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Chiral Mercaptoaryl-oxazolines as Ligands in Asymmetric Catalysis: Enantioselective Cu-Catalyzed 1,4-Addition of Grignard Reagents to α,β-Unsaturated Ketones

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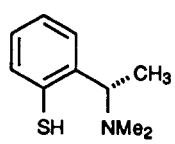
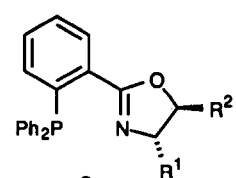
Abstract: *Copper(I) thiolate complexes derived from chiral mercaptophenyl-oxazolines* **3** *have been studied as enantioselective catalysts for the 1,4-addition of Grignard reagents to α,β-unsaturated ketones. For cyclic enones enantioselectivities increase in the sequence cyclopentenone (16-37 % ee) < cyclohexenone (60-72 % ee) < cycloheptenone (83-87 % ee).*

A number of chiral organocopper reagents have been described which undergo 1,4-addition to α,β-unsaturated carbonyl compounds with high enantioselectivity.[1,2] Despite substantial progress in this field, synthetically useful methods, which require catalytic rather than stoichiometric amounts of a chiral copper complex, are still lacking. Only few examples of copper-catalyzed 1,4-additions are known which proceed with significant enantioselectivity. In the addition of butylmagnesium chloride to cyclohexenone, Lippard *et al.*[3] obtained up to 74% ee, using Cu(I) complexes of chiral aminotropone imines as catalysts. Copper(I) complexes with thiosugar derivatives, a class of ligands developed by Spescha[4], afforded up to 60% ee in this reaction. Van Koten *et al.*[5] reported selectivities of up to 70-80% ee for the reaction of methylmagnesium iodide with benzylideneacetone catalyzed by a Cu(I) thiolate complex derived from ligand **1**. The structure of the chiral aminothiol **1** attracted our attention in connection with our work on chiral phosphino-oxazolines **2** which we[6] and others[7] found to be highly effective ligands for enantioselective Pd-catalyzed allylic alkylations. We hoped that analogous mercaptophenyl-oxazolines **3**, which resemble van Koten's aminothiol **1**, would be useful controller ligands for enantioselective Cu-catalyzed 1,4-additions.



1



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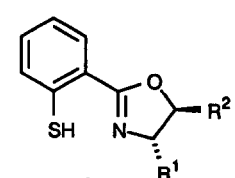
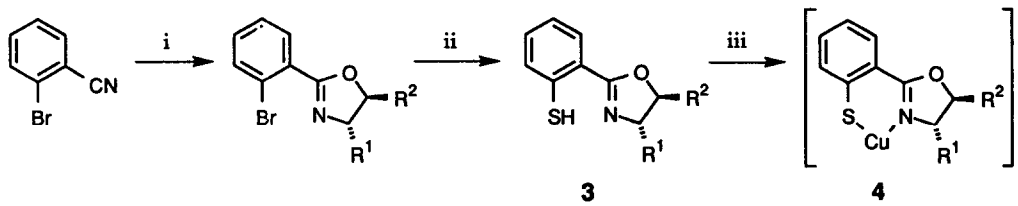


3

In an analogous manner to P,N-ligands **2**, enantiomerically pure mercaptophenyl-oxazolines **3** are readily prepared from amino alcohols, using the two-step sequence shown in Scheme 1. 2-Bromobenzonitrile was converted to the corresponding oxazolines in 50-80% yield by zinc-catalyzed condensation with amino alcohols according to the method of Witte and Seeliger.[6,8] Lithium-bromine exchange with *n*-butyllithium, followed by reaction with elemental sulfur[9] and subsequent work-up with aqueous acid afforded the desired ligands **3** in 30-60% yield. Starting from commercially available amino alcohols, a variety of differently substituted ligands is readily accessible.

Scheme 1



3 **4**

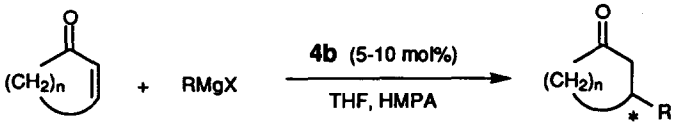
(i) amino alcohol, $ZnCl_2$ (2.5 mol%), chlorobenzene, reflux.
(ii) *n*-BuLi, THF, -78 °C; S_8, THF, -78 °C; HCl, H_2O.
(iii) *n*-BuLi, THF, -78 °C; CuI, THF, -20 °C.

a	$R^1 = CH_3$	$R^2 = H$
b	$R^1 = i$-Pr	$R^2 = H$
c	$R^1 = t$-Bu	$R^2 = H$
d	$R^1 = CH_2Ph$	$R^2 = H$
e	$R^1 = CH_2OSiMe_2t$-Bu	$R^2 = Ph$

Copper(I) thiolate complexes derived from ligands **3** were found to be efficient catalysts for enantioselective conjugate addition of Grignard reagents to cyclic enones (Table 1). The catalysts were prepared *in situ* by complexation of CuI with the lithium salt of the corresponding ligand.[10] The best results were obtained when the Grignard reagent was slowly added at -78 °C to a THF solution containing the catalyst, the substrate, and 2 equiv. of hexamethyl phosphoric triamide (HMPA).[11] Under these conditions, the desired 3-alkylketones were formed in good yield and with high regioselectivity (>94% 1,4- *vs.* 1,2-addition). For a comparison of the different ligands **3a-e**, the reaction of BuMgCl with cyclohexenone was chosen. The methyl and isopropyl derivatives **3a** and **3b** were found to be the most effective ligands, whereas the bulky *tert*-butyl derivative **3c** gave markedly lower enantioselectivities (**3a**: 58% ee, **3b**: 60% ee, **3c**: 15% ee, **3d**: 52% ee, **3e**: 47% ee). Similar selectivities were obtained using butylmagnesium bromide instead of the chloride.

It is well known that the solvent as well as polar additives, such as HMPA, and trialkylchlorosilanes can have a strong influence on the reactivity and selectivity of organocopper compounds.[12] In our case too, proper selection of the reaction medium is crucial. In pure THF or diethyl ether, very low enantiomeric excesses were observed. Significant enantioselectivities were only obtained in the presence of HMPA or 1,3-dimethylimidazolidin-2-one (DMI), which was almost as effective as HMPA (53% *vs.* 60% ee for the reaction of BuMgCl with cyclohexenone). In contrast to the findings of Lippard *et al.*[3], who recorded the highest enantiomeric excess in the presence of HMPA and trialkylchlorosilanes, addition of Me_3SiCl resulted in a substantial loss of selectivity, whereas $Ph_2(t\text{-Bu})SiCl$ had essentially no effect.

Table 1. Enantioselective 1,4-Addition of Alkylmagnesium Halides to Cycloalkenones[11]



Enone	4b [equiv.]	RMgX	Temp. [°C]	Yield [%]	ee[a] [%]
2-Cyclopentenone	0.05	*n*-BuMgCl	-78	30	16
„	0.05	*i*-PrMgCl	-78	43	37
2-Cyclohexenone	0.05	*n*-BuMgCl	-78	67	60
„	0.05	*n*-BuMgBr	-78	65	54
„	0.05	*i*-PrMgCl	-78	71	72
„	0.05	„	-45	89	68
2-Cycloheptenone	0.05	*n*-BuMgCl	-78	24	83
„	0.10	„	-78	50	83
„	0.10	*i*-PrMgCl	-78	55	87
„	0.10	„	-45	71	71

a) Determined by ^{13}C-NMR analysis after conversion to the corresponding ketals with (*R,R*)-(–)-2,3-butanediol.[13] All products had positive $[\alpha]_D$-values. Based on the sign of optical rotation, the configuration of 3-butylcyclopentanone and 3-butylcyclohexanone is (*R*).[2a,14]

Isopropylmagnesium chloride gave consistently higher enantioselectivities than *n*-BuMgCl in the reactions with cyclopentenone, cyclohexenone, and cycloheptenone. Phenylmagnesium bromide, on the other hand, afforded virtually racemic products. The enantioselectivity increased with the ring size of the cycloalkenone, from disappointingly low ee values for cyclopentenone to a maximum of 87% ee for cycloheptenone. Preliminary experiments with acyclic enones such as benzylideneacetone gave selectivities below 20% ee.

The results obtained with cycloheptenone are encouraging. For the first time, such high levels of enantioselectivity have been accomplished in a Cu-catalyzed 1,4-addition. The selectivities with other enones, however, still need to be improved substantially. In order to achieve this goal, further modification of the ligand structure, as well as a better understanding of the reaction mechanism and the catalyst structure will be necessary.

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10. A recrystallized sample of the Cu(I) complex derived from **3b** (elemental analysis in accord with formula [{**4b**}$_n$]) gave very similar selectivities as the corresponding catalyst generated *in situ*.
11. Experimental procedure: To a solution of ligand **3b** (13.3 mg, 60 μmol) in 5 mL of THF was added *n*-butyllithium (1.58 M in hexane; 38 μL, 60 μmol) at -78 °C. After 10 min the solution was transferred through a cannula to the reaction flask containing a suspension of CuI (9.5 mg, 50 μmol) in 5 mL of THF at -78 °C. The mixture was warmed to -20 °C and stirred at this temperature for 30 min. The resulting homogeneous brownish solution was cooled to -78 °C. HMPA (0.35 mL, 2.0 mmol) was added and stirring was continued for 5 min until all HMPA had dissolved. After addition of 2-cyclohexen-1-one (96 μL, 1.0 mmol), a 0.5 M solution of isopropyl magnesium chloride in THF (2.0 mL, 1.0 mmol) was added dropwise over a period of 2 h. The resulting orange solution was stirred at -78 °C for an additional 2 h. After hydrolysis with 5 mL of saturated aqueous NH_4 solution, the mixture was extracted with Et_2O. The ether phase was washed twice with aqueous HCl and twice with water. Flash chromatography on silica gel with *n*-pentane/EtOAc (5:1) afforded 100 mg (71%) of 3-isopropylcyclohexanone (72% ee; $[\alpha]_D$ = +13.6, c = 1.9 in $CHCl_3$, 23 °C). The enantiomeric purity was determined by ^{13}C-NMR analysis after ketalyzation with (*R,R*)-(–)-2,3-butanediol.[13]
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