Hz)  $\text{H}_c$ , 2.34 (3 H, s)  $\text{H}_h$ , 2.03 (3 H, s)  $\text{H}_a$ , 1.24 (3 H, d)  $\text{H}_e$ , and 0.8 g of a product, b.p.  $150^\circ\text{C}/30$  Pa, MS mol. wt., obs.  $336.208 \pm 0.003$ , calc. for  $\text{C}_{23}\text{H}_{28}\text{O}_2$  336.209. The product has tentatively been assigned the following structure:



*Reaction of trans-4-(4-methoxyphenyl)-3-buten-2-one with  $\text{LiMe}_2\text{Cu}$ .* Distillation of the crude product (3.2 g) gave 4-(4-methoxyphenyl)-2-pentanone (2.8 g, 73%) b.p.  $105-107^\circ\text{C}/13$  Pa, IR  $1715\text{ cm}^{-1}$ ,  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.04 (2 H, d,  $J_{fg}$  8.6 Hz)  $\text{H}_f$ , 6.74 (2 H, d)  $\text{H}_g$ , 3.68 (3 H, s)  $\text{H}_h$ , 3.17 (1 H, qdd,  $J_{de}$  7.0 Hz)  $\text{H}_d$ , 2.62 (1 H, dd,  $J_{bc}$  16.0 Hz,  $J_{bd}$  7.6 Hz)  $\text{H}_b$ , 2.53 (1 H, dd,  $J_{cd}$  6.8 Hz)  $\text{H}_c$ , 1.98 (3 H, s)  $\text{H}_a$ , 1.15 (3 H, d)  $\text{H}_e$ .

*Reaction of trans-4-(4-chlorophenyl)-3-buten-2-one with  $\text{LiMe}_2\text{Cu}$ .* GLC indicated a quantitative yield of 4-(4-chlorophenyl)-2-pentanone (3.0 g, 77% after distillation) b.p.  $112^\circ\text{C}/13$  Pa, IR  $1715\text{ cm}^{-1}$ ,  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.23 (2 H, d,  $J_{fg}$  8.6 Hz)  $\text{H}_f$ , 7.13 (2 H, d)  $\text{H}_g$ , 3.28 (1 H, qdd,  $J_{bd}$  9.2 Hz,  $J_{cd}$  7.6 Hz)  $\text{H}_d$ , 2.71 (1 H, dd)  $\text{H}_b$ , 2.62 (1 H, dd,  $J_{bc}$  6.6 Hz)  $\text{H}_c$ , 2.04 (3 H, s)  $\text{H}_a$ , 1.25 (3 H, d,  $J_{de}$  7.0 Hz)  $\text{H}_e$ .

*Preparation of chiral lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate.* *R*- or *S*-*N,N*-dimethyl-1-phenylethylamine<sup>24</sup> (20 mmol) was lithiated by stirring it with butyllithium (20 mmol) in ether (30 ml) at  $20^\circ\text{C}$  for 45-60 h. Dropwise addition of this chiral 2-(1-dimethylaminoethyl)phenyllithium reagent to methylcopper (from 22 mmol of methyllithium and  $\text{CuI}$  in ether, 30 ml) at  $0^\circ\text{C}$  followed by stirring for 30 min or until Gilman Test I<sup>25</sup> was negative, gave the chiral lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate.

*Chiral lithium butyl- or phenyl-[2-(1-dimethylaminoethyl)phenyl]cuprates* were prepared in the same way as above except that butyl-<sup>26</sup> or phenylcopper<sup>27</sup> were used in place of methylcopper. The reaction temperature for the butyl

mixed cuprate was  $-40^{\circ}\text{C}$ . All the chiral mixed cuprates were used immediately after preparation and without isolation for the subsequent conjugate addition reaction.

*General procedure for the reaction of chiral mixed cuprates with  $\alpha,\beta$ -unsaturated aldehydes and ketones.* An  $\alpha,\beta$ -unsaturated aldehyde or ketone (18 mmol) was added all at once to the mixed cuprate (20 mmol, calc. as a monomer) in ether at 0 to  $-5^{\circ}\text{C}$ . The mixture was stirred for 30–60 min and was then partitioned between ether and aqueous  $\text{NH}_3/\text{NH}_4\text{Cl}$ . The basic material was removed from the ether solution by extraction with 2 M HCl. *N,N*-Dimethyl-1-phenylethylamine was recovered in 55–65% yield after distillation,  $[\alpha]_{578}^{20} + 65.20^{\circ}$  and  $-66.37^{\circ}$  (neat), respectively lit.<sup>28</sup>  $[\alpha]_{\text{D}}^{25} - 67^{\circ}$  (neat) for the (-)-*S*-amine. There was no change in optical activity compared to the starting material. Further work-up was analogous to that described above.

*Reaction of 3-phenylpropenal with (+)-lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate.* The crude reaction mixture was treated with  $\text{K}_2\text{Cr}_2\text{O}_7$  in acid.<sup>29</sup> 3-Phenylbutanoic acid (1.1 g, 31%) was isolated, b.p.  $80^{\circ}\text{C}/30$  Pa, lit.<sup>30</sup> m.p.  $37-39^{\circ}\text{C}$ , IR  $1725\text{ cm}^{-1}$ ,  $[\alpha]_{578}^{20} - 0.1^{\circ}$  (c 0.100, benzene). For (-)-*R*-3-phenylbutanoic acid  $[\alpha]_{\text{D}} - 60.0^{\circ}$  (benzene) has been reported.<sup>31</sup> The reaction was repeated with (-)-lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate. Distillation of the crude product gave 3-phenylbutanal (0.36 g, 13%), b.p.  $80^{\circ}\text{C}/65$  Pa,  $[\alpha]_{578}^{25} + 1.5^{\circ}$  (c 0.020,  $\text{CHCl}_3$ ). Trace amounts of the 1,2-addition product, 4-phenyl-3-buten-2-ol, were detected by GLC analyses.

*Reaction of 4-phenyl-3-buten-2-one with (+)- and with (-)-lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate.* Distillation of the crude products gave 4-phenyl-2-pentanone (1.66 g, 52%, 2.25 g, 78%) b.p.  $72-73^{\circ}\text{C}/13$  Pa, lit.<sup>20</sup> b.p.  $64-65^{\circ}\text{C}/60$  Pa, IR  $1715\text{ cm}^{-1}$ ,  $[\alpha]_{578}^{20} + 0.01^{\circ}$  (neat, -*R*\*) and  $-0.01^{\circ}$  (+*R*\*) resp. Lit.<sup>31</sup>  $[\alpha]_{\text{D}} - 74.5^{\circ}$ .

*Reaction of 4-(4-methylphenyl)-3-buten-2-one with (+)- and (-)-lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate.* Distillation of the crude products gave 4-(4-methylphenyl)-2-pentanone, (2.1 g, 60%), b.p.  $100^{\circ}\text{C}/27$  Pa,  $[\alpha]_{578}^{25} + 0.05^{\circ}$  (c 0.300,  $\text{CHCl}_3$ ) and  $-0.06^{\circ}$  (neat), respectively, lit.<sup>28</sup>  $[\alpha]_{\text{D}} + 46.5^{\circ}$  (neat). Trace amounts of products of higher molecular weight were obtained, MS mol.wt., obs. 350.174  $\pm 0.003$ , calc. for  $\text{C}_{22}\text{H}_{30}\text{O}_2$  350.225 corresponding to a dimer of the initially formed enolate,  $[\text{CH}_3-\text{C}_6\text{H}_4-\text{CH}(\text{CH}_3)-\text{CH}(\text{COCH}_3)]_2$  and MS mol.wt., obs.  $462.257 \pm 0.003$  calc. for  $\text{C}_{33}\text{H}_{44}\text{O}_2$  462.256.

*Reaction of 4-(4-methoxyphenyl)-3-buten-2-one with (-)-lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate.* Cup distillation of the crude product gave 4-(4-methoxyphenyl)-2-pentanone (2.9 g, 75%), b.p.  $142^{\circ}\text{C}/40$  Pa,  $[\alpha]_{578}^{25} - 0.01^{\circ}$  (neat). The NMR (270 MHz,  $\text{CDCl}_3$ , chiral shift reagent  $\text{Eu}(\text{III})\cdot\text{tris}(3\text{-tri-$

fluoromethylhydroxymethylene)-*d*-camphor) indicated a small enantiomeric excess ca. 1%. Hypobromite oxidation<sup>22</sup> gave 3-(4-methoxyphenyl)-butanoic acid, m.p.  $57-58^{\circ}\text{C}$  lit.<sup>33</sup> m.p.  $64-65^{\circ}\text{C}$ ,  $[\alpha]_{578}^{20} + 4.0^{\circ}$  (c 0.033, benzene). Trace amounts of a high molecular weight product were isolated, MS, mol.wt., obs. 368.191  $\pm 0.003$ , calc. for  $\text{C}_{23}\text{H}_{30}\text{O}_4$  368.198. The product has been assigned the structure:  $\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CH}(\text{CH}_3)-\text{CH}(\text{COCH}_3)-\text{CH}(\text{C}_6\text{H}_4-\text{OCH}_3)-\text{CH}_2-\text{COCH}_3$ .

*Reaction of 4-(4-chlorophenyl)-3-buten-2-one with (+)- and (-)-lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate.* The (+) form of the mixed cuprate (30 mmol) was reacted with the enone (4.9 g, 27 mmol). After distillation 4-(4-chlorophenyl)-2-pentanone (4.2 g, 80%) was isolated, b.p.  $112^{\circ}\text{C}/30$  Pa,  $[\alpha]_{578}^{20} + 2.3^{\circ}$  (c 0.050,  $\text{CHCl}_3$ ). The NMR (270 MHz,  $\text{CDCl}_3$ , shift reagent) indicated a small enantiomeric excess, ca. 1%. When the (-) form of the cuprate was reacted with the enone (5 mmol), 0.8 g of 4-(4-chlorophenyl)-2-pentanone (80%) was isolated,  $[\alpha]_{578}^{20} - 0.4^{\circ}$  (c 0.230, benzene).

*General procedure for the reaction of chiral mixed cuprates with  $\alpha,\beta$ -unsaturated esters in diethyl ether.* The unsaturated ester was added all in one portion, to a preparation of a chiral mixed cuprate (20 mmol, calc. as a monomer) in diethyl ether at the temperatures indicated in Table 2. The mixture was stirred for 45 to 60 min. The reaction was essentially complete within a few minutes (GLC). The work-up was performed as above. The products were characterized by comparison (b.p., m.p., IR, GLC and NMR) with authentic samples as described before.<sup>10</sup> Table 2 gives further details of the various reactions, the yields and the specific rotations of the products. The reported specific rotation of (-)-*R* methyl 3-phenylbutanoate is  $[\alpha]_{\text{D}} - 44.3$  (c 0.010, benzene).<sup>31</sup>

*Reaction of methyl crotonate with (-)-lithium phenyl[2-(1-dimethylaminoethyl)phenyl]cuprate in toluene.* 2-(1-Dimethylaminoethyl)phenyllithium (20 mmol) and phenylcopper (20 mmol) were prepared separately in ether. Most of the ether was pumped off and dry toluene was added. The remaining ether was evaporated. The toluene solution of 2-(1-dimethylaminoethyl)phenyllithium was added to the slurry of phenylcopper in toluene over 5 min at  $0^{\circ}\text{C}$ . The mixture was stirred for 40 min at  $0^{\circ}\text{C}$ . Gilman Test I was then negative. Methyl crotonate (5 mmol) was added all at once, and stirring was continued at 0 to  $+5^{\circ}\text{C}$ . After 1 h only a small fraction of the crotonate had reacted (GLC). The temperature was raised gradually to room temperature and the stirring was continued for 2 h. The reaction mixture was worked up in the usual way. Some biphenyl from the preparation of phenyllithium was isolated. After distillation methyl 3-phenylbutanoate (0.44 g, 49%) was isolated, b.p.  $65-70^{\circ}\text{C}/130$  Pa,  $[\alpha]_{578}^{25} - 0.02^{\circ}$  (c 0.220, ethanol).

Reaction of methyl crotonate with (-)-bromo-magnesium phenyl[2-(1-dimethylaminoethyl)-phenyl]cuprate in diethyl ether. (-)-2-(1-Dimethylaminoethyl)phenylcopper (20 mmol) was prepared by addition of (-)-2-(1-dimethylaminoethyl)phenyllithium (20 mmol) to CuI (20 mmol) in ether (10 ml) at 0°C over a period of 30 min. A yellow precipitate of 2-(1-dimethylaminoethyl)phenylcopper appeared. The stirring was continued at 0°C for 30 min and then at room temperature for 15 min. Gilman Test I was then negative. Phenyl magnesium bromide (prepared from 20 mmol of bromobenzene and 20 mmol of Mg in 30 ml of ether) was added to the copper compound over 15 min at 0 to +5°C. The mixture was stirred for 30 min. A green, dark precipitate was formed. Methyl crotonate (5 mmol) was added, and the mixture was stirred for 30 min. GLC analyses indicated that the reaction was complete within this time. After the usual work-up, column chromatography and distillation, methyl 3-phenylbutanoate (0.23 g, 26%) was isolated, b.p. 65°C/130 Pa,  $[\alpha]_{D}^{25} -0.16^{\circ}$  (c 0.105, ethanol).

Oxidation of lithium methyl [2-(1-dimethylaminoethyl)phenyl]cuprate. Oxygen was bubbled through a preparation of lithium methyl [2-(1-dimethylaminoethyl)phenyl]cuprate for 5 min at -5°C. The colour changed from black to brown. After work-up and distillation 46% of the *N,N*-dimethyl-1-phenylethylamine was recovered. *N,N*-Dimethyl-1-(2-methylphenyl)ethylamine (2%), b.p. ca. 75–80°C/130 Pa, lit.<sup>34</sup> b.p. 94–95°C/22.6 kPa <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>): δ 7.4 (4 H, m), 3.7–3.2 (1 H, m), 2.5 (3 H, s), 1.6 (6 H, s), 1.1 (3 H, d); MS mol. wt., obs. 163.109 ± 0.003, calc. for C<sub>11</sub>H<sub>17</sub>N 163.136, and 2,2'-bis-(1-dimethylaminoethyl)biphenyl (19%), b.p. 100°C/30 Pa. MS: M<sup>+</sup> = 296, <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>): δ 7.6–7.1 (8 H, m), 3.5–2.9 (2 H, m), 2.1 (12 H, s), 1.3 (6 H, d), were the only products. The same oxidation was performed with lithium di[2-(1-dimethylaminoethyl)phenyl]cuprate. After work-up and distillation *N,N*-dimethyl-1-phenylethylamine (19%) and 2,2'-di-(1-dimethylaminoethyl)biphenyl (38%) were isolated.

**Acknowledgement.** This work has been supported by a grant from the Swedish Board of Technical Development. M.T.R. was awarded a research fellowship from the International Seminar of Chemistry and Physics at Uppsala University supported by the Swedish International Development Agency. We thank Professor Martin Nilsson for valuable discussions.

## 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. Vineyard, B. D., Knowles, W. S., Sabacky, M. J., Bachman, G. L. and Winekauff, D. J. *J. Am. Chem. Soc.* 99 (1977) 5946.
6. Fryzuk, M. D. and Bosnich, B. *J. Am. Chem. Soc.* 99 (1977) 6262.
7. Inouye, Y. and Walborsky, H. M. *J. Org. Chem.* 27 (1962) 2706.
8. Kawana, M. and Emoto, S. *Bull. Chem. Soc. Jpn.* 39 (1966) 910.
9. Meyers, A. I. and Whitten, C. E. *J. Am. Chem. Soc.* 97 (1975) 6266.
10. Nilsson, M., Rahman, M. T. and Ullenius, C. *Acta Chem. Scand. B* 31 (1977) 514.
11. van Koten, G. and Noltes, J. G. *J. Chem. Commun.* (1972) 940.
12. Ashby, E. C., Lin, J. J. and Watkins, J. J. *J. Org. Chem.* 42 (1977) 1099.
13. Gustafsson, B. and Ullenius, C. *Tetrahedron Lett.* (1977) 3171.
14. Gustafsson, B., Hansson, A.-T. and Ullenius, C. *To be published.*
15. Olsson, T., Rahman, M. T. and Ullenius, C. *Tetrahedron Lett.* (1977) 75.
16. Gustafsson, B., Nilsson, M. and Ullenius, C. *Acta Chem. Scand. B* 31 (1977) 667.
17. Voskuil, W. and Arens, J. F. *Org. Synth.* 43 (1968) 47.
18. Gilman, H. and Morton, Jr., J. W. *Org. React.* 8 (1954) 258.
19. Houben-Weyl, *Methoden der Organischen Chemie*, Thieme, Stuttgart 1976, Vol. VII:2b, p. 1483.
20. House, H. O. and Umen, M. J. *J. Org. Chem.* 38 (1973) 3893.
21. Adams, R. and Garber, J. D. *J. Am. Chem. Soc.* 71 (1949) 522.
22. Braude, E. A., Jones, E. R. H. and Stern, E. S. *J. Chem. Soc.* (1946) 396.
23. Rupe, H., Clar, G., St. Pfau, A. and Pattner, P. *Helv. Chim. Acta* 17 (1934) 372.
24. Gram, D. J., Gaston, L. K. and Jäger, H. *J. Am. Chem. Soc.* 83 (1961) 2183.
25. Gilman, H. and Schulze, F. *J. Am. Chem. Soc.* 47 (1925) 2002.
26. Corey, E. J. and Posner, G. H. *J. Am. Chem. Soc.* 90 (1968) 5615.
27. Costa, G., Camus, A., Gatti, L. and Marsich, N. *J. Organometal. Chem.* 5 (1966) 568.
28. Craiz, C. J., Chan, R. P. K. and Roy, S. K. *Tetrahedron* 23 (1967) 3573.
29. *Oxid. Org. Chem.* 5 (1965) 152. Part A.
30. Weidler, A.-M. and Bergson, G. *Acta Chem. Scand.* 18 (1964) 1484.
31. Cookson, R. C. and Kemp, J. E. *Chem. Commun.* (1971) 385.
32. Houben-Weyl, *Methoden der Organischen Chemie*, Thieme, Stuttgart 1952, Vol. VIII, p. 415.
33. Woodruff, E. H. and Pierson, E. J. *Am. Chem. Soc.* 60 (1938) 1075.
34. Jones, F. N. and Hauser, C. R. *J. Org. Chem.* 27 (1962) 1542.

Received April 6, 1978.