71. Enantioselective Copper-Catalyzed 1,4-Addition of *Grignard* Reagents to α,β-Unsaturated Carbonyl Compounds

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The enantioselective copper-catalyzed 1,4-addition of *Grignard* reagents to α,β-unsaturated carbonyl compounds was studied with the following Cu^I compounds as catalyst precursor and 1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose (Hsiig) as chiral ligand: CuI, iodo[bis(dibutylsulfide)]copper(I), [Cu(siig)], [Cu(siig)(pp)] (pp = 1,2-bis(diphenylphosphinoethene), and tetrakis[iodo(tributylphosphine)]copper(I). The addition of BuMg halides to cyclohex-2-en-1-one was tested under several reaction conditions. The chemical yields and regioselectivities for this reaction were, in all cases, larger than 90 and 98%, respectively, and independent of the experimental conditions. The enantioselectivity was strongly dependent on the reaction conditions and reached a maximum of 60%. Several other substrates were also tested in the above reaction. The X-ray crystal structure for [Cu(siig)(pp)] was determined by X-ray crystallography.

Introduction. – One recognized synthetic challenge of the 90's is the development of effective methods for enantioselective C–C bond formation. Among these, the Cu^I-catalyzed addition of *Grignard* reagents to α,β-unsaturated carbonyl compounds has received increasing attention over the past decade (for reviews, see [1]). However, only two very specific catalytic enantioselective versions of this reaction are known [2] [3]. We report here a new catalytic system for this reaction.

Results. – *Copper(thiosurgar) Complexes*. The reaction of tetrakis(acetonitrile)copper(I) hexafluorophosphate with the lithium salt of 1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose (Hsiig, **1**) in Et_2O gave a yellow solid with the presumed composition of [Cu(siig)] (**2**). Purification of this compound by chromatography gave two compounds with identical ^{1}H-NMR spectra but with different melting points. However, neither compound gave analytical results in good agreement with the above formulation. As we were unsuccessful in finding a method of purification for **2**, we characterized this new copper-thiolate compound by forming derivative with 1,2-bis(diphenylphosphino)ethene (pp, **3**) which gave [Cu(siig)(pp)] (**4**) in analytically pure form.

It was also possible to obtain crystals of this compound suitable for an X-ray diffraction analysis. Its structure is dimeric (see *Fig.*), with the two Cu-atoms bridged by the S-atoms of the thiolate ligands. A selection of bond lenghts and angles is given in *Table 1*[1]). Similar copper sulfur four-membered rings are well known in the literature

[1]) A complete list is available from the authors upon request.

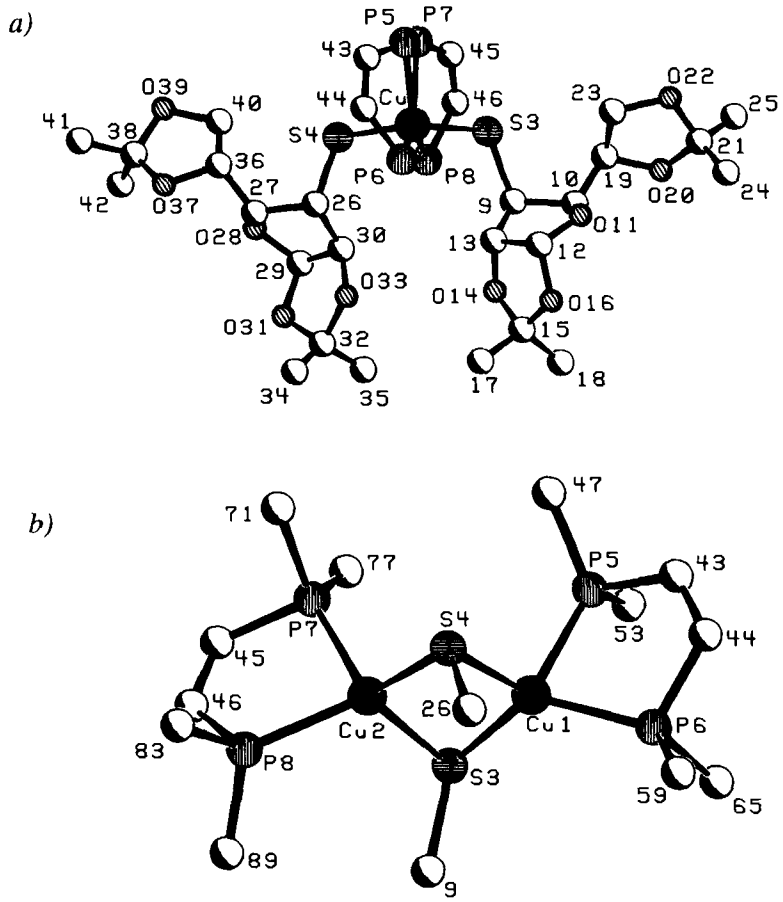


Figure. *The Structure of [Cu(siig)(pp)]* **4**. *a*) Viewed down the Cu–Cu bond (the Ph rings of the phosphine ligands have been omitted for clarity); *b*) the coordination polyhedron.

Table 1. *Selected Bond Distances* [Å][a]) *and Bond Angles* [°][a]) *in [Cu(siig)(pp)]* (**4**)

Bond distances			
Cu(1)–Cu(2)	2.797(3)	Cu(2)–S(3)	2.351(5)
Cu(1)–S(3)	2.337(5)	Cu(2)–S(4)	2.339(6)
Cu(1)–S(4)	2.361(5)	Cu(2)–P(7)	2.293(6)
Cu(1)–P(5)	2.304(5)	Cu(2)–P(8)	2.289(7)
Cu(1)–P(6)	2.271(6)		
Bond angles			
S(3)–Cu(1)–S(4)	105.4(1)	S(3)–Cu(2)–P(7)	105.8(2)
S(3)–Cu(1)–P(5)	112.9(2)	S(3)–Cu(2)–P(8)	113.2(3)
S(3)–Cu(1)–P(6)	127.5(3)	S(4)–Cu(2)–P(7)	113.9(2)
S(4)–Cu(1)–P(5)	108.5(2)	S(4)–Cu(2)–P(8)	127.4(2)
S(4)–Cu(1)–P(6)	114.2(3)	P(7)–Cu(2)–P(8)	88.3(3)
P(5)–Cu(1)–P(6)	86.1(3)	Cu(1)–Cu(2)–P(8)	73.3(1)
S(3)–Cu(2)–S(4)	105.7(3)	Cu(1)–S(4)–Cu(2)	73.1(2)

[a]) Numbers in parentheses are estimated standard deviations in the least significant digits.

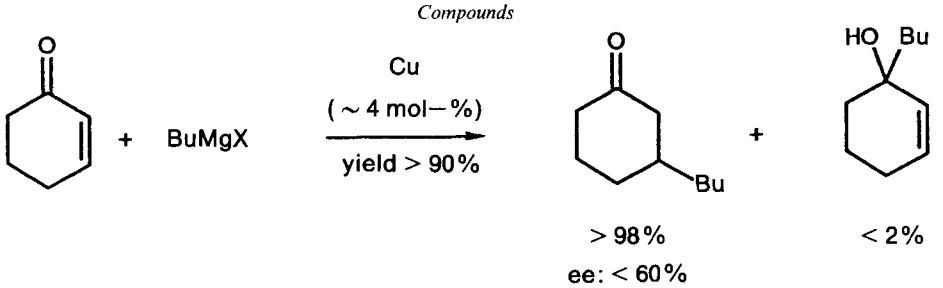
[4–6]. The coordination geometry at the Cu-atoms is represented by a distorted tetrahedron, and the geometry at the S-atoms reflects a distorted trigonal pyramid. The two substituents at the S-atoms are in a mutual *cis*-arrangement relative to the copper sulfur ring. The copper sulfur ring is not planar. The plane Cu(1)–S(3)–Cu(2) forms an angle of 160° with the plane Cu(1)–S(4)–Cu(2). This is in contrast to most of the known copper sulfur four-membered rings, which are usually planar. However, an example for a similar non-planar copper sulfur four-membered ring has been reported [5].

It is noteworthy that the molecular-weight determination of [Cu(siig)(pp)] (**4**) in CH_2Cl_2 gave a molecular weight of 780 g/mol, which is compatible with a monomeric structure.

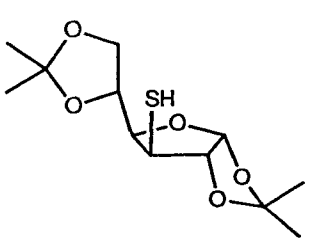
Both copper compounds **2** and **4** were used as catalyst precursors in the 1,4-addition of *Grignard* reagents to α,β-unsaturated carbonyl compounds.

Enantioselective Cu-Catalyzed 1,4-Addition of BuMg Halides to Cyclohex-2-en-1-one. The above copper(thiolate) complexes were used as catalyst precursors in the title reaction whereby only [Cu(siig)] (**2**) showed a high catalytic activity. Since the preparation of analytically pure **2** failed and since [Cu(siig)(pp)] (**4**) had only a low catalytic activity and showed no enantioselectivity, we also used Hsiig (**1**) in presence of the following Cu^I salts as catalyst precursors: CuI, iodobis(dibutylsulfido)copper(I), and tetrakis[iodo(tributylphosphine)copper(I)]. The addition of BuMg halides to cyclohex-2-en-1-one was used as a test reaction (*Scheme 1*). The catalytic reaction was carried out by slow simultaneous addition of a solution of BuMg halide and a solution of cyclohex-2-en-

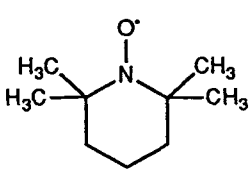
Scheme 1. *The Enantioselective, Copper-Catalyzed 1,4-Addition of* Grignard *Reagents to α,β-Unsaturated Carbonyl Compounds*



Cu': – CuI + 3 BuLi + Hsiig
– $[Cu(Bu_2S)_2I]$ + 3 BuLi + Hsiig
– [Cu(siig)] + 2 BuLi
– $[Cu(Bu_3P)I]_4$ + 3 BuLi + 0.7TEMPO• + Hsiig



Hsiig, **1**



TEMPO•

1-one to a solution of the starting cuprate prepared *in situ* at low temperature. The starting cuprate was prepared by adding 2 equiv. of BuLi to a solution of [Cu(siig)] (**2**) or by adding 3 equiv. of BuLi and 1 equiv. of Hsiig (**1**) to the Cu^I salt at low temperature in the appropriate solvent. The crude reaction product, 3-butylcyclohexan-1-one, was then transformed into the diastereoisomeric ketals by reaction with enantiomerically pure (*R,R*)-butane-2,3-diol [7] or (*R,R*)-pentane-2,4-diol in order to determine the enantiomeric excess.

Under all reaction conditions tested, we obtained good chemical yields (> 90%) determined by GC with an internal standard and very good regioselectivities (1,4- to 1,2-product > 98%). The enantioselectivity was not very dependent on the Cu^I salt used and ranged between 50 and 60%. Interestingly, the enantioselectivity was dependent on the halide of the *Grignard* reagent. Thus, we found that with [Cu(siig)] (**2**) only BuMgBr gave good ee's (60%). The other catalyst precursors gave the highest ee, when BuMgCl was used (up to 58%). The most reproducible reaction system was obtained when tetrakis[iodo(tributylphosphine)copper(I)] and 2,2,6,6-tetramethylpiperidin-*N*-oxyl (TEMPO·), a radical scavenger (*Method A*), were used. When we added a small amount of H_2O to the reaction system, the same results were obtained (*Method B*, for an interpretation of this uncommon feature, see below). Thus, we tried to optimize the reaction condition using of tetrakis[iodo(tributylphosphine)copper(I)]. The experiments carried out and their results are summarized in *Tables 2–4*.

Table 2 shows a list of the variation of single reaction parameters.

Table 2. *Variation of Reaction Parameters*

Parameter changed[a])	x_s	ee_s [%]	x	ee [%]	x	ee [%]	x	ee [%]
t_1	10 min	50	15 h	50				
t_2	8 min	50	5 min	40	70 min	46	200 min	58
V_1	10 ml	50	2 ml[b])	11	100 ml	12		
V_2	8 ml	50	2 ml	10	30 ml[c])	49	5 ml[d])	30
Equiv. of starting cuprate	1	50	0.5	29	2	41		
Equiv. of TEMPO·	0.7	50	0.35	46	0.7	46	7[e])	6
Equiv. of BuMgCl	25	50	50	12				
Equiv. of cyclohex-2-en-1-one	25	50	50[f])	7				
Equiv. of **1**	1	50	2[g])	19				
Equiv. of BuLi	3	50	1	17				
Temp.	–78°	50	0°	16 (38)[h])	–30°	26	116°[i])	3

[a]) Standard conditions: *Method A:* starting cuprate: $[Cu(Bu_3P)I]_4$ + Hsiig (**1**) + 3 BuLi + 0.7 TEMPO· in 10 ml of Et_2O) (V_1) at –78° (T); stirring for 10 min (t_1); simultanous addition of cyclohex-2-en-1-one (25 equiv.) and BuMgCl (25 equiv.) each in 8 ml of Et_2O (V_2) over a time of 13 min (t_2). ee: 50%; ee: 50%.

[b]) Cyclohex-2-en-1-one/3-butylcyclohexan-1-one 1:30.

[c]) t_2 = 30 min.

[d]) t_2 = 8 min.

[e]) Cyclohex-2-en-1-one/3-butylcyclohexan-1-one 1:13.

[f]) 1-Butylcyclohex-2-en-1-ol/3-butylcyclohexan-1-one 1:15.

[g]) 4 equiv. of BuLi.

[h]) All solutions were degassed by a freeze-pump cycle.

[i]) Cyclohex-2-en-1-one/3-butylcyclohexan-1-one 1:4; *Method B:* as *Method A*, except for the addition of 0.28 equiv. of H_2O to the solution of the starting cuprate and to the cyclohex-2-en-1-one solution.

Table 3. *Change of Reagents Used in the Catalysis*

Standard reagent[a])	ee_s [%]	New reagent[b])	ee [%]	Configuration
BuLi	50	BuMgCl	10	*S*
BuLi	50	PhLi	24	*S*
BuMgCl	50	BuLi	0	*S*
BuMgCl	50	BuMgBr[c])	48	*S*
BuMgCl	50	BuMgBr[d])	42	*S*
BuMgCl	50	BuMgI	6	*S*
BuMgCl	50	Bu_2Mg[e])	10	*R*
BuMgCl	50	BuMgCl + 0.7 equiv. TEMPO·	42	*S*
BuMgCl	50	BuMgI + MgI_2 (saturated solution)[f])	7	*S*
Et_2O	50	$Et_2O/MgCl_2$ (saturated solution)[g])	50	*S*
[Cu(Bu$_3$P)I]	50	[Cu(Bu_2S)$_2$I]	5	*S*
	50	+ 34 mg [Cu(Bu$_3$P)I] + 2 equiv. BuLi	33	*S*
0.7 TEMPO·	50	1 *p*-Benzoquinone	10	*S*
0.7 TEMPO·	50	0.3 *p*-Benzoquinone	42	*S*
0.7 TEMPO·	50	0.6 Anthracen	45	*S*
0.7 TEMPO·	50	1.1 Tetracyclooctadiene	38	*S*
0.7 TEMPO·	50	0.7 4-Hydroxy-TEMPO·	50	*S*
0.7 TEMPO·	50	0.6 Anthracen + 0.6 in BuMgCl solution	33	*S*
Et_2O		THF[h])[i])	13	*R*
Et_2O		THF[i])[k])	16	*R*
Et_2O		THF[j])	6	*R*
Et_2O		CH_2Cl_2[h])[i])	0	
Et_2O		CH_2Cl_2[i])[k])	0	
Et_2O		NEt_3[h])[l])	6	*S*
		Hexan[h])	0	

[a]) Standard conditions see *Table 2*.
[b]) No sign: the old reagent was substituted by the new one; +: Standard reaction condition plus the new reagent.
[c]) The cannula was dipped into the reaction solution.
[d]) The solutions of 2-cyclohex-2-en-1-one and BuMgCl were added dropwise to the reaction solution.
[e]) Cyclohex-2-en-1-one/3-butylcyclohexan-1-one 1:16.
[f]) MgI_2 was added to the reaction solution prepared as described in [8].
[g]) Prepared as described in [9].
[h]) BuMgCl 2M in Et_2O.
[i]) *Method B* (see *Table 1*).
[k]) The BuMgBr solution was evaporated to dryness and then dissolved in the appropriate solvent.
[l]) The alkylating reagent was Bu_2Mg.

In some further experiments, we examined the effects of changing some reagents in our catalytic system. These results are summarized in *Table 3*.

As the addition of TEMPO· had a positive effect on the reproducibility of the enantioselectivity, we examined the influence of other radical scavengers. These results are also shown in *Table 3*, in addition to the results we obtained by varying the solvent. As can be seen, the use of Et_2O as solvent gave the best yields as well as regio- and enantioselectivities.

In a further set of experiments, we measured the enantioselectivity as a function of the turnover numbers of the reaction (*Table 4*). For this purpose, we took small samples (*ca.* 0.5 ml) from the reaction solution.

Table 4. *Enantioselectivities after Different Turnovers of the Reaction*

Parameter	Turnover	ee [%]	Turnover	ee [%]	Turnover	ee [%]	Turnover	ee [%]	Turnover	ee [%]
Variation[a])	4.8	30	9.6	43	14.4	47	19.2	47	25	47
Method B[b])	25	50	50	37	90	28				
$V_1 = 14$ ml;										
$V_2 = 2$ ml	4.8	12	9.6	15	14.4	13.	19.2	10	25	10
$V_1 = 100$ ml[c])	5.7	18	11.5	17	14.4	18	19.2	15	25	12
$V_2 = 50$ ml[d])	4.8	26	9.6	40	14.4	36	19.2	31	25	29
$Et_2O/MgCl_2$										
(saturated solution)[e])	4.8	13	9.6	52	14.4	51	19.2	49	25	50
$Et_2O/MgCl_2$										
(saturated solution)[f])	1.9	7	5.7	22	11.5	42		25	46	
BuLi substituted by										
BuMgCl; without										
TEMPO·	1	12	5.7	12	11.5	11	17.1	11	25	7

[a]) Standard conditions see *Table 2. Method B:* As *Method A*, except for the addition of 0.28 equiv. of H_2O to the solution of the starting cuprate and to the cyclohex-2-en-1-one solution.

[b]) Addition time. 25 equiv. = 22 min; 50 equiv. = 28 min; 90 equiv. = 36 min.

[c]) Cyclohex-2-en-1-one/3-butylcyclohexan-1-one 1:20.

[d]) $t_1 = 8$ min.

[e]) Prepared as described in [9].

[f]) $MgCl_2$ was prepared by heating $MgCl_2 \cdot 6\ H_2O$ to 200° for 6 h on high vacuum.

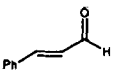
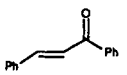
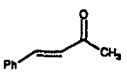
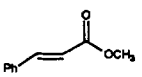
[g]) Cyclohex-2-en-1-one/3-butylcyclohexan-1-one 1:16.

The substitution of BuMgCl by Bu_2Mg and the use of THF as solvent resulted in decrease of ee by 6% ((*R*)-enantiomer in excess). The chemical yields and the regioselectivities were lower than in the standard experiment. By carring out the reaction with 90 equiv. of cyclohex-2-en-1-one and 90 equiv. of BuMgCl, each in 30 ml of Et_2O, we found an ee of 28% (*Method B*). In this experiment, we also determined the enantioselectivity after 25 and 50 turnovers. The observed ee were 50% and 37%, respectively.

Catalysis with Other Substrates. By carrying out the reaction with other substrates, we found that the reaction condition described above were very specific. Thus, we found that PhMgBr gave an ee of 20%. However, the enantioselectivity was independent of the method of preparation of the starting cuprate. Thus, we obtained the same ee, when the starting cuprate was prepared using PhLi or BuLi. The chemical yield was 60% (isolated yield). The ratio of 1,2- to 1,4-product was 1:5. Also the addition of the substrate solutions over a period of 2 h had no effect either on the enantioselectivity or on the product ratio (1,2-/1,4-product 1:8). In addition to cyclohex-2-en-1-one, we tested the α,β-unsaturated carbonyl compounds listed in *Table 5*. In all cases, low ee were obtained, and in some cases the 'wrong' compound or no product at all was formed. These reactions were carried out under standard conditions. By performing the reaction with the above substrates without Hsiig (**1**), we obtained the same chemical yield and regioselectivity.

Discussion. – A full rationalization of our results is not possible at this stage, and many of them are quite puzzling. Nevertheless, there are some trends which seem to be quite general, and the following conclusions can be drawn. The high 1,4-selectivity

Table 5. *Results with Different α,β-Unsaturated Carbonyl Compounds*[a])

Substrate	1,4-Product/ 1,2-product	ee [%] (1,4-product)	Remarks
	0:100		ee = 0 (determined with GC (column CD 18))
	100:1	< 20	yield 90%
	low 1,4-product formation		mixture of products
			no reaction
	10:1	10	yield 54%

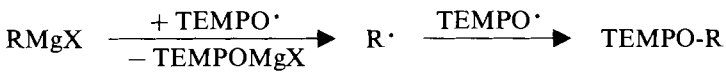
[a]) Standard conditions see *Table 2*.

obtained in all experiments shows that the reaction is Cu-mediated (by performing the reaction without Cu under the same conditions, a 1:1:1 mixture of cyclohex-2-en-1-one, 1-butylcyclohex-2-en-1-ol, and 3-butylcyclohexan-1-one was obtained). The same 1,4-selectivity and chemical yield resulted by carrying out the reaction either with CuI or tetrakis[iodo(tributylphosphine)copper(I)] in the absence of Hsiig (**1**). We could not establish the extent of the catalysis caused by **1** in addition to that due to the Cu^{I} salts. By carrying out the reaction with an excess of tetrakis[iodo(tributylphosphine)copper(I)] (1 equiv.), we obtained an enantioselectivity of 33%. This decrease can be due to several factors (see also below). If we assume that the chiral and the achiral catalysts do not interact with each other, then the calculated ratio of $k_{achiral}/k_{chiral}$ would be 0.5.

A variation of the time to form the starting cuprate had no effect on the enantioselectivity of the reaction. This implies that the cuprate formation is completed after 10 min, and that this cuprate is stable for at least 15 h at −78°. This result can be interpreted by assuming that under the reaction conditions all Cu complexes are in equilibrium, however, it might also be considered that a metastable state of the catalytically active complex is formed.

An interesting point is to understand the role of the radical scavenger. The fact that only the addition of TEMPO· to the solution of the starting cuprate had a positive effect on the enantioselectivity makes the situation more complicated (the addition of TEMPO· to the substrate solution resulted in a decrease of the enantioselectivity to 42%). Furthermore, it is known that TEMPO· has a low reactivity towards oxygen radicals (RO·) [10] and is inert towards peroxy radical (RO_2·) [11] [12]. A further complication is that TEMPO· reacts with organolithium and *Grignard* reagents as shown in *Scheme 2*.

Scheme 2



The resulting product is the same as that one obtains by the reaction of TEMPO· with the corresponding carbon nucleophile [13]. Therefore, we have to conclude that BuLi reacts with carbon radicals which may be present in the reaction system as well as with TEMPO·. In this way, TEMPO· destroys the most reactive BuLi. It is the BuLi which is aggregated with alcoholates which are formed by the reaction of oxygen with BuLi. The latter could be responsible for the low reproducibility of the enantioselectivity [14]. The role of the added H_2O could be interpreted in a similar way.

The dependence of the enantioselectivity on the halide used in the *Grignard* reagent could be a consequence of the position of the *Schlenk* equilibrium. Thus, we tried to carry out the reaction with Bu_2Mg, because, in this reagent, the *Schlenk* equilibrium lays totally on one side. The result was a decrease of ee by 10% ((*R*)-enantiomer in excess). Because of the low enantioselectivity found with Bu_2Mg, we tried to shift the *Schlenk* equilibrium to the other side by adding the appropriate magnesium halide. However, no effect on the enantioselectivity was observed. Therefore, we tried to shift the *Schlenk* equilibrium using different solvents such as Et_3N or THF. In the presence of Et_3N, the *Schlenk* equilibrium lays far on the side of the mixed *Grignard* reagent, whereas in THF it lays on the other side [15]. The enantioselectivity in both solvent was low. Therefore, we believe that the influence of the salt and solvent effects are more complex than expected. Similar effects are quite common for cuprate reactions [16–18].

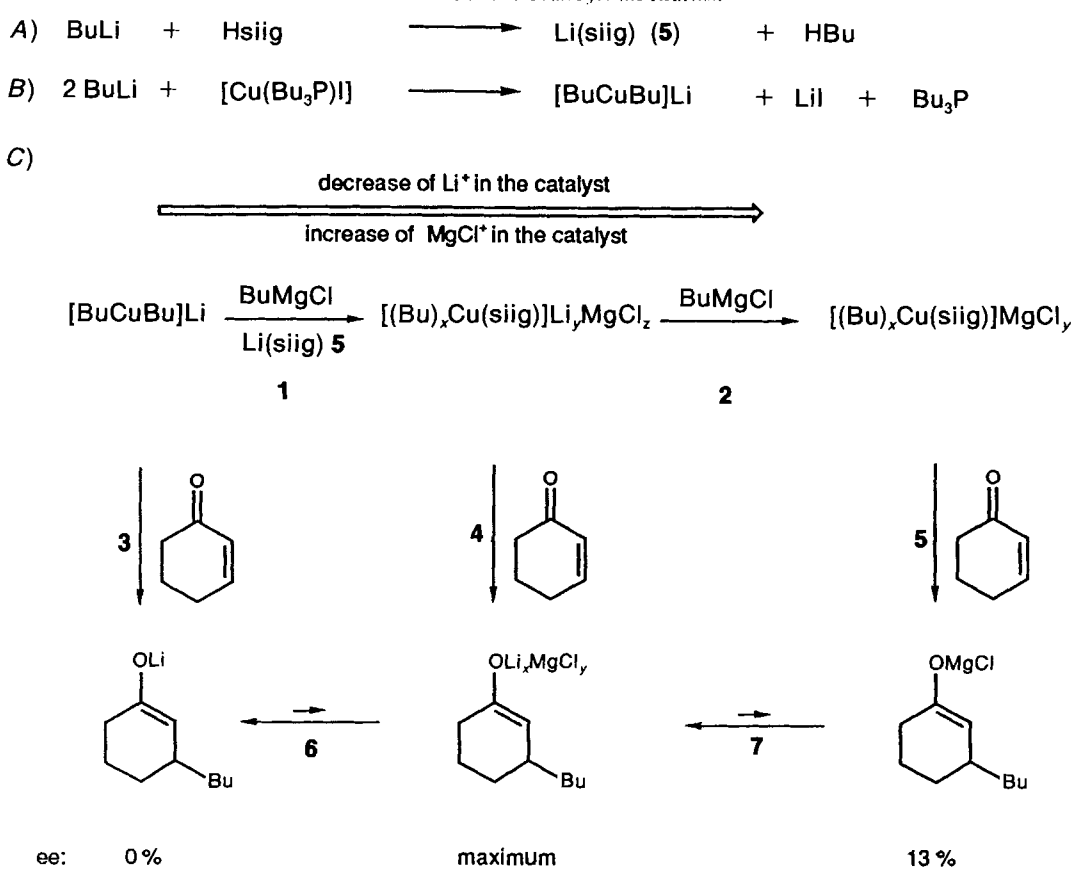
The variation of other reaction parameters such as addition time (t_2), starting volume (V_1), addition volume (V_2), and equivalents of catalyst precursor has the common feature that it only changes the ratio catalyst precursor/cyclohex-2-en-1-one and BuMgCl. As can be seen, there is a range of this ratio in which a good enantioselectivity results. These observations and the enantioselectivity, which is obtained after different turnover numbers, can be interpreted as follows.

Different aggregates are formed during the course of the reaction, which are in equilibrium with each other. Furthermore, the position of this equilibrium is strongly dependent on the concentration of each reagent, and each aggregate is catalytically active and gives a different enantioselectivity. Interestingly, these aggregates had no effect on the regioselectivity of the reaction.

Further studies showed that all three metals have to be used in the reaction system. If we replaced the BuLi used in the generation of the starting cuprate by a *Grignard* reagent, the enantioselectivity decreased to 13% and was constant over the course of the reaction. Substitution of the alkylating *Grignard* reagent by BuLi resulted in a total loss of the enantioselectivity.

The above interpretation can be summarized as shown in *Scheme 3*. The stoichiometries in *Scheme 3* are only formal: *x*, *y*, and *z* have a different value in each complex. The course of the reaction as sketched in *Scheme 3* should be understood as follows.

Scheme 3. *A Possible Course for the Reaction*



Reactions 1 and *2* show that, in the course of the reaction, a cuprate is formed which gives maximal enantioselectivity. This cuprate is a mixed cuprate, which includes all three metal (*i.e.* Cu, Mg, and Li) as well as [Li(siig)] (**5**). *Reaction 3* in *Scheme 3* shows that the starting cuprate is achiral. The reaction product of this achiral cuprate is, of course, racemic. The important aspect of *Reaction 3* is that, during product formation, the starting cuprate loses lithium ions and, thus, **5** and the *Grignard* reagent are incorporated in the cuprate (*Reaction 1* in *Scheme 3*). The loss of lithium ions is slow and is not complete after 2 turnovers. By analogy with *Reaction 3*, the cuprate formed in *Reaction 2* gradually loses lithium ions. This continual loss of lithium ions results in the formation of a lithium-ion-free cuprate. The enantioselectivity of the reaction with this lithium-ion-free cuprate is 13% as mentioned above (*Reaction 5* in *Scheme 3*). *Equilibria 6* and *7* show a further way how the cuprate can lose lithium ions.

Conclusion. – Our investigation of a new catalytic system for the enantioselective Cu-catalyzed 1,4-addition of *Grignard* reagents resulted in good chemical yields and regioselectivities for our test reaction. The observed enantioselectivities are among the

best known for the catalytic version of this reaction. The disadvantage of our reaction system is its low application range. This seems to be quite common for cuprate reactions (*e.g.*, see [19]). However, work on this project is still in progress in the hope of finding more general reaction conditions and better ee by varying the protecting groups on our ligand.

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Experimental. – *General.* All catalytic reactions were carried out using standard *Schlenk* technique under Ar. Et_2O, THF, and hexane were dried over Na/benzophenone and distilled before use. Other solvents were purified as described in [20]. Hsiig (**1**) was prepared as described in [21], and tetrakis(acetonitrile)copper(I) hexafluorophosphate as described in [22]. BuLi and (*R,R*)-butane-2,3-diol were used as received from *Fluka,* while cyclohex-2-en-1-one, also from *Fluka,* was distilled before use. BuMgCl was used as received (*Aldrich*), and BuMgBr was prepared as a ~ 1M stock soln. in Et_2O. The ^{1}H-, ^{13}C-, and ^{31}P-NMR spectra were recorded on a *Bruker* 250-MHz instrument. GC Analyses were performed using a *Carlo Erba GC 6000 Vega Series,* equipped with a *SE 54* (0.25 mm × 25 m) capillary column, flame ionization detector, and a *SIC Chromatocorder 12* integrator.

[Cu(siig)] (**2**). BuLi soln. (1.46 ml, 2.33 mmol; 1.6M in hexane) was added to a soln. of 635 mg (2.33 mmol) of 1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose (**1**) in 20 ml of Et_2O, at r.t. The resulting soln., after stirring at r.t. for 10 min, was added to a suspension of 870 mg (2.33 mmol) of tetrakis(acetonitrile)copper(I) hexafluorophosphate in 10 ml Et_2O. After stirring this suspension for 1 h, most of the solid dissolved, and 30 ml of H_2O were added to the mixture. The resulting two-phase mixture was vigorously stirred for 10 min, then the phases were separated, and the org. phase was dried ($MgSO_4$) and evaporated. The resulting yellow solid was chromatographed on silica gel. One product was eluted with AcOEt and a second product with MeOH. M.p. of the two compounds ranged between 100° and 135°. The elemental analyses of the two products were variable (calc.: C 42.35, H 5.65; found: C 39–45; H 5.5–6.5). ^{1}H-NMR ((D$_9$)toluene; 90°): 6.30 (J(1,2) = 3.4, H–C(1)); 5.13 (H–C(2)); 4.92 (J(4,5) = 9.0, J(5,6) = 6.0, J(5,6′) = 4.5, H–C(5)); 4.43 (J(3,4) = 3.6, H–C(4)); 4.26 (J(6,6′) = 8.7, H–C(6)); 4.13 (H–C(6′)); 4.06 (H–C(4)); 1.48 (6 H); 1.42, 1.25 (CH_3). ^{13}C-NMR ((D$_9$)toluene): 113.1; 111.2; 106.6; 91.2; 82.1; 76.1; 69.3; 52.2; 28.5; 27.7; 27.6; 26.9.

[Cu(siig)(pp)] (**4**). A soln. of 135 mg (3.98 mmol) [Cu(siig)] (**2**) in 5 ml of Et_2O was added to a suspension of 157 mg (3.98 mmol) 1,2-bis(diphenylphosphino)ethene (pp) in 20 ml of Et_2O at r.t. To the resulting mixture, acetone was added, until almost all the solid dissolved (*ca.* 5 ml). After filtration, the soln. was evaporated to dryness. The resulting solid was recrystallized from toluene/hexane: 140 mg (1.90 mmol; 48%) of **4**. M.p. 150°. ^{1}H-NMR ((D$_9$)toluene): 7.54–6.88 (*m*, 22 H, 1,2-bis(diphenylphosphino)ethene); 5.24 (1 H); 4.9 (1 H); 4.43–4.24 (*m*, 4 H); 3.08 (1 H); 1.54, 1.39, 1.34, 1.16 (CH_3); (all signals br.). ^{13}C-NMR ((D$_9$)toluene): 109.8; 107.6; 105.2; 83.0; 76.8; 66.5; 59.5; 27.4; 27.1; 26.2. (The signals of 1,2-bis(diphenylphosphino)ethene partly overlapped with those of (D$_9$)toluene signals.) ^{31}P-NMR ((D$_9$)toluene): –10.4 (br.). Anal. calc.: C 62.07, H 5.62; found: C 61.85, H 5.73.

Crystallization of **4**. Hexane was added to a soln. of **4** in toluene, until a precipitate formed, the resulting mixture was placed at –30° for *ca.* 2 h and then heated to reflux, until almost all the solid dissolved and then left to cool slowly to r.t. This procedure was repeated, until large crystals resulted.

Typical Catalytic Reaction Procedure Using **2** *as Catalyst Precursor.* A soln. of 0.09 ml (0.15 mmol) of BuLi (1.6M in hexane) was added to a soln. of 25 mg (0.074 mmol) of **2** in 10 ml of Et_2O at –78°. The resulting soln. was kept at –78° for 10 min. Two Et_2O solns. (8 ml each), one containing cyclohex-2-en-1-one (225 mg, 2.3 mmol) and the other containing BuMgBr (2.3 mmol), were then added dropwise and simultaneously *via* a syringe pump over 13 min. After the addition was complete, the mixture was stirred at –78° for 10 min and quenched with a sat. NH_4Cl soln. (*ca.* 15 ml). Mesitylene (30 µl; internal standard for the GC) was then added. A sample of the org. layer, filtered over neutral aluminium oxide, used for GC (temp. program: 80°, heating up to 250° (20°/min); yield 92%). The remainder of the mixture was transferred to a separatory funnel, and, after separation, the org. phase was dried ($MgSO_4$). After filtration and evaporation, the crude product was used for the determination of the enantiomeric excess. This procedure gave 60% ee.

Typical Catalytic Reaction Procedure Using [Cu(Bu$_3$P)I]$_4$ as Catalyst Precursor. Method A. A 0.169 mM soln. of Hsiig (**1**; 0.52 ml, 0.088 mmol) in Et_2O was added to a soln. of 34 mg (0.022 mmol) of tetrakis[iodo(tributylphos-

phine)copper(I)] and 10 mg (0.064 mmol) of 2,2,6,6-tetramethylpiperidin-*N*-oxyl (TEMPO·) in 10 ml of Et_2O at r.t. The resulting soln. was cooled to −78°. Then, 0.17 ml (0.27 mmol) BuLi (1.6M in hexane) was added and the resulting soln. stirred for 10 min at −78°. Two Et_2O solns. (8 ml each), one containing cyclohex-2-en-1-one (225 mg, 2.3 mmol) and the other containing BuMgCl (2.3 mmol), were then added simultaneously *via* a syringe pump over 13 min. After the addition was complete, the mixture was quenched with a sat. NH_4Cl soln. (*ca.* 15 ml). The workup and determination of the ee were carried out as described for the catalytic procedure using **2** as catalyst precursor. Yield: 92%; ee: 50%.

Method B. A 0.169 mM soln. of **1** (0.52 ml (0.088 mmol)) in Et_2O was added to a soln. of 34 mg (0.022 mmol) of tetrakis[iodo(tributylphosphine)copper(I)] and 10 mg (0.064 mmol) of 2,2,6,6-tetramethylpiperidin-*N*-oxyl (TEMPO·) in 10 ml of Et_2O at r.t. The resulting soln. was cooled to −78°. Then, 0.19 ml (0.31 mmol) of BuLi (1.6M in hexane) was added and the resulting soln. stirred for 10 min at −78°. Then, 0.5 µl (0.028 mmol) of H_2O were added through the needle of the micro syringe, which dipped into the soln.: subsequently; two Et_2O solns. (8 ml each), one containing cyclohex-2-en-1-one (25 mg, 2.3 mmol) and H_2O (0.5 µl, 0.028 mmol) and the other containing BuMgCl (2.3 mmol), were then added simultaneously *via* a syringe pump over 13 min. After the addition was complete, the mixture was quenched with a sat. NH_4Cl soln. (*ca.* 15 ml). Workup and determination of ee were carried out as described for the catalytic procedure using **2** as catalyst precursor. Yield: 94%; ee: 50%.

Typical Catalytic Reaction Procedure Using CuI as Catalyst Precursor. BuLi (0.14 ml, 0.22 mmol; 1.6M in hexane) was added to a suspension of 14 mg (0.074 mmol) of CuI in 10 ml of Et_2O at −78°. The suspension was stirred for *ca.* 3 min over the cooling bath and then 10 min at −78°. The color changed from grey to black. Now, 0.56 (0.074 mmol) of 0.132 mM soln. of **1** in Et_2O was then added at −78° and stirring continued for 10 min. Two Et_2O solns. (8 ml each), one containing cyclohex-2-en-1-one (225 mg, 2.3 mmol) and the other containing BuMgCl (2.3 mmol), were then added simultaneously *via* a syringe pump over 13 min. After the addition was complete, the mixture was quenched with a sat. NH_4Cl soln. (*ca.* 15 ml). Workup and determination of ee were carried out as described for the catalytic procedure using **2** as catalyst precursor. Yield: 90%; ee: 50%.

Typical Catalytic Reaction Procedure Using [Cu(Bu$_2$S)$_2$I] as Catalyst Precursor. [Cu(Bu$_2$S)$_2$I] (42.7 mg (0.088 mmol)) was added with a micro syringe to a soln. of 0.17 ml (0.27 mmol) of BuLi (1.6M in hexane) in 10 ml of Et_2O at −78°. The resulting soln. was stirred for 10 min at −78°. Then, 0.56 ml (0.074 mmol) of a 0.132 mM soln. of **1** in Et_2O were added at −78°. The soln. was stirred for 10 min. Two Et_2O solns. (8 ml each), one containing cyclohex-2-en-1-one (225 mg, 2.3 mmol) and the other containing BuMgCl (2.3 mmol), were then added simultaneously *via* a syringe pump over 13 min. After the addition was complete, the mixture was stirred for 10 min and then quenched with a sat. NH_4Cl soln. (*ca.* 15 ml). Workup and determination of ee were carried out as described above. Yield: 90%; ee 50%.

Determination of ee. 3-Butylcyclohexan-1-one. Acetalization with (*R,R*)-butane-2,3-diol and determination of ee by ^{13}C-NMR-spectroscopy: we followed the procedure described by *Hiemstra* and *Wynberg* [7]. The ^{13}C-NMR spectra were recorded with a size of 32 K and a relaxation delay of 2 s.

Acetalization with (R,R)-Pentane-2,4-diol. A suspension of 10 µl of 3-butylcyclohexan-1-one, 20 mg (0.2 mmol) of (*R,R*)-pentane-2,4-diol, 50 mg *Amberlyst 15* (activated at 130°), and 1 g of molecular sieves (*Union Carbide*, type 3 Å, activated at 250° at high vacuum) in 15 ml of Et_2O was stirred at r.t. overnight. The solids were separated by centrifugation, and the resulting soln. was used for the determination of ee by GC (temp. program: 150° isotherm). Only traces of substrate were found.

3-Phenylcyclohexan-1-one. We used the same procedure as described for 3-butylcyclohexan-1-one (temp. program: 150°, heating up to 250° (30°/min)).

3-Butyl-5-pentanolide. Acetalization with (*R,R*)-butane-2,3-diol: a soln. of 10 µl of 3-butyl-5-pentanolide 20 mg (0.2 mmol) of (*R,R*)-butane-2,3-diol, 100 µl Me_3SiCl, and 4 µl Me_3SiTf in 15 ml of Et_2O was stirred overnight at r.t. It was then extracted with a Na_2CO_3 soln. and the Et_2O phase filtered over *Alox*. The resulting soln. was used for the determination of ee by GC (temp. program: 150° isotherm). Thereby, only traces of substrate were found.

1,3-Diphenylheptane-1-one. The ee was determined with HPLC (*Chiracel* o.d., 25 × 0.46 cm i.d., eluant. 0.25% i-PrOH in hexane, flow rate 0.5 ml/min, UV detector).

Single-Crystal X-Ray Analysis. $C_{76}H_{82}O_{10}P_4S_2Cu_2$, f.w. = 1470.6, monoclinic, space group C_2, a = 26.146(2) Å, b = 13.385(1) Å, c = 23.514(2) Å, β = 91.51(1)°, V = 8226 Å^3, z = 4. The cell constants were determined from a least-squares fit of the setting angles for 25 accurately centered reflections. A *Philips PW 1100* automatic diffractometer was used for data collection using graphite monochromated MoK_α radiation. The intensities of 7800 independent reflections with $\Theta < 50°$ were measured, of which 5240 were classified as observed with $I > 3\sigma(I)$. Raw intensities were reduced to structure factor amplitudes by correction for scan speed, background, and *Lorentz* and polarizations effects. Absorption corrections were not applied. The structure were solved by direct methods

(SDP MULTAN 82). The structure was refined by full-matrix least-squares calculations with anisotropic displacement parameters for Cu-, S-, and P-atoms to a final R value of 0.072. Some disordered solvent was detected in the crystal. Surprisingly, a five-membered ring was found, which is not compatible with the solvent used. It could be that this five-membered ring is simulated by desorder in the crystal. A table of positional parameters has been deposited as *Supplementary Material.*

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