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CONJUGATE ADDITION OF CHIRAL LITHIUM METHYL[*o*(CYCLOHEXYLDIMETHYLAMINOMETHYL)PHENYL]CUPRATE TO METHYL 3-PHENYL-2-PROPENOATE AND 4-PHENYL-3-BUTEN-2-ONE

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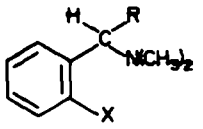
Abstract—Chiral lithium methyl[*o*-(cyclohexyldimethylaminomethyl)phenyl]cuprate reacts with methyl 3-phenyl-2-propenoate and 4-phenyl-3-buten-2-one to give the conjugate addition products, viz. methyl 3-phenylbutanoate and 4-phenylpentan-2-one respectively. The reaction rates and chemical yields (30–60%) are lower than in corresponding reactions with lithium dimethylcuprate and lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate respectively. Lithium halides in the reaction favour the formation of one enantiomer. The highest asymmetric induction obtained is 4.4%.

Due to their specificity as nucleophilic reagents, lithium organocuprates, LiR_2Cu, are widely used for C–C bond formations, e.g. in conjugate addition to α,β-unsaturated carbonyl compounds[1,2] and in displacements with inversion at sp^3-hybridized C atoms.[3–5] Mixed cuprates, LiRR'Cu, have been used in order to utilize valuable R groups more economically.[6] It could be possible to create chiral surroundings for the conjugate addition with a chiral, nontransferable ligand, R*, in the cuprate.

Reaction between mixed cuprates, LiRR*Cu (R = Me, Ph, and Bu; R* = (±)-*o*-(1-dimethylaminoethyl)phenyl (R*H; Fig. 1a)), and α,β-unsaturated carbonyl compounds, give the conjugate addition product almost quantitatively.[7] With the chiral nonracemic ligand R*, some optical activity has been observed in the 1,4-adduct.[8,9] The ligand R* precipitates as the corresponding copper compound, R*Cu.

One of the critical points in this approach to asymmetric synthesis should be the composition of the reagent and thus the presence and role of the chiral ligand in the transition state. This could be compared with the reaction of an organometallic reagent with a chiral substrate, e.g. an α,β-unsaturated ester of an optically active alcohol. The asymmetric induction can be fairly high in such cases.[10,11]

Copper has been suggested to act as a nucleophile in several reactions of lithium diorganocuprates.[5,12] A one-electron transfer has also been proposed as the initial step for the conjugate addition,[13] but free radicals have



1a: R = CH_3, X = H
1b: R = *c*-C_6H_{11}, X = H
1c: R = *c*-C_6H_{11}, X = Br

Fig. 1.

not been detected. Such mechaniams should not exclude the possibility of obtaining asymmetric induction.

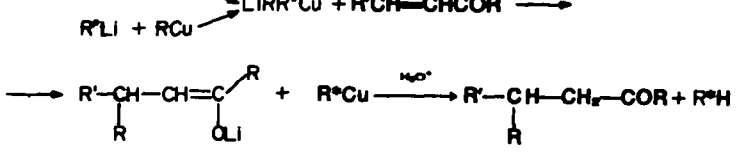
The organocuprates may be involved in different equilibria, including disproportionation,[3] association with lithium halides,[6] or aggregation to clusters.[14]

The amino group in organometallic 2-(dimethylaminomethyl)phenyl reagents makes the reagent more stable[15] and also reduces the freedom of rotation within the reagent.

It was considered appropriate to use a more bulky amino ligand in the reagent, in order to investigate the possibilities of obtaining asymmetric induction and also to study the composition of the reacting reagent. The 2-(dimethylaminocyclohexylmethyl)phenyl group R* was chosen for this investigation (R*X; Fig. 1b).

The conjugate additions studied were the Me addition to methyl 3-phenyl-2-propenoate (Fig. 2a) and 4-phenyl-3-buten-2-one (Fig. 2b).

(−)-*R*-3-Phenylbutanoic acid $[\alpha]_D = -60.0°$[16] has been correlated to (−)-*R*-4-phenylpentan-2-one $[\alpha]_D = -74.5°$ *via* the (−)-*R*-methyl ester $[\alpha]_D = -44.3°$.[17]



Scheme 1.

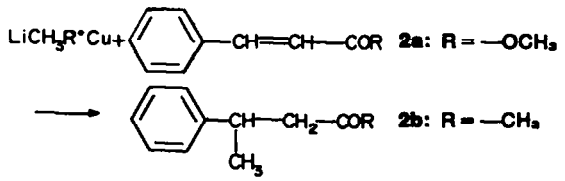


Fig. 2.

RESULTS

N-(Cyclohexylphenylmethyl) N,N-dimethylamine (Fig. 1b) was prepared and treated with BuLi.[18] The lithiation was not complete even after one week. Therefore *o*-bromo N-(cyclohexylphenylmethyl) N,N-dimethylamine, was synthesized (Fig. 1c) and lithiated with BuLi[18] or with t-BuLi. A second equivalent of t-BuLi reacts with the bromoalkane formed to produce LiBr.[19]

The lithiated amine added to carefully prepared methylcopper (e.g. free from CuI) rapidly gave a homogeneous solution. The lithiated amine itself adds instantly to methyl 3-phenyl-2-propenoate, while the mixed reagent reacts slowly to give the methyl 1,4-adducts with methyl 3-phenyl-2-propenoate and 4-phenyl-3-buten-2-one. The chemical yields are lower and the reactions are slower when the cyclohexyl-substituted amine is used instead of the Me-substituted amine (Table 1).[7,9]

The colour of the reagent solution varied with the method of preparation. In exp. 1 (Table 1) a greenish-grey reagent was obtained, while the reagent in exp. 2 was brown. After addition of a substrate to a reagent rich in LiX the solution turned yellow but remained homogeneous. When less LiX was present a green precipitate was formed at the end of the reaction.

It has been observed that lithium halides enhance the rate of a 1,4-addition.[8] Such an effect could not be observed in the reactions studied in this work. The amounts of by-products increased in the reactions at low concentration of LiX.

When methyl 3-phenyl-2-propenoate was treated with the chiral cuprate prepared from lithium[*o*-(cyclohexyldimethylaminomethyl)phenyl] and methylcopper the specific rotation of the 1,4-adduct, methyl 3-phenylbutanoate, was 0.6° (1.4% e.e.). With 4-phenyl-3-buten-2-one as the substrate, the highest specific rotation of the 1,4-adduct, 4-phenylpentan-2-one, was −3.3° (4.4% e.e.) obtained with a cuprate prepared from an excess of halide-free methylcopper.[20]

DISCUSSION

It is obvious that a cuprate is formed from methylcopper and lithium[*o*-(cyclohexyldimethylaminomethyl)-phenyl]. The large ligand in the cuprate decreases the reactivity compared with lithium dimethylcuprate and lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate. This strongly suggests that the ligand participates in the rate-determining step. Moreover, the enhanced asymmetric induction suggests that the bulky ligand takes part in the transition state giving the 1,4-adduct. These observations support the hypothesis that the reacting species is a mixed cuprate.

In both reactions studied, a reagent containing less lithium halides seems to enhance the formation of the (−)-*R*-enantiomer. This suggests that lithium halides participate in the cuprate complexes. The formation of a LiRXCu cuprate, totally free from R*Li, is not probable

Table 1. 1,4-Addition of chiral lithium methyl[*o*-(cyclohexyldimethylaminomethyl)phenyl]cuprate to methyl 3-phenyl-2-propenoate (a) at 0° and 4-phenyl-3-buten-2-one (b) at −30°. The cuprate was used in 10% molar excess. Two equivalents of t-BuLi (exps. 1 and 3) gave one equivalent of ArLi and one of LiBr

Exp. nr	Substrate	1,4-Add. prod.	Lithiating agent	MeLi quality	Reaction time min	GLC yield %	Isol. yield %	$[\alpha]_{578}^{18}$ and conc. (c, C_6H_6)	Optical yield %	Absol. conf.
1	a	d	t-BuLi	MeLi (LiBr)	60	45	31	+0.6 (0.010)	1.4	S
2	a	d	BuLi	commercial	60	30	20	+0.3 (0.021)	0.7	S
3	b	e	t-BuLi	MeLi (LiBr)	20	60	41	−1.1 (0.036)	1.5	R
4	b	e	BuLi	MeLi (LiBr)	30	55	24	−2.6 (0.011)	3.5	R
5	b	e	BuLi	commercial[f]	15	50	21	−3.3 (0.018)	4.4	R

d = Methyl 3-phenylbutanoate; e = 4-phenylpentan-2-one. [f]The methylcopper was purified prior to use, in order to remove lithium halides, and used in excess.

since this would generate a free or complexed lithium compound; $(LiRR^*Cu)_n + LiX \rightleftharpoons LiRXCu + R^*Li(LiRR^*Cu)_{n-1}$. This situation can be compared with the one in which more than one equivalent of RLi is added to RCu causing a 1,2-addition, when the conjugate addition is slow.[21]

The fact that the chiral cuprate gives more of the (−)-*R*-enantiomer when it reacts with 4-phenyl-3-buten-2-one and more of the (+)-*S*-enantiomer when it reacts with methyl 3-phenyl-2-propenoate seems interesting. Comparison with earlier results[9] shows that the enantiomeric excess of methyl 3-phenylbutanoate is less than expected. This, together with the observed "salt effect", suggests that more than one directing tendency is operative when the chiral cuprate reacts with methyl 3-phenyl-2-propenoate. These competing tendencies could be expected to be more general and also to be additive in other systems.

Further experiments are under way to study the possibilities of obtaining a higher asymmetric induction.

EXPERIMENTAL

Reactions were performed and products analysed as described earlier.[7-9] MeLi was synthesized from bromomethane (Merck) and Li (Merck) in diethyl ether. BuLi (Merck) and t-BuLi (Fluka) were commercially supplied. The commercial MeLi was supplied by Merck. The strength of the reagents was determined prior to use.

N-(Cyclohexylphenylmethyl)-N,N-dimethylamine. Cyclohexylphenylmethylamine[22] (20 g) was dimethylated according to the method described for 1-phenylethylamine.[23] The crude amine was eluted from a column containing 1 kg of alumina (active neutral) with light petroleum containing 15% diethyl ether, yield 9.5 g (41%) b.p. 85°/13 Pa. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.35–7.10 (5 H, m), 3.00 (1 H, d, J 8.2 Hz), 2.10 (6 H, s); 2.0–0.8 (11 H, m). Abs. mass 217.183.

Lithiation of N-(cyclohexylphenylmethyl)-N,N-dimethylamine. The amine (10 mmol) was mixed with BuLi (10 mmol) in ether (10 ml), but only small amounts of lithiated amine were detected even when the reaction time was extended to 1 week. After addition of chlorotrimethylsilane,[7] less than 10% silylated product could be detected (GLC, OV-17). The IR peak at 2233 cm^{-1} (C-D) after deuteriolysis varied from very small to undetectable. Abs. mass 218.193.

(2-Bromophenyl)cyclohexylmethylamine. 2-Bromobenzoic acid (0.5 mol) (Fluka, pract.) was treated with $SOCl_2$ (2 mol) and pyridine (*ca.* 0.5 ml). After 4 hr the mixture was warmed to 50–60° and kept overnight. The excess of $SOCl_2$ was evaporated and dry toluene (50 ml) was added and thoroughly evaporated. The acid chloride was used without further purification.

At the same time, cyclohexylmagnesium bromide (0.6 mol) in ether was prepared. The Grignard reagent, cooled to −70°, was then slowly added to the 2-bromobenzoyl chloride in ether (400 ml) at *ca.* −50°, with the aid of glass tubing and N_2-pressure. The addition of the Grignard reagent was stopped when no more acid chloride could be detected (GLC). After usual work-up and concentration, the product (126 g) was reacted with $HCOONH_4$[24] (2.5 mol) at 180° for 23 hr. After 8 hr, excess water was removed under vacuum to maintain the temp at 180°. After 23 hr only 1–2% of unreacted ketone could be detected (GLC). Work-up[24] resulted in 49.1 g (36.6%) of (2-bromophenyl)cyclohexylmethylamine b.p. 101°/13 Pa. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.50 (1H, dd), 7.41 (1H, dd), 7.30 (1H, ddd), 7.06 (1H, ddd), 4.13 (1H, d, J 7.2 Hz), 2.0–0.8 (11 H, m). MS (IP 65 eV): m/e = 267.055 (M^+, 0.4%); 226 (16%); 224 (17%); 186 (97%); 184 (100%).

Resolution of (2-bromophenyl)cyclohexylmethylamine. (+)-Tartaric acid (14.4 g) was dissolved in dry acetone (400 ml) by heating. The amine (25.2 g) was added and the ppt was dissolved by addition of MeOH (85 ml). After standing in the refrigerator for 24 hr, the mother liquor was decanted from the crystals. The crystals were dissolved in a hot mixture of acetone (400 ml) and MeOH (30 ml) and left in the cold for 24 hr. This salt was recrystallised three times from acetone. The salt was then treated with ammonia and the free amine extracted with ether, dried and concentrated. In this way 2.5 g of the amine were obtained $[\alpha]_{578}^{25} = -30.8°$ c 0.068 ($CHCl_3$). A fraction showing $[\alpha]_{578}^{25} = -27.9°$ c 0.081 was *ca.* 88% optically pure as determined by NMR analysis using the chiral shift reagent europium(III)tris(3-trifluoromethylhydroxymethylene)-d-camphor (Ciba–Geigy).

(+)-o-Bromo-N-(cyclohexylphenylmethyl)-N,N-dimethylamine. (−)-(*o*-Bromophenyl)cyclohexylmethylamine (2.5 g) was dimethylated[23] and purified by distillation, yield 2.1 g (76%) b.p. 101°/13 Pa. $[\alpha]_{578}^{25} = +33.6°$ c 0.053 ($CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.5–7.0 (4H, m), 3.92 (1H, d, J 9.2 Hz), 2.15 (6 H, s), 2.5–0.8 (11 H, m). MS (IP 65 eV): m/e = 295.092 (M^+, 0.4%); 214 (93%); 212 (100%).

General procedure for the conjugate additions. Methylcopper was carefully prepared from copper(I)iodide (4.0 mmol) and MeLi (4.0 mmol) in ether in 0.5 hr at 0°. In exp. 5, the methylcopper was prepared from 10 mmol of reagents and used in undetermined excess after removal of lithium halides by twice centrifuging the methylcopper and removing the supernatant liquid. *o*-Bromo-N-(cyclohexylphenylmethyl)-N,N-dimethylamine (4.0 mmol) was lithiated with either BuLi (4.0 mmol) or t-BuLi (8.0 mmol) at −78° in ether. The soln was allowed to reach room temp. and the lithiated amine was transferred to the MeCu slurry, which immediately dissolved. The reagent was then stirred for 1 hr at 0°. With 4-phenyl-3-buten-2-one as the substrate, the reagent was cooled to −35° before the addition of the substrate (3.6 mmol) in ether. Methyl 3-phenyl-2-propenoate (3.6 mmol) was added at 0°. The reactions were followed by GLC and worked up when the substrate had been consumed. The 1,4-addition products were isolated by distillation after the basic components had been removed by extraction with 0.2 M HCl. The yields and conditions are summarised in Table 1.

Products. The 1,4-adducts, methyl 3-phenylbutanoate and 4-phenylpentan-2-one, had spectral data identical with those of authentic samples.

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