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Lithium Methylorganocuprates Containing Chiral 2-(*N*-Methyl-2-pyrrolidinyl)-, 2-(*N*-Methyl-2-piperidinyl)- or 2-(1-*N*,*N*-Dimethylaminoethyl)-phenyl Groups. A Comparison of Addition to Two Acyclic Enones

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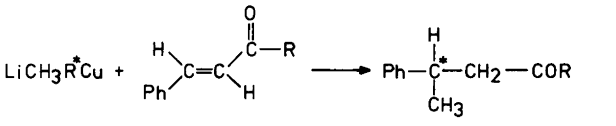
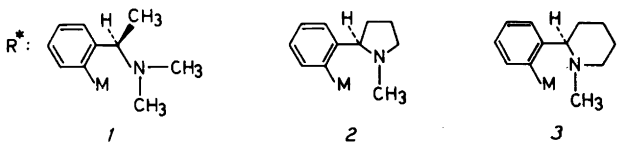
Conjugate addition of the title cuprates to 4-phenyl-3-buten-2-one or 5-phenyl-2,2-dimethyl-4-penten-3-one at −35 °C gave 4-phenyl-2-pentanone or 5-phenyl-2,2-dimethyl-3-hexanone, respectively, in high chemical yields (80–98%). The enantiomeric excess, however, was only of the order of 1 %.

Both enantiomers of *N*-methyl-2-phenylpyrrolidine and of *N*-methyl-2-phenylpiperidine were obtained by resolution with *R,R*-(+)-tartaric acid and *R,R*-(−)-*O,O*-dibenzoyltartaric acid, respectively.

Mixed organocuprates, LiRR*Cu, containing a chiral 2-(1-dimethylaminoethyl)phenyl group (*1c*) add the group R (methyl, butyl, phenyl) to prochiral α,β-unsaturated carbonyl compounds.[1,2] However, only a small degree of asymmetric induction has been obtained so far. We have now also studied the reactions of some related mixed chiral cuprates in conjugate addition to see if the arrangement at the chiral carbon in these ligands affects the stereodifferentiating ability of the cuprate towards enones. The 2-(*N*-methyl-2-pyrrolidinyl)-phenyl (*2*) and 2-(*N*-methyl-2-piperidinyl)phenyl (*3*) groups were chosen partly due to the similarity to nicotine. The bonding in the cyclic amines should lead to fairly static complexation within the cuprates prepared from cyclic amines *2* and *3* compared to the dynamic behaviour of compound *1* as ligand in lithium diorganocuprates.[3] A more rigid structure in the mixed, chiral cuprates could lead to an improved stereodifferentiation in the



R: methyl t-butyl
4 5



a M=H *b* M=Li *c* M=LiCuCH$_3$ *d* M=Cu

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addition reaction with prochiral α,β-unsaturated carbonyl compounds.

The parent amines (*1a*–*3a*) were prepared by standard methods. The absolute configuration of *N*-methyl-2-phenylpyrrolidine (*2a*) is known.[4] When we used tartaric acid for resolution we obtained almost three times higher specific rotation for (*S*)-(−)-*N*-methyl-2-phenylpyrrolidine than is reported for the product obtained by resolution with *O,O*-dibenzoyltartaric acid. We also could isolate (*R*)-(+)-*N*-methyl-2-phenylpyrrolidine with equal specific rotation, of opposite sign, by recrystallisation of the precipitate formed in the concentrated mother liquor of the first recrystallisation.

The *N*-methyl-2-phenylpiperidine (*3a*) was resolved in the same way with *O,O*-dibenzoyltartaric acid. The absolute configuration of (*R*)-(+)-*N*-methyl-2-phenylpiperidine was determined by methylation of (*R*)-(+)-2-phenylpiperidine.[5]

N,N-Dimethyl-1-phenylethylamine (*1a*) was prepared from commercial (*R*)- and (*S*)-1-phenylethylamine. A sample of *1a* was recrystallised as the picrate and the recovered amine gave a specific rotation somewhat higher than that reported previously. The amines (*1a*–*3a*) were lithiated with butyllithium and the lithium compounds (*1b*–*3b*) reacted with "halide-free" methylcopper to afford the mixed, chiral methylorganocuprates (*1c*–*3c*). (*E*)-4-Phenyl-3-buten-2-one (*4*) and (*E*)-2,2-dimethyl-5-phenyl-4-penten-3-one (*5*) were chosen as substrates. The reactions were conducted at −35 or 0 °C with molar ratio reagent "LiMeR*Cu": substrate 4:1. The results are summarised in Table 1 and show that while the chemical yields are high, inductions are low. Earlier[2] additions of cuprate *1c* to *4* are reported to give inductions of <0.1 %, while our result for the same cuprate/substrate is of the order of 1 %. The conditions differ in that we used "halide-free" methylcopper and that we added it to the lithiated amine. Further we used cuprate in excess and performed the reaction at lower temperature.

We have mainly used the ^{1}H NMR technique with a chiral europium salt[6] for the estimation of enantiomeric excess of the conjugate addition products. With 4-phenyl-2-pentanone the enantiomeric excess was calculated by integration of the two partly overlapping doublets from the conjugate-added methyl group. With this method, the measured values for this compound are, however, poor in precision and accuracy. With 5-phenyl-2,2-dimethyl-3-hexanone the enantiomeric excess was calculated by integration of the resolved singlets of the *t*-butyl group.

In the course of the conjugate addition a precipitate appeared which we assume to be the copper compounds *1d*–*3d*. After hydrolytic work-up, 80–85 % of the amines were recovered with unchanged rotation. The residue of basic material after distillation was found to consist of the corresponding biaryls from the starting amines. These were formed during the preparation of the cuprate reagents. The formation of two diastereomeric biaryls from *1a*, with one in excess, indicated that the starting amine *1a* was not optically pure.

Both the purity of copper(I) halide and the form

Table 1. 1,4-Addition of chiral lithium methylorganocuprates, LiMeR*Cu, to 4-phenyl-3-buten-2-one (*4*) and 5-phenyl-2,2-dimethyl-4-penten-3-one (*5*). R* = 2-(1-dimethylaminoethyl)phenyl (*1*), 2-(*N*-methyl-2-pyrrolidinyl)phenyl (*2*) or 2-(*N*-methyl-2-piperidinyl)phenyl (*3*). Reactions were run in ether-hexane to give 4-phenyl-2-pentanone and 5-phenyl-2,2-dimethyl-3-hexanone. The enantiomeric yield was measured from ^{1}H NMR, 270 MHz, with Eu(facam), and optical sign by correlation with optical rotation. The ratio "LiMeR*Cu": substrate was 4:1. Reaction time one hour.

Chiral ligand (R*) in cuprate	Substrate	Temp./ °C	Isolated 1,4-add. prod./%	E.e. Eu(facam)/ %(opt. sign.)	E.e. opt. rot./ %	$[\alpha]_D^{22}$/°	c/g ml^{-1} in benzene	Conf.[a]
(*S*)-(−)-*1*	*4*	−35	85	7 (+)	1.1	+0.83	0.05	*S*
(*S*)-(−)-*2*	*4*	−35	98	5 (+)	1.0	+0.78	0.07	*S*
(*S*)-(−)-*3*	*4*	−35	89	4 (−)				*R*
(*S*)-(−)-*1*	*5*	−35	82	3 (−)				
(*R*)-(+)-*2*	*5*	−35	80	1 (−)				
(*S*)-(−)-*3*	*5*	−35	91	1 (+)				
(*R*)-(+)-*1*	*5*	0	98	1 (+)		+0.28	0.16	

[a] According to the results in Refs. 13 and 14.

in which it is added to the organolithium compound can affect the product pattern in conjugate additions.[7] Disproportionation of the cuprate and formation of other organometallic species than those expected can compete with the mixed cuprate for the substrate or cause other types of reaction.

Impurities in copper(I) iodide might cause the following disproportionation:[7]

$$(LiMeR^*CuO)_2 \rightarrow 2\ Cu^\circ + R^* - R^* + 2\ MeLi.$$

The formation of dimeric amines and a black copper-containing precipitate supports this suggestion. With methyllithium produced during the preparation of the mixed cuprate, the continued addition of methylcopper to the solution of lithiated amine until obtainment of a negative Gilman test I[8] would lead to formation of lithium dimethylcuprate. This lithium dimethylcuprate would compete with the chiral mixed cuprate in the conjugate addition and thus have an adverse effect on the enantiomeric excess.

EXPERIMENTAL

All handling and reactions of organometallic reagents were carried out under dry, oxygen-free nitrogen. Diethyl ether was distilled from sodium benzophenone ketyl. Commercial butyllithium (Merck) in hexane and methyllithium (Fluka) in ether were used after titration.[9] Commercial copper(I) iodide (Fluka) was used. Reaction mixtures were hydrolysed with aqueous ammonia saturated with ammonium chloride. Products were generally distilled in a Büchi short path/Kugelrohr distillation apparatus.

N-*Methyl-2-phenylpyrrolidine.* A solution of *N*-methyl-2-pyrrolidone (0.5 mol) in ether (100 ml) was added slowly to phenyllithium (0.5 mol) in ether at 0 °C. The mixture was stirred for 1 h at room temperature and was then hydrolysed with water. The product was sensitive to air so the ether phase was evaporated under nitrogen. The residue was dissolved in ethanol (200 ml) and hydrogenated in a Parr apparatus at 350 kPa over 0.2 g platinum oxide. The product was distilled to give *N*-methyl-2-phenylpyrrolidine in 70 % yield, b.p. 74–76 °C/670 Pa, lit.[4] 82–84 °C/1.6 kPa.

Resolution of N-*methyl-2-phenylpyrrolidine.* (*R,R*)-(+)-Tartaric acid (0.35 mol) was added to racemic *N*-methyl-2-phenylpyrrolidine (0.35 mol) dissolved in ethanol (210 ml). The mixture was warmed, filtered, slowly cooled to 15 °C and seeded. The precipitate formed on cooling to 0 °C was filtered off, washed with cold ethanol (20 ml) and redissolved in ethanol (140 ml) by warming. At room temperature the solution was seeded with crystals from the previous crop. With slow cooling, crystals appeared which were filtered off at about 17 °C, washed, dissolved in ethanol (160 ml) and the procedure repeated. The isolated salt was treated with aqueous ammonia–ether. The ether phase was dried and evaporated and the amine distilled at 120 °C/100 Pa to give (*S*)-(−)-*N*-methyl-2-phenylpyrrolidine in 9% yield, $[\alpha]_D^{25} = -152.2°$ (neat), lit.[4] $[\alpha]_D^{20} = -53.65°$ (neat). GLC and NMR data were identical with those of the racemic amine.

The mother liquor from the first crystallisation was concentrated to half its volume and was cooled to 0 °C to give a precipitate. After fourfold application of the previous procedure followed by work-up, (*R*)-(+)-*N*-methyl-2-phenylpyrrolidine was obtained in 8.5 % yield, $[\alpha]_D^{25} = +156.5°$ (neat).

N-*Methyl-2-phenylpiperidine.* *N*-Methyl-2-phenylpiperidine was prepared from *N*-methyl-2-piperidone (0.21 mol) as described for *N*-methyl-2-phenylpyrrolidine to give *N*-methyl-2-phenyl-piperidine in 74 % yield, b.p. 85–87 °C/530 Pa, lit.[10] 52–54 °C/20 Pa.

Resolution of N-*methyl-2-phenylpiperidine.* (*R,R*)-(−)-*O,O*-Dibenzoyltartaric acid (66 mmol) was added to racemic *N*-methyl-2-phenylpiperidine (66 mmol) in ethanol (750 ml). The mixture was warmed, filtered and slowly cooled to room temperature. The precipitate was filtered off, washed and, redissolved in ethanol (500 ml) to give a new precipitate on cooling. The recovered precipitate was dissolved in ethanol (400 ml) and the isolated salt formed was decomposed with aqueous ammonia and ether. The ether extract was dried and evaporated and the amine was distilled at 140 °C/100 Pa to give (*S*)-(−)-*N*-methyl-2-phenylpiperidine in 14 % yield, $[\alpha]_D^{25} = -155.0°$ (neat). GLC and NMR data were identical with those of the racemic amine. The mother liquor from the first crystallisation was cooled to 0 °C. The precipitate formed was isolated and hydrolysed to give 6 g partially enriched (*R*)-(+)-*N*-methyl-2-phenylpiperidine, $[\alpha]_D^{25} = +82.7°$ (neat).

Partial resolution and methylation of 2-phenylpiperidine. (*R,R*)-(−)-*O,O*-Dibenzoyltartaric acid (25 mmol) was added to racemic 2-phenylpiperidine[5] (25 mmol) in ethanol (90 ml). The mixture was warmed, filtered and slowly cooled to 0 °C and seeded. Crystals formed slowly. They were filtered off and the salt was decomposed in aqueous ammonia and ether. The ether phase was dried, evaporated and the amine distilled at 120 °C/100 Pa to give (*R*)-(+)-2-phenylpiperidine[5] in 40 % yield, $[\alpha]_D^{20} = +31.8$ (neat), lit. $[\alpha]_D = +35.3$ (neat).

(*R*)-(+)-2-Phenylpiperidine (6.1 mmol) was dissolved in formic acid (6 ml) with cooling. Aqueous formaldehyde (13 mmol) was added and the mixture

was boiled for 18 h. Then concentrated hydrochloric acid (10 mmol) was added and excess formic acid and formaldehyde evaporated. The residue was dissolved in water, made alkaline with ammonia and the solution extracted with ether. The ether phase was dried, evaporated and the residue distilled at 130 °C/100 Pa to give (*R*)-(+)-*N*-methyl-2-phenylpiperidine in 94 % yield, $[\alpha]_D^{20} = +61.9$ (neat).

N,N-*Dimethyl-1-phenylethylamine.* *N,N*-Dimethyl-1-phenylethylamine, (*R*) and (*S*), were prepared from (*R*)- and (*S*)-1-phenylethylamine, respectively.[11] A sample of (*R*)-(+)-*N,N*-dimethyl-1-phenylethylamine, 2.8 g, $[\alpha]_D^{25} = +68.25°$ (neat), in ethanol (175 ml) was mixed with saturated picric acid in methanol (40 ml) with warming. On cooling, crystals formed. Filtration and washing with ethanol gave yellow needles (4.95 g), m.p. 140–142 °C. Hydrolysis with aqueous ammonia and then 1 M NaOH and work-up gave (*R*)-(+)-*N,N*-dimethyl-1-phenylethylamine (1.6 g), $[\alpha]_D^{25} = +73.1°$ (neat), lit.[12] $[\alpha]_D^{25} = -67°$ (neat).

Preparation of lithium methylorganocuprates. The following procedure was used for the preparation of chiral mixed cuprates, starting from *N,N*-dimethyl-1-phenylethylamine, *N*-methyl-2-phenylpyrrolidine or *N*-methyl-2-phenylpiperidine. Amine (10 mmol) and butyllithium (10 mmol) were stirred in ether (25 ml) for at least three days until Gilman test II[8] was negative. Methylcopper was prepared by addition of methyllithium (11 mmol) to a stirred suspension of copper(I) iodide (11 mmol) in ether (6 ml) at −5°C. The mixture was stirred for one hour and was then centrifuged and the ether phase removed. The solid was washed twice with ether and was then suspended in ether and added *via* syringe to the solution of lithiated amine at 0 °C. When the last of the methylcopper was added the colour of the mixture always turned from yellow to dark. The solution was green and contained fine black particles. Gilman test I was negative. The mixture was used directly. A sample for GLC always showed the formation of a heavy basic compound, 15–20 %, which we found to be the biaryls of the amines.

Conjugate addition to enones. The following procedure was used for the reaction of cuprates with 4-phenyl-3-buten-2-one or 5-phenyl-1,1-dimethyl-4-penten-3-one (Table 1): A solution of 2 mmol of the enone in 2 ml ether was added to the cuprate reagent. The reaction mixture was hydrolysed after one hour. The ether phase was extracted three times with 2 M hydrochloric acid, washed with water, dried and evaporated. The residue was distilled at 120–140 °C/100 Pa. Purity was checked by GLC and NMR and the yield was determined by weight.

The combined aqueous solutions were made basic with ammonia and extracted with ether. After washing the ether with water, drying and evaporation, the residue was distilled at 120–140 °C/130 Pa. The amine was recovered to 80–85 % in all cases leaving a heavy residue that mainly contained the symmetrical biphenyl derivative of the starting amine. The residue distilled at 200–240 °C/20 Pa.

4-Phenylpentan-2-one. IR 1715 cm^{-1}, ^1H NMR (270 MHz, $CDCl_3$): δ 7.32–7.12 (5 H, m), 3.28 (1 H, m, *J* 7 Hz), 2.8–2.58 (2 H, m), 2.05 (3 H, s), 1.27 (3 H, d, *J* 7 Hz). Lit.[13] $[\alpha]_D = -74.5°$. Enantiomeric yield was determined by optical rotation or by integration of the doublets of the conjugate-added methyl group which resolved on mixing 15 mg ketone and 14 mg tris[3-trifluoroacetyl-*d*-camphorato]europium(III), Eu(facam)$_3$, in 1 ml CCl_4: benzene-d_6 (1:1).

2,2-Dimethyl-5-phenylhexan-3-one. IR 1710 cm^{-1}, ^1H NMR (270 MHz, $CDCl_3$): δ 7.28–7.2 (5 H, m), 3.35 (1 H, q, *J* 7.0 Hz), 2.75–2.7 (2 H, m), 1.22 (3 H, d, *J* 7.0 Hz), 1.05 (9 H, s). MS (70 eV): *m/e* 204 (M^+, 15), 105 (100). Enantiomeric yield was determined by integration of the singlets of the *t*-butyl group which resolved on mixing 15 mg ketone and 11 mg Eu(facam)$_3$ in 1 ml CCl_4: benzene-d_6 (1:1).

(*R,R*)-(+)-*2,2′-Bis(1*-N,N-*dimethylaminoethyl)biphenyl.* ^1H NMR (270 MHz, $CDCl_3$): δ 7.7–7.0 (8 H, m), 3.03 (2 H, q, *J* 6.7 Hz), 2.08 (12 H, s), 1.29 (6 H, d, *J* 6.7 Hz). MS (70 eV): *m/e* 296 (M^+). $[\alpha]_D^{21} = +123.4°$ (*c* 0.12, CH_2Cl_2).

(*R,R*)-(+)-*2,2′-Bis(*N-*methyl-2-pyrrolidinyl)biphenyl.* ^1H NMR (270 MHz, $CDCl_3$): δ 7.75–7.0 (8 H, m), 3.16 (1 H, t, *J* 8 Hz), 2.86 (1 H, t, *J* 8 Hz), 2.15 (6 H, s), 2.11–1.6 (10 H, m). MS (70 eV): *m/e* 320 (M^+, 4), 234 (100). M.p. 103–106 °C. $[\alpha]_D^{22} = 301.5°$ (*c* 0.31, CH_2Cl_2).

(*S,S*)-*2,2′-Bis(*N-*methyl-2-piperidinyl)biphenyl.* MS (50 eV): *m/e* 348 (M^+, 70), 333 (65), 276 (65), 248 (100), 98 (60).

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REFERENCES

1. Gustafsson, B., Nilsson, M. and Ullenius, C. *Acta Chem. Scand. B 31* (1977) 667.
2. Hansson, A.-T., Rahman, M. T. and Ullenius, C. *Acta Chem. Scand. B 32* (1978) 483.
3. van Koten, G. and Noltes, J. G. *J. Am. Chem. Soc. 101* (1979) 6593.
4. Cervinka, O., Fabryova, A. and Strejcek, F. *Collect. Czech. Chem. Commun. 40* (1975) 3183.

5. Vetuschi, C., Ottolino, A. and Tortorella, V. *Gazz. Chim. Ital. 105* (1975) 935.
6. Sievers, R. E. and Kime, K. A. *Aldrichimica Acta 10(4)* (1977) 54.
7. House, H. O. and Wilkins, J. M. *J. Org. Chem. 43* (1978) 2443.
8. Houben–Weyl, *Methoden der Organischen Chemie*, Thieme, Stuttgart 1970, XIII/1, p. 22.
9. Watson, S. C. and Eastham, J. F. *J. Organomet. Chem. 9* (1967) 165.
10. Bestmann, H. J. and Ruppert, D. *Chem. Ztg. 96* (1972) 411.
11. Cope, A. C., Ciganek, E., Fleckenstein, L. J. and Meisinger, M. A. P. *J. Am. Chem. Soc. 82* (1960) 4651.
12. Craig, J. C., Chan, R. P. K. and Roy, S. K. *Tetrahedron 23* (1967) 3573.
13. Cookson, R. C. and Kemp, J. E. *Chem. Commun.* (1971) 385.
14. Weidler, A.-M. and Bergson, G. *Acta Chem. Scand. 18* (1964) 1483.

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