Short Communications

Reaction of Chiral Lithium Hetero(butyl)cuprates with 2-Cyclohexenone and 4-Phenyl-3-buten-2-one

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In previous papers we have described reactions of mixed, chiral homocuprates, LiR*Cu, with $\alpha,\beta$-unsaturated carbonyl substrates.\textsuperscript{1−3} Some asymmetric induction has been observed in the 1,4-adducts, supporting the hypothesis that the chiral ligand, R*, in a mixed cuprate participates in the transition state of the addition reaction.

It has been shown that mixed heterocuprates, LiHet(R)Cu, are valuable reagents for conjugate additions (Het = R'O or R'S).\textsuperscript{4} In the present investigation some chiral heterocuprates have been used to obtain asymmetric induction in conjugate additions (Reaction 1).

\[
\text{LiR'O(Bu)Cu + R'' - CH = CH - CO - R''} \rightarrow \text{R'' - CH(Bu) - CH$_2$ - CO - R''}
\] (1)

The alcoholates and thiolates, respectively, of \((-\text{-}2\)-butanol 1, \((-\text{-}2\text{-})\text{-}2\text{-methylbutanol 2, \((-\text{-})\text{-}N\text{-}methylprolinol 3, \((-\text{-})\text{-}menthol 4, \text{(+\text{-})neomethylthiol 5, \((-\text{-})\text{-}cyclohexylbenzenemethanethiol 7 were chosen as chiral ligands R'O and R'S. The heterocuprates Li(Het)BuCu were prepared by reacting butyl lithium with the corresponding copper(I) alcoholate or thiolate, prepared from the lithium alcoholate and copper(I) iodide. 2-Cyclohexenone and 4-phenyl-3-buten-2-one were used as substrates.}

In the reaction of lithium hetero(butyl)cuprate (in a small excess) with 2-cyclohexenone, the formation of the conjugate addition product, 3-butyl-cyclohexanone, is fast and almost quantitative, compare Table 1. The enantiomeric excess (e.e.) varies between 0 and 15\%, with the best result obtained with 3 as the chiral ligand. Attempts to determine the e.e. by NMR spectroscopy using chiral shift reagents failed.

When 5-methyl-2-cyclohexenone was treated with lithium menthoxycuprate, a small kinetic resolution was observed. Analysis of the excess substrate showed $\left[\alpha\right]_{578}^{25} + 6.6^o$ (c 0.067, CHCl$_3$, 7\% e.e.).\textsuperscript{5} The reaction product, 3-butyl-5-methyl-cyclohexanone, showed $\left[\alpha\right]_{578}^{25} - 5^o$ (c 0.019, CHCl$_3$), and the NMR spectrum (270 MHz) indicated only

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Isol. yield %</th>
<th>$\left[\alpha\right]_{578}^{25}$</th>
<th>c, CHCl$_3$</th>
<th>e.e. %</th>
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<tr>
<td>5</td>
<td>THF</td>
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<td>THF</td>
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<td>0</td>
<td>0.026</td>
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Table 1. Addition of chiral LiHet(Bu)Cu to 2-cyclohexenone (10 mmol) at - 70 °C for 15 min. Molar ratio: 1:15. GLC yield of 3-butylcyclohexanone ca. 90 %.

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Table 2. Reaction of chiral LiHet(Bu)Cu with 4-phenyl-3-buten-2-one at \(-20\) to \(0\) °C with formation of 4-phenyloctan-2-one and dimer 8.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Reaction time min</th>
<th>Yield of 4-phenyloctan-2-one/% GLC</th>
<th>[(\alpha)](_{578})</th>
<th>GLC yield of 8/%</th>
<th>Molar ratio</th>
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<td>33</td>
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</table>

one diastereomer, probably the \(trans\)-substituted cyclohexanone.\(^6\)

Attempts to react 2-cyclohexenone with LiHet-(Me)Cu or LiHet(Pb)Cu, in which the chiral ligands 4 or 5 were used, resulted only in the formation of less volatile products.

The reactions of lithium hetero(1-butyl)cuprates with 4-phenyl-3-buten-2-one were very sensitive to the size of the chiral ligand and to the choice of solvent. The results are summarized in Table 2. The expected product, 4-phenyloctan-2-one, was formed in competition with a dimer, 4-acetyl-3,5-diphenylcyclohexanone, 8, of 4-phenyl-3-buten-2-one. The same dimer 8 was obtained upon treatment of 4-phenyl-3-buten-2-one with lithium triphenylmethoxide or with lithium heterocuprates prepared from methyl- or phenylnithium with 4 or 6 as ligands and is probably formed \(\textit{via}\) two Michael additions of enolate ions.\(^7,8\)

![Diagram](image)

Our results show that there are narrow limits to the synthetic utility of heterocuprates. The addition of a methyl group seems to be very sensitive to the reaction conditions. Crabbé \textit{et al.}\(^9\) have reported the transfer of methyl from other LiHet(Me)Cu reagents, while Posner \textit{et al.}\(^4\) have reported the failure to transfer methyl from Li(t-BuO)MeCu to 2-cyclohexenone. Alkyl groups other than the methyl group can successfully be transferred to highly reactive enones like 2-cyclohexenone.

The asymmetric inductions obtained in this investigation are two to three times higher than those obtained previously by us with chiral mixed homocuprates.\(^1-3\) Crabbé \textit{et al.}\(^9\) have reported the formation of 3-butylicyclohexanone with [\(\alpha\)]\(_D\) +0.8.\(^10\) It is interesting to note that the small chiral ligand 1 induces optical activity of the same magnitude as the very bulky ligand 6, which was synthesised especially to study the effect of the size of the chiral ligand. The high e.e. obtained with neomethylthiol 5 as ligand was thought to be partly due to the chelating effect of the sulfur atom. This hypothesis seems, however, less likely when the observed low optical induction obtained with 7 as the chiral ligand is taken into account.

Our results show that asymmetric induction is possible in reactions with chiral cuprates and that by variation of the conditions the enantiomeric excess can be increased.

\textit{Experimental.} The chiral ligands \((\textit{--})-N\text{-methylprolinol 3}, b.p. 52 °C/0.2 kPa,\(^11,12\) \((\textit{+})\text{-neomethylthiol 5,}\(^13\) \((\textit{--})\text{-cyclohexylbenzenemethanol 6,}\(^14,15\) and \((\textit{+})\text{-cyclohexylbenzenethanol 7}\(^14\) were synthesised using standard procedures. The crude thiol 7 was separated from by-products by partitioning between cyclohexane and 4 M NaOCH\(_3\) in methanol. The methanol solution was acidified, extracted with cyclohexane and dried. Distillation afforded pure thiol 7, 61 \% b.p. 90 °C/13 Pa, [\(\alpha\)]\(_{2.58}\) +29.4° (c 0.053, ether).

Preparation of the cuprates and their reactions with \(\alpha,\beta\)-unsaturated substrates were performed as described previously.\(^1-4\)

3-Butylcyclohexanone was resolved\(^16\) and its optical rotation measured after each of four recrystallisations: (yield \%, [\(\alpha\)]\(_{2.58}\) 1: 49 \%, 14°; 2: 45 \%, 17.6°; 3: 41 \%, 19.2°; 4: 48 \%, 19.3°.

\textit{Isolation of products.} The conjugate addition products 3-butylicyclohexanone and 4-phenyloctan-2-one were isolated by distillation and their NMR and IR spectra compared with those of authentic materials. When 1 and 2 were used as ligands, the crude reaction product was distilled through a short column, while ligand 3 was removed prior to distillation by extraction with 2 M HCl. When 4, 5, 6 or 7 were used as ligands, the crude reaction mixture was treated with benzoyl chloride in pyridine prior to distillation. The purity of the products was checked by GLC. 3-Butylcyclohexa-

none is pure, while 4-phenyloctan-2-one shows traces of starting material. The distilled products were free from any trace of chiral ligands.

The separation of the dimer 8 was achieved by prep. TLC (ether; light petroleum 60:40), m.p. 99—
100 °C, IR (KBr): 1720 cm⁻¹, abs. mass 292.141. ¹H NMR (270 MHz, CDCl₃): δ 1.63 (3H, s), 2.67 (1H, dd, J₀₋₁ 15 Hz, H₂), 2.74 (1H, dd, J₀₋₄ 15, H₂), 3.02 (1H, dd, J₀₋₄ 6.0, J₀₋₄ 1.0, H₀), 3.20 (1H, dd, J₀₋₄ 10.0, H₀), 3.42 (1H, m, J₀₋₄ 6.0, H₀), 3.52 (1H, m, J₀₋₄ 5.0, H₀), 3.62 (1H, m, J₀₋₄ 7.5, H₀), 7.03 (2H, d), 7.23 (8H, m).

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