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STEREOSELECTIVITY IN THE TRANSFER OF THE 2-(1-DIMETHYLAMINOETHYL)PHENYL GROUP, R^*, FROM LiR^*_2Cu AND $Li(R^*)(2\text{-THIENYL})Cu$ TO ENONES

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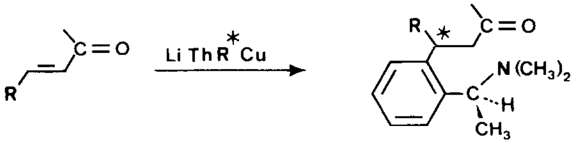
Summary: One diastereomer is formed in large excess (98 - 76 % diastereomeric excess) on addition of the 2-(1-dimethylaminoethyl)phenyl group, R^*, to 3-penten-2-one, 2-cyclohexenone, 4-phenyl-3-buten-2-one, and 5-phenyl-2,2-dimethyl-4-penten-3-one.

Much work is presently devoted to the search for reactions forming carbon-carbon bonds and giving chiral products of high enantiomeric purity.[1] Promising results have been obtained in diastereoselective additions of organocopper reagents to chiral unsaturated esters.[2,3]

Enantioselective conjugate addition using chiral cuprates is an attractive approach to chiral 1,4-addition products and several attempts have been published.[4] In earlier work[4d,j] we tried the R and S-2-(1-dimethylaminoethyl)phenyl group R^* as chiral ligand in mixed cuprates transferring methyl, butyl or phenyl groups to prochiral enones to give the corresponding conjugate addition products in high chemical yields but in rather low enantiomeric excess (<5%). Higher e.e. is achieved on transfer of a 2-pyridyl group (23%) using the same chiral ligand, R^*.[5]

Addition of cuprates to chiral enones is highly sensitive towards remote control of stereochemistry. For example axial attack by cuprates on cyclic enones is sensitive to substituents on the ring and this leads to high preference for attack on one face of the ring, giving essentially one diastereomer.[6]

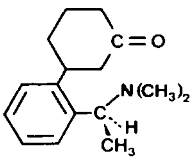
In this work we demonstrate the diastereodifferentiating effect of the chiral group R* on addition to prochiral enones. The chiral, enantiomerically pure lithium bis[2-(1-dimethylaminoethyl)phenyl] cuprate, LiR$^*_2$Cu,[7] and lithium[2-(1-dimethylaminoethyl)phenyl](2-thienyl)cuprate, LiR*ThCu, have been added to 2-cyclohexenone (1), 3-penten-2-one (2), 4-phenyl-3-penten-2-one (3), and 5-phenyl-2,2-dimethyl-4-penten-3-one (4).



The additions gave the conjugate addition products from transfer of the R* group with high diastereoselectivity and in good to high chemical yields, see Table. The diastereomeric excess was determined both by GC on 50 m Carbowax 20 M quartz capillary column and by ^{1}H-NMR spectroscopy (270 MHz). In the Table d.e. $\geqslant$98 % indicates that only one diastereomer was observed, at lower d.e. both diastereomers were observed both by ^{1}H-NMR spectroscopy and by GC.

Table. Diastereomeric excess (d.e.) and isolated yields from conjugate additions of LiR$^*_2$Cu and LiR*ThCu to enones 1 - 4 in ether at 0 °C, giving 3-[2-(1-dimethylaminoethyl)]phenylcyclohexanone (5), 4-[2-(1-dimethylaminoethyl)]phenyl-2-pentanone (6), 4-[2-(1-dimethylaminoethyl)]phenyl-4-phenyl-2-butanone (7) and 5-[2-(1-dimethylaminoethyl)]phenyl-5-phenyl-2,2-dimethyl-3-pentanone (8), respectively. Substrate:reagent ratio, 1:1.2.

	1 2-Cyclo- hexenone	2 E-3-Penten-2-one	3 E-4-Phenyl-3- penten-2-one	4 E-5-Phenyl-2,2-dimethyl-4-penten-3-one
LiR$^*_2$Cu				
D.e., %	$\geqslant$98	80	$\geqslant$98	76
Yield, %	87	30	50	67
LiR*ThCu				
D.e., %	$\geqslant$98	82	$\geqslant$98	$\geqslant$98
Yield, %	57	70	44	42



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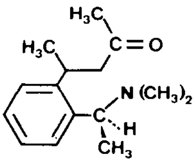

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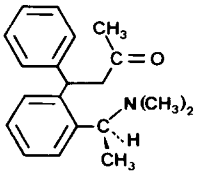

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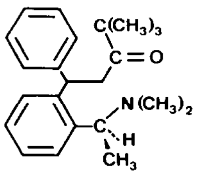

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The diastereomers are typically obtained in a 99:1 ratio indicating a very high enantioface differentiation in the addition. When $R^{*}Li$ was used in a control experiment for the transfer of the R^{*} group to enone 4 a mixture of 1,2- and 1,4-addition products was obtained. The 1,4-addition adduct was a diastereomeric mixture, ratio 3:97, with the opposite diastereomer dominating compared to the addition of $LiR^{*}_{2}Cu$ or $LiR^{*}ThCu$. Enones 1, 2, and 3 reacted with $R^{*}Li$ to give the 1,2-addition products only. The isolation of the other diastereomer in the addition of $R^{*}Li$ made verification of NMR and GC data for the $LiR^{*}_{2}Cu$ and $LiR^{*}ThCu$ additions possible.

It should be noted that $LiR^{*}ThCu$ transfers the R^{*} group and retains the thienyl group bonded to copper. The thienyl group could probably be utilized in other mixed cuprates also. As shown in the Table the mixed $LiR^{*}ThCu$ also shows a higher degree of enantioface differentiation in the transfer of the R^{*} group to enone 4. The chemical yields are somewhat lower. However, the R^{*} group is better utilized in the mixed cuprate and no biaryl R^{*}-R^{*} is formed in its preparation as is the case with $LiR^{*}_{2}Cu$. This also simplifies the work up.

The high stereoselectivity obtained in this work indicates that it should be possible to obtain enantioselectivity in 1,4-additions also of achiral R groups from chiral, mixed cuprates to prochiral enones. When the configurations of the addition products have been determined we hope to provide a more detailed interpretation of the stereoselectivity of the reaction.

General procedure, $LiR^{*}ThCu$: 2-Thienyllithium (5 mmol), from thiophene (6 mmol) and butyllithium (5 mmol) in ether at r.t. (10 ml, 40 min), was slowly added to an ether slurry of powdered copper(I) iodide (10 ml, 5 mmol).[8] Optically pure S-$R^{*}Li$, prepared from S-(-)-$R^{*}H$ and butyllithium (ether, r.t., three days)[8] was added to the yellowish slurry of 2-thienylcopper at r.t. (about 5 min), until Gilman test I was positive.[9] The dark solution was cooled to 0 °C and the substrate was added. The reaction was complete within 15 min (GC sampling). The mixture was hydrolysed with aqueous ammonium chloride. After work up, including acid extraction, the residue was distilled on a short path/Kuglrohr distillation apparatus.

$LiR^{*}_{2}Cu$: $R^{*}Li$ was added dropwise to an ether slurry of powdered copper(I) iodide (10 ml, 5 mmol) at 0 °C (about 5 min) till Gilman test I was positive. Following the procedure above, the distilled product mixture was flash chromatographed (silica, 0.8 M triethylamine in petr. ether). Structures were checked by 270 MHz ^{1}H-NMR spectroscopy and high-resolution MS (peak matching).

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