Enantioselective Conjugate Addition of Grignard Reagents to Enones Catalyzed by Chiral Zinc(II) Complexes

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of products given in Table III were calculated.

Reaction of 6a/7a with DL-Dithiothreitol. (a) On a Preparative Scale. **7a** (704 mg, 1 mmol) was dissolved in a stirred mixture of 1,4-dioxane (25 mL) and water (30 mL), DL-DTT (154 mg, 1 mmol) was added, and the colorless precipitate was filtered off after 30 min. Recrystallization from acetonitrile gave 140 mg (48.1%) of pure **9a**, mp 148–150 °C, identical in every respect with **9a** previously described.[2]

(b) ^{1}H NMR Monitored Reactions. A solution of **6a** was prepared by dissolving **7a** (10 mg, 14 μmol) in CD_3OD (1 mL), pH <1.0 (20 μL of 20% DCl per mL of CD_3OD) and DL-DTT (5.2 mg, 34 μmol) was added. **6a** did not react with the excess of DL-DTT (molar ratio 1:2.4) during 46 h. For the reaction with the thiol to start, the pH had to be increased to 3.0.

Under neutral conditions, **7a** (12–13 mg/mL) in CD_3CN was reduced with increasing amounts of DL-DTT (1.18, 2.35, 5.80 mg/mL) to the corresponding sulfide **9a**. This reaction could be easily followed in a quantitative manner by NMR as there were some well-separated characteristic signals for the starting materials as well as for the products. Selected signals: **7a**, δ 4.02 (4′-OCH_3), 7.28 (H-5′), 8.92 (H-6′); **9a**, δ 3.88 (4′-OCH_3), 6.91 (H-5′), 8.38 (H-6′); DL-DTT, δ 2.62 (CH_2S), 3.60 (CHO); cyclic oxidation product of DTT, δ 2.84–3.06 (CH_2S), 3.44–3.48 (CHO). From the integrals of these signals, the amount of DL-DTT consumed for the reduction of 1 mol of **7a** to **9a** was calculated for different DL-DTT/**7a** ratios: These values are 0.78, 0.82, and 0.88 mol for the initial mole ratios DL-DTT/**7a** = 0.41, 0.83, and 2.21, respectively.

Registry No. **1a**, 86604-68-4; **1b**, 73590-58-6; **1c**, 110374-18-0; **2a**, 102804-86-4; **2b**, 102353-88-8; **3a**, 126543-60-0; **4a**, 126543-62-2; **4b**, 126543-64-4; **4c**, 126543-66-6; **5a**, 126543-68-8; **5c**, 126543-70-2; **6a**, 126543-72-4; **6b**, 126578-23-2; **6c**, 126543-74-6; **7a**, 126543-75-7; **7b**, 126578-24-3; **9a**, 86604-69-5; **9b**, 73590-85-9; DTT, 27565-41-9; 2-mercaptoethanol, 60-24-2.

Enantioselective Conjugate Addition of Grignard Reagents to Enones Catalyzed by Chiral Zinc(II) Complexes

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Various chiral zinc(II) complexes catalyze the asymmetric 1,4-addition of Grignard reagents to α,β-unsaturated ketones with high chemoselectivities (yields of 1,4-adducts, 83–99%), high regioselectivities (1,4/1,2 ratios up to 499) and modest enantioselectivities (ee up to 33%). A study of several factors, i.e. ligand, solvent, counterions, order and rate of additions, temperature, and the nature of Grignard reagents, that influence the regio- and enantioselectivities is given. Based on the addition of isopropylmagnesium halides to 2-cyclohexenone as a model reaction, it was established that the highest enantioselectivities are reached with in situ prepared zinc complexes derived from optically active diamino alcohol ligands using lithium bases in tetrahydrofuran as the solvent. A mechanistic rationalization is given.

Conjugate addition reactions are among the most important methods for carbon–carbon bond formation with a central role for organocopper reagents.[1] Much effort has been devoted to chemo- and stereoselective additions of organocuprates, and considerable progress has been made using so-called second generation organocopper reagents,[2] by the use of organocopper catalysts[3] and in asymmetric conjugate addition via organocuprates. Following the early work of Kretchmer[4] on asymmetric induction in conjugate addition via organocopper(I) reagents in the presence of (−)-sparteine, numerous approaches to achieve asymmetric conjugate addition have been described.[5] High diastereoselectivities have been achieved using chiral enones and chiral enonates[6] and cuprates with chiral transferable ligands.[7] Impressive results were obtained by several groups on cuprates with chiral nontransferable ligands. Leyendecker and co-workers[8] reported the addition of Me_2CuLi to chalcone, using 4(*S*)-(*tert*-butylthio)-(*S*)-prolinol as tridentate chiral ligand with ee's as high as 94%. Optical yields ranging from 41 to 83% were reported by Dieter and Tokles[9] in a systematic investigation of conjugate additions to enones employing chiral organo(hetero)cuprates based on (*S*)-proline-derived chiral nontransferable ligands. Up to 50% ee was reached in asymmetric additions of chiral amidocuprates.[10] Corey and co-workers[11] reported the enantioselective addition of chiral cuprate reagents to 2-cycloalkenones (ee 75–95%) using (+)- and (−)-ephedrine derived chiral ligands. Lippard[12] recently described the first catalytic conjugate addition of Grignard reagents to 2-cyclohexenone (ee 4–14%) in the presence of a chiral copper(I) catalyst employing chiral *N,N′*-dialkyl-substituted aminotroponeimines as ligands. In recent years a parallel development on conjugate addition by organozinc reagents is seen, initiated by the discovery of Isobe and co-workers[13] of the facile

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Table I. Conjugate Addition of i-PrMgBr to 2-Cyclohexenone Catalyzed by Zinc Complexes

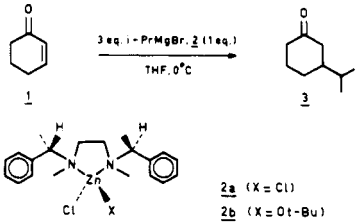
entry	catalyst (mol %)	reaction[a] conditions	1,4/1,2[b] ratio	yield,[c] %	ee,[d] %
1	–	A	3	25	–
2	**5** (0.1)	A	5.7	81	–
3	**6** (0.1)	A	19	88	–
4	**7** (1.0)	A	49	91	18
5	**8** (1.0)	A	32.3	90	16
6	**8** (1.0)	B	99	90	26
7	**8** (1.0)	C	32	95	26

[a] Reaction conditions employed: (A) Reactions were carried out by adding equimolar Et_2O solutions of i-PrMgBr to a THF solution of the catalyst followed by the addition of equimolar amounts of 2-cyclohexenone (see also the Experimental Section). (B) As A except reverse addition of i-PrMgBr and 2-cyclohexenone solutions; addition time 15 min; total reaction time 30 min. (C) As B except for addition time of 50 min; total reaction time 90 min. [b] Ratios determined by GLC. [c] Isolated yield of 1,4-adduct. [d] Determined by the ratio of diastereomeric ketals (see text).

conjugate addition of lithium triorganozincates. Subsequent studies resulted in selective alkyl group transfer from mixed lithiumtrialkylzincates,[14] the use of alkoxides as nontransferable ligands for zinc complexes,[15] and 1,4-additions of Grignard reagents mediated by *N,N,N',N'*-tetramethylethylenediamine zinc dichloride.[16] Langer and Seebach[17] reported the enantioselective addition (ee 16%) of lithium trialkylzincates to 2-cyclohexenone using (*S,S*)-1,4-bis(methylamino)-2,3-dimethoxybutane as a chiral cosolvent. In this article we describe the first results of the enantioselective 1,4-additions of Grignard reagents catalyzed by chiral zinc(II) complexes. This study was initiated by the challenging goal to develop efficient catalysts for the enantioselective 1,2- and 1,4-addition of organometallic reagents and the following observations: (i) Asymmetric induction in 1,4-additions using an organozincate with either a chiral diamine or a chiral alkoxide ligand was seen.[15] (ii) Preliminary studies indicated a catalytic effect of various zinc complexes on the 1,4-addition of Grignard reagent to enones.[16]

Results

In initial experiments employing the trialkylzincate prepared from isopropylmagnesium bromide and optically active (*S,S*)-*N,N'*-dimethyl-*N,N'*-bis(1-phenylethyl)-1,2-ethylenediamine zinc dichloride (**2**), 2-cyclohexenone was converted into 3-isopropylcyclohexanone (**3**) with a low though significant (5%) ee (eq 1).[15] The exchange of one



(1)

isopropyl group for a *tert*-butoxide group in the zincate resulted in an increase of both the yield (94%) and the ee (14%).

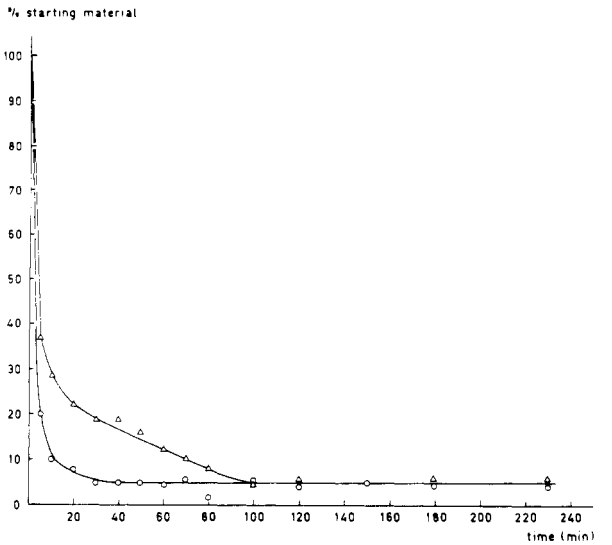
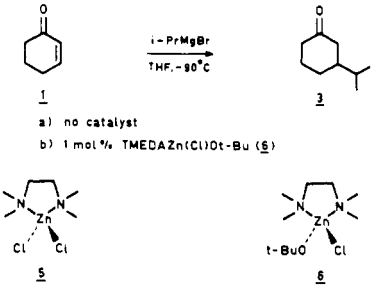


Figure 1. Decrease of 2-cyclohexenone (**1**) versus time in the reaction with i-PrMgBr at −90 °C in THF: (△) no catalyst, (○) using 1.0 mol % TMEDAZn(OtBu)Cl (**6**).

Furthermore the use of the (1*S*,2*R*,5*R*)-menthyloxy group as a nontransferable ligand in the tetramethylethylenediamine (TMEDA) zincate mediated 1,4-addition shown in eq 1 gave **3** with an ee of 9%. Much to our surprise, employing 1 mol % of a zinc(II) catalyst, prepared in situ from $ZnCl_2$ and (2*S*,2'*S*)-2-(hydroxymethyl)-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (Mukaiyama's ligand, **4A**) (Figure 2), in the conjugate addition of isopropylmagnesiumbromide to **1** afforded 3-isopropylcyclohexanone in 91% isolated yield with an ee of 18% and a 1,4/1,2 ratio of 98/2 (see Table I, entry 4). These results prompted us to study systematically the conjugate addition of Grignard reagents mediated by catalytic amounts of zinc(II) complexes in order to devise a catalytic process for enantioselective conjugate addition.

Catalytic Activity. The use of catalytic amounts (0.1 mol %) of $TMEDAZnCl_2$ (**5**) substantially increases both the yields of 1,4-adducts and the 1,4/1,2 ratios in the conjugate addition of Grignard reagents to enones. Table I, entry 2, gives the result for a typical case. The use of an alkoxide as a nontransferable ligand, as is present in catalyst **6**, increases yield and selectivity in stoichiometric[15] and catalytic reactions (entry 3). Variable amounts of 1,4- and 1,2-adducts are generally found in the Grignard addition to enones.[18] An extensive literature search learned that numerous ambiguous data exist on the extent of 1,4-adduct formation and the formation of condensation product by the Grignard reagent itself in metal-mediated additions to enones. In order to assess the extent of the competing uncatalyzed conversion of enones by Grignard reagents we studied the model reaction depicted in eq 2.



(2)

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Table II. Asymmetric Conjugate Addition of Grignard Reagents to 2-Cyclohexenone: Effects of Temperature, Alkyl Group, Halides, and Alkali Metal[a]

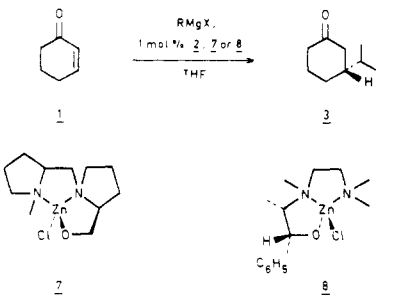
entry	Grignard reagent (RMgX) R	X	temp, °C	catalyst	1,4/1,2[b] ratio	yield,[c] %	ee,[d] %
1	Et	Br	-90	7	2.7	68	4
2	i-Pr	Br	-90	7	49	91	18
3	*n*-Bu	Br	-90	7	5.7	74	5
4	i-Pr	Cl	-90	7	499	97	22
5	i-Pr	I	-90	7	5.1	65	9
6	*n*-Bu	Cl	-90	7	49	96	9
7	*n*-Bu	I	-90	7	4.3	69	0
8	i-Pr	Cl	-90	8	249	97	17
9	i-Pr	Br	-90	8	32.3	92	26
10	i-Pr	I	-90	8	3.0	49	3
11	i-Pr	Cl	0	8	9.0	81	7
12	i-Pr	Cl	0	**2a**	7.3	75	7
13	i-Pr	Cl	-90	**2a**	142	97	17
14	i-Pr	Cl	-90	**2b**[e]	166	95	21
15	i-Pr	Cl	-90	**2b**[f]	193	89	11
16	i-Pr	Cl	-90	**2b**[g]	142	93	17

[a] Reaction conditions, see Table I, procedure B (1.0 mol % catalyst). [b] Ratios determined by GLC. [c] Isolated yield of 1,4-adduct. [d] Determined by the ratio of diastereomeric ketals (see text). [e] Using LiOtBu in the preparation of **2b**. [f] Using NaOtBu in the preparation of **2b**. [g] Using KOtBu in the preparation of **2b**.

The conversion of 2-cyclohexenone by i-PrMgBr both uncatalyzed (a) and catalyzed by TMEDAZnCl (OtBu) (**6**) (b) is shown in Figure 1. A clear rate enhancement due to the presence of the zinc complex is seen. Furthermore the catalyzed reaction yields mainly 1,4-adduct as 81% of **3** and 13% condensation products[18] were isolated. In contrast herewith the uncatalyzed Grignard addition gave 55% of condensation products and only 40% of **3** after 3 h.

It should be noted that adding more than 1 equiv of alkoxide to the diaminezinc halides (such as **5**) resulted in inactive catalysts. Furthermore control experiments showed that $ZnCl_2$ itself can act as a catalyst for the 1,4-addition of Grignard reagents. A typical result is the formation of 3-isopropylcyclohexanone in 81% yield from the addition of i-PrMgBr to **1** mediated by 5 mol % $ZnCl_2$. In addition it was established that no significant asymmetric induction (ee <5%) occurred in the uncatalyzed 1,4-addition of i-PrMgBr in the presence of the chiral ligand **4A**. Next the influence of the order of addition and the rate of addition of the reagent on the yield and the regio- and enantioselectivity was examined (Table I, entries 5, 6). For these experiments a catalyst (with the proposed structure **8**) was prepared from the lithium salt of ligand **4B** and $ZnCl_2$. Although the yield of **3** did not depend upon the order of addition, both regioselectivity and enantioselectivity increased when the Grignard reagent was added to the mixture of enone and catalyst. A lower addition rate (entries 6, 7) did not affect the ee of **3** but had a reverse effect on the yield and the selectivity. Similar effects were observed when the neutral ligands were employed in preparing the catalysts or when $TMEDAZnCl_2$ (**5**) or chiral zinc complex **2** was used. Based on these data and the reasons mentioned above the asymmetric additions (vide infra) were performed under standard conditions with in situ prepared zinc catalysts using a procedure in which the Grignard reagents are added to the substrates with an addition time of 15 min (Table I, reaction conditions B).

Asymmetric Induction in the 1,4-Addition. The low though significant enantioselectivities in the 1,4-addition to 2-cyclohexenone using catalytic amounts of homochiral zinc complex **2** or in situ prepared zinc complexes initiated the study of several variables of this reaction. Table II (entries 1–3) show the effect of changing the alkyl group in RMgBr in the Grignard addition to **1** mediated by 1 mol % of chiral catalyst (eq 3). The zinc catalyst, presumably



(3)

of structure **7**, was prepared in situ by stirring equimolar amounts of dry $ZnCl_2$ and ligand **4A** at room temperature followed by deprotonation of the alcohol group in the ligand by *n*-BuLi.

It is clear from these experiments that i-PrMgBr gave the best results, although this picture might change when different ligands are used in the preparation of the catalyst. The effect of the modification of the halide in isopropyl and *n*-butyl Grignard reagents was studied with catalysts prepared from ligands **4A** and **4B** (Table II, entries 2–10). We assume that zinc complexes **7** and **8** are initially formed using ligands **4A** and **4B**. Again higher enantioselectivities were obtained with the isopropyl Grignard compared to the *n*-butyl Grignard. The effect of the halide modification can be summarized as follows: (a) Grignard reagents from alkyl iodides gave the worst results (yield, regioselectivity, and enantioselectivity). (b) In all cases the highest chemical yields and 1,4/1,2 ratios were achieved with Grignard reagents prepared from alkyl chlorides. (c) The influence of chloride or bromide on the enantioselectivities cannot be readily translated to catalysts prepared from different ligands as opposite results were obtained with ligands **4A** and **4B** (entries 2, 4 and 8, 9). The effect of the temperature on the addition of i-PrMgBr to **1** is shown in Table II (entries 8, and 11–13) using catalysts prepared from ligands **4B** and **4L** (eq 3).

As expected both regioselectivity and enantioselectivity improved by decreasing the temperature from 0 to -90 °C. Also a favorable effect on the chemical yield was observed. In 1,4-addition reactions mediated by organocopper(I) reagents it has been observed that lithium ions may have

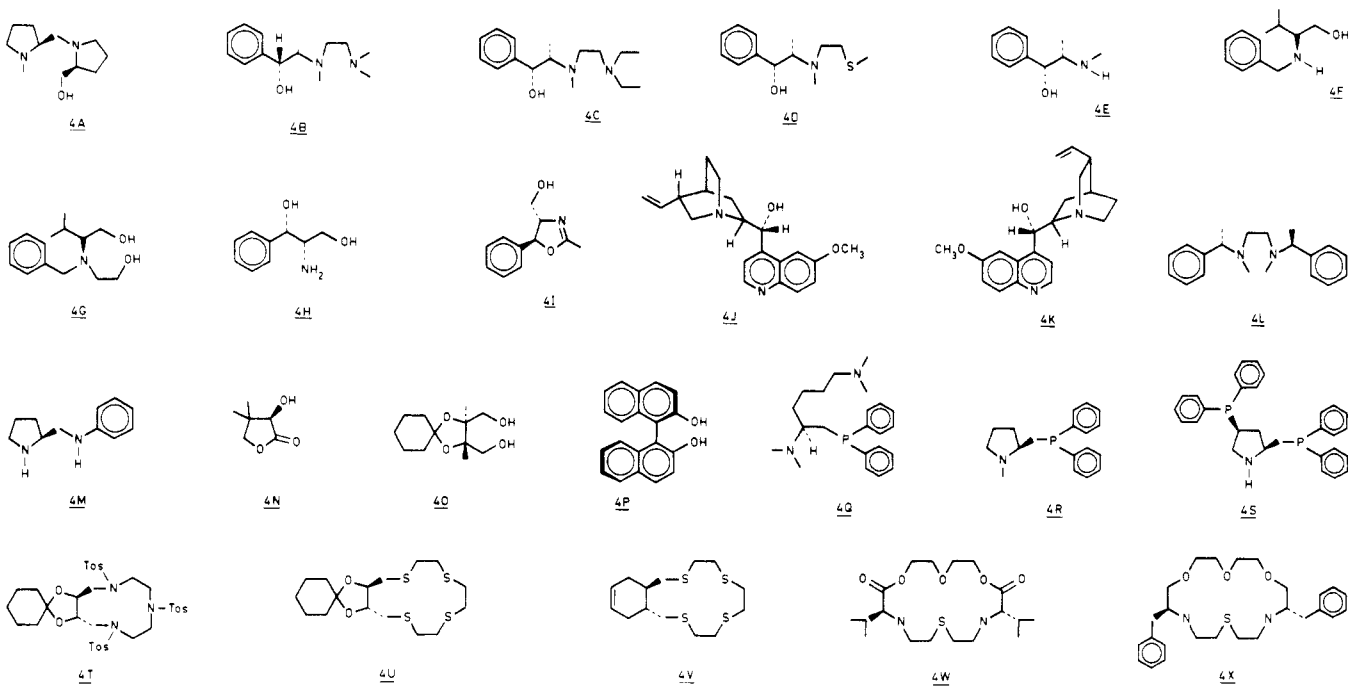


Figure 2. Structures of the chiral ligands **4A–X**.

an important role (Li^+ coordination) in these reactions.[12] To reveal the importance of such an effect in the present reactions the influence of the counterion in the alkoxide employed for the catalyst preparation was briefly investigated. Complex **2a** was converted into the active zinc catalyst **2b** using lithium, sodium, or potassium *tert*-butoxide and subsequently used in the addition of i-PrMgCl to **1**. Small though significant improvements in the enantioselectivities are observed in the order Na^+, K^+, Li^+ (Table II, entries 14–16).

Ligand Modification. 2-Cyclohexenone was the substrate in these studies, and the ratio of isopropylmagnesium halide to enone was 1.1. Reactions were run on a 10-mmol scale at concentrations of approximately 0.2 M, following the procedure described above. The lithio salts of the amino alcohol ligands were prepared by deprotonation using *n*-butyllithium. Deprotonation was complete as no *n*-butyl adducts were found. All reactions were run at −90 °C using 1 mol % of zinc catalyst in situ prepared from $ZnCl_2$. The regioselectivity was determined by GLC calibrated with authentic product using an internal standard. The reported chemical yields of **3** are isolated yields of pure 1,4-adduct after distillation. The ee was determined by the ^{13}C NMR method[19] employing the (*R*,*R*)-butane-2,3-diol ketals. The absolute configuration was based on ^{13}C NMR following the analysis given by Corey et al.[11]

Figure 2 shows the chiral ligands used in this study. Four categories can be distinguished: (i) diamines and amino alcohols; (ii) alcohols and diols; (iii) phosphines and aminophosphines; (iv) crown ethers. The results of the screening of ligands **4A–X** are summarized in Table III. On the basis of the halide effect previously described, we used i-PrMgBr for the Corey type ligands[11] **4B**, **4C**, and **4D** and i-PrMgCl in all other cases. Excellent chemical yields of **3** were obtained in all cases (lowest yield 83%). Furthermore high regioselectivity was observed with 1,4/1,2 ratios varying between 11.5 (ligand **4C**) and 490 (ligand **4A**). These selectivities compare favorably with related cuprate additions[1] and organocopper catalyzed 1,4-additions.[12] Significant enantiomeric yields (>5%) were obtained for several of the chiral ligands investigated. The highest ee's were reached with ligands **4A** (ee = 22%) and **4B** (ee = 26%). It is noted that both these ligands are diamino alcohols. In only three other cases ee's exceeding 20% were reached: with amino alcohol **4F** (chemical yield 91%, 21% ee); diamine **4M** (89%, 21% ee) and bis-β-naphthol (**4P**) (91%, 21% ee). Further examination of the results in Table III show that amino alcohols and diamine ligands (category i) gave the highest enantioselectivities. The phosphines (iii, **4Q**, **4R**, **4S**) gave only

Table III. Effect of the Chiral Ligand[a]

entry	ligand	ratio 1,4/1,2[b]	yield,[c] %	ee,[d] %
1	**4A**	499	97	22
2	**4B**[e]	99	90	26
3	**4C**[e]	11.5	87	17
4	**4D**[e]	15.6	83	14
5	**4E**	249	93	17
6	**4F**	99	91	21
7	**4G**	110	85	17
8	**4H**	332	95	15
9	**4I**	165	92	16
10	**4J**	249	96	13
11	**4K**	99	87	5
12	**4L**[f]	141	93	17
13	**4M**[g]	199	89	21
14	**4N**	141	97	3
15	**4O**	141	95	11
16	**4P**	199	91	21
17	**4Q**	124	88	4
18	**4R**	99	87	4
19	**4S**	99	95	6
20	**4T**	165	96	8
21	**4U**	141	94	16
22	**4V**	165	99	17
23	**4W**	165	87	6
24	**4X**	49	89	10

[a] Reactions at −90 °C in THF using 1 mol % in situ prepared catalyst from $ZnCl_2$ and i-PrMgCl (see text). [b] Based on GLC. [c] Isolated yield of 1,4-adduct. [d] Determined by the ratio of diastereomeric ketals (see text). [e] Using i-PrMgBr. [f] Adding 1 mol % KOtBu. [g] When 1 mol % KOtBu is added during preparation of the zinc complex: ratio 1,4/1,2 = 249, yield = 82%; ee = 16%.

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Table IV. Effect of the Amount of Catalyst[a]

entry	ligand (mol %)	Grignard reagent (X in i-PrMgX)	ratio 1,4/1,2[b]	yield,[c] %	ee,[d] %
1	**4A** (1)	Br	49	91	18
2	**4A** (5)	Br	99	92	29
3	**4B** (1)	Cl	249	97	17
4	**4B** (5)	Cl	332	97	19
5	**4B** (100)	Cl	49	93	27
6	**4B** (1)	Br	99	90	26
7	**4B** (5)	Br	32.3	92	33
8	**4C** (1)	Br	11.5	87	17
9	**4C** (5)	Br	32.3	85	22
10	**4D** (1)	Br	15.7	83	14
11	**4D** (5)	Br	19	89	20
12	**4L**[e] (1)	Cl	165	95	21
13	**4L**[e] (5)	Cl	165	98	27
14	**4L**[f] (1)	Cl	14.2	93	17
15	**4L**[f] (100)	Cl	9	71	24

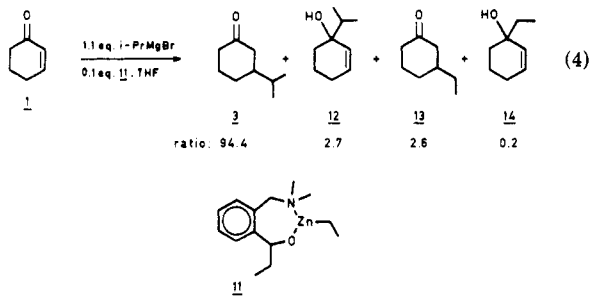
[a] Reactions of i-PrMgX and 2-cyclohexenone at −90 °C in THF using catalysts prepared in situ from $ZnCl_2$. [b] Determined by GLC. [c] Isolated yield of 1,4-adduct. [d] Determined by the ratio of diastereomeric ketals (see text). [e] Adding 1 mol %, respectively 5 mol %, of LiOtBu. [f] Adding 1 mol %, respectively 100 mol %, of KOtBu.

low ee's although chemical yields and 1,4/1,2 ratios are high. Chiral alcohols and crown ethers (ii and iii) gave enantioselectivities ranging from very low (3% ee for **4N**) to values comparable with those for diamines. In this respect the 21% ee reached with the bis-β-naphthol (**4P**) derived zinc catalysts is remarkable. The large stereocontrol by the ligand **4P** in asymmetric synthesis has ample precedent.[20]

Table IV summarizes the effect of the amount of catalyst on the chemical yield, regioselectivity, and enantioselectivity for four amino alcohol ligands and one diamine ligand. In the latter case equimolar amounts of lithium and potassium *tert*-butoxide are added as we have previously shown[15] that alkoxides improve both the catalytic activity and the stereoselectivity using zinc complexes prepared from diamines. A 5-fold increase of the amount of chiral catalyst markedly increased the ee in all cases whereas comparable yields and 1,4/1,2 ratios are found as for the 1 mol % cases. Stoichiometric use of chiral zinc complexes derived from **4B** and **4L** led to a decrease of chemical yield and selectivity but not to a substantially further improvement of the ee's. The best results in the catalytic enantioselective addition of i-PrMgBr to **1** so far were obtained with 5 mol % of zinc catalyst prepared from ligand **4B** leading to an ee of 33%.

Finally a number of experiments were conducted to get insight into the nature of the actual zinc complex that undergoes 1,4-addition. The reaction of TMEDAZn $(i\text{-Pr})_2$ (**9**) or TMEDAZn (i-Pr)OtBu (**10**), prepared from respectively **5** and **6** and i-PrMgBr, with 2-cyclohexenone did not yield any 1,4-adduct. Addition of 1 equiv of i-PrMgBr to **9** or **10** resulted, however, in 80% and 94% of 3-isopropylcyclohexanone, respectively. This indicates that a halide or alkoxide ligand bound to a (di)alkylzincate is essential or that complex formation between a Grignard reagent and an alkylzincate (as for **10**) is necessary to obtain an active species for 1,4-addition. The ligand-accelerated addition of dialkylzincates to aldehydes has been well examined in recent years.[21] To study the possible intermediacy of dialkylzinc species in the conjugate addition first a solution of diethylzinc was added to 2-cyclohexenone, but no trace of reaction was observed. Addition of 10% TMEDA and KOtBu (based on Et_2Zn) resulted in 10% 3-ethylcyclohexanone. A "salt effect" was not observed as addition of $ZnCl_2$ or $MgCl_2$ did not result in further product formation. Addition of 10% i-PrMgBr to the mixture of Et_2Zn and 2-cyclohexenone initially treated with 10% TMEDA, KOtBu resulted in the conversion of 20% of starting material to provide 12% 3-ethylcyclohexanone and 8% 3-isopropylcyclohexanone. This result indicates that both ethyl and isopropyl groups are transferred upon addition of i-PrMgBr to the zinc complex prepared in situ from Et_2Zn and TMEDA, KOtBu.

Subsequently the well-characterized racemic monoethyl zinc complex **11**[22] containing an amino alcohol bidentate ligand was employed. Addition of i-PrMgBr to **1** using 10 mol % of **11** resulted in four addition products, **3** and **12**–**14**, with the 1,4-adducts as the major ones (eq 4). Both



(4)

11

isopropyl and ethyl groups are again transferred resulting in an isolated yield of **3** of 86%. Enantiomerically pure monoethylzinc compound **11** is a crystalline dimeric complex. The dimeric structure (**11b**) was recently established by X-ray analysis.[22] Employing 5 mol % of **11b** in the conjugate addition of i-PrMgBr to **1**, there was obtained the 1,4-adduct **3** in 87% yield with an ee of 9%. Furthermore 1.4% 3-ethylcyclohexanone was obtained.

A catalytic effect of diaminezinc complexes on the addition of alkyllithium reagents was also seen although no synthetically useful results were obtained. Thus the addition of *n*-butyllithium to **1** in the absence or presence of 10 mol % TMEDAZn(OtBu)Cl resulted in 3-butylcyclohexanone in <0.5% and 9% yields, respectively. An attempt to study the zinc complexes described above by ^{67}Zn NMR[23-25] in THF solution did not result in detectible signals that could be ascribed to actual zinc complexes involved in the 1,4-addition.

Discussion

This study describes the first results on asymmetric 1,4-additions of Grignard reagents to enones catalyzed by organozinc complexes. Preliminary investigations quickly revealed that (i) various zinc complexes improved yields and selectivities in the conjugate addition of Grignard reagents and (ii) the enantioselectivity depends on a number of variables. Therefore we devoted this study with a few zinc complexes on the effect of temperature, halide,

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and counterion as well as the variation of a limited number of classes of chiral ligands to assess some of the more important factors that govern these asymmetric additions. 2-Cyclohexenone was chosen as the substrate to make comparison with literature results on various asymmetric cuprate additions possible. In the major part of this work isopropyl Grignard reagents were used as these showed the highest induction in preliminary studies. The enantiomeric excess was determined in all cases by ^{13}C NMR analysis of the (2*R*,3*R*)-2,3-butanediol ketals[19] in order to eliminate reproducibility effects with optical rotation measurements or HPLC analyses of small amounts of **3**.[10] The 3*R* absolute configuration is assigned to **3** obtained with most aminoalcohol ligands, on the basis of ^{13}C NMR data using the analysis followed by Corey[11] and Posner[26] and coworkers. When the configuration at the chiral centers of the crucial vicinal amino alcohol group was inverted, as is the case when quinidine (**4K**) was used instead of quinine, (3*S*)-**3** was formed. In an early stage we studied the method of executing the addition as well as solvent modifications. Yields of conjugate additions run in ether were low compared to THF. This result contrasts with cuprate additions were often the reverse solvent effect is observed.[10] It was shown that slow addition (15 min) of i-PrMgX to the solution containing the substrate and catalyst (method B) gave higher regio- and enantioselectivities although a further increase in addition time did not lead to further improvement. The effect of the order of addition might be ascribed to diminished uncatalyzed 1,4-addition of RMgX and suppression of condensation reactions due to excess free Grignard reagent.[18] From Figure 1 it can be seen that both catalyzed and uncatalyzed conversions of 2-cyclohexenone with i-PrMgBr are fast reactions, i.e. 80% conversion in 5 min employing 1 mol % catalyst. Although a major part of the product isolated from the uncatalyzed reaction is not the 1,4-adduct, it is possible that a substantial part of racemic **3** is formed via the noncatalyzed route. This points to an important factor in the present study; the competing uncatalyzed reaction is not completely suppressed and can (in part) be responsible for the rather low ee's obtained so far. The formation of chiral Grignard reagents by ligand coordination[28,29] can only have a minor effect on the asymmetric induction as control experiments indicate.

The most extensive part of this investigation deals with the effect of chiral ligand structure. A few conclusions can be drawn: (i) The conjugate addition is fast and surprisingly selective with all ligands tested. The lowest isolated yield of **3** was 83% and the worst 1,4/1,2 ratio 11.5 (Table III). (ii) The better chiral ligands were amino alcohols. (iii) Phosphine and alcohol ligands gave hardly any asymmetric induction except for bis-β-naphthol, which gave a remarkable high (ee 21%) enantioselectivity. (iv) A significant improvement of the enantioselectivity was due to the presence of lithium cations. The low selectivity with phosphines might be ascribed to poor complexation with zincates.[27] Comparing the zinc-mediated conjugate additions described here and the related copper-mediated asymmetric additions, it is interesting to note that amino alcohols are also the better chiral auxiliaries in several organocuprate additions. Using the best amino alcohol ligands **4A**, **4B**, **4C**, and **4D** and the chiral diamine **4L** we investigated some other variables. The ee's were dependent on the halide used. As the higher enantioselectivities were observed with i-PrMgCl for the Mukaiyama type ligand **4A** and with i-PrMgBr for the Corey type ligand **4B** these combinations were also employed in further investigations. The nature of the halide effect is unknown, but similar changes in optical yields upon halide modification have been observed in cuprate additions.[10] Incorporation of these external ligands (including solvent) in the catalyst complex cannot be excluded.[9] As expected the optical yields increase at lower temperature but only approximately 2-fold increases of the ee's are observed (Table II) in going from 0 °C to −90 °C. This corresponds well with the temperature effect observed in conjugate additions of heterocuprates,[9,10] i.e. for an (*S*)-α-naphthylethylamide cuprate an ee of 20% at 0 °C and 30% at −78°[10] was found. A significant improvement of the enantioselectivity due to the presence of lithium cations was observed with the lithium salts of aminoalcohols or upon addition of lithium alkoxides to diamine ligands in the zinc-catalyzed reaction. It is well precedented that lithium is readily chelated by amine and alcohol (ether) containing ligands[31] and that chelated Li^+ can associate with alkylmetals, e.g. alkylcopper[9,11] and alkylzinc[30] moieties. In the ephedrine-based asymmetric cuprate additions devised by Corey et al.,[11] the presence of electrophilic lithium is crucial for the reaction to occur.[32] In the present system the Li effect might in the same way point to the presence of coordinated lithium in the chiral Zn complex which could reinforce binding of i-PrMgX or 2-cyclohexenone and consequently improve the selectivity. It is furthermore demonstrated that raising the amount of zinc complex from 1 to 5 mol % results in higher ee's for five selected ligands[33] (Table IV). We attribute this concentration effect mainly to suppression of the uncatalyzed 1,4-addition of i-PrMgX. In the present study the highest enantioselectivities so far were obtained with zinc complex **8**, resulting in 3-isopropylcyclohexanone with ee's of 26% and 33% using 1 mol % and 5 mol % of **8**, respectively. These selectivities, although still rather low, compare favorably with earlier results in stoichiometric organocopper additions. For instance ee's of 80–89% were reached[9,11] with chiral ligand to substrate ratios 110–350 times the ratios used here. The same holds for the enantioselective 1,4-addition of organozincates described by Langer and Seebach with optical yields up to 24% (ligand–substrate ratio over 10^3 times the ratios used here). The ee's are also significant when compared to recent studies by Lippard and co-workers[12] who described the first asymmetric conjugate addition of Grignard reagents to 2-cyclohexenone catalyzed by chiral organocopper(I) complexes (ee's up to 14% with 2 mol % catalyst). Finally it must be emphasized that the complexity of organozinc and organocopper additions in general, the not well defined structures, the aggregation of these metal complexes and the lack of detailed mechanistic insight combined with the sensitivity of the present system to substrate, Grignard

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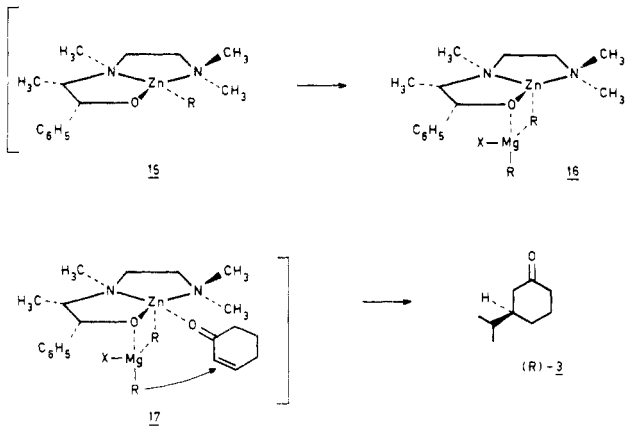
Scheme I



reagent, ligands, and halides makes it difficult to postulate a catalytic cycle. The enantioselective additions with a diamino alcohol derived catalyst can be rationalized however by a model shown in Scheme I. Various results and literature data support this scheme. $ZnCl_2$ reacts first with the alkoxide derived from **4B** and subsequently with i-PrMgBr to provide complex **15** containing a tetracoordinated (sp^3) Zn(II) monoalkyl species.[34] A related tetrahedrally surrounded Zn complex was recently proposed by Oppolzer to rationalize the stereochemical results of the diamino alcohol catalyzed asymmetric addition of dialkylzincates.[33] A Li analogue of **15** was proposed as the key complex in enantioselective cuprate additions[11] and dialkylzinc additions.[30] Furthermore a recent X-ray structure of a monoalkylaminoalkoxide chelated zinc(II) complex was shown to be dimeric in nature with a tetrahedrally coordinated Zn.[35] The dimeric complex was readily dissociated by external monodentate ligands, i.e. aldehyde or R_2Zn.[35] In the case of **15** the structure shown may be one among various complexes in equilibrium; coordination of Mg salts or dimerization via pentacoordinated Zn[34] cannot be excluded. Binding of the Grignard reagent via coordination of the Mg to the oxygen exo to the bicyclic Zn complex results in the active catalyst complex **16**. This is consistent with the catalytic 1,4-addition of i-PrMgBr using monoalkyl complex **11**. Alternatively **16** contains an R-bridged four-membered bimetallic structure as is proposed to be the crucial structural entity in binuclear Zn catalysts for 1,2-addition[35] and Li–Cu reagents for 1,4-additions.[11] Activation of the enone via coordination to Zn involves a pentacoordinated Zn(II) intermediate **17**.[27,34] In this stage a third metal (i.e. Li) might be involved as proposed for cuprate additions.[11] Finally transfer of the Mg-bound alkyl group results in the formation of (*R*)-**3**. Scrambling of both R groups could occur—as was observed with complex **11** and i-PrMgBr—depending upon the geometry of the binuclear complex.[36] The results described here clearly indicate that extensive mechanistic study will be necessary in order to be able to synthesize rationally designed ligands for Zn catalysts that produce high enantioselectivities in the conjugate addition of Grignard reagents. Such studies are in progress.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300S spectrometer. The gas chromatographic analyses were performed on a methyl–silicone gum column (15 m × 0.53 mm × 2.65 μm) at 110 °C.

Materials. Products were identified by co-injection with authentic samples. Decane was used as an internal standard. All reactions were carried out under a N_2 atmosphere with oven-dried glasware. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone under a N_2 atmosphere. The Grignard reagents were prepared under a N_2 atmosphere in ether and titrated in THF with an 1 N solution of s-BuOH in xylene using bipyridyl as indicator. Only Grignard reagents whose normality exceeded 2 N were used. The following compounds were commercially available and used without further purification: 2-cyclohexenone (Janssen); (2*S*,2*S*')-(−)-2-(hydroxymethyl)-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (**4A**, Merck); ephedrine [(1*R*,2*S*)-2-(methylamino)-1-phenyl-1-propanol, **4E**, Aldrich]; (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol (**4H**, Merck); (4*S*,5*S*)-(−)-4,5-dihydroxy-4-(hydroxymethyl)-2-methyl-5-phenyloxazole (**4I**, Merck); quinine (**4J**, Janssen); quinidine (**4K**, Janssen); 5-(−)-2-(anilinomethyl)pyrrolidine (**4M**, Merck); D-(−)-pantolactone [D-(−)-2-hydroxy-3,3-dimethyl-γ-butyrolactone, **4N**, Janssen]; (*S*)-(−)-1,1'-bi-2-naphthol (**4P**, Janssen); (2*S*,4*S*)-(−)-4-(diphenylphosphino)-2-[(diphenylphosphino)-methyl]pyrrolidine (**4S**, Merck).

The zinc complex of (*S*,*S*)-(−)-*N*,*N*'-dimethyl-*N*,*N*'-bis(1-phenylethyl)-1,2-ethylenediamine (entry 10, **4L**) was prepared as previously described.[15] The compounds **4C**, **4D**, **4F**, **4G**, **4O**, **4Q**, **4R**, **4T**, **4U**, **4V**, **4W**, and **4X** were kindly provided by J. Buter and Prof. R. M. Kellogg. Compound **11** was provided by W. Menge and Prof. H. Wynberg. Compound **4B** was prepared according to Corey.[11] The $ZnCl_2$ stock solution was prepared as described by Isobe.[13] The (*R*,*R*)-butane-2,3-diol used for the ketalization was prepared according to Hiemstra.[19]

Conjugate Addition of Grignard Reagents to 2-Cyclohexenone Using Chiral Zn(II) Complexes Prepared in Situ. This procedure is typical for all ligands except **4B**, **4C**, **4D**, **4L** (and complex **11**). To a stirred solution of ligand **4A** (19.8 mg, 0.1 mmol) (entry 1, Table III) in 20 mL of THF was added at room temperature a $ZnCl_2$ solution (53 μL of a 1.9 N solution in THF, 0.1 mmol). After the mixture was stirred for 5 min at room temperature 2-cyclohexenone (960 mg, 10.0 mmol) was added followed by a decrease of the temperature of the reaction mixture to −90 °C (methanol/N_2(l)). At −90 °C a mixture of isopropylmagnesium chloride in ether (2.9 mL of a 3.8 N solution, 11.0 mmol) and 30 mL of THF was added dropwise in 15 min. After being stirred for 15 min the reaction was quenched with saturated NH_4Cl (50 mL) and extracted with ether (3 × 50 mL). After drying (Na_2SO_4) a GLC sample was taken. Evaporation followed by bulb-to-bulb distillation yielded pure 3-isopropylcyclohexanone (1.36 g, 9.7 mmol, 97%).

Conjugate Addition Using Zinc Complexes Prepared in Situ from 4B, 4C, and 4D as Catalyst. At room temperature a $ZnCl_2$ solution (53 μL of a 1.9 N solution in THF, 0.1 mmol) was added to a stirred solution of ligand **4A** (23.6 mg, 0.1 mmol) in 20 mL of THF. After 5 min of stirring *n*-butyllithium (63 μL of a 1.6 N solution in hexane, 0.1 mmol) was added and the mixture was stirred for another 5 min followed by the addition of 2-cyclohexenone (960 mg, 10.0 mmol). Subsequently, cooling of the mixture to −90 °C was followed by the dropwise addition (15 min) of a mixture of 4.4 mL of a solution of isopropylmagnesium bromide (2.5 N in ether, 11.0 mmol) and 30 mL of THF. After 15 min the reaction was worked up as described in the previous procedure to provide pure **3** in 97% yield.

Conjugate Addition Using (*S*,*S*)-*N*,*N*'-Dimethyl-*N*,*N*'-bis(1-phenylethyl)-1,2-ethylenediamine Zinc Dichloride (2a) as Catalyst. To a solution of **2a** (43.4 mg, 0.1 mmol) in 20 mL of THF was added at room temperature KOtBu (11.2 mg, 0.1 mmol). After the mixture was stirred for 5 min (room temperature) 2-cyclohexenone (960 mg, 10.0 mmol) was added and the mixture was subsequently cooled to −90 °C. At this temperature a mixture of 2.9 mL of a solution of isopropopylmagnesium chloride (3.8 N in ether, 11 mmol) and 30 mL of THF were added

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(36) It is remarkable that in the enantioselective 1,2-additions of dialkylzinc reagents scrambling did occur when an amino alcohol ligand was used (involving tetracoordinated Zn(II))[35] and no scrambling was seen with a diamino alcohol ligand (involving pentacoordinated Zn(II)).[33]

dropwise (15 min). After 15 min the reaction mixture was worked up as described in the previous procedure to yield 1.30 g (9.3 mmol, 93%) of 3-isopropylcyclohexanone.

Conjugate Addition Using 11 as Catalyst. To a stirred solution of zinc complex 11 (28.6 mg, 0.1 mmol) in 10 mL of THF was added 2-cyclohexenone (96 mg, 1.0 mmol). After 5 min the reaction mixture was cooled down to −90 °C and a mixture of isopropylmagnesium bromide (0.44 mL of a 2.5 N solution in Et_2O, 1.1 mmol) and 15 mL of THF was added dropwise (15 min). After being stirred for an additional 15 min the reaction mixture was worked up as previous described to yield 120 mg (0.86 mmol, 86%) 3-isopropylcyclohexanone.

Procedure for Following the Reaction with GLC. At −90 °C 2-cyclohexenone (960 mg, 10 mmol) is added at once to a stirred mixture of tetramethylethylenediamine (TMEDA) (25.2 mg, 0.1 mmol), zinc chloride (11.2 mg, 0.1 mmol), KOtBu (142 mg, 1.0 mmol), decane (internal standard), and isopropylmagnesium bromide (4.4 mL of a 2.5 N solution in ether, 11.0 mmol) in 50 mL of THF. At 10-min intervals samples of 0.1 mL were taken. These samples were immediately quenched with wet THF and injected in the GLC. After 3 h at −90 °C the reaction mixture was quenched and worked up using the standard procedure except that also the amount of condensation product was determined. For the reference reaction the same procedure was followed except that the reaction mixture contained no TMEDA, Zinc chloride, and KOtBu. GLC retention times (oven temperature 110 °C, flow 76.8 mL/min He): 2-cyclohexenone, 2.80 min; decane, 4.25 min; 1-isopropyl-2-cyclohexene-1-ol, 6.20 min; 3-isopropylcyclohexanone, 8.37 min.

Conversion to the Diastereoisomeric Ketals and Analysis by ^{13}C NMR. A mixture of 3-isopropylcyclohexanone (100 mg, 0.7 mmol), (*R,R*)-2,3-butanediol (100 mg, 1.1 mmol), and *p*-toluenesulfonic acid (15 mg) in 30 mL of toluene was treated under reflux in a 100-mL round-bottom flask equipped with a Dean-Stark trap for 5–16 h. After cooling to room temperature K_2CO_3 (1 g) was added followed by washing the reaction mixture with water, saturated K_2CO_3 and brine. Drying over Na_2SO_4 was followed by evaporation of the toluene, resulting in a ketal (usually >90% isolated yield, in all respects identical with independently prepared samples and data in agreement with those reported) which was dissolved in $CDCl_3$. A ^{13}C NMR spectrum was recorded and determination of the integrated carbon resonance (C_2 and C_3 of the ketal) of the diastereoisomers provided the relative amounts of diastereoisomers present.

Procedure for the Diethylzinc Additions. To a mixture of 2-cyclohexenone (96 mg, 1.0 mmol) and TMEDA (116 mg, 1.0 mmol) in tetrahydrofuran (10 mL) stirred at 0 °C under a N_2 atmosphere was added diethylzinc (1 mL of a 1.0 N solution in toluene). The mixture was subsequently analyzed at 5-min intervals. Potassium *tert*-butoxide (11.2 mg, 0.1 mmol) was added, and after being stirred for 0.5 h the products were analyzed by GC. Product formation was confirmed by comparison with independently prepared samples of 3-ethylcyclohexanone and 1-ethyl-1-hydroxycyclohexane.

Addition of $MgBr_2$ (184 mg, 1.0 mmol) or $ZnCl_2$ (68 mg, 0.5 mmol) did not result in further conversion. Following an identical procedure but adding i-PrMgBr (0.08 mL of a 1.25 N solution in ether, 0.1 mmol) instead of $MgBr_2$ followed by stirring for 5 min resulted in a mixture of 3-isopropylcyclohexanone (7.8%), 3-ethylcyclohexanone (2.0%), 1-isopropyl-1-hydroxycyclohexane (0.2%), and 1-ethyl-1-hydroxycyclohexane (>0.1%) (GC analysis).

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Synthesis of 1,1′-Bis(2-amino-2-carboxyethyl)ferrocene (1,1′-Ferrocenylbis(alanine))

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The 1,1′-disubstituted ferrocenyl amino acid **1** (1,1′-ferrocenylbis(alanine)) was synthesized by two different routes. Optically acitive **1** was obtained by asymmetric hydrogenation of the bis(didehydroamino acid) derivatives **2** followed by deprotection. The bis(didehydroamino acid) derivatives were prepared by a palladium-catalyzed coupling between 1,1′-diiodoferrocene and suitably protected 2-amidoacrylates. Alternatively, racemic **1** was obtained via the bis(nitro ester) **6**. The key step in this synthesis was the one-step conversion of the nitro compound **6** into the Boc-protected amino acid derivative **3a**.

The mutual interaction of aromatic rings of aromatic amino acid residues in proteins and peptides has recently been discussed by several authors.[1] These investigations show that aromatic side chains of proteins and even of smaller peptides tend to arrange their aromatic rings in domains with relatively short distances between the rings. The interaction between aromatic rings seems to contribute largely to the stabilization of the tertiary structure of a protein, and it has even been suggested that *aromatic–aromatic interaction* forms an important class of noncovalent bonding besides hydrogen bonds, electrostatic interactions, and van der Waals interactions.[1b] Incorporation of aromatic amino acids, with a covalent link between their aromatic rings, into peptides and proteins would give possibilities to further study the biological consequences of this concept experimentally. To date, there are some interesting reports in the literature of synthetic work concerning covalent linkages between aromatic side chains in peptides.[2,3] One example is the introduction of an azo-bridge between tyrosine and phenylalanine residues

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